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Disruption is Personal: RWE and AI changing the game for Personalized Medicine

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ABSTRACT

Conventional clinical trial approach deals with data from patients enrolled in a designated trial and represents a small portion of the actual patient population. Real world evidence (RWE) is developed using Real world data (RWD) that reflects use of broader, more heterogeneous populations and utilize variety of sources like clinical data, administrative/claims data, patient-generated/reported data, and emerging data sources including social media. Personalized medicine based on RWE adopts a data-driven approach and aims to design the best treatment option tailored to individual patients, using predictive analytics from a large data set. Artificial Intelligence tools like Neural Network and Deep Learning algorithms can act in tandem to generate more decisive outcomes than the traditional stratified approach, as every patient is different. Linking real-world clinical, healthcare and genomic data with the help of Deep Genomics and next-gen cognitive assistance can create study populations that provide generalizable evidence for precision medicine interventions.

INTRODUCTION

Very few drugs are actually effective when considering broader patient population globally. They either act on a subset of population, or work in different ways on different people. There are several reasons for the same, but the difference in genetic makeups (genome), proteins in our body (proteome), metabolites (metabolome) and microbial flora (microbiome) affect how drugs work. Conventional medical approach is “one size fits all”, which is a gross generalization of treatments given against a disease. At this age of personalization, when even doing home interior, we look for that “personal touch”; when big e-commerce companies pushing the recommender system for showing customer choice specific products---- then medicine should also become more patient-specific.

However, to accomplish that specificity---- the cost and time to develop drugs can increase due to delays in creating patient pools, difficulty in finding patients with the right genetic makeup, and the need to increase the length of trials to find drugs that will work for greater portions of the population. Changing the way of design and administering treatment trials, using real-world big data to bring personalized medicine to drug trials and research, has the potential to reduce costs, faster development of new drugs, and improve outcomes. At this crux, Deep learning, Artificial Intelligence, Internet of Things and Blockchain technologies can create amazing wonder if used properly [Ref_4, Ref_5]. Ultimately, this procedure holds possibility of faster drug development with lesser risk and can create win-win situation for pharmaceutical companies and patients alike [Ref_1, Ref_4, Ref_8].

A PARADIGM SHIFT FOR DEVELOPING MEDICINES: TRADITIONAL TO PERSONAL

In the last few decades, there is a transformation in biomedical sciences towards data-driven medical research complementing well-established hypothesis driven knowledge discovery. This is contributed by the reduced cost of high throughput genome sequencing, and outstanding development of data science and computing technologies [Ref_1]. We are at a crucial juncture of time when huge amount of data is readily available and churning out insights helps creating newer business opportunities. The pharmaceutical industry is moving beyond traditional, statistical approaches to leverage disruptive technologies like machine learning and other cognitive approaches [Ref_2]. Instead of developing treatments for populations and making the same medical decisions based on a few similar physical characteristics among patients, future of medicine shifting towards prevention, personalization, and precision.

Precision medicine requires viewing each patient as an individual rather than an average, random sample, and it helps get the right medication to the right patient at the right time. Precision medicine holds the potential to substantially enhance efficacy and outcomes by integrating disease-specific factors, patient-specific factors,

environmental/sociocultural considerations, quality of life and functionality considerations, and economic outcome analyses. One goal is to effectively stratify at-risk patients for targeted prevention. Precision medicine involves several steps: developing a therapeutic hypothesis, determining which patients respond and why, and creating robust mechanisms for identifying those patients. The process includes thinking about delivery of the drug, the biomarker response, and the diagnostic tool for identifying the proper patients [Ref_3]. As therapies are identified based on analytics, clinical trials and medical treatment can become more effective.

REAL WORLD EVIDENCE AND ITS CONNECTION TO PERSONALIZED MEDICINE

Real World Evidence (RWE) is promising to answer the hard questions in health care, such as what works, for whom, why does it work, and in what context. All of these questions are at the heart of value-based personalized medicine with value-based care [Ref_3].

RWD AND RWE

RWD or Real-world data is the patient data collected in real-world setting and outside of controlled clinical trials. RWD can come from a variety of sources, for example:

- Electronic health records (EHRs)
- Claims and billing activities
- Product and disease registries
- Patient-generated data including in home-use settings and patient reported outcomes surveys
- Data gathered from other sources, like wearables data collected via mobile devices, that can inform on health status

On the other hand, RWE or Real-world evidence is the downstream insight that comes from analysing RWD. RWE provides insight beyond traditional clinical trial data, adding the potential to link data from different sources [Ref_2, Ref_3]. RWE is expected to translate into:

- Improved trial efficiency
- Identification of potential new indications
- Generation of a real-world perspective on risks/benefits to make informed decisions beyond traditional clinical trials.

For all of these, RWE is influencing the health care market and has been getting attention on the regulatory side.

REGULATORY PERSPECTIVE FOR RWD AND RWE

From regulatory perspective, FDA has been exploring ways to further support industry use of RWE as a part of clinical studies under the agency's RWE framework. A growing number of researchers think RWD/RWE need to be supportive of enhanced diversity in trial populations and the number of patients needed for clinical studies, whereas many others have encouraged the FDA to consider how RWE / RWD may be used to help provide information on effects of the drug in these broader patient populations.

REAL WORLD, BIG DATA?

Now as the real-world data is coming from various sources, with huge volume and with multiple characteristics like text, image, video etc.----by virtue of 3V—volume, velocity and veracity-- they become Big Data [Ref_2]. Clinics and hospitals have been amassing large quantities of complex data within patient medical records -- including handwritten notes, X-ray results, blood samples, vital signs, DNA sequences, and more for several years. It is challenging to analyse this humongous amount of data to mine appropriate insight.

DISRUPTIVE AND EMERGING TECHNLOGIES IN ACTION

It is exciting to find that not only the data sources available for real world is expanding, but also the platform technologies and data science techniques to analyze RWE are making major strides.

- Most of the investments for developing new capabilities in the RWE space are leveraging cloud data platforms compared to on premise platforms. The cloud can quickly ingest and analyze the data and create external data sandboxes to collaborate with external partners.

- A number of the Big Data analytic techniques that have been developed and leveraged in other industries, can be leveraged now for pharmaceutical and healthcare as well. Pharmaceutical companies are moving away from traditional warehousing approaches to utilizing tools that are more suited to the variety and complexity of real-world data.

THE PATH TO REACH INSIGHTS

Technology industry buzzwords – AI (Artificial Intelligence), ML(Machine Learning), NLP(Natural Language Processing) - to name a few - have been making their way into the public vernacular more and more in recent years. For pharma and biotech industries, the applications of these buzzwords are far reaching, particularly when it comes to processing large data sets to generate RWE. There are five main ways that these innovative technologies can be utilized to improve efficiencies in real world data ingestion, normalization and outcomes research.

- When ingesting massive amounts of secondary data from dissimilar sources, there is a need to link and normalize the data into a common data model to generate meaningful insights. In the past, this normalization could only be done manually, and could take a prohibitive amount of time. Now with NLP and ML, the entire end-to-end process can be automated and insights can be generated in a fraction of the time.

- In patient treatment pathways, ML can be used to analyze and compare treatment effectiveness of a particular drug or therapy and ensure, from a payer's perspective, the prescribed treatment is meeting value expectations

- In the near future, physicians would be able to rely on AI to better determine if a patient is at high risk for developing certain diseases. Based on available secondary data sources and learned predictive modelling, a patient's profile can be aligned with these models to identify markers that would determine risk levels.

- As the data getting collected primarily in EHR, we have better access to RWD now and ability to track patient behavior and treatment adherence. ML can also be applied to these data sets and used to predict which patients are more likely to discontinue a drug or therapy for a chronic disease. With these analyses, pharma and biotech companies can then take action to focus on improving patient adherence.

As evident, the technology advancements of AI, ML and NLP offer pharma and biotech companies the power to increase meaningful RWE output, decrease time to insights, and make the most of the vast data sources now available. An RWE technology platform that delivers smart data processing, analysis and outcomes offers an unparalleled opportunity to capitalize on these computing advancements. When used as part of an overall comprehensive RWE strategy, AI, ML, and NLP innovations can enhance drug development, improve patient treatment and access, and drive valuable new business opportunities [Ref_10] .

WHY PERSONALIZED MEDICINES REQUIRE RWE AND DISRUPTIVE TECHNOLOGIES INTERVENTION?

Data is the foundation for patient-centric, precision medicine clinical trials. The life sciences industry has historically relied almost exclusively on randomized controlled clinical trials for data, while making little use of real-world data (RWD) from patients. In some ways, existing patient data is essentially huge for a complete clinical trial. This data can be normalized to facilitate the search retrospectively for benchmarks and trends that can be leveraged to improve care. By collecting, organizing, and extracting from existing data sets, clinicians and researchers can assess how specific sets of patients reacted over several years. Data can also be utilized from direct and indirect sources to achieve a more holistic perspective on each patient, so there is now an enormous volume of qualitative and quantitative data for advancing precision medicine. As churning out insights from large volume of data is becoming easier due to the intervention of newer technologies, we are more prepared towards the targeted drugs [Ref_3].

HOW MACHINE LEARNING AND AI CAN LEVERAGE THE CHANGE

To explore humongous amount of data, it requires significant computing power. As a result, algorithms that can learn by themselves at an unprecedented rate i.e deep learning will have significant impact on its efficiency. An approach

that uses the cognitive capabilities of physicians on a new scale, i.e artificial intelligence, will help finding best decisions at faster rate.

ARTIFICIAL INTELLIGENCE

AI is able to learn from each piece of data that is given and rapidly re-evaluate its analysis as more data received. This ability to rapidly analyze data, and potential correlations, creates more comprehensive and holistic view into a patient's health [Ref_4, Ref_5, Ref_6]. Some of the newer avenues, which AI is opening as below:

- AI can interpret and aggregate imaging, text, handwritten notes, test results, sensor data, and even demographic and geo-spatial data. This helps speeding up data acquisition, segregation and store better.
- AI will be able to cross reference data, find commonalities and draw insights that were previously impossible due to data silos or the sheer amount of time it would take for a human to crunch the numbers
- It can also consider seemingly unrelated or outside factors that doctors and researchers may not immediately see as relevant. For example, environmental factor, such as elevation, humidity and proximity to certain dense mineral deposits, factories or agriculture, may also be considered during drug efficiency.

Precision medicine often requires the study of rare cohorts, and the ability to rapidly query a data set and identify patients who meet certain criteria requires that the criteria be pre-specified, accurately captured, and represented similarly across all source data sets. Examples for AI applications towards finding new, precision medicines [Ref_6] :

- AI has been applied to extract and study millions of patient records with the goal of understanding how cancer spreads and reoccurs. This is an example of AI being able to pour through large amounts of genomic data in a quick manner, so doctors can draw conclusions.
- AI is currently being used to study scans of healthy brains and brains affected by Alzheimer's to learn and identify the telling systems of the disease.
- AI is also getting utilized for sweeping through large amounts of data, identifying variables and predicting avoidable hospitalizations in diabetes patients.
- AI has been utilized to identify patterns in large data sets of genetic information and medical records, looking for mutations and linkages to disease.

DISRUPTION IS PERSONAL

The focus here will be to discuss how disruptive technologies helping personalized medicines development, and how they hold potential to solve problems commonly found in traditional trials.

RECRUTIMENT CHALLENGE

The recruitment process is often the most time-consuming and expensive step of a trial. According to a 2016 study 18% of cancer trials that launched between 2000 and 2011 as part of the US National Cancer Institute's National Clinical Trials Network failed to find even half the number of patients they were seeking after three or more years of trying, or had closed entirely after signing up only a few volunteers. An estimated 20% of patients with cancer are eligible to participate in such trials, but fewer than 5% actually do [Ref_5]. Many are hoping that AI can make a difference. One branch of AI, called natural language processing (NLP), enables computers to analyze the written and spoken word. ML and in particular deep reinforcement learning empowers systems to automatically analyze EHR and clinical trial eligibility databases, find matches between specific patients and recruiting trials, and recommend these matches to doctors and patient for participating in a given clinical trial. Utilizing social media analytics is also a preferred method for finding and recommending trial participants. These can potentially enhance reach and efficiency of the trial recruitment, and expedite targeted medicine development [Ref_4].

HETEROGENEITY OF COHORT

AI-powered patient-matching algorithms could lead to more-diverse trial cohorts, by giving anyone in need a chance to participate — not just those who know the right doctor or who live near large health-care institutions. In real world situation, the assessment of suitability would use patient-specific diagnostic genome, proteome and metabolome-

wide profiling to determine whether biomarkers which the drug targets are sufficiently strong represented in the patient profile or not. NLP and computer vision algorithms can play a vital role, by two ways--- choosing patients who are more likely to have a measurable clinical endpoint, or 'prognostic enrichment', and identifying a population more capable of responding to a treatment, also termed as 'predictive enrichment' [Ref_3, Ref_4].

MORE EYES ON TRIAL: IMPROVEMENT OF MONITORING

Patient dropouts caused by a lack of adherence to trial protocols require additional recruiting efforts, which lead to trial delays and substantial additional costs. A linear increase of the non-adherence rate in a trial leads to an exponential increase in additional patients required to maintain the statistical power of the outcomes. Improved patient monitoring and coaching methods during ongoing trials can be used to minimize the adherence burden. It can also make endpoint detection more efficient, and thus reduce dropout and non-adherence rates. AI techniques, in combination with wearable technology, offer new approaches to develop power efficient, real-time, and personalized patient monitoring systems. Wearable sensors and video monitoring can be used to automatically and continuously collect patient data, thereby relieving the patient of this task. ML, and particularly Deep Learning (DL) models can be used to analyze data in real-time for detecting and logging events of relevance. AI also has an important role to play in image-based endpoint detection. ML technologies hold potential for rapid detection of diseases from medical images and can also reduce the cost associated with image-based studies. AI and ML methods may also be used to dynamically predict the risk of dropout for a specific patient, to detect the onset of patient behavior that suggest difficulty to adhere to the trial protocol. The use of deep reinforcement learning algorithms help simulating the optimal treatment dose at reduced toxicity to have desired treatment effect, and thereby it can reduce the risk of patient dropout and in turn can increase trial efficiency [Ref_4, Ref_8] .

COGNITIVE COMPUTING

Algorithms for analyzing, and continuously correlating, contextualizing, and filtering raw data in real-time directly at the point of sensing, will be necessary to extract actionable information. Deep learning (DL) models in combination with on-sensor data pre-processing and curation systems allow this task to be accomplished.

There is significant potential for the use of cognitive sensors for neurology drug trials, taking a personalization approach. The predominant type of data which most of these sensor types measure is time-series data. Although DL has traditionally focused on analyzing imagery data using deep convolutional neural networks, recent work has demonstrated that custom-designed neural network models are also uniquely suitable to analyze complex time-series streams [Ref_9] .To run DL algorithms continuously in real-time at the point of sensing, ultra-low-power consumption mobile processors are needed. Advances in developing both novel AI hardware and AI software techniques over the years have led to several versions of such AI-tailored mobile processing solutions now being available for real-life use.

Recently, first cognitive-sensing applications have emerged in the field of applied neuroscience for monitoring and interpreting brain activity, diagnostics, and predictive prevention in epilepsy and mental disorders, deep-brain stimulation, brain–machine interfacing, and bionics. There are the feasibility of using mobile AI for real time epileptic seizure detection. The same DL algorithm can be utilized across multiple patient cohorts, and automatically adapts to the individual disease patterns of each patient as they evolve and change over time. The demonstrated monitoring systems remain operational over extended periods without the need for any third-party input, and will thus become the personal seizure detector and predictor for each patient. Wearable devices and ML models also shown to automatically detect cognitive and emotional states and prediction, and to assess quality of sleep (among other parameters) in neurology trials [Ref_4].

The balanced amalgamation of AI, Internet of things (IoT), and healthcare can produce more medical-grade devices with advanced analytics capabilities for continuous real-time monitoring of patients and disease progression. These devices might make cognitive sensing an effective tool for improving the performance of personalized medicine trials. It is important to note that, data integrity and safety occupy a central role in the conception, implementation, and exploitation of digital disease diaries: patients, doctors, and regulatory bodies will rely on the integrity and safety of sensitive patient data and of analytical insights derived from it. The data security guidance should be HIPAA-compliant environment. In addition, advanced generations of AI-based monitoring and data-housing platforms will employ Blockchain technology for ensuring trusted and traceable multiparty communication and monitoring data.

CONCLUSION

Personalized medicine development can take advantage of a myriad of disruptive technologies to be utilized for developing treatments, practicing medicine, and delivering care. Currently, large amount of multi-omics data, imaging, medical devices and EHR data collected from large-scale cohorts and population studies have the potential to be implemented in personalized medicines discovery. Advanced machine learning techniques like deep learning and platforms for cognitive computing represents the future toolbox for data driven analysis of biomedical big data. However, infusing innovation that changes established processes is a difficult task and it should be approached and implemented with caution. Although AI has the potential to influence numerous steps of clinical trial design from preparation to execution, there are chances of failure as well. Need of the hour is , data scientists and medical scientists should jointly define achievable use cases where the application of well-understood AI tools to clinical trial design promises the greatest improvement of overall trial performance. Usable AI technology first needs to be tested alongside the existing technology which it aims to complement or replace, and the benefit must be demonstrated in an explainable, ethical and scalable way – to users as well as to regulatory bodies. This approach may ensure AI adoption into the clinical trial ecosystem, making trials faster and holding the potential to lowering failure rates and R&D costs. It may not be an exaggeration to say that we have lot of data and diverse technologies at hand, but suitable amalgamation of them is still at nascent stage, considering biomedical data. RWE is a stepping-stone or link for data to medicine, and integration of disruptive technologies with RWE will curve the future path of personalized, precision medicines and herald a new dawn in healthcare.

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11. Also publicly available information through various search engines, published reports etc.

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