Artificial Intelligence Demystified and How Can it Help Clinical Development

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Disclosure

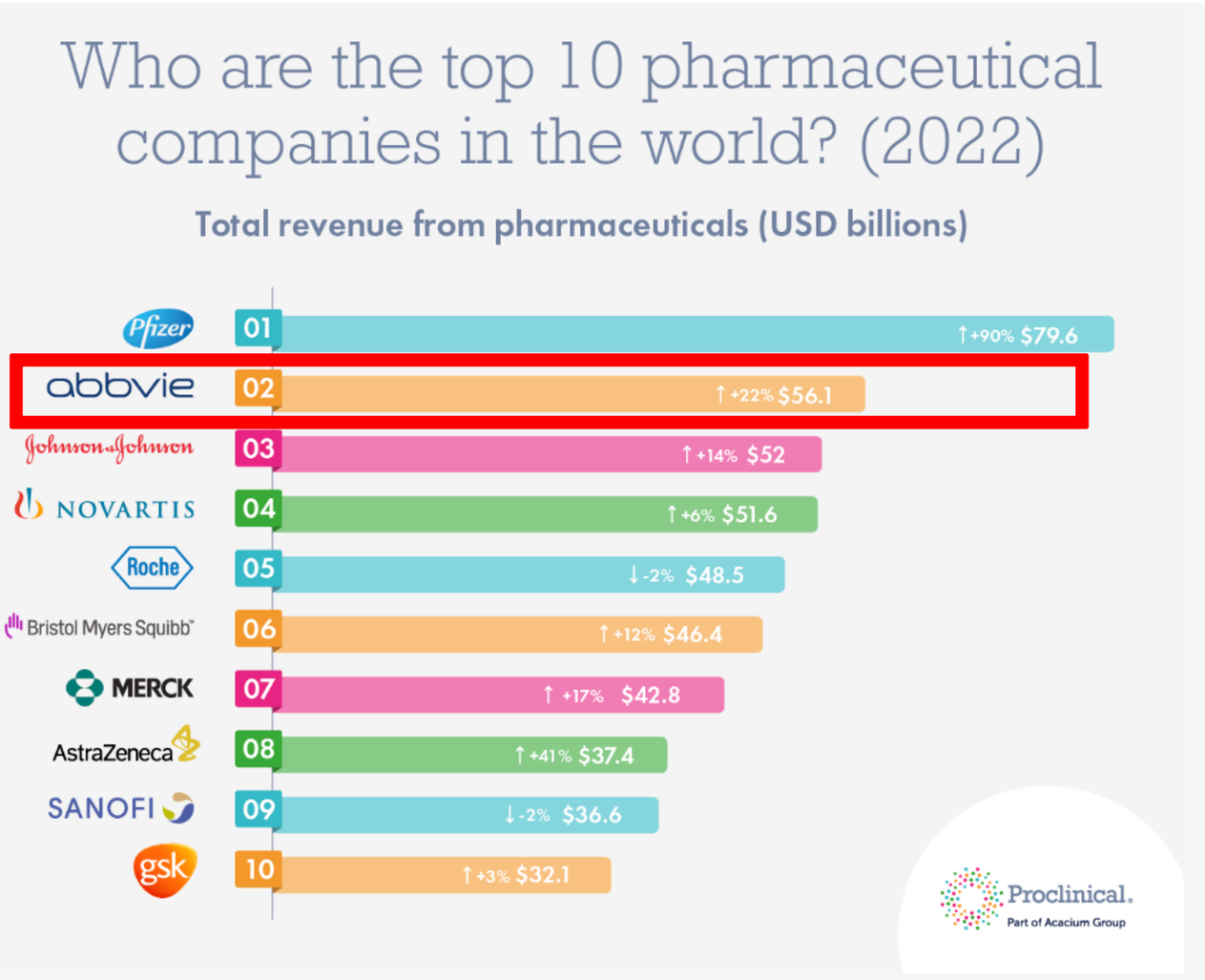
- The comments provided here are solely those of the presenters and are not necessarily reflective of the positions, policies or practices of presenters' employers.

- This publication was neither originated nor managed by AbbVie, and it does not communicate results of AbbVie-sponsored Scientific Research

Outline

- Brief AbbVie Intro
- Maturity of Artificial Intelligence Methodology and New Technology
- Statisticians and Data Scientists
- Several Use Cases in AbbVie Development

AbbVie in 2022



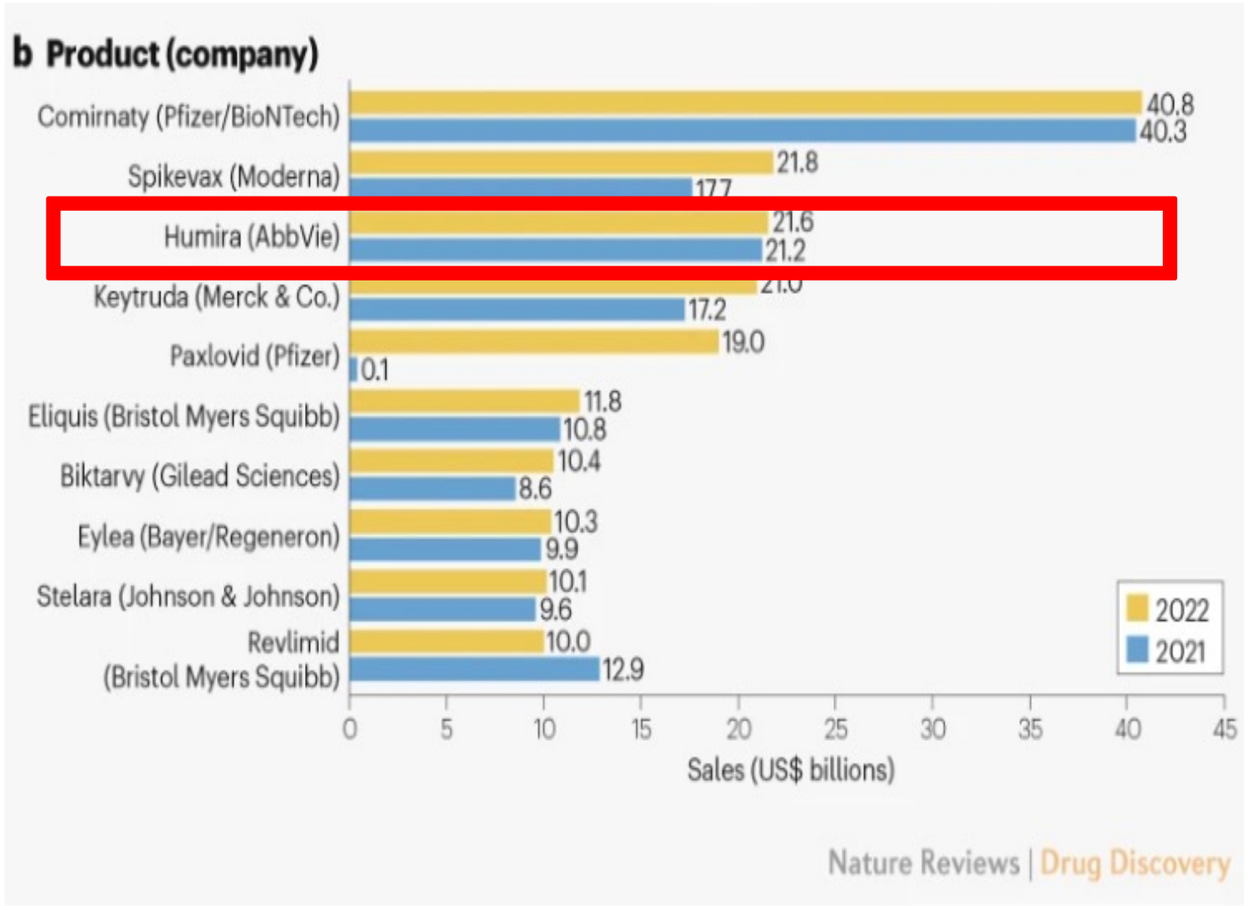


Fig. 1 | Top companies and drugs by sales in 2022. a, Top ten companies by sales of prescription and over-the-counter drugs. **b**, Top ten drugs by sales globally. Source: EvaluatePharma.

AbbVie R&D Pipeline in 2023

ABBVIE'S RESEARCH PIPELINE

At a glance: Pipeline highlights

Our R&D work fuels a dynamic and diverse pipeline that continues to advance and deliver new medicines and solutions for patients. Our pipeline includes ~75 programs in mid- and late-stage development and ~60 programs in early-stage development.

EXPLORE OUR RESEARCH PIPELINE >

PROGRESS

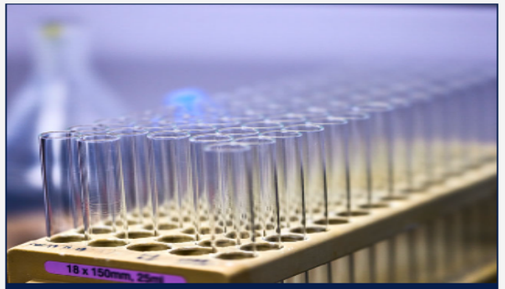
~50
new molecular entities

PROGRAMS

75+
clinical programs

IMPACT

75+
conditions treated



INVESTMENT

$7.1b
R&D investment in 2022

PRIORITIES

Core focus areas:

- Immunology →
- Oncology →
- Neuroscience →
- Eye Care →
- Aesthetics →
- Other Specialties →

Statistical Sciences and Analytics in AbbVie

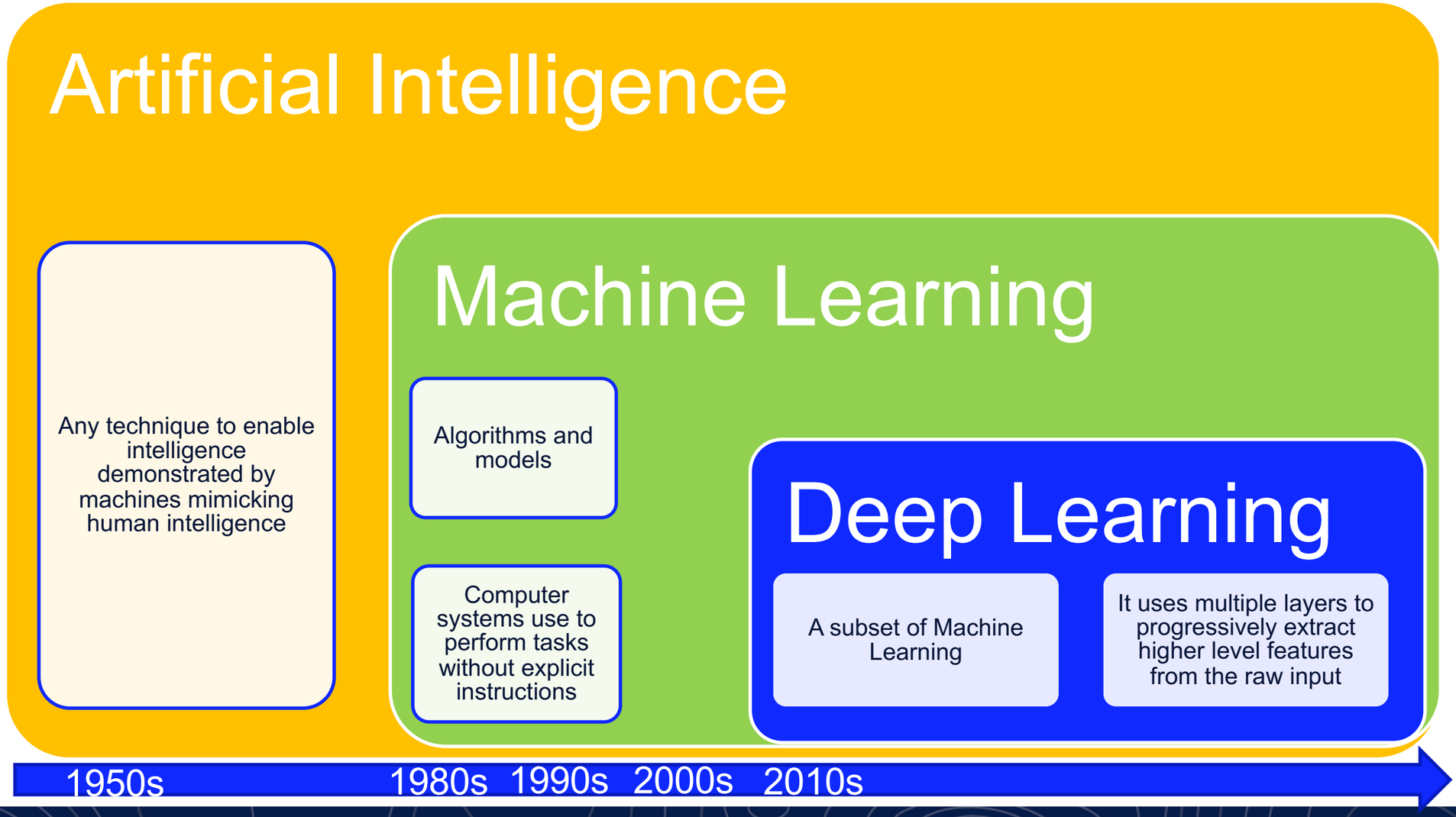
- More than 200 Ph.D statisticians supporting 6 Therapeutic Areas including Immunology, Oncology, Neuroscience, Aesthetics, Eye Care and Specialty

- Supporting key R&D functions and projects in Non-clinical, CMC, Exploratory Biomarker, Phase 1, Phase 2, Phase 3, Statistical Innovation Group (SIG), Medical Affairs and HTA, Safety, Digital Science, and Data Science and Analytics

- Frequentists, Bayesians and (statistical) data scientists

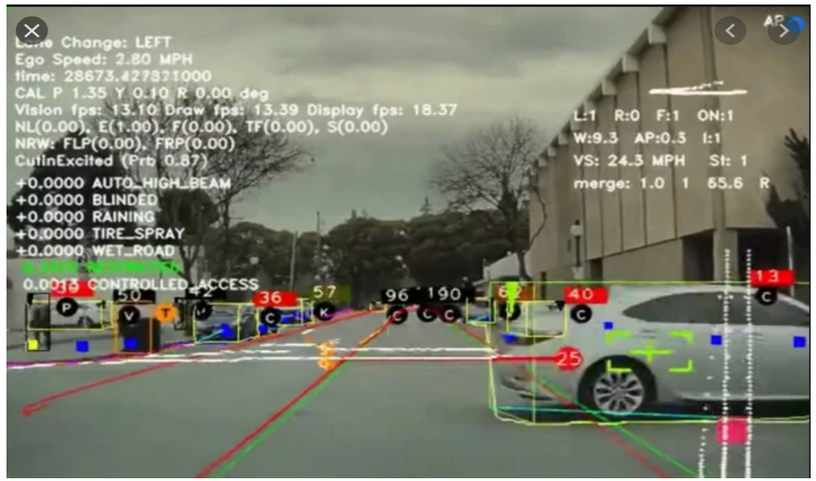
- SIG has the luxury to collaborate with lots of functions in and out of Clinical Development

Machine Learning and Artificial Intelligence



Amazing Machine Learning Use Cases in IT Industry

"Google's AlphaGo Defeats Chinese Go Master in Win for A.I."



"Tesla's Deep Learning at Scale: Using Billions of Miles to Train Neural Networks"

"BOSTON DYNAMICS' ROBOTS ARE PREPARING TO LEAVE THE LAB — IS THE WORLD READY?"

Some Machine Learning Use Cases in Health Care Industry

- Discovery
  - “Artificial intelligence-created medicine to be used on humans for first time” BBC News, Jan. 30, 2020
  - “XXX company has launches trial for AI-discovered drug in a trial to treat idiopathic pulmonary fibrosis”, Pharma.com, Dec. 15, 2021
  - “The target was identified by AI and the module was designed using AI, meaning it is AI-discovered and AI designed” CISION PR Newswire, Feb.24, 2022

- Genetics and genomics
  - Machine learning applications in genetics and genomics, Nature Reviews 2015
  - Artificial intelligence in clinical and genomic diagnostics, Genome Medicine, 2019

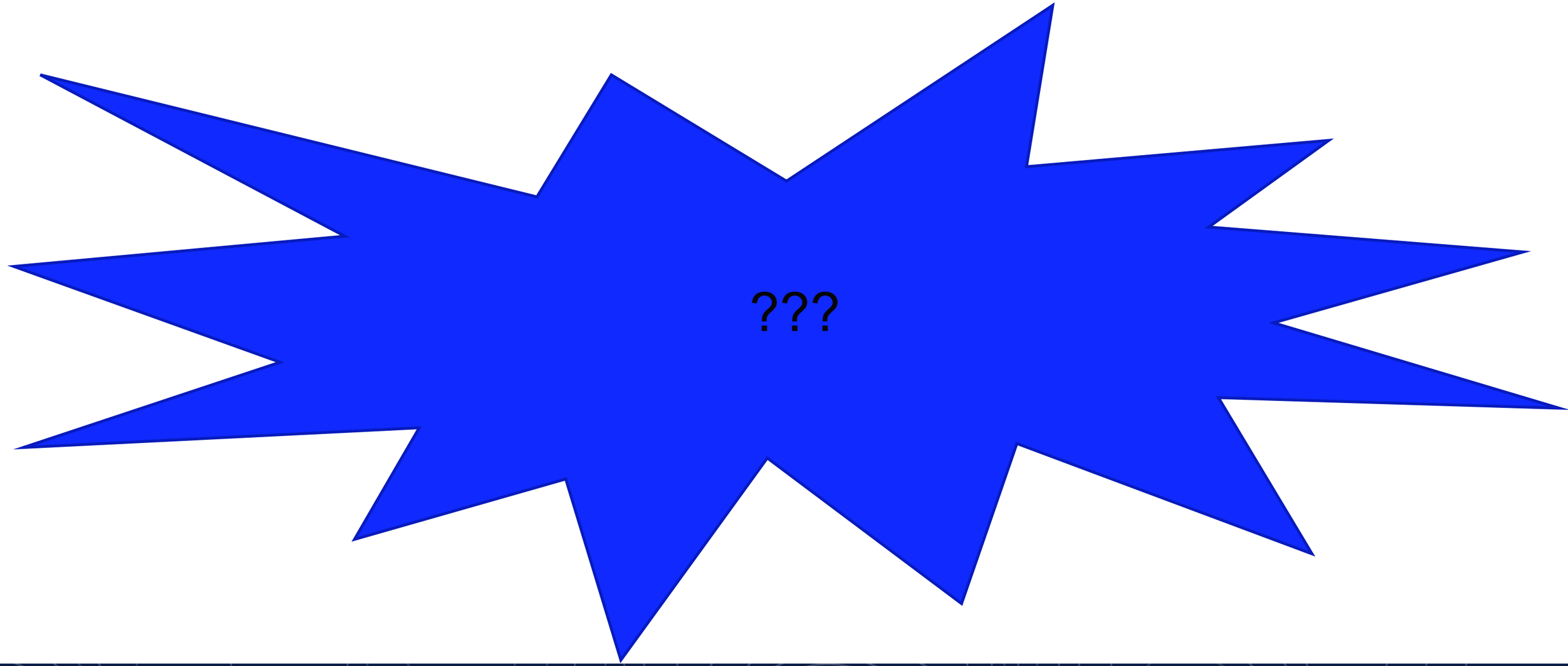
- Medical Imaging
  - Oncology:
    - Melanoma: CNN has shown to perform better to identify melanoma than dermatologists, Annual of Oncology 2018
    - Breast: AI is better than radiologists, NYT, 1/1/2020
  - Eye disease:
    - John Hopkins has developed AI algorithms to identify age-related macular degeneration (AMD), John Hopkins Medicine, 07/01/2019

- Medical Devices
  - “The state of artificial intelligence-based FDA-approved medical devices and algorithms: an online database” 09/11, 2020
  - “Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan” from FDA, 2021

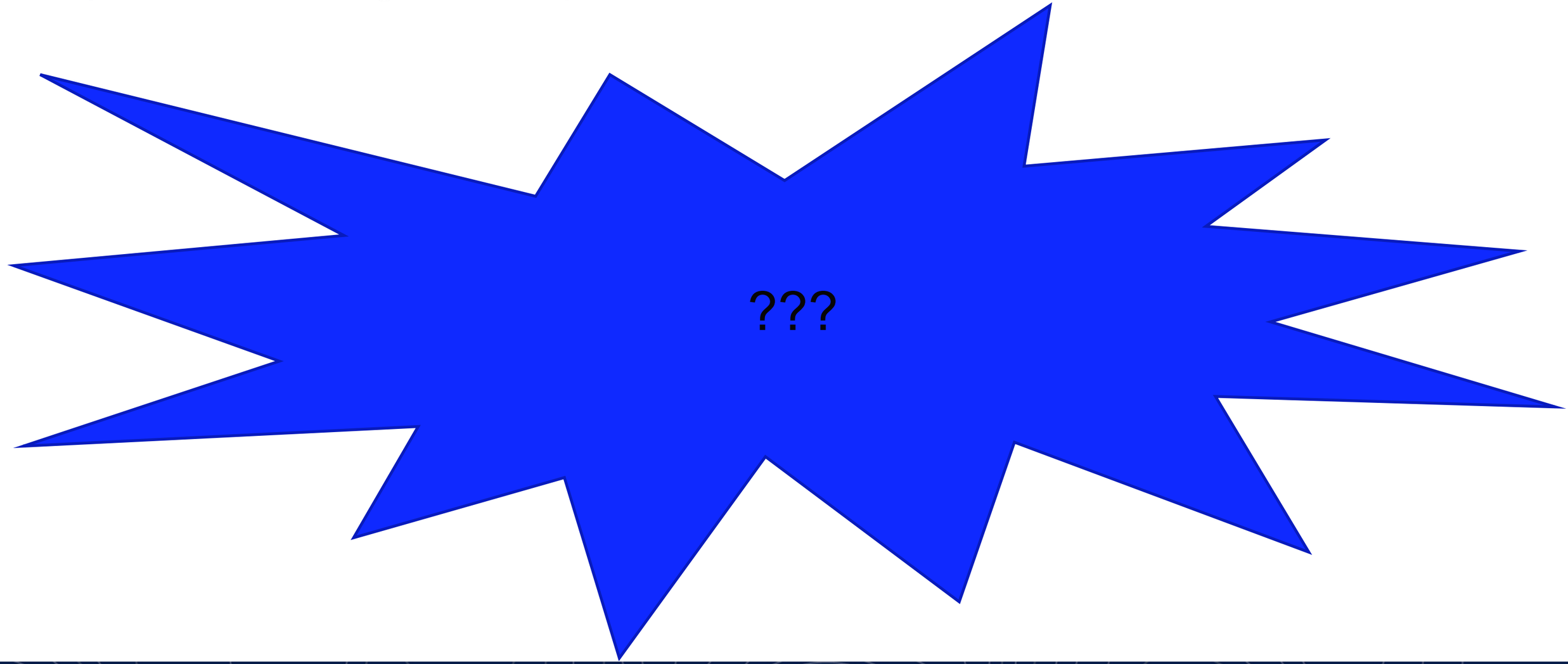
Methodology Evolvement Over Time

- 1990s: Early neural networks (gradient-descent optimization)
- 1995: Support Vector Machine (SVM) (decision boundaries optimization)
- 2000: Decision trees, random forest and gradient boosting machines (gbm)
  - Gbm is one of the best if not *the* best
- 2010: Deep learning (convolutional neural network/recurrent neural network)
  - Convnets becomes the go-to algorithm for all computer vision tasks
  - Has completely replaced SVM and decision trees in a wide range of applications
  - Winner of the industry wise competition ImageNet since 2012
- 2016 - 2017: Kaggle (industrial competition) was dominated by two approaches
  - Gradient Boosting Machines (structural data, XGBoost)
  - Deep learning (perceptual problem like image classification, Keras)
- 2019 – 2021: Transformer networks (BERT, GPT-3 etc.) are becoming more and more popular
- 2022 – present: Generative AI and Large Language Models (LLMs) becomes new norm (GPT-3.5, GPT-4, BARD, LLaMa1, LLaMa2 etc)

How Would Machine Learning/AI Help Clinical Drug Development?



How Would Statisticians Embrace the Era and Contribute More to Help Clinical Drug Development?

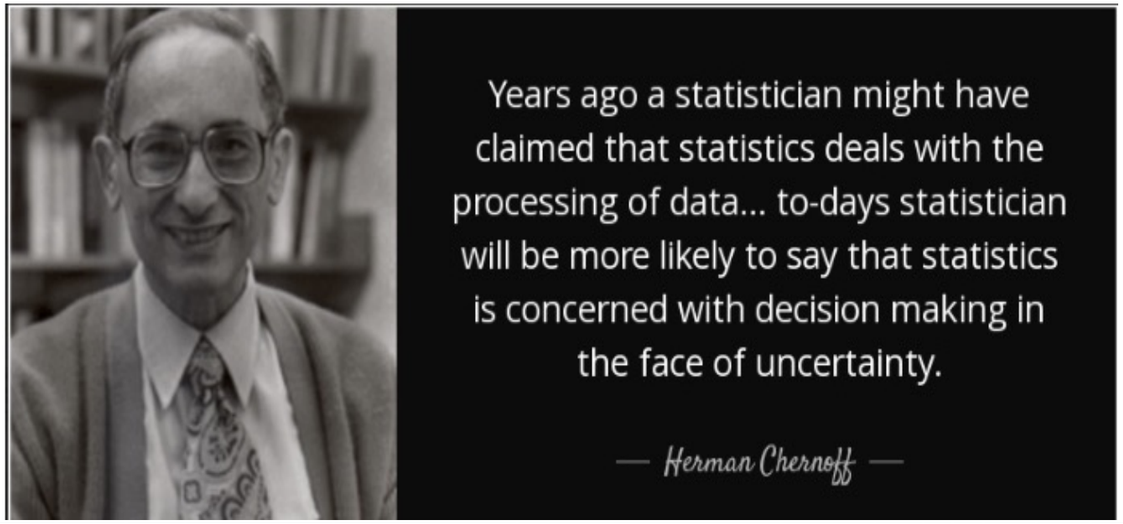


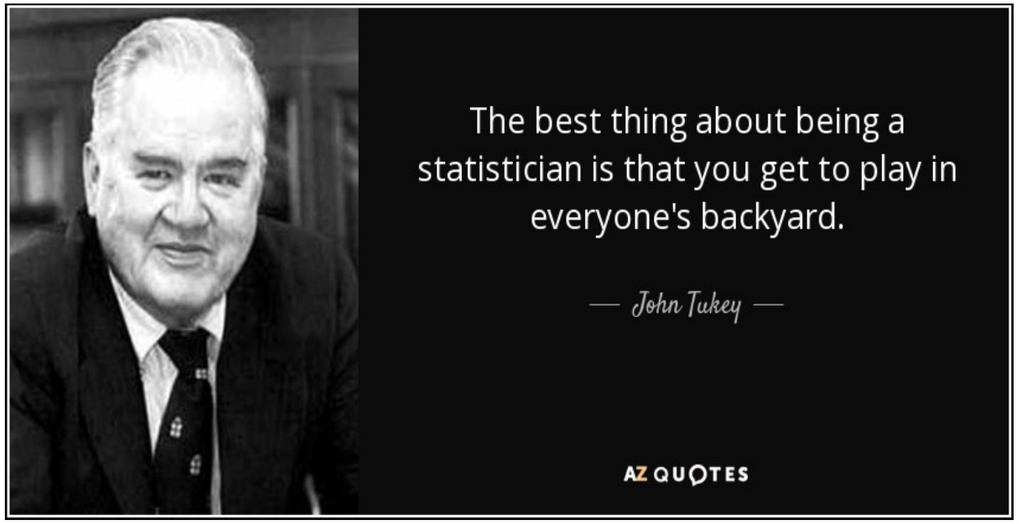
Statistics and Statistician

- Merriam-Webster: a branch of mathematics dealing with the collection, analysis, interpretation, and presentation of masses of numerical data

**"In God we trust.
All others must bring data."**

- Dr. W. Edwards Deming

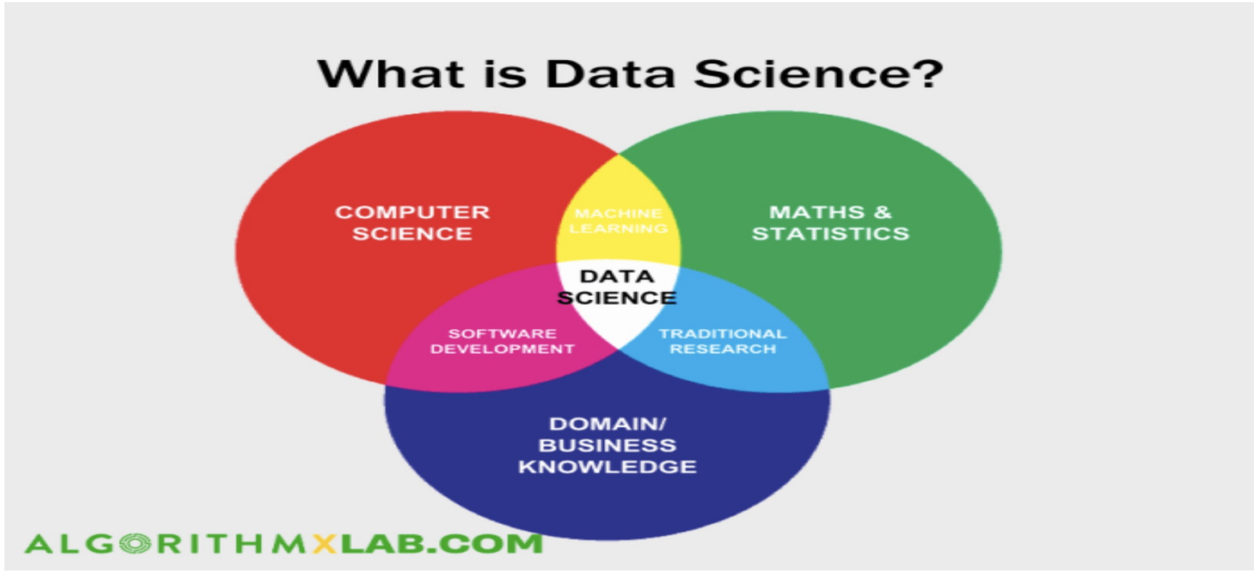


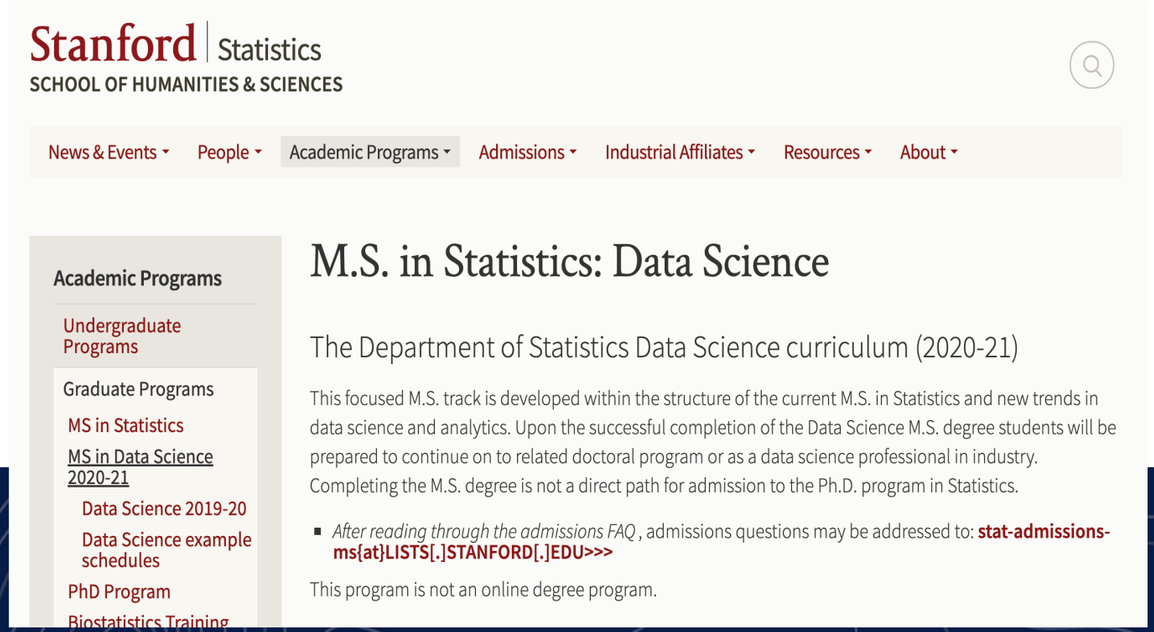


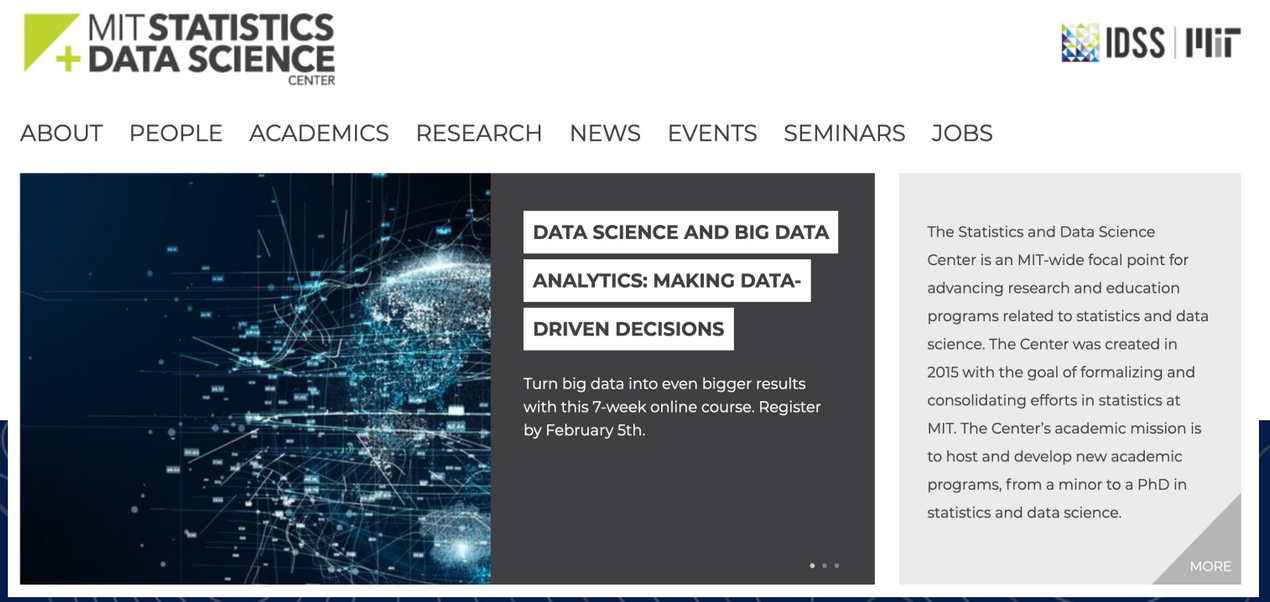
Data Science and Data Scientist

- Wikipedia: Data science is a "concept to unify statistics, data analysis and their related methods" in order to "understand and analyze actual phenomena" with data.

- It uses techniques and theories drawn from many fields within the context of mathematics, statistics, computer science, domain knowledge and information science.







Way Cooler Terminology in Data Science

$$y = f(x)$$

	In Statistics	In Supervised Learning
y	Dependent Variable	Target Variable (Label)
x	Independent Variable	Features
$y_i - \hat{y}_i$	Prediction Error	Loss
$\sum_{i=1}^{n} \lvert y_i - \hat{y}_i \rvert$/n	Mean Absolute Error	L1 Loss Function
$\sum_{i=1}^{n} (y_i - \hat{y}_i)^2$/n	Mean Square Error	L2 Loss Function
When y is a binary response	Logistic regression	Classification model
Get f()	Run a regression	Run a model
Binary classification results	2 x 2 contingency table	Confusion Matrix

Way Cooler Terminology in Data Science

$$y = f(x_1, x_2, x_3, \ldots, x_i)$$

	In Statistics	In Supervised Learning
Create x_i	Derive independent variables	Create features
Technique to handle categorical independent variables	Create dummy variables	One-hot encoding
Data manipulation techniques for independent variables	Transformation, imputation, etc.	Feature engineering
A simple non-negative, non-linear function of x	y= Max(0,x)	Rectified Linear Unit (ReLU) Activate Function
People who create derived data	Statistical programmer	Data engineer
People who do data analysis and modeling	Statistician	Data scientist

Analogy between Simple Machine Learning and Statistics

In Supervised Learning	In Statistics
I linked lots of different data sources together	I created a derived data set
I did intensive feature engineering	I derived lots of variables
I ran several models	I did several exploratory analyses
I tried Random Forest, SVM and Neural Network	I tried linear regression, logistic regression and multivariate regression
The prediction performance is evaluated on sensitivity and specificity	I looked at the Rsquare and Adjusted Rsquare
Random Forest model is the best	Logistic regression fits the data best

True Beauty and Essence of AI and Machine Learning

- Prediction Driven Deep Learning

- The capability to leverage different type of complicated data sources like imaging, voice, video, unstructured texts, high frequency longitudinal sensor data, genetic data etc. that traditional statistical models cannot handle well.

- The capability to leverage computational power to optimize prediction

Statistical Innovation Group Expertise and Publications/Manuscripts

Natural Language Processing (NLP)

"Natural language processing to identify lupus nephritis phenotype in electronic health records" (2023)

"Bertsurv: Bert-based survival models for predicting outcomes of trauma patients" (2023)

"Characterizing design patterns of EHR-driven phenotype extraction algorithms" and many more…

Imaging Deep Learning

"A one-step deep learning framework for psoriasis area and severity prediction trained on interventional clinical trial images" (submitted)

"Unlocking the Potential of Proprietary Clinical Development Datasets for Image-Based Machine Learning Models" (submitted) and many more

Enrollment Prediction

Leveraging Deep Learning and NLP to Co-build an **End-to-End Platform** to Predict Trial Duration and Site Enrollment for different stages from Portfolio Planning, Protocol Design to Trial Execution

"Real time monitoring and prediction of time to endpoint maturation in clinical trials" (2022) and many more

Rare Event Prediction and Novel Digital Endpoint

"A Machine Learning Case Study to Predict Rare Clinical Event of Interest: Imbalanced Data, Interpretability and Practical Considerations" (submitted)

"Quantifying Nocturnal Scratch in Atopic Dermatitis: A Machine Learning Approach Using Digital Wrist Actigraphy" (In prep)

and many more

Medical Imaging: Deep Learning to Predict PASI Score

Patient photos captured by cell phone APP

Body detection

Lesion segmentation

Severity classification

Computer vision algorithms

PASI score for physician

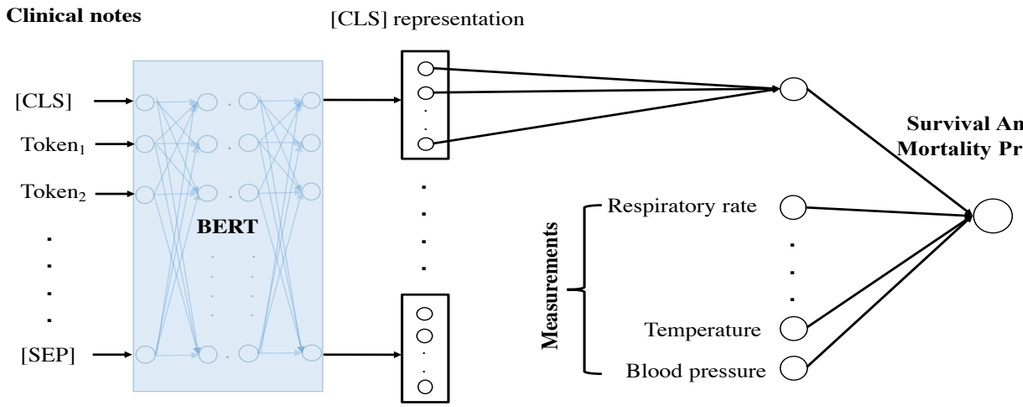
Working closely with digital science team to ensure the success of project

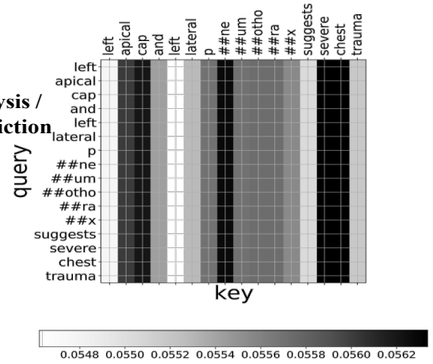
Developing a robust deep learning algorithm for PASI score prediction

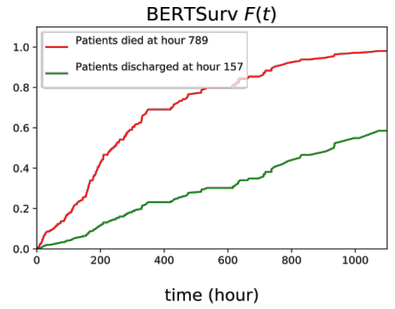
Establishing internal capability of computer vision on medical imaging

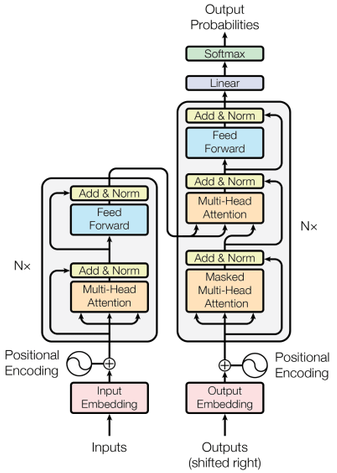
- Trained and validated 145 DCNN (deep convolutional neural network) models
- Achieved Vendor proposed MTP goal MAE=2.0~3.5 (potentially saved $1.5~3M)

Natural Language Processing in Computational Phenotyping, Patient Safety, and Risk Prediction









Projects

- NLP for lupus nephritis computational phenotyping in EHR
- NLP in patient safety: adverse drug events detection
- BERT-Based Survival Models for Predicting Outcomes of Trauma Patients

Our achievement

Developed a model to utilized both ICD, lab features and clinical notes

- Implemented NER to extract >1000 features from clinical notes
- Improved F1 from **0.41 -> 0.79**

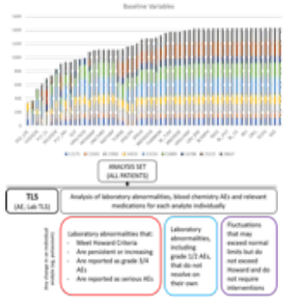
Fine tuned various LLMs to detect adverse drug events

- Fine tuned BERT, Roberta, Roberta-large, Bio_ClinicalBERT, GPT2, and ChatGPT;
- Improved F1 from **0.70 -> 0.76**

Developed a novel BERT-based architecture to model time-to-event (death) outcome

- Survival outcome: c-index = 0.7 > 0.68 (cox model)
- Visualized BERT's attention heads to extract patterns in clinical notes

ML Predictive Modeling to Predict Rare Safety Event



Clinical Data

Our Robust Non-standard ML Pipeline

Challenge:

- Complex target events: 3 primary target events, 6 secondary target events
- Extreme imbalanced data: <10% patients have rare events
- Non-standard ML outcome requests: an interpretable criteria instead of a model in black-box

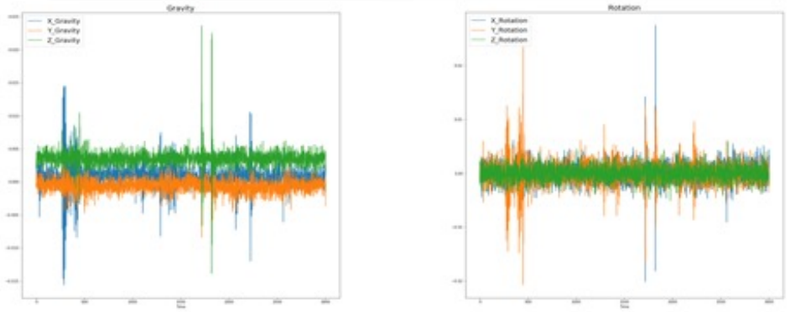
Our Achievement:

- Design hierarchical event paths to capture multiple severity groups of events
- Applied state of arts approaches to conquer imbalanced data issue. (e.g. cost sensitive, SMOTE)
- Explored and evaluated 60 models (e.g. XGBoost, RF, NN, Decision Tree…)
- Developed a robust ML pipeline with multiple optimization criteria to avoid potential bias and overfitting
- Achieved an interpretable binary-tree criteria with comparable performance as complicated models but readable by human

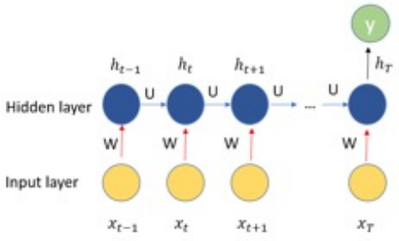
Digital Endpoint Development in Atopic Dermatitis

- Wearable sensors (e.g., Apple Watch) on wrists can objectively record motion that could be further utilized to predict scratching
  - Actigraphy data collected by the built-in accelerometer
- Scratch ground truths identified from continuous video recording
- Deep Learning techniques applied to build scratch algorithm
  - Traditional RNNs with LSTM cells
  - Advanced techniques for sequence data: Attention-based networks, transformers

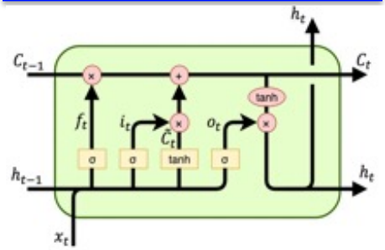
Actigraphy data: Gravity and Rotation



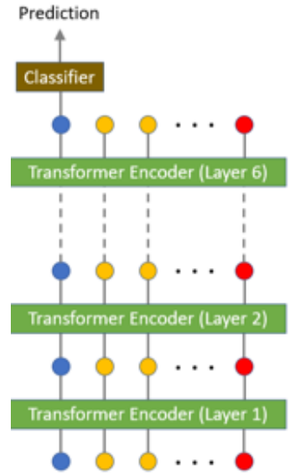
RNN Architecture



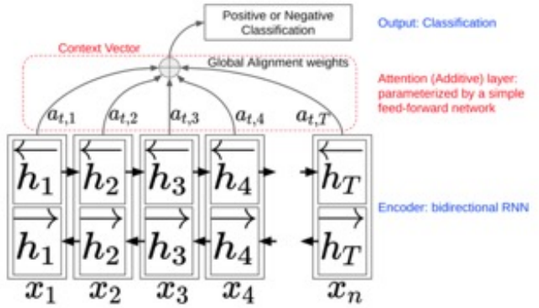
LSTM Cell



Transformer



Attention-based RNN



Summary

- Drug development paradigm is evolving and there is an increasing need for statistical innovation
- AI methodology is pretty mature, powerful and fast evolving.
- Simple ML is just like basic statistical methods that every statistician should know
- Deep learning and the capability to leverage more complicated data sources is critical
- Statisticians as a profession should and can evolve, embrace and drive the problem solving and application of the right AI methodology at the right place to help the business