Continuous Glucose Sensors in Diabetes

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DirecNet

DIABETES RESEARCH IN CHILDREN NETWORK

DirecNet

- NIH funded collaborative study group
- Objective: to critically evaluate the clinical usefulness of current and future glucose sensors in youth with TIDM

Centers in DirecNet

- Coordinating Center
  - Jaeb Center for Health Research, Tampa, FL
- Clinical Centers
  - University of Colorado: Denver, CO
  - Children's Hospital of Iowa: Iowa City, IA
  - Nemours Children's Clinic: Jacksonville, FL
  - Stanford University: Stanford, CA
  - Yale University: New Haven, CT

Questions

- What criteria should be used for approval of new sensors?
- Can continuous glucose monitoring data be used as outcome measures for evaluation of the safety and efficacy of new diabetes treatments?

The answer to both questions depends on

SENSOR ACCURACY

DirecNet Inpatient Accuracy

Cygnus Glucowatch Biograpgher II

Medtronic MiniMed CGMS

DirecNet Inpatient Accuracy Study

Assess the accuracy of the GWB2 and the CGMS in comparison with reference, central laboratory, plasma glucose measurements in an inpatient setting in diabetic children.

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Inpatient Accuracy Study Procedures

- 90 Subjects, age 1- 17
- 26 hour in-patient CRC Admission
- Reference BG q1hr day, q30min night
- 1-2 CGMS and GWB worn simultaneously
- Spontaneous BG, Hyper- and Hypoglycemia

DirecNet Inpatient Accuracy Study

Principal Measures of Accuracy in DirecNet Study

Point to Point Differences between Sensor and Reference Glucose Levels

- Difference
- Absolute difference
- Relative difference
- Relative absolute difference (RAD)**

** [sensor-reference]/reference x100=%RAD

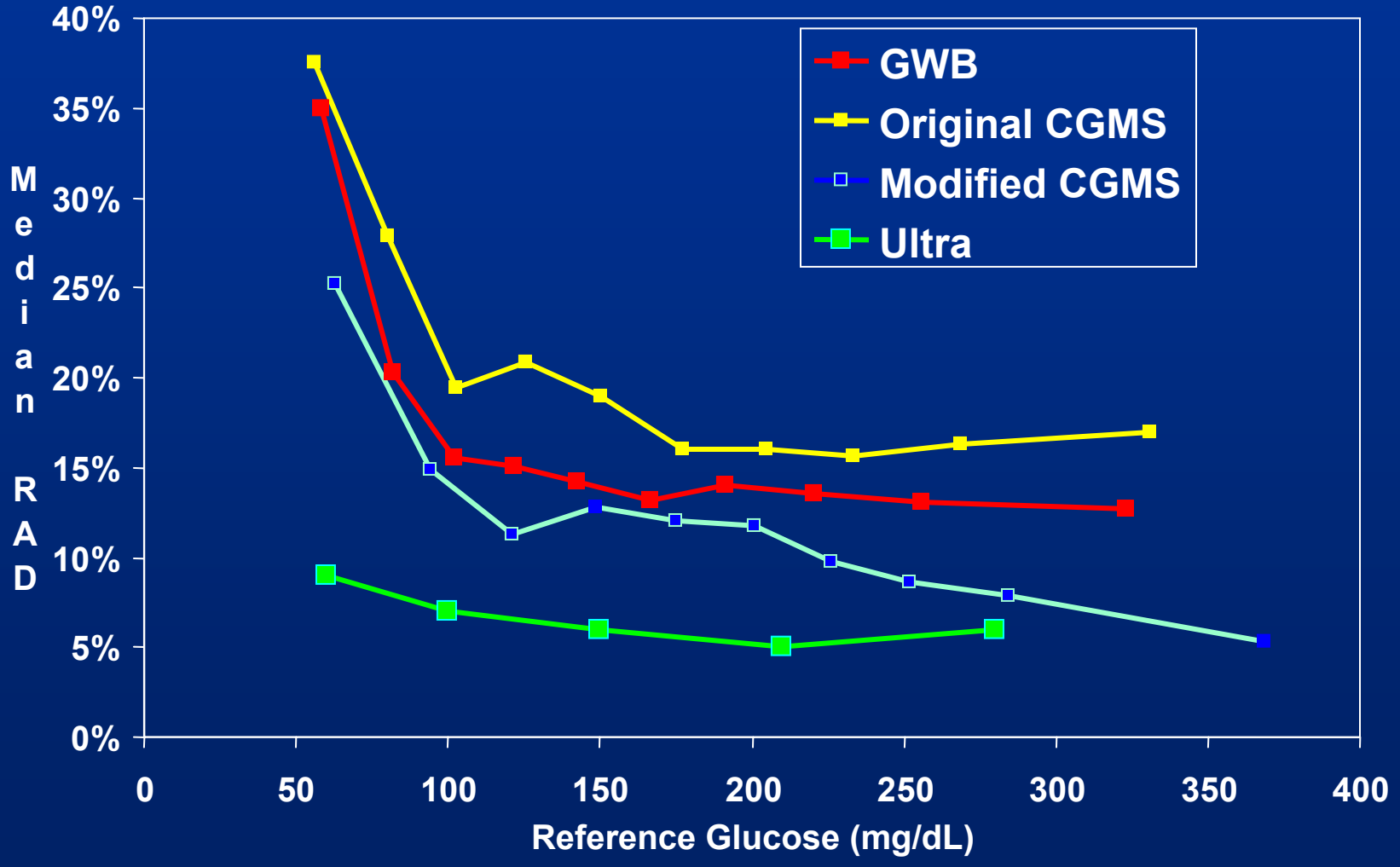
ISO Criteria

- If reference glucose > 75 mg/dL, sensor glucose within ± 20%;
- If reference glucose ≤ 75 mg/dL, sensor glucose within ± 15 mg/dL;
- Data expressed as the % of paired values meeting criteria

Results

	n	r	Mean RAD	Median RAD	within ISO
GW2	3,672	0.86	22%	16%	60%
CGMS (original)	5,658	0.77	26%	19%	53%
CGMS (modified)	1,120	0.92	16%	11%	72%
Ultra	2,068	0.97	7%	6%	94%

Effect of Glucose Concentration on Accuracy - Assessed by Median RAD%



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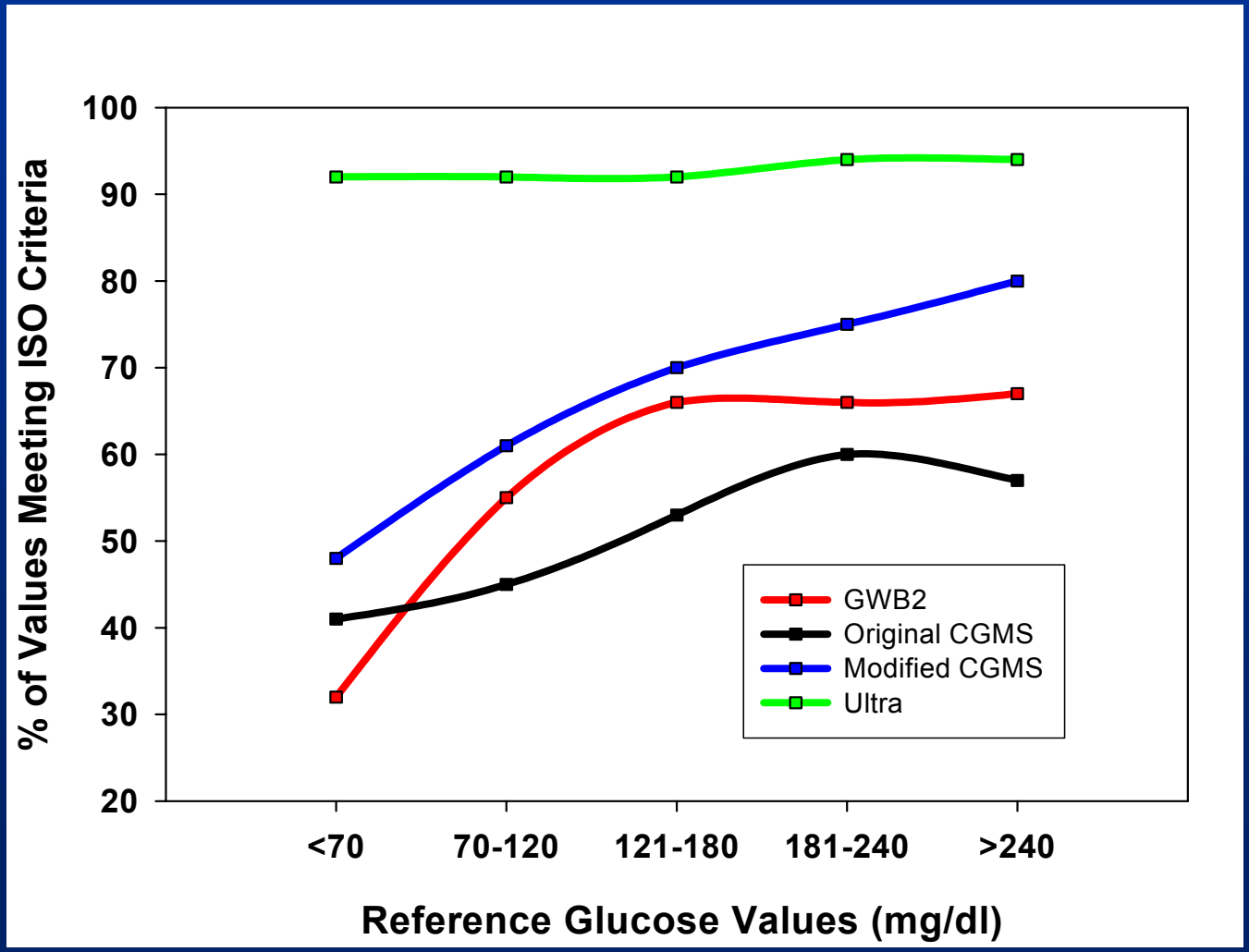


Detection of Hypoglycemic Events

Reference Glucose <60 mg/dl (IV insulin)

	GWB2	CGMS (orig)	CGMS (mod)
# events	48	51	3
#detect by sensor	12	26	2

Sensor Glucose <60/mg/dl at night

# events	18	26	3
#confirmed by ref.	10	8	3

GW2 Sensitivity and False Alarm rate for detection of hypoglycemia

Alarm Setting (mg/dl)	Sensitivity	False Alarm Rate
60	23%	51%
80	59%	67%
100	84%	80%
120	92%	85%

Hypoglycemia Sensitivity and False Alarm Rate Modified CGMS

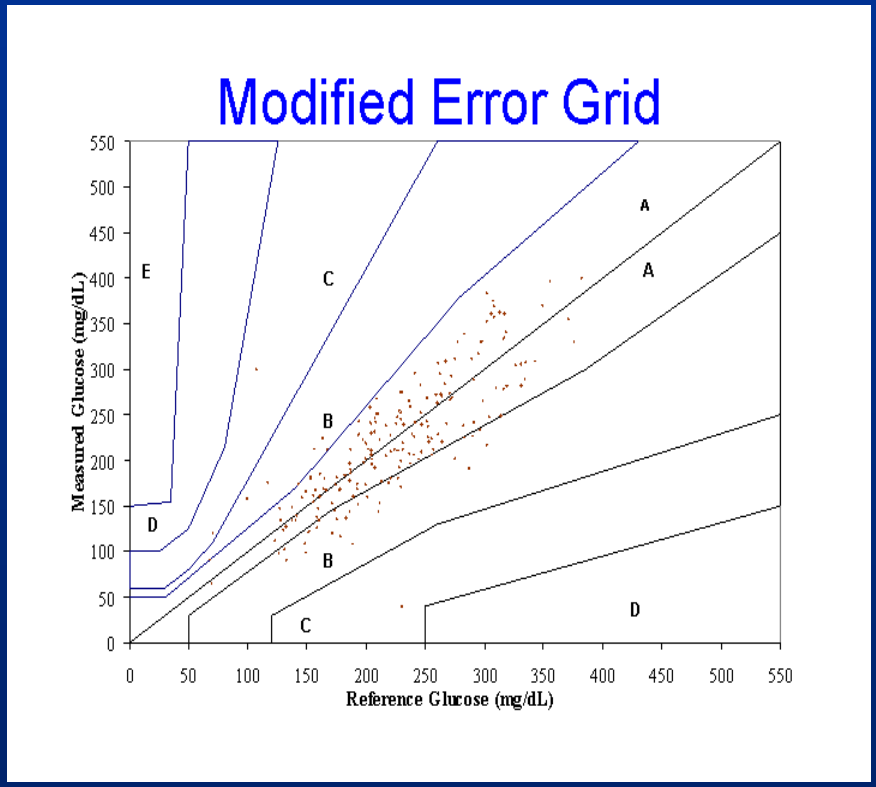
Alarm Setting (mg/dl)	Sensitivity	False Alarm Rate
60	49%	58%
80	84%	64%
100	100%	75%
120	100%	84%

Other Point-to-Point Measures To Validate Accuracy

- Clark Error Grid Analysis
- R values (correlations)

Error Grid Analysis

- Purpose to distinguish clinically meaningful vs. less important errors in glucose measurements.
- Divides measurement errors into zones to distinguish increasing clinical significance of errors.



- Sensor accuracy often measured by the percentage of points falling in zones A+B.

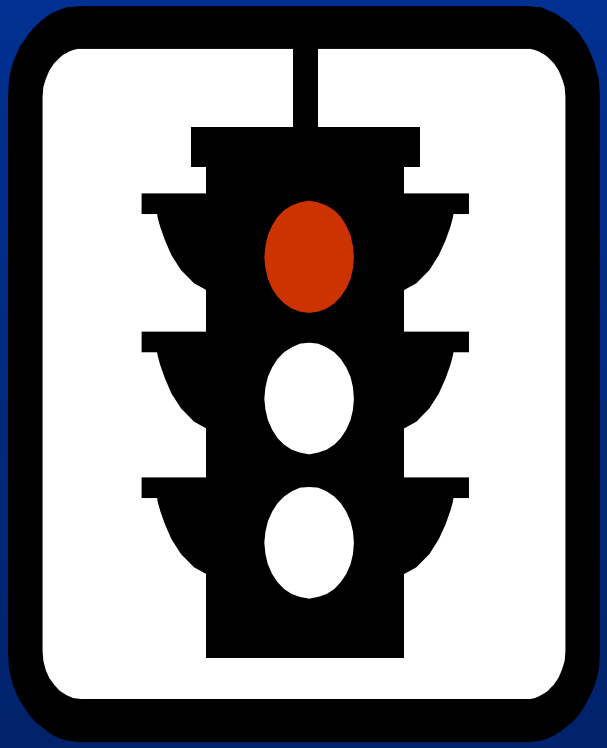
Problems with Error Grid Analysis

- Zones A and B on error grids are large enough that even inaccurate sensors will hit them the majority of the time.
- Current insulin dose adjustments based on much smaller variations in glucose than in past
- Can give a misleading notion of sensor accuracy through chance agreement.

When we randomly shuffled sensor and reference glucose pairings (10,000 simulations) A&B zone=76%

Correlation Analyses

Value limited because r's sensitive to amount of variation in glucose levels



R value simulations

- 4 simulated sensors, each has identical accuracy.
- Sensor value equal to the “true” value plus a normally distributed error with standard deviation = 25 mg/dL.
- Vary the range of true glucose values for each sensor.

Simulated Sensors with Identical Accuracy

(N = 10,000 data pairs per sensor)

Sensor	Range of True Glucose	Pearson Correlation
1	175-225	0.50
2	150-250	0.76
3	100-300	0.92
4	50-350	0.96

Limitations of Point-to Point Assessments of Accuracy

- Do not capture the near continuous nature of glucose sensors.
- Difficult to assess trends.
- How well do sensors characterize acute changes in glucose?

Possible physiologic contributions to "error" between plasma and sensor glucose levels

- Variability in plasma and interstitial glucose gradients
  - Euglycemic-hyperinsulinemic clamp increases plasma to interstitial gradient and lowers sensor glucose levels
- Lag time between plasma and interstitial glucose levels

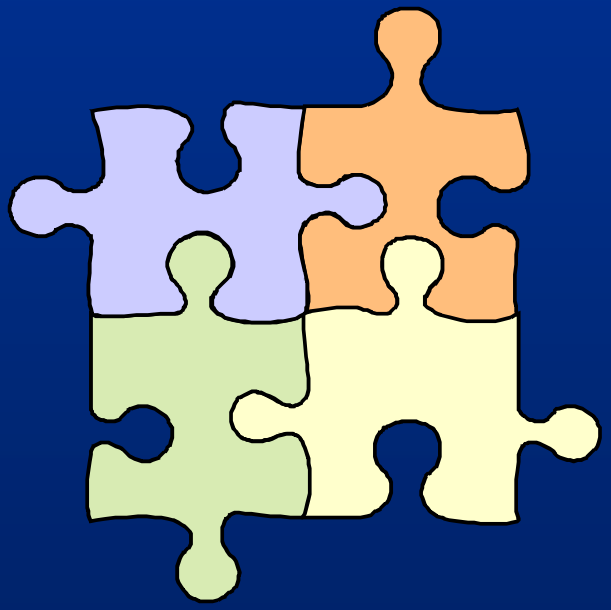
Future Accuracy Study Designs

- Diverse populations
  - Age, non-diabetes, type 1, type 2, hypoglycemic disorders, post-transplant
- Inpatient study with frequent sampling
  - CLIA-certified laboratory methods
- Collection of out-patient accuracy data
  - Is a well characterize meter sufficient?

Future Studies: Beyond Accuracy

- Will the use of sensor systems in clinical management lower HbA1c levels and/or the risk of hypoglycemia?
- Will patients use them?
- How will patients and clinicians deal with reams of data from 24/7 sensor systems? Who will support the effort required to implement and effectively utilize these technologies?

Other part of the puzzle: Are current sensors accurate enough as outcome measures for diabetes therapy?



Answer depends on what you are measuring

Mean glucose values

- Yes, but
- HbA1c values easier and better

Hyperglycemia

- Yes, current sensors are reasonably accurate in hyperglycemic range
- CGMS data are masked to patient
- Metrics: meal related excursions, AUC or time of day above cut-offs, etc

Glycemic Variability

- Sensors provide a good measure of glucose variability
- Metrics: MAGE, M-value, SDS, etc.

Unanswered Therapeutic Question: What is the clinical significance of changes in variability and/or reductions in hyperglycemia independent of changes in HbA1c levels?

Hypoglycemia

- No
- Current Systems Not Accurate Enough

Promise of the Future

Closed-loop artificial pancreas

The Guardian- Continuous Glucose Monitoring with Telemetry

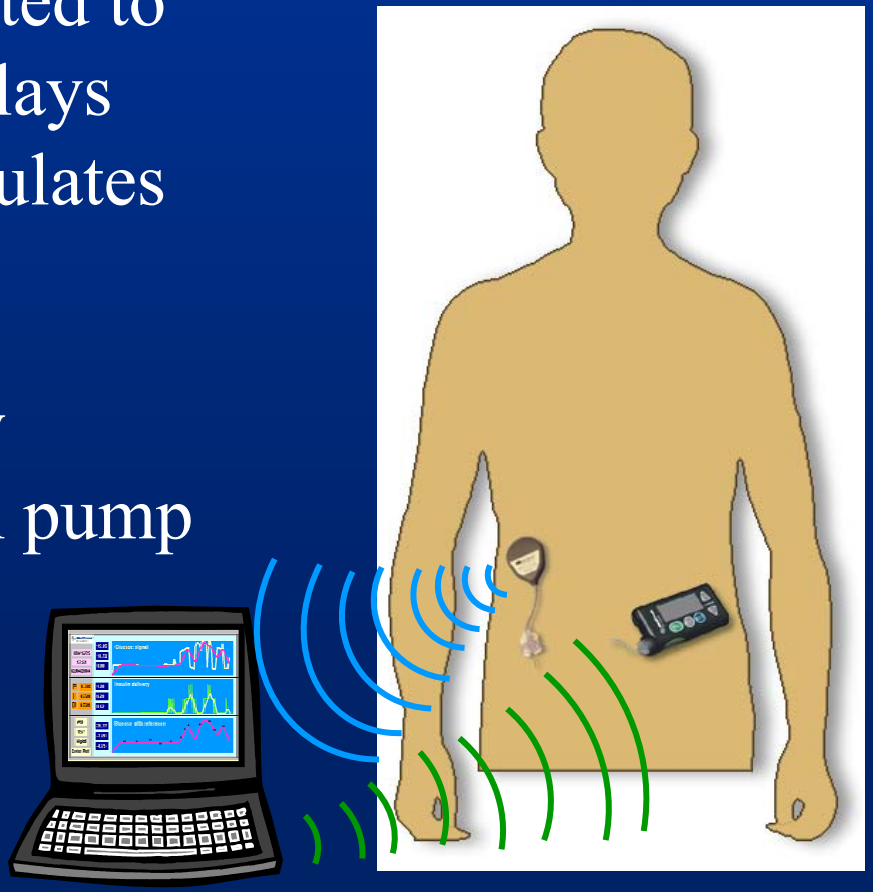
- “Real time” glucose readings
- Wireless communication from sensor to monitor
- High and low glucose alarms

Closed-loop Development System

Sensor signals are transmitted to a laptop computer that displays the sensor glucose and calculates rate of insulin delivery.

The rate of insulin delivery is transmitted to the insulin pump

Final System:
Signal from Sensor to Pump



Sensor-regulated overnight insulin delivery

Greatest danger:

- Sensor glucose> plasma glucose
- Extra insulin infused when true glucose normal

Solution:

- Set target value at 120 mg/dl
- If sensor> plasma by 50%
  - Back to basal insulin infusion at plasma glucose of 80 mg/dl
- If sensor> plasma by 100%
  - Back to basal insulin infusion at plasma glucose of 60 mg/dl