Machine learning for precision medicine

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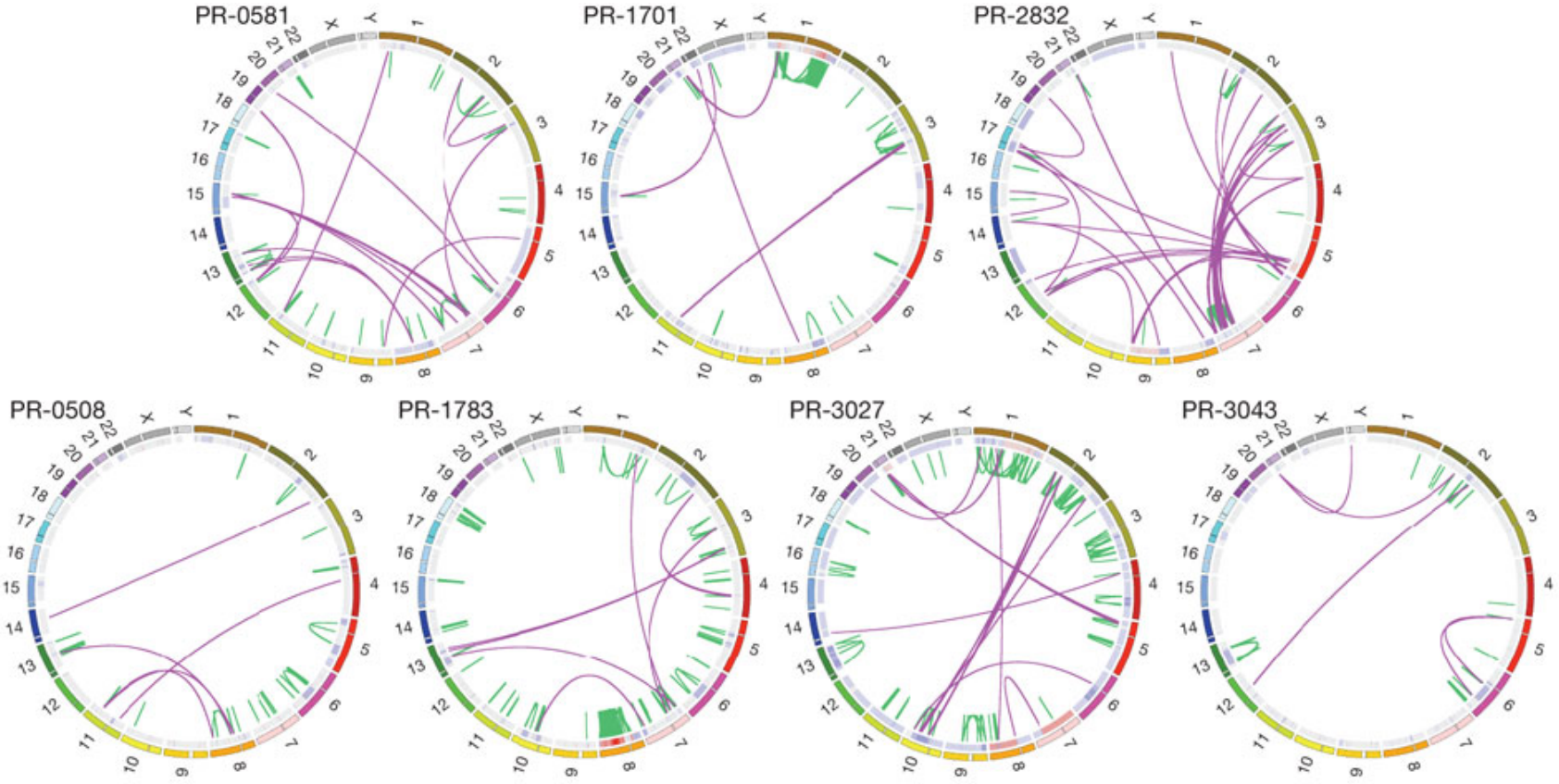
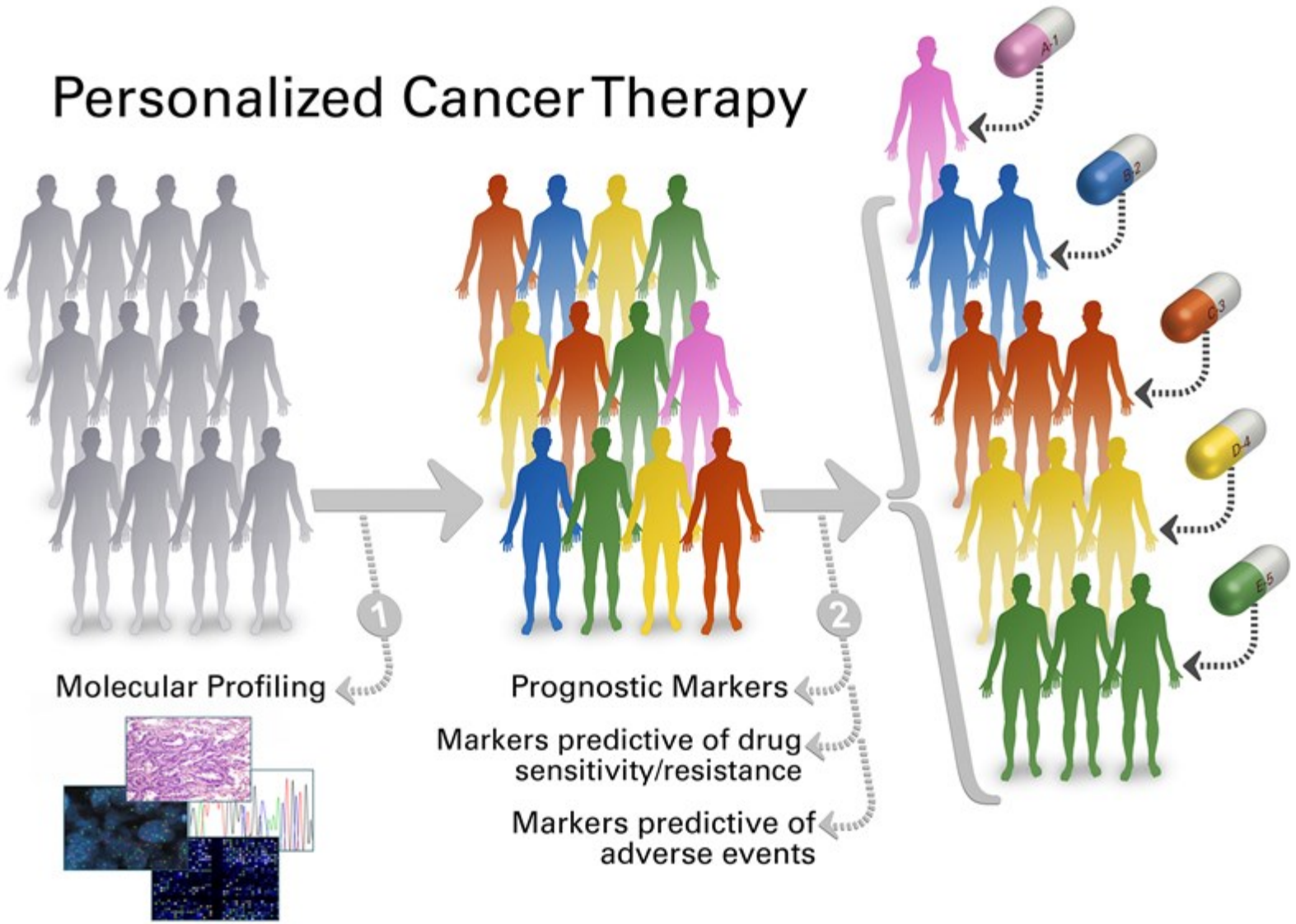
All cancers are different



All happy families are alike; each unhappy family is unhappy in its own way.

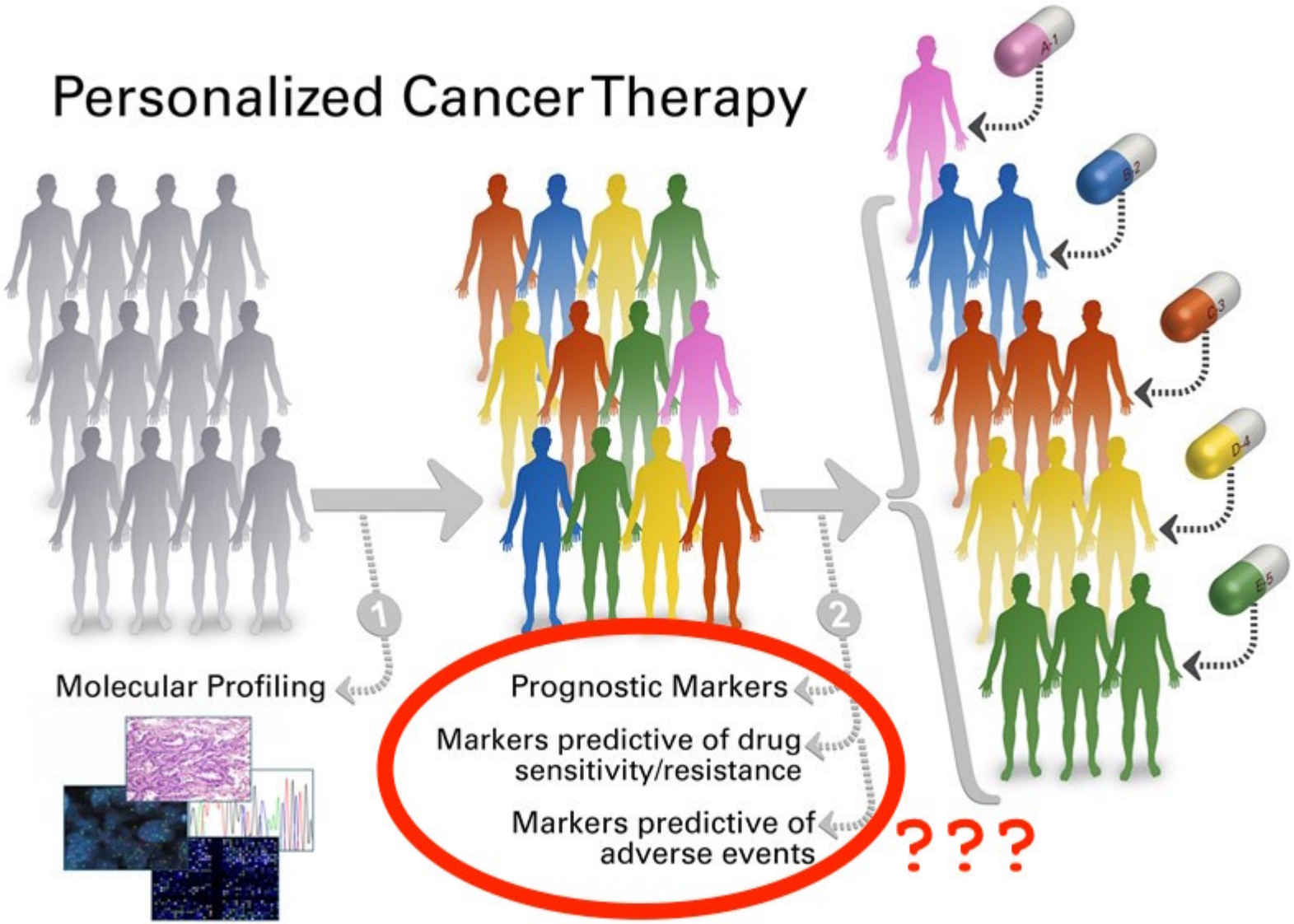
- Leon Tolstoy, Anna Karenina.

The future of medicine



https://pct.mdanderson.org

The future of medicine



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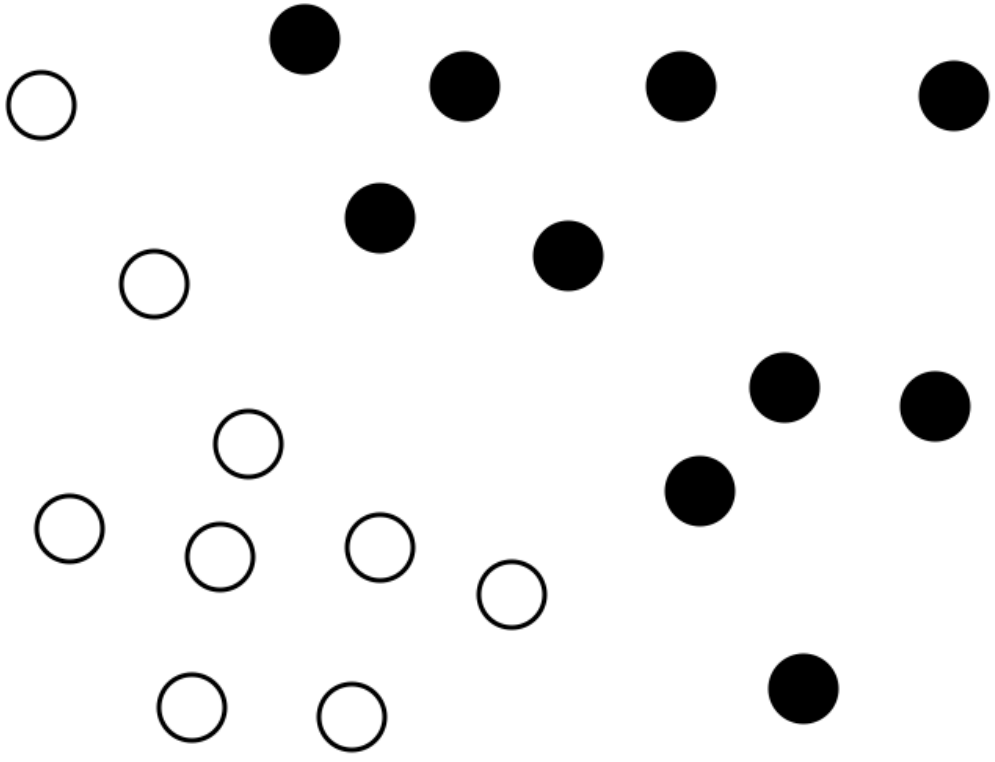
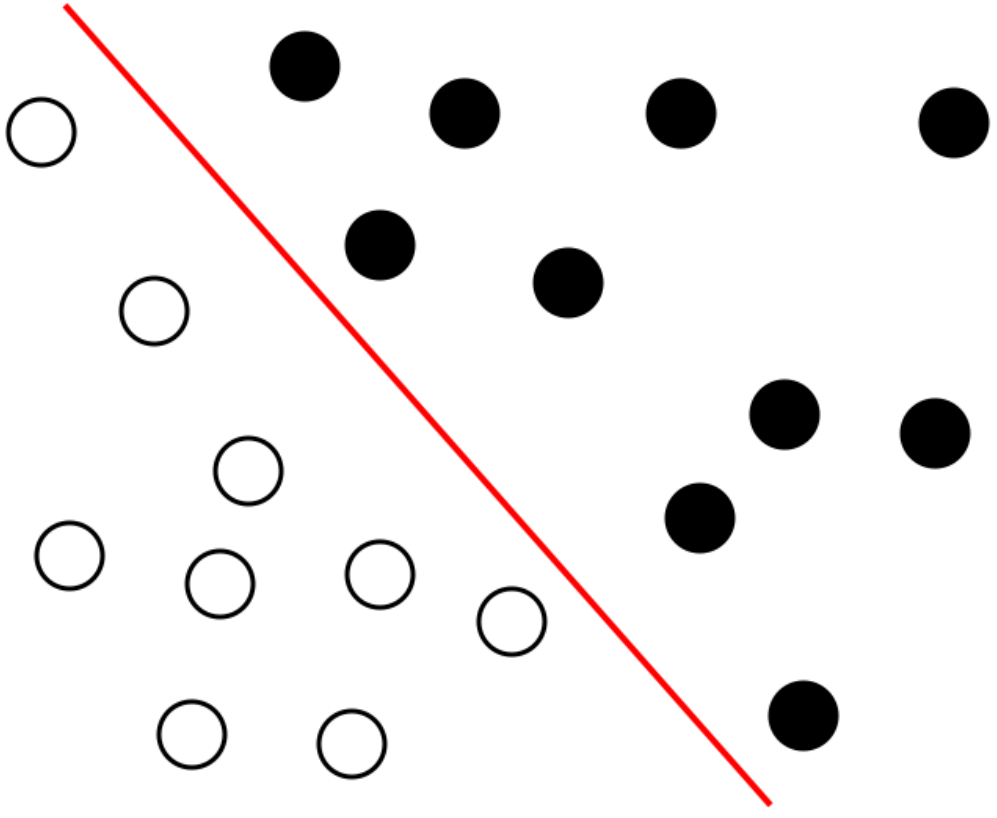
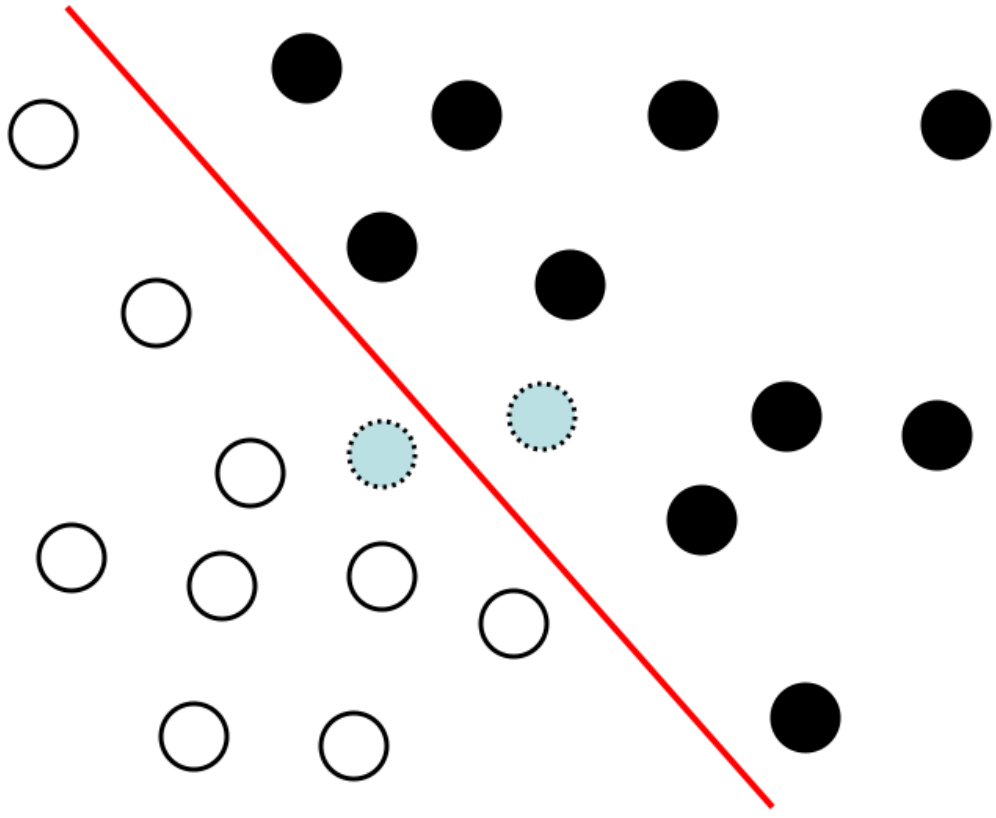
Machine learning



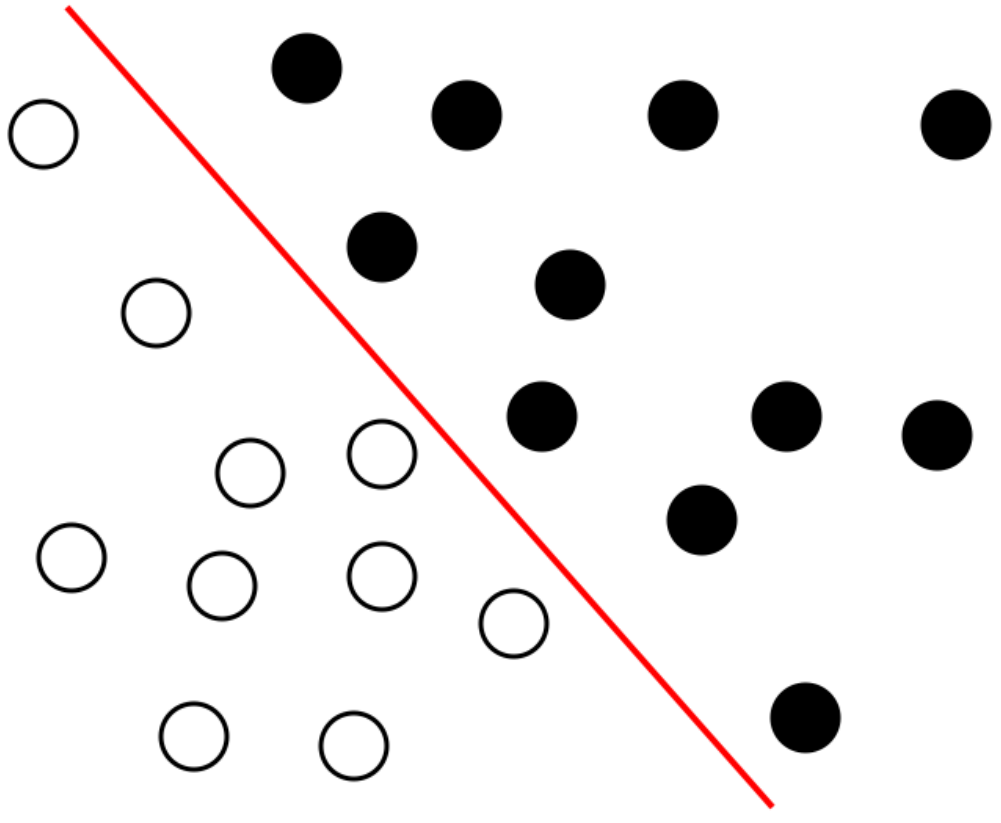
Machine learning



Machine learning



Machine learning

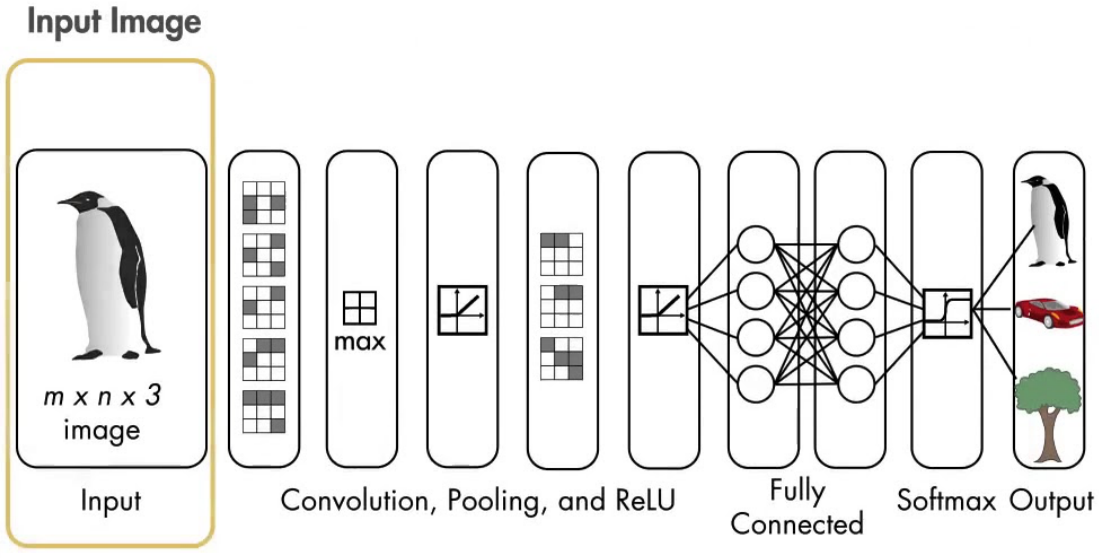


Modern ML works well!

Turing Award Won by 3 Pioneers in Artificial Intelligence

Ingredients

1. Collect big, labeled data (eg, 10M images)
2. Use a model well adapted to the data (eg, CNN)

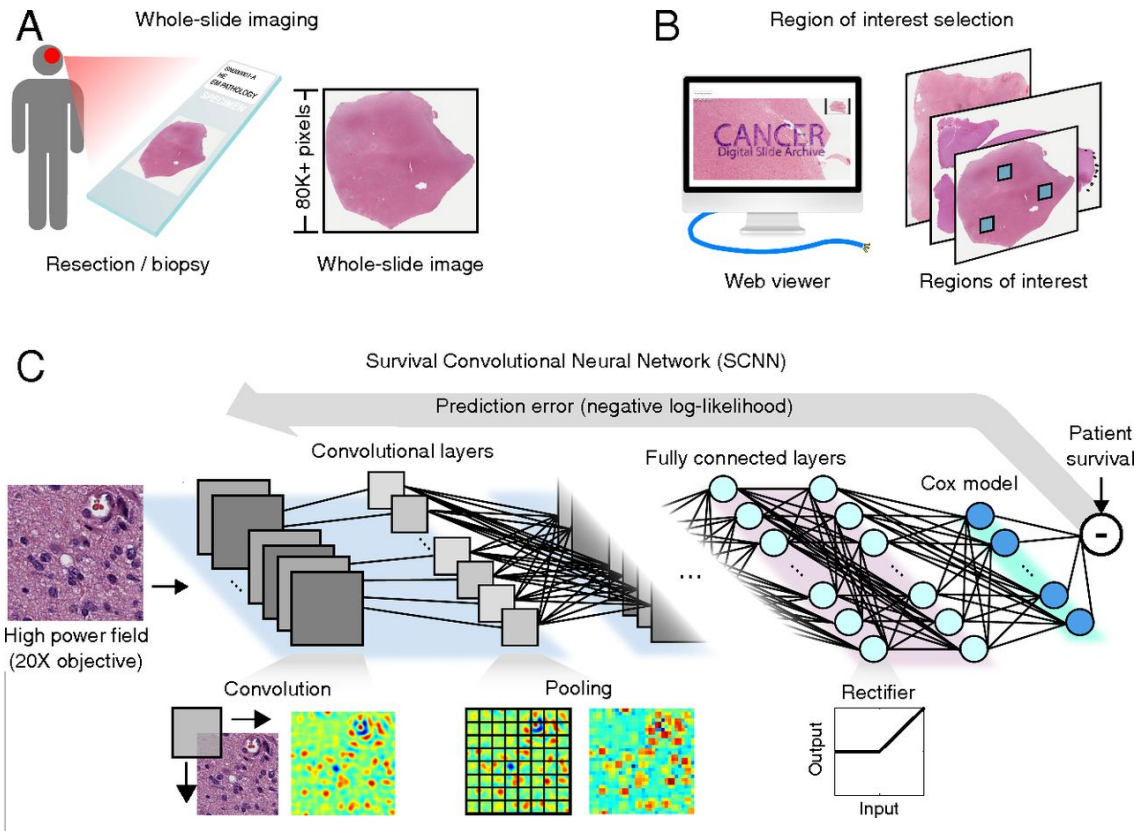


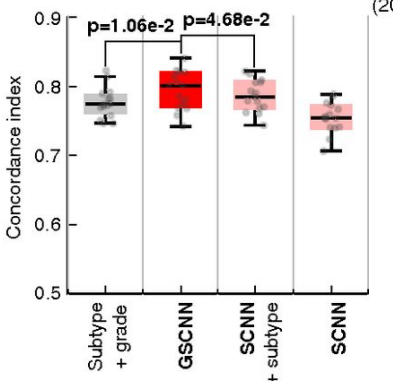
(from `https://www.youtube.com/watch?v=gjK70r0Rqzs`)

3. Large computational power + know-how ("alchemy"?)

Many applications: object/face recognition in images, machine translation, speech recognition, go, self-driving cars, trading, recommender systems, chemistry, material science...

Promising applications in health: images, texts, ..?

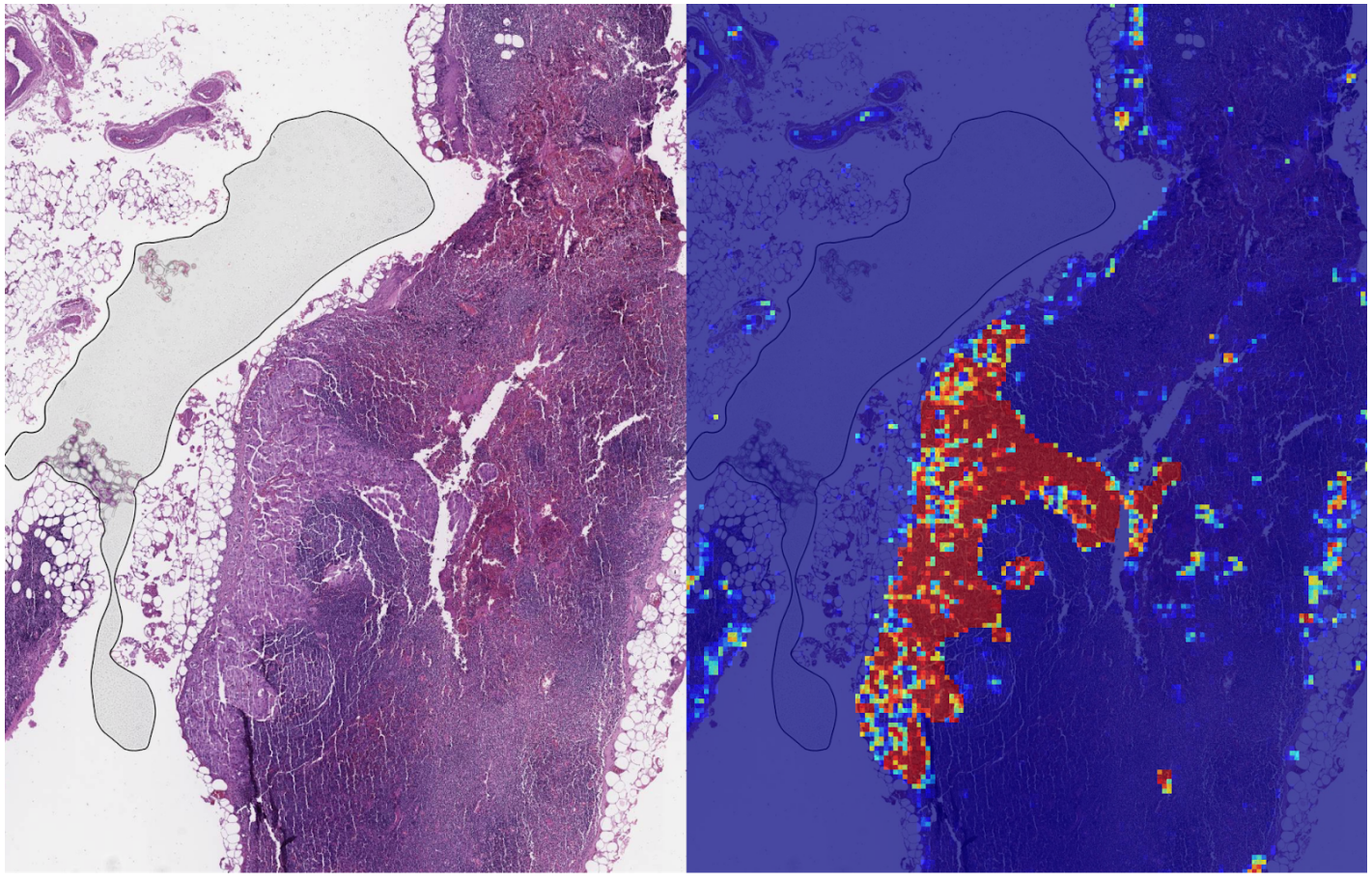




(Mobadersany et al., 2018)

Also: high-content screening, digital pathology, radiomics, skin diagnosis, EHR, ...

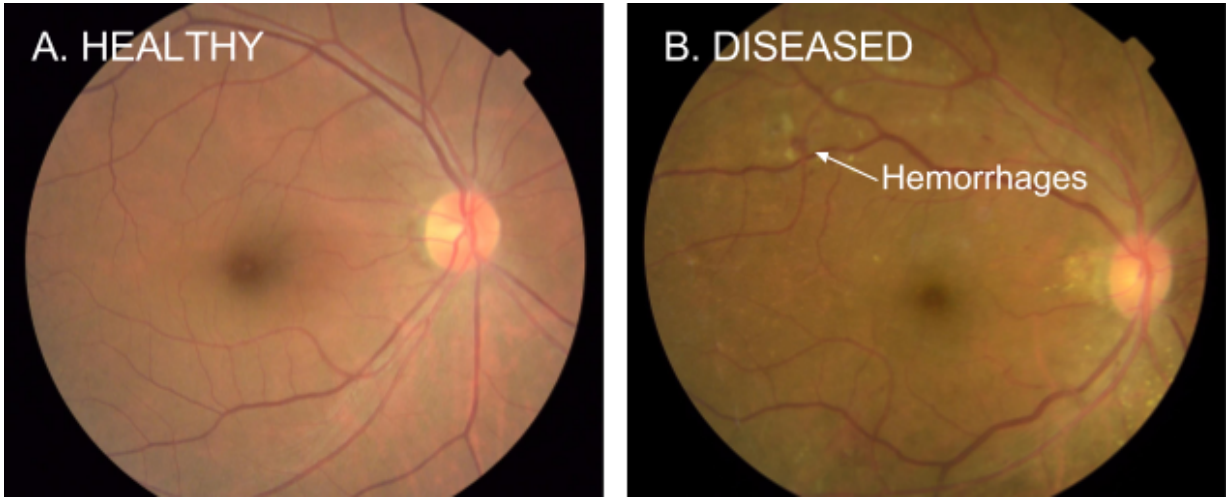
Ex: breast cancer metastasis detection (LYNA)

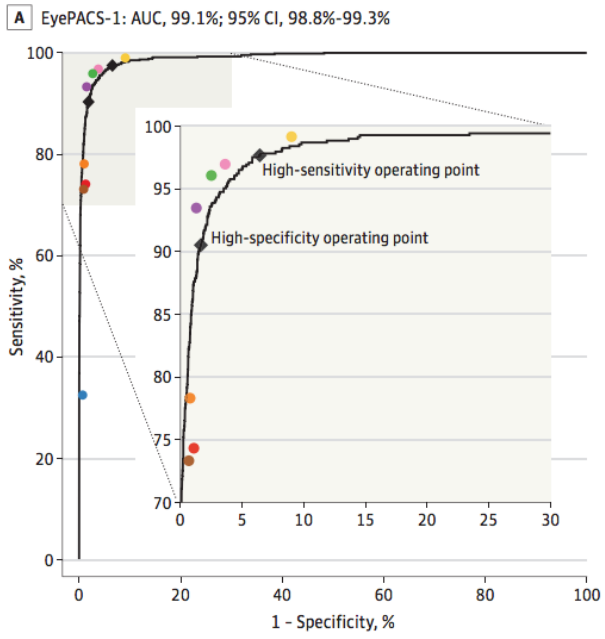


https://ai.googleblog.com/2018/10/applying-deep-learning-to-metastatic.html

- Trained on 270 (large) images, 99% accuracy
- halves average slide review time for expert pathologists

Ex: Diabetic retinopathy (DR) detection

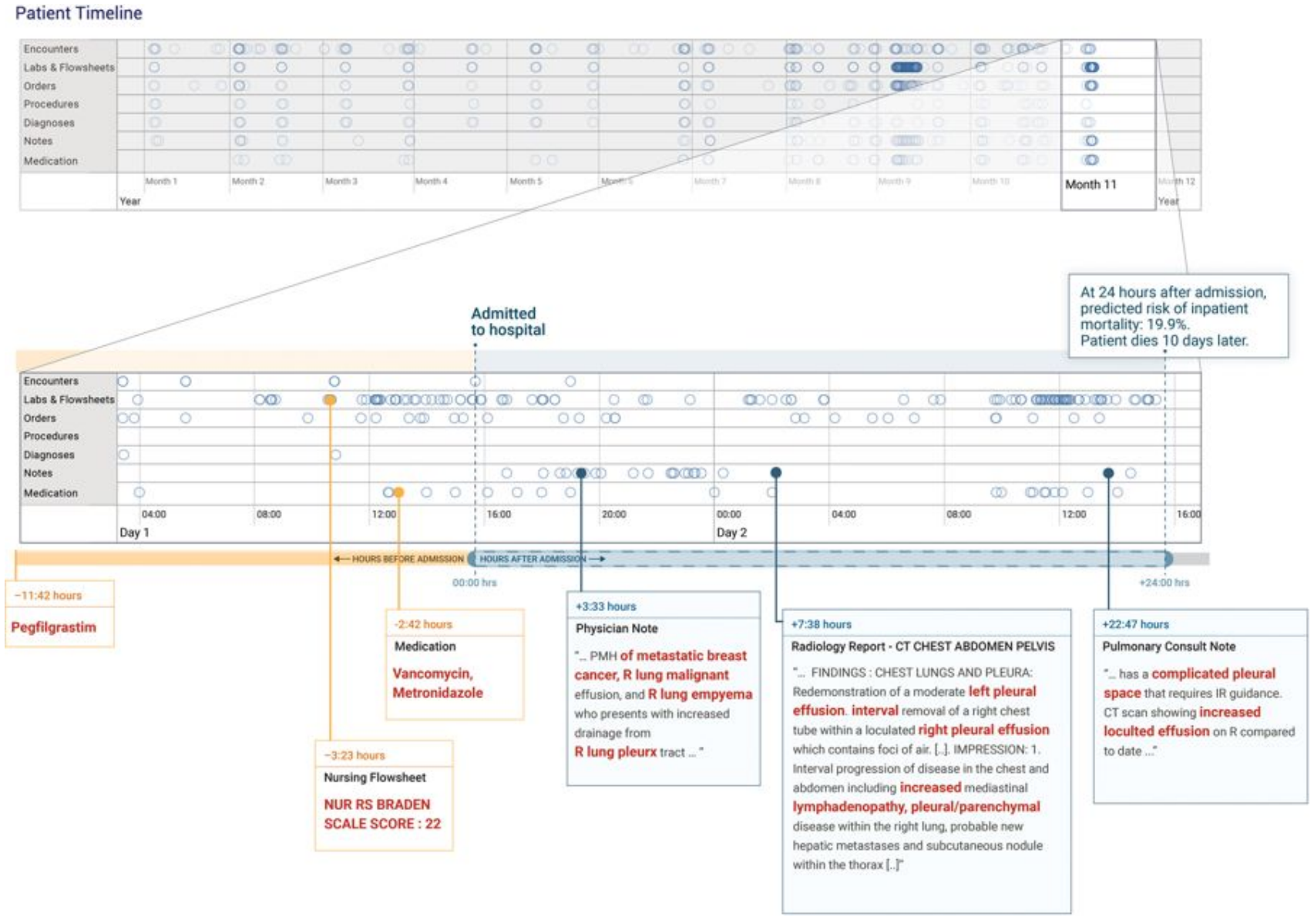




https://ai.googleblog.com/2016/11/deep-learning-for-detection-of-diabetic.html

- Fastest growing cause of blindness, with nearly 415 million diabetic patients at risk worldwide
- Lack of medical expertise for good diagnosis in many parts of the world
- System trained on 128k annotated images.

Ex: Clinical predictions from electronic health records



https://www.nature.com/articles/s41746-018-0029-1/figures/3

Ex: Reading antibiograms on a smartphone

ASTAPP : A FREE DIAGNOSTIC TOOL FOR ANTIBIOTIC RESISTANCE TESTING

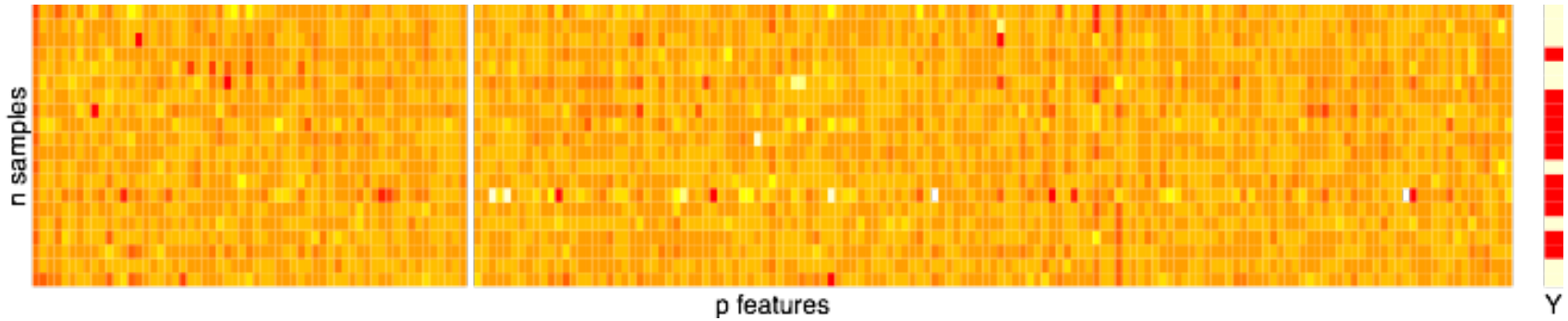
MEDECINS SANS FRONTIERES
LA FONDATION

Laboratoire de Mathématiques et Modélisation d'Évry
LaMME
université évry val-d'essonne
HENRI MONDOR
Google

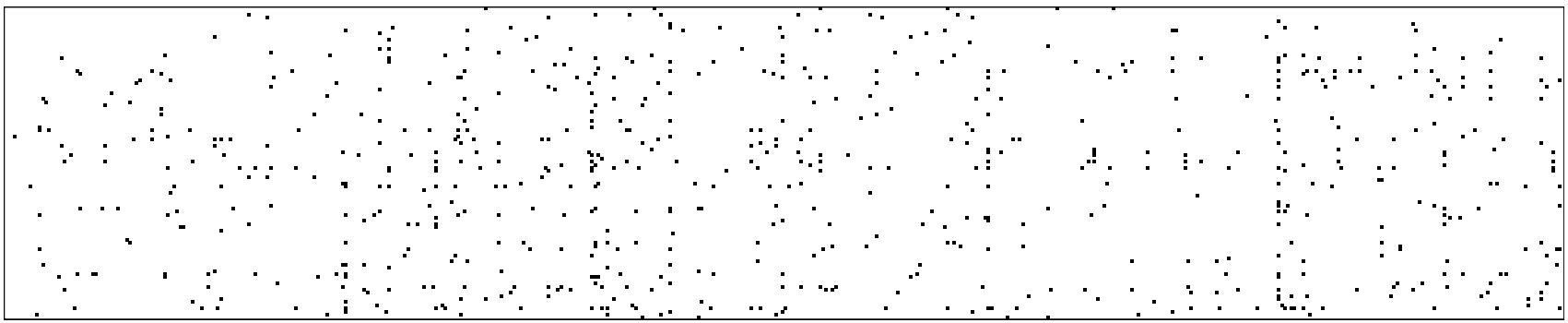
https://fondation.msf.fr/en/projects/astapp-free-diagnostic-tool-antibiotic-resistance-testing

More challenging data

- Gene expression



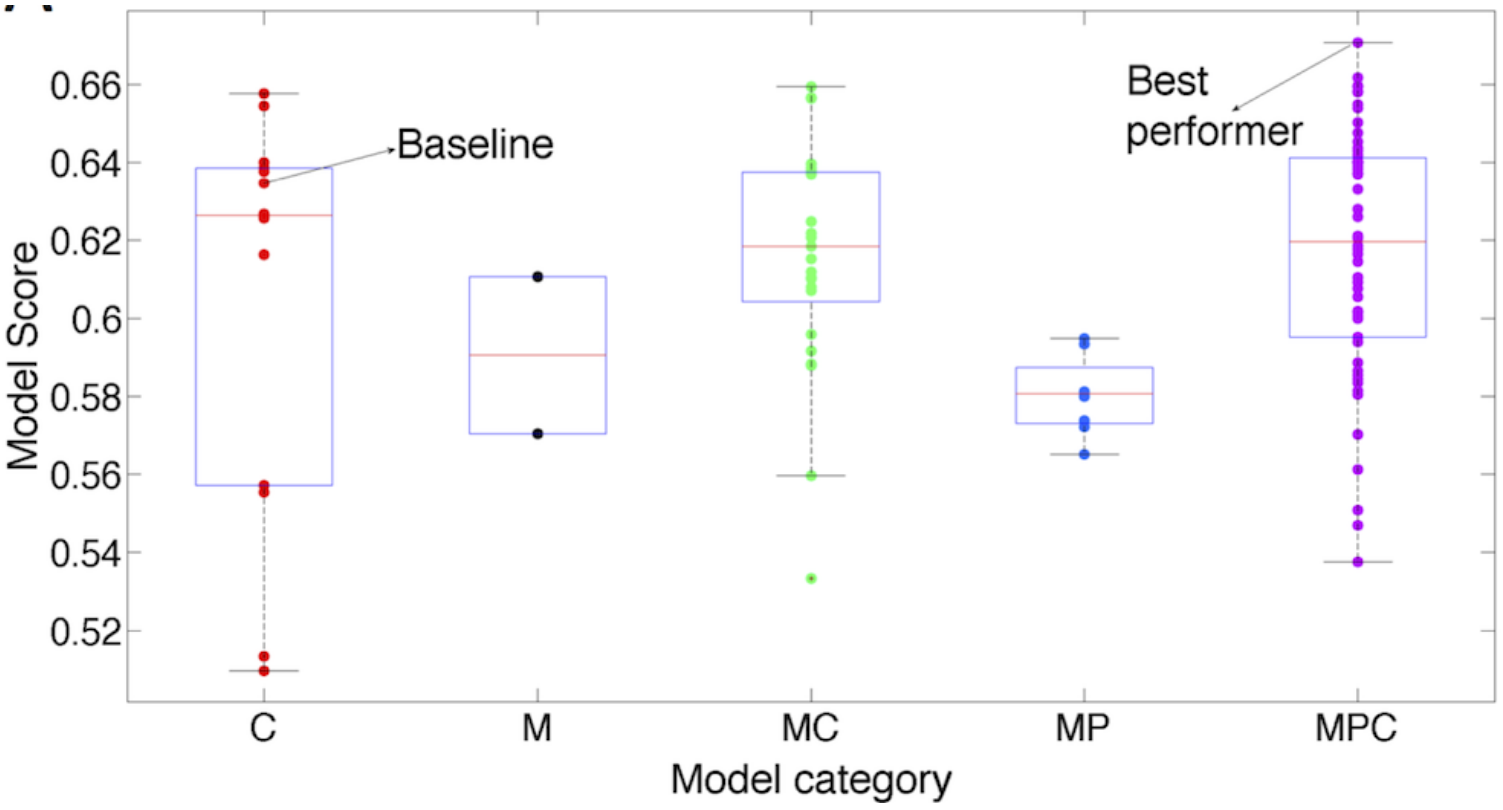
- Somatic mutations



- $n = 10^2 \sim 10^4$ (patients)
- $p = 10^4 \sim 10^7$ (genes, mutations, copy number, ...)
- Data of various nature (continuous, discrete, structured, ...)
- Data of variable quality (technical/batch variations, noise, ...)

Consequence: limited accuracy

Breast cancer prognosis competition, $n = 2000$, Bilal et al (2013)



- C: 16 standard clinical data (age, tumor size, ...)
- M: 80k molecular features (gene expression, DNA copy number)
- P: incorporate prior knowledge

Consequence: unstable biomarker selection

Gene expression profiling predicts clinical outcome of breast cancer

Laura J. van 't Veer*†, Hongyue Dai†‡, Marc J. van de Vijver*†, Yudong D. He‡, Augustinus A. M. Hart*, Mao Mao‡, Hans L. Peterse*, Karin van der Kooy*, Matthew J. Marton‡, Anke T. Witteveen*, George J. Schreiber‡, Ron M. Kerkhoven*, Chris Roberts‡, Peter S. Linsley‡, René Bernards* & Stephen H. Friend‡

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70 genes (Nature, 2002)

Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer

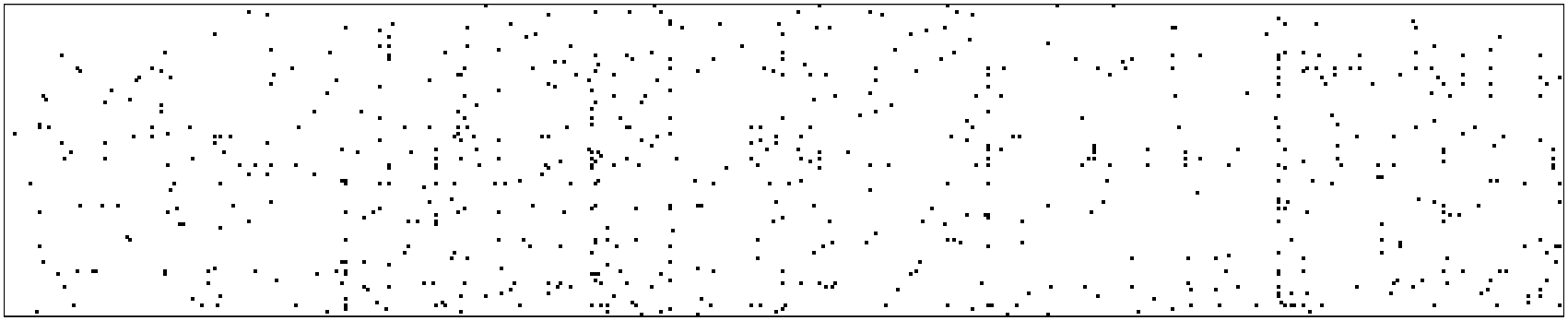
Yixin Wang, Jan G M Klijn, Yi Zhang, Anieta M Sieuwerts, Maxime P Look, Fei Yang, Dmitri Talantov, Mieke Timmermans, Marion E Meijer-van Gelder, Jack Yu, Tim Jatkoe, Els M J J Berns, David Atkins, John A Foekens

76 genes (Lancet, 2005)

3 genes in common

van 't Veer et al. (2002); Wang et al. (2005)

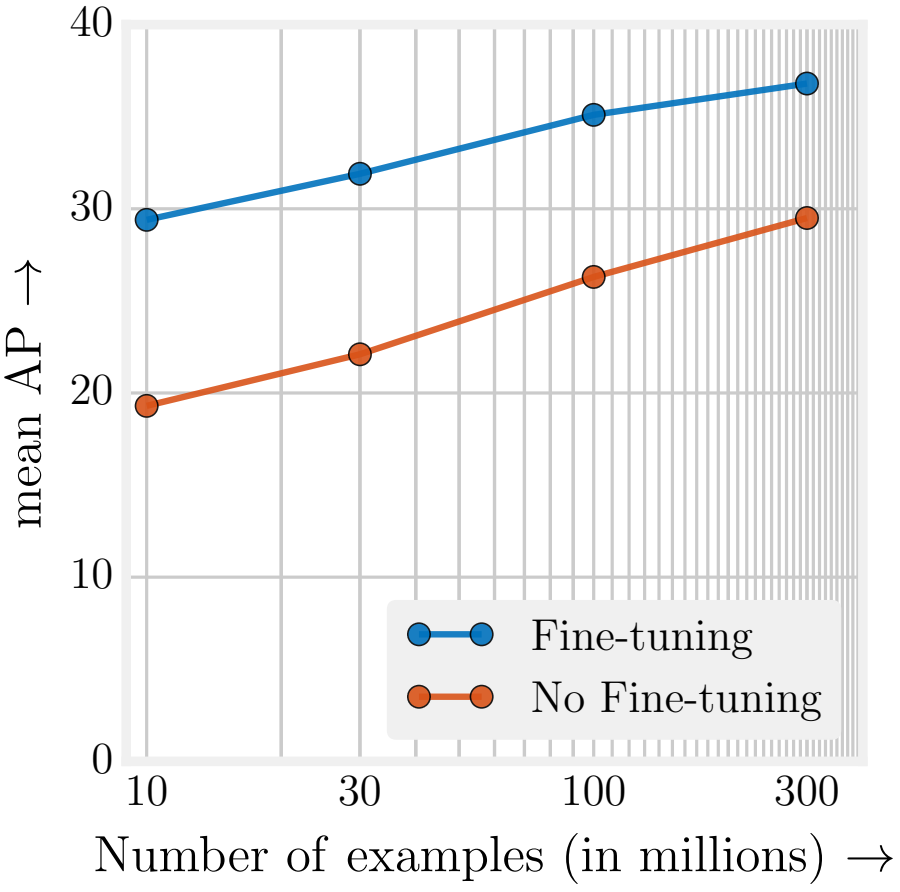
What to do?

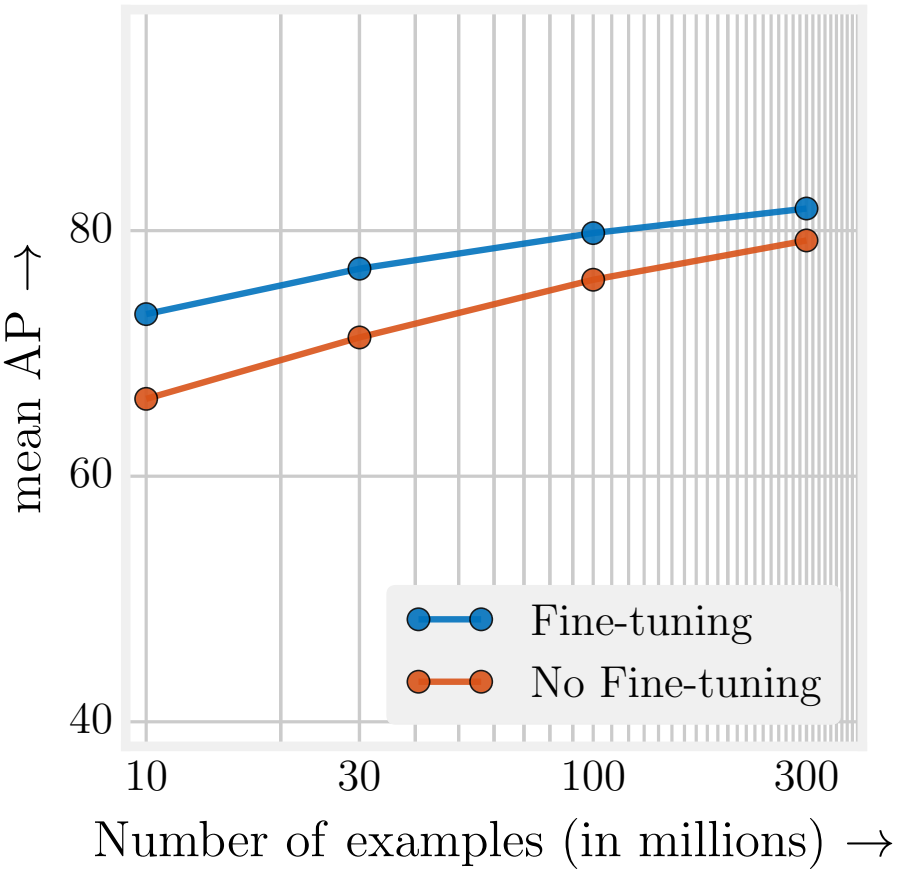


- Get more data
  - with labels
  - sharing data (or models) is crucial
  - of good quality
- Improve the models
  - include prior knowledge (biology, structure of noise, invariants...)
  - balance model complexity vs data available

More data helps

...but performance increases slowly. How much can be afford?

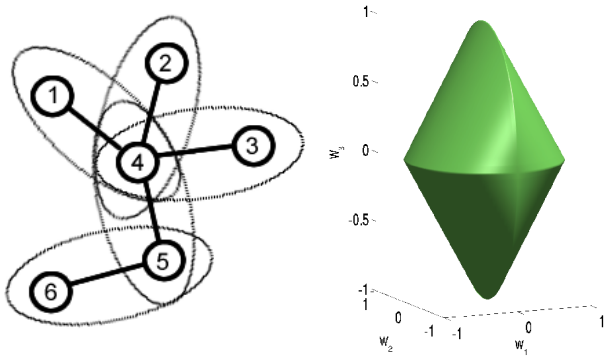




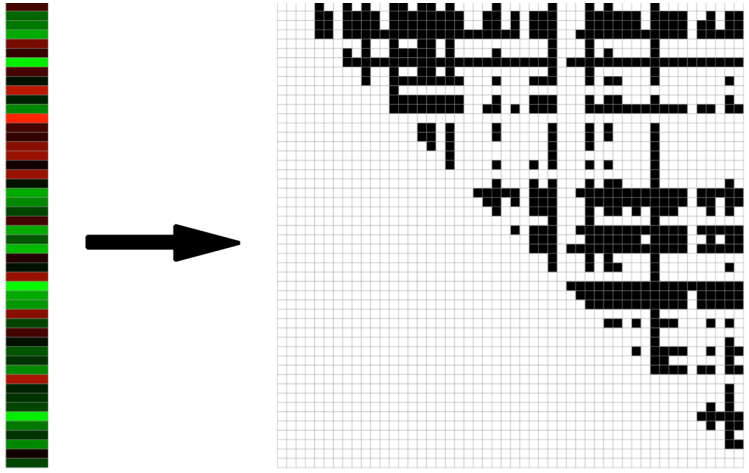
Object detection performance on two benchmarks (COCO minimal, left, and PASCAL VOC 2007, right) as a function of the number of labeled images used to train the model (Sun et al., 2017).

Some research directions

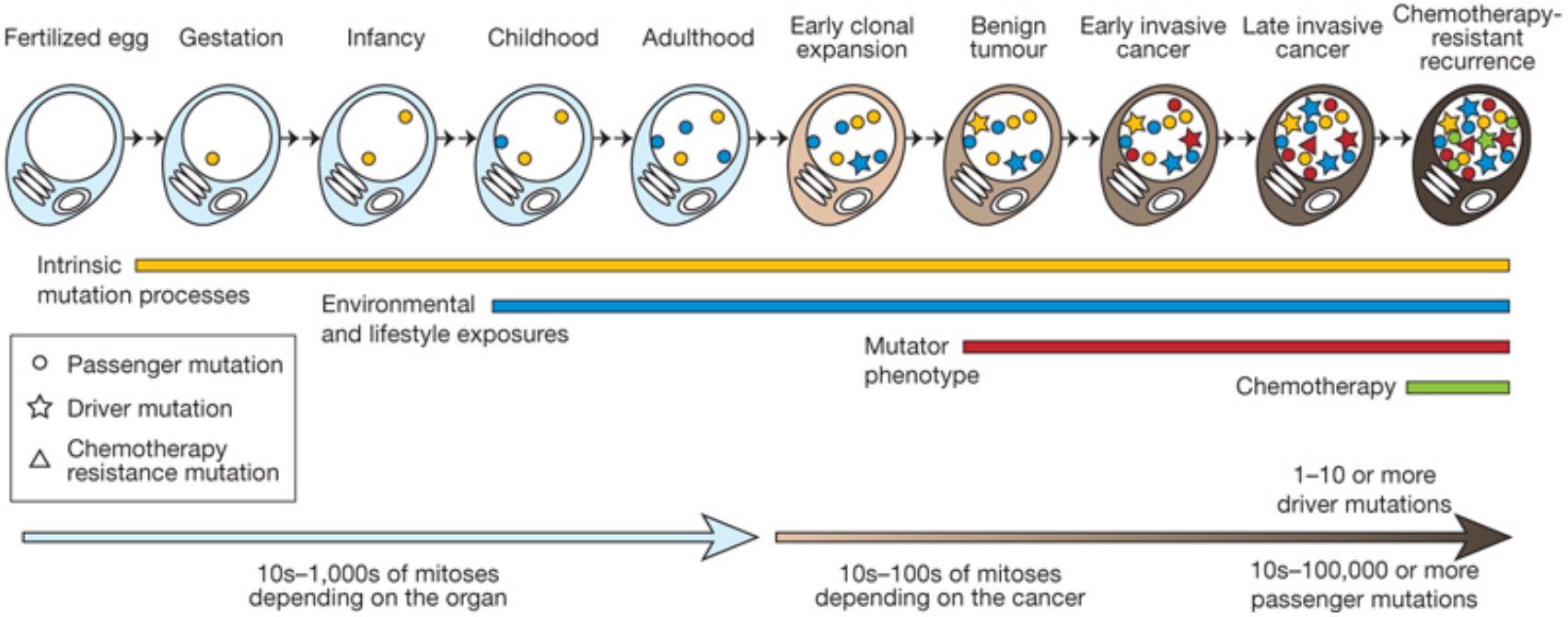
- Regularize and incorporate prior knowledge

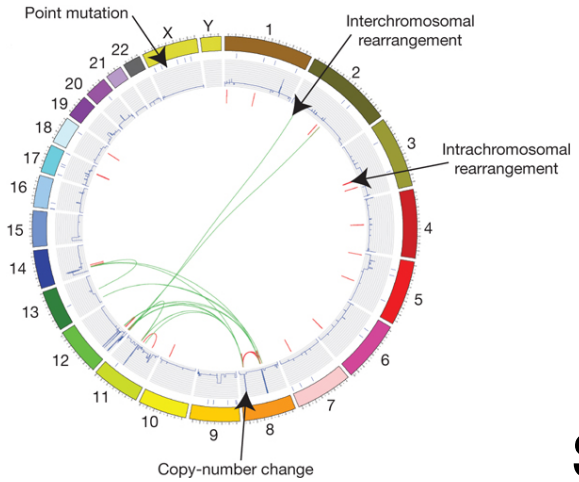


- Find a better representation



Ex: somatic mutations in cancer

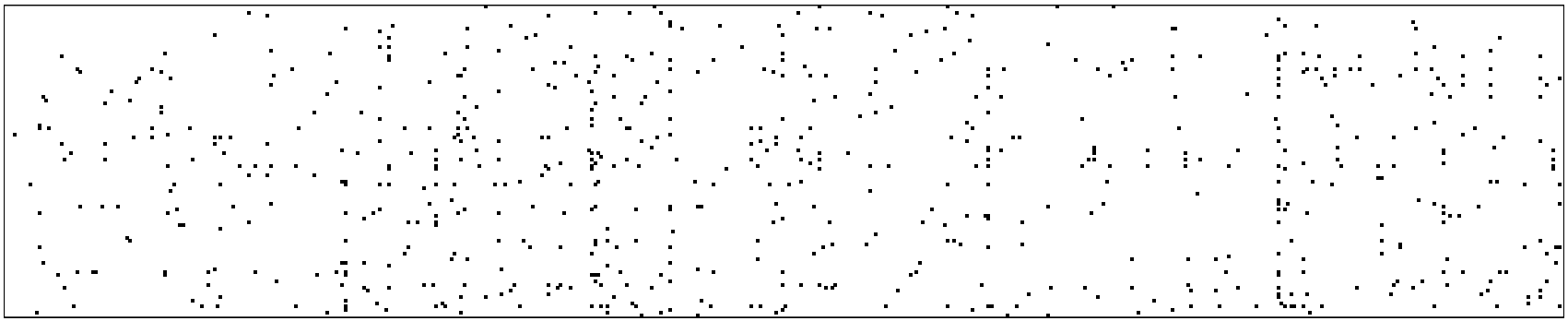




Stratton et al. (2009)

Large-scale efforts to collect somatic mutations

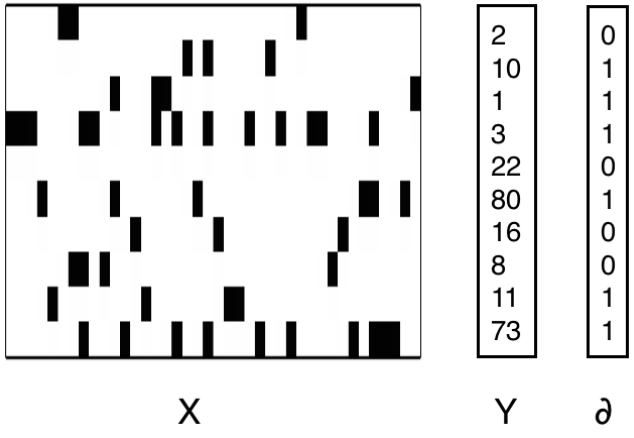
- 3,378 samples with survival information from 8 cancer types
- downloaded from the TCGA / cBioPortal portals.

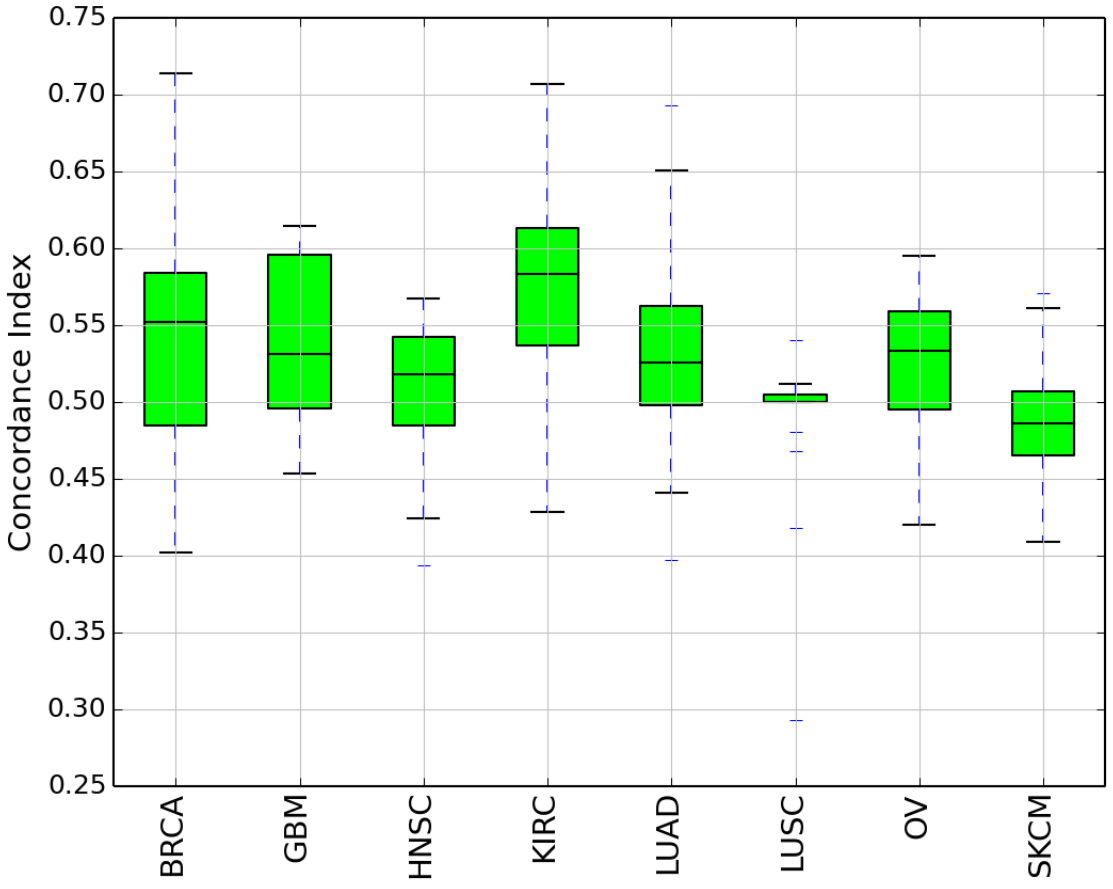


Cancer type	Patients	Genes
LUAD (Lung adenocarcinoma)	430	20 596
SKCM (Skin cutaneous melanoma)	307	17 463
GBM (Glioblastoma multiforme)	265	14 750
BRCA (Breast invasive carcinoma)	945	16 806
KIRC (Kidney renal clear cell carcinoma)	411	10 609
HNSC (Head and Neck squamous cell carcinoma)	388	17 022
LUSC (Lung squamous cell carcinoma)	169	13 590
OV (Ovarian serous cystadenocarcinoma)	363	10 195

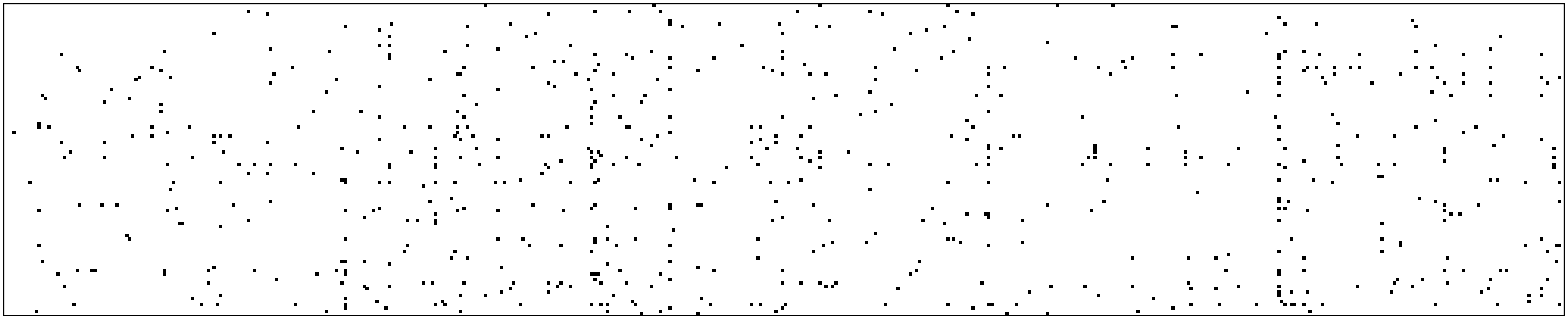
Survival prediction from raw mutation profiles

- Each patient is a binary vector: each gene is mutated (1) or not (2)
- Silent mutations are removed
- Survival model estimated with sparse survival SVM
- Results on 5-fold cross-validation repeated 4 times





Approach: change representation?



Can we replace

$$x \in \{0,1\}^p \quad \text{with } p \text{ very large, very sparse}$$

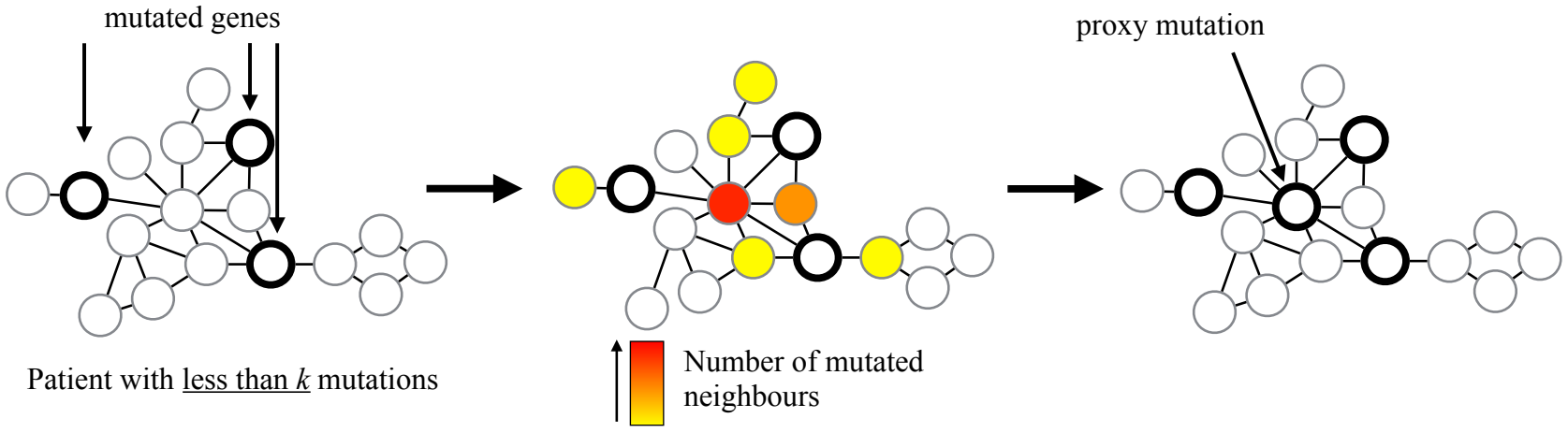
by a representation with more information shared between samples

$$\Phi(x) \in \mathcal{H}$$

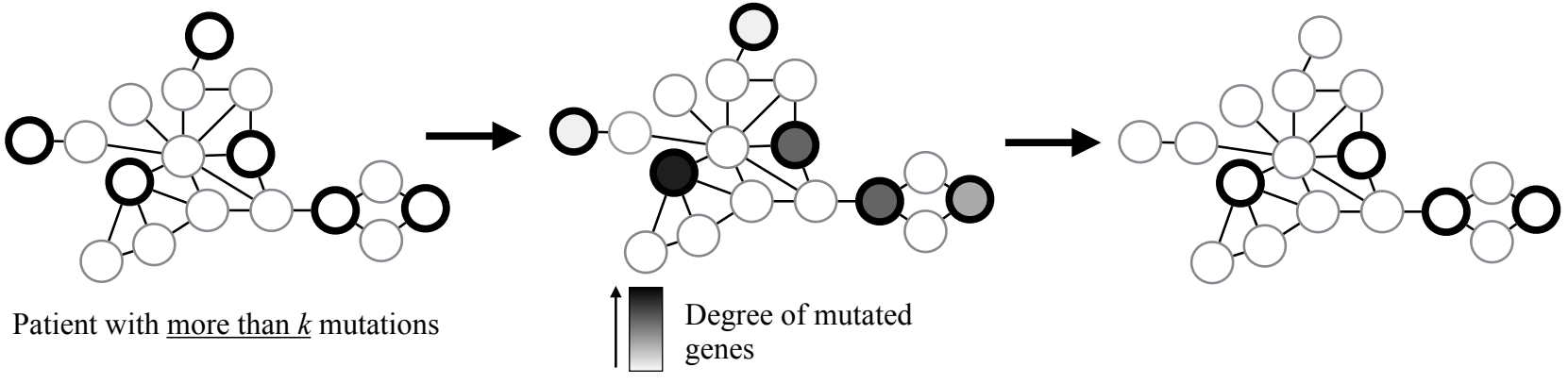
that would allow better supervised and unsupervised classification?

NetNorm (Le Morvan et al., 2017)

1. Add mutations for patients with few (less than K) mutations

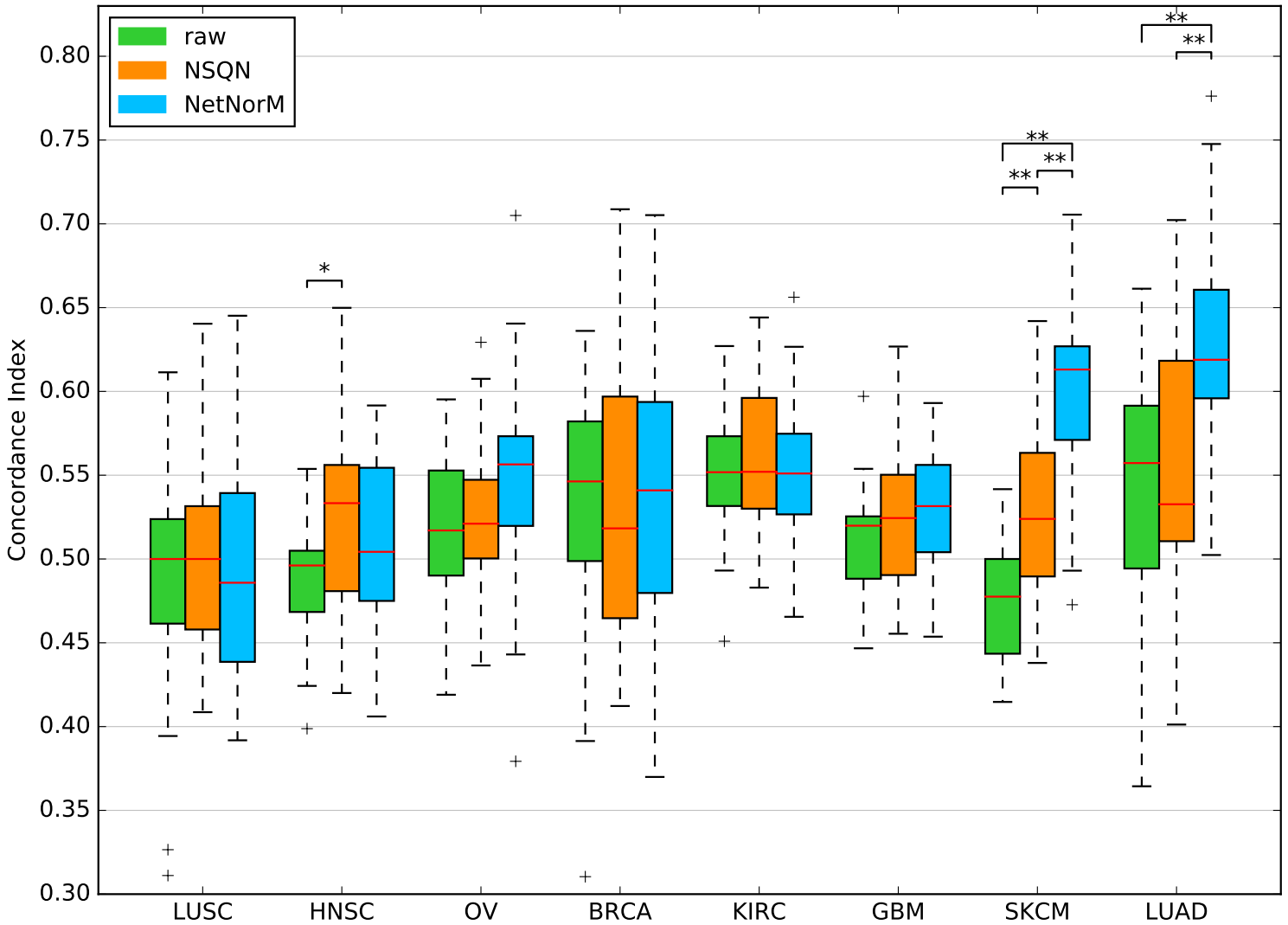


2. Remove mutations for patients for many (more than K) mutations



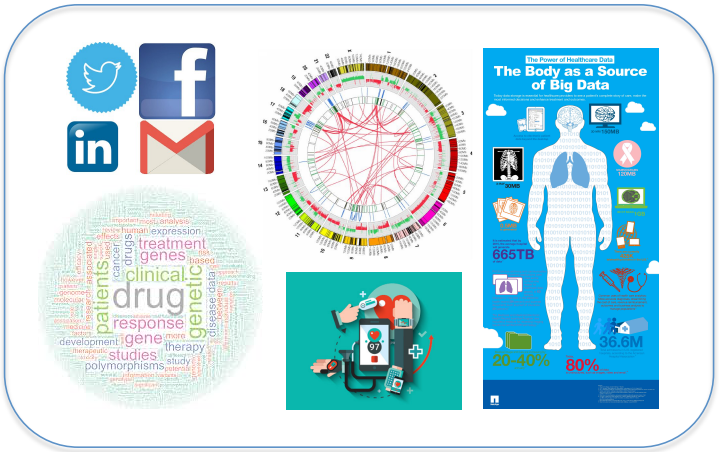
In practice, K is a free parameter optimized on the training set, typically a few 100's.

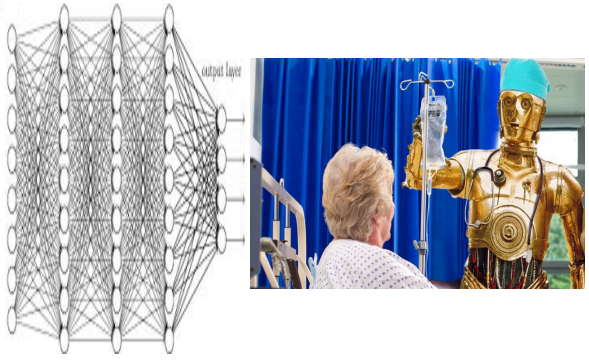
Results



Use Pathway Commons as gene network.
NSQN = Network Smoothing / Quantile Normalization (Hofree et al., 2013)

Conclusion





- Lots of data, increasing role of ML (particularly with images, texts)
- Omics data is more challenging
- Getting more data is important, but unlikely to allow ML-based methods to reach their best
- Active research
  - allowing data sharing (federated learning, differential privacy, ...)
  - new representations and learning algorithms for complex data
  - new experimental design strategies, causality inference

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