CPAD Industry Co-Director Remarks

October 27, 2020

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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

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

• 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
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

• Integrated Model yields highly accurate classification results

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

Please email questions to ykarten@c-path.org
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/](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
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

Get AI/ML advanced algorithms to extract information from instruments

What has happened?

Develop Multi-modal algorithms to predict outcome

What will happen?

Predict Individual trajectories or treatment efficacy/safety outcomes

What should be done?

User Virtual bodies (partly) as patients in clinical trials

Would this work?

Descriptive/Diagnostic
Prognostic/Predictive
Prescriptive
In-silico prescriptive
In-silico drug trial/approval process

Please email questions to ykarten@c-path.org
Key Challenges

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

https://doi.org/10.1038/s41746-019-0148-3
Key Recommendations for Industry

• 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


• Hilton, et al, Digital Medicine. *Personalized predictions of patient outcomes during and after hospitalization using artificial intelligence*