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Precision Medicine Symposium 2023

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MEDICINE

PMCOE Research Projects:

1. Adult Primary Care
2. Alzheimer's Disease
3. COVID-19
4. Cystic Fibrosis
5. Kidney Disease
6. Lung Cancer
7. Multiple Sclerosis
8. Myositis
9. Neonatal Critical Care
10. Neurocritical Care
11. Ophthalmology
12. Pediatric Genetic Syndromes with Aortopathy
13. Pulmonary Embolism
14. Psychosis
15. Rehabilitation
16. Schizoaffective Disorder
17. Scleroderma
18. Miscellaneous/Developing Centers

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Adult Primary Care PMCOE

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Adult Primary Care PMCOE

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

- To learn about the profile and care processes of patients with diabetes using data in the OMOP Common Data Model and the Atlas tool.

Interested in Collaboration?

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Precision Medicine Symposium

Primary Care PMCOE: Characterizing Individuals with Diabetes in Johns Hopkins Medicine from 2016 to Present: Demonstration of Use of OMOP and ATLAS with the APC-COE Registry

Shanshan Lin, Jodi B. Segal

Focus

Background: The extract, transform, and load (ETL) process restructured the Electronic Health Records (EHR) data to the OMOP Common Data Model (CDM), which lays the groundwork for prospective large-scale network analysis.

Objectives:

(1) To learn about the profile and care processes of our patients with diabetes in primary care across Johns Hopkins Medicine (JHM);

(2) To demonstrate the use of data in the OMOP CDM with the Atlas tool.

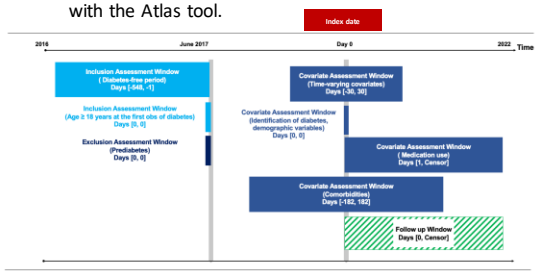


Figure 1. Graphical depiction of the study design for patients observed to have an incident diabetes occurrence

Method and Analytics

Data source: The Adult Primary Care Center of Excellence (APC-COE) projection includes all EHR data from patients who saw a primary care clinician in any of our 42 clinics since 2016.

Study design: Retrospective cohort analysis. We established three cohorts:

(1) Incident diabetes (Figure 1)

(2) Diabetes (without diabetes-free period compared to cohort for incident diabetes)

(3) All patients (patients with observation start date after 2016-01-01).

Diabetes definition[1]:

(1) Diagnosis code: ≥ 1 inpatient visit diagnosis or ≥ 2 outpatient visit diagnosis. Diagnosis codes include 250.x, 357.2, 366.41, 362.01–362.07;

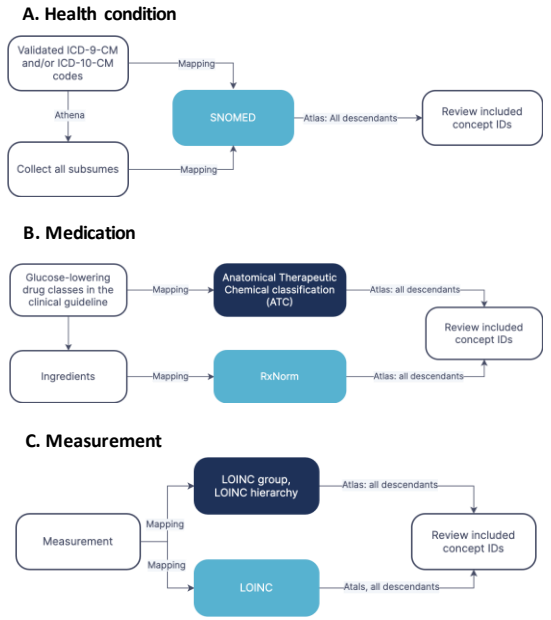
(2) Prescription: ≥ 1 prescription of glucose-lowering drug;

(3) Measurement: having either HbA1c at ≥ 6.5%, fasting plasma glucose at ≥ 126 mg/dL, or random plasma glucose at ≥ 200 mg/dL.

Covariates: Characteristics were generated with the built-in features in Atlas, adapted according to our research interests.

Results and Highlights

Product 1. A standardized process of constructing the concept sets for health condition, medication, and measurement of interest



Note: light blue: standard concepts; **dark blue**: classification concepts; **mapping**: the process of translating source code to standard code

Product 2. The conduct of a usual descriptive analysis using Atlas, along with advanced visualizations

Table 1. Baseline characteristics of individuals from the three cohorts

Characteristics	All Patients (N = 369331)	Diabetes (N = 62374)	Incident Diabetes (N = 45963)
Age, years			
18-39.9	143115 (38.7)	8482 (13.6)	5016 (10.9)
40-64.9	157823 (42.7)	31918 (51.2)	22723 (49.4)
65-85.9	62157 (16.8)	20188 (32.4)	16583 (36.1)
≥ 85	6236 (1.7)	1786 (2.9)	1641 (3.6)
Sex, N (%)			
Female	217397 (58.9)	34925 (56.0)	25422 (55.3)
Male	151843 (41.1)	27447 (44.0)	20539 (44.7)
Race, N (%)			
Black or African American	98075 (26.6)	23338 (37.4)	17685 (38.5)
White	213658 (57.9)	30306 (48.6)	22158 (48.2)
Asian	9944 (2.7)	870 (1.4)	469 (1.0)
American Indian or Alaska Native	1586 (0.4)	336 (0.5)	266 (0.6)
Native Hawaiian or Other Pacific Islander	628 (0.2)	117 (0.2)	83 (0.2)
Ethnicity, N (%)			
Hispanic or Latino	11477 (3.1)	57595 (92.3)	42748 (93.0)
Not Hispanic or Latino	335839 (90.9)	1154 (1.9)	616 (1.3)
Index year, N (%)			
2016	174111 (47.1)	18454 (29.6)	-
2017	78495 (21.3)	11329 (18.2)	4 (0.0)
2018	32859 (8.9)	5722 (9.2)	21056 (45.8)
2019	25554 (6.9)	5103 (8.2)	6387 (13.9)
2020	20954 (5.7)	4603 (7.4)	4374 (9.5)
2021	20764 (5.6)	5772 (9.3)	4998 (10.9)
2022	12339 (3.3)	6473 (10.4)	5284 (11.5)
2023	4255 (1.2)	4918 (7.9)	3860 (8.4)
Body Mass Index, kg/m², mean (SD)	**28.8 (7.5)**	**29.7 (8.0)**	**29.9 (8.1)**

Figure 2. A sunburst plot showing the trajectory of the prescription history of glucose-lowering medication for patients observed as having incident diabetes

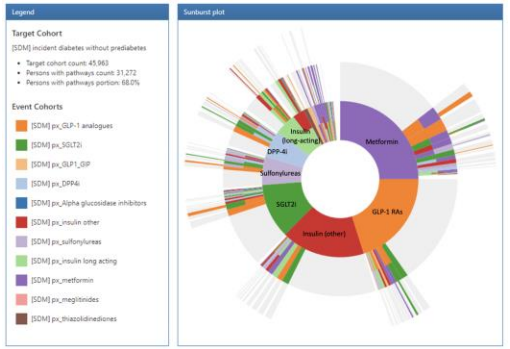


Figure 3. The counts and percentages of coded comorbidities 6 months prior and after the index date for patients with diabetes (yellow: diabetic health conditions)

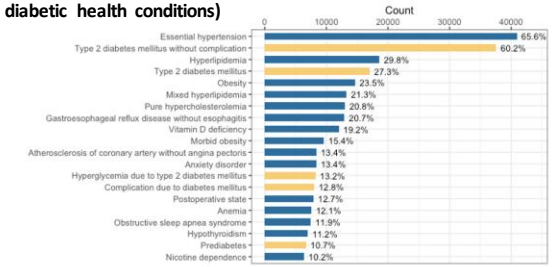
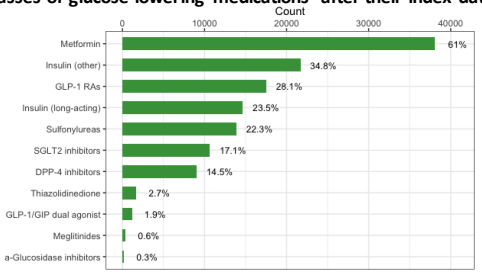


Figure 4. The counts and percentages of patients prescribed 11 classes of glucose-lowering medications after their index dates



Limitations

1. Data availability: There is no detailed information available about medication use, such as day supply and quantity, but it can be imported.
2. Interpretation:
   a. Sunburst plot (Figure 2): it describes the prescription pattern of physicians rather than the medication receipt by patients.
   b. Bar chart (Figure 3): The default feature output in the characterization analysis displays the coded comorbidities. To more meaningfully describe comorbid conditions, we need to customize a feature by aggregating the SNOMED codes.
3. Validation: There is a validated algorithm for creating a cohort of individuals with diabetes, but this is not often the case.

Conclusion

1. The diabetes prevalence in our health system, at 16.9%, exceeds the national estimate of 11.3% [2].
2. The cohorts of individuals with diabetes have the expected clinical characteristics.
3. The use of data in OMOP CDM with the Atlas tool minimizes researchers' effort in data cleaning. Nevertheless, additional support, such as SQL programming and R packages in HADES library are necessary to facilitate research with more sophisticated study designs.

Next Steps

1. Address remaining questions with SQL programming
2. Prepare for research involving incidence rate analysis, causal estimation, or prediction;
3. Prepare for a large-scale network analyses

[1] Nichols GA, Desai J, Elston Lafata J, et al. Construction of a multisite DataLink using electronic health records for the identification, surveillance, prevention, and management of diabetes mellitus: the SUPREME-DM project. *Prev Chronic Dis*. ElSayed NA, Aleppo G, Aroda VR, et al. [2] National Diabetes Statistics Report, 2022

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Precision Medicine Symposium

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.

Goal: To test the impact of virtual care usage on quality metrics used for performance measurement.

Methods and Analytics

- *Design:* mixed-design etiologic study using data from patients receiving primary care from January 2020 through December 2021
- *Participants:* Eligible patients had at least one primary care contact. Eligible physicians had 10 or more patient contacts.
- *Exposures:* Quartile of virtual visits per physician per month calculated as the percentage of total visits conducted by phone or video (Q1 is lowest).
- *Main Measures:* Six metrics used by institution for value-based reimbursement, measured monthly at physician-level
- *Models: generalized* linear mixed models, using Poisson or negative binomial distributions; with random intercepts for physicians nested in clinics and with a first-order autoregressive structure on the residuals by month; controlled for physician-level patient covariates by month

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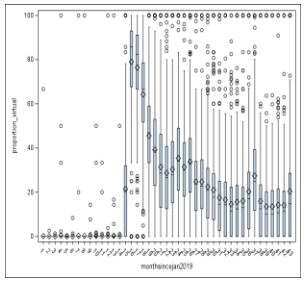
Results

Table 1. Patient Characteristics by Physicians' Virtual Usage Category 2020-2021[a]

	Quartile 1[b] (n=171 physicians)	Quartile 2 (n=171 physicians)	Quartile 3 (n=171 physicians)	Quartile 4 (n=169 physicians)
Unique patients (N)	8638	56,307	70,620	64,525
Total visits (median 25th,75th)	521 (244, 2541)	4481 (2746, 5461)	4949 (3485, 5670)	4575 (1980, 5751)
Age (mean years, s.d.)	58.7 (18.7)	52.4 (17.5)	51.2 (17.1)	50.3 (17.3)
Female gender, N (%)	4879 (56)	31313 (56)	43084 (61)	40134 (62)
Black race, N (%)	2794 (33)	15489 (28)	18907 (27)	18035 (28)
English as primary language, N (%)	8325 (96)	55605 (99)	69170 (98)	63144 (98)
Maryland resident, N (%)	8174 (95)	52298 (94)	64492 (91)	59397 (92)
MD/DC/VA/DE/PA resident, N (%)	8459 (98)	54652 (97)	69377 (98)	63375 (98)
ADI decile 10: most disadvantaged, N (%)	1052 (12)	3525 (6.3)	3204 (4.5)	3319 (5.1)
Metropolitan resident, N (%)	8277 (99)	54807 (99)	69026 (99)	62880 (99)
Micropolitan resident, N (%)	45 (0.54)	553 (1)	358 (0.51)	289 (0.46)
Small town resident, N(%)	20 (0.24)	91 (0.16)	118 (0.17)	142 (0.22)
Rural resident, N (%)	18 (0.22)	75 (0.14)	52 (0.07)	59 (0.09)

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

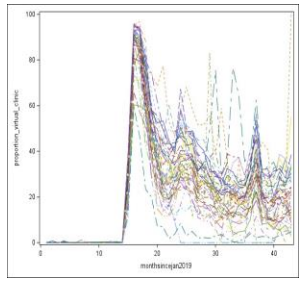


Figure 2a. Average Adjusted Rates of Meeting Blood Pressure Control Metric, by Quartile of Virtual Visits

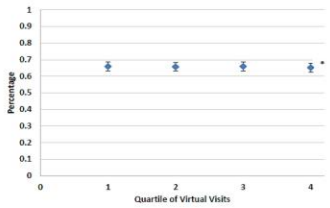


Figure 2b. Average Adjusted Rates of Meeting Hemoglobin A1c Control Metric, by Quartile of Virtual Visits

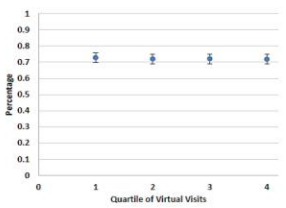
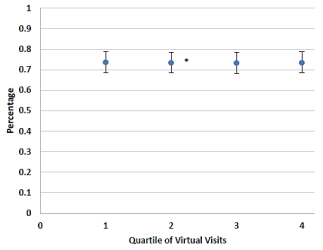


Figure 2c. Average Annual Adjusted Rate of Meeting Breast Cancer Screening Metric, by Quartile of Virtual Visits



*P<0.05 relative to Quartile 1

Figure 2d. Average Annual Adjusted Rate of Meeting Colon Cancer Screening Metric, by Quartile of Virtual Visits

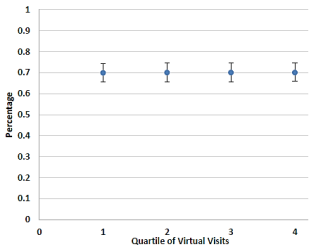
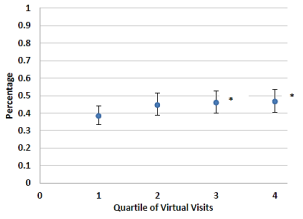
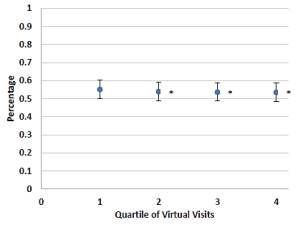


Figure 2e. Average Adjusted Rates of Meeting Diabetic Exam Screening Metric, by Quartile of Virtual Visits



*P<0.0001 relative to Quartile 1

Figure 2f. Average Adjusted Rates of Meeting Medicare Annual Wellness Visit Metric , by Quartile of Virtual Visits



*P<0.0001 relative to Quartile 1

Table 2. Incidence rate ratios comparing each quartile to lowest quartile of virtual care use [a]

Quartile of Virtual Care Use	Blood Pressure Control 95% CI			Breast Cancer Screening 95% CI			Colon Cancer Screening 95% CI			Diabetic Eye Exam Completion 95% CI			Medicare Annual Wellness Visit Completion 95% CI		
1 (lowest)	1.00	-		1.00	-		1.00	-		1.00	-		1.00	-	
2	0.997	0.991	1.002	1.000	1.000	1.004	1.002	1.000	1.004	1.163	1.149	1.177	0.978	0.974	0.983
3	1.000	0.994	1.006	1.000	1.000	1.004	1.002	1.000	1.004	1.198	1.182	1.214	0.974	0.969	0.978
4	0.990	0.983	0.997	1.000	1.000	1.004	1.002	1.000	1.004	1.215	1.197	1.233	0.971	0.965	0.976

Limitations

- This was an ecologic analysis, although we also had detailed individual-level data that was used for adjustment
- Analyses answer the question of the *contextual effect* of heavy virtual care delivery on the whole population in primary care
- Confounding and effect modification by physician is possible
- There are many other outcomes of importance for primary care delivery including patient satisfaction measures

Conclusions

- Variation in use of virtual care across clinics but modest relative to variation by month
- Some quality metrics were modestly impacted by high virtual primary care usage; the absolute differences in rates were small.
- Provides reassurance to physicians and their health systems that telemedicine use may not adversely impact quality metrics

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Ebele Okoli, MS – SPH

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

Funding: Johns Hopkins Office of Telemedicine

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Precision Medicine Symposium

Standardizing Diabetes Medication Data in the Adult Primary Care PMCOE

Team: Michael Chiu, Samantha Pitts, Lisa Yanek

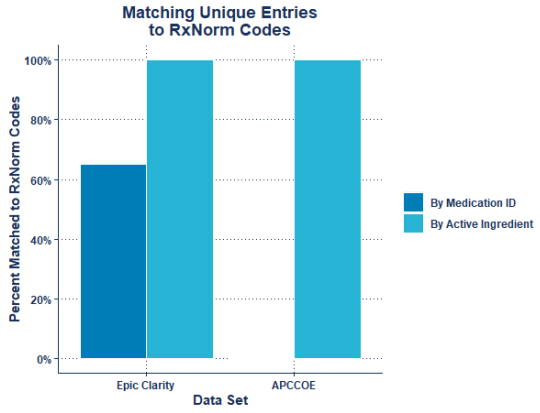
Focus

- Medication data must be standardized before they can be used in studies
- RxNorm codes provide a method of standardization
- The APCCOE medications failed to match RxNorm codes for analysis
- We used active ingredients to identify the missing RxNorm codes

Method and Analytics

- Data sources were the Epic Clarity (n=173,352) and Adult Primary Care Center of Excellence medications from First Data Bank therapeutic class "ANTIHYPERGLYCEMICS" that failed to match to RxNorm codes (n=2,449)
- The branded drug data set was generated using RxNav
- We used two algorithms to extract active ingredients and drug classes in both data sets (Figure 1)
- Entries in both data sets were then matched to RxNorm codes using active ingredients and exploratory analyses were performed

Figure 2. The proportion of unique entries that successfully matched to an RxNorm code in each data set.



Results and Highlights

- Active ingredients matched more unique entries to RxNorm codes than medication ID in both the Epic Clarity and APCCOE data sets (Figure 2)
- Almost all identified medications were monotherapies (Figure 3)
- Four medications constituted about 70% of all prescriptions in the APCCOE data for both monotherapy and combination therapies (Figure 4)
- These exploratory analyses validated the drug information extracted using the algorithms

Figure 1. The workflow to filter, extract, and match the data. The top left quadrant describes the process to select non-insulin diabetes from the raw Epic Clarity data set. The bottom left quadrant shows the steps using the algorithms to extract active ingredients and drug classes from each entry. The right half illustrates the procedure to match RxNorm codes using active ingredients.

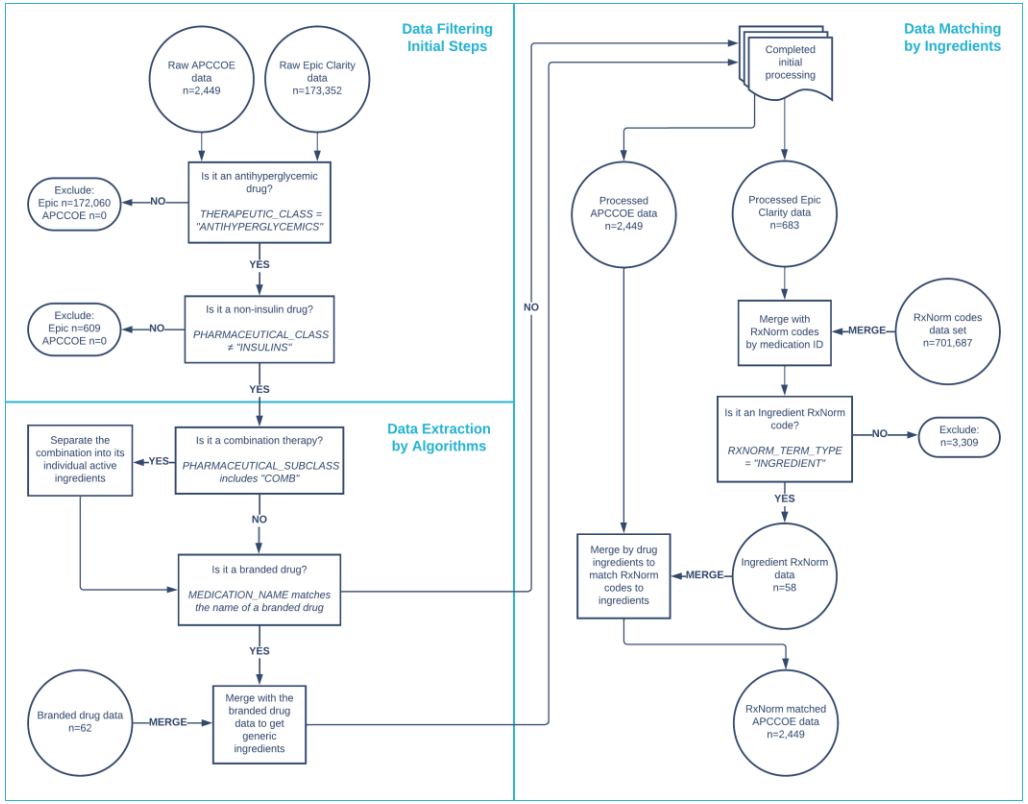
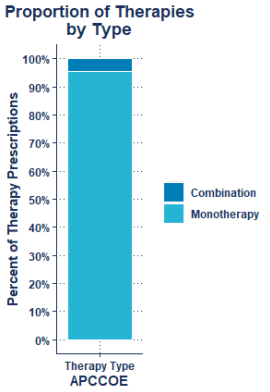


Figure 3. All combinations contain two active ingredients.



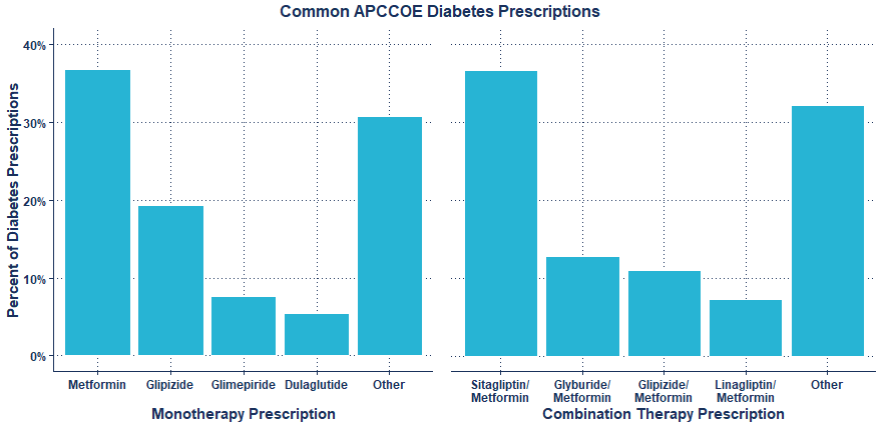
Conclusion

- APCCOE prescription data were matched to RxNorm codes using using active ingredients to provide completeness for data analysis
- Health system medication data may require novel methods to identify and classify them using standard terminology
- The methods and results require validation
- Standardized data can now be included in epidemiologic studies, which allows the APCCOE to gain insights into prescription practices

Next Steps

- Additional analyses will be performed to assess prescription of GLP-1 receptor agonists and SGLT2 inhibitors in diabetes patients
- Standardized data can be combined with data from other health systems to gain population-level insights on prescription practices
- Prescription practices can be carefully analyzed to ensure that patients are receiving the best of available treatments

Figure 4. The four most common therapies are depicted in the bar graphs for each type of therapy and the rest are categorized as "Other."



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Prescribing of evidence-based medications for the prevention of adverse cardiovascular events and progression of chronic kidney disease among patients with diabetes

Samantha Pitts, Lisa Yanek, Justin Wu, Alisa Zayas, Erin Michos, Nes Mathioudakis, Nisa Maruthur

Precision Medicine Symposium

Adult Primary Care COE

Focus

- Glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium-glucose transport protein-2 inhibitors (SGLT2i) reduce adverse cardiovascular events and progression of kidney disease among high-risk patients with diabetes
- In prior studies, few eligible patients received a GLP-1 RA or SGLT2i, with racial disparities in their use
- The proportion of eligible patients in primary care at Johns Hopkins with diabetes who have been prescribed a GLP-1 RA and SGLT2i is unknown

SGLT2i and GLP-1 RA indication by condition

Condition	SGLT2i*	GLP-1 RA*
ASCVD or CV high risk#	☑	☑
Chronic kidney disease (CKD)+	☑	☑
Heart failure (HF)	☑	

*Not all SGLT2I and GLP-1 RA have proven benefits for each indication
#ASCVD: Atherosclerotic cardiovascular disease; CV: Cardiovascular
+ SGLT2i is preferred in CKD, with GLP-1 RA if SGLT2i is not tolerated/contraindicated

Method & Analytics

- Identified patients in the Adult Primary Care COE with:
  - Type 2 diabetes, determined by at least one ICD-10 diagnosis code (E11 – E14)
  - At least one visit to a Johns Hopkins primary care location in the prior 12 months
- Further identified patients with additional conditions by ICD-10 code:
  - ASCVD (I20 – 25)
  - HF (I50)
  - CKD (N18)
- Defined patients as having a medication order for a GLP-1 RA or SGLT2i if they had at least one medication order identified
  - Active medication order: Order is less than 12 months old and has ended or been discontinued
  - Prior medication order: Order is identified but not active

Results and Highlights

We identified 26,478 patients with diabetes, of whom 7,837 (29.6%) had **ASCVD**, 6,506 (24.6%) had **CKD**, and 3,837 (14.5%) had **HF**. (Table 1)

Among patients with diabetes:

- ~30% of patients with **CKD** or **ASCVD** had an active medication order for an **SGLT2i** or **GLP-1 RA** (Figure 1)
- 20.1% of patients with **HF** had an active medication order for an **SGLT2i** (Figure 2)
- ~ 17% of patients with **CKD** or **ASCVD** had an active medication order for an **SGLT2i** (Figure 2) or **GLP-1 RA** (Figure 3)
- An additional 15 – 20% of patients had at least one prior medication order for an **SGLT2i** or **GLP-1 RA**

Table 1: Demographics of patients with diabetes in primary care in the past 12 months

Demographic characteristic	n (%) - except as noted
Age, mean +/- SD	64.1 +/- 13.9
Female	14,104 (53.3%)
White	12,845 (48.5%)
Black	9,759 (36.9%)
Asian	1,198 (4.5%)
Hispanic	977 (3.7%)

Figure 1: Active and prior SGLT2i or GLP-1 RA medication orders among patients with diabetes and CKD or ASCVD

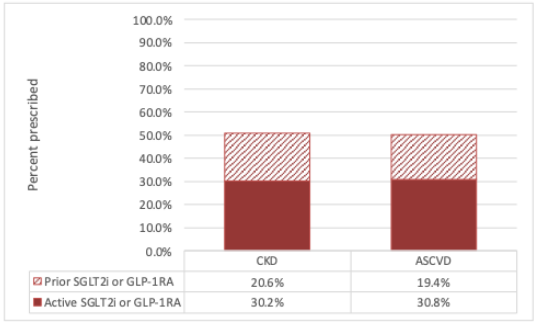


Figure 2: Active and prior SLGT2i medication orders among patients with diabetes and HF, ASCVD, or CKD

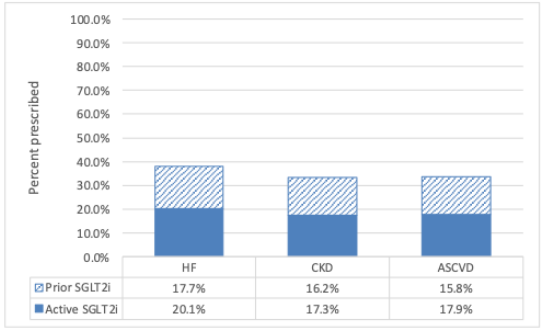
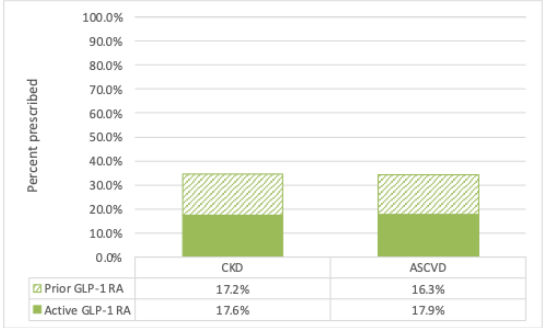


Figure 3: Active and prior GLP-1 RA medication orders among patients with diabetes and CKD or ASCVD



Conclusions

- Fewer than 1/3 of patients with diabetes and CKD or ASCVD had an active medication order for an SGLT2i or GLP-1 RA
- Only 1/5 of patients with diabetes and HF had an active medication order for an SGLT2i
- No more than 1/2 of patients with diabetes an an indication had evidence of any medication order (active or prior) for an SGLT2i or GLP-1 RA.
- Increasing the use of these evidence-based medications would reduce the risk of adverse cardiovascular events and progression of kidney disease in patients with diabetes.

Limitations

- We analyzed all SGLT2i and GLP-1 RA medications, not just those with proven benefits for each condition.
- We relied on ICD-10 codes, which may not adequately identify the study population.
- We did not include glomerular filtration rate or proteinuria in the definition of CKD, which are criteria for the use of SGLT2i.

Next Steps

Additional study is necessary to:

- Refine the definitions of the target populations (e.g., CKD with estimated glomerular filtration rate <60 or proteinuria)
- Examine differential prescribing by race, ethnicity, and language preference
- Understand barriers to prescribing to guide interventions to improve the use of SGLT2i and GLP1 RA among high-risk populations with diabetes

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Precision Medicine Symposium

Identifying and classifying medications for hypertension

Ching-Huan Wang, John Scott, Lisa Yanek, Samantha Pitts

Adult Primary Care COE

Focus

- Extracting relevant medications from clinical datasets is challenging due to the number of medication names and formulations for each ingredient.
- ATC[1] and EPC[2] are standard classification systems which are mapped to RxNorm codes for medication ingredient and formulation identification.
- Epic uses a proprietary system (FDB[3]) to classify medications and not all medications can be mapped to RxNorm codes.
- We sought to develop a standards-based approach to identify and extract anti-hypertensive medications from Epic.

Method & Analytics

Phase 1: Identification and classification of medications in the Clarity medication table (Fig. 1).

Figure 1. Tasks of Phase 1

Original columns in the Clarity dataset

MEDICATION_ID	NAME	GENERIC_NAME
97794	EXFORGE HCT 5MG-160 MG-12.5MG TABLET	amlodipine 5 mg-valsartan 160 mg-hydrochlorothiazide 12.5 mg tablet

Task 1: Exact drug names

DRUG_1	DRUG_2	DRUG_3
amlodipine	valsartan	hydrochlorothiazide

Task 2: Assign drug classes

DRUG_1	DRUG_2	DRUG_3
Calcium Chanel Blockers - Dihydropyridines	Angiotensin II Receptor Blockers (ARBs)	Diuretic – Thiazide and Related

Active ingredient extraction

- Extracted active ingredients from medications' generic name (variable, GENERIC_NAME)
- Next, extracted ingredients from simple generic code (variable, SIMPLE_GENERIC_C) if generic name was missing or invalid

Pharmacologic class assignment

- Assigned pharmacologic classes to extracted ingredients using the PHARMACEUTICAL_SUBCLASS of medications with only one ingredient.

Phase 2: Identification of angiotensin converting enzyme inhibitors (ACEi) via NLM vs. Epic pathways

- Queried the NLM RxNav API[4] using ATC and EPC classes to identify all unique ACEi ingredients and their corresponding RxNorm codes
- Identified medications in the Clarity medication table by ACEi ingredient RxNorm codes and by a string search of GENERIC_NAME and NAME for ingredients – "NLM pathway"
- Queried the COE for medications identified as ACEi by the NLM pathway, and compared this to using FDB pharmaceutical subclasses – "Epic pathway"

Results and Highlights

Phase 1:

- Using generic name, we extracted at least one ingredient from 2,314 (91.9%) unique medications, with failures due to missing or invalid generic names (Fig. 2 , Table 1)
- Adding a search of the simple generic code decreased failures in ingredient extraction by 77.5%, to 46 (1.8%) unique medications
- 2,390 (96.7%) of unique medications matched to at least one pharmacologic class

Phase 2:

- The NLM pathway for ACEi identified 570 unique medications in the Clarity medication table, including all 371 identified by the Epic pathway (Fig. 3)
- This resulted in a small increase in medications orders identified in the COE dataset – 27 unique medications and 818 medication orders

Figure 2. Identification and classification of medications

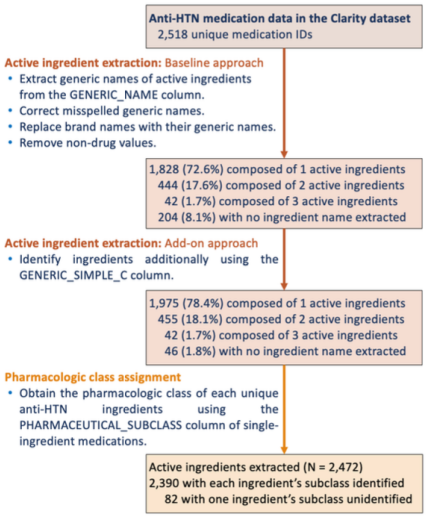
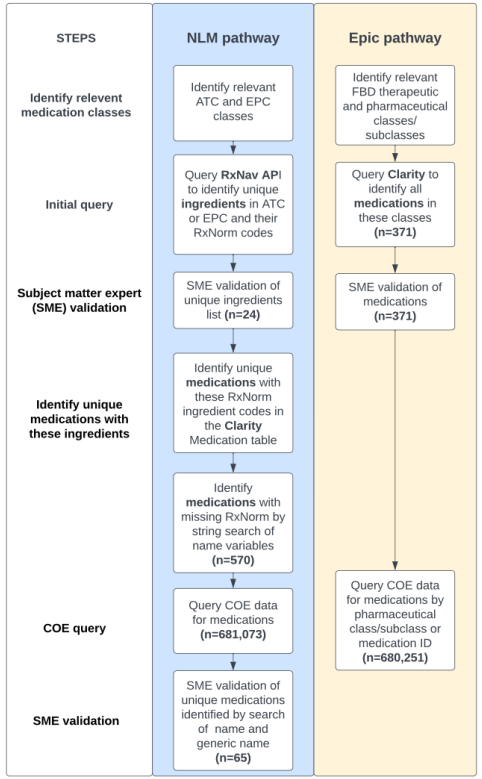


Table 1. Invalid generic names in Clarity data

Reason	Example	Correct value
Misspelling	• amlodipin • hydrochlorothiaz	→ amlodipine → hydrochlorothiazide
Brand name	• Bumex • zaroxyln	→ bumetanide → metolazone
Non-drug texts	• avenous • osm	→ nicardipine → (Not an ingredient)
Limitation of text extraction*	• Sodium	→ nitroprusside

* The first word and the word following a hyphen in the GENERIC_NAME column was extracted as an active ingredient; however, sodium nitroprusside starts with "sodium."

Figure 3. Comparison of NLM and Epic pathways for ACEi



Conclusions

The NLM pathway for ACEi:

- Identified all ACEi found by the Epic pathway
- Used standard classification systems and nomenclature for identification of medications
- Identified ingredients rather than medications
- As a result, required SME review of a small set of ingredients – rather than a longer list of medications – with a small additional review of medications
- These characteristics lend it to automation with reduced need for curation by an SME
- Using generic name and simple-generic codes to identify medication ingredients is feasible
- Some gaps remain due to missing or invalid information

Next Steps

- Compare performance of NLM and Epic pathways with additional medication classes

Abbreviations and acknowledgements

We would like to thank Brant Chee for sharing his work using ATC, EPC and RxNorm for medication data and Michael Chiu for his parallel work on diabetes medications.

[1]ATC: Anatomical Therapeutic Chemical classification system

[2]EPC: Established Pharmacologic Class

[3]FDB: First Data Bank

[4]NLM: National Library of Medicine

RxNav: https://lhncbc.nlm.nih.gov/RxNav/

API: application programming interface

The Richman Family Precision Medicine Center of Excellence in Alzheimer's Disease

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The Richman Family Precision Medicine Center of Excellence in Alzheimer's Disease

Vision

- Provide early detection, prognosis, and/or predicting response to available medications; develop new blood tests to better monitor treatment response; and, using blood-derived stem cells, test whether patients will be helped by emerging medication treatments.

Mission

- Translate research into clinical care by defining patients who respond optimally to currently available and emerging therapies. Identify new therapeutic targets based on refined and granular understanding of disease mechanisms.

Research Aims

- Generate patient-derived iPSCs and differentiate them into hindbrain organoids to study drug responses targeting neuropsychiatric symptoms in Alzheimer's Disease.

Interested in Collaboration?

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Precision Medicine Symposium

The Richman Family Precision Medicine Center of Excellence in Alzheimer's Disease: Hindbrain organoids from patient-derived iPSCs to evaluate pharmacological treatment for neuropsychiatric symptoms in Alzheimer's disease

Team: Cristina Zivko, Ram Sagar,, Ariadni Xydia, Constantine G. Lyketsos, Vasiliki Machairaki

Focus

Alzheimer's disease (AD) is a neurodegenerative disorder and the most common cause of dementia. Almost all AD patients eventually suffer from neuropsychiatric symptoms (NPS; e.g., agitation, depression) whose emergence correlates with dysfunctional serotonergic systems. Our aim is to generate hindbrain organoids containing serotonergic neurons using induced Pluripotent Stem Cells (iPSCs)[3] from healthy volunteers or AD patients with and without NPS. The organoids can be used to study AD, NPS, and to evaluate individual differences in disease progression, NPS development, and/or pharmacological treatment response.

Method & Analytics

- iPSC lines were generated from peripheral blood monocytes (PBMCs) of 3 healthy individuals and from 3 AD patients, two of which were diagnosed with NPS.
- The 6 iPSC lines were differentiated into hindbrain organoids. The presence of serotonergic neurons was confirmed by quantitative RT-PCR, flow cytometry, detection of released serotonin in the extracellular environment, and confocal fluorescence microscopy.
- Escitalopram oxalate (selective serotonin reuptake inhibitor) was used on the organoids to evaluate treatment response by ELISA.

Conclusion and Next Steps

We successfully generated hindbrain organoids from human iPSCs. Organoids from different people respond differently to the application of escitalopram *in vitro*, possibly revealing distinct subgroups of AD patients.

We propose that this 3D platform might be effectively used for drug screening purposes to predict patients with NPS most likely to respond to treatment with escitalopram.

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Results and Highlights

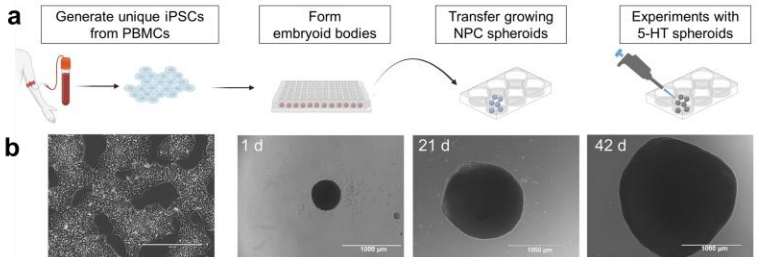

Figure 1: Generation of 5-HT-organoids from iPSCs. Schematic overview of the differentiation protocol (**a**) and representative brightfield (BF) images of cells and the organoids at different stages (adherent iPSCs, organoids at days 1, 21 and 42) (**b**).

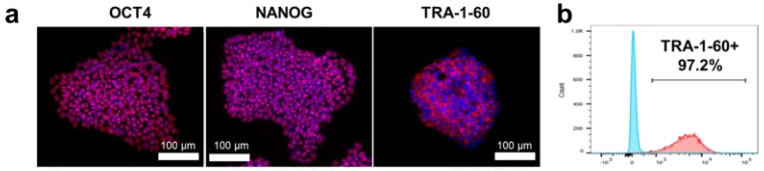

Figure 2: Reprogramming of PBMCs into iPSCs. Fluorescence microscopy imaging upon staining of iPSCs with pluripotency markers Oct4, Nanog and TRA-1-60 confirms the successful reprogramming (**a**). The enrichment of TRA-1-60 positive cells was additionally validated by flow cytometry (**b**).

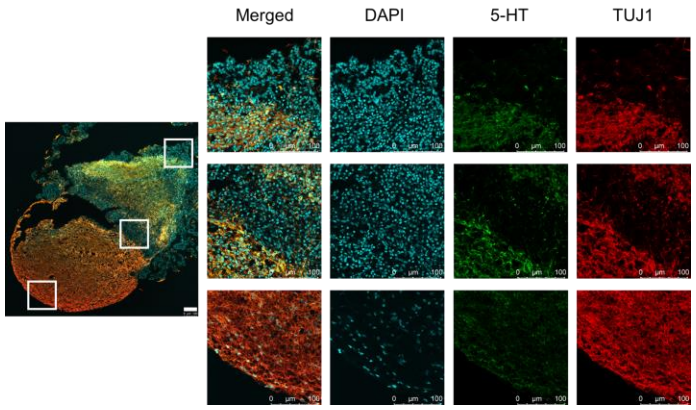

Figure 3: Immunocytochemistry for the 5-HT organoids. Confocal images of the organoids show distinct regions of differentiated cells (scale bar: 100 µm).

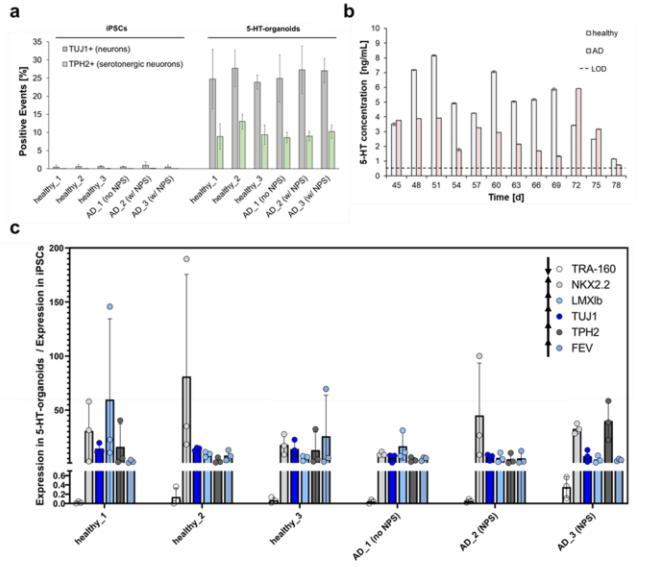

Figure 4: Characterization of 5-HT-organoids. All 6 iPSC lines were successfully differentiated into organoids containing serotonergic neurons as evidenced by the detection of TUJ1 and, more specifically, TPH2 by flow cytometry (**a**) (mean ± SD, n=3). The secretion of 5-HT from two representative samples of the organoids was measurable above the lower limit of detection (LOD=0.49 ng/mL) for over a month after the initial 42 d required for differentiation (**b**) (mean ± SD, n=1). Detailed analysis of different markers by qRT-PCR for all 6 cell lines further validated the differentiation (**c**) (mean ± SD, n=3).

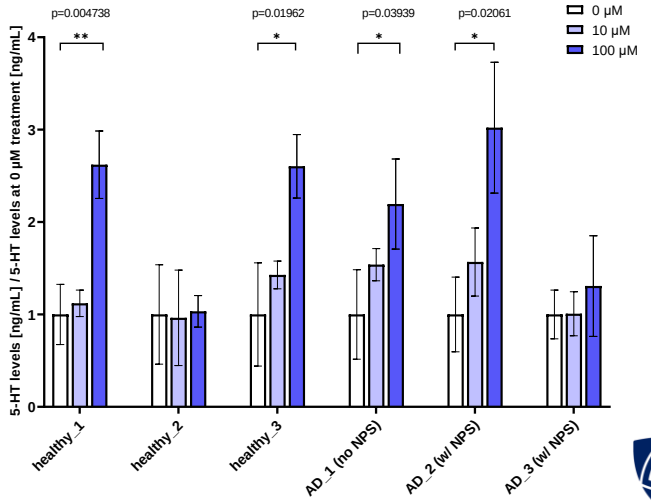

Figure 5: Serotonin release from 5-HT-organoids upon 1 h treatment with different concentrations of escitalopram oxalate (mean ± SD, n=3). Response to the drug was dose-dependent when present. Furthermore, our 3D in vitro platform indicated that human iPSC-derived hindbrain organoids from different people respond differently to the same dose of drug. For individuals healthy_1 and AD_3 there was no observable change in extracellular 5-HT with treatment, whereas for the others there was a 2 to 3-fold increase in 5-HT.. While 1h of treatment was sufficient to elicit such a response, the higher 100 µM dosage was necessary.

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COVID PMCOE: Addressing the Challenges of Precision Medicine Data Management

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COVID-19 PMCOE

Vision

- Understand the factors that underlie the pathobiology of COVID-19, the progression to severe illness or death, and the effectiveness of therapeutic interventions in order to provide personalized care to patients infected with SARS-CoV-2.

Mission

- Improve the care of patients infected with SARS-CoV-2 by learning about COVID-19 pathobiology, likelihood of disease progression and impact of specific therapeutic interventions. We aim to provide this information to clinicians, patients and family members at the point of care.

Research Aims

- To characterize the longitudinal trajectories of patients infected with SARS-CoV-2 to inform research questions and clinical care.
- To develop prediction models of COVID-19 severe disease and death that can be used at the point of care to inform treatment decisions, resource allocation and discussions with patients and families.
- To examine the impact of different treatment interventions on COVID-19 outcomes.
- To explore racial and social inequities in COVID-19 diagnosis and management.

Interested in Collaboration?

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Precision Medicine Symposium

The Johns Hopkins Precision Medicine Center of Excellence for COVID-19
Validation of Calculated Sequential Organ Failure Scores in a COVID-19 Registry

Team: Elizabeth K. Zink, PhD, RN, Joshua F. Betz, MS , Natalie Wang , Brian T. Garibaldi, MEHP, FACP, FRCP (E)

Focus

- Frameworks for allocation of scarce resources (ASR) have not been validated in COVID-19.
- The JH ASR was developed in anticipation of a mechanical ventilator shortage.
- The Sequential Organ Failure Assessment (SOFA) score is a key component of the JH ASR
- The SOFA score has 6 domains: respiratory, cardiovascular, hepatic, renal, neurologic and coagulation.
- It is unclear if SOFA scores derived from electronic health record (EHR) data are comparable to manually abstracted scores.

Method and Analytics

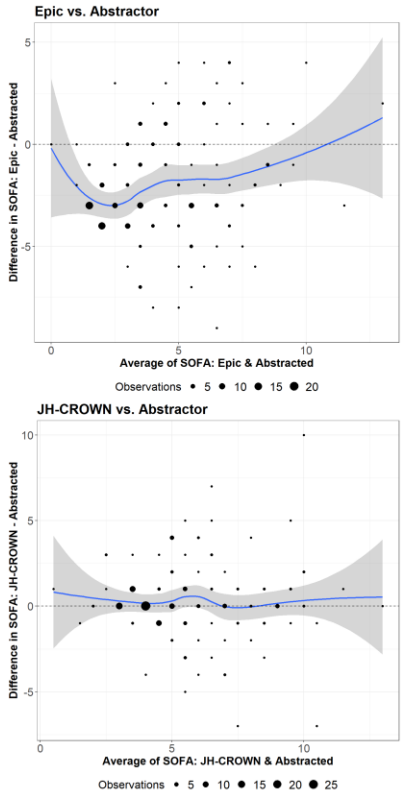
- The JH-CROWN registry includes all patients admitted to the Johns Hopkins Health System with a laboratory-confirmed diagnosis of COVID-19.
- 250 patients who underwent mechanical ventilation (MV) were randomly selected from CROWN
- SOFA scores were manually calculated by trained abstractors in the 24 hours preceding MV, with 10% of cases reviewed by two expert moderators.
- Intraclass correlation (ICC) between abstractors and moderators was assessed using a linear mixed effects model with random effects for case and reviewer.
- EHR SOFA scores, SOFA scores calculated from data elements in JH-CROWN (CROWN SOFA) and manually abstracted scores were compared.

Results and Highlights

- Abstractors were able to calculate a SOFA score for 191 patients.
- Completeness of EHR SOFA subscores ranged from 14% (95% CI: 10-20%) for respiratory to 63% (95% CI: 56-69%) for coagulation; completeness in EHR total SOFA score was 88% (95% CI: 83-92%)
- Completeness of CROWN SOFA subscores ranged from 91% (95% CI: 86-94%) for cardiac to 99% (95% CI: 96-100%) for neurologic; completeness in CROWN total SOFA score was 87% (95% CI: 81-91%).
- EHR and manually abstracted SOFA scores differed by 2 or more points in 76% of cases (95% CI: 69-82%)
- CROWN and manually abstracted SOFA scores differed by 2 or more points in 27% of cases (95% CI: 20-34%).
- EHR SOFA scores were on average 2.1 points lower than manually abstracted scores (95% CI: 1.8, 2.5)
- CROWN SOFA scores were on average 0.3 points higher than manually abstracted scores (95% CI: -0.1, 0.6).
- The ICC between abstractors and moderators was 0.82 (95% CI: 0.69, 0.92).

Variable	Value	Sample: N=191
Age	Years: Median [IQR]	68 [57, 76]
Sex	2. Male	127 (66.5%)
	1. Female	64 (33.5%)
Race	1. White	69 (36.1%)
	2. Black	72 (37.7%)
	3. Asian	9 (4.7%)
	4. Other	38 (19.9%)
	NA. Not obtained	3 (1.6%)
Ethnicity	0. Not Hispanic/Latino	158 (82.7%)
	1. Hispanic/Latino	32 (16.8%)
	NA. Not obtained	1 (0.5%)
Admission to Mechanical Ventilation	Days: Median [IQR]	2.3 [0.6, 4.2]
SOFA: Abstracted	Median [IQR]	5 [4, 7]
SOFA: Epic	Median [IQR]	3 [1, 5]
Missing	N (%)	23 (12.0%)
SOFA: JH-CROWN	Median [IQR]	5 [4, 7]
Missing	N (%)	25 (13.1%)

Table 1: Characteristics of patients with a SOFA score able to be abstracted. SOFA was assessed in the 24 hours prior to initiating mechanical ventilation.



Figures 1: Bland-Altman plots of agreement between SOFA scores from abstractors and Epic (top) and JH-CROWN (bottom). A smoothed average (LOESS – blue line) shows the average difference across the range of the score. Ideally, the average should coincide with the horizontal dashed line, indicating no average difference in scoring.

Conclusion

- Automated EHR tools can process large amounts of clinical data to inform processes such as resource allocation.
- The importance of clinical and contextual verification cannot be overstated.
- CROWN SOFA scores (as compared to EHR SOFA scores) demonstrated superior agreement with manually abstracted SOFA scores.
- EHR SOFA domain scores had a high degree of missingness, resulting in a score of 0, causing underestimation of illness severity, particularly in respiratory domain.
- SOFA Scores calculated by EPIC should be modified to avoid underestimating severity in research and practice.
- This analysis will assist in the development of better methods to predict mortality, allocate scarce resources, and address public concerns regarding equity during crises.

Next Steps

- Refinement of specifications for the cardiac and neurologic domains of the CROWN SOFA score will be made to improve the agreement between CROWN and abstracted scores.
- Recommendations to improve the coding specifications in the EHR for SOFA will be made.

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Addressing the Challenges of Precision Medicine Data Management Using the COVID-19 PMCOE Registry

Vision

- Understand the factors that underlie the pathobiology of COVID-19, the progression to severe illness or death, and the effectiveness of therapeutic interventions in order to provide personalized care to patients infected with SARS-CoV-2.

Mission

- Improve the care of patients infected with SARS-CoV-2 by learning about COVID-19 pathobiology, likelihood of disease progression, and impact of specific therapeutic interventions. We aim to provide this information to clinicians, patients and family members at the point of care.

Research Aims

- Furthering precision medicine by reducing the costs and barriers associated with managing precision medicine data.

Interested in Collaboration?

Contact us at:

Email / Teams
jbetz@jhu.edu / jbetz2

Github:
Username: jbetz-jhu
Repo:
JH-inHealth/crwn-data-pipeline

Precision Medicine Symposium

The Johns Hopkins Precision Medicine Center of Excellence for COVID-19
Addressing the Challenges of Precision Medicine Data Management

Team: Joshua F. Betz MS, Brian T. Garibaldi MD MEHP, Matthew L. Robinson MD

Focus

- EMR data require considerable processing to produce analysis-ready data.
- Sharing of data management code is complicated by lack of standardization across data projections.
- Development of a flexible, readable, and well-documented workflow suitable for sharing is necessary

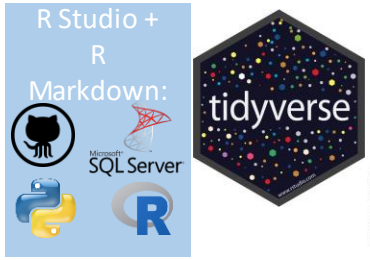
Method and Analytics

- Workflow code was developed in an inHealth Github repository, designed for the Crunchr containers with R versions 4.0 and 4.2.
- Credentials were managed using the Linux Secret Service and `keyring` package in R.
- Varying table and column names were addressed using an abstraction layer: names were retrieved from project-specific configuration files managed by the `config` package, and inserted into `dplyr` queries using 'non-standard evaluation' in R.
- Metadata tables were used to avoid 'hard-coding' measure names and values of interest. Range checks (high/low) were implemented using metadata tables.
- Comorbidities were extracted using the `comorbidity` package in R. Height, weight, and BMI values were cleaned using robust Z-scores to identify potential data entry errors in values or units.
- Labs, vitals and meds, were extracted from flowsheets and CCDA provisioned tables. Regular expressions were used to standardize unit labels.
- SQL Server command line tools were used to bulk copy processed data to the database.

Results and Highlights

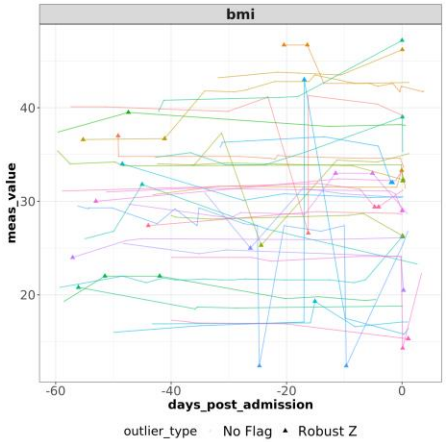
Data are extracted from CCDA curated tables and flowsheets. Queried data are cleaned, and then saved to the scratch projection. Cleaned data are further processed for Q4H/Q6H/Q24H summaries from admission and initiation of mechanical ventilation: min, median, mean, max, count, first, and last. Scores (WHO COVID-19 severity, SOFA, etc.) are calculated from summaries. Reports visualize quality and completeness.

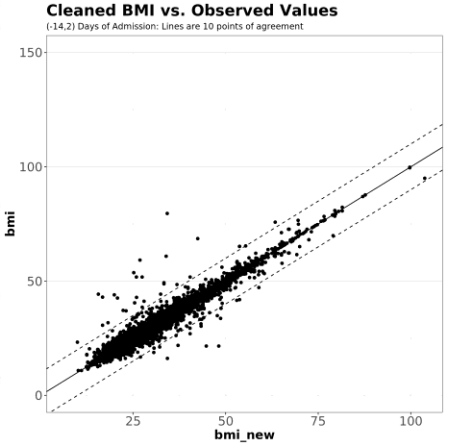
R Studio + R Markdown:

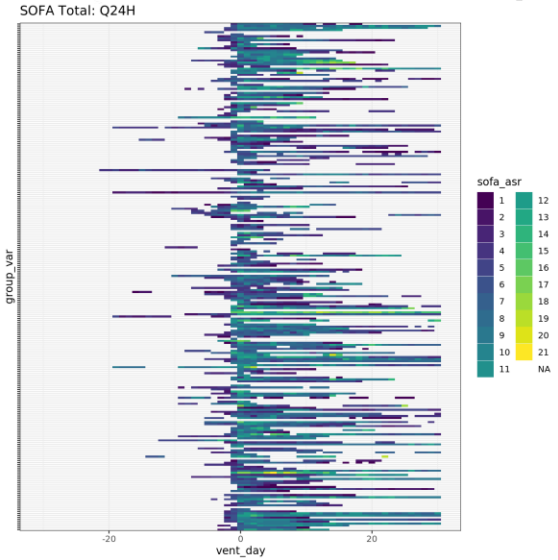


Configuration & Workflow:

1. Update and install Linux/R packages
2. Secure credentials in keyring
3. Create project-specific configuration
4. Run .Rmd reports and check results







meas_id	variable	low	high
301250	map_arterial	0	300
301360	map_cuff	0	300
304600914	map_cuff	0	300

o2_device	category	rank
Nasal cannula	nasal cannula	2
RAM nasal cannula	~~nasal cannula~~ **NIPPV**	~~3~~ **9**
Venturi Mask	mask	3
Face Mask	mask	3

Tables 1-2: Examples of using metadata tables to select, group, and filter raw values. Data processing can be modified just using the tables without editing the underlying code.

Figures 1-3: (Clockwise from top left) Visualizations of (1) trajectories of BMI with outliers, (2) original vs. cleaned BMI data, and (3) completeness of data produced by the workflow.

Conclusion

- Data management remains a significant challenge, even using a common data model.
- R Studio naturally integrates with GitHub, allowing for version control and easy access to its software development tools.
- R Markdown combines R, SQL, and Python in a single notebook or report, combining their strengths and facilitating collaboration.
- 'Non-standard evaluation' in R allows for flexibility in code evaluation that is not possible in SQL and Python.
- Metadata can serve as documentation of code and control how code behaves.
- Bulk copy significantly reduces the time necessary to write data to a database.
- Moving towards a shared workflow for common data elements can improve data quality and reduce data management costs.

Next Steps

- The existing repository is based on the CCDA and Epic data model.
- Further work is necessary to query the primary data from OMOP format data projections.

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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 establish human nasal epithelial (HNE) cell culture from people with CF (pwCF) and CF carriers for in vitro assessment of cellular response to treatment with CFTR modulator therapies.
- Aim 2: To return insights from in vitro HNE testing to clinical practice to inform treatment decisions for pwCF.
- Aim 3: To establish a biorepository for primary HNE cells to allow for in vitro study of various molecular strategies for restoration of CFTR function.

Interested in Collaboration?

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Precision Medicine Symposium

Cystic Fibrosis Precision Medicine Center of Excellence

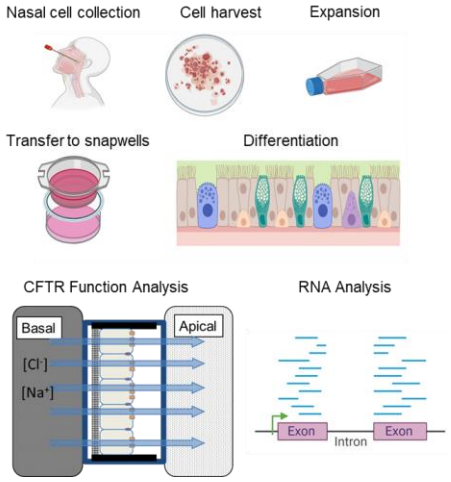
Audrey Pion, Erin Kavanagh, Anya Joynt, Lori Vanscoy, Garry Cutting, Christian Merlo, Neeraj Sharma

Focus

The CF PMCOE studies a cohort of ~1000 individuals of all ages with CF and with CFTR-related disorders, utilizing a variety of different data streams including clinical (EPIC), genomic, environmental, and laboratory data. This project focuses on use of primary human nasal epithelial cell cultures (HNE) to serve as a reliable in vitro system for evaluation of response of CFTR variants that are not yet approved for CFTR-targeted therapies. Functional analysis of these cultured cells reflects the contribution of both alleles to CFTR function and considers the patient's entire genomic context.

Method and Analytics

To date, 80 HNE samples have been collected from the CF individuals, as well as their parents and healthy controls (IRB#00116966).



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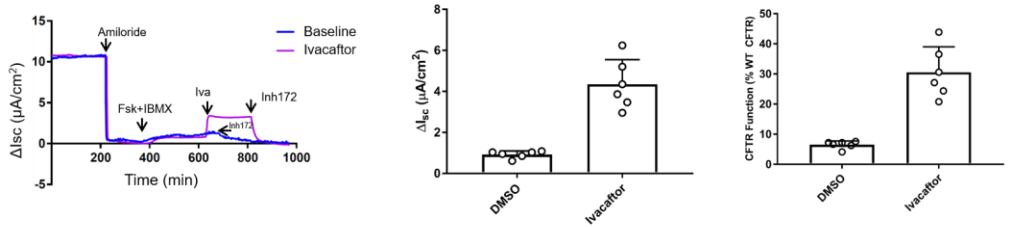
Results and Highlights

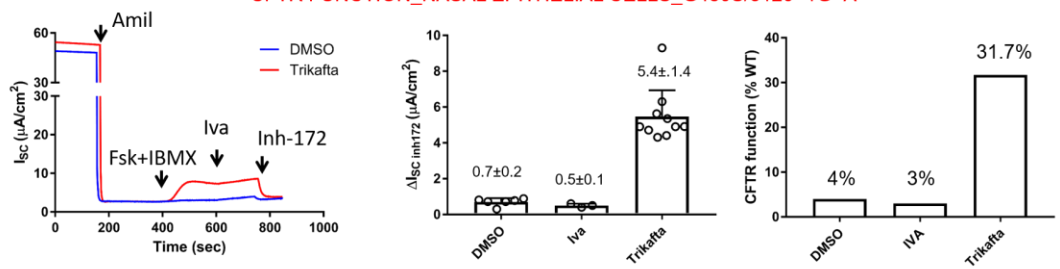
A

CFTR FUNCTION_NASAL EPITHELIAL CELLS_Q359R/621+1G>T Siblings



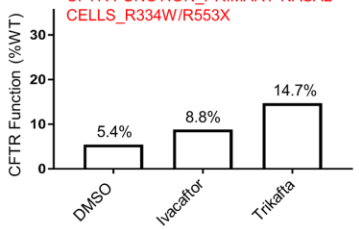
B

CFTR FUNCTION_NASAL EPITHELIAL CELLS_G480S/3120+1G>A



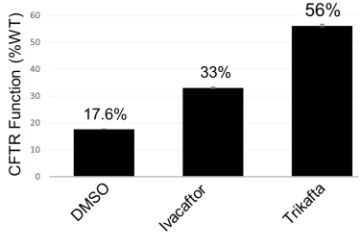
C

CFTR FUNCTION_PRIMARY NASAL CELLS_R334W/R553X



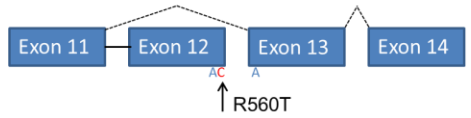
D

CFTR FUNCTION_PRIMARY NASAL CELLS_R117H-7T-TG10/5T-TG12



E

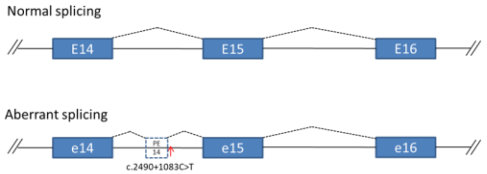
CFTR SPLICING_NASAL EPITHELIAL CELLS_R560T/621+1G>T



- R560T results in aberrant splicing resulting in no recovery of CFTR function by the modulator treatments

F

CFTR SPLICING_NASAL EPITHELIAL CELLS_CARRIER PARENT WT/C.2490+1083C>T



- Inclusion of pseudoexon, resulting in leaky splicing producing minor fraction of normal spliced product tested by Expression Minigene

G

Initiation of modulator treatment in CF individuals based on primary cell data and clinical response

- Q359R Sibling 1: Symptoms completely resolved. Sweat chloride decreased to <10mmol/L from 55 mmol/L after initiation of therapy. BMI increased to normal range.
- Q359R Sibling 2: Sweat chloride decreased to 14mmol/L from 60mmol/L after initiation of therapy. Spirometry improved to an FVC of 101%, FEV1 101%, and FEV1/FVC 100%.
- G480S/3120+1G>T: Significant clinical improvement observed. Sweat chloride concentration dropped to 46mmol/L from 119mmol/L. Initial PFTs were FVC 47%, FEV1 29%, and FEV1/FVC 83%; which increased to FVC 70%, FEV1 50%, and FEV1/FVC 72%.

Conclusion

- We emphasize the importance of using HNE cells to determine which modulators, either individually or in combination, result in maximum functional restoration. E.g Ivacaftor alone to Q359R, Trikafta to G480S.
- R334W variant was previously believed to be unresponsive, but our studies demonstrate a clinically significant increase in function to 14% with Trikafta treatment.
- Through RNA analysis, we can assess the impact of variants on splicing, such as c.1679G>C (R560T) and c.2490+1083C>T, and predict the response to modulators.

Next Steps

To establish a primary cell repository that will help:

- Investigate molecular genetics of CF-causing variants.
- Assess CFTR function recovery through modulator treatment.
- Evaluate antisense oligos ASOs for splicing restoration.
- Identify a suitable method for delivering gene editing materials.

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Kidney Precision Medicine Center of Excellence

Director: Chirag Parikh, MD, PhD

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Bleeding complications after native kidney biopsy associated with aspirin use

Vision

- Expanding native kidney biopsy procedures while maintaining safety

Mission

- Examine potential risk factors for bleeding complications and improve clinical decision making

Research Aims

- Examine the association of aspirin use prior to the time of kidney biopsy and
  - Drop in hemoglobin level within 72 hours of kidney biopsy
  - Need for packed red blood cell transfusion within 7 days following kidney biopsy

Interested in Collaboration?

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Kidney PMCOE

Precision Medicine Symposium

Bleeding complications after native kidney biopsy associated with aspirin use

Steven Menez, David Hu, Heather Thiessen Philbrook, Jack Bitzel, Yumeng Wen, Mohamed G Atta, Derek M Fine, J Manuel Monroy-Trujillo, John Sperati, Samir C Gautam, Celia P. Corona-Villalobos, Chirag R Parikh

KPMCOE

Focus

Significant bleeding complications after native kidney biopsies include the following:

- Drop in hemoglobin (Hgb)
- Need for blood (pRBC) transfusion
- Persistent bleeding requiring embolization

Anti-platelet agents such as aspirin are often discontinued for 7 days or more prior to kidney biopsy, with the goal to reduce the risk of bleeding complications. However, such a wait in biopsy timing leads to a delay in kidney disease diagnosis and may have a negative impact on time-sensitive therapeutic decision-making.

Method and Analytics

2,722 Kidney biopsies performed at Johns Hopkins Hospitals 2019-2022

Exclusions
- Missing lab measurements (1,413)
  - Transplant biopsy (384)
- Mass / malignancy biopsy (22)
- Outpatient biopsy (192)

711 inpatient biopsies with hemoglobin before and after biopsy

Using logistic regression, we examined the association between aspirin usage and

- Drop in hemoglobin (Hgb) level within 72 hours of kidney biopsy
- Packed red blood cell (pRBC) transfusion within 7 days of kidney biopsy

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Results and Highlights

The mean Hgb drop post-biopsy was 0.6 g/dL. A total of 183 (26%) patients had a Hgb drop over 1 g/dL, while 43 (6.0%) patients experienced a Hgb drop over 2 g/dL.

		Time of Last Aspirin Use			
		Within 3 days of biopsy (n=86)	3-6 days before biopsy (n=95)	6-365 days before biopsy (n=112)	No history within 1 year (n=418)
At the time of biopsy	Age (years)	64 (16)	62 (15)	60 (14)	52 (17)
	Female	40 (47%)	37 (39%)	50 (45%)	217 (52%)
	BMI	28.9 (7.4)	29.6 (7.9)	29.8 (8.6)	29.2 (8.5)
Pre-biopsy	Hemoglobin (g/dL)	9.51 (1.89)	9.51 (1.96)	8.85 (1.65)	9.39 (1.96)
	Platelet count (10^3/L)	240 (81.3)	252 (123)	249 (125)	250 (123)

Compared to patients with no prior aspirin use within a year, those who stopped aspirin within 3 days of kidney biopsy did not have a significantly higher risk of either Hgb drop ≥ 1 g/dL or ≥ 2 g/dL.

Outcome	Aspirin Use Before Biopsy	n (%) Event	Odds Ratio (95 % CI)	
			Unadjusted	Adjusted pre-biopsy Hgb and platelet count
Hgb Drop ≥ 2 g/dL	No History	26 (6%)	reference	
	Within 3 days	9 (10%)	1.76 (0.75, 3.78)	1.69 (0.70, 3.76)
	3-6 days	3 (3%)	0.49 (0.12, 1.44)	0.44 (0.10, 1.33)
	6-365 days	5 (4%)	0.70 (0.23, 1.73)	0.90 (0.29, 2.28)
Hgb Drop ≥ 1 g/dL	No History	104 (25%)	reference	
	Within 3 days	29 (34%)	1.54 (0.92, 2.51)	1.51 (0.90, 2.51)
	3-6 days	27 (28%)	1.20 (0.72, 1.95)	1.17 (0.69, 1.94)
	6-365 days	23 (21%)	0.78 (0.46, 1.28)	0.90 (0.52, 1.50)
pRBC Transfusion	No History	70 (17%)	reference	
	Within 3 days	14 (16%)	0.97 (0.50, 1.76)	1.11 (0.56, 2.13)
	3-6 days	16 (17%)	1.01 (0.54, 1.79)	1.16 (0.60, 2.15)
	6-365 days	26 (23%)	1.50 (0.89, 2.48)	1.21 (0.69, 2.06)

Conclusion

- Discontinuation of aspirin within 3 days of biopsy was not associated with increased odds of significant bleeding complications.
- These risks could be discussed when consenting patients where urgent biopsy diagnosis is necessary for timely therapeutic decision-making.

Next Steps

We plan to replicate this analysis in a prospective observational cohort of patients undergoing kidneys biopsies at Johns Hopkins (Novel Approaches in the Investigation of Kidney Disease (NAIKiD) Study) to examine the association between aspiring usage and adjudicated post-biopsy outcomes that require detailed chart abstraction:

- Blood transfusion directly related to biopsy
- Hematoma formation
- Jet formation
- AV fistula formation

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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

Kidney PMCOE

Chirag Parikh, Heather Thiessen Philbrook, Steven Menez, Dipal Patel, Jack Bitzel, Prakash Nadkarni

Focus

The primary goal of the Kidney PMCOE is to transform the care of patients with kidney disease.

Current Initiatives include

- Curation of high-quality renal focused data
- Integration of evidence-based medicine into clinical care
- Facilitating of clinical research
- Supporting quality improvement initiatives in clinical care

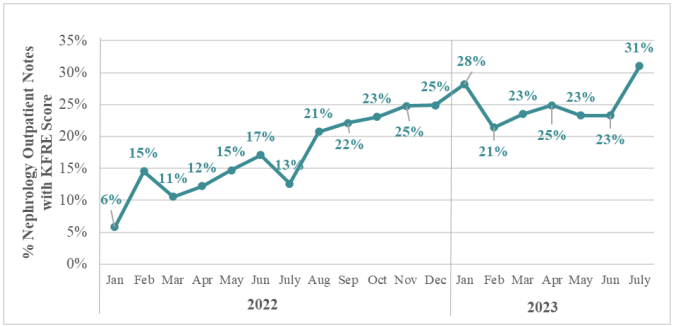
Curation of high-quality data

KPMCOE strives to curate high-quality data for use in research and clinical care. We have ~100 standardized definitions of labs, diagnoses, and procedures.

We recently developed an approach for mapping detailed EPIC medication records to a hierarchical medication classification framework, allowing for improved identification of prescribed medications. One application of this approach is to identify prescriptions by medication class to display in a patient dashboard (Patient Insight).

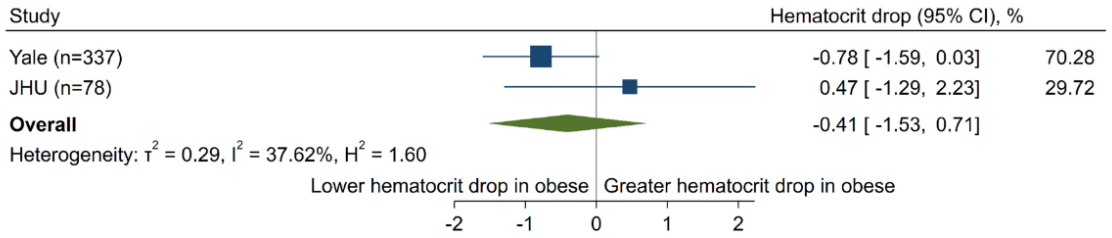
Supporting Evidenced-based Medicine in Clinical Care

In 2022, the kidney failure risk equation (KFRE) was added to the EPIC storyboard utilizing the curated data from KPMCOE. In the first half of 2023, roughly 25% of nephrology outpatient progress notes included the KFRE score.



Facilitating Clinical Research

In a prospective cohort of outpatients undergoing clinically indicated kidney biopsies, patients with obesity did not have a larger drop in hematocrit compared to those without obesity (Long Q, Menez S et al. Kidney360 2023; 4(1):98-101)

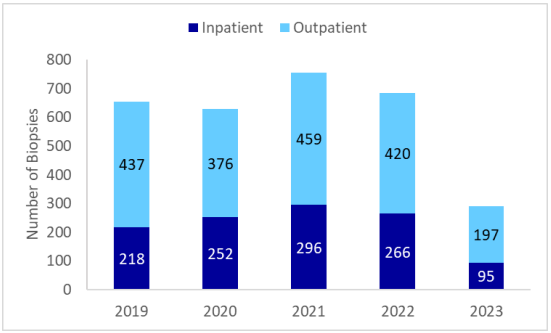


As a pilot test, one nephrology provider developed and successfully disseminated an electronic patient-reported outcome measure in nephrology clinic to assess patient health-related quality of life. (Patel D, Thavarajah S, Bitzel J et al. CJASN 2023)

	ePROM respondents (n = 264)	ePROM non-respondents (n = 583)
Patient characteristics		
Age in years (mean ± S.D.)	66 ± 14	67 ± 14
Male gender, n (%)	161 (61%)	309 (53%)
Black race, n (%)	95 (36%)	297 (51%)
History of diabetes, n (%)	132 (50%)	303 (52%)
History of hypertension, n (%)	251 (95%)	542 (93%)
eGFR in ml/min/1.73m² (mean ± S.D.)	33 ± 16	33 ± 16
2-year kidney failure risk equation[7] (KFRE) score in % (mean ± S.D.)	16 ± 25	15 ± 24
Average ePROM score (mean ± S.D.)		
General health (1-5)	2 ± 0.9	
Overall health (1-10)	7 ± 2	
Composite physical symptom (0-100)	83 ± 14	
Composite mental health (0-100)	65 ± 20	

Quality Improvement in Clinical Care

KPMCOE has several quality improvement initiatives to improve efficiency of patient care. A recent initiative created a dashboard with details on kidney biopsies.



Next Steps

- Continue support of ongoing research projects and newly created disease-specific sub-studies (Acute Kidney Injury, Kidney Transplantation, Kidney Biopsy and Chronic Kidney Disease)
- Support and support clinical trials and new research initiatives
  - O'Brien Kidney Center Grant on Health Equities in Kidney Disease
- QI metric development
- Implement patient dashboards for Kidney transplant patients

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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

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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

Precision Medicine Symposium

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:

1. **Reveal genomic features** associated with exposure/risks and therapy response; and
2. **Interventional care tools and pathways** that enable efficient matching of precise therapy to individual patients with NSCLC; and
3. **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

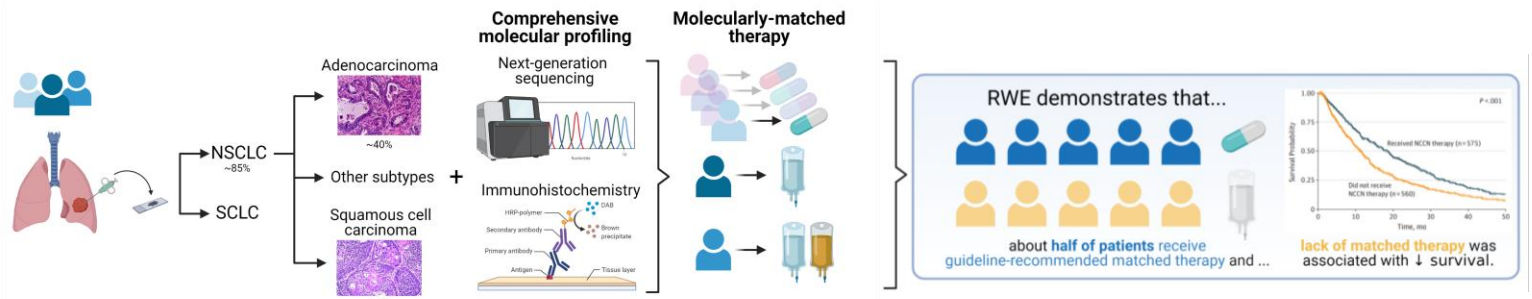
Implementation of a **Thoracic Cancer Data Commons** built on the **Precision Medicine Analytics Platform (PMAP)** for integration of complex molecular, clinical and research data

- Ascertainment of prognostic and predictive **biomarkers for adaptive treatment** of patient
- Development of novel deep learning models from the aggregation of clinical, genomic, radiomic – or **multi-omic data –** to learn from our patients

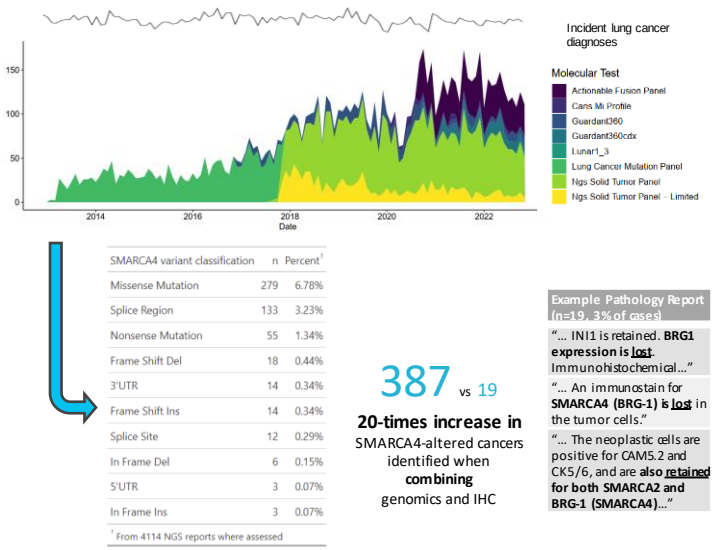
Next Steps

- Matching patient genotypes to clinical "phenotypes"
- Deepen translational features in the Data Commons: cfDNA, WES, RNAseq, TCRseq NGS, radiomics
- Build predictive models of clinical outcomes

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



Results – Genomic features driving precision lung cancer care: patterns and features for exposures and trials



SMARCA4 variant classification	n	Percent[1]
Missense Mutation	279	6.78%
Splice Region	133	3.23%
Nonsense Mutation	55	1.34%
Frame Shift Del	18	0.44%
3'UTR	14	0.34%
Frame Shift Ins	14	0.34%
Splice Site	12	0.29%
In Frame Del	6	0.15%
5'UTR	3	0.07%
In Frame Ins	3	0.07%

[1] From 4114 NGS reports where assessed

387 vs 19

20-times increase in SMARCA4-altered cancers identified when **combining** genomics and IHC

Example Pathology Report (n=19, 3% of cases)

"... INI1 is retained. **BRG1 expression is lost.** Immunohistochemical..."

"... An immunostain for **SMARCA4 (BRG-1) is lost** in the tumor cells."

"... The neoplastic cells are positive for CAM5.2 and CK5/6, and are **also retained for both SMARCA2 and BRG-1 (SMARCA4)**..."

Figure 1. Identifying patterns of SMARCA4-altered lung cancers for clinical trial considerations: genomics versus immunohistochemistry.
Top, Incident diagnoses of lung cancer and changes in respective clinical comprehensive molecular profiling (cCMP) since the inception of testing in the Thoracic Cancer Data Commons PMAP database. **Bottom,** Patterns of SMARCA4 mutations in over 4,000 cCMP reports identifying up to n=387 candidates for a SMARCA-directed clinical trial (left table) versus review of pathological reports identifying only n=19 patients by immunohistochemical (IHC) staining.

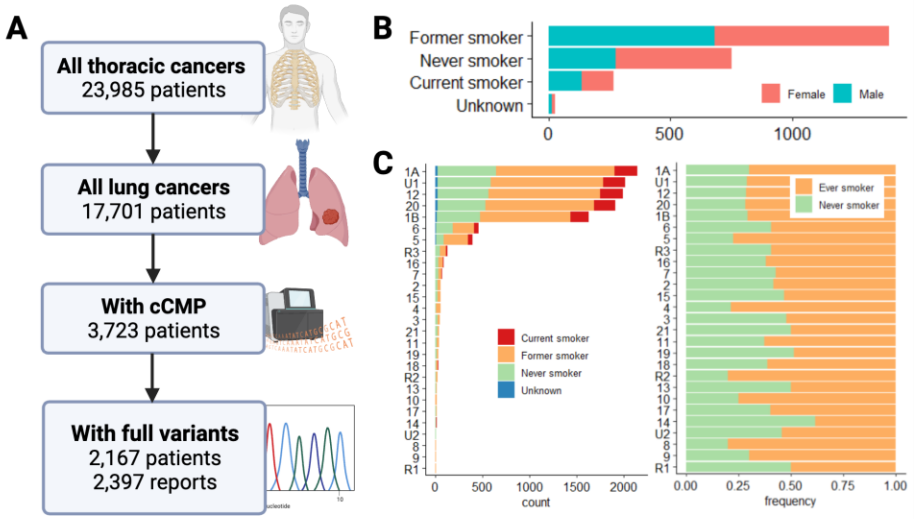


Figure 2. Revealing genomic features associated with exposure/risks in lung cancer.
A, Patient population with lung cancer and clinical comprehensive molecular profiling (cCMP) and full variant reports identified via the Thoracic Cancer Data Commons PMAP database. **B,** Patient-identified tobacco smoking status and gender in the identified cohort with the majority of patients reporting a history of prior tobacco smoking ("Former smoker"). **C, left** Single-base pair substitution-based mutational signatures from n=1,997 cCMP tests with sufficient variant-level data (>50 variants found per test) assessed for molecular signatures using `deconstructSigs` (Rv4.3) as described previously (Alexandro, Nature 2013)[3]. **C, right** Known ever-smoking status were enriched for smoking-related signatures (signatures 4 & 5), whereas never-smokers were enriched for uncharacterized defects in DNA maintenance (signature 14).

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
3. Alexandrov LB et al. Nature 2013. doi:10.1038/nature12477

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Multiple Sclerosis PMCOE

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Multiple Sclerosis PMCOE

Goals:

The Johns Hopkins MS PMCOE was launched in April 2017 with two primary goals:

1. Identify clinical, imaging, and blood biomarkers of long-term disability risk
2. Translate evidence to clinical trials aiming to identify new therapeutic strategies to prevent disability and promote repair in people with MS

Interested in Collaboration?

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Research Aims:

- Technology-enabled tracking of neurologic functional performance and systematic clinical data capture at every clinic visit via an internally-developed Smartform
- Baseline and annual non-invasive imaging of optic nerve damage using optical coherence tomography (OCT)
- Collection of blood at biannual clinic visits for research to identify biomarkers of prognosis and treatment response
- Standardization of annual surveillance brain magnetic resonance imaging (MRI) across (and beyond) the Johns Hopkins Health System
- Home-based collection of data regarding environmental and lifestyle exposures that may be relevant to the prognosis of MS.

COE Achievements:

- The COE includes 13 MS neurologists as well as experts in MS epidemiology, neuroimaging, neuropsychology, and neurorehabilitation
- Over 2,000 people with MS have participated in the PMCOE.
- The Johns Hopkins MS Smartform is being widely adopted across other prominent institutions throughout the US.
- 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.
- Smartform data, with other Epic-derived data, is being used to more specifically determine if a given person will likely benefit from brain MRI scan at a given timepoint (early estimates suggesting ~60% of patients are correctly classified as not requiring a new scan).

Multiple Sclerosis PMCOE: "Filling Research Gaps with Routine Clinical Imaging"

Team: Blake Dewey, Kate Fitzgerald, Peter Calabresi, Ellen Mowry

Precision Medicine Symposium

Focus

- Imaging is a core component of the MS PMCOE
- Analysis of routine clinical images is hampered by logistical, technical, and regulatory challenges
- PMAP allows the MS PMCOE to collect, curate, and analyze images stored in clinical systems
- Using routine clinical imaging extends imaging follow-up for research studies
- Harmonization methods allow for more images to be considered for research analyses

Method and Analytics

- The MS PMCOE MR imaging projection includes >5,700 patients and >15,600 MR imaging sessions that are ready for volumetric analysis
- Analysis-ready scans include:
  - Multiple contrasts
  - >= 1 3D-acquired image
- Analysis tasks include whole-brain segmentation, lesion segmentation, and cortical reconstruction

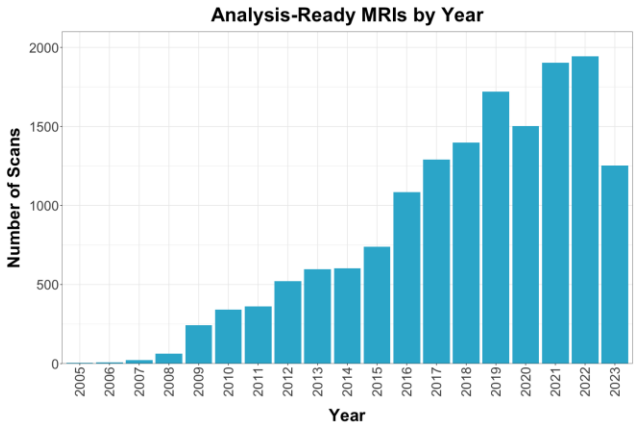

Figure 1: Number of analysis-ready MRIs in the MS-PMCOE imaging projection for each year. 2023 represents Jan-Aug, 2023.

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Results and Highlights

- Rapid increase in scan availability in recent years is shown in Figure 1
  - Nearly 2,000 analysis-ready scans acquired in both 2021 and 2022 (2023 projected to be similar)
- Increase is due to improving technology and standardizing of high-quality scans for people with MS
- The potential for longitudinal analysis is shown in Figure 2
  - Many patients have little or no follow-up imaging
  - There are ≈2,543 patients with some follow-up, ≈1,100 with ≥5 years, ≈300 with ≥10 years

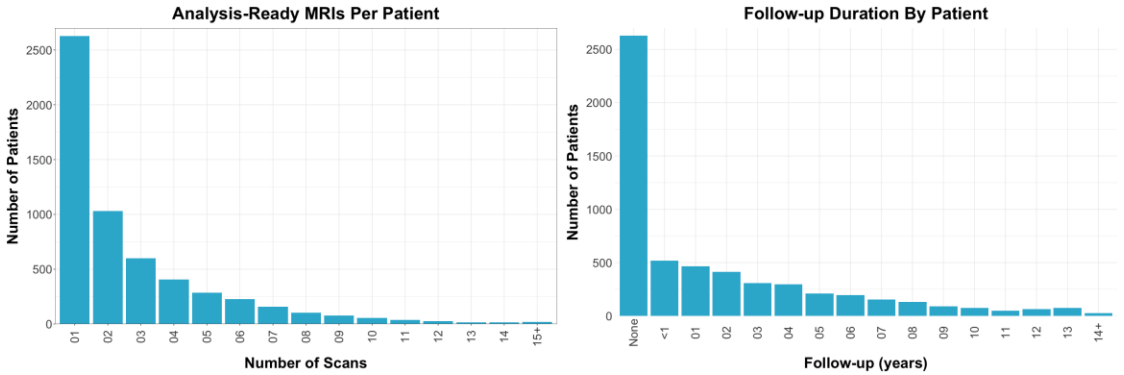

Figure 2: Histograms of the number of analysis-ready scans acquired (left) and duration of analysis-ready imaging follow-up (right) of patients in the MS-PMCOE. For follow-up duration, "None" refers to patients that only have one scan (no follow-up).

- Analysis-ready scans can be used to enrich research cohorts (with IRB approval) to lengthen follow-up or enroll more subjects (can't or wouldn't commit to a research-only MRI)
- Multiple studies have extended (or are looking to) their cohorts (or cohort follow-up) using MS PMCOE data
  - Two examples (HEAL-MS and MS-Genetics) are shown in Figure 3

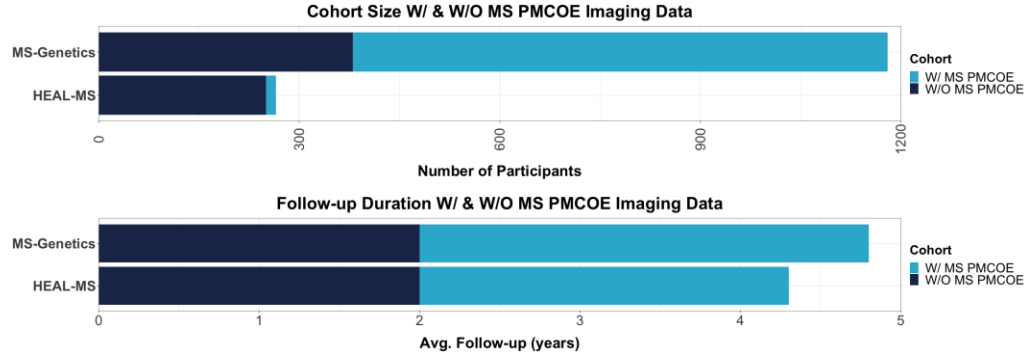

Figure 3: Stacked bar charts of cohort size (top) and follow-up duration (right) in two research studies of people with MS. Bar charts are divided into data available to the research study with (W/) and without (W/O) imaging data from the MS PMCOE.

Conclusion

- The MS PMCOE has a defined imaging cohort for investigation of neuroimaging outcomes in people with MS
- The cohort continues to acquire 1000s of analysis-ready scans per year with history of nearly 20 years
- Most patients in the cohort have follow-up imaging enabling longitudinal analysis
- Research studies that enroll participants from the MS Center at JHMI can leverage routine clinical images to enrich their cohorts

Next Steps

- Ongoing analysis of all analysis-ready images from the MS PMCOE
- Generating quantitative results for on-going and future studies
- Investigating spinal cord imaging in MS PMCOE
  - ~1.5x increase in scans
- Improving harmonization techniques to include even more routine clinical images (e.g., low-resolution 2D images)
  - ~5x increase in scans

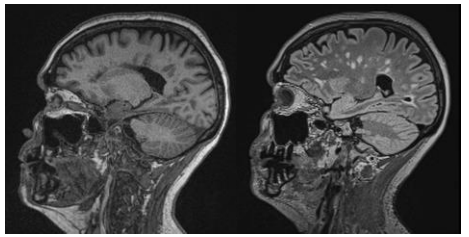

Figure 4: Example 3D high-resolution T_1-weighted (left) and T_2-FLAIR (right) images from an MS patient in the imaging cohort. These images are representative of the standardized MS MRI protocol.

Acknowledgements: We would like to thank the PMCOE providers, coordinators, staff, and collaborators who made this work possible.

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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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Precision Medicine Symposium

Myositis PMCOE

Christopher Mecoli, William Kelly, and Lisa Christopher-Stine on behalf of the Myositis Center

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. 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. To date we have automated electronic consenting, biospecimen management including DNA, RNA, sera, and PBMCs, and developed myositis-specific SmartForms within EPIC.

Ongoing Projects and Highlights

(1) We are leveraging the common data model 'Observational Medical Outcomes Partnership' (OMOP) to perform network studies within the international myositis and Observational Health Sciences and Informatics (OHDSI) communities [Figure 1].

- Within the International Myositis Assessment and Clinical Studies Group (IMACS), we are developing both minimum and optimum datasets in the structure of OMOP. This multi-site international network will facilitate clinical trial recruitment, enable comparative effectiveness studies, and provide adequate statistical power for genetic association studies
- Over 30 sites in >10 countries around the world are engaged in this initiative

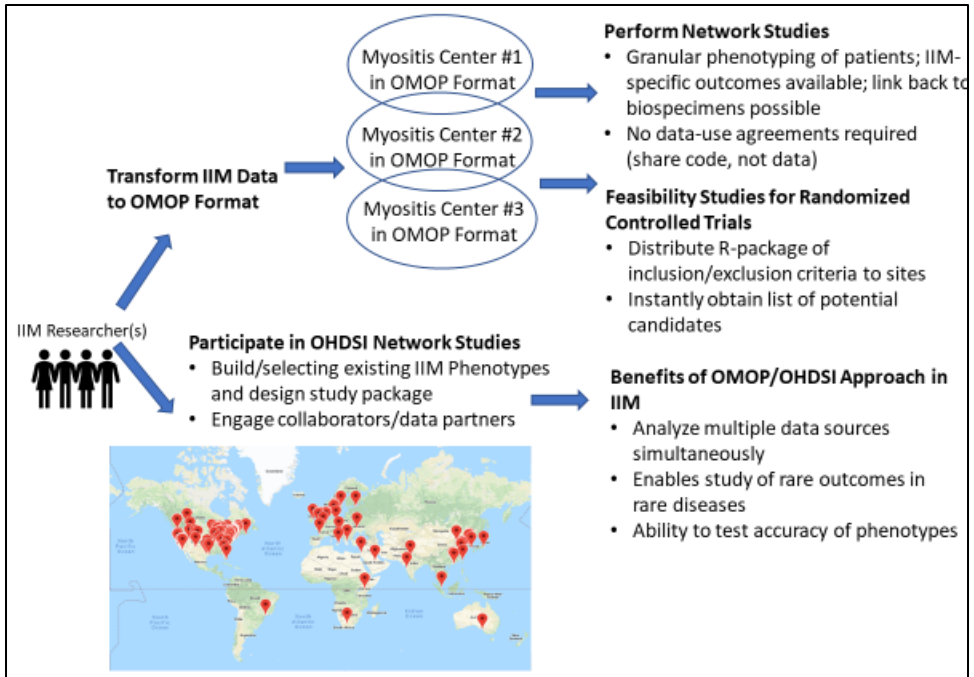

Figure 1: Benefits of Common Data Model (e.g. OMOP) Adoption

(2) Our myositis longitudinal cohort within PMAP, paired with biospecimens, has enabled commercial partnerships in 2022-2023.

- Identifying novel drug targets in dermatomyositis, necrotizing myopathy, and inclusion body myositis
- Developing and validating commercial biomarkers (myositis-specific autoantibody panels) to facilitate rapid diagnosis and management decisions in both the inpatient and outpatient settings

(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 IIM patients. We are now in the process of building a cancer prediction tool to inform clinical decision-making in collaboration with Stanford University and the University of Pittsburgh. This tool will be embedded within EPIC to facilitate a future multi-site clinical trial assessing the tool's value in a real-world setting

(4) Reducing FTEs required to effectively run the Myositis FTE.

- Through use of SmartForms and PMAP, we have saved the equivalent of 3 research coordinator FTEs annually
- Study feasibility and clinical trial eligibility have gone from a process taking weeks to queries that take minutes

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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 build a model to identify premature infants most at risk for high morbidity and mortality using their response to different treatments and available data?
- Can this model be developed into an objective EHR tool that could facilitate dynamic individualized counseling in the Neonatal Intensive Care Unit?

Interested in Collaboration?

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NICU PMCOE: Analyzing Premature Infants' Response to Surfactant Therapy

Flora Yazigi MD, Sai Manasa Kalyanam MEng, Kartikeya Makker MD, Jen Park MS, Hrishikesh Kambli MS, Khyzer B Aziz MD

Precision Medicine Symposium

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Background

- Advances in neonatal care are enabling higher survival rates of extremely premature (<29 weeks gestation) and extremely low birth weight infants (<1000g).
- A vast majority of these infants suffer from neonatal respiratory distress syndrome (NRDS), commonly due to surfactant deficiency, which is crucial for preventing lung alveoli collapse.
- Surfactant administration and respiratory support, both invasive and non-invasive, are standard interventions for NRDS.
- The response to surfactant treatment, especially in terms of oxygen and respiratory support needs, is inconsistent among neonates.
- The neonatal sequential organ failure assessment (nSOFA) score measures patient severity of illness, including respiratory support needs & degree of organ dysfunction.

Objectives

- To assess in detail the surfactant response by tracking changes in organ dysfunction from birth to either death or discharge, factoring in gestational age and time, particularly in extremely preterm infants.
- **Hypothesis**: Distinct modifiable and non-modifiable maternal, fetal, and neonatal factors will differentiate surfactant responders from non-responders.

Method and Analytics

- A retrospective cohort study at a single center assessed inborn, extremely preterm infants with very low birth weight from July 2016 to June 2023 using the NICU PMAP Registry (~35,000 records). Hourly neonatal sequential organ failure assessment scores were tracked until discharge or death. We developed replicable phenotype definitions using SQL and analyzed the data with Python.

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Results and Highlights

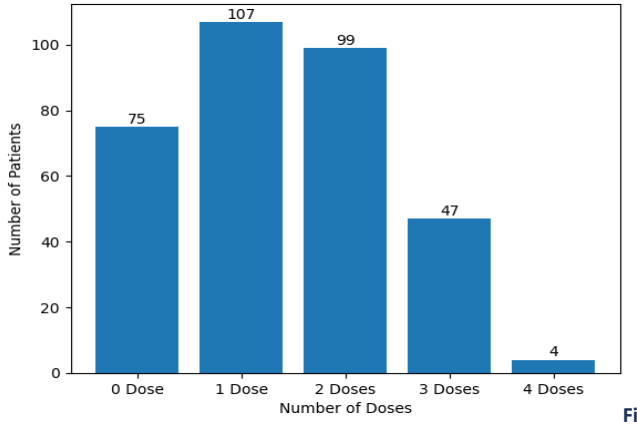

Figure 1. Distribution of Patients Based on Number of Surfactant Doses. Histogram of number of patients and doses of surfactant administered. Total of 332 patients.

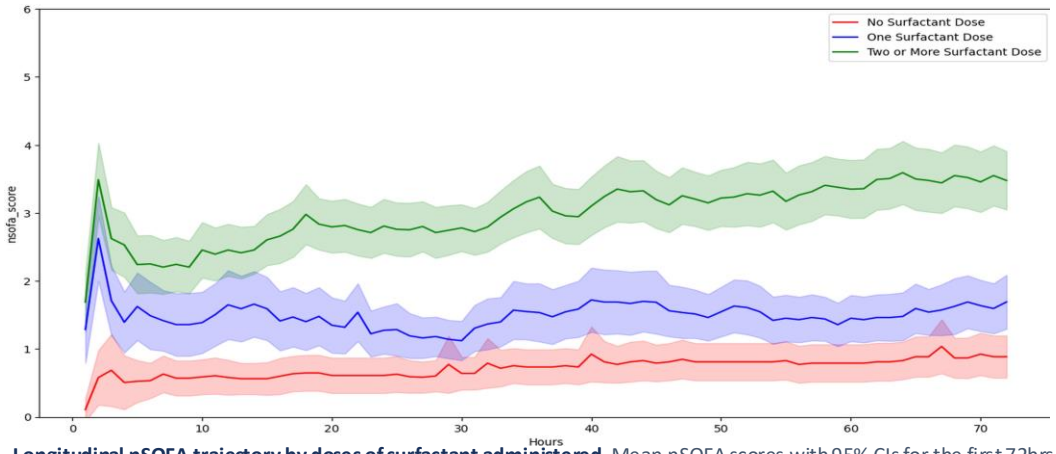

Figure 2. Longitudinal nSOFA trajectory by doses of surfactant administered. Mean nSOFA scores with 95% CIs for the first 72hrs of life for all patients. Higher nSOFA trend observed in infants given ≥2 surfactant doses (green band) compared to one (blue) and none (red). Peak scores around 1-5hrs, reflecting typical post-birth surfactant administration; secondary peak at ~12hrs of life coinciding with usual second dose administration. Distinct differentiation among the three groups at these intervals.

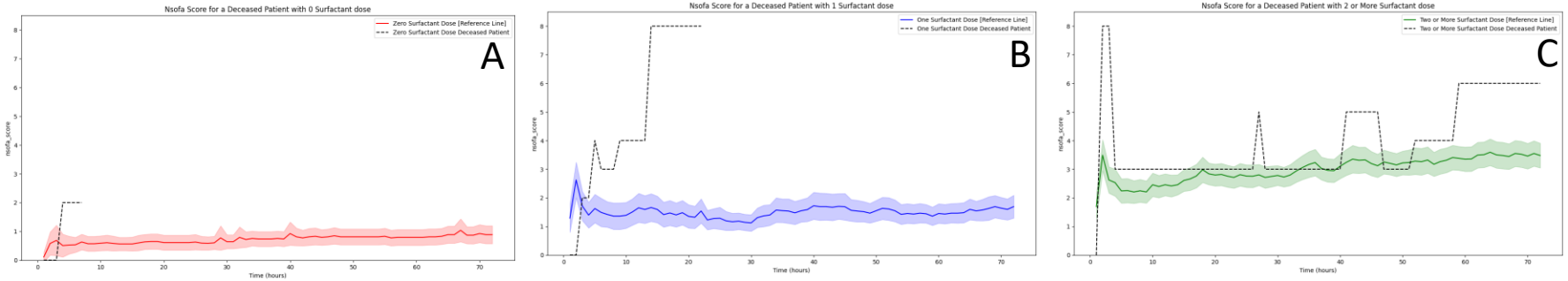

Figure 3. Example patient level nSOFA profiles for non-survivors relative to matched epoch. Mean nSOFA scores with 95% CIs for the first 72hrs of life for all patients. Dashed line represents non-survivor. Complex, shared decisions often dictate care for extremely premature and extremely low birth weight infants. Situations where no surfactant is given due to parental preference, equipment size constraints, and/or major anomalies (A). Cases where surfactant administration results in complications such as pneumothorax or pulmonary hemorrhage, preventing repeat dosing (B). Some patients face severe pulmonary hypoplasia that is not responsive to surfactant (C).

Conclusion and Next Steps

- Using birth weight and gestational age, we discerned nSOFA profiles based on surfactant doses (none, one, or ≥2).
- Next, we'll examine the NICU PMAP registry features to test our hypothesis and identify maternal, fetal, and neonatal factors influencing key outcomes
- Our main analysis will target survivors treated with surfactant who develop bronchopulmonary dysplasia (BPD), aiming to create a BPD prediction model and personalizing existing care paradigms (therapies) for improved outcomes.

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Neurocritical Care PMCOE

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Neurosciences Critical Care PMCOE

- **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 with an emphasis on three types of modeling:
  - Predictive modeling (Prognostic enrichment)
  - Treatment response modeling (Predictive enrichment)
  - Health economics modeling (efficiency, cost, generalizability)
- 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 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 deterioration index 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

CICL –Classification of Intra-Cranial Pressure Waveforms to identify clamped external ventricular drain signals by applying Machine Learning using the PMCOE-NCC Data Repository

Rohan Mathur [1,2], Sudha Yellapantula [4], Lin Cheng[1,3], Peter H. Dziedzic [1,2], Eusebia Calvillo[1,2,3], Jose I. Suarez[1,2,3]

[1]Division of Neurosciences Critical Care, Department of Anesthesiology & Critical Care Medicine, JHSOM ;
[2]Department of Neurology, JHSOM; [3]Department of Neurosurgery, JHSOM, [4]Medical Informatics Corp., Houston TX

Background

Management of elevated intracranial pressure (ICP) is important in preventing secondary brain injury, in patients with acute brain injuries admitted to the intensive care unit. External Ventricular Drains (EVDs) are the current gold standard in invasive ICP monitoring, and generate a continuous ICP waveform, from which a mean ICP value is generated. A major unmet need is to create better predictive models of impending elevations in ICP. However, the use of the ICP waveforms to develop predictive models is limited by the fact that EVDs produce accurate waveforms only when they are clamped (i.e. drainage is turned off). Typically, this is intermittently done for variable intervals every hour.

In large retrospective datasets, information about whether the EVD is clamped or draining or if there is noise, is not captured or labelled.

This project showcases an innovative means of labelling a large dataset of physiological waveforms and demonstrates how it is used to train a machine learning classification algorithm to segment and classify ICP segments from an EVD as clamped or not

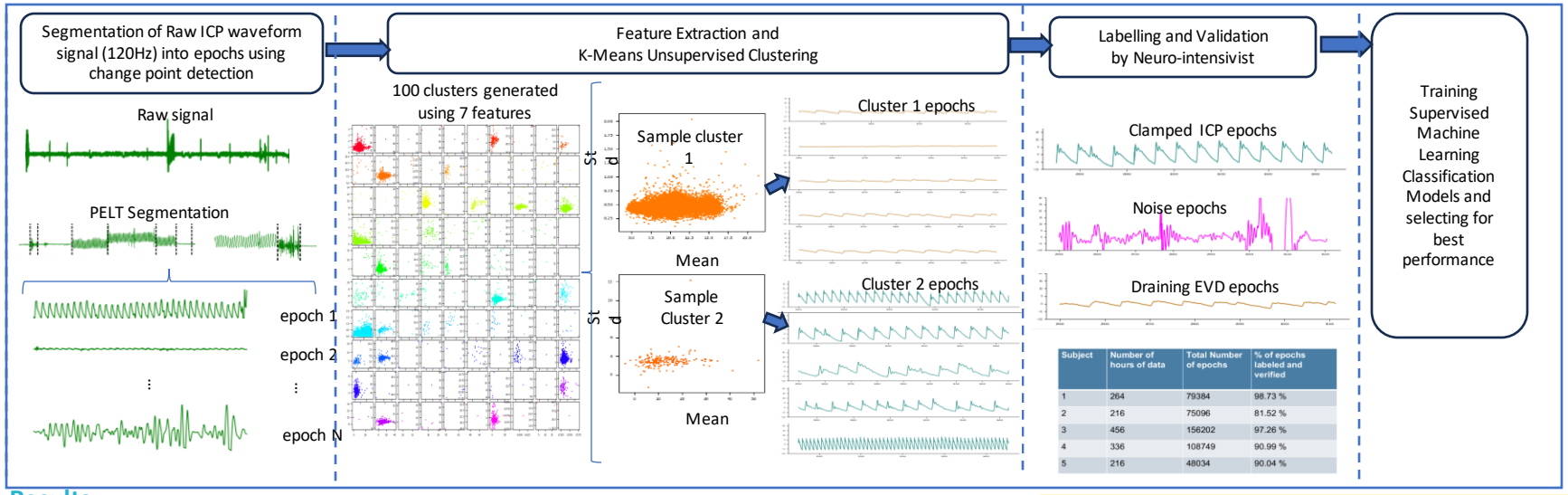
Methods

Initial Patient Selection

5 patients with acute brain injuries that underwent ICP monitoring with an EVD, were identified through a search of the Precision Medicine Center of Excellence in Neurocritical Care Data Repository (PMCOE-NCC), and the entire duration of their ICP waveforms was extracted, totaling 1488 hours (approx. 62 days) of high frequency ICP waveform data, sampled at 120Hz.

Generation of a Labelled and Validated Dataset

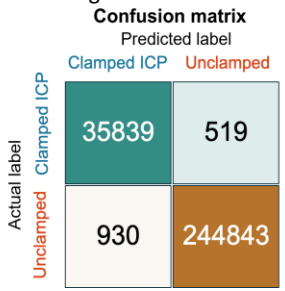
The labelling process first involved segmenting the ICP waveform time series from each patient into epochs using the PELT change-point detection algorithm. PELT identifies and segments the time-series where the statistical properties of the time-series change. The data was divided to create a training dataset, and a validation dataset. Next, multiple statistical features were extracted for each segment, and K-Means unsupervised clustering was used to generate individual clusters of segments, each with similar statistical properties. Next, using a uniform methodology, segments from each cluster was extensively sampled and labelled by a neuro-intensivist. This process involved visualization of the segment along multiple different time axes, allowing for visualization of the segment and its neighboring segments for minutes and hours. These labelled and validated epochs were then used to train supervised machine learning algorithms. The best algorithm based on accuracy and efficiency metrics was selected.



Subject	Number of hours of data	Total Number of epochs	% of epochs labeled and verified
1	264	79384	98.73 %
2	216	75096	81.52 %
3	456	156202	97.26 %
4	336	108749	90.99 %
5	216	48034	90.04 %

Results

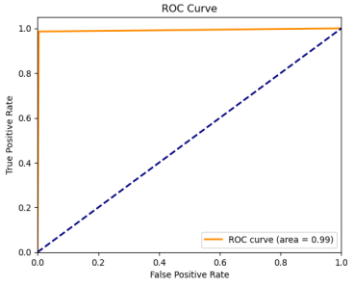
After 10-fold cross validation, and testing various Machine Learning Classification models, the confusion matrix, accuracy statistics and Receiver-Operating Curve (ROC) of our best performing model are presented in the figure below.



Classify **Clamped ICP** vs **NOT Clamped ICP**

Area under ROC curve	99.10% ± 0.001
Recall	98.57% ± 0.002
Positive predictive value	97.47% ± 0.003
F1 score	98.02% ± 0.002

(10 fold cross validation)



Summary and Next Steps

CICL is a machine-learning based classification algorithm that rapidly and accurately identifies clamped ICP waveform segments

This algorithm paves the way for rapid high throughput processing of ICP waveform data which will allow for their use in prediction model development

Next steps include validating patient generalizability and studying the application of this algorithm prospectively in real time

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Precision Medicine Symposium

PMCOE-NCC - Automated Identification of Patients who developed critical care needs after Elective Neurosurgical Intracranial Tumor Resection

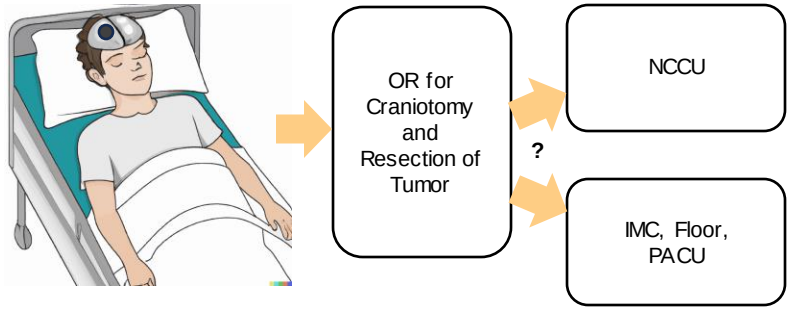
Rohan Mathur[1,2], Vishank Shah[1,2,4], Tamas Budavari[5], Niteesh R. Potu[1,2], Peter H. Dziedzic[1,2], Lin Cheng[1,3,4], Eusebia Calvillo[1,2,3,4]
Bill King, William S. Anderson[3], Robert D. Stevens[1,2,3,4] Jose I. Suarez[1,2,3,4]
[1]Division of Neurosciences Critical Care, JHSOM, [2]Department of Neurology, JHSOM, [3]Department of Neurosurgery, JHSOM,
[4]Department of Anesthesiology & Critical Care medicine, JHSOM, [5]Dept. Of Applied Mathematics and Statistics, Whiting School of Engineering, JHU

BACKGROUND

Patients diagnosed with intracranial tumors, after consultation with a neurosurgeon, present to the hospital at a scheduled date for surgical resection of their intracranial tumors. Post-operatively, they are routinely admitted to the Neurosciences Critical Care Unit for monitoring.

The Problem

- Only some of these patients develop clinical issues that require care that can only be provided in the NCCU; Most receive care that may be able to be delivered in less resource-intensive environments within the hospital.
- Scarce Resource such as intensive care provision and monitoring can be better allocated by Identifying those patients that will truly develop ICU needs



To tackle this problem, it is first important to identify exactly what counts as care that can only be provided in an ICU and determine how to identify those patients in a data repository. Furthermore, given that the PMCOE Data Repository is being updated with new patient information on a weekly basis, the identification algorithm should be automated so that these patients can be routinely and rapidly identified.

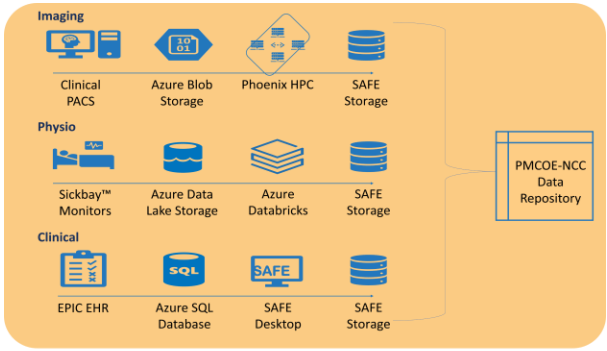
THE QUESTION

In a retrospective analysis of the PMCOE-NCC data repository, how do you identify those patients undergoing elective neurosurgical resection of their brain tumors that received care that can only be delivered in the ICU environment?

METHODOLOGY

Data Source

The Precision Medicine Center of Excellence in Neurocritical Care Data Repository contains clinical EMR data, physiological waveform data and Imaging data from all patients that have been admitted to the Neurosciences Critical Care Units at Johns Hopkins. Through querying and screening these patient records, research questions of interest can be explored.



Inclusion Criteria for patient selection

- Adult Patient (18 years or older)
- Diagnosis of a brain tumor based on ICD-10 code screening
- Elective admission to the hospital for resection of the brain tumor with Neurosurgery. Excluded patients who went to the OR after being first admitted to the hospital in an acute symptomatic presentation
- Directly admitted to the NCCU after their surgery
- Information was stored in the PMCOE-NCC Data Repository

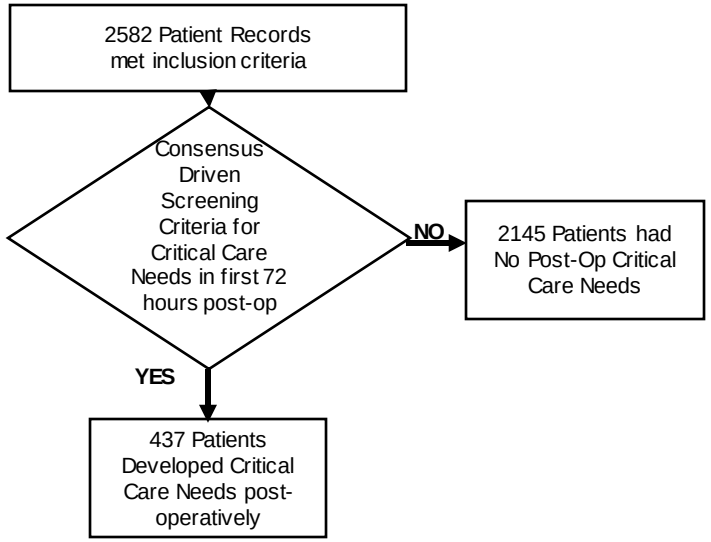
Screening Criteria for ICU Needs

Consensus driven criteria were developed by a team of four neuro-intensivists. These include:

- Administration of specific medications that can only be administered in an ICU
- ICU Specific procedures including intubation; high-flow nasal canula; non-invasive positive pressure ventilation; central venous catheter placement; ventriculostomy management
- ICU specific diagnoses
- Restricted the time frame for development of critical care needs to 72 hours post-op

RESULTS

The PMCOE-NCC Data Repository was screened including patients from July 1, 2016, to August 31, 2023. 2582 eligible patients were identified. Among these, the algorithm identified 437 patients that demonstrated needs that could only be addressed in the Neurocritical Care Setting. Of these, 341 patients were administered critical care medications, 106 had critical care orders, and 136 had critical diagnoses codes entered.



DISCUSSION

- The Precision Medicine Center of Excellence in Neurocritical Care (PMCOE-NCC) aims to effectively identify patients who would most likely benefit in the resource-intensive neurocritical care environment from those who can fare equally well in a less resource-intensive environment such as intermediate care units or the floor.
- Identifying patients that developed critical care needs in the first 72 hours after elective surgical resection of their brain tumors is the first step in developing a model that will ultimately use pre-operative and intra-operative data to triage patients to the appropriate level of post-operative care. Such a model could potentially improve resource allocation and improve patient care.

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Wilmer Precision Ophthalmology PMCOE

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Wilmer Precision Ophthalmology Center of Excellence

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

- Provide fine-grained predictions for conversion to wet age-related macular degeneration (AMD) in patients with dry AMD
- Identify the optimal intravitreal anti-VEGF medication for patients with retinal vascular diseases at treatment initiation

Interested in Collaboration?

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Predicting Imminent Conversion to Neovascular Age-related Macular Degeneration Using OCT Volumes and Deep Learning

T. Y. Alvin Liu, M.D.[1,2]; Yuxuan Liu, M.S.[1]; Neslihan Dilruba Koseoglu, M.D.[1]; Craig K. Jones, Ph.D.[1,2,3]

1 Wilmer Eye Institute, 2 Malone Center for Engineering in Healthcare, 3 Department of Computer Science, Johns Hopkins University School of Medicine, Baltimore, MD

Introduction

- Age-related macular degeneration (AMD) is the most common cause of irreversible central vision loss in patients over age 50.[1]
- Most AMD patients lose vision due to neovascular AMD (NVAMD).
- Average risk for progression over 5 years can be estimated using AREDs criteria.

Objective

- The goal of the current study is to analyze 3D optical coherence tomography (OCT) volumes using deep learning (DL) and to create a model that will predict imminent conversion (within 6 months) from non-neovascular to NVAMD. We chose a 6-month time frame, as it is a more actionable time frame as compared to 5 years.

Materials and Methods

- **33,189 3D OCT scans from 2,084 patients with AMD were split into a training (70%) and validation (20%) and hold-out test set (10%) Data partition was performed at the patient level.**
- **The conversion date was defined as the first anti-VEGF injection date based on previous work[2].**
- **For training, all scans were center cropped into 496 x 512 x 24 (width x height x # line scans per volume). Then, the signal intensity was scaled with zero mean and unit standard deviation.**
- **Data augmentation with transformations and random flipping along vertical axis were applied with a probability of 50%.**
- **A 3D ResNet-50 model[3] was used as backbone, along with a Stochastic Gradient Descent optimizer (learning rate = 1e-4) and a learning rate scheduler.**
- **Best model parameters were selected based on best balanced accuracy during validation.**
- **All processing done in Azure Machine Learning Studio within the Precision Medicine Analytics Platform**

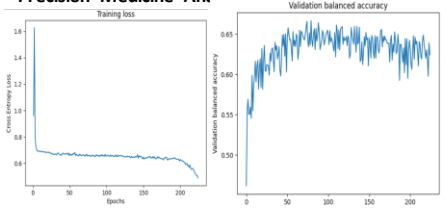

Fig 1. Training loss (left) and validation balanced accuracy (right).

Results

- **The hold-out test set contained 2051 OCT volumes from 136 patients.**
- **On the hold-out test set, the model achieved a 68.8% balanced accuracy and 0.75 Area Under Curve (AUC). When set to a "sensitive" mode with a sensitivity of 80%, the model achieved a specificity of 45%. When set to a "specific" mode with a specificity of 80%, the model achieved a sensitivity of 57%.**

		Actual Values: YES	Actual Values: NO
Predicted Values	N=2051		
Predicted Values	YES	TP = 94	FP = 451
Predicted Values	NO	FN = 59	TN = 1447

Table 1. Test set confusion matrix : "yes" is yes conversion within 6 months and "no" is no conversion within 6 months; threshold = 0.5.

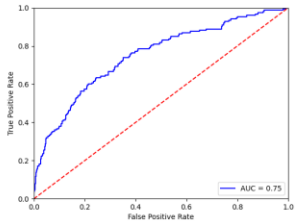

Fig 2. Test set AUC

		Actual Values: YES	Actual Values: NO
Predicted Values	N=109		
Predicted Values	YES	TP = 27	FP = 45
Predicted Values	NO	FN = 8	TN = 29

		Actual Values: YES	Actual Values: NO
Predicted Values	N=544		
Predicted Values	YES	TP = 39	FP = 106
Predicted Values	NO	FN = 39	TN = 360

		Actual Values: YES	Actual Values: NO
Predicted Values	N=152		
Predicted Values	YES	TP = 28	FP = 44
Predicted Values	NO	FN = 12	TN = 68

Table 2. Confusion matrixes for subgroups within the test set: first converted eye in patients with NVAMD OU (left), second converted eye in patients with NVAMD OU (middle), first converted eye in patients with unilateral NVAMD (right). Threshold = 0.5.

	Sensitivity	Specificity
First Eye in OU patients	**80.0%**	37.4%
	32.1%	**80.0%**
Second Eye in OU patients	**80.0%**	44.3%
	47.4%	**80.0%**
Unilateral converted eye	**80.0%**	49.4%
	48.7%	**80.0%**
Never converted eye		**79.5%**

Table 3. Model subgroup performance with threshold set at 80% sensitivity and 80% specificity.

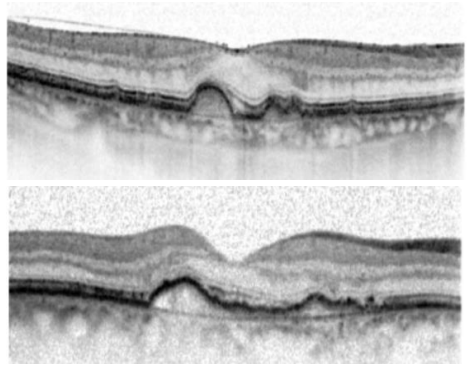

Fig 2. Sample correct predictions by our model in the hold-out test set. Ground truth: no conversion within 6 months (top); yes conversion within 6 months (bottom)--- note the presence of a double layer sign.

Conclusion and Future Work

- Our model showed reasonably robust performance in predicting imminent conversion to NVAMD using only a single OCT volume as input.
- In contrast to previous work[2] that only included patients with known NVAMD in one eye, our model was trained and tested with OCT images from both patients with known NVAMD in one eye and patients without previous history of NVAMD.
- Future work will include incorporating tabular clinical data into model training and testing.

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Pediatric Genetic Syndromes with Aortopathy Precision Medicine Center of Excellence

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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

Kasper Center of Excellence for Pediatric Genetic Syndromes with Aortopathy

Johns Hopkins Team Leadership: Hal Dietz, Tony Guerrerio, Gretchen MacCarrick
NIH Collaborators: Allyson Mateja, Marjohn Rasooly, Samara Levin, Alaina Magnani, Caeden Dempsey, Erica Brittain, Alison M Boyce, Pamela A. Frischmeyer-Guerrerio

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 overall phenotype 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 to make critical decisions about their prognostic counseling, the frequency and extent of imaging, the screening of family members, the use of medications, and which additional features of the phenotype to screen for and treat.

In addition to vascular disease, some patients with Loeys-Dietz Syndrome are prone to osteopenia and osteoporosis with fractures after minimal to no trauma. Identification of those patients who require additional screening and treatment may prevent significant morbidity in those susceptible to fracture while avoiding unnecessary screening in others.

Method & Analytics

Patients underwent clinical evaluation
- history
- physical exam
- DXA scan
- blood work

Whole body DXA score
- patients <18yo
  - adjusted for height and age.
  - Used adjusted whole body DXA score (whole body minus head)
- patients ≥18 yo.
  - Unadjusted whole body DXA score

- Skeletal features used in the predictive models were assessed by clinicians with LDS expertise

Results and Highlights

Who has low DXA scores? (Figures A and B)
- 9.1% of adults and 50% of children had Whole body DXA Z-scores < -2
- Type 5 LDS appeared to have higher Z-scores but limited sample size
- 60% of patients experienced ≥1 lifetime fracture. Median number of lifetime fractures was 1 (range: 0-6)
- Fractures were most common in children with types 1 and 2 LDS but were more evenly distributed across LDS types in adults

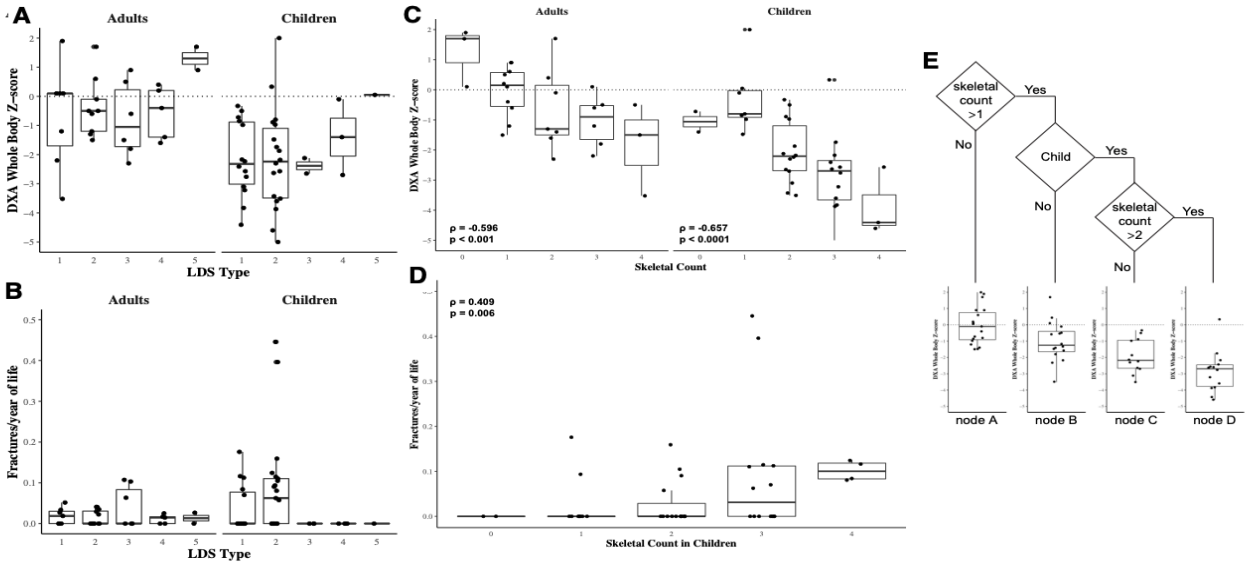
What clinical features are associated with low DXA scores? (Figures C and D)
- Skeletal abnormalities in LDS include scoliosis, pes planus, arachnodactyly, spondylolisthesis, and camptodactyly
- Patients were scored for the number of skeletal features they manifested
- Whole body DXA Z-score was inversely correlated with the total number of skeletal features in adults and children
- Number of fractures per year of life correlated with skeletal count in children

Can we develop an algorithm to help clinicians identify those at risk? (Figure E)
- Only 2 clinical and laboratory features were significant in predicting DXA whole body Z-score: skeletal features count and binary age (adult vs. child)

Table 1: Demographic data, laboratory data, and skeletal features of patients with a genetic diagnosis of LDS.

	Overall	Adults	Children
n	77	33	44
LDS Type 1	22 (28.6%)	7 (21.2%)	15 (34.1%)
LDS Type 2	33 (42.9%)	12 (36.4%)	21 (47.7%)
LDS Type 3	10 (13.0%)	7 (21.2%)	3 (6.8%)
LDS Type 4	9 (11.7%)	5 (15.2%)	4 (9.1%)
LDS Type 5	3 (3.9%)	2 (6.1%)	1 (2.3%)
Age	22.07 (17.38)	38.54 (14.20)	9.72 (4.42)
Male	31 (40.3%)	11 (33.3%)	20 (45.5%)
BMI (%)	20.26 (6.60)	25.73 (6.13)	16.17 (2.99)
DXA Whole Body Z-score[a]	-1.36 (1.62)	-0.45 (1.29)	-2.06 (1.50)
DXA Spine Z-score[b]	-1.17 (1.20)	-1.03 (1.37)	-1.27 (1.06)
P1NP Z-score (Adults Only)[c]		-0.08 (1.47)	
CTX Z-score (Adults Only)[c]		0.54 (1.34)	
Count of LDS Skeletal Features	2.87 (1.10)	2.67 (1.20)	3.02 (1.02)
Scoliosis	41 (53.2%)	18 (54.5%)	23 (52.3%)
Pectus Deformity	42 (54.5%)	18 (54.5%)	24 (54.5%)
Pes planus	64 (83.1%)	24 (72.7%)	40 (90.9%)
Arachnodactyly	38 (49.4%)	14 (42.4%)	24 (54.5%)
Spondylolisthesis	4 (5.2%)	3 (9.1%)	1 (2.3%)
Cervical spine abnormalities	16 (20.8%)	4 (12.1%)	12 (27.3%)
Camptodactyly	16 (20.8%)	7 (21.2%)	9 (20.5%)

Continuous variables are presented as mean (SD). Categorical variables are presented as n (%)
[a] 4 adults and 6 children with missing data
[b] 5 adults and 8 children with missing data
[c] 4 adults with missing data



Conclusion

- 33% of adults and 59% of children with LDS exhibited poor bone health (whole body DXA Z-score ≤ - 1)
- No significant differences in DXA scores across the different types of LDS
- Children with LDS types 1 and 2 had significantly more fractures/year than those with types 3-5 (p=0.02)
- 61% of LDS patients experienced ≥ 1 fracture in their lifetime
- Children exhibited worse bone health compared to adults with LDS. We strongly suspect this represents a referral and/or survival bias and not that DXA scores improve with age
- The number of skeletal features a patient exhibits strongly predicts their likelihood of having a low DXA score and fractures.
- A decision tree using the number of skeletal features and binary age (adult vs. child) predicts those at risk for skeletal morbidity

Next Steps

- We recommend that bone density assessment be performed as part of routine care in all patients with LDS.
- Patients should be counseled on
  - dietary and lifestyle interventions to optimize bone health
  - maintaining adequate calcium intake
  - Monitor vitamin D levels and supplement if low
  - Promoting safe weight-bearing physical activity
  - Avoiding additional risks such as smoking and alcohol use.

We have now started treating patients with bisphosphonates and are working to identify those that respond to this treatment.

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Pulmonary Embolism (PE)
PMCOE

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PE PMCOE

Vision

- Our vision is to improve outcomes for patients at risk of PE by preventing the life-threatening consequences that occur in more severe forms of this condition due to delayed detection.

Mission

- We aim to develop a computational model for prediction of PE in critically ill patients that leverages clinical data reflecting their physiological complexity.

Research Aims

1) PE Prediction: As described above, we aim to develop a computational model for prediction of PE in critically ill patients.

2) Feature discovery through the modeling process, identifying physiological markers of PE not currently known.

Interested in Collaboration?

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Precision Medicine Symposium

Development of a Machine Learning Model for Pulmonary Embolism Prediction in Intensive Care

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[1]Department of Biomedical Engineering, [2]Department of Anesthesiology and Critical Care Medicine

Focus

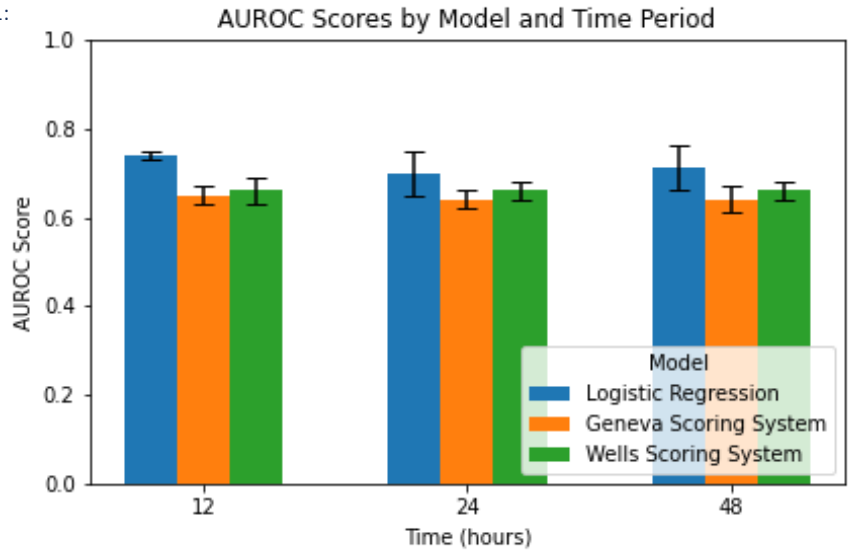
- Pulmonary embolism (PE) is a frequent and life-threatening complication in hospitalized patients whereby a thrombus occludes blood flow in the pulmonary artery or its branches.
- Current Pulmonary Embolism (PE) scoring systems (e.g., Modified Wells Scoring System, Revised Geneva Scoring System, and the Pulmonary Embolism Rule Out Criteria, have limited predictive accuracy, in part because they may not consider the physiological complexity of acutely ill patients.
- There is an unmet need for more accurate methods that can forecast the likelihood for developing PE.

Methods and Analytics

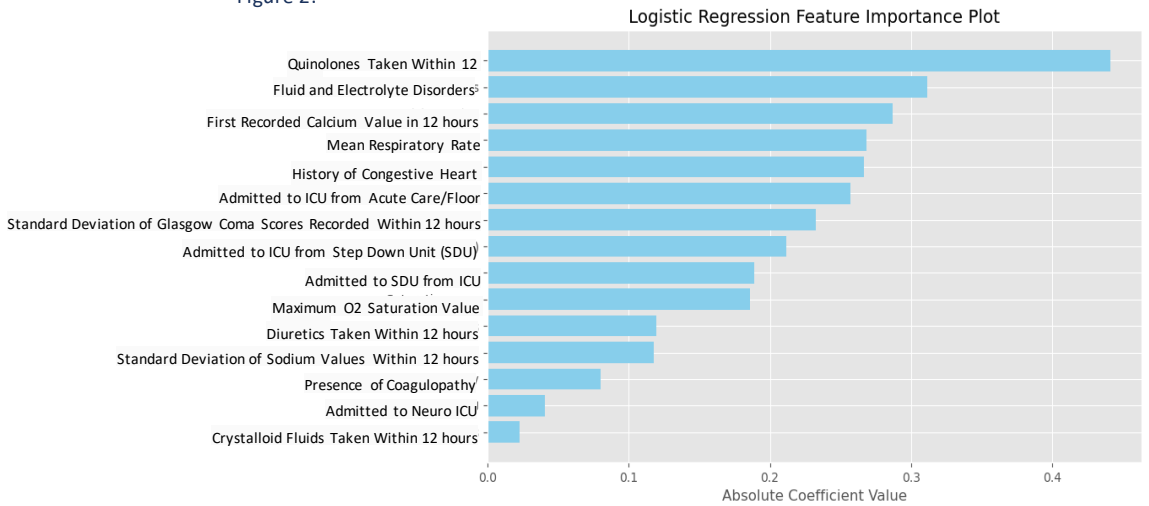
- Employed a large, multicenter database (eICU) containing >200,000 ICU admissions from 208 hospitals across the US
- Gathered and analyzed 2,799 unique ICU stays where a diagnosis of PE is recorded
- Due to a lack of a reliable determination of when the PE truly took place, we stratified our time-dependent data into three difference observation windows (12hrs, 24hrs, and 48hrs) for our PE and non-PE patients.
- Aggregated clinical data contains laboratory, demographic, vital sign, comorbidities, medications, and more.
- Trained multiple different machine learning (ML) models: decision tree, random forest (RF), gradient boosting (XGBoost, CatBoost, and GBoost), generalized linear models (GLM), support vector machine (SVM), and artificial neural network (ANN)
- Compared models to current PE risk scoring models (Wells and Geneva risk scoring models). Risk scoring models are modified to adapt to the limitations of the dataset.
- Figure 3. demonstrates inclusion & exclusion criteria

Results and Highlights

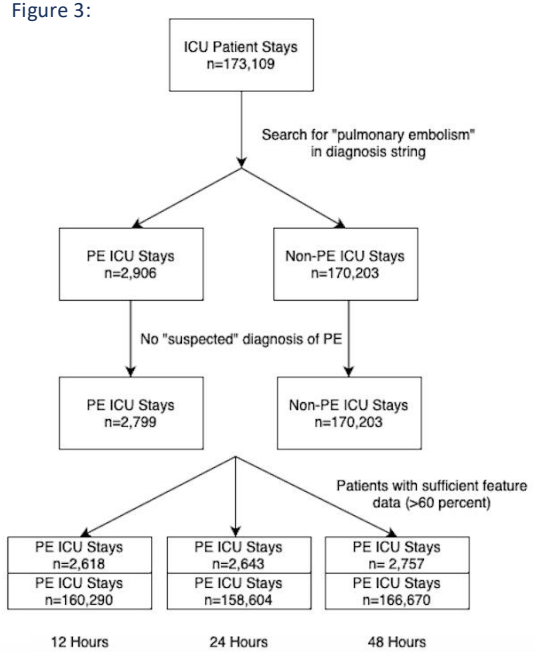
- These models stood out for their superior performance: XGBoost, CatBoost, ANN, and Logistic Regression.
- AUROCs for logistic regression and the risk scoring models are in Figure 1.
- Figure 2. presents the feature importance plot of the best performing model (by AUROC) across all time periods and models (12hr Logistic Regression).
- Figure 1:



- Figure 2:



- Figure 3:



Conclusion

- The following results demonstrate the potential of these models to predict the onset of PE in critically ill ICU patients
- The model further allows us to understand additional variables of interest that are currently ignored by PE risk scoring models.

Next Steps

- Following external validation, this study aims to validate the model prospectively to determine its performance in a real-world setting.

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Psychosis PMCOE

The Johns Hopkins Schizophrenia Center

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Psychosis PMCOE

Vision

- Our PMCOE wishes to establish a new, more effective method of precision patient care for patients with psychosis in a wide range of medical conditions.

Mission

- We aim to develop a new precision care for patients with psychosis. A novel biomarker and medicine will be applied to patients with psychosis in a wide range of medical conditions, resulting in a mechanism-driven targeted approach with less side effects than traditional antipsychotics.

Research Aims

- To dissect the pathophysiology of psychosis with accompanying cognitive deficits, particularly focusing on lysosomal deficits and augmented cellular autofluorescence (AF).
- To apply this biological knowledge to a wide range of medical conditions that accompany psychosis beyond the boundary of psychiatry and other medical specialties. We **hypothesize** that the lysosomal deficits underlie a subset opatients who show psychotic manifestations in a cross-disease manner.
- To apply a novel high-throughput method of detecting cellular AF for biospecimens from a wide range of medical conditions that accompany psychosis, hopefully that this method will be a tool in conducting clinical trials with an ongoing developing compound that targets the lysosomal deficits.

Interested in Collaboration?

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Precision Medicine Symposium

Psychosis PMCOE

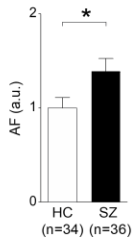
Focus

1) To dissect the pathophysiology of psychosis with accompanying cognitive deficits, particularly focusing on lysosomal deficits and augmented cellular autofluorescence (AF).
2) To apply this biological knowledge to a wide range of medical conditions that accompany psychosis beyond the boundary of psychiatry and other medical specialties. We **hypothesize** that the lysosomal deficits underlie a subset of patients who show psychotic manifestations in a cross-disease manner.
3) To apply a novel high-throughput method of detecting cellular AF for biospecimens from a wide range of medical conditions that accompany psychosis, hopefully that this method will be a tool in conducting clinical trials with an ongoing developing compound that targets the lysosomal deficits.

Background

Our group originally discovered and studied lysosomal deficits, featured with augmented cellular autofluorescence (AF) in neuronal cells from patients with psychotic disorders. The level of AF is also associated with specific domains of cognitive deficits associated with psychosis (NIH RO1 grant: MH107730). The cellular deficits resemble the cellular pathology reported in lysosomal storage disorders, which are accompanied by cognitive and mental symptoms. In collaboration with a pharmaceutical industry, we have conducted this phenotype-based compound screening and the final candidate compounds are under toxicology and safety testing prior to clinical trials. We are also optimizing a high-throughput method of detecting cellular AF from blood samples.

A



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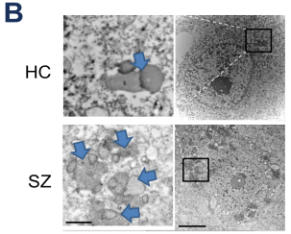

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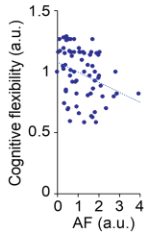


D

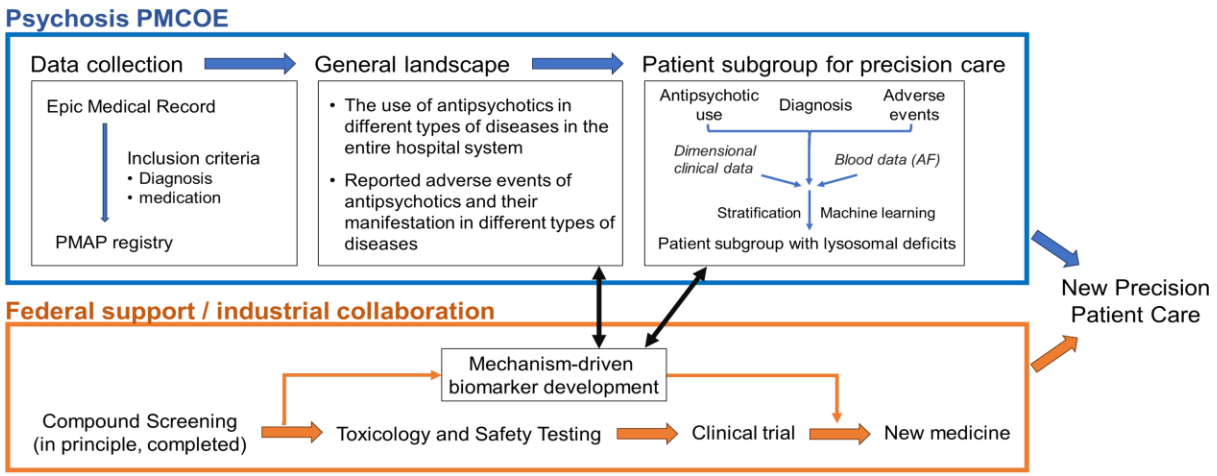
	1st Visit		2nd Visit	
	Patients	Controls	Patients	Controls
Psychiatric evaluation	273	N/A	73	N/A
Neuropsychological test (NP)	193	201	65	55
Olfaction test	143	149	52	47
Olfactory neuronal culture cells	137	96	14	14
Fibroblasts	128	103	22	31
CSF	41	25	5	6
Blood	369	245	88	73
Structure /resting state fMRI (3T)	134	124	40	41
MRS (7T)	96	114	35	46

E

	Blood	Blood + NP	Blood + NP + 3T	Blood + NP + 7T	Blood + NP + 3T + 7T
HC	245	201	116	98	96
SZ/SA	199	171	90	67	63

A) Significant increase in cellular AF in blood cells of patients with schizophrenia (SZ) compared with those of healthy subjects.(HC)
B) Lysosomal deficits in SZ patients (data from a collaborator Dr. Roberts in UAB).
C) Significant relationship between blood AF and cognitive inflexibility.
D) Bio-samples and data from patients and healthy subjects in the Johns Hopkins Schizophrenia Center (JHSZC): a collection by other projects including the NIH Conte Center project in parallel to this PMCOE project.
E) Bio-samples and data from patients and healthy subjects for a pilot AF study, which will provide a scientific foundation prior to this PMCOE project. SA, schizoaffective.

Study design



Next step

1) We will investigate a hospital-wide landscape of psychosis, paying an attention to antipsychotic use and its adverse events.
2) In accordance with the development and refinement of a novel high-throughput method of detecting cellular AF and a novel compound that targets the lysosomal deficits with psychosis, we will define a subgroup of a subset of patients who show psychotic manifestations in a cross-disease manner.

Conclusion

1) By defining lysosome deficits-mediated psychotic manifestation, we will investigate a novel landscape of psychosis in a cross-disease manner beyond the boundary of psychiatry and other medical specialties.
2) Based on the precision medicine-guided approach, we will stratify patients with psychosis, mainly using a novel high-throughput method of detecting cellular AF.
3) We hope that the efforts of this PMCOE project, in combination with other projects under federal support/industrial collaboration, will lead to a new precision care for patients with psychosis.

Members

- Investigators: Nicola Cascella, Jennifer Coughlin, Koko Ishizuka, Akira Sawa (PI), Kun Yang (data science leader)
- Consultants and advisors: William Eaton, Donald Geman, Laurent Younes
- Staff members: Maeve Schumacher (lead of this poster)
- Research manager: Yukiko Lema

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Rehabilitation
Precision Medicine Center of Excellence

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Rehabilitation Precision Medicine Center of Excellence

Vision

- To improve personalized rehabilitation by combining large-scale electronic medical record data with prospectively collected data on real-world function

Mission

- To understand how to provide the right rehabilitation to the right patient at the right time

Research Aims

- 1) Develop and test approaches for subgrouping patients based on shared characteristics
- 2) Develop and test predictive models of patient recovery trajectories
- 3) Develop and test predictive models of adverse health events (e.g., rehospitalization, emergency department visits)

Interested in Collaboration?

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Precision Medicine Symposium

Gait speed and gait asymmetry relate to the accuracy of Fitbit Inspire 2 step counts in persons post-stroke (Rehab PMCOE)

Junyao Li[1], Jan Stenum[1,2], Margaret A. French[1], Ryan T. Roemmich[1,2]
[1]Department of Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine; [2]Center for Movement Studies, Kennedy Krieger Institute

Focus

Introduction

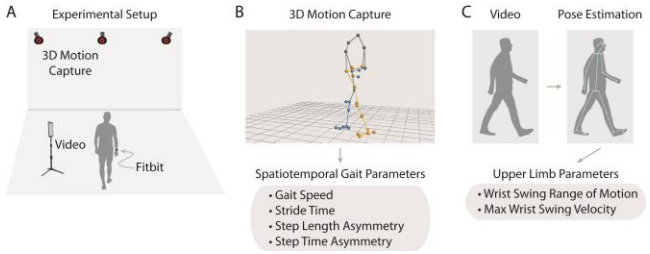
- Low physical activity (PA) is associated with poor health outcomes in individuals recovering from stroke
- Real-time PA monitoring with wearables like Fitbit may allow for identification of patients at risk
- Real-time PA monitoring requires that wearable devices accurately measure and record data in patient populations
- Step counts are often inaccurate in persons with gait impairment
- We do not yet understand how to identify patients who may/may not be good candidates for accurate PA monitoring

Purposes and Hypotheses

- We **hypothesize** that **1)** the Fitbit would generally undercount steps in persons post-stroke at the group level, and **2)** gait speed, gait asymmetry, and metrics of arm swing would predict step count error
- The **purposes** of this work were to **1)** understand how well a newer model of wearables measures step counts in persons post-stroke, and **2)** identify clinically observable gait impairments that affect step count accuracy

Methods & Analytics

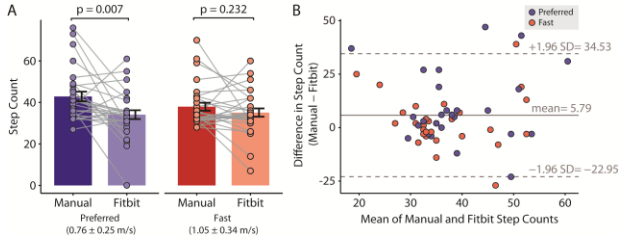
- 29 individuals (10 male, 62 ± 12 y.o.) with stroke wore a Fitbit Inspire 2 and walked overground at both their preferred and fastest comfortable speeds in a three-dimensional motion capture laboratory
- We recorded simultaneous digital video and motion capture recordings to measure whole-body movement kinematics
- We recorded manual and Fitbit-derived step counts to assess accuracy



Results and Highlights

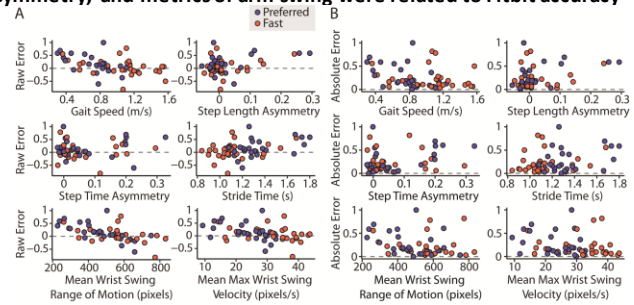
1. The Fitbit tended to undercount steps in persons post-stroke when walking at preferred but not fast speeds

- **A)** When persons post-stroke walked at their preferred walking speeds (blue; mean ± SD: 0.76 ± 0.25 m/s), there was a significant difference between the manual and Fitbit step counts (p=0.007)
- This difference was not present when persons post-stroke walked at their fastest comfortable speeds (red; mean ± SD: 1.05 ± 0.34 m/s; p=0.232)
- **B)** We provide a Bland-Altman to show inaccuracy as a function of step counts



2. We observed that gait speed, gait asymmetry, and metrics of arm swing were related to Fitbit accuracy

- We assessed discrepancies in Fitbit step counts relative to manual counts using two metrics: Raw Error (a measure of bias) and Absolute Error (a measure of accuracy)
- **A)** Raw Error was significantly associated with gait speed, step length asymmetry, metrics of arm swing, and stride time
- **B)** Absolute Error was significantly associated with gait speed, step length asymmetry, step time asymmetry, metrics of arm swing, and stride time
- These relationships were similar across both preferred (blue) and fast speed (red) overground walking trials



3. Gait speed and gait asymmetry predict Fitbit step count accuracy

- We used linear mixed effect modeling to understand which of the parameters mentioned above predicted the Absolute Error across all data (i.e., both preferred and fast speed trials)
- We performed the modeling because we observed significant collinearity in the data (e.g., arm swing metrics are significantly associated with walking speed)
- We tested several models that included all metrics mentioned above
- Linear mixed effect modeling revealed that gait speed and step length asymmetry were significant predictors of Absolute Error in the most parsimonious model
- Additional modeling (shown in next column) demonstrated that arm swing can be substituted for gait speed as a significant predictor of Absolute Error

Gait Parameter	Model 1[1]	Model 2[1]	Model 3[1]	Model 4[1]
Gait Speed	-0.51*** (-0.75, -0.27)	-0.37** (-0.63, -0.12)	-0.34 (-0.89, 0.21)	-0.23 (-0.91, 0.41)
Step Time Asymmetry		0.04 (-0.29, 0.37)	0.07 (-0.25, 0.41)	0.08 (-0.26, 0.41)
Step Length Asymmetry		0.35** (0.05, 0.65)	0.30* (0.01, 0.60)	0.26 (-0.06, 0.60)
Mean Maximum Wrist Swing Velocity			0.25 (-0.27, 0.78)	0.30 (-0.26, 0.84)
Mean Wrist Swing Range of Motion			-0.33 (-0.77, 0.10)	-0.38 (-0.83, 0.09)
Stride Time				0.16 (-0.40, 0.67)
Model Comparison Metrics				
Marginal R^2	0.27	0.40	0.42	0.42
Change in Marginal R^2		0.13	0.02	0
Conditional R^2	0.55	0.61	0.62	0.65
χ^2 p-value		0.02**	0.30	0.66

***p <0.001; **p <0.05; *p < 0.1

[1]Standardized beta coefficients and 95% confidence intervals.

Results (continued)

Gait Parameter	Model 1A[1]	Model 2A[1]	Model 3A[1]	Model 4A[1]
Mean Maximum Wrist Swing Velocity	0.02 (-0.42, 0.45)	0.04 (-0.37, 0.45)	0.25 (-0.27, 0.78)	0.30 (-0.26, 0.84)
Mean Wrist Swing Range of Motion	-0.53** (-1.01, -0.05)	-0.41* (-0.84, 0.02)	-0.33 (-0.77, 0.10)	-0.38 (-0.83, 0.09)
Step Time Asymmetry		0.14 (-0.18, 0.46)	0.08 (-0.25, 0.41)	0.08 (-0.26, 0.41)
Step Length Asymmetry		0.33** (0.03, 0.63)	0.30* (0.01, 0.60)	0.26 (-0.06, 0.60)
Gait Speed			-0.34 (-0.89, 0.21)	-0.23 (-0.91, 0.41)
Stride Time				0.16 (-0.40, 0.67)

Conclusion

- Fitbit Inspire 2 devices tend to undercount steps in persons post-stroke
- Gait speed and gait asymmetry affect the accuracy of Fitbit-derived step counts in persons post-stroke
- Clinicians and researchers can use these findings to estimate the suitability of individual patients or research participants for remote physical activity monitoring using wearable devices

Acknowledgements

This work was supported by funding from the Sheikh Khalifa Stroke Institute, the National Institutes of Health (grant number 1F32HD108835-01), and the American Heart Association (23IPA1054140).

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Precision Medicine Symposium

Identifying unique subgroups of individuals after stroke using heart rate and steps to characterize physical activity (Rehab PMCOE)

Lily Koffman[1], Ciprian Crainiceanu[1], Ryan T. Roemmich[2,3], Margaret A. French[2]

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Focus

Introduction

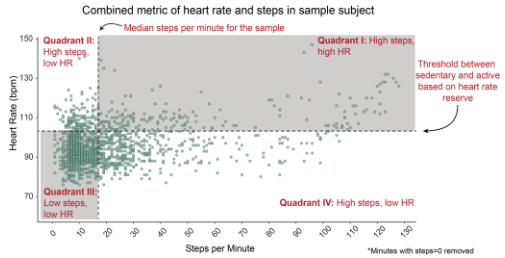
- Low physical activity (PA) is associated with poor health outcomes in individuals recovering from stroke
- Real-time PA monitoring with wearables like Fitbit may allow for identification of patients at risk
- Change in heart rate (HR) in response to PA can provide additional health information
- HR/PA relationship may illuminate unique subgroups
- Quantifying this relationship is challenging and has not been explored in individuals with stroke

Purposes and Hypothesis

- The **purposes** of this work were to **1)** propose a combined metric to reflect the PA/HR relationship, **2)** identify subgroups with distinct PA patterns, and **3)** examine the association between these subgroups and clinical outcomes
- We **hypothesize** that metrics of PA, including a combined steps/HR metric, identify subgroups of patient that may be associated with clinical metrics

Methods & Analytics

- 70 individuals (38 male, 39 white, 61 ± 13 y.o.) with stroke wore a Fitbit Inspire 2 for 1 year. A 2-week window from this period was used in the analysis
- Individuals were included if they wore the device >75% of minutes from 7am-10pm for ≥10 days

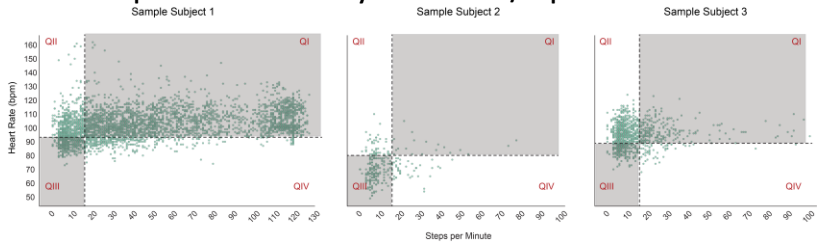


- Metrics included in a k-means **clustering algorithm**: steps/day, percent sedentary time, resting HR, time in quadrant I, II, and IV, and mean steps during high steps/high HR minutes

Results and Highlights

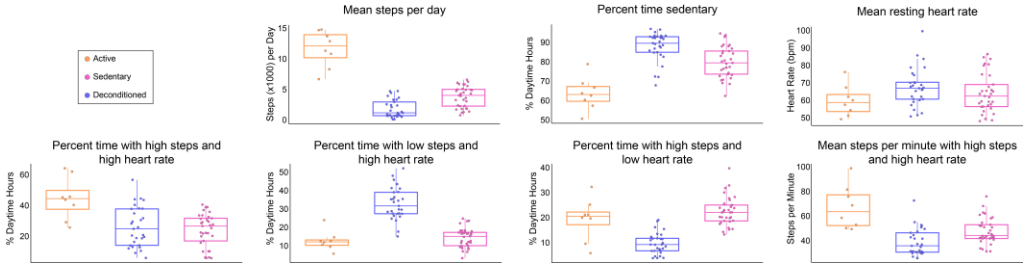
1. Percent time spent in each "quadrant" as defined by combined HR/step metric varies between individuals

- Some individuals (sample subject 1) spend a large proportion of minutes in QI (high steps/high HR), while others spend more time in QIII (sample subject 2) or QII (sample subject 3)



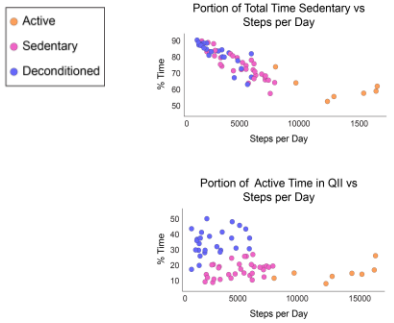
2. K-means clustering identified 3 subgroups: Active (n=8), Sedentary (n=29), and Deconditioned (n=33)

- All clustering variables except resting HR different between groups (p<0.01)
- Active had higher time with high steps/high HR, more steps per day, less sedentary time (p<0.01) than deconditioned and sedentary
- Deconditioned and sedentary differed most on time with low steps/high HR and time with high steps/high HR (p<0.01)



3. Subgroups are evident by examining the combined heart rate and step metrics

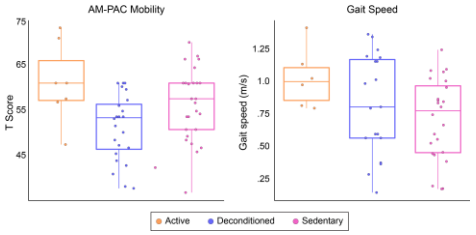
- Sedentary and deconditioned are similar when examining sedentary time vs. steps per day, but are distinct when considering the HR/steps metric



4. Clusters differ on select clinical metrics of mobility, specifically AM-PAC Mobility (p<0.01)

- Pairwise comparisons for AM-PAC Mobility show differences between active and deconditioned (p=0.04) and sedentary and deconditioned (p<0.01)

Cluster	Age at Enrollment n (%)	Time Since Stroke in months mean (SD)	Beta Blockers n (%)	Male n (%)	White race n (%)	Employed n (%)
Active	64.2 (5.9)	21.3 (48.5)	6 (75)	6 (75)	5 (63)	2 (25)
Deconditioned	67.6 (10.3)	36.5 (56.6)	17 (59)	15 (52)	18 (62)	6 (21)
Sedentary	54.5 (13.0)	29.7 (52.7)	19 (56)	17 (52)	16 (48)	13 (39)



Conclusion

- Combined HR/steps metrics based on proportion of time in HR/step categories differs between individuals
- K-means clusters formed with combined HR/steps metric identifies three distinct PA subgroups
- Subgroups differ on AM-PAC Mobility
- Distinct PA patterns suggest different interventions for sedentary vs. deconditioned individuals

Next Steps

- Cluster stability over longer periods of time
  - Exploratory analysis split 2-week sample into two 1-week periods and recalculated clusters for each period

Week 1 \ Week 2	Active	Decond.	Sed
Active	6	1	1
Decond.	0	23	5
Sed.	1	3	30

- Cluster movement as predictive of adverse events (i.e., hospital admissions, emergency room visits)

Acknowledgements

This work was supported by funding from the Sheikh Khalifa Stroke Institute and the National Institutes of Health (grant number 1F32HD108835-01 and 2R01NS060910-14A1)

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1. Schrack, J. A., Leroux, A., Fleg, J. L., Zipunnikov, V., Simonsick, E. M., Studenski, S. A., Crainiceanu, C., & Ferrucci, L. (2018). Using Heart Rate and Accelerometry to Define Quantity and Intensity of Physical Activity in Older Adults. The journals of gerontology. Series A, Biological sciences and medical sciences, 73(5), 668–675. https://doi.org/10.1093/gerona/glx029
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Rehabilitation
Precision Medicine Center of Excellence

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Rehabilitation Precision Medicine Center of Excellence

Vision

- To improve personalized rehabilitation by combining large-scale electronic medical record data with prospectively collected data on real-world function

Mission

- To understand how to provide the right rehabilitation to the right patient at the right time

Research Aims

- 1) Develop and test approaches for subgrouping patients based on shared characteristics
- 2) Develop and test predictive models of patient recovery trajectories
- 3) Develop and test predictive models of adverse health events (e.g., rehospitalization, emergency department visits)

Interested in Collaboration?

Contact us at:

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Precision Medicine Symposium

Gait speed and gait asymmetry relate to the accuracy of Fitbit Inspire 2 step counts in persons post-stroke (Rehab PMCOE)

Junyao Li[1], Jan Stenum[1,2], Margaret A. French[1], Ryan T. Roemmich[1,2]

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

Focus

Introduction

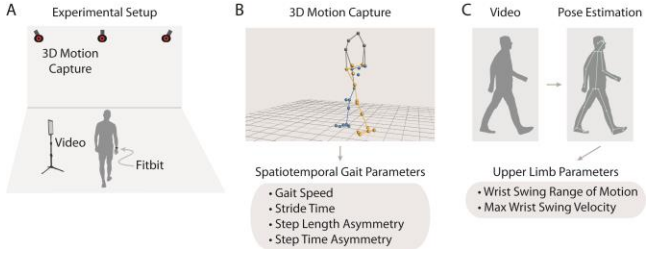
- Low physical activity (PA) is associated with poor health outcomes in individuals recovering from stroke
- Real-time PA monitoring with wearables like Fitbit may allow for identification of patients at risk
- Real-time PA monitoring requires that wearable devices accurately measure and record data in patient populations
- Step counts are often inaccurate in persons with gait impairment
- We do not yet understand how to identify patients who may/may not be good candidates for accurate PA monitoring

Purposes and Hypotheses

- We **hypothesize** that **1)** the Fitbit would generally undercount steps in persons post-stroke at the group level, and **2)** gait speed, gait asymmetry, and metrics of arm swing would predict step count error
- The **purposes** of this work were to **1)** understand how well a newer model of wearables measures step counts in persons post-stroke, and **2)** identify clinically observable gait impairments that affect step count accuracy

Methods & Analytics

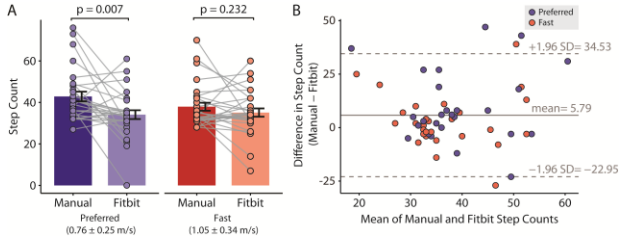
- 29 individuals (10 male, 62 ± 12 y.o.) with stroke wore a Fitbit Inspire 2 and walked overground at both their preferred and fastest comfortable speeds in a three-dimensional motion capture laboratory
- We recorded simultaneous digital video and motion capture recordings to measure whole-body movement kinematics
- We recorded manual and Fitbit-derived step counts to assess accuracy



Results and Highlights

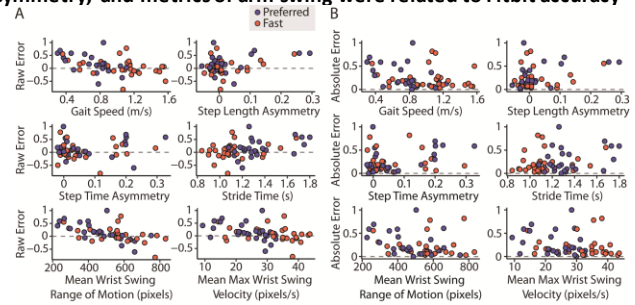
1. The Fitbit tended to undercount steps in persons post-stroke when walking at preferred but not fast speeds

- **A)** When persons post-stroke walked at their preferred walking speeds (blue; mean ± SD: 0.76 ± 0.25 m/s), there was a significant difference between the manual and Fitbit step counts (p=0.007)
- This difference was not present when persons post-stroke walked at their fastest comfortable speeds (red; mean ± SD: 1.05 ± 0.34 m/s; p=0.232)
- **B)** We provide a Bland-Altman to show inaccuracy as a function of step counts



2. We observed that gait speed, gait asymmetry, and metrics of arm swing were related to Fitbit accuracy

- We assessed discrepancies in Fitbit step counts relative to manual counts using two metrics: Raw Error (a measure of bias) and Absolute Error (a measure of accuracy)
- **A)** Raw Error was significantly associated with gait speed, step length asymmetry, metrics of arm swing, and stride time
- **B)** Absolute Error was significantly associated with gait speed, step length asymmetry, step time asymmetry, metrics of arm swing, and stride time
- These relationships were similar across both preferred (blue) and fast speed (red) overground walking trials



3. Gait speed and gait asymmetry predict Fitbit step count accuracy

- We used linear mixed effect modeling to understand which of the parameters mentioned above predicted the Absolute Error across all data (i.e., both preferred and fast speed trials)
- We performed the modeling because we observed significant collinearity in the data (e.g., arm swing metrics are significantly associated with walking speed)
- We tested several models that included all metrics mentioned above
- Linear mixed effect modeling revealed that gait speed and step length asymmetry were significant predictors of Absolute Error in the most parsimonious model
- Additional modeling (shown in next column) demonstrated that arm swing can be substituted for gait speed as a significant predictor of Absolute Error

Gait Parameter	Model 1[1]	Model 2[1]	Model 3[1]	Model 4[1]
Gait Speed	-0.51*** (-0.75, -0.27)	-0.37** (-0.63, -0.12)	-0.34 (-0.89, 0.21)	-0.23 (-0.91, 0.41)
Step Time Asymmetry		0.04 (-0.29, 0.37)	0.07 (-0.25, 0.41)	0.08 (-0.26, 0.41)
Step Length Asymmetry		0.35** (0.05, 0.65)	0.30* (0.01, 0.60)	0.26 (-0.06, 0.60)
Mean Maximum Wrist Swing Velocity			0.25 (-0.27, 0.78)	0.30 (-0.26, 0.84)
Mean Wrist Swing Range of Motion			-0.33 (-0.77, 0.10)	-0.38 (-0.83, 0.09)
Stride Time				0.16 (-0.40, 0.67)
Model Comparison Metrics				
Marginal R^2	0.27	0.40	0.42	0.42
Change in Marginal R^2		0.13	0.02	0
Conditional R^2	0.55	0.61	0.62	0.65
χ^2 p-value		0.02**	0.30	0.66

***p <0.001; **p <0.05; *p < 0.1

[1]Standardized beta coefficients and 95% confidence intervals.

Results (continued)

Gait Parameter	Model 1A[1]	Model 2A[1]	Model 3A[1]	Model 4A[1]
Mean Maximum Wrist Swing Velocity	0.02 (-0.42, 0.45)	0.04 (-0.37, 0.45)	0.25 (-0.27, 0.78)	0.30 (-0.26, 0.84)
Mean Wrist Swing Range of Motion	-0.53** (-1.01, -0.05)	-0.41* (-0.84, 0.02)	-0.33 (-0.77, 0.10)	-0.38 (-0.83, 0.09)
Step Time Asymmetry		0.14 (-0.18, 0.46)	0.08 (-0.25, 0.41)	0.08 (-0.26, 0.41)
Step Length Asymmetry		0.33** (0.03, 0.63)	0.30* (0.01, 0.60)	0.26 (-0.06, 0.60)
Gait Speed			-0.34 (-0.89, 0.21)	-0.23 (-0.91, 0.41)
Stride Time				0.16 (-0.40, 0.67)

Conclusion

- Fitbit Inspire 2 devices tend to undercount steps in persons post-stroke
- Gait speed and gait asymmetry affect the accuracy of Fitbit-derived step counts in persons post-stroke
- Clinicians and researchers can use these findings to estimate the suitability of individual patients or research participants for remote physical activity monitoring using wearable devices

Acknowledgements

This work was supported by funding from the Sheikh Khalifa Stroke Institute, the National Institutes of Health (grant number 1F32HD108835-01), and the American Heart Association (23IPA1054140).

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Precision Medicine Symposium

Identifying unique subgroups of individuals after stroke using heart rate and steps to characterize physical activity (Rehab PMCOE)

Lily Koffman[1], Ciprian Crainiceanu[1], Ryan T. Roemmich[2,3], Margaret A. French[2]

[1]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health; [2]Department of Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine; [3]Center for Movement Studies, Kennedy Krieger

Focus

Introduction

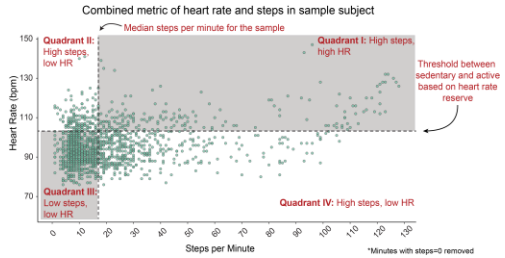
- Low physical activity (PA) is associated with poor health outcomes in individuals recovering from stroke
- Real-time PA monitoring with wearables like Fitbit may allow for identification of patients at risk
- Change in heart rate (HR) in response to PA can provide additional health information
- HR/PA relationship may illuminate unique subgroups
- Quantifying this relationship is challenging and has not been explored in individuals with stroke

Purposes and Hypothesis

- The **purposes** of this work were to **1)** propose a combined metric to reflect the PA/HR relationship, **2)** identify subgroups with distinct PA patterns, and **3)** examine the association between these subgroups and clinical outcomes
- We **hypothesize** that metrics of PA, including a combined steps/HR metric, identify subgroups of patient that may be associated with clinical metrics

Methods & Analytics

- 70 individuals (38 male, 39 white, 61 ± 13 y.o.) with stroke wore a Fitbit Inspire 2 for 1 year. A 2-week window from this period was used in the analysis
- Individuals were included if they wore the device >75% of minutes from 7am-10pm for ≥10 days

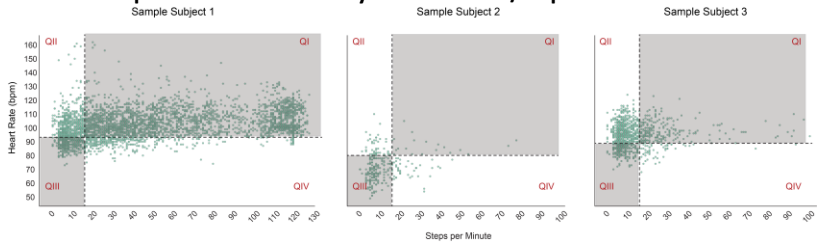


- Metrics included in a k-means **clustering algorithm**: steps/day, percent sedentary time, resting HR, time in quadrant I, II, and IV, and mean steps during high steps/high HR minutes

Results and Highlights

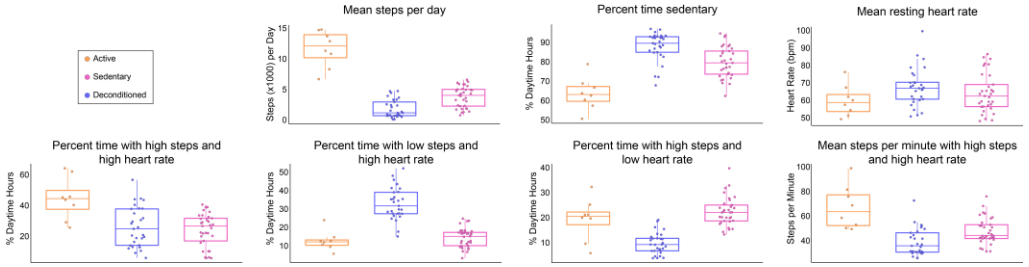
1. Percent time spent in each "quadrant" as defined by combined HR/step metric varies between individuals

- Some individuals (sample subject 1) spend a large proportion of minutes in QI (high steps/high HR), while others spend more time in QIII (sample subject 2) or QII (sample subject 3)



2. K-means clustering identified 3 subgroups: Active (n=8), Sedentary (n=29), and Deconditioned (n=33)

- All clustering variables except resting HR different between groups (p<0.01)
- Active had higher time with high steps/high HR, more steps per day, less sedentary time (p<0.01) than deconditioned and sedentary
- Deconditioned and sedentary differed most on time with low steps/high HR and time with high steps/high HR (p<0.01)



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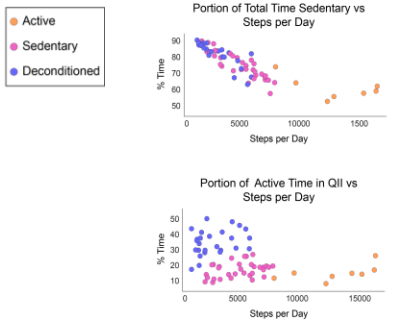

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- Pairwise comparisons for AM-PAC Mobility show differences between active and deconditioned (p=0.04) and sedentary and deconditioned (p<0.01)

Cluster	Age at Enrollment n (%)	Time Since Stroke in months mean (SD)	Beta Blockers n (%)	Male n (%)	White race n (%)	Employed n (%)
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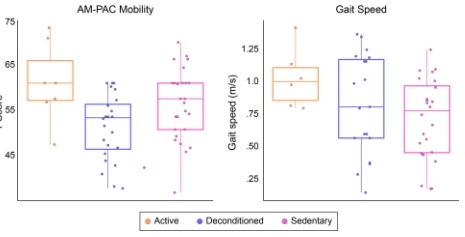

Conclusion

- Combined HR/steps metrics based on proportion of time in HR/step categories differs between individuals
- K-means clusters formed with combined HR/steps metric identifies three distinct PA subgroups
- Subgroups differ on AM-PAC Mobility
- Distinct PA patterns suggest different interventions for sedentary vs. deconditioned individuals

Next Steps

- Cluster stability over longer periods of time
  - Exploratory analysis split 2-week sample into two 1-week periods and recalculated clusters for each period

Week 1 \ Week 2	Active	Decond.	Sed
Active	6	1	1
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References

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Schizoaffective Disorders PMCOE

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Schizoaffective Disorders PMCOE

Vision

- Improve the outcomes for schizoaffective patients by establishing disease subtypes based on treatment response.

Definition

- Schizoaffective disorder is broadly defined to include schizophrenia with or without prominent mood symptoms.

Research Aims

1. Subtype the clinical phenotype of schizoaffective disorder based on treatment response.
2. Subtype schizoaffective disorder based on EEG and neuroimaging signature.
3. Use biological samples to establish the neurobiological distinction among schizoaffective disorder subtypes.
4. Establish precision therapeutics for schizoaffective disorder.
5. Use data analytics of the Johns Hopkins EMR to establish a learning health system for care of schizoaffective disorder patients.

Interested in Collaboration?

Contact PI Dr. Russell Margolis

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Precision Medicine Symposium

A Comparison of Frequency Oddball and Visual Stroop Event-Related Potentials in Treatment Resistant and Ultra-Treatment Resistant Schizophrenia

Schizoaffective Disorders PMCOE

Team: Andor BODNÁR, Yifan MO, Claire MCCAULLEY, Arlene CUERDO, Lilian ZHONG, Clare BETHANY, Malika HARPER, Jay LEONARD, Christopher ROSS, Fred NUCIFORA, & Russell MARGOLIS

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Focus

Schizoaffective disorder, defined as schizophrenia with or without prominent mood symptoms, is a heterogenous disease that affects ~1% of the population. 30% of patients do not respond to standard antipsychotic medicines (treatment-resistant schizophrenia, TRS), and ~30% of TRS do not respond to the atypical agent clozapine (ultra-treatment-resistant schizophrenia, UTRS). We hypothesize that neurobiological differences underlie these subtypes of schizoaffective disorder. We are exploring these differences with multiple tools, including EEG to measure differential electrophysiological responses to auditory and visual stimuli. We selected event-related potential (ERP) amplitude changes to assess preattentive and attentional control processes.

Methods and Analytics

Patients were recruited from Johns Hopkins Bayview Community Psychiatry Program. All 18 schizoaffective disorder patients were on clozapine, after failing two or more typical antipsychotic medications. Treatment response to clozapine was defined based on PANSS total score (TRS ≤ 58, N=11, Age = 34.6 SD = 14.7, F/M = 1/10; UTRS > 58, N=7, Age = 31 SD = 6.5, F/M = 3/4). All patients had normal hearing. Patients with visual impairment wore glasses throughout EEG experimentation. EEG data in both schizoaffective disorder groups were recorded using Brain Vision Recorder software. 32 electrodes were mounted in a fitted cap with a standard 10-20 layout. Electrodes on the cap were initially referenced to the electrode at the vertex (FCz). Average electrode impedances was < 20 kΩ. The EEG data were sampled at 1000 Hz. In EEG preprocessing steps, electrodes were average referenced, and spherical interpolation was limited to 10-15% of electrodes. After epoch rejection, high (0.5 Hz) and low (60Hz) pass filtering was applied to the EEG data. Independent component analyses of preprocessed EEG data were performed; non-brain-related components were rejected. In the passive frequency oddball experiment, patients listened to 200 pure tone sounds (80% standard, 500 Hz; 20% deviant, 750 Hz). Patients silently counted deviant sounds. In the visual Stroop experiment, patients responded to 200 trials where 50% of trials were congruent (ink color and word meaning are the same, e.g., red or blue) and 50% of trials were incongruent (ink color and word meaning are different, e.g., red or blue). 2 (Group: TRS vs. UTRS) by 2 (Stimulus type: standard vs. deviant AND congruent vs. incongruent) Analysis of Variance was performed on central-parietal electrodes during P200 and P300 time-windows to assess differences in amplitude. Multiple regression analysis was performed on clinical (PANSS) and electrophysiological measurements. This study was approved by the Johns Hopkins IRB.

This study was supported by NIMH T32MH015339, the Abramson Fund, and Johns Hopkins inHealth.

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Results and Highlights

Figure 1: Visual Stroop Experiment (P200)

- 1st row, TRS in Blue, UTRS in Green. 2nd row sig. P-values.
- Topographic map of TRS (1st row) vs. UTRS (2nd row), P-value is in the 3rd row
- Diminished P200 (120-175ms) amplitude in both congruent and incongruent trials in UTRS compared to TRS patients (F = 7.02, p = .018, η2 = .32) at left frontal electrodes
- Preattentive visual information processes appear to be more impaired in UTRS patients

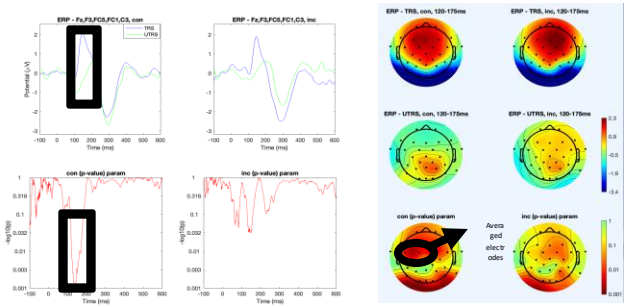


Figure 2: Visual Stroop Experiment (P300)

- Diminished P300 (310-430ms) amplitude in both congruent and incongruent trials in UTRS compared to TRS patients (F = 11.77, p = .004, η2 = .44) at central-parietal electrodes
- Attention control appears more impaired in UTRS

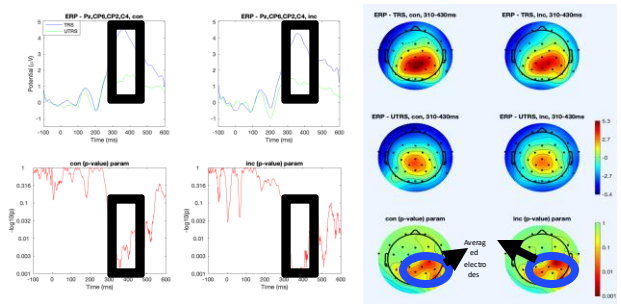


Figure 3: Passive Frequency Oddball Experiment (P200)

- Diminished P200 (130-160ms amplitude during deviant oddb trials in UTRS compared to Tl patients (F = 5.93, p = .027, η2 .27) at central-parietal electro
- Also, a trend towards significa (F = 4.05, p = .061, η2 = .20) a left frontal electrodes
- Preattentive auditory informat processes are impaired in UTF patients

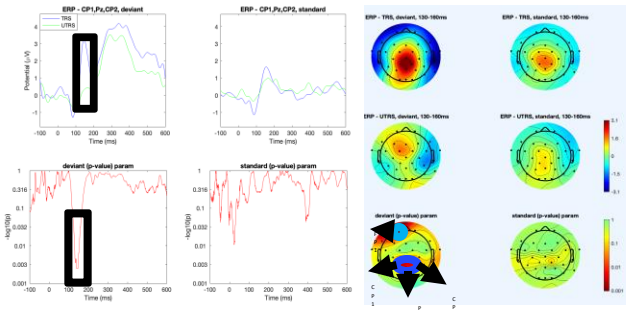


Figure 4: Negative correlation between total PANSS and averaged amplitude for visual Stroop at P200 (frontal electrodes) and P300 (parietal electrodes) time-windows

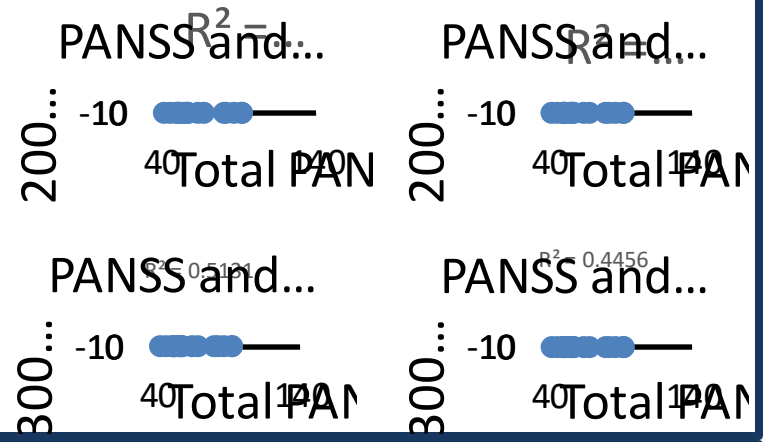
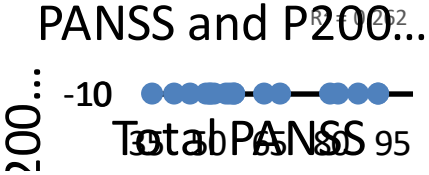


Figure 5: Negative correlation between total PANSS and averaged central-parietal amplitude for deviant frequency oddball trials at P200 time-window



Conclusion and Next Steps

Taken together, these preliminary ERP findings suggest that deficits in preattentive sensory processing and attentional control in both visual and auditory modality may distinguish UTRS from TRS. These results support expansion of this study, including adding patients who respond to standard antipsychotics and healthy controls. Longitudinal studies before and after starting clozapine will be necessary to distinguish whether the ERP differences observed here reflect severity of symptoms or unique neurobiological differences between TRS and UTRS subtypes of schizoaffective disorder.

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Scleroderma
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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

- Identify patients at high risk of progressive disease across a broad spectrum of complications: interstitial lung disease, pulmonary hypertension, cardiomyopathy, among others.
- Detect emerging complications at an earlier stage of disease using novel biomarker, ambulatory device and quantitative imaging strategies.
- Identify patients who are most likely to respond to different treatment strategies.
- Prospectively define whether immunologically distinct subgroups predict clinical outcomes and treatment responsiveness.
- Construct an individual level predictive model of a patient's likely trajectory and outcome.

Interested in Collaboration?

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Precision Medicine Symposium

Probabilistic clustering of longitudinal trajectories of scleroderma patients

Ji Soo Kim*, Yizhen Xu*, Rachel Wallwork, Laura Hummers, Ami Shah†, Scott Zeger†

Joint first authors*, joint senior authors†

Focus

- Autoantibodies are used clinically as tools to identify scleroderma patients with distinct risks of disease progression and complications
- For example, anti-topoisomerase 1 (anti-topo) positive patients have higher risk of interstitial lung disease, yet we lack tools to identify patients who are likely to progress from those likely to remain stable over time (**Figure 1**)
- Can scleroderma patients be further separated into subgroups based upon their longitudinal biomarkers?

Method and Analytics

- We used the population of anti-topo positive patients that, a priori, we would expect to be more homogeneous
- We use a multivariate linear mixed model so that the subgroups can be identified by the joint trajectories of the two measures, FVC and DLCO, while accounting for the correlation between them
- The model also accounts for baseline characteristics including age of onset, sex, race, and cutaneous subtype

Results and Highlights

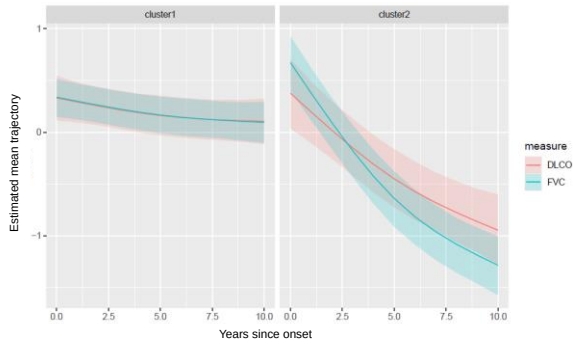

Figure 1. Estimated average trajectories of FVC and DLCO in standardized scale for each identified cluster among anti-topo positive patients. The values are quantile normalized so that observations within each measure follow the standard normal distribution. Cluster 1 (left) consists of patients with stable trajectories for both measures, and cluster 2 (right) with faster progressing trajectories.

- 289 anti-topo positive patients
  - "stable" group (151 patients): both biomarkers changed little from the date of disease onset (**Figure 1** left panel)
  - "progressor" group (138 patients): a steep decline in both measures (**Figure 1** right panel)
- The two-subgroup model was statistically significantly better than the others – the model with one group and models with more than two groups

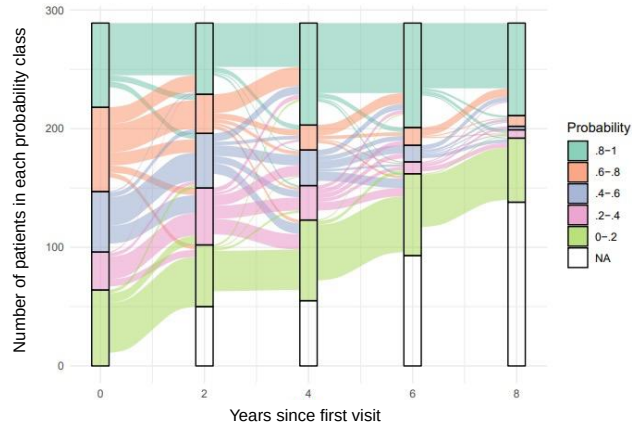

Figure 2. Flowchart demonstrating changes in the probability of being in the stable cluster (p_{it}) of 289 anti-topo positive patients. p_{it} at baseline (0 years since first visit) are more evenly distributed across the five probability groups indicating there is low certainty of group membership for most patients. As more FVC and DLCO data are observed, p_{it} is closer to 0 or 1 for most patients demonstrating increase in certainty.

- Our algorithm produces an updated individualized probability of belonging to the stable group at any given time (**Figure 2**)
- At baseline when no FVC and DLCO values are observed, the probability is calculated based on only clinical and demographic characteristics
- More precise estimations are obtained as more longitudinal observations become available

Conclusion

- Using our model, we can further risk-stratify homogeneous subgroup of patients sharing same baseline characteristics

Next Steps

- By identifying patients where there is tremendous uncertainty at baseline, we can now study biomarkers that may enhance risk prediction beyond known parameters
- Investigate variables highly associated with fast progressors among anti-topo positive patients with high uncertainty at baseline that can possibly lead to new biomarker discovery

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Precision Medicine Symposium

Distinct scleroderma autoantibody profiles stratify patients for cancer risk at scleroderma onset and during disease course

Ji Soo Kim, Adrianne Woods, Laura Gutierrez-Alamillo, Maureen Laffoon, Fredrick M. Wigley, Laura K. Hummers, Antony Rosen, Scott Zeger, Robyn T. Domsic, Livia Casciola-Rosen, Ami A. Shah

Focus

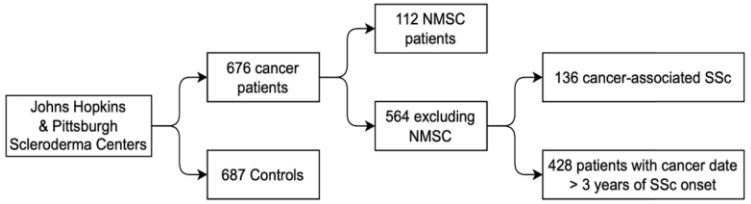
- Are scleroderma autoantibodies, alone or in combination, useful tools for cancer risk stratification?
- An array of scleroderma immune responses examined to study association with risk of cancer

Method and Analytics

- Scleroderma cancer and controls from Johns Hopkins and University of Pittsburgh Scleroderma Centers were studied
- Cancer cases identified using data on PMAP
- Sera assayed by Lineblot and ELISA for autoantibodies against centromere, topoisomerase 1, RNA polymerase III (POLR3), PM/Scl, Th/To, NOR90, U3RNP (Fibrillarin), Ku, Ro52, U1RNP, and RNPC3 (U11/U12 RNF)
- Logistic regression models constructed to examine whether distinct autoantibodies associated with overall cancer at any time and cancer-associated scleroderma
- ORs estimated from logistic regression models including each autoantibody as a predictor, adjusting for age at scleroderma onset, sex, race, cutaneous subtype, and history of smoking
- The effects of having >1 autoantibody on cancer further examined using random forest analysis

Results and Highlights

Study Population



NMSC = Non-melanoma Skin cancer: SSc = scleroderma

Distinct immune responses associate with increased or decreased risk of cancer

Autoantibody	Adjusted OR (95% CI)	
	Cancer-associated scleroderma	Overall cancer
POLR3	2.28 (1.33-3.91)**	1.47 (1.03-2.11)*
Centromere	0.39 (0.20-0.74)**	0.69 (0.51-0.93)*
Monospecific Ro52	2.58 (1.05-6.30)*	2.19 (1.29-3.74)**
U1RNP	0.32 (0.11-0.93)*	0.63 (0.43-0.93)*
Th/To	0.41 (0.18-0.97)*	0.72 (0.48-1.08)

* = P < 0.05; ** = P < 0.01

- Anti-POLR3 and monospecific anti-Ro52 associated with an increased overall cancer risk, whereas anti-centromere and anti-U1RNP associated with lower risk

Distinct combinations of 5 scleroderma immune responses may stratify patients for cancer risk

- Anti-POLR3 or anti-Ro52 alone associated with a higher predicted probability for cancer
- Patients with anti-Ro52 who also have anti-Th/To have a moderate cancer risk, as do patients who are negative for anti-POLR3, anti-centromere and anti-Ro52
- Anti-centromere or the combination of anti-Ro52 and anti-U1RNP have the lowest risk

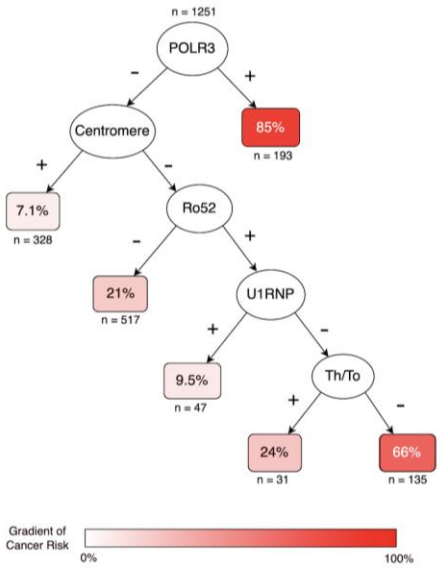


Figure 1. Summary tree of the random forest model showing top five autoantibodies for estimating cancer risk in our population. Positivity or negativity of an autoantibody dictates a decision rule at each tree node, classifying patients into two subgroups. The number and percentage of cohort patients meeting criteria and their predicted cancer risk are shown at each terminal node.

Conclusion

5 distinct scleroderma immune responses, alone or in combination, may be useful tools to stratify scleroderma patients' cancer risk

Next Steps

Further study examining cancer risk in autoantibody subgroups relative to the general population is warranted

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PMAP Research Projects

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PMAP Working Group: Social Determinants of Health

Vision

- To allow for the consideration of social determinants of health (SDoH) as a core component of precision medicine

Mission

- To expand the availability of social determinants of health (SDoH) by building and maintaining a dataset available to CoEs through PMAP

Research Aims

- Phase 0 – Consolidate and Enhance Current Census Data in PMAP
- Phase 1 – Develop plan to get the right data moving from broad phenotypes (area level exposure)
- Phase 2 – Move to individual level
- Phase 3 - Capture all SDoH elements that seem beyond reach

Interested in Collaboration?

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Expansion of Neighborhood-level Social Determinants of Health Available in PMAP

Team: Kathryn C. Fitzgerald, Aparna Natarajan, Sharon Penttinen, and Theodore J. Iwashyna

Precision Medicine Symposium

Focus

- Social determinants of health (SDoH) are upstream social and economic conditions, related to where people are born, grow, live, work, and age that impact individual and group differences in health status (**Figure 1**).
- SDoH incorporate relevant factors that are measured at both an individual and neighborhood-level.
- The Precision Medicine Analytics Platform (PMAP) currently includes information for each patient related to several neighborhood-level indicators of SDoH that are derived the census block geographical unit.
- The currently available resource is limited to a relatively limited set of seven indicators and is largely restricted to patients residing in census blocks groups located in Maryland.

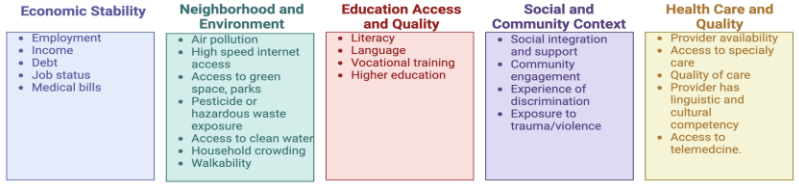

Figure 1. A sample of SDoH targeted for inclusion in the updated SDoH table.

Method & Analytics

- Collated information from publicly available sources for various SDoH domains
  - Census block group
  - Census tract
- Sources of information included in the updated table
  - American Community Survey for 2011-2015 and 2016-2020
  - Area Deprivation Index (ADI) for 2011-2015 and 2016-2020
  - US Census for 2010 and 2020
  - USDA indicators of food accessibility
  - Index of relative rurality (IRR)
  - Persistent poverty
  - Historical redlining
  - Rural-Urban Commuting Area (RUCA) codes
  - Green space (Washington, DC and Baltimore
  - Superfund sites indicating hazardous waste targeted for clean-up by EPA
  - Social vulnerability index for 2010, 2012, 2014, 2018, and 2020
- Expanded a code library to allow investigators to derive census block groups from geocodes available in Epic
  - Allow derivation of census block groups beyond Maryland

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Results and Highlights

- Developed a PMAP accessible and linkable table (and data dictionary) in which >500 neighborhood-level SDoH indicators are available for the entire US.
  - Most indicators available at census block group (**Figure 2**) or census tract
  - Table and relevant measures available using 2010 and 2020 census geographies
- This resource extends the scope of neighborhood-level measures to additional census measures as well as other neighborhood characteristics including food accessibility, rurality, historical redlining, green space, toxic waste site location, among others.
  - Some of the selected indicators are summarized in **Figure 3**.
- Interested investigators can link to this table through two methods: (1) leveraging patient geocodes; and (2) using the existing block group identifiers included as a part of the existing census table.
- We also provide a shared code repository that will allow investigators to perform the geocode to census-block group linkage, thereby extending the availability of neighborhood level indicators of SDoH beyond Maryland (**Figure 4**).

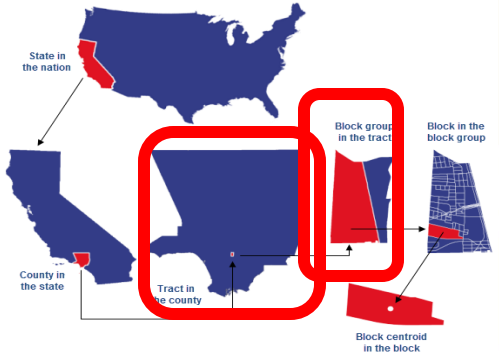

Figure 2. Geographic levels included for the updated table. The red boxes denote the selected geographies

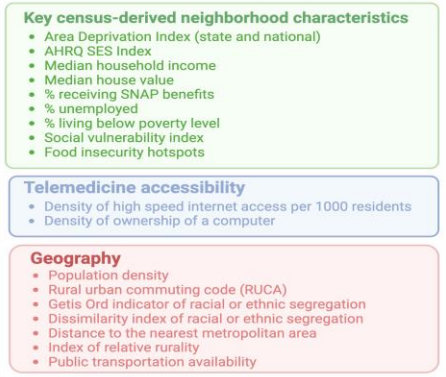

Figure 3. Selected indicators included in the updated table.

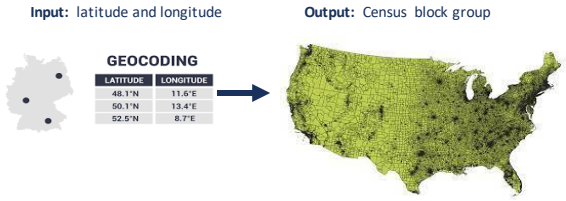

Figure 4. Schematic of provide code as one of the ways investigators can link to the new table

Conclusion

- We provide an expanded neighborhood-level table of indicators of SDoH available to all PMAP users for use in ongoing or future research studies.
- This resource will allow for more detailed consideration of SDoH for studies across PMAP projects.
- The table will be available as a part of the SQL server where PMAP is hosted (i.e., similar to PMAP dictionaries).

Next Steps

- We are working to add further measures including indicators of crime, additional environmental hazards among others.
- Any questions about the table or provded code, please email Kate (fitzgerald@jhmi.edu)
- Office hours with introduction to the table will be held in October

JOHNS HOPKINS SCHOOL of MEDICINE

Improving Accuracy and Efficiency of Medication Data Classification in Electronic Health Record Data

Vision

- Efficiently and effectively identify prescription medication records from electronic medical record data

Mission

- Develop a standardized and convenient process to programmatically extract medication records for use in both research and clinical care

Research Aims

- Create a linkage to an existing medical language system to facilitate the use of pre-existing and standardized relationship hierarchies
- Design a user-friendly interface for the extraction of medications and complex medication classes
- Compare brute-force approaches to medication classification to a programmatic approach

Interested in Collaboration?

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Kidney
Precision Medicine
Center of Excellence

Precision Medicine Symposium

Improving Accuracy and Efficiency of Medication Data Classification in Electronic Health Record Data

Jack Bitzel, Heather Thiessen-Philbrook, Steve Menez, Chirag Parikh, Prakash Nadkarni

KPMCOE

Background

The accurate categorization of medications is a crucial requirement when utilizing electronic health record (EHR) data in research and clinical settings.

Johns Hopkins' EHR stores medication data at a detailed level, complicating the identification and extraction of medication data from a high classification level.

Specific Aims

- Design a classification process that will provide Principal Investigators with accurate medication information from any level of classification
- Minimize manual involvement in the classification of medication records

Methods

- Establish a link between JHU medication records and unified medical language system (UMLS) concepts
- Query UMLS hierarchical relationships to identify concepts of interest
- Obtain JHU medication data

Results

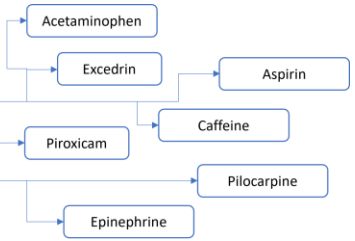
To test our process, we focused on a single, large class of medications: non-steroidal anti-inflammatory drugs (NSAIDs).

NSAID Linkage example of JHU Medical records and UMLS concepts

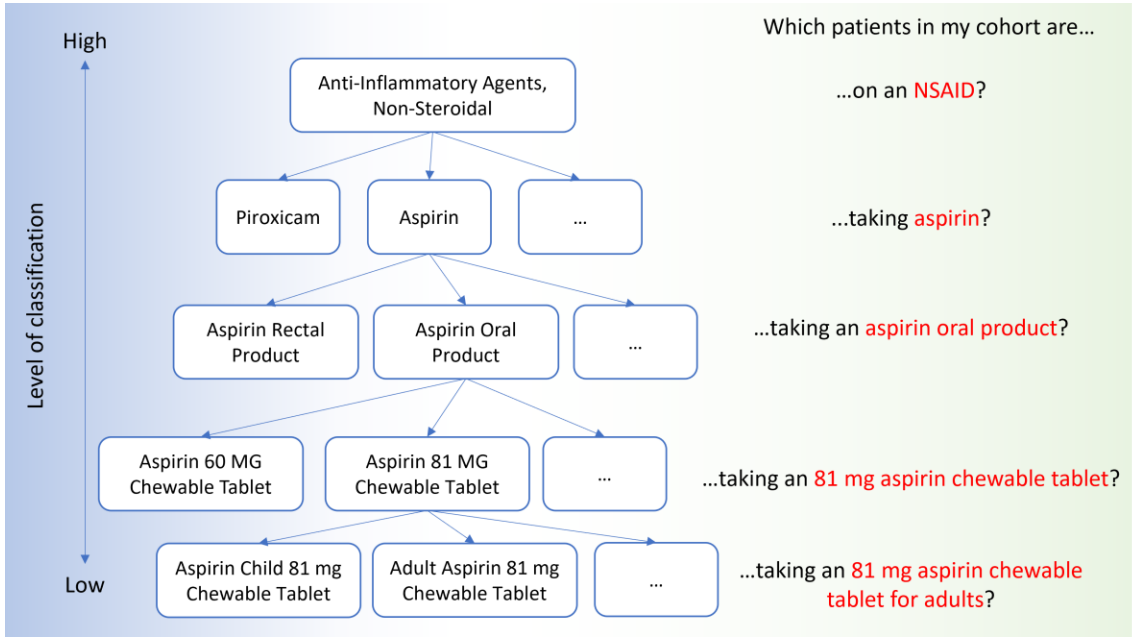
JHU Medication records

medication_name	simple_generic	generic_name
EXCEDRIN EXTRA STRENGTH ORAL	aspirin/acetaminophen/caffeine	aspirin-acetaminophen-caffeine oral
FELDENE ORAL	piroxicam	piroxicam oral
PILOCARPINE 2 %-EPINEPHRINE EYE DROPS	pilocarpine HCl/epinephrine bi	pilocarpine 2 %-epinephrine eye drops

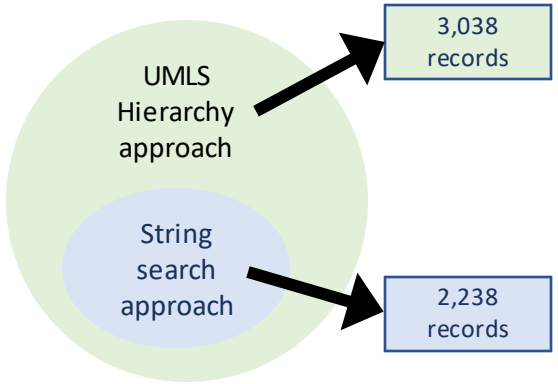
UMLS Concepts



UMLS relationship hierarchy given NSAIDs as initial concept



To determine the accuracy of our process, we compared it to a brute-force approach using simple string searches, which rely on pharmacological knowledge or extensive Google searches.



The UMLS hierarchy approach extracted 800 additional medication records that the string-search approach had missed, such as bromfenac, valdecoxib, and nepafenac.

Conclusions and Next Steps

Our hierarchical approach provides a reliable, exhaustive method for classifying medication data stored in EHR. Future research includes creating a process suitable for integration into a production environment.

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Hyperacute Prediction Of Targeted Temperature Management Outcome After Cardiac Arrest

Jocelyn Hsu[1,2], Han B. Kim[1,2,3], Kirby Gong[1,2,3],
Tej Azad[4], Robert D. Stevens[1,3]

1 Laboratory of Computational Intensive Care Medicine
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Overview

Motivation

- Targeted temperature management (TTM) has been widely regarded as a promising therapy in the resuscitation of cardiac arrest patients primarily because it is believed to improve neurological function. However, the benefits of TTM have not been consistently observed across trials. Moreover, TTM is resource intensive and can lead to serious adverse effects.

Mission

- Our goal is to develop a machine learning model capable of identifying patients most likely to benefit from TTM would have a unique data signature. Such a model could enable greater precision in the selection of potential TTM candidates, establishing a baseline for personalized cardiac arrest treatment, and enable cohort enrichment for future clinical trials.

Research Aims

- 1. Predict the discharge outcome of postcardiac arrest patients receiving TTM by training a ML model with physiological data and TTM treatment data.
- 2. Identify specific features that are associated with favorable outcome following TTM.

Interested in Collaboration?

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Precision Medicine Symposium

Hyperacute Prediction of Targeted Temperature Management Outcome After Cardiac Arrest

Jocelyn Hsu[1,2], Han B. Kim[1,2,3], Kirby Gong[1,2,3], Tej Azad[4], Robert D. Stevens[1,3]

1 Laboratory of Computational Intensive Care Medicine
2 Department of Biomedical Engineering, Whiting School of Engineering
3 Department of Anesthesiology and Critical Care Medicine
4 Department of Neurosurgery
Johns Hopkins University School of Medicine

Focus

Targeted temperature management (TTM) has been widely regarded as a promising therapy in the resuscitation of cardiac arrest patients primarily because it is believed to improve neurological function [1, 2, 3, 4]. However, the benefits of TTM have not been consistently observed across trials [5, 6]. Moreover, TTM is resource intensive and can lead to serious adverse effects [7].

The aims of this study were twofold. First, to predict the discharge outcome of postcardiac arrest patients receiving TTM by training a ML model with physiological data and TTM treatment data. Second, to identify specific features that are associated with favorable outcome following TTM. We hypothesized that patients most likely to benefit from TTM would have a unique data signature. Such a model could enable greater precision in the selection of potential TTM candidates, establishing a baseline for personalized cardiac arrest treatment, and enable cohort enrichment for future clinical trials.

Method and Analytics

Data were extracted from the multicenter Philips eICU - Clinical Research Database [8]. Patients were included if they were adults admitted to ICU after cardiac arrest. Since TTM is not consistently recorded in eICU, we analyzed temperature time series recorded in the first 24 hours after ICU admission. We designated as TTM any instance of a patient whose body temperature decreased to < 36°C after admission and remained below that threshold for > 12h in the first 24h after admission. All patients with potentially erroneous recordings, as signified by infeasible body temperatures less than 20°C included in the database, were excluded from the study. A total of 444 patients meeting these criteria were identified. Among the latter, neurological outcome data was available for 310 patients. The two outcome variables were survival at discharge and neurological function at discharge. Neurological function was defined using the motor subscore of the Glasgow Coma Scale (mGCS). A mGCS of 6 signifies a patient who is awake and able to follow verbal commands, while an mGCS < 6 implies greater neurological impairment.

Variables used to predict outcome were extracted from clinical data collected from the time of ICU admission to the time when TTM was initiated or 12 hours post admission, whichever came first. This interval was selected as the window during which treatment decision-making was most likely occurring. Patient data included demographics; medical history; laboratory test results for the first 12 hours of ICU admission or up to the start of TTM treatment, whichever came first; type of initial heart rhythm detected; and length of CPR administered, if the CA was witnessed. Mean, standard deviation, minimum, maximum, first, and last values recorded were derived for physiologic time series and laboratory data.

We employed three modeling methods: generalized linear modeling (GLM), random forest (RF), and gradient boosting (XG). Hyperparameters used were the default for each package to allow for equal comparison across the different models. Models were 10-fold cross-validated and resampled 10 times once again. The models were used to assess patient mortality status at hospital discharge and neurological status following TTM treatment.

Results and Highlights

Mortality Outcome Prediction

The best performing model, GLM, achieved an AUROC of 0.86 ± 0.04, accuracy 0.76 ± 0.04, sensitivity 0.75 ± 0.09, specificity 0.77 ± 0.07, precision 0.83 ± 0.04, and F_1 0.78 ± 0.05 across 10 cross-validations (Fig. 1a).

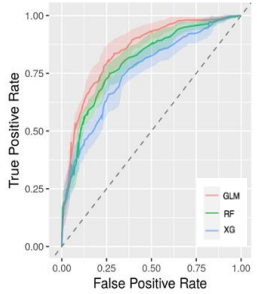
Some of the highest scoring SHAP (most informative) features included the last pH recording, last platelet count data point, last white blood cell (WBC) count, and first lactate recording, where first refers to the first recording captured for the patient after hospital admission and last for the final value recorded prior to the start of TTM (Fig. 1b). Higher values of the last pH and platelet count had a high contribution towards predicting survival, whereas higher values of first lactate value and last WBC count had a low contribution towards survival. However, lower values of last pH and platelet count had a low contribution towards predicting death while lower values of first lactate level and last WBC count recorded had higher contributions towards predicting death.

Neurological Outcome Prediction

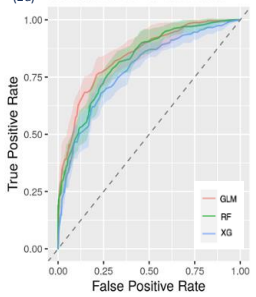
For neurological function prediction, GLM performed slightly better than RF, with an AUROC of 0.75 ± 0.03, accuracy 0.66 ± 0.05, sensitivity 0.69 ± 0.08, specificity 0.64 ± 0.10, precision 0.57 ± 0.07, and F_1 0.61 ± 0.04. Similar to mortality predictions, top predictive features were identified via forward selection with 0.5 threshold, and models improved significantly, with GLM achieving an AUROC of 0.85 ± 0.03, accuracy 0.77 ± 0.05, sensitivity 0.71 ± 0.10, specificity 0.80 ± 0.12, precision 0.73 ± 0.08, and F_1 0.71 ± 0.04 across 10 cross-validations (Fig. 2a).

We also used SHAP to rank features for predicting neurological outcome. We observed some similar top predictive features such as last pH measured, which also demonstrates positive correlation with mGCS. Other features include minimum monocyte count, which also highly contributes towards mGCS of 6 predictions, and last FiO2 levels and first base excess lab test, both of which highly contribute towards patient outcomes with mGCS less than 6 (Fig. 2b).

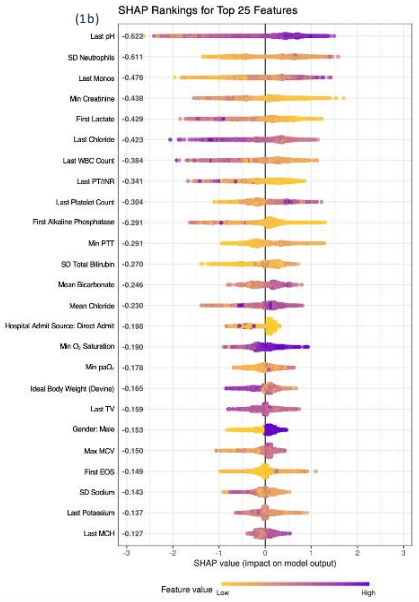
(1a) ROC curves for 10 outer folds



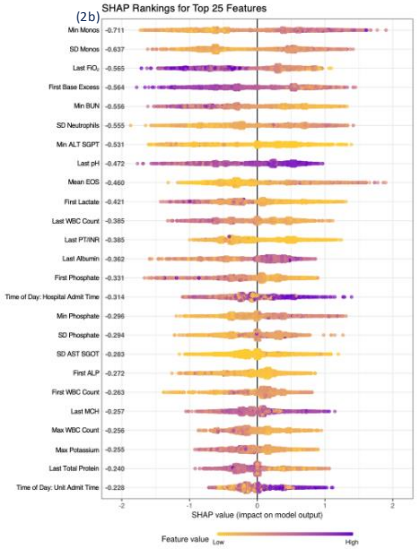
(2a) ROC curves for 10 outer folds



(1b) SHAP Rankings for Top 25 Features



(2b) SHAP Rankings for Top 25 Features



Conclusion

Overall, our study provides insight into physiologic and laboratory features that impact outcomes in cardiac arrest patients receiving TTM. By limiting the dataset to incorporate only the most predictive features via forward selection, our models were able to better capture the correlations between individual features and results, as indicated by the increased performance of models.

There are several limitations in this study. The cardiac arrest patients in the dataset were not designated as recipients of TTM treatment or not. This resulted in the need to develop an algorithm to check for temperature data points to determine whether TTM was administered. Some TTM patient temperature data fluctuate quite significantly, and these patients would have been excluded from the study had their temperatures oscillated above and below 36°C. TTM was also not administered in the same manner across all patients as the eICU dataset incorporated patients across various hospitals. Furthermore, we were unable to externally validate our result and confirm generalizability due to lack of access to other additional cardiac arrest datasets, but cross-validation was implemented to prevent overfitting. As this was a retrospective study, some labels and features that could potentially provide useful insight into patient outcome were not available, such as Cerebral Performance Category (CPC) scores that could be used to evaluate neurological outcome.

Next Steps

We plan to investigate how different aspects of TTM, such as rates of cooling, rewarming, duration of cooling, and offset of TTM administration, could affect outcomes. Additionally, we will optimize models with further hyperparameter tuning to evaluate the best prediction outcomes that GLMs can achieve. Once we gain access to other datasets and can externally validate that the models robustly predict mortality and mGCS outcomes across different patient data, we will design a clinical trial specifically for cardiac arrest patients who are potentially candidates of TTM. This will enable us to gather more clinically predictive features and evaluation labels, such as CPC, serum biomarkers, and imaging and EEG data. It is expected that such work could enable personalized therapies to maximize favorable outcome in cardiac arrest patients.

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Johns Hopkins School of Medicine

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Clinical Implementation of Actionable Pharmacogenomics Testing at Johns Hopkins

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Pharmacogenomics

- **Vision**
  Clinical care and research studies will be informed by high-quality pharmacogenomics testing alongside practical and timely decision-support tools

- **Mission**
  Provide targeted genotyping of metabolic genes for clinical care and research investigations

- **Research Aims**
  Elucidate the impact of clinical pharmacogenomics testing on patient care, adverse drug events, and therapeutic efficacy; Enable increased accessibility of pharmacogenomics testing and education for all patients and providers; Support investigations of new and emerging gene-drug pairs in precision medicine research.

Interested in Collaboration?

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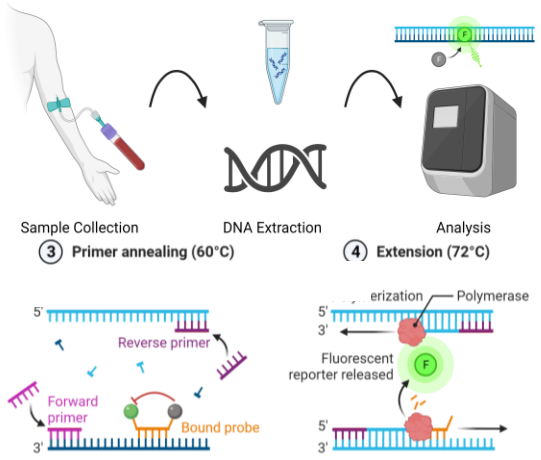
Precision Medicine Symposium

Clinical Implementation of Actionable Pharmacogenomics Testing at Johns Hopkins

Isabel Snyder, Jonathan Merran, Mark Marzinke, Claire Knezevic

Background

Drug response is a key factor in the success of treatment regimens; applying genomic data to inform prescribing decisions is a proactive form of precision medicine. Proactive pharmacogenomic (PGx) testing identifies patient-specific drug-gene interactions and provides evidence-based guidance for appropriate drug selection and dosing before initial drug administration. PGx-guided prescribing mediates the variability of drug response and reduces the probability of adverse drug-related events. Previously, Johns Hopkins patients could only have PGx testing performed by third party laboratories, and results were available only as pdf uploads into the patient chart.



Method and Analytics

The pharmacogenetic panel is simple for patients and providers: it requires one blood draw, and the data is available to view within 3-7 days. Genomic DNA is extracted from whole blood, combined with designated PCR primers and two targeted fluorescent probes, each probe corresponding to either the reference or variant allele. The TaqMan® Genotyper software determines the assay call is determined as either homozygous reference, heterozygous, or homozygous variant. From this data metabolic phenotypes can be assigned: poor, intermediate, normal, rapid and ultrarapid.

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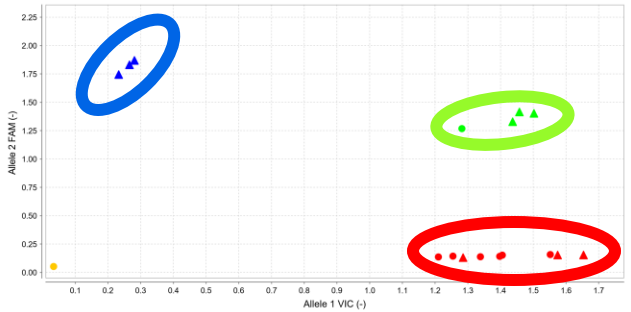
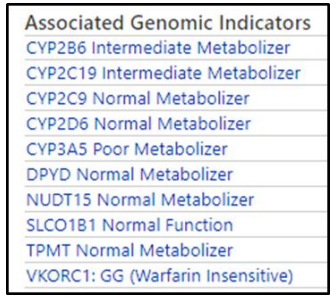
Results and Highlights

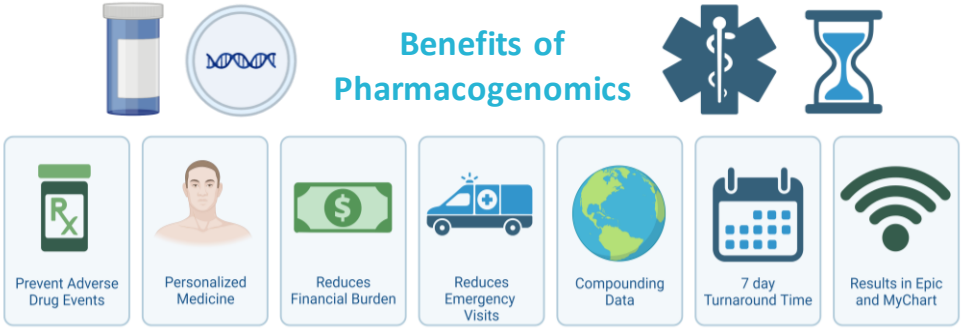
The JH Actionable Pharmacogenomics Panel was validated for clinical testing. The PGx panel consists of 39 variant-specific assays covering 11 different genes with over 70 actionable drug pairings based on Clinical Pharmacogenetic Implementation Consortium guidelines. With seamless integration into EPIC, genotypes and metabolic phenotypes are reported directly within Epic Labs tab. Metabolic phenotypes are also presented as Genomic Indicators, an Epic functionality that highlights clinically actionable variants and their associated medications. These Genomic Indicators enable clinical decision support tools to be deployed during prescribing activities to guide selection of drug dosage and type.



Allelic Distribution plot, includes references (triangles) and samples (circles). The angle of the signal and clustering with reference data helps determine the call. If there are equal amounts of fluorescence from both VIC and FAM fluorophores, a heterozygous allele is called (green). Signal from just VIC flurophore results in a homozygous reference call (red) and just FAM results in a homozygouse variant call (blue).

Example PGx panel results with genotypes for each gene (left) and associated Epic Genomic Indicators (right):





PGx Panel Genes and Affected Medications

Gene	Affected Medications (CPIC Level A)
ABCG2	rosuvastatin
CYP2B6	efavirenz, sertraline, nevirapine
CYP2C19	clopidogrel, voriconazole, several antidepressants, proton pump inhibitors
CYP2C9	warfarin, phenytoin, fluvastatin, several NSAIDs
CYP2D6	atomoxetine, codeine, tramadol, several antidepressants, ondansetron, tamoxifen
CYP3A5	tacrolimus
DPYD	fluorouracil, capecitabine
NUDT15	azathioprine, mercaptopurine, thioguanine
SLCO1B1	simvastatin, atorvastatin, rosuvastatin, lovastatin, fluvastatin, pitavastatin, pravastatin
TPMT	azathioprine, mercaptopurine, thioguanine
VKORC1	warfarin

Conclusion

Pharmacogenomics supports the goals of precision medicine by giving the correct drug at the optimal dose from the start of treatment, improving patient care and reducing costs. A recent study with over 5,000 participants observed a $7,000 reduction in direct medical charges per person, a 7% reduction in emergency department visits, and a 15% reduction in inpatient days after PGx panel testing and pharmacist medication review [1]. A multi-center European study also demonstrated an almost 30% drop in adverse drug reactions after the use of a 12-gene PGx panel [2]. With in-house PGx testing at Johns Hopkins, results will follow the patient through their lifetime to provide stable, consistent care, with clinical decision support tools that can be continually updated to reflect the most current medical literature and treatment guidelines. Clinical implementation of the Johns Hopkins PGx Panel is a key component of our work to incorporate metabolic profiles into patient care to avoid adverse pharmacological events and improve treatment efficacy.

References

https://cpicpgx.org/
Figures created with Biorender.com and taken from TaqMan Genotyper Software (ThermoFisher Scientific).
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JOHNS HOPKINS SCHOOL of MEDICINE

Development and Assessment of Novel Continuous Glucose Monitoring (CGM) Metrics Using Time Series Analysis

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Development and Assessment of Novel Continuous Glucose Monitoring (CGM) Metrics using Time Series Analysis

Joseph Sartini[1], Mike Fang[1], Mary R. Rooney[1], R. Nisha Aurora[2], Naresh Punjabi[3], Elizabeth Selvin[1], Joe Coresh[1], Scott Zeger[1]

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Precision Medicine Symposium

Background: CGM

- Wearable sensor capturing interstitial glucose
- Measured every 15 min for wear period of 14 days
- All data from Abbott Libre Pro

Sensor and Placement: adapted from https://www.freestylle.abbott/in-en/home.html

- Preeminent existing metrics:
  - Mean glucose: average reading
  - Standard deviation: variation around the mean
  - Time in range: proportion of measures in normal 70-180 mg/dL range

Existing metrics do not capture shape nor patterns in CGM and have tenuous associations with comorbidities

Development and Reliability

- We developed our novel metric, the Glucose Color Index (GCI), using time-series analysis – see methods
- Within-person consistency assessed through test-retest r^2
- HYPNOS: N=141 adults with type 2 diabetes; no insulin
- 2 CGM wear periods, 3 months apart
- Median age of 61 yrs

Clinical Utility

- Associations with each comorbidity derived as odds ratio (OR) per standard deviation from logistic regression model
- ARIC: N=301 older adults with diabetes
- 1 CGM wear period and comorbidity indicators
- Median age of 82 yrs

Methods: The Periodogram p_ω

- Linear transform into frequency domain
- Decomposition of signal variance into components at the fundamental frequencies – defined by sampling schema to be $\omega_j = (2\pi j)/n$ for total samples n and integers j
- Regression interpretation of p_ω for time series x_t:

$$x_t = \sum_{j=1}^{\frac{n}{2}} [\alpha_j \cos(\omega_j t) + \beta_j \sin(\omega_j t)]$$

where $p_{\omega_j} \propto \alpha_j^2 + \beta_j^2$

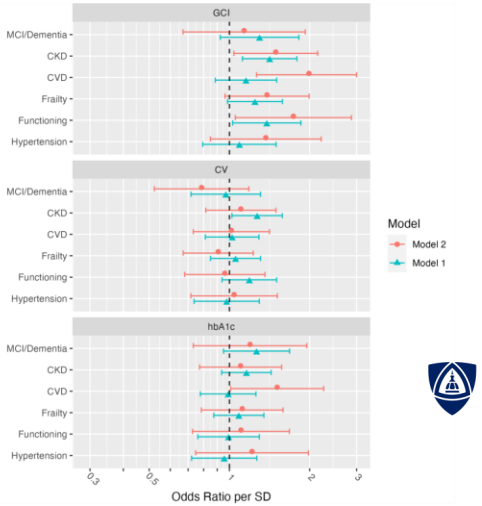
Results

Table 1: Comparative Assessment of Reliability

Test-Retest Correlations of Standard Metrics		
Metric	r^2	r^2 Adjusted for Other Existing Metrics
Mean Glucose	0.73	0.24
Time in Range	0.73	0.23
Coefficient of Variation	0.73	**0.59**
Test-Retest Correlations of Novel Metric		
Metric	r^2	r^2 Adjusted for Existing Metrics
GCI	**0.75**	**0.55**

Adjustment accomplished through calculation of linear model residuals.

Figure 1: Assessment of Clinical Utility



Associations between biomarkers, including GCI, and comorbidities in ARIC participants with diabetes. Model 1 adjusts for the demographic factors of age, sex, and race. Model 2 adjusts for these demographic features and diabetes condition covariates: duration of diabetes and indicator of diabetes medication use.

Conclusion

The GCI is a reproducible new CGM metric based upon the time series periodogram which is, above and beyond existing CGM measures, consistent within persons and strongly associated with major comorbidities

Methods: Calculating the Glucose Color Index

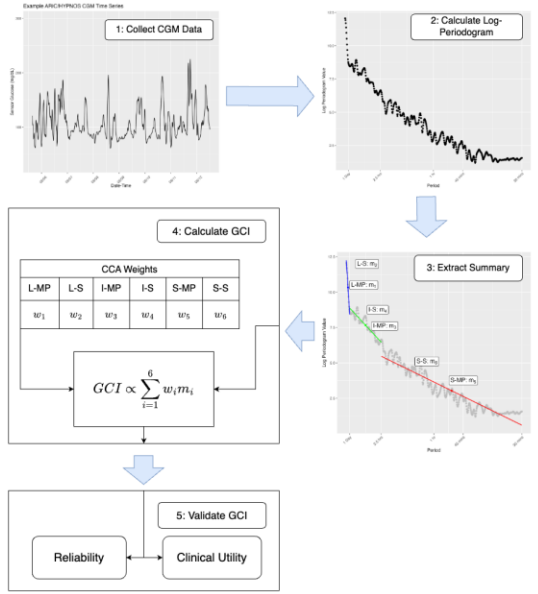


Figure 2: GCI Calculation and Evaluation

1. Collect and pre-process raw CGM data
2. Periodogram calculated for each CGM wear period
3. Fit piece-wise linear model over 3 frequency bands (long L, intermediate I, and short periodicity S), extract slopes S and midpoints MP to approximate log-periodogram
4. 1-number summary Glucose Color Index (**GCI**) derived using Canonical Correlation Analysis (CCA)
   - Assume the 6 shape parameter values are I.I.D. drawn as X_i for period i, such that each period has its own multivariate distribution
   - Find weighting $\hat{w}$ with maximal test-retest r^2:

$$\hat{w} = \underset{w \in \mathbb{R}^6}{\operatorname{argmax}} \{Cor(w^T X_1, w^T X_2)\}$$

$$= \underset{w \in \mathbb{R}^6}{\operatorname{argmax}} \frac{w^T Cov(X_1, X_2) w}{\sqrt{w^T Var(X_1) w}\sqrt{w^T Var(X_2) w}}$$

5. Verify the reliability and clinical utility of the GCI

Pharmacogenetics eConsult for JHHS Clinicians

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Division of Clinical Pharmacology

Vision

- To use germline pharmacogenetic information in routine clinical practice to improve medication outcomes.

Mission

- Build evidence for pharmacogenetic associations through discovery research, demonstrate clinical utility in pragmatic studies, and develop infrastructure to seamlessly integrate pharmacogenetic data into routine clinical workflows.

Research Aims

- Identify ideal candidates for pharmacogenetic testing
- Demonstrate improved clinical outcomes through pharmacogenetics-guided care

Interested in Collaboration?

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Precision Medicine Symposium

Pharmacogenetics eConsult for JHHS Clinicians

James M. Stevenson, PharmD, MS; Claire E. Knezevic, PhD; Kathy Sapitowicz; Helen K. Hughes, MD, MPH; Mark A. Marzinke, PhD

Background

Pharmacogenetics refers to the influence on an individual's genetics on medication efficacy or adverse drug reactions. Pharmacogenetics can be useful in current clinical practice. Here, we are specifically referring to germline pharmacogenetics rather than somatic/tumor genetics. For example, germline variation in genes encoding drug metabolizing enzymes are known to affect dose requirement or likelihood of efficacy or adverse drug reactions for dozens of medications.

However, many healthcare providers have received inadequate training in the field. eConsults are a mechanism for provider-to-provider consultation with an expert in a specialized field.

Implementation

The Epic electronic health record includes functionality to deliver asynchronous eConsults. In the first quarter of 2023, the Office of Telemedicine and Division of Clinical Pharmacology collaborated to launch a Pharmacogenetics eConsult service. The service provides a method for timely, but asynchronous clinical expertise when considering testing or after results are available. The eConsult is available at all mid-Atlantic JHHS facilities regardless of whether the testing has been performed within the health system or with a third party.

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Results and Highlights

As intended, the Pharmacogenetics eConsult has been used by clinicians to discuss patients in which testing is being considered as well as patients with existing pharmacogenetic results. Turnaround time is <2 days. There is currently no charge to patients for the Pharmacogenetics eConsult.

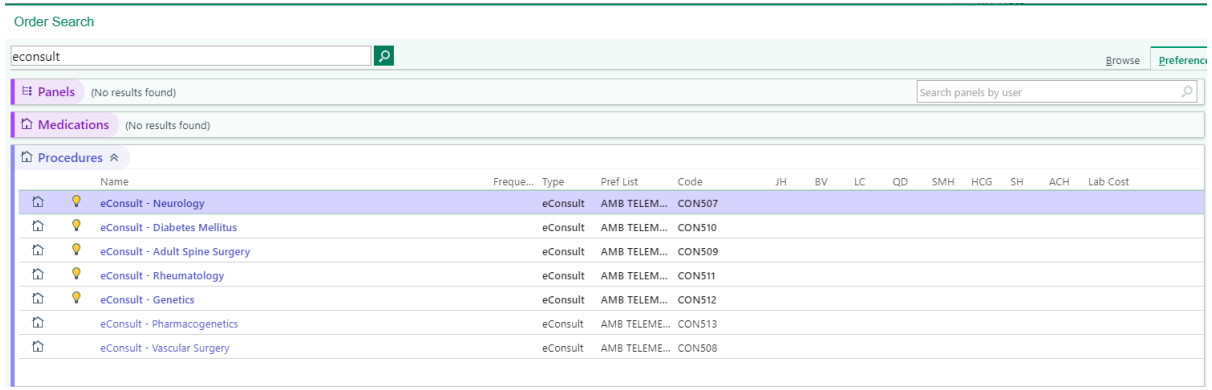

Figure 1. Ordering the pharmacogenetics eConsult

Timing	Provider	Context/question	Response
Pre-test	Primary care physician	36 y/o F with anxiety and ADHD has multiple treatment failures due to efficacy and ADRs	Explained testing options, costs, and which medications it could shed light on
Post-test	Primary care physician (geriatrics)	67 y/o F with hypertension, Ehlers Danlos, and potential dysautonomia. Wondering about *MTHFR* gene results from 23andMe data	Clinical use of *MTHFR* genotype is not recommended. Third-party interpretation of 23andMe data is not appropriate for clinical use.
Pre-test	Ambulatory care pharmacist (internal med)	37 y/o M with hx of Stevens-Johnson syndrome from albuterol	PGx is most useful for explaining dose-dependent toxicity. PGx can predict SJS from certain medications, but not albuterol.

Table 1. Examples of pharmacogenetics eConsults

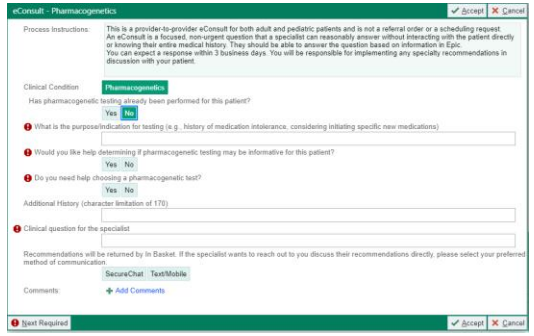

Figure 2. Pharmacogenetics eConsult intake form

Conclusion

The Pharmacogenetics eConsult is a convenient way for JHHS providers to seek pharmacogenetics expertise in an efficient and timely manner within the electronic health record.

Next Steps

We are currently considering automated ways to incorporate the option for a pharmacogenetics eConsult when new orders are placed for pharmacogenetic testing, such as the Hopkins-based Actionable Pharmacogenomics Panel.

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Streamlined Extracellular Vesicle Loading: Harnessing Protein-Specific Subpopulations Through Direct Electroporation

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Corinna Torabi

Department of Mechanical Engineering

In this study, we present a novel method for encapsulating protein-specific subpopulations of nanoscale extracellular vesicles with miRNA directly through electroporation, eliminating the need for laborious follow-up purification and sorting procedures.

Our study introduces a promising avenue for advancing the production of genetic cargo-loaded extracellular vesicles, paving the way for more effective and targeted gene therapies for a wide range of diseases.

Interested in Collaboration?

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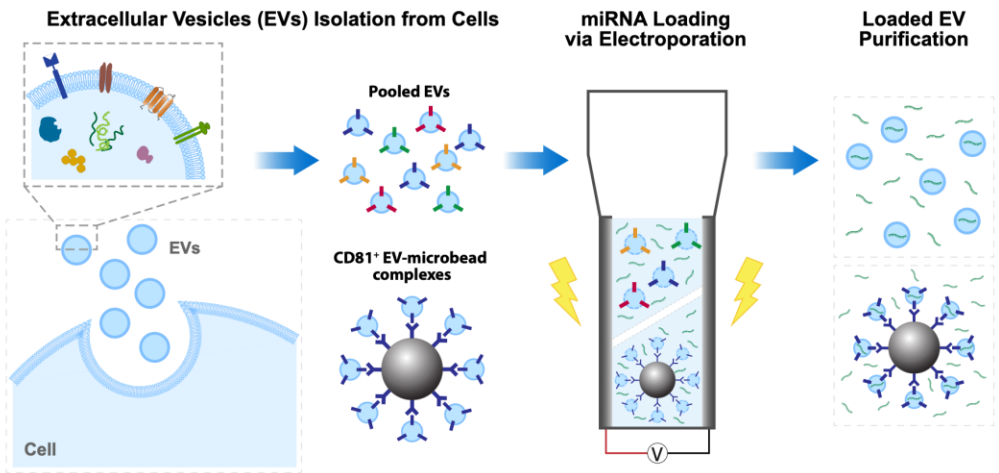
Johns Hopkins inHealth Precision Medicine Symposium

Streamlined Extracellular Vesicle Loading: Harnessing Protein-Specific Subpopulations Through Direct Electroporation

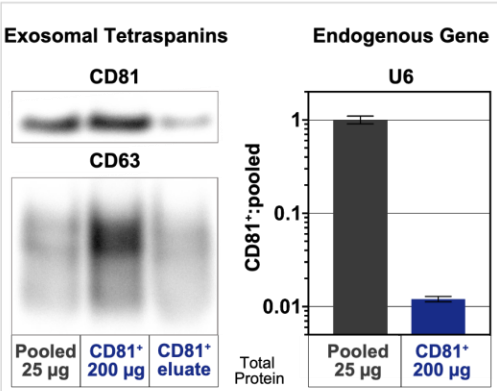
Corinna Torabi and Soojung Claire Hur
Department of Mechanical Engineering | Johns Hopkins University | Baltimore, MD

Johns Hopkins Whiting School of Engineering

EV-Mediated Delivery of Gene Therapy Agents

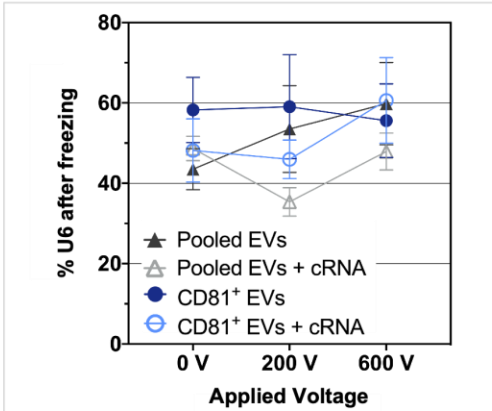


EV Characterization



CD81⁺ EV-microbeads have enriched levels of CD81⁺.

EV Integrity



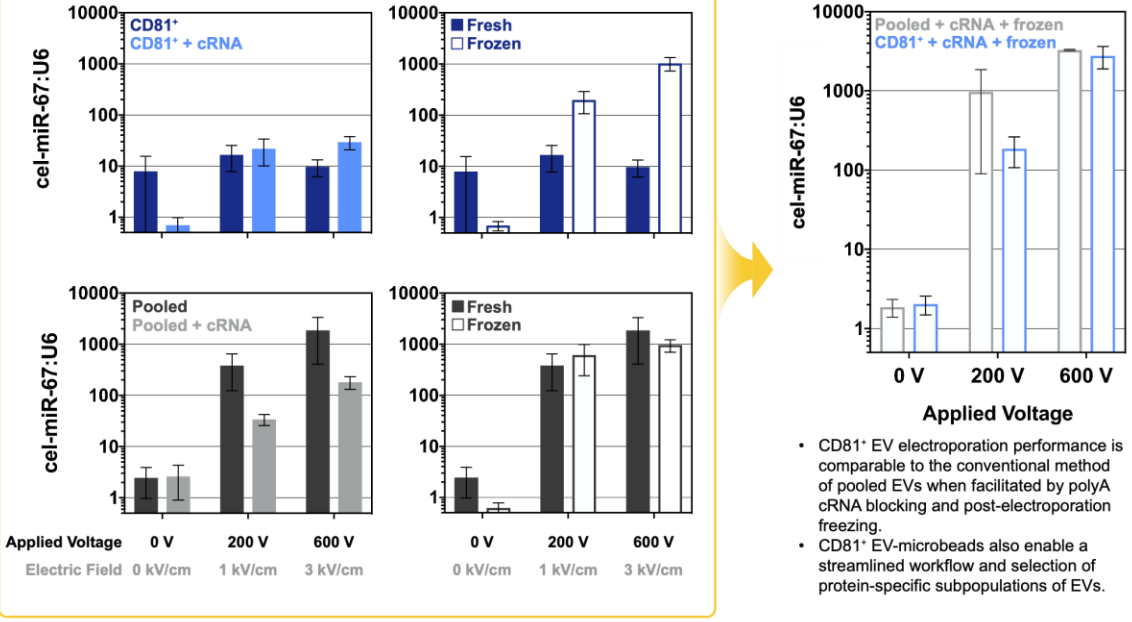
Consistent expression of EV endogenous control after freezing for all conditions

Accurate Detection of Electroporation-Loaded miRNA

polyA cRNA reduces non-specific RNA binding

Freezing destroys unloaded residual miRNA

Purified EVs are loaded with miRNA



- CD81⁺ EV electroporation performance is comparable to the conventional method of pooled EVs when facilitated by polyA cRNA blocking and post-electroporation freezing.
- CD81⁺ EV-microbeads also enable a streamlined workflow and selection of protein-specific subpopulations of EVs.

Conclusions

We have designed a novel protein-specific EV electroporation process that provides significant advantages over exisiting methods:

- Simplified workflow
- Improved purity
- Accurate detection of EV miRNA contents
- Eliminate the need for post-electroporation EV selection
- Opportunity to integrate with microfluidic technology for automated microscale electroporation and multiplexing of protein targets

PCR relative expression calculated using Pfaffl Method adaptation of $2^{-\Delta\Delta C_T}$

Acknowledgements

Thomas Pisanic, Ph.D. Johns Hopkins University, Institute for NanoBioTechnology

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David Lyden, Ph.D. Weill Cornell Medical College, Department of Pediatrics, Department of Cell and Developmental Biology

National Science Foundation

The Hartwell Foundation

Hur Lab µFluidic Biophysics

Consumer Health Information Technology to Engage and Support ADRD Care Partners

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Consumer Health Information Technology to Engage and Support ADRD Care Partners

Vision

- Persons with cognitive impairment and other disabilities may benefit from managing their health virtually, but they and their care partners have been largely excluded from research on consumer health information technology (CHIT) interventions.

Mission

- To increase evidence regarding the role and use of CHIT and of novel, scalable, high-impact CHIT-supported interventions to improve Alzheimer's Diseases and Related Dementias (ADRD) assessment, care, and management.

Research Aims

- Aim 1: To produce new knowledge of individual, contextual, and organizational factors that affect patient portal use and evidence regarding the effects of access and use of such technologies on ADRD care quality and outcomes.

- Aim 2: To understand how persons with ADRD (mild through severe), caregivers, clinicians, and other relevant stakeholders (e.g., case managers, direct care workers, residential care staff) perceive and use consumer health information technology and identify novel technology-supported interventions that hold promise to improve ADRD care and management across the spectrum of residential and care delivery settings.

Interested in Collaboration?

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Precision Medicine Symposium

Consumer Health Information Technology to Engage and Support ADRD Care Partners

Team: Aleksandra Wec, Jennifer L. Wolff, Kelly T. Gleason, MJ Wu, Danielle S. Powell, Danielle Peereboom, Jamie M. Smith, Julia G. Burgdorf, Halima Amjad, Ariel R. Green, Stephanie K. Nothelle, Chanee D. Fabius, Catherine M. DesRoches, Chen-Tan Lin, Catherine A. Riffin, and Hillary D. Lum (Funder: NIH NIA grant R35AG072310)

Focus

- Persons with cognitive impairment and other disabilities may benefit from managing their health virtually but have been largely excluded from research on patient portal interventions

Project Goal: Increase evidence regarding the role and use of consumer health information technology (CHIT) and CHIT-supported interventions to improve assessment, care, and management of Alzheimer's Disease and Related Dementias (ADRD).

Method and Analytics

Data Source

Johns Hopkins Health System (JHHS) electronic health record and patient portal (2017 to 2022).

Sample Characteristics

Established JHHS patients 65 yrs and older (n = 49,382)

- Mean age: 76.6 years old
- 57.3% female
- 67.2% White, 23.4% Black, 3.3% Asian or Pacific Islander, and 6.1% Another Race
- **6.4% of patients had a dementia diagnosis**

Methods

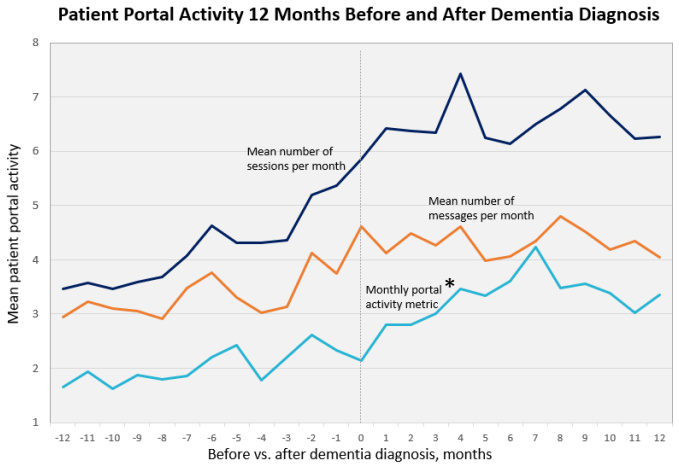
*Portal activity metric: ratio of **number of portal sessions** to **number of clinical encounters**

Dementia diagnosis: based on International Classification of Diseases, 10th edition (ICD-10) codes and patient's problem list

Results and Highlights

71.5% of patients were registered for the portal

Portal registration **did not differ** by **dementia diagnosis** (with vs. without) for patients.



Patients **with dementia** (vs. without) were **more likely** to have a **registered care partner** with **shared access** to their portal account.

Yet, **care partner registration** remained low at **10.4%** for patients with dementia.

For patients with dementia, care partners **authored most** messages, most commonly while **logged in with patient identity credentials**.

This work has been published in:

1. Gleason, K. T., Wu, M. M., Wec, A., Powell, D. S., Zhang, T., & Wolff, J. L. (2023). Patient Portal Use Among Older Adults With Dementia Diagnosis. *JAMA Internal Medicine*.

2. Gleason, K. T., Wu, M. M., Wec, A., Powell, D. S., Zhang, T., Gamper, M. J., ... & Wolff, J. L. (2023). Use of the patient portal among older adults with diagnosed dementia and their care partners. *Alzheimer's & Dementia*.

Conclusion

Our work highlights the need to:

- ✓ **Better identify, engage, and support care partners** of persons with ADRD via the patient portal.
- ✓ Understand the potential of **embedded interventions** delivered via the portal.

Next Steps

Ongoing analyses using focus on:

- Portal use during home health episodes
- Portal use and the Medicare annual wellness visit
- Portal-based deprescribing intervention
- Accuracy of natural language processing to identify authors of portal messages
- Portal use to better support care partners

To read more about our work scan the QR code:

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Management of Nonalcoholic Fatty Liver Disease in a Primary Care Setting

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Management of Nonalcoholic Fatty Liver Disease in a Primary Care Setting

Vision

- Prove there is a need for further education on the outpatient management of NAFLD among primary care physicians.

Mission

- Improve management of fatty liver disease within the primary care setting

Research Aims

- To better understand how PCPs are diagnosing and managing NAFLD in their practices.

Interested in Collaboration?

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Management of Nonalcoholic Fatty Liver Disease in a Primary Care Setting

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BACKGROUND

- The prevalence of nonalcoholic fatty liver disease (NAFLD) has grown exponentially in recent years.
- NAFLD is quickly becoming one of the leading causes of cirrhosis in the United States.
- Primary care physicians (PCPs) are often the first to encounter patients with NAFLD, as it is most often diagnosed incidentally.
- Several recent guidelines have been published detailing optimal NAFLD management.
- How PCPs are diagnosing and managing NAFLD in practice is unknown.

HYPOTHESIS

Few patients with NAFLD in the primary care setting are receiving evidence-based evaluation and follow up designed to prevent the progression of NAFLD to NASH / cirrhosis and its complications.

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METHODS

Dataset:
- 370,000 patients in the Adult Primary Care Center of Excellence (APCCOE) patient registry with a primary care appointment between July 1, 2016 – September 17, 2023

Study Population:
- 10,334 Adults who had at least one primary encounter during this time where NAFLD or NASH was billed.

Extraction:
- Completed by the core for clinical research data acquisition within Microsoft SQL Server Management Studio and RStudio
- NAFLD and NASH population extracted using ICD-10 codes K75.1 or K76.0
- Those with advanced fibrosis or cirrhosis were identified as those who also had ICD-10 codes K74.60 or K74.02

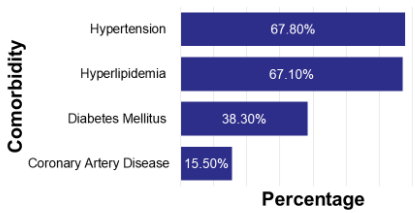
Descriptive data analyses:
- Frequencies and percentages for categorical variables
- Means and standard deviations or medians and interquartile ranges for continuous variables.

RESULTS

Patient Demographics and Comorbidities at the Time of NAFLD Diagnosis (N=10,334)

Diagnosis		**Mean Weight**	210.6 lbs
• NAFLD	93.1%		
• NASH	16.7%		
Gender		**Mean BMI**	33.2 kg/m^2
• Female	53.8%		
• Male	46.1%		
• Non-Binary	<0.01%		
• Other	<0.01%		
Mean Age	52.8 yrs	**BMI Category**	
Distribution		• Underweight	0.3%
• 18-25	2.3%	• Normal Weight	8.7%
• 26-35	9.9%	• Overweight	26.6%
• 36-49	27.1%	• Obesity Class I	30.1%
• 50-64	39.2%	• Obesity Class II	18.7%
• >65	21.4%	• Obesity Class III	14.9%

Presence of Comorbidities



Mean Laboratory Values at First NAFLD Visit		% Missing Lab Data
Aspartate Aminotransferase (0-37)	34.7 U/L	14%
Alanine Aminotransferase (0-40)	44.1 U/L	13.8%
Platelets (150-350)	260 K/cu mm	54.6%
Total Bilirubin (0-1.2)	0.58 mg/dL	1.7%
Albumin (3.5-5.3)	5.87 g/dL	99.7%
INR (excluding those on Warfarin; 0.8-1.1)	1.91	60.9%
Hemoglobin A1c (normal <5.6, pre-diabetes 5.7-6.4, diabetes >6.5)	6.22	16.1%
Lipid Panel		
Cholesterol (0-200)	186 mg/dL	4.3%
Triglycerides (0-150)	159 mg/dL	4.7%
HDL (>40)	48.9 mg/dL	4.4%
LDL (<70)	108 mg/dL	5.4%

Treatment Received

	Overall population	Those with Advanced Fibrosis or Cirrhosis
Prescriptions		
SGLT-2	10.5%	18%
GLP-1	21.5%	26.1%
Vitamin E	8.2%	18%
Statin	54%	65.5%
Thiazolidinediones	35.6%	44.6%
Referred to Hepatology	0.7%	12.2%
Seen by hepatologist	3.8%	16.8%
Referred to Nutrition	24.2%	35%
Seen by nutritionist	18.4%	15.6%
Imaging ordered at diagnosis		
Ultrasound elastography	2.7%	6.2%
Fibroscan	3.1%	9.1%
MRE Liver	0.6%	0.7%
Liver Biopsy	2.7%	13.4%
Repeat Imaging		
Ultrasound Elastography	0.2%	0.5%
Fibroscan	0.9%	1.4%
MRE Liver	0.1%	0.2%
Liver Biopsy	0.2%	1.7%

CONCLUSIONS

- In general, PCPs are not screening, stratifying, referring, or managing patients with NAFLD according to guidelines.
- While the Fib-4 score has been shown to be an excellent predictor of fibrosis, 15% of patients did not have AST or ALT values, and 55% did not have a platelet count
- Less than 1% of all patients and <15% of those with advanced fibrosis/cirrhosis were referred to hepatology
- Follow up imaging, or biopsies was done in < 4% of high-risk patients, despite recommendations for repeat fibrosis screening every 1-3 years.

LIMITATIONS

- NAFLD management has been evolving with recommendations published at various points throughout the study period
- We were not able to access provider notes for further details on counseling or patient engagement with care
- Data was only obtained from one healthcare system, limiting our knowledge of outside referrals or results.

IMPLICATIONS

There is a strong need to enhance education around NAFLD and its management particularly within primary care and preventative settings.