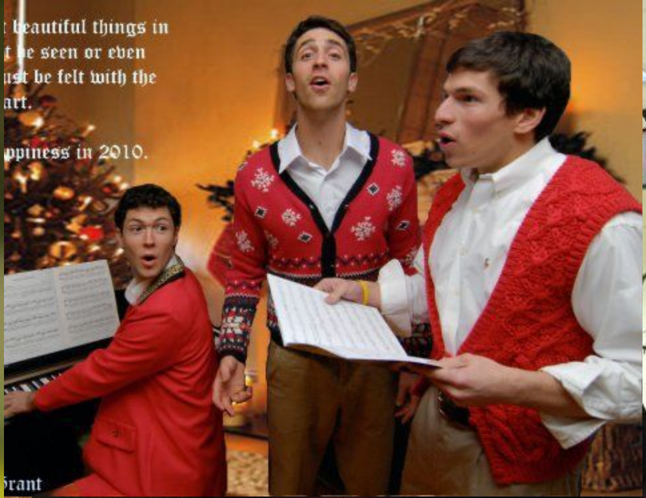
From Chasing My Cure to Every Cure:
Unlocking the lifesaving potential of FDA-approved medicines

GRANT MITCHELL, MD, MBA
Co-Founder & CEO, Every Cure

November 15, 2023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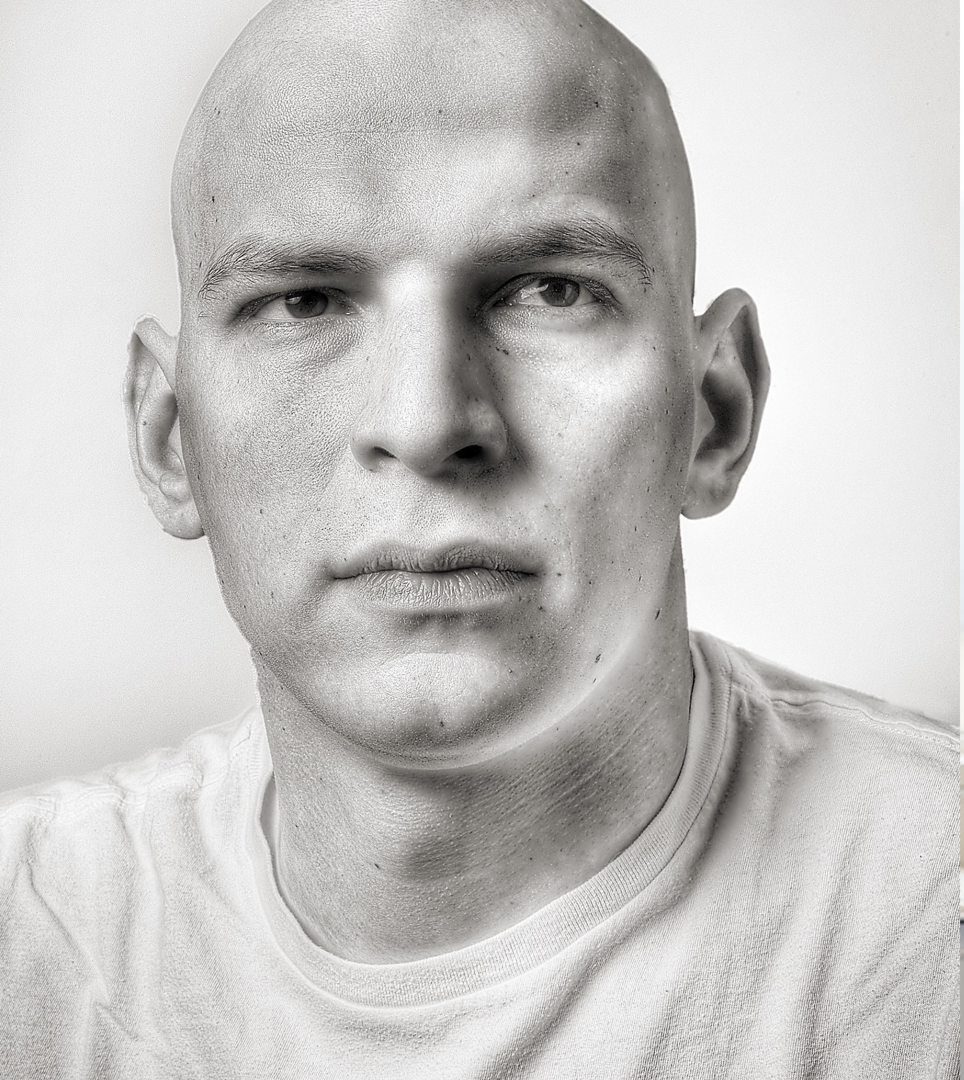
Grant

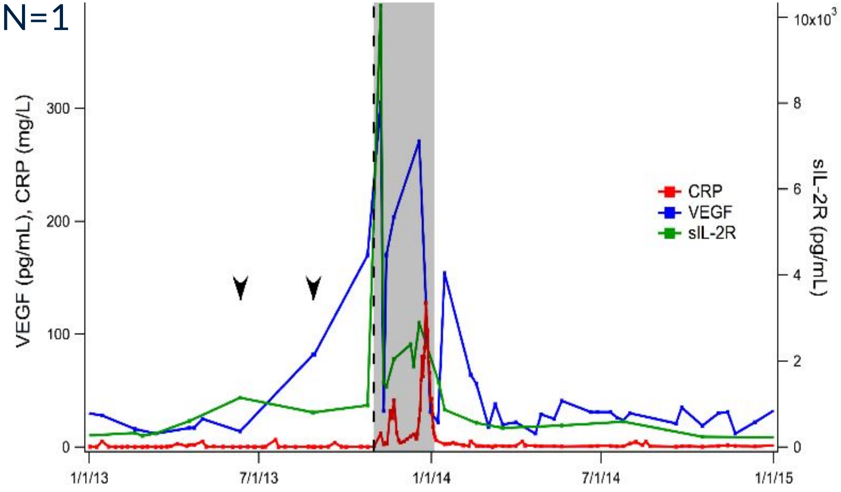

EXIT





Elevated VEGF and T cell activation in iMCD

N=1



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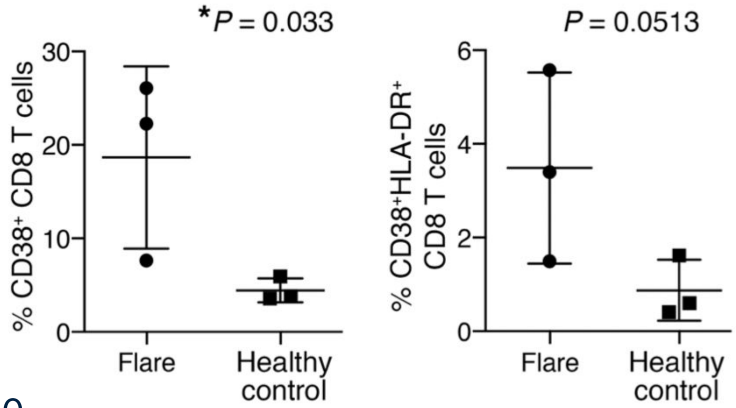
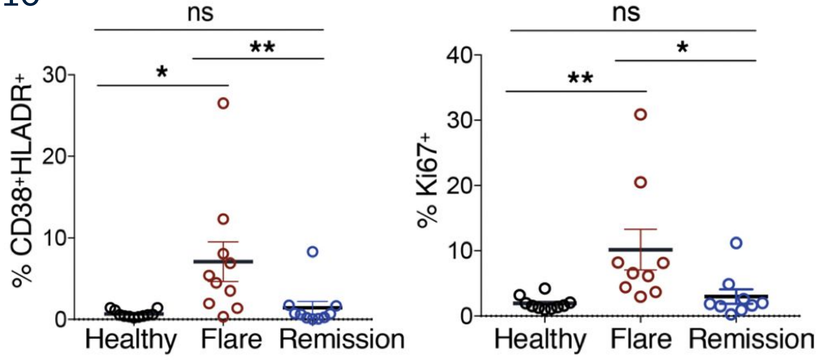
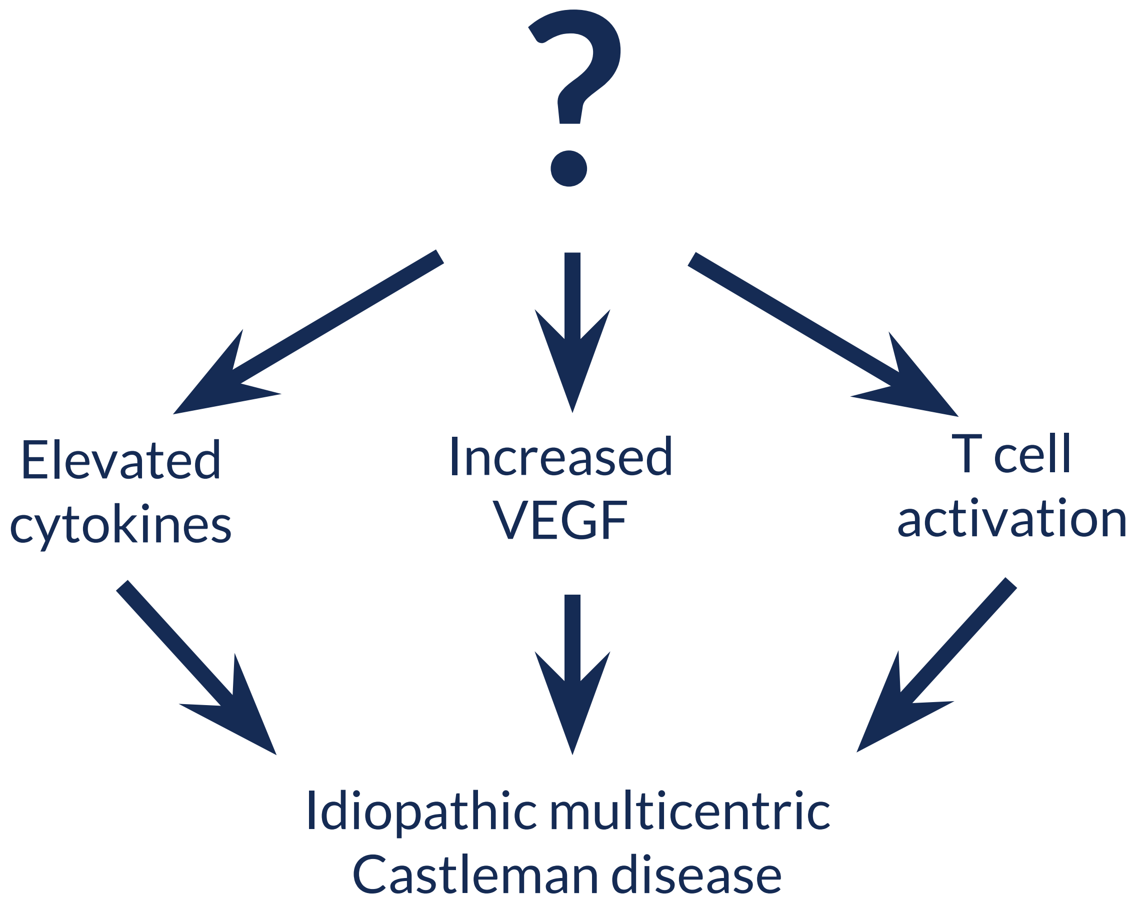


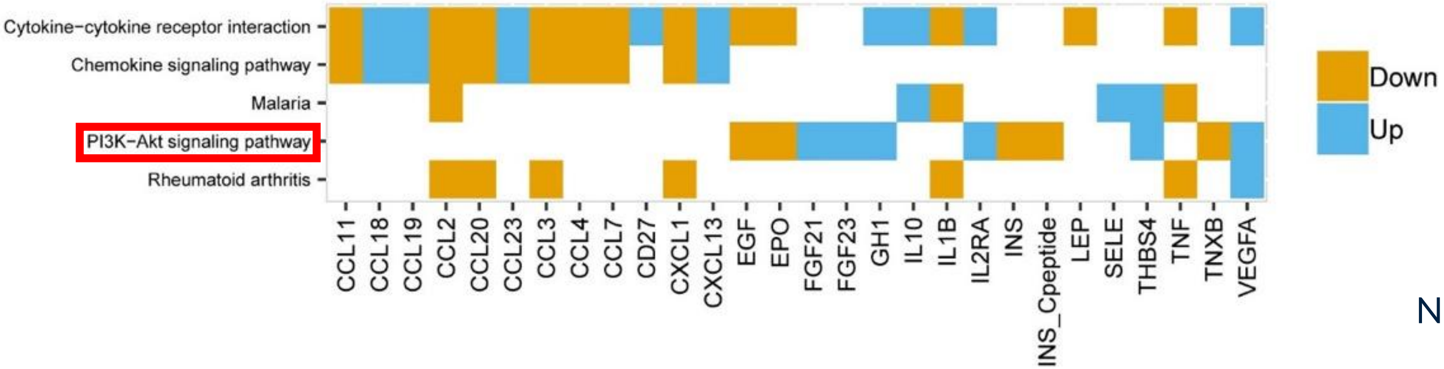
N=10



Fajgenbaum et al. JCI. 2019.
Pai et al. JCI Insight. 2020


?
Elevated cytokines
Increased VEGF
T cell activation
Idiopathic multicentric Castleman disease

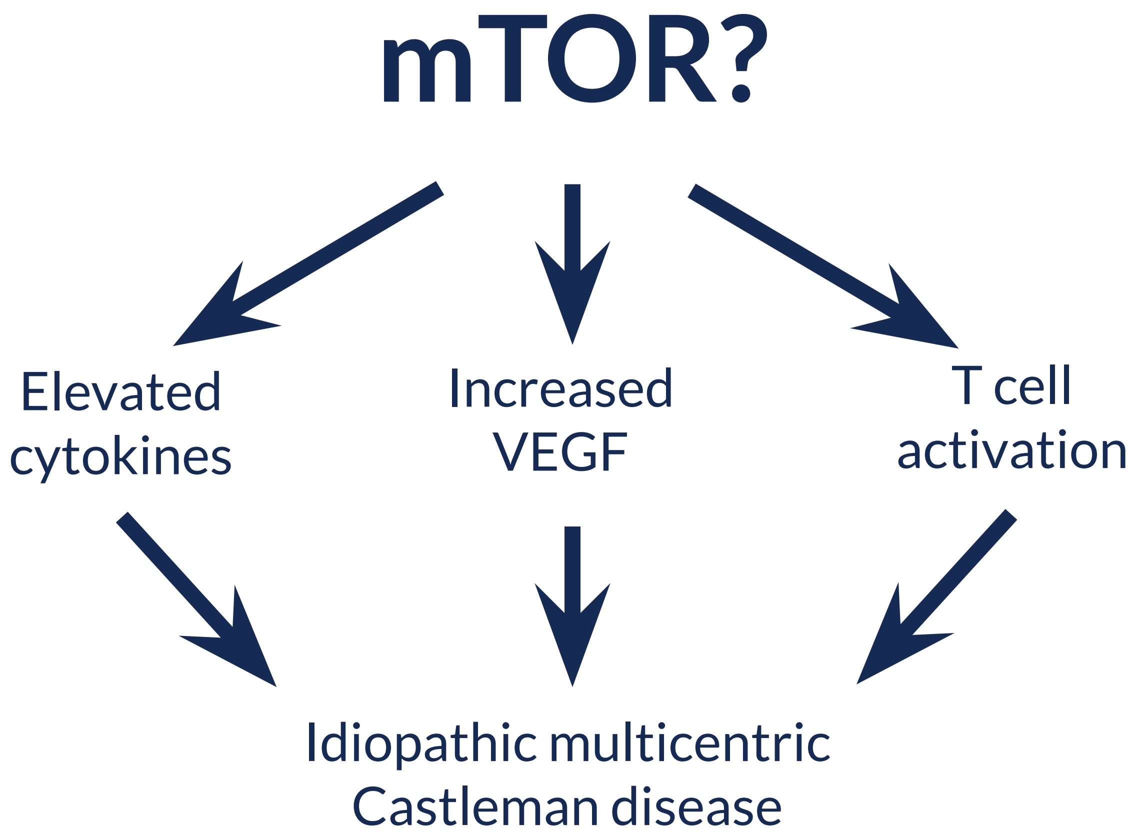
mTOR signaling enriched in iMCD



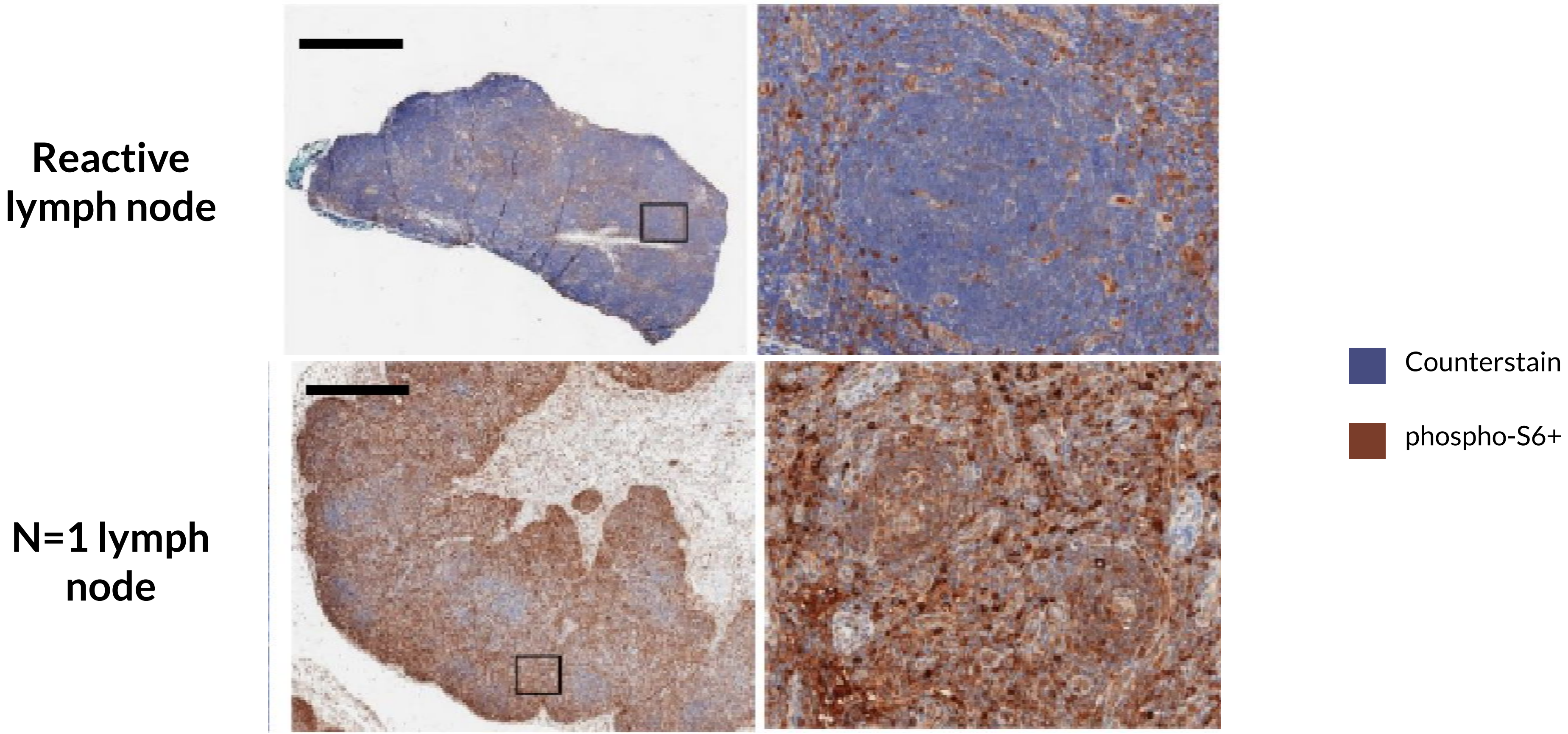
N=1

IPA of SOMAscan Flare 3		
	Top five canonical pathways	-log(p-value)
1	PI3K Signaling in B Lymphocytes	5.26
2	mTOR Signaling	4.64
3	Protein Kinase A Signaling	4.64
4	Synaptic Long Term Potentiation	4.15
5	G Beta Gamma Signaling	4.15

Fajgenbaum et al. JCI. 2019.

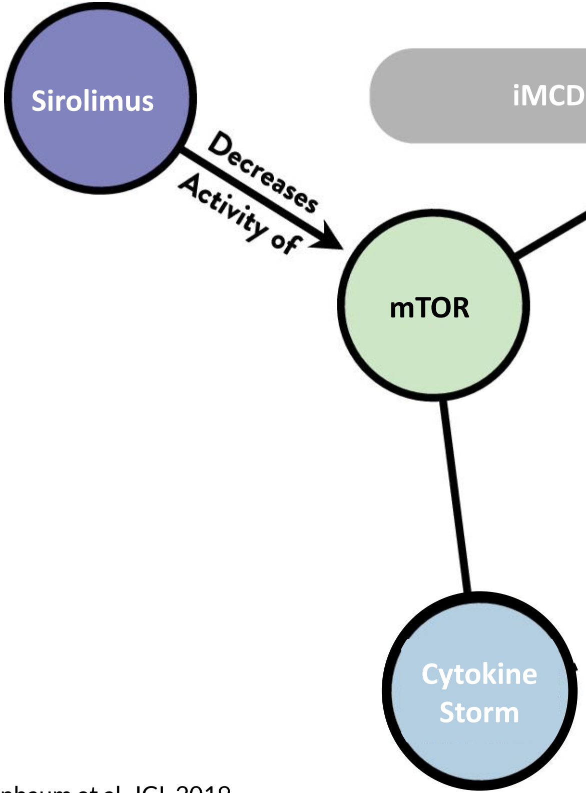

mTOR?
Elevated cytokines
Increased VEGF
T cell activation
Idiopathic multicentric Castleman disease

Immunohistochemistry for phospho-S6, a marker of mTOR activation



Fajgenbaum et al. JCI. 2019.

Sirolimus identified for iMCD by uncovering mechanistic insights




Above, Clarice Maggio, a nurse... port on Dr. David Fajgenbaum'... through which he will receive t... the Hospital of the University o... Pennsylvania. Left, the doctor, ... Castleman disease, with his wif... home in Philadelphia.

Doctor, Cure Thyself

On the brink of death, a physician with a rare disease decides to become his own test subject.

By KATIE THOMAS

They called him the Beast.

David Fajgenbaum was the fittest of his friends at the University of Pennsylvani... medical school, a 6-foot-3 gym... former quarterback...

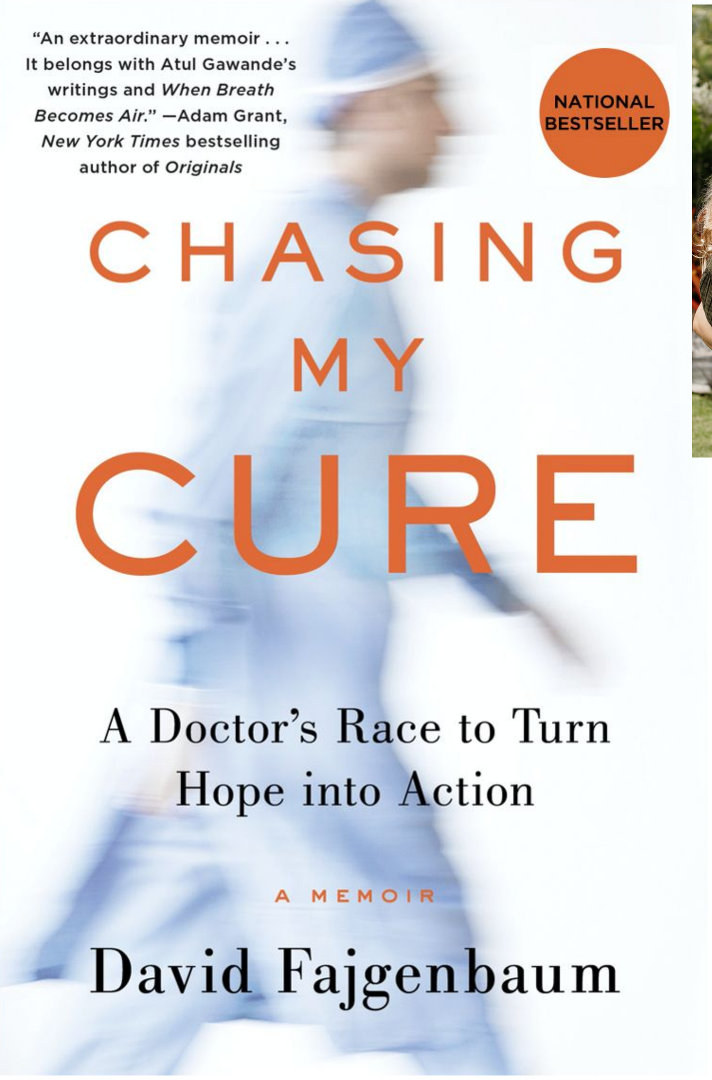
his former roommate, Gra... used to walk to w... would ar...

The New York Times

SUNDAY, FEBRUARY 5, 2017

"All the News ... Print"

Fajgenbaum et al. JCI, 2019.
Arenas & Fajgenbaum. Blood, 2020.



CSTL
Center *for* Cytokine Storm Treatment & Laboratory

QuantumBlack
AI by McKinsey

Nashville Biosciences.

AdhereTech

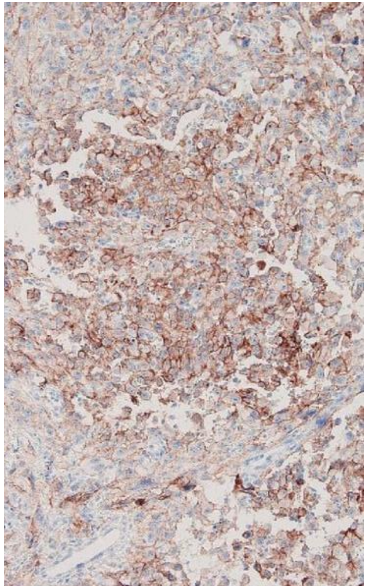
CSTL
Center *for* Cytokine Storm Treatment & Laboratory

NIH
National Heart, Lung, and Blood Institute

FDA

Uncovered an angiosarcoma treatment hiding in plain sight

AS — PDL1 — PD1-i




National Comprehensive Cancer Network®
NCCN

Guidelines for Soft Tissue Sarcoma

Panel Discussion/References

The panel consensus supported including the following subtype for nivolumab ± ipilimumab:
- For myxofibrosarcoma, UPS, dedifferentiated liposarcoma, cutaneous angiosarcoma, and undifferentiated sarcomas

OR
- For TMB-H (≥10 mutations/megabase [mut/Mb]) regardless of soft tissue sarcoma sub-type

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Recruiting — Testing the Addition of Nivolumab to Chemotherapy in Treatment of Soft Tissue Sarcoma

Recruiting — Trial of Sunitinib and/or Nivolumab Plus Chemotherapy in Advanced Soft Tissue and Bone Sarcomas

Recruiting — Nivolumab and Ipilimumab in Treating Patients With Rare Tumors

2013 paper links PD1/PDL1 and angiosarcoma (AS)

Testing **confirmed increased PDL1** in 2016

First AS patient treated with PD1 inhibitor in **remission >7 years**

Recommended by NCCN and clinical trials underway

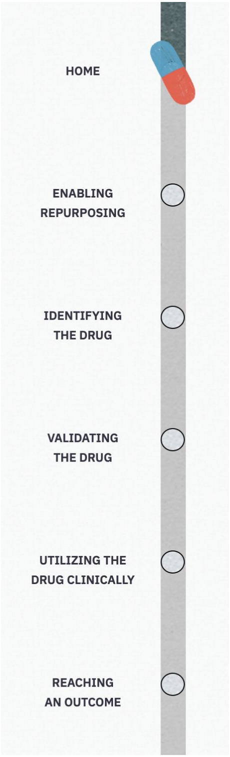
Kim et al. PLOS ONE. 2013.

EVERY CURE

Built a ROADMAP with CZI for rare disease drug repurposing

- 723 respondents from rare disease community, including 21% of all rare disease organizations
- Provides paths for rare disease-specific data-driven drug repurposing

www.everycure.org/roadmap



Korsunska et al. 2023 (in submission).

How many cures sit on the pharmacy shelf…

...while the data able to link these drugs and diseases hide in plain sight?

3,000+
DRUGS

THAT ARE APPROVED FOR
3,000 DISEASES

9,000 DISEASES

WITH NO APPROVED THERAPIES

3,000+

DRUGS

THAT ARE APPROVED FOR

3,000 DISEASES


ACNE PIMPLES
Acne Medication 5
ALBUTEROL SULFATE
INHALATION SOLUTION
ALBUTEROL SULFATE
INHALATION SOLUTION
ALBUTEROL SULFATE
INHALATION SOLUTION
align
MAJOR
Calcium
Centrum

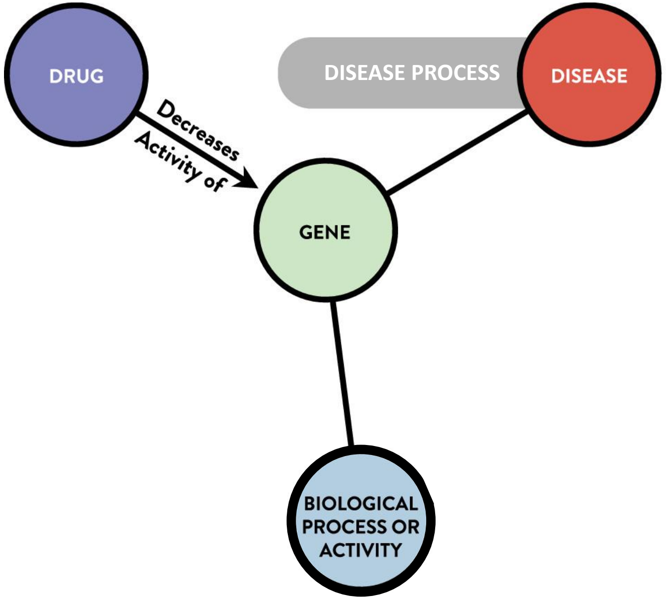
“

There is a missing link in the system that isn't filled by NIH, FDA, or pharma...
No one is responsible for making sure that drugs are fully utilized across diseases.

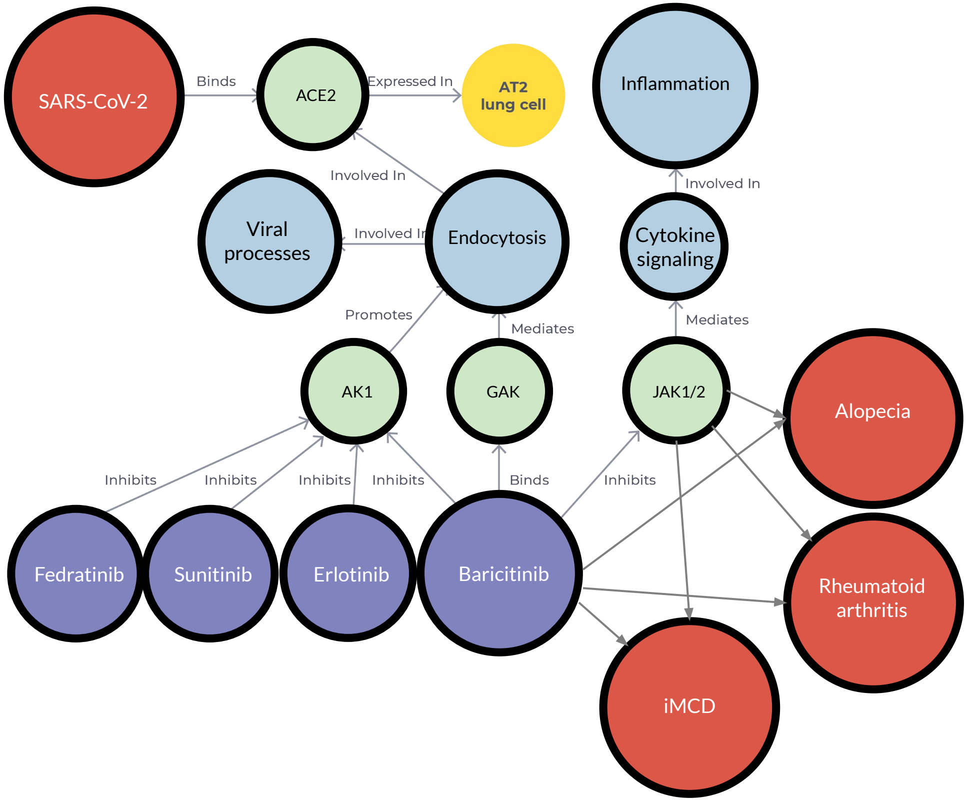
— JANET WOODCOCK, MD
PRINCIPAL DEPUTY COMMISSIONER, FDA

Baricitinib identified for COVID by applying AI to knowledge graphs

Framework for knowledge graph connections



Example of COVID knowledge graph connections



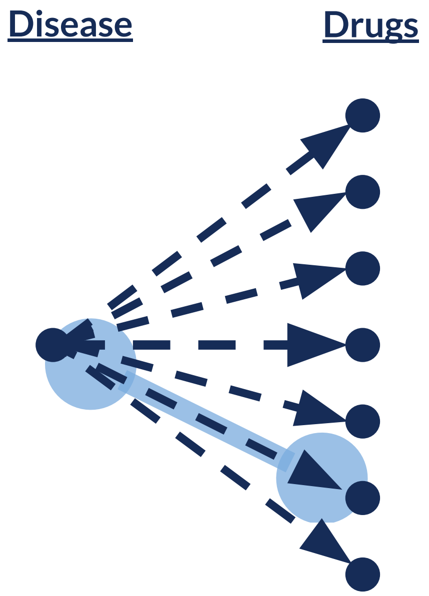
Richardson et al. *Lancet* **395**, e30–e31 (2020).
Selvaraj et al. *EClinicalMedicine* **49**, 101489 (2022).
Marconi et al. *Lancet Respir Med* **9**, 1407–1418 (2021).

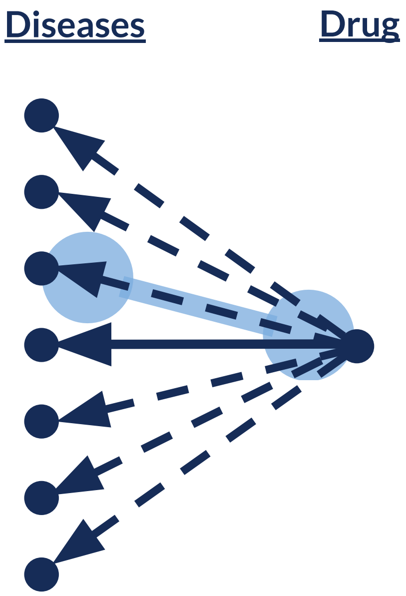
EVERY CURE

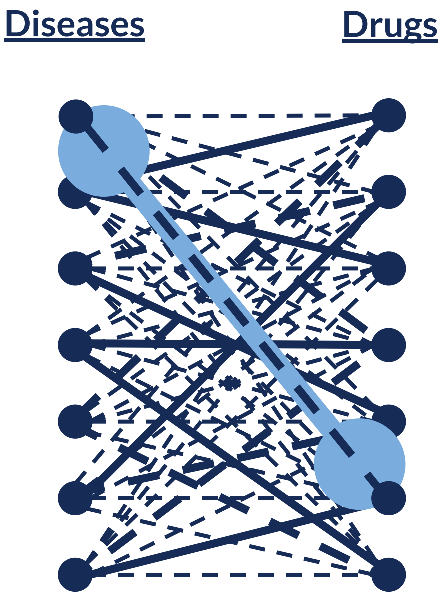
Unleashing the potential of *every* approved medicine to **treat *every* disease and *every* patient possible**

Advancing a new field of systematic pharmaco-phenotyping to save lives

Traditional Drug Repurposing + **Drug Repurposing: Indication Expansion** = **Therapeutic Crosspurposing / Systematic Pharmacophenotyping**



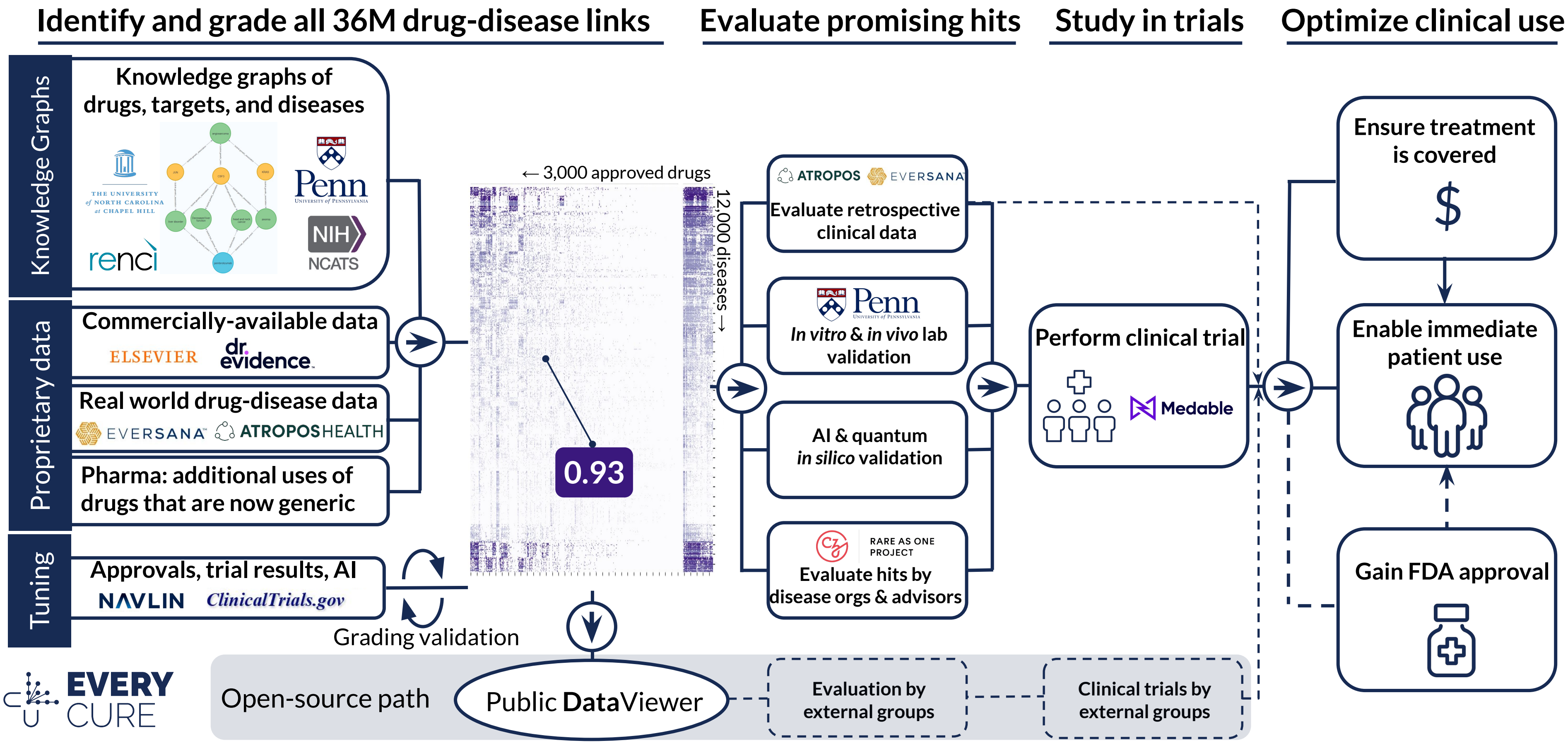




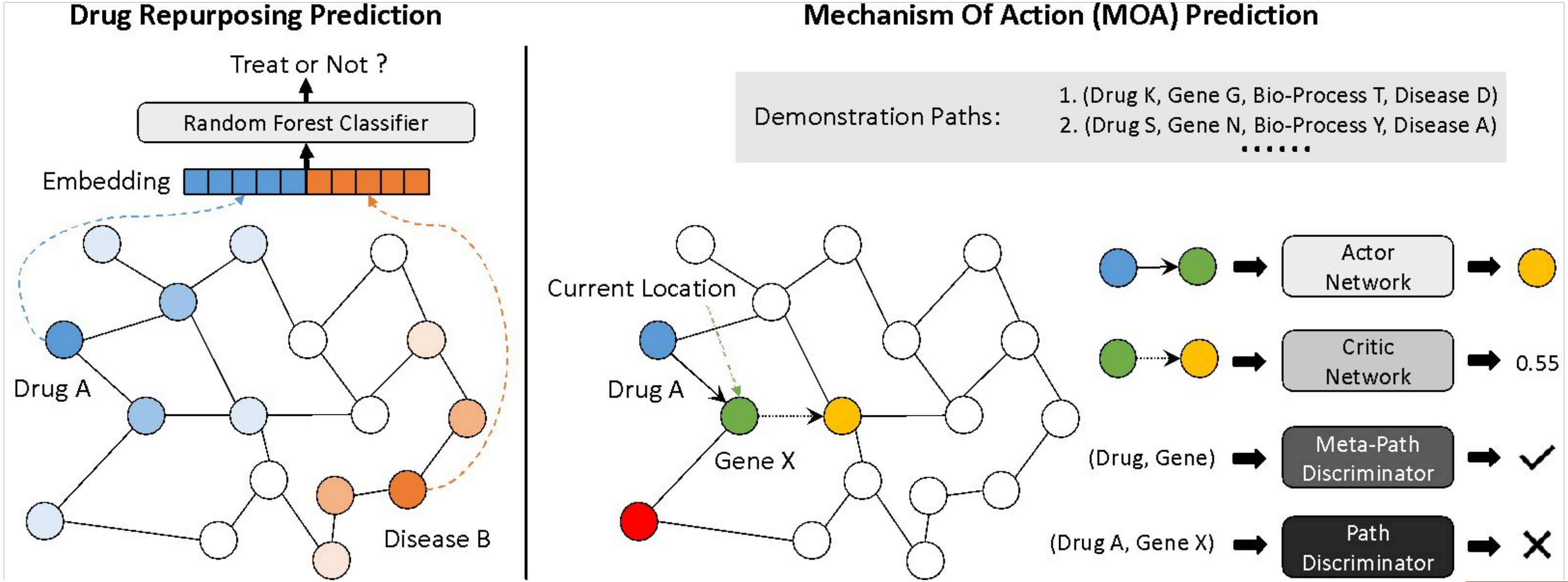
Korsunska, et al. 2023 (in submission).

EVERY CURE

Every Cure combines federally-funded knowledge graphs, proprietary data, and AI to grade all 36M drug-disease links and advance top hits



We are using 5 independent algorithms to grade treatment opportunities



Mu et al., KGML-xDTD: A KG-based ML Framework for Drug Treatment Prediction and Mechanism Description. bioRxiv. 2022.

First ‘All drugs vs All diseases’ analysis generated promising results!

Rank	Drug	Mechanism	Score
1	ADALIMUMAB	Anti-TNF	0.83735989
2	RITUXIMAB	B cell depletion	0.83385483
3	CERTOLIZUMAB PEGOL	Anti-TNF	0.82613921
4	CYCLOPHOSPHAMIDE	cytotoxic	0.81639938
5	METHYLPREDNISOLONE	corticosteroid	0.81590714
6	PREDNISONE	corticosteroid	0.80920972
7	SECUKINUMAB	Anti-IL17A	0.80650303
8	TRASTUZUMAB	Anti-HER2	0.80566249
9	TRIAMCINOLONE	corticosteroid	0.80365282
10	CISPLATIN	cytotoxic	0.80064139
63	Ruxolitinib	JAK1/2	0.77005478
177	Temsirolimus	mTOR	0.75333104
253	Sarilumab	IL-6	0.74729794

Unpublished.
Mu et al., bioRxiv. 2022.
Pierson et al., Blood Advances, 2021.

Our partners and key relationships in saving lives

EVERY CURE

Partners

CHAN ZUCKERBERG INITIATIVE

Flagship Pioneering

ELEVATE PRIZE

LYDA HILL PHILANTHROPIES

dr. evidence

EVERSANA™

CSTL Center for Cytokine Storm Treatment & Laboratory

CDCN CASTLEMAN DISEASE COLLABORATIVE NETWORK

CLINTON GLOBAL INITIATIVE

aws

somalogic

monarch INITIATIVE

Medable

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

WORLDWIDE CLINICAL TRIALS

ELSEVIER

CuresWithinReach

CDRC CURE DRUG REPURPOSING COLLABORATORY

ATROPOS HEALTH

UAB HUGH KAUL PRECISION MEDICINE INSTITUTE

PennState

Key relationships

medidata

NIH National Center for Advancing Translational Sciences

janssen

REAGAN-UDALL FOUNDATION for the Food and Drug Administration

DATAVANT

Google Health

BROAD INSTITUTE

FDA

healx

GSK

AstraZeneca

UNM SCHOOL of MEDICINE

SANDBOXAQ™

Wolters Kluwer

MILKEN INSTITUTE FasterCures


EMOTIONAL CONCUSSIONS
live your best life
inspire


APPOINTMENT

Lessons learned and future directions

- Lots of drug repurposing opportunities are waiting to be uncovered, confirmed, and/or advanced into clinical practice.
- We need to accurately prioritize repurposing opportunities for further evaluation.
- We can rapidly identify promising candidates but validating them in model systems is critical to maximizing impact and de-risking clinical trials.
- Don’t reinvent the wheel/ROADMAP.
- Every Cure would LOVE to partner with you!
  - Share data with us for integration into the knowledge graph
  - Evaluate promising hits
  - Perform clinical trials together
- Please share open opportunities with potential mission-driven candidates: everycure.org/joinus (e.g., CTO, CMO, Head of Data Science, Head of Engineering, etc)

david@everycure.org

EveryCure.org

Thank you to our scientific partners and collaborators!

INSTITUTION	GROUP PI	DATABASE	APPROACH
Pennsylvania State University	Koslicki	RTX-KG2	KGML-xDTD
Scripps Research Institute	Su	BTE	Case Based Reasoning/Neural Nets
RENCI	Tropsha/Bizon	ROBOKOP	Rule Mining/Resistance Distance
UAB Precision Medicine Institute	Might	RTX-KG2	Druggability Index
Institute for Systems Biology	Huang/Baranzini	SPOKE	Weighted Path Search
Monarch Initiative	Haendel	MONARCHKG	

NIH National Center for Advancing Translational Sciences

monarch INITIATIVE

UAB HUGH KAUL PRECISION MEDICINE INSTITUTE

CHAN ZUCKERBERG INITIATIVE

Flagship Pioneering

CSTL Center for Cytokine Storm Treatment & Laboratory

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

PennState

dr. evidence

EVERSANA™

CDCN CASTLEMAN DISEASE COLLABORATIVE NETWORK

somalogic™

REAGAN-UDALL FOUNDATION for the Food and Drug Administration

CLINTON GLOBAL INITIATIVE

CuresWithinReach

Medable

medidata

WORLDWIDE CLINICAL TRIALS

ELSEVIER

Janssen

CDRC CURE DRUG REPURPOSING COLLABORATORY

ATROPOSHEALTH

EveryCure.org/joinus

drug_name	prob	treated_labeled_by_kg2	rk_match	rk_lit_treats	rk_biolink_treats	rk_hetio_treats	rk_drugcentral_treats	rank	percentile
OLANZAPINE	0.91726815	TRUE	TRUE	TRUE	TRUE	FALSE	FALSE	63123	0.00101289
DICHLORVOS	0.89301168	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	115918	0.00186006
TIOTROPIUM	0.88688865	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	130370	0.00209196
ASENAPINE	0.88518213	FALSE						134420	0.00215695
CANRENOATE	0.88382046	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	137699	0.00220957
FLUOXETINE HYDROCHLORIDE	0.88297934	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	139781	0.00224297
ISRADIPINE	0.88138511	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	143693	0.00230575
ENTINOSTAT	0.88001326	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	147065	0.00235986
AMIFAMPRIDINE PHOSPHATE	0.87888067	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	149928	0.0024058
LITHIUM	0.8782279	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	151574	0.00243221
CARBAMAZEPINE	0.87798044	TRUE	TRUE	TRUE	FALSE	FALSE	FALSE	152191	0.00244211
CYCLOPHOSPHAMIDE	0.87779645	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	152657	0.00244959
PROPRANOLOL HYDROCHLORIDE	0.8777245	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	152823	0.00245225
OLANZAPINE	0.87671313	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	155339	0.00249262
FLUVASTATIN	0.8751996	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	159157	0.00255389
CLOZAPINE CHLORIDE	0.87335519	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	163699	0.00262677
DOMPERIDONE	0.86844223	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	176096	0.0028257
OLANZAPINE	0.86770766	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	178047	0.002857
TRIFLUOPERAZINE	0.867064	FALSE	TRUE	TRUE	FALSE	FALSE	FALSE	179618	0.00288221
DOMPERIDONE	0.86651505	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	181002	0.00290442
AMIODARONE HYDROCHLORIDE	0.86442496	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	186445	0.00299176
PRIMAQUINE PHOSPHATE	0.86419384	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	187017	0.00300094
PRIMAQUINE PHOSPHATE	0.86412991	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	187186	0.00300365
BETAXOLOL	0.86398843	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	187578	0.00300994
VINPOCETINE	0.86372367	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	188282	0.00302124

BICIFADINE	0.86365795	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	188460	0.00302409	FALSE
TIOTROPIUM	0.86353385	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	188772	0.0030291	FALSE
ILOPERIDONE	0.86317312	FALSE	TRUE	TRUE	FALSE	FALSE	FALSE	189683	0.00304372	FALSE
DIGOXIN	0.86257529	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	191207	0.00306817	FALSE
OLANZAPINE	0.86175336	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	193335	0.00310232	FALSE
antidepressant	0.86173558	TRUE	TRUE	FALSE	TRUE	FALSE	FALSE	193377	0.00310299	FALSE
CELIPROLOL HYDROCHLORIDE	0.861629	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	193663	0.00310758	FALSE
ISOPROTERENOL HYDROCHLORIDE	0.86153537	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	193876	0.003111	FALSE
GLIMEPIRIDE	0.86124756	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	194660	0.00312358	FALSE
SIMVASTATIN	0.86111103	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	194994	0.00312894	FALSE
ETOMIDATE	0.86025575	FALSE	TRUE	TRUE	FALSE	FALSE	FALSE	197267	0.00316541	FALSE
LANSOPRAZOLE	0.86004845	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	197818	0.00317426	FALSE
VILAZODONE	0.85952518	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	199228	0.00319688	FALSE
FLUVASTATIN	0.85900637	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	200611	0.00321907	FALSE
NIMODIPINE	0.85891182	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	200868	0.0032232	FALSE
PALIPERIDONE	0.85873475	TRUE	TRUE	TRUE	FALSE	FALSE	TRUE	201304	0.00323019	FALSE
PRIMAQUINE PHOSPHATE	0.85818893	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	202740	0.00325324	FALSE
Azathioprine sodium	0.8581483	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	202856	0.0032551	FALSE
SULPIRIDE	0.85791303	FALSE	TRUE	TRUE	FALSE	FALSE	FALSE	203509	0.00326557	FALSE
FLUVASTATIN	0.85773323	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	203966	0.00327291	FALSE
FLUVASTATIN	0.85768632	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	204084	0.0032748	FALSE
LOVASTATIN	0.85762238	FALSE	TRUE	TRUE	FALSE	FALSE	FALSE	204247	0.00327742	FALSE
THIOPENTAL	0.85748542	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	204623	0.00328345	FALSE
CERIVASTATIN	0.85719481	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	205300	0.00329431	FALSE
CANDESARTAN	0.85710199	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	205534	0.00329807	FALSE

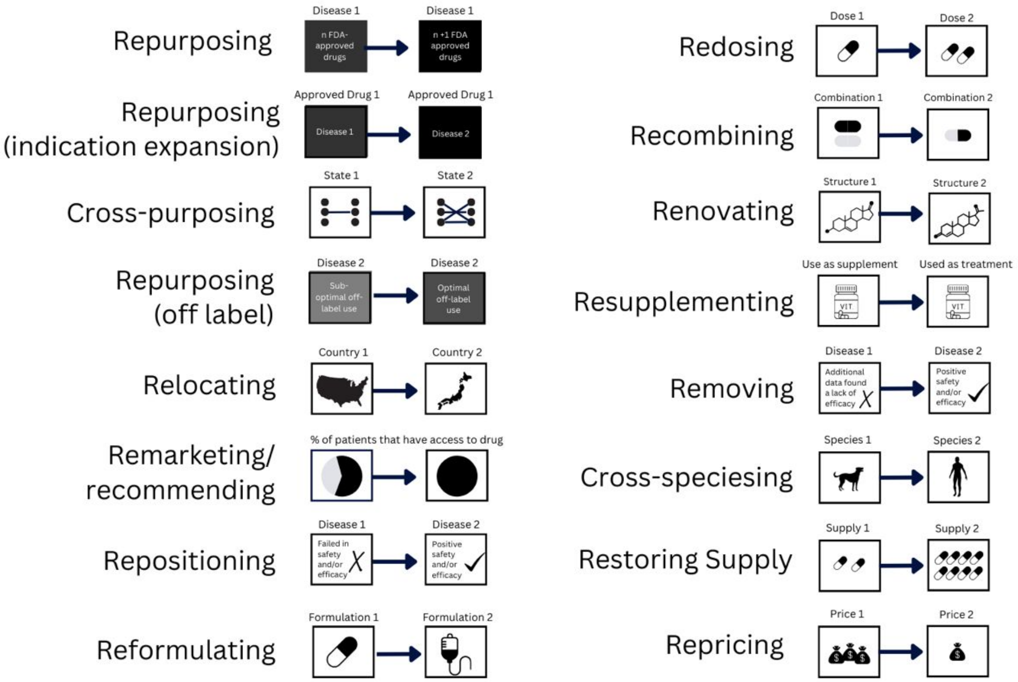
Our Roadmap

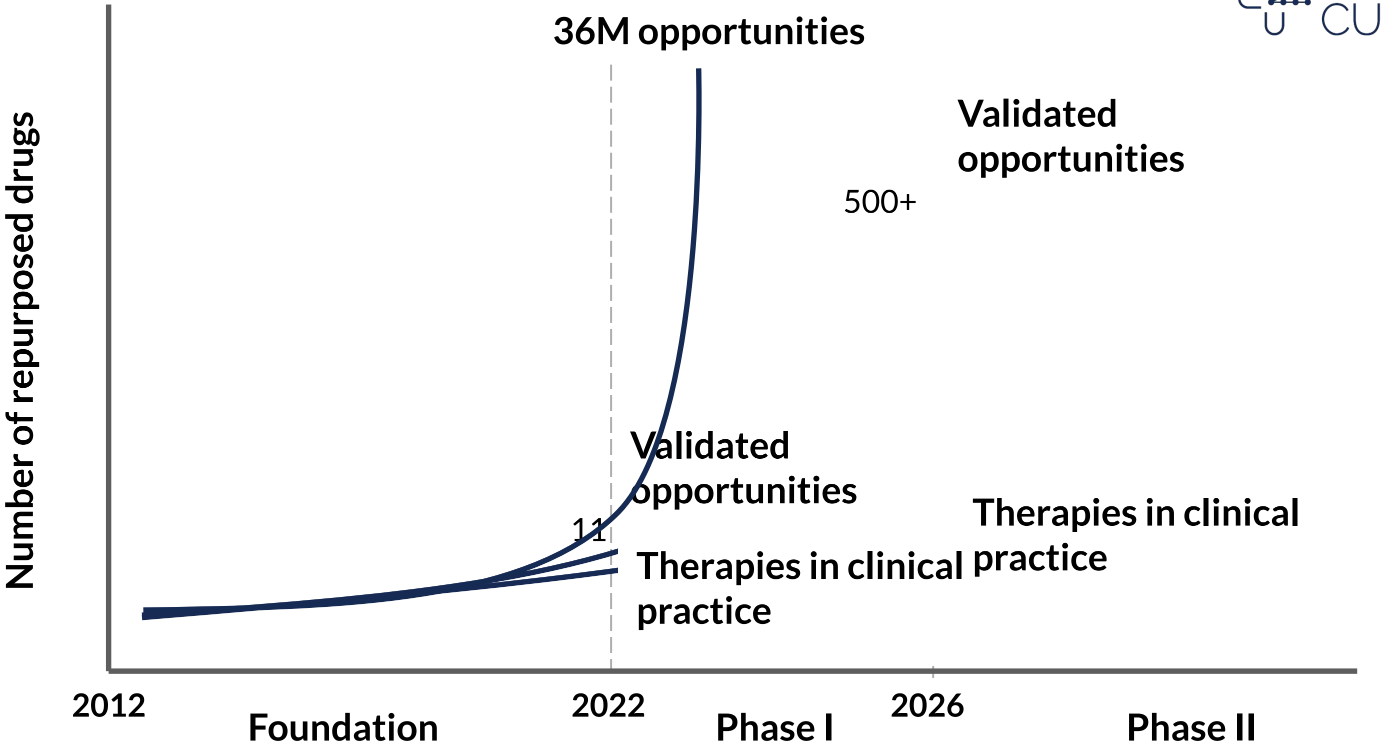
1. Build out the team (e.g., CTO, CMO, Head of Data Science, Head of Data Engineering, etc)
2. Establish benchmark datasets + knowledge graphs for computational drug repurposing
3. Integrate proprietary data and generate 'omics data to enhance the datasets + KGs
4. Refine ranking algorithms for "all drugs" vs "all diseases" query and release publicly
5. Utilize framework for selecting drug-disease hits for further evaluation
6. Evaluate promising hits in *in silico* and clinical studies as well as *in vitro* and *in vivo* studies
7. Perform clinical trials of high-impact drug repurposing opportunities
8. Optimize the use of medicines to alleviate suffering for more patients with more diseases


CELEBRATION OF
TO
Science


brightens your life

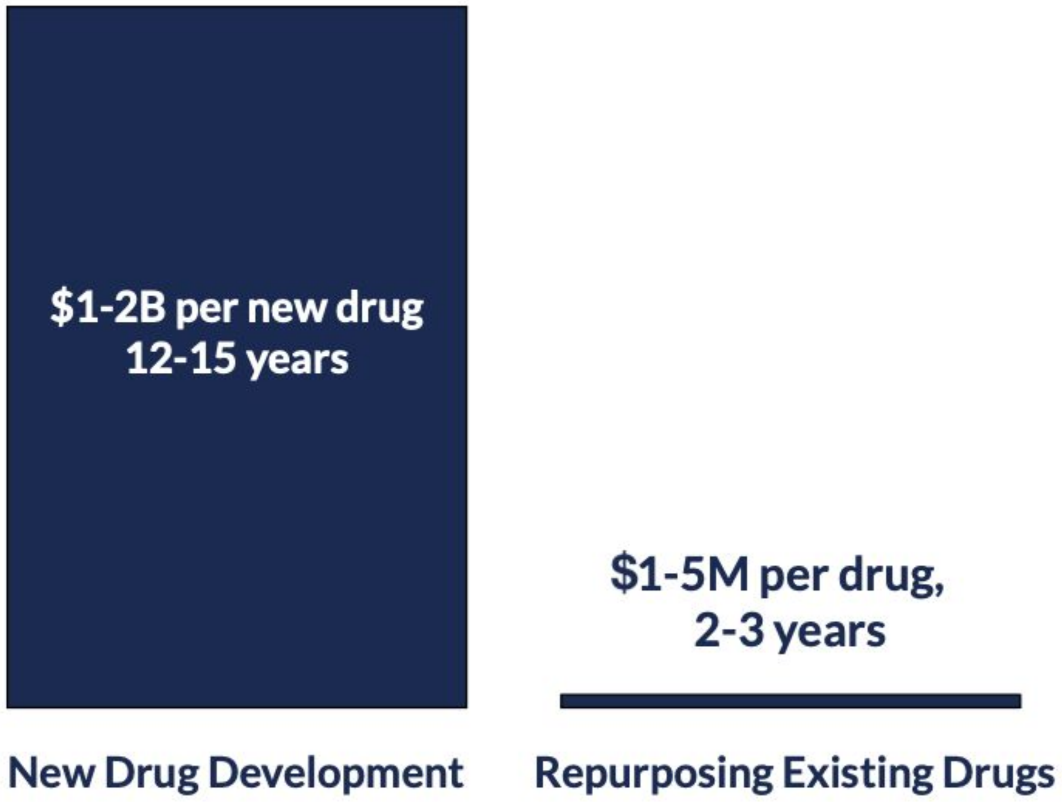
Paths towards Optimal Therapeutic Utilization



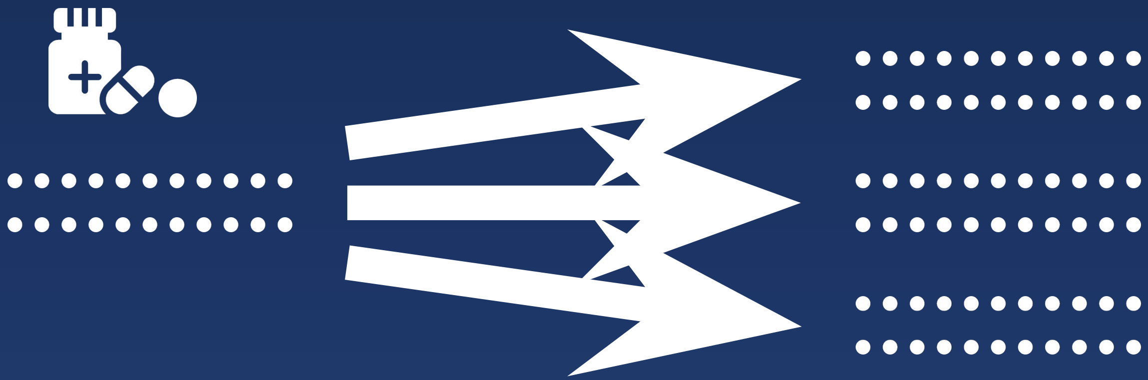


Goal:	Establish process	Build scalable AI engine	Save more lives
Cost:	$10M	$10M	$1-5M/ disease

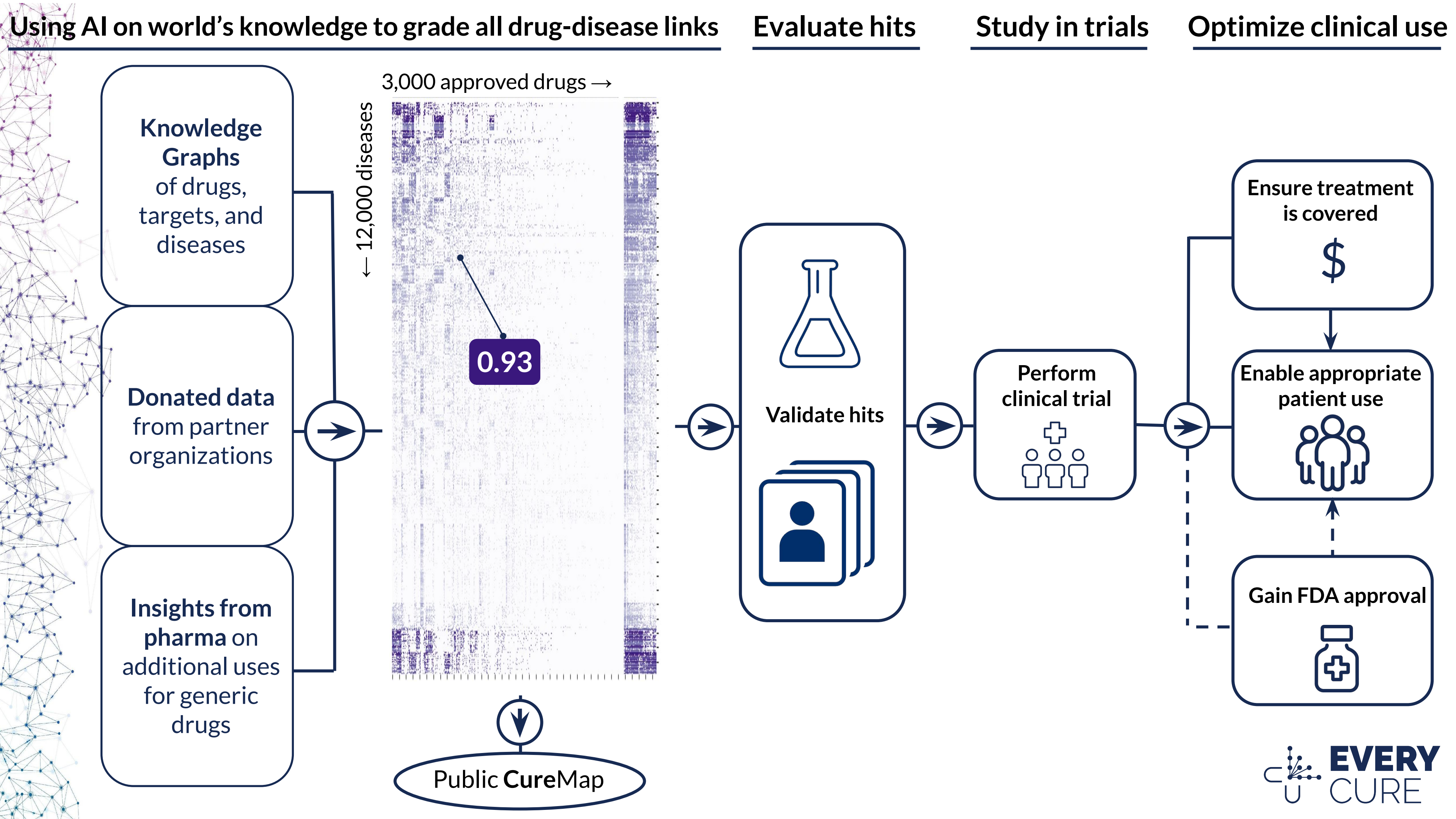
ResearchAmerica. Estimated U.S. Medical and Health R&D Investments, by Source, 2020.


$1-2B per new drug
12-15 years
$1-5M per drug,
2-3 years
New Drug Development
Repurposing Existing Drugs

THROUGH COMBINING AND ANALYZING EXISTING DATA



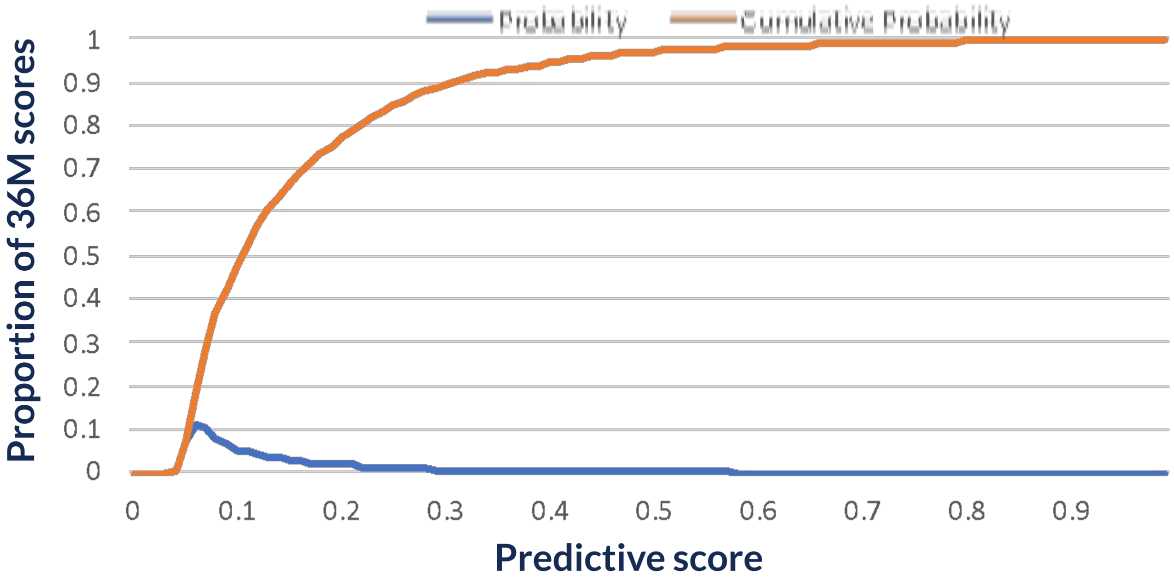
WE CAN DISCOVER NEW USES
FOR EACH AND EVERY DRUG



Using AI on world's knowledge to grade all drug-disease links
Evaluate hits
Study in trials
Optimize clinical use
Knowledge Graphs of drugs, targets, and diseases
Donated data from partner organizations
Insights from pharma on additional uses for generic drugs
3,000 approved drugs →
← 12,000 diseases
0.93
Public CureMap
Validate hits
Perform clinical trial
Ensure treatment is covered
$
Enable appropriate patient use
Gain FDA approval
EVERY CURE

The first ‘All vs All’ query generated promising results

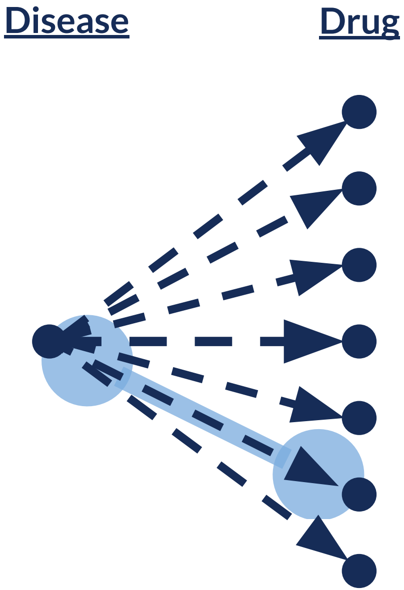
- Distribution of 36M scores came out as expected (50% have probability < 0.1)
- Top hits were anticipated (primarily approved indications)



Unpublished.
Mu et al., bioRxiv. 2022.

Advancing a new field of systematic pharmaco-phenotyping to save lives

Traditional Drug Repurposing



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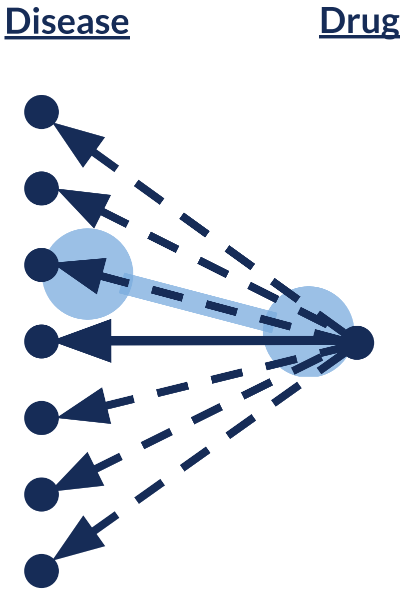
Drug Repurposing: Indication Expansion



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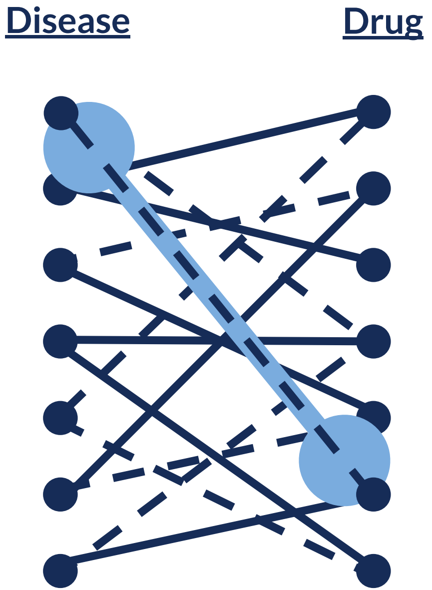
Therapeutic Crosspurposing / Systematic Pharmacophenotyping



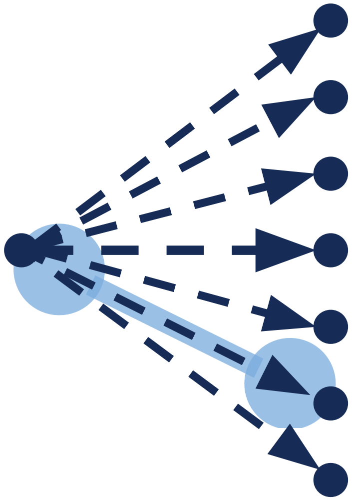
Korsunska, et al. 2023 (in submission).

EVERY CURE

Advancing a new field of systematic pharmaco-phenotyping to save lives

Traditional Drug Repurposing

<u>Disease</u> <u>Drug</u>



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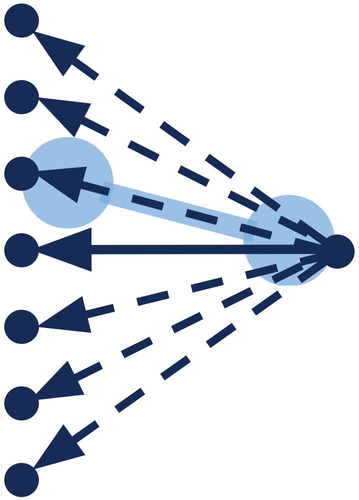
Drug Repurposing: Indication Expansion

<u>Disease</u> <u>Drug</u>



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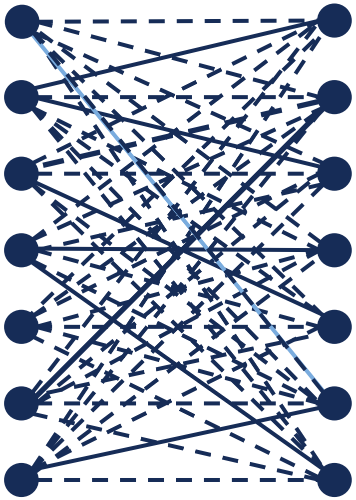
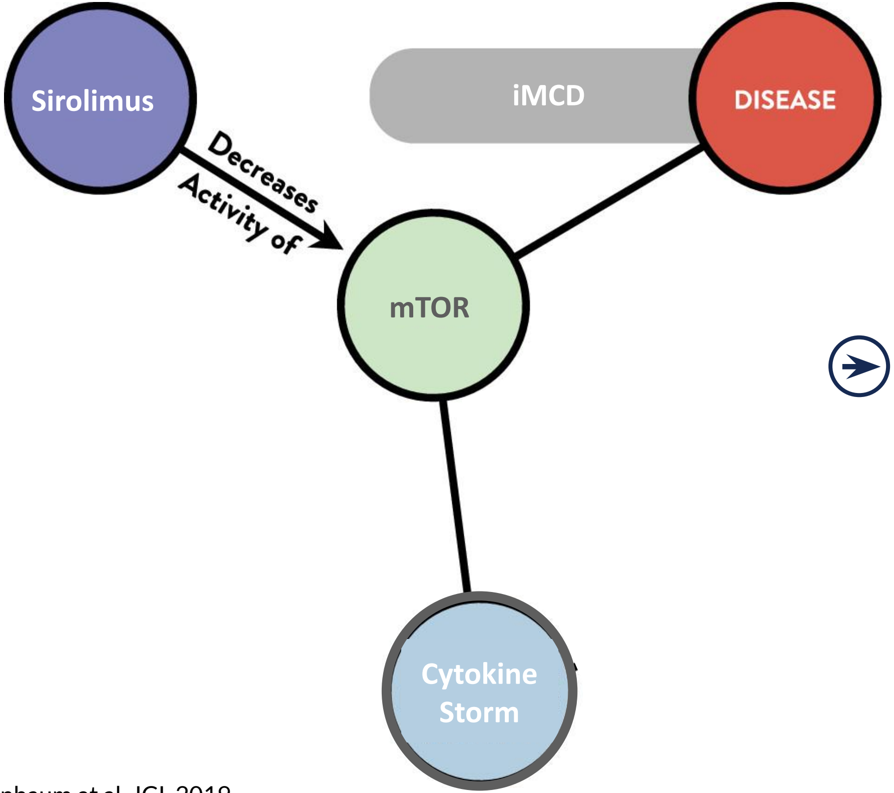
Therapeutic Crosspurposing / Systematic Pharmacophenotyping

<u>Disease</u> <u>Drug</u>



Korsunska, et al. 2023 (in submission).

Sirolimus identified for iMCD by uncovering mechanistic insights



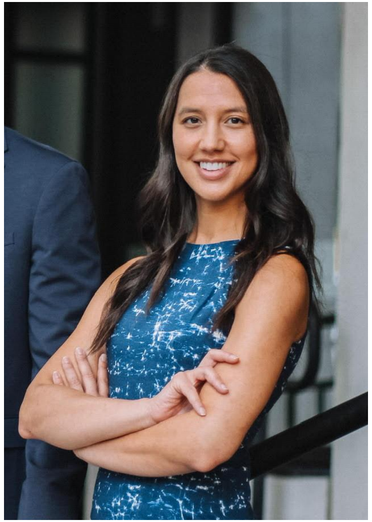
T cell activation and mTOR signature

Fajgenbaum et al. JCI, 2019.
Arenas & Fajgenbaum. Blood, 2020.

Grant Mitchell, MD, MBA
AI-driven indication expansion

QuantumBlack
AI by McKinsey

Tracey Sikora
Novel clinical trial design



Penn

Daniel Korn, PhD
KG-driven drug repurposing

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