Curing Type 1 Diabetes: What the Future Holds

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City of Hope

Disclosures

- Grant/Research Support from Viacyte, Inc.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced company or its product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Prevalence of diabetes across different ethnic groups and regions.*
- *Highlight ethnic groups that have healthcare disparities.*

City of Hope Diabetes and Endocrine Center

- Duarte

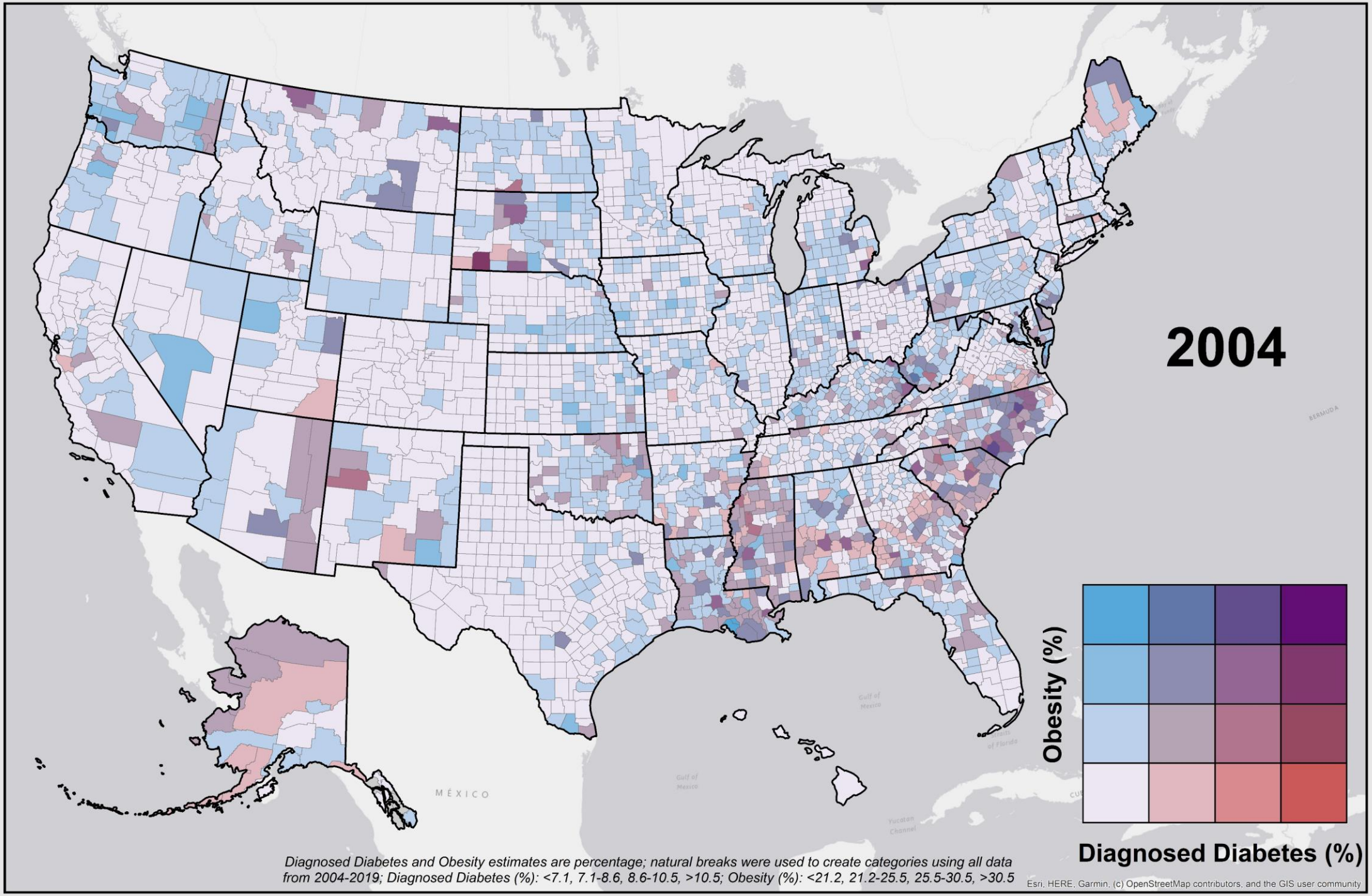
- Orange County

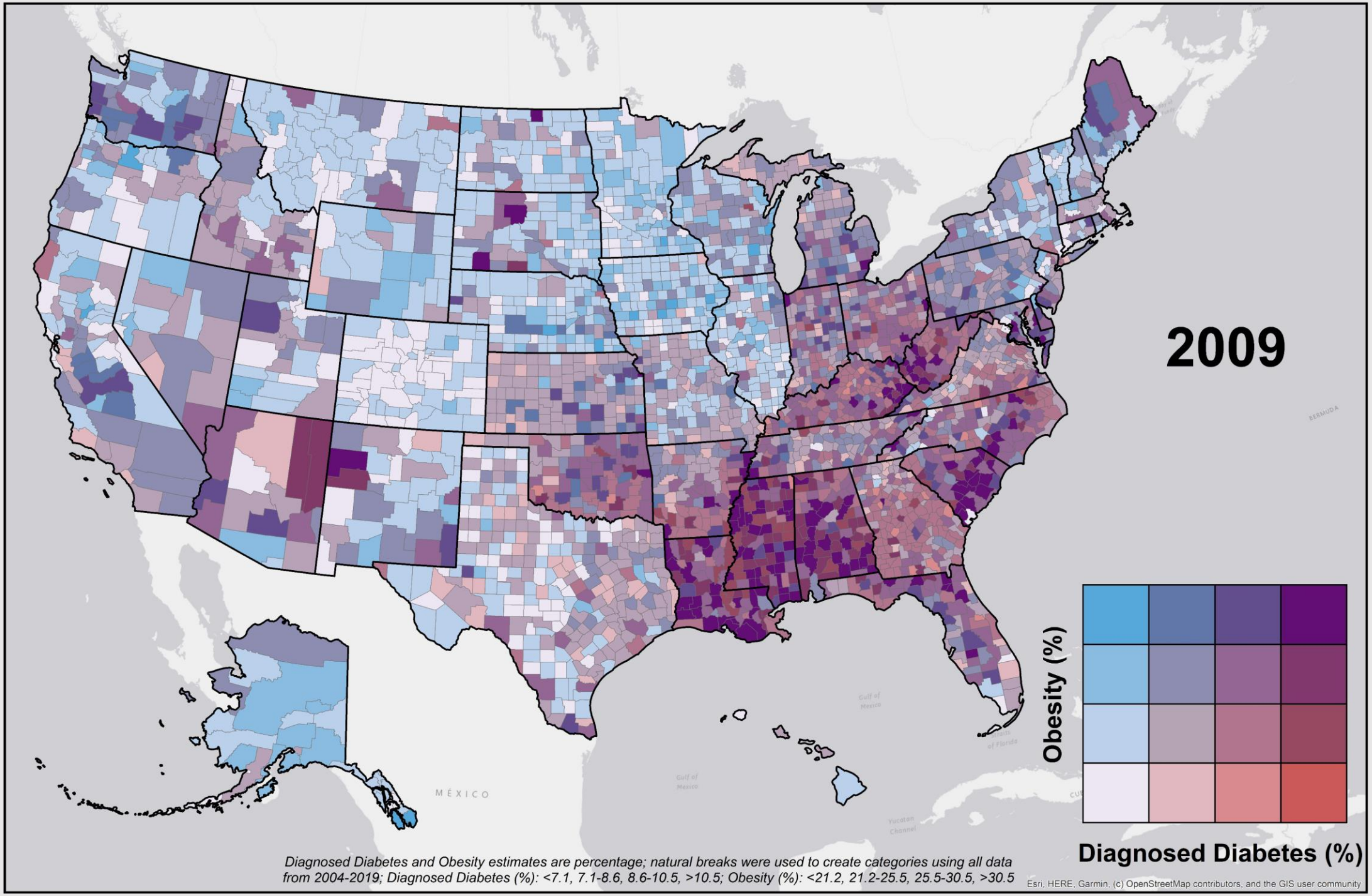
- South Pasadena

Classification of Diabetes

Diabetes is a syndrome, not a single disease entity

- Type 1 Diabetes (Juvenile onset, IDDM)
- Type 2 Diabetes (Adult onset, NIDDM)
- Specific Diabetes Types due to known underlying causes
  Monogenic diabetes (MODY gene mutations)
  Exocrine pancreas diseases (pancreatitis, cystic fibrosis)
  Drug or chemical induced (steroid, HIV, CPI, etc)
  Posttransplantation
  Post pancreatectomy
- Gestational Diabetes
- Neonatal Diabetes
- Other rare forms of diabetes


2004
Obesity (%)
Diagnosed Diabetes (%)
MÉXICO
Gulf of Mexico
Yucatan Channel
BERMUDA
Diagnosed Diabetes and Obesity estimates are percentage; natural breaks were used to create categories using all data from 2004-2019; Diagnosed Diabetes (%): <7.1, 7.1-8.6, 8.6-10.5, >10.5; Obesity (%): <21.2, 21.2-25.5, 25.5-30.5, >30.5
Esri, HERE, Garmin, (c) OpenStreetMap contributors, and the GIS user community


2009
Obesity (%)
Diagnosed Diabetes (%)
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Gulf of Mexico
Yucatan Channel
BERMUDA
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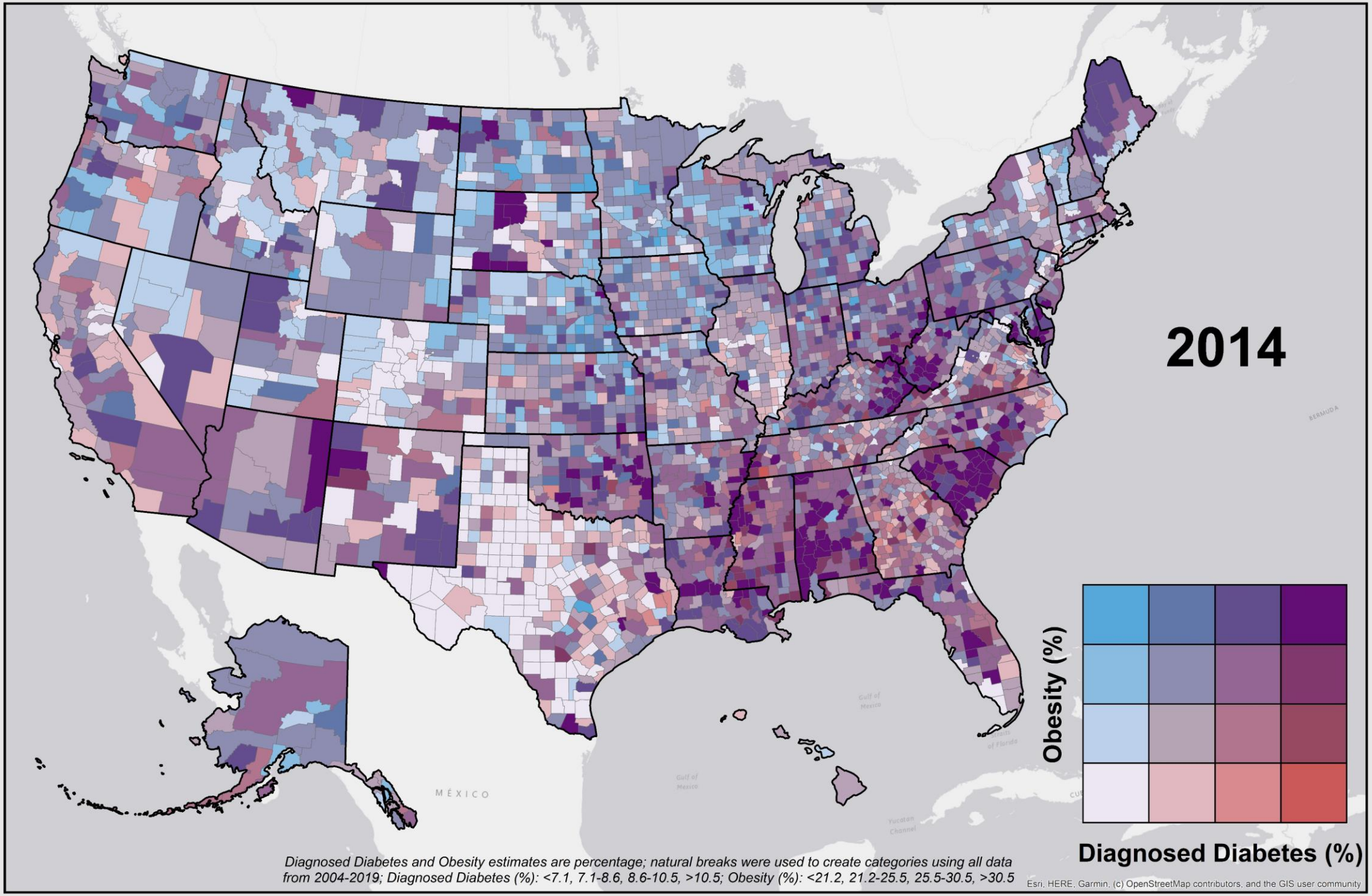
2014
Obesity (%)
Diagnosed Diabetes (%)
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Yucatan Channel
BERMUDA
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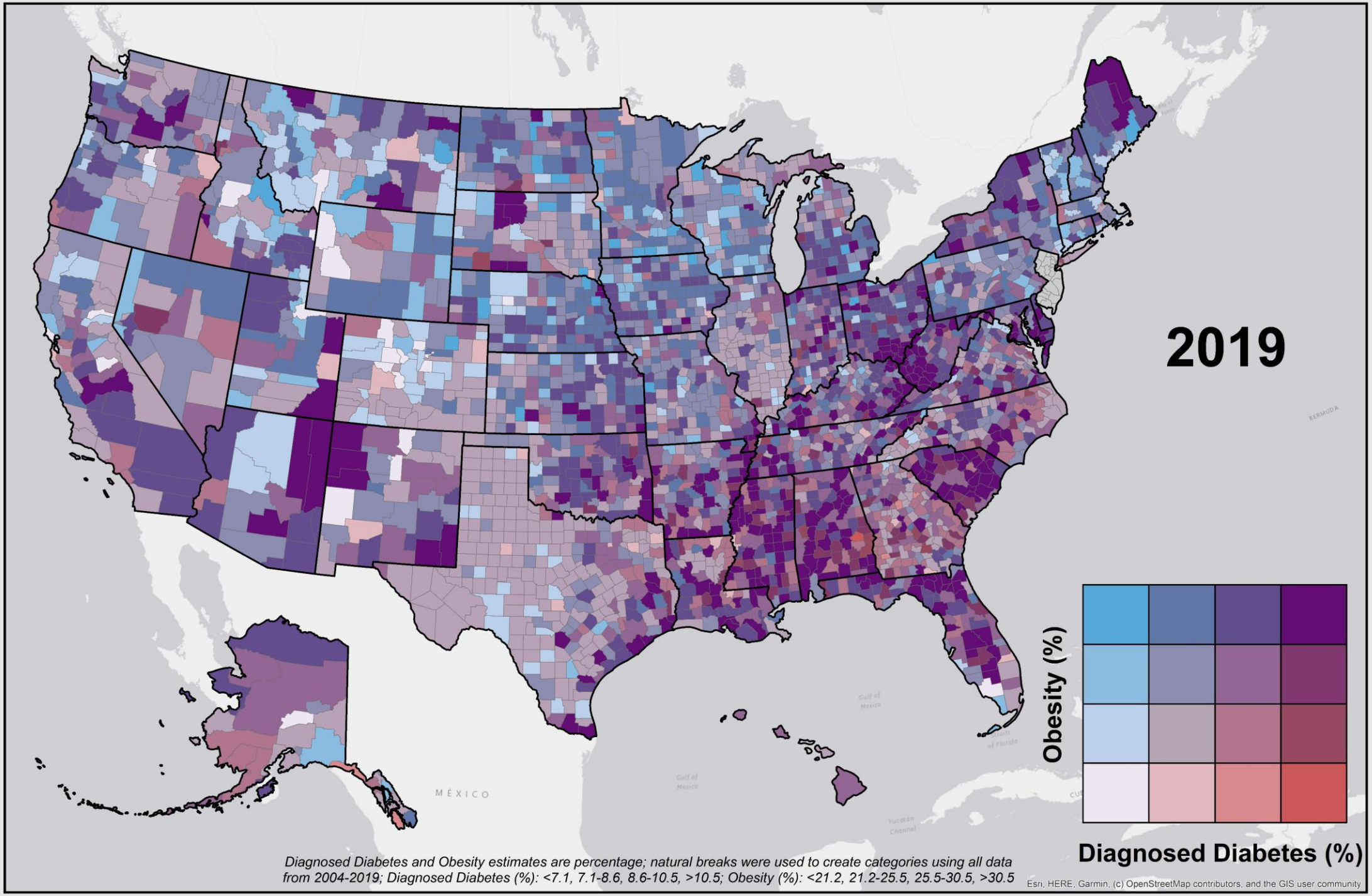
2019
Obesity (%)
Diagnosed Diabetes (%)
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BERMUDA
Diagnosed Diabetes and Obesity estimates are percentage; natural breaks were used to create categories using all data from 2004-2019; Diagnosed Diabetes (%): <7.1, 7.1-8.6, 8.6-10.5, >10.5; Obesity (%): <21.2, 21.2-25.5, 25.5-30.5, >30.5
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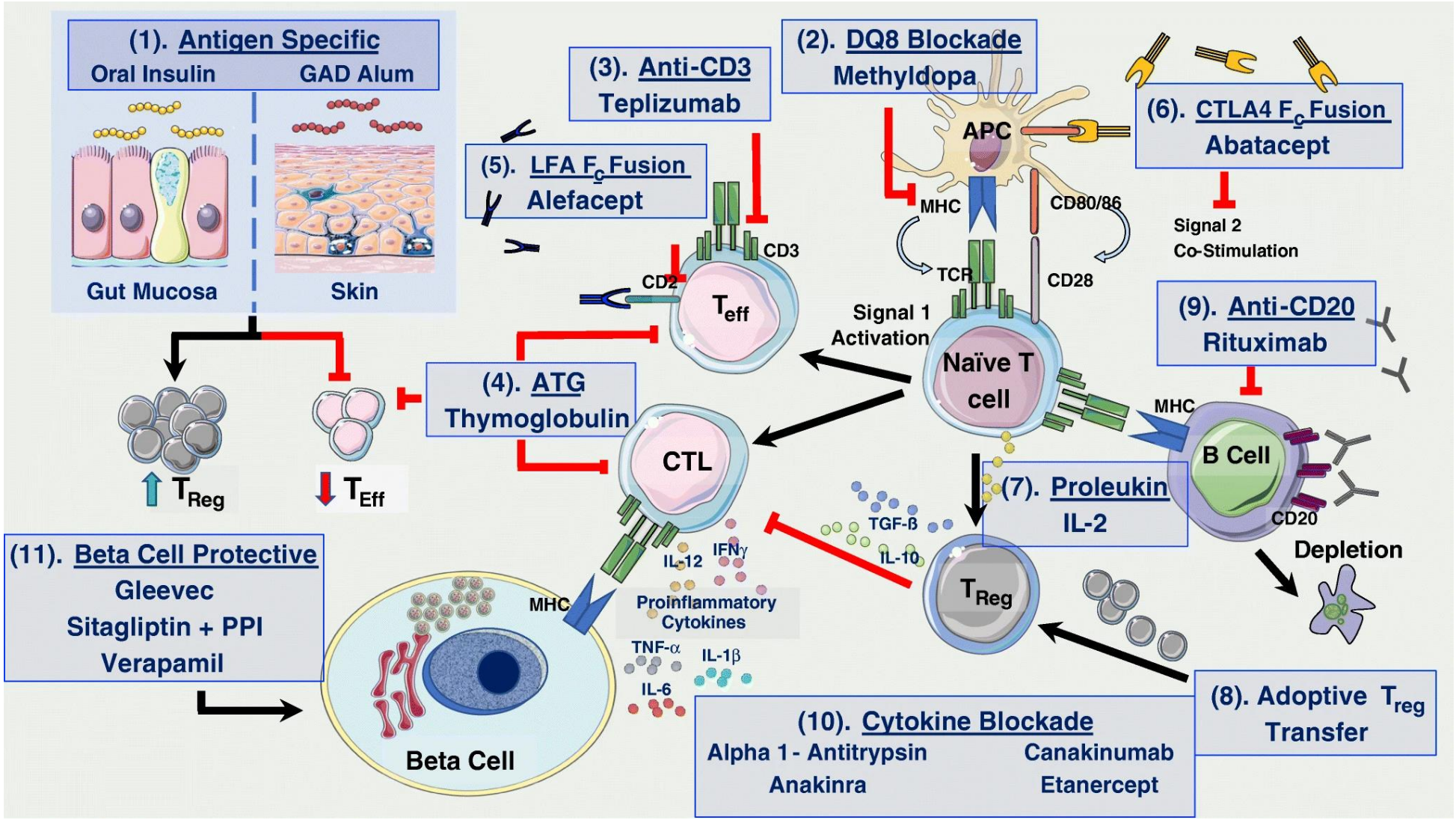
Current State of Diabetes in the United States

- Total: 37.3 million people have diabetes (11.3% of the US population)
- Diagnosed: 28.7 million people, including 28.5 million adults
- Undiagnosed: 8.5 million people (23.0% of adults are undiagnosed)
- Prediabetes:
  Total: 96 million people aged 18 years or older have prediabetes (38.0% of the adult US population)

  65 years or older: 26.4 million people aged 65 years or older (48.8%) have prediabetes

Immune Mechanisms and Pathways Targeted in Type 1 Diabetes

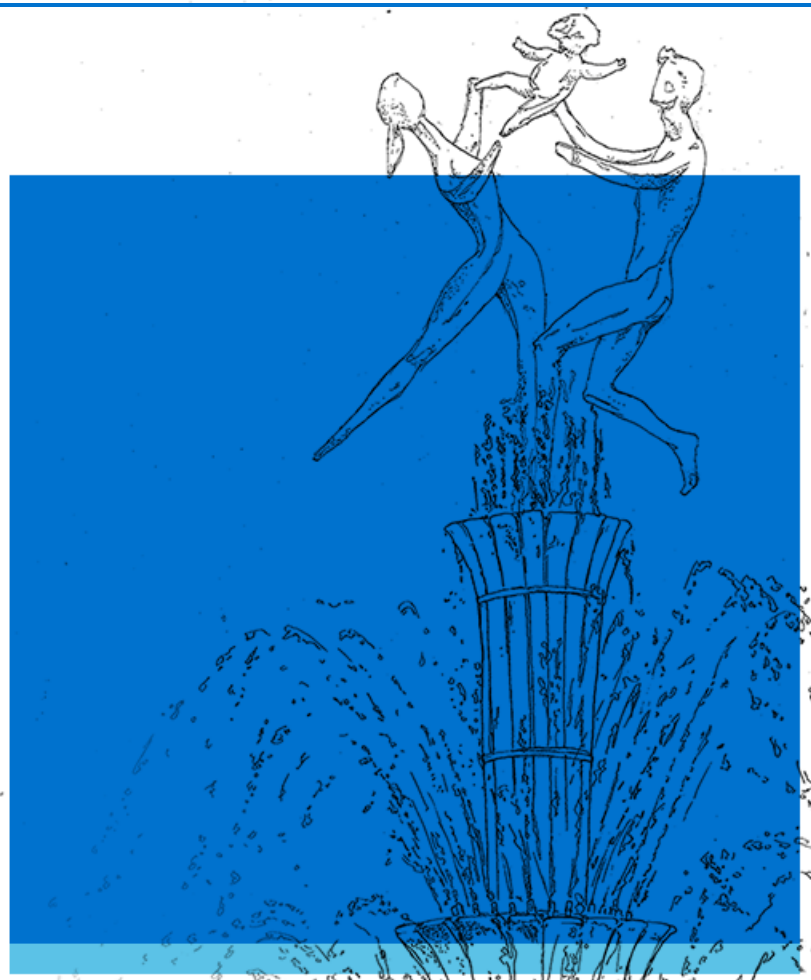


Curr Diab Rep 18, 90 (2018). https://doi.org/10.1007/s11892-018-1066-5

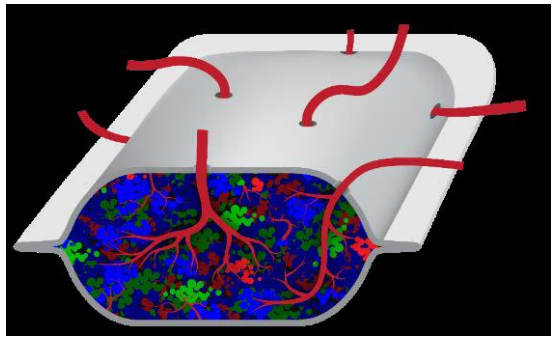
Unique Opportunity for Diabetes Research Breakthrough at COH

- COH diabetes basic science laboratories have been at the forefront of scientific discoveries in the past 50 years since the invention of synthetic human insulin.
- COH physicians and scientists have pioneered cell-based therapies for leukemia and blood cancers.
- Now we are ready to combine COH expertise in cell therapies with basic science discoveries to conduct trailblazing diabetes clinical study and push for potential cure in diabetes and its complications.

Viacyte Trial



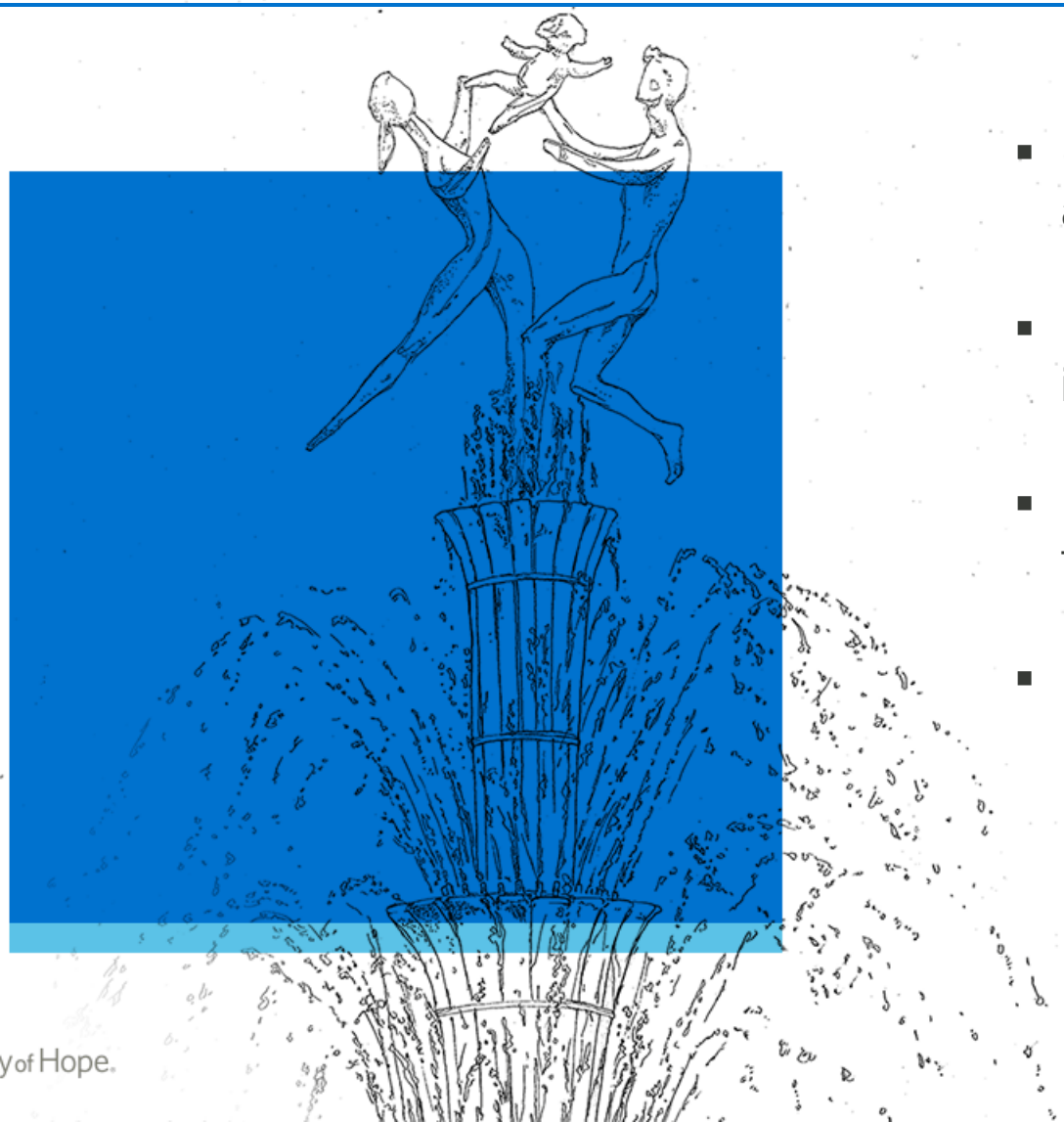
- First in human study to evaluate the efficacy of stem cell-derived islet transplantation for type 1 diabetes.



Encapsulated for Transplantation

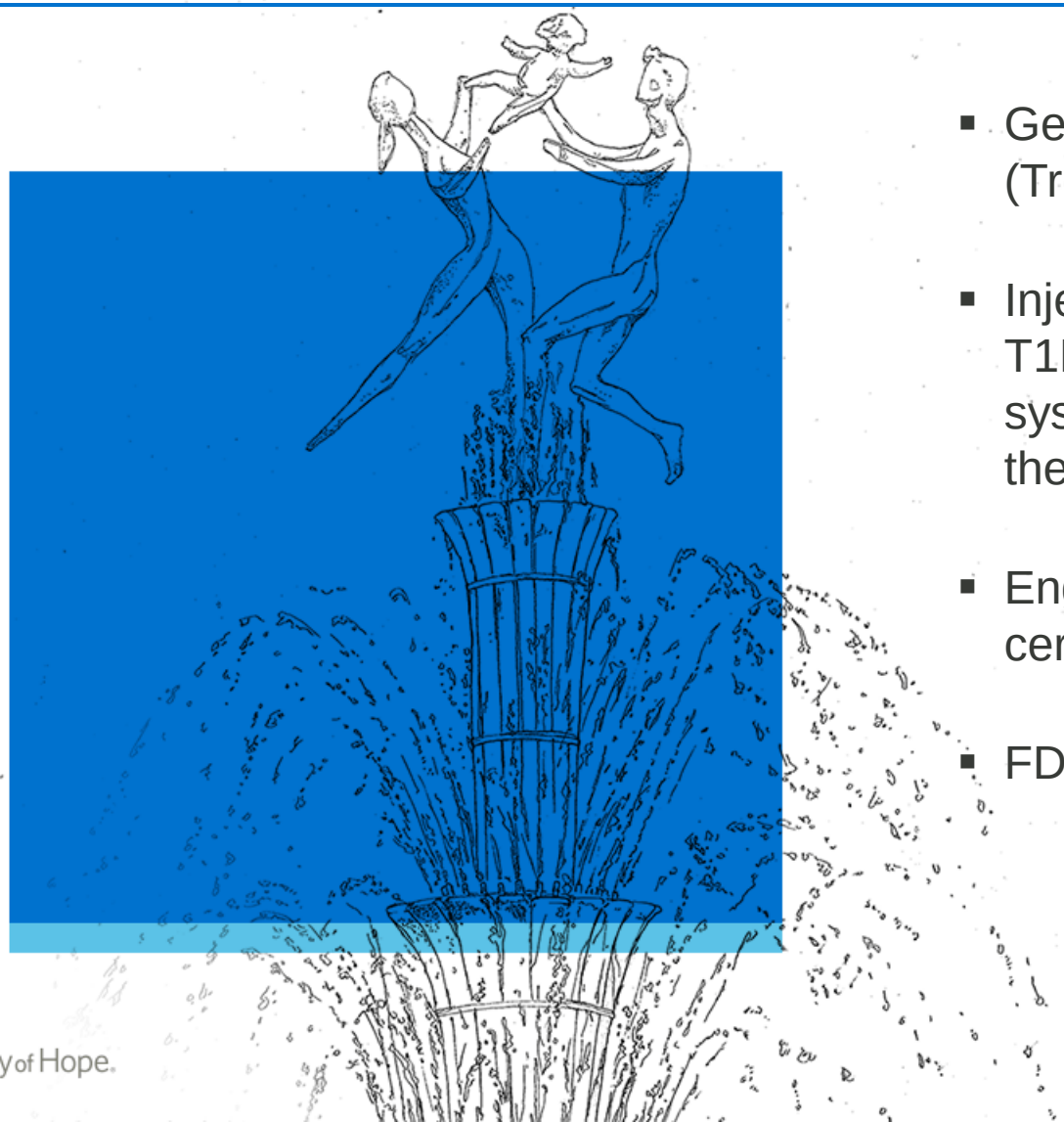
- Next generation product with genetic editing does not require immunosupression.
- Trial starts in December 2020 at City of Hope and will move to the next generation product in 2023.

LR90 Trial



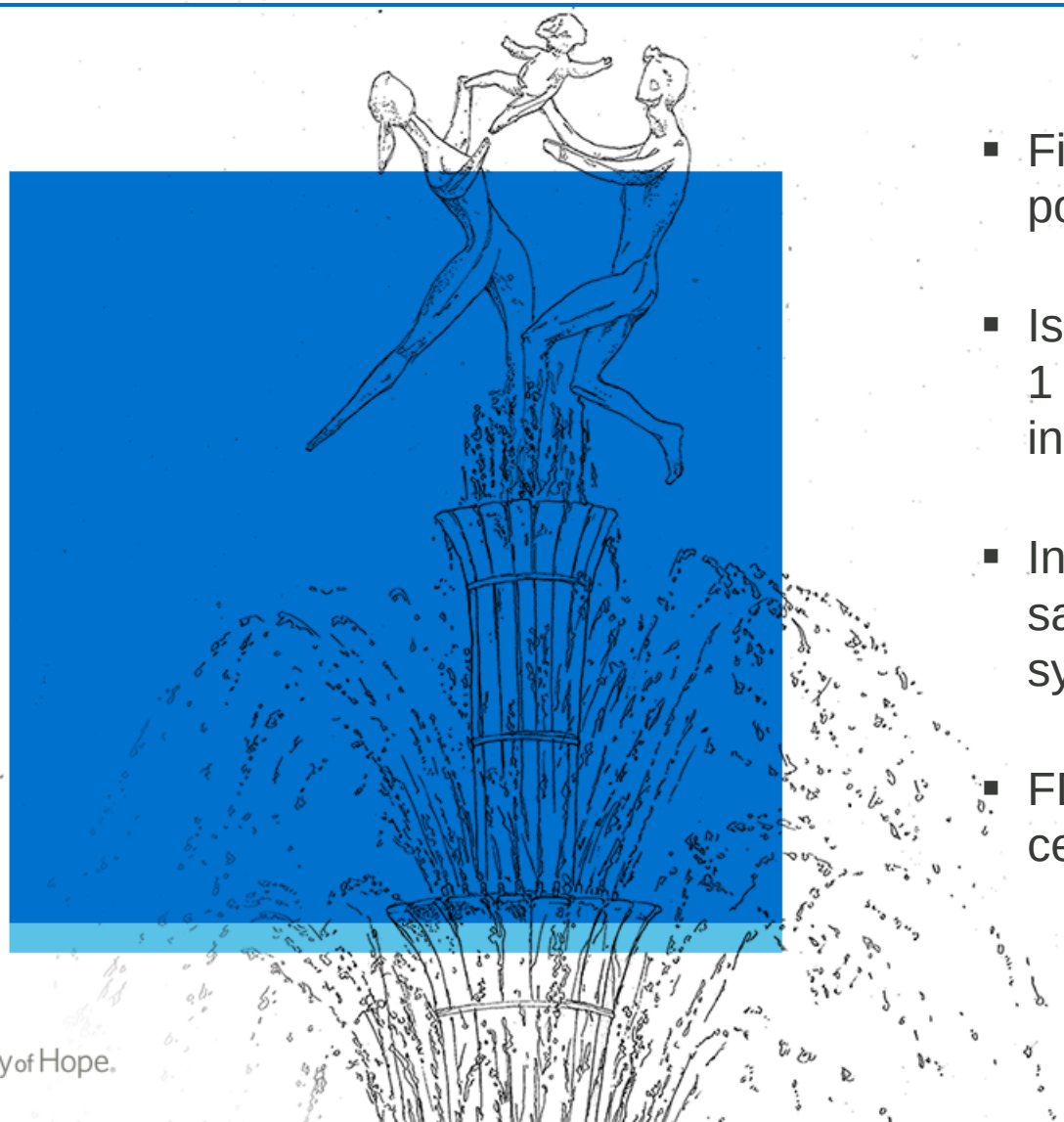
- First in Human Study to Evaluate the Efficacy of a new drug for diabetic neuropathy.
- No drug is currently available to effectively improve progression of neuropathy.
- In the last stage of pre-clinical development – formulation.
- FDA submission in 2022-2023.

CD6-CAR-Treg Trial



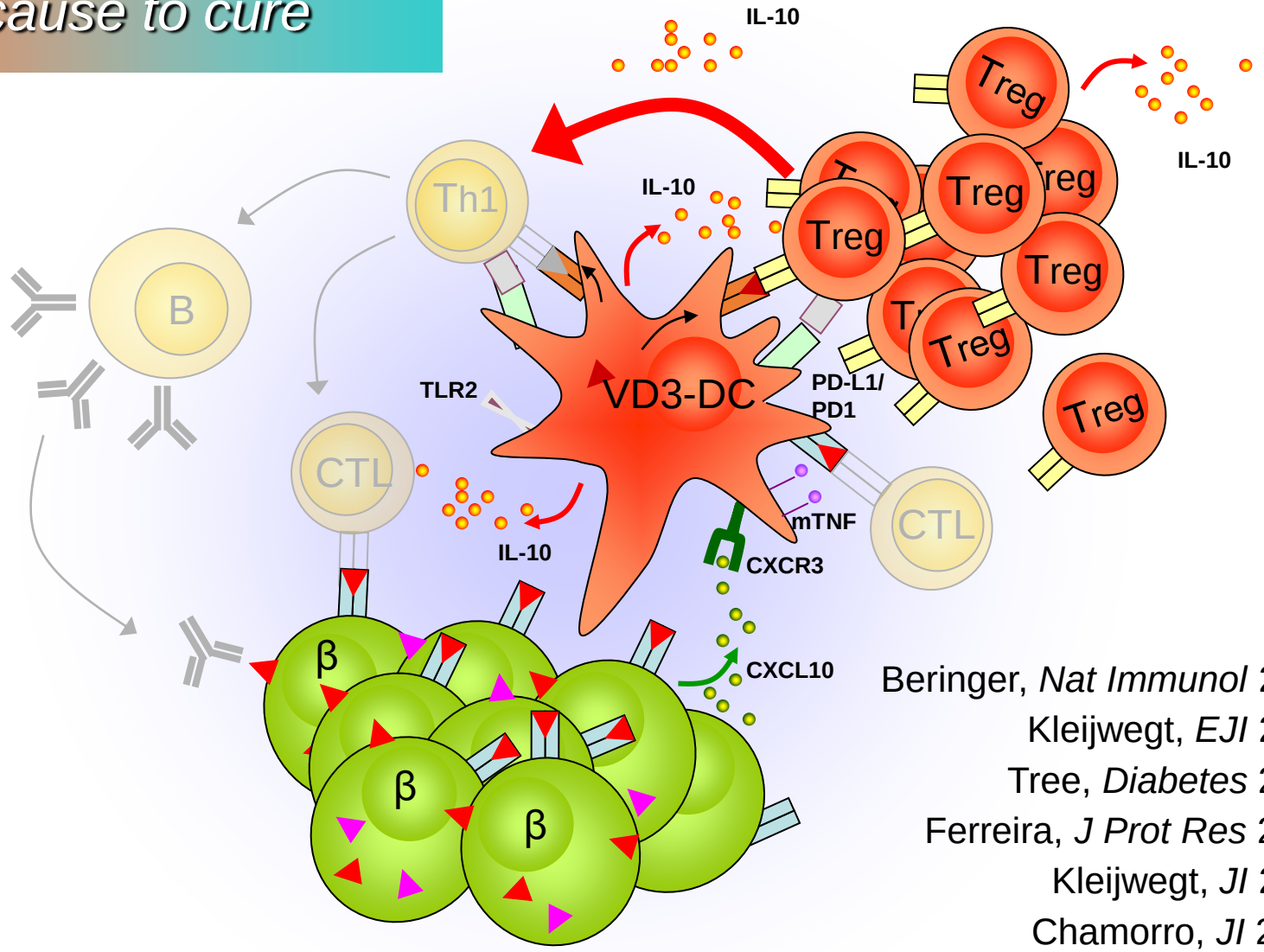
- Genetic Engineering of human immune cells (Treg) from Type 1 diabetes in the laboratory.
- Inject the engineered immune cells back to each T1D patient to restore normalcy in the immune system and stop immune system from attacking the beta cells in pancreas.
- Engineering run and qualification run in GMP certified facility in 2021.
- FDA submission in 2022-2023.

TolDC Trial – A Vaccine



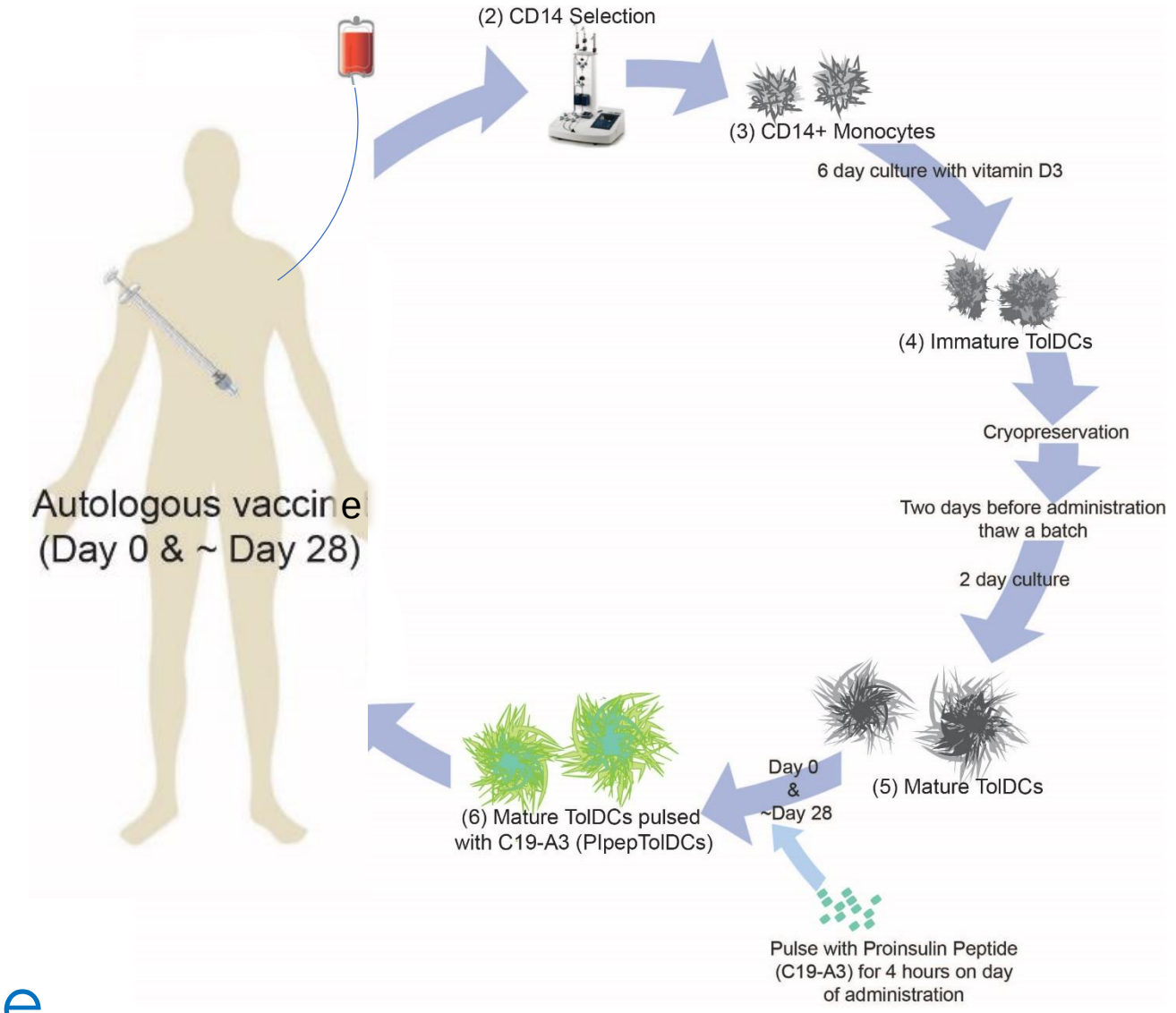
- First in human study to evaluate the efficacy of a potential vaccine for Type 1 Diabetes.
- Isolate immune cells (dendritic cells) from Type 1 diabetes patient and teach them to adapt to insulin-producing cells in the laboratory.
- Inject the trained dendritic cells back to the same patient. The cells will coach the immune system not to attack the beta cells in pancreas.
- FDA approved. Study started in 2022. Actual cell vaccine injection scheduled for Q4 2022.

Type 1 diabetes
From cause to cure



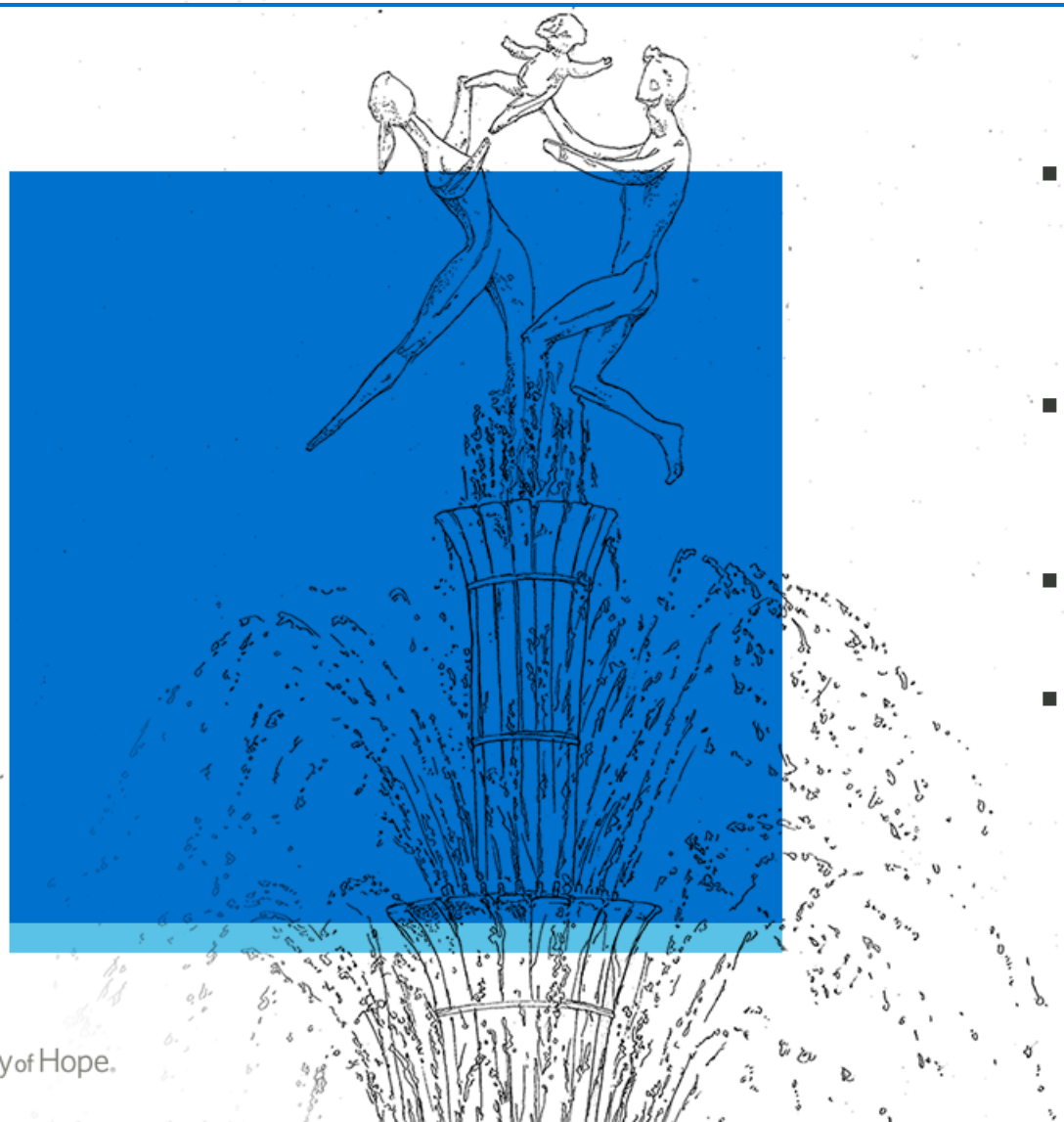
Beringer, *Nat Immunol* 2015
Kleijwegt, *EJI* 2013
Tree, *Diabetes* 2011
Ferreira, *J Prot Res* 2011
Kleijwegt, *JI* 2011
Chamorro, *JI* 2009
Roep, *CEI* 2010
Kleijwegt, *JI* 2010
Unger, *EJI* 2009

Manufacturing

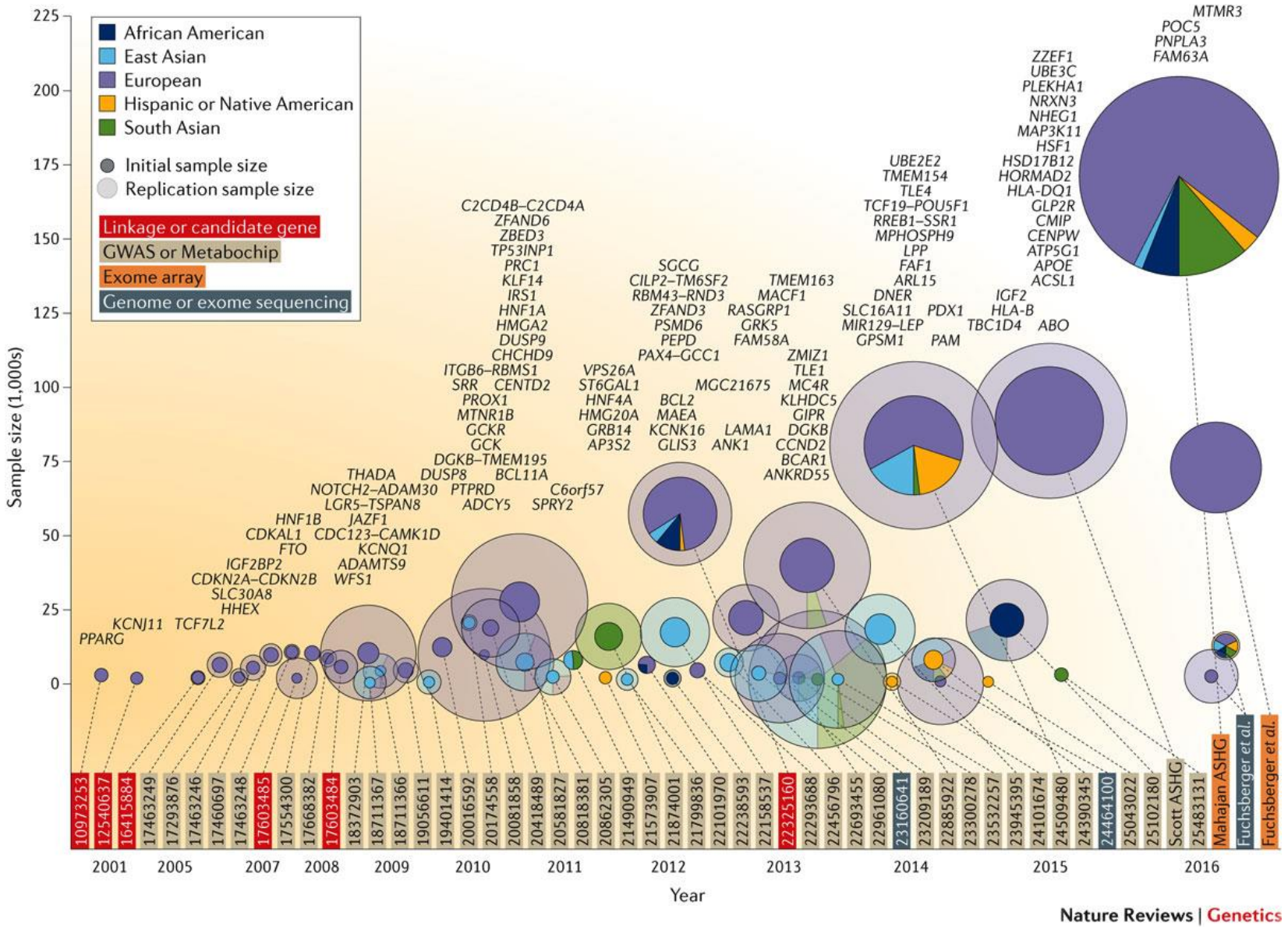


Nikolic, *Lancet Diabetes & Endocrinol* 2020

Islet Imaging Trial



- Inability to determine the volume of pancreas islets in human has been a bottleneck for Type 1 and Type 2 diabetes research.
- Novel imaging scan to determine the volume of islets in human.
- FDA submission 2021.
- Clinical trial to begin soon.


African American
East Asian
European
Hispanic or Native American
South Asian
Initial sample size
Replication sample size
Linkage or candidate gene
GWAS or Metabochip
Exome array
Genome or exome sequencing
Sample size (1,000s)
Year
Nature Reviews | Genetics
MTMR3
POC5
PNPLA3
FAM63A
ZZEF1
UBE3C
PLEKHA1
NRXN3
NHEG1
MAP3K11
HSF1
HSD17B12
HORMAD2
HLA-DQ1
GLP2R
CMIP
CENPW
ATP5G1
APOE
ACSL1
UBE2E2
TMEM154
TLE4
TCF19–POU5F1
RREB1–SSR1
MPHOSPH9
LPP
FAF1
ARL15
DNER
SLC16A11
PDX1
MIR129–LEP
GPSM1
PAM
IGF2
HLA-B
TBC1D4
ABO
C2CD4B–C2CD4A
ZFAND6
ZBED3
TP53INP1
PRC1
KLF14
IRS1
HNF1A
HMGA2
DUSP9
CHCHD9
ITGB6–RBMS1
SRR
CENTD2
PROX1
MTNR1B
GCKR
GCK
DGKB–TMEM195
SGCG
CILP2–TM6SF2
RBM43–RND3
ZFAND3
PSMD6
PEPD
PAX4–GCC1
TMEM163
MACF1
RASGRP1
GRK5
FAM58A
ZMIZ1
TLE1
MC4R
KLHDC5
GIPR
DGKB
CCND2
BCAR1
ANKRD55
VPS26A
ST6GAL1
HNF4A
HMG20A
GRB14
AP3S2
MGC21675
BCL2
MAEA
KCNK16
GLIS3
LAMA1
ANK1
THADA
DUSP8
BCL11A
NOTCH2–ADAM30
PTPRD
C6orf57
LGR5–TSPAN8
ADCY5
SPRY2
HNF1B
JAZF1
CDKAL1
CDC123–CAMK1D
FTO
KCNQ1
IGF2BP2
ADAMTS9
CDKN2A–CDKN2B
WFS1
SLC30A8
HHEX
KCNJ11
TCF7L2
PPARG
10973253
12540637
16415884
17463249
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23160641
23209189
22885922
23300278
23532257
23945395
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24390345
24464100
25043022
25102180
Scott ASHG
25483131
Mahajan ASHG
Fuchsberger et al.
Fuchsberger et al.
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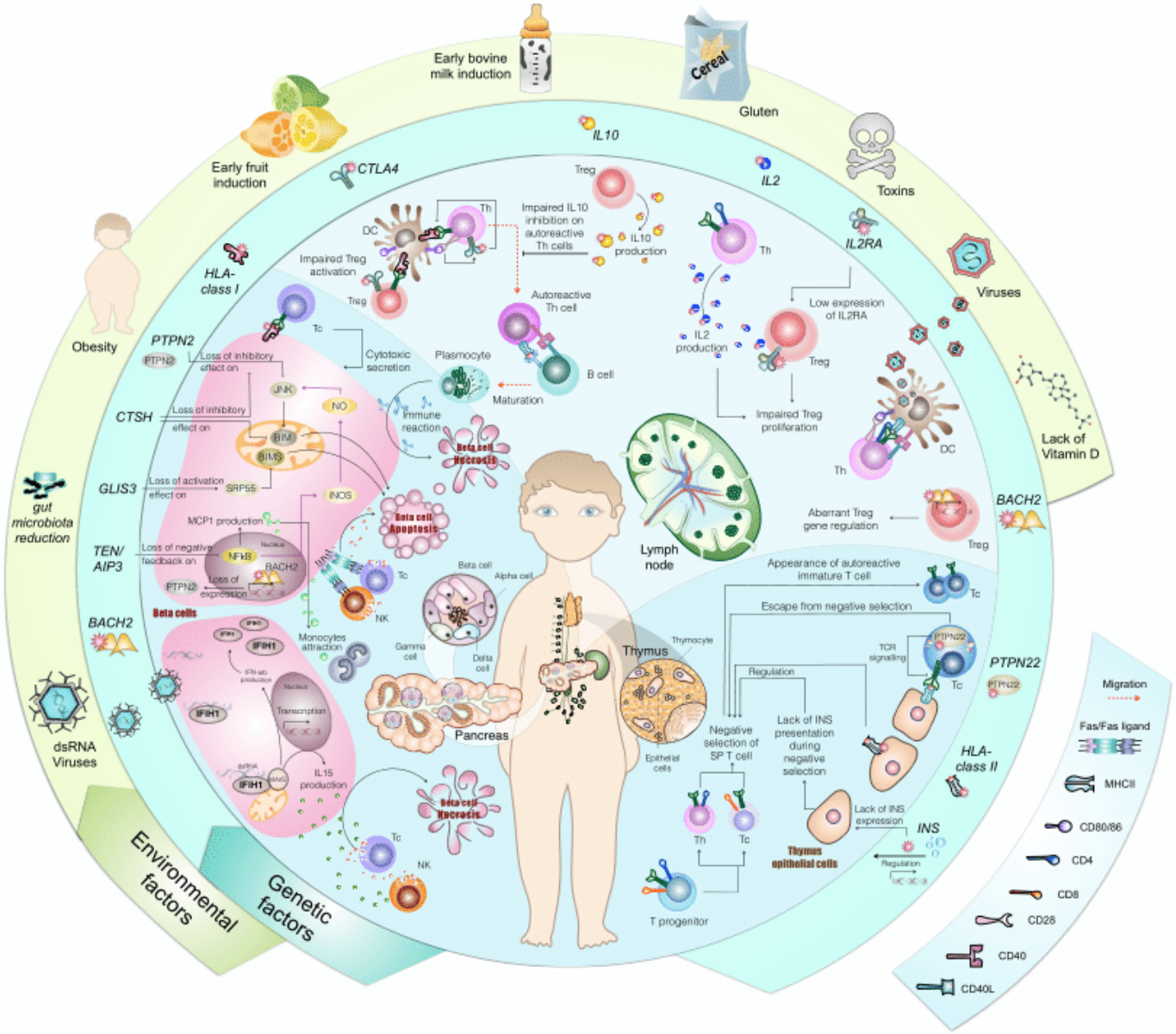
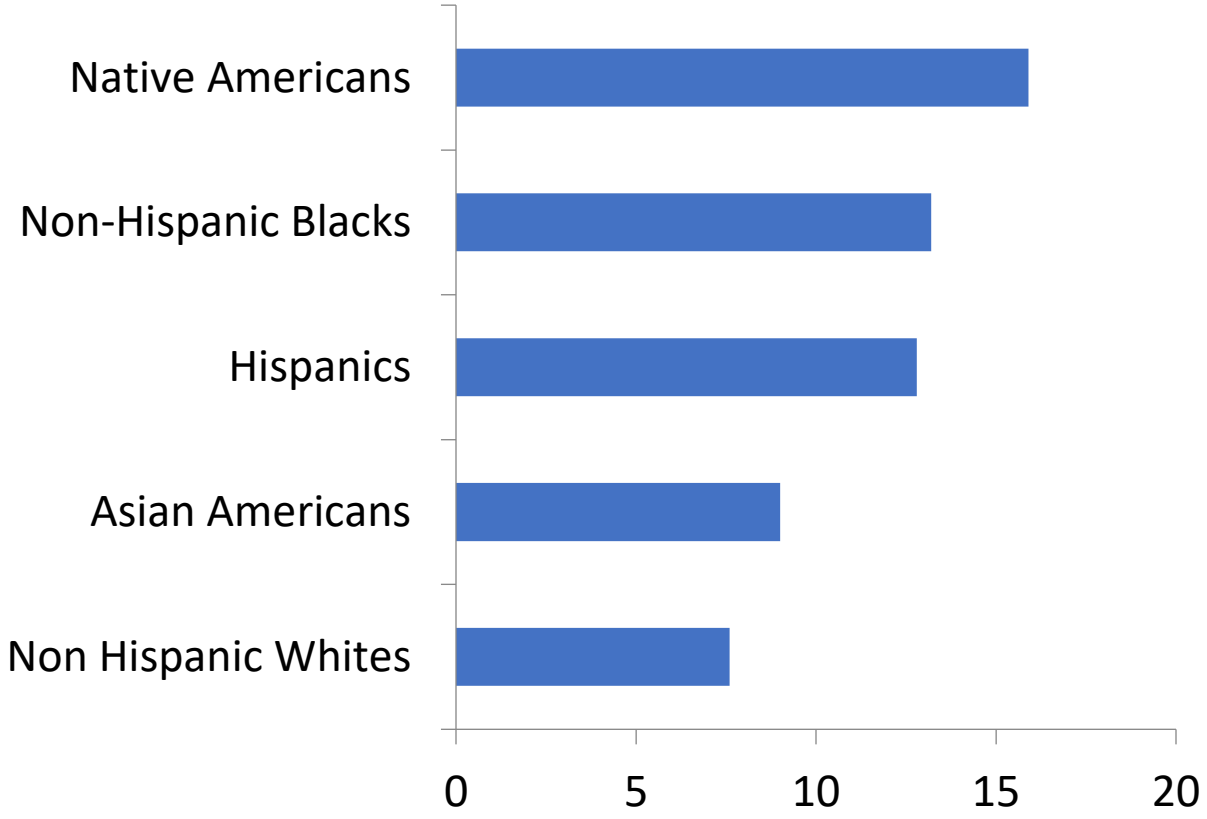


Abbreviations:

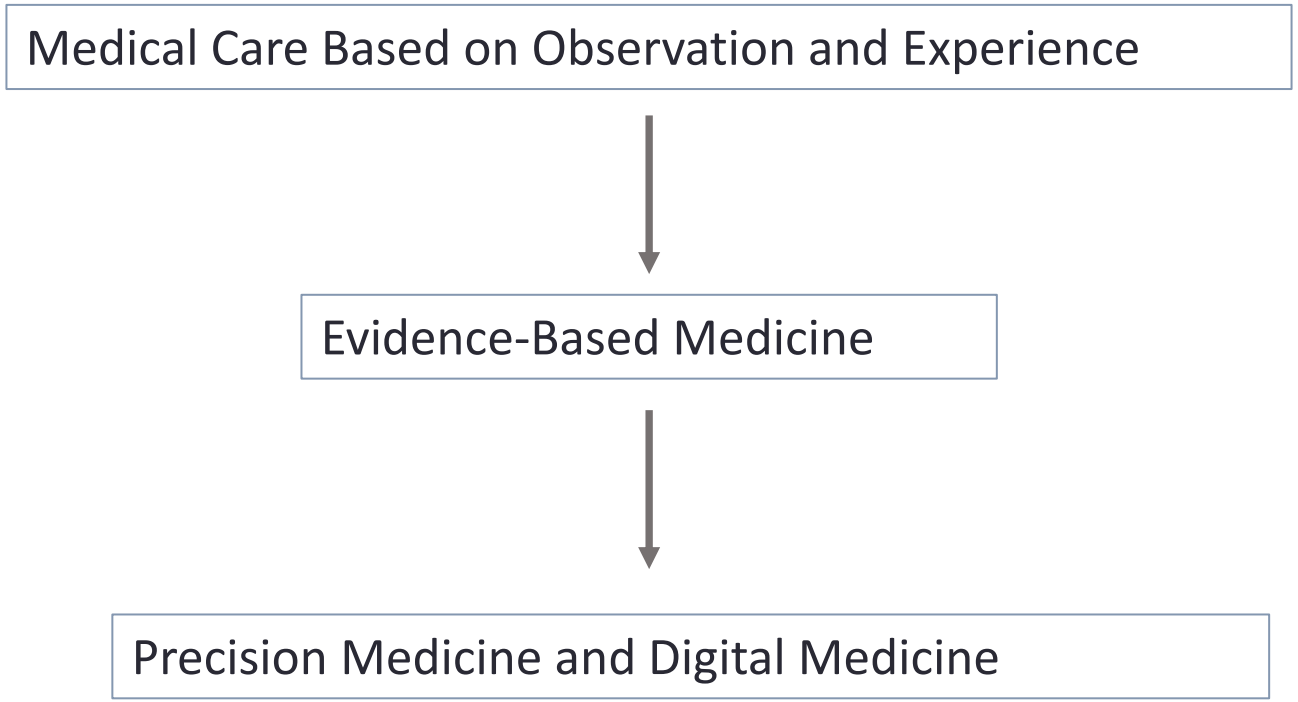
- **AIP3**: Actin Interacting Protein 3
- **CTLA4**: Cytotoxic T-Lymphocyte Associated protein 4
- **CTSH**: Cathepsin H
- **GLIS3**: GLIS Family Zinc Finger 3
- **HLA**: Human Leukocyte Antigen
- **IFIH1**: Interferon Induced with helicase C Domain 1
- **IL**: Interleukin
- **IL2RA**: Interleukin 2 Receptor subunit Alpha
- **INS**: Insulin
- **JNK**: c-Jun N-terminal Kinases
- **MAVS**: Mitochondrial Antiviral-Signaling
- **PTPN2**: Protein Tyrosine Phosphatase, Non-Receptor Type 2
- **PTPN22**: Protein Tyrosine Phosphatase, Non-Receptor Type 22
- **BACH2**: BTB Domain and CNC Homolog 2

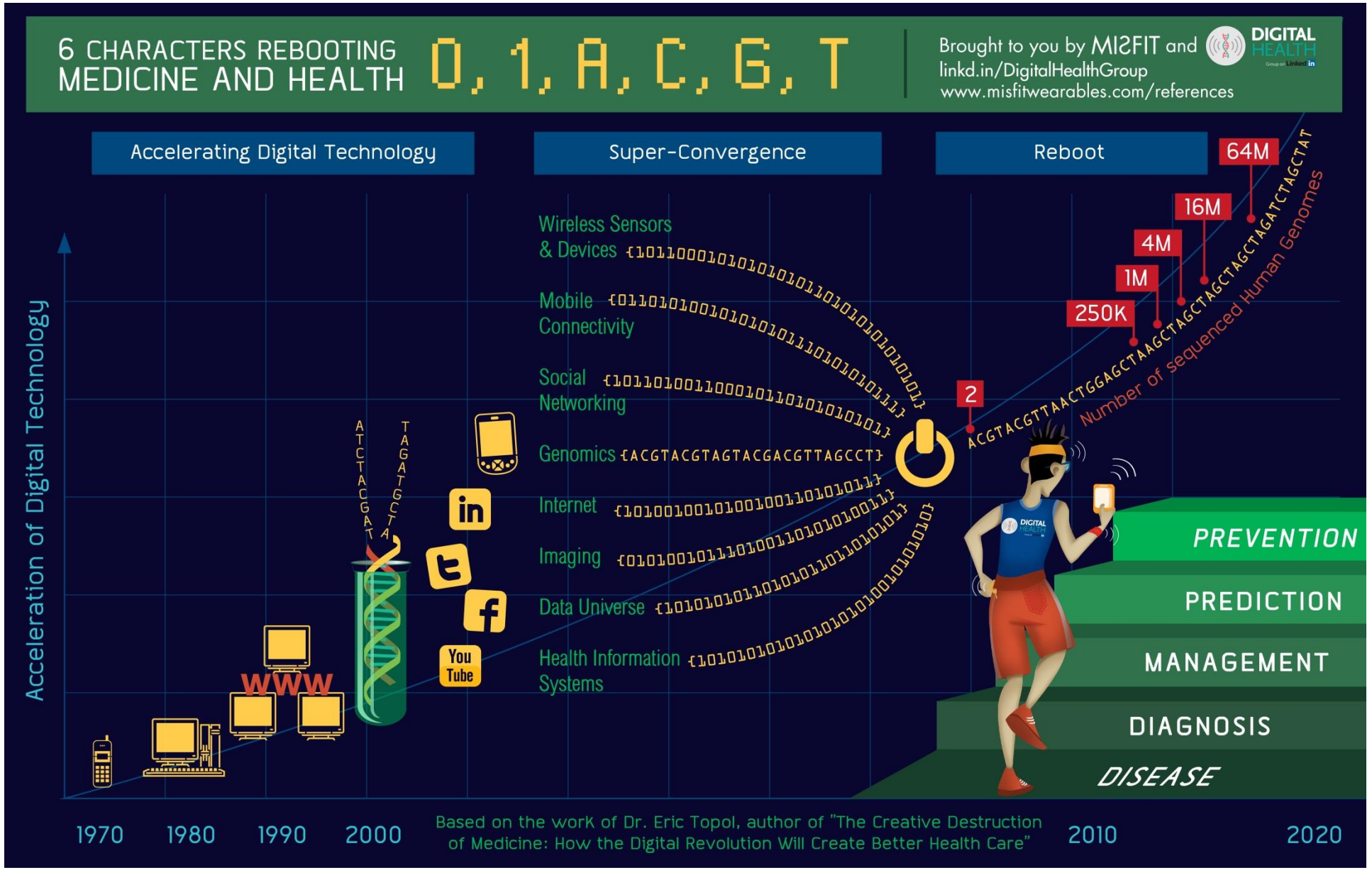
Cell Journal 20(3):294-301

U.S. Diabetes Prevalence by Ethnic Group



Evolution of Medicine





Paul Sonnier, Wikipedia

New Paradigm Shift in Diabetes Care - Precision Medicine

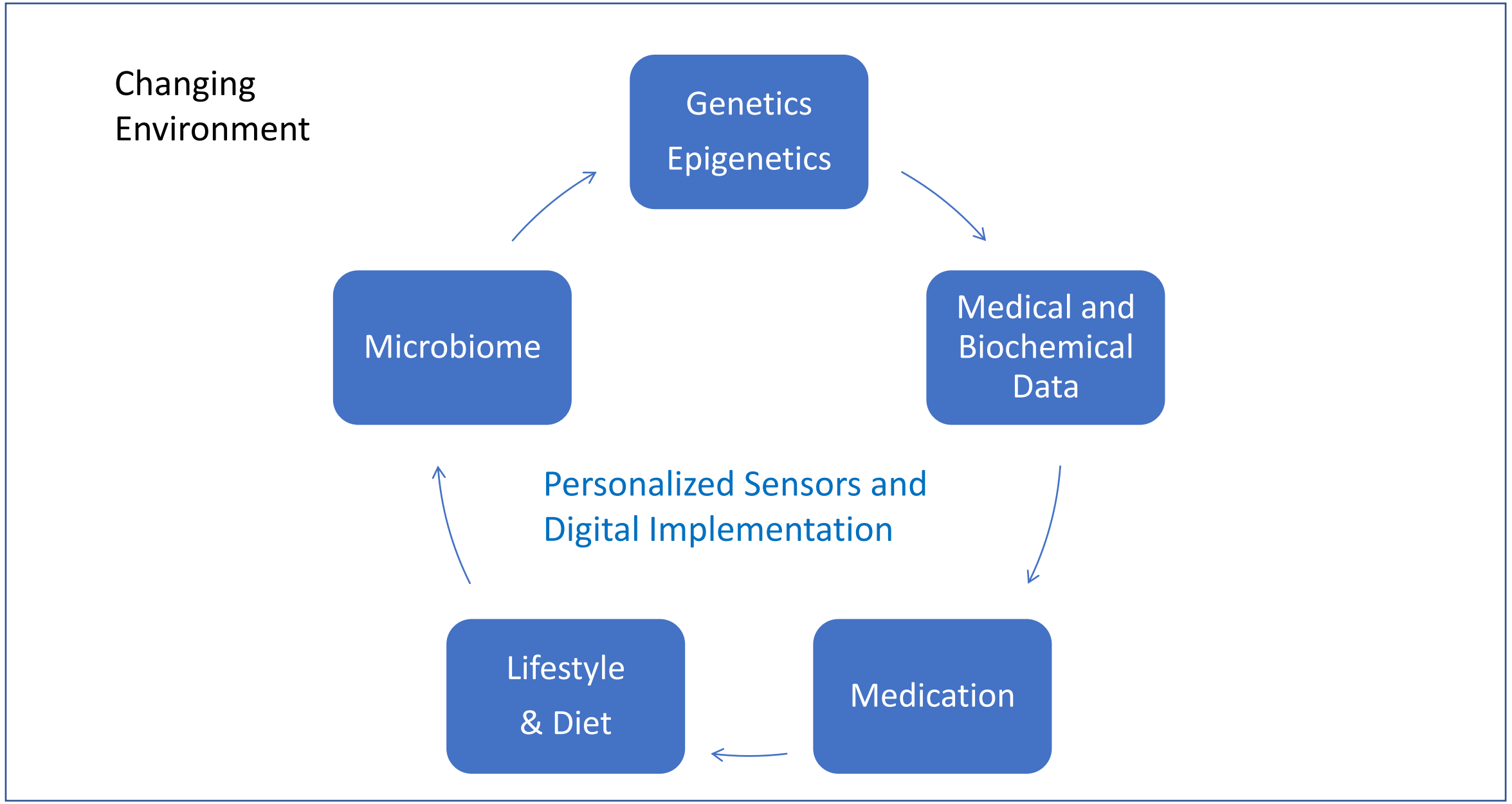
Previous Approach

- High blood sugar
- Obesity/Insulin resistance
- First and second line therapy
- Passive risk management
- Acute care
- Office records

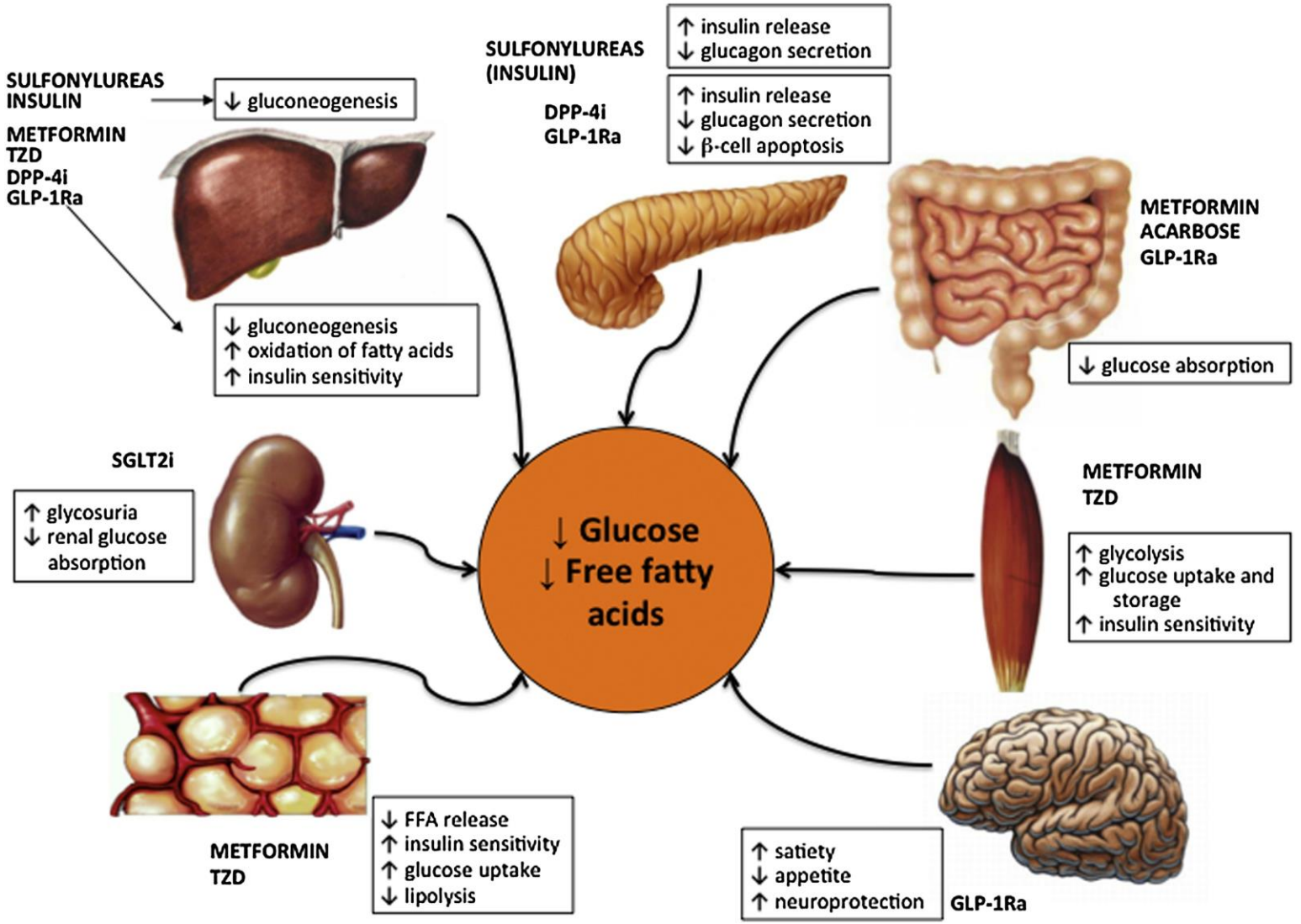
New Approach

- Biochemical Defect(s)
- Genetics
- Individualized Treatment
- Prevention & Early Detection
- Prolong Life
- Integrated Information System

Personalized Metabolic Predication and Precision Medicine



Drug Treatments for Type 2 Diabetes and Their Sites of Action



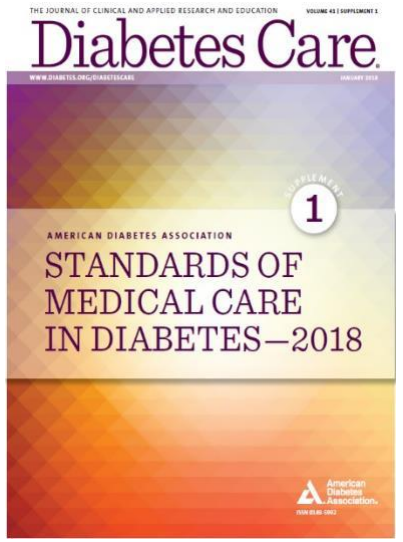
Mazzotti et al. Digestive and Liver Dis 2017. 49(3): 235-240

Medications for T2DM with Cardiovascular Benefits

SGLT2 Inhibitors	GLP-1 Receptor Agonists
Endothelial cell oxidative Stress	Endothelial cell oxidative stress
Inflammation and atherosclerosis	Inflammation and atherosclerosis
Glucose lowering effect	Glucose lowering effect
Natriuretic/diuretic effect	Natriuretic/diuretic effect
Rennin-Angiotensin	Renin-Angiotensin
Nephropathy protection	Nephropathy protection
Increase beta hydroxybutyrate	

Therapeutic Advances Over Past 20 Years

ADA Standards of Care
1989

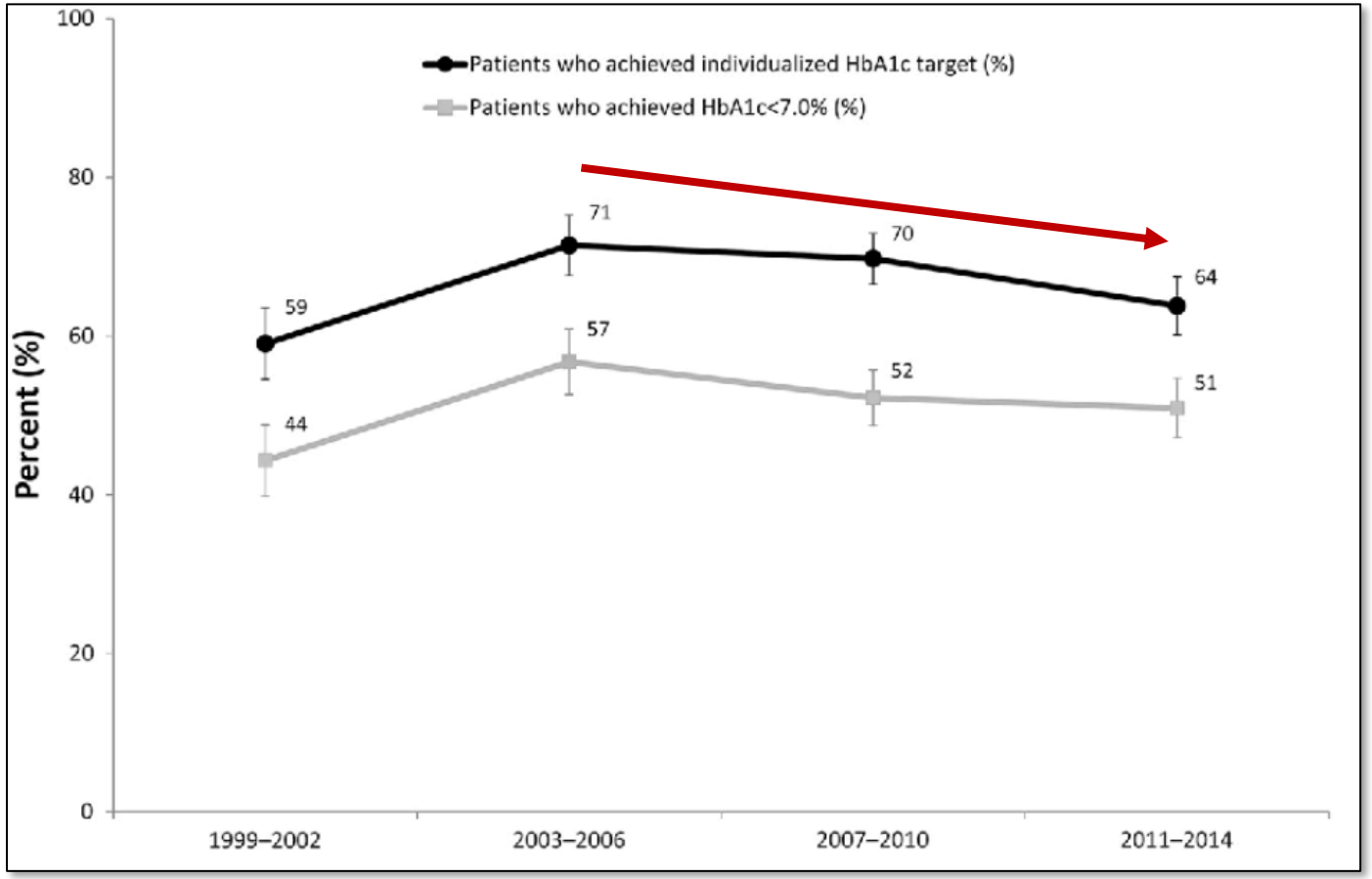


Insulin
SFU
Metformin
αGlucosidase inhibitor
Rapid-acting insulin
Basal insulin
TZD
Meglitinide
GLP-1R agonist
Pramlintide
DPP-4 inhibitor
Bromocriptine
SGLT-2 Inhibitor

1920 1960 1970 1980 1990 2000 2010 2014

Despite increasing number of new diabetes medications and technologies …

- Achievement of individualized targets declined from 69.8% to **63.8%**



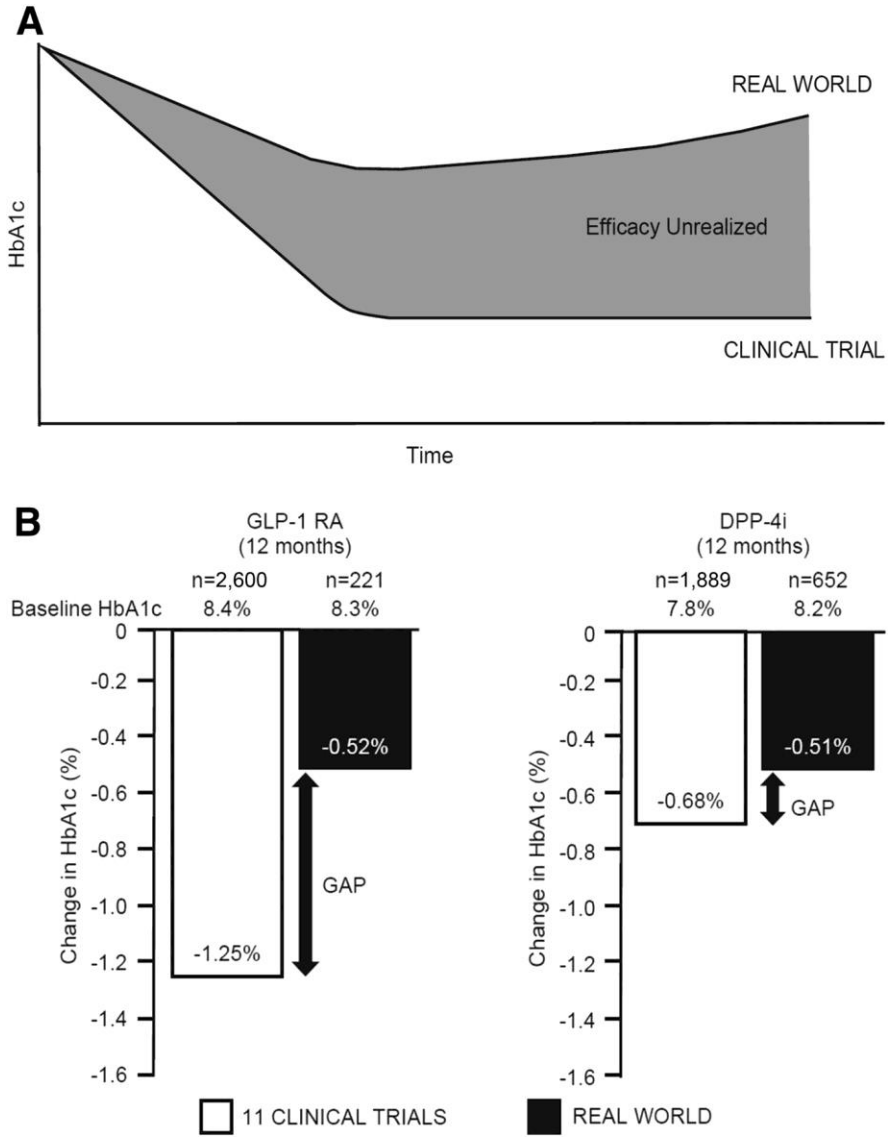
Carls G . Huynh J . Tuttle *et al*. Achievement of Glycated Hemoglobin Goals in the US Remains Unchanged Through 2014. Diabetes Ther 2017;8:863–873

What are Real World Data and where do they come from?

Real world data are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.
RWD can come from a number of sources, for example:

- ❑ Electronic health records (EHRs)
- ❑ Claims and billing activities
- ❑ Product and disease registries
- ❑ Patient-generated data including in home-use settings
- ❑ Data gathered from other sources that can inform on health status, such as mobile devices

A1c Reductions in Tightly Controlled Clinical Trials Are Not Being Translated into Real-World Outcomes.



Steven V. Edelman, and William H. Polonsky. Diabetes Care 2017;40:1425-1432

American Diabetes Association.

What's wrong with this picture?

- Decline in % of patients at HbA1c <7%
- At best, only about 50% of patients at Goal
- Increase in % of patients with very poor control
- Unacceptable level of morbidity and mortality
- Diabetes-related costs to society are tremendous

ALL THIS DESPITE MORE THAN 40 NEW T2D TREATMENT OPTIONS APPROVED SINCE 2005

Blind Spot in Current Medical Care

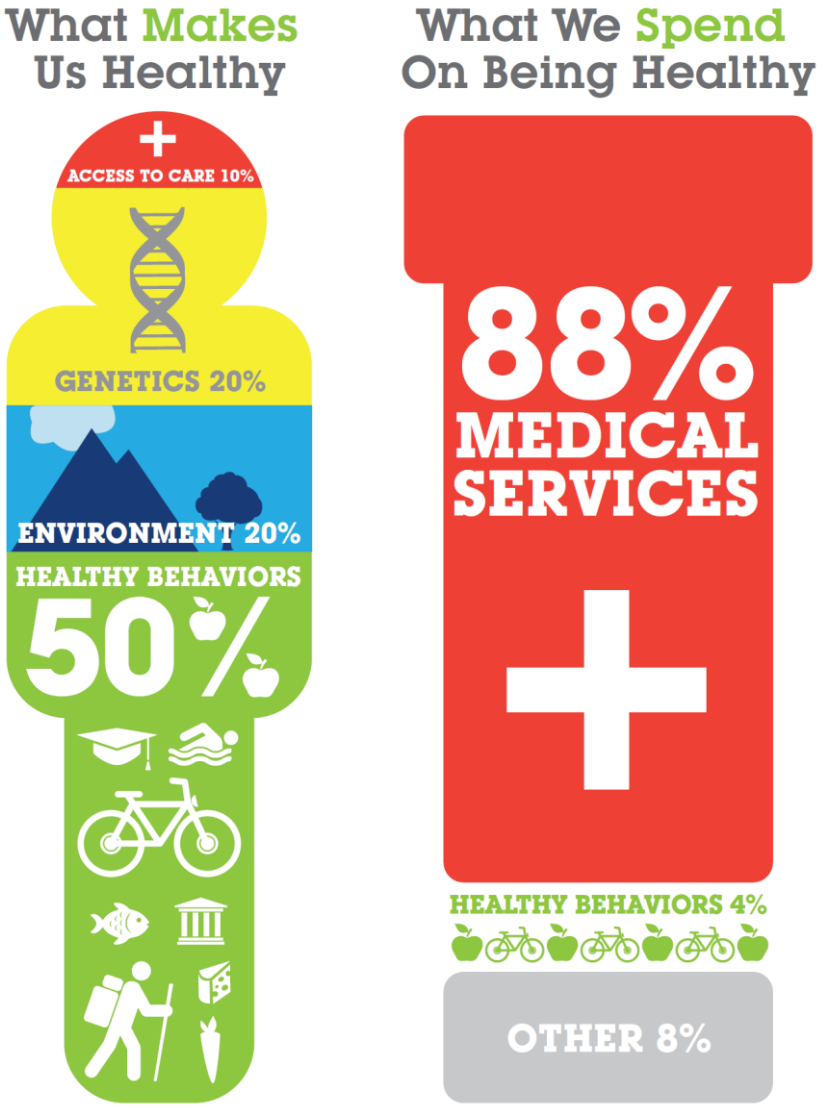
Francis Crick, 1966 – The ultimate aim of the modern movement in biology is to explain all biology in terms of physics and chemistry.

Research commonly carried out by breaking the biological processes down to pieces and determining the connection between the parts.

Biological activity does not arise just from the specificity of the individual molecules that are involved. Environmental/lifestyle factors heavily Influence our health.

Lifestyle factors are frequently neglected by current healthcare practice.

Human is a complex species in a complicated environment.
We need overall precision medicine that include effective lifestyle therapy.



Source: WHO