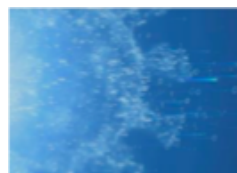




*AI for drug efficacy and safety.*



**XIV FORESIGHT TRAINING COURSE**

*The health emergency: regulatory crash and future perspectives*  
December 10<sup>th</sup>, 2021



FONDAZIONE  
PER LA RICERCA FARMACOLOGICA  
**GIANNI BENZI**  
ONLUS

researchers

**“Machines will not replace physicians, **but** physicians using AI will soon replace those not using it”**

-Antonio Di Ieva THE LANCET

researchers

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(19\)32626-1/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)32626-1/fulltext)

Nov 15, 2019: DOI:[https://doi.org/10.1016/S0140-6736\(19\)32626-1](https://doi.org/10.1016/S0140-6736(19)32626-1)

1. Tech co: AI/healthcare.

2. We map all drugs against all targets and all diseases.

3. Pre-clinical/early clinical in rare diseases of mitochondrial origin.

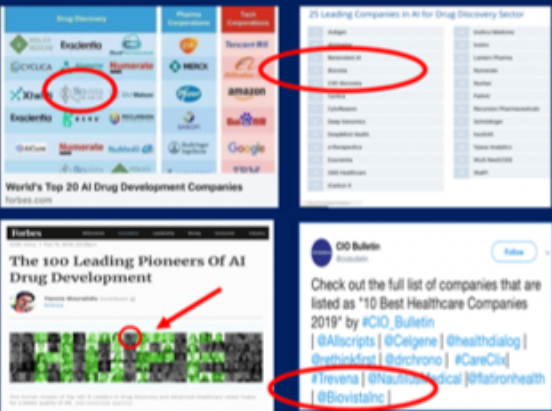
Partners

2009-2019

2020-2021-



Recognition



Healthcare:	Top 10
Development:	Top 20
Discovery:	Top 25
AI Pioneers:	Top 100
Forbes; CIO Bulletin; Deep Knowledge Analytics; Business Insider	



[X]pandemia™



Biovista Personalized Medicine



# Not all AIs are created equal: e.g. ML is domain-specific

2. It needs “training sets” or models of known “somethings”.



1. ML **matches** and **classifies** against known scenarios.

3. ML does not predict or offer “unknown-unknowns”.

Many Moves –

*But few elements  
to move*



Few Moves –

*But many elements  
to move*

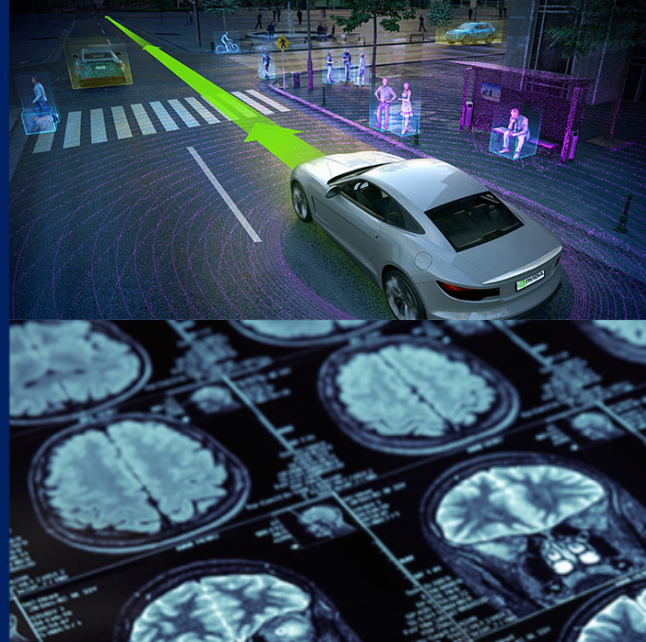
Many Moves –

*But few elements  
to move*



Few Moves –

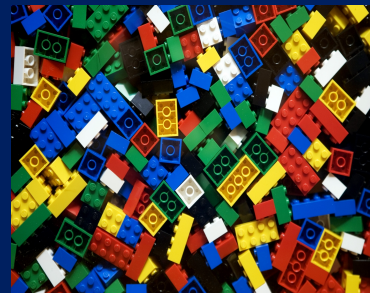
*But many elements  
to move*



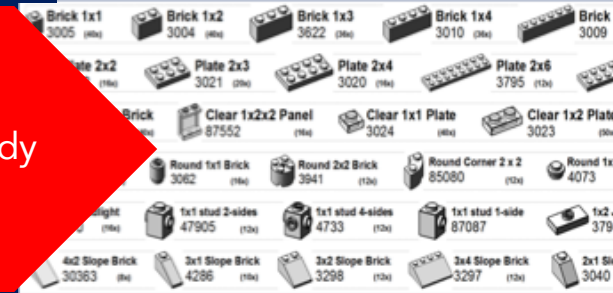
But...Medicine has  
**MANY MOVES** and  
**MANY ELEMENTS**

# A different AI doctrine: Machine Building

## Typical ML-AI



Machine Learning  
extracts what's already  
there



## Biovista



Machine Building™  
builds  
possible answers



# How Project Prodigy™ works

1.	2.	3.	4.
Data ingestion and extraction.	Individual profile building.	Database generation.	Predictions.
48 categories; Over 30 sources	Over 2 MM profiles.  48-dimensional profile for every drug, disease, gene, side effect etc.	All vs. All database of drugs- diseases-genes-side effects	Individual profiles are compared and ranked, built again by recombining their elements, and re- ranked.

1100010100010010  
0010111001001000  
1110100101001101  
1001100101100110  
1101001000111011



# Use Case #1: Multiple Sclerosis - New targets/assets, 100 days

## Problem Statement:

1. In MS, can we find **new targets** and then new therapeutic entities?
2. We want a **different class** than auto-immune drugs that have major side effects.
3. We need this **very quickly**.

1

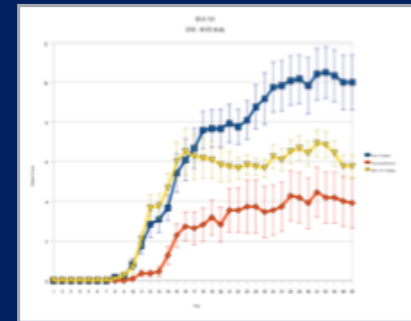
Classical Hypothesis: Auto-Immune MoA  
**OBVIOUS**


2

New Hypothesis:  
**Mitochondrial dysfunction MoA**  
**NON-OBVIOUS**

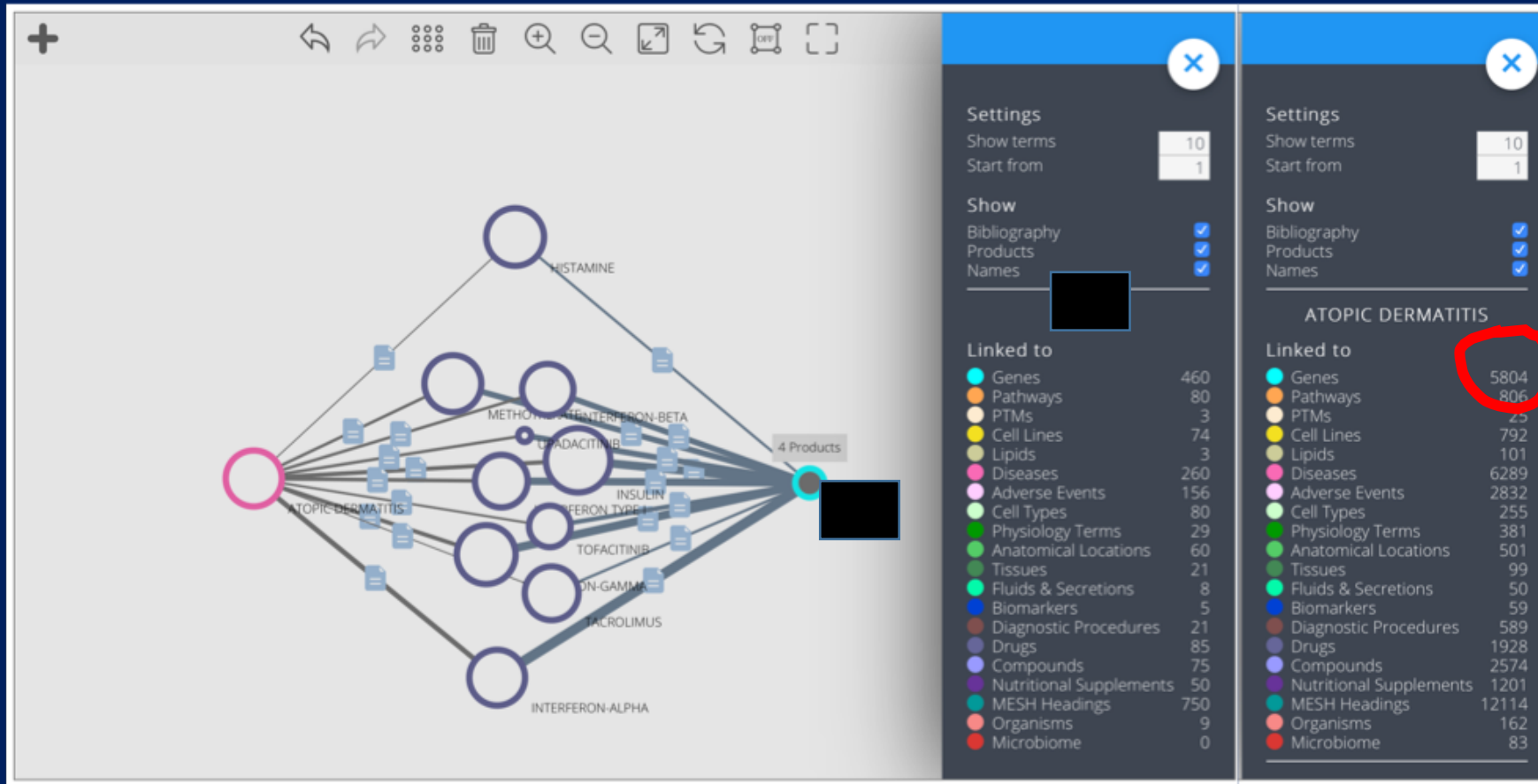
3

4



	
US010172854B2	
(12) <b>United States Patent</b> Deferereos et al.	(10) Patent No.: <b>US 10,172,854 B2</b> (45) Date of Patent: <b>*Jan. 8, 2019</b>
(54) <b>COMPOSITIONS AND METHODS FOR TREATING MITOCHONDRIAL DISEASES</b>	3,630,200 A 12/1971 Higuchi
(71) Applicant: <b>BIOVISTA, INC.,</b> Charlottesville, VA (US)	3,847,770 A 11/1974 Radlow et al.
(72) Inventors: <b>Spyros Deferereos, Athens (GR); Andreas Persidis, Athens (GR)</b>	3,916,899 A 11/1975 Thomson et al.
(73) Assignee: <b>BIOVISTA, INC.,</b> Charlottesville, VA (US)	3,959,470 A 5/1976 Madhok et al.
	4,008,719 A 2/1977 Thomson et al.
	4,087,610 A 8/1987 Vassilatos
	4,769,027 A 9/1988 Baker et al.
	4,879,208 A 11/1989 Wagner et al.
	5,079,595 A 10/1991 Le Grange
	5,073,543 A 12/1991 Marshall et al.
	5,120,548 A 6/1992 McClelland et al.
	5,354,506 A 10/1994 Adkins et al.

# Use Case #2: Atopic dermatitis target ID and initial chemistry



1. Identified and ranked 5,804 targets.
2. Identified 9 initial chemistries.

# Use Case #3: Nieman Pick A target ID and initial chemistry

**SOCIAL MEDIA**  
MY Yahoo! Pageflakes Add to Google MY MSN Windows Live netvibes newsqator Bloglineزور

**Biovista announces strong preclinical results for two drugs targeting Niemann-Pick Disease Type A**

*Biovista announces strong preclinical results for two drugs targeting Niemann-Pick Disease Type A identified by Biovista's Project Prodigy.*

Send Like Be the first of your friends to like this.

Online PR News – 12-January-2017 – Charlottesville, VA, Jan 11th, 2017 – Biovista Inc. today announced that two drugs targeting Niemann-Pick Disease Type A (NPA), have shown strong positive results in the Acid Sphingomyelinase ASM knock-out (ASMKO) mouse model. Both repositioning candidates (BVA-901A and BVA-901B) tested by the laboratory of Dr. M.D. Ledesma at the Madrid Center for Molecular Biology "Severo Ochoa" (CBMSO) promoted significant sphingomyelin hydrolysis in vitro in hippocampal ASMKO mouse neurons. The drug candidates were identified using Biovista's Project Prodigy big data inference engine in drug repositioning mode.

"We are pleased with this latest positive outcome from Project Prodigy and these initial results that confirm the predicted efficacy of these two candidates, in particular because we are seeing significant hydrolysis of sphingomyelin. We will continue working with both candidates to further confirm the purported mechanism of action and quantify expected efficacy before we proceed with our IND application" said Andreas Persidis, Ph.D., CEO of Biovista. "We are also happy that our collaboration with Wylder Nation Foundation (WNF) that started with the 2015 BeHeard science challenge hosted by the Rare Genomics Institute has yielded these early success results" added Dr. Persidis.

The results were obtained using the ASMKO model of NPA. "We are excited by these results obtained using an animal model that faithfully reproduces the human disease. We believe they open new perspectives for finding a cure for NPA patients" said Dr Ledesma. "We remain very optimistic about the potential that one of these drug candidates will significantly improve the most severe neurological manifestations of Niemann-Pick Type A, and we are currently in the process of planning in vivo studies to further validate these initial in vitro results," said Steven Laffoon, Co-Founder and President of Wylder Nation Foundation.

**Contact Information**  
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+1.434.971.1141  
<http://www.biovista.com/>  
**CONTACT AUTHOR**

Biovista / Ochoa  
Center for Molecular  
Biology (Madrid)

# Use Case #4: Prioritizing assets – optimal asset use

	A	B	C	D	E	F
	Company / Disease Target	Year of Biovista Repositioning	New Use and Disease Identified by Biovista	Subsequent Published Conflormatory Papers	Year of Literature Confirmation	Level of Evidence
1						
2						
3	PHARMA 1					
4	REDACTED	2010	REDACTED	PMID= 258 REDACTED	2015	Animal
5	REDACTED			PMID= 222	2012	Animal
6	REDACTED	2010	REDACTED	PMID= 253	2015	Animal
7				PMID= 221	2012	Animal
8	REDACTED	2010	REDACTED	Not confirmed		
9	REDACTED	2010	REDACTED	Not confirmed	2010	Animal
10	REDACTED	2010	REDACTED	PMID= 228 REDACTED	2012	Animal
11	REDACTED	2010	REDACTED	Not confirmed		
12						
13	PHARMA 2					
14	REDACTED	2011	REDACTED	PMID= 262 REDACTED	2015	In Vitro
15	REDACTED	2011	REDACTED	PMID= 258	2015	Animal
16				PMID= 2558	2015	Animal
17				PMID= 248	2014	Animal
18				PMID= 248	2015	Human
19	REDACTED	2011	REDACTED	Not confirmed		
20	REDACTED	2011	REDACTED	Not confirmed		
21						
22						
23	PHARMA 3					
24	REDACTED	2012	REDACTED	Not confirmed		
25		2012	REDACTED	PMID= 256 REDACTED	2015	Review
26		2012	REDACTED	Not confirmed		
27		2012	REDACTED	PMID= 244 REDACTED	2014	Genetic Association Study, Human
28						
29	REDACTED	2012	REDACTED	Not confirmed		
30		2012	REDACTED	Not confirmed		
31		2012	REDACTED	Not confirmed		
32						
33	NOTE 1: "Not Confirmed" means that there is no third party study in the literature linking the specific drugs and/or mechanisms to the repositioned diseases. It does not mean that the repositionings failed. It means they have not been studied and reported to date.					
34						
35	NOTE 2: "PMID" is the PubMed Identification Code for each literature citation.					

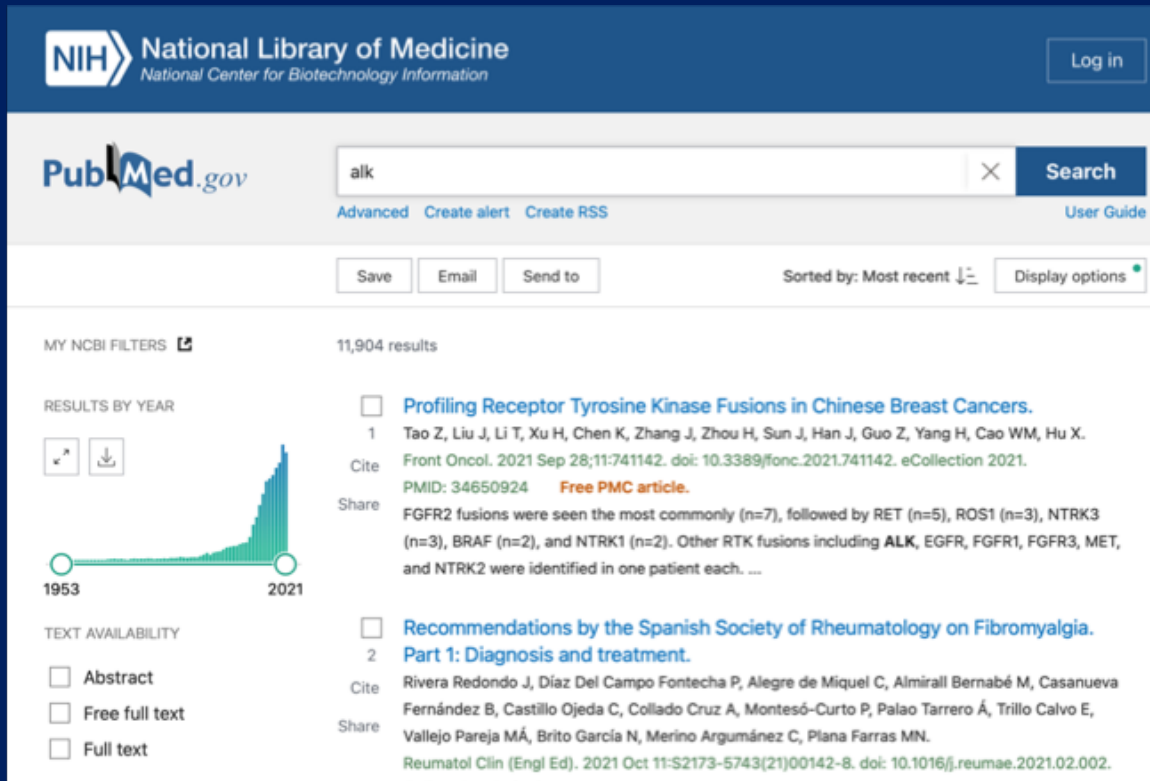
Six Assets: Prioritize/Predict

Performance:

*Benefit: 64%, 3-5 years prior*

# Use Case #5: Prioritizing indications for repositioning

ALK: 11,904 papers; How many diseases?  
397 Days (30 papers /day) to extract/FTE



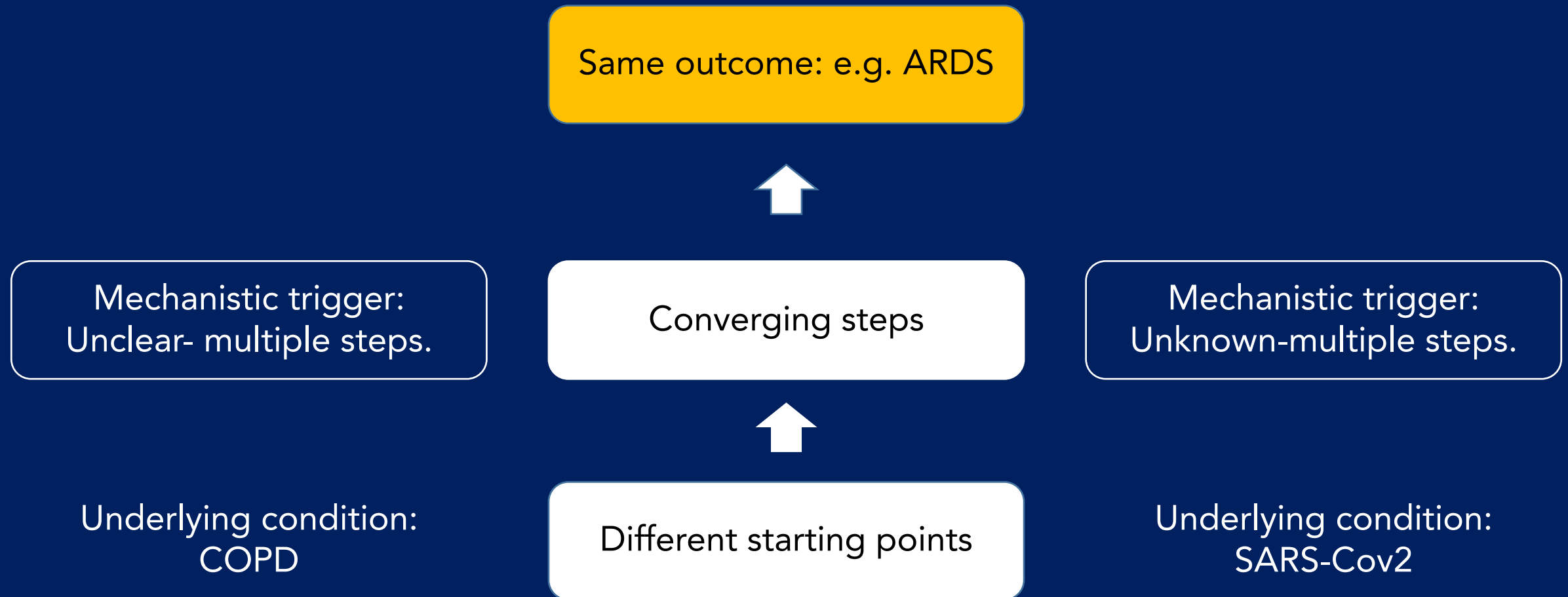
The screenshot shows a sidebar menu for the term 'ALK'. The menu is titled 'ALK' and has a close button (X) in the top right corner. The menu lists various categories and their associated counts. The 'Diseases' category is highlighted with a red circle. The categories and their counts are:

Category	Count
Genes	4454
Pathways	499
PTMs	20
Cell Lines	560
Diseases	2641
Cell Types	243
Physiology Terms	201
Anatomical Locations	388
Tissues	78
Fluids & Secretions	28
Biomarkers	54
Diagnostic Procedures	361
Drugs	628
Compounds	870
Nutritional Supplements	319
MESH Headings	5170
Organisms	64
Microbiome	15

Below the list, there are sections for 'Synonyms' and 'Resources'. The 'Synonyms' section lists 'CD246' and 'MUTANT ANAPLASTI...'. The 'Resources' section lists 'Wikipedia', 'NCBI Entrez', 'NCBI Gene', 'UniProt', 'Gene Ontology', 'MESH', 'Reactome', and 'KEGG'.

2,641 disease set  
"seen" in 0.1 sec,  
updated  
constantly

# Use Case #6: Post Covid-19, targets and rapid prototype drugs



# The world before and after Covid-19



Cover Date:  
15 May 2017

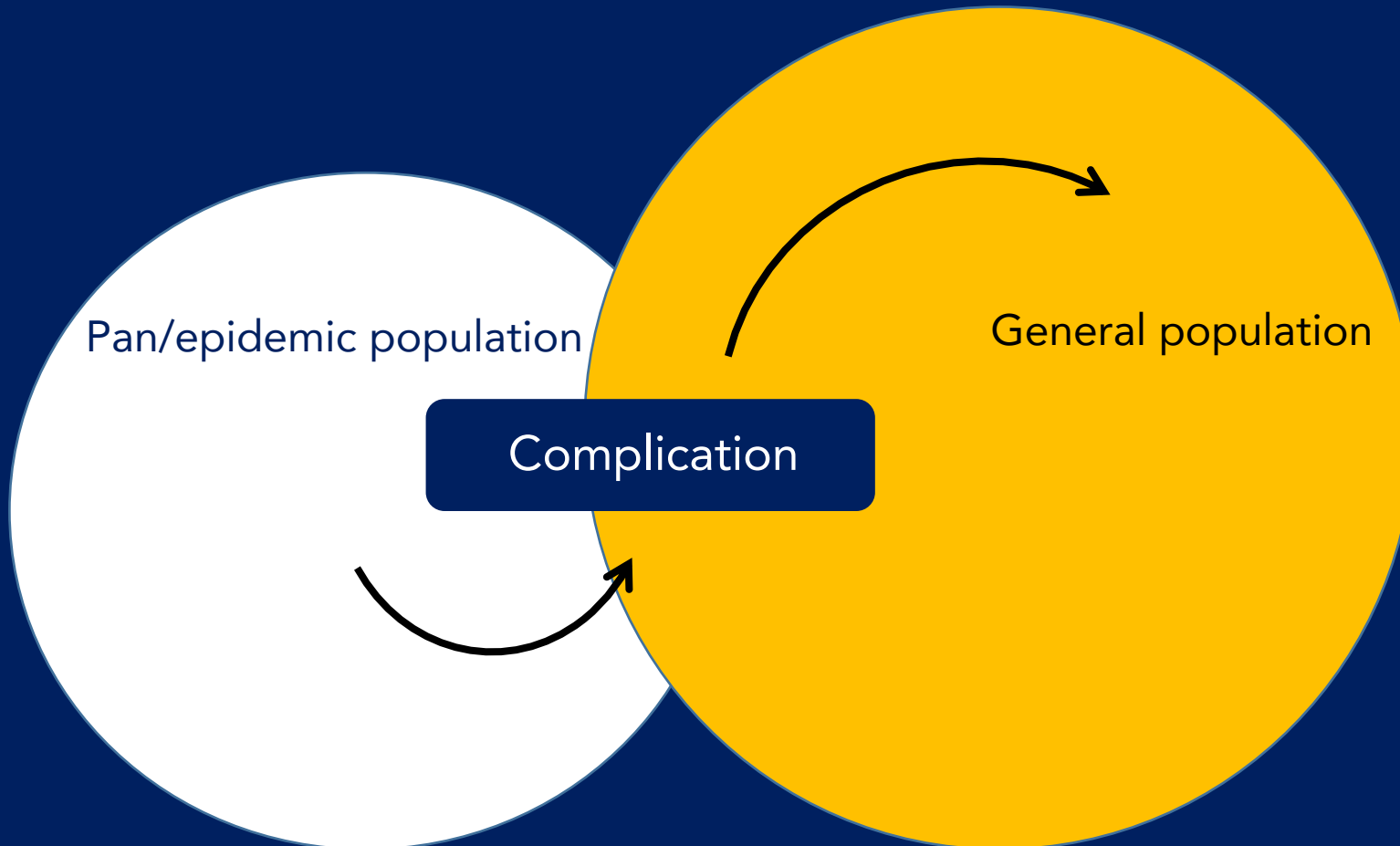


Cover Date:  
27 June 2020



Cover Date:  
April 2021

Core idea: Use Covid-19 as the new starting point to develop medicines for other diseases.

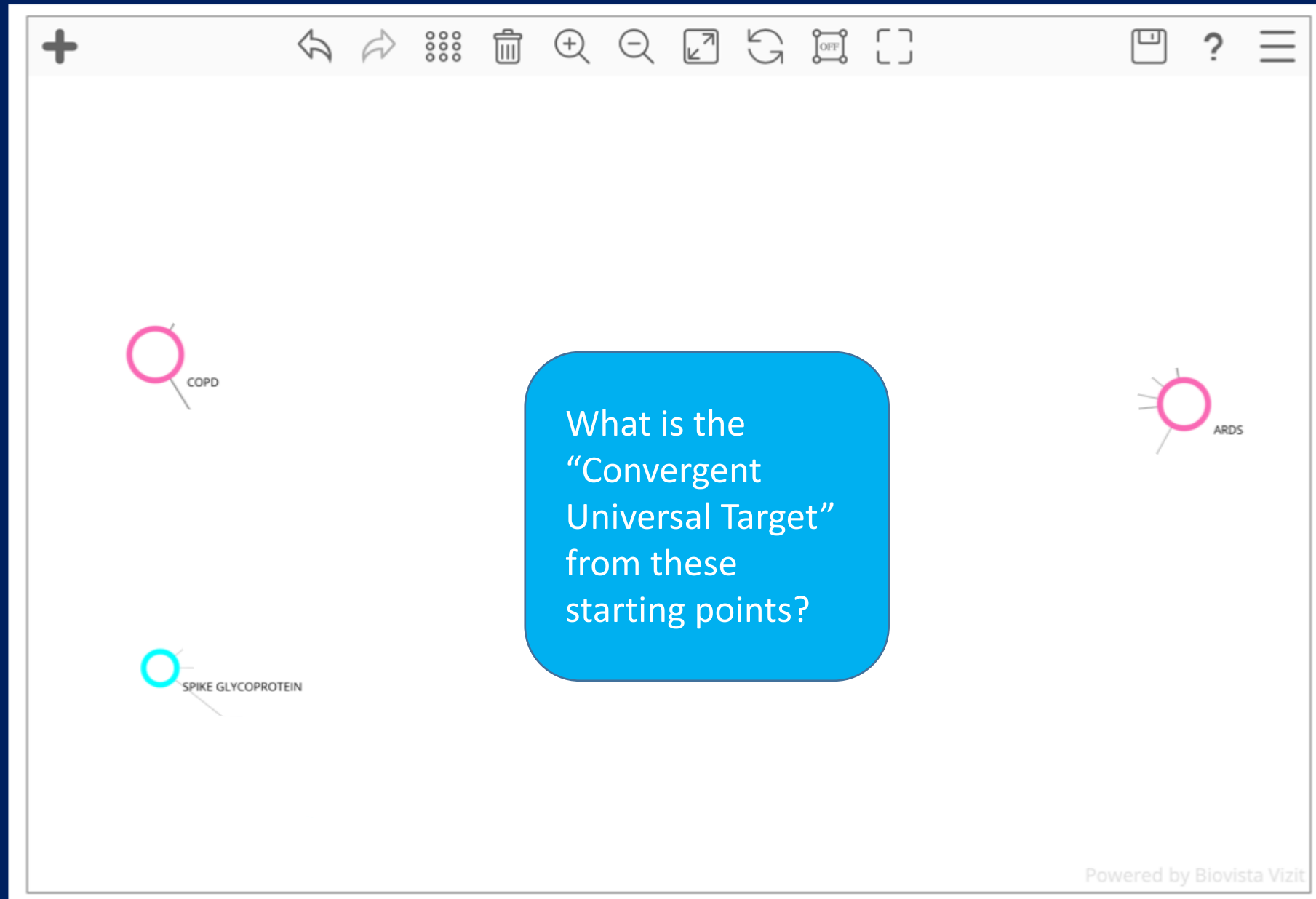


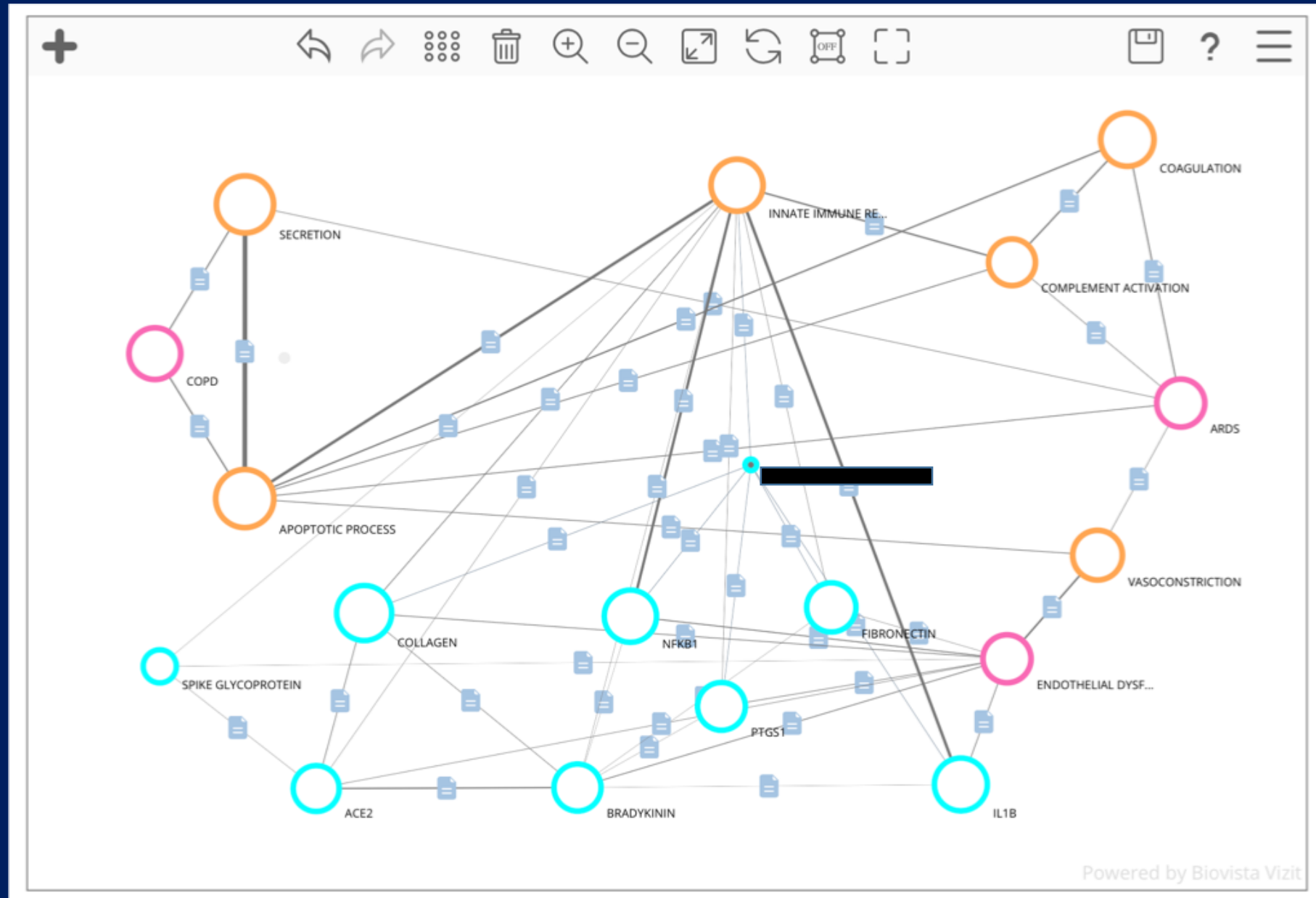
**What is a PASC**  
complication in Covid-19  
is a stand-alone disease  
already. Examples:

**ARDS**  
**Epilepsy**  
**Kawasaki**  
**Kidney dysfunction**  
**Myasthenia**  
**Pancreatitis**

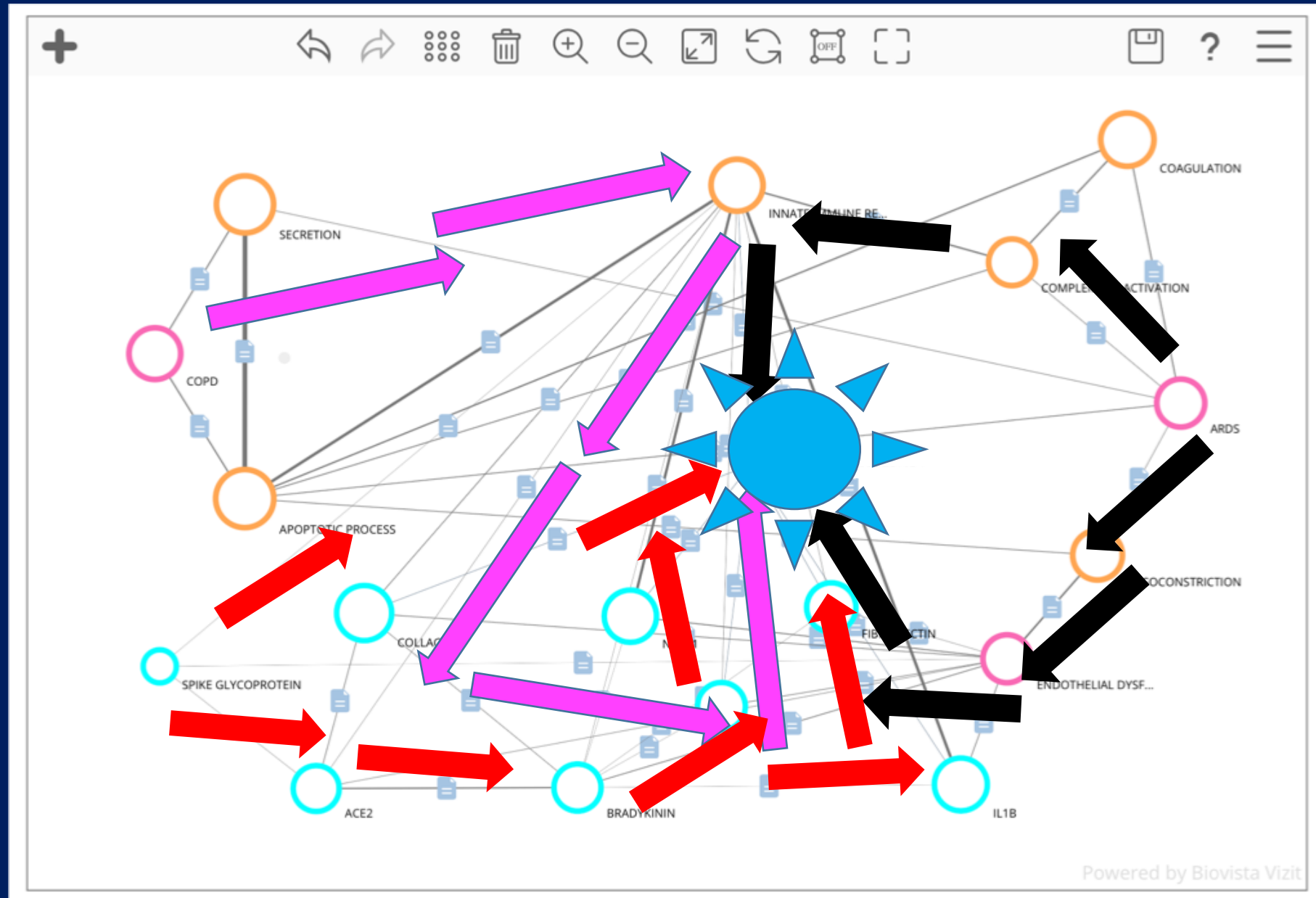
...

# Learning from different starting points





# Three different starting points: One new target set.



# Current data for just the first patient group: ARDS

COPD

Linked to	
Genes	9455
Pathways	1041
PTMs	36
Cell Lines	1141
Lipids	79
Diseases	7022
Adverse Events	3192
Cell Types	278
Physiology Terms	449
Anatomical Locations	567
Tissues	109
Fluids & Secretions	50
Biomarkers	86
Diagnostic Procedures	1067
Drugs	2081
Compounds	2077
Nutritional Supplements	684
MESH Headings	12739
Organisms	169
Microbiome	87
Synonyms	
• CHRONIC AIRFLOW ...	
• CHRONIC AIRWAY D...	
• PULMONARY DISEAS...	
• CHRONIC OBSTRUCT...	
• HYPERACTIVE AIRW...	
• OBSTRUCTIVE PULM...	
• CHRONIC AIRWAY O...	
• CHRONIC OBSTRUCT...	
• COPD - CHRONIC O...	
• COPD, CHRONIC OB...	
• CHRONIC OBSTRUCT...	
• CHRONIC IRREVERS...	

SARS-COV-2

Linked to	
Genes	2221
Pathways	330
PTMs	14
Cell Lines	458
Lipids	25
Diseases	3340
Adverse Events	1790
Cell Types	166
Physiology Terms	293
Anatomical Locations	343
Tissues	70
Fluids & Secretions	37
Biomarkers	20
Diagnostic Procedures	534
Drugs	871
Compounds	447
Nutritional Supplements	343
MESH Headings	5728
Organisms	80
Microbiome	22
Synonyms	
• 2019-NCOV EPIDEMIC	
• 2019 NOVEL CORON...	
• COVID19	
• HCOV-19	
• 2019-NCOV	
• CORONAVIRUS DISE...	
• SEVERE ACUTE RES...	
• SARS-COV-2 INFEC...	
• COVID-19	
• COVID-19 VIRUS I...	
• SARS-COV2	
• 2019 NOVEL CORON...	

Raw data:

18,003 initial triggers

Deep triage:

New target family  
Four initial NTE candidates

ARDS

Linked to	
Genes	4275
Pathways	607
PTMs	24
Cell Lines	571
Lipids	71
Diseases	5253
Adverse Events	2522
Cell Types	214
Physiology Terms	350
Anatomical Locations	465
Tissues	85
Fluids & Secretions	44
Biomarkers	50
Diagnostic Procedures	626
Drugs	1502
Compounds	1329
Nutritional Supplements	441
MESH Headings	9388
Organisms	107
Microbiome	40
Synonyms	
• ADULT RESPIRATOR...	
• ADULT RESPIRATOR...	
• ARDS, HUMAN	
• A.R.D.S.	
• ACQUIRED RESPIRA...	
• ADULT RESPIRATOR...	
• SHOCK LUNG	
• ADULT RESPIRATOR...	
• RESPIRATORY DIST...	
• ADULT HYALINE ME...	
• RESPIRATORY DIST...	
• HUMAN ARDS	

# Use case #7: Benefit AND Risk - Linking target biology to SAEs



The screenshot shows the top of a web page for the journal "Diabetes Care" by the American Diabetes Association. The header includes navigation links like Home, Current Issue, Archive, Contact Us, Subscribe, Help, Alerts, and Podcasts. Below the header is a red banner. The main content area features a CrossMark logo and the article title "Hypothyroidism Is a Risk Factor for New-Onset Diabetes Mellitus: A Cohort Study" by Naomi Gronich et al. The abstract is partially visible, starting with "OBJECTIVE To identify risk factors for the development of statin-associated diabetes mellitus (DM)." The right sidebar contains a "This Article" section with links to the abstract, full text (PDF), PDF Plus, Supplementary Data, and various services like email alerts and citation management.

American Diabetes Association. **Diabetes Care.**

Home | Current Issue | Archive | Contact Us | Subscribe | Help | Alerts | Podcasts

CrossMark

### Hypothyroidism Is a Risk Factor for New-Onset Diabetes Mellitus: A Cohort Study

Naomi Gronich<sup>1,†</sup>, Spyros N. Deftereos<sup>2</sup>, Idit Lavi<sup>1</sup>, Andreas S. Persidis<sup>2</sup>, Darrell R. Abernethy<sup>3</sup> and Gad Rennert<sup>1,4</sup>

Corresponding author: Naomi Gronich, [gronichn@clalit.org.il](mailto:gronichn@clalit.org.il).

#### Abstract

**OBJECTIVE** To identify risk factors for the development of statin-associated diabetes mellitus (DM).

**RESEARCH DESIGN AND METHODS** The study was conducted in two phases. Phase one involved high-throughput in silico processing of a large amount of biomedical data to identify risk factors for the development of statin-associated DM. In phase two, the most prominent risk factor identified was confirmed in an observational cohort study at Clalit, the largest health-care organization in Israel. Time-dependent Poisson regression multivariable models were performed to assess rate ratios (RRs) with 95% CIs for DM occurrence.

**This Article**

Published online before print  
June 12, 2015; doi:  
10.2337/14c4-4355  
Diabetes Care June 12, 2015

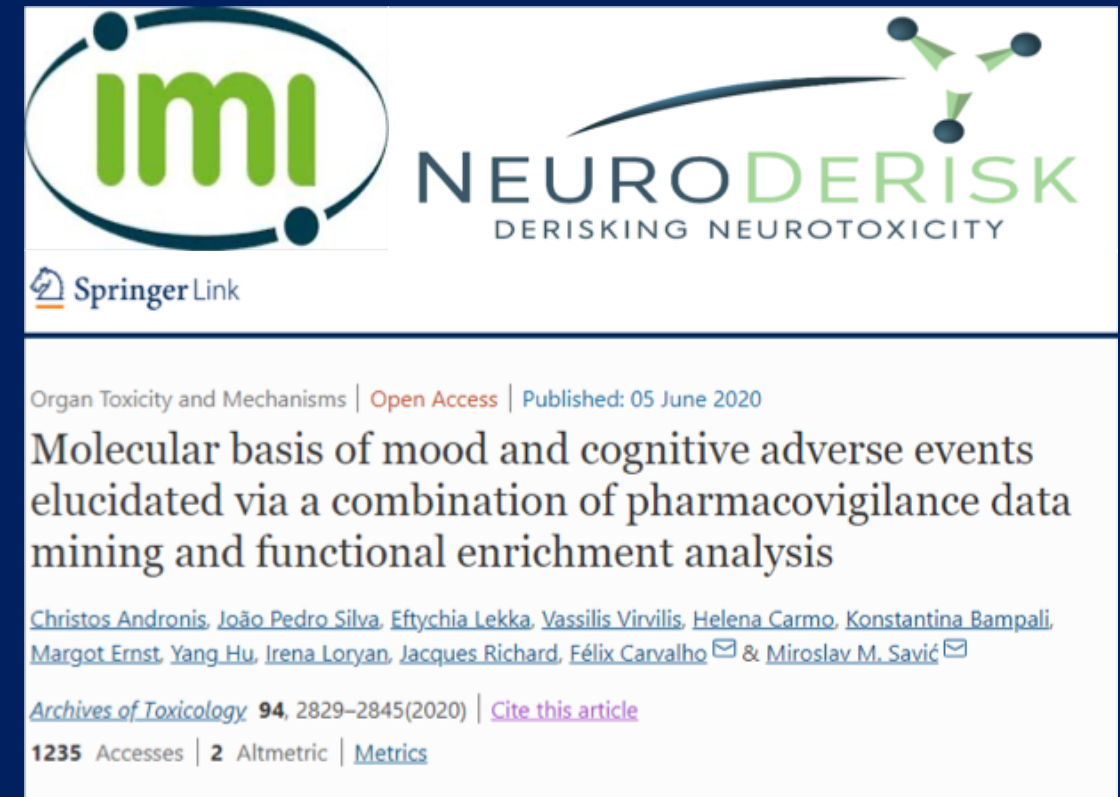
» Abstract  
Full Text (PDF)  
PDF Plus  
Supplementary Data

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PMID: 26070591 DOI: [10.2337/dc14-2515](https://doi.org/10.2337/dc14-2515)



The screenshot shows the top of a web page for the journal "NeuroDERISK" by imi. The header includes the imi logo and the journal title "NEURODERISK" with the subtitle "DERISKING NEUROTOXICITY". Below the header is a Springer Link logo. The main content area features the article title "Molecular basis of mood and cognitive adverse events elucidated via a combination of pharmacovigilance data mining and functional enrichment analysis" by Christos Andronis et al. The abstract is partially visible, starting with "Organ Toxicity and Mechanisms | Open Access | Published: 05 June 2020". The right sidebar contains a "This Article" section with links to the abstract, full text (PDF), PDF Plus, Supplementary Data, and various services like email alerts and citation management.

imi

### NEURODERISK

DERISKING NEUROTOXICITY

Springer Link

Organ Toxicity and Mechanisms | Open Access | Published: 05 June 2020

### Molecular basis of mood and cognitive adverse events elucidated via a combination of pharmacovigilance data mining and functional enrichment analysis

Christos Andronis, João Pedro Silva, Eftychia Lekka, Vassilis Virvilis, Helena Carmo, Konstantina Bampali, Margot Ernst, Yang Hu, Irena Loryan, Jacques Richard, Félix Carvalho & Miroslav M. Savić

Archives of Toxicology 94, 2829–2845(2020) | Cite this article

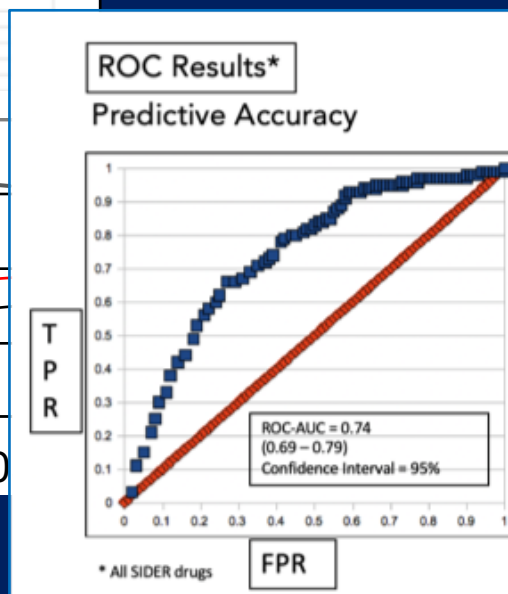
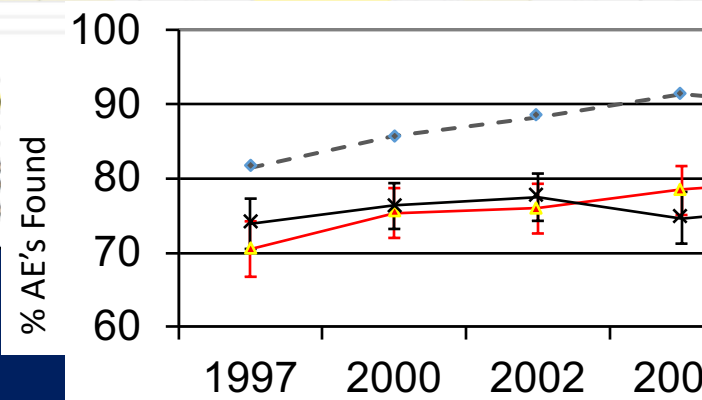
1235 Accesses | 2 Altmetric | Metrics

<https://doi.org/10.1007/s00204-020-02788-1>

# Benchmarking benefit AND Risk: 5-year study

Sample for Benefit: *103 drugs*  
 Sample for Risk : *All approved APIs*

	A	B	C	D	E	F
	Company / Disease Target	Year of Biostats Repositioning	New Use and Disease Identified by Biostats	Subsequent Published Conformational Papers	Year of Literature Confirmation	Level of Evidence
1						
2	PHARMA 1					
3	REDACTED	2010	REDACTED	PMID= 258 REDACTED	2015	Animal
4	REDACTED	2010	REDACTED	PMID= 222	2012	Animal
5	REDACTED	2010	REDACTED	PMID= 253	2015	Animal
6	REDACTED	2010	REDACTED	PMID= 221	2012	Animal
7	REDACTED	2010	REDACTED	Not confirmed	2010	Animal
8	REDACTED	2010	REDACTED	PMID= 225 REDACTED	2012	Animal
9	REDACTED	2010	REDACTED	Not confirmed		
10	REDACTED	2010	REDACTED	Not confirmed		
11	REDACTED	2010	REDACTED	Not confirmed		
12						
13	PHARMA 2	2011	REDACTED	PMID= 262 REDACTED	2015	In Vitro
14	REDACTED	2011	REDACTED	PMID= 256	2015	Animal
15	REDACTED	2011	REDACTED	PMID= 2558	2015	Animal
16	REDACTED	2011	REDACTED	PMID= 248	2014	Animal
17	REDACTED	2011	REDACTED	PMID= 248	2015	Human
18	REDACTED	2011	REDACTED	Not confirmed		
19	REDACTED	2011	REDACTED	Not confirmed		
20						
21	PHARMA 3	2012	REDACTED	Not confirmed		
22	REDACTED					
23						
24						
25						
26						



Performance:

*Benefit: 64%, 3-5 years prior*

*Risk: 70%+, 5 years prior*

# Novelty vs. Risk

Obvious; Known



Non-Obvious

Literature:	Significant-Explicit	Recent; Indirect	Sparse; Non-explicit
IP:	Crowded; Unlikely	Possible	Available
Models:	Multiple	Few	Unclear
Clinical:	Available	Starting	N/A
Market:	Follower	Follower	Leader

Type:

Risk:

Reward:

I

No/Little

Follower

II

Moderate

Possible

III

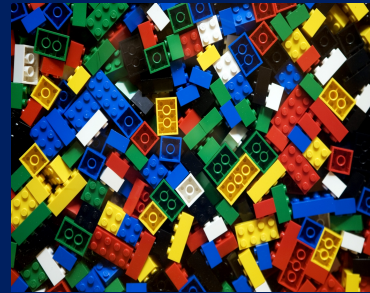
Riskier

Very High

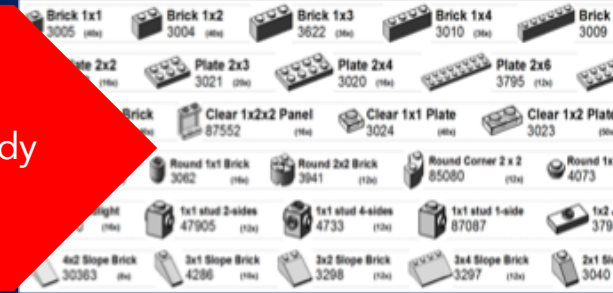
# Summary

I have target(s):	I need target(s):	I need initial drugs fast
Prioritization SAE impact Subpopulations	MoA audit	MoA matching
Indication audit	Prioritization SAE impact Subpopulations	Prioritization SAE impact Subpopulations
Novelty vs Obviousness	Novelty vs Obviousness	Novelty vs Obviousness

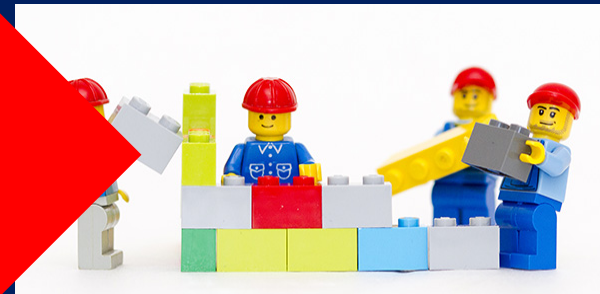
# Summary



Machine Learning  
extracts what's already  
there



Machine Building™  
builds  
possible answers



# THANK YOU!



FDA: Darrell Abernethy

Clalit: Naomi Gronich, Idit Lavi,  
Gad Rennert

Biovista: Spyros Deftereos, Effie Lekka,  
Vassilis Virvilis, Christos Andronis,  
Andreas Persidis

Aris Persidis, [arisp@biovista.com](mailto:arisp@biovista.com)