Johns Hopkins inHealth

Precision Medicine Symposium 2022

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ePoster Presentation:

Research Underway by our Precision Medicine Centers of Excellence

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Wilmer Precision Ophthalmology Center of Excellence

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Wilmer Precision Ophthalmology COE

Vision

Harness the power of artificial intelligence, multimodal ophthalmic imaging and big data to provide previously-unavailable stratification, prognostication and treatment recommendations for patients with ophthalmic diseases.

Mission

Usher in an era of personalized ophthalmic care and transform the field of ophthalmology using artificial intelligence.

Research Aims

Risk predictions: can we develop an algorithm that provides fine-grained predictions for conversion to wet age-related macular degeneration (AMD) in patients with dry AMD?

Treatment recommendations: can we identify the optimal intravitreal anti-VEGF medication for patients with retinal vascular diseases at treatment initiation?

Interested in Collaboration?

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Wilmer Precision Ophthalmology Center of Excellence

Focus

- Retinal vascular diseases include neovascular (wet) age-related macular degeneration (AMD), diabetic retinopathy and retinal vein occlusion.
- The standard of care for treatment of retinal vascular diseases is repeated intravitreal injections of anti-VEGF medications, one of the most expensive classes of medications.
- Our initial focus is on AMD, the leading cause of central vision loss in the elderly.
- Our initial focus is on optical coherence tomography (OCT) imaging, the most commonly-used imaging modality in ophthalmology.

Key question #1: can we provide fine-grained predictions for when a patient with dry AMD will convert to wet AMD?

Key question #2: can we predict which patients will do well in the long-term on Bevacizumab, the most cost-effective anti-VEGF medication for wet AMD?

Method & Analytics

- Deep-learning-based analysis of OCT images with 3D neural networks.
- Serial and different versions (raw version vs. segmented version) of OCT images will be included.
- Ensemble machine learning models incorporating both imaging and tabular data.

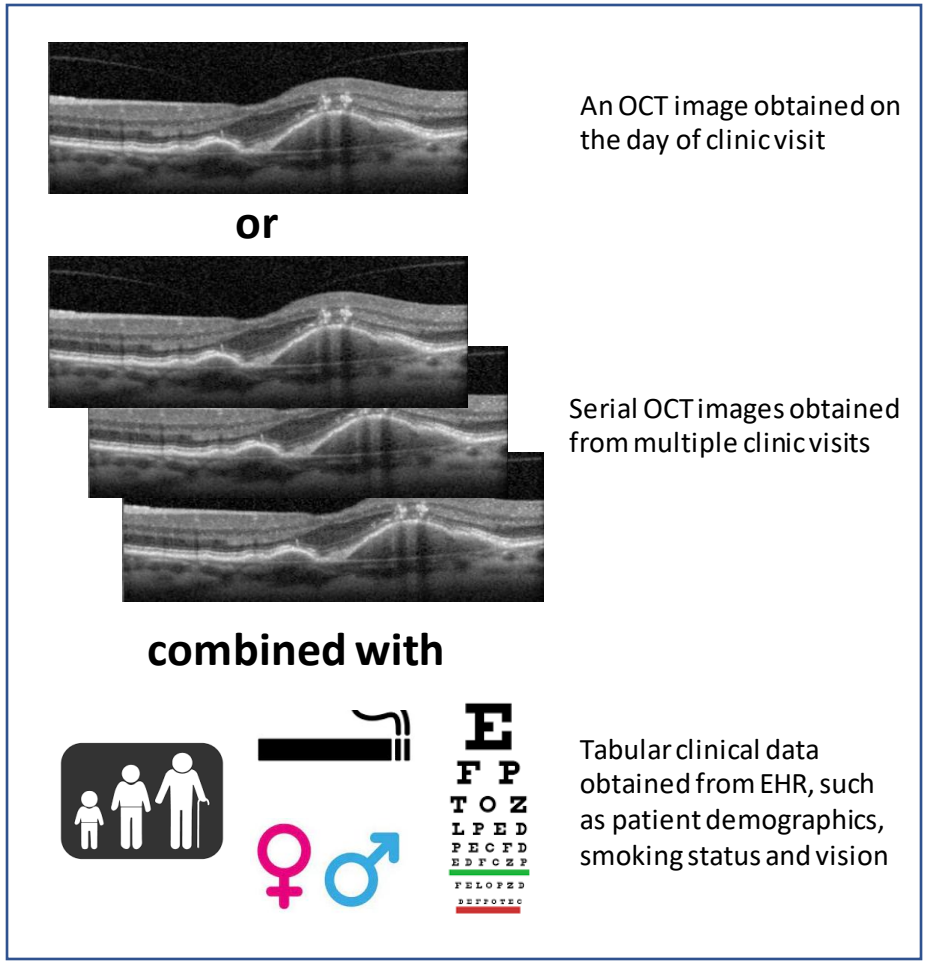

Figure 1: A diagram highlighting the proposed clinical decision tool to be deployed in an out-patient clinic setting.

Results and Highlights

- Curated an OCT dataset from 3000 patients with wet AMD, one of the largest curated AMD OCT datasets in the world.
- OCT segmentation is currently underway.
- Trained a preliminary 3D neural network for **Key question #1**.

Next Steps

- Investigate how to incorporate serial OCT data and tabular clinical data into model training and testing.
- Obtain external independent datasets for validation.

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Precision Medicine Center of Excellence for Patient Safety and Quality

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Patient Safety and Quality PMCOE

- **Vision:**
  Transform the science and delivery of patient safety and quality using precision medicine approaches
- **Mission**
  Develop innovative insights and operational solutions to improve safety, quality, and efficiency throughout Johns Hopkins Medicine, and apply these solutions broadly within healthcare.
- **Research Aims**
  - Synthesize heterogeneous data to identify previously invisible risks and opportunities
  - Build novel interventions to prevent patient safety events and achieve National patient safety goals
  - Tailor patient care to prevent healthcare-associated complications in identified subgroups

Interested in Collaboration?

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Patient Safety and Quality PMCOE

Focus

Transform the science and delivery of safety and quality using precision medicine approaches

The Armstrong Institute for Patient Safety and Quality provides an infrastructure that oversees, coordinates and supports patient safety and quality efforts across the Johns Hopkins integrated health care system.

The focus of the Patient Safety and Quality PMCoE is to develop innovative insights and operational solutions to improve safety, quality, and efficiency throughout Johns Hopkins Medicine, and apply these solutions broadly within healthcare.

Method & Analytics

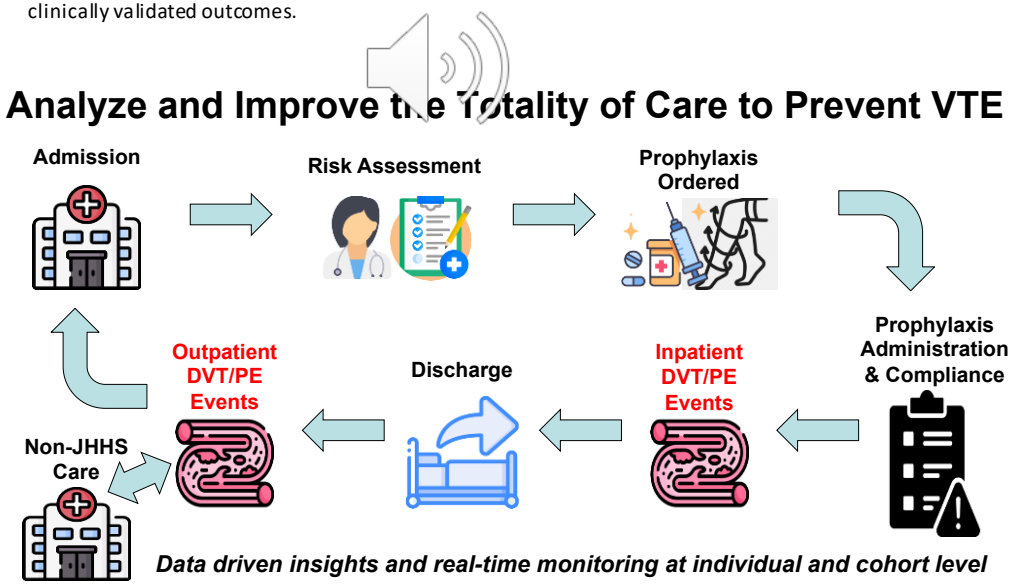
The Patient Safety and Quality PMCoE leverages systems engineering and mission assurance methodologies proven in other domains where JHU is also a global leader. This integrated end-to-end system perspective is key to solving these critical and complex challenges.

Analytically, the PMCoE employs a comprehensive set of Epic-derived data. Various discrete data elements are combined in complex algorithms to provide data science insights at present. Additional data elements critical to solving these problems are identified and will be incorporated as more advanced natural language processing tools become available.

Results and Highlights

This transformational work addresses many of The Joint Commission's 2022 National Patient Safety Goals and Johns Hopkins Medicine strategic priorities.

- Identification of risk to patient safety involves the curation and synthesis of various clinical and operational data elements in novel ways. The PMCoE developed a proof-of-concept system to help prevent wrong-site procedures, to be activated when a case is posted for a procedure.
- Benchmarking and improvement of clinical care currently relies on large teams of trained abstractors searching patient records manually to find and infer critical information. A major initiative is underway to develop a robust system of machine-assisted abstraction tailored for the data challenges of clinical registries, with technical leadership by the Predictive Analytics Core at Johns Hopkins All Children's.
- Combining the expertise of JHM clinicians and APL data scientists, the PMCoE established the analytic foundation to develop a revolutionary new system to prevent hospital-associated venous thrombosis. The system is designed to analyze, improve, and facilitate the full continuum of care for each inpatient: medical history – admission risk assessment – ordering/administration of prophylaxis – post-discharge follow-up – clinically validated outcomes.



Conclusion

The JHU inHealth Precision Medicine Platform is transforming the science and delivery of health care safety and quality. The ability to synthesize heterogeneous data from disparate sources leads to the identification of previously invisible risks and opportunities.

Health systems across the U.S. and around the world strive diligently to eliminate preventable harm, achieve the best possible outcomes, and improve the value of health care. JHU inhealth enables the development of novel and more effective interventions to prevent patient safety events.

Patient risk assessment can now be more accurate and rigorous. Prophylaxis can now be tailored for more specific subgroups to prevent health-care associated complications.

The PSQ PMCoE provides multifaceted advancements to help JHM deliver on the promise of medicine.

Next Steps

These innovations are under continued development in collaboration with the Applied Physics Laboratory (APL) and the Center for Pediatric Data Science and Analytics Methodology at the Johns Hopkins All Children's Hospital.

Further advanced applications are under formulation within the Armstrong Institute in collaboration with APL and the Whiting School of Engineering. These involve broader applications in surgical data science and ambient intelligence.

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Scleroderma Precision Medicine Center of Excellence

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Scleroderma Precision Medicine Center of Excellence

- **Vision:**
  Scleroderma is a heterogeneous disease with significant variability in a patient's disease expression and clinical trajectory. Our precision medicine program in scleroderma will lead to improved understanding of a patient's disease course, provide opportunities for early detection of complications and development of more targeted treatment approaches.
- **Mission**
  The mission of The Johns Hopkins Scleroderma Center is to provide outstanding, holistic clinical care while seeking to better understand the causes and best treatment approaches for scleroderma. The Scleroderma Precision Medicine Center of Excellence is harnessing the revolution occurring in big data and computational science to neutralize disease complexity and variability.
- **Research Aims**
  1) Identify patients at high risk of progressive disease across a broad spectrum of complications: interstitial lung disease, pulmonary hypertension, cardiomyopathy, among others.

  2) Detect emerging complications at an earlier stage of disease using novel biomarker, ambulatory device and quantitative imaging strategies.

  3) Identify patients who are most likely to respond to different treatment strategies.

  4) Prospectively define whether immunologically distinct subgroups predict clinical outcomes and treatment responsiveness.

  5) Construct an individual level predictive model of a patient's likely trajectory and outcome.

Interested in Collaboration?

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Precision Medicine Symposium 2022

Scleroderma Precision Medicine Center of Excellence

Ji Soo Kim, Laura Hummers, Scott Zeger, Ami Shah

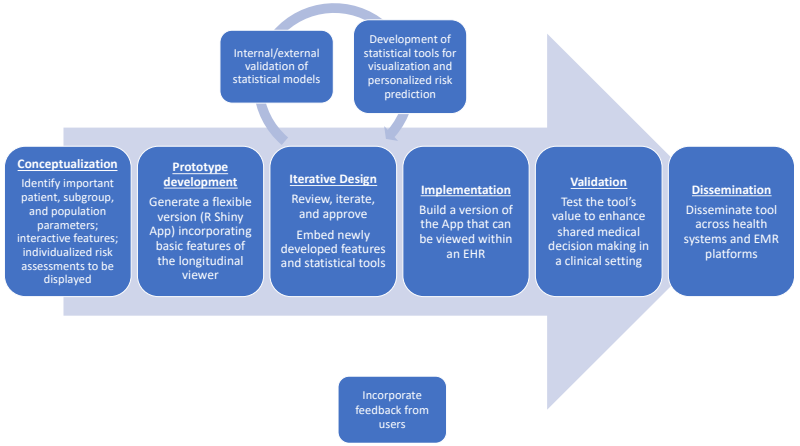
Focus

- In complex multisystem diseases, physicians integrate information from baseline risk factors and prior trajectory to assess risk of progression, major events, and need for higher-risk therapies
- This cognitive process is not generalizable across physicians, particularly in rare diseases. It is also time-consuming and costly.

Using Johns Hopkins Scleroderma PMCOE data (n > 4,000), we developed a Visualization App and analysis platform that:

1) visually communicates key clinical data about a patient's current state
2) computes and displays each patient's disease trajectory in selected domains relative to a clinician-selected patient subgroup with similar characteristics
3) calculates risks of future critical events.

Pathway to tool development harnessing patient and population level longitudinal data



This iterative process encompasses developing statistical models and visualization tools to communicate disease trajectory and personalized risk estimates, with opportunity to rapidly test and validate new features over time.

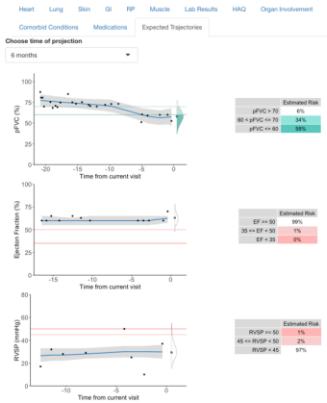
Visualizing individual patient's data with interactive filters for the reference population

(a)

(b)

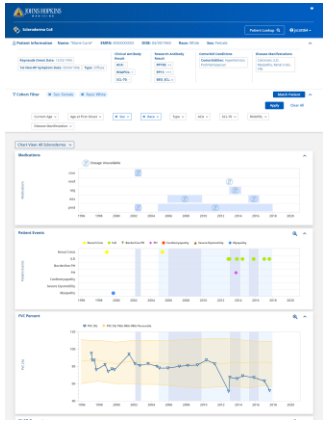
The Visualization App presents individual patient's data relative to those who share specific subgroup characteristics, providing insight into how the reference population changes the interpretation and one's perspective

Computing risk estimates for cardiopulmonary outcomes



- Individualized predictions are calculated by fitting a Multivariate Bayesian mixed model
- Method harnesses information in multiple correlated measures within and across patients to improve prediction
- Risks of multiple outcomes can be calculated simultaneously

Embedding Visualization App in EMR



- Patient Insight, embedded in Epic, illustrates an individual patient's trajectory across multiple organ systems (cardiac, pulmonary, cutaneous, GI, renal, peripheral vascular, muscle) and includes reference trajectory data for patients in the Johns Hopkins Scleroderma Center
- Filters can be deployed to compare an individual patient to others who share subgroup characteristics, such as race, cutaneous subtype and autoantibody type

Conclusions & Implications

- Development of predictive analytics at a patient level and decision support tools is an iterative process that requires evaluation at many steps
- These approaches foster development of a continuous learning health system in rheumatology by creating a tool that provides real-time estimates of the risk of major complications
- A high risk of future progression could result in more intensive monitoring, earlier initiation of therapy, and utilization of combination treatment strategies
- A low risk of progression could result in less screening tests being performed and cost savings over time

Next Steps

- Study the tool's potential to enhance shared medical decision-making including patients' and providers' perspectives
- Test whether the provider's medical judgement combined with the model is synergistic and performs better than either alone
- Externally validate statistical modelling
- Disseminate the tool to other academic centers
- Assess whether these measures improve patient outcomes and reduce costs

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Rehabilitation PMCOE

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Rehabilitation PMCOE

- **Vision:**
  Change the model of rehabilitation from a "one size fits all" approach toward a data-driven, patient-specific approach. We focus on constructing subgroups of individuals based on their level of function as a whole-person by leveraging real-world digital monitoring techniques (e.g., wearable devices and artificial intelligence for measuring motor function, as well as web and mobile applications for measuring cognitive and psychosocial function) and large-scale electronic health record data. Comprising our collaborative team are clinician-scientists who develop clinically-relevant research questions and translate findings back into clinical care, engineers who develop new ways of collecting data about a patient's functional status, and data scientists who develop techniques for big data analysis and predictive modeling through machine learning and biostatistics.
- **Mission**
  Provide the right intervention to the right patient at the right time.
- **Research Aims**
  - Improve the rigor of real-world measurement of whole-person functional status.
  - Identify patient subgroups that will be most responsive to particular interventions.
  - Develop and deliver patient-specific interventions that improve whole-person function.

Interested in Collaboration?

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Precision Medicine Symposium 2022

Rehabilitation PMCOE: Development of a digital application to automatically collect and manage physical activity data

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[1]Department of Physical Medicine and Rehabilitation, Johns Hopkins University, Baltimore, MD; [2] Center for Movement Studies, Kennedy Krieger Institute, Baltimore, MD

Introduction

- Physical activity has been linked to numerous negative health outcomes, including mortality and hospital readmission.
- Measuring physical activity via wearable devices, such as the Fitbit, has the potential to improve health outcomes; however, there are barriers to using these devices.
- **Here we describe the development of a digital application that assists in overcoming these barriers and improves the feasibility of using wearable devices to shape clinical care and health outcomes.**

Advantages to using wearable devices

Continuous data

Large amounts of data

Measurement of real-world activity

Barriers to using wearable devices

Time to set up/get data

Patient Compliance

Large amounts of data

Metrics that related to health outcomes?

Data Flow

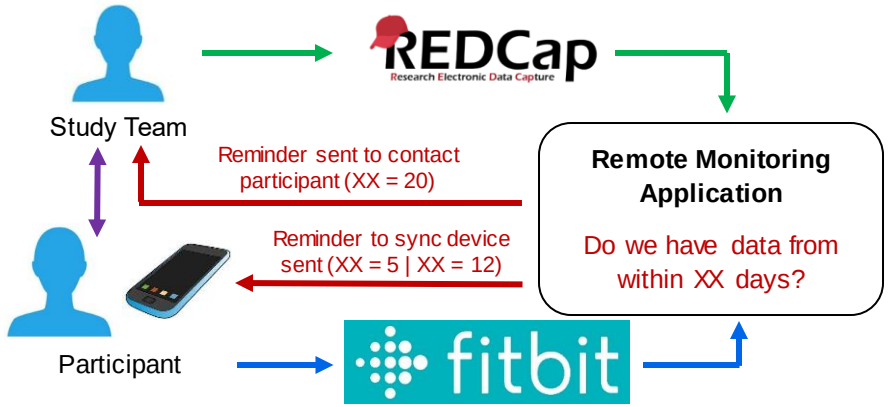
Step 1: Enrollment – shown in **purple**

Step 2: Study set up – shown in **green**

Step 3: Application automatically extracts data – shown in **blue**

Step 4: Series of logic to check data and contact participant as needed – shown in **red**

Step 5: Application data synced with clinical data – shown in **orange**



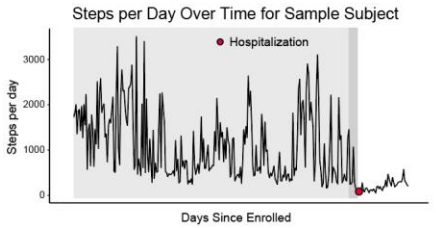
Summary of Use

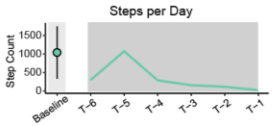
This automated flow of data from wearable devices:

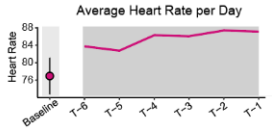
1. Reduces the time to access data
2. Reduces study team burden to ensure patient compliance
3. Streamlines the management of large amount of data
4. Integrates data from wearable devices with medical record data
5. Facilitates exploration of metrics related to health outcomes

Preliminary Work

Question: Do data from wearable devices predict hospital admissions in individuals with COPD?







Preliminary data suggest that wearable device data may predict hospital admission in individuals with COPD.

Next Steps

- Extracting additional metrics from the Fitbit, including sleep and GPS data.
- Expanding the application for use with other wearable devices.
- Identification of key metrics from wearable devices that relate to health outcomes.
- Development of predictive models that utilize these key metrics.
- Feeding summary data from the wearable devices back into the medical record system for clinicians to use in clinical care.

References and Acknowledgements

1. Lang CE, Barth J, Holleran CL, Konrad JD, Bland MD. Implementation of Wearable Sensing Technology for Movement: Pushing Forward into the Routine Physical Rehabilitation Care Field. Sensors (Basel) 2020;20(20).
2. Leroux A, Xu S, Kundu P, Muschelli J, Smirnova E, Chatterjee N et al. Quantifying the Predictive Performance of Objectively Measured Physical Activity on Mortality in the UK Biobank. J Gerontol A Biol Sci Med Sci 2021;76(8):1486-94.
3. Phillips SM, Cadmus-Bertram L, Rosenberg D, Buman MP, Lynch BM. Wearable Technology and Physical Activity in Chronic Disease: Opportunities and Challenges. Am J Prev Med 2018;54(1):144-50.

We would like to thank the Johns Hopkins University's Technology Innovations Center, specifically Kirby Smith, Will Green, Zach Deering, Nick Cannon, and Chris Doyle, for technical support in building the application. We would also like to thank Sharon Penttinen for serving as the liaison between the technical team and the research team. Lastly, we thank the Sheikh Khalifa Stroke Institute for their financial support.

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Rehab PMCOE: The Feasibility Of Remotely Monitoring Physical, Cognitive, And Psychosocial Function In Individuals With Stroke or Chronic Obstructive Pulmonary Disease

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Precision Medicine Symposium 2022

Introduction

- Current clinical assessments of physical, cognitive, and psychosocial function are limited by their low information content and infrequency.
- Remote monitoring may provide valuable information about function as it is collected in the real world and can provide more detailed information at a higher frequency.
- However, the feasibility of remote monitoring and the compliance of individuals with remote monitoring is a barrier.
- Here, we evaluate adherence and the required resources related to monitoring 1) physical function and 2) cognitive and psychosocial function in individuals with chronic obstructive pulmonary disease (COPD) and stroke during a three-month period.

Methods & Analytics

Participants

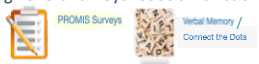
Individuals with stroke or COPD who had access to wifi and owned a smart phone were enrolled [n= 73 (36F; COPD=35); 64.4±14.6 yo]

Remote Monitoring for 3 Months

Physical Function

Fitbit Inspire 2: Continuously

Cognitive and Psychosocial Function



At enrollment and every 4 weeks (4 total)

At enrollment and the end of 3 months (2 total)

Feasibility Metrics

Physical Function

Minutes Worn Per Day (Wear Time)

Wear Time Over Time

Resource needed to promote adherence

Cognitive and Emotional Function

Number of Sessions Completed Per Person

Assessment Completion Rate Over Time

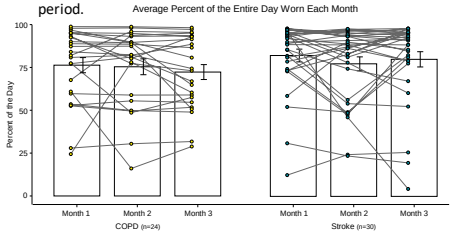
Resource needed to promote adherence

Results and Highlights

Physical Function

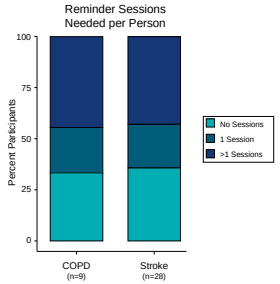
1. Most participants consistently wear their Fitbit the majority of the time.

On average, participants wore their Fitbit 77.5±19.9% (~18.6 hours) of the day. NO significant difference was found between average wear time over the 3-month period.



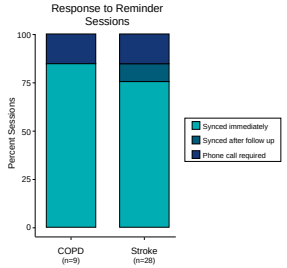
2. Most participants need to be reminded to wear their Fitbit.

On average, participants needed 0.68 ± 0.81 reminders per month.



3. Most participants are responsive to the automatic reminders.

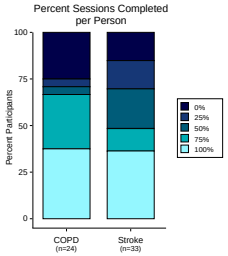
76.7% of reminder sessions resulted in immediate device syncing.



Cognitive and Psychosocial Function

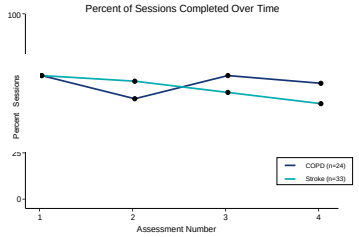
1. Most participants complete their assessment the majority of the time.

61% of the 228 initiated sessions were completed; on average, each participant completed 2.44±1.5 of the 4 possible sessions.



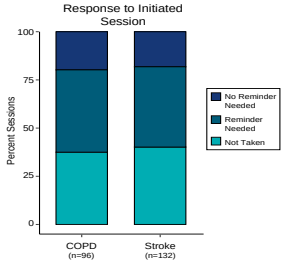
2. The percentage of assessments completed remains stable over time.

There was NO significant reduction in the proportion of completed assessments from assessment 1 to assessment 4 for both groups.



3. Automatic reminders may be necessary to promote assessment completion.

For those who have completed at least one assessment, an average of 1.13±0.57 reminders were needed per person per completed session.



Conclusions

- Overall, individuals with stroke and COPD were compliant with remote monitoring of physical function as evident by the high number of minutes the device was worn.
- Compliance with remote cognitive and psychosocial health assessments dropped slightly over time for both groups; however, the change was not statistically significant.
- Dedicated resources such as our automated reminder system help promote high adherence to remote monitoring.
- There is NO statistical difference in adherence as well as resources needed to monitor the physical, cognitive, and psychosocial function between the two groups of patient populations.

Next Steps

- Individuals enrolled in this study have agreed to participate for one year; thus, we will continue to monitor feasibility and compliance.
- Additional work will:
  - Identify patient subgroups that are likely to need additional assistance to be compliant with remote monitoring approaches.
  - Examine longitudinal trends in physical, cognitive, and emotional function.
  - Develop predictive models of key health events from remotely collected data.
  - Assess the implementation of these remote monitoring approaches into standard practice.

Acknowledgements

We would like to acknowledge the individuals who participated in this project as well as the clinicians, who have assisted in recruitment. We would also like to thank the Technology and Innovation Center, specifically Kirby Smith, Will Green, Zach Deering, and Nick Cannon, for the development of the application that collects the data used in this work. We would also like to acknowledge the Sheikh Khalifa Stroke Institute for financial support of this work.

References

1. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D et al. How we design feasibility studies. Am J Prev Med 2009;36(5):452-7.
2. French MA, Roemmich RT, Daley K, Beier M, Penttinen S, Raghavan P et al. Precision Rehabilitation: Optimizing Function, Adding Value to Health Care. Arch Phys Med Rehabil 2022;103(6):1233-9.
3. Block VJ, Bove R, Zhao C, Garcha P, Graves J, Romeo AR et al. Association of Continuous Assessment of Step Count by Remote Monitoring With Disability Progression Among Adults With Multiple Sclerosis. JAMA Netw Open 2019;2(3):e190570.
4. Katzan I, Schuster A, Kinzy T. Physical Activity Monitoring Using a Fitbit Device in Ischemic Stroke Patients: Prospective Cohort Feasibility Study. JMIR Mhealth Uhealth 2021;9(1):e14494.
5. Thompson LI, Harrington KD, Roque N, Stenger J, Correia S, Jones RN et al. A highly feasible, reliable, and fully remote protocol for mobile app-based cognitive assessment in cognitively healthy older adults. Alzheimers Dement (Amst) 2022;14(1):e12283.
6. Singh S, Strong RW, Jung L, Li FH, Grinspoon L, Scheuer LS et al. The TestMyBrain Digital Neuropsychology Toolkit: Development and Psychometric Characteristics. Journal of clinical and experimental neuropsychology 2021;43(8):786-95.
7. Collins JE, Yang HY, Trentadue TP, Gong Y, Losina E. Validation of the Fitbit Charge 2 compared to the ActiGraph GT3X+ in older adults with knee osteoarthritis in free-living conditions. PLoS One 2019;14(1):e0211231.
8. Beukenhorst AL, Burke KM, Scheier Z, Miller TM, Paganoni S, Keegan M et al. Using Smartphones to Reduce Research Burden in a Neurodegenerative Population and Assessing Participant Adherence: A Randomized Clinical Trial and Two Observational Studies. JMIR Mhealth Uhealth 2022;10(2):e31877.

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Data Science for Quality & Finance: Project K

Johns Hopkins Precision Medicine Analytics Platform (JH-PMAP)

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Data Science for Quality & Finance: Project K

- **Vision:**
  To use scalable machine learning models to know precisely how Johns Hopkins Medicine's care is measured, and engineering methods to move decisions as close as possible to the point of care
- **Mission**
  To improve the quality of the data that informs Johns Hopkins Medicine's operational decision making and measurements of external performance, financial reimbursements, and reputational scoring
- **Research Aims**
  On average greater than 50% of cases require coding edits, which leads to uncertainty and administrative costs

Interested in Collaboration?

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Data Science for Quality & Finance: Project K

Focus

Design a scalable solution and build:

A data lake that stores daily snapshots of select pieces of the EMR, coding, and billing systems capturing **lineage**

A platform of pipelines to **enrich** that data with scores

A platform to run statistical **models** against those data

Methods

Using time-series data structures
- No data is thrown away

Automated data quality checking

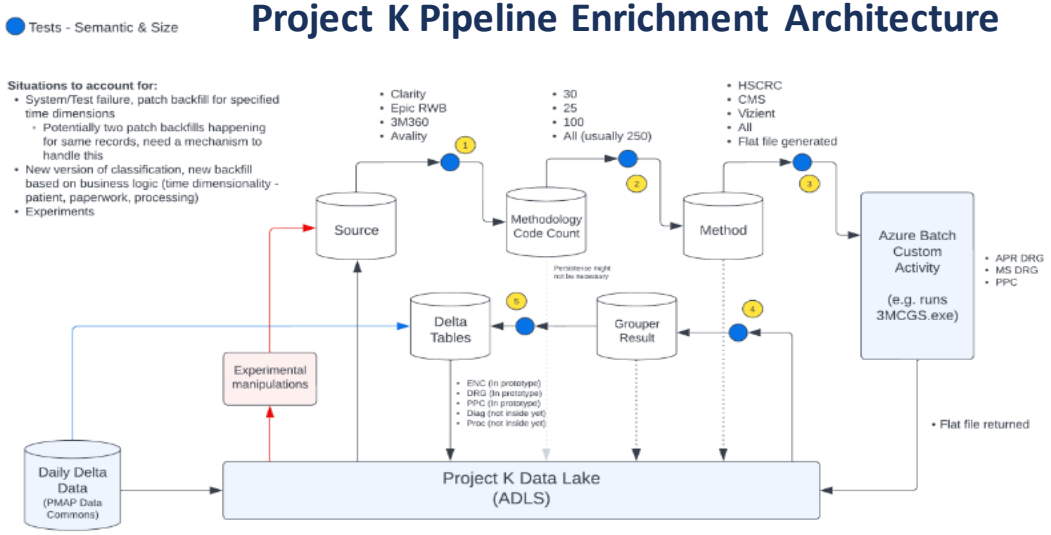
Using Agile software development practices

Using DevOps practices and designs
- Continuous Integration/Continuous Development
- Infrastructure as Code

Engaging with industry leaders
- Databricks
- Lovelytics LLC

Platform Tools & Highlights

Project K Pipeline Enrichment Architecture



Azure components

- Azure DevOps (ADO) for Continuous Integration Continuous Development
- Version Control – Azure DevOps & github
- Storage – Databricks Delta Tables, Azure Data Lake
- Computational Environment – Databricks Cluster & Azure batch custom activity

MLOps

- MLFlow
  - Experiment Tracking
  - Saving Models
  - Model Monitoring
- hyperopt
  - Hyperparameter tuning
  - Runs on Databricks Orchestrator

Infrastructure Tooling

- Terraform
- Apache Airflow
- Databricks Job Orchestration

Analytics

Machine learning monitoring of data volumes, depths of diagnosis and procedure coding anomaly detection

Learning thresholds for quality and scoring variances.

Sequence to sequence models – diagnosis code predictions day by day

Administrative resource intensity measurement – record touches over time

End-to-end Counterfactuals – What happens when obesity is coded at 27% vs 12%

Next Steps

1. Implement MLOps

2. Feedback loop and display layers for operational managers

3. Ingest additional sources of data. Ex: External Claims

4. Further downstream analytics and measurement enrichments. Ex: AHRQ SAS based programs such as Patient Safety Indicators

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Primary Care Precision Medicine Center of Excellence

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Primary Care Precision Medicine Center of Excellence

- **Vision:**

- Healthy people and communities enabled by the delivery of the best interventions for health promotion and disease prevention, diagnosis, and treatment for each patient in primary care.

- **Mission**
  To accelerate discovery and translation of research into primary care practice. We will achieve this with precision data and analytics that enables a learning health system, working in partnership with patients, families, clinicians, researchers, and communities.

- **Research Aims**

- Neighborhood Differences: We are using tools of spatial analysis to improve the care in communities with high risks of adverse outcomes among their residents.
- Individualized Treatment : We are developing analytic methods to identify the best medication addition for patients who need intensified treatment of a chronic condition.
- Develop Registries: We support researchers in developing registries of patients with important primary care needs such as hypertension control, transgender health, complex care, and disabilities.
- Learning about Barriers: We are developing a Comprehensive Diabetes Assessment tool that will help identify barriers to individuals' attaining their best diabetes outcomes.
- Data Linkage: We integrate rich data from public sources into our data platform to learn about the needs of individuals living in diverse neighborhoods.
- Linkage to Services: We use data and analytics to link patients to services, within and outside of the health system, for management of their chronic conditions.

Interested in Collaboration?

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Precision Medicine Symposium 2022

(Adult) Primary Care Center of Excellence
The Telemedicine Challenge

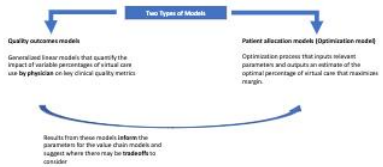
Focus

- Virtual care, specifically the synchronous clinician-patient interactions occurring over telephone or video, was broadly implemented in many health systems during the pandemic of COVID-19
- Little evidence to date about its *effectiveness* and *value* for the delivery of primary care
- Needed is additional evidence of its impact on care quality, patient outcomes and satisfaction, contribution to inequities in care and outcomes, and clinician satisfaction and burnout.
- Additionally, practice *revenue* must be evaluated to assess the ongoing viability of this mode of primary care delivery.

Goal: *To model the expected revenue from some mix of virtual and in-person primary care in a practice.*

Method & Analytics

- We assume that both modes of care delivery are equally appropriate for most clinical situations under consideration ("exchangeable")
- Using 2 models:



- **Quality outcome models**

$$\log(E[Y_{ijt}\,|u_i, v_j]) = \log(N_{ijt}) + \beta_0 + u_i + v_j + \beta_1 X_{1ijt} + \beta_2 X_{2ijt} + \cdots$$
$$Y_{ijt}|u_i, v_j \sim Poisson(\mu_{ijt})$$
$$u_i \sim Normal(0, \sigma_u^2)$$
$$v_j \sim Normal(0, \sigma_v^2)$$

Where:
Y_{ijt} is the count outcome for physician i in clinic j in month t
u_i is the random intercept for physician i
v_j is the random intercept for clinic j
N_{ijt} is the offset (denominator) for outcome Y_{ijt} as needed
X_{1ijt}, X_{2ijt} etc are the fixed effect physician and clinic level covariates including the **main covariate of interest (category of virtual care percentage)** and clinic-level characteristics of the patients (age, sex, ACG) and clinic characteristics (urban/rural) and calendar month.

Model written to run in SAS using GLIMMIX procedure

- ***Patient allocation models***
  - Base case: fixed number of physicians and fixed number of rooms
  - Choice variable is the # of exchangeable patients seen in-person and # seen virtually
  - Constraints include: total # of patients, cost of quality
  - Objective function seeks to maximize revenue
  - Inputs for the model came from analysis of data from the Primary Care COE (40 clinics, 400 clinicians, 400,000 patients, 800,000 visits)

Results and Highlights

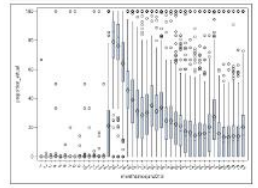
Medical Demography

Visit Characteristics by **Physicians'** Virtual Usage Category 2020-2021

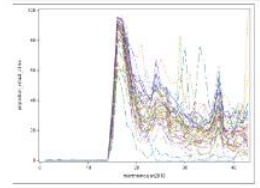
	Physician Never Virtual n=70 physicians	Physician Light Virtual n=257 physicians	Physician Heavy Virtual n=356 physicians
Age (mean years)	51.65 (17.9)	53.73 (17.7)	50.71 (17.2)
Total visits (median 25th,75th)	48 (36, 409)	4127 (1747, 5388)	4870 (2721, 5747)
Unique patients (N)	1202	58011	140895
Female gender, N (%)	713 (59.3)	32054 (55.2)	86650 (61.5)
Black race, N (%)	536 (49.9)	15654 (27.3)	38989 (28.0)
English primary language, N (%)	1098 (91.3)	57190 (98.5)	137974 (97.9)
Maryland resident, N (%)	1153 (95.9)	53777 (92.7)	129448 (91.8)
ADI decile 10: most disadvantaged, N (%)	241 (20.0)	3892 (6.71)	6976 (4.95)
Metropolitan resident, N (%)	1163 (99.2)	56283 (98.6)	137561 (99.2)
Rural resident, N (%)	3 (0.26)	88 (0.15)	113 (0.08)

category definition: never virtual (never a virtual visits in 2020-21); light virtual (virtual percentage is below overall median (22 visits) percentage for 2020-21), heavy virtual (virtual percentage is above median percentage 2020-21)

Proportion of telemedicine use by physician

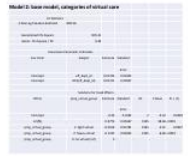


Proportion of telemedicine use within each clinic



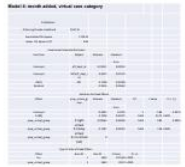
Quality Outcomes Models
[Subset of Clinicians in JHOC/Res.Clinic/ Greenspring]

BP control



Higher virtual care categories, less control of BP

A1c out of control



Higher virtual categories, more out of control A1c

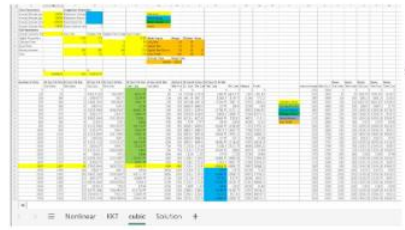
Breast Cancer screening

HIGHEST virtual category, slightly fewer mammograms

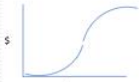
Patient Allocation Models

Managerial question

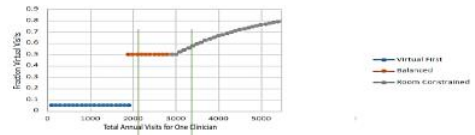
With a given panel of patients, if the clinic can control where patients are seen, what proportion of visits should be virtual to maximize the profit at the physician and clinic level?



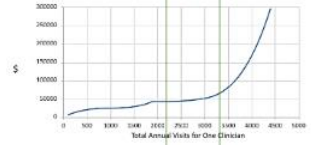
The team's insight was to optimize with a cubic function (concave/convex) so that the relationship between cost and # of visits could be first concave and then convex at the visit count goes up (reflecting reality).



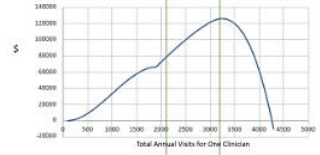
Proportion of Virtual Visits



Minimum Cost vs. Number of Visits



Profit vs. Number of Visits



Conclusion

Variation in use of virtual care across clinics but modest relative to variation by month

Preliminary quality models suggest that the quality metrics may not be met with heavy virtual care use. (Possibly a *higher* cost of quality with virtual care)

Profit peaks at 3200 visits or physicians working at 80% of capacity. In the absence of room constraints, the optimum would be 3700 visits. Because we need to move patients to virtual care when there are capacity issues, we lose about $8000.

Our model predicts:
1)If cost of quality is identical between sites of care, then having both options lowers total cost of quality.
2)With *equal* marginal cost of quality across sites, a *middle level* of virtual care is optimal. Mix tilts towards site with higher quality.

We remain uncertain if quality is equivalent. Work is ongoing.

Next Steps

Proceed with quality models in full data.

Report results to Office of Telemedicine to inform their decisions

Respond to upcoming AHRQ P50 award about telemedicine in primary care

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Samantha Pitts, MD, MPH – Director, Adult Primary Care COE

Funding: Johns Hopkins Office of Telemedicine

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Schizoaffective Disorders PMCOE

Director: Russell L. Margolis, M.D.
Co-Director: Frederick Nucifora, Jr, PhD, DO,MHS

- **Vision:**
  To improve the outcomes for patients with schizoaffective disorders (broadly defined to include schizophrenia with varying degrees of affective symptoms) by establishing disease subtypes based on treatment response
- **Mission**

  1) To develop methods that distinguish schizoaffective subtypes prior to the onset of treatment, as a guide to choosing among current treatments. 2) To determine the neurobiological underpinnings of the subtypes, with the goal of facilitating the development of novel treatments. 3) To use health system data to change clinical practice.

Research Aims

Aim 1: Deep clinical phenotyping of a large population of patients

Aim 2: Development of novel 7T MRI methods to determine brain signatures of patient subgroups.

Aim 3: Study patient and engineered iPSCs and induced neurons to determine the cellular phenotypes that correlate with patient subtypes.

Aim 4: Use mouse models to explore pathophysiological correlates of mutations associated with schizoaffective disorder

Aim 5: Use EHR data to characterize patient subtypes based on treatment response.

Interested in Collaboration?

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Precision Medicine Symposium 2022

Schizoaffective Disorders PMCOE:

Investigating the translational value of Ank3 knockout mouse for drug development in schizoaffective disorders

Bashiri K[1], Kim J[1], Li J[1], Hsieh E[1], Margolis RL[1], Ross CA[1]

1. Dept of Psychiatry, Johns Hopkins School of Medicine, Baltimore, MD.

Focus

Several studies have indicated the link between the genetic loss of function at ANK3 with bipolar disorder and schizophrenia. Previously, our group generated a mouse model for bipolar disorder with a conditional homozygous deletion (AnkG-cKO) of ANK3 in excitatory neurons of the adult forebrain. The AnkG-cKO mice showed behavioral hyperactivity that was reversed by the anti-mania drugs lithium and valproic acid. We hypothesized that functional dysregulations of transcriptomics could replicate human data on bipolar disorder to assess the model's translational value for drug development studies.

Method & Analytics

Cerebral cortical tissues were collected from AnkG-cKO (2 females and 2 males), and control mice (2 females and 2 males). Nuclei were sorted using DAPI, 90% of NeuN (pos), and 10% of NeuN (neg) events (figure 1). Libraries were constructed based on the 10X Chromium protocol. From each sample, 5000 nuclei were included for sequencing 400 million read-pairs of PE150. Alignment was performed by "STAR" using "CellRanger". Cell typing was done based on "Allen Brain Cell Types". Differential expression analysis between AnkG-cKO and control mice within each cell subtype was performed by "Loupe Browser".

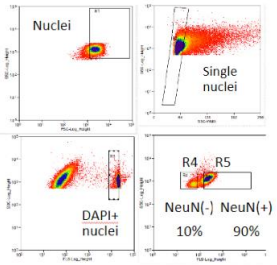

Fig 1. FACS gating

Results and Highlights

Among the neuronal cell population, 88% of neurons were classified as glutamatergic neurons and 12% as GABAergic neurons (figure 2). Transcriptional changes between AnkG-cKO and control were almost exclusively among glutamatergic neurons (figure 3) and were mostly related to the male models. Pathways enrichment analysis of the upregulated features demonstrated the following GO terms: protein autophosphorylation, regulation of postsynapse organization, regulation of neuron projection development, and regulation of MAPK cascade on top (Figure 4), all of which were found in the human postmortem brain of bipolar disorder in prior studies.

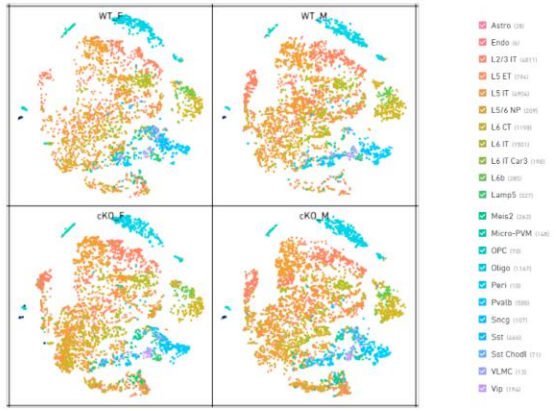

Fig 2. t-SNE visualization of the snRNA-seq data using Allen Brain Institute's annotation. WT_F, WT_M, cKOF and cKO-M represent control females, control males, AnkG cKO females, and AnkG-cKO males, respectively.

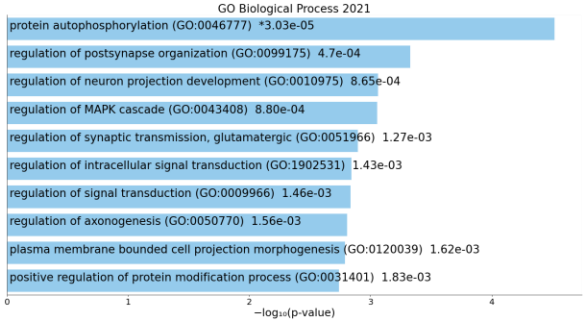

Fig 4. Using upregulated genes in AnkG-cKO mice, enriched GO Biological pathways, revealed terms consistent with human studies on bipolar disorder. As expected, postsynaptic organization and synaptic transmission were among the enriched pathways.

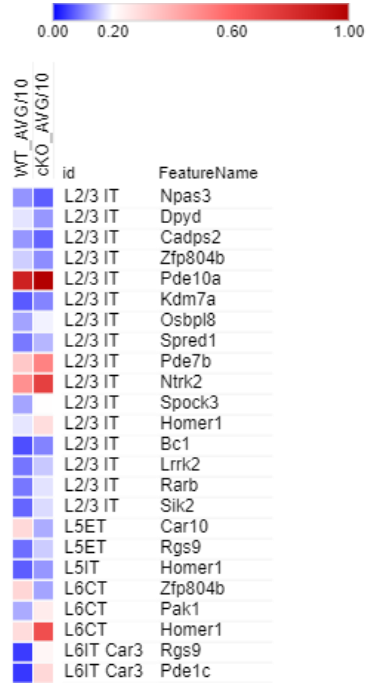

Fig 3. Differentially expressed (DE) genes (FeatureName) between AnkG-cKO (cKO_AVG/10) and control mice (WT_AVG/10) in different neuronal cell types (id). Among the DE genes, Homer1 was found to be increased in different cell types, compatible with recent studies on the interaction between AnkG and Homer postsynaptic scaffolding proteins.

Conclusion

AnkG-cKO mice have revealed transcriptional changes consistent with human data on bipolar disorder. This study lends further weight to the translational value of this model for drug development studies in bipolar disorder. ANK3 and Homer1 are potential targets for designing mood stabilizers, although more studies are warranted to identify the causal role of their alterations in the development of schizoaffective disorders.

Next Steps

The gene expression changes in AnkG-cKO mice will be retested by using male animals that possess the majority of transcriptional dysregulations and the mechanism of lithium in rescuing behavioral hyperactivity will be studied. Additionally, the isoform of the upregulated transcript of Homer 1 will be identified to provide a better insight into the pathogenetic mechanism of Ank3 deletion in the development of schizoaffective disorders.

The Abramson Fund

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Precision Medicine Symposium 2022

Schizoaffective Disorders PMCOE:

Better functional capacity and cognitive performance in clozapine responders compared to non-responders: A cross-sectional study

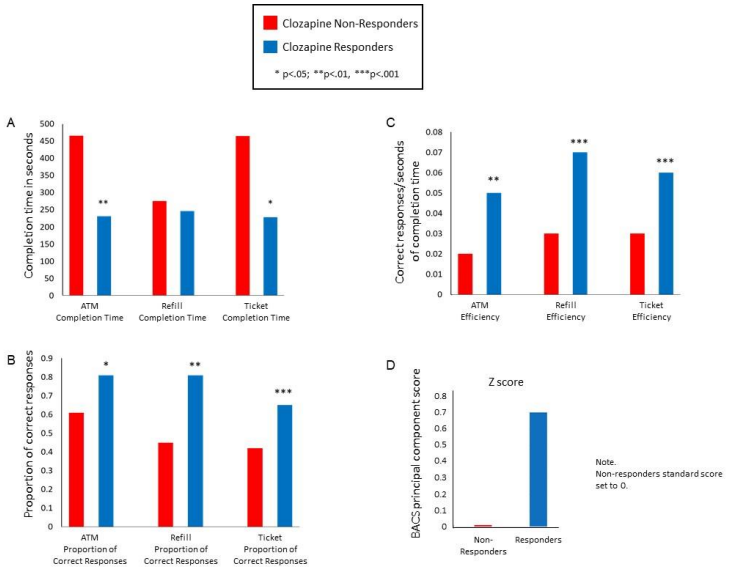
Focus

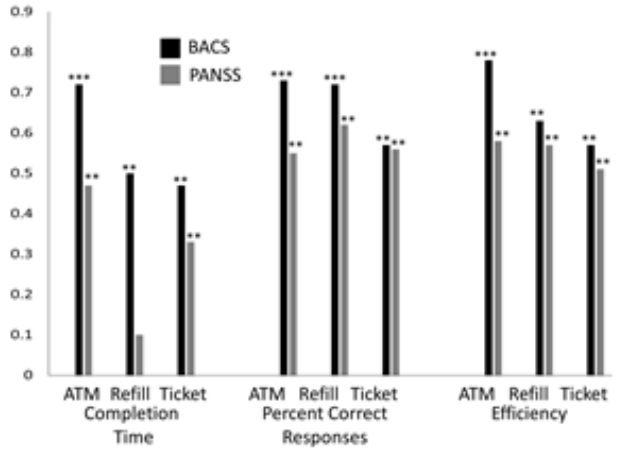
Schizoaffective disorder (SCZ; defined as schizophrenia with varying degrees of affective symptoms) is associated with considerable everyday disability, associated with impairment in tests of cognitive performance and on measures of functional capacity. However, the association among symptom status, cognitive functioning, and functional capacity in treatment refractory patients who respond only to the atypical agent clozapine, and not to conventional antipsychotic medicines (TRS), has not been compared to patients who respond neither to conventional antipsychotics nor clozapine (ultra-treatment resistant SCZ; UTRS). In this study, we examine clozapine-treated patients and compare cognitive and functional capacity performance across response status using the University of Miami Computer-Based Functional Assessment System (CFAS).

Method & Analytics

27 clozapine-treated SCZ patients treated at Johns Hopkins Bayview, previously designated as treatment refractory, were assessed with the Positive and Negative Symptoms Scale (PANSS). Patients were considered clozapine-responders (TRS) if they had a PANSS score ≤ 58 and non-responders (UTRS) if PANSS was > 58. Cognition was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS), and level of function was determined using three validated computerized tests of functional capacity: ATM Banking, Ticket Purchase, and Prescription Refill.

Results and Highlights





Completion times and percent of correct responses for the ATM, and Ticket Purchase tasks were significantly better in TRS than UTRS patients. TRS patients were significantly more efficient in all three tasks, as assessed by the ratio of correct answers/time. BACS composite scores were significantly better in the TRS patients. The BACS significantly correlated with time to completion, percent correct and efficiency for each test, while PANSS total scores correlated with every CFAS score other than time to completion on prescription refill. PANSS negative scores were significantly correlated with CFAS performance, and in all cases negative subscale scores were more strongly correlated with CFAS performance than positive scores.

Conclusion

Our study indicates that for patients on clozapine, lower symptom burden is correlated with better cognition and functional capacity. Symptom scores prior to clozapine treatment are not available, but it is likely that the clozapine-responding group had substantially higher symptoms before treatment, as they met clinical criteria for treatment-resistance. We speculate that the better cognitive and functional performance in this group post-clozapine treatment was also related to clozapine. The implication is that clozapine improves cognitive performance and functional capacity as well as clinical symptoms, further supporting the use of clozapine in patients who do not respond to other antipsychotic medicines. The results also further support our hypothesis that clozapine-response can be used generate patient sub-groups.

Next Steps

1. Replicate results prospectively.
2. Investigate the clinical, imaging and biological differences between TRS and UTRS patient subtypes.
    A. Identify biomarkers to determine who will respond to clozapine
    B. Identify the pathophysiological differences between TRS and UTRS forms of SCZ.

Authors:
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[1]Dept of Psychiatry, Johns Hopkins School of Medicine, Baltimore, MD, [2]University of Miami Miller School of Medicine

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Precision Medicine Symposium 2022

Schizoaffective Disorders PMCOE:

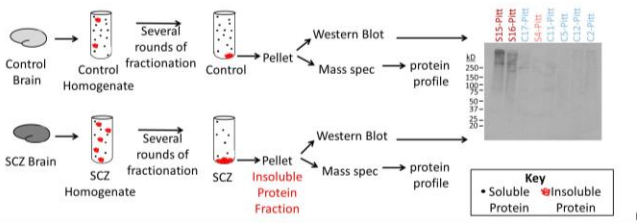
Focus

The mechanisms leading to schizoaffective disorder (a term including schizophrenia with varying degrees of affective symptoms) are likely to be diverse. However, there may be common pathophysiological pathways for as yet undefined patient subsets. In the present study, we hypothesized that disruption of protein quality control can lead to protein insolubility for a subset of patients.

Method & Analytics

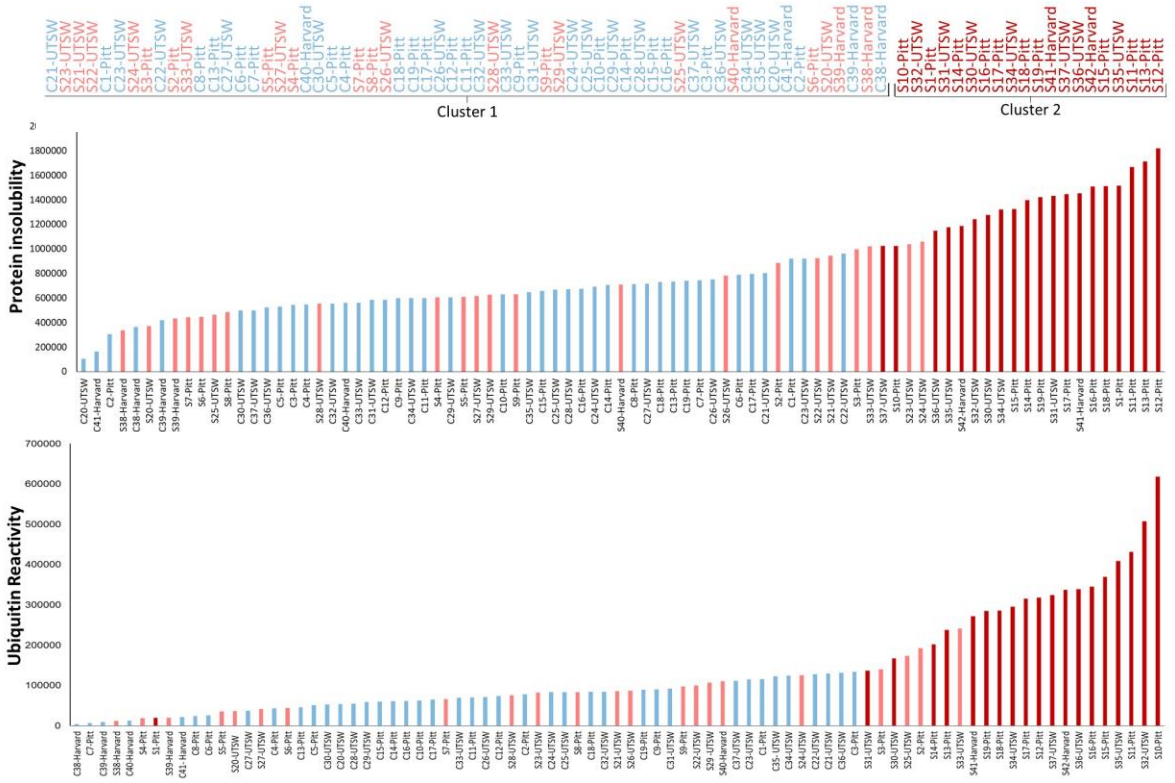
Prefrontal cortex or superior temporal gyrus from autopsy brains of individuals with schizoaffective disorder provided by the University of Pittsburgh, University of Texas Southwestern, and Harvard were subjected to cold sarkosyl fractionation, separating proteins into soluble and insoluble fractions. All pellet samples were analyzed to quantify insoluble protein levels and ubiquitin reactivity, normalized to total homogenate protein. We then performed mass spectrometry analysis to identify the contents of the insoluble pellets. The potential biological relevance of the detected proteins was assessed using Gene Ontology Enrichment Analysis and Ingenuity Pathway Analysis.

Sarkosyl Fractionation and Study Design



Results and Highlights

A subset of patients with schizoaffective disorder showed an increase in protein insolubility and ubiquitination in the insoluble protein fraction. Mass spectrometry of the insoluble fraction revealed that cases with increased insolubility and ubiquitination showed a similar pattern of peptide clustering by principal component analysis. The proteins that were significantly altered in the insoluble pellet were enriched for terms relating to axon target recognition as well as nervous system development and function.



Figures. Hierarchical clustering analysis **(top)** identified two clusters based on protein insolubility and ubiquitination (**Cluster 1 and Cluster 2**). 20 SCZ brains have increased protein insolubility and ubiquitination compared to 23 SCZ brains and 40 controls. The same brains that clustered together in the individual samples clustered together in the combined sample, with the exception of brain S1, which switched to the positive cluster, and brain S33, which dropped out of the positive cluster. Brains in Cluster 2 have significantly greater protein insolubility **(middle)** and ubiquitination **(bottom)** than brains in Cluster 1.

Conclusion

Protein insolubility and ubiquitination are present in a subset of schizoaffective disorder brains. Brains with increased insolubility and ubiquitination exhibited a similar protein expression. The insoluble proteins were enriched for pathways relating to axon target recognition and nervous system development and function. This study suggests a pathological process related to protein insolubility for a subset of patients with schizoaffective disorder.

Next Steps

Protein insolubility may provide pathogenic mechanisms for specific clinical phenotypes. We aim to determine the clinical symptoms that associate with protein aggregation.

A better understanding of the aggregation process and the consequences of aggregation could lead to improved nosology and provide novel targets for therapeutics. To pursue this mechanism, we aim to develop cell models from patient populations, and cell and animal models with specific mutations associated with schizoaffective disorder.

Authors: Nucifora LG[1], MacDonald ML[2], Lee BJ[1], Peters ME[1], Norris AL[1], Orsburn B[1], Yang K[1], Gleason K[3], Margolis RL[1], Pevsner J[1], Tamminga C[3], Sweet RA[2], Ross CA[1], Sawa A[1], Nucifora FG Jr.[1]

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Kidney Precision Medicine Center of Excellence

Director: Chirag Parikh, MD, PhD

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Kidney PMCOE

- **Vision**
  Transform the care of patients with kidney disease, from prevention to diagnosis to treatment, strive to provide patient-centered and best-practice care, and provide diverse opportunities for patients to participate in cutting- edge research to potentially alter the landscape of kidney disease
- **Mission**
  Change how we care for patients at risk of and suffering from kidney disease and modernize kidney research
- **Research Aims**
  - Measure clinical outcomes in patients with both acute kidney injury and progressive chronic kidney disease, applying risk assessments in real-time
  - Improve clinical phenotyping of patients with acute kidney injury
  - Identify barriers to optimal clinical care and target areas for quality improvement initiatives
  - Identify key patient subgroups to enrich enrollment in prospective observational studies and clinical trials

Interested in Collaboration?

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Precision Medicine Symposium 2022

Kidney Precision Medicine Center of Excellence

Focus

The Johns Hopkins Kidney PMCOE was launched in the fall of 2020 with the primary goal of transforming the care of patients with kidney disease.

Initiatives within the Kidney PMCOE have sought to improve patient-centered and best-practice care while increasing opportunities for patients to participate in cutting-edge, innovative research.

Method & Analytics

The kidney failure risk equation (KFRE), which has been globally validated to determine 2 and 5-year risk of kidney failure (needing dialysis or kidney transplant), has been engineered into Epic and is now available to all providers in Epic, using a simple dot phrase (.kfre).

The Novel Approaches in the Investigation of Kidney Disease (NAIKiD) Study has enrolled patients at Johns Hopkins Hospital scheduled for clinically indicated native kidney biopsies to contribute extra urine, blood, and kidney tissue samples towards building a biorepository.

Through the Kidney PMCOE, patient data and biomarker measurements at the time of kidney biopsy can be linked with longitudinal data from Epic to determine trends in kidney function over time and measure adverse kidney outcomes systematically.

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Results and Highlights

In addition the .kfre dotphrase available to all providers in Epic, Nephrology providers are able view a KFRE tab on their Epic sidebar (**Figure 1**). Nephrology providers are also able to open a dedicated dashboard within pre-charting or open encounters to view these risk scores, as well as a graphical representation of kidney function over time that includes estimated glomerular filtration rate overlaid with measurement of albuminuria (**Figure 2**).

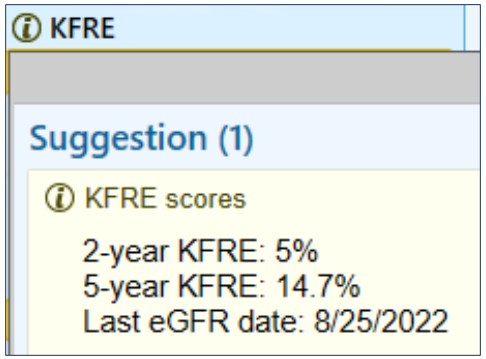

Figure 1. KFRE pop-up on Epic sidebar

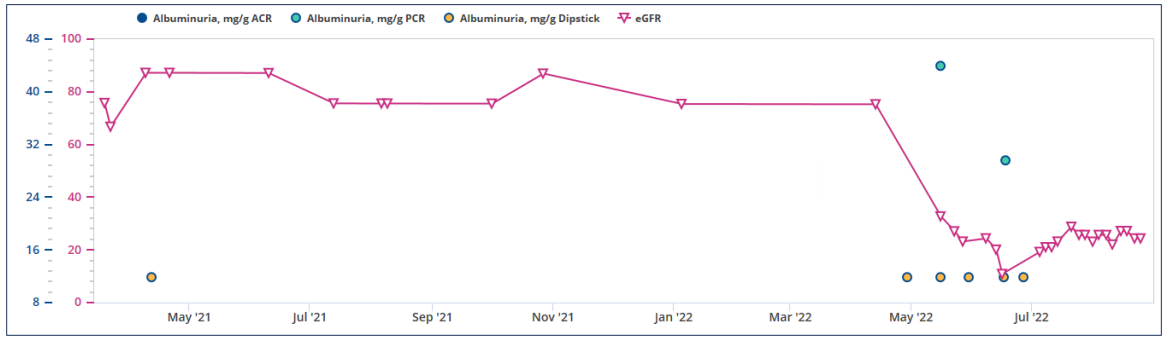

Figure 2. Albuminuria with overlay of estimated glomerular filtration rate over time

The NAIKiD Study began enrollment of inpatients at JHH for urine, blood, and kidney tissue collection in September 2020 and expanded enrollment to outpatients in February 2022, with a total of 164 patients enrolled as of 8/25/2022 (**Table 1**). We are able to link Epic data to participants to evaluate outcomes such as changes in hemoglobin after kidney biopsy (**Figure 3**).

Characteristic	Overall (N=164)	Inpatient (n=113)	Outpatient (n=51)
Age (Mean, SD)	54.6 (16.4)	53.2 (15.8)	57.6 (17.5)
Male (N, %)	77 (47%)	58 (51%)	19 (37%)
Biosamples			
Urine	142 (87%)	96 (85%)	46 (90%)
Blood	134 (82%)	92 (81%)	44 (86%)
Kidney tissue	138 (84%)	98 (87%)	40 (78%)

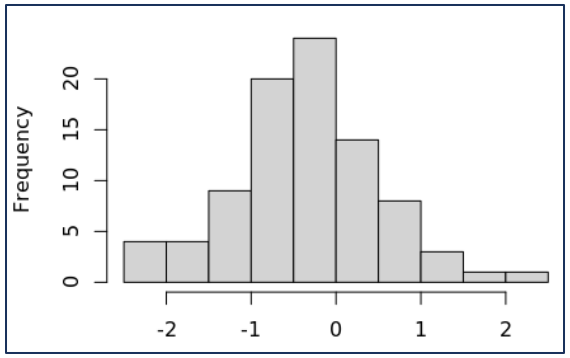

Figure 3. Hemoglobin change 24 hours after kidney biopsy (g/dL).

Conclusion

The Kidney PMCOE has established a number of ongoing initiatives to improve clinical decision making in real time, as well as foster clinical research projects for the future.

Next Steps

- Expand Patient Insight dashboard to all providers in Epic, currently limited to Nephrology providers
- Develop quality improvement initiatives across the Division of Nephrology to improve efficiency of patient care in both inpatient care and outpatient clinics
- Increase multi-disciplinary research with investigators within the institution and amongst Nephrology collaborators outside Johns Hopkins
- Explore opportunities to team with experts in industry to enhance the transition of successful innovations into clinical care

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Funding sources: UH3DK114866 (Kidney Precision Medicine Project), P30DK079310 (O'Brien Kidney Center at Yale), K23DK128538

Office hours: 1-2PM EST on 9/22/22

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Kasper Center of Excellence for Pediatric Genetic Syndromes with Aortopathy

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Kasper Center of Excellence for Pediatric Genetic Syndromes with Aortopathy

- **Vision:**
  The creation of a comprehensive and dynamic database that integrates granular information regarding diagnosis, disease gene, underlying mutation, modifying genetic or environmental variation, age, gender, personal medical history, results of imaging, family history, physical manifestations, and response to prior interventions to recognize patterns within patient subgroups with strong predictive value.

- **Mission**
  Our main goal is the creation of a polyfactorial risk score that takes into account clinically accessible factors basing the decision to proceed with surgery on objective criteria, avoiding unnecessary surgery in stable patients and hastening surgery in patients for whom delay would possibly result in aortic dissection with its attendant morbidity and mortality.

- **Research Aims**
  1) Polyfactorial risk score: As described above, visualized as a graph showing risk of aneurysm/dissection/surgery over the coming months.

  2) Automated calculation of arterial tortuosity. Development of a machine learning algorithm that identifies the vertebral arteries and calculates the tortuosity index.

  3) Evaluate patterns in strain measurements in the aorta, left atrium, and left ventricle in in patients with vascular EDS potentially providing a novel indicator of the risk of aortic complications in these patients

  4) Evaluate if corneal topography can distinguish Marfan Syndrome from other connective tissue disorders and be used as a diagnostic criteria

Interested in Collaboration?

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Precision Medicine Symposium 2022

Kasper Center of Excellence for Pediatric Genetic Syndromes with Aortopathy

Focus

Our center focuses on connective tissue disorders that are characterized by aortic aneurysm and risk of vascular rupture (ex: Marfan Syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos). We know that the spectrum of severity in inherited presentations of aortic aneurysm is wide, both within and between specific diagnoses. As it stands, we currently use limited information about the underlying diagnosis and the size and rate of growth of an individual's aorta to make critical decisions about their prognostic counseling, the frequency and extent of imaging, the screening of family members, the use of medications, and the timing and type of surgery to consider. We seek to create a polyfactorial risk score that considers all clinically accessible factors, basing the decision to proceed with surgery on objective criteria, avoiding unnecessary surgery in stable patients and hastening surgery in patients for whom delay would possibly result in aortic dissection with its attendant morbidity and mortality.

Method & Analytics

We have assembled a cohort of nearly 3000 patients with genetic syndromes with aortopathy. Our primary focus has been appropriate phenotyping and classification of the cohort. To this aim we have worked to create Epic smart forms for standardization of phenotype data as well as vascular measurements obtained from echos, MRAs and CTAs. With this data we have begun preliminary work toward the following goals:

1) Identifying patients with a more severe clinical course who may benefit from earlier aortic root surgery
2) Development of an automated method of calculating the tortuosity index of the vertebral arteries using MRAs and CTAs
3) Evaluate patterns in strain measurements in the aorta, left atrium, and left ventricle in in patients with vascular EDS potentially providing a novel indicator of the risk of aortic complications in these patients
4) Evaluate if corneal topography can distinguish Marfan Syndrome from other connective tissue disorders and be used as a diagnostic criteria

Results and Highlights

Loeys-Dietz syndrome (LDS) is an aggressive aortopathy characterized by aortic and arterial aneurysms/ dissections. Although in general, TGFBR2=TGFBR1>SMAD3>TGFB2>TGFB3 in severity, there is variable expression of vascular, craniofacial, GI and skeletal presentations with some patients severely affected and others with the same variant only mildly affected. While poor outcomes in childhood arerare, vascular catastrophes do occur in this age group. We undertook to examine the TGFBR2 cohort seen at Johns Hopkins University for genotype-phenotype correlation

TGFBR2 N=140				
Occurrence of Vascular Event in Childhood	**Number Affected**	**Type of Vascular Event**	**Genotypes**	**Totals**
1st	46	Aortic root replacement	**R528H/C (16)-32%*** D446G (3) L347P, P427A/L, M434L, D446G/N, R460H/L (2) +21 unique variants	**50 (36%)**
	2	Mitral valve repair		
	1	Ascending aortic dissection		
	1	Aortic valve/root replacement		
2nd	6	Ascending arch aneurysm repair/ dissection	**R528H/C (11)-61%**	**18 (13%)**
	3	Re-do aortic root replacement		
	2	Graft pseudoaneurysm repair		
	2	Coronary pseudoaneurysm repair		
	2	Mitral valve repair		
	1	Subclavian artery repair		
	1	Aortic valve replacement		
	1	Cerebral hemorrhage		
3rd	3	Ascending arch aneurysm repair/ dissection	**R528H/C (8)-89%**	**9(6%)**
	3	Descending aortic dissection		
	2	Subclavian artery repair/dissection		
	1	Aortic graft pseudoaneurysm repair/ rupture		

Total Deaths N=18 (13%)				
Age at Death (Yrs)	**Number**	**Diagnosis**	**Genotypes**	**Totals**
<19	2	Descending aortic dissection	**R528H/C**	**N=5 (28%)** all female & 80% R528H/C
	1	Arch surgery complications	S449F	
	1	Subclavian artery dissection	**R528H/C**	
	1	Unknown	**R528H/C**	
19-31	2	Ascending aortic dissection	V276D	**N=5 (28%)**
	1	Renal artery dissection	**R528H/C**	
	1	Descending aortic dissection	C533R	
	1	Unknown	D524N	
>31	1	Ascending aortic dissection	A355P	**N=8 (44%)**
	1	Mitral valve surgery complication	R495X	
	1	Cerebral hemorrhage	R460H/C	
	1	Aortic arch surgery complication	G253V	
	4	Unknown		

- 20/140 patients in our TGFBR2 cohort (14%)
- Only one familial occurrence
- 17/20 have had aortic root surgery
- Those with R528H/C who had not had surgery at time of data collection were 2, 3, and 18 yo

- Average age (y) for surgery
  - R528H/C and female: 6
  - R528H/C and male: 11
  - All other TGFBR2 variants: 22

Conclusion

While out data suggest that those with R528 variant may require more aggressive surgical practices, there are those with this variant who have a milder course . These individuals show remarkable protection despite overt predisposition. By focusing on these individuals, we hope to uncover the mechanism for this protective modification of their phenotype and work to mimic it through manipulation of medications, environment, lifestyle, etc.

Next Steps

Although the variants presented here appear to have a more severe course, there still exists a significant phenotypic variability both in patients with these variants and in patients with other variants. Additionally, there are significant other complications of connective tissue disease and we do not have an effective means to predict which patients will be affected by these complications and which will not. Our work will continue to refine our predictive capabilities to identify those individuals at risk for events for which early surgical intervention will decrease the morbidity and mortality of these events. We will also undertake to identify modifying features of a patient's course providing insight into the pathophysiology of the disease.

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Precision Medicine Symposium 2022

Prostate Cancer PMCOE: Active Surveillance

Predicting True Pathologic Gleason Score (PGS) During Active Surveillance for Prostate Cancer: Calibration of the Johns Hopkins ActiveCare Model in 5 Large Active Surveillance Cohorts

Christian P. Pavlovich[1], Daan Nieboer[2,3], Mufaddal Mamawala[1], Aki Nishimura[4], Patricia Landis[1], Katarzyna Macura[5], Jonathan Epstein[6], Jozien Helleman[2], Bruce Trock[1], and the Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) consortium
Brady Urological Institute[1], Departments of Biostatistics[4], Radiology[5], Pathology[6] Johns Hopkins School of Medicine
Departments of Urology[2] and Public Health[3] - Erasmus University Medical Center, Rotterdam

Focus

We developed a Bayesian latent state model to predicts *true pathologic Gleason score (PGS)* for men on active surveillance (AS) for low risk prostate cancer[1,2]. This model is run weekly at our institution to help counsel patients. In the present work, we sought to recalibrate our current model to five external cohorts to assess its accuracy and wider applicability.

Method & Analytics

Our "ActiveCare" model predicts PGS of individual AS patients from their demographic, longitudinal PSA, and serial biopsy data, using various regression models (Fig 1.). The overall model is first trained on a dataset that includes patients whose PGS has been confirmed at radical prostatectomy (RP), then predicts unobserved, true PGG for other patients (Fig 2.). We shared the model code with the Global Action Plan Prostate Cancer Active Surveillance (GAP3) initiative, which houses data from 27 AS cohorts (v3.3). Our model was first externally validated using data from five of the largest AS cohorts in GAP3 (Milan, MSKCC, MUSIC, PRIAS, UCSF), and then recalibrated to the each of these cohorts. The ability of the recalibrated ActiveCare model to discriminate between patients with and without PGG >1 was assessed using the area under the ROC (AUC).

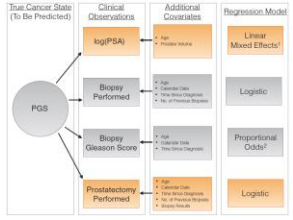

Fig 1. ActiveCare Model Inputs

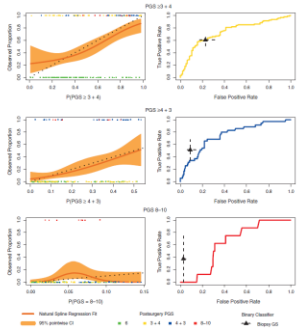

Fig 2. ActiveCare Model Performance at Johns Hopkins for predicting PGS at various cutoffs

Results and Highlights

The ActiveCare model was validated and calibrated to each of the five largest cohorts in GAP3 (7,697 patients overall, Table 1). Median age of patients at diagnosis was 65 and median PSA ranged from 4.6-5.7.
The percentage of AS patients who underwent RP ranged from 9%-26%. The percentage of patients with PGG > 1 at RP ranged from 64%-87%.
At external validation, AUCs ranged from 0.5-0.6. However, by calibrating our model to each cohort, we achieved AUCs competitive with or exceeding those of other prognostic models to date (0.64-0.79) with the added benefit that our model predicts true PGS (rather than biopsy grade group).

		JHU	Milan	MSKCC	MUSIC	PRIAS	UCSF
N		1,311	884	1,006	768	3,519	1,520
Age at diagnosis		66 (62-69)	65 (60-70)	63 (57-68)	65 (60-69)	66 (61-71)	63 (57-68)
PSA at diagnosis		4.8 (3.6-6.2)	5.7 (4.5-7.2)	4.6 (3.4-6.2)	5.2 (4.2-6.8)	5.6 (4.5-7.1)	5.4 (4.2-7.4)
PGS	1	131 (51%)	23 (28%)	53 (28%)	17 (13%)	130 (34%)	73 (18%)
	2	79 (31%)	39 (48%)	104 (56%)	78 (58%)	192 (50%)	241 (60%)
	3	37 (14%)	13 (16%)	21 (11%)	31 (23%)	42 (11%)	62 (15%)
	4	9 (4%)	7 (9%)	9 (5%)	8 (6%)	23 (6%)	26 (7%)
# of patients with RP		256 (20%)	82 (9%)	187 (19%)	134 (17%)	387 (11%)	402 (26%)

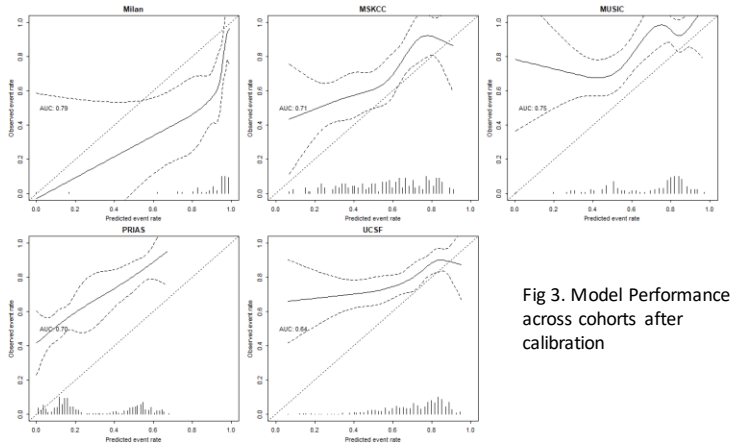

Fig 3. Model Performance across cohorts after calibration

Conclusi

Upon recalibration, our ActiveCare model was able to discriminate between PGS across disparate AS cohorts with good accuracy excepting in one cohort.

Next Steps

Further work to improve across-cohort calibration using hierarchical modeling to allow for borrowing of information across cohorts is underway. In addition, future work to improve the model is underway:

- Addition of longitudinal MRI information
- Calibration across cohorts with MRI information included
- Development of a web-based interface for such a model

References

Coley RY, Zeger SL, Mamawala M, Pienta KJ, Carter HB.
Eur Urol. 2017 Jul;72(1):135-141.
Prediction of the Pathologic Gleason Score to Inform a Personalized Management Program for Prostate Cancer.

Coley RY, Fisher AJ, Mamawala M, Carter HB, Pienta KJ, Zeger SL. Biometrics. 2017 Jun;73(2):625-634.
A Bayesian hierarchical model for prediction of latent health states from multiple data sources with application to active surveillance of prostate cancer.

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Treating Every Pancreatic Cancer Patient as an “Exceptional” Patient

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Pancreatic Cancer PMCOE

- **Vision:**
  The Johns Hopkins Pancreatic Cancer (PaC) PMCOE was launched in November 2017 with the primary goals of both identifying clinical, genomic, and imaging biomarkers of "Exceptional" patients and translating this evidence into the discovery of new therapeutic strategies
- **Mission**
  Treating every pancreatic cancer patient as an exceptional one.
- **Research Aims**
  Pancreatic Cancer PMCOE delivers on the promise of precision medicine through five core foci of integrated care and research:

- a Nation's first multidisciplinary clinic for pancreatic cancer as a "one-stop shop" for patients;
- a standardized pathway for clinical NGS test ordering, tracking, reporting and data capture;
- an Openspecimens system that track biospecimens from clinical trials and also from biobanking protocols;
- a PMCOE registry database to capture clinical and genomic data and the EPIC structured data projection
- a user friendly platform that images the registry database for flagging actional genetic alterations and for cohort discovery.

Interested in Collaboration?

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Precision Medicine Symposium 2022

Pancreatic Cancer PMCOE

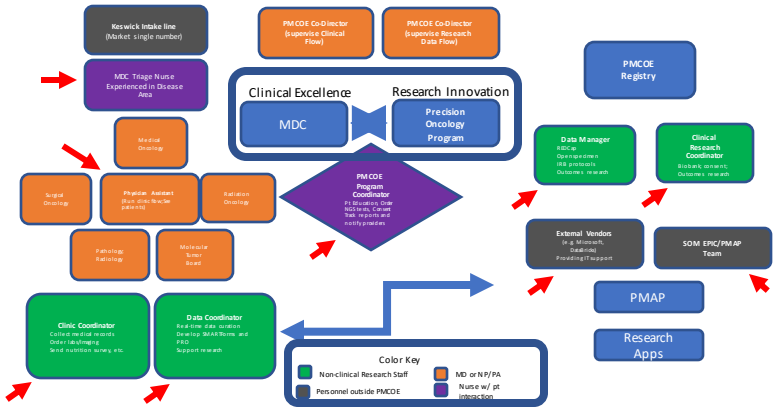
Focus

Pancreatic Cancer PMCOE delivers on the promise of precision medicine through five core foci of integrated care and research:

- a Nation's first multidisciplinary clinic for pancreatic cancer as a "one-stop shop" for patients;
- a standardized pathway for clinical NGS test ordering, tracking, reporting and data capture;
- an Openspecimens system that track biospecimens from clinical trials and also from biobanking protocols;
- a PMCOE registry database to capture clinical and genomic data and the EPIC structured data projection
- a user friendly platform that images the registry database for flagging actional genetic alterations and for cohort discovery.

Venues

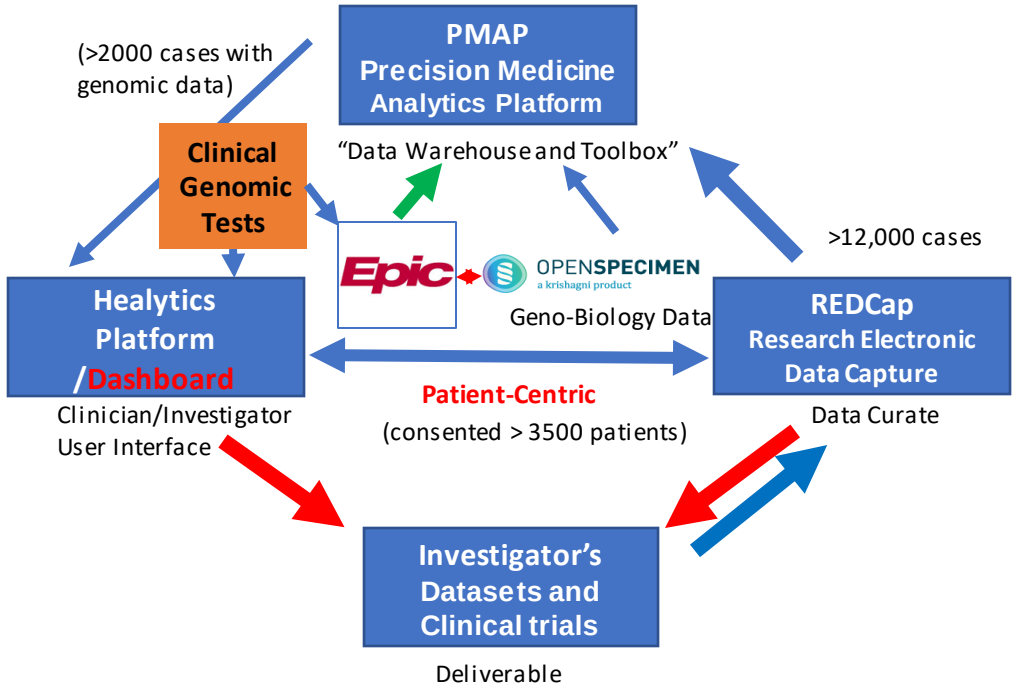
Pancreatic Cancer Precision Medicine Multi-Disciplinary Clinic



Results and Highlights

- Since its inception, over 3,000 pancreatic cancer patients have participated in the PMCOE.
- The Johns Hopkins Pancreatic Cancer PMCOE Registry is one of the largest disease specific registry with more than 13,000 patient records and is being leveraged for clinical genomic test results from approximately 1,500 recent patients.
- It is also being used, with other Epic-derived data, to generate predictive models to more specifically identify patients with exceptional responses to the treatments and to discovers the genomic and imaging biomarkers that predict the responses to the treatments.
- The PMCOE Registry REDCap database has provided clinical datasets, historical control cohorts, and biospecimens that are tracked by Openspecimens to support over 40 active research projects per year.

Build a precision medicine electronic health data ecosystem (EPHDE)



Conclusion

Through supporting multiple projects, the Pancreatic Cancer PMCOE program is able to identify potential clinical, genomic, and imaging biomarkers to predict patient's outcome and also translate this evidence into the discovery of new therapeutic strategies that are currently being tested in the ongoing clinical trials (publications bleow).

Next Steps

To demonstrate that the precision oncology practice at the Pancreatic Cancer PMCOE can improve the patients' long-term outcomes.

Publications in 2022 using PMCOE clinical and genomic registry

Li et al. Cancer Cell 2022
Ivey et al. .World J Surg. 2022
Reddy et al. Gastrointest Oncol. 2022
Javed et al. Curr Probl Diagn Radiol. 2022
Xie F et al. .JCO Precis Oncol. 2022
Seppälä et al. Clin Cancer Res. 2022
Hill CS et al. .Pract Radiat Oncol. 2022
Reddy AV et al. Gastrointest Oncol. 2022
Hill C et al. .Cancer Med. 2022
Hill CS et al. Ann Surg Oncol. 2022
Shi DD et al. .Lancet Oncol. 2022
Reddy AV et al. Curr Oncol. 2022

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Neonatal Precision Medicine Center of Excellence

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Neonatal PMCOE

- **Vision:**
  To identify, quantify, and define early predictors of clinical outcomes and lower barriers to research and personalized medicine for all neonates
- **Mission**
  Develop the infrastructure and expertise that will allow for personalized evaluation, counseling, management, and **prevention** of neonates at risk for adverse outcomes
- **Research Aims**
  - Can we develop a tool for timely identification of neonatal ICU factors that impact on ultimate brain health?
  - Can we unify nuanced neonatal data collection into the OMOP common data model format?
  - Can we develop an objective and quantifiable scoring system to predict dynamic individualized in-hospital and longer term neonatal outcomes which are EHR compatible and scalable?

Interested in Collaboration?

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Precision Medicine Symposium 2022

Neonatal Brain Injury: Hypoxic Ischemic Registry to Augment Research and Improve Patient Care

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Introduction

- Neonates with Hypoxic Ischemic Encephalopathy (HIE) are at high risk for significant morbidity and mortality
- Therapeutic Hypothermia (TH) is the only strategy proven to provide neuroprotection to infants with HIE
- Infant with HIE generate millions of clinical data points during their initial neonatal intensive care unit (NICU) admission.
- HIE research is limited by:
  - Underpowered 'small' datasets
  - Narrowly focused research studies
  - Labor intensive and siloed data collection

Objectives

- Develop a comprehensive clinical data set specific to patients undergoing TH for HIE via the Johns Hopkins Precision Medicine Analytics Platform (PMAP) that utilizes the OHDSI OMOP CDM (Observational Health Data Sciences and Informatics Observational Medical Outcomes Partnership, Common Data Model).

Key Terms

- **CDM:** Formats used to store electronic health record (EHR) data in a consistent way – **OHDSI** is a CDM which utilizes **OMOP** terminology
- **Atlas** is an open source application used with **OHDSI/OMOP** to provide a unified interface for data and analytics
- **Cohort Definition** is a computable inclusion/exclusion criteria for events to identify a list of patients for a period of time
- **Data Element Definition** is a computable list of which data elements/concepts to be included
- **Database projector** takes a **cohort definition** (list of patients) and a data specification to project that data to a database at a regular interval.

Methods

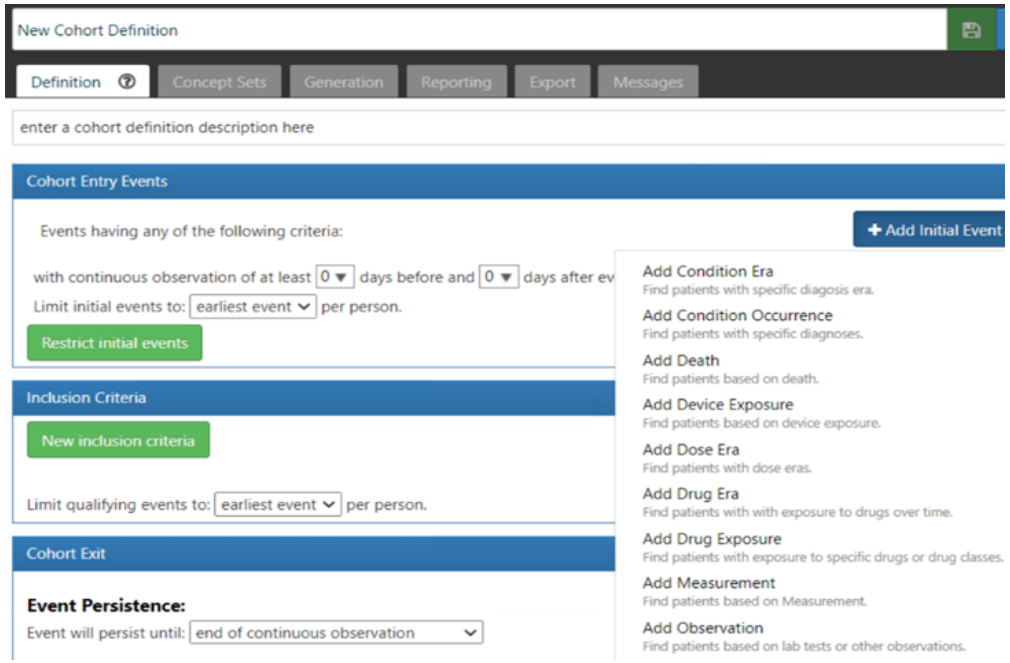

Figure 1. Atlas application interface to define and build study cohorts

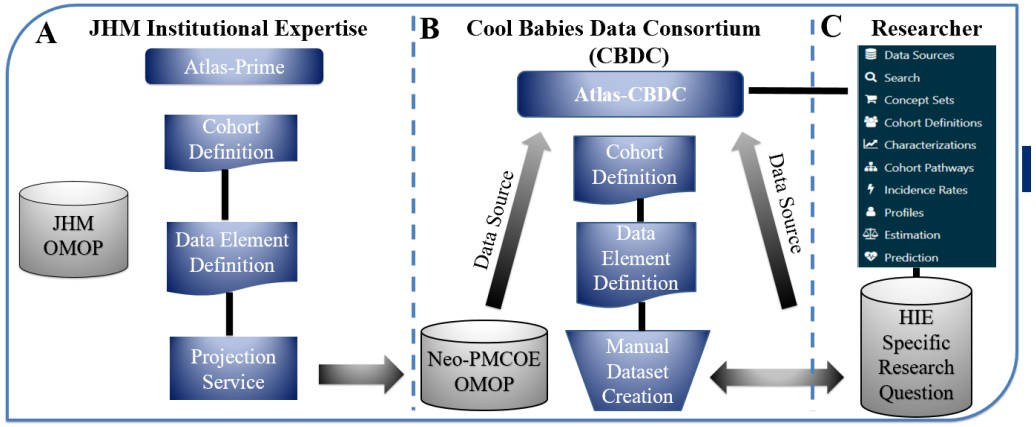

Figure 4. OMOP on PMAP Schematics A. JHM, in conjunction with the OHDSI/OMOP establishes Atlas Prime and terminology. B. CBDC is an automated central HIE registry among participating institutions. C. Researcher interface with CBDC

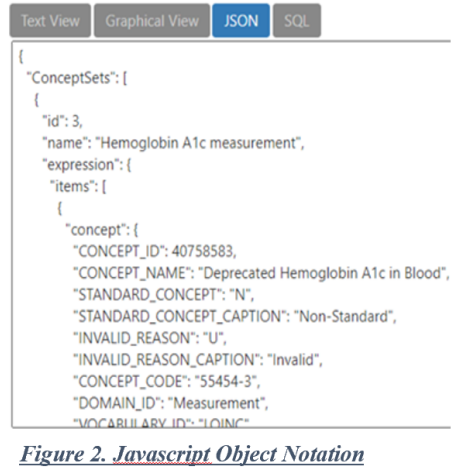

Figure 2. Javascript Object Notation (JSON) automatically populated by Atlas for a particular project. for sharing and exchanging data.

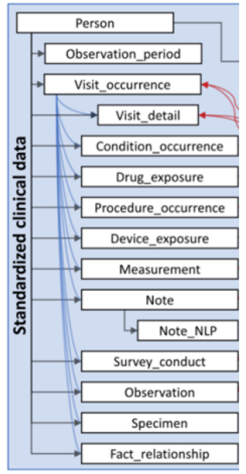

Figure 3. OMOP Standardized clinical data elements.

Conclusion & Future Directions

- Lower the activation energy for collaboration and research
- "Living" registry
- Institutional participation – multicenter R01
- OMOP CDM will be applicable to all of neonatology for various diseases and discrete questions
- Incorporate other CDMs that are routinely used in the US

Abbreviations

- Hypoxic Ischemic Encephalopathy (**HIE**)
- Therapeutic Hypothermia (**TH**)
- Neonatal Intensive Care Unit (**NICU**)
- Precision Medicine Analytics Platform (**PMAP**)
- Johns Hopkins Medicine (**JHM**)
- Common Data Model (**CDM**)
- Observational Health Data Sciences and Informatics (**OHDSI**)
- Observational Medical Outcomes Partnership (**OMOP**)
- Cool Babies Data Consortium (**CBDC**)

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Neonatal PMCOE: Acute Kidney Injury in Extremely Preterm Infants

UFHealth Shands children's Hospital

Focus

- Among patients admitted to the neonatal ICU (NICU), the frequency of AKI ranges from 18-70%.Short-termmortality risk as well as long-term kidney complications including hypertension are associated with neonatal AKI. Neonatal AKI is commonly defined using age-modified Kidney Disease: Improving Global Outcomes (KDIGO) criteria wherein the severity of AKI is determined by the magnitude of changes in serum creatinine (sCr) or urine output (UOP). However, the longitudinal incidence of AKI from birth to death or discharge in this unique population, including the criterion and values that substantiated AKI, as well as the temporal relationship of AKI to neonatal severity of illness and adverse in-hospital outcomes remains unclear.

Method & Analytics

- We comprehensively measured AKI from birth to death or discharge using >13,000 sCr values (NICU hospitalization) and >2500 measures of UOP (first week of life)in436 inborn, extremely premature (<29 weeks completed gestation), extremely low birth weight (<1000 grams)infants with special attention to the frequency and to what KDIGO component substantiated AKI (UOP or Cr). We examined clinical characteristics of patients that developed AKI, when AKI developed, impact of AKI on adverse in-hospital outcomes, the relationship of AKI with medication dosing, mortality andq1 hour measures of severity of illness including cardiovascular dysfunction. We also used Shapley Additive Explanations(SHAP)-based analysis and visualization of clinical variables in an NICU population to convey importance of each variable as a singular entity and relative to competing risks.

Results and Highlights

Figure 1. First-week acute kidney injury (AKI) in the extremely low birth weight, extremely preterm infant. A. Frequency of AKI by day of life among all patients in the cohort. **B.** Distribution of AKI type by day of life among those with AKI. **C.** *Kidney Disease: Improving Global Outcomes* (KDIGO) criterion met for AKI by day of life among those with AKI. **Note this work is by currently under review.*

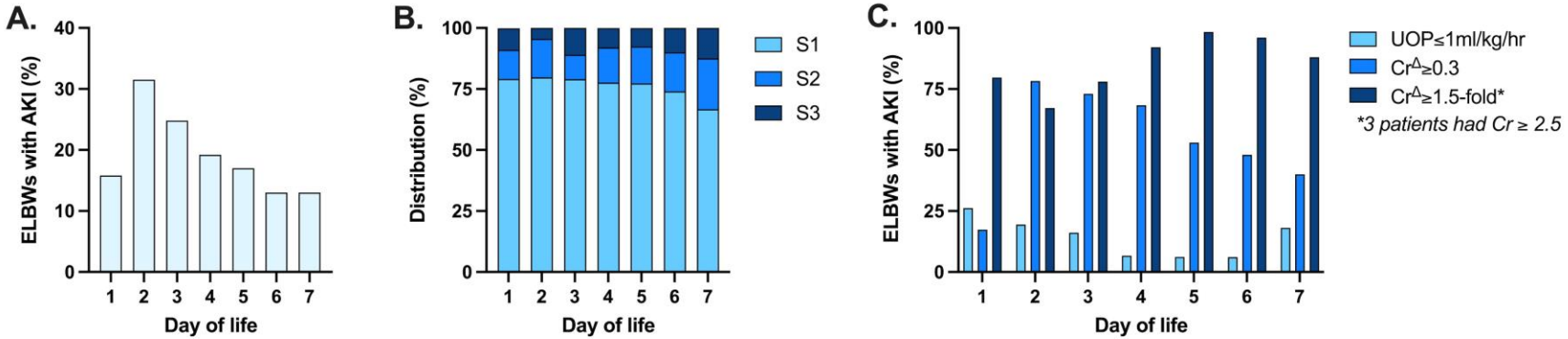
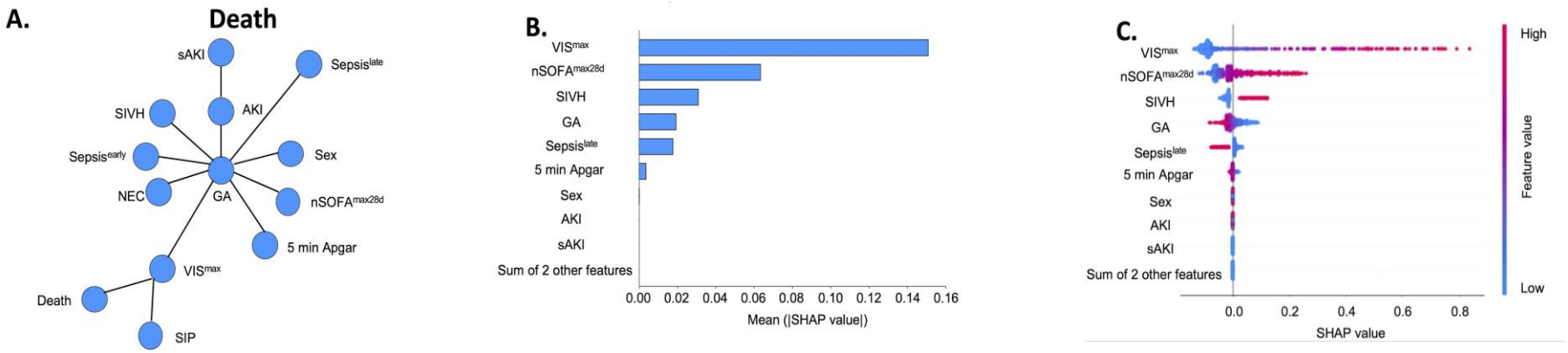


Figure 2. Structural Models and SHAP Values. A. Structural model for death (anytime) as the primary node. Structural models illustrate relationships between individual clinical variables/outcomes (features) and death (primary node). Lines and circles represent undirected relationships among variables using the maximum likelihood estimation. **B.** SHAP feature importance for death (anytime) as mean absolute Shapley Values. Sum of 2 other features (variables) includes spontaneous intestinal perforation and early onset sepsis. **C.** SHAP summary plot for death (anytime)**.** SHAP feature important and summary plots visually represent the importance of individual variables, effects on the model, and directionality of effect. ***Note this work is by currently under review.*



Conclusions: AKI was common in ELBWs, primarily in the first week of life, was inversely associated with gestational age, and followed organ (primarily cardiovascular) dysfunction. AKI considered as the primary pathway to mortality was rare and amelioration of AKI to modify the outcome of death was not well supported.

Next Steps: In this collaboration with Dr. Wynn at University of Florida, we demonstrate the ability analyze granular data from an outside academic center within our PMAP platform; next we will use PMAP and the OMOP common data model to study a wide array of neonatal pathologies and research questions.

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Path to Precision in Neurocritical Care

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PMCOE FOR NEUROCRITICAL CARE

Vision

Leverage high-resolution multi-dimensional data, mechanistic hypotheses, and advanced modeling (including artificial intelligence) to effectively and efficiently enhance the care and outcome of critically ill neurological patients

Mission

- To establish and scale a data-driven research program in neurocritical care
- To create an institutional resource for research in Precision Therapeutics
- To secure funding via federal agencies (NIH, NSF) and industry partnerships

Research Aims

Aim 1. To develop and validate a highly accurate risk prediction score for post-operative neurosurgical complications.

Aim 2. To develop and validate a highly accurate risk prediction index of neurological (and physiologic) deterioration for patients admitted to the NCCU (Aim 2A). To predict timely and safe discharge of patients from the NCCU (Aim 2B).

Aim 3. To determine the efficacy and cost-effectiveness of the NCCU triage score and neurologic/physiologic deterioration indices by testing them in clinical trials evaluating feasibility safety, clinical outcome, and health-economic endpoints.

Interested in Collaboration?

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Precision Medicine Symposium 2022

PMCOE for Neurocritical Care

Focus

- Neurocritical Care focuses on the care of critically ill patients with primary or secondary neurological and neurosurgical disorders
- The neurocritical care unit (NCCU) is a data-intensive and clinically complex environment
- There is a significant untapped opportunity to improve decision-making in neurocritical care by leveraging methods from data science & informatics
- The NCCU PMCOE is designed to address unmet needs in detection, diagnosis, classification, treatment, prevention, and prognostication as they relate to patients treated in the NCCU

Method & Analytics

- Large and comprehensive data repository containing NCCU patient-level data from multiple sources including electronic health record (EHR), high-frequency physiologic data, and neuroimaging
- Each electronically controlled bed is equipped with a monitor GE Carescape (GEC), a connectivity interface Capsule Neuron Computing Hub (CNCH), used for sensor/devices not compatible with GEC, and a clinical workstation linked to the JHH Clinical Intranet (including EHR/EPIC)
- Synchronization compatibility issues were addressed using an agnostic FDA-approved, commercially available analytic platform, (Sickbay™) [Figure 1]

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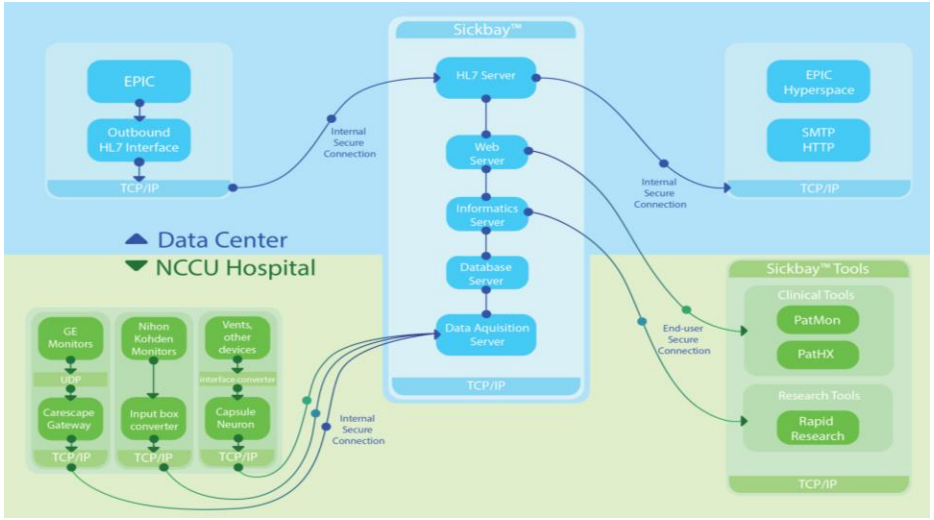

Figure 1: A workflow diagram demonstrating the flow of data through the Sickbay™ system. Briefly, physiological data is collected by monitors at bedside, transferred through the Sickbay™ system and to analysis tools and the EHR/EPIC.

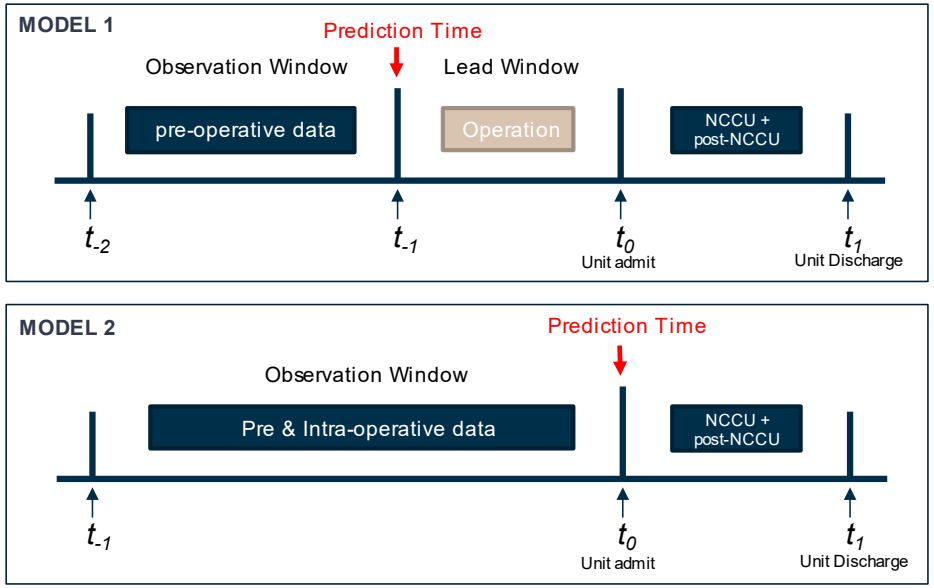

Figure 2: A timeline diagram demonstrating two options for predictive modeling.

Results and Highlights

- Complete EHR/EPIC data collected from 14,000 NCCU patients from 2016-2022
- High-frequency data collected from 7,000 NCCU patients from 2018-2022
- Neuroimaging segmentation currently underway
- Current focus is addressing Aim 1 (Develop and validate a highly accurate risk prediction score for post-operative neurosurgical complications)
- We will evaluate two time windows for prediction modeling: pre- and pre + intra-operative [Figure 2]
- Generalized linear models, random forest, and gradient boosting machine (among others) will be used for predictive modeling
- Model performance will be compared using multiple metrics to determine not only the best performing model between modeling methods, but also the most clinically tractable models

Conclusion

It is feasible to construct a complex and multidimensional repository of Neurocritical care data to develop prediction models of outcome.

Next Steps

- Finalize neuroimaging segmentation and processing
- Curate high-frequency physiological data
- Train, test and validate prediction models

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NCCU PMCOE: "Analyzing Multi-Modal Datasets in PMAP"

Focus

- The NCCU PMCOE research goals require multi-modal data to be used for analysis and prediction
- Data fall into three main modalities: imaging, physiological ("physio"), and clinical/EHR
- Large scale modalities like imaging and physio data require optimized processing due to their size and compute requirements
- High dimensionality data (again imaging and physio) require dimensionality reduction before incorporating into predictive models

Conclusion

- Data in the NCCU PMCOE is collected from multiple sources
- Complex and high dimensionality data requires optimized storage and compute power
- Databricks and the Phoenix HPC provide powerful analysis options for big datasets
- Multi-modal data after preliminary analysis can be collected and used in predictive modeling within PMAP

Next Steps

- Imaging in PMAP is being transferred to a XNAT instance for future processing
- Patient encounter timelines are being created to align data from different sources
- Features of interest need to be evaluated for predictive value
- Neuroimaging segmentation is on-going
- Databricks is being explored as a common processing system for all NCCU data sources

Imaging

- Brain MRIs are collected and segmented for brain tumors
- Segmentation pipeline involves multiple state-of-the-art methods for image analysis including super-resolution, registration and segmentation using AI
- Segmentations produce volumes for tumor classes (enhancing, core, edema)
- Future analysis will include tumor location

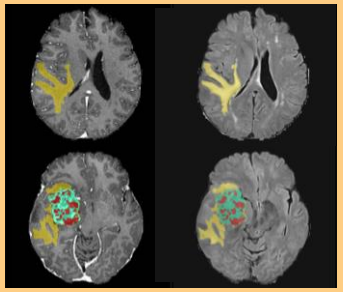

Figure 1: Example brain tumor segmentation from the NCCU PMCOE cohort

Physio

- Physio data are collected from Sickbay™ connected devices
- Time-series data includes ECG, blood pressure, intracranial pressure, pulse ox, etc.
- Many data types have 100s of measurements per second -> huge datasets
- Analysis will include windowed statistical metrics and functional data analysis
- Databricks provides optimized storage and compute to extract these large datasets quickly for analysis

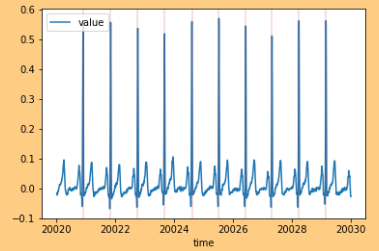

Figure 2: Example ECG window with heartbeat detection overlaid

Clinical

- Clinical/EHR data from EPIC is projected into a MSSQL database accessed through SAFE
- Data including demographics, static clinical measurements, and medications will all be considered for possible inclusion in the predictive model
- EHR data are also used to build a "patient encounter timeline" so that a patient can be tracked throughout their hospital stay even through different units
- This timeline allows alignment of the multi-modal data by identifying points of care in different arenas (e.g., bed identification for Sickbay™)
- Complications can also be tracked and codified from EHR data, an important step to target patients when attempting to predict their care requirements

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Myositis PMCOE

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Myositis PMCOE

- **Vision:**
  To use our multidisciplinary approach, trajectory analysis, and novel subgroup identification to tailor the monitoring and treatment of the disease to the individual.

- **Mission**
  To leverage the longitudinal nature of our clinical cohort, coupled with prospectively collected biospecimens, to better classify unique phenotypes of IIM.

- **Research Aims**
  (1) Identifying distinct patient trajectories related to muscle, lung, joint, and skin involvement.

  (2) Determining clinical and biological predictors of response to different treatment regimens.

  (3) Tailoring cancer screening recommendations to distinct subgroups of myositis patients.

Interested in Collaboration?

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Myositis PMCOE

Background of Myositis

Idiopathic Inflammatory Myopathies (IIM, commonly referred to as simply 'myositis') comprise a group of rare chronic autoimmune diseases affecting multiple organ systems that can lead to substantial morbidity and mortality. While many of the underlying mechanisms of IIM remain unknown, the disease expression can impact the muscles, lungs, joints, skin, and heart. The diseases can be subclassified based on clinical type (dermatomyositis, polymyositis, necrotizing myopathy) or biomarkers in the blood such as autoantibodies (e.g. anti-Jo1, anti-NXP2, anti-HMGCR). Current therapies for IIM are generally nonspecific, are not targeted to individual disease pathologies, and often are prescribed on a 'trial and error' basis.

Launch of Myositis PMCOE

The Johns Hopkins Myositis Precision Medicine Center of Excellence was launched in 2018 with the vision of increasing the efficiency of healthcare delivery to patients with IIM and to use our multidisciplinary approach, trajectory analysis, and novel subgroup identification to tailor the monitoring and treatment of the disease to the individual. Our mission is to leverage the longitudinal nature of our clinical cohort, coupled with prospectively collected biospecimens, to better classify unique phenotypes of IIM. Precise phenotyping allows for a directed personalized approach to potentially better identify early signs of disease flare, determine appropriate clinical trial candidates that represent more homogenous groups, and eliminate the longstanding trial and error approach of therapeutic decision making. To date we have streamlined electronic consenting, automated biospecimen collection including DNA, RNA, sera, and PBMCs, and developed myositis-specific SmartForms within EPIC.

Ongoing Projects and Highlights

(1) Identifying distinct patient trajectories related to muscle, lung, and skin involvement.

- Using prospectively collected SmartForm data, we are identifying distinct trajectories within our cohort related to organ-specific complications. This is performed through serial strength training and CK/aldolase lab testing (muscle), pulmonary function testing and HRCT reports (lung), and CDASI activity scores (skin) [Figure 1].

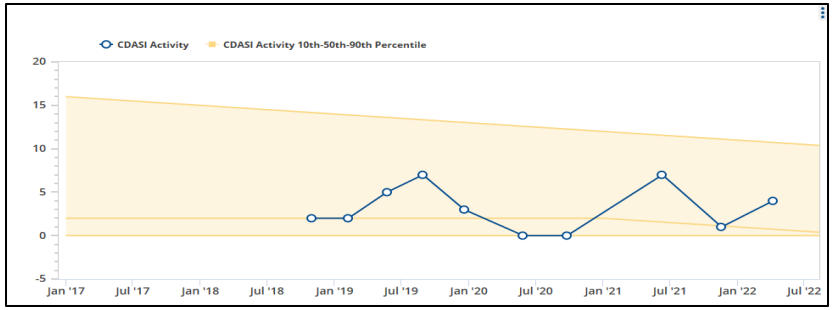

Figure 1: Skin trajectory over time compared to entire cohort (shaded yellow)

(2) Determining clinical and biological predictors of response to different treatment regimens.

- We are currently collaborating with the Applied Physics Laboratory using the All of Us Illumina array to genotype a subgroup of our cohort, with the goal of predicting adverse events and ineffectiveness of common 1st line agents used to treat myositis.

(3) Tailoring cancer screening recommendations to distinct subgroups of myositis patients.

- We have validated several novel biomarkers to improve risk-stratification for contemporaneous cancer, a complication occurring in up to 10% of patients. We now seek to expand this work and build a cancer prediction tool to inform clinical decision-making, embedded within EPIC and also available as a public-facing website.

(4) Develop a myositis-specific vocabulary for Observational Medical Outcomes Partnership (OMOP).

- A myositis-specific vocabulary will enable the pooling of disparate myositis cohorts, validate findings, and facilitate network studies using real-world data. We are working with key stakeholders in the myositis community to accomplish this goal.

(5) Development of visualization tool within EPIC to inform patient/clinician/referring provider decision-making [Figure 2].

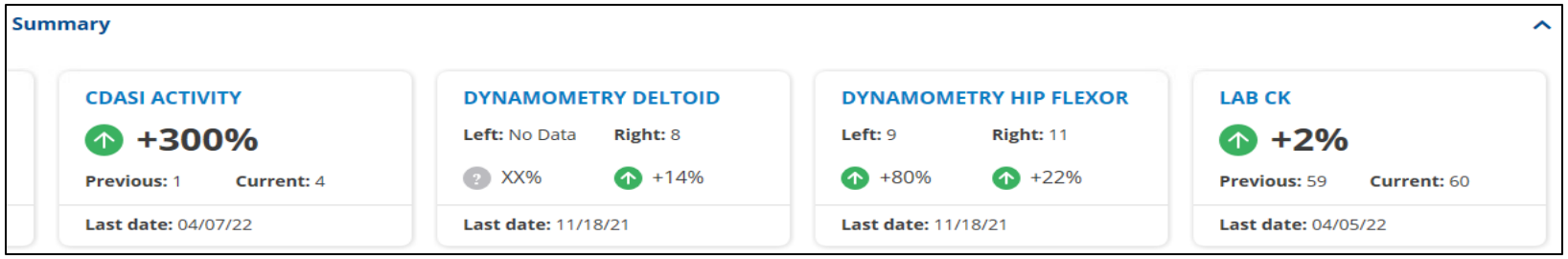

Figure 2: Key Metrics for Clinical Decision-Making

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Multiple Sclerosis (MS) PMCOE

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Multiple Sclerosis PMCOE

Launched: April 2017

The Johns Hopkins MS PMCOE was launched in April 2017 with the primary goals of both identifying clinical, imaging, and blood biomarkers of long-term disability risk as well as translating this evidence to clinical trials to identify new therapeutic strategies to prevent disability and promote repair in people with MS. With a team that includes 12 MS neurologists as well as experts in MS epidemiology, neuroimaging, neuropsychology, and neurorehabilitation, the expanded center delivers on the promise of precision medicine through five core foci of integrated care and research: 1) technology-enabled tracking of neurologic functional performance (via the sponsored MS PATHS project) and systematic clinical data capture at every clinic visit via an internally-developed Smartform; 2) baseline and annual non-invasive imaging of optic nerve damage using optical coherence tomography (OCT); 3) collection of blood at biannual clinic visits for research to identify biomarkers of prognosis and treatment response; 4) standardization of annual surveillance brain magnetic resonance imaging (MRI) across (and beyond) the Johns Hopkins Health System; and 5) home-based collection of data regarding environmental and lifestyle exposures that may be relevant to the prognosis of MS.

Since its inception, over 2,000 people with MS have participated in the PMCOE. The Johns Hopkins MS Smartform is enabling efficient collation of information relevant to MS state and is being leveraged to graphically project the individual disease course for a given patient. It is also being used, with other Epic-derived data, to generate predictive models to more specifically determine if a given person will likely benefit from brain MRI scan at a given timepoint, with early estimates suggesting ~60% of patients can be correctly classified as not requiring a surveillance scan. The Johns Hopkins MS Smartform is being widely adopted across other prominent institutions throughout the US. Concomitantly, an ongoing project is evaluating the performance of serum neurofilament light chain (sNfL) as a prognostic biomarker and monitoring tool in MS.

https://www.hopkinsmedicine.org/inhealth/precision-medicine-centers/multiple-sclerosis/index.html

Office Hours:

Interested in collaborating? Join us for office hours: Friday, September 23@1:00PM
https://jhjhm.zoom.us/j/5704293332
Host: Ellen Mowry, emowry1@jhmi.edu

Precision Medicine Symposium 2022

MS PMCOE: "Long term exposure to ambient air pollution is associated with markers of neuronal injury in people with multiple sclerosis"

Eleni Vasileiou, MD; Kathryn Fitzgerald, ScD

Focus

- Multiple sclerosis (MS) is a neuroinflammatory disorder of the central nervous system and contributors to its heterogeneity remain poorly understood
- Neurofilament light chain (NfL) is a nerve sheath protein released in the serum during incidents of neuronal damage (**Figure 1**)
- Serum NFL (sNfL) levels have been associated with clinical and radiologic outcomes in MS and can be used as a sensitive biomarker of disease activity

- High ambient air pollution exposure is associated with neuroinflammation in the general population
- Here, we assessed the association of air pollution with sNfL levels

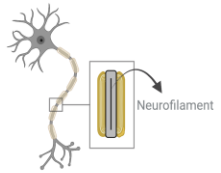

Figure 1. Neurofilament light chain released during events of neuronal injury

Method & Analytics

- Annual fine particulate matter of diameter ≤2.5μm ($PM_{2.5}$), ozone(O_3) and nitric oxide (NO_2) exposure were estimated using spatial resolution of 1km an updated over follow-up.
- Estimates were linked to geocoded addresses updated in each clinical encounter on the Precision Medicine Analytics Platform (PMAP)
- Pollution exposure was estimated as the cumulative average of the recorded exposure over follow-up and prior to sNfL blood draw. (**Figure 3**)
- sNfL was measured using a high-throughput immunoassay (Siemens), and age-specific cut-points of sNfL and Z-scores were derived from a comparable cohort of healthy controls (n=201)
- Statistical analyses were performed using generalized linear models
- Analyses were adjusted for multiple sociodemographic, neighborhood, comorbid, and MS-related characteristics derived from the PMAP

Results and Highlights

- Pollution exposure for the 1113 MS patients included was recorded over a median of 7.1 years prior to sNfL blood draw. Cohort characteristics at the time of sNfL measurement are presented in **Table 1**

		Quantile of PM 2.5				
	Overall	1st	2nd	3rd	4th	5th
Number of participants	1113	223	222	223	222	223
Age, mean (SD)	47.16 (12.3)	47.48 (12.3)	47.29 (12.3)	47.89 (12.7)	46.14 (11.7)	47.01 (12.6)
Male Sex, n (%)	276 (24.8)	57 (25.6)	65 (29.3)	42 (18.8)	53 (23.9)	59 (26.5)
White Race, n (%)	837 (75.2)	173 (77.6)	177 (79.7)	153 (68.6)	162 (73.0)	172 (77.1)
Years of education, mean (SD)	15.71 (2.55)	15.76 (2.43)	16.00 (2.42)	15.66 (2.77)	15.80 (2.60)	15.33 (2.51)
Current smoker, n (%)	101 (9.1)	18 (8.1)	22 (9.9)	19 (8.5)	23 (10.4)	19 (8.5)
BMI >30	394 (35.4)	82 (36.8)	72 (32.0)	78 (35.0)	77 (34.7)	86 (38.6)
Disease duration, n (%)						
0-6	268 (24.1)	74 (33.2)	47 (21.2)	46 (20.6)	45 (20.3)	56 (25.1)
7-21	581 (52.2)	96 (43.1)	134 (60.3)	120 (53.9)	122 (55.4)	108 (48.4)
Progressive MS (%)	330 (29.6)	74 (33.2)	66 (29.7)	66 (29.6)	59 (26.6)	65 (29.1)
Treatment class, n(%)						
Injectable	342 (30.7)	68 (30.5)	67 (30.2)	74 (33.2)	65 (29.3)	68 (30.5)
Infusion	309 (27.8)	56 (25.1)	74 (33.3)	51 (22.9)	68 (30.6)	60 (26.9)
Oral	278 (25.0)	59 (26.5)	49 (22.1)	55 (24.7)	55 (24.8)	60 (26.9)
EDSS, mean (SD)	2.73 (1.95)	2.75 (1.98)	2.54 (1.97)	2.80 (1.94)	2.57 (1.80)	2.97 (2.06)

EDSS: expanded disability scale status

- $PM_{2.5}$ exposure were associated with higher sNfL Z-scores (per 1SD increase in $PM_{2.5}$: 0.16; 95%CI: 0.08-0.24; p<0.001)
- Similar trend in sNfL z-scores was identified when O_3 was assessed (per 1SD increase in O_3: 0.08; 95%CI: 0.00-0.17; p=0.05). This trend was not observed for NO_2

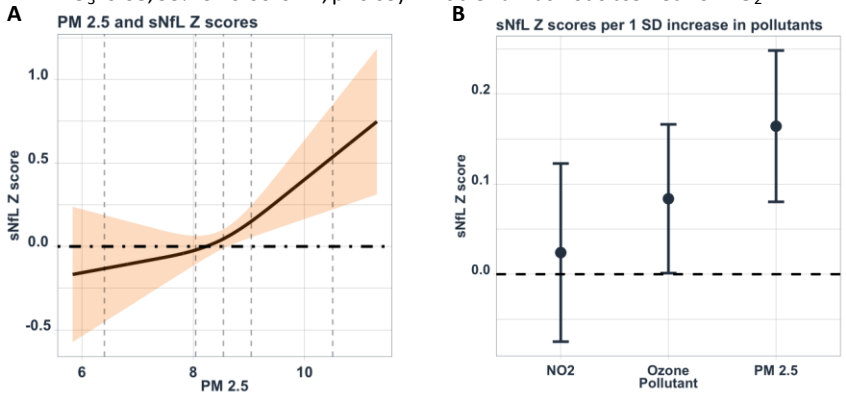

Figure 2: **A.** Restricted cubic splines model depicting the association of sNfL z-scores with levels of $PM_{2.5}$. Vertical dotted lines denote the 2.5th, 25th, 50th, 75th and 97.5th percentile of PM_{25} distribution; **B.** sNfL z-scores per 1 standard deviation (SD) increase in NO_2, O_3 and PM_{25}. All analyses were adjusted for age, gender, race, disability status, disease duration, disease modifying treatment, disease subtype, BMI, diabetes, smoking status, population density in area of residence, years of education

- Higher composite pollution exposure was associated with higher sNfL Z-scores (per 1SD increase in pollution mixture: 0.14; 95%CI: 0.02-0.25; p=0.02)
- Results remained unaltered when restricting to participants without a change of address during follow-up or when using sNfL levels >97.5th

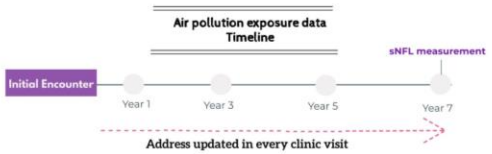

Figure 3. Timeline of air pollution data. Pollution exposure was estimated as the cumulative average over a median time of 7 years of follow-up.

Conclusion

- Higher ambient air pollution was significantly associated with increased subclinical measures of disease activity in people with MS

Next Steps

- Unravel the magnitude of the impact of ambient pollution on disease prognosis in PwMS by evaluating additional biomarkers of MS activity like optical coherence tomography (OCT)
- Examine the interplay of environmental, socioeconomic and lifestyle factors on differential MS outcome.

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Multiple Sclerosis PMCOE: "Curating a Large-Scale Clinical Imaging Dataset in PMAP"

Focus

- Imaging is a core component of the MS PMCOE
- Analysis of images derived from clinical care is hampered by logistical, technical, and regulatory challenges
- PMAP allows the MS PMCOE to collect, curate, and analyze images stored in clinical systems

Method & Analytics

- The MS PMCOE MR imaging projection includes >14,000 patients and >70,000 MR imaging sessions
- DICOM images were selected for projection from the vendor neutral archive (VNA) using specific procedure codes for MRIs regularly used in MS care
- Images are projected from the VNA to Azure Blob Storage for use in analysis (totals 5.79TiB of data)

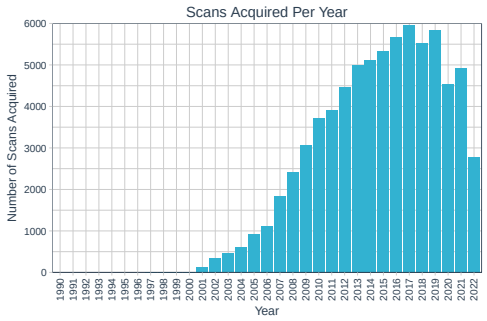

Figure 1: Number of scans in the MS-PMCOE imaging projection for each year. A small number of scans were acquired before 2001 but are not visible in this figure. 2022 represents Jan-Aug

Results and Highlights

- The rapid increase in scan availability in recent years is shown in Figure 1, with nearly 6,000 scans acquired in some years (also see the effect of the COVID-19 pandemic in 2020 and 2021)
- The potential for longitudinal analysis is shown in Figure 2. While many patients have little or no follow-up imaging, there are ≈3,800 patients with ≥5 years, ≈1,600 with ≥10 years, and ≈400 with ≥15 years follow-up

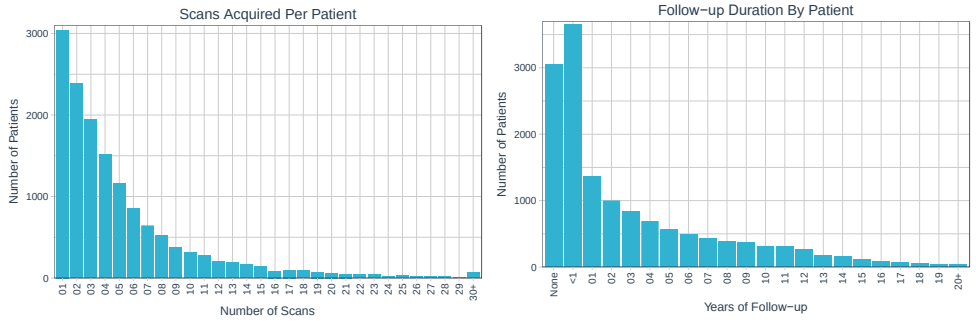

Figure 2: Histograms of the number of scans acquired (left) and length of imaging follow-up duration (right) of patients in the MS-PMCOE. For follow-up duration, "None" refers to patients that only have one scan (no follow-up).

- Historical scans have varying quality. Since 2015, the MS Clinic implemented standardized scanning (JH MS). JH MS scans increase from ≈10% of brain scans in 2015 to ≈41% in 2022 (Figure 3).

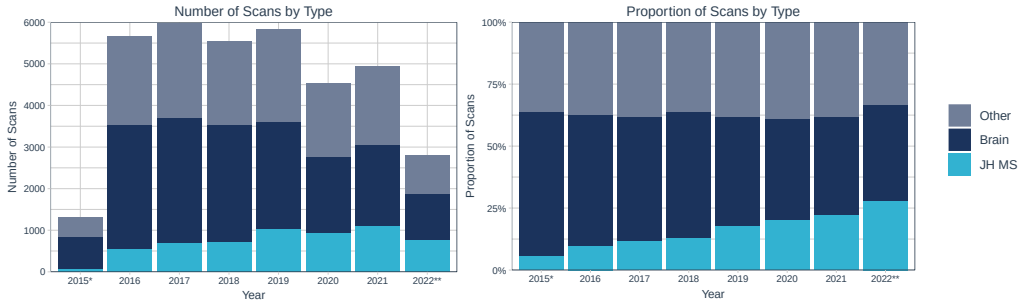

Figure 3: Histograms of raw scan counts (left) and normalized proportions (right) in the imaging cohort by year (2015-2022). Histograms are divided into standardized (JH MS), brain, and other scans (such as spine scans). *2015 represents Oct-Dec. **2022 represents Jan-Aug

Conclusion

- The MS PMCOE has a defined imaging cohort for investigation of neuroimaging outcomes in MS
- The cohort continues to acquire 1000s of images per year with history of >20 years
- Most patients in the cohort have follow-up imaging enabling longitudinal analysis
- Image quality is highly variable, especially across time, but standardized scans are becoming more popular

Next Steps

- Imaging in PMAP is being transferred to a XNAT instance for future processing
- In-depth investigation of the images to triage images based on quality
- Triaged images will guide technical research for incorporating historical data
- Analysis will begin on standardized scans to produce initial imaging outcomes

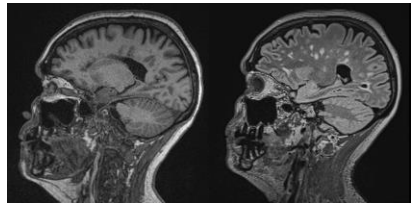

Figure 4: Example 3D high-resolution T_1-weighted (left) and T_2-FLAIR (right) images from an MS patient in the imaging cohort. These images are representative of the standardized MS MRI protocol.

Precision Medicine Symposium 2022

MSCOE: Reducing Need for MRI Scans Using Readily-Available Patient Information

Michael S. Robinette, Elias S. Sotirchos, Kathryn C. Fitzgerald, Blake E. Dewey, John Scott, Peter A. Calabresi, William Gray-Roncal, Ellen M. Mowry

Focus

- MS is a complex disease, which manifests differently across patient populations
- MRI is the gold standard for assessing lesion load but costly and difficult to access
- Identifying patients most likely to benefit from an MRI scan will reduce unnecessary scans and burden on patients
- Using patient data that can be easily collected extends clinical utility of predictive models

Method & Analytics

- **Goal**: identify patients who are highly unlikely to have developed new brain lesions on MRI scans using readily-available patient information
- Data from 2017 onward leveraged from MS Performance Test and SmartForm for patients in the MS PMCOE
- Prediction goal: does the patient have one or more new brain lesions on their next MRI scan?
- Our patient population consists of 889 patients. 13% of these patients have one or more new brain lesions at their next scan
- Data considered:
  - NeuroQOL scores (Anxiety, Depression, Fatigue)
  - Patient-Determined Disease Steps (PDDS)
  - Medication history (aggressive, traditional)
  - Demographics (age, sex)
  - Relapse information
  - Previous lesion information
  - Visit Date
- For prediction, we use logistic regression with 5-fold stratified cross validation for handling class imbalance
- Low-risk patients are identified using a thresholding approach; patients with a prediction probability less than 10% are predicted as not having new lesions

Results and Highlights

- We have identified a sizable proportion of MS patients who are especially unlikely to have one or more new brain lesions on MRI scan (62% of total population)
- Regression coefficients show factors that may be affecting presence of new lesions
  - Aggressive medication and being older have strong negative effects on presence of new lesions
  - New lesions on the previous scan and higher PDDS are predictive of new lesions at next scan
  - Recently changing to an aggressive medication is predictive of having new lesions – closely monitoring these patients may be the best course of action
- There is only a small subset of patients with new lesions that is not classified correctly (2.3%)

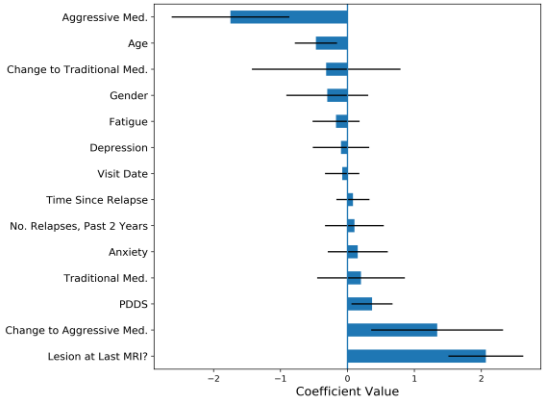

Figure 1: Coefficients for 5-fold cross validated logistic regression, depicted with 95% confidence intervals

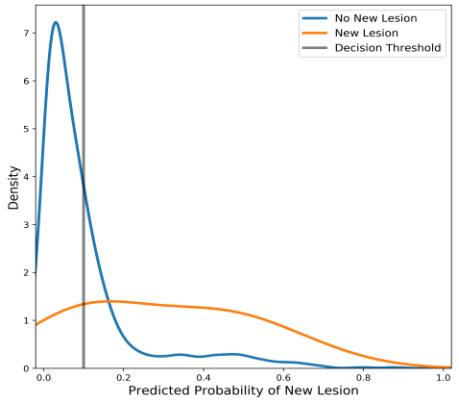

Figure 2: Predicted probability distributions based on true presence of new lesions on their next scan

Target	Count
No new lesion (0)	776
New lesion (1)	113
Total	**889**

Table 1: Target class distribution for the patient population

		True	
		0	1
Predicted	0	**TN**: 555	**FN**: 25
	1	**FP**: 221	**TP**: 88

Table 2: Confusion matrix for prediction results, based on true and predicted labels using the 10% decision threshold

Conclusion

- Using readily-available patient information, we are able to correctly identify a large subset of patients unlikely to have new brain lesions while minimizing patient risk
- Using these predictors potentially extends utility of this method to clinical settings outside of the MS PATHS consortium
- These results could be used in conjunction with clinical guidance to determine if new MRI scans are likely to show new lesions

Next Steps

- External validation with networked MS PATHS data, featuring over 18,000 unique patients from 11 sites
- Prospective validation, testing tools in clinic to validate performance with current JHM patients
- Validation from other MS clinicians and

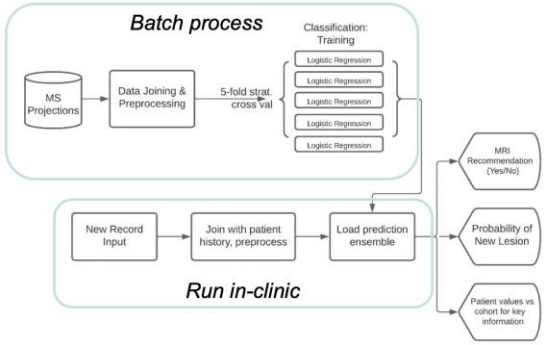

Figure 3: Tool process diagram for clinical care, consisting of a batch process, run at scheduled intervals, and an on-demand process, to be run in clinic, as well as possible display outputs

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Mood Disorders PMCOE

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Precision Medicine Center of Excellence on Mood Disorders

Focus

The Precision Medicine Center of Excellence (PMCoE) on Mood Disorders brings together a multi-disciplinary team of clinicians and researchers with expertise in genomics and informatics sciences to advance the care of patients with mood disorders, including depression (MDD) and bipolar disorder (BP).

- Mood disorders are common and debilitating mental illness that are among the leading causes of suicide and disability worldwide
- Approximately two-thirds of patients will fail first-line treatments and nearly one-third will fail multiple treatments and be designated as treatment-resistant.
- A significant challenge in treating mood disorders is the considerable heterogeneity in the clinical course, severity of illness and response to available treatments.
- To address this challenge, our PMCoE is working to establish a learning health system for mood disorders in which we integrate our clinical and research activities to more efficiently learn from our patients while we provide them with best-evidence care and then rapidly translate what we learn back into improved care.
- We have gathered and are analyzing electronic health record data on over 200,000 patients with mood disorders seen in the Department of Psychiatry and the Johns Hopkins Community Physicians to examine how patients with mood disorders are treated across the health system and the impact on outcomes.
- We are currently building on this learning health framework to pursue four driving initiatives. We provide an overview of these four initiatives here.

Overview

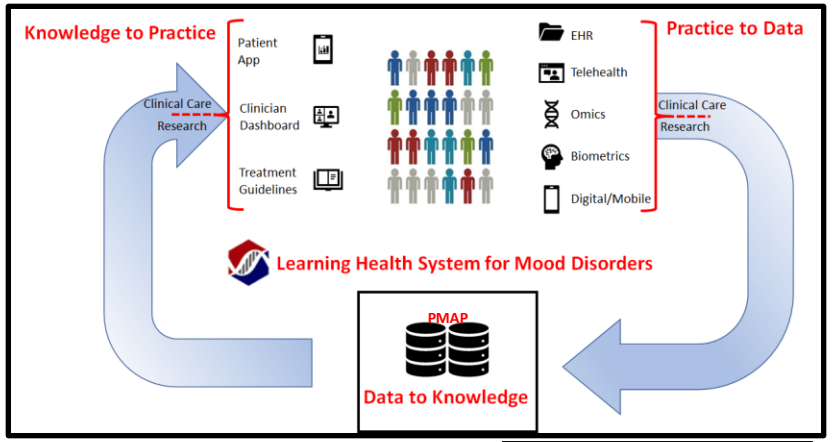
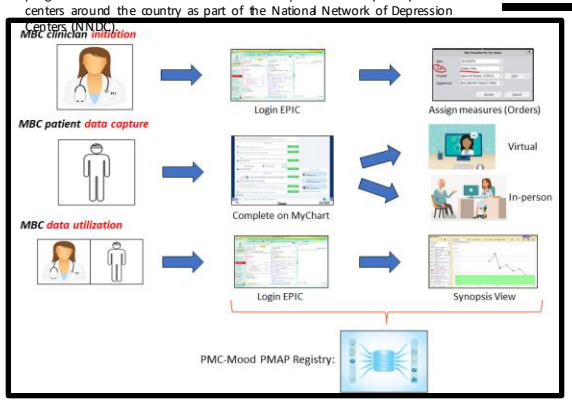


Figure 1. Conceptual model of learning health network. We are building a learning health system to achieve the goals of precision medicine for mood disorders. We are developing tools that leverage electronic health records, telepsychiatry, genomics, biometrics and digital devices to turn practice into data. We are then using the PMAP platform to bring this data together to turn data into knowledge. And, finally, we aim to advance treatment guidelines and build a clinician dashboard with patient data visualization and a patient mobile app to translate knowledge into practice for improved outcomes of our patients with mood disorders.

Figure 2. Schematic of Mood Outcomes Program. We have developed and implemented a measurement-based care program as an engine for our learning health system. As part of the Mood Outcomes Program, we collect patient reported outcome measures (PHQ9, GAD7 and CSSR-S) from patients at every clinic visit to facilitate patient-engaged care and enable prospective research with the electronic health records. We have implemented the program in mood disorders clinics across the Department of Psychiatry and at centers around the country as part of the National Network of Depression Centers (NNDC).

PMAP Registry		BP (n=22,181)	MDD (n=242,045)
Age	<18	184	6,120
	18-65	18,652	162,443
	>65	3,345	73,482
Sex	Female	13,206	161,747
	Male	8,969	80,219
	Other	6	69
	Unknown	1	10
Race	Am Indian	122	800
	Asian	558	7,421
	Black	7,265	60,533
	White	13,061	156,125
	Pac Islander	27	252
	Other	965	13,424
	Multi-race	0	28
	Unknown	183	3,451



Local implementation: Bayview CPP serving >4,000 adult and >2,000 pediatric patients.

National implementation: Over 26 Centers of Excellence across the country in the NNDC

Driving Projects

The Telepsychiatry Study

1. Examine the impact of the transition to telepsychiatry on the process of care, content of care, outcomes of care, and costs of care in patients with depression.
2. Examine if changes in process, content, outcomes and costs of care with telepsychiatry vary by type of service (primary vs. specialty) and patient characteristics (age, sex, race/ethnicity, insurance, clinical acuity).

Goal: To identify patient and clinic level factors which predict more effective use of telepsychiatry for providing care to patients with depression that improve outcomes at a cheaper cost.

The Bipolar Cohort Study

1. Ascertain, consent, biosample and longitudinally follow 1,000 patients with BP within our learning health system.
2. Characterize the heterogeneous trajectories of illness and outcomes of BP patients in real-world settings, with a particular focus on historically under-represented and under-served sub-groups of patients.
3. To evaluate the clinical utility of using polygenic risk scores to predict course of illness and response to treatments.

Goal: To develop genetic risk scores that identify different sub-groups of BP patients and can guide treatment decisions in real world settings.

EEG and Treatment Response in Mood Study:

1. Identify objective Slow wave Sleep (SWS) parameters associated with response to Esketamine treatment in subjects (N=30) with Treatment Resistant Depression.
2. Measure treatment associated changes in continuous wave Functional Near-Infrared Spectroscopy (CW-fNIRS) as a proxy measure of the Glymphatic System and perform mediation analyses, testing the hypothesis that changes in GS may be the physiologically relevant activity for symptom improvement.

Goal: To identify novel EEG and CW-fNIRS predictors of response to Ketamine, a novel fast-acting therapy for depression with heterogeneous clinical effects.

The MindLAMP Study

1. Consent 50 participants with MDD, 50 participants with BP, and 50 healthy controls and follow longitudinally for three months.
2. Assess the acceptability and feasibility of using a smartphone app (MindLAMP) and a wearable device (Oura ring) to follow patients and track “digital phenotypes”.
3. Develop preliminary “digital phenotypes” that correlate with changes in mood trajectories over time.

Goal: To develop “digital” early warning signals for detecting the onset of a depressive or manic episodes requiring early intervention to prevent serious adverse outcomes.

Next Steps

To take what we learn from the driving projects and translate them into new knowledge and tools for advancing precision-guided treatment decisions and improving outcomes of our patients with mood disorders.

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Huntington's Disease PMCOE

Director: Christopher A. Ross, M.D., Ph.D.

- **Vision:**
  To cure a disease like Huntington's disease (HD), it is critical to know the mechanisms involved in the disease pathogenesis and target potential therapeutic pathways to slow down or stop the progression of HD. Using multiplex model system, we will be able to evaluate the effect of small compounds in different HD model systems to reduce the mHTT induced neuronal toxicity, then further translate findings to preclinical and/or clinical trials to treat HD patients and related neurological disorders.

- **Mission**

  1) To setup different model systems to screen small molecules which potentially could be translate to clinical trial. These systems include primary neuronal cultures from different HD mouse, immortalized striatal mouse cells expressing mHTT and human-derived iPSC or iSPNs.
  2) Validating findings from screening platform in mouse models.
  3) Evaluate potential and optimize for clinical trials.

- **Research Aims**

  Aim 1: Setup reliable screening system for small compounds in different platforms.
  Aim 2: Validating the findings from screening in HD specific model systems.
  Aim 3: Mechanistic studies for validated compounds and
  Aim 4: Pre-clinical test of efficient compounds.
  Aim 5: Optimize for clinical trials based on preclinical study.

Interested in Collaboration?

Contact HD PMCOE Director Christopher A. Ross at:

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caross@jhu.edu

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Huntington's Disease PMCOE:

Multiplex platform studies to identify the therapeutic targets and discover new treatment for Huntington's disease

Focus

HD (Huntington's disease) is a fatal neurodegenerative disease with no cure. The symptoms include motor disorders, psychiatric disturbance and cognitive declines. The causative gene is discovered for decades. However, there is still a great demands to understand the mechanisms to develop therapeutic strategy. We focus on screen small molecules to reduce neuronal toxicity induced by mHTT. Further studying the response of HD cells to those small molecules will elucidate the mechanism and move forward to develop efficient treatment for HD patients.

Method & Analytics

We had preliminary data from our in vitro kinase assay indicating that kinase can target specific amino acid on huntingtin protein, which can modify toxicity of mHTT.

Screening: We will screen small molecules that have high relevant to HD pathogenesis using our HD cell model systems.

Validating: small molecules that can protect neurons from mHTT toxicity will be tested in HD specific models, e.g. HD mouse primary neurons and human HD patients derived iPSCs.

Translating: small molecules that can protect in cell models will be administrated in HD mouse models and efficacy will be evaluated with different readout to explore the exact mechanisms and potentiation as treatment targets.

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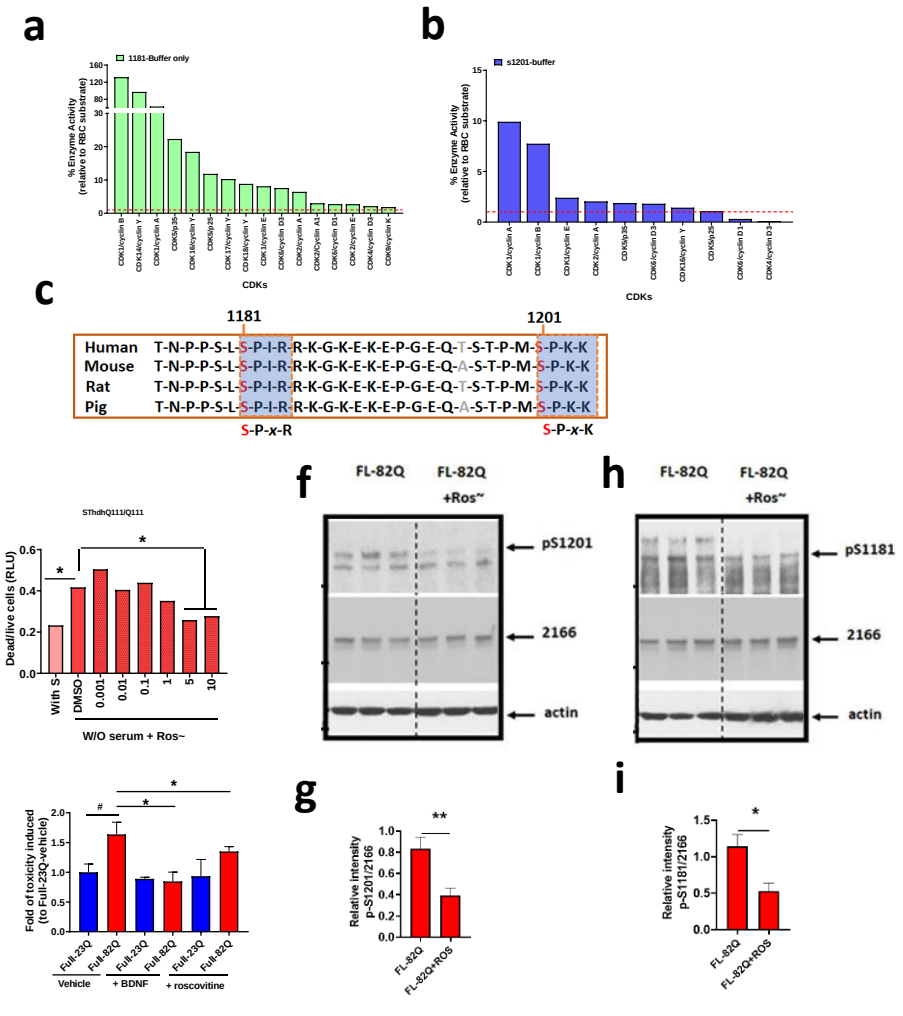
Results and Highlights

SCREENING: Our in vitro kinase assay targeting the post-translational modification (PTMs) sites of mHTT indicated that CDKs affected serine 1181(S1181) and 1201 (S1201) of huntingtin protein (a, b). These 2 serine sites have CDK5 consensus sequence (c).

VALIDATING: We validated that roscovitine (one candidate small molecule from in vitro kinase assay) protected cells from mHTT induced toxicity (d, e). We confirmed that roscovitine specifically targets serine 1181 and serine 1201 of mutant huntingtin protein (f, g, h, and i). We further confirmed the specificity of roscovitine on S1181 and S1201 by modifying these serine (S) sites to alanin (A) and aspartate (D). When serine (S) is modified to alanine (A), it reduced toxicity on both S1181 (S→A) and S1201 (S→A), but not for S→aspartate (j). Specifically knock-down CDK5 ameliorated the cell toxicity of mHTT (k).



Conclusion

- PTM sites of mHTT including S1181 and S1201, are potential therapeutic targets for lowing mHTT toxicity.
- PTMs of mHTT can be targeted using small molecules , like CDKs inhibitor, roscovitine.
- Roscovitine can protect neurons from mHTT induced cell toxicity.
- Roscovitine targets CDK5 to protect cell from mHTT toxicity which is confirmed by knocking down CDK5 in mHTT expressing cells.
- Roscovitine is a promising candidates to treat HD.
- In vitro kinase assay is a useful tool to screen small molecules that can be translated to preclinical and clinical trials.

Next Steps

- **TRANSLATING:** Test the efficacy of roscovitine in HD mouse model.
- Validating more small molecules that can reduce mHTT toxicity and further translate for preclinical trials.
- Further mechanism study of HD pathogenesis can provide detailed and effective therapeutic strategies for different stages of HD.

Authors: Jing Jin[1], Asvini Krishnaprakash[1], Mali Jiang[1], Tamara Ratovitski[1] and Christopher A. Ross[1 2 3] **

1 Division of Neurobiology, Department of Psychiatry, Johns Hopkins University (JHU) School of Medicine (SOM), Baltimore, MD, USA.

2 Departments of Neurology, Neuroscience and Pharmacology, JHU SOM, Baltimore, MD, USA.

3 Department of Pharmacology and Molecular Sciences, JHU SOM, Baltimore, MD, USA.

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Huntington's Disease PMCOE:

Drug Screening on Juvenile and adult-onset HD Immortalized Striatal Precursor Neurons Generated from Patient-Derived iPS Cells

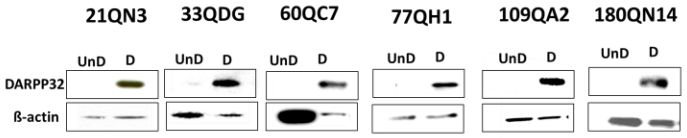
Focus

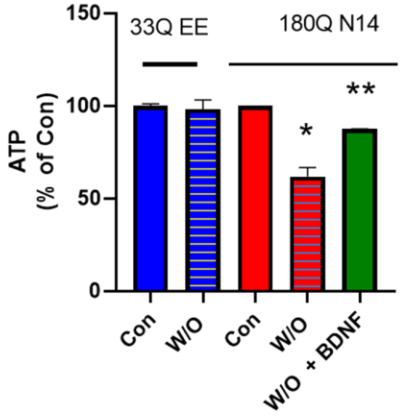
Huntington's disease (HD) is an autosomal dominant inherited neurodegenerative disease caused by an expanded CAG trinucleotide repeat in the huntingtin gene. In general, juvenile onset patients carrying long CAG expansion (over 70 CAGs). Previously we generated immortalized striatal precursor neurons (ISPNs) with different repeat length which recapitulated HD-like phenotypes. Further we developed a drug screening cellular platform for drug screening and target validation. We are performing screening tests using libraries of kinase inhibitors and diverse chemical compounds on ISPNs with 180 CAG. Further, we will test these compounds on the neurons derived from iPSC of adult-onset patients.

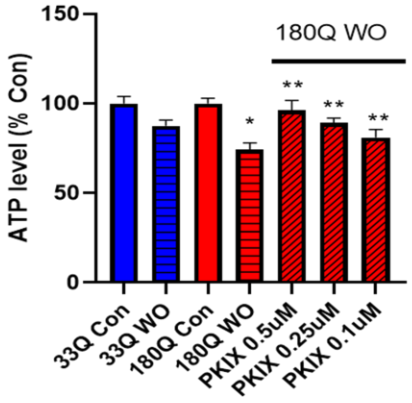
Method

Precursor ISPNs with the 33 or 180 CAG repeats were stressed by growth factor and nutrients withdrawal (W/O) for 24 hr. Meanwhile, kinase inhibitors was added at the indicated concentration. ATP levels were measured, and the results are presented as MEAN+SE normalized as % of the value of control (Con) group (n=3). One-way ANOVA was performed. * p<0.05 vs 180Q Con. ** p<0.05 vs 180Q W/O.

Results and Highlights







We generated the ISPNs with different CAG repeat length which includes both cells from juvenile and adult–onset cases. There were significantly higher levels of toxicity in HD 180Q ISPN lines compared with normal control lines after BDNF withdrawal. Z' factor: 0.6-0.8. Replacement of BDNF (40-50 ng/ml) attenuated mutant HD-induced toxicity. Small molecules kinase inhibitor PKX dose dependently rescued mHTT toxicity in HD 180Q ISPNs using CellTiter-Glo Luminescent Cell Viability Assay.

Conclusion

- HD ISPNs are more vulnerable to cellular stress than the non-disease controls.
- Small molecules can rescue mHTT toxicity in HD ISPNs using CellTiter-Glo Luminescent Cell Viability Assay.
- The ISPNs derived from HD iPSCs is a useful cellular model platform for target validation and drug screening.

Next Steps

1. Establish the cellular toxicity assay in HD ISPNs with different CAG repeat length.
2. Screen drugs on the different ISPN lines with specificly differentiate the drug response to ISPNs from adult and juvenile onset patients.

Authors:

Mali Jiang[1], Ronald Wang[1], Ritika Miryala[1], Tianze Shi[1], Rashi Sultania[1], Emma Whelan[1], Anthony Tang[1], Kimberly Mae Bockley[1], Evelyn Zhang[1], Jing Jin[1], Tamara Ratovitski[1] and Christopher A. Ross[1,2]

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Chronic Obstructive Pulmonary Disease (COPD) PMCOE

Directors: Nadia N. Hansel, Robert A. Wise

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Chronic Obstructive Pulmonary Disease Precision Medicine Center of Excellence

- **Vision:**
  Chronic Obstructive Pulmonary Disease is a highly prevalent disease associated with significant morbidity, mortality, and burden on the healthcare system. The COPD PMCOE seeks to raise the standards of excellence in assessment and management of COPD through exceptional clinical care and cutting-edge research geared towards individualized medicine that will improve health outcomes.
- **Mission**
  We are focused on identifying clinical and biologic characteristics that define high-risk subgroups and developing novel clinical interventions that improve outcomes and are also cost-effective, all towards a goal of establishing optimal treatment models for patients with COPD.
- **Research Aims**
  - Understand individuals who have a rapid decline in lung function
  - Characterize frequent exacerbators and high healthcare utilizers
  - Evaluate comorbid conditions and the impact on clinical outcomes
  - Assess the role of physical and cognitive functioning in COPD
  - Develop a biorepository to understand biologic underpinnings in high-risk subgroups
  - Examine immune function dysregulation in COPD
  - Examine social determinants of health as they relate to COPD outcomes

Interested in Collaboration?

Contact us at:

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Aparna Balasubramanian
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Lung Function Trajectories using EHR data in Chronic Obstructive Pulmonary Disease

Cervantes, C., Balasubramanian, A., Gearhart, A., Chee, B., Subbarao, S., Putcha, N., Fawzy, A., McCormack, M., Singh, A., Wise, R.A, Hansel, N.N

Focus

- Lung function decline is a key outcome in multiple respiratory conditions including Chronic Obstructive Pulmonary Disease (COPD).
- Rapid lung function decline is associated with increased symptoms, exacerbations, and mortality.
- Clinicians often make assessments using trends in pulmonary function tests to estimate trajectories in patients, but real-world pulmonary function testing (PFT) data is confounded by clinical indications, uncontrolled testing settings, variable quality of tests, inconsistent timing and frequency, and extreme values.
- Leveraging the COPD PMCOE, we have conducted analyses to better understand various aspects of lung function change using real-world clinical data

Method & Analytics

- COPD PMCOE includes Johns Hopkins Healthcare system patients ≥30 years old with:
  - ICD-10 diagnosis code for COPD, *OR*
  - Forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio < 0.7 or the lower limit of normal, *OR*
  - ACG grouping for COPD
- Individuals with ≥3 outpatient PFTs over ≥1 year
- Excluded lung transplant or resection
- Rate of change calculated as mL/yr and %/yr
- Five methods were used to estimate change in FEV_1 including non-regressive methods (Total Change as a simple average slope from first and last PFT, Average Change as the average of all slopes between PFTs) and regressive methods (Huber, RANSAC, and Quantile)
- Descriptive statistics were calculated including means with standard deviations, medians, minimum, and maximum values to compare distributions by methods
- Clinical characteristics at or prior to first PFT were evaluated by bins of estimated rate of change

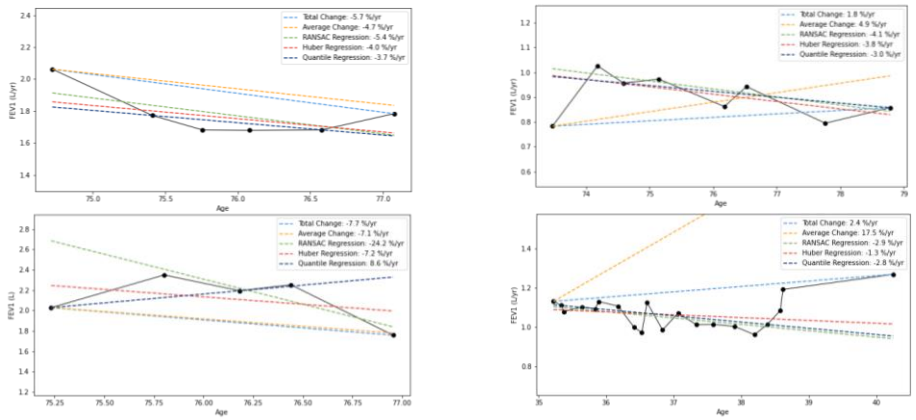
Results and Highlights

- COPD PMCOE contains 69,111 patients; 53.6% were female, 27.0% were African American, and 27.3% were current smokers at time of first record (26.0% at time of last record)

Modeling PFT Decline

- 1417 patients met inclusion criteria with a baseline mean FEV_1 of 1.7 ± 0.8 L
- Median number of PFTs was 5 and time between PFTs was 147 days
- Demographics were similar to the entire COPD PMCOE including age, sex, race, and smoking status

Figure 1 – Lung function trajectories can vary drastically by method



- Non-regressive methods struggle with first/last FEV_1 extremes or short intervals
- Regression methods differ in instances with potentially informative outliers

Table 1 – Average Change yields unrealistic extremes

	Min	Mean	Median	SD	Max
Total Change	-1101	-37.1	-31.7	147.1	1246.5
Average Change	-3761	48.7	-16.0	472.0	7445.3
RANSAC Regression	-2210	-36.4	-35.1	224.6	2253.0
Huber Regression	-1089	-39.8	-34.0	141.1	1246.5
Quantile Regression	-1183	-39.3	-32.7	150.6	1246.5

All values are reported as mL/yr change in FEV_1

- Most methods offer similar average or median rates of change, but have differing extremes
- Huber Regression tends to minimize extremes while including all data in estimation

Table 2 – Huber %/yr estimates associated with clinical characteristics

	λ < -10% (N=138)	-10≤λ<-5% (N=233)	-5≤λ <0% (N=629)	0≤λ <5% (N=279)	λ ≥ 5% (N=136)
Age (yrs)	62 ± 12	62 ± 12	61 ± 13	57 ± 15	59 ± 14
Current Smoker, n (%)	18 (13.0%)	28 (12.0%)	44 (7.0%)	20 (7.2%)	11 (8.1%)
FEV1 (L/s)	1.7 ± 0.8	1.7 ± 0.8	1.9 ± 0.8	1.9 ± 0.8	1.5 ± 0.7
DLCO (mL/min/mmHg)	10.5 ± 5.4	12.2 ± 6.0	13.6 ± 5.5	13.3 ± 5.6	12.3 ± 6.0
% All-Cause Hosp. in year prior, n (%)	53 (38.4%)	78 (33.5%)	158 (25.1%)	79 (28.3%)	47 (34.6%)
% COPD Hosp. in year prior, n (%)	4 (2.9%)	6 (2.6%)	10 (1.6%)	3 (1.1%)	1 (0.7%)

- Increased age, current smoking, reduced DLCO, and increased hospitalizations are associated with more rapid lung function decline
- Improving lung function is unexplained and is similarly associated with smoking, DLCO, and all-cause hospitalizations

Conclusions

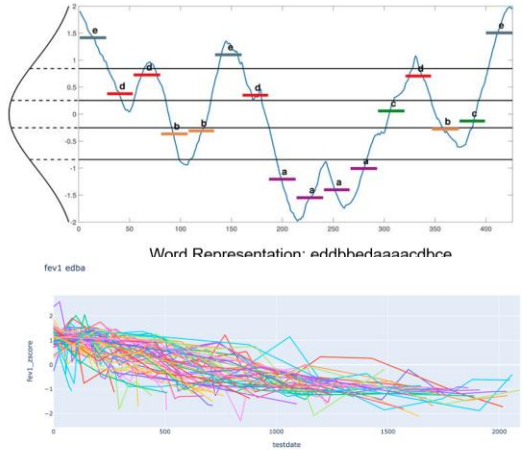
- Real world PFT data is riddled by concerns related to how, when, and why testing is performed
- Methods to estimate a lung function trajectory must consider these complexities to generate estimates that are feasible and accurate
- Regression methods are more reliable than methods traditionally used in the literature, due to i) frequent occurrences of short intervals and ii) outlier first or last PFTs, likely reflective of acute clinical worsening.
- Regression methods treat outliers with varying consideration, but in the absence of clinical context, we identified Huber regression to be the most accurate method for defining PFT trajectories

Next Steps

- Predicting clinical outcomes using estimates of rate of change in lung function
- Using patterns of PFTs (increasing, decreasing, static) as a novel lens by which to examine associations between PFTs and clinical outcomes

Exploratory Data Analysis With SAX

- Symbolic Aggregate ApproXimation (SAX) to look at groups of patterns in PFTs
- Apply a letter to each FEV_1 z-score from at least four time points, with an alphabet range of a-e to generate four-letter words



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Cystic Fibrosis
Precision Medicine Center of Excellence

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Cystic Fibrosis PMCOE

Director: Garry Cutting, MD
Co-Director: Lori Vanscoy, MD

- **Vision:**
  To improve the outcomes and quality of life for all individuals with Cystic Fibrosis (CF) by identifying subgroups with similar disease complications and trajectories to inform individualized diagnostics and treatments.
- **Mission**
  To fully harness all available clinical, genetic, social, and patient-derived information to deliver safe, beneficial, and cost-effective treatments to all individuals with CF. To facilitate collaboration with the CF Foundation and with pharmaceutical companies in early phase development and clinical trials of novel precision treatments for CF.
- **Research Aims**
  Aim 1: To project comprehensive longitudinal disease trajectories at the point of care to improve clinic operations and enhance shared decision-making.

  Aim 2: To understand impacts of telehealth on patient outcomes, adherence to established clinical care guidelines, and clinic operations.

  Aim 3: To create risk prediction models for lung disease progression, CFTR modulator drug response, and development of CF-related diabetes.

Interested in Collaboration?

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Cystic Fibrosis (CF) Precision Medicine Center of Excellence

Focus

The CF PMCOE studies a cohort of ~1000 individuals of all ages with CF and with CFTR-related disorders, who receive or who have received care at the Johns Hopkins Pediatric or Adult CF programs in Baltimore and at the All Children's CF program in Florida. We are utilizing a variety of different data streams to accurately identify subgroups of individuals with similar disease trajectories and complications to inform not only future research but also personalized diagnostics and treatment decisions.

Data Sources of Interest

- Clinical Data from EPIC
- Genetic information, including disease-causing mutations + modifier genes
- Medical imaging
- Social Determinants of Health
    - Environmental exposures
    - Economic factors (including health insurance, food insecurity, transportation needs)
- Patient-generated, remotely collected data
    - Home spirometry
    - Continuous glucose monitoring
    - Physiologic data (Fitbit, Apple watch as examples)

Active Projects

- **Creation of Longitudinal Patient Insight Visualization**
    - This project will assemble longitudinal disease markers in a unified visualization available to the patient and provider at the point of care to inform shared clinical decision-making.
    - The visualization will allow for comparison to individuals with similar disease features.

- **Evaluating the Telehealth Experience for Individuals with Cystic Fibrosis**
    - During the COVID-19 pandemic, routine clinical care for individuals with CF largely shifted to telemedicine format and is now being delivered in a hybrid model that incorporates both in-person and telemedicine visits.
    - This project is assessing impacts of the telemedicine mode of care delivery on adherence to CFF clinical care guidelines and on disease trajectories.
    - This project also seeks to identify social determinants of health that are associated with telemedicine visit completion.

- **Facilitate Data Sharing with the CF Foundation(CFF) National Patient Registry**
    - >95% of individuals with CF have consented to share their clinical data with the US CF Foundation Patient Registry
    - Currently, data entry into the CFF Patient Registry is a manual process, which is labor-intensive and error prone because of its reliance on human transcription of data.
    - This project will automate up to 90% of CFF Patient Registry data entry, saving EACH of our CF programs up to 0.5 FTE per year of labor, while substantially increasing timeliness and accuracy of data sharing.

Projects in Development

- **Predicting development of CF-related diabetes**
- **Understanding impacts of Cystic fibrosis transmembrane regulator modulator drugs on exocrine/endocrine pancreatic function**
- **Utilizing machine learning analysis of chest x-rays to predict lung function in children and adolescents with CF**
- **Understanding disease liability for individuals with a single CFTR mutation**

Next Steps

- **Creation of Cystic Fibrosis Biorepository**

- **Incorporation of home spirometry and CGM data into our clinical data repository**

Core CF PMCOE Team Members

- **Department of Genetic Medicine**
    - Garry Cutting, MD
    - Neeraj Sharma, DVM, PhD
- **Eudowood Division of Pediatric Respiratory Sciences**
    - Lori Vanscoy, MD
    - Peter Mogayzel, Jr, MD, PhD
- **Johns Hopkins Division of Pulmonary & Critical Care Medicine**
    - Noah Lechtzin, MD, MHS
- **Johns Hopkins All Children's Hospital Pediatric Pulmonology**
    - Deanna Green, MD, MHS
- **BEAD Core/Biostatistics**
    - Jiajun Wu
- **JH Technology Innovation Center**
    - Sharon Penttinen (project manager)

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Bladder Caner
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Bladder Cancer PMCOE

David J. McConkey, PhD

Focus

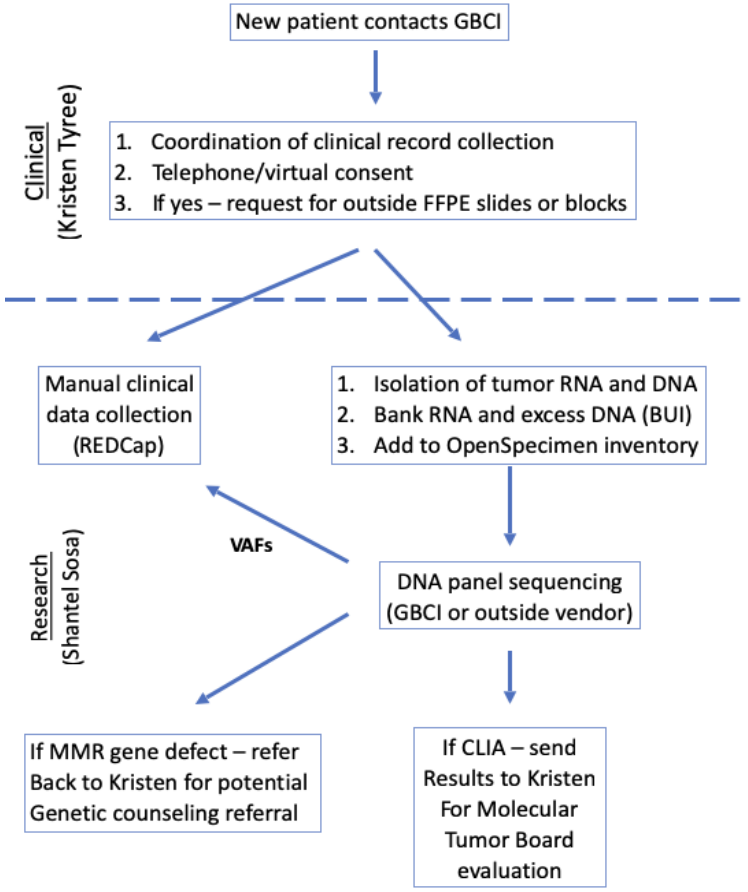
Urothelial (bladder) cancers are clinically diverse and highly heterogeneous at the genomic level. Recent studies indicate that urothelial cancers can be grouped into subtypes based on the presence or absence of specific DNA damage and repair (DDR) gene defects and basal versus luminal gene expression profiles. Our near-term goal is to establish a framework for prospective, longitudinal collection of clinical and genomic data from all consenting patients seen at our specialized multi-disciplinary clinics (MDCs). In the first phase we are launching this effort in patients seen at our upper tract urothelial cancer (UTUC) MDC

Method & Analytics

The UTUC MDC recently recruited a nurse navigator (Kristen Tyree) to serve as a point-of-contact for all new and existing patients diagnosed with UTUC being seen at Johns Hopkins. She will consent patients to the Bladder PMCOE's eFormR clinical registry and Brady Urological Institute's J1380 tissue collection protocols, arrange for outside imaging and tissue to be sent to Johns Hopkins, and connect patients to the PMCOE's Data Coordinator (Stan Rapiey). Stan will work with Kristen to prospectively populate the UTUC's REDCap database and coordinate tissue collection and panel DNA sequencing using an in-house custom panel. The clinical and sequencing data will be uploaded monthly to the PMAP, and additional data streams (i.e., urine and plasma liquid biopsy results, scanned H&E images and clinical imaging data) will be added to the PMAP as methods for ingesting them become available.

Results and Highlights

Preliminary sequencing results from UTUC patients treated with neoadjuvant chemotherapy suggest that DNA damage and repair mutations are not major determinants of response. The REDCap clinical data collection effort is being leveraged in a national collaborative project aimed at predicting glomerular filtration rates (GFRs) in patients treated with definitive surgery (nephroureterectomy). This project is the first in what is expected to be a series of clinical publications from the UTUC Collaborative Network (UCAN), involving investigators from Johns Hopkins, MD Anderson, UT Southwestern Medical Center, Mayo, Moffitt, Penn State, and MSKCC.



Conclusion

Prospective sequencing and clinical data collection have already increased the quality and impact of the UTUC's research programs, and the UTUC portion of the GBCI's website is far and away the most heavily trafficked. As a consequence of this visibility, the UTUC MDC has attracted significant philanthropic investment, and new patient referrals to the UTUC MDC are also increasing rapidly.

Next Steps

The UTUC portion of the Bladder Cancer PMCOE has launched completely this month. The next measurement that needs to be integrated into the PMAP is urine tumor DNA profiling; in-house efforts to develop a robust assay are underway, and we are also launching a research collaboration with Convergent, who have already established a CLIA assay that can be used to estimate prognosis and to quantify minimal residual disease (MRD). Scanned H&Es and clinical imaging data are the next measurements that are being targeted for integration. The UTUC research program will leverage the PMCOE as a "core" in the multi-investigator extramural grants that are being prepared by the group, including a SPORE.

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ARVC
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Novel Late-gadolinium Enhanced Cardiac Magnetic Resonance-based Computational Heart Paradigm Predicts Optimal Ventricular Tachycardia Ablation Targets in Arrhythmogenic Right Ventricular Cardiomyopathy

Yingnan Zhang, Adityo Prakosa, Eric Sung, Alessio Gasperetti, Richard Carrick, Cynthia A. James, Stefan L. Zimmerman, Crystal Tichnell, Brittney Murray, Hugh Calkins, Harikrishna Tandri, Natalia Trayanova

Precision Medicine Symposium 2022

Introduction

Background:

- Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a leading inherited cause of ventricular tachycardia (VT) in young adults, especially athletes.
- Arrhythmogenic substrates include structural and electrical remodeling in the right ventricle.
- Catheter ablation is the most common treatment for VT in ARVC patients; however, identification of optimal ablation target is challenging.
- Non-invasive prediction of ARVC re-entrant VT circuits could provide a thorough pre-ablation evaluation of the arrhythmogenic substrate and identify specific region(s) to target during the ablation procedure.

Hypothesis:

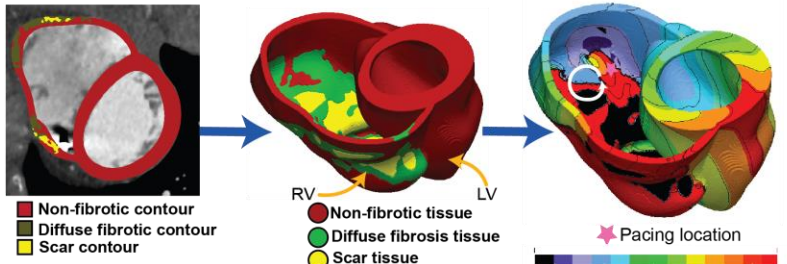
- Right Ventricular Cardiomyopathy Ablation Targeting (RVCAT) is a novel digital-heart paradigm to accurately predict the optimal VT ablation targets of ARVC patients.

Method & Analytics

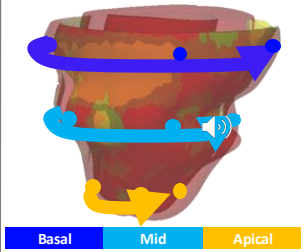
Cohort

- As a retrospective study, eight patients diagnosed with definite right ventride (RV) dominant type ARVC were selected from Johns Hopkins ARVC database to test this novel modeling methodology.
- All the patients in this cohort had clinical VT and been through ablation procedures.
- All the patients in this cohort had clear RV enhancement identified on LGE-CMR.

MRI-based Model Creation

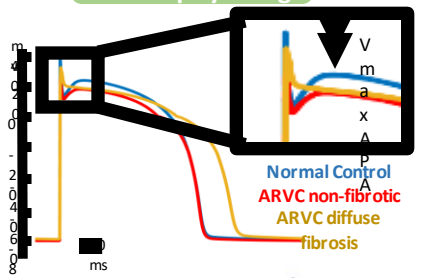


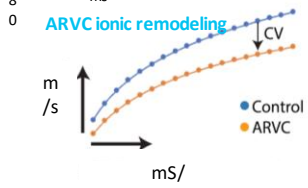
Simulation Protocol



- We constructed 3D computational models of ARVC patients' hearts from LGE-CMR scans with observed RV hyperenhancements representing arrhythmogenic structural substrates.
- For each model, rapid pacing was performed from 9 different sites on the RV, covering anterior, lateral and inferior regions in basal, mid and apical heart segments.

Genetically-driven Electrophysiolog

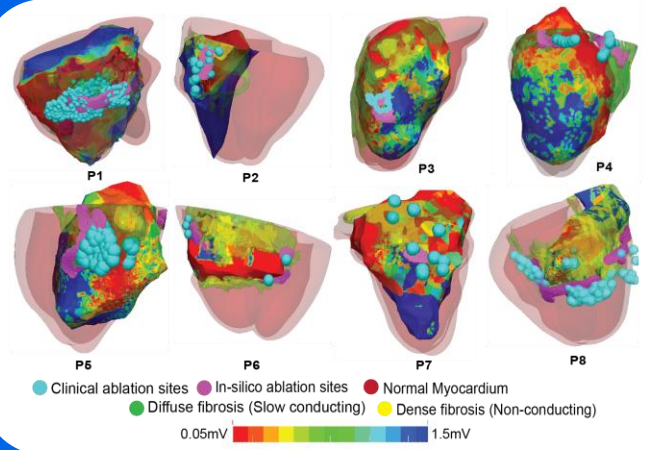


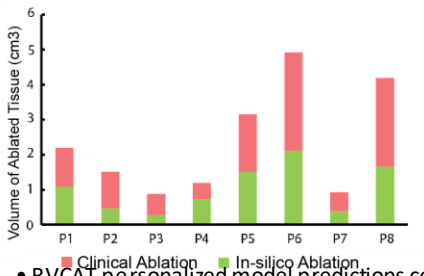


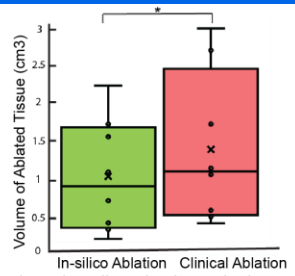
ARVC conduction remodeling

- Genetically-driven ARVC single-cell model has been developed for *DSG2* pathogenic variant.
- Decreased CV in ARVC due to both ionic channels and gap junctions remodeling.

Results and Highlights







- RVCAT personalized model predictions correlated well with clinical observations.
- Simulated VT circuit locations matched the clinical description.
- Substrate distribution in models matched low-voltage zones in EAM.
- Ablation targets predicted by RVCAT coincided with clinical ablations.
- Results showed that the volume of RVCAT ablation lesions was significantly smaller than that of clinical ablations (1.02 ±0.68 versus 1.45 ±0.91, $p<0.05$, Fig C).

Conclusion

- RVCAT is a novel digital-heart technology for optimal ARVC VT ablation guidance that can be potentially integrated into clinical workflows for augmenting therapeutic precision.

Next

- VT properties across different ARVC genotypes will be investigated using genotype-specific computational virtual heart model.
- FAT infiltration will be integrated into current scar-based model to study the impact of both structural substrates on arrhythmogenic propensity.

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Neurofibromatosis
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Neurofibromatosis PMCOE

Director: Jaishri Blakeley, MD

- **Vision:**
  Application of continually updated clinical data to create predictive nomograms that support diagnostic and surveillance strategies for rare tumor predisposition conditions to reduce patient and care system burden and improve outcomes.
- **Mission**
  Improve diagnostic accuracy for people living with NF1 to reduce health insecurity, eliminate unnecessary testing and associated spending and improve the speed and accuracy of diagnosis and treatment with the ultimate goal of broadly improving patient outcomes.
- **Research Aims**
  Aim 1: Assess the predictive power of clinical data elements collected during clinical care in characterizing people with Neurofibromatosis Type 1 (NF1) as high versus low risk for malignancy?
  - Aim 1b: Is there differential predictive power of tumor or germline mutational status versus imaging features versus clinical factors for predicting risk of malignant conversion in people with NF1 associated benign peripheral nerve tumors?
- Aim 2: Assess the accuracy of multifactorial prediction calculators for risk of malignancy in people with NF1
- Aim 3: Model the cost-effectiveness of data driven predictive calculators versus current diagnostic approaches for people with NF1?

Interested in Collaboration?

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Neurofibromatosis PMCOE

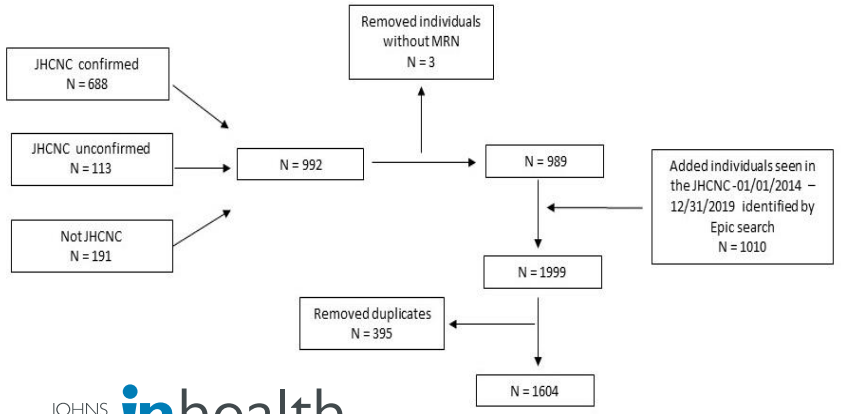
Focus

The Neurofibromatosis (NF) PMCOE uses a curated registry of roughly 1600 people with the neurogenetic conditions NF1 and NF2, SMARCB1 and LZTR1 related schwannomatosis who receive their care at the Johns Hopkins Comprehensive NF Center. Curated clinical registries are updated with clinical features, germline and tumor genetic results, and imaging features to create predictive nomograms to identify people at high versus low risk of malignancy. Ultimately, these nomograms will be applied clinically to inform diagnostic screening and surveillance with the goals of early detection and better cancer outcomes in high risk individuals and reduced health care strain and cost for low risk individuals.

Method & Analytics

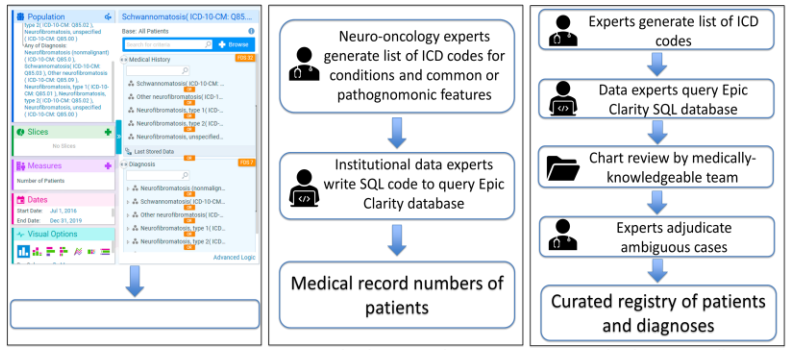
People seen at the multidisciplinary Johns Hopkins Comprehensive NF Center are evaluated to determine if they meet the criteria for NF1 and NF2, SMARCB1 and LZTR1 related schwannomatosis. Key demographic data, the basis of the diagnosis (clinical criteria or genetics), manifestations, and specialties involved, mutli-parametric imaging, non-imaging diagnostic studies, surgeries, pathology, medications and treatments and outcomes.

The database is curated to ensure that patients are accurately identified by their specific diagnosis.



Active Projects

- **Evaluation of relationship between history of "high risk" clinical features and development of MPNST in people with NF1**
- **Assessment of the impact of COVID-19 on people with NF1, NF2 and Schwannomatosis via the National COVID Cohort Collaborative (N3C) and NF PMCOE**
  - Jineta Banerjee, Jaishri Blakeley, Joshua Roberts, Eric Scheiss, Children's Tumor Foundation Clinical care Advisory Board
- **Comparing Methods Used to Identify Patients with Rare Tumor Predisposition Syndromes in the Electronic Health Record**
  - Macy Early, John Gatti, Bronwyn Slobogean, Bonnie Woods, Robert Ackerman, Anil Mathur, Joshua Roberts, Jaishri Blakeley



Method 1: Epic Slicer-Dicer

Method 2: Epic Clarity search with data experts

Method 3: Manually-curated registry

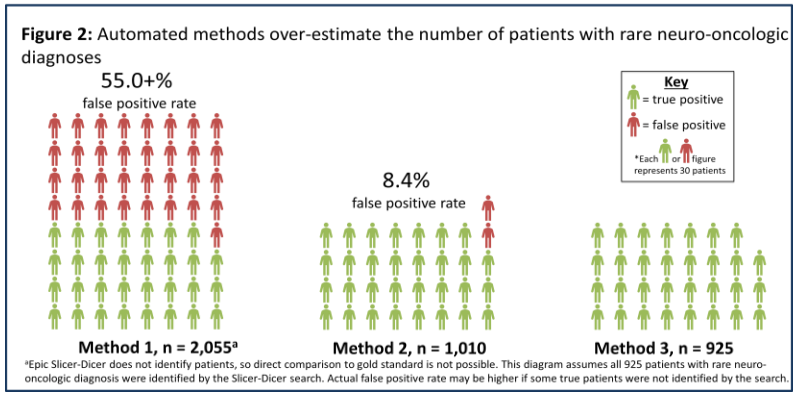


Figure 2: Automated methods over-estimate the number of patients with rare neuro-oncologic diagnoses

[a]Epic Slicer-Dicer does not identify patients, so direct comparison to gold standard is not possible. This diagram assumes all 925 patients with rare neuro-oncologic diagnosis were identified by the Slicer-Dicer search. Actual false positive rate may be higher if some true patients were not identified by the search.

Conclusion

- Curated registry or rare conditions with complicated diagnostic criteria enable confidence in retrospective data analysis not possible with application of ICD10 codes only to EHR.
  - Encourages engagement of partner specialties (i.e. otolaryngology, neurosurgery) for assessment of various outcomes.
  - Enables partnership with patient advocacy organizations and national patient registries
- Large volume of excellent, regularly updated data is required for generating predictive nomograms.

Next Steps

- Complete data entry and curation for all people with NF1 diagnosed with MPNST.
- Coordinate with external genetic testing centers to directly enter genetic test results into the laboratory section of EPIV for integration into PMAP (not PDF)
- Complete dedicated MRI data collection forms
  - Use this data to generate models of relative risk of MPNST based on clinical, genetic and radiographic features with retrospective data.
  - Test the best performing model prospectively.
- Publish the studies completed in 2022.

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Advancing Precision Oncology in Lung Cancer

*Answering the Call to **Action**: Actionable Alterations in Non-Small Cell Lung Carcinoma*

Joseph (Joe) C. Murray, MD, PhD
Co-Director of the Lung Cancer Precision Medicine Center of Excellence

Valsamo (Elsa) Anagnostou, MD, PhD
Co-Director of the Lung Cancer Precision Medicine Center of Excellence
Director, Molecular Oncology Laboratory & Thoracic Biorepository
Co-Leader, Molecular Tumor Board

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Lung Cancer PMCOE

- **Vision**

Enhance the outcomes for lung cancer patients through integrative data-driven approaches that deliver precise diagnosis and personalized treatment

- **Mission**

Build a learning health system that delivers a comprehensive clinical and molecular understanding of our lung cancer patients to improve their pathways to diagnosis, enable guideline-driven personalized care, and increase access to translational research

- **Aims**

  - Identifying molecularly matching therapies – for ***every*** patient
  - Discovering novel predictive biomarkers – for **prognosis** and **response**
  - Adapting treatment strategies – where guidelines are limited

Interested in Collaboration?

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Precision Medicine Symposium 2022

Lung Cancer PMCOE: Advancing Precision Oncology in Lung Cancer

Joseph Murray, MD, PhD • Valsamo Anagnostou, MD, PhD • Julie Brahmer, MD on behalf of the Lung Cancer PMCOE Team

Background

In the US, even with numerous molecularly-matched therapies in non-small cell lung cancer (NSCLC), **only half of patients receive appropriate molecular testing for these therapies[1].** Furthermore, *even with* appropriate testing, **only half of those patients receive the appropriate matched therapy[2]** leading to decreased overall survival. Although oncologists aim to deliver tailored clinical care to patients, integration of molecular & clinical data is needed to improve precision oncology – and identify new therapeutic strategies – for all patients with NSCLC.

Aims

We aim to develop

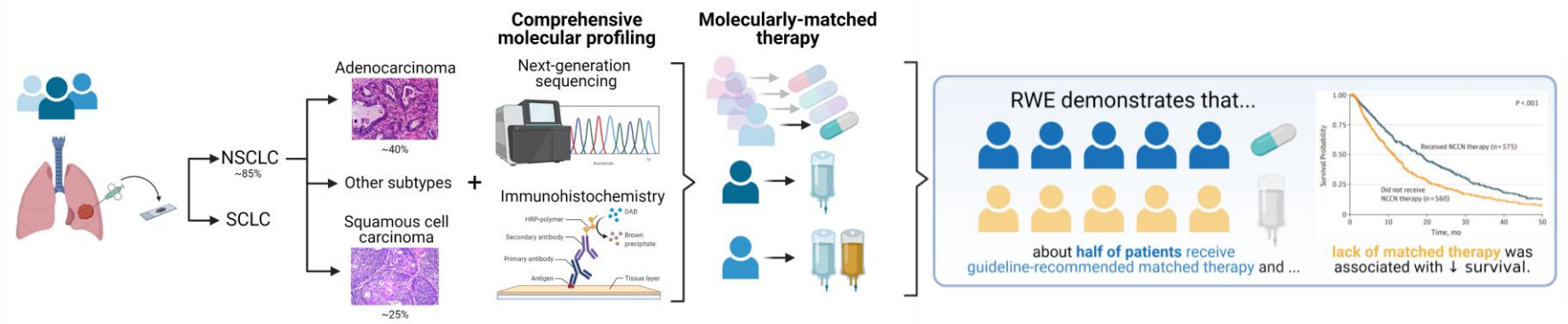
1. **Interventional care tools and pathways** that enable efficient matching of precise therapy to individual patients with NSCLC; and
2. **A learning health system** for patients and clinicians that utilizes real-world data (RWD) to generate real-world evidence (RWE), to improve outcomes for patients with NSCLC.

Strategies

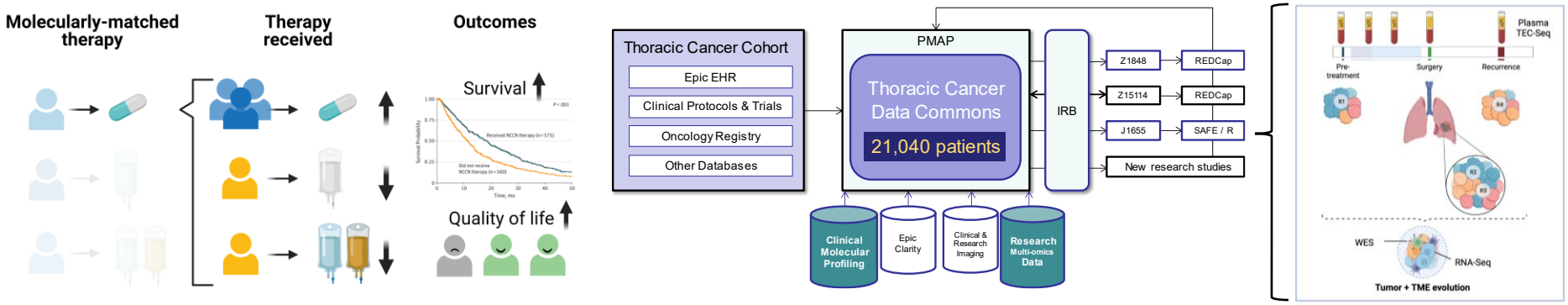
Our strategies include:

- Implementation of a **Thoracic Cancer Data Commons** built on the **Precision Medicine Analytics Platform (PMAP)** for integration of complex molecular, clinical and research data
- Novel deep learning models from the aggregation of clinical, genomic, radiomic – or **multi-omic data –** to learn from our patients
- Development of prognostic and predictive **biomarkers for adaptive treatment** of patient

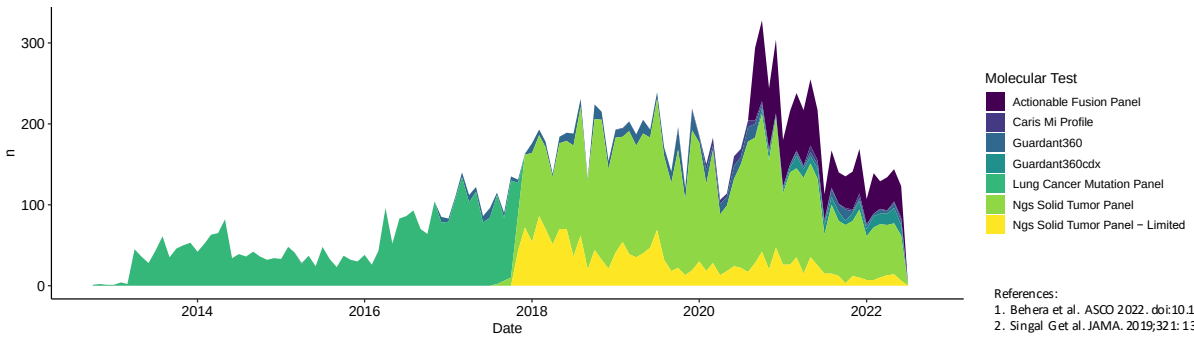
Challenge – Translating molecular testing to clinical benefit for patients with non-small cell lung cancer (NSCLC)



Vision – Improving outcomes through matched therapies, while building sustainable resources to discover therapies where matches are lacking.



Results – Prevalence and diversity of molecular testing requires meaningful integration



Next Steps

- Integrate genomic and clinical data
- Develop patient "phenotypes"
- Deepen translational features in the Data Commons, including: cfDNA, WES, RNAseq, TCRseq NGS; and radiomic features
- Build predictive models of clinical outcomes

References:
1. Behera et al. ASCO 2022. doi:10.1200/JCO.2022.40.16_suppl.9128
2. Singal G et al. JAMA. 2019;321:1391–1399. doi:10.1001/jama.2019.3241

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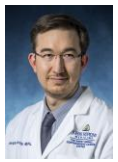
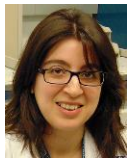
Acknowledgements – Our Team

- **Co-Directors**: Joe Murray, MD, PhD & Elsa Anagnostou, MD, PhD
  - Prior directorship: Julie Brahmer, MD & Victor Velculescu, MD, PhD





- **Multidisciplinary Team**
  - **UAD –** Julie Brahmer, MD • Kristen Marrone, MD • Patrick Forde, MD
  - **Multidisciplinary Disease Management Team**
    - K. Ranh Voong, MD, MPH
    - Stephen Broderick, MD, MPHS



- **Data Research Manager**: Durrant Barasa
- **Biostatistician**: Robert Scharpf, PhD
- **Project Manager & Development**: Sharon Penttinen & the inHealth Team

Our group has well 30,000 citations of our published research in lung cancer genomics and therapy, with a broad range of NIH/NCI R & P-series, foundational, and industry grant support.

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Heart Failure with Preserved Ejection Fraction PMCOE

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Heart Failure with Preserved Ejection Fraction PMCOE

- **Vision:**
  The vision of the Heart Failure with Preserved Ejection Fraction (HFpEF) PMCOE is to bring together clinicians and basic-translational researchers in a collaborative effort to improve diagnosis, treatment, and outcomes for patients with HFpEF.
- **Mission**
  Our mission in the HFpEF PMCOE is to understand risk factors, identify prognostic markers, uncover disease mechanisms, with the goal of detecting therapeutic targets for patients with HFpEF through collaborative clinical-translational and basic science research.
- **Research Aims**
  Our multi-faceted research program aims include: 1. Clinical Trials: phase 2-3 clinical trials in HFpEF; 2. Clinical Research: including registry-based observational studies, and broader population-based studies on outcomes in HFpEF; 3. Basic-translational Research: including biomarker and human myocardial tissue-based studies to understand underlying disease mechanisms.

Interested in Collaboration?

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Precision Medicine Symposium 2022

Heart Failure with Preserved Ejection Fraction PMCOE

Co-Directors: Kavita Sharma, MD and David Kass, MD

Focus

Heart Failure with Preserved Ejection Fraction (HFpEF) constitutes half of all heart failure in the United States, with an estimated 3.5 million adults affected, and is predicted to be the predominant form of hospitalized heart failure over the coming decade. There remain very limited therapies for this disease, with high morbidity and mortality in patients in hospitalized patients with HFpEF.

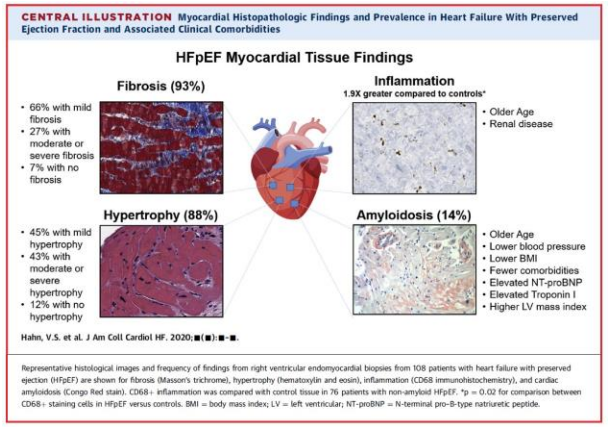
The HFpEF PMCOE aims to bring together clinicians and basic-translational researchers in a collaborative effort to improve diagnosis, treatment, and outcomes for patients with HFpEF. Here we highlight some of our basic-translational research including first-in-human myocardial tissue-based studies to understand underlying disease mechanisms.

Method & Analytics

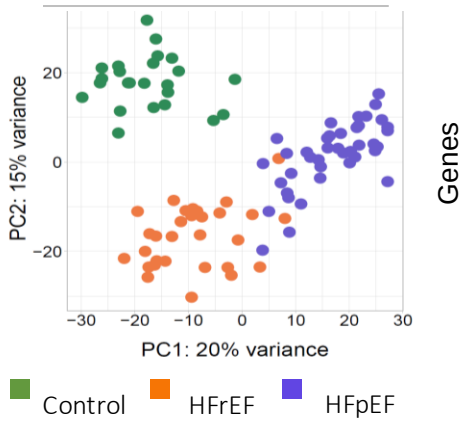
Our myocardial tissue-based studies are based on prospectively obtained right ventricular endomyocardial biopsy samples at the time of right heart catheterization procedures for diagnostic testing in patients referred from the JHU HFpEF Clinic. All patients included have qualifying hemodynamic, clinical, and echocardiographic criteria for the diagnosis of HFpEF. Myocardial tissue from HFpEF patients was compared to those with HF reduced ejection fraction (HFrEF) and controls (donor hearts) for histopathologic analysis and myocardial transcriptomics with machine learning analysis to identify subgroups within HFpEF.

Results and Highlights

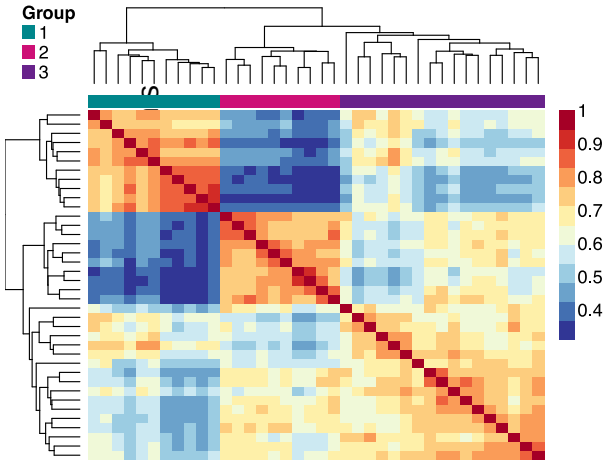
HFpEF Myocardial Histopathology

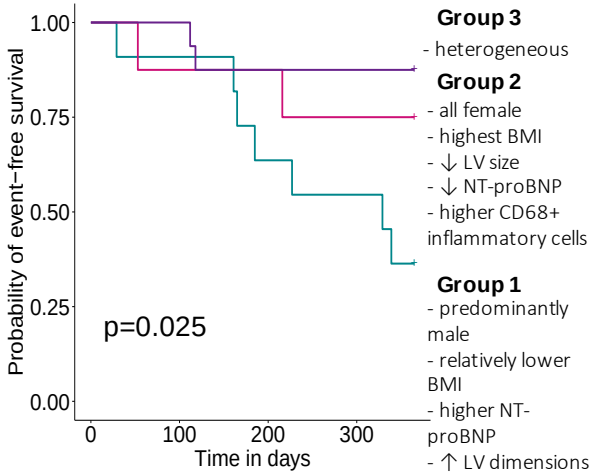


HFpEF Myocardial Transcriptomics v. HFrEF



HFpEF Myocardial Transcriptomics and Phenotype Identification





Group 3
- heterogeneous

Group 2
- all female
- highest BMI
- ↓ LV size
- ↓ NT-proBNP
- higher CD68+ inflammatory cells

Group 1
- predominantly male
- relatively lower BMI
- higher NT-proBNP
- ↑ LV dimensions
- ↑ pulmonary vascular load

Conclusion

HFpEF remains a major unmet need in cardiovascular medicine today. The growing predominant clinical phenotype is characterized by metabolic co-morbidities such as obesity, diabetes, and dyslipidemia. Myocardial tissue-based studies offer insights into underlying disease mechanisms, and the potential to identify therapeutic targets for this population.

Next Steps

The JHU HFpEF PMCOE research program aims to continue to pursue mechanistic studies from human blood and myocardial tissue to understand disease mechanisms in HFpEF. Ongoing and future studies include gene sequencing from blood and tissue, single-cell sequencing from tissue, and proteomics studies. We aim to pursue hemodynamic studies where both arterial and coronary sinus blood sampling are assessed for metabolite uptake and degradation by the heart with exercise, as well as a cardiac PET imaging-based study comparing myocardial metabolic activity in HFpEF patients to matched patients with similar co-morbidities yet without the heart failure syndrome. From our HFpEF registry, we aim to further study predictors of disease severity and progression from patients enrolled from the JHU HFpEF Clinic.

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COVID PMCOE

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Precision Medicine Center of Excellence for COVID-19

The Clinical Challenge

- Most patients with COVID-19 recover with simple supportive care
- Severe COVID-19 usually occurs early in hospitalization
- COVID-19 therapies work best early in disease course, before severe disease onset
- Identifying patients with risk of severe disease may help guide therapeutics to patients most in need
- COVID-19 severity prediction is a moving target: variants, vaccines, evolving treatment strategies
- Most machine learning methods use cross-sectional data from a single time-point to predict an outcome – but clinical status changes rapidly in COVID-19
- Clinicians have insufficient time to manually enter a long list of variables into a prediction tool

Method & Analytics

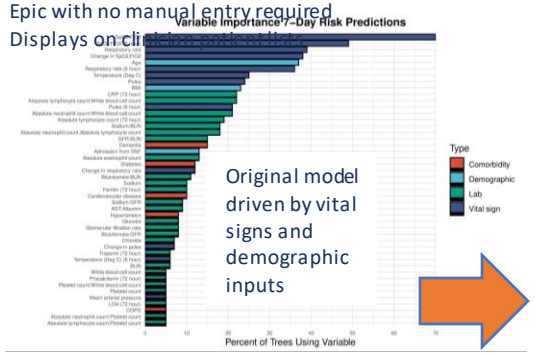
Patient population
- Patients hospitalized with COVID-19 in 5 JHM hospitals
- Data source: JH-CROWN

Model construction and evaluation
- Random Forests for Survival, Longitudinal, and Multivariate (RF-SLAM) extends random forests:
  - Evaluates longitudinal data
  - Considers time-dependent predictor variables
  - Bins time-varying covariates into discrete person-time units (6-hours for this model)

Model deployment
- Random forests execute slowly
  - Too slow for instant reporting using web-based tools
  - Too computationally demanding for direct EHR (Electronic Health Record) integration
- Summary classification and regression trees (CaRT) provide:
  - Simplified visualization for clinician interpretation
  - Rapid results for a web interface
  - EHR integration with Predictive Model Markup Language (PMML)
- Ensemble models with dynamic user input limits clinician inputs

Results and Highlights

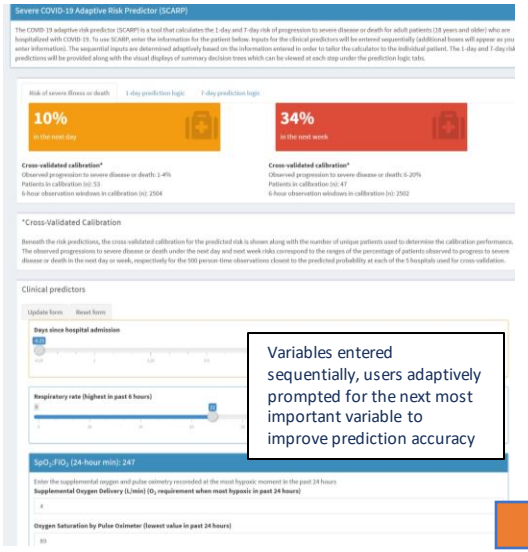
Severe COVID-19 Adaptive Risk Predictor (SCARP)
- Predicts 1- and 7-day risk of progression to severe COVID-19
- Applicable at any day in the first 7 days of hospital admission
- Tailors input dynamically to the most predictive variables (web version)
- PMML version integrated into Epic at all 5 JHM hospitals
- Gathers clinical features directly from structured data in Epic with no manual entry required
- Displays on cli



Original model driven by vital signs and demographic inputs

Model: RF-SLAM
Data: JH-CROWN on PMAP
Language: R
User input: specification file
Platform: RStudio

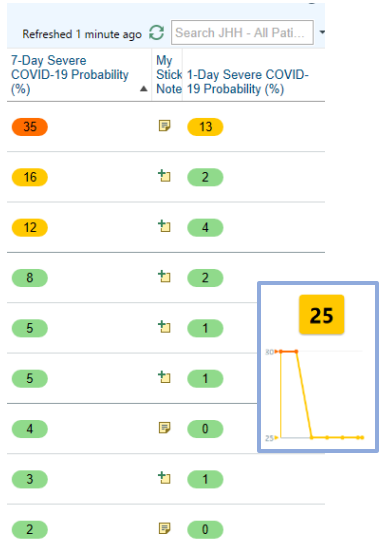
https://rsconnect.biostat.jhsph.edu/covid_trajectory/



Variables entered sequentially, users adaptively prompted for the next most important variable to improve prediction accuracy

Model: Ensemble Classification and Regression Trees (CaRT)
Data: RPART specification file
Language: R
User Input: Dynamic manual entry (1-6 inputs)
Platform: Shiny Web host

Screenshot from Epic Patient List



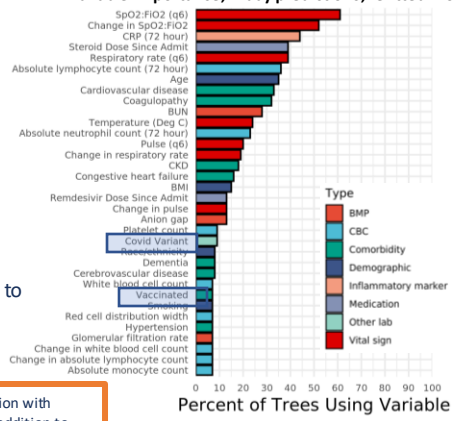
Model: CaRT
Data: Chronicles
Language: PMML
User Input: none
Platform: Epic

Shortcomings of original model
- Fitted prior to:
  - Emergence of SARS-CoV-2 variants
  - Widespread vaccination
  - Consistent steroid and remdesivir use
- Not prospectively validated

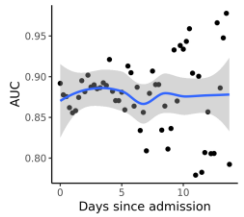
Refitted model
- Excludes hospitalizations prior to September 2020
- Considers vaccine status, variant, and treatment

Despite their strong association with inpatient outcomes, limited addition to clinical prediction

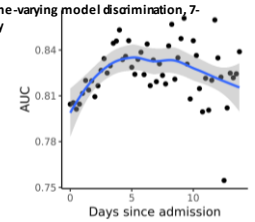
Variable importance, 7-day predictions, refitted model



Time-varying model discrimination, 1-day



Time-varying model discrimination, 7-day



Conclusion

- RF-SLAM successfully considers longitudinal data for clinical prediction
- Integrating clinical prediction into the EHR is challenging but possible
- The contribution of individual variables to model performance may be counterintuitive

Next Steps

- Implement updated model which incorporates vaccine status, variant, and treatment into the online and EHR version
- Apply RF-SLAM and adaptive risk prediction to other applications

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Asthma Precision Medicine Center of Excellence

Director: Meredith C. McCormack, MD MHS

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Asthma PMCOE

- **Vision:**
  Asthma is a chronic disease affecting 25 million people, including 6 million children. Our vision is to advance the field of asthma with new approaches for specific subgroups, including novel personalized therapies at the individual level and integrated precision approaches at the system level.
- **Mission**
  We seek to define the drivers of asthma and develop therapies and customized approaches targeting lifestyle and behavioral factors absent from current asthma guidelines. Our specific initial focus includes obese asthma patients, as these patients are prone to more severe, worse outcomes and are at an increased risk of hospitalization and a lower quality of life.
- **Research Aims**
  We aim to explore and model internal and external exposures that are common triggers of asthma exacerbations across the lifespan. Our goal is to identify opportunities for interventions that span from the individual to systems-level that will improve health and lives of those with asthma.

Interested in Collaboration?

Contact us at:

Phone:
(410)502-2806
(410)550-1060

Email:
mmccor16@jhmi.edu
breathe@jhu.edu

Asthma Precision Medicine Center of Excellence

Scott E, Balasubramanian A, Koehl RJ, Wu TD, Eakin M, Koehler K, Zaitchik B, Waugh D, Zeger S, McCormack MC

Precision Medicine Symposium 2022

Focus

- Asthma is a complex, heterogenous disease with a high morbidity often related to asthma exacerbations.
- Asthma exacerbations occur when a trigger is presented to a susceptible host.
- Factors contributing to susceptibility include both internal and external factors, some of which may be behavioral.
- The Asthma PMCOE aims to better characterize these factors to identify high-risk subgroups and estimate the risk of an exacerbation in any given individual.
- The ultimate goal is to define strategies to reduce exacerbations and improve the lives of those with asthma.

Method & Analytics

- Asthma PMCOE consists of individuals:
  - Age>5 years old
  - From any JHM site including Johns Hopkins Hospital, Bayview Medical Center, Suburban, Sibley, Howard County, All Children's Hospital
  - ICD-10 code for Asthma (J45) OR ICD-10 code for cough, wheeze, or shortness of breath (R group)
- Asthma Exacerbations defined by ICD-10 code consistent with asthma exacerbation only in the inpatient setting (emergency, observation, or inpatient visits)
- Linear mixed models were developed for each of six biomarkers: FEV_1, eosinophil count, IgE, HbA1c, HDL, LDL.
- Biomarker trajectories were modelled as a function of patient characteristics and include random effects at the patient-level.
- Using a proportional hazards model, the risk of asthma exacerbation was estimated as a function of patient characteristics, biomarker trajectories, and recent biomarker observations.

Environmental and Socioeconomic Factors

- The interplay of environmental factors such as chronic pollutant/heat exposure and socioeconomic factors measured by metrics such as Area Deprivation Index (ADI) and Social Vulnerability Index (SVI) impact susceptibility and act as triggers for exacerbations
- Figure 1 demonstrates the distribution of ADI in the Asthma PMCOE cohort. Notably median ADI among Black individuals was higher than White individuals (median (Q1,Q3): 43 (24,72) vs 20(10, 34), p<0.001)
- Figure 2 is a heatmap of the interaction between SVI and temperature

Figure 1. Distribution of ADI in Asthma PMCOE

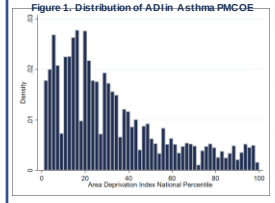
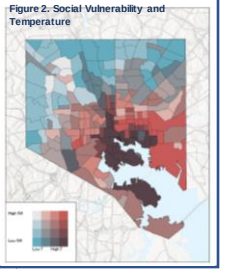
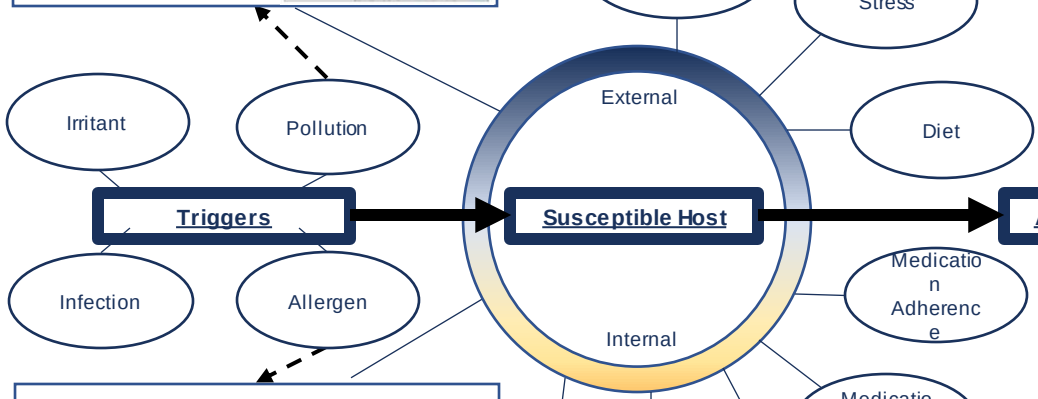


Figure 2. Social Vulnerability and Temperature

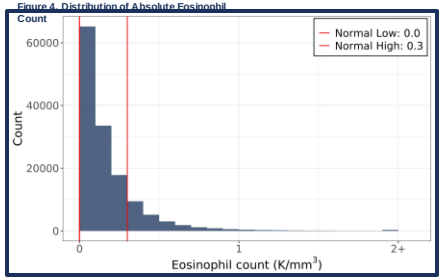




Allergic Inflammation

- Allergic inflammation was commonly identified, with 29% having at least one absolute eosinophil count >0.3 K/mm³ in their follow up time (Figure 4)
- Elevations in Immunoglobulin E were also common with a median IgE of 110 kU/L, (Q1 26, Q3 436.5), and 13% having an IgE above 1000

Figure 4. Distribution of Absolute Eosinophil Count



- Asthma PMCOE consists of 454,599 individuals, with 78,600 (17%) children, 270,326 (59%) female, and 140,056 (31%) identifying as Black
- Over half of individuals (N=254980, 56%) carried an Asthma ICD-10 code (J45 group), with the remaining having respiratory symptom ICD-10 codes (R group)
- 30% of patients came from Johns Hopkins Hospital or BMC, and 3% came from All Children's Hospital

Observed Exacerbations in the EHR

- 27,953 inpatient exacerbations were observed using ICD-10 diagnosis code criteria from 16,338 patients
- Table 1 describes the distribution of asthma exacerbation inpatient encounters in the cohort among those with at least one exacerbation over a median follow up time of 3.7 years
- Most inpatient encounters for exacerbations were ED visits, as demonstrated in Figure 3
- Males more commonly exacerbated as children, while females more commonly exacerbated as adults
- Children tended to have exacerbations resulting in ED visits while adults had more observation or inpatient admissions (Table 2)

Table 1. Distribution of Inpatient Exacerbations

	Number (Percent) of Individuals (N=16,338)
1 exacerbation	11804 (72%)
1–2 exacerbations	2324 (14%)
>2 exacerbations	2210 (14%)

Figure 3. Inpatient Exacerbations by Location

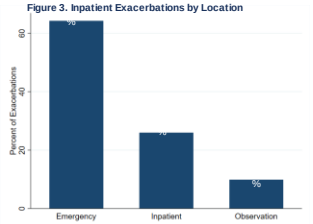


Table 2. Inpatient Exacerbations Location by Age,

	Children N=14209		Adults N=13672	
	Male N=8605	Female N=5604	Male N=4682	Female N=8802
Emergency	6515 (75%)	4162 (74%)	2812 (58%)	4387 (50%)
Inpatient	1572 (18%)	1093 (20%)	1361 (28%)	3219 (37%)
Observation	518 (6%)	349 (6%)	689 (14%)	1196 (14%)

Modeling Exacerbations

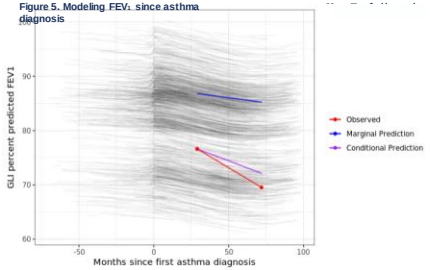
- For each biomarker, linear mixed models: $Y_{ik} = X_{ik}\beta_k + Z_{ik}b_{ik} + \varepsilon_{ik}$ where i corresponds to patient and k corresponds to biomarker. X_{ik}, Z_{ik} are the fixed effects and random effects design matrices for patient i, biomarker k, respectively. Figure 5 demonstrates results from this model for FEV_1.
- We assume:

$$\varepsilon_i \sim N(0,\Sigma)$$

$$b_i \sim N(0,D)$$

$$Y_{ik} \sim N(X_{ik}\beta_k, ZDZ^T + \Sigma)$$

Figure 5. Modeling FEV_1 since asthma diagnosis



- We will develop a joint model of biomarkers to examine how they covary over time followed by a model of exacerbations using proportional hazard models
- Risk of asthma exacerbation: $\lambda(t|X_i, Y_i) = \lambda_0(t)\, e^{X_i\Gamma + Y_i\delta}$ where $X_i = \left(X_{i1}^T, \ldots, X_{ik}^T\right)^T$ and $Y_i = \left(Y_{i1}^T, \ldots, Y_{ik}^T\right)^T$
- We can separate the risk of exacerbation associated with a person's trajectories from the risk associated with the biomarker values by changing the hazard model above to: $\lambda(t|X_i, b_i, Y_i) = \lambda_0(t)\, e^{X_i\Gamma + b_i\alpha + (Y_i - X_i\beta - Z_i b_i)\delta}$

Conclusions & Next Steps

Asthma is a complex disease with emerging insight into specific phenotypes and endotypes . The Asthma PMCOE seeks to better understand asthma exacerbations as a key outcome by defining biomarkers of relevance. The overarching goal is to identify new approaches to treat high risk subgroups and improve the lives of those living with asthma.

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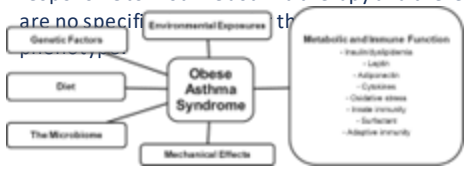
Metformin Use and Risk of Asthma Exacerbation Among Asthma Patients

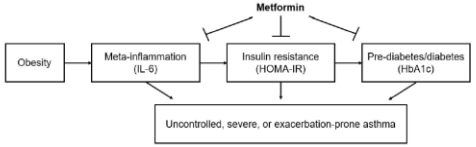
Wu TD, Fawzy A, Akenroye A, Keet C, Hansel NN, McCormack MC

Focus

- An overarching goal of the JH Asthma PMCOE is to advance the understanding and treatment of overweight and obese individuals with asthma.
- More than 40% of the 250 million people living with asthma in the U.S are obese.
- Obese individuals with asthma are at increased risk for more severe asthma and for asthma morbidity.
- Obese individuals with asthma are less responsive to first line asthma therapy and there are no specifi th



- The drivers of the excess asthma morbidity among obese individuals are multifactorial.
- There is increasing recognition that metabolic dysfunction may be a unique contributor to asthma.



- We sought to determine the association of metformin use and asthma exacerbation in an electronic health record (EHR)-based cohort of individuals with asthma and diabetes.
- We hypothesized that metformin use would be associated with lower risks of asthma-related steroid prescription, emergency department visit, and hospitalization.

Results and Highlights

Characteristics of Study Population

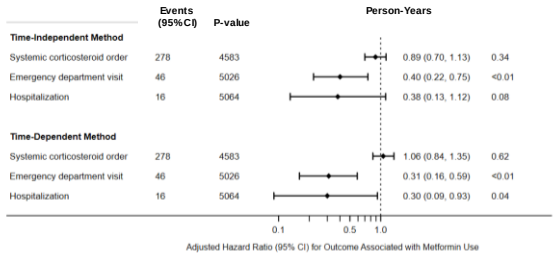
Characteristic	Metformin non-users	Metformin users	Standardized difference**
Number	888	861	
Age, mean (SD)	55.1 (14.3)	53.3 (13.6)	0.13
Female sex, n (%)	650 (73)	638 (74)	0.02
Race, n (%)			0.07
Black	456 (51)	413 (48)	
White	349 (39)	355 (41)	
Other	83 (9)	93 (11)	
Smoking status			0.04
Current	90 (10)	97 (11)	
Former	272 (31)	254 (30)	
Never	526 (59)	510 (59)	
Insurance type			0.17
Medicaid	123 (14)	106 (12)	
Medicare	287 (32)	229 (27)	
Tricare	79 (9)	107 (12)	
Private/other	399 (45)	419 (49)	
Body mass index, mean (SD)	37.1 (9.1)	37.4 (8.8)	0.03
Asthma medications*			
Inhaled corticosteroid	286 (32)	298 (35)	0.05
Long-acting beta agonist	167 (19)	167 (19)	0.02
Leukotriene modifier	126 (14)	127 (15)	0.02
Diabetes medications*			
Sulfonylurea	106 (12)	208 (24)	0.32
Thiazolidinedione	13 (2)	22 (3)	0.08
Glucagon-like peptide-1 agonist	15 (2)	24 (3)	0.07
Dipeptidyl peptidase 4 inhibitor	36 (4)	87 (10)	0.24
Insulin	172 (19)	160 (19)	0.02
Hemoglobin A1c, %, mean (SD)	7.7 (1.7)	7.6 (2.0)	0.05
Charlson Comorbidity Index	0.36 (0.73)	0.22 (0.49)	0.21

*medication classes with less than 1% prevalence in all groups are not listed
** a larger standardized difference reflects a greater difference between groups, values above 0.1 are considered statistically significant; SD: standard deviation

Methods & Analytics

- Patients with asthma and diabetes treated in the Johns Hopkins Health System between 4/1/2013 and 5/31/2018 (n=1,749) were followed after testing of hemoglobin A1c for (1) prescription for oral steroid, (2) emergency visit, (3) and hospitalization for asthma
- Time to event after HbA1c testing was estimated by Cox proportional hazards, adjusted for sociodemographic variables, comorbidities, drug use, and body mass index
- Metformin exposure was modeled as time-independent or time-dependent (figure)

Association between Metformin use and asthma

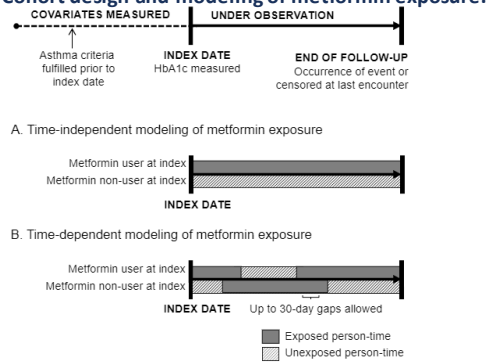


*Models adjusted for age, sex, race, smoking, BMI, insurance, HbA1c, diabetes medications (GLP-1 and TZD)

Summary of Results

- Metformin use was associated with lower hazard of systemic corticosteroid orders and asthma-related emergency visits in both modeling approaches, and with lower hazard of asthma-related hospitalization only in the time-dependent approach
- Asthma-related emergency department visits and hospitalizations were uncommon overall
- Associations were not mediated by hemoglobin A1c

Cohort design and modeling of metformin exposure.



Participants are followed from the index date, defined as date of HbA1c measurement, until the occurrence of event or censoring at the last healthcare encounter. Metformin exposure was assessed as time-independent (A) based on the presence or absence of a metformin order on the index date or time-dependent (B).

Conclusions

- Metformin use was associated with lower risk of asthma exacerbation independent of glycemic dysfunction and body mass index
- Limitations include examination of prevalent metformin users, risk of healthy user biases, and misclassification related to use of electronic health record data
- Results build rationale for prospective studies and future clinical trial

Next Steps

- American Lung Association grant secured to fund feasibility study to inform design of definitive multicenter trial of metformin for asthma
- NHLBI R34 resubmission for pilot study of metformin for asthma underway
- Patients from the Asthma PMCOE registry will be invited to participate if eligible
- Individuals who do not already meet the clinical indications for metformin are the target candidates
- Analyses to investigate the associations between newer therapies for diabetes (GLP1 agonists) and asthma outcomes.
- Ongoing work with the asthma PMCOE to define other factors that contribute to the increased prevalence and morbidity to asthma among overweight and obese.
- Ultimately aim to have customized therapies for individuals who are overweight and obese with asthma.

References

Wu TD, Fawzy A, Akenroye A, Keet C, Hansel NN, McCormack MC. Metformin Use and Risk of Asthma Exacerbation Among Asthma Patients with Glycemic Dysfunction. J Allergy Clin Immunol Pract. 2021 Nov;9(11):4014-4020. PMID: 34293503.

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Biclustering and Supervised Machine Learning Approaches for Subgroup Discovery and Cognitive Decline Prediction in Alzheimer's Disease

Hannah P. Cowley, Nathanael Kuo, Michael Robinette, Roy Adams, Anil Mathur, Milap Nowrangi, Peter Zandi, & Kenichi Oishi

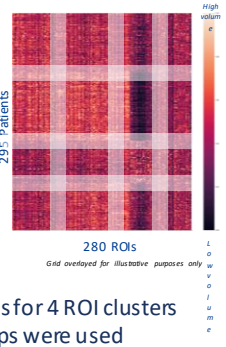
Two Projects | One Aim

A major goal of the Richman Family Precision Medicine Center of Excellence (PMCoE) is to **leverage big data for patient subtyping**, with applications to diagnostics and therapeutics.

- **Biclustering Analysis:** Simultaneously identify patient clusters and region of interest (ROI) sub-groups using clinical magnetic resonance imaging (MRI)
- **Supervised Machine Learning (ML):** Train explainable ML models to predict cognitive decline using clinical and research MRI

Biclustering Analysis Methods

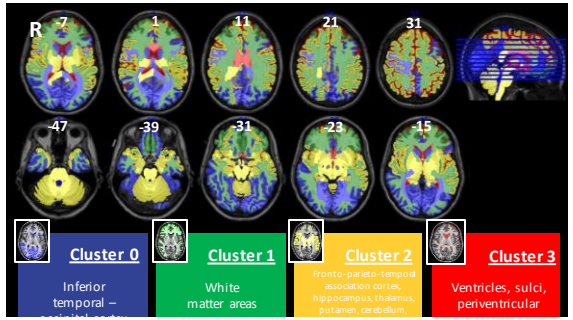
- Parcellated T1-weighted scans of JH MATC patients (N=295)
- Brain volume per ROI is expressed as a ratio of total brain volume for each individual patient
- Clustering was implemented using the spectral biclustering algorithm
- Clustering specifications for 4 ROI clusters and 4 patient sub-groups were used
- Results were joined to clinical data in PMAP projection database



Supervised ML Methods

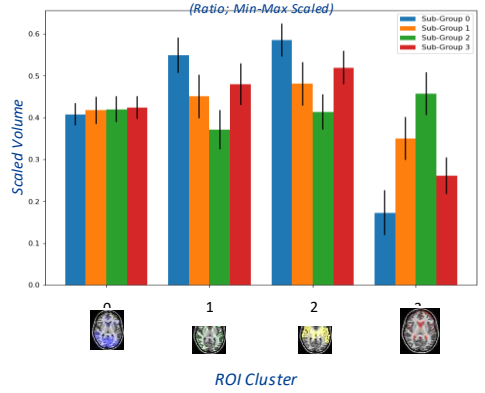
- Traditional ML and deep learning (DL) models, as well as classification and regression models, were trained
- Datasets included parcellated scans with associated difference in Mini-Mental State Exam (MMSE) scores from the Alzheimer's Disease Neuroimaging Initiative (ADNI; N=3838) and from the PMCoE (N=127)

Biclustering Analysis Results

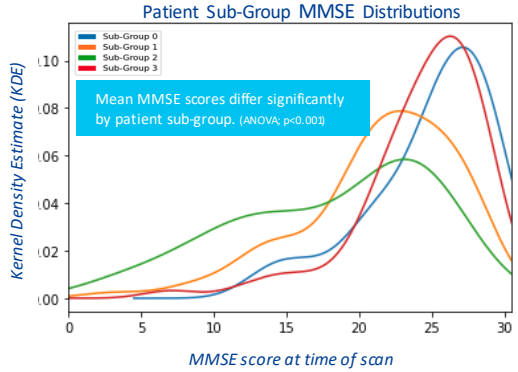


Mean Volume by ROI Cluster and Patient Sub-Group

(Ratio; Min-Max Scaled)

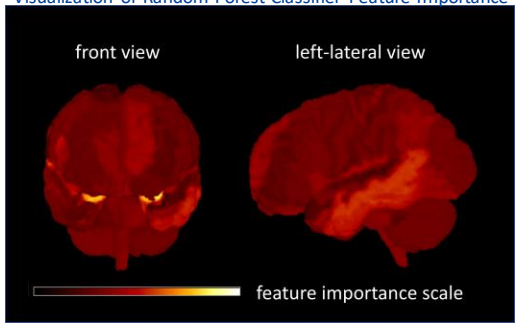


Patient Sub-Group MMSE Distributions



Supervised ML Results

Visualization of Random Forest Classifier Feature Importance



Biclustering Analysis Conclusions

- Despite noise in the clustering results, promising results are found in this small dataset
- Patient sub-groups may exhibit different atrophy patterns: volumes within ROI cluster 3 (ventricles, sulci, periventricular caps) may be especially informative for distinguishing patient sub-groups
- There is evidence to suggest that the data-driven clustering has identified clinically-significant patterns: lower MMSE (more impaired) in patient sub-groups 1 and 2 correspond to higher volume (more atrophy) in ROI cluster 3

Supervised ML Conclusions

- Models seem to be overfitting given the limited size of the training dataset
- A domain shift is observed between the two datasets that is currently being explored
- The hippocampus region of the brain seem to be most correlated with cognitive decline

Next Steps

- Continued funding for these efforts through externally-funded grants. Validate the existing results and advance current methods.
- Validation of clustering results using a larger PMCoE dataset
- Publication of findings for each effort

Acknowledgements

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Primary Care
Precision Medicine Center of Excellence

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Primary Care Precision Medicine Center of Excellence

- **Vision:**
- Healthy people and communities enabled by the delivery of the best interventions for health promotion and disease prevention, diagnosis, and treatment for each patient in primary care.

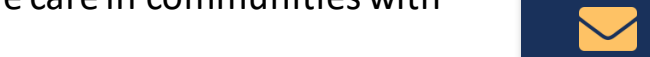
- **Mission**

To accelerate discovery and translation of research into primary care practice. We will achieve this with precision data and analytics that enables a learning health system, working in partnership with patients, families, clinicians, researchers, and communities.

- **Research Aims**
- Neighborhood Differences: We are using tools of spatial analysis to improve the care in communities with high risks of adverse outcomes among their residents.
- Individualized Treatment : We are developing analytic methods to identify the best medication addition for patients who need intensified treatment of a chronic condition.
- Develop Registries: We support researchers in developing registries of patients with important primary care needs such as hypertension control, transgender health, complex care, and disabilities.
- Learning about Barriers: We are developing a Comprehensive Diabetes Assessment tool that will help identify barriers to individuals' attaining their best diabetes outcomes.
- Data Linkage: We integrate rich data from public sources into our data platform to learn about the needs of individuals living in diverse neighborhoods.
- Linkage to Services: We use data and analytics to link patients to services, within and outside of the health system, for management of their chronic conditions.

Interested in Collaboration?

Contact us at:



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Precision Medicine Symposium 2022

(Adult) Primary Care Center of Excellence
The Telemedicine Challenge

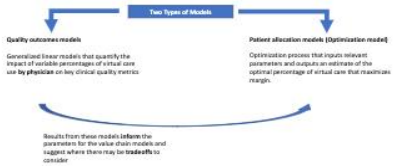
Focus

- Virtual care, specifically the synchronous clinician-patient interactions occurring over telephone or video, was broadly implemented in many health systems during the pandemic of COVID-19
- Little evidence to date about its *effectiveness* and *value* for the delivery of primary care
- Needed is additional evidence of its impact on care quality, patient outcomes and satisfaction, contribution to inequities in care and outcomes, and clinician satisfaction and burnout.
- Additionally, practice *revenue* must be evaluated to assess the ongoing viability of this mode of primary care delivery.

Goal: *To model the expected revenue from some mix of virtual and in-person primary care in a practice.*

Method & Analytics

- We assume that both modes of care delivery are equally appropriate for most clinical situations under consideration ("exchangeable")
- Using 2 models:



- **Quality outcome models**

$$\log(E[Y_{ijt} \mid u_i, v_j]) = \log(N_{ijt}) + \beta_0 + u_i + v_j + \beta_1 X_{1,ijt} + \beta_2 X_{2,ijt} + \cdots$$
$$Y_{ijt} \mid u_i, v_j \sim Poisson(\mu_{ijt})$$
$$u_i \sim Normal(0, \sigma_u^2)$$
$$v_j \sim Normal(0, \sigma_v^2)$$

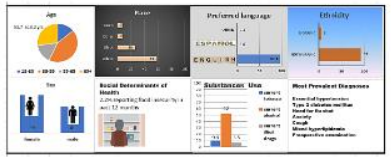
Where:
Y_{ijt} is the count outcome for physician i in clinic j in month t
u_i is the random intercept for physician i
v_j is the random intercept for clinic j
N_{ijt} is the **offset** (denominator) for outcome Y_{ijt} as needed
$X_{1,ijt}, X_{2,ijt}$, etc are the fixed effect physician and clinic level covariates including the **main covariate of interest (category of virtual care percentage)** and clinic-level characteristics of the patients (age, sex, ACG) and clinic characteristics (urban/rural) and calendar month.

Model written to run in SAS using GLIMMIX procedure

- ***Patient allocation models***
  - Base case: fixed number of physicians and fixed number of rooms
  - Choice variable is the # of exchangeable patients seen in-person and # seen virtually
  - Constraints include: total # of patients, cost of quality
  - Objective function seeks to maximize revenue
  - Inputs for the model came from analysis of data from the Primary Care COE (40 clinics, 400 clinicians, 400,000 patients, 800,000 visits)

Results and Highlights

Medical Demography



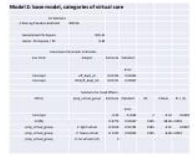
Visit Characteristics by **Physicians'** Virtual Usage Category 2020-2021

	Physician Never Virtual n=70 physicians	Physician Light Virtual n=257 physicians	Physician Heavy Virtual n=356 physicians
Age (mean years)	51.65 (17.9)	53.73 (17.7)	50.71 (17.2)
Total visits (median 25th,75th)	48 (36, 409)	4127 (1747, 5388)	4870 (2721, 5747)
Unique patients (N)	1202	58011	140895
Female gender, N (%)	713 (59.3)	32054 (55.2)	86650 (61.5)
Black race, N (%)	598 (49.9)	15654 (27.3)	38989 (28.0)
English primary language, N (%)	1098 (91.3)	57190 (98.5)	137974 (97.9)
Maryland resident, N (%)	1153 (95.9)	53777 (92.7)	129448 (91.8)
ADI decile 10: most disadvantaged, N (%)	241 (20.0)	3892 (6.71)	6976 (4.95)
Metropolitan resident, N (%)	1163 (99.2)	56283 (98.6)	137561 (99.2)
Rural resident, N (%)	3 (0.26)	88 (0.15)	113 (0.08)

category definition: never virtual (never a virtual visits in 2020-21); light virtual (virtual percentage is below overall median (22 visits) percentage for 2020-21), heavy virtual (virtual percentage is above median percentage 2020-21)

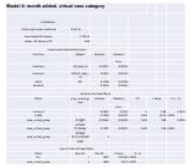
Quality Outcomes Models
[Subset of Clinicians in JHOC/Res.Clinic/ Greenspring]

BP control



Higher virtual care categories, less control of BP

A1c out of control

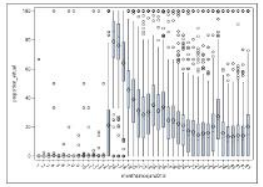


Higher virtual categories, more out of control A1c

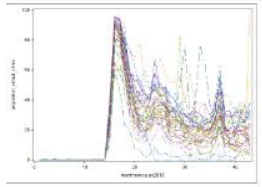
Breast Cancer screening

HIGHEST virtual category, slightly fewer mammograms

Proportion of telemedicine use by physician



Proportion of telemedicine use within each clinic

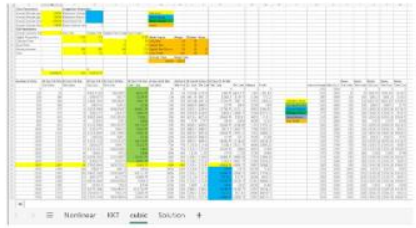


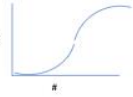
Patient Allocation Models

Managerial question

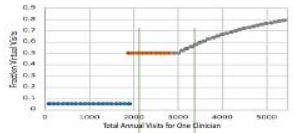
With a given panel of patients, if the clinic can control where patients are seen, what proportion of visits should be virtual to maximize the profit at the physician and clinic level?

The team's insight was to optimize with a cubic function (concave/convex) so that the relationship between cost and # of visits could be first concave and then convex at the visit count goes up (reflecting reality).

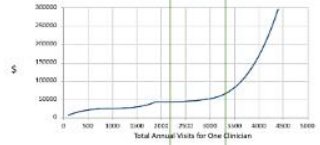




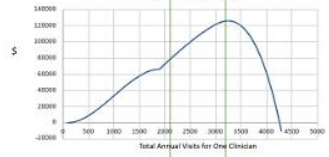
Proportion of Virtual Visits



Minimum Cost vs. Number of Visits



Profit vs. Number of Visits



Conclusion

Variation in use of virtual care across clinics but modest relative to variation by month

Preliminary quality models suggest that the quality metrics may not be met with heavy virtual care use. (Possibly a *higher* cost of quality with virtual care)

Profit peaks at 3200 visits or physicians working at 80% of capacity. In the absence of room constraints, the optimum would be 3700 visits. Because we need to move patients to virtual care when there are capacity issues, we lose about $8000.

Our model predicts:
1) *If* cost of quality is identical between sites of care, then having both options lowers total cost of quality.
2) With *equal* marginal cost of quality across sites, a *middle level* of virtual care is optimal. Mix tilts towards site with higher quality.

We remain uncertain if quality is equivalent. Work is ongoing.

Next Steps

Proceed with quality models in full data.

Report results to Office of Telemedicine to inform their decisions

Respond to upcoming AHRQ P50 award about telemedicine in primary care

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Funding: Johns Hopkins Office of Telemedicine

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Machine Learning Operations (MLOps) in Healthcare

Precision Medicine Symposium 2022

MLOps in Healthcare

J. Vince Pulido, Yem Mekonnen, Brant Chee, Suma Subbarao

Focus

Machine Learning Operations (MLOps) is a core function of Machine Learning (ML) engineering, focused on streamlining the process of taking ML models to production, and then maintaining and monitoring them. MLOps is a collaborative function, often requiring data scientists, software engineers, and IT staff. By adopting an MLOps approach, enterprises can increase the pace of model development and methodically transition ML capabilities to production.

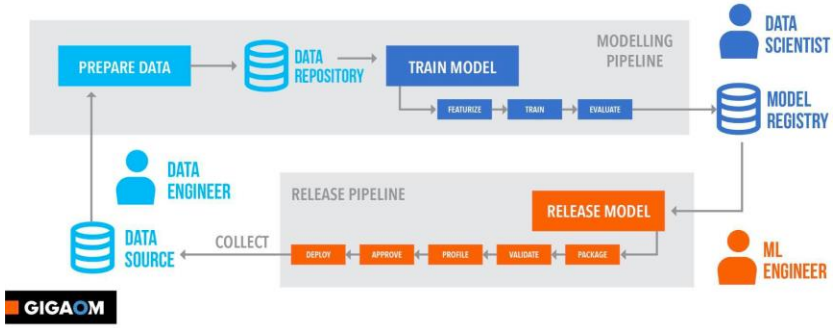
While it is slowly becoming more prevalent in the wider industry, MLOps has not been widely accepted for use within the healthcare setting. This is due to healthcare's unique regulatory, and ethical requirements, combined with the traditional approach to the practice of medicine. For this work, we introduce a systematic roadmap for healthcare institutions to develop their MLOps capabilities.

Framework

We adopted the MLOps Maturity Model and addressed the five core components [1] as tailored to the healthcare setting:

1. **Strategy:** an institution's ability to align MLOps with its executive priorities
2. **Architecture:** the ability to manage artifacts and computing resources
3. **Processes:** activities and resources allowing the management of multi-disciplinary teams to perform MLOps
4. **Modeling:** the process of delivering models for clinical use
5. **Governance:** ability to control and secure resources and artifacts of MLOps

Levels	0	1	2	3	4
Strategy	• No initiative for multi—disciplinary collaboration • Leadership skeptical of value ML/MLOps provides to the organization	• Small and siloed data science initiatives • Few leaders understand the value of ML	• Small group of data scientist, data engineers and software developers are given resources to coordinate • External partners are allowed and enabled to collaborate and provide data	• Large, well-integrated teams coordinating with healthcare workers • Executive leadership begin to track effects of MLOps (e.g. financial, patient outcomes)	• Metrics are showing improvements in operations and patient outcomes • Engineers and healthcare workers are embedded on the same teams
Architecture	• Data siloed, designed for one-off integration • Data not prepared for ML	• Health data is ready for siloed ML experiments • Annotation tools integrated into computing systems • Data architecture is still immature	• Most health data is enabled for ML • Data pipeline is mature and robust	• Health data is well-cataloged and managed for ML projects • Automated data pipelines in place	• Comprehensive architecture to govern all data • Architecture and its surrounding practices are tuned to increase efficiency for the institution
Modeling	• Manual process for model training • Low amount of experiments	• Basic experiment tracking, no model management	• Experiment tracking and model management in place • Policy exists to ensure high quality of annotations (e.g. inter-rater variability) • Methods addressing class imbalance and rare data	• All output of ML models are reasonable and auditable • Scale of data increases (e.g. from external partners, adversarial examples)	• Models are validated clinically (i.e. prospectively), studying the downstream impacts of the model • Methods addressing bias, explainability, model drift etc.
Processes	• No MLOps practices adopted • No agile software development practices	• DevOps adopted for software development • Software logging (i.e. warnings, security, etc.)	• Data is under version control • Manual logging of clinical outcomes	• All training artifacts are under version control • Healthcare providers have understanding of the processes	• Automatic logging of clinically relevant results (i.e. patient outcomes)
Governance	• No policy or guidance on use of models	• No universal policy or guidance on use of models, only within working groups • No concept of bias and explainability • HIPPA guidelines only considered per project	• Deployed models may contain model bias, limiting their utility and trustworthiness • Model releases are tracked • Consideration for HIPPA guidelines ingrained in data pipelines	• Attempts to remove bias in the model • Model releases are tracked • HIPPA guidelines ingrained in data pipelines	• Institution-level ethics practices are considered • Well-defined information privileges • Model biases are maximally mitigated



Highlights

A healthcare institution's adoption level could be graded as falling into one of these categorical levels. Using this framework, healthcare institutions can self-assess their readiness level to adopt and progress their MLOps culture and capabilities.

References

[1] McKnight, W., (2020)Delivering on the Vision of MLOps A maturity-based approach

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