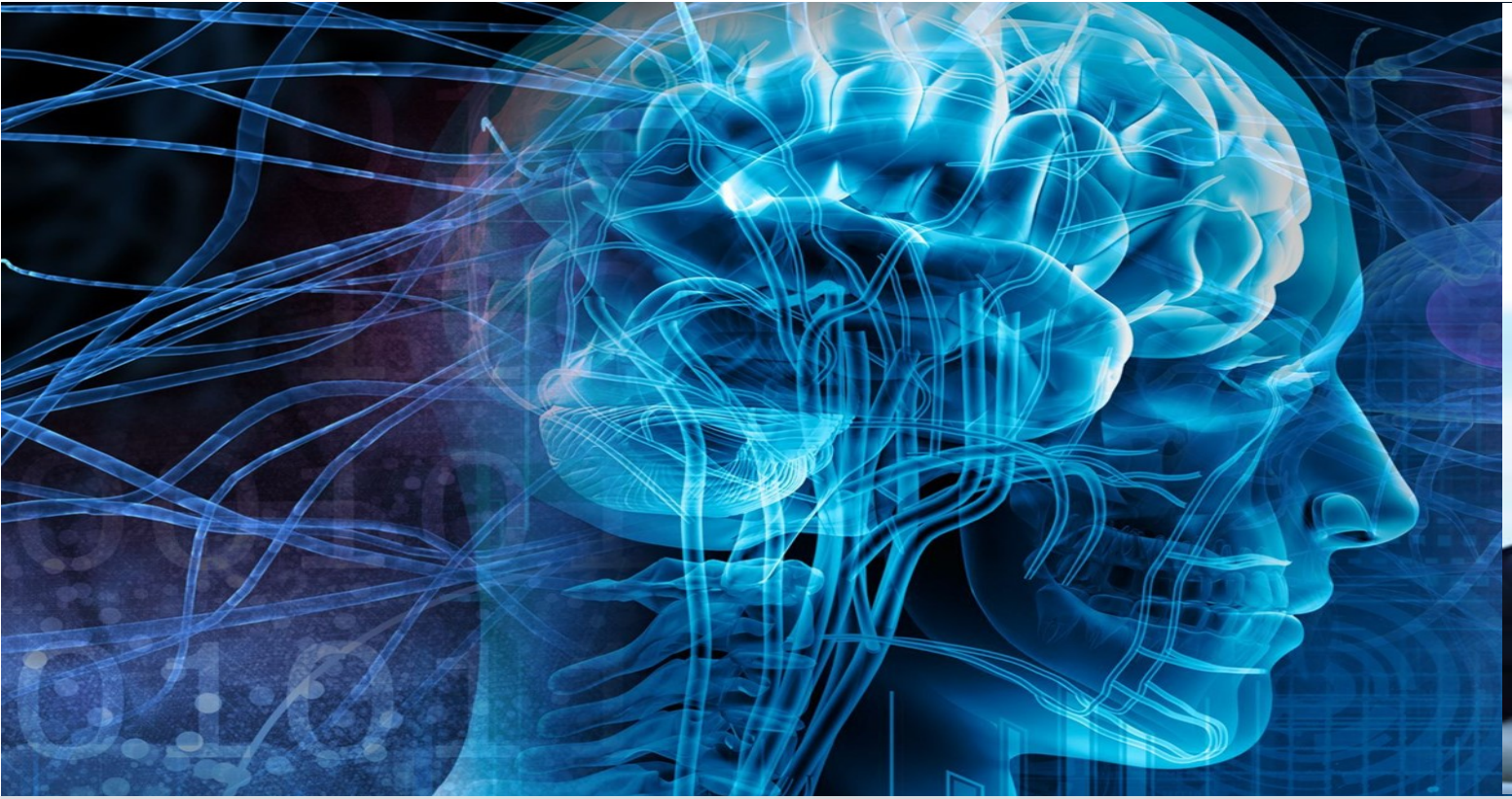

CPAD Industry Co-Director Remarks

October 27, 2020

Nusrat Rabbee

NBG Head of Statistical Methodologies & Data Science, Eisai Co., Ltd.

CRITICAL PATH INSTITUTE 15 YEARS

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Why AI/ML is needed to improve clinical trials?

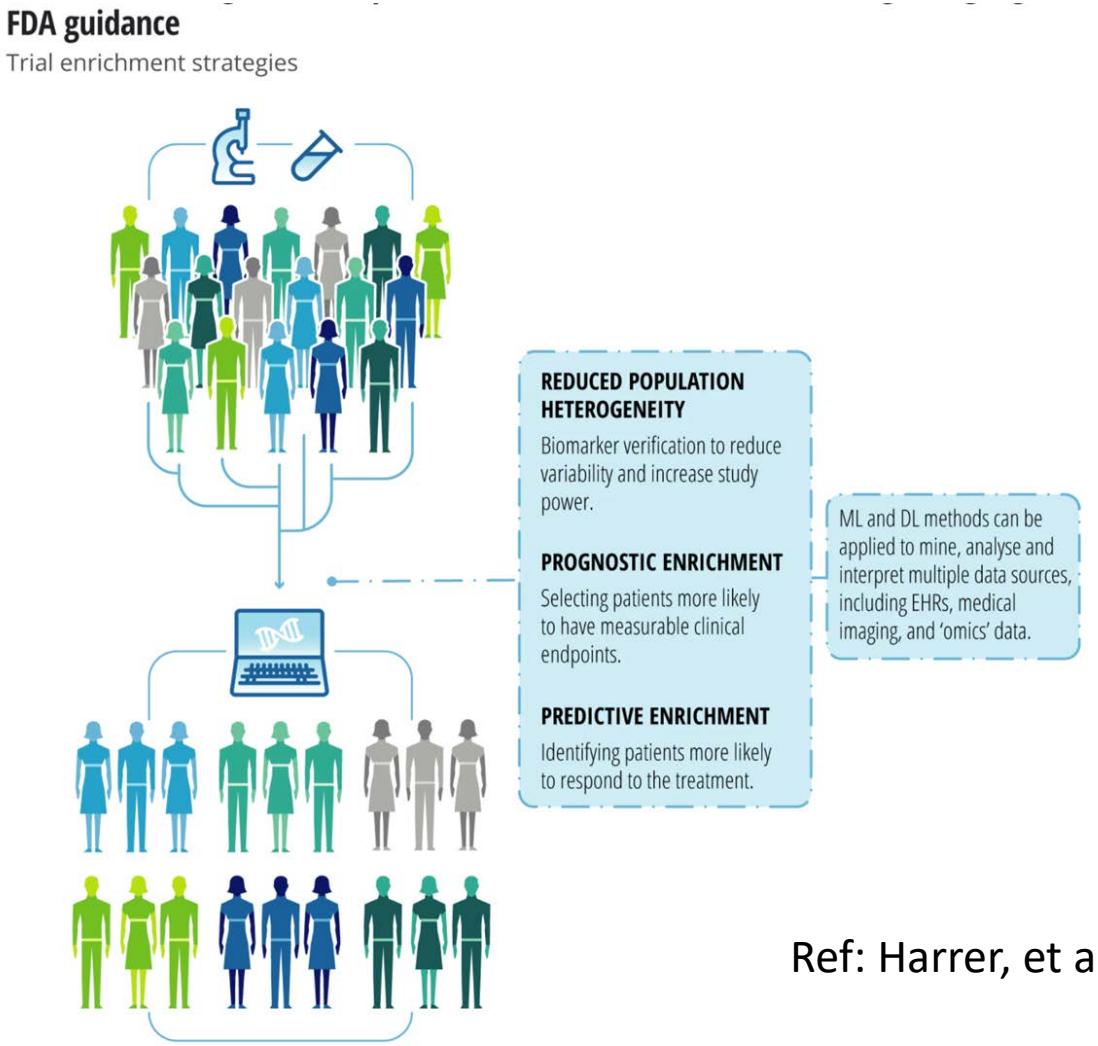
- Patient diagnosis
- Patient selection
- Understand response (efficacy/safety) to therapy
- Predict outcome of trial

Example Oct 2020 of what is happening

Genentech enters partnership with Imbio to develop AI-powered imaging diagnostics for lung diseases for use with clinical trials, as well as more broadly by physicians.

"This collaboration is a great example of Imbio's strategy to meet the growing interest by medical device and pharmaceutical companies in using imaging biomarkers and imaging AI to facilitate diagnosis of respiratory diseases," CEO David Hannes said.

Focusing on AI/ML applications
Trial Enrichment Strategies



AI/ML can help by patient selection via:

1. **Reduce patient heterogeneity/improve screening**
   - EMR technology, etc. is useful; or improve screening through ML

2. **Build prognostic model**
   - Choose patients with measurable clinic endpoint (DPM like CTS)

3. **Build of predictive model**
   - Identify people likely to respond

Ref: Harrer, et al. 2019.

Focusing on AI/ML applications Trial Enrichment Strategies

AI/ML applications are prevalent in all aspects of the clinical trial.

Focusing on trial enrichment/trial modernization & improvement from these aspects:

- Patient diagnosis/screening tools
- Patient prognostic and predictive signature
- Patient trajectory development

I will highlight ***4 areas of innovation:***

- I. Need continually improving AI/ML algorithms for evolving unstructured and/or big data from advancing instruments
- II. Need multi-modal algorithms to build integrative picture of the system
- III. Need advanced algorithms to build personalized trajectories of disease
- IV. Need in-silico trial capabilities to replace/reduce human/animal experimentation

I. Need AI/ML technology ("big data science") to extract/combine insights from big data in clinical trials

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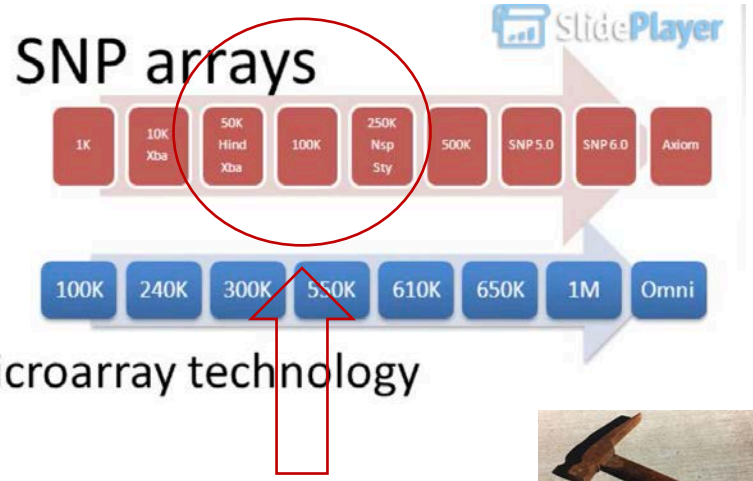
- Big data science should track big data



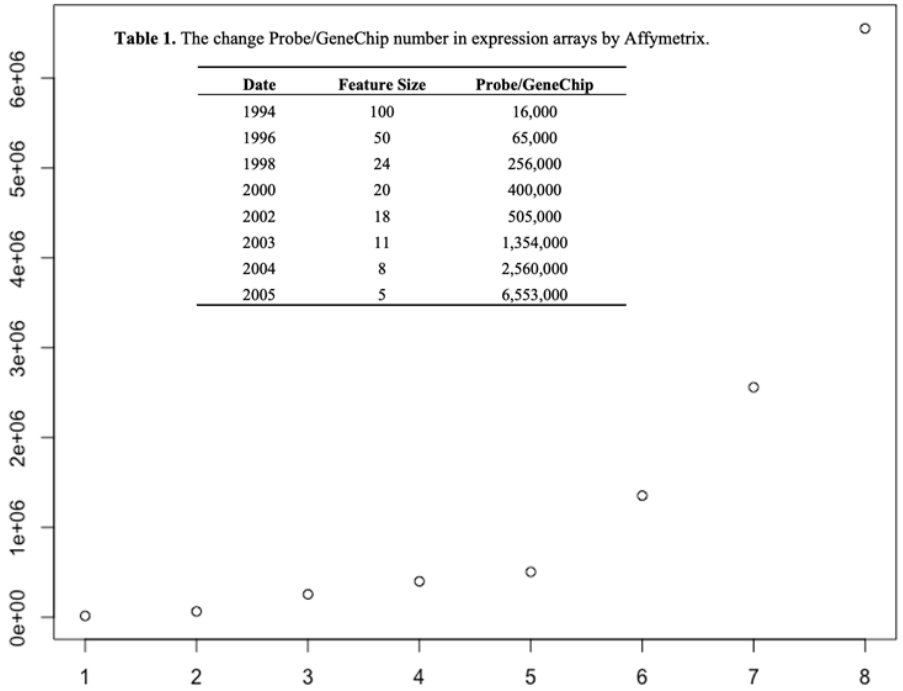
- Affymetrix
- Illumina
- Probes on microarray technology

Co-invented the RLMM algorithm which enables Affy to go from 50k to 500k and now ~1m SNPs (CRLMM).

- Moore's law for hardware applies to software

Table 1. The change Probe/GeneChip number in expression arrays by Affymetrix.

Date	Feature Size	Probe/GeneChip
1994	100	16,000
1996	50	65,000
1998	24	256,000
2000	20	400,000
2002	18	505,000
2003	11	1,354,000
2004	8	2,560,000
2005	5	6,553,000



I. Need AI/ML technology ("**big data** science") to extract/combine insights from **big data** in clinical trials

- With advanced instruments (like MRI scanners, digitized medical records, IoT) – we need algorithms to read and extract information from these sources
  - Need AI/ML, Bayesian approaches to borrow information, and combined machine learning (ML) and Bayesian methods
    - Traditional statistical/biostatistical methods not suitable
  - Need high-performance computing environment
  - Need good quality and quantity of data

- Thus we need to continually improve & integrate big data and big science into clinical trial to modernize drug development

II. Multi-modal algorithms – integrative approach through AI algorithms

- Integrative Approach on combined data for detecting biomarkers for

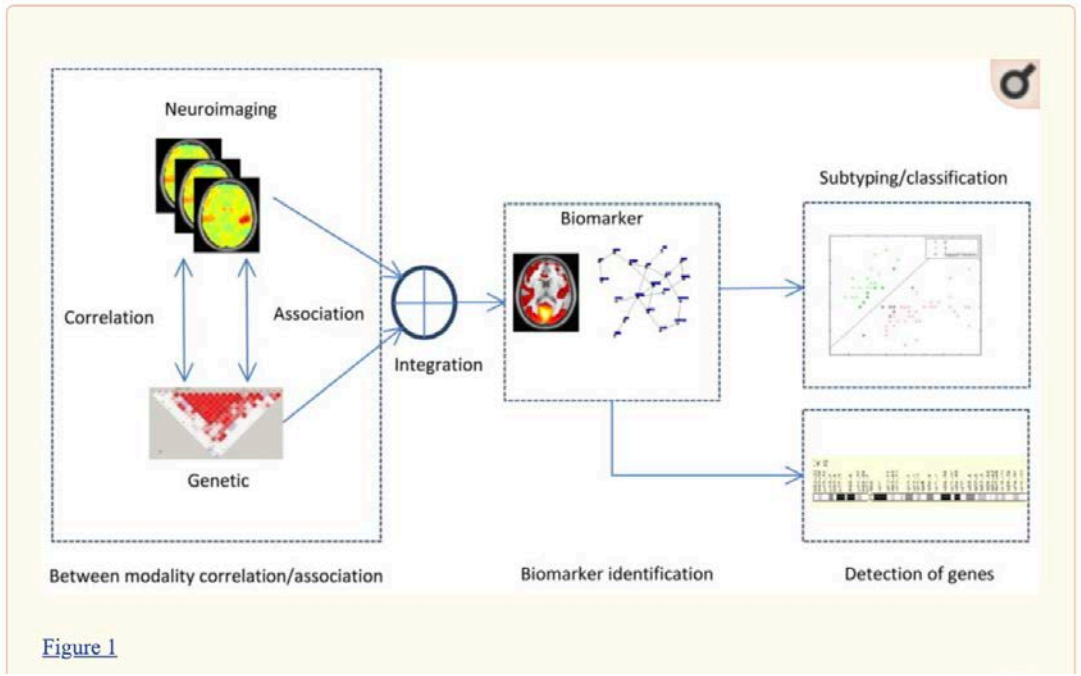
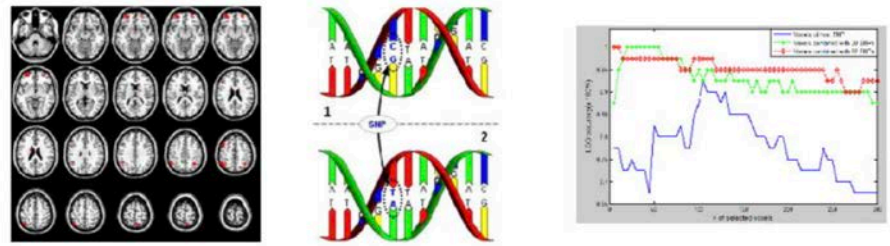


Figure 1

- Integrated Model yields highly accurate classification results

Figure 7



Integration of fMRI (a) and SNP (b) with our proposed sparse models[2]results in better classification of schizophrenia and healthy controls than using just fMRI data or SNPs only. In (c), blue line is the classification result without using combined data, while the red and green lines are the results by combing fMRI with SNP markers with different numbers, showing higher classification accuracy.

Ref: Lin, et al., J NeuroSci Methods. Sparse models for correlative and integrative analysis of imaging and genetic data (2014)

II. Multi-modal algorithms - applications

Perfect Storm: Advanced Instruments + Big Medical Data + Computational Infrastructure + Advanced AI Algorithms

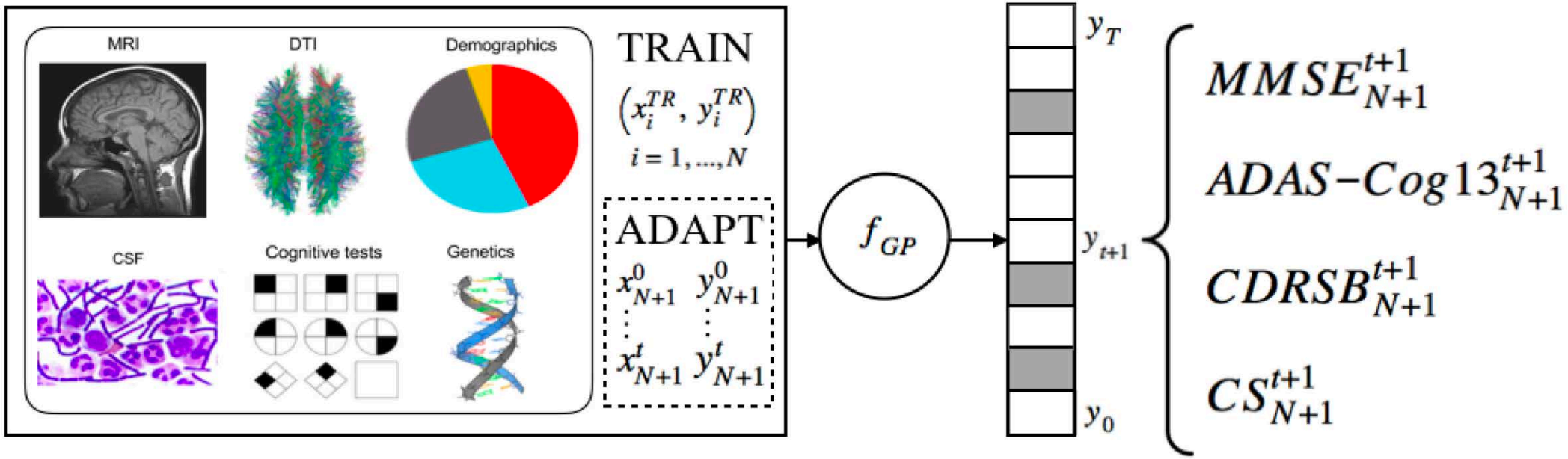
- Rapid advances in experimental instruments and protocols
- Imaging, wearable, sequencing data are being generated at an unprecedented rate contributing significantly to the current and coming biomedical data
- Unprecedented advances in computational infrastructure and
- Breakthrough in advanced AI algorithms **(like deep learning methods CNN)**

Facts:

- Although broadly implemented elsewhere – applications in healthcare is starting
- Unique opportunity because of vast potential in integrated genomics data with histopathological imaging data
  - May create breakthroughs in diagnosis, treatment, and monitoring at molecular and tissue levels.

Artificial intelligence can be used with genomics, imaging, IoT data to make breakthroughs in biomedical and translational research for computer-aided applications: patient screening, risk stratification, safety event detection/monitoring, disease trajectory

III. Personalized Trajectories
Which factors are influencing each patient?

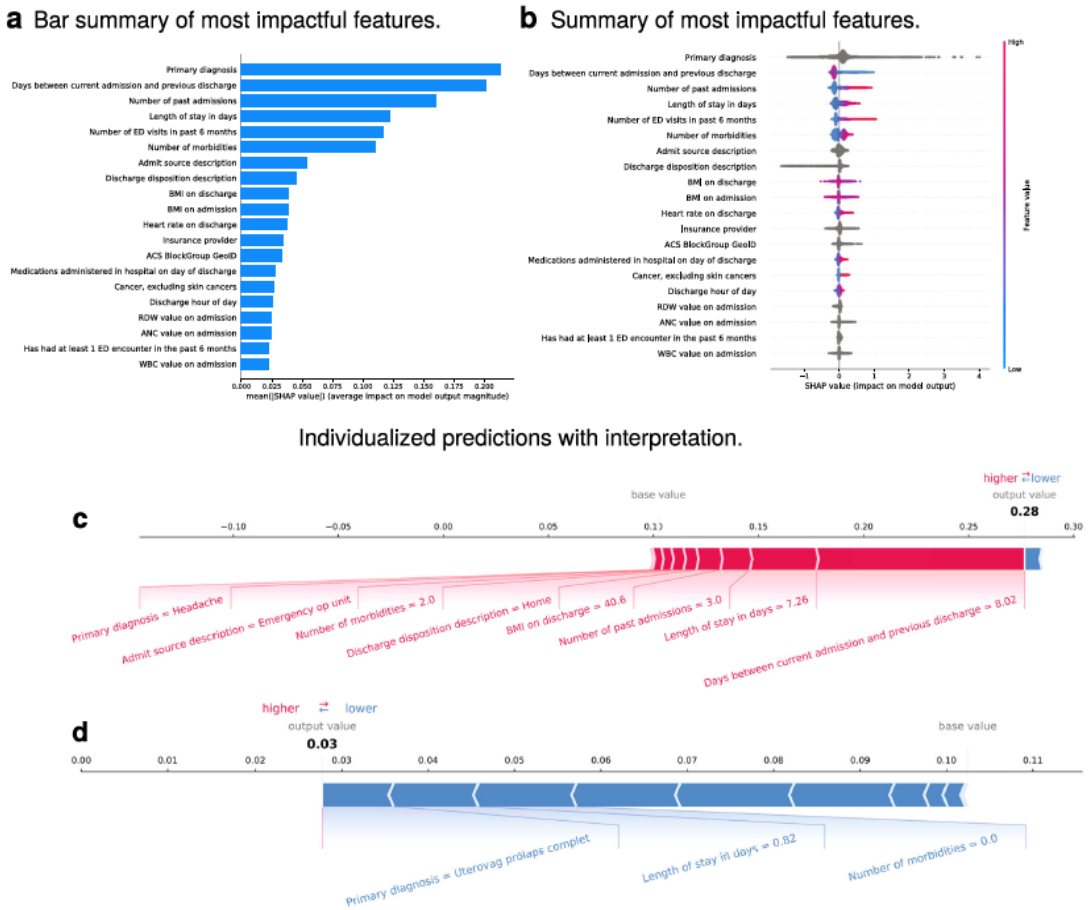


- Train a population model for Disease Progression using multi-modal data (GP)
- Adapt the GP model sequentially over time to a new subject (pGP)

Leads to significant improvements in the prediction performance of the future clinical status and cognitive scores for target subjects when compared to the population model.

III. Personalized Trajectories - applications

- Temporal personalization of disease trajectories leads to significant improvements in disease progression and conversion predictions
- Significant recent advances in artificial intelligence (AI), machine learning (ML), and deep learning (DL) yielded compelling innovations making this possible
- These advances lead to algorithms that reliably extract important variables and explain model decisions; verifying that clinically relevant variables are included and so mechanism is understood and may lead to new insights and hypotheses



Ref: Hilton, et al

IV. In-Silico Clinical Trials (ISCT) with Virtual Bodies

- In-silico is **the term scientists use to describe the modeling, simulation, and visualization of biological and medical processes in computers**. The emergence of in silico medicine is a result of the advance of medical computer science over the last 20 years.
  - (ref: https://medicalfuturist.com/in-silico-trials-are-the-future/)

- Traditional clinical trials costing billions of dollars – with many drugs not approved
  - So consider conducting clinical trials (Phase I /partly /wholly) in virtual bodies that mimic the human physiology
  - AI + simulations + knowledge of personalized medicine all coming together

IV. In-Silico clinical Trials (ISCT) with Virtual Bodies -Why?

- Use ‘software as a medical device’ regulatory pathway
- If computer models can guide the diagnostic, prognostic, or therapeutic decision for individual patients, why should they not be able to advise on the safety and efficacy of new medical products?
- Cost of health care innovation too high and pace too slow
  - Regulatory process is very slow and complex
- In-silico is adopted in many other industries
  - Aerospace, chemical, nuclear, energy
- Variety of approaches like bioinformatics, systems biology, computational biochemistry, physiology-based pharmacokinetics, physiology-based and biophysics-based mechanistic models, non-linear system identification methods, Bayesian modelling, Big Data Science, and AI/ML methods including causal machine learning
  - Each is specific; but together very powerful ability to do “in-silico” trials
- May change the regulatory process; need regulatory support to reduce animal + human experimentation
  - Reduce, refine, and replace clinical trials

IV. In-Silico Clinical Trials with Virtual Bodies -Example

A transformative innovation Gemini™, the in-silico patient, will drive better drug development, clinical trial design, and generation of real-world evidence in multiple myeloma

- GNS Healthcare, an AI-driven precision medicine company, today announced the launch of Gemini™, the *in-silico* multiple myeloma patient. **The *in-silico* patient is a highly accurate computer model of disease progression and drug response at the individual patient level.** Clinical development applications include discovering markers of response/nonresponse for clinical trial design, predicting optimal combination therapies, and running head-to-head *in-silico* trials. Market access applications include generating evidence for line of therapy switching and optimizing treatment sequencing.

Capture Value & Create Value From Data in Clinical Trials Through AI/ML

Key Challenges
Ref: Shah, et al 2019 (Nature)

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Challenges and Considerations

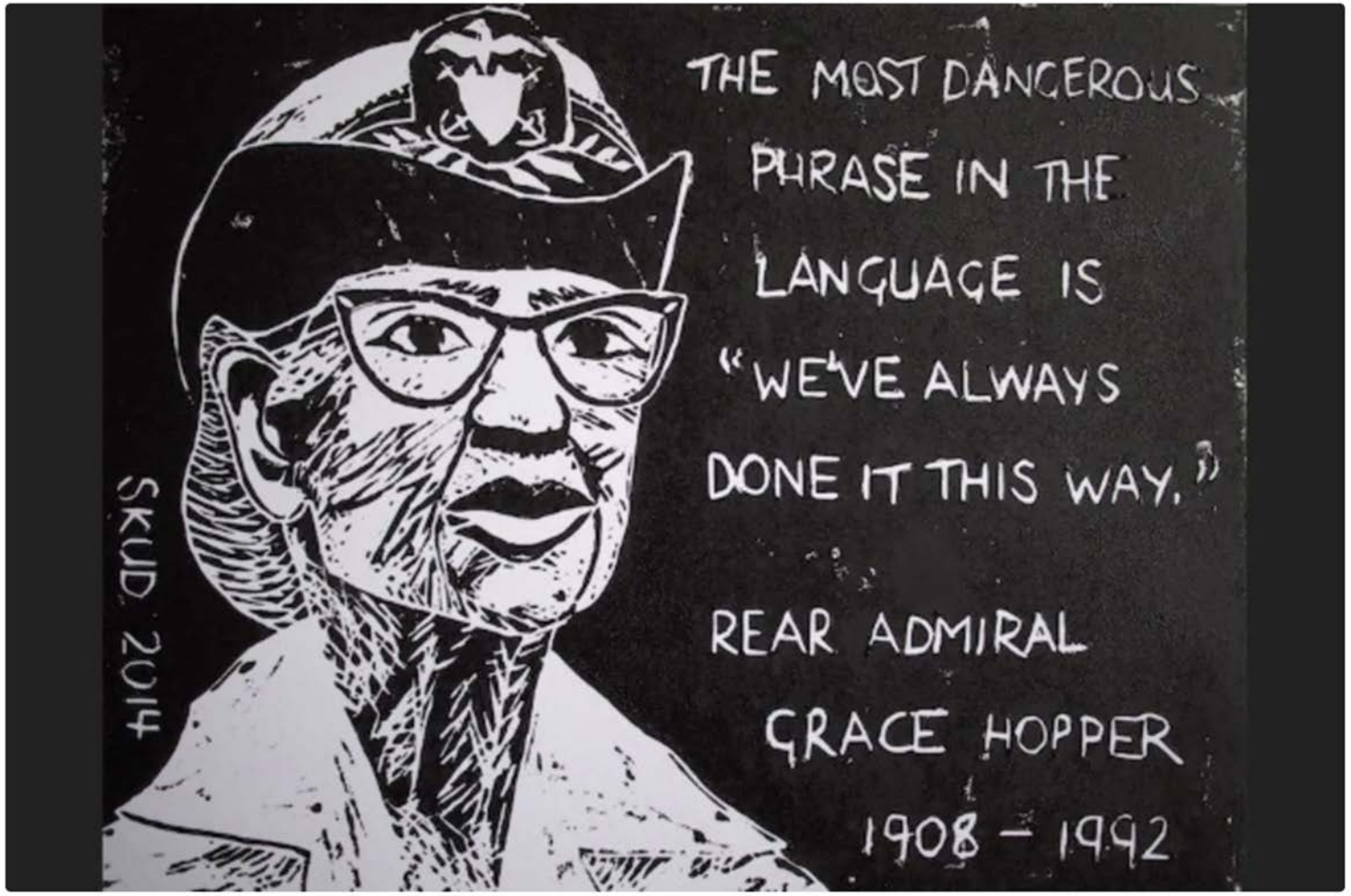
- Academia – Industry: Overcome limitations of current computer science deep learning models to generalize complex clinical data sets
  - Partner with AI/ML industry to turn models into software
- All: Inadequate repository of high volumes of labeled data sets for training deep learning algorithms
- Industry: Lack of internal strategies to implement AI/ML technology to modernize clinical trials
- Regulatory: Need regulatory framework for dealing with relevant ethics issues and validation issues for de-risking use of AI and ML based prediction and decision support in clinical trials

Ref: Shah, P., Kendall, F., Khozin, S. *et al.* Artificial intelligence and machine learning in clinical development: a translational perspective. *npj Digit. Med.* **2,** 69 (2019). https://doi.org/10.1038/s41746-019-0148-3

Key Recommendations for Industry
Ref: Shah, et al 2019 (Nature)

- Maximize AI and ML opportunities by focusing on data aggregation and easier access to data within and across industry comprising pharma & biotech
- Share data in a pre-competitive manner (such as, with CPAD) across industry, regulatory staff and academics to generate insights faster and collaboratively
  - Small biotechs benefit from publicly available tools and insights
- Put statistics/computer science experts in relevant initiatives in order to build core capabilities and interdisciplinary teams
- Leverage external advisors from academic research groups or from companies dedicated to developing AI tools

Thank you!


THE MOST DANGEROUS PHRASE IN THE LANGUAGE IS "WE'VE ALWAYS DONE IT THIS WAY."
REAR ADMIRAL GRACE HOPPER
1908 – 1992
SKUD 2014

Additional References – Dr. Rabbee's Presentation

- Lin D, et al. *Sparse models for correlative and integrative analysis of imaging and genetic data.* J Neurosci Methods. 2014 Nov Harrer, et al, ScienceDirect 2019. *Artificial Intelligence for Clinical Trial Design*
- Hilton, et al, Digital Medicine. *Personalized predictions of patient outcomes during and after hospitalization using artificial intelligence*
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