UNLEARN

Use of artificial intelligence within drug development programs

Promoting Effective Drug Development Programs:
Opportunities and Priorities for FDA's Office of New Drugs

Charles Fisher, Ph.D.
Founder and CEO, Unlearn.AI
November 7, 2019

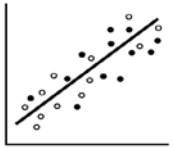
Unlearn.AI: a science-based company creating computational innovations to benefit patients and improve healthcare

Jon Walsh Ph.D. Charles Fisher Ph.D. Aaron Smith Ph.D.

Company overview:
Founded in 2017
Started by 3 ML scientists
Background in Pharma R&D
Focused on unsupervised learning
9 employees
San Francisco, CA

Curated clinical trial data.

Sophisticated machine learning.



Rigorous statistical analysis.

The last decade has seen tremendous progress in machine learning (ML) and artificial intelligence (AI)

Divam Gupta

thispersondoesnotexist.com

TITLE: A randomized controlled trial of renal denervation for resistant hypertension.

OBJECTIVE: Renal denervation is recommended as a method of treatment for patients with resistant hypertension who are at high risk for hypertension. The objective of this study was to determine the effectiveness of renal denervation in hypertensive patients.

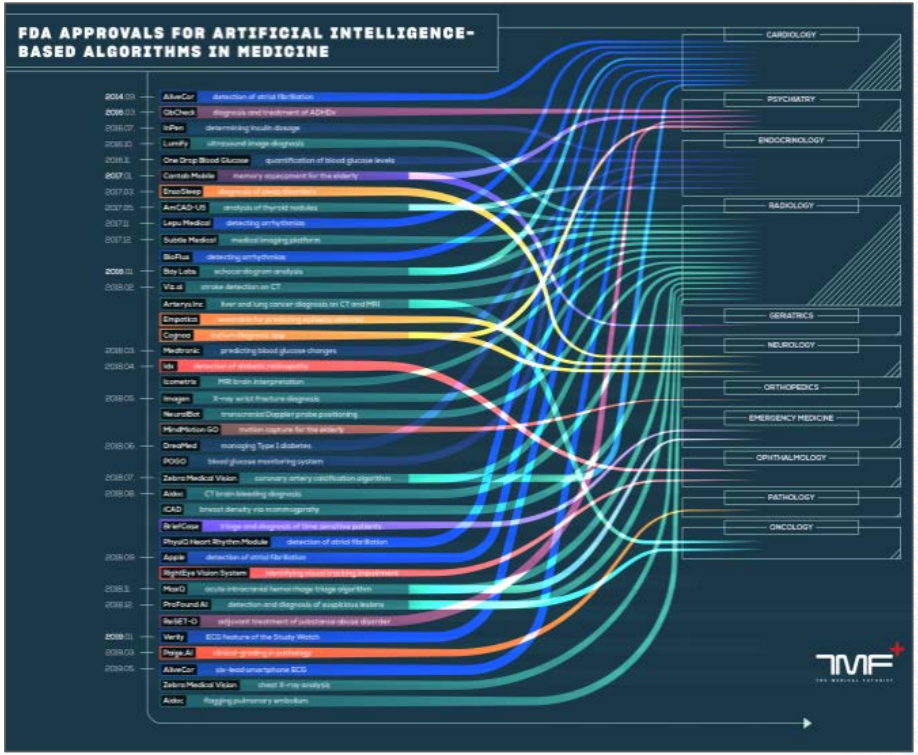
METHODS: We evaluated the effects of renal denervation on hypertension, cardiovascular events, and renal function in renal transplant recipients who were treated with renal denervation.

RESULTS: A total of 160 patients were included. Renal denervation was more effective than renoprotectant in decreasing blood pressure and improving renal function (AUC0.87, P < 0.01) and on neutropenia (AUC0.93, P < 0.01). In the reverse order, renal denervation was superior to pruritus in reducing blood pressure and improving renal function. In the final analysis, all doses of renal denervation were superior to apixaban (AUC 0.80, P < 0.01). When all the dose and the dose of renal denervation were compared, renal denervation was more effective in decreasing blood pressure (AUC 0.77, P < 0.01) and improving renal function (AUC 0.76, P < 0.01). The serum level of arginase, chylomicron, and calcitonin were higher in patients who received renal denervation.

CONCLUSIONS: Renal denervation is effective in reducing blood pressure and improving renal function in patients with resistant hypertension. Use of renal denervation may decrease blood pressure and improve renal function.

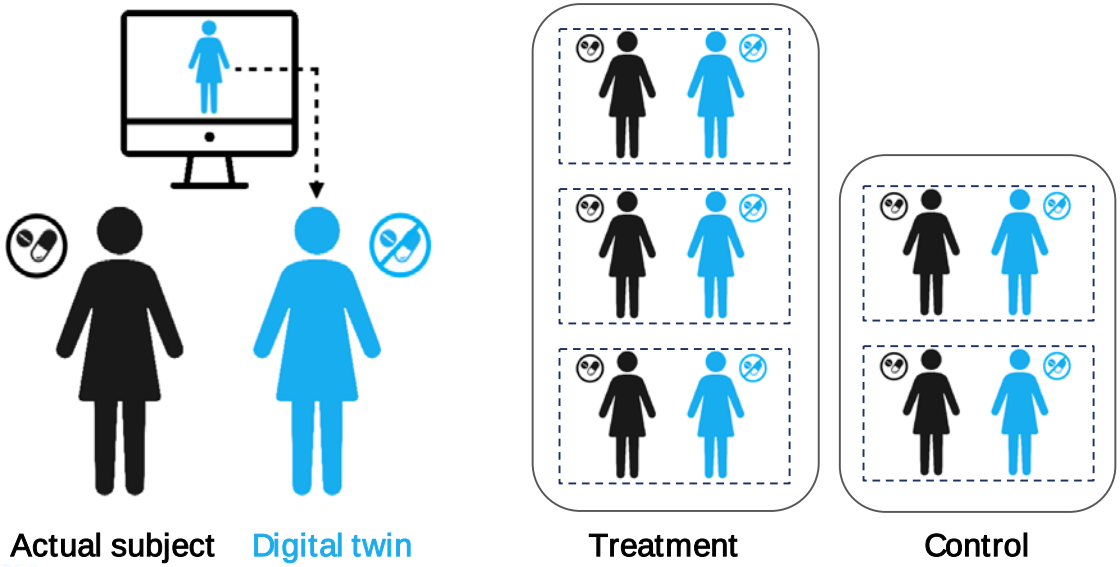
TRIAL REGISTRATION: ClinicalTrials.gov, number NCT015274006. Registered on 13 August 2015.

James Howard



The Medical Futurist

Unlearn uses ML to create digital twins that allow us to ask "what would have happened to a specific subject in a clinical trial if he or she had received a placebo?"



Example of synthetic AD patient data

	Age (years):	73			Sex:							Female		
	Race:	White			Region:							North America		
	Height (cm):	167			ApoE e4 Count:							1		
	Diagnosis:	AD			Past Cardiovascular event:							No		
	Time (months)	Baseline	3	6	9	12	15	18	21	24	27	30	33	36
ADAS	ADAS Commands	1	3	3	1	3	4	2	3	3	4	4	3	2
	ADAS Comprehension	1	2	2	1	1	2	0	1	2	3	2	4	2
	ADAS Construction	2	3	3	3	1	0	1	1	2	2	1	1	1
	ADAS Delayed Word Recall	10	10	10	10	10	10	10	10	10	10	10	10	10
	ADAS Ideational	1	2	2	2	1	2	4	3	3	3	2	3	3
	ADAS Naming	1	2	2	2	4	3	2	2	3	3	2	2	2
	ADAS Orientation	5	5	5	6	8	7	6	6	8	8	7	7	8
	ADAS Remember Instructions	4	4	5	5	4	5	5	4	5	5	5	5	5
	ADAS Spoken Language	2	2	1	0	0	0	1	1	2	3	4	3	5
	ADAS Word Finding	1	2	2	0	1	1	0	1	3	3	3	4	5
	ADAS Word Recall	8	9	9	10	10	10	10	9	9	8	10	9	10
	ADAS Word Recognition	12	5	10	11	11	7	9	12	10	12	10	12	12
	ADAS Total	48	49	54	51	54	51	50	53	60	64	60	63	65
MMSE	MMSE Attention Calculation	1	2	3	0	0	0	0	0	1	0	0	1	1
	MMSE Language	7	4	5	7	7	6	4	6	4	6	4	5	6
	MMSE Orientation	6	6	2	2	4	1	3	0	3	3	0	3	2
	MMSE Recall	0	0	0	0	0	0	0	0	1	0	0	1	0
	MMSE Registration	3	3	3	2	1	2	2	3	3	2	3	2	3
	MMSE Total	17	15	13	11	12	9	9	9	12	11	7	12	12
Clinical	Weight (kg)	56	57	60	55	61	67	68	65	64	68	66	67	71
	Systolic Blood Pressure (mmHg)	156	132	131	156	166	130	117	113	128	109	129	138	124
	Diastolic Blood Pressure (mmHg)	67	85	82	79	88	60	66	61	65	60	63	77	75
	Heart Rate (bpm)	78	71	72	72	59	59	59	72	61	66	66	70	87
Biomarkers	Alanine Aminotransferase (µkat/l)	0.18	0.31	0.18	0.15	0.26	0.29	0.32	0.30	0.20	0.13	0.15	0.19	0.27
	Alkaline Phosphatase (µkat/l)	1.78	1.16	1.63	1.12	1.30	1.43	1.00	1.93	1.18	1.02	2.43	1.61	0.99
	Aspartate Aminotransferase (µkat/l)	0.32	0.22	0.34	0.30	0.31	0.25	0.27	0.26	0.25	0.20	0.24	0.24	0.30
	Cholesterol (mmol/l)	7.13	5.52	5.72	5.48	4.99	5.22	5.42	5.10	5.61	6.61	5.27	5.49	6.07
	Creatine Kinase (mg/dl)	0.48	1.35	0.45	0.28	0.89	0.35	0.53	0.62	0.86	0.49	0.42	0.26	0.28
	Creatinine (mg/dl)	1.30	1.27	1.27	1.02	1.21	1.40	1.30	1.10	1.06	0.99	1.16	0.86	0.93
	Gamma Glutamyl Transferase (iu/dl)	1.39	1.90	2.45	3.18	2.45	3.14	2.15	1.45	1.97	1.89	1.56	1.96	1.56
	Hematocrit (counts)	0.39	0.47	0.44	0.49	0.43	0.40	0.39	0.37	0.37	0.40	0.40	0.44	0.41
	Hemoglobin (g/dl)	13.87	14.16	13.44	13.75	13.26	13.10	12.14	12.73	12.40	13.96	13.34	12.05	15.24
	Hemoglobin A1C (%)	5.54	5.82	5.78	6.12	6.20	6.82	7.45	6.61	6.59	6.63	6.61	5.65	5.61
	Indirect Bilirubin (mg/dl)	0.29	0.39	0.33	0.61	0.28	0.33	0.37	0.68	0.43	0.68	0.42	0.63	0.37
	Potassium (mmol/l)	4.38	3.78	4.69	4.56	4.71	4.61	4.76	4.49	4.13	4.36	3.80	4.70	3.92
	Sodium (mmol/cl)	1.42	1.41	1.43	1.42	1.44	1.37	1.38	1.39	1.43	1.38	1.40	1.46	1.38
	Triglycerides (g/l)	2.48	1.94	1.64	3.56	1.64	1.20	1.51	1.37	0.61	2.26	1.60	3.31	1.87

Fisher, Smith, and Walsh for the Critical Path for Alzheimer's Disease (2019) Scientific Reports

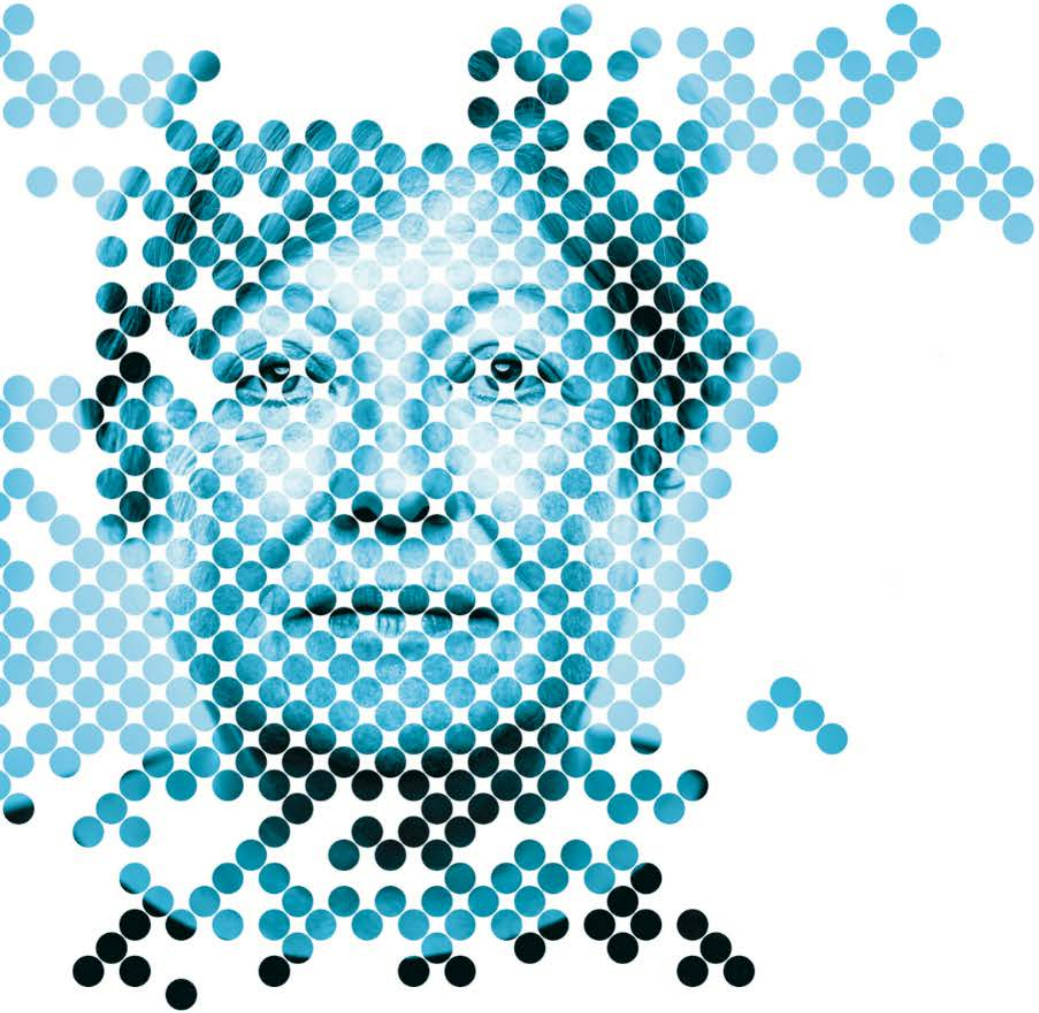
UNLEARN

We recommend that CDER develop a framework describing how AI tools may be used within drug development programs

For example, CDER could

- clarify how some AI applications for drug development could be qualified within FDA's Drug Development Tool Qualification Programs
- promote new pathways in which sponsors and other stakeholders may obtain feedback from FDA about specific uses of AI-based tools
- develop demonstration projects to facilitate the use of AI tools in drug development to support regulatory decision-making

The above concrete actions would alleviate regulatory uncertainty and would open the door to innovative approaches that will make drug development more efficient and help deliver new treatments to patients who need them as quickly as possible.



It's about **giving data life** through machine learning that transforms a trial's statistical power.

It's about time.

Charles K. Fisher, PhD
drckf@unlearn.ai

UNLEARN