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The Impact of AI, Real World Evidence, Precision Medicine and Mobile Health Technology on Streamlined Clinical Trials

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ABSTRACT

Today's therapies are developed to be more personalized, precise, and real-time data-driven than ever, yet the clinical trials in which they are tested deliver results based on the average response from a given trial. Further, new therapies are tested in clinical practice by physicians caring for patients that might never have been included in such trials. These patients are different from their experimental cohorts in myriad ways: they have different genetics, may suffer from additional diseases and likely have a history of taking different medications. This gap between clinical research and practice explains why promising new medicines often do not find uptake in clinical practice. To bridge this implementation gap, clinical trials will make increasing use of Real-World Data, mobile health technology and data that is specific to the individual patient. Indeed, having been digitized over the past decade, clinical trials are now bound to become more pragmatic, incorporating patient-specific data from IoT-enabled medical devices, digital health apps, and even digital biomarkers.

INTRODUCTION

We see three major themes in the way we are approaching health care and life sciences. The first one is that we are getting away from the disruption and starting to transform our health care and life sciences industries. There are still many challenges and hurdles on this journey, especially when it pertains to validation and readiness for implementation in clinical trials and daily patient care. The second theme pertains to being fit for the future from a regulatory perspective. Finally, we conclude with our third theme providing examples of advanced analytics/AI for clinical practice (clinical reality). ROC or AUC does not equal clinical effectiveness. Many of our partners and customers understand this as they have been using analytics for many years. The ability to use the right analytic tools in the right circumstances impacts clinical reality.

1.FROM DISRUPTION TO TRANSFORMATION

1.1 DIGITIAL TRANSFORMATION AND ARTIFICIAL INTELLIGENCE

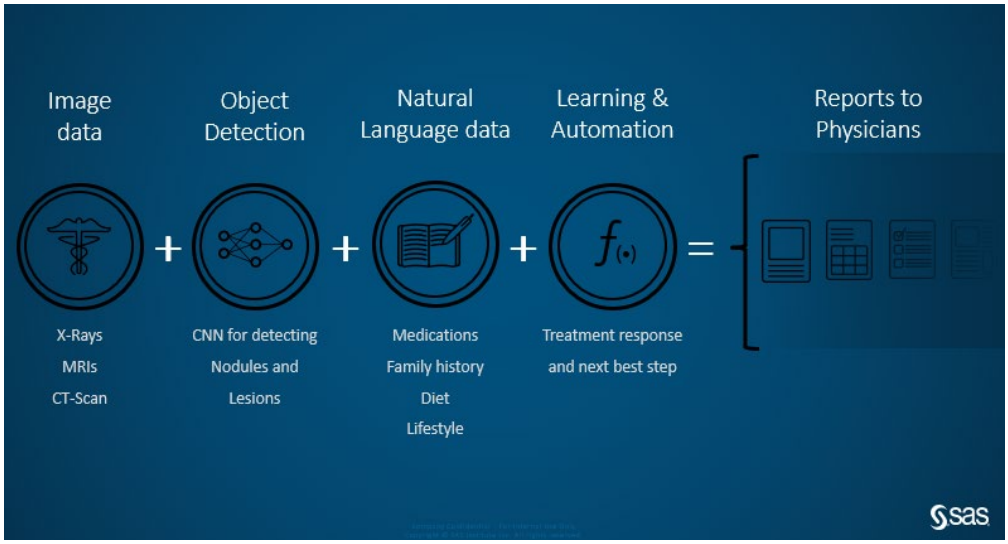
A mind-boggling amount of healthcare and life sciences data is generated annually, namely about a trillion gigabytes of data, according to latest estimates. Thanks to the emergence of advanced analytical approaches such as machine learning (ML) and deep learning (DL), it has only recently become possible to make sense of such massive data sets. This has been described in the book by Eric Topol ("Deep Medicine, How Artificial Intelligence can make healthcare human again") and in the Nature Medicine article ("Medicine in the digital age") that appeared at the start of this year (2019).

AI is what is driving a lot of the conversation today, as well as expectations. And rightfully so. Algorithms like deep learning as embedded in computer vision, can process and analyze data at a volume and complexity we humans simply never could. While there are applications where AI alone can drive positive results, there are many more applications and use cases where AI in combination with a broader set of analytics is what delivers bigger results. Over the years, SAS has developed a deep set of analytical capabilities, for any data and any usage.

Artificial intelligence (AI), and deep learning more precisely, among the leading technological tools beginning to be used in the interpretation of medical images and electronic health records.

EXAMPLE1: HUMAN LIMITATIONS IN TUMOR ASSESSMENTS

Colorectal cancer is the third-most common cancer worldwide, and it spreads to the liver in about half the patients. The best way to treat this type of cancer is to remove it. But some tumors are too large to be removed, and these patients must undergo systemic therapy, such as chemotherapy to shrink the tumors. After a period of treatment, tumors are manually evaluated using computerized tomography (CT) scans. At that time, medical professionals can see if a tumor shrunk or changed in appearance. How a tumor reacts to systemic therapy determines whether lifesaving surgery is possible or if a different chemotherapy regimen is necessary. This manual approach takes time and presents many challenges. Together with SAS, Amsterdam University Medical Center (AUMC) is transforming tumor evaluations with AI. It uses computer vision technology and deep learning models in SAS Visual Data Mining and Machine Learning to increase the speed and accuracy of chemotherapy response assessments. Data scientists also take advantage of the SAS Deep Learning With Python (DLPy) API to create deep learning models. Capabilities like automatic segmentation help doctors quickly identify changes in the shape and size of tumors and note their color.



EXAMPLE2: AI MAKING USE OF DATA GOVERNANCE: HOW TO MAKE PROCESS/PRODUCT INNOVATIONS

At PharmaSUG Tokyo 2018, Shionogi presented how they were generating semi-automatically SAS analysis programs using AI resulting in 20% business improvement.

System Outline (V1.0) - The necessary information for program creation is collected from existing planning documents. The training data is based on External Standard Metadata (CDISC) and Internal Clinical Trial Data from past studies. Programs are verified by manual efforts.

Governance Strategy – SAS® Viya® extends the SAS Platform to enable everyone – data scientists, business analysts, developers and executives alike – to collaborate and realize innovative results faster. It is an open analytics platform that's accessible from the interface or coding language of your choice (SAS, Python, Lua, R, etc.), giving you the freedom to experiment, act and achieve. By providing the perfect balance of choice and control, the SAS Platform enables you to orchestrate your analytics journey to ensure *optimal returns on your investments in data, talent and different analytic technology.*

System Outline (V2.0) – In the next phase Shionogi converted sentences and tables into jpg files (image data). It was confirmed that the analysis content can be correctly identified from the images of plan document. Using heat maps, it is possible to lead to the discovery of new knowledge by considering where the machine discriminated based on. Applying Convolutional Neural Network (CNN) resulted in an increase from 20% (V1.0) to 33% (V2.0) business improvement.

Finally, AI was used to semi-automatically generate QC results using QC Plan (word doc), Log Files (Execution Result of batch File), Excel / SAS and other deliverables.

1.2 INTERNET OF MEDICAL THINGS (IOMT) AND ITS ROLE IN ENABLING PATIENT-CENTRIC CLINICAL TRIALS

A lot of patient information remains buried in the form of unstructured text information, and it is estimated that about 50% of valuable clinical information for any patient is hidden in physicians' notes, images, voice recordings and other types of unstructured information. If the objective of precision medicine ("the right therapy for the right patient at the right time") is to be realized, more strategies and technology for unlocking data will be needed. Sensor/wearable technologies have the potential to transform our ability to monitor physiology not only in the clinical trial and outpatient settings, but also in the context of health and wellness. The use of wearable technologies in clinical trials can reduce the need for site visits (remote monitoring), as well as decrease the length of these visits for both clinicians and patients (QOL). Getting data from wearables earlier gives a better signal detection for what's really going on with these patients. Many site activities can be done remotely or automatically using technology. What cannot be replaced is the human element, specifically the relationship between the physician and the patient. To the extent that sites can focus on that and improve that aspect of their practices, technology will serve as an enabler.

EXAMPLE1: SENSOR BASED ANALYSIS OF MOVEMENT FOR QANTIFICATION OF PAIN, DISCOMFORT AND DISEQUILIBRIUM.

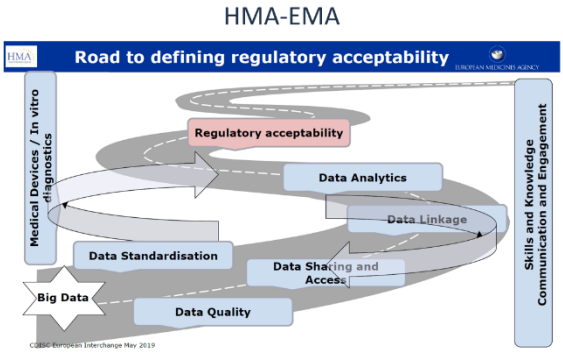
There is a large body of literature describing the application of sensing technology to study and understand many aspects of human motion. Many clinicians and researchers have reported on the use of sensors and imaging to compare movement in normal and pathological states and to quantify therapeutic effect. Such analyses are often complex and expensive. Rapid advances have been made in the development of smaller inexpensive, sensitive and capable sensors such as High Definition Web Cams and Multi-Axis Inertial Measurement Units. During the presentation we will describe the application of machine learning techniques to study clinically relevant movement and develop robust correlates between pathology, pain, discomfort and disequilibrium from streaming sensor data. Such analyses facilitate the discreet quantification of therapeutic effect of pharmacological and mechanical therapies and identification of real-time, autonomous, algorithm based Digital Mobility Outcomes. Further, such analyses are designed to facilitate their use in tele-medicine and remote monitoring applications.

SAS is also a full industry partner of ASSIST since 2015.The NSF Nanosystems Engineering Research Center (NERC) for Advanced Self-Powered Systems of Integrated Sensors and Technologies (ASSIST) develops and employs nano-enabled energy harvesting, energy storage, nanodevices, and sensors to create innovative, battery-free and body-powered wearable health monitoring systems. This center of excellence received funding from the National Science Foundation (NSF) in 2012 for five years of research, renewable out until 2022.

1.3 INCREASED USAGE OF REAL-WORLD EVIDENCE IN LIFE SCIENCES

The regulatory landscape is changing when it comes to Real world evidence. End of last year, US FDA released their Framework for Real World Evidence Program. Earlier this year, recommendations for a path towards understanding the acceptability of evidence derived from 'Big data' in support of the evaluation and supervision of medicines by regulators were published as part of a summary report of the Heads of Medicines Agencies (HMA) - EMA Joint Big Data task force.

This is good news as it shows that the consideration of real word data in Marketing Authorization Applications will become the norm in the upcoming years. As the RWE environment is becoming more regulated, it is clear that the approach to analysis of real-world data as well as the interpretation of real-world evidence needs to be done according to high standards and with scientific rigor. This is only possible with tools that provide complete data transparency, while allowing cutting-edge analytics and modern methods to be applied.



Dr. Alison Cave, EMA, Principal Scientific Administrator. Pharmacovigilance and Epidemiology Department. CDISC European Interchange - May 2019 (Amsterdam).

EXAMPLE1: PFIZER USES EHR DATA TO SUPPORT EXPANDED INDICATION FOR BREAST CANCER DRUG

In April 2019, US FDA approved a new indication for Pfizer's Ibrance (palbociclib) in combination with an aromatase inhibitor or fulvestrant to include men with certain types of metastatic breast cancer. The approval is based on RWD from electronic health records and post marketing reports of Ibrance in male patients sourced from three databases: IQVIA Insurance database, Flatiron Health Breast Cancer database and the Pfizer global safety database, according to Pfizer.

EXAMPLE2: LANDMARK SCHIZOPHRENIA DATA THAT BRINGS HOPE IN BREAKING THE CYCLE OF HOSPITALIZATION AND INCARCERATION RECEIVES FDA APPROVAL FOR INCLUSION IN INVEGA SUSTENNA (PALIPERIDONE PALMITATE) LABEL.

One other relevant public example is Invega Sustenna, the Johnson & Johnson long-acting antipsychotic. These data came from the Paliperidone Palmitate Research In Demonstrating Effectiveness (PRIDE) study. This was a pragmatic real-world trial, a randomized trial that used measures that are collected in clinical practice. It showed a six-month delay in relapse for those that got this long-acting injection compared to a basket of seven antipsychotic pills, and the FDA did approve adding to the product's label in 2018. See also relevant article "What's scary, and appealing, about real-world evidence" (March, 2019) for additional insights.

2.FROM REGULATION TO OPPORTUNITY

2.1 PERSONAL DATA PROTECTION

Understanding, and ensuring compliance with, data protection laws like the GDPR presents an ongoing challenge for the pharmaceutical industry, and one that is set to get more complex given this ever-changing landscape and new regulations coming down the track.

2.2 AI / ML REGULATION

There is a need for more evidence, risk appreciation and regulation as underlined by the Software as a Medical Device (SAMD) paper published by the FDA. The FDA is considering a total product lifecycle-based regulatory framework for these technologies that would allow for modifications to be made from real-world learning and adaptation, while still ensuring that the safety and effectiveness of the software as a medical device is maintained.

2.3 DATA SHARING / TRANSPARENCY

While better global regulatory alignment for clinical trials is needed, the benefits and collaboration opportunities will make a big difference in patient care and will help government bodies and academia push forward to support transparent data. Industry leaders, researchers and peers recently assembled in Heidelberg (June 2019) for the 6th Clinical Trial Data Transparency Forum to discuss how the life sciences industry will build off the success of the data sharing movement. They discussed ways to support growth, sustainability and evolution within the industry - and explored new horizons in the advancement of transparency.

2.4 ETHICAL RULES

It's clear that a combination of explainable AI - where you can see what input elements contributed to the decision- and risk management of the remaining unexplained parts, just like we do with unexplained clinical treatments will be needed. AI will need to be treated like any therapy: based on evidence, not on complete understanding of causality.

3.FROM ANALYTICS TO CLINICAL PRACTICE (REALITY)

3.1 AI PROVIDES AN OVERVIEW OF HOSPITAL ACQUIRED INFECTIONS

In the ***Region of Southern Denmark***, AI technology and deep insights play an important role in patient safety. Combining many years of clinical experience with modern technology from SAS®, ***Lillebælt hospital*** can now monitor and predict the risk of hospital-acquired infections in patients.

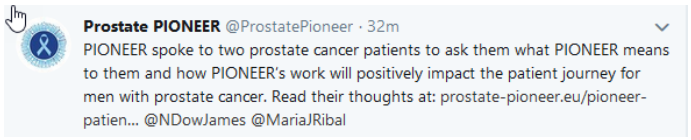
3.2 COMMUNITY BASED GENETICS STUDY USES SAS® MACHINE LEARNING AND AI TO IMPROVE POPULATION HEALTH IN NEVADA

The ***Healthy Nevada Project***, developed by Renown Institute for Health Innovation (Renown IHI), is one of the first community-based population health studies in the United States. By combining genetic data, environmental data and individual health information, researchers and physicians are gaining new insight into population health, enabling personalized health care while improving the health and well-being of entire communities in Nevada. The Project comes at a time when the state continues to struggle with poor health outcomes and excess costs. Nevada ranks near the bottom of overall health rankings in the U.S. and suffers from high mortality rates for chronic conditions like heart disease, cancer and chronic respiratory disease. Data scientists apply machine learning and artificial intelligence capabilities to the DNA results generated by personal genomics partner, Helix.

3.3 IMI PIONEER – THE EUROPEAN NETWORK OF EXCELLENCE FOR BIG DATA IN PROSTATE CANCER

The IMI PIONEER is one of the "big data for better outcomes" (BD4BO) of the public-private research consortium funded by industry (including SAS) and the European Commission.

PIONEER harness the power of big data (and AI/ML) to transform the field of prostate cancer research from the perspective of all relevant stakeholders including clinicians, pharmaceutical companies, payers and most importantly patients. Together we can ***ensure each individual patient receives the right treatment for them at the right time***.



Patient representatives, Erik Briers and Ken Mastris, reflect on the relevance of PIONEER for prostate cancer patients. https://prostate-pioneer.eu/pioneer-patient-testimonials/

4.CONCLUSION

We see artificial intelligence and advanced analytics being used in 3 different ways. The first one is **OPERATIONAL EFFICIENCY** in Clinical Development and Healthcare. The 2nd focus is **CLINICAL SCIENCE AND POPULATION HEALTH**. Enabling faster access to Care and support for physicians (e.g. Deep learning for computer vision & biological signals, IoMT -wearables/sensors/devices, modern Clinical Trial Designs, Patient Engagement - chatbots, RWE - cohort analysis, matching patients, enrolment simulation etc.). Finally, to **SUPPORT WITH REGULATION & COMPLIANCE** such as Auto-Coding, Regulatory Intelligence, Pharmacovigilance (Literature Follow Up, Social Media Analysis) with Natural Language Processing.

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