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Development of a Tool to Assess Hypoglycemia Risk in Patients with Type 2 Diabetes

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The speaker has no actual or potential conflict of interest in relation to this presentation.

Background

- More than 34 million US adults have diabetes (~1 in 10) and 90-95% have type 2¹
- In severe cases, can result in loss of consciousness, seizure, head injury, and other injuries to self or others²
- Severe hypoglycemia: requiring assistance of another person to administer carbohydrate, glucagon, or other resuscitative actions³
- Many risk factors for hypoglycemia

<https://www.cdc.gov/diabetes/basics/type2.html>.

Leckie A, et al. Diabetes Care. 2005 Jun; 28(6): 1333-1338.

Workgroup on Hypoglycemia, American Diabetes Association. Diabetes Care. 2005 May;28(5):1245-9.

Risk Factors for Hypoglycemia

- Older age (> age 77)
- Medication-related
 - Insulin
 - Sulfonylurea
 - Beta blocker
 - Antidepressant
- Alcohol use
- Cognitive dysfunction
- Kidney dysfunction
- Untreated hypothyroidism
- Post-gastric bypass surgery
- Pregnancy
- Labile blood glucose
- Skipping meals
- Significant exercise

Borzi V, et al. Diabetes Res Clin Pract. Volume 115;2016:24-30.

True B, et al. Am J Psychiatry. 1987 Sep;144(9):1220-1221.

Leak D, et al. J Lab Clin Medicine. 1962 Nov 1;60(5):811-817.

Salehi M, et al, J Clin Endocrinol & Metab, 2018 Aug;103(8):2815–2826.

Current Literature

Hypoglycemia Associated With Hospitalization and Adverse Events in Older People⁵

Study Design	Population-based cohort study over 4 year follow-up
Baseline Characteristics	85,370 patients in cohort; 440 identified with severe hypoglycemia (0.5%) Mean age 75, female 51% 93% had diagnosis of diabetes in severe hypoglycemia subgroup
Results	<ul style="list-style-type: none">- Hospitalized hypoglycemia was independently associated with increased mortality (60% vs 19% mortality if no hypoglycemia)<ul style="list-style-type: none">- Higher risk if more hypoglycemic episodes ($P < 0.001$)- Hospitalized hypoglycemia independently associated with subsequent hospitalizations ($P < 0.001$) and recurrent hypoglycemia ($P < 0.001$)
Conclusion	Hypoglycemia severe enough for hospitalization put patients at substantially increased risk of morbidity and mortality Older patients were even more at risk

Current Literature

Development and Validation of a Tool to Identify Patients With Type 2 Diabetes at High Risk of Hypoglycemia-Related Emergency Department or Hospital Use⁶

Objective	Develop and validate a tool to categorize risk of hypoglycemic-related utilization in patients with T2D	
Study Design	<ul style="list-style-type: none">• Recursive partitioning, split-sample design• Classification tree of potential predictors• Validation using 3 sample patient groups	
Inclusion/Exclusion	ICD-9: hypoglycemia	ICD-9: SSTIs or osteomyelitis
Outcomes	Hypoglycemia-related ED or hospital use, 12 months follow-up	
Baseline Characteristics	<ul style="list-style-type: none">• 165,148 patients screened• Mean age 63.9 years, 47.6% female	

Karter A, et al. JAMA Intern Med. 2017 Oct 1;177(10):1461-1470.

Current Literature

Development and Validation of a Tool to Identify Patients With Type 2 Diabetes at High Risk of Hypoglycemia-Related Emergency Department or Hospital Use⁶

Results	<ul style="list-style-type: none">- Annual rate of 1+ hypoglycemia-related ED/hospital encounter: 0.49%- Risk stratification: 6 patient-specific inputs<ul style="list-style-type: none">- Prior hypoglycemia-related utilization- Insulin use- Sulfonylurea use- Prior year ED use- Chronic kidney disease stage- Age- Internal validation sample categorized 2.0% high risk, 10.7% intermediate risk, and 87.3% low risk- 12-month hypoglycemia-related utilization rates: 6.7%, 1.4%, and 0.2%
Key Points	<ul style="list-style-type: none">- Six inputs to categorize hypoglycemia risk- Target interventions, reduce hypoglycemic risk, improve safety/QOL

Self Assessment Question #1

Which of the following factors may contribute to hypoglycemic risk?

- a. Sedentary lifestyle
- b. Use of long-acting insulin
- c. History of severe hyperglycemia
- d. Presence of severe lung disease

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Self Assessment Question #2

Which of the following patients would likely have the highest risk of severe hypoglycemia?

- a. 82 year-old female with type 2 diabetes, cognitive disease, hypothyroidism, 3 hospitalizations in previous year, and use of basal insulin, bolus insulin, and a sulfonylurea
- b. 24 year-old pregnant female currently taking propranolol for migraine prophylaxis
- c. 45 year-old male with type 2 diabetes and hypertension taking metformin, long acting insulin and lisinopril
- d. 68 year-old male with type 2 diabetes and alcoholism, hospitalized once in previous year, and currently noncompliant with medications

Self Assessment Question #2

Which of the following patients would likely have the highest risk of severe hypoglycemia?

- a. **82 year-old** female with type 2 diabetes, **cognitive disease**, **hypothyroidism**, **3 hospitalizations in previous year**, and use of **basal insulin**, **bolus insulin**, and a **sulfonylurea**
- b. 24 year-old pregnant female currently taking **propranolol** for migraine prophylaxis
- c. 45 year-old male with type 2 diabetes and hypertension taking **metformin**, long acting **insulin** and lisinopril
- d. 68 year-old male with type 2 diabetes and **alcoholism**, **hospitalized once in previous year**, and currently noncompliant with medications

Setting

- Parkview Health
 - 10 hospital health system
 - Close to 800,000 patients
 - Northeast Indiana and Northwest Ohio
- More than 100 PPG locations



Study Purpose

- Known risk factors for hypoglycemia
- Can we use patient-specific information to predict individual hypoglycemic risk?
- Can we create a screening tool to identify patients and help guide clinical therapy?

Study Design

- Retrospective, single center study
- Time frame: 1/1/2019 to 12/31/2020
 - 1/1/2019 to 12/31/2019: baseline period
 - 1/1/2020 to 12/31/2020: analysis period

Study Design

Inclusion

- Type 2 diabetes
- 18 years or older
- “Active” patient of Parkview Health

Exclusion

- Type 1 diabetes
- Gestational diabetes
- Latent or dormant diabetes
- Active pregnancy diagnosis in the study period
- Deceased prior to 1/1/2021

Baseline Characteristics

41,425
patients

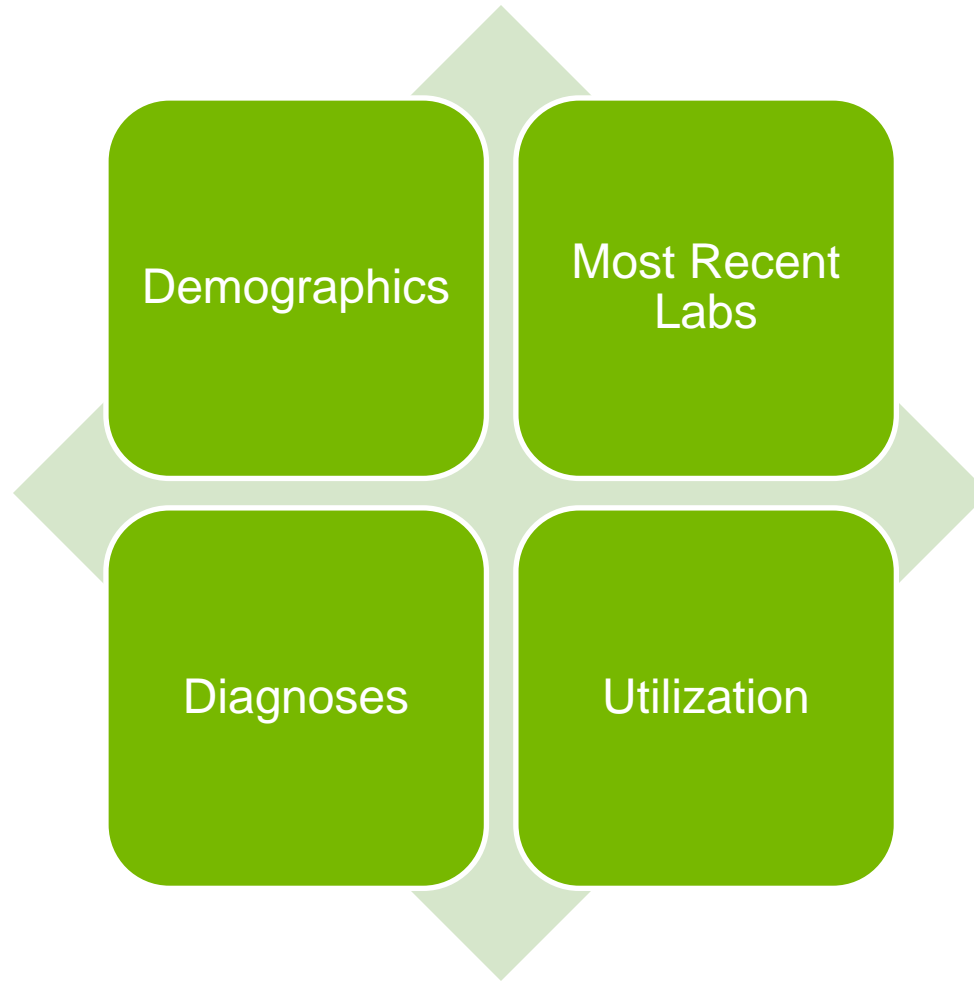
Mean age:
64 years

49.4%
female

Predictive Model

- Created in partnership with Business Intelligence
- Data extraction and deidentification
- Ensemble forest model
- “Machine learning”
 - Model training, correction, repeat

Features (Risk Factors)



Features (Risk Factors)

Demographics

- Age
- Gender
- Height
- Most recent weight
- Most recent BMI

Most Recent Labs

- HbA1c
- Blood glucose
- Serum creatinine
- BUN
- Estimated GFR

Features (Risk Factors)

Diagnoses

- Cognitive disease (Alzheimer's, dementia)
- Hypothyroidism
- Gastric bypass surgery
- Pregnancy
- Current alcohol use (any amount)

Utilization

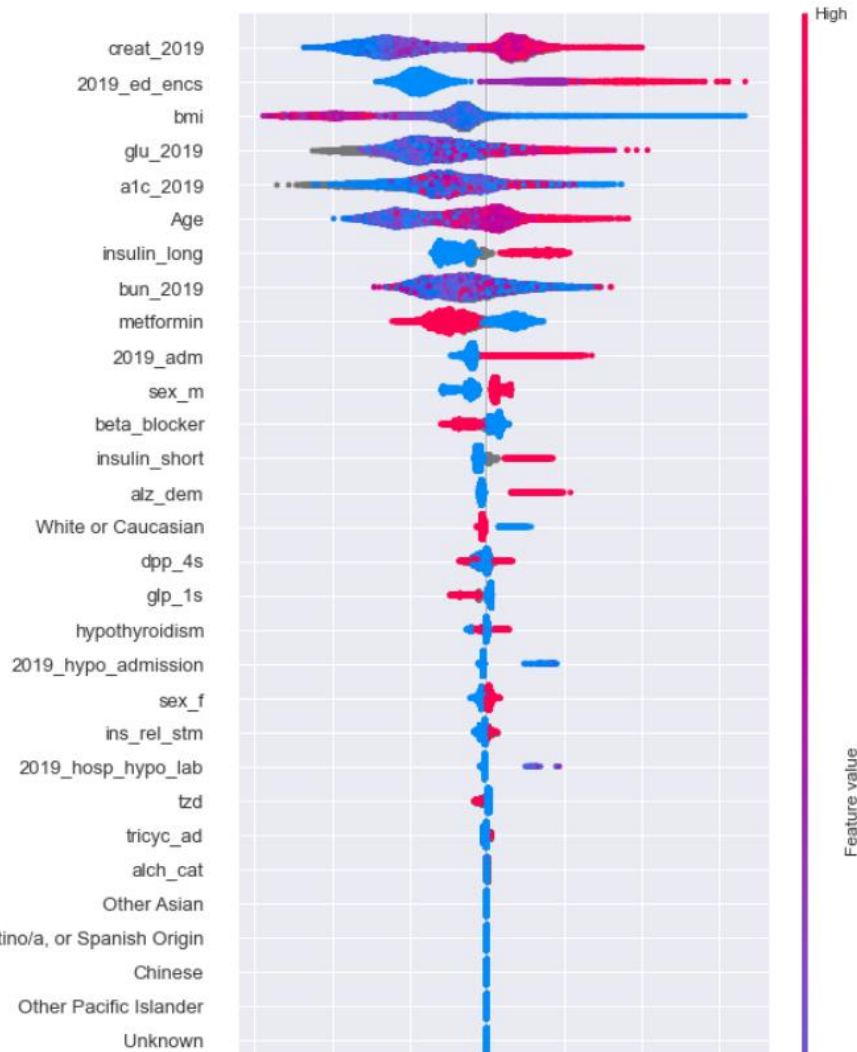
- Number of previous ED/hospital-related hypoglycemic episodes
- Number of previous ED encounters for any reason
- Walk-in clinic encounters for any reason

Outcomes of the Model

- Model has potential to predict 5 outcomes:
 - Hypoglycemia-related ED encounter
 - Hypoglycemia-related hospital admission
 - All-cause ED encounter
 - All-cause hospital admission
 - Hypoglycemic event during ED encounter or hospital admission (<70 mg/dL)

Results: Influential Variables

```
shap.summary_plot(shap_values, X_test, max_display = X_test.shape[1])
```



- Top influential variables for each model outcome
- **Red** = positive influence
- **Blue** = negative influence
- **Purple** = variable influence

Results: Influential Variables

Hypoglycemia-related ED Encounter	Hypoglycemia-Related Hospital Admission	All-Cause ED Encounters	All-Cause Hospital Admission	Hypoglycemia During Encounter
A1c	Previous ED enc	Previous ED enc	Previous ED enc	SCr
Glucose	A1c	BUN	Age	Previous ED enc
SCr	Glucose	SCr	SCr	BMI
Previous ED enc	SCr	Glucose	Previous hosp adm	Glucose
BUN	BMI	A1c	BUN	A1c
Age	Long-acting insulin	Age	Glucose	Age
BMI	Age	BMI	A1c	Long-acting insulin
Long-acting insulin	Metformin	Previous hosp adm	Metformin	BUN
DPP-4	Previous hosp adm	Female	BMI	Metformin
Beta blocker	BUN	Metformin	Long-acting insulin	Previous hosp adm

**variables sorted in order of highest influence to lowest influence for each outcome

Results: Non-Influential Variables

Green = non-influential variable

White = influential variable

	Hypoglycemia-Related ED Encounter	Hypoglycemia-Related Hospital Admission	All-Cause ED Encounters	All-Cause Hospital Admission	Hypoglycemia During Encounter
Ethnicity	Green	Green	Green	Green	Green
Sex	Green	Green	Green	Green	Green
Previous hypoglycemia-related ED enc.	White	Green	Green	Green	Green
Previous hypoglycemia during admission	Green	Green	Green	Green	White
Gastric bypass surgery	Green	White	Green	Green	Green
SGLT-2	Green	Green	White	Green	Green
TZD	White	Green	White	White	White
TCA	White	Green	White	White	White
Cognitive disease	White	Green	White	White	White
Alcohol use	White	White	White	White	Green

Model Performance: AUC

- Area under the curve
- Healthcare models: > 0.8 is desirable
- Previous hypoglycemic risk models: 0.83
- At Parkview:
 - All-cause ED encounters or all-cause hospital admissions: 0.75
 - ED or hospital encounters for hypoglycemia: 0.82

Model Performance: Precision and Recall

- **Precision:** What proportion of positive identifications was actually correct?
- **Recall:** What proportion of actual positives was identified correctly?

	All-Cause Encounters		Hypoglycemia-Related Encounters	
	ED Encounters	Hospital Admissions	ED Encounters	Hospital Admissions
Precision	0.49	0.21	0.01	0.03
Recall	0.54	0.54	0.67	0.60

Discussion/Limitations

- ED and hospital encounters as a PROXY
 - Ideally prevent all hypoglycemic events, not just in “measurable locations”
- Limited by numbers
- Data from 2019 and 2020
 - Final version would be “real-time” data

Future Directions

Implementation into Parkview Health EHR

Guide for physicians

Interventions

- Continuous glucose monitor
- Hypoglycemia education
- Medication modification
 - Glucagon prescription
- Referral
 - Dietician
 - Diabetes education
 - Endocrinology
 - Ambulatory Care Pharmacist

Conclusion

- Many known hypoglycemia risk factors
- Factors are unique to each patient
- Predictive model helps determine unique AND specific risk—helps guide therapy

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