Real World Evidence Stream

Leveraging Real World Data to Provide Deeper Insight to Treatment Effects in Clinical Trials

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ABSTRACT

Measuring true effects of a treatment is foundational to assessing a drug product's efficacy. In clinical trials, researcher rely on a biomarker explicitly measured at baseline to determine any change throughout trial. This measurement is a point estimate at best; it is not confirmed with another reading or measurement. Furthermore, it is not known if this is a patient's normal value or if it is an abnormal value for that patient. Clinical trials do not currently account for intrapersonal variability in biomarker measurements. Thus, efficacy is prone to the impact of unmeasured variability and introduction of error and potential bias. This discussion aims to explore options and methods that could mitigate this conundrum. Leveraging machine learning methods to assess and predict intra-patient variability on a given measurement using a patient's longitudinal Electronic Medical Record (EMR) allows researchers to evaluate a more accurate efficacy of a drug product. Moreover, researchers could further stratify likelihood of efficacy of a treatment compared to a real baseline adjusted for within subject variability allowing for more personalized medicine. Study designs could accommodate and account for this more precise measurement of a primary or secondary variable with more sophisticated methods and technology. The natural and ethical evolution of efficacy assessment warrants researchers to capitalize and leverage novel methods that are no longer a theory but available to put into practice.

INTRODUCTION (HEADER 1)

Measuring true effects of a treatment is foundational to assessing a drug product's efficacy. In clinical trials, researchers rely on a biomarker explicitly measured at baseline to determine any change throughout trial. This measurement is a point estimate at best; it is not confirmed with another reading or measurement. Furthermore, it is not known if this is a patient's normal value or if it is an abnormal value for that patient. Clinical trials do not currently account for intrapersonal variability in biomarker measurements. Thus, efficacy is prone to the impact of unmeasured variability and introduction of error and potential bias. This discussion aims to explore options and methods that could mitigate this conundrum. For example, Tacrolimus, a calcineurin inhibitor, is an immunosuppressant used in post-transplantation maintenance therapy. The drug has a narrow therapeutic range and requires periodic therapeutic drug monitoring. Although many studies have reported the effects of intra-patient variability of tacrolimus on survival, rejection, and complications in renal transplant recipients, very few studies have reported these effects in liver transplant recipients. In another study by Polidori et al (Polidori 2018), the results show that intra-patient variation accounts for about 15.8% of the total variation, inter-patient variation accounts for about 84.2% of the total variation, and the coefficient of variation (CV) in intra-patient variation is 15.8%. In this study, the variability associated with intra-patient variation demonstrates that there may be clinically significant impacts related it that may need to be addressed or at least considered in reviewing efficacy.

These considerations are even more pertinent when considering personalized precision medicine as proposed in the work of Park et al in 2021. Identifying and addressing pronounced differences across and within individuals is crucial when considering the impact of each patient's uniqueness on their treatment options and efficacy. Factoring in intra-patient variability allows physicians and

researchers to identify natural clusters and subtypes of patients to adequately treat them and optimize the best possible outcome.

When EHRs are adapted to FHIR standards, the data are structured and semantically interoperable, making it easier to aggregate and analyze. FHIR adaptor technology yields opportunities for researchers across the healthcare and life sciences continuum to more readily access and analyze RWD, especially data sourced from EMRs. With the volumes of data available in these formats, Artificial Intelligence and machine learning systems are becoming more prevalent in clinical research, from running predictive models to performing image analytics to aid in diagnoses.

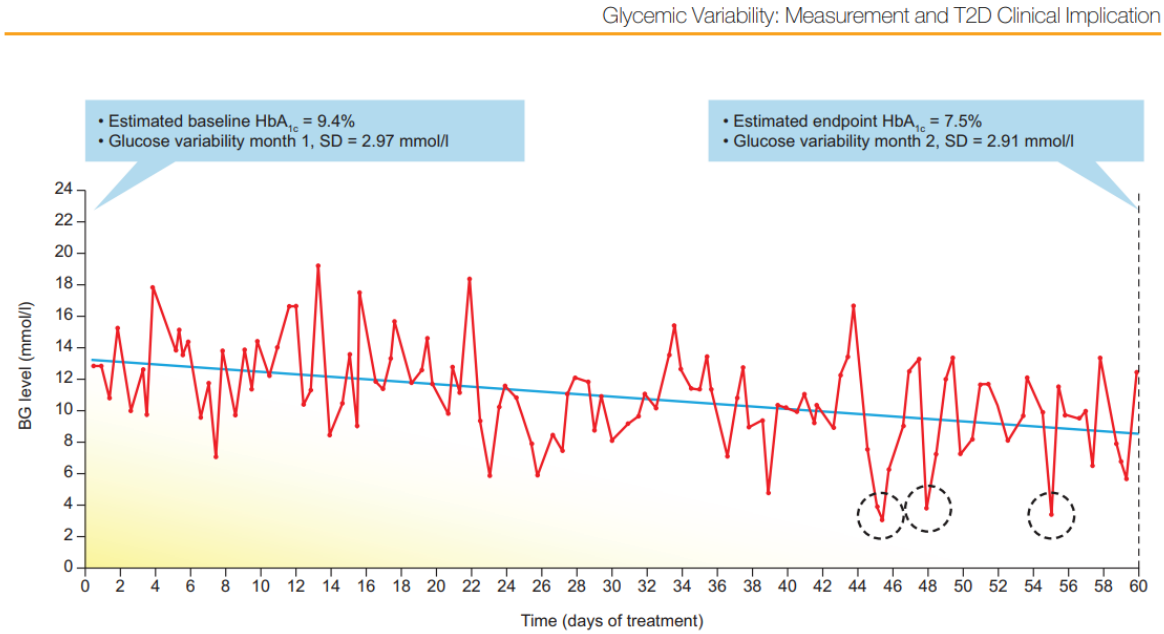


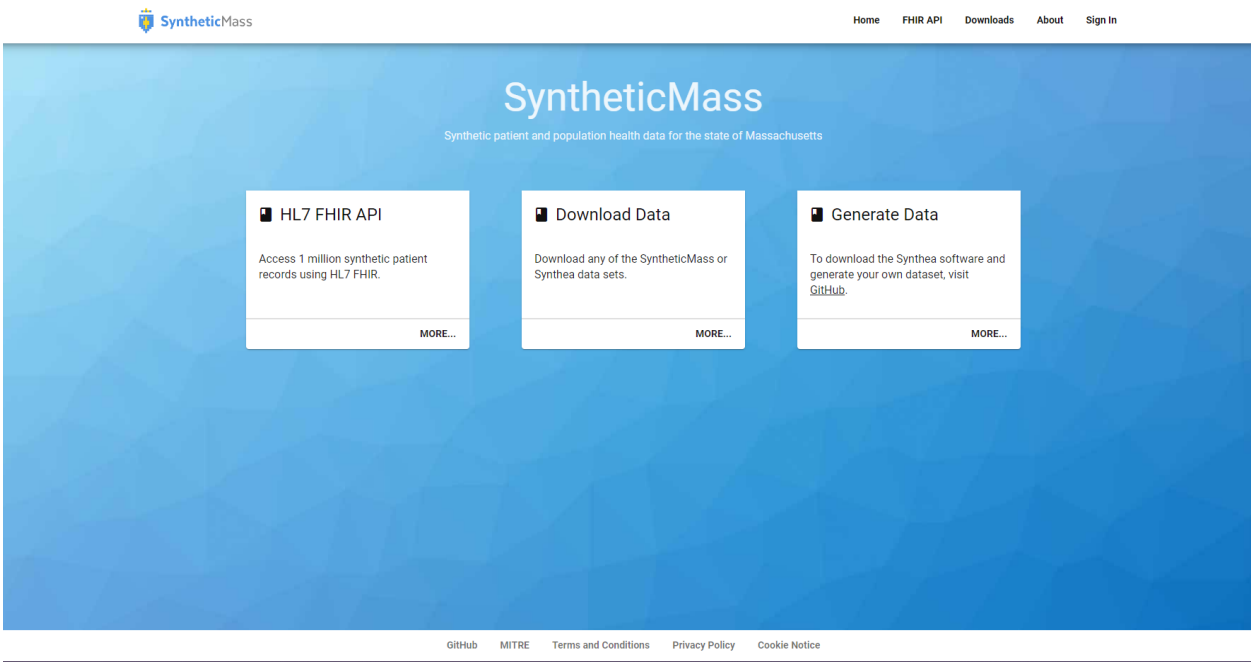
FIGURE 1. Risk of hypoglycemia and improved glycemic control. Self-monitored blood levels of glucose recorded over 60 days. A downward trend in blood levels of glucose is evident; levels of HbA_{1c} (estimated by the use of a linear formula) decreased from 9.4% at baseline to 7.5% by the end of the observation period. However, glucose variability remained relatively unchanged from the first to the second month of observation, which resulted in 3 hypoglycemic episodes (<3.9 mmol/L) registered by self-monitoring blood glucose at days 45, 48 and 55 (dotted circles). Reproduced with permission from Springer Nature: Nature Reviews Endocrinology, Metrics for glycaemic control—from HbA1c to continuous glucose monitoring, Kovatchev, 2017.[3] Abbreviations: HbA_{1c}, hemoglobin A_{1c}; SD, standard deviation.

Guillermo E. Umpierrez, Boris P. Kovatchev, Glycemic Variability: How to Measure and Its Clinical Implication for Type 2 Diabetes, Am J of the Med Sci, Volume 356, Issue 6, 2018, 518-527, ISSN 0002-9629, https://doi.org/10.1016/j.amjms.2018.09.010.

METHODS

Synthetic patient EMR data was generated using SytheticMass to mimic in FHIR format using opensource and SAS® code. The data was later ingested into an advanced analytics platform that supports multilingual programming including R, Python and SAS as well as a graphical user interface. Data were directly connected to using the FHIR adaptor on the analytics platform.

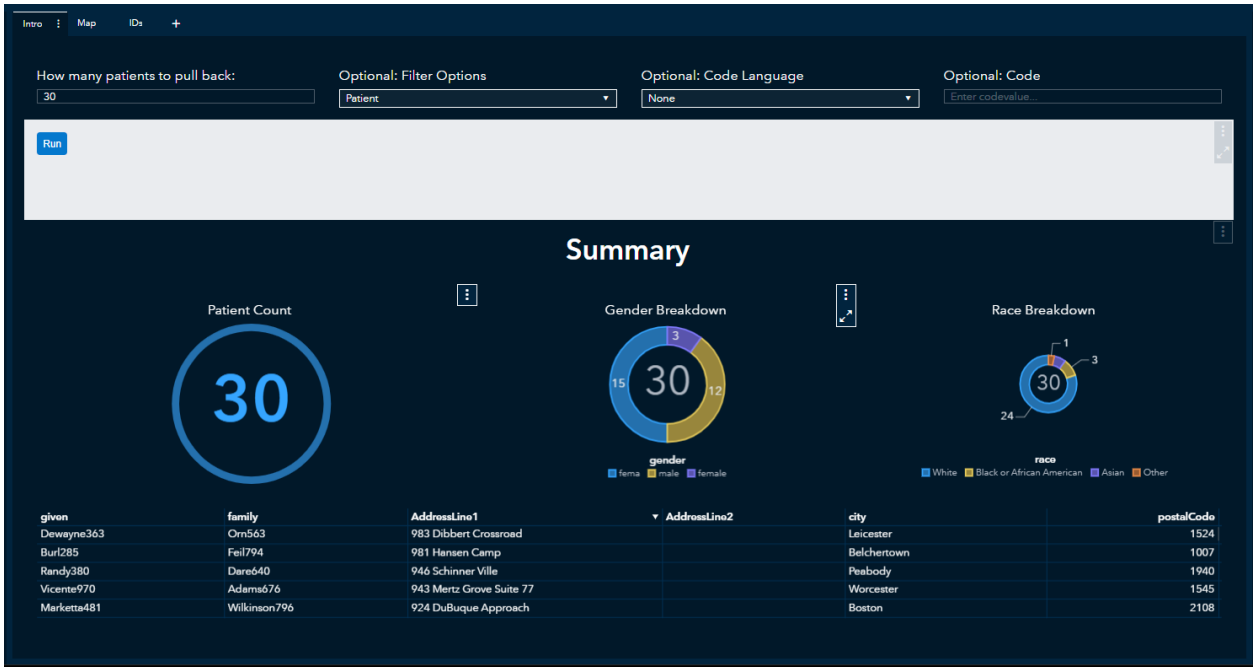
Patient information was then visually analyzed to assess diversity, equity and inclusive representation of the study population. Geographic distribution of patients was assessed and differences in demographic distribution were noted. These data were analyzed using more advanced predictive and machine learning methods.

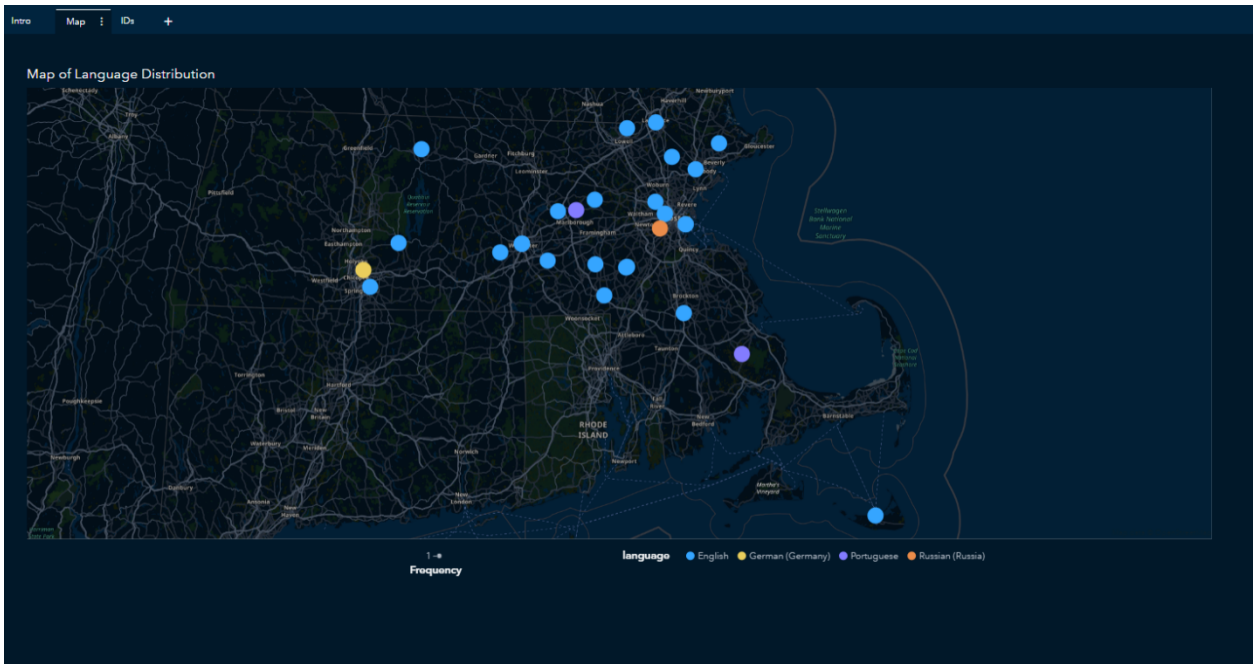


IMPORTANCE OF A HIGH COMPUTING PLATFORM

A high computing platform is essential for running complex analytics and RWD analysis because it provides the computational power, memory capacity, scalability, and reliability required to process large datasets, perform advanced calculations, and derive valuable insights efficiently and effectively.

SAS Health offers an extraordinary opportunity to advance patient care and treatment through improved efficiencies in data and analytics frameworks, which ultimately will allow health care payers and providers to deliver better outcomes, more quickly.





given	family	Medical Record Number	Driver's License	Social Security Number	Passport Number
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Al123	Daugherty69	af324ccb-9837-45cc-b39f-2f77f99429eb	S99980980	999-93-2747	X70569062X
Allegra202	O'Connell601	4fcc744e-7191-4f81-8717-b910837f5ee2		999-94-3248	
Angla303	Homenick806	643d00f0-c49a-43df-839b-b7e8d4cf0fd8		999-14-5453	
Astrid395	Koch169	15cd4083-8a2c-4a0c-be30-ccbf860ce8b2	S99977603	999-76-5212	X23669981X
Burl285	Feil794	b99333dd-dc81-43ab-8aee-a3147a0e6b74	S99911736	999-11-9181	X87664340X
Carmelo33	Kirlin939	959b05e1-f5c7-4dbd-8e04-bde111be0d21		999-50-2988	
Cruz300	Wyman904	f87ebd0e-359d-4d78-a58e-bb914dddecee	S99988755	999-46-3430	X8435178BX
Danny396	Mraz590	632b48b2-06d5-44e5-b518-c5eca0fe4765	S99927572	999-86-8119	X22332887X
Daren950	Spencer878	60829189-4a97-47b1-9b63-74bb5a2f9ff4	S99936630	999-64-3262	X2149378X
Dewayne363	Orn563	b69db372-a049-4af5-ac3f-35c11a455b8a		999-75-9587	
Dominque770	Schumm995	ac0d224d-beb6-4f00-aae1-77492372430e	S99963375	999-33-2191	X2074231X
Gregg522	Hettinger594	a238ebf2-392b-44be-9a17-da07a15220e2	S99942098	999-99-7515	X19416767X
Izetta651	Hintz995	f39d0979-c774-4109-bcca-8fd54d37577c	S99914066	999-95-5645	X80347960X

CONCLUSION

In an age where we are witnessing an explosion of data volumes and formats, bigger compute engines and best-in-class emerging analytical methods, it is unethical for researchers and drug manufacturers to continue developing medicines the same way we have been for the last 30 years. The opportunities presenting themselves with novel sources of data, compute power and innovative analytical methods lend to more accurate and diverse trials, real-time insights, more precise personalized medicines and shorter time to market.

Instead of taking simple snapshots in time, we are now able to analyze and consider the whole physiological pattern of an individual patient throughout a clinical trial. Medicines that target disease states with narrow treatment windows or subtypes of patients will especially benefit from

the novel data sources, powerful compute and emerging complex advanced analytics to generate robust insights from intricately linked federated data.

Leveraging machine learning methods to assess and predict intra-patient variability on a given measurement using a patient's longitudinal Electronic Medical Record (EMR) allows researchers to evaluate a more accurate efficacy of a drug product. Moreover, researchers could further stratify likelihood of efficacy of a treatment compared to a real baseline adjusted for within subject variability allowing for more personalized medicine. Study designs could accommodate and account for this more precise measurement of a primary or secondary variable with more sophisticated methods and technology. The natural and ethical evolution of efficacy assessment warrants researchers to capitalize and leverage novel methods that are no longer a theory but available to put into practice.

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