Machine Learning and Computational Medicine for Clinical development, Patients, and Regulators

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Massachusetts Institute of Technology
Cambridge, MA

Disclosures: none

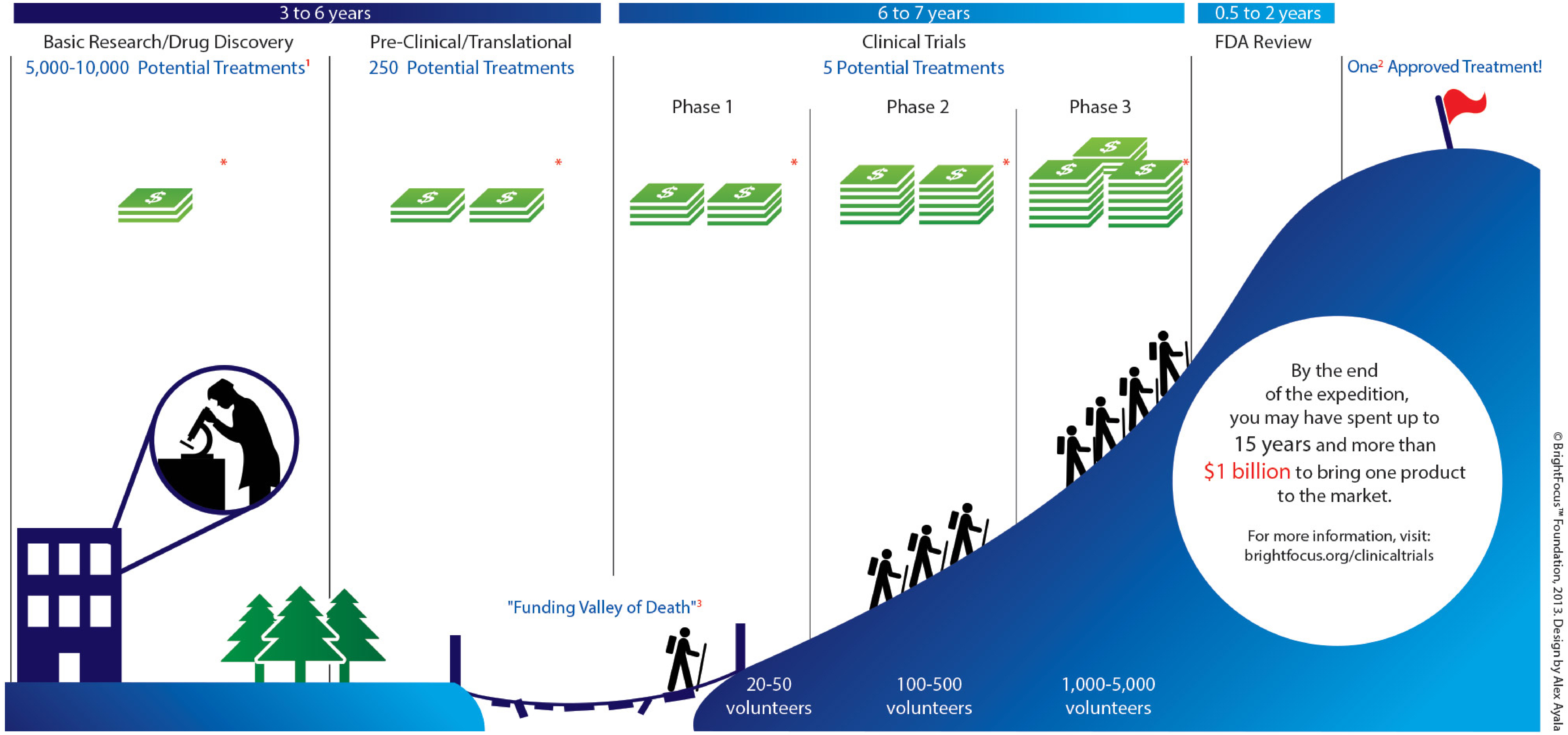
Current Drug Development Paradigm

An Uphill Battle

Imagine leading an expedition where every step is more difficult than the last...

BrightFocus™ Foundation
Cure in Mind. Cure in Sight.

The long journey begins in the lab, where scientists spend years testing thousands of ideas. Next, crossing the so-called "Funding Valley of Death" requires the resources and time needed to complete clinical trials, testing safety and effectiveness among what could end up being thousands of volunteers. At the end of this steep financial and scientific climb: Food and Drug Administration approval for a new treatment. Ultimately, it may have taken up to 15 years and more than $1 billion to bring this treatment to the market.



1 Although we are using the word "treatment," clinical trials also involve medical research studies in which people participate as volunteers to test new methods of prevention, screening, and diagnosis of disease.

2 After approval, the product is manufactured for sale on the market, and the process enters Phase 4 (Post-Marketing Monitoring/Clinical Trials). At this point, the FDA monitors for public safety and adverse events, and the sponsor company may begin Phase 4 Clinical Trials to obtain information about long-term effects or to test the product in special patient populations.

3 The "Funding Valley of Death" is the financial challenge many promising treatments face in having the opportunity to be scientifically tested in a clinical trial. In many cases, further financial support or partnerships are necessary to proceed.

* The cost of bringing a drug to market depends on a number of variables, but could be more than $1 billion, including approximately $50-840 million for Basic Research/Drug Development and Pre-Clinical/Translational research, and approximately $50-970 million to complete all three Phases of the Clinical Trials.

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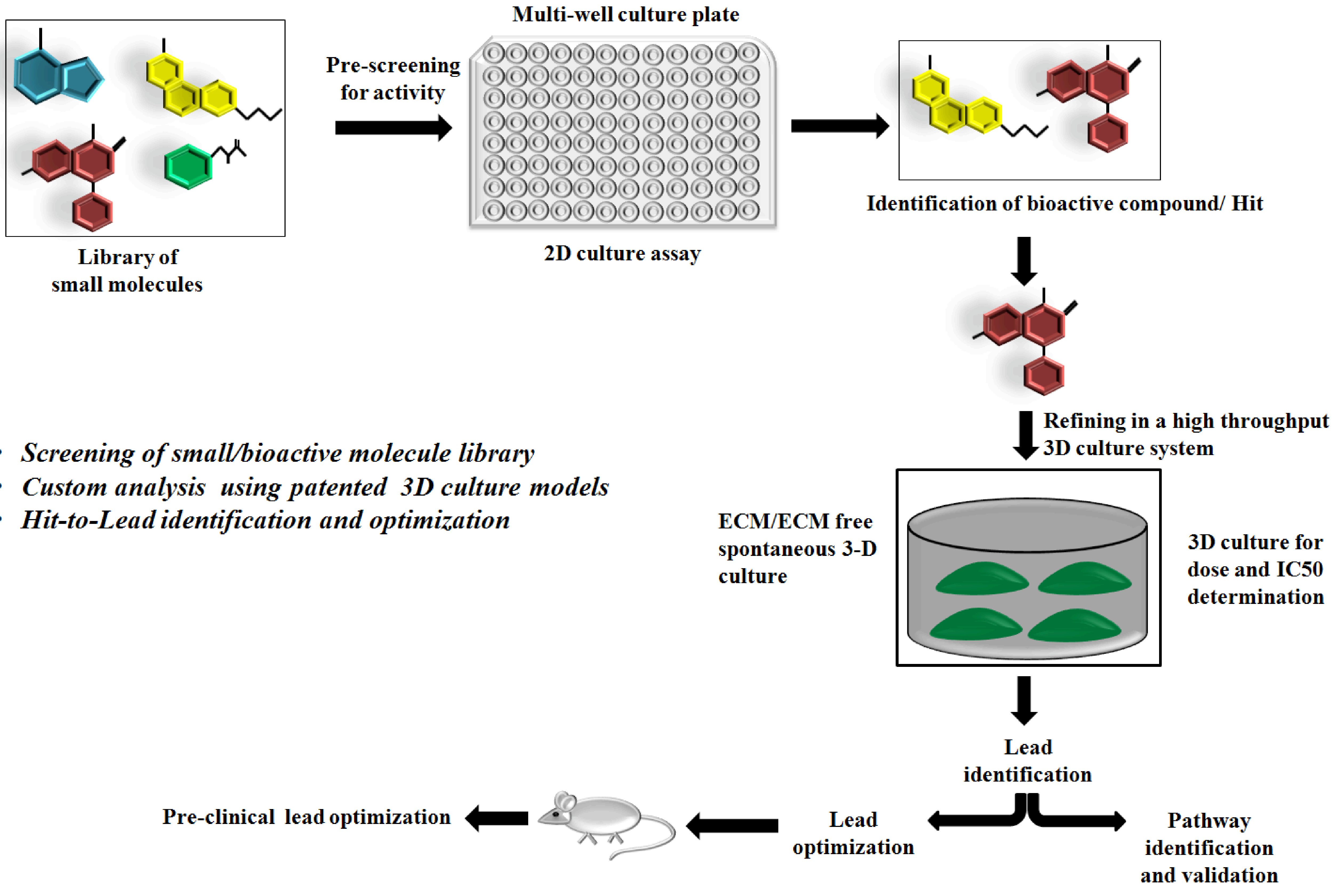
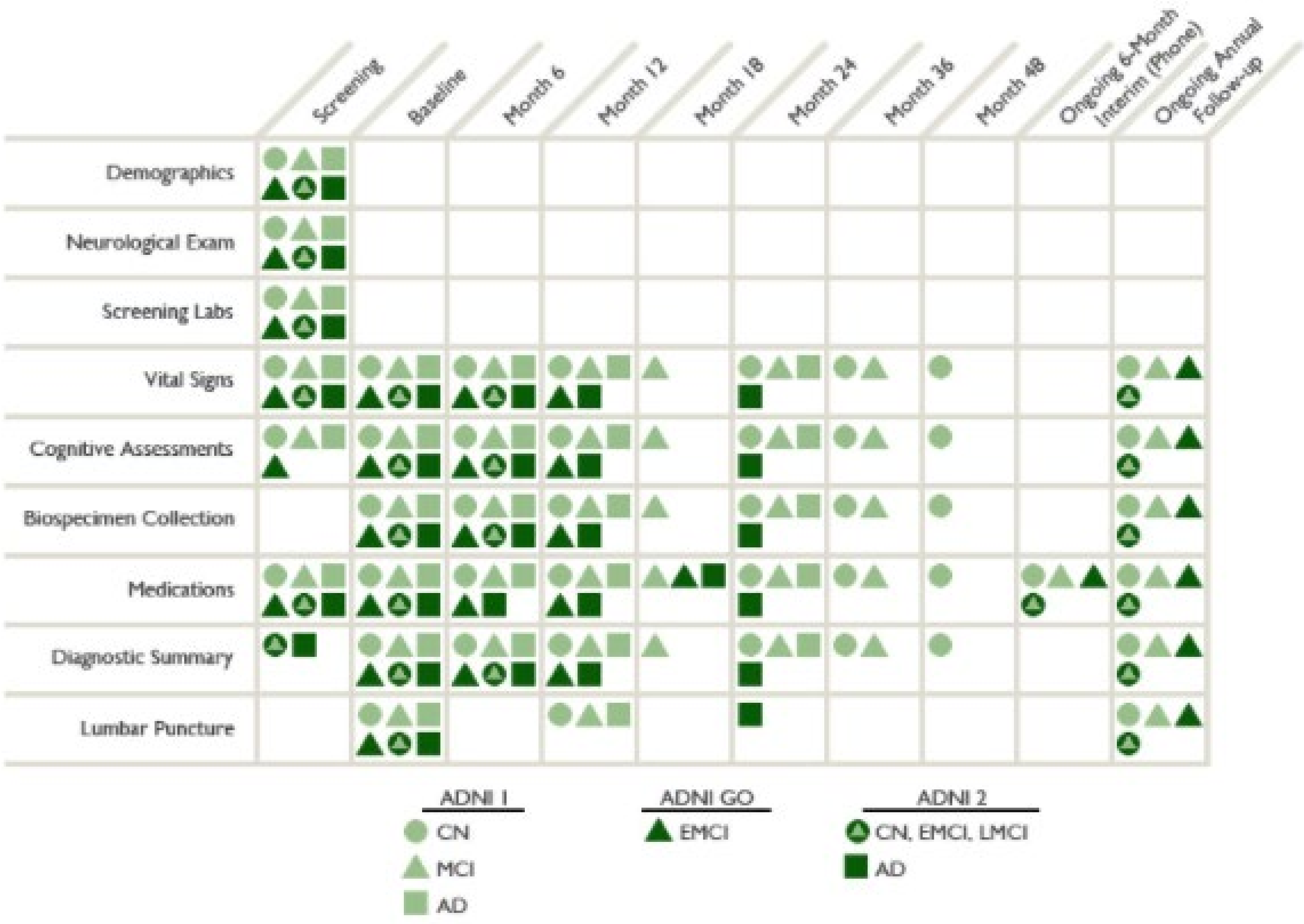
Advanced Analytics for Clinical Datasets are Challenging



- *Screening of small/bioactive molecule library*
- *Custom analysis using patented 3D culture models*
- *Hit-to-Lead identification and optimization*



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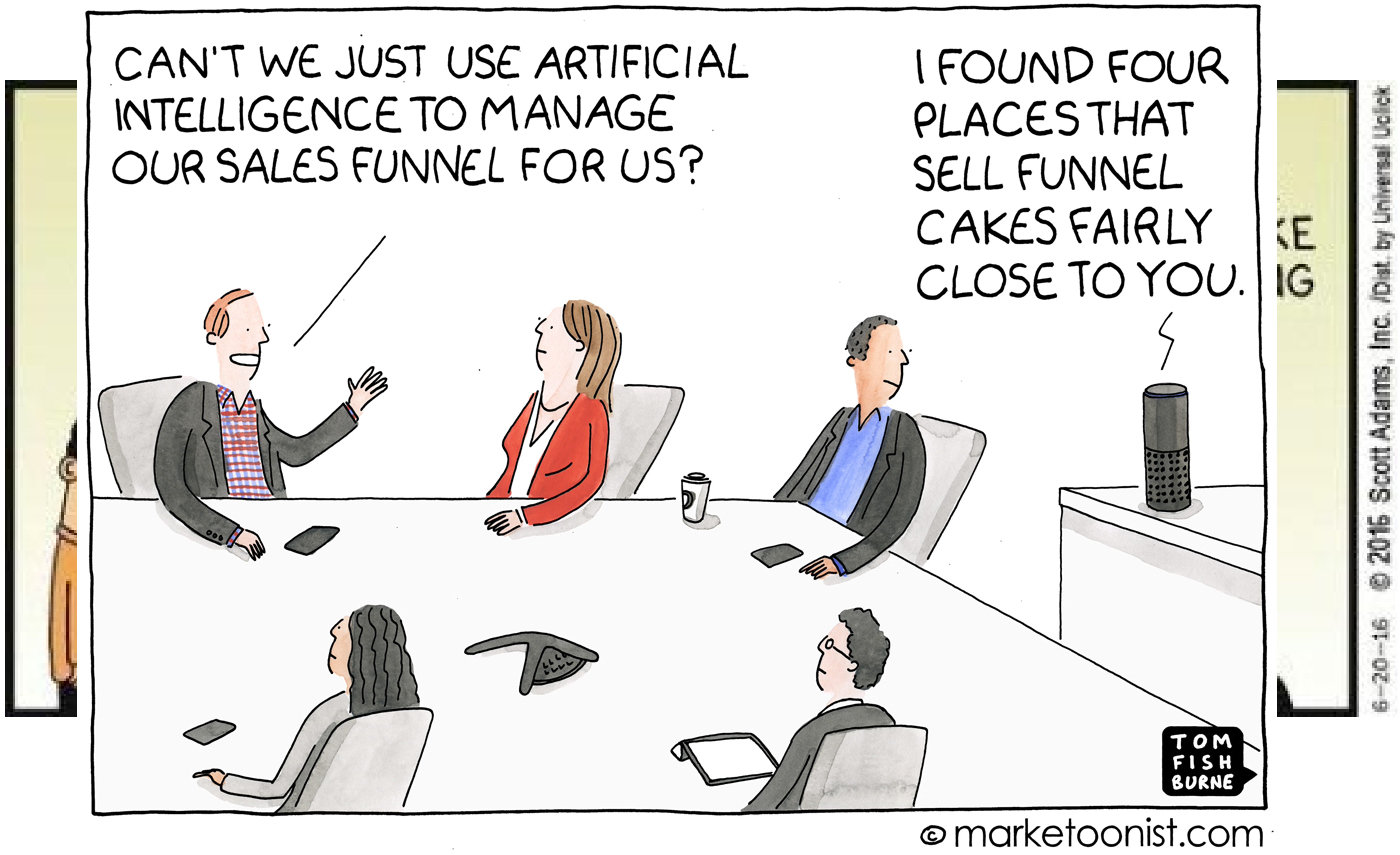

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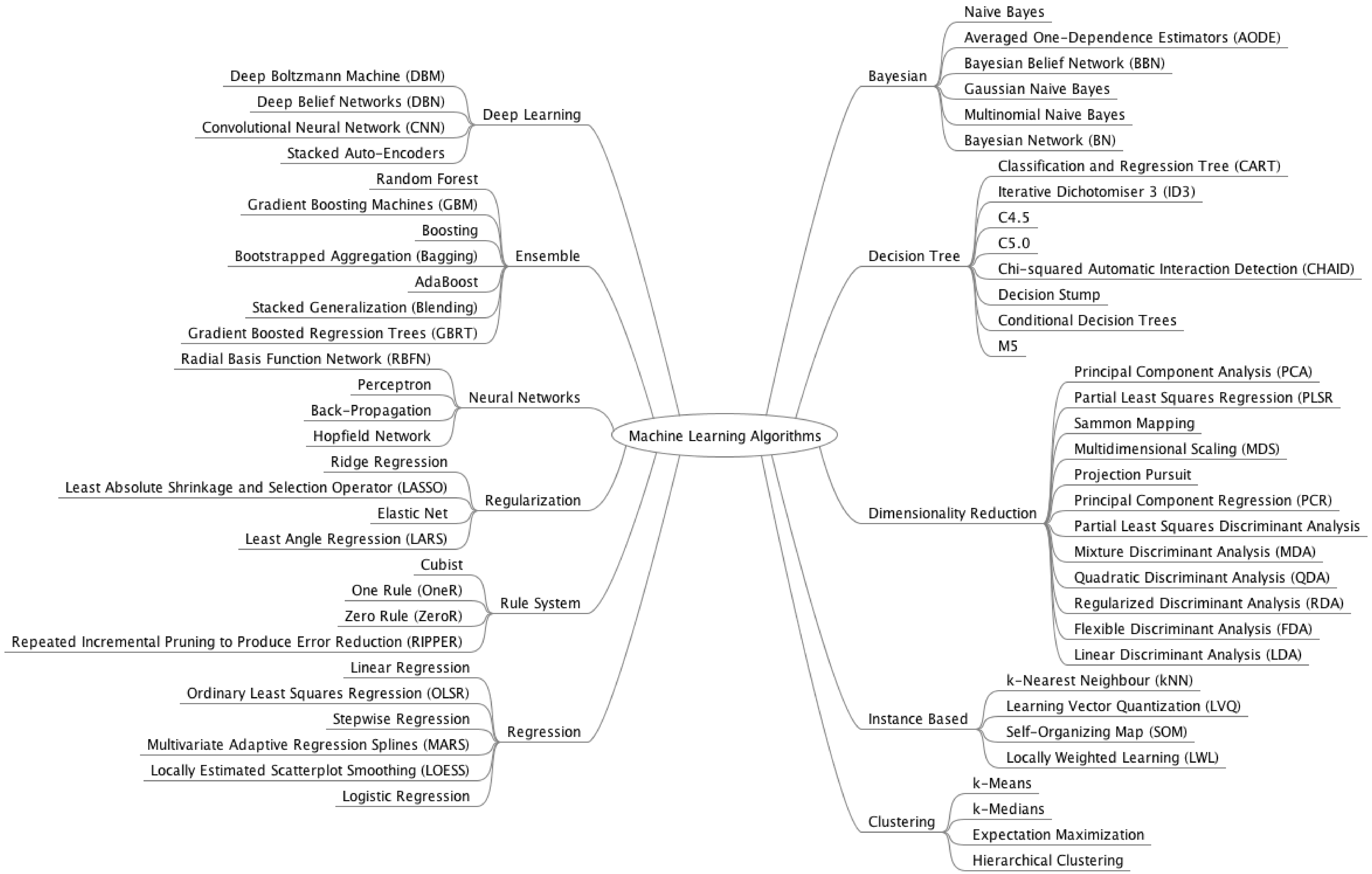
Limitations and applications of machine learning (and AI)
(Automation vs. Knowledge vs. Intelligence)



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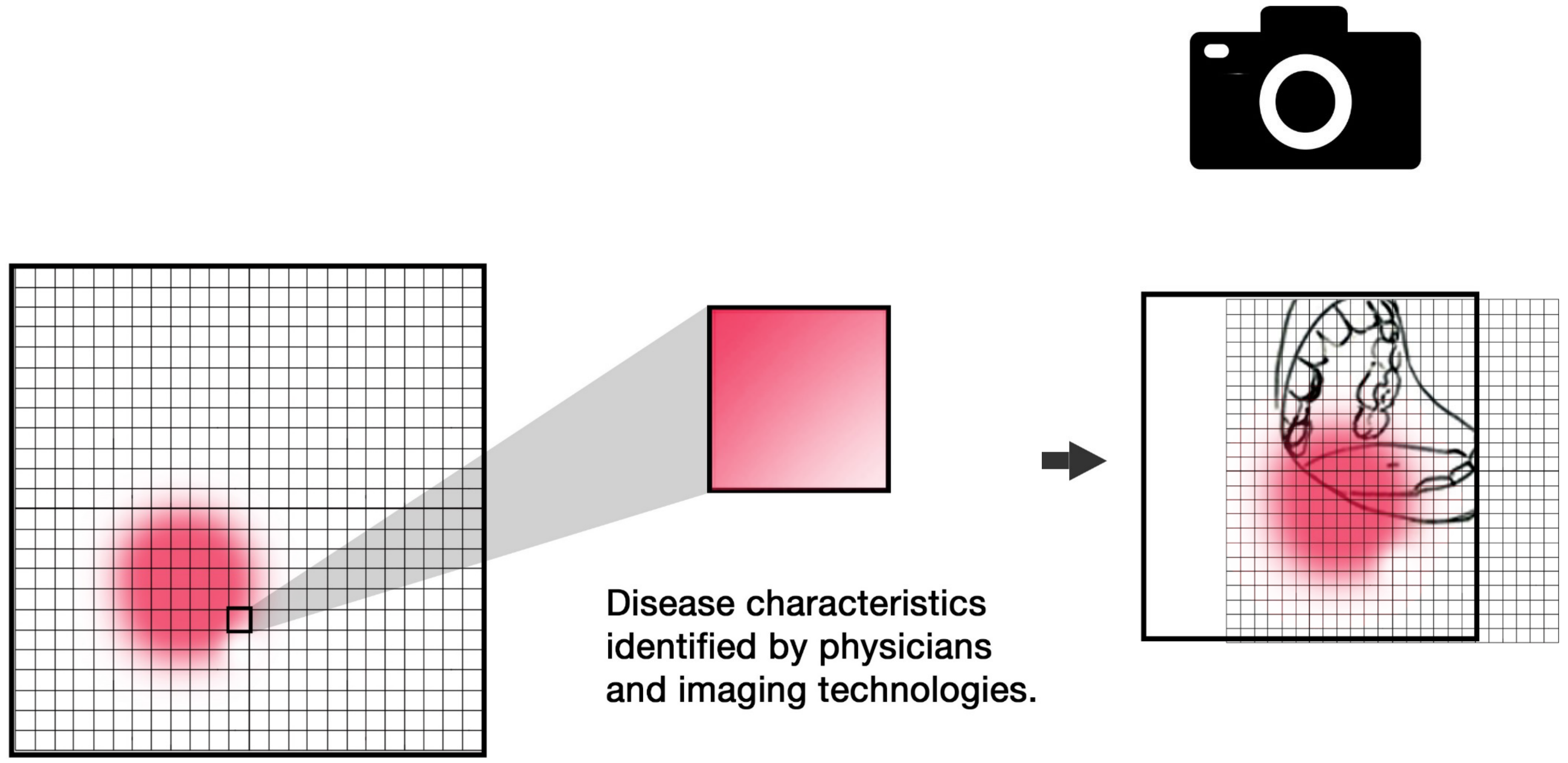
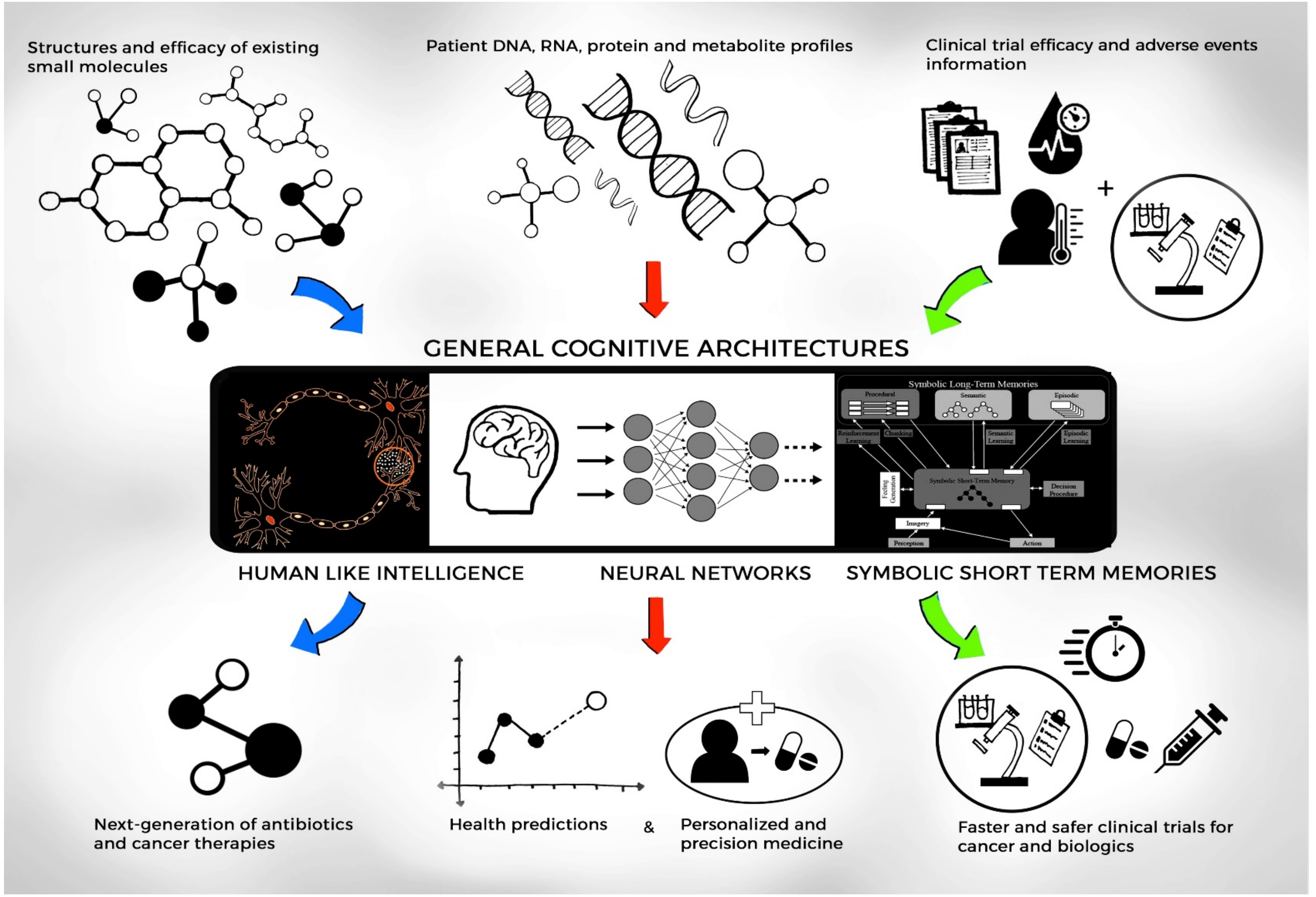
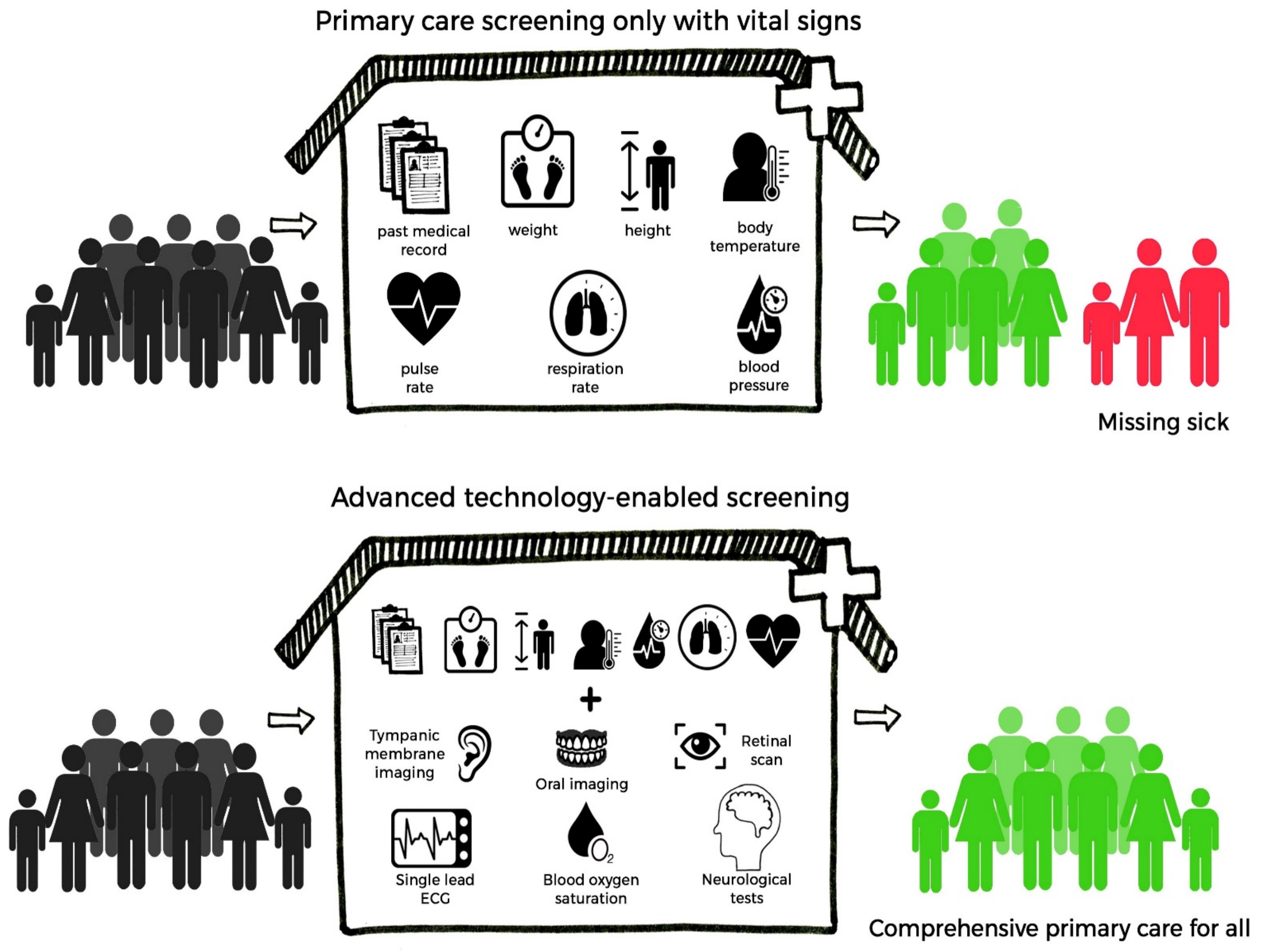
Research Areas



Medical imaging technologies using unorthodox artificial intelligence for early disease diagnoses



Novel ethical and explainable artificial intelligence based digital medicines and treatments



Point-of-care medical technologies for real world data and evidence generation

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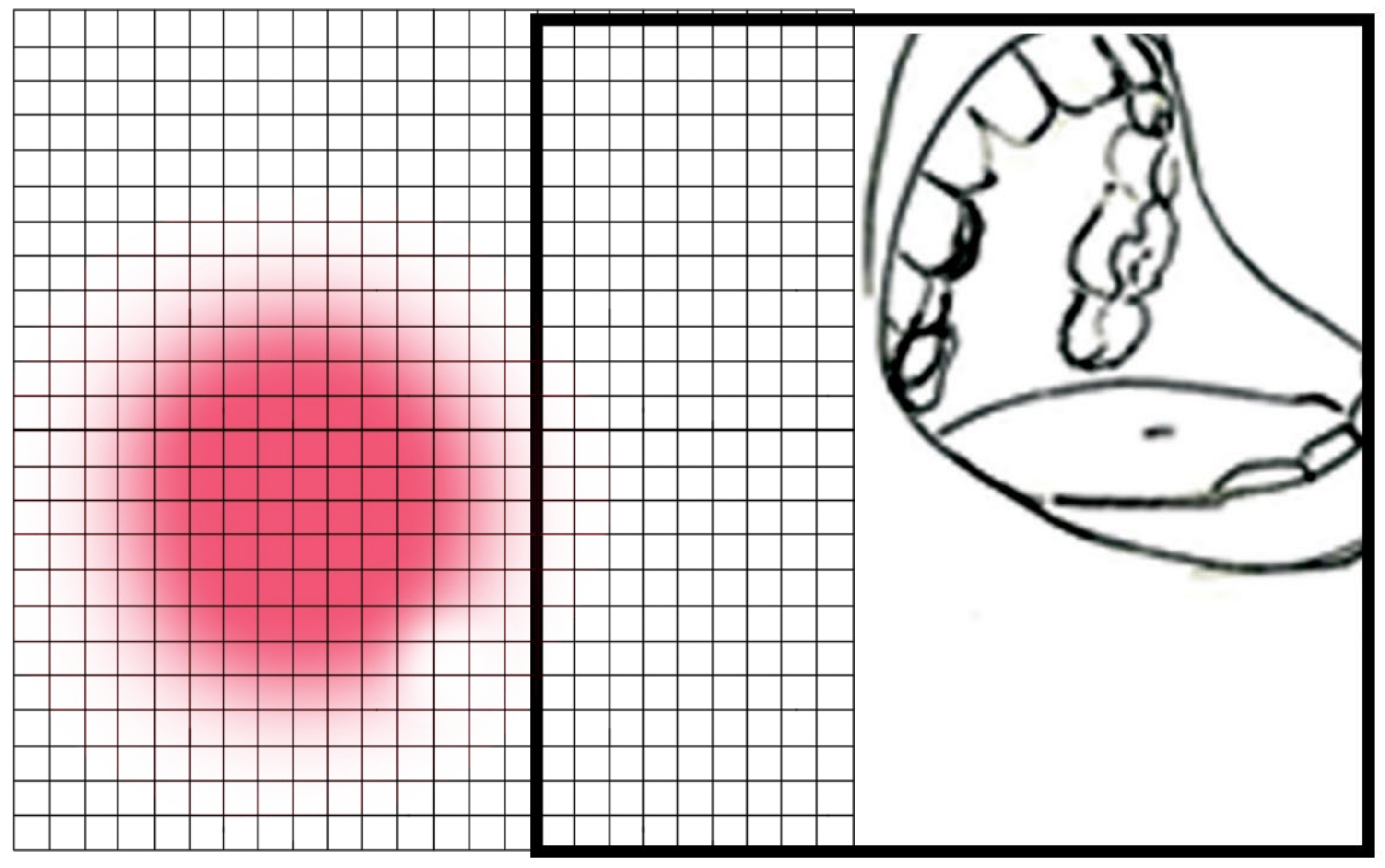
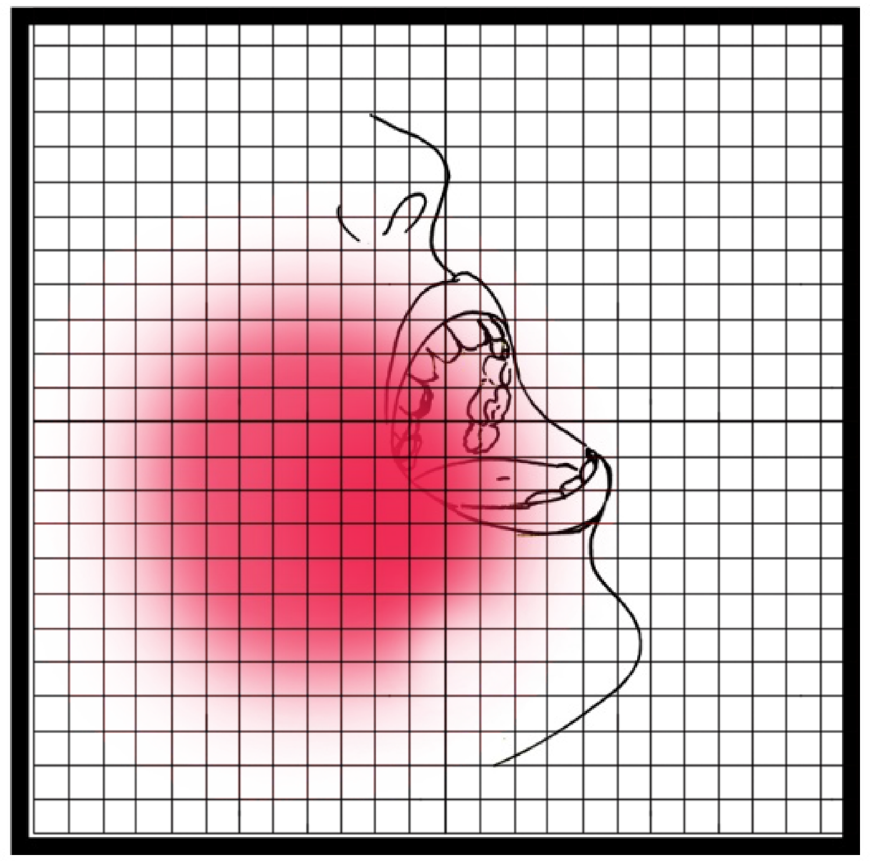
Unorthodox Image Processing and Biomarker Generation





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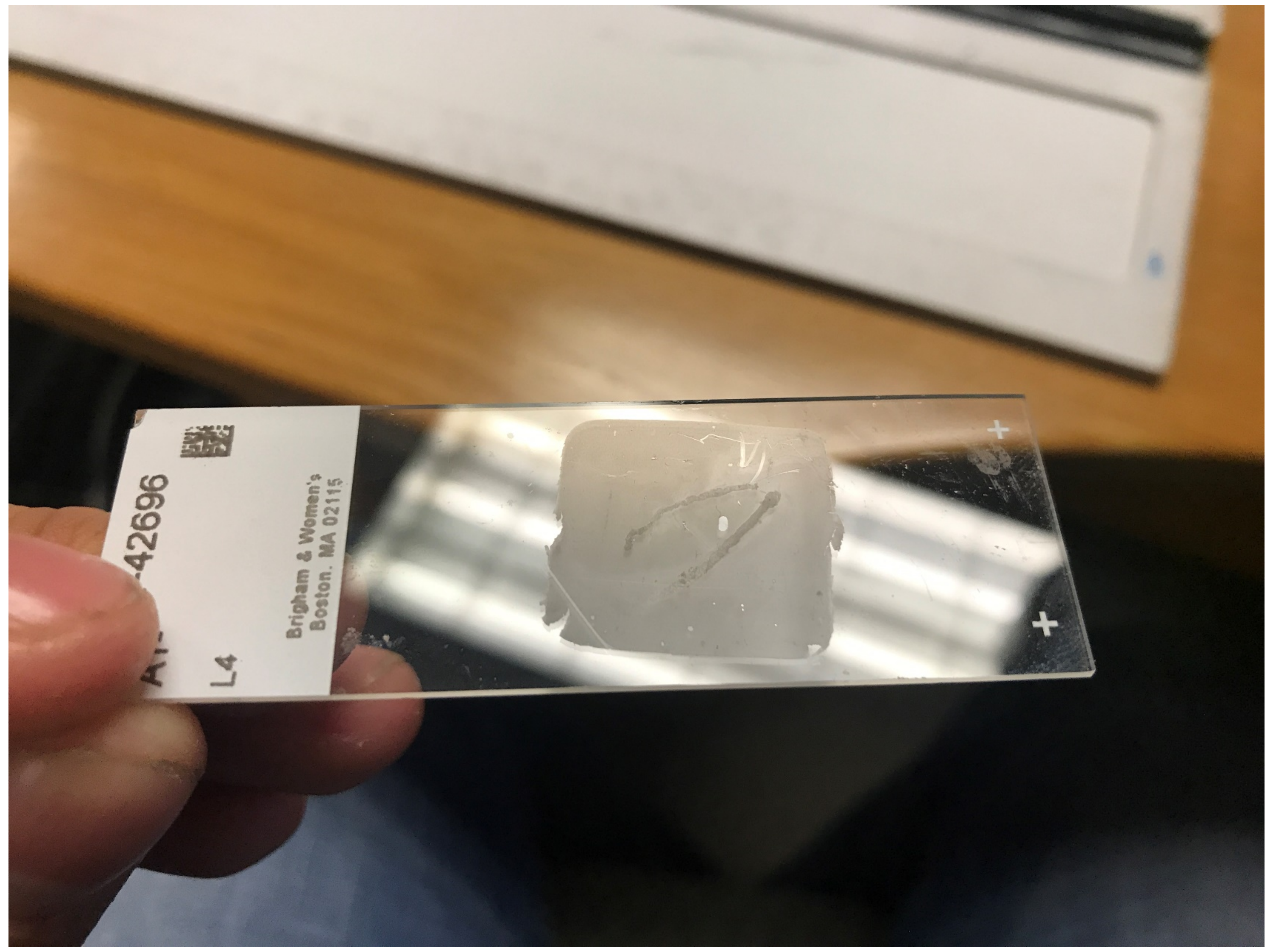
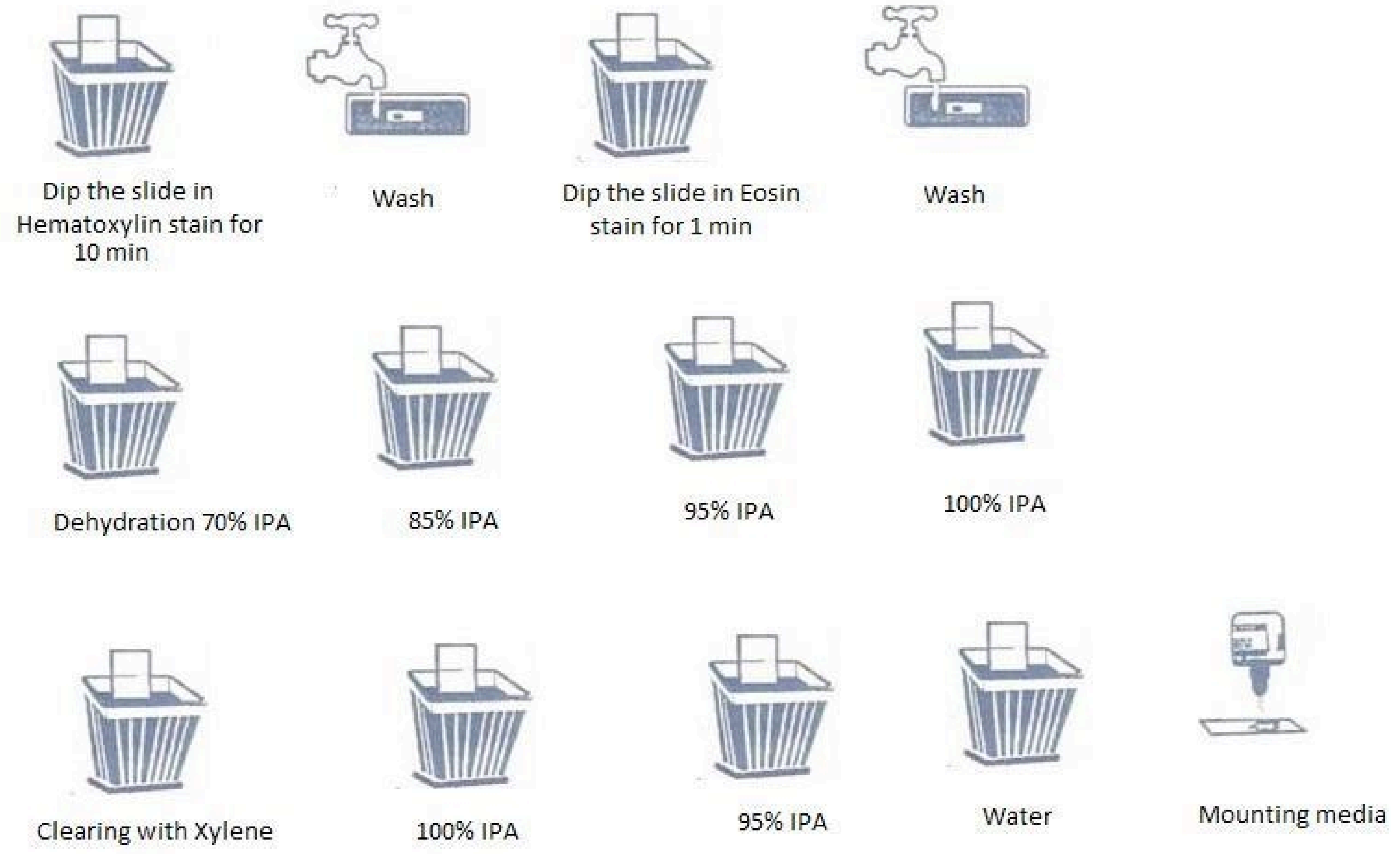
Computational Histological Staining and Destaining of Prostate Core Biopsy RGB Images with Generative Adversarial Neural Networks





Collaboration with Brigham and Womens Hospital

Computational histological staining and destaining of prostate core biopsy RGB images with generative adversarial neural networks
A. Rana, G. Yauney, A. Lowe and Pratik Shah
2018 17th IEEE International Conference of Machine Learning and Applications, DOI: 10.1109/ICMLA.2018.00133

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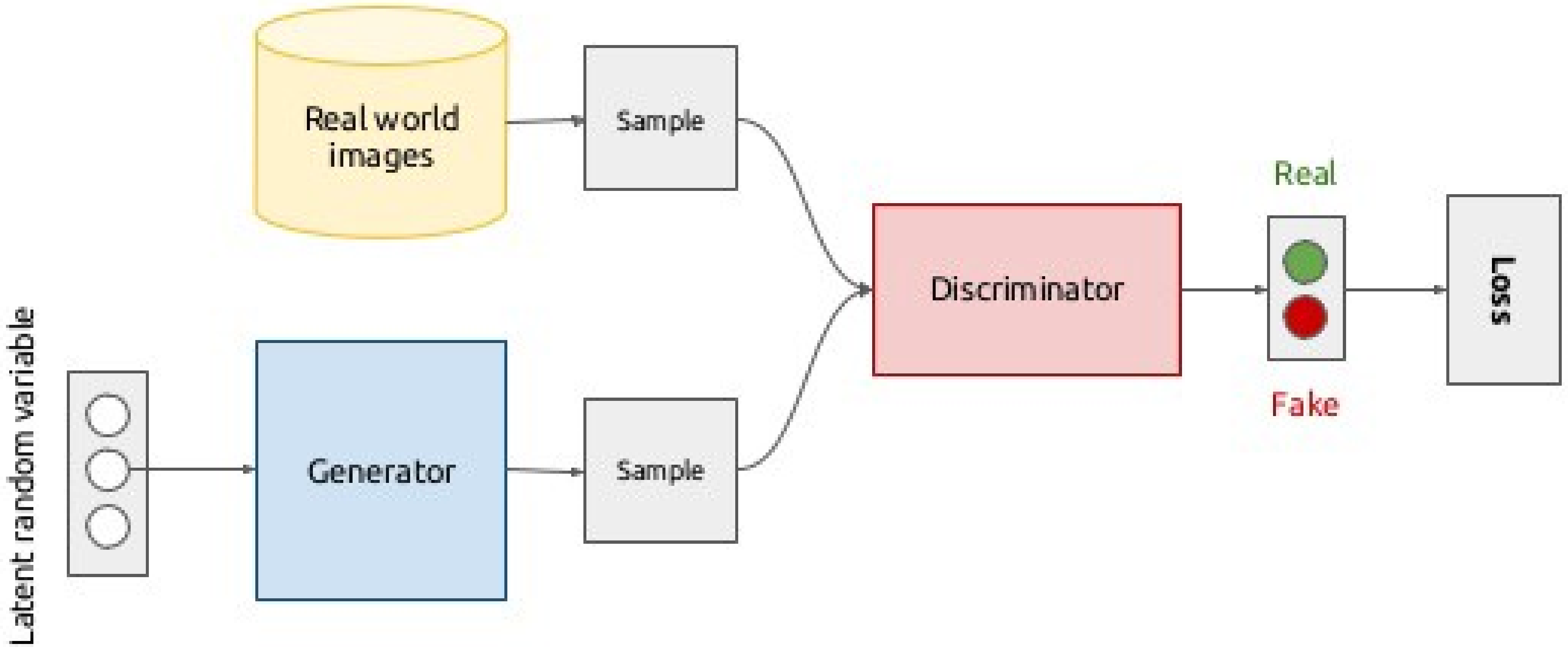
Generative Adversarial Neural Networks for New Medical Knowledge

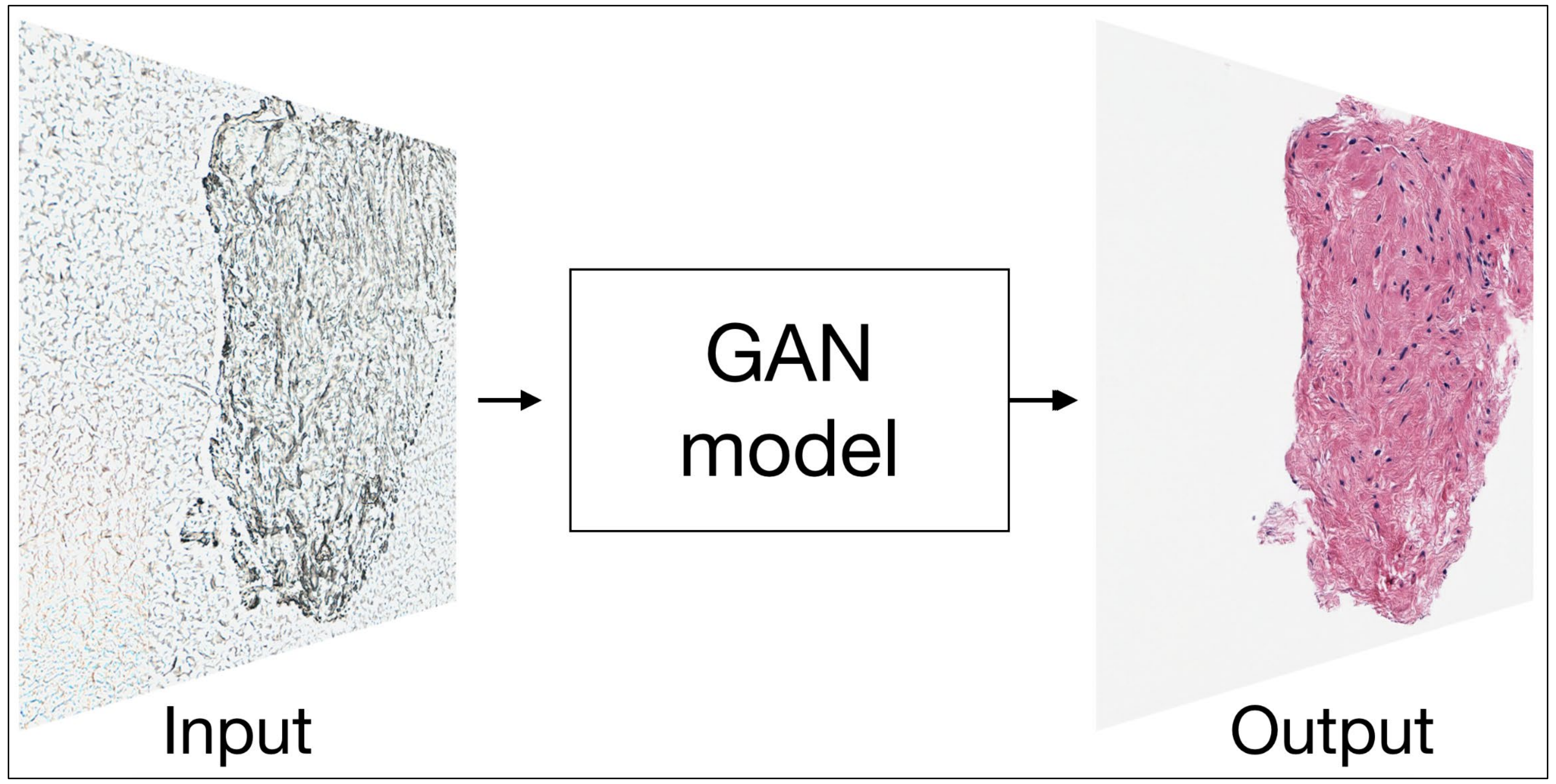


synthetic data/images

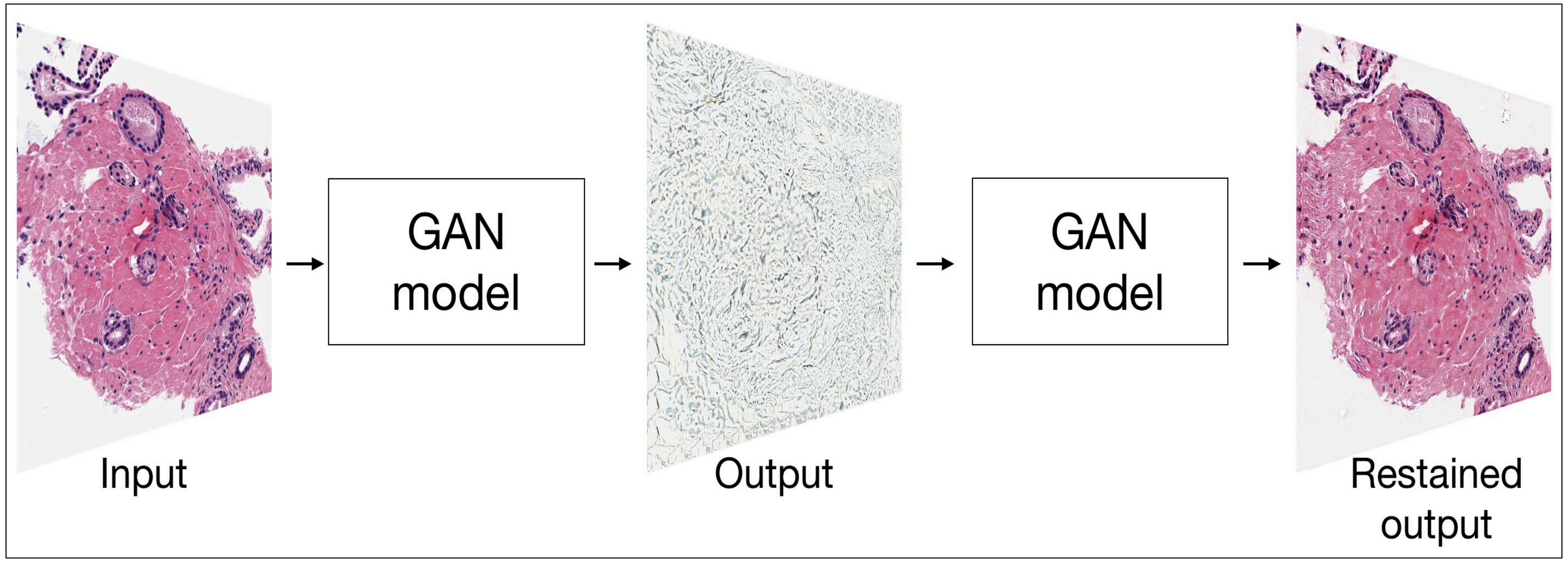
realistic looking high resolution images

$$\min_G \max_D V(D, G) = \mathbb{E}_{\boldsymbol{x}\sim p_{\text{data}}(\boldsymbol{x})}[\log D(\boldsymbol{x})] + \mathbb{E}_{\boldsymbol{z}\sim p_{\boldsymbol{z}}(\boldsymbol{z})}[\log(1 - D(G(\boldsymbol{z})))].$$

H & E Staining and Destaining of Prostate Core Biospy Images



Computational staining



Computational destaining

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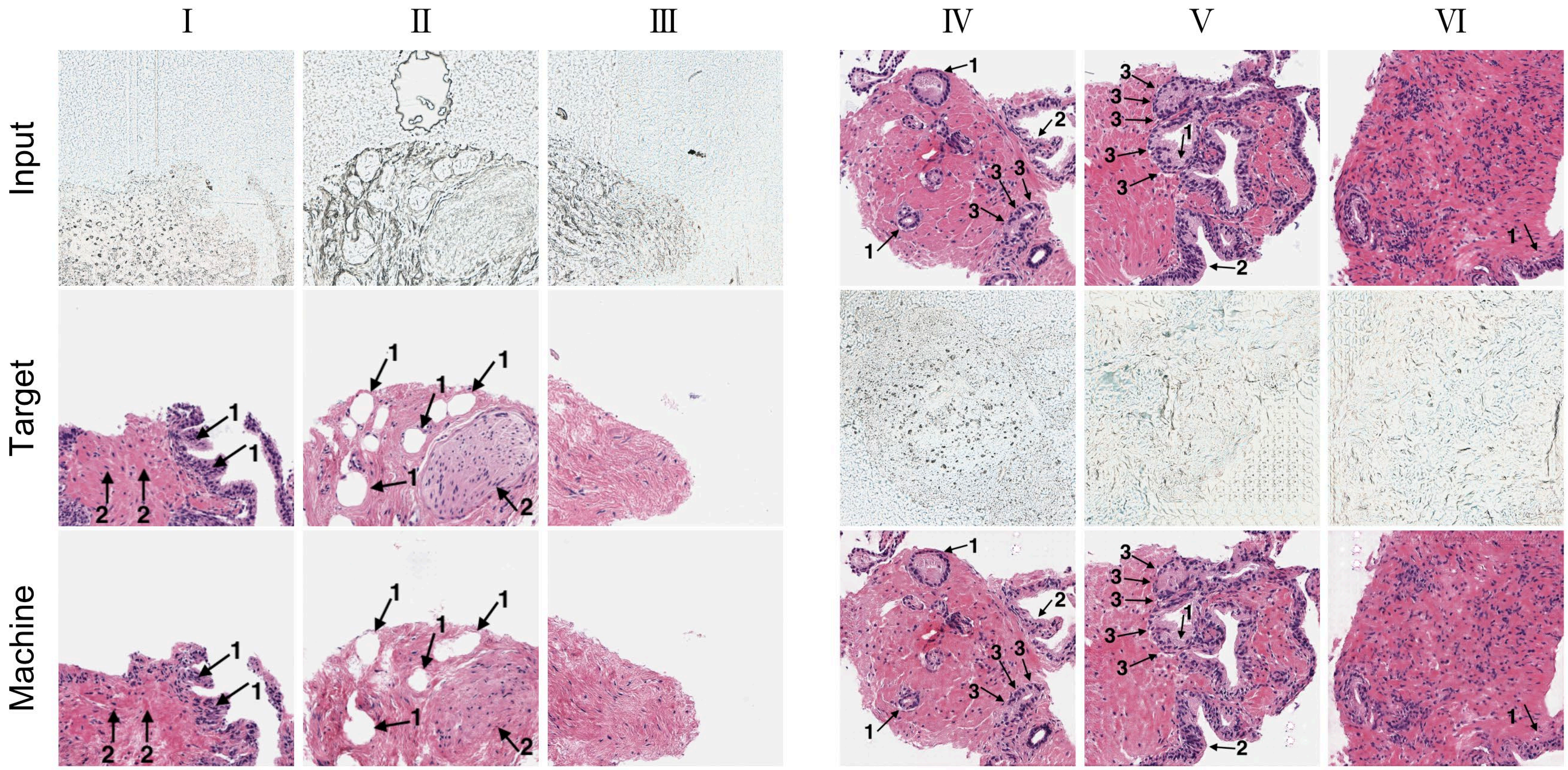
Computational Staining and Destaining of Prostate Cancer Biopsy



Computational staining

Computational destaining

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Images and Machine learning

- **Data standards and generalization**
- **Detailed validation studies with physician raters**
- **Deployment and testing: New clinical trials for algorithms, software as medical device and integration at point of care (need based)**
- **Regulation and communication with physician and patients**
- **Case studies with other hospitals and data for generalization**

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“Explainable” Machine Saliency for Medical Knowledge

Collaboration with Beth Israel Deaconess Medical Center

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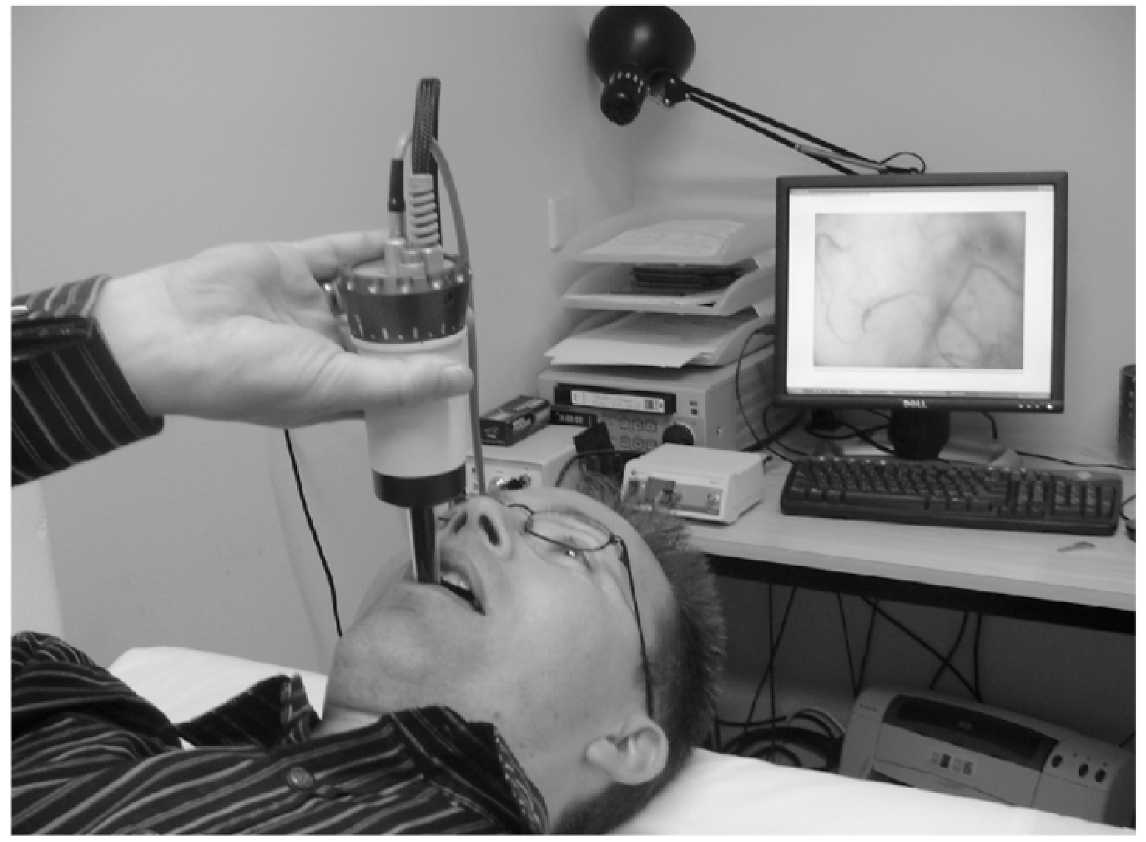
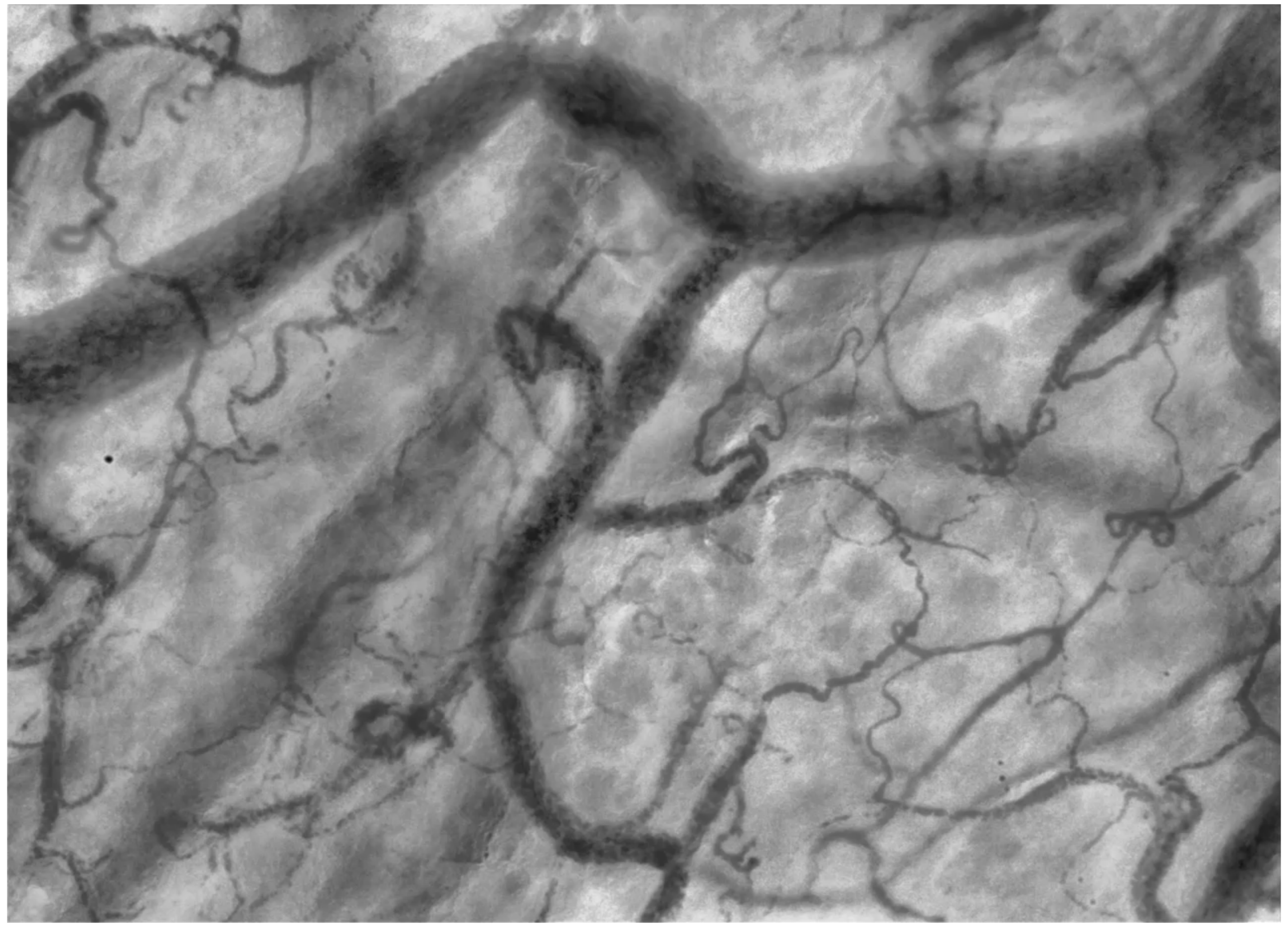
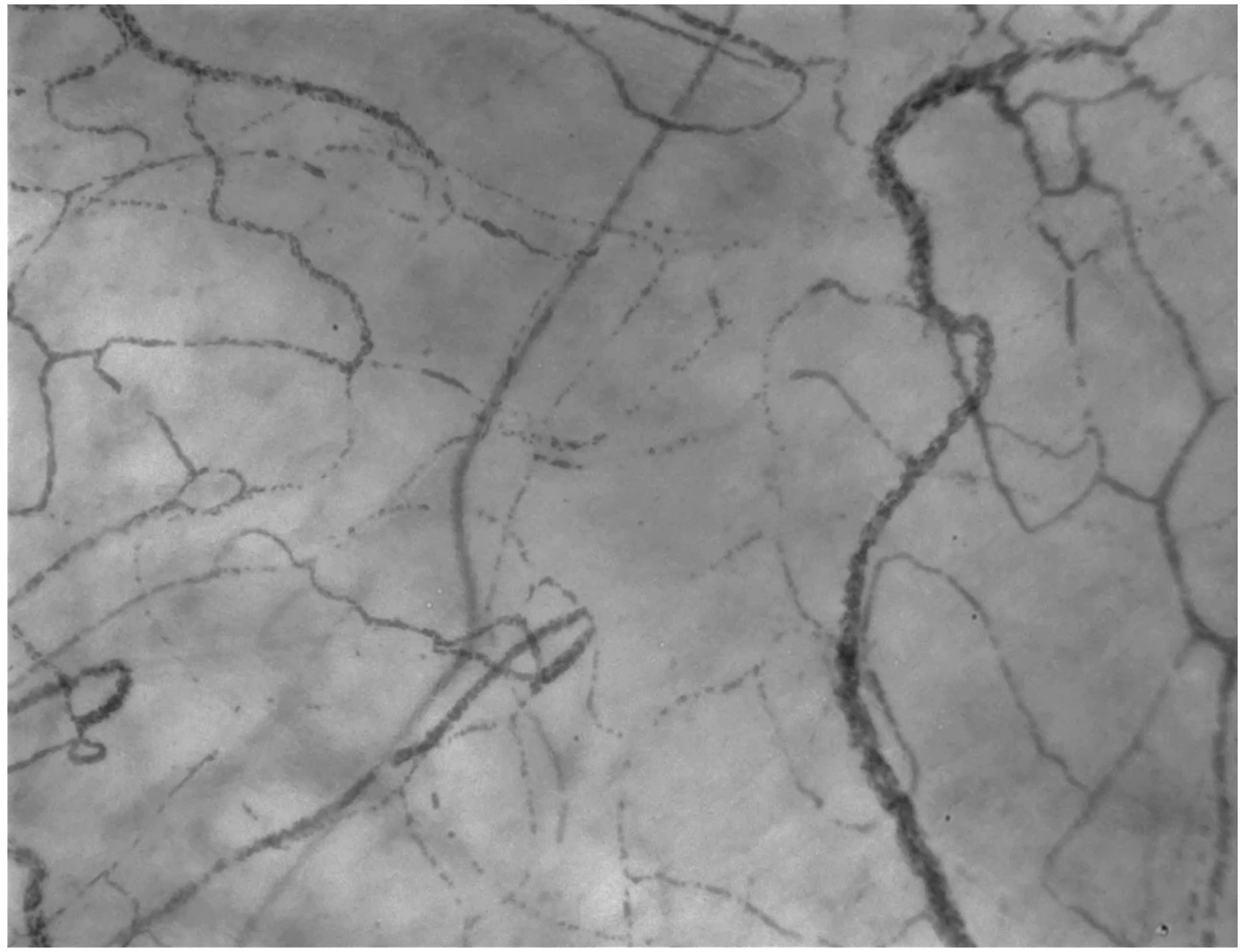




Healthy Patient



Septic Patient

Machine learning algorithms for classification of microcirculation images from septic and non-septic patients
P. Javia, Rana A and Pratik Shah
17th IEEE International Conference of Machine Learning and Applications, DOI: 10.1109/ICMLA.2018.00097

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Collaboration with Beth Israel Deaconess Medical Center

Neural Network based Learning from Microcirculation Videos

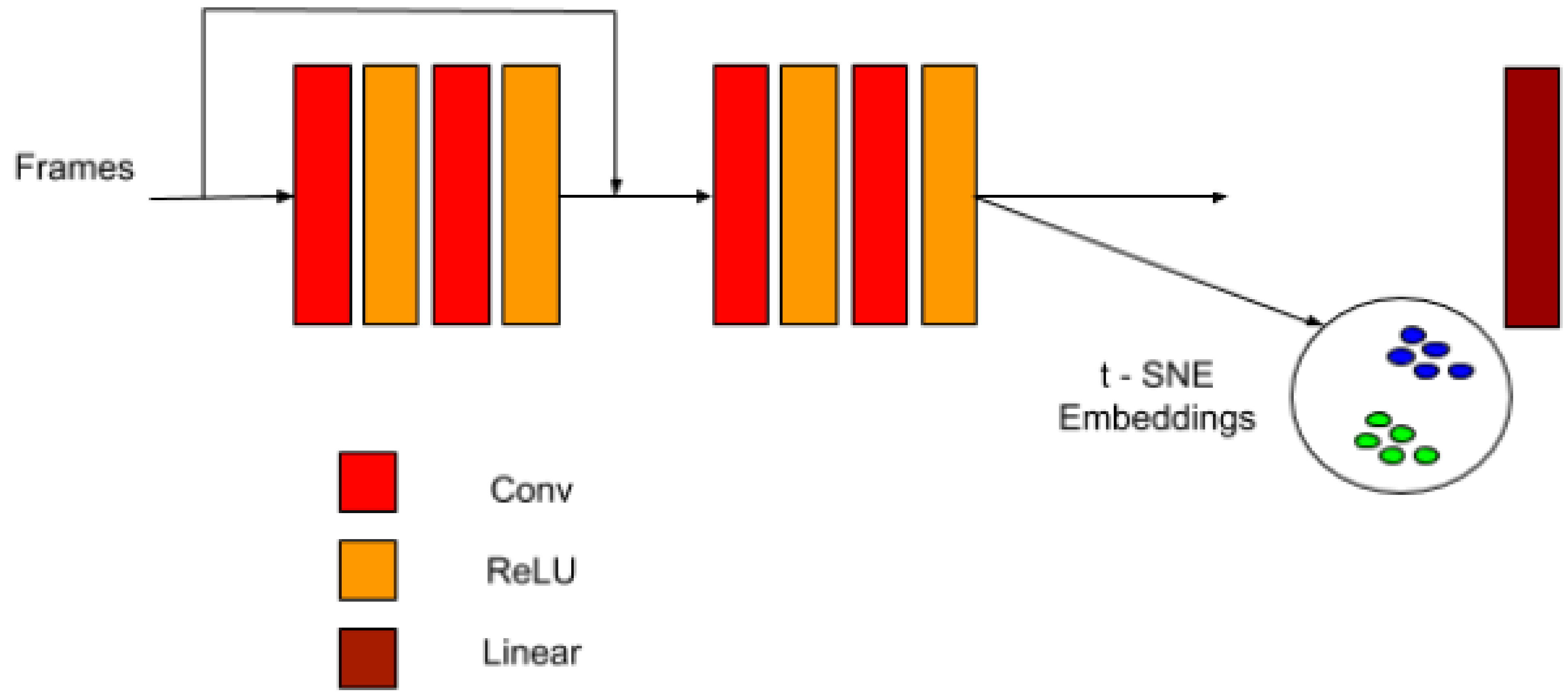

Fig. 2: The last convolutional layer used for visualization of t-SNE embedding.

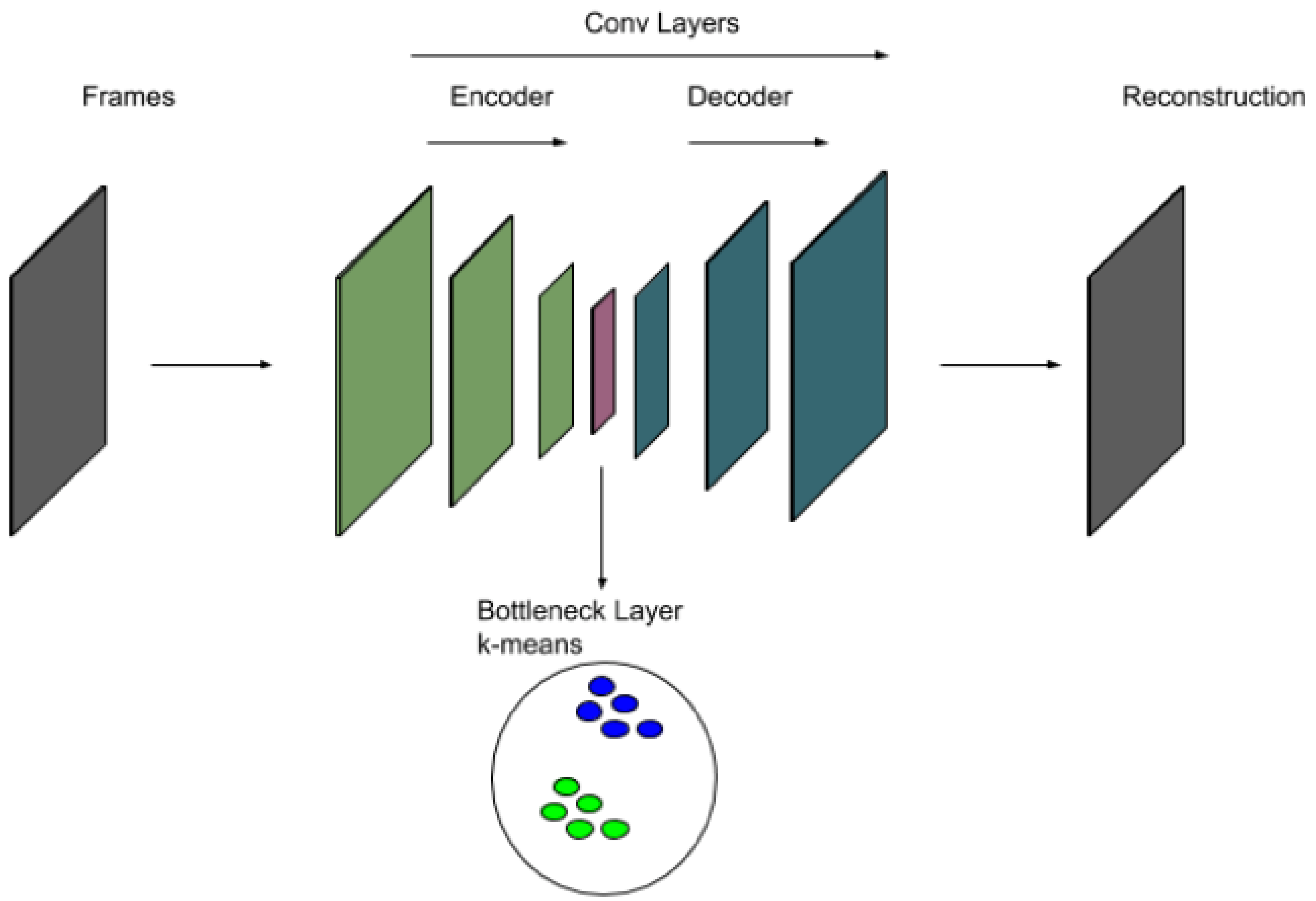

Fig. 3: Feature vector from the trained autoencoder used for k-means clustering and visualization.

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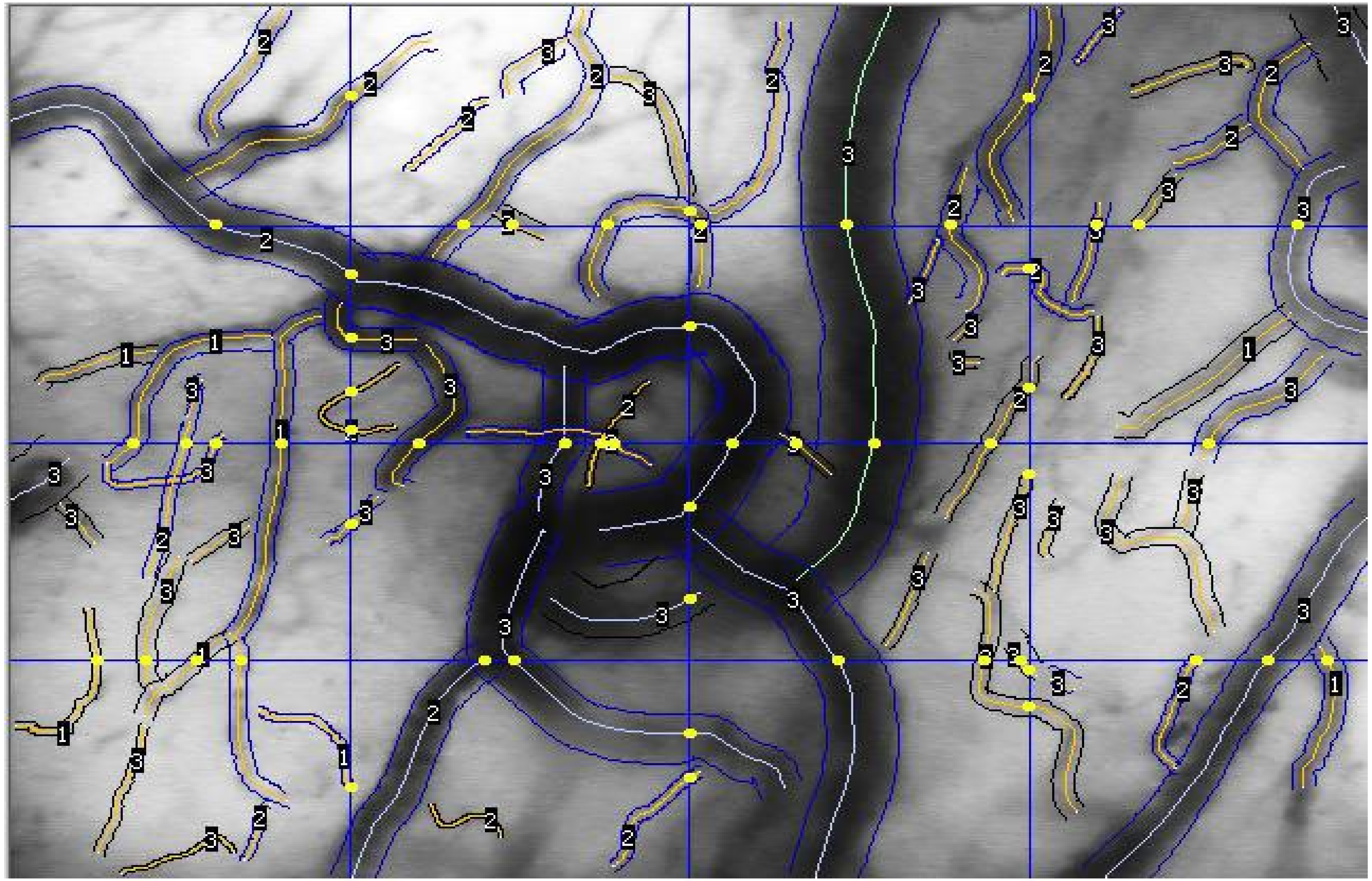
Image and Clinical Analysis by Human Experts vs. Algorithms

- Frame Average
- Vessel Segmentation
- Blood Flow Analysis
  - –Microvascular Flow Index (MFI)
  - –Portion of Perfused Vessels (PPV)
  - –Perfused Vessel Density (PVD)
  - –Heterogeneity Index
  - –Total Vessel Density



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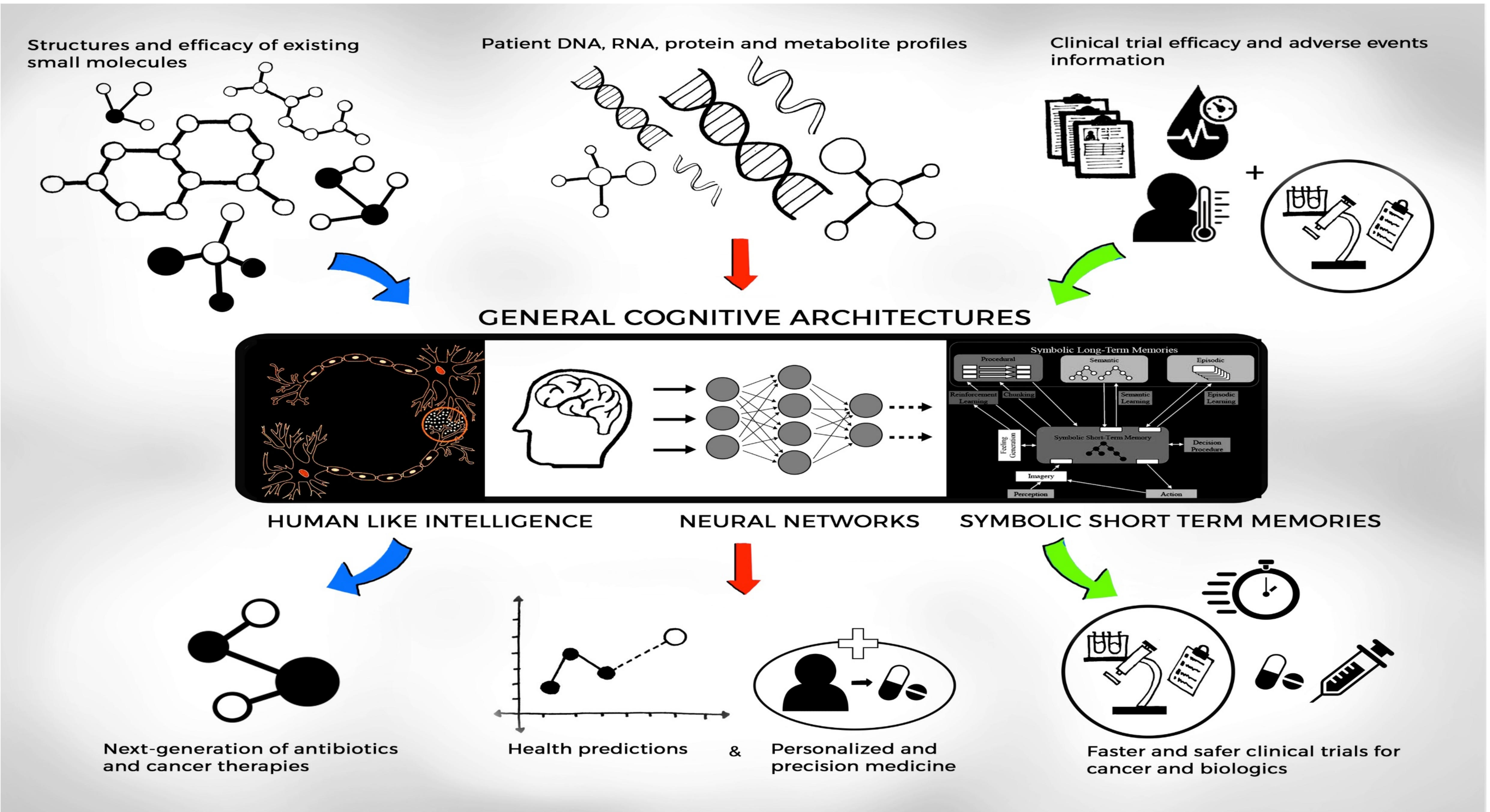
Machine Learning and AI for Clinical Trial Design



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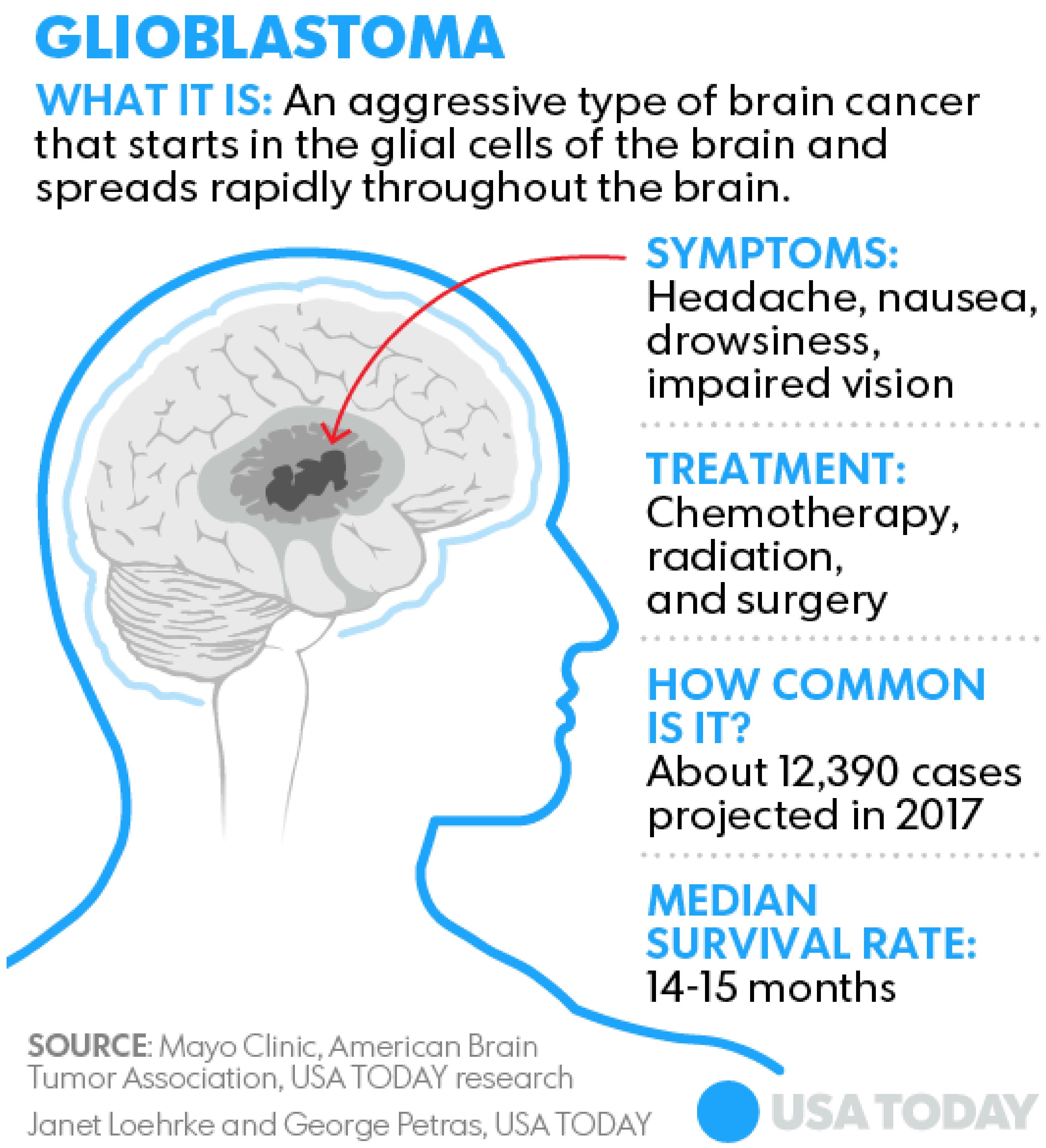
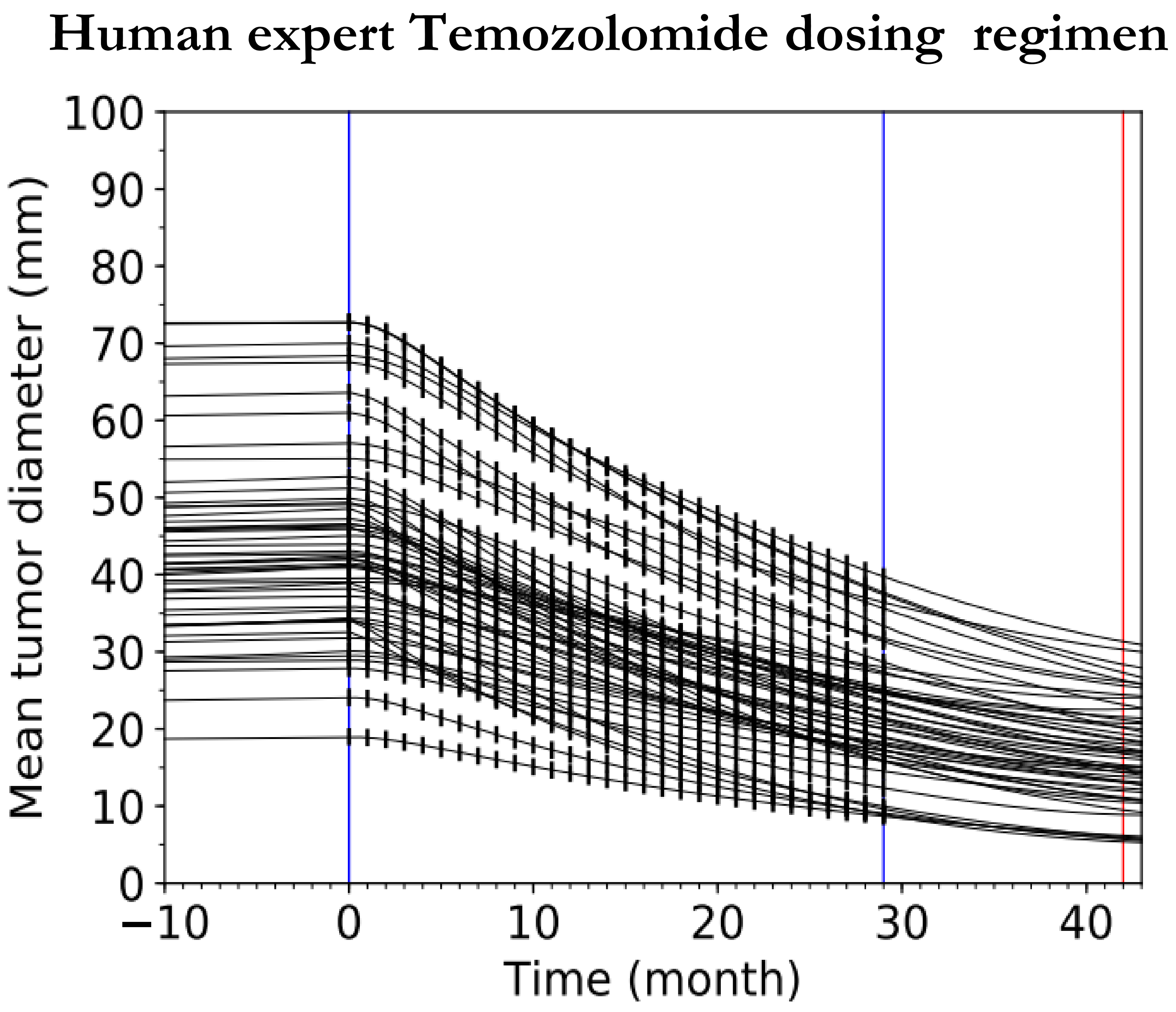
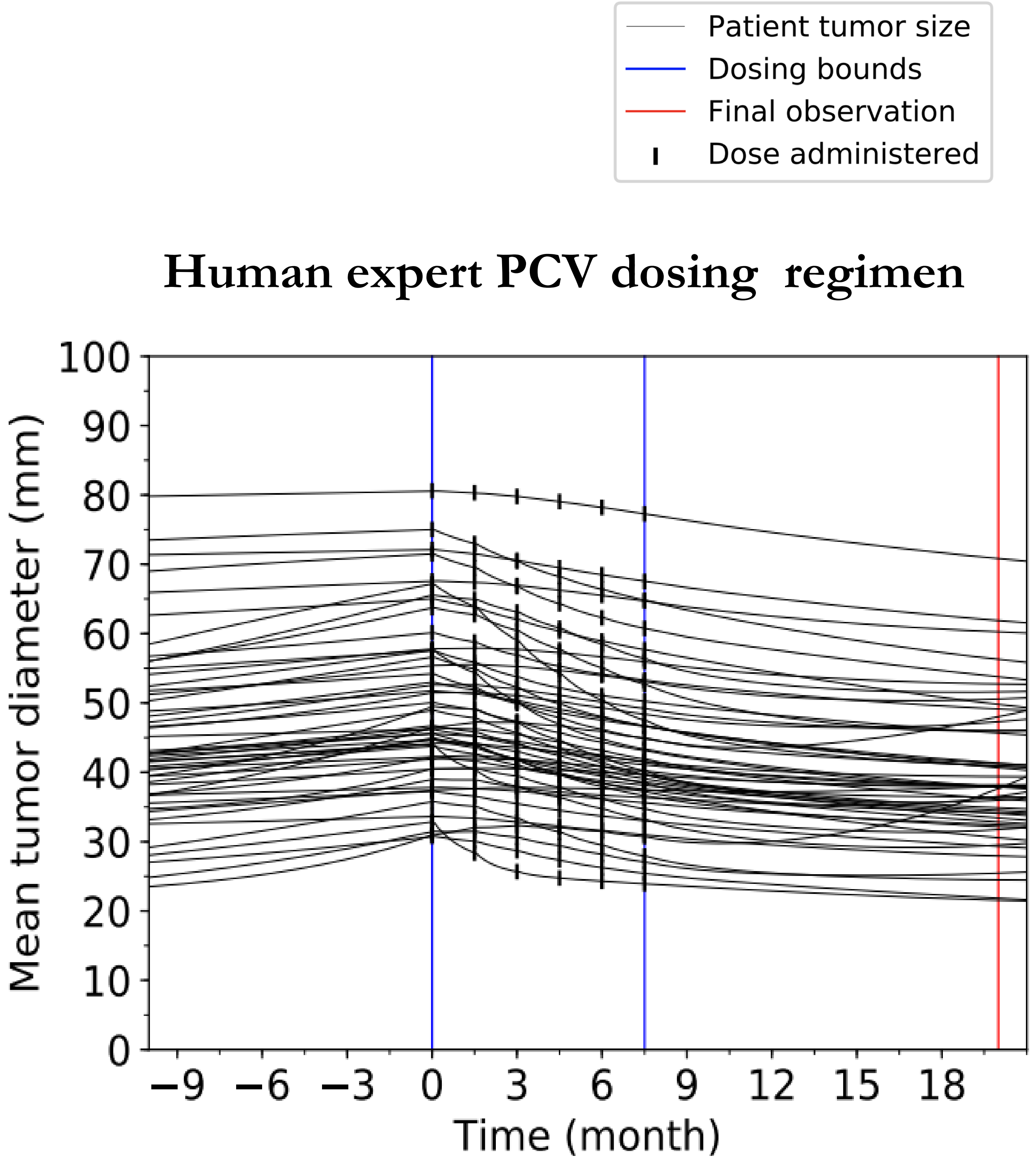
Glioblastoma Treatment and Toxicity with Chemo-and-Radiotherapy







Reinforcement learning with action-derived rewards for chemotherapy and clinical trial dosing regimen selection

G. Yauney and Pratik Shah

Proceedings of the 3rd Machine Learning for Healthcare Conference, PMLR 85:161-226

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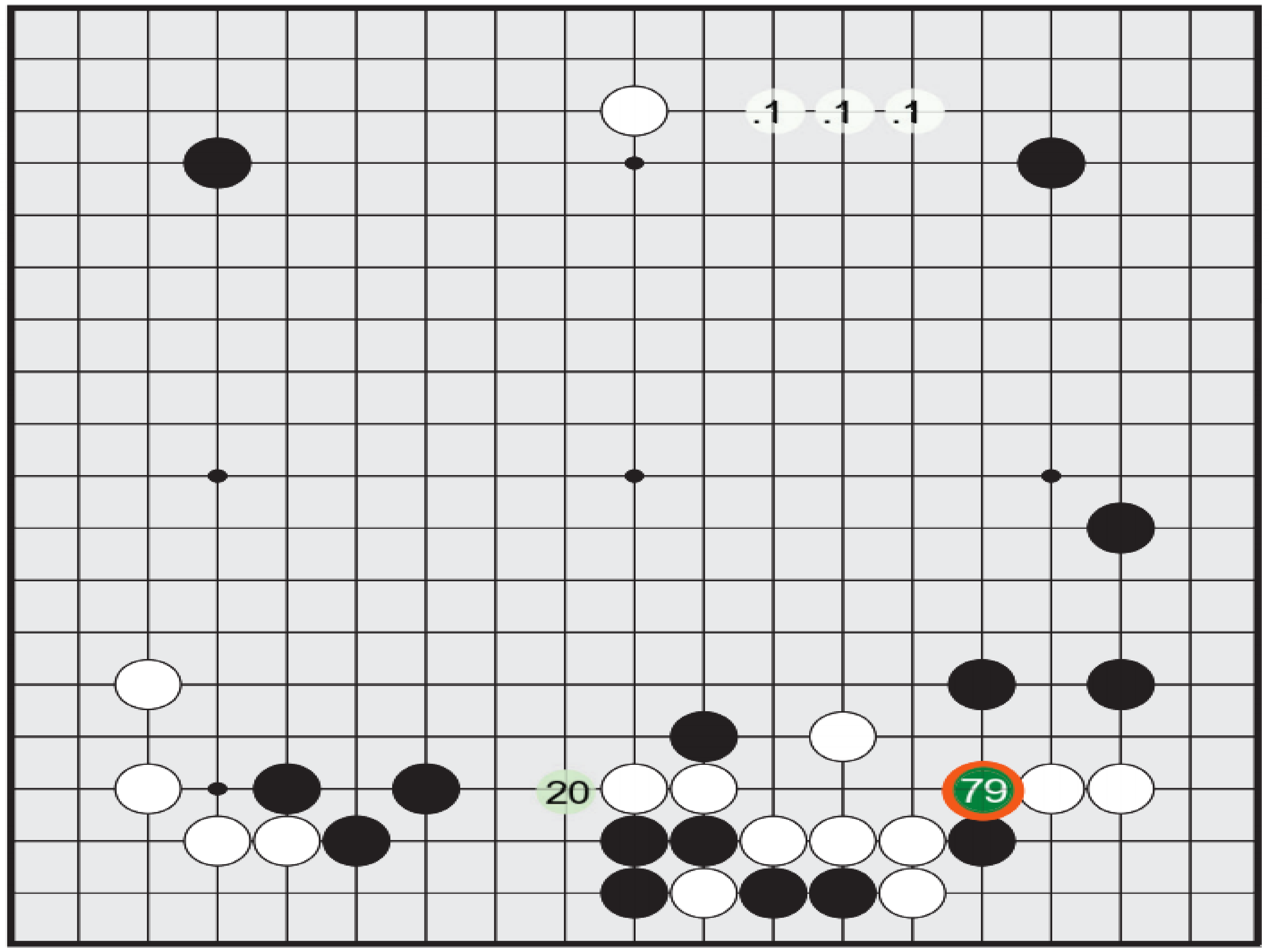
Reinforcement Learning

Formal definition:

- States
- Actions
- Transition
- Reward
- Discount factor

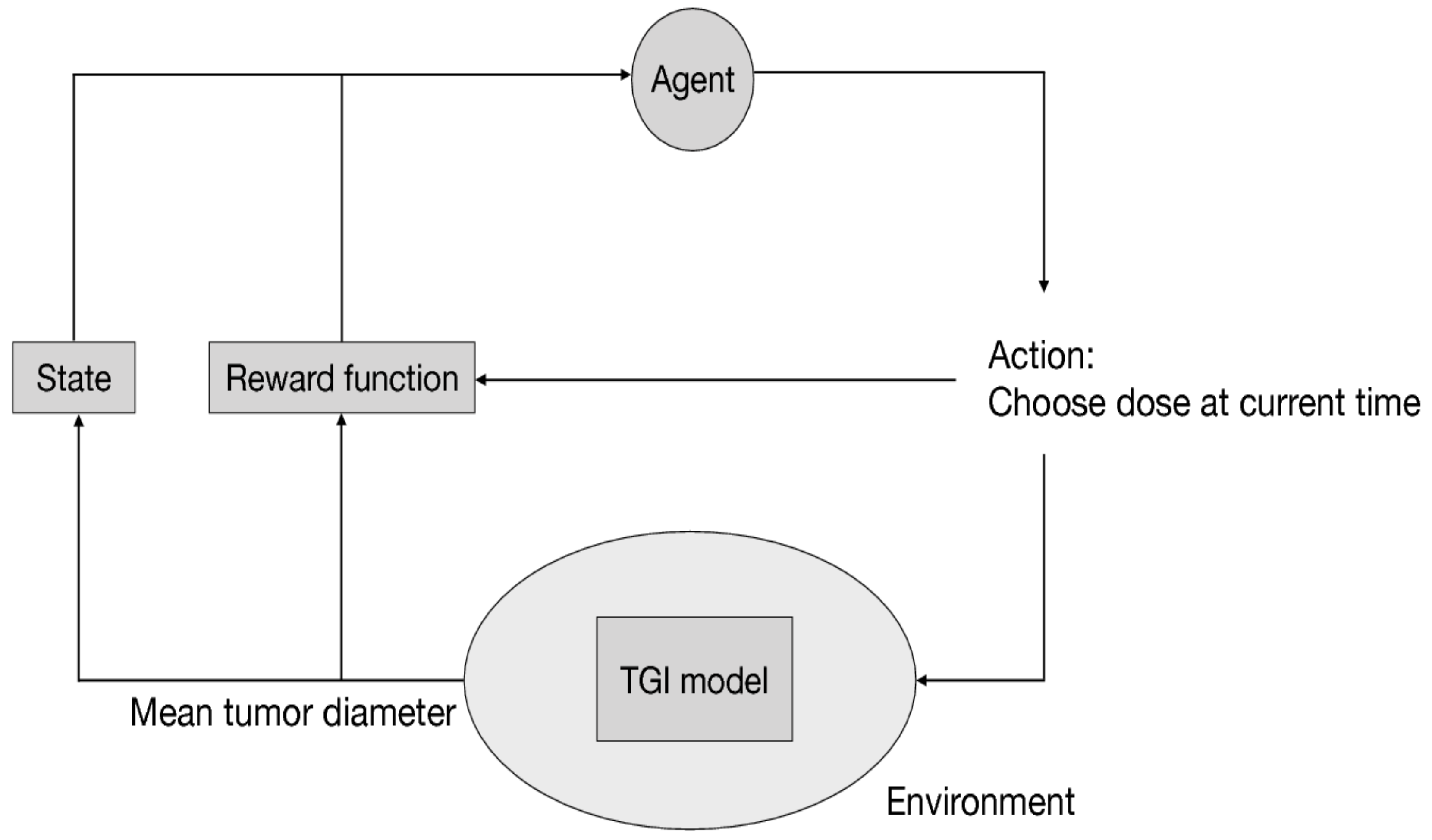


Silver, David, Aja Huang, Chris J. Maddison, Arthur Guez, Laurent Sifre, George Van Den Driessche, Julian Schrittwieser et al. "Mastering the game of Go with deep neural networks and tree search." *Nature* 529, no. 7587 (2016): 484-489.

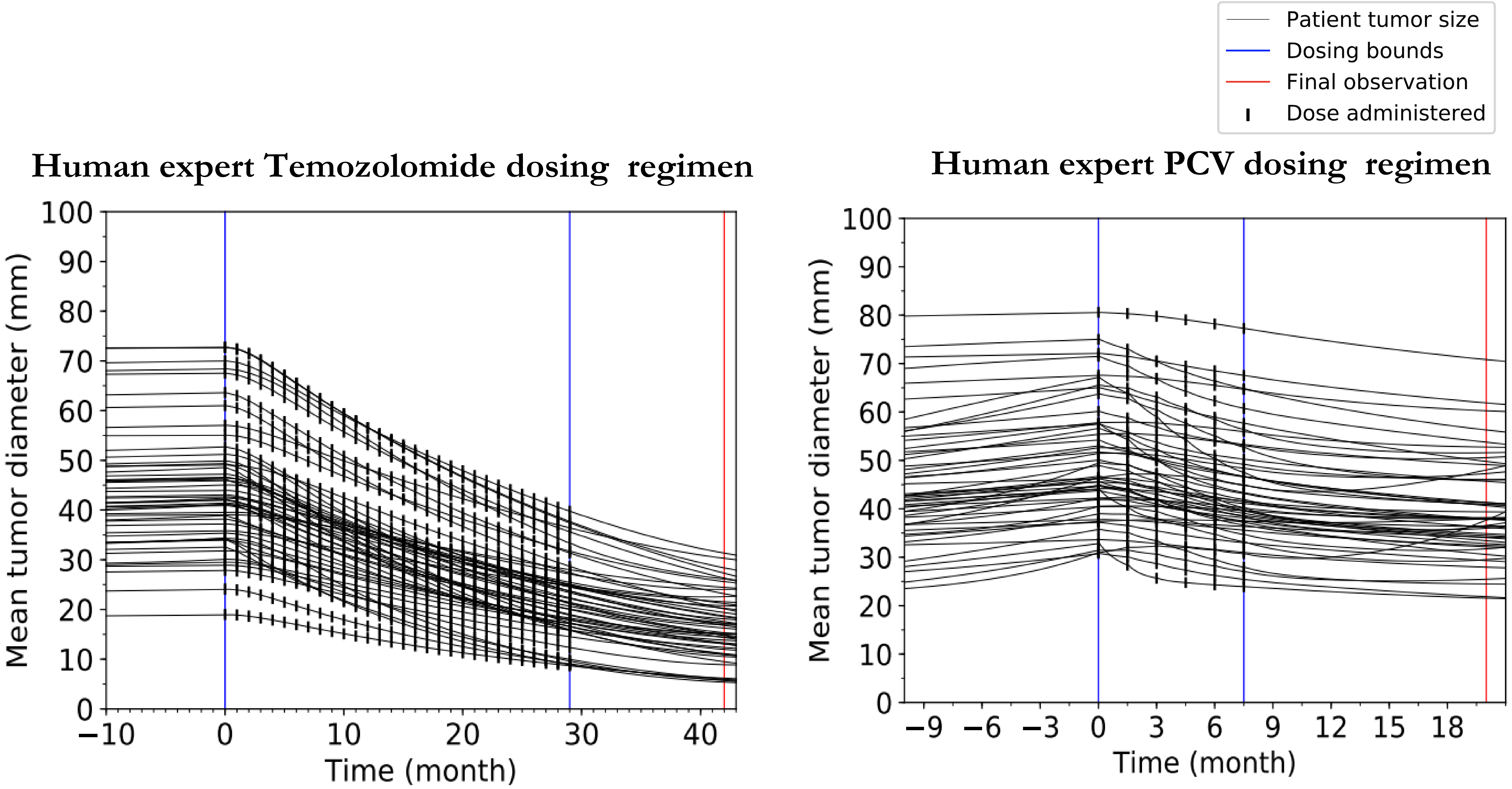
Sutton & Barto, *Reinforcement Learning: an Introduction.* Cambridge: MIT Press: 1996

Mnih, Volodymyr, Koray Kavukcuoglu, David Silver, Andrei A. Rusu, Joel Veness, Marc G. Bellemare, Alex Graves et al. "Human-level control through deep reinforcement learning." *Nature* 518, no. 7540 (2015): 529-533.

Learning environment, rewards and penalties



The reinforcement learning agent interacts with an environment containing a tumor growth inhibition (TGI) model. The reward is determined in part by the values used for the reinforcement learning model's state and the agent's most recent action.



Off-Policy deep Q learning

$$Q^*(s,a) = R(s,a,s') + \gamma \sum_{s' \in S} T(s,a,s') \max_{a'} Q^*(s',a')$$

Actions are sampled according to an epsilon-greedy strategy, after which the optimal action from each state can be found:

$$\pi^*(s) = \mathrm{argmax}_a Q^*(s,a)$$

$R = c\,(MTD_t - MTD_{t'})$ - penalty . concentration
$R_{final} = c_{final}\,(MTD_{initial} - MTD_{final})$

C= 1, Cfinal=10

TMZ penalties= 1 and 5

PCV penalties= 1 and 10

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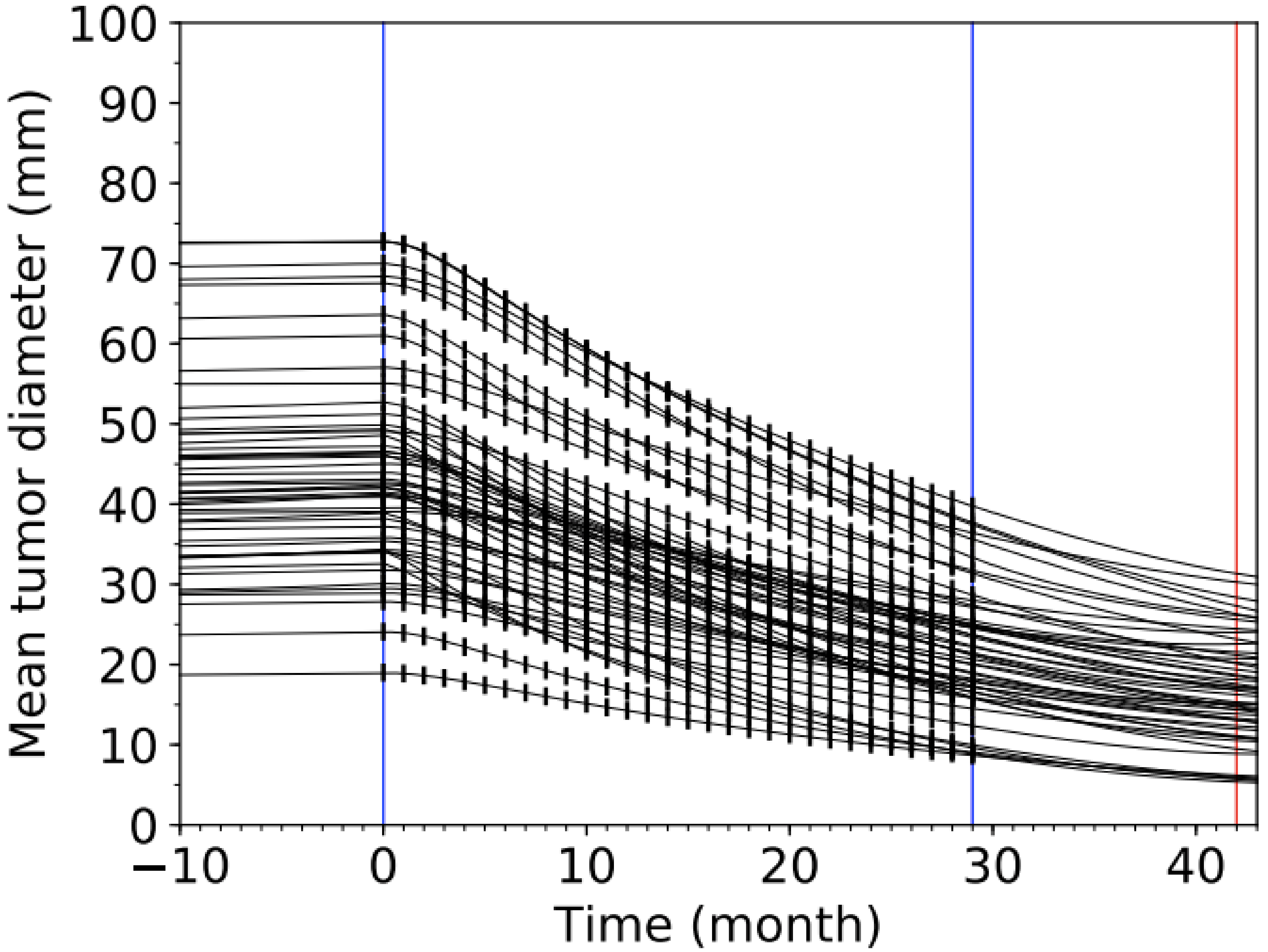
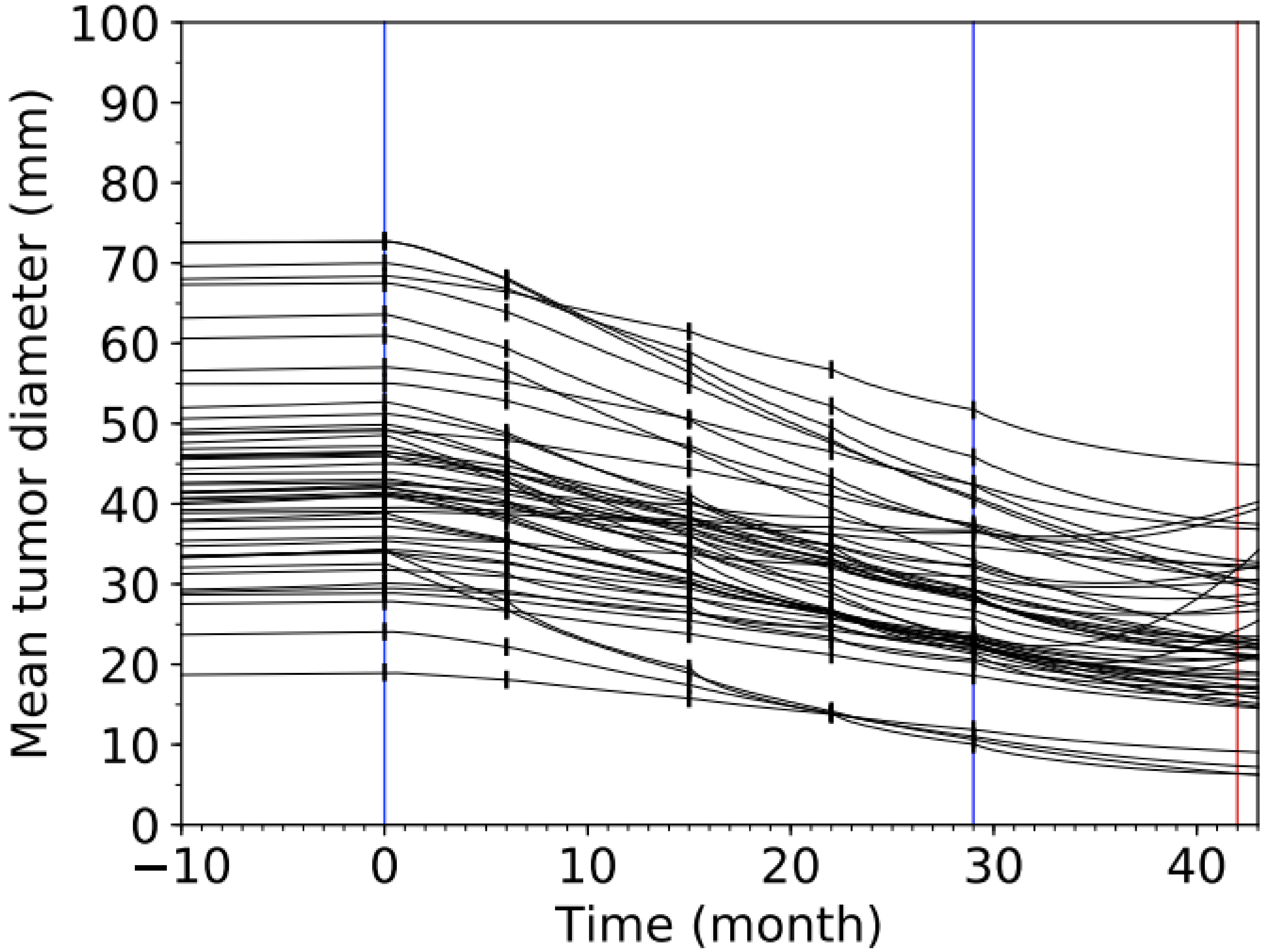
Digital Therapeutics and Algorithmic Design of Clinical Trials

Goal: Reduce number of doses for all patients

Human experts



Machine policy



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Digital Therapeutics and Algorithmic Design of Clinical Trials

Goal: Reduce number of doses for all patients

	Month of trial																													
Dosing regimen	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Expert	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Machines	✓	✓	✓	.	✓	.	.	.	.	✓	.	.	.	✓	.	.	.	✓	.	.	.	.	✓	.	.	.	✓	.	.	.

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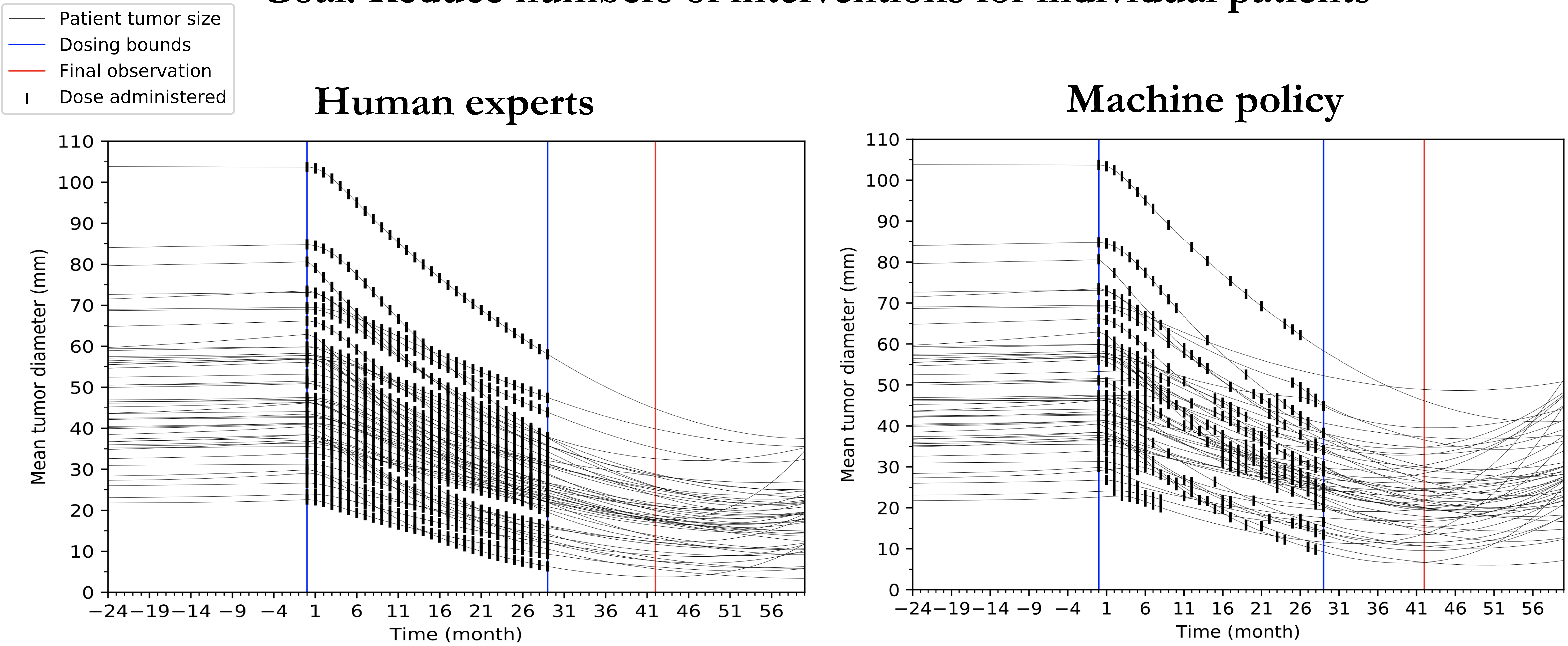
Digital Therapeutics and Algorithmic Design of Clinical Trials

Goal: Reduce numbers of interventions for individual patients



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Learned policies with penalties and MTD reductions in TMZ cohort trials

			Month of trial																													
	Conc.	Penalty	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
A		None	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
B	Fixed	Small	1	1	1	0	1	0	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0	1	0	0	0	1	0	0	0
C		Large	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	1
D		None	1	1	1	1	.25	.75	1	1	.75	.75	.75	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
E	Variable	Small	1	1	.75	.75	0	0	.25	.5	0	.5	0	0	.5	0	.5	0	0	.5	0	0	.5	0	.5	0	0	.25	.5	0	0	.5
F		Large	1	.5	0	0	0	0	0	0	.25	.25	0	.25	.25	0	.25	0	.25	0	.25	.25	0	.25	0	.25	.25	0	.25	.25	0	.25

Table 2: Learned policies for trial-based TMZ experiments where all simulated patients received the same dose each month. Agents with a fixed concentration could give a unit dose, whereas agents with a variable concentration could give doses at 25%, 50%, 75%, and 100% of the unit dose's concentration. Penalty: size of the dose penalty the agent tried to minimize while maximizing mean tumor diameter reduction. Conc: concentration.

	Trial parameters			Average MTD change			
	Treatment	Conc.	Type	Expert policy	No penalty	Small penalty	Large penalty
A	TMZ	Fixed	Patient	-61.04% ± 11.63%	-60.95% ± 11.64%	-51.89% ± 15.31%	-35.97% ± 17.05%
B	TMZ	Fixed	Trial	-62.18% ± 10.50%	-62.17% ± 10.51%	-54.09% ± 14.05%	-46.27% ± 17.93%
C	TMZ	Variable	Patient	-60.51% ± 10.68%	-60.23% ± 10.80%	-39.35% ± 46.02%	-7.15% ± 40.80%
D	TMZ	Variable	Trial	-62.86% ± 11.41%	-62.72% ± 11.43%	-54.03% ± 15.21%	-45.69% ± 18.06%

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Language, Literacy and Vocabulary of Machine Learning Research for Improving Health outcomes

- Inclusion and diversity in datasets are key to engender a fair clinical development process driven by algorithms
- Causal inferences and data standards should be implemented
- Machine learning and humans: synergy not competition
- Black box: Saliency, explicability and explainability is important but not rate-limiting
- Deployment and testing: New clinical trials for algorithms to be piloted
- Regulation and communication with patients and physicians to de-risk technology
- Automation vs. Knowledge vs. Intelligence
- It is a new field. We can do it right together vs. operating in silos

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Artificial Intelligence in Clinical Development to Improve Public Health: Key recommendations

- New models and technologies for health research: digitally empowered researchers, physicians, regulators, patients and citizens
- Addressing current and near-term artificial intelligence (AI), machine learning (ML), medical imaging and neural network capabilities as they pertain to digital medicines and improving health
- Safer, faster and effective real world evidence driven clinical trials and novel digital endpoints
- Developing a sustainable model to bridge the gap between AI and data science experts, life sciences communities and physicians
- Encrypted ML, AI and other data sharing platforms to protect confidential information; and
- Collaborations with leaders and experts from within MIT, government, foundations, life sciences, universities, patient advocacy groups and technology corporations.

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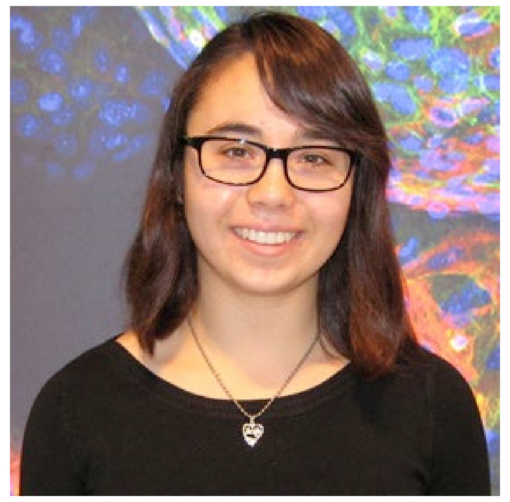
Research Staff & Students


G. Yauney


Sharon Wu


A. Rana


Keith Angelino


Perikumar Javia


Gaurav Bhatia


Alicia Chong


Judy Chang

Collaborators


Dr. Francis Kendall


Dr. Nate Shapiro


Dr. Ali Muftu


Dr. SV Subramanian


Dr. Ali Lowe

Institutions and Funding

National Institutes of Health

NIH National Cancer Institute

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FDA

BWH

AAAS-Lemelson Invention Ambassadors

Tufts Medical Center

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Open Positions in my Lab at MIT

Postdoc computer science/vision/math: Machine learning + medical imaging

Postdoc computer science/stats/math: Machine learning + RWE

Postdoc/Research scientist: Machine learning + X

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Peer-Reviewed Medical Technology Research

- Gregory Yauney, Keith Angelino, David A. Edlund, **Pratik Shah**★ **"Convolutional Neural Network for Combined Classification of Fluorescent Biomarkers and Expert Annotations using White Light Images"** 2017 17th International Conference on Bioinformatics and Bioengineering, DOI: 10.1109/BIBE.2017.00-37

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