

SUPPLEMENTAL MATERIAL:

TABLE S1: Diagnostic Performance Characteristics for the Prediction of 6 to 12-Month DKA of of Baseline Capillary Ketone Levels Comparing the Methods of Multivariable Logistic Regression and Gradient-boosted Machine Learning.

Definition	Parameter*	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Multivariable Logistic Regression							
Parameter favoring Sensitivity	0.02687631	100%	54%	6%	100%	2.2	0
	0.02764701	91%	63%	7%	99.5%	2.5	0.1
	0.02894822	82%	72%	8%	99%	2.9	0.3
	0.02900737	73%	72%	7.5%	99%	2.6	0.4
	0.02937560	64%	74%	7%	99%	2.5	0.5
Parameter favoring Specificity	0.03178361	55%	85%	10%	98%	3.7	0.5
Optimal Parameter	0.02894822						
Gradient-Boosted Trees							
Parameter favoring Sensitivity	0.021557570	100%	72%	10%	100%	3.5	0
	0.035842448	91%	77%	11%	99.6%	4.0	0.1
	0.045249164	82%	81%	12%	99%	4.3	0.2
	0.051601917	73%	82%	11%	99%	4.1	0.3
	0.057568878	64%	83%	11%	99%	3.8	0.4
Parameter favoring Specificity	0.087452292	55%	92%	18%	99%	6.9	0.5
Optimal Parameter	0.035842448						

*Parameter is a probability value derived from the MVLr and GBT models (model-based probability)

Table S2
Case definitions for ketoacidosis adjudication:

	Certain KA		Potential KA					Unlikely KA	Unlikely KA but ketosis	Unclassifiable
pH	≤7.3	N/A	≤7.3	N/A	N/A	N/A	N/A	Blood BHB ≤1.5 and/or pH >7.3 (if pH N/A, then bicarb. >18)	Blood BHB >1.5 to <3.8 and one of the below: - pH >7.3 - bicarb. >18 (if pH N/A) - no hist. ^{3/} sympt. reported ⁴	If only one of the below is available: - pH ≤7.3 - bicarb. ≤18 - suggestive hist. ³ - typical sympt. ⁴
Bicarb. [mEq/L]	<15		≤18	15 to 18	N/A	N/A	N/A			
Blood BHB [mmol/L]	>1.5	>1.5	>1.5		>1.5	>1.5	≥3.8 ¹			
Urine ketones when blood BHB N/A ²	≥++	≥++	≥++		≥++	≥++	++++			
Suggestive history ³ or typical KA symptoms reported ⁴			Y	Y		Y				
CEC assessment of case category	X	X	X	X	X	X	X	X	X	X

Legend:

Please see Figure S2 for Overview of Outcome Classification.

KA = ketoacidosis; N/A = data not available

1. For potential KA, a blood BHB value ≥3.8 mmol/L was to be confirmed by an additional measurement ≥3.8 mmol/L within 24 h. A single BHB value ≥3.8 mmol/L without symptoms/suggestive history was to be regarded as unlikely KA but ketosis.

2. ++/+++ is equivalent to moderate/large, which translates to 1.5 to 2.9 mmol/L blood BHB; ++++ is equivalent to very large, which translates to ≥3 mmol/L blood BHB.

3. Suggestive history means pump failure, insulin dose omission, illness, improper sick day plan, etc.

4. Typical KA symptoms means neurological (confusion, drowsiness, loss of consciousness, etc.) and non-neurological symptoms (dehydration, nausea/vomiting, abdominal pain, kussmaul breathing, etc.).

The occurrence of 2 BHB values ≥3.8 mmol/L within 60 min constituted clinically the same reading, it was required that 2 BHB values ≥3.8 mmol/L within 24 h be separated by more than 60 min (in the absence of any other parameters) to fulfil the criterion needed for the classification of such an event as potential ketoacidosis.

The CEC assessed ketoacidosis severity using pH per ADA criteria as the primary differentiator (mild: pH 7.25 to 7.30; moderate: pH 7.00 to 7.24; severe: pH <7.00). If pH was not available then bicarbonate level was used (mild: 15 to 18 mEq/L; moderate: 10 to <15 mEq/L; severe: <10 mEq/L). If bicarbonate values were also not available, then the degree of neurological symptoms was to be used (mild: alert; moderate: alert/drowsy; severe: stupor/coma). Note that the final case assessment was at the discretion of the CEC members and allowed deviations from the above definitions of severity, if needed.

FIGURE S1:
Receiver Operating Characteristic (ROC) Curve for the Prediction of 6 to 12-Month DKA of Baseline Capillary Ketone Levels Comparing the Methods of Gradient-boosted Tree (GBT) and Multivariable Logistic Regression (MVLRL) Machine Learning.

AUC, Area Under the Curve for the Receiver Operating Characteristic Curve.

Figure S2:**KETOACIDOSIS EVENT IDENTIFICATION AND CASE CATEGORIZATION BASED ON ADJUDICATION: Summary of ketoacidosis trigger identification, adjudication parameters and case definitions:****Legend:**

*2 BHB readings ≥ 3.8 mmol within 24 hours in the absence of symptoms to fulfill the criterion of potential ketoacidosis

The following are details related to triggers which were used to identify potential ketoacidosis events that were sent for adjudication:

- Any AE where the electronic case report form tick box 'ketoacidosis' had been ticked
- Selected trigger search terms indicative of ketoacidosis and/or DKA
- Selected trigger search terms indicative of acetonemia, when accompanied by reported symptoms suggestive of ketoacidosis, accompanied by a report of hospitalization, and/or reported as an SAE
- Any BHB value >1.5 and <3.8 mmol/L, when accompanied by reported symptoms suggestive of ketoacidosis, accompanied by a report of hospitalization, and/or reported as an SAE
- Any BHB value ≥ 3.8 mmol/L, based on laboratory data (any source) and investigator-confirmed readings from the e-diary

Single or multiple triggers consisting of BHB values >1.5 and <3.8 mmol/L without accompanying typical ketoacidosis symptoms, hospitalization, or SAE reporting were classified as ketosis and did not undergo adjudication. In addition to the events identified using the triggers above, a periodic review was performed of all AEs to identify additional events for adjudication.

The events identified by the triggers or by periodic review were adjudicated by the CEC according to the case definitions defined in c, taken from the CEC Charter for Ketoacidosis and Severe Hypoglycaemia Events.

Case definitions for ketoacidosis adjudication:

KA = ketoacidosis; N/A = data not available

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3. Suggestive history means pump failure, insulin dose omission, illness, improper sick day plan, etc.
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The occurrence of 2 BHB values ≥ 3.8 mmol/L within 60 min constituted clinically the same reading, it was required that 2 BHB values ≥ 3.8 mmol/L within 24 h be separated by more than 60 min (in the absence of any other parameters) to fulfil the criterion needed for the classification of such an event as potential ketoacidosis.

The CEC assessed ketoacidosis severity using pH per ADA criteria as the primary differentiator (mild: pH 7.25 to 7.30; moderate: pH 7.00 to 7.24; severe: pH < 7.00). If pH was not available then bicarbonate level was used (mild: 15 to 18 mEq/L; moderate: 10 to < 15 mEq/L; severe: < 10 mEq/L). If bicarbonate values were also not available, then the degree of neurological symptoms was to be used (mild: alert; moderate: alert/drowsy; severe: stupor/coma). Note that the final case assessment was at the discretion of the CEC members and allowed deviations from the above definitions of severity, if needed.