THE ARTIFICIAL PANCREAS:

Models, Signals, and Control in Diabetes

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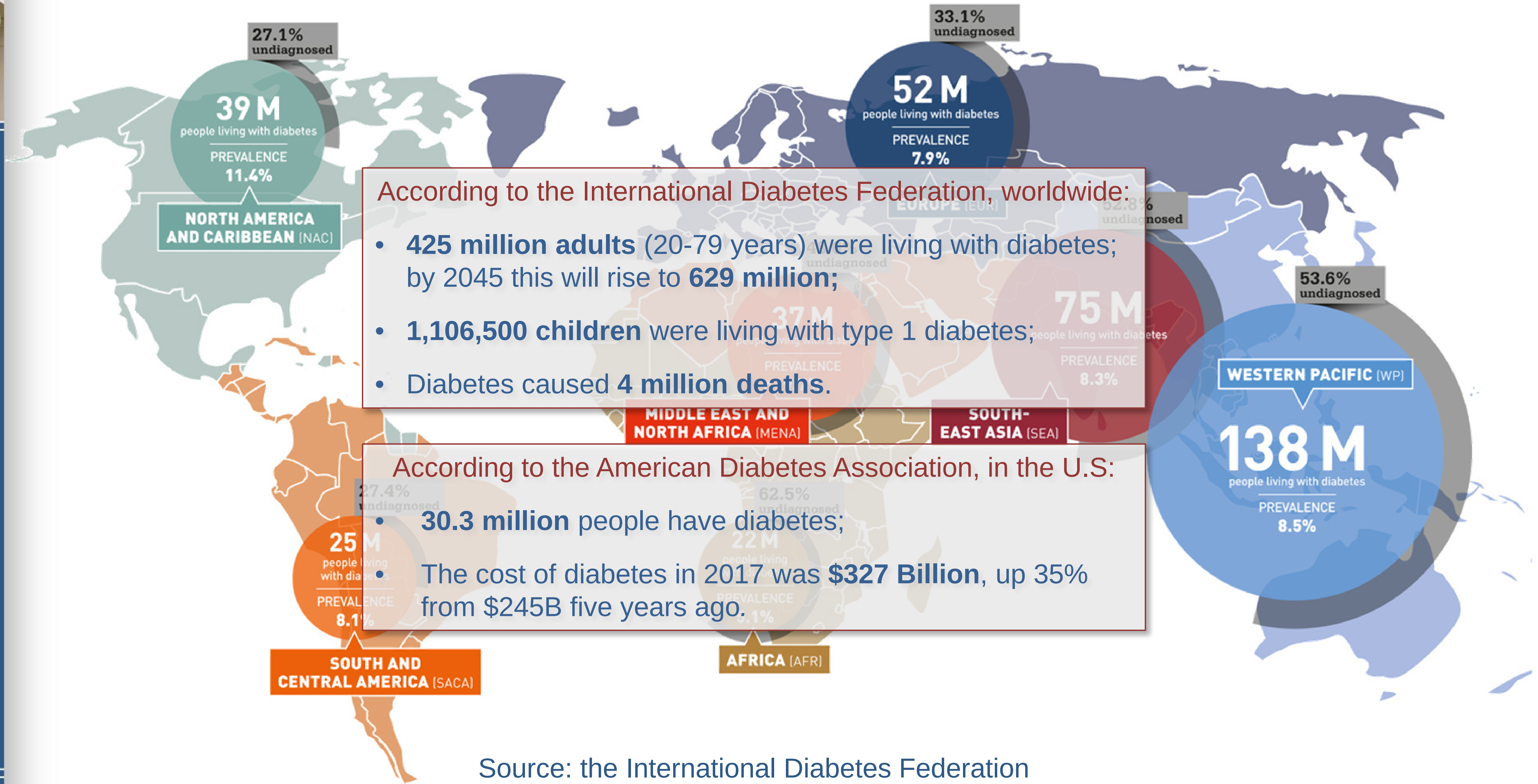
The Map of Diabetes in 2017



According to the International Diabetes Federation, worldwide:

- **425 million adults** (20-79 years) were living with diabetes; by 2045 this will rise to **629 million;**
- **1,106,500 children** were living with type 1 diabetes;
- Diabetes caused **4 million deaths.**

According to the American Diabetes Association, in the U.S:

- **30.3 million** people have diabetes;
- The cost of diabetes in 2017 was **$327 Billion**, up 35% from $245B five years ago.

Source: the International Diabetes Federation

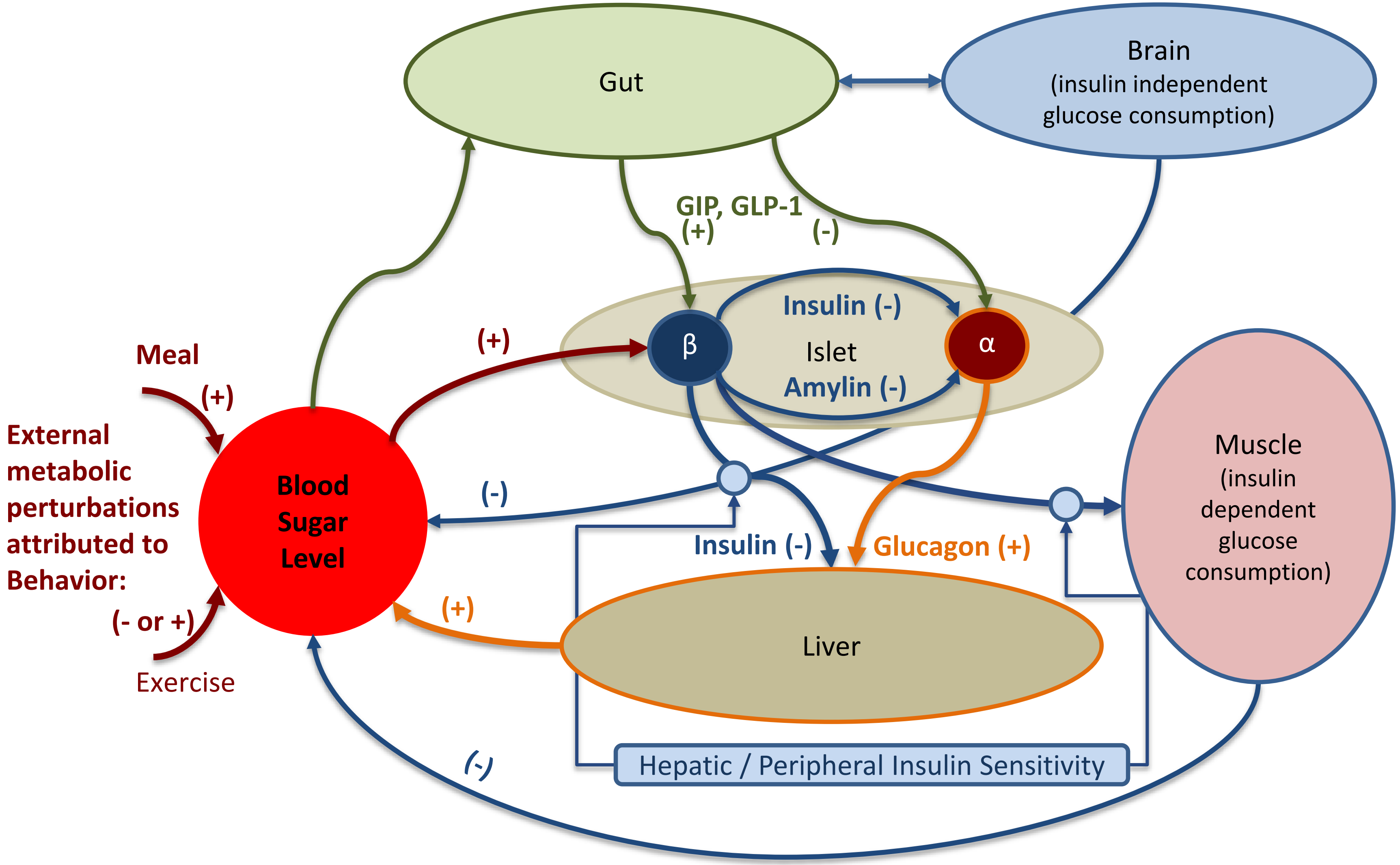
IN THIS PRESENTATION:

- ✓ Metabolic models – *in silico* pre-clinical trials replacing animal studies;
- ✓ The Artificial Pancreas – automated closed-loop control of diabetes – and the International Diabetes Closed Loop (iDCL) Trial;
- ✓ Diabetes Data Science – UVA's PrIMeD project.

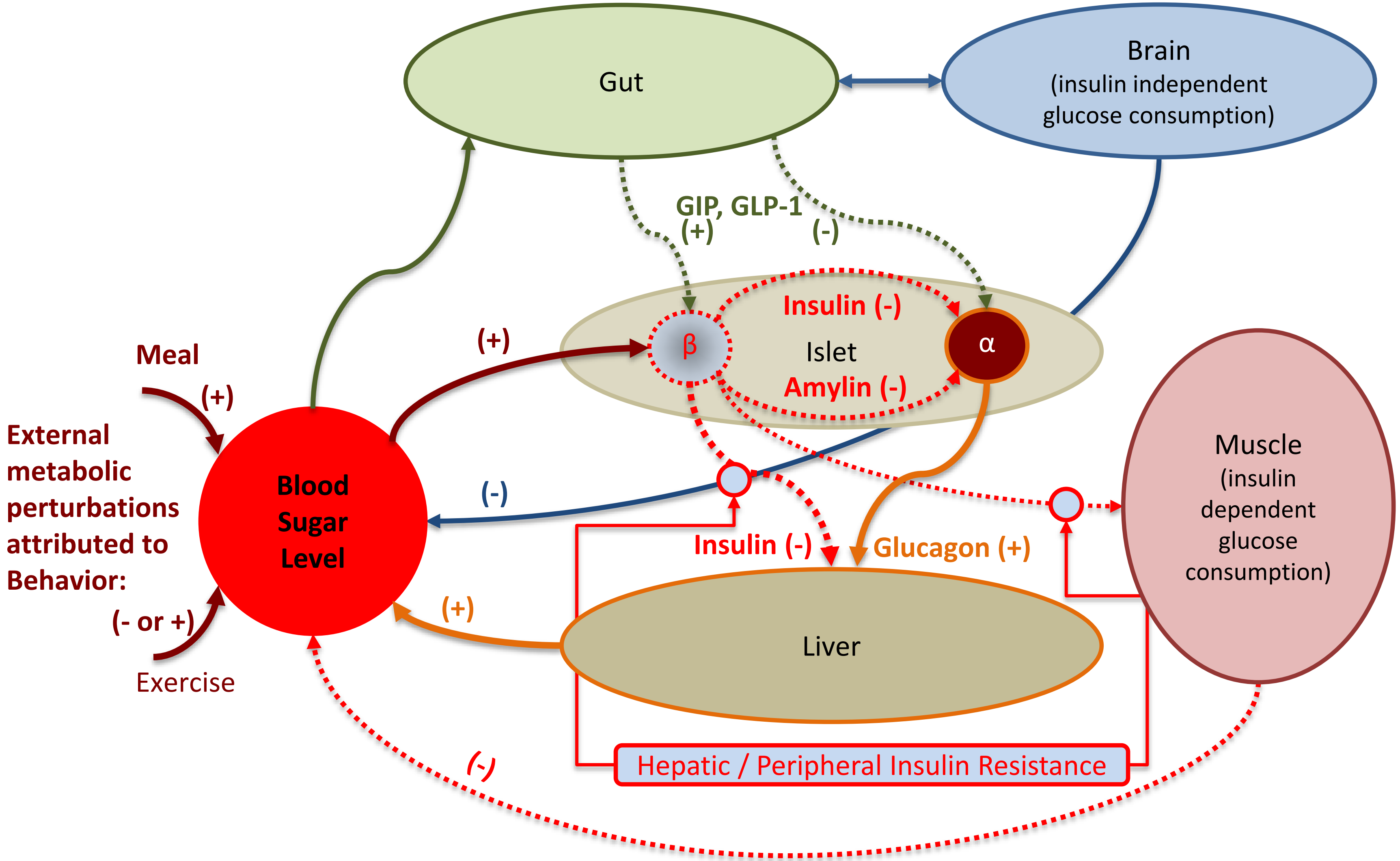
Models and *In Silico* Pre-clinical Trials

All models are wrong, but some are useful (George E.P. Box)

Step 1: Understand The Human Glucose Control Network in Health



Step 2: Identify Metabolic Network Deviations in Diabetes



Gut

Brain
(insulin independent
glucose consumption)

GIP, GLP-1
(+)
(-)

Insulin (-)

β

Islet

α

Amylin (-)

Meal
(+)

External
metabolic
perturbations
attributed to
Behavior:

(- or +)

Exercise

(+)

Blood
Sugar
Level

(-)

Insulin (-)

Glucagon (+)

Muscle
(insulin
dependent
glucose
consumption)

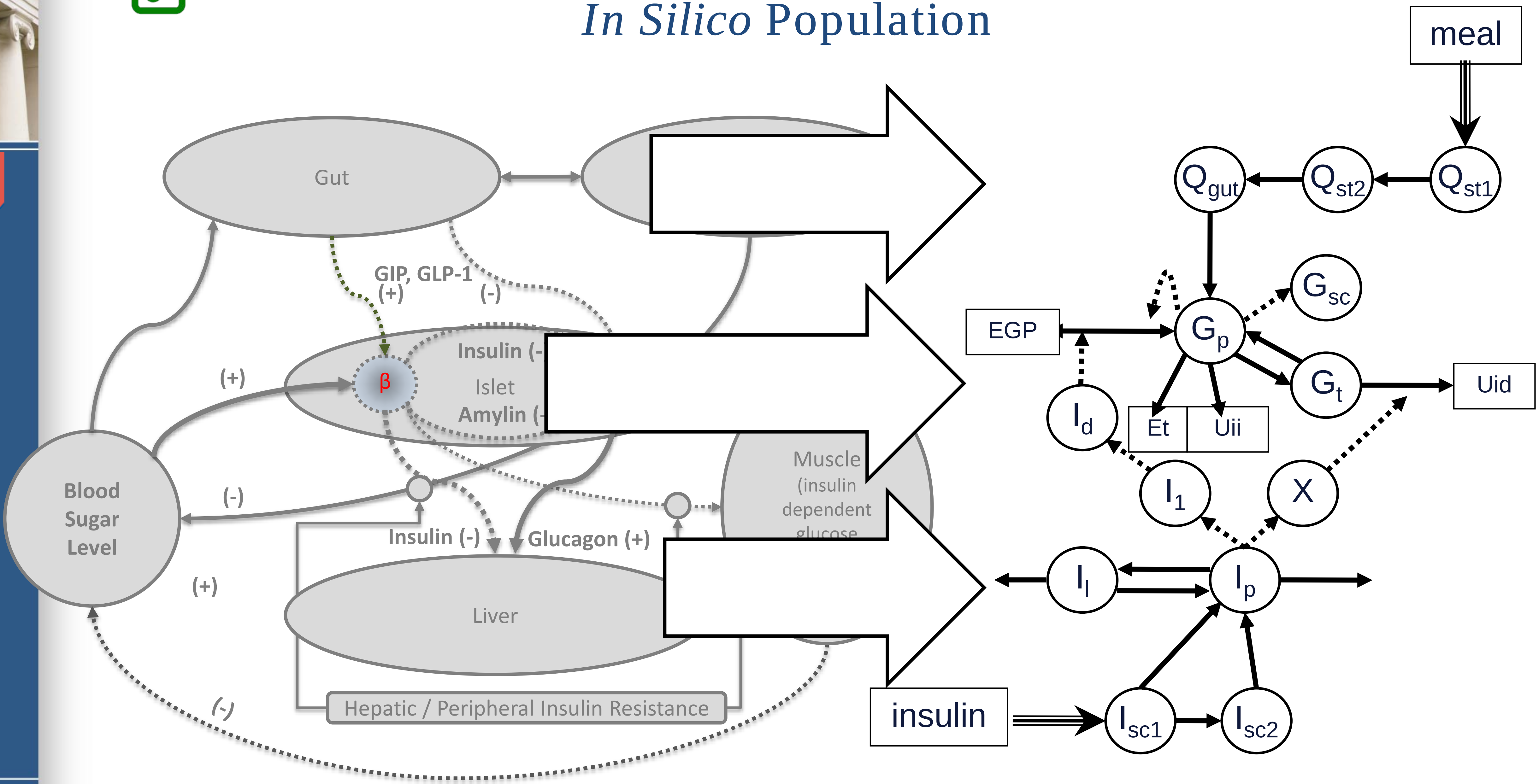
(+)

Liver

Hepatic / Peripheral Insulin Resistance

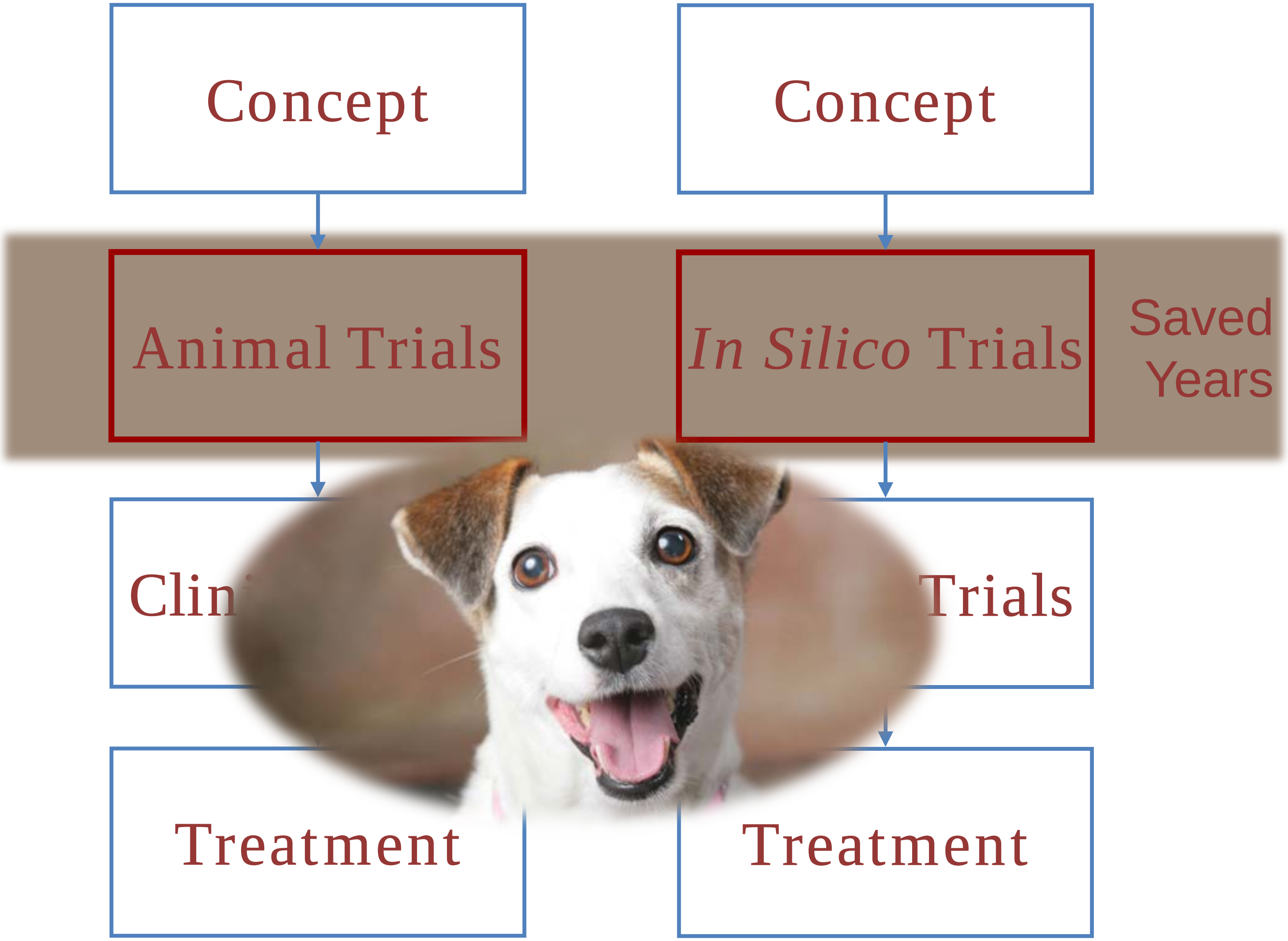
(-)

<u>Step 3:</u> Build a Quantitative Model and Create *In Silico* Population



Step 4: Evaluate Treatment Options in Computer Simulation to Enable/Optimize Clinical Trials

- Metabolic simulation environment introduced in 2008 and continually developed since;
- Equipped with 300 virtual "subjects" in three age groups. Each virtual "subject" can be screened, measured, and treated;
- FDA Label: Accepted for approximation of human glucose/insulin utilization, interstitial sensor performance, and subcutaneous insulin delivery;
- Accepted as a substitute to animal trials for the pre-clinical testing of insulin treatments and artificial pancreas algorithms.



Concept

Animal Trials

Clin

Treatment

Concept

In Silico Trials

Trials

Treatment

Saved Years

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The Artificial Pancreas

Any sufficiently advanced technology is indistinguishable from magic (Arthur C. Clarke)

The Optimization Problem of Diabetes:

Blood Sugar Level <50 mg/dl (very low!)

✓

Blood Sugar Level 90-100 mg/dl (normal)

> 180 mg/dl (high)

Diabetes Technology Timeline:

Iletin, Eli Lilly & Co, 1923

Backpack insulin & glucagon pump

Intravenous glucose control:

Albisser et al; Mirouze, Selam et al. Pfeiffer et al.

The Minimal Model of Glucose Kinetics. Bergman & Cobelli, 1979

Subcutaneous Continuous Glucose Monitoring

Minimed CGMS, 1999

Blood glucose meters & insulin pumps becoming smaller

1920s

1960s

1970s

1980s

1990s

2000s

Models of diabetes becoming larger & more complex

Insulin discovered Frederick Banting

The Auto Syringe (Dean Kamen)

Ames Reflectance Meter

First use of s.c. insulin pump

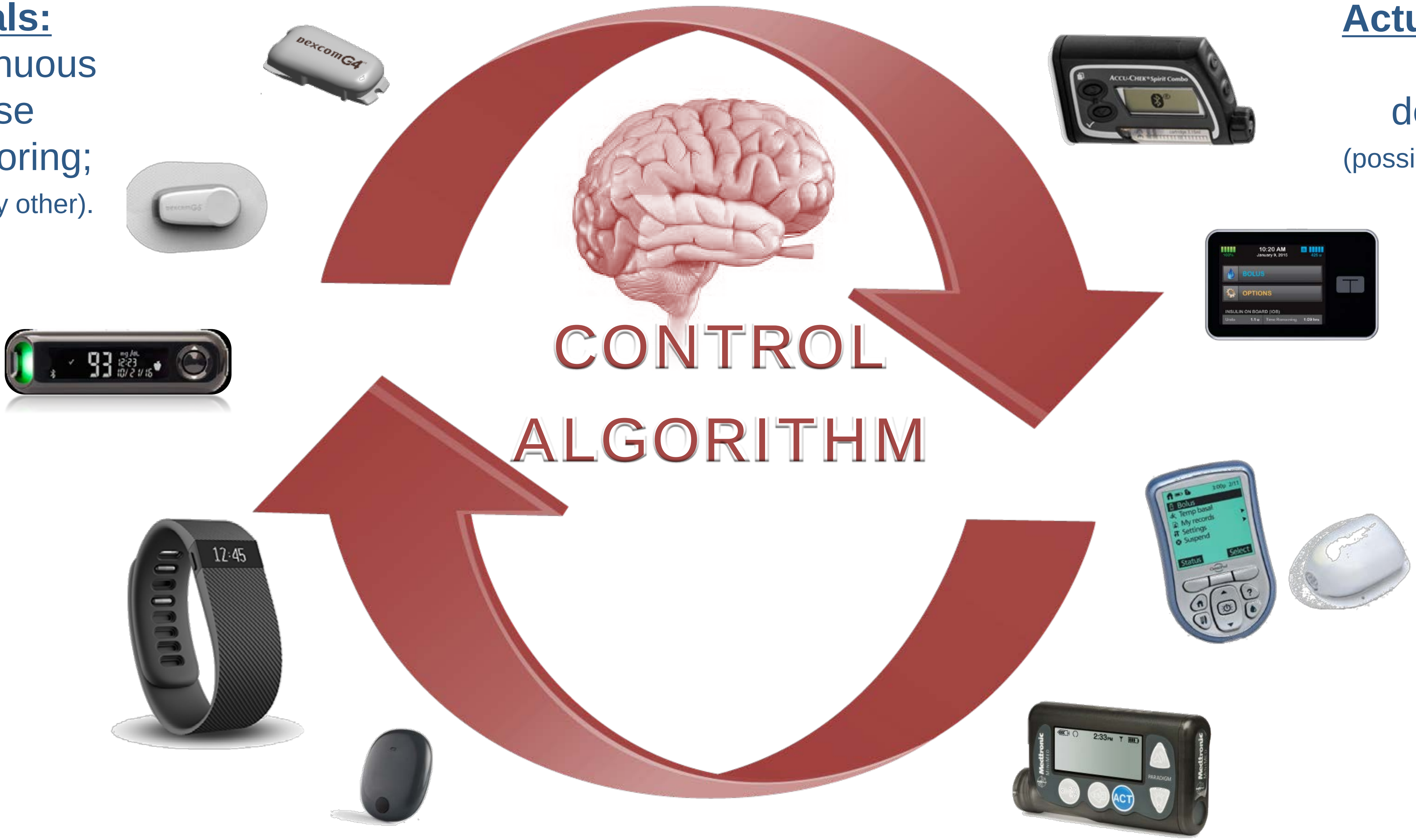
Tamborlane et al; Pickup et al.

Risk Analysis of blood glucose fluctuations. Kovatchev et al. 1997-98

Automated Closed-Loop Control of Diabetes

Signals:
Continuous glucose monitoring;
(possibly other).

Actuators:
Insulin delivery;
(possibly other).



2008-2010: First Inpatient Studies

- Linked continuous glucose sensor and insulin pump
- Automated insulin delivery using a control algorithm

2012: First Wearable AP Introduced by UVA

- The Diabetes Assistant (DiAs) ran on a smart phone;
- Linked wirelessly glucose sensor and insulin pump;
- Automated and optimized insulin delivery.

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17 May 2012

nature

DIABETES OUTLOOK

Closed-loop algorithms can run on smartphones; this version shows insulin delivery and glucose level.

Health, formed the Interagency Artificial Pancreas Working Group to identify and work through any clinical and scientific challenges. Meanwhile, government funding bodies in the United States and Europe, as well as many medical device companies, started spending tens of millions of dollars to encourage the development of an artificial pancreas.

In the wake of rapid progress, a handful of independent research groups launched human clinical trials, and several algorithms are being tested (see 'Control issue'). For the most part, studies have been conducted under the controlled confines of the hospital setting, often with participants hooked up to laptop computers and intravenous backup systems that limit their mobility, as Moynihan was. But some investigators have taken their devices to the next level.

At the Princess Margaret Hospital for Children in Perth, Australia, Medtronic is running its algorithm on a BlackBerry smartphone. In Italy and France, researchers are using mobile phones and tablet computers to conduct trials in hotels — not hospitals — with doctors and engineers in separate rooms in case safety problems arise. "The patients wanted to go home with it," says Eric Renard, a diabetes specialist at Montpellier University Hospital in France who is leading the hotel-based trial. "After only a few hours, they say they're completely different. Never before have they had this feeling that they don't have to think about their disease." In March 2012, the FDA approved a similar trial using the same technology at the University of

speed up insulin delivery or slow down glucose absorption will help."

A RISKY PROPOSITION

Although developers of artificial pancreases have differing opinions about the best closed-loop design, all agree that safety must remain a top priority as more authority is handed over to the device. "Hypoglycaemia is extraordinarily dangerous. You lose consciousness and then you have seizures and you die if someone doesn't help you," warns Steven Russell, a diabetes specialist at MGH who is collaborating with Damiano on the trials in Boston. "Giving over control entirely to a machine is a high-risk proposition," he says, making it imperative that the process be "done properly".

To help make the safe transition to a fully closed-loop system that requires minimal human input, many experts and companies are advancing hybrid control algorithms that are only partly automated. "We want to take iterative steps to closing the loop," says John Mastrototaro, vice-president of global medical, scientific and health affairs at Medtronic's diabetes division in Northridge, California.

The first such product could be Medtronic's Paradigm Veo, an insulin pump that automatically turns off when a sensor reports that glucose levels have fallen below a certain level. Already available in Europe, this 'low glucose suspend' system is now undergoing in-home testing in the United States, and is expected to receive regulatory approval in 2013.

Subsequent partly automated systems will

2013: First International Multi-Site Feasibility Trials of Outpatient Closed Loop Control

Charlottesville,
Virginia


[redacted]

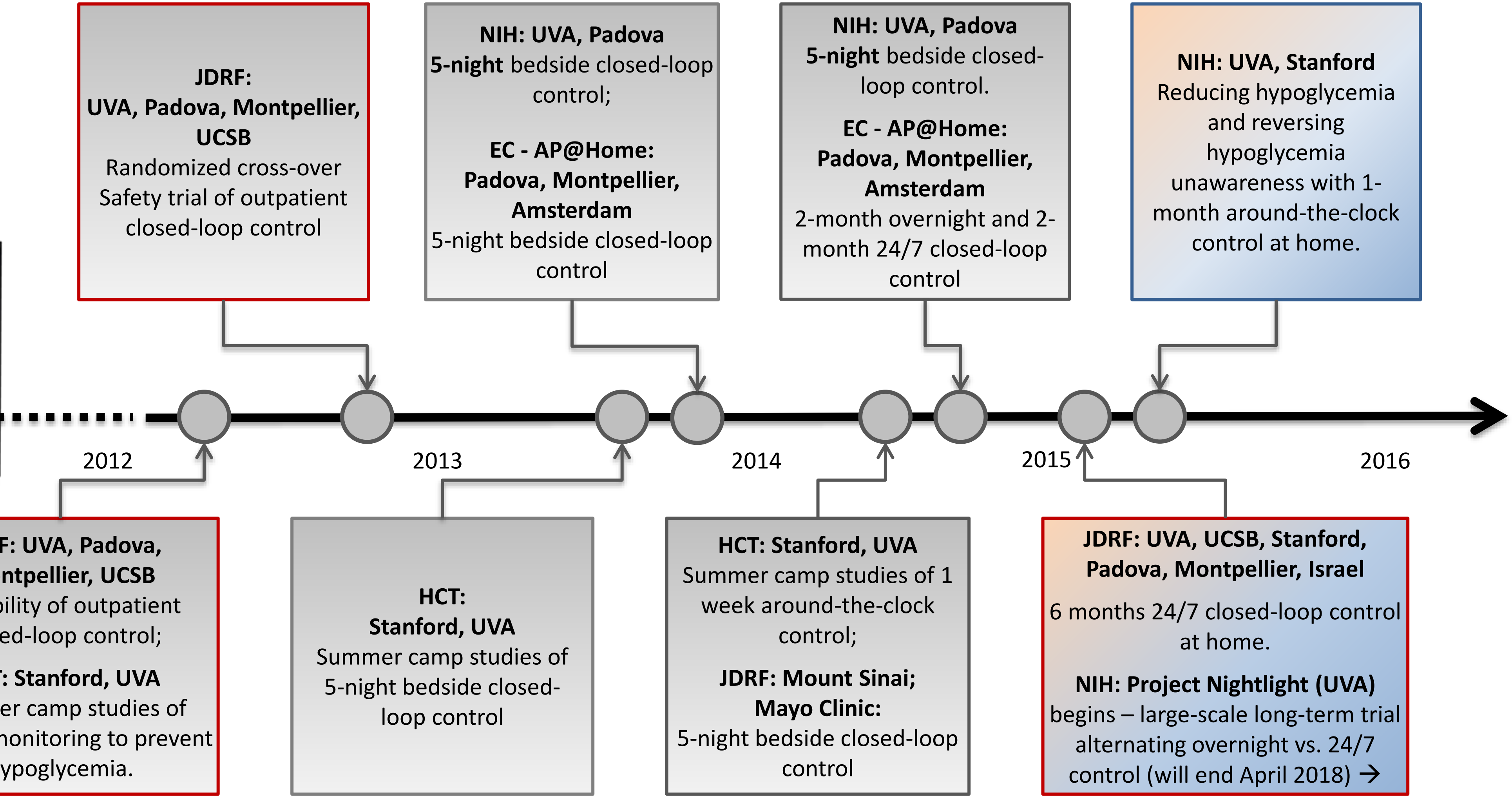
Montpellier,
France

Padova,
Italy

Santa Barbara,
California

Clinical Trials 2013-2015

(funded by NIH, JDRF, the Helmsley Charitable Trust, and the European Commission)



JDRF: UVA, Padova, Montpellier, UCSB
Feasibility of outpatient closed-loop control;

HCT: Stanford, UVA
Summer camp studies of remote monitoring to prevent hypoglycemia.

JDRF:
UVA, Padova, Montpellier, UCSB
Randomized cross-over Safety trial of outpatient closed-loop control

HCT:
Stanford, UVA
Summer camp studies of 5-night bedside closed-loop control

NIH: UVA, Padova
5-night bedside closed-loop control;

EC - AP@Home:
Padova, Montpellier, Amsterdam
5-night bedside closed-loop control

HCT: Stanford, UVA
Summer camp studies of 1 week around-the-clock control;

JDRF: Mount Sinai; Mayo Clinic:
5-night bedside closed-loop control

NIH: UVA, Padova
5-night bedside closed-loop control.

EC - AP@Home:
Padova, Montpellier, Amsterdam
2-month overnight and 2-month 24/7 closed-loop control

JDRF: UVA, UCSB, Stanford, Padova, Montpellier, Israel

6 months 24/7 closed-loop control at home.

NIH: Project Nightlight (UVA) begins – large-scale long-term trial alternating overnight vs. 24/7 control (will end April 2018) →

NIH: UVA, Stanford
Reducing hypoglycemia and reversing hypoglycemia unawareness with 1-month around-the-clock control at home.

2012

2013

2014

2015

2016

Meta-Analysis by the End of 2015

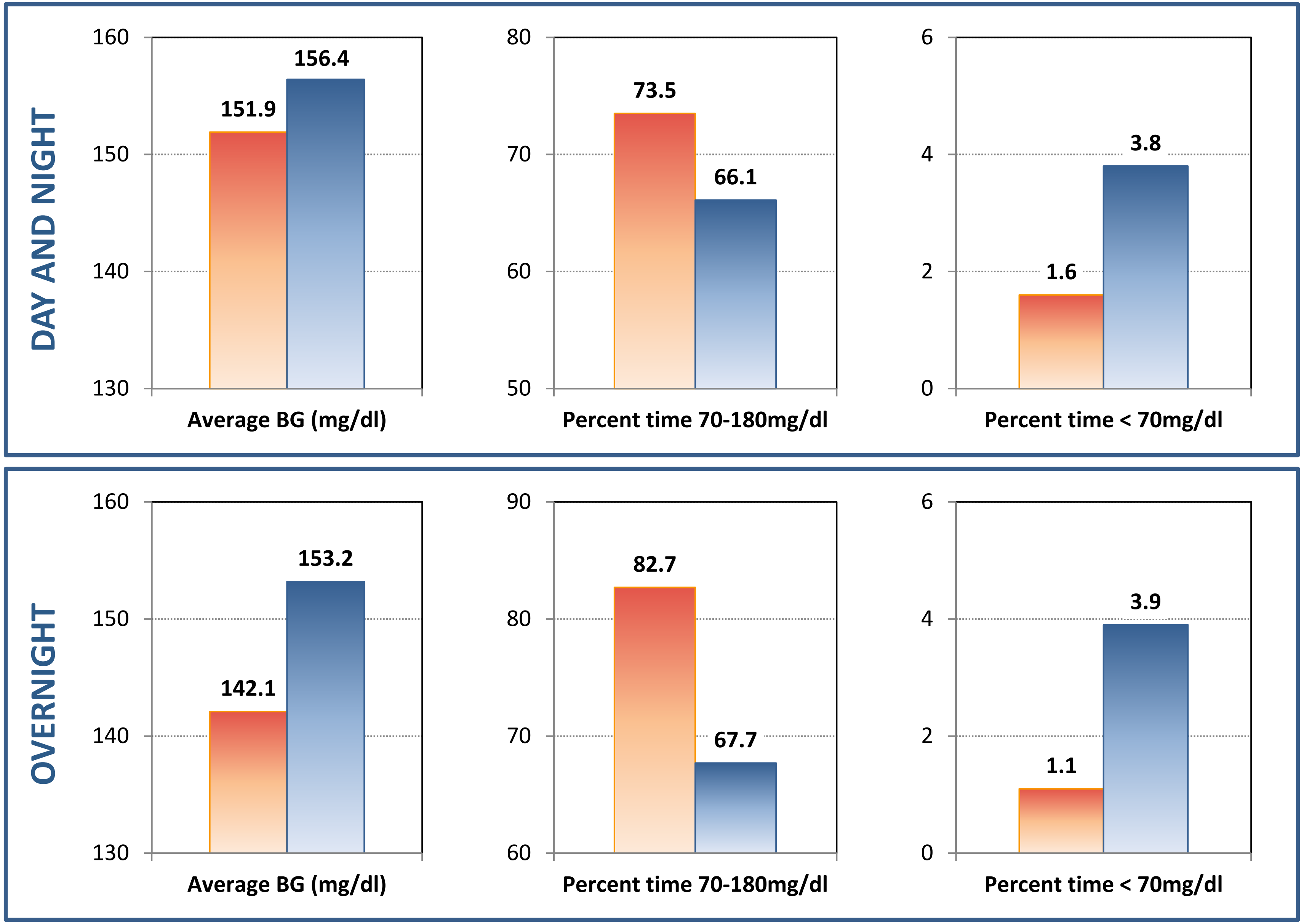
18 Clinical Trials;

12 IDEs issued by FDA;

Regulatory approvals in Italy, France, Holland, Israel.

320 patients;

155,000 hours (~18 years) of system use



🟧 Closed Loop: Sensor, Pump, and Control Algorithm

🟦 Sensor and Pump; no Control Algorithm

2016 - 2018: Stress Tests–The AP Ski Trials

January 2016: First 5-Day Ski Camp on Closed-Loop Control Wintergreen, Virginia, elevation 3,515’ (1,071 meters); Children, ages 12-18.

April 2016: Ski Camp on Closed-Loop Control Breckenridge, Colorado, elevation 12,840’ (3,914 meters)

January-April 2018 and January 2019: Virginia, California, Colorado using *Control IQ* – a new commercial closed-loop system based on UVA’s control algorithm (Tandem Diabetes Care).

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Diabetes Care

WWW.DIABETES.ORG/DIABETESCARE

DECEMBER 2017

Improving the Clinical Value and Utility of CGM Systems: Issues and Recommendations: A Joint Statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group

J.R. Petrie, A.L. Peters, R.M. Bergenstal, R.W. Holl, G.A. Fleming, and L. Heinemann

Closed-Loop Control During Intense Prolonged Outdoor Exercise in Adolescents With Type 1 Diabetes: The Artificial Pancreas Ski Study

M.D. Breton, D.R. Cherñavsky, G.P. Forlenza, M.D. DeBoer, J. Robic, R.P. Wadwa, L.H. Messer, B.P. Kovatchev, and D.M. Maahs

Time Trends of Dietary and Lifestyle Factors and Their Potential Impact on Diabetes Burden in China

Y. Li, D.D. Wang, S.H. Ley, M. Vasanti, A.G. Howard, Y. He, and F.B. Hu

Burden of Mortality Attributable to Diagnosed Diabetes: A Nationwide Analysis Based on Claims Data From 65 Million People in Germany

E. Jacobs, A. Hoyer, R. Brinks, O. Kuss, and W. Rathmann

SPECIAL ARTICLE COLLECTION:
Continuous Glucose Monitoring and Risk of Hypoglycemia

American Diabetes Association

ISSN 0149-5992

2017-2020: The International Diabetes Closed-Loop Trial

NIH/NIDDK Grant UC4 DK 108483;
N>400 PARTICIPANTS IN FOUR CLINICAL PROTOCOLS AT:

- University of Virginia
- Harvard University
- Mount Sinai School of Medicine
- Mayo Clinic
- Barbara Davis Diabetes Center
- Stanford University
- William Sansum Diabetes Center
- University of Montpellier (France)
- Caen University Hospital (France)
- University of Padova (Italy)
- Coordinated by the Jaeb Center for Health Research

- ✓ Protocol 1: N=126 participants for 3 months. Establish mobile closed-loop control as viable treatment for type 1 diabetes (completed; met its objectives as reported in November 2018);
- ✓ Protocol 2: N=72 participants for 3-6 months. Generate safety and efficacy data satisfying E.U. regulatory requirements (awaiting EU regulatory approvals; to begin in February-March, 2019);
- ✓ Protocol 3: N=168 participants for 6-9 months. Pivotal Trial to generate safety and efficacy data satisfying FDA requirements. Began in June 2018 using the Control IQ system (Tandem/Dexcom); to be completed in April 2019;
- ✓ Protocol 4: Pilot test a new-generation adaptive closed-loop control system developed at Harvard (expected to begin in June 2019).

Control-IQ

Dexcom G6

The Progression of UVA’s AP Technology:

from Research

DiAs (UVA, 2012)
Sensor: Dexcom Seven plus or G4;
Insulin Pump: Roche or Tandem

to Industry

inControl (TypeZero, 2015)
Sensor: Dexcom G4 or G5;
Insulin Pump: Roche or Tandem

to Clinical Practice

Control-IQ
(Tandem, 2017)
dexcom G6

TO DATE:	
Days of system use	>50,000 (~137 years)
Clinical trial participants	>660
Clinical trials	33
Research sites on four continents	15

THE NEXT RESEARCH FRONTIER:

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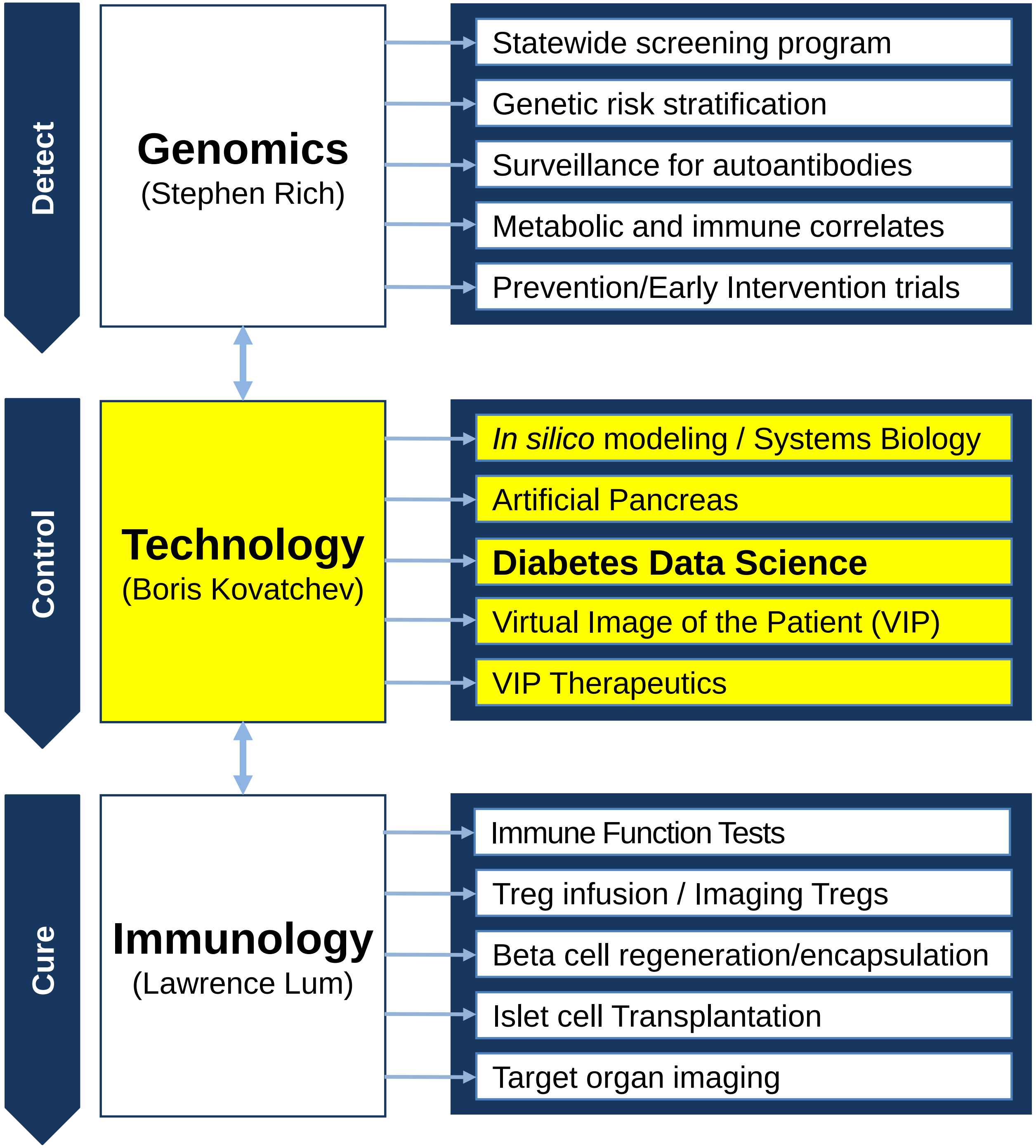
PrIMeD

Precision Individualized Medicine for Diabetes

$17M Strategic Investment in diabetes made by UVA in 2017



Detect

Genomics
(Stephen Rich)

- Statewide screening program
- Genetic risk stratification
- Surveillance for autoantibodies
- Metabolic and immune correlates
- Prevention/Early Intervention trials

Control

Technology
(Boris Kovatchev)

- *In silico* modeling / Systems Biology
- Artificial Pancreas
- **Diabetes Data Science**
- Virtual Image of the Patient (VIP)
- VIP Therapeutics

Cure

Immunology
(Lawrence Lum)

- Immune Function Tests
- Treg infusion / Imaging Tregs
- Beta cell regeneration/encapsulation
- Islet cell Transplantation
- Target organ imaging

UNIVERSITY NEWS

A Historic Day at the Rotunda and a New School for the University's Third Century

January 18, 2019 • Caroline Newman, cfn8m@virginia.edu

UNIVERSITY of VIRGINIA: WITH $120 MILLION GIFT UVA PLANS NEW SCHOOL OF DATA SCIENCE

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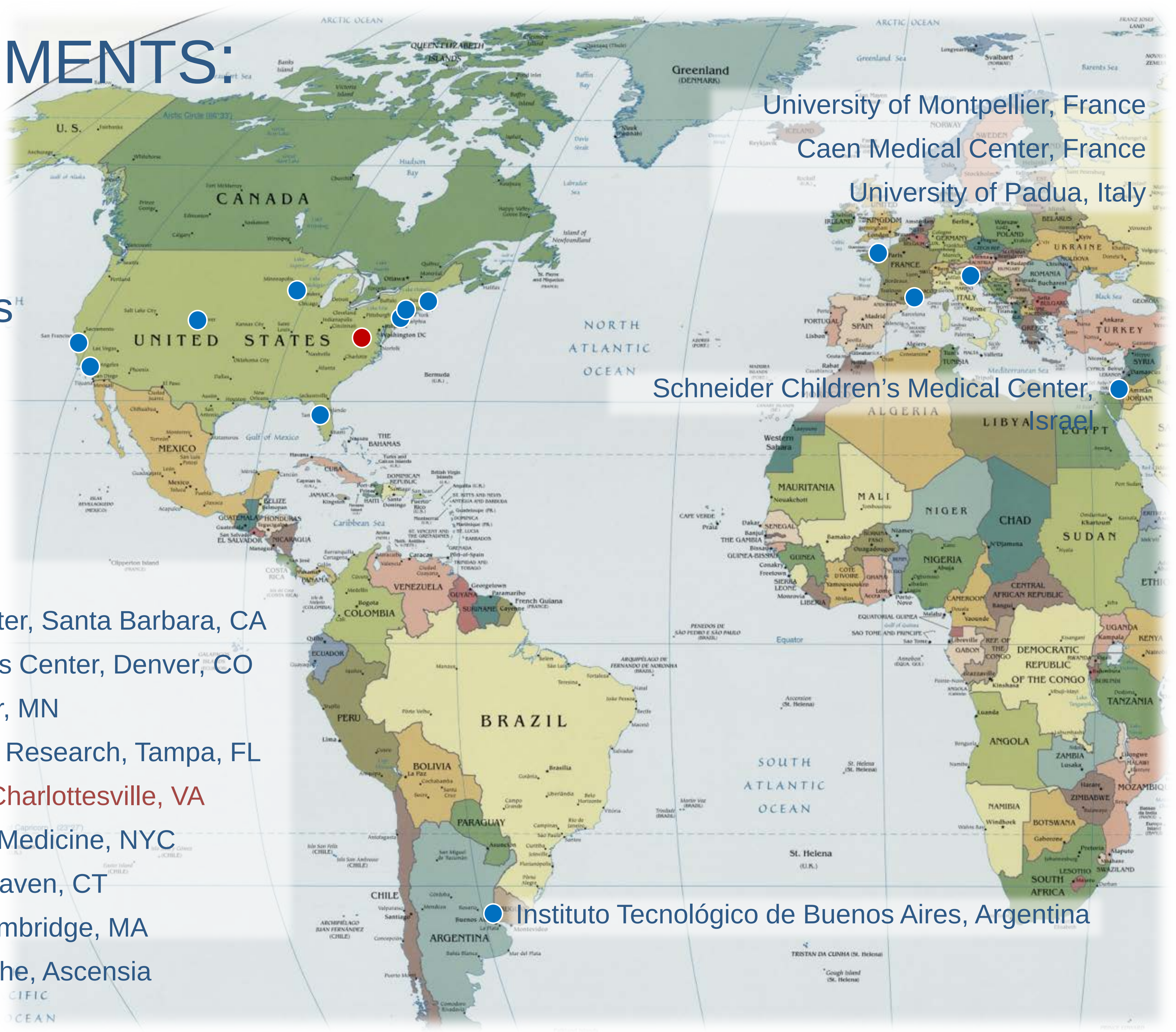
UVA's PrIMeD Project;

UVA's Center for Diabetes Technology, and our International Research Network and Industry Partners :



University of Montpellier, France

Caen Medical Center, France

University of Padua, Italy

Schneider Children's Medical Center, Israel

Instituto Tecnológico de Buenos Aires, Argentina

Stanford University

Sansum Diabetes Center, Santa Barbara, CA

Barbara Davis Diabetes Center, Denver, CO

Mayo Clinic, Rochester, MN

Jaeb Center for Health Research, Tampa, FL

University of Virginia, Charlottesville, VA

Mount Sinai School of Medicine, NYC

Yale University, New Haven, CT

Harvard University, Cambridge, MA

Dexcom, Tandem, Roche, Ascensia