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

Sherrine Eid, MPH, Global Head, Epidemiology, RWE, and Observational Research
Soundarya Palanisamy, Sr Industry Advisor, Health & Life Sciences Practice

What is Intra-Patient Variability

- The fluctuations in biomarker measurements over time.
- Fluctuations typically occur without clear cause.
- High Intra-Patient Variability is associated with poor long-term outcome.

Today

- Clinical Trials rely on point estimates throughout the trial.
  - Usually compare a **BASELINE** estimate to a **FINAL** estimate
- At best, a clinical trial could have up to 60 measurements of a particular biomarker

- Problem
  - Intra-Patient Variability is not captured
  - Is the measured baseline value the normal value or an abnormal reading for any given subject…now what about for 1,000?
  - How can researchers truly determine efficacy of a product when Intra-Patient Variability was NOT accounted for?

Contributing Factors

- Data limitations
- Technology limitations
- Methodology limitations

Why Now?

- New (acceptable) sources of data
- New technology
- New methods

Who Cares?

Transplant Recipients

Received: 23 March 2021 | Accepted: 6 April 2021

DOI: 10.1111/bcp.14865

COMMENTARY

BJCP BRITISH PHARMACOLOGICAL SOCIETY

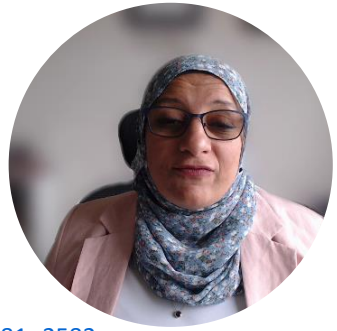
A new method to calculate intra-patient variability in tacrolimus concentrations

Teun van Gelder

Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands

Correspondence
Teun van Gelder, Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA, Leiden, The Netherlands.
Email: t.van_gelder1@lumc.nl

In this issue of the journal, Yin et al. publish their study on a new method to calculate intra-patient variability (IPV) in tacrolimus concentrations in kidney transplant patients.[1] IPV reflects the fluctuations in tacrolimus concentrations over time, in patients on maintenance treatment, treated with a stable dose. Clinicians taking care of 1343 kidney transplant patients was divided into two groups, with either a high TVS (>0.30) or low TVS (<0.30). The threshold was based on a ROC analysis and divided the population into two groups of almost equal size (655 patients in the low TVS group and 688 in the high TVS group). In a multivariate analysis, TVS was an independent



van Gelder, T. A new method to calculate intra-patient variability in tacrolimus concentrations. Br J Clin Pharmacol. 2022; 88(6): 2581- 2582. doi:10.1111/bcp.14865

sas

…and more

- **Patients with Breast Cancer Lymph Node Metastases**
  - Diest, P., Fleege, J., Matze-Cok, E. and Baak, J. (1992), Intra-patient variation between breast cancer axillary lymph node metastases using quantifiable features. Histopathology, 21: 257-262. https://doi.org/10.1111/j.1365-2559.1992.tb00384.x
- **Patients with Breakthrough Cancer Pain**
  - Intra-and inter-patient variability of baseline pain intensity scores during breakthrough pain in cancer. Allen W, Burton, Marilene Filbet, Ravi Tayi, Michael Sidney Perelman, and Alastair D. Knight. Journal of Clinical Oncology 2012 30:15_suppl, e19578-e19578
- **Patients with Diabetes**
  - F. Iacono, L. Magni and C. Toffanin, "Personalized LSTM models for glucose prediction in Type 1 diabetes subjects," 2022 30th Mediterranean Conference on Control and Automation (MED), 2022, pp. 324-329, doi: 10.1109/MED54222.2022.9837153.
- **Patients with Parkinson's Disease**
  - Wu G, Baraldo M, Furlanut M. Inter-patient and intra-patient variations in the baseline tapping test in patients Parkinson's disease. Acta Neurol Belg. 1999 Sep;99(3):182-4. PMID: 10544726.
- **Patients with COPD**
  - Sapey E, Bayley D, Ahmad A, et alInter-relationships between inflammatory markers in patients with stable bronchitis: intra-patient and inter-patient variabilityThorax 2008;63:493-499.

The Concept

Interpatient Variability

Intra-patient Variability

Methods

Previous

- ANCOVA
- Chi Square
- Mann-Whitney U
- Linear Regression

"Novel"

- Dynamic structural equation modeling
- Deep learning (image analytics)
- Co-efficient of Variation
- Edge computing
- Machine Learning (ML)
- Artificial Intelligence (AI)
- Deep Learning (DL)

Example: Glycemic Variability

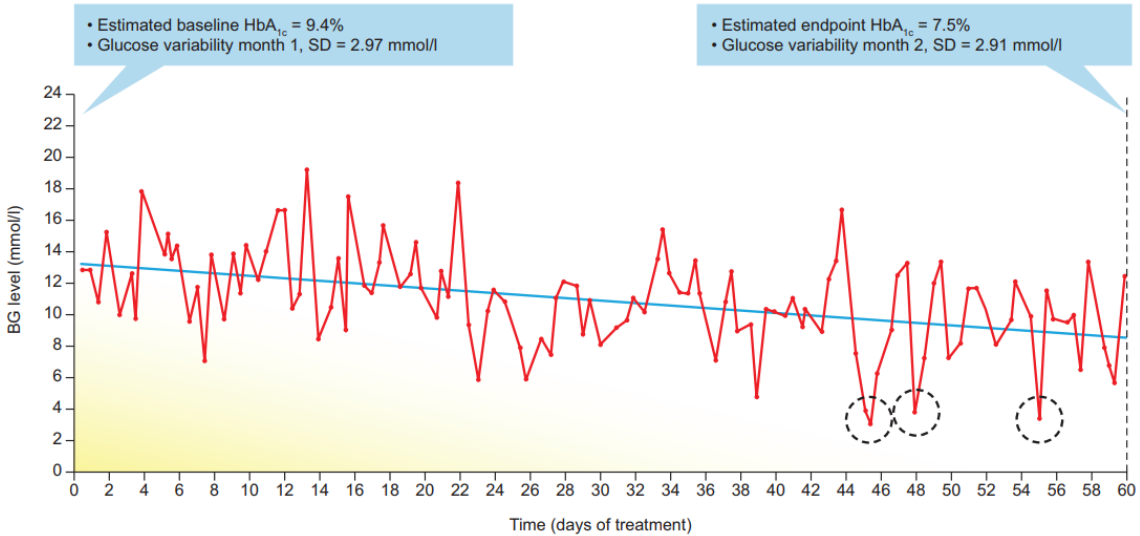


FIGURE 1. Risk of hypoglycemia and improved glycemic control. Self-monitored blood levels of glucose recorded over 60 days. A downward trend in blood levels of glucose is evident; levels of HbA_{1c} (estimated by the use of a linear formula) decreased from 9.4% at baseline to 7.5% by the end of the observation 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.

Glycemic Variability

Glycemic Variability: Measurement and T2D Clinical Implication

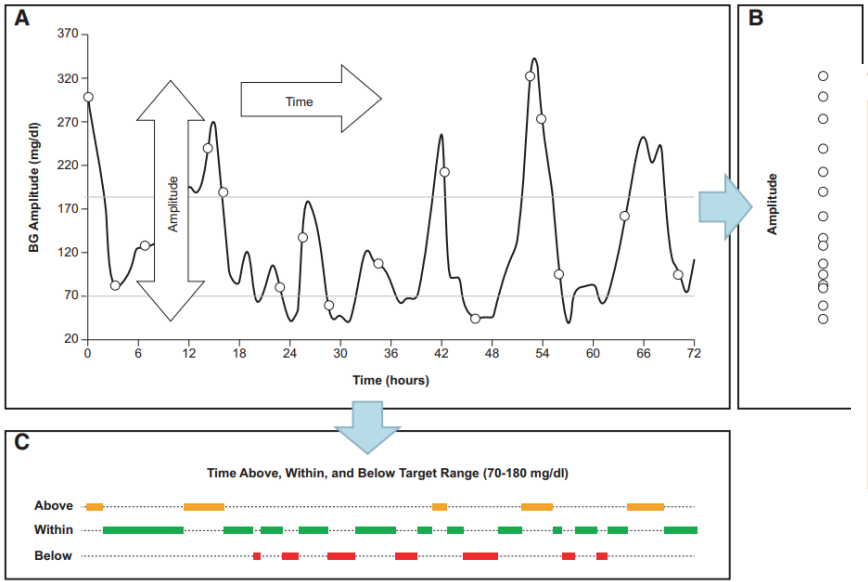


FIGURE 2. Principal components of GV. Glucose fluctuations are a process in time that has 2 dimensions—amplitude and time (A). Projected along its amplitude axis, this process is measured by metrics such as SD or MAGE (B). Projected along its time axis, this process is assessed by temporal characteristics, such as time within target range and time spent in hypoglycemia or hyperglycemia (C). Reproduced with permission from Kovatchev et al.[37] Glucose variability: timing, risk analysis and relationship to hypoglycemia in diabetes, American Diabetes Association, 2016. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association. Abbreviations: BG, blood glucose; MAGE, mean amplitude of glycemic excursions; SD, standard deviation.

TABLE 1. Metrics used to describe GV parameters.

Metric	Description
***Amplitude* of GV (temporal resolution range: hours to days)**	
MAGE	Diabetes-specific metric of the amplitude of glucose excursions. Mean of glycemic excursions from nadir to peak blood glucose level and vice versa that are > 1 SD of blood glucose mean (it takes into account glycemic peaks and nadirs occurring daily, but does not account for the total number of fluctuations; it depends on sampling frequency; ambiguity as to where peaks and nadirs begin and end)[38]
SD	Variation around the mean blood glucose (intra-day or inter-day)[2]
CV = SD/mean	Magnitude of variability relative to mean blood glucose[18,39]
LBGI	Measure of frequency and magnitude of hypoglycemia (amplifies hypoglycemic excursions without accounting for hyperglycemia)[13]
HBGI	Measure of frequency and magnitude of hyperglycemia (amplifies hyperglycemic excursions without accounting for hypoglycemia)[40]
***Timing* of GV (based on CGM; temporal resolution range: minutes to hours)**	
Time within, above or below target range	Quantitative measure of time spent in an individual's target glucose range, time spent below this range, and time spent above this range. All values are needed to provide an assessment of overall glycemic control[18]

Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation; GV, glycemic variability; HBGI, high blood glucose index; LBGI, low blood glucose index; MAGE, mean amplitude of glycemic excursions; 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

- Ketone bodies were modelled using a random effects model
- Intra- and inter-subject variability were characterized using a population intraclass correlation coefficient.
- Associations between changes in serum ketone bodies and changes in other measurements were assessed using a stepwise regression model.
- Manual process

Received: 18 October 2017 | Revised: 2 January 2018 | Accepted: 11 January 2018
DOI: 10.1111/dom.13224

WILEY

BRIEF REPORT

Intra- and inter-subject variability for increases in serum ketone bodies in patients with type 2 diabetes treated with the sodium glucose co-transporter 2 inhibitor canagliflozin

David Polidori PhD[1] | Hiroaki Iijima PhD[2] | Maki Goda BSc (Agr.)[2] | Nobuko Maruyama BPharm[2] | Nobuya Inagaki MD, PhD[3] | Peter A. Crawford MD, PhD[4]

[1]Janssen Research & Development, LLC, San Diego, California
[2]Ikuyaku. Integrated Value Development Division, Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan
[3]Department of Diabetes, Endocrinology and Nutrition, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[4]Departments of Medicine, and Biochemistry, Molecular Biology, and Biophysics, University of Minnesota, Minneapolis, Minnesota

Correspondence
David Polidori, PhD, Janssen Research & Development, LLC, 3210 Merryfield Row, San Diego, California 92121.

Sodium glucose co-transporter 2 (SGLT2) inhibitors have been associated with increased serum ketone body levels in patients with type 2 diabetes mellitus (T2DM). In the present analysis we evaluated serum ketone body levels and variability in 1278 Japanese patients with T2DM treated with canagliflozin 100 or 200 mg. Similar mean increases in ketone body concentrations of ~2-fold were seen with both canagliflozin doses. The median (inter-quartile range) percent change from baseline was 62% (0;180) for acetoacetate and 78% (2;236) for β-hydroxybutyrate. Approximately two-thirds of the variability in each ketone measure was attributed to intra-subject variability. Intra-subject variability was higher for serum ketones than other metabolites. Patients in the lowest response tertile exhibited no increase in ketones. Those in the highest response tertile tended to be male and have higher fasting plasma glucose levels, lower insulin levels, and longer T2DM duration at baseline. Moreover, changes in serum ketones were not fully explained by changes in

Polidori, D, Iijima, H, Goda, M, Maruyama, N, Inagaki, N, Crawford, PA. Intra- and inter-subject variability for increases in serum ketone bodies in patients with type 2 diabetes treated with the sodium glucose co-transporter 2 inhibitor canagliflozin. *Diabetes Obes Metab.* 2018; 20: 1321– 1326. https://doi.org/10.1111/dom.13224

Imagine

We could connect to the whole person in real time

- Leverage connections to Electronic Medical Records and devices
- Leverage cloud storage repository and computing
- Extract measures
- Analyze variability and patterns
- Decide
  - Alert Care Team
  - Flag data point

Today

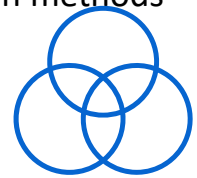
Data and Architecture

- Real World Data
  - EHR, Devices, and IoT, etc.
  - Interoperability (SMART, FHIR, API, etc.)
  - Digital endpoints (SMART watches, phones, sensors, etc.)
  - Electronic Patient Reported Outcomes (ePRO) and Electronic Data Capture (EDC) integration
  - Internet of Medical Things (IoMT)

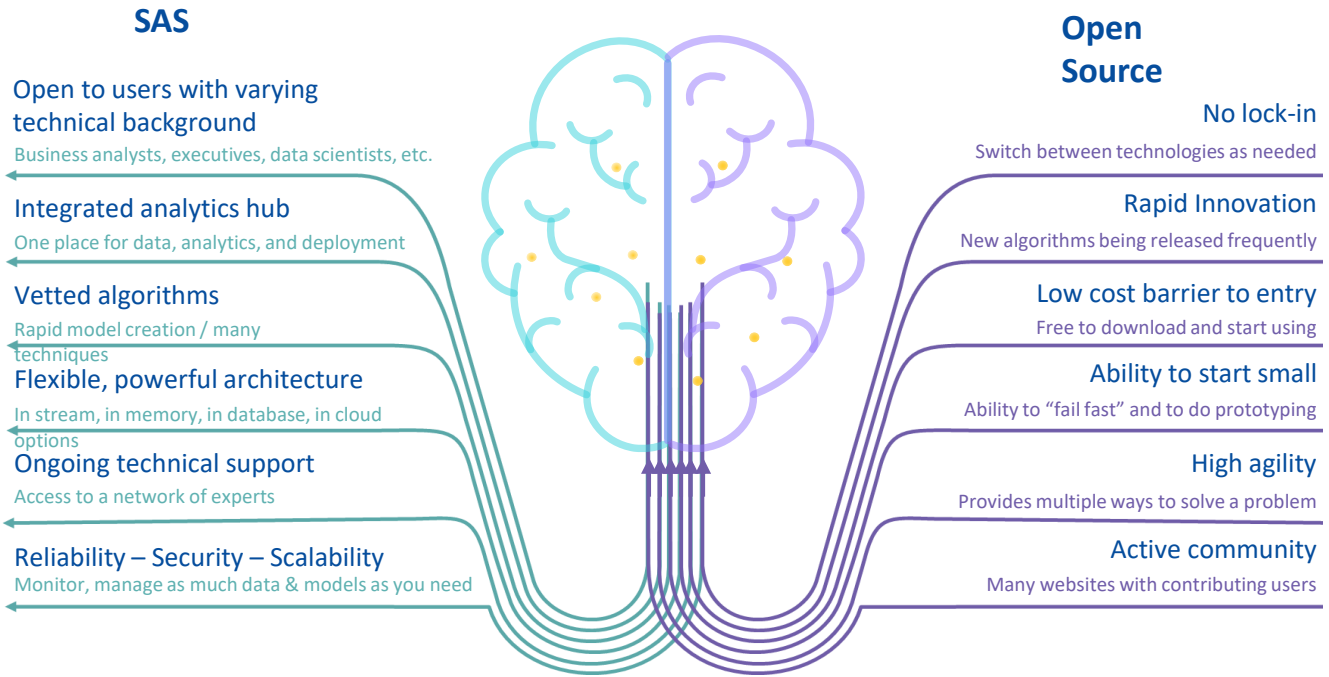
- Scalable and Flexible Cloud computing
  - In-memory distributed processing
  - High compute engines
  - Massive Parallel Processing
  - Cloud-based Data Management
  - Expanding ecosystems

Advanced Analytics

- Advanced analytics
  - Machine Learning
  - Artificial Intelligence
  - Automatically Inferred Clusters for bootstrapping personalization of supervised detection methods
  - Supervised and unsupervised ML to detect context and infer proximal outcomes
  - Improved digital extraction and computational phenotyping and interpretability
  - Deep Learning
  - Edge Computing
  - Event Stream Processing

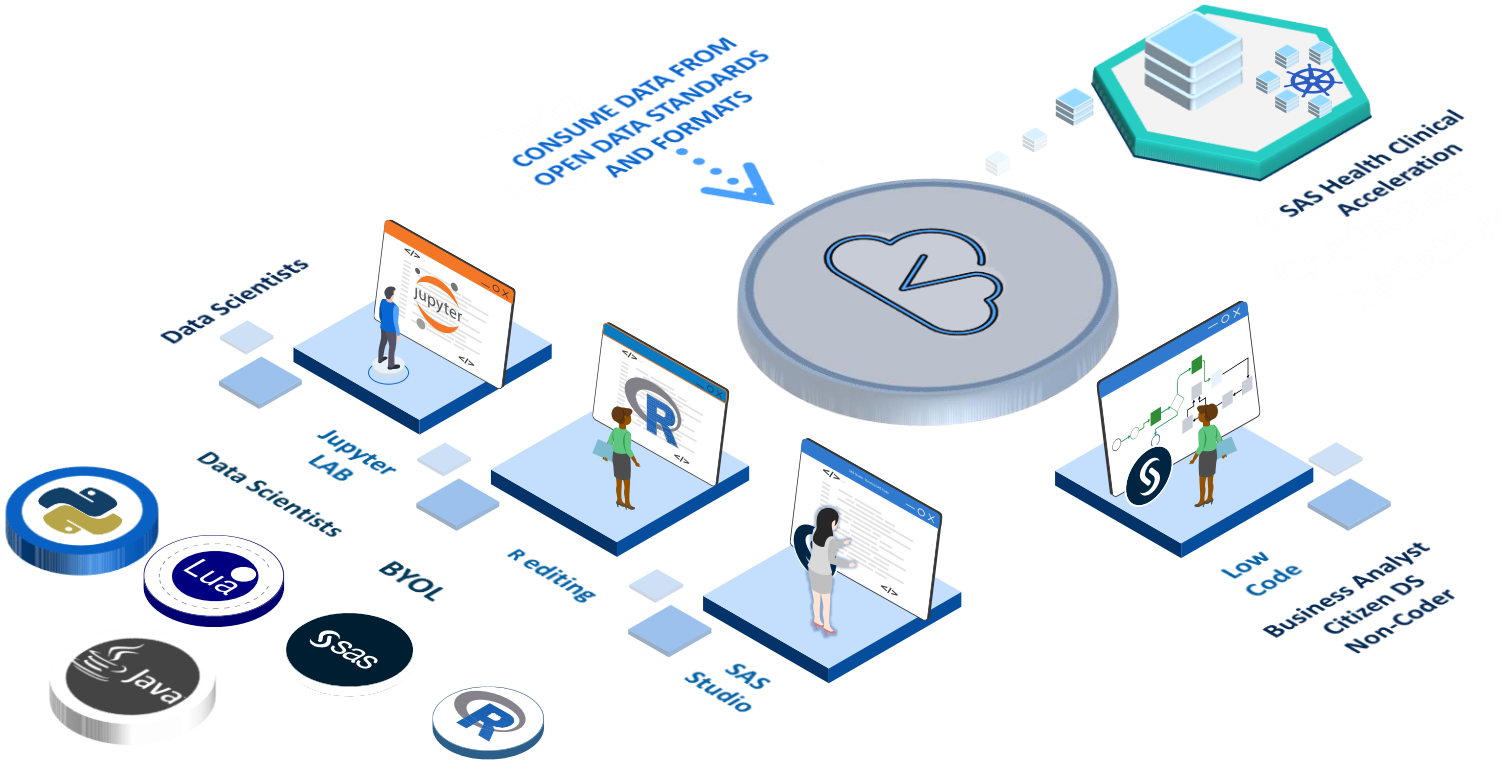


Benefits of SAS and Open Source



An integration of the two technologies, SAS and open source, unlocks a whole spectrum of analytics to different user backgrounds, stimulating the democratization of analytics.

Working with the language of your choice – interoperability is key



Digital Transformation

Natural and ethical evolution

- Trial Design
  - Micro-randomization
  - Multi-modal patient engagement
  - Trial optimization
  - Address disparities
  - Decentralized/Individualized trials

Current Application -Methods

- Leveraged Synthea data- SyntheticMass
- Connected to data using API connections
- Leveraged FHIR adaptors across sources
- Queried patient records directly through API connection
- Evaluated validity criteria and pulled final patient cohort
- Visually analyzed geographic distribution of demographic characteristics and all SDOH variables
- Can now assess all patient level data and calculate intra-patient and interpatient variability, identify level of DEI achieved, and even apply to External/Synthetic Control Arms

SyntheticMass

Synthetic patient and population health data for the state of Massachusetts

HL7 FHIR API

Access 1 million synthetic patient records using HL7 FHIR.

MORE...

Download Data

Download any of the SyntheticMass or Synthea data sets.

MORE...

Generate Data

To download the Synthea software and generate your own dataset, visit GitHub.

MORE...

Intro | Map | IDs | +

How many patients to pull back: 30

Optional: Filter Options: Patient

Optional: Code Language: None

Optional: Code: Enter codevalue...

Run

Summary

Patient Count

Gender Breakdown

gender

fema male female

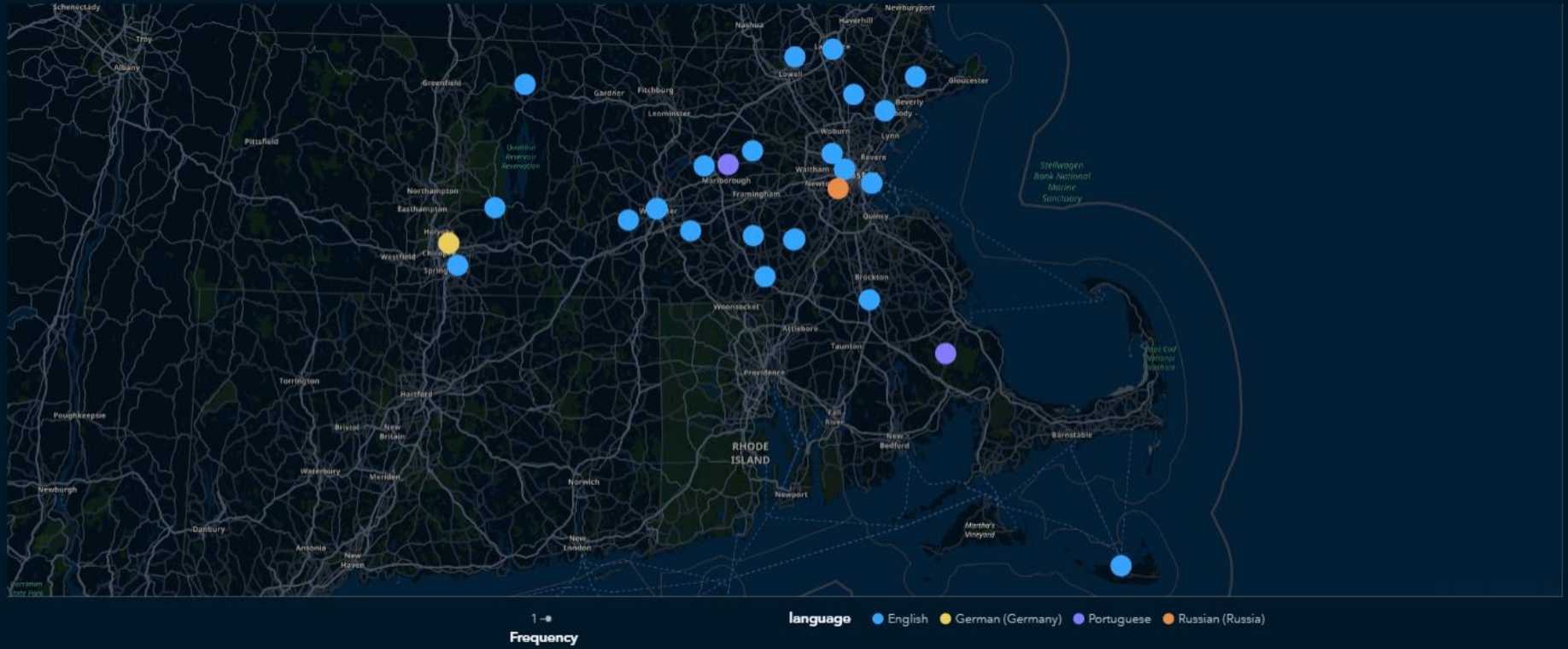
Race Breakdown

race

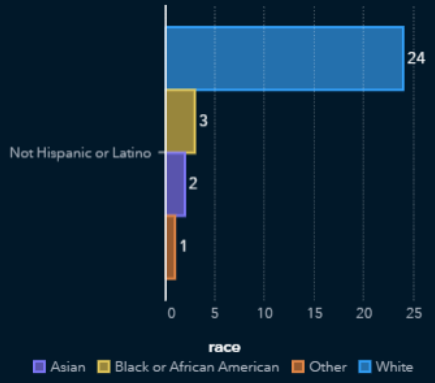
White Black or African American Asian Other

given	family	AddressLine1	AddressLine2	city	postalCode
Dewayne363	Orn563	983 Dibbert Crossroad		Leicester	1524
Burl285	Feil794	981 Hansen Camp		Belchertown	1007
Randy380	Dare640	946 Schinner Ville		Peabody	1940
Vicente970	Adams676	943 Mertz Grove Suite 77		Worcester	1545
Marketta481	Wilkinson796	924 DuBuque Approach		Boston	2108

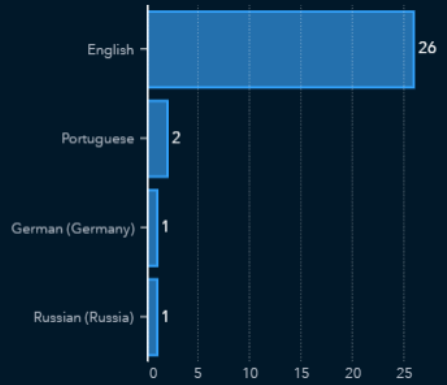
Map of Language Distribution



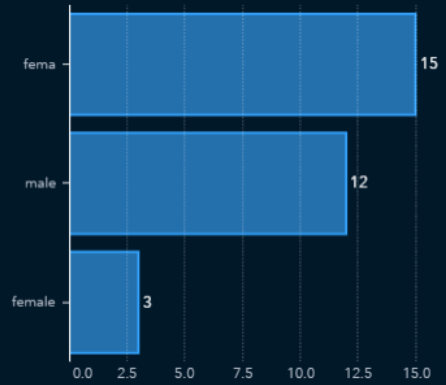
Ethnicity and Race



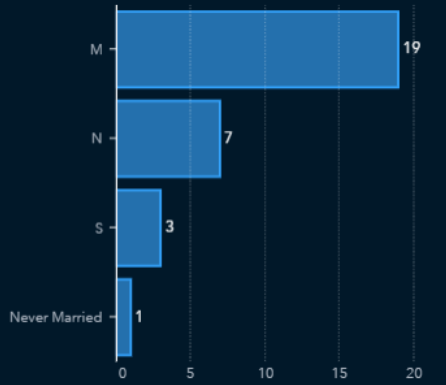
Language



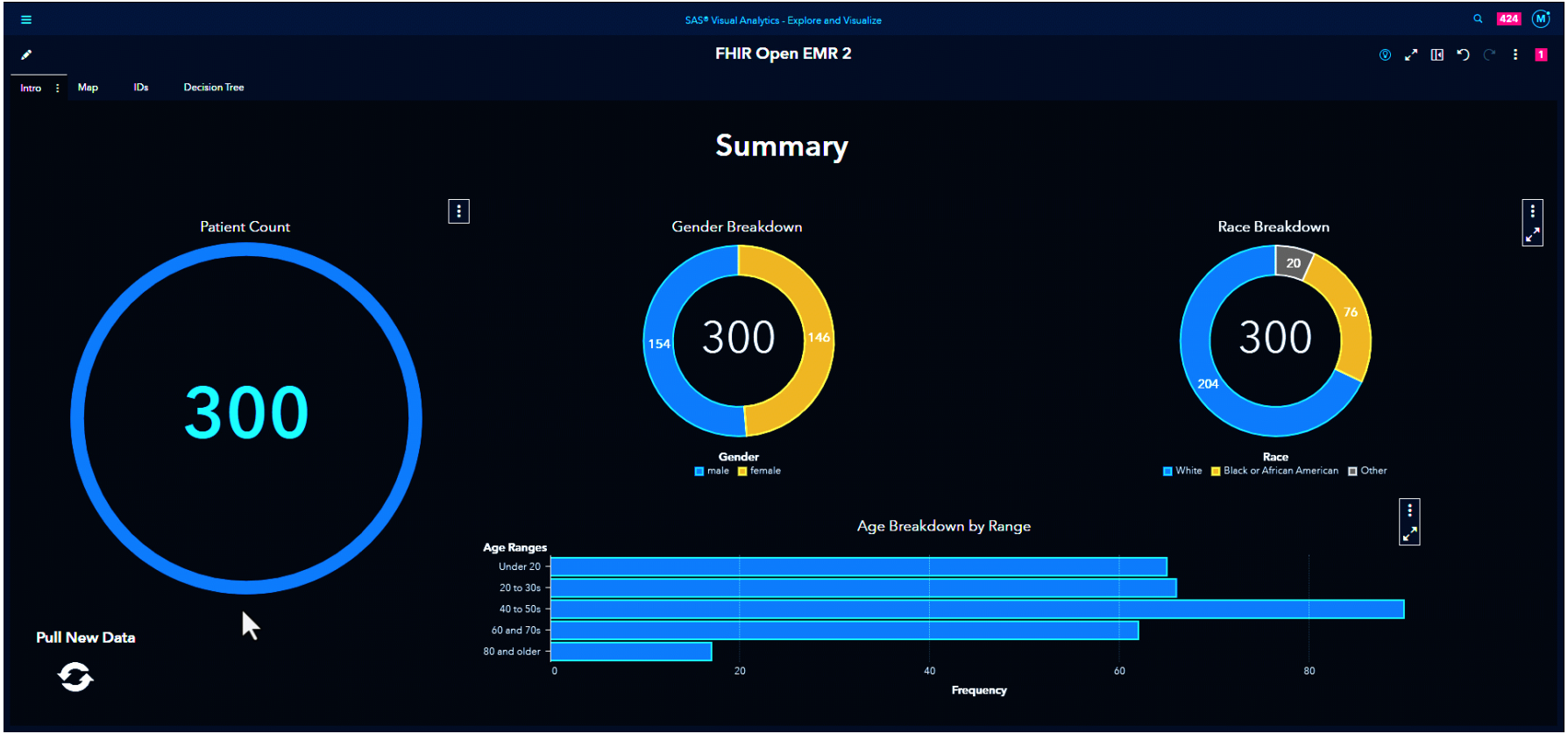
Gender



Marital Status



given	family	Medical Record Number	Driver's License	Social Security Number	Passport Number
Adaline602	Koch169	aca39bdc-0d62-4e6b-8b6e-9a451dab6231	S99936519	999-14-4205	X7209357X
Al123	Daugherty69	af324ccb-9837-45cc-b39f-2f77f99429eb	S99980980	999-93-2747	X70569062X
Allegra202	O'Connell601	4fcc744e-7191-4f81-8717-b910837f5ae2		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	X84351788X
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

- Study designs could accommodate and account for more precise measurement of a primary or secondary variable with better access to novel **data** sources, more sophisticated **methods** and **technology** accommodating intra-patient variability.
- The natural and ethical evolution of efficacy assessment warrants researchers to capitalize and leverage novel methods that are no longer a theory but available and have **already been put into practice**.
- We can impact the **accuracy** and **precision** of efficacy evaluation
- We can **shorten** clinical trial duration and **lower cost** leveraging RWD.

References

- Inan OT, Tenaerts P, Prindiville SA, Reynolds HR, Dizon DS, Cooper-Arnold K, Turakhia M, Pletcher MJ, Preston KL, Krumholz HM, Marlin BM, Mandl KD, Klasnja P, Spring B, Iturriaga E, Campo R, Desvigne-Nickens P, Rosenberg Y, Steinhubl SR, Califf RM. Digitizing clinical trials. NPJ Digit Med. 2020 Jul 31;3:101. doi: 10.1038/s41746-020-0302-y. PMID: 32821856; PMCID: PMC7395804.
- Polidori, D, Iijima, H, Goda, M, Maruyama, N, Inagaki, N, Crawford, PA. Intra- and inter-subject variability for increases in serum ketone bodies in patients with type 2 diabetes treated with the sodium glucose co-transporter 2 inhibitor canagliflozin. Diabetes Obes Metab. 2018; 20: 1321–1326. https://doi.org/10.1111/dom.13224
- van Gelder, T. A new method to calculate intra-patient variability in tacrolimus concentrations. Br J Clin Pharmacol. 2022; 88(6): 2581- 2582. doi:10.1111/bcp.14865
- Intra-and inter-patient variability of baseline pain intensity scores during breakthrough pain in cancer. Allen W, Burton, Marilene Filbet, Ravi Tayi, Michael Sidney Perelman, and Alastair D. Knight. Journal of Clinical Oncology 2012 30:15_suppl, e19578-e19578
- F. Iacono, L. Magni and C. Toffanin, "Personalized LSTM models for glucose prediction in Type 1 diabetes subjects," 2022 30th Mediterranean Conference on Control and Automation (MED), 2022, pp. 324-329, doi: 10.1109/MED54222.2022.9837153.
- Wu G, Baraldo M, Furlanut M. Inter-patient and intra-patient variations in the baseline tapping test in patients with Parkinson's disease. Acta Neurol Belg. 1999 Sep;99(3):182-4. PMID: 10544726.
- Sapey E, Bayley D, Ahmad A, et alInter-relationships between inflammatory markers in patients with stable COPD with bronchitis: intra-patient and inter-patient variabilityThorax 2008;63:493-499.

Thank you !