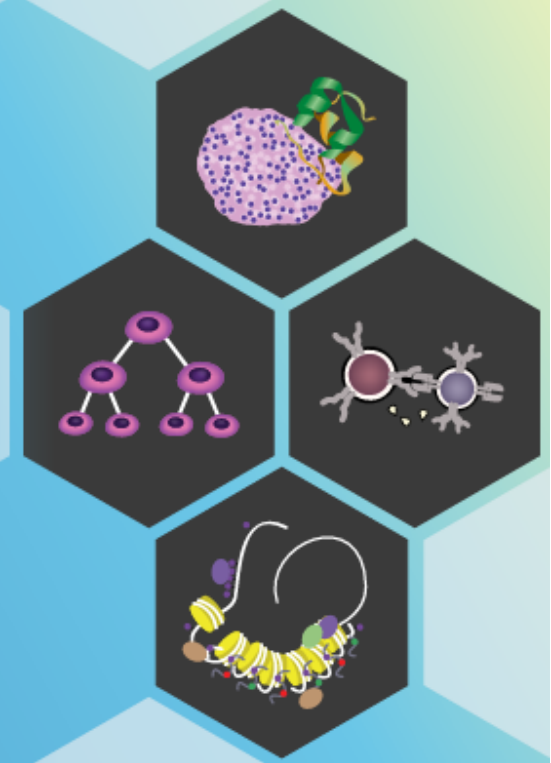
2024 RACHMIEL LEVINE-ARTHUR RIGGS

Diabetes Research Symposium

Heterogeneity of Type 2 Diabetes: Genotypes



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Assistant Professor, Harvard Medical School

Director, MGH Diabetes Genetics Clinic

Associate Member, Broad Institute of MIT and Harvard

Disclosures

- Grant/Research Support from Novo Nordisk.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their 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.

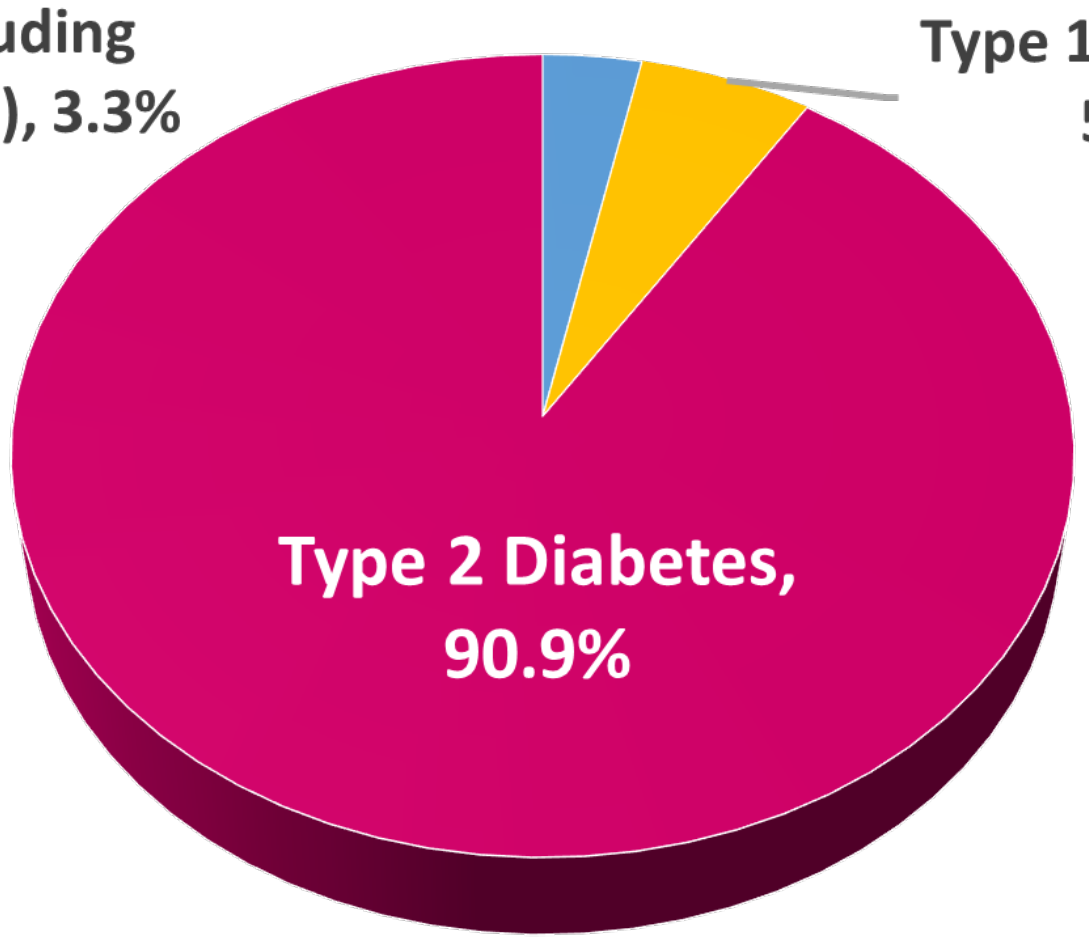
EXEMPTION:

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.

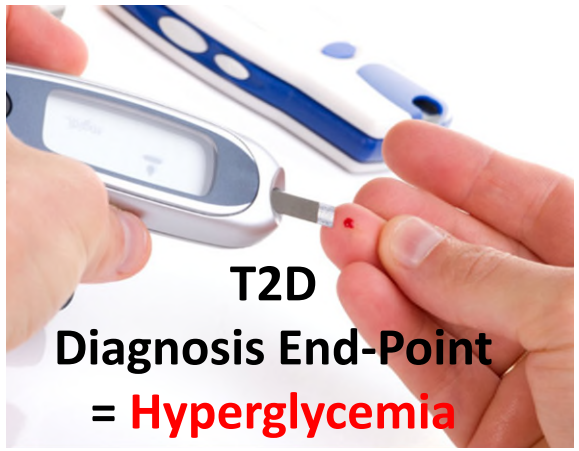
The following CLC & IB components will be addressed in this presentation:

- *Diversity in clinical presentations of metabolic disease.*
- *Recognition of bias that exists in tools available to screen for monogenic diabetes.*

The problem: Type 2 diabetes diagnosis is based on non-specific endpoint related to different underlying etiologies

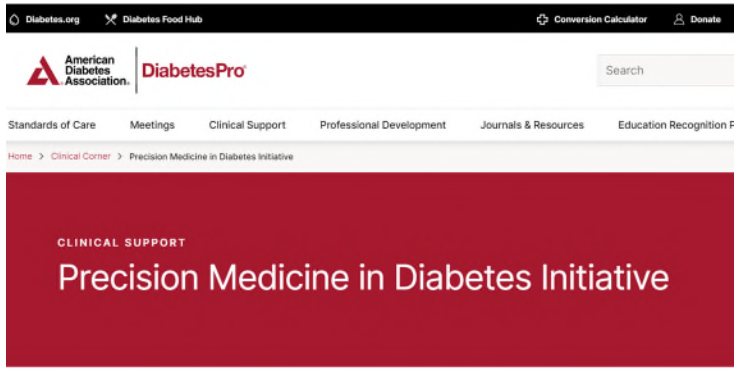


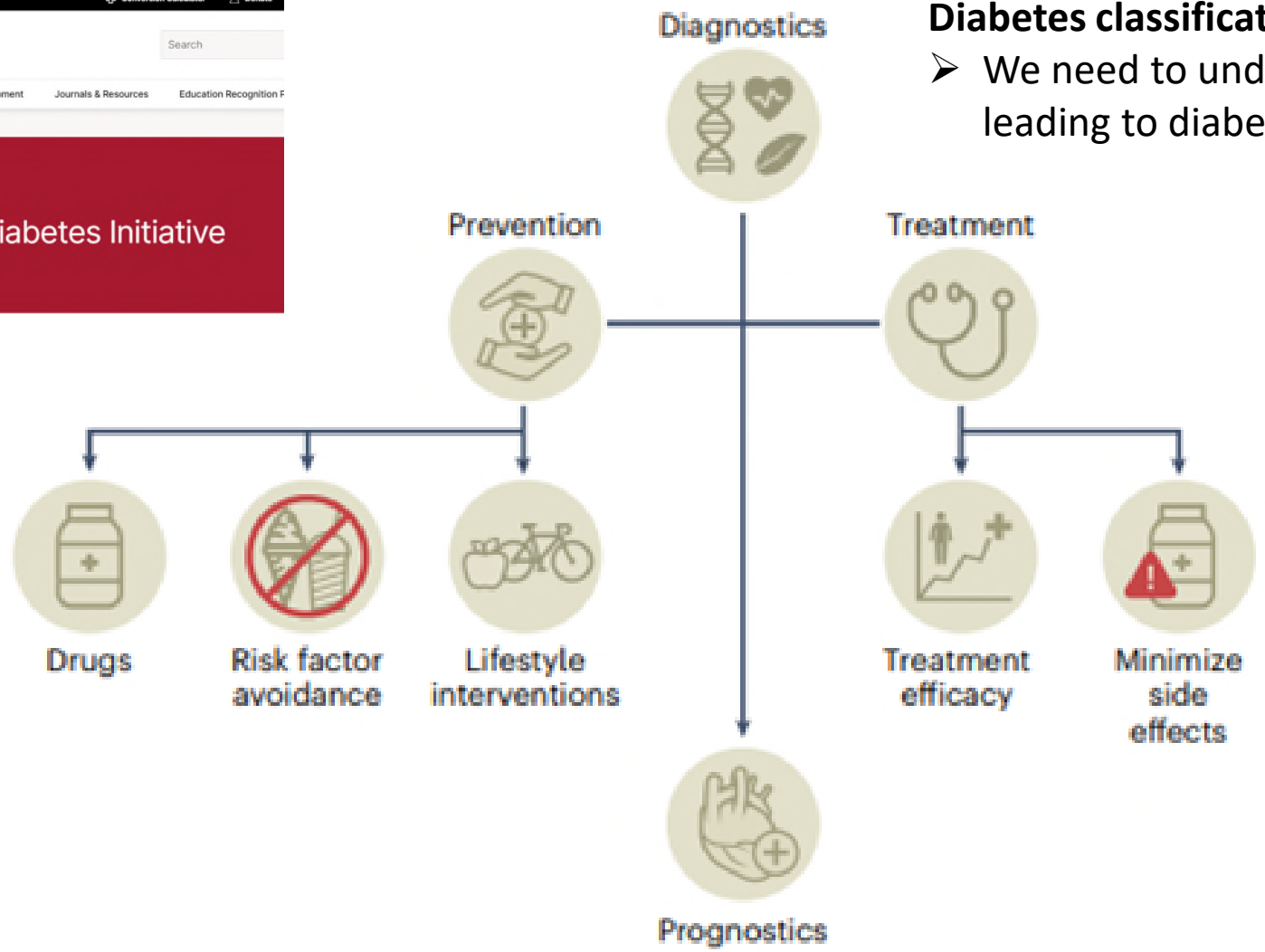
"Waste bucket diagnosis"



MMWR Morb Mortal Wkly Rep. 2018 Mar 30; 67(12): 359–361.

Pillars of Precision Medicine in Diabetes



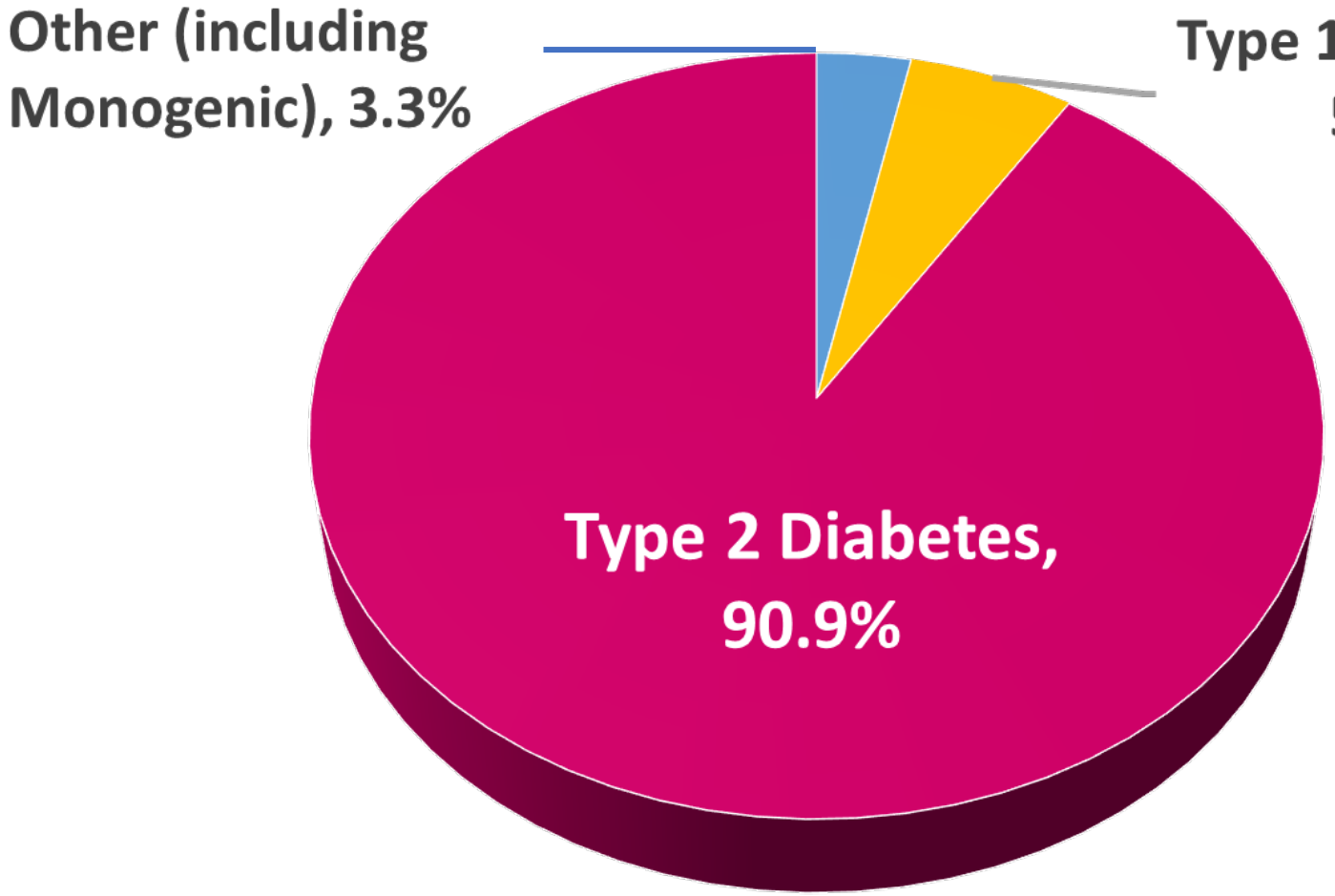


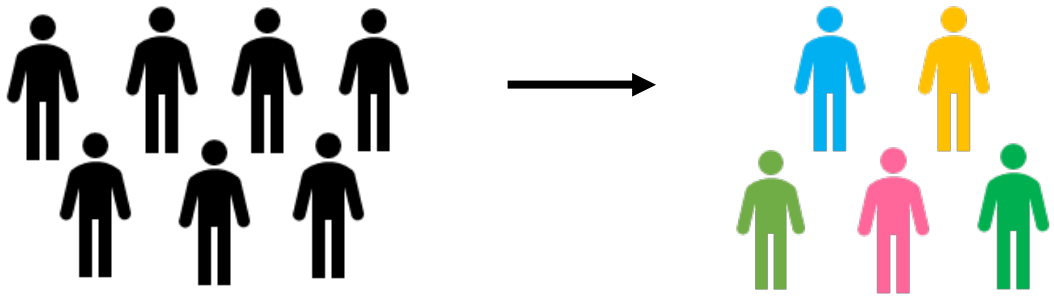
Diabetes classification is rudimentary

- We need to understand the causal pathways leading to diabetes development.

2nd International Consensus Report on Gaps and Opportunities for the Clinical Translation of Precision Diabetes Medicine, *Nature Medicine*, 2023

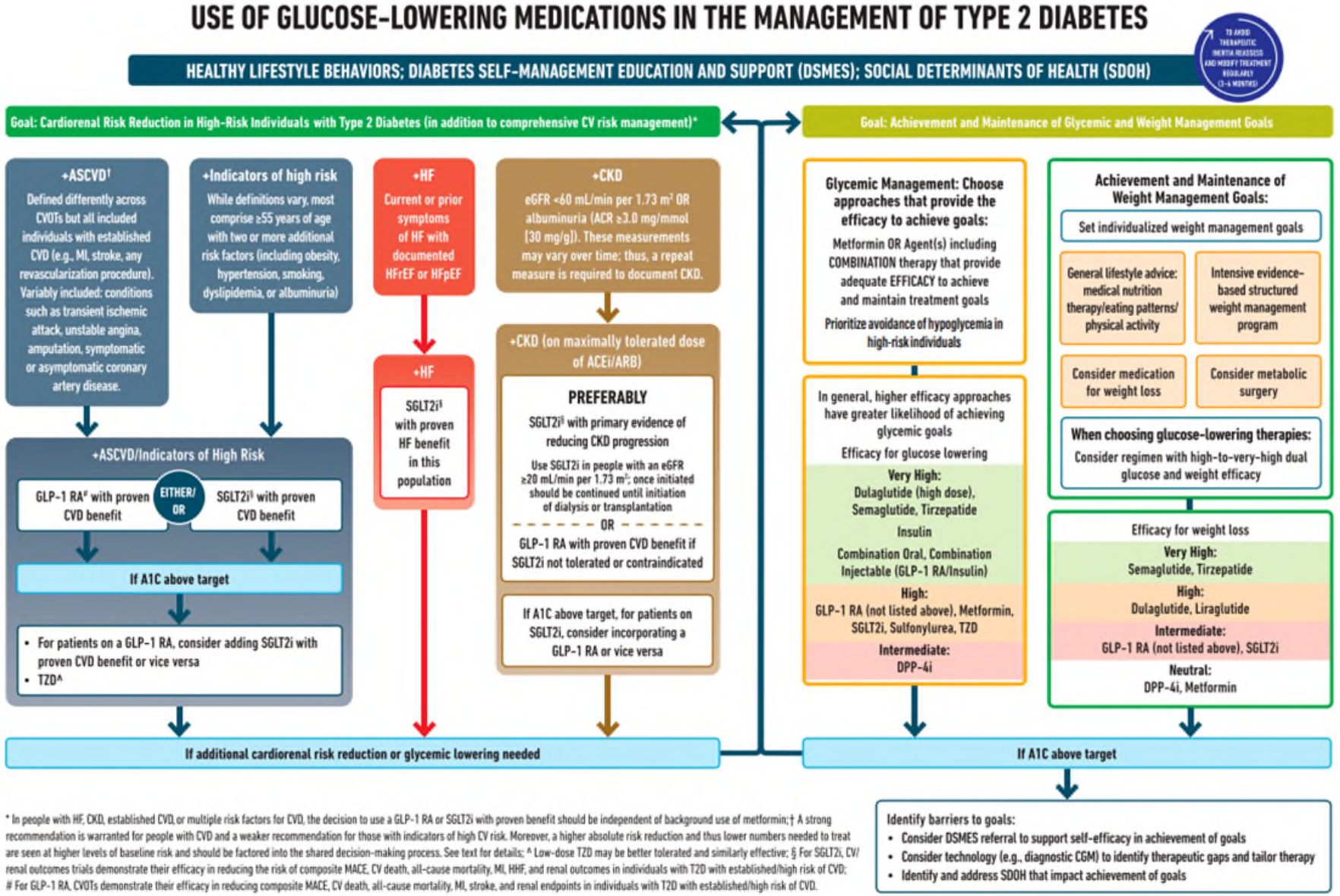
Can we improve classification of diabetes?

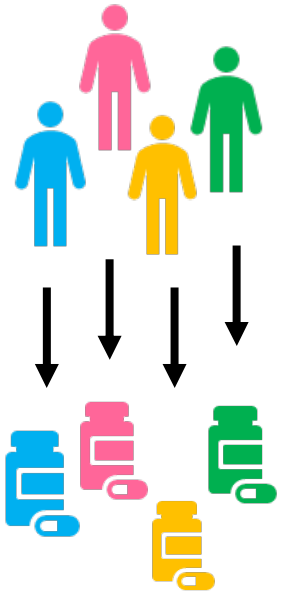




Ideally informed by disease mechanism

Current T2D treatment approach does not consider underlying disease pathophysiology





Standards of Care in Diabetes - 2024

To improve T2D management, can we target underlying disease mechanisms rather than just treating the symptom?

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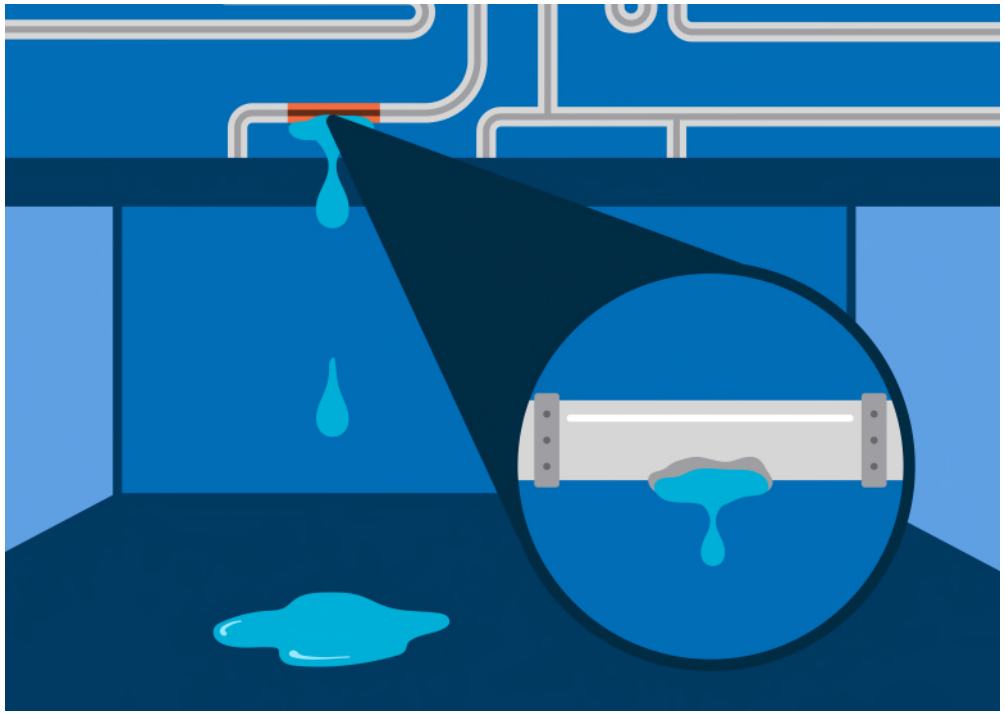
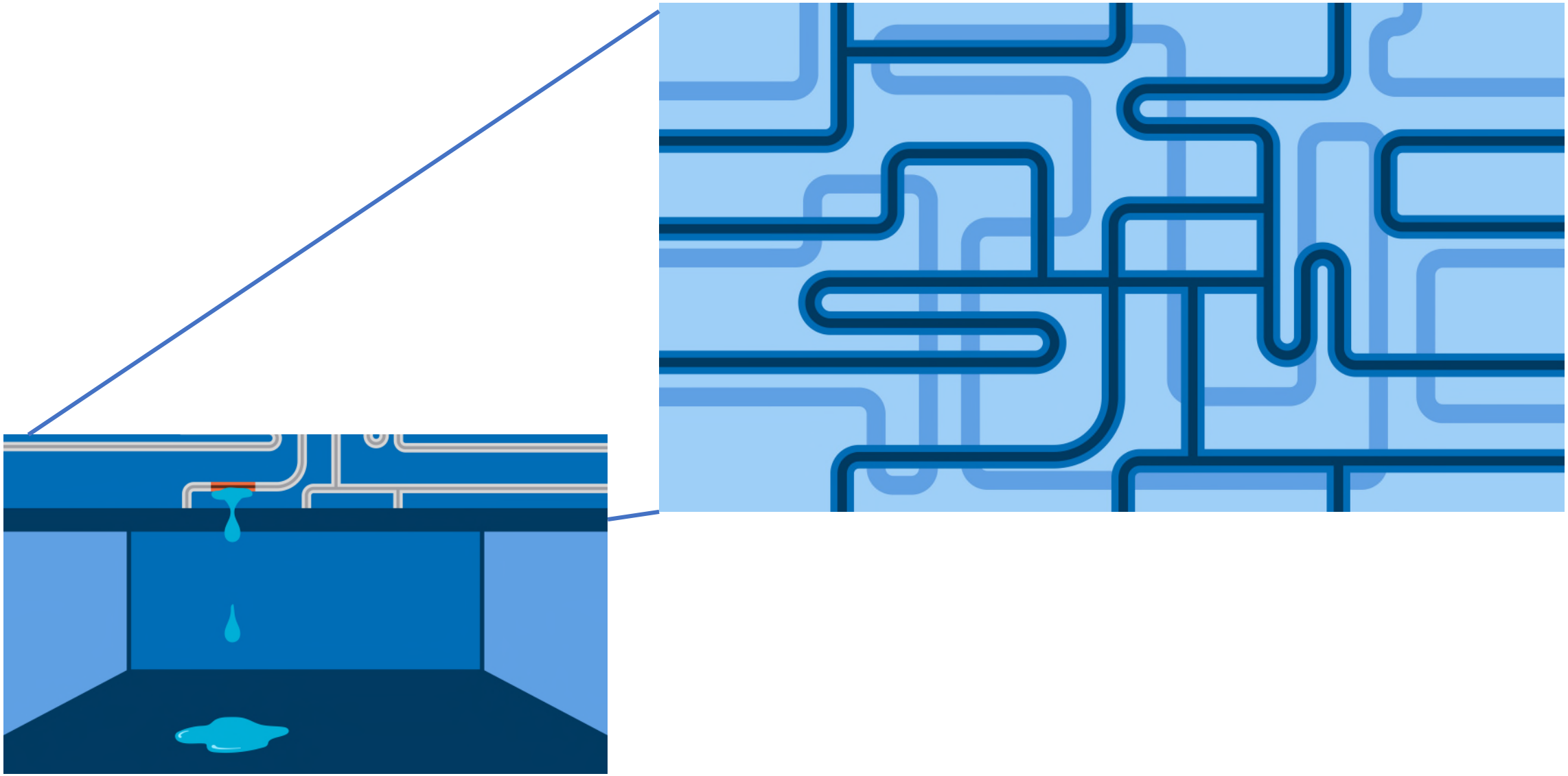
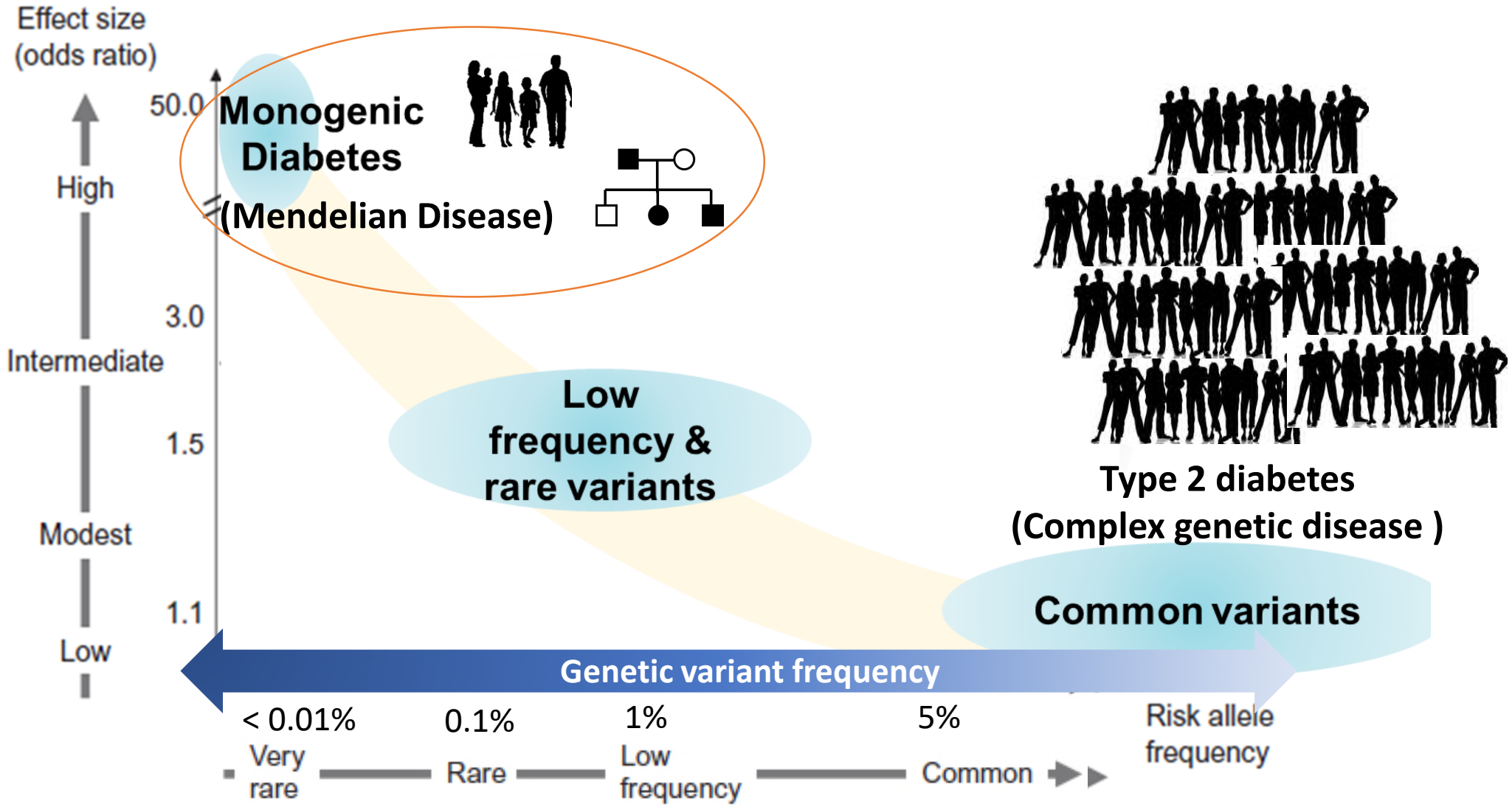


How can we understand the complex network of pathways leading to type 2 diabetes?



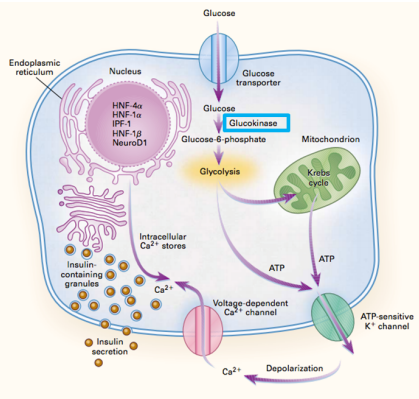
Spectrum of Genetic Contribution to Diabetes

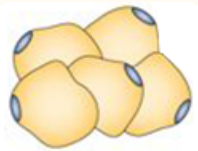


Adapted from Udler MS, Florez JC: Diabetes. *Genomic and Precision Medicine: Primary Care,* 3rd ed. 2017

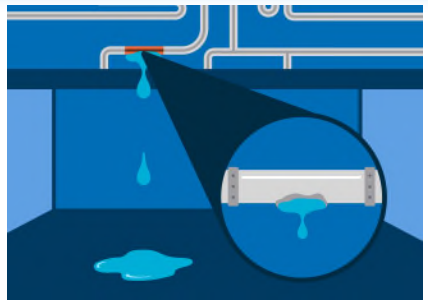
Monogenic Diabetes as Endotypes, Highlighting Disease Mechanisms

Gene → Disease mechanism → Treatment





Distinct genetic pathways
lead to diabetes
and inform management

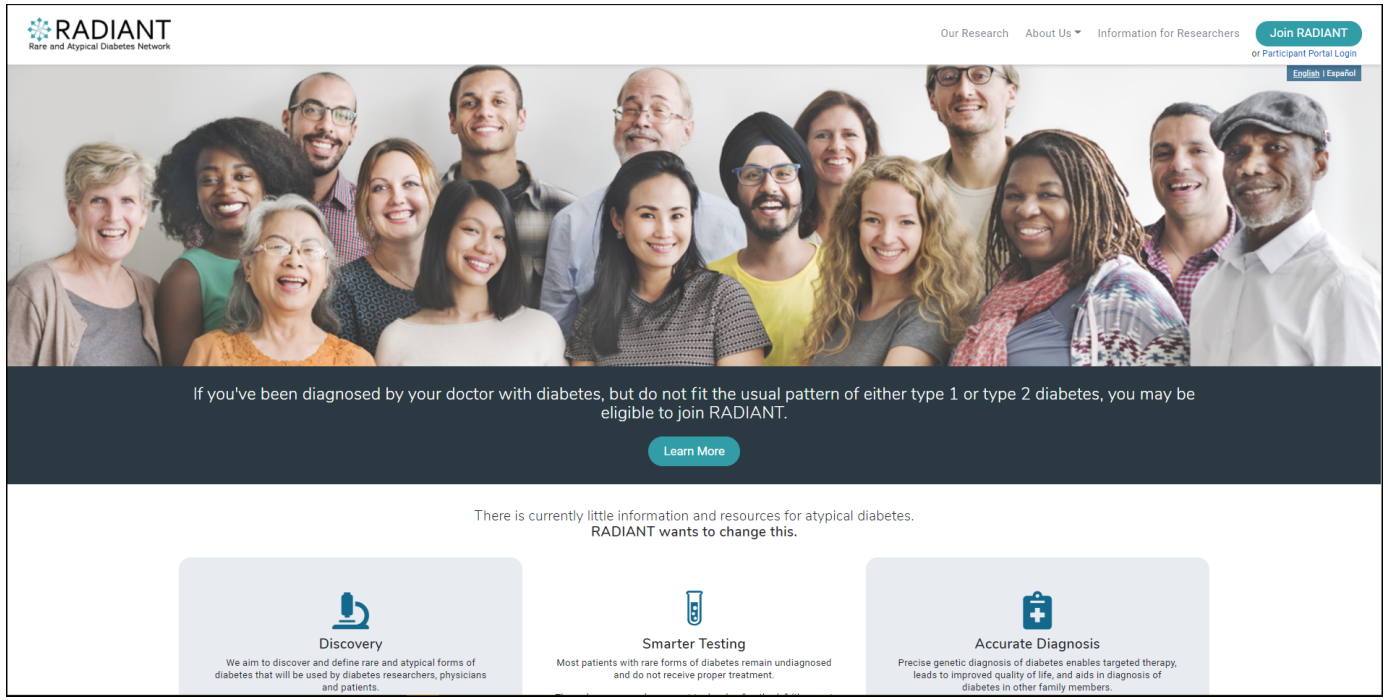


Pearson *et al*., Lancet 2003; Shields *et al*. Diabetologia 2010; Murphy *et a*l. Nat Clin Practice, End & Metabolism, 2008; Fajans *et al*, NEJM 2001.

Are there <u>new</u> subtypes of T2D to be discovered?

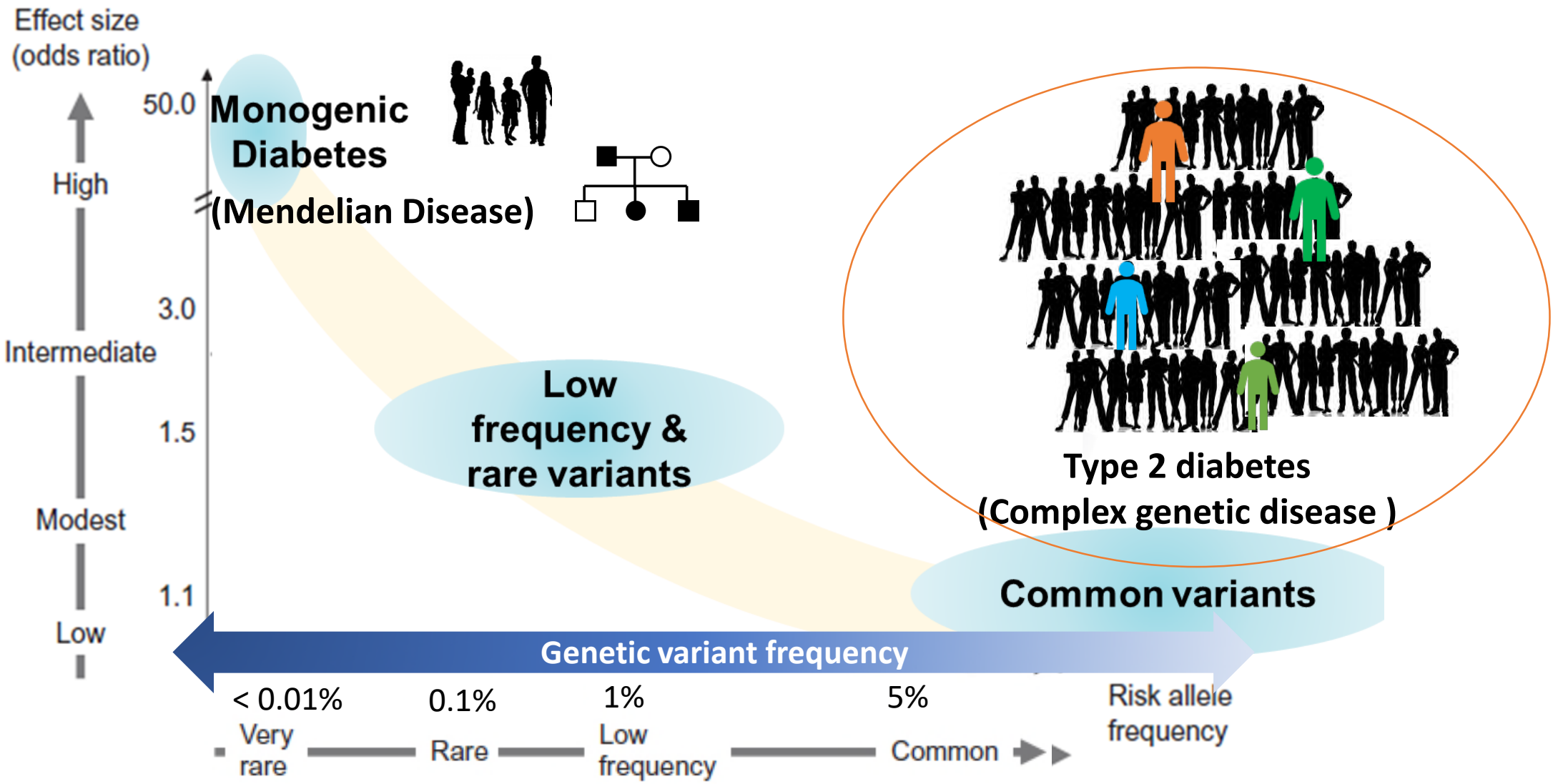
RADIANT study: www.atypicaldiabetesnetwork.org

- U-54 NIDDK multi-site national **study of individuals with Atypical Diabetes**
- <u>Free whole genome sequencing</u> for eligible participants
- Ideal patients are those whose “type” of diabetes is not clear to you



RADIANT
Rare and Atypical Diabetes Network

Spectrum of Genetic Contribution to Diabetes



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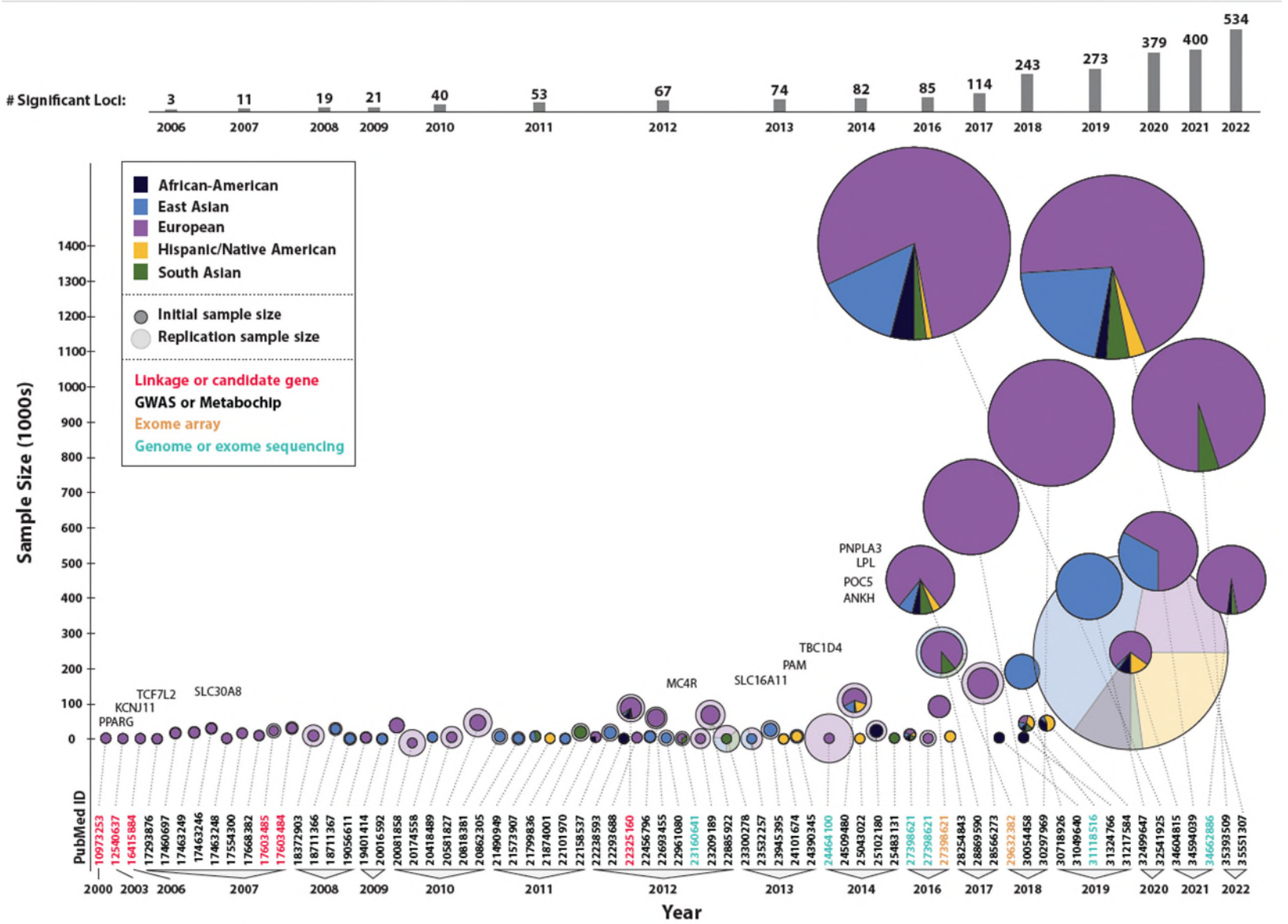
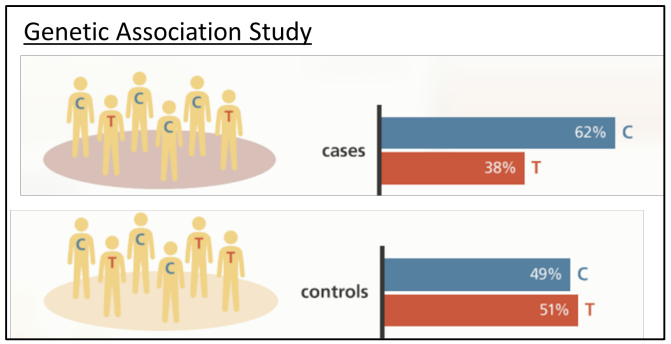
Massive genetic discovery for type 2 diabetes: a window to understanding disease mechanisms



>600 genetic loci associated with T2D



Kreienkamp, Voight, Gloyn, Udler. Genetics of Type 2 Diabetes, Diabetes in America, *2024*

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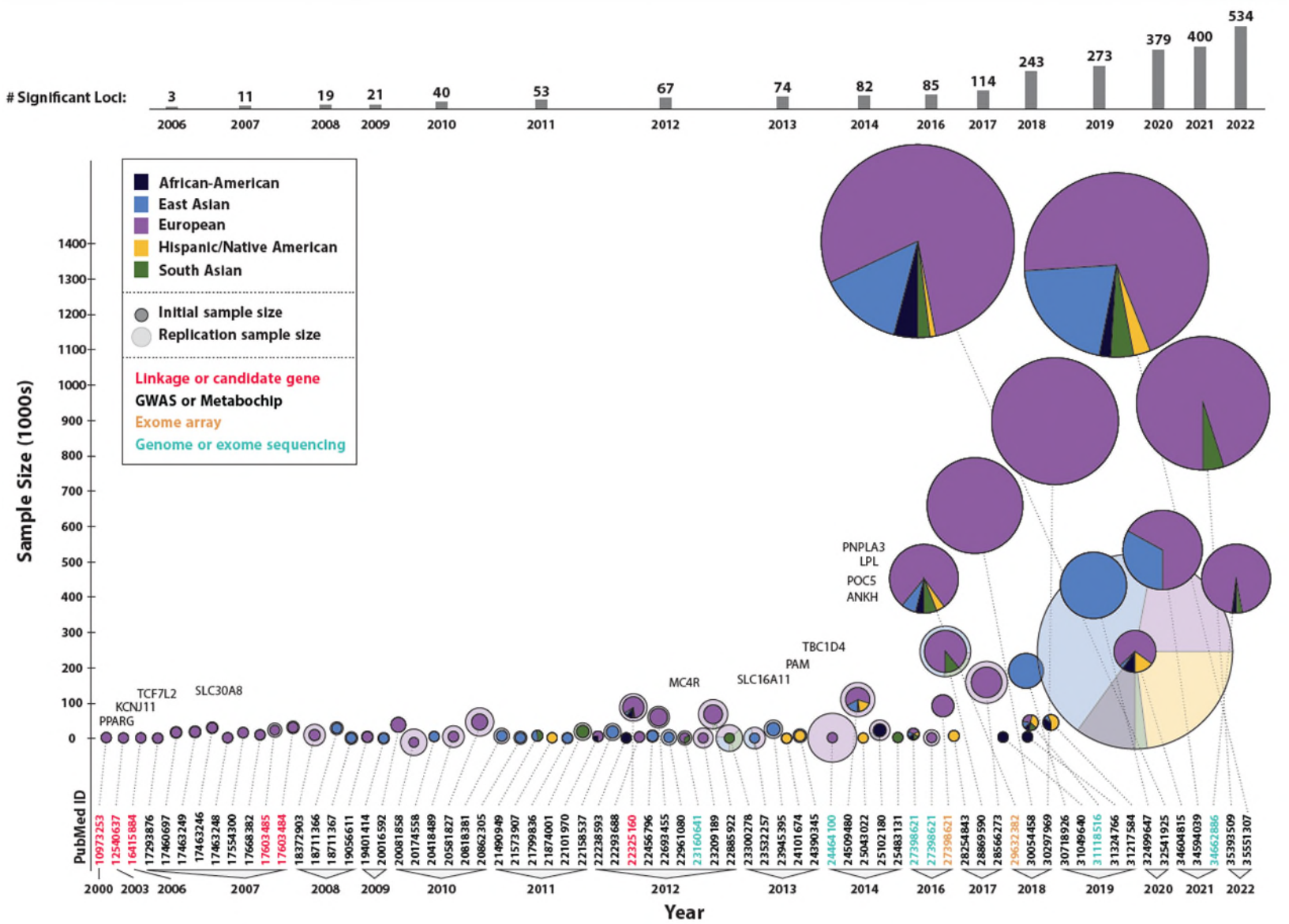
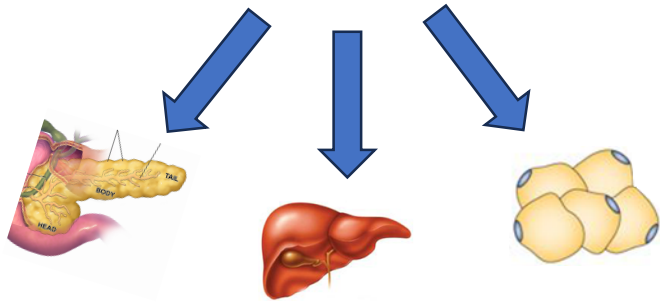


>600 genetic loci associated with T2D

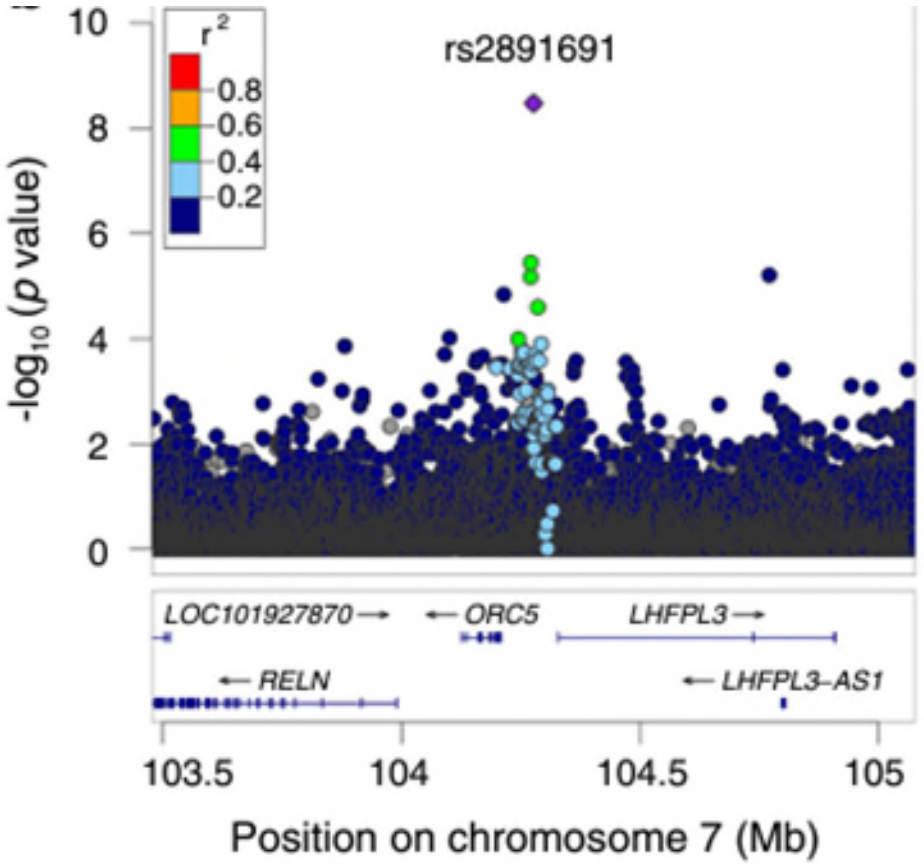
Separate into disease mechanisms



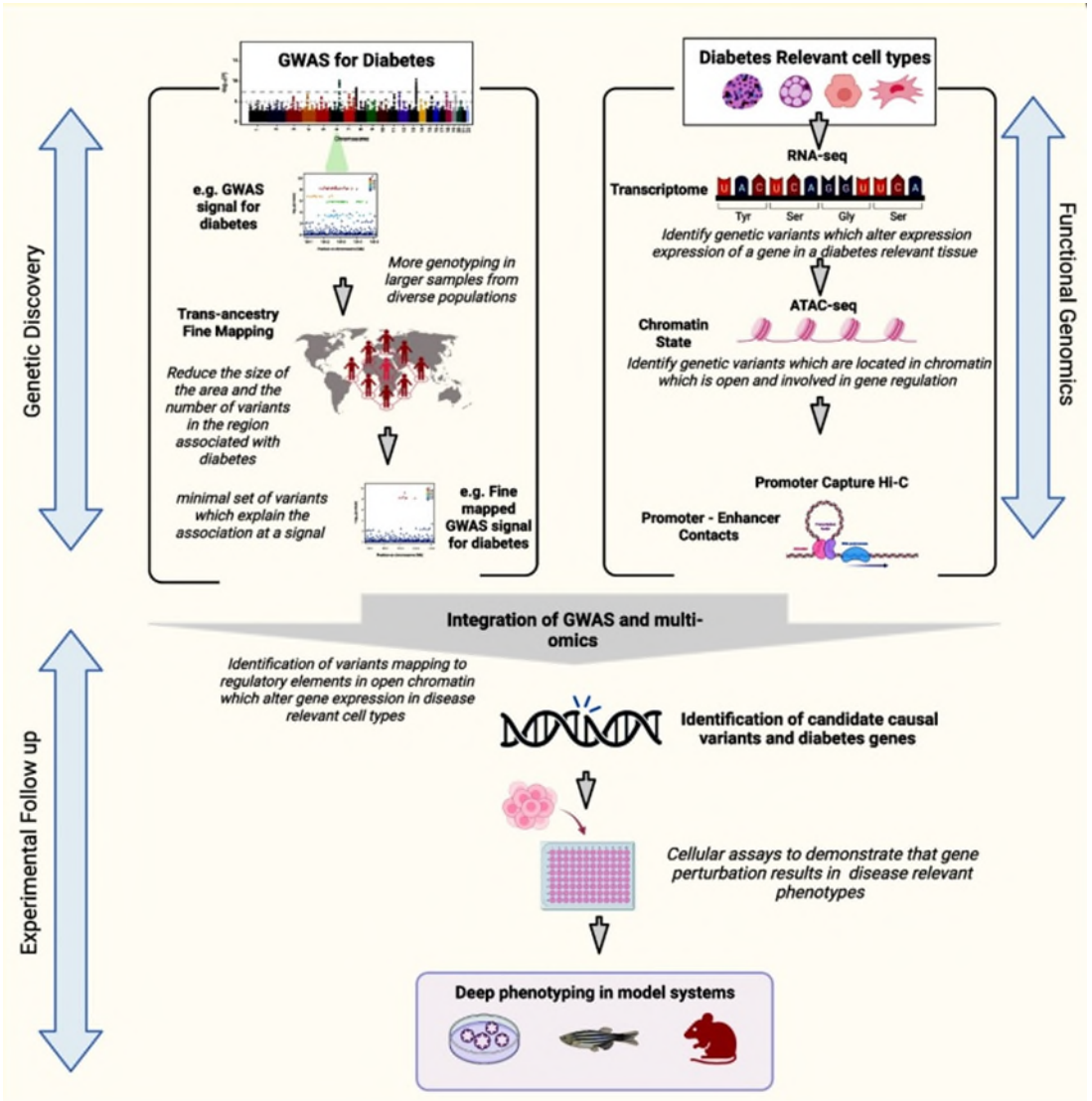
Kreienkamp, Voight, Gloyn, Udler. Genetics of Type 2 Diabetes, Diabetes in America, *2024*

Challenge is connecting loci to disease mechanisms

Issue: ***Unknown causal variants, genes***



Huerta-Chagoya et al Diabetologia, 2023



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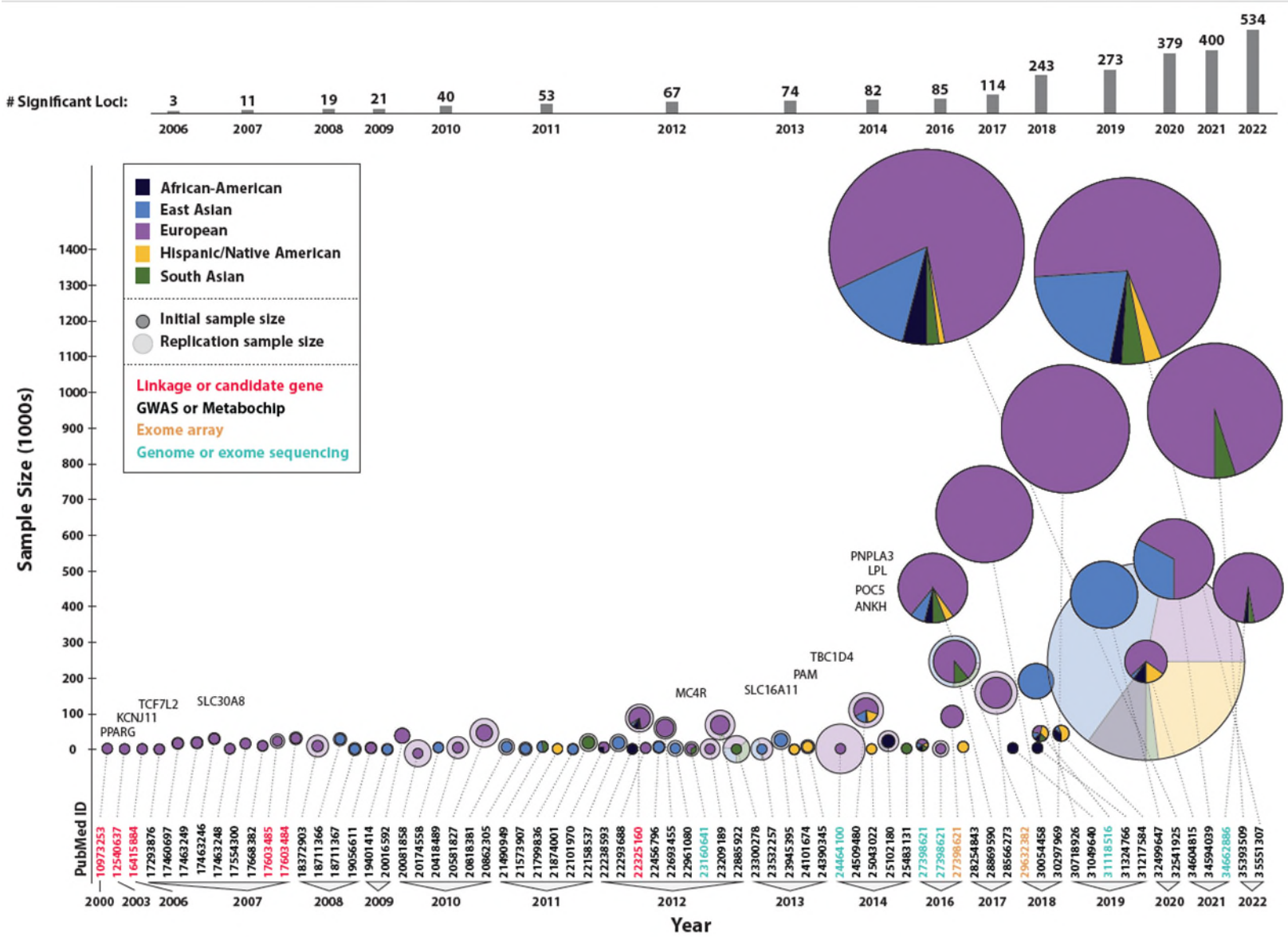

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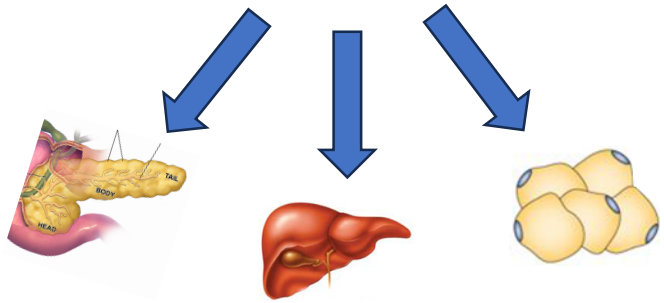

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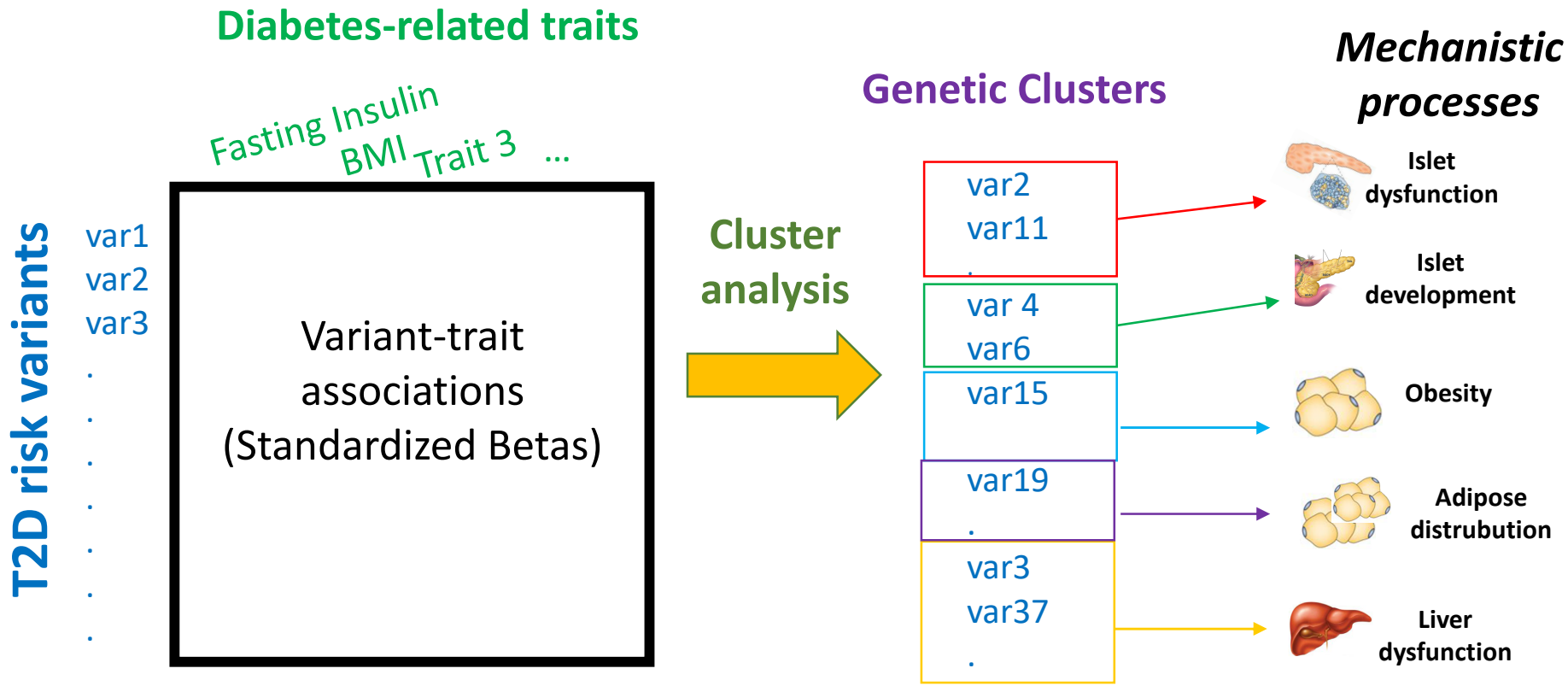
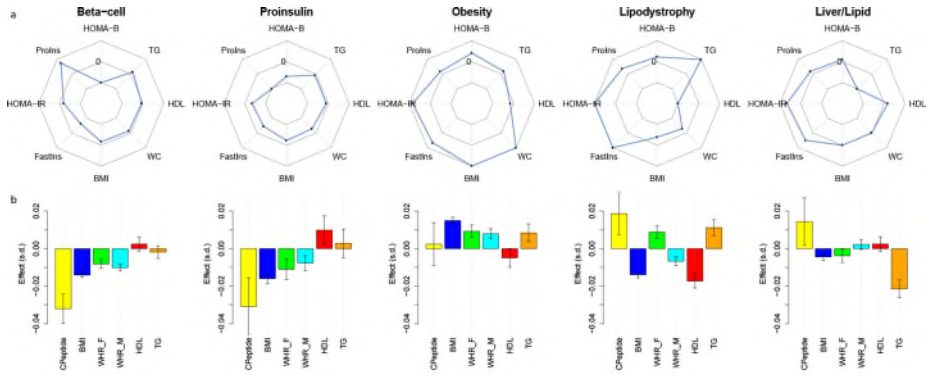
Connect variants to mechanistic processes using clustering of variant-trait associations



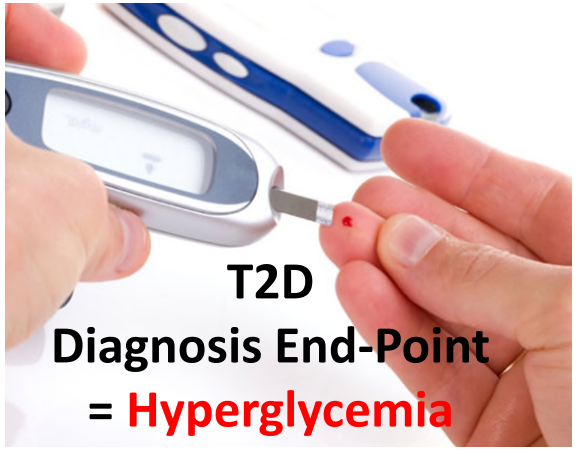
T2D genetic variants representing loci, aligned by T2D-risk increasing allele

5 Salient genetic clusters of T2D robust across methods



Udler *et al*, PLOS Medicine, 2018

- 94 SNPs, 47 Traits

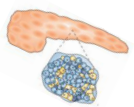


Mahajan *et al*, Nature Genetics, 2018

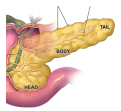
- 94 SNPs, 12 Traits

Insulin Deficiency

Proinsulin +

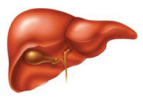


Proinsulin -

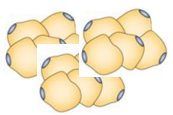


Insulin Resistance

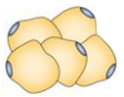
Liver/Lipid dysfunction



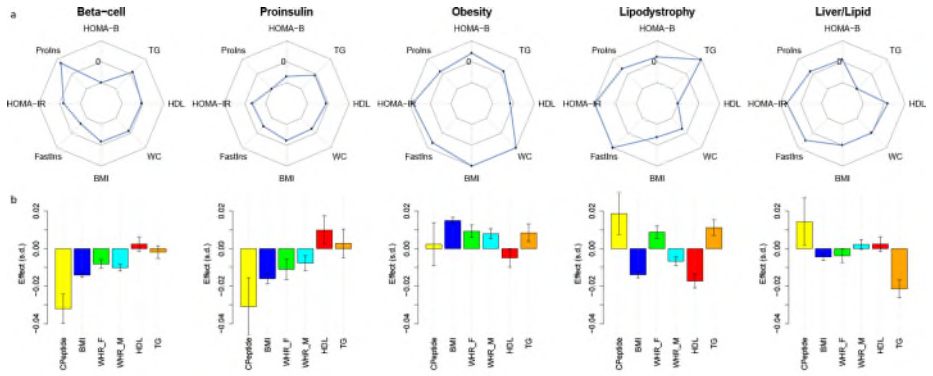
Lipodystrophy

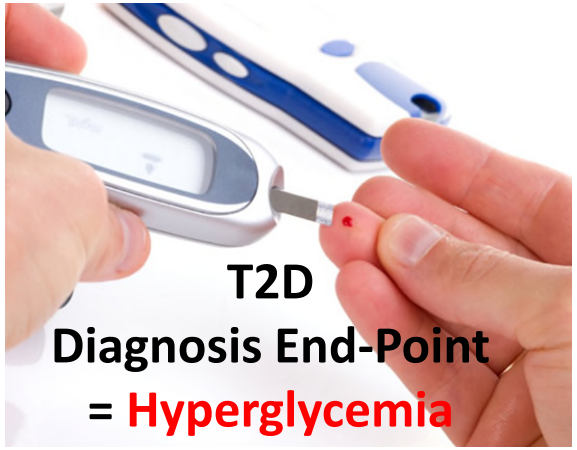


Obesity



5 Salient genetic clusters of T2D robust across methods





Udler *et al*, PLOS Medicine, 2018

- 94 SNPs, 47 Traits

Mahajan *et al*, Nature Genetics, 2018

- 94 SNPs, 12 Traits

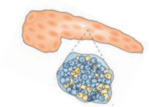
Kim *et al* Diabetalogia, 2023

- 323 T2D variants, 64 traits
- 10 clusters

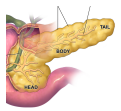
Introduced high-throughput pipeline

Insulin Deficiency

Proinsulin +



Proinsulin -



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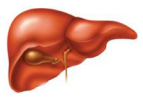
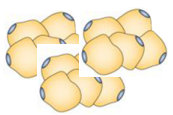
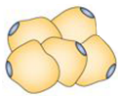
Liver/Lipid dysfunction



Lipodystrophy



Obesity



T2D Multi-ancestry Genetic Clusters

Article

Genetic drivers of heterogeneity in type 2 diabetes pathophysiology

Nature

https://doi.org/10.1038/s41586-024-07019-6
Received: 22 March 2023
Accepted: 3 January 2024
Published online: 19 February 2024
Open access
Check for updates

Type 2 diabetes (T2D) is a heterogeneous disease that develops through diverse pathophysiological processes[1,2] and molecular mechanisms that are often specific to cell type[3,4]. Here, to characterize the genetic contribution to these processes across ancestry groups, we aggregate genome-wide association study data from 2,535,601 individuals (39.7% not of European ancestry), including 428,452 cases of T2D. We identify 1,289 independent association signals at genome-wide significance ($P < 5 \times 10^{-8}$) that map to 611 loci, of which 145 loci are, to our knowledge, previously unreported. We define eight non-overlapping clusters of T2D signals that are characterized by distinct profiles of cardiometabolic trait associations. These clusters are differentially enriched for cell-type-specific regions of open chromatin, including pancreatic islets, adipocytes, endothelial cells and enteroendocrine cells. We build cluster-specific partitioned polygenic scores[5] in a further 279,552 individuals of diverse ancestry, including 30,288 cases of T2D, and test their association with T2D-related vascular outcomes. Cluster-specific partitioned polygenic scores are associated with coronary artery disease, peripheral artery disease and end-stage diabetic nephropathy across ancestry groups, highlighting the importance of obesity-related processes in the development of vascular outcomes. Our findings show the value of integrating multi-ancestry genome-wide association study data with single-cell epigenomics to disentangle the aetiological heterogeneity that drives the development and progression of T2D. This might offer a route to optimize global access to genetically informed diabetes care.

- T2D-GGI, 2.5M Multi-ancestry GWAS
  - 1,289 SNPs, 37 traits
  - Method: Unsupervised hierarchical clustering
  - # Clusters = 8

nature medicine

Article

https://doi.org/10.1038/s41591-024-02865-3

Multi-ancestry polygenic mechanisms of type 2 diabetes

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Accepted: 6 February 2024
Published online: 05 March 2024
Check for updates

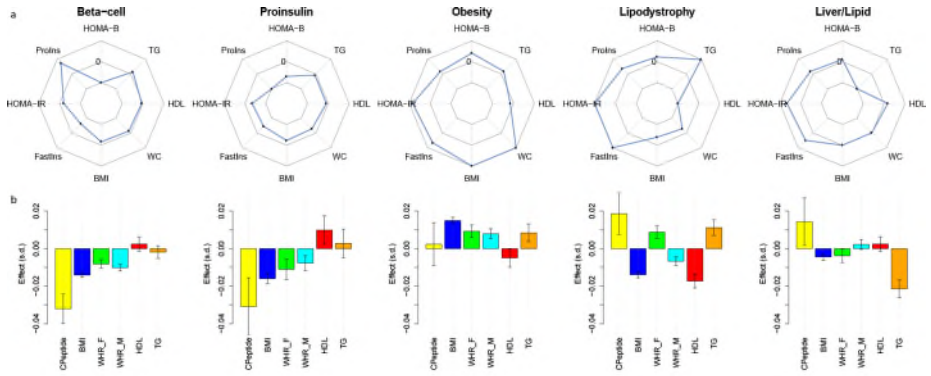
Kirk Smith[1,2,3,19], Aaron J. Deutsch[1,2,3,4,19], Carolyn McGrail[5], Hyunkyung Kim[1,2,3,6,7], Sarah Hsu[3,8], Alicia Huerta-Chagoya[1,2,3], Ravi Mandla[1,2,3], Philip H. Schroeder[1,2,3], Kenneth E. Westerman[3,4,8], Lukasz Szczerbinski[1,2,3,9,10], Timothy D. Majarian[3,8,18], Varinderpal Kaur[1,2,3], Alice Williamson[11,12], Noah Zaitlen[13,14,15], Melina Claussnitzer[1,2,3,4,16], Jose C. Florez[1,2,3,4], Alisa K. Manning[3,4,8], Josep M. Mercader[1,2,3,4], Kyle J. Gaulton[17] & Miriam S. Udler[1,2,3,4]

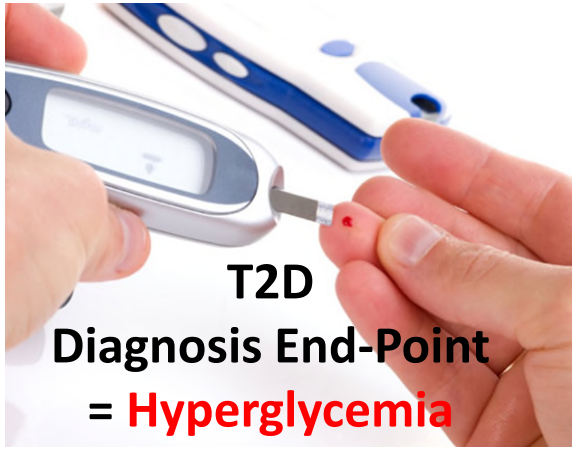
Type 2 diabetes (T2D) is a multifactorial disease with substantial genetic risk, for which the underlying biological mechanisms are not fully understood. In this study, we identified multi-ancestry T2D genetic clusters by analyzing genetic data from diverse populations in 37 published T2D genome-wide association studies representing more than 1.4 million individuals. We implemented soft clustering with 650 T2D-associated genetic variants and 110 T2D-related traits, capturing known and novel T2D clusters with distinct cardiometabolic trait associations across two independent biobanks representing diverse genetic ancestral populations (African, $n = 21,906$; Admixed American, $n = 14,410$; East Asian, $n = 2,422$; European, $n = 90,093$; and South Asian, $n = 1,262$). The 12 genetic clusters were enriched for specific

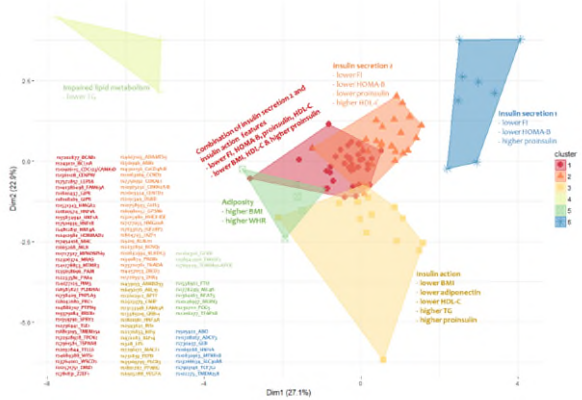
- MA + individual diverse study populations
  - 650 SNPs, 110 traits
  - bNMF soft clustering
  - # Clusters = 12

a broader range of biological mechanisms and provide preliminary insights

5 Salient genetic clusters of T2D robust across methods







Udler *et al*, PLOS Medicine, 2018
- 94 SNPs, 47 Traits

Mahajan *et al*, Nature Genetics, 2018
- 94 SNPs, 12 Traits

Kim *et al* Diabetalogia, 2023
- 323 T2D variants, 64 traits
- 10 clusters

Introduced high-throughput pipeline

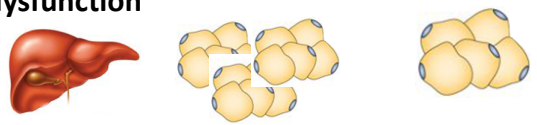
Smith, Deutsch *et al*, Nature Medicine 2024 – Multi-ancestry
- 650 T2D variants, 110 traits
- 12 clusters

Insulin Deficiency

Proinsulin + **Proinsulin -**

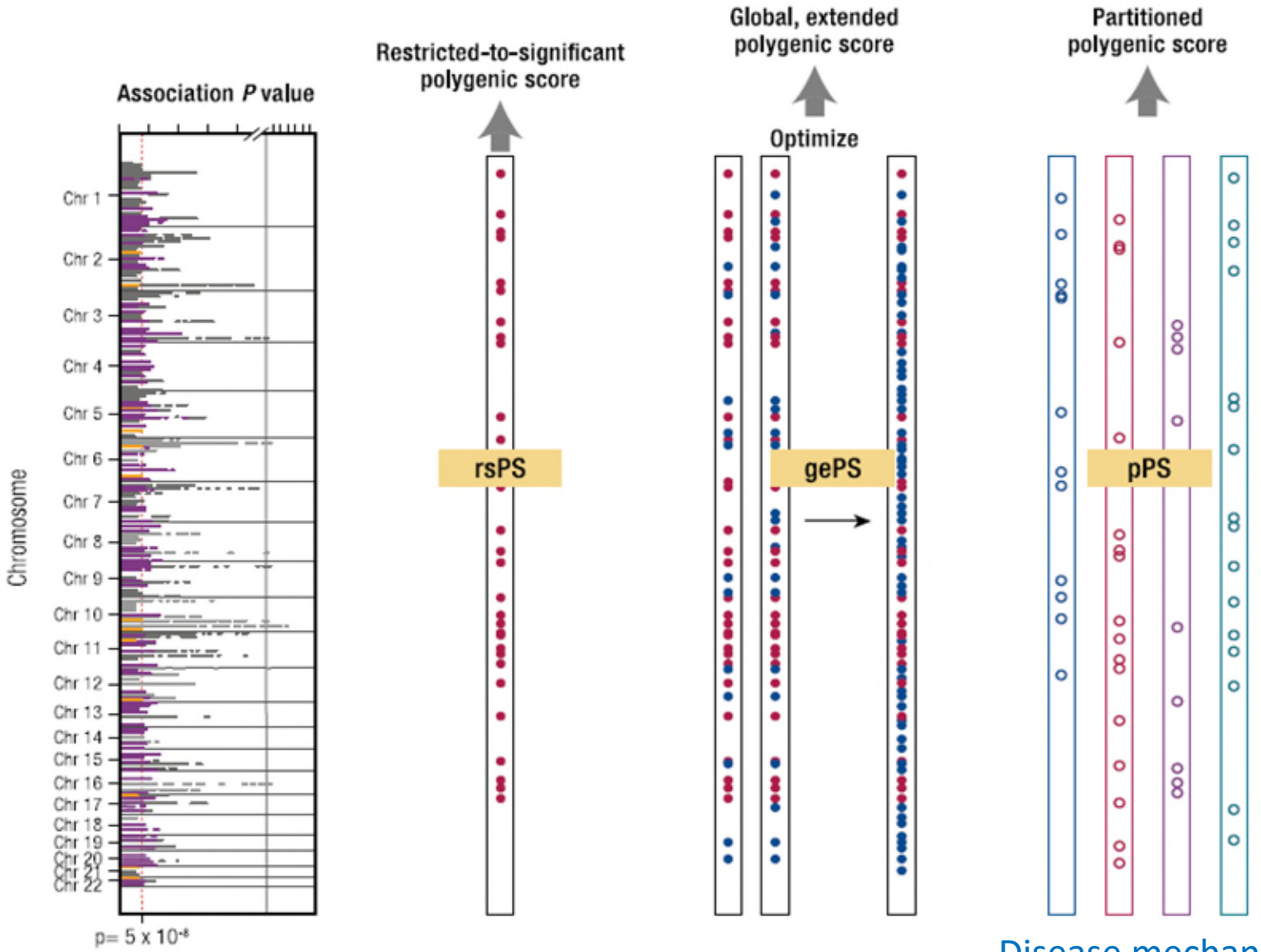
Insulin Resistance

Liver/Lipid dysfunction **Lipodystrophy** **Obesity**



T2D Global Genomics Initiative, Nature, 2024
-Multi-ancestry
- 1289 SNPs, 37 SNPs
- 8 clusters

Genetic clusters can be used to generate partitioned polygenic scores

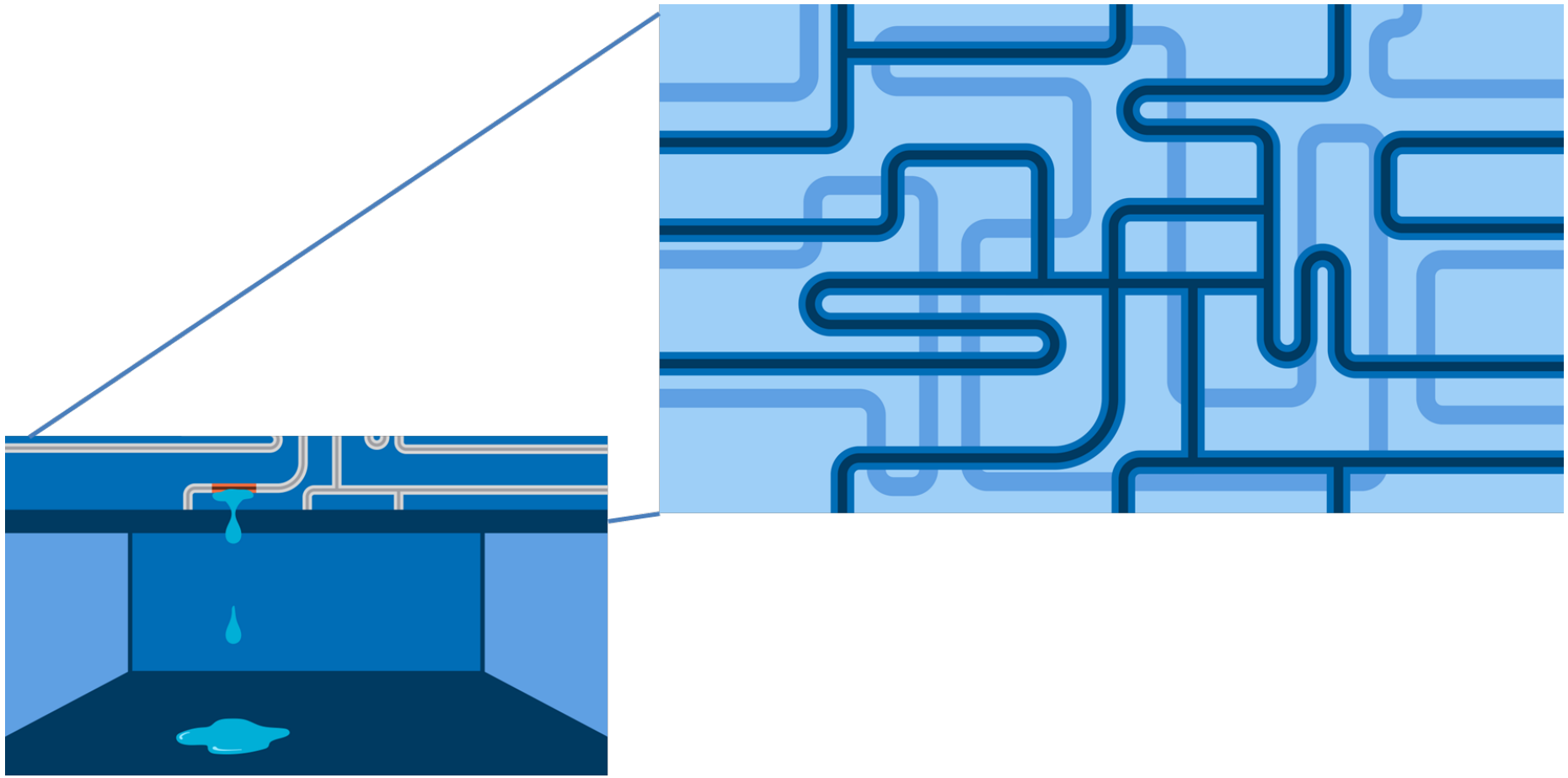


Disease mechanisms

Udler, Mahajan, Florez, McCarthy, Endocrine Reviews, 2019

What can we learn from T2D genetic clusters?

Inform on **mechanistic heterogeneity** of T2D and **improve understanding of disease pathogenesis** → *blueprint of the network of disease pathways*



12 T2D genetic clusters capture disease processes, some shared with monogenic disease

Table 1 | Overview of multi-ancestry T2D genetic clusters

Cluster (no. of variants)	Expected physiological impact	Key top-weighted traits	Key top-weighted loci	Suspected mechanism	Note
Beta Cell 1 (82)	Insulin deficiency	CIR (–), disposition index (–)	*CDKAL1, C2CD4A, HHEX, ST6GAL1, LDHB, TET2*	Beta cell function, glucose homeostasis	Recaptures part of Beta Cell cluster from Udler et al.[3] and Beta Cell 1 from Kim et al.[4]
Beta Cell 2 (40)	Insulin deficiency	HbA1c female (+), FG adjBMI (+), glucose male (+), proinsulin (+)	*GCK, TCF7L2, SLC30A8, SLC2A2, ADCY5, DGKB*	Beta cell function, insulin processing	Recaptures part of Beta Cell cluster from Udler et al.[3] and Beta Cell 2 from Kim et al.[4]
Proinsulin (16)	Insulin deficiency	Proinsulin (–), VAT (–)	*ARAP1/STARD10, LINC01512*	Insulin synthesis	Recaptures Proinsulin cluster from Udler et al.[3] and Kim et al.[4]
Obesity (76)	Insulin resistance	BMI male (+), SAT (+), waist circumference female (+), trunk fat % female (+)	*FTO, MC4R, TMEM18, BDNF*	Obesity-mediated insulin resistance	Recaptures Obesity cluster from Udler et al.[3] and Kim et al.[4]
Hyper Insulin (41)	Insulin resistance	Disposition index (+), CIR (+)	*PDE3A, RBM6, TRAF3, CNTN2*	Insulin secretion, inflammation	Recaptures Hyper Insulin cluster from Kim et al.[4]
Cholesterol (5)	Insulin resistance	CRP male (+), cholesterol (–), apolipoprotein A (+)	*APOE, NECTIN2, TM6SF2, POLK/HMGCR*	Cholesterol metabolism	New cluster in this study
Lipodystrophy 1 (47)	Insulin resistance	GFAT adjBMI (–), VAT/GFAT ratio (+), adiponectin (–)	*VEGFA, CCFC92, LINC01625/CITED2, GRB14/COBLL1, FAM13A*	Fat distribution-mediated insulin resistance	Recaptures Lipodystrophy cluster from Udler et al.[3] and Kim et al.[4]
Lipodystrophy 2 (29)	Insulin resistance	ALT (+), ISI adjAgeSexBMI (–), AST (+), GGT (+)	*PNPLA3, PPARG, LOC646736/IRS1, PEPD, ANKRD55, ERLIN1*	Hepatic steatosis	New cluster in this study; split from previous Lipodystrophy cluster
Liver-Lipid (7)	Insulin resistance	TG female (–), SHBG male (+), IGF female (+), albumin male (–)	*GCKR, FADS1, PPIP5K1*	Liver/lipid metabolism	Recaptures Liver-Lipid cluster from Udler et al.[3] and Kim et al.[4]
Bilirubin (2)	Unclear	Bilirubin (+)	*UGT1A3*	Bilirubin metabolism	New cluster in this study
SHBG-LpA (3)	Unclear	SHBG male (–), LpA female (+), estradiol female (–)	*SHBG, SLC22A3, STAG1*	SHBG and LpA metabolism	Merged from LpA and SHBG clusters from Kim et al.[4]
ALP Negative (6)	Insulin resistance	ALP (–), RBC count (–), hemoglobin concentration (–)	*ABO, FADS1*	Unclear	Recaptures ALP Negative cluster from Kim et al.[4]

Smith, Deutsch et al Nature Medicine, 2024

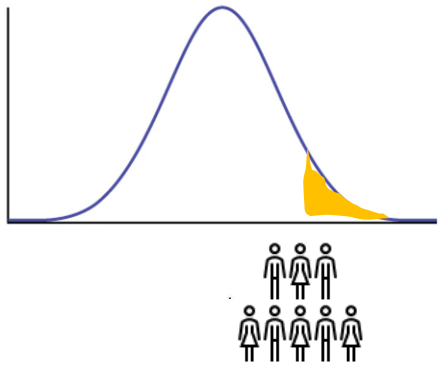
12 T2D genetic clusters capture disease processes, some shared with monogenic disease

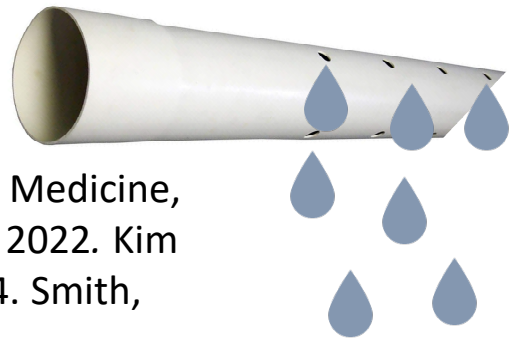
Type 2 Diabetes

Lipodystrophy-like T2D genetic cluster (partitioned polygenic score)

- **T2D risk**
- **Insulin resistance without obesity**
- **Triglycerides**
- **Visceral fat**

- **Subcutaneous fat**
- **HDL cholesterol**



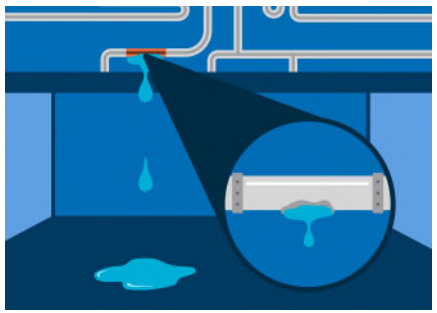


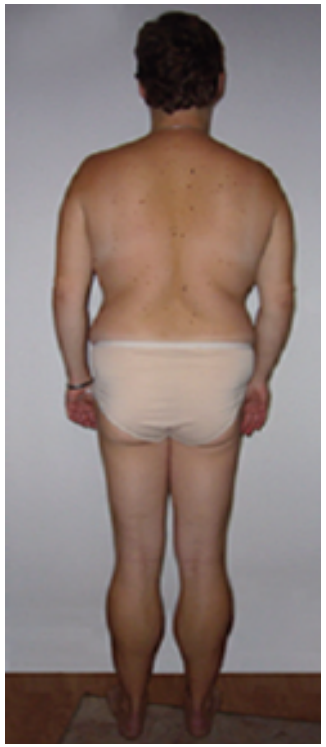
Monogenic disease

Familial Partial Lipodystrophy (rare variant)

- **T2D risk**
- **Insulin resistance without obesity**
- **Triglycerides**
- **Visceral fat**

- **Subcutaneous fat**
- **HDL cholesterol**

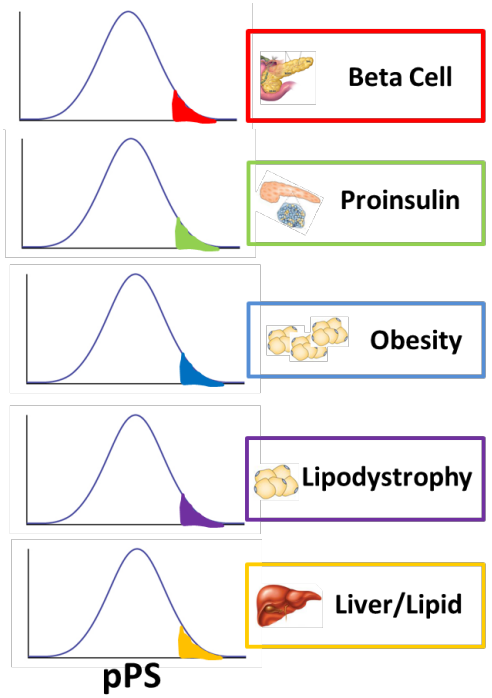




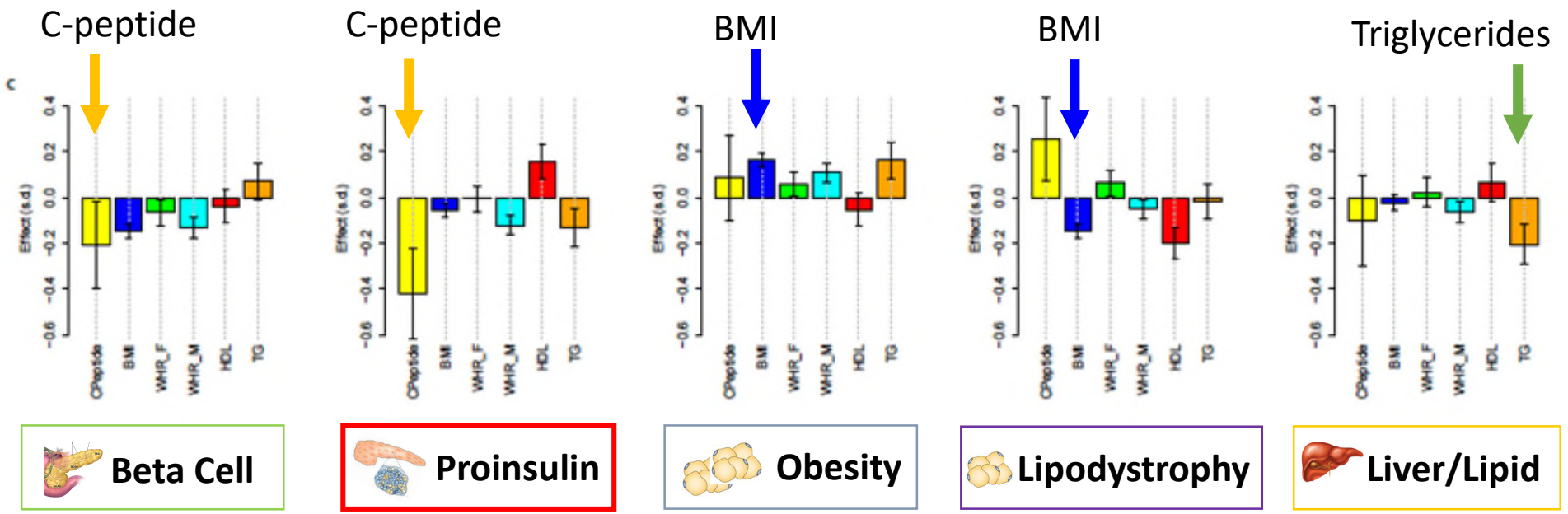
Ludtke et al., 2007

Yaghootkar et al, Diabetes 2014; Udler *et al*, PLoS Medicine, 2018; DiCorpo, LeClaire, Cole *et al*, Diabetes Care 2022. Kim et al Diabetologia 2023; Suzuki et al, Nature, 2024. Smith, Deutsch et al Nature Medicine, 2024

T2D partitioned polygenic scores dissect patient clinical heterogeneity (in aggregate)

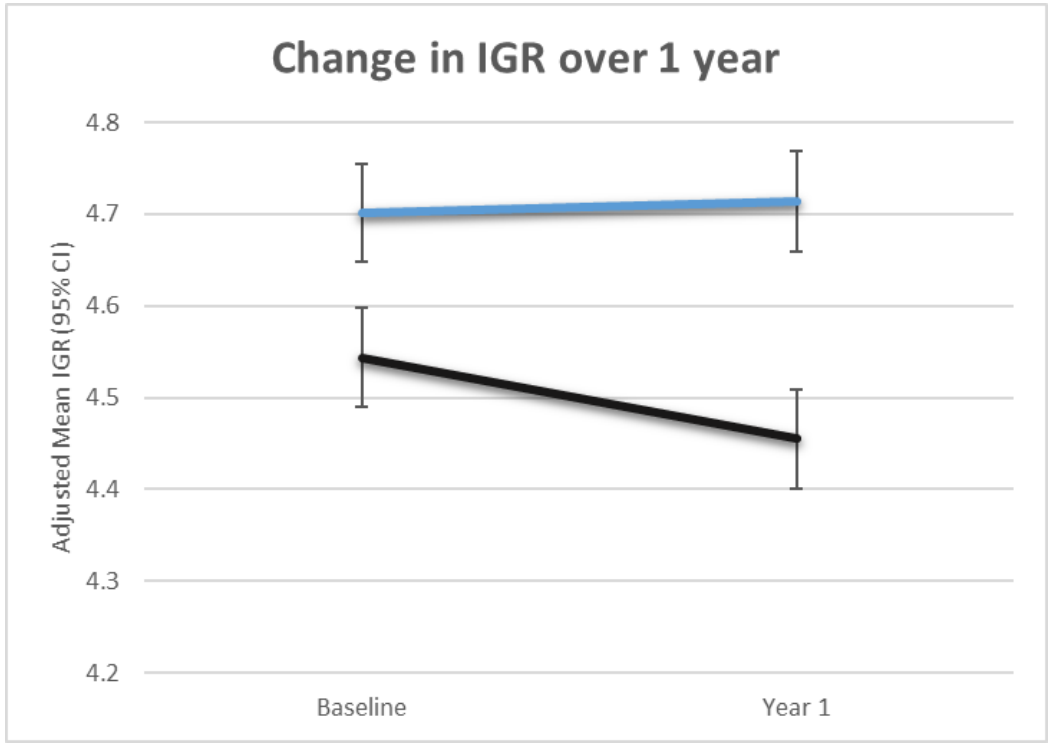


- 17,364 individuals with T2D
- Calculate each person's process-specific polygenic scores (**pPS**) for each cluster
- Compare those in top 10% pPS uniquely in each cluster to all others with T2D.

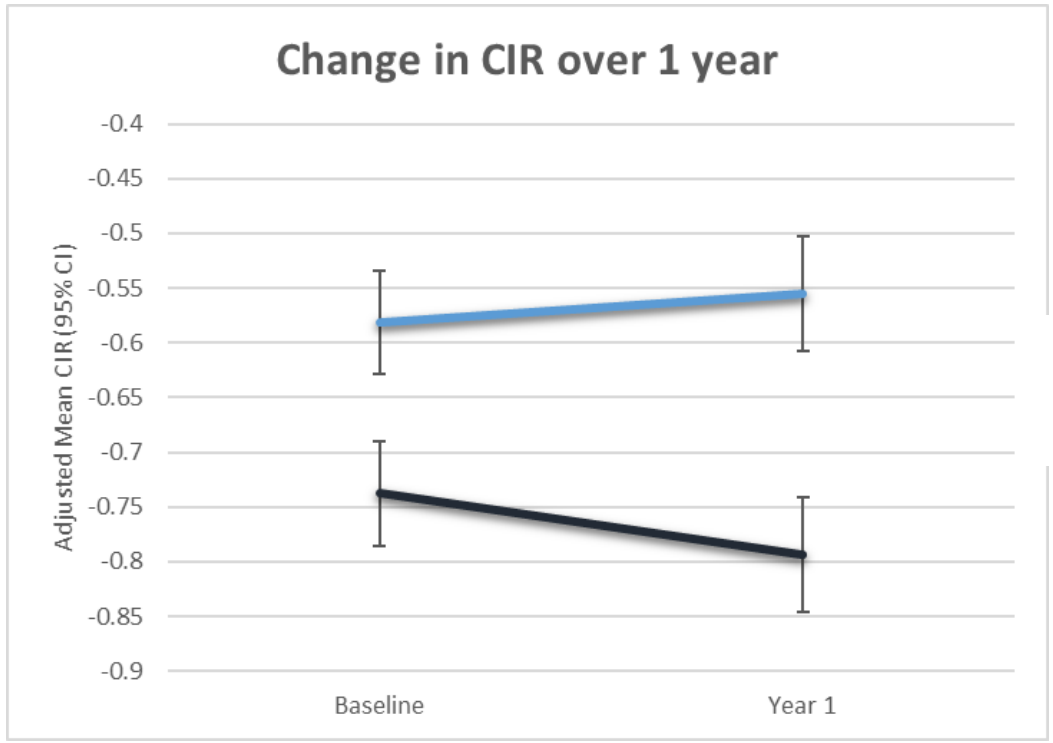


Udler *et al*, PLoS Medicine, 2018; Kim et al Diabetologia 2023; Smith, Deutsch et al Nature Medicine 2024

Increased “beta cell” T2D partitioned polygenic scores is associated with longitudinal beta cell decline



P<0.001



P<0.001

Insulinogenic Index (IGR) = ($Insulin_{30}$ – $insulin_0$)/($Glucose_{30}$-$Glucose_0$)

Corrected Insulin Response (CIR) = $Insulin_{120}$/($Glucose_{120}$ x [$Glucose_{120}$-70])

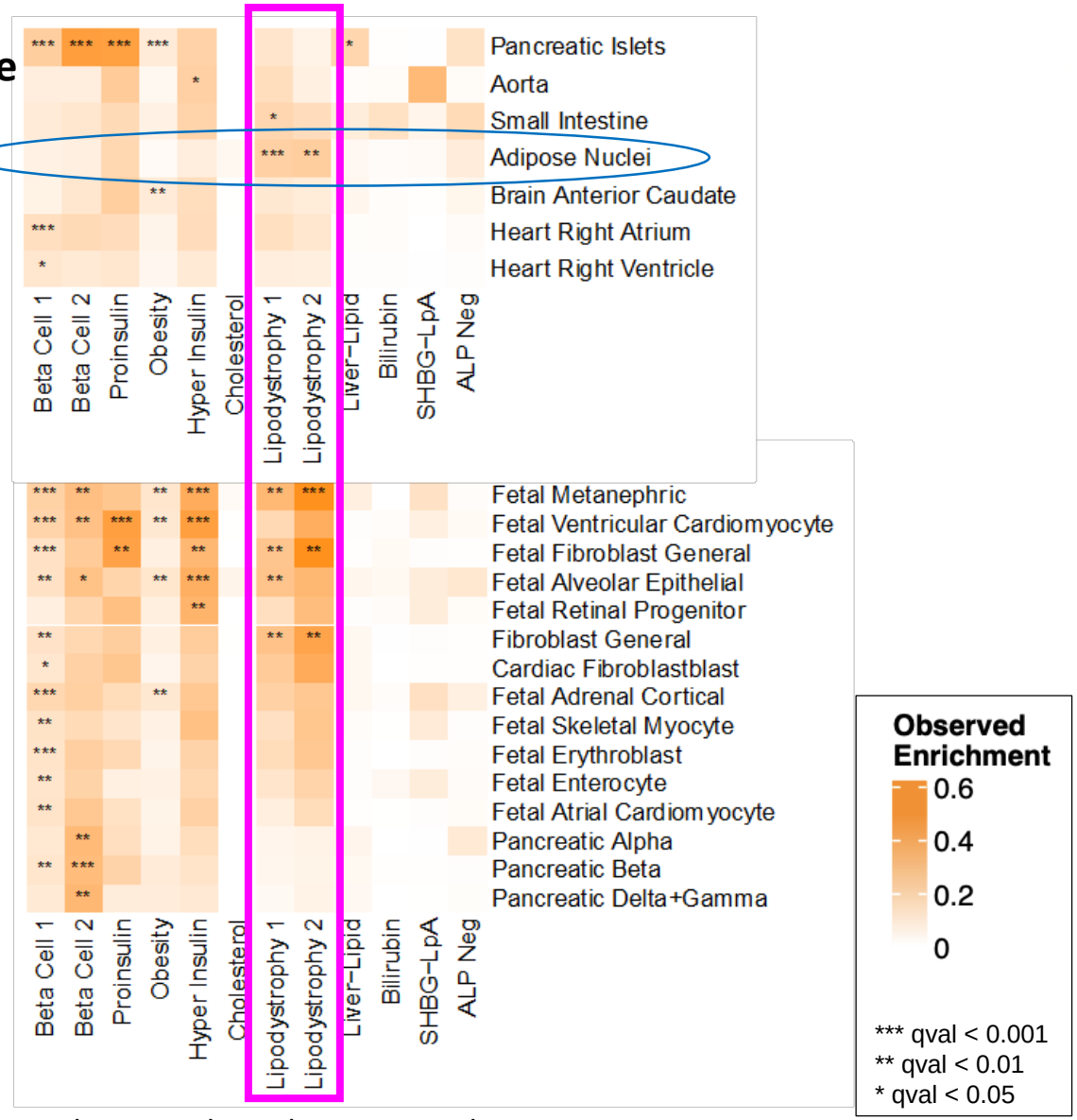
Diabetes Prevention Program

Billings et al, *Diabetes*, 2024

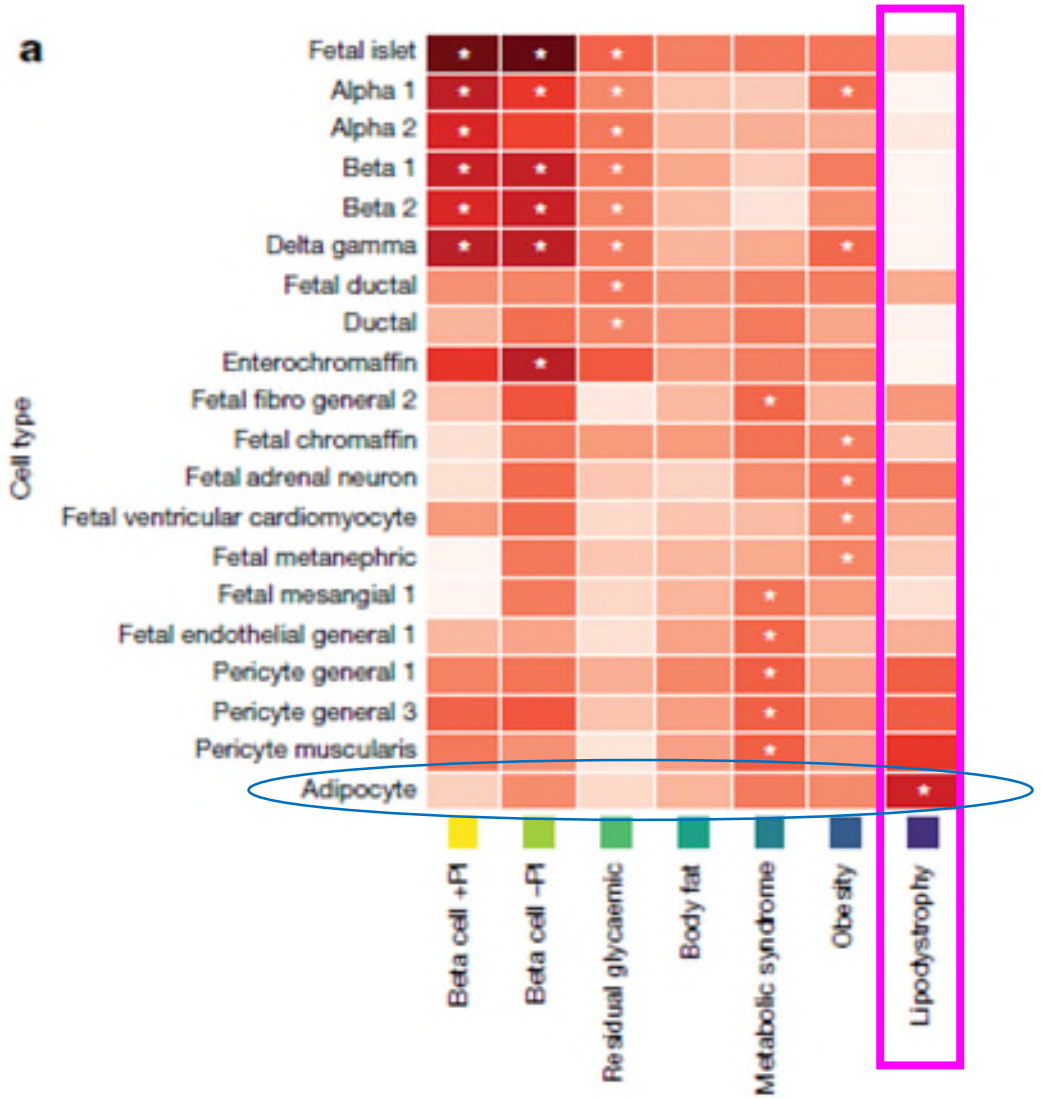
Genetic clusters connect disease processes to tissues/cells

Bulk tissue

Single cell

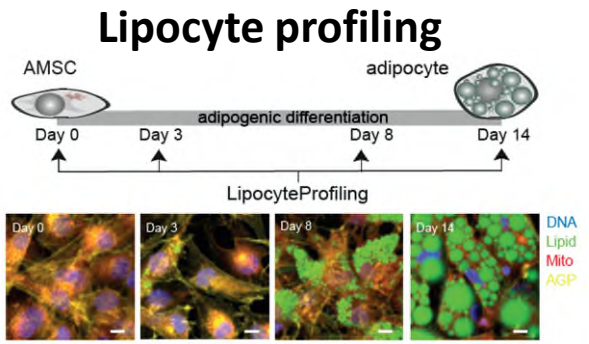


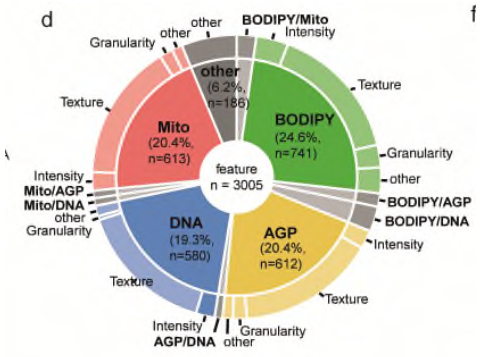
Smith, Deutsch et al Nature Med, 2024



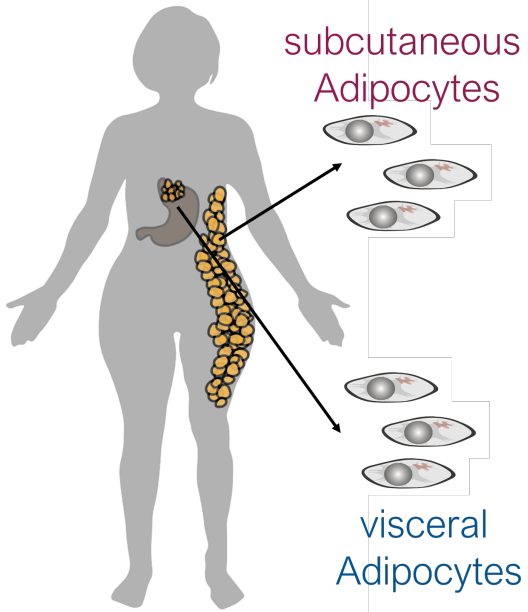
Suzuki et al Nature, 2024

T2D partitioned polygenic scores define cellular phenotypes





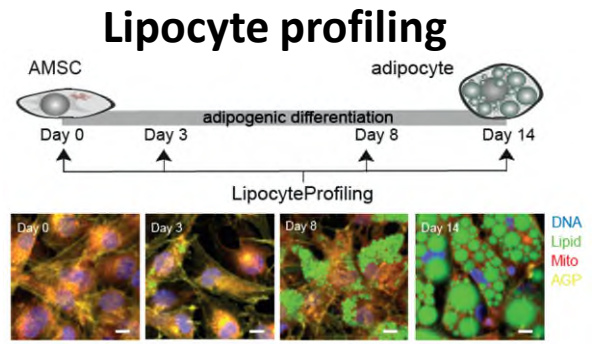
adipose-tissue-derived mesenchymal stem cells

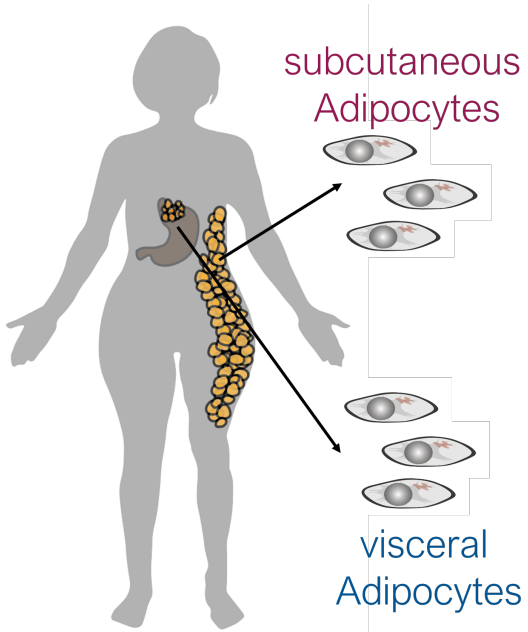


Subcutaneous N=29
Visceral N=35

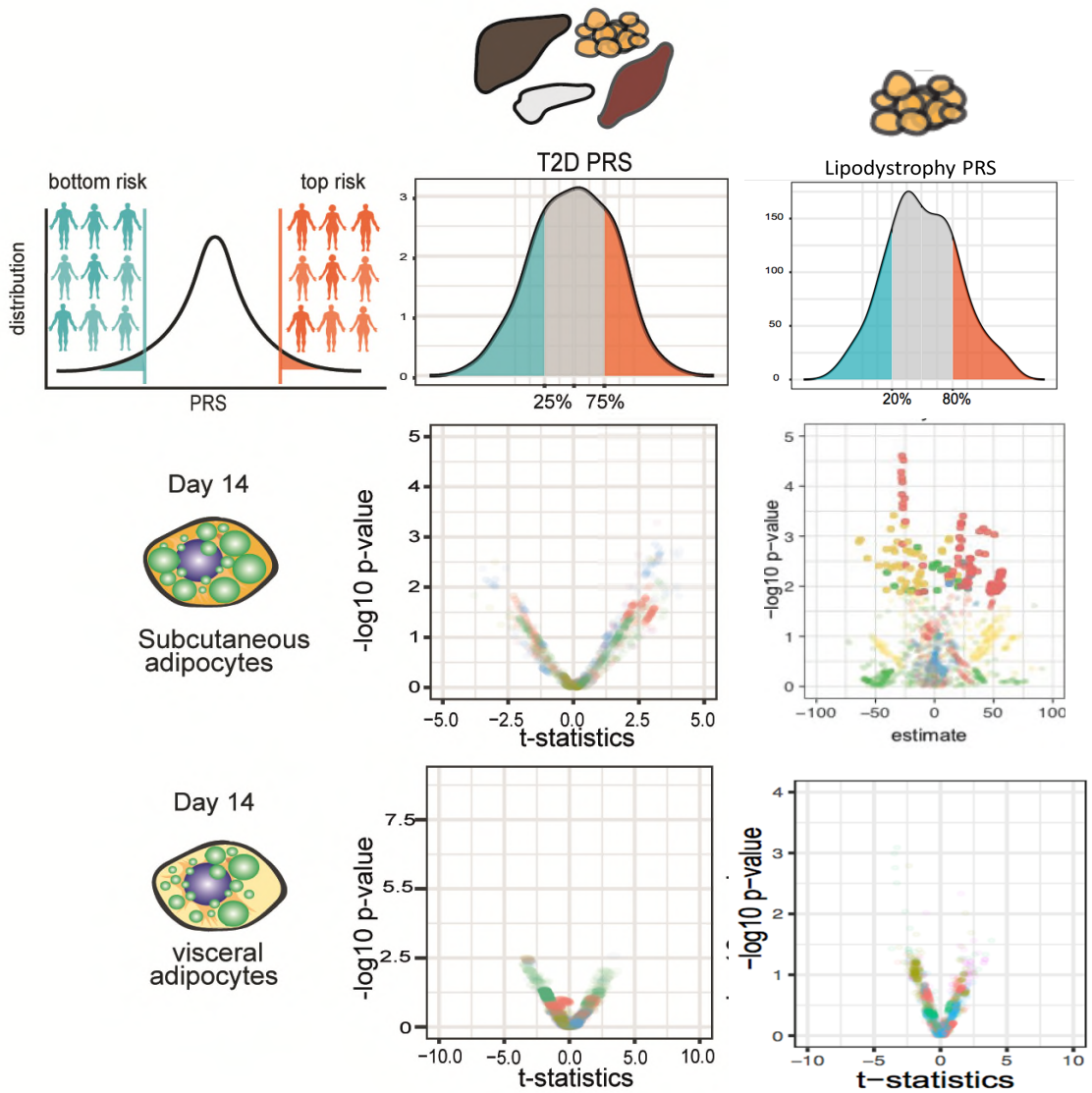
Laber, Strobel…, Claussnitzer, Cell Genomics 2023

T2D partitioned polygenic scores define cellular phenotypes





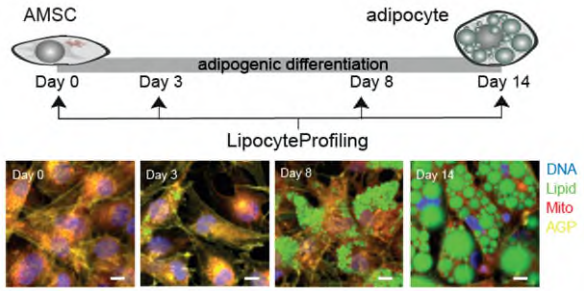
Subcutaneous N=29
Visceral N=35

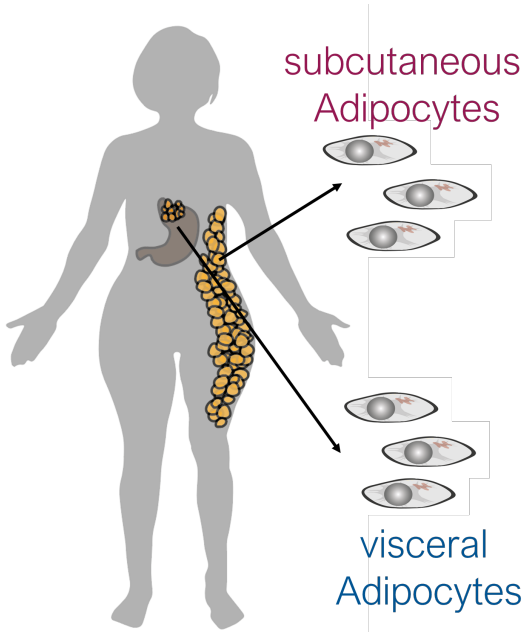


Laber, Strobel…, Claussnitzer, Cell Genomics 2023

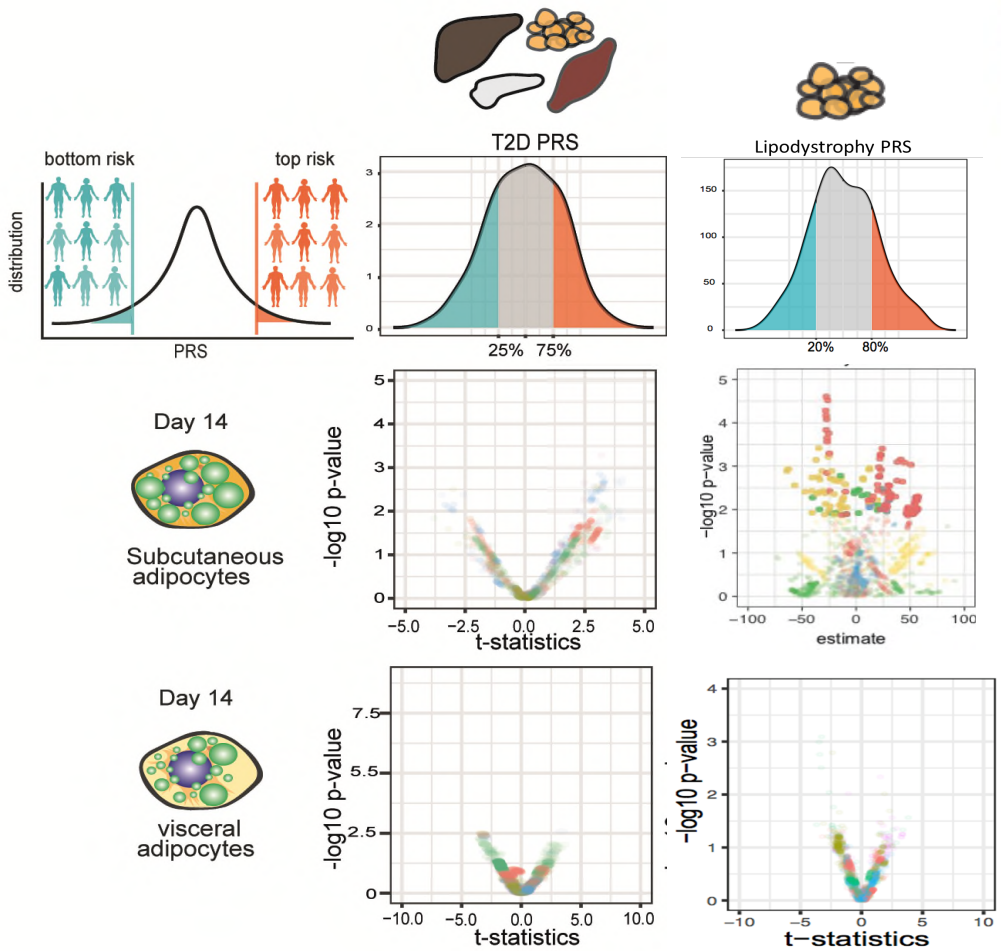
T2D partitioned polygenic scores define cellular phenotypes

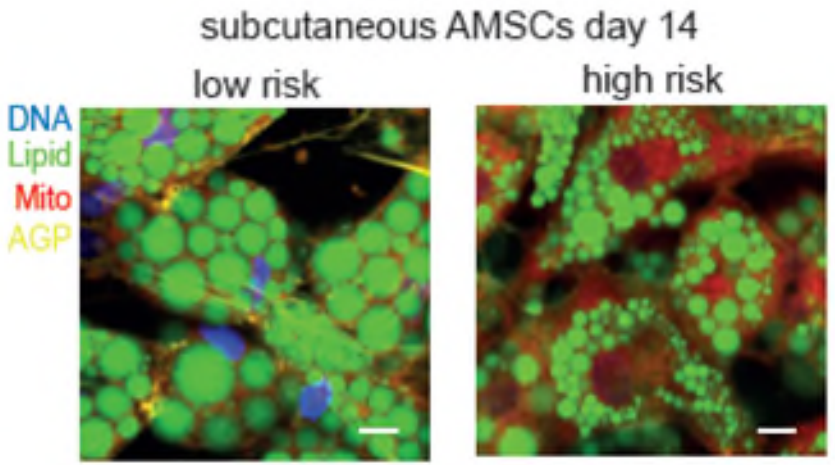
Lipocyte profiling





Subcutaneous N=29
Visceral N=35





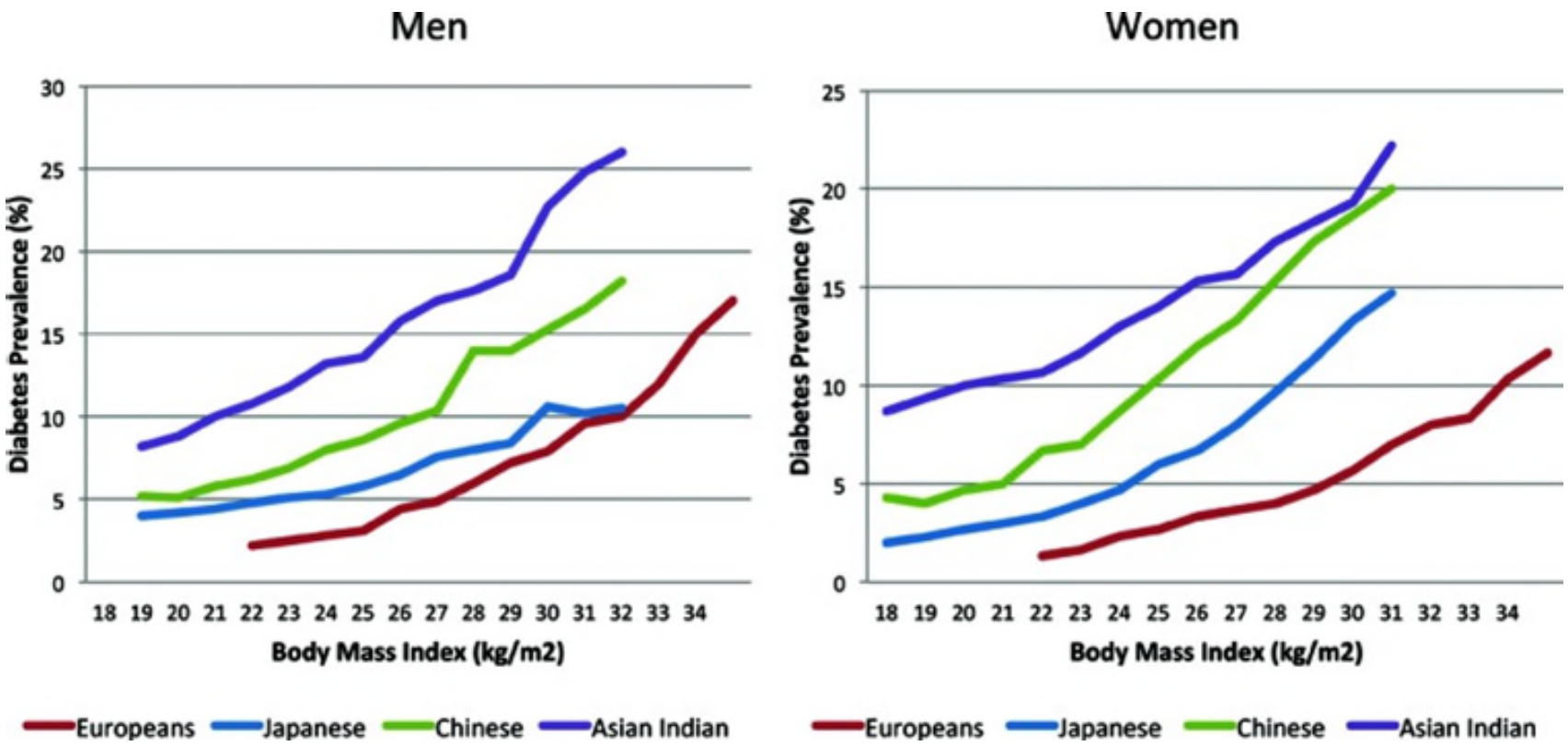
High vs low lipodystrophy partitioned score

- decreased lipid accumulation
- increased mitochondrial activity
- → fat storage reduced in subcutaneous adipocytes

Laber, Strobel…, Claussnitzer, Cell Genomics 2023

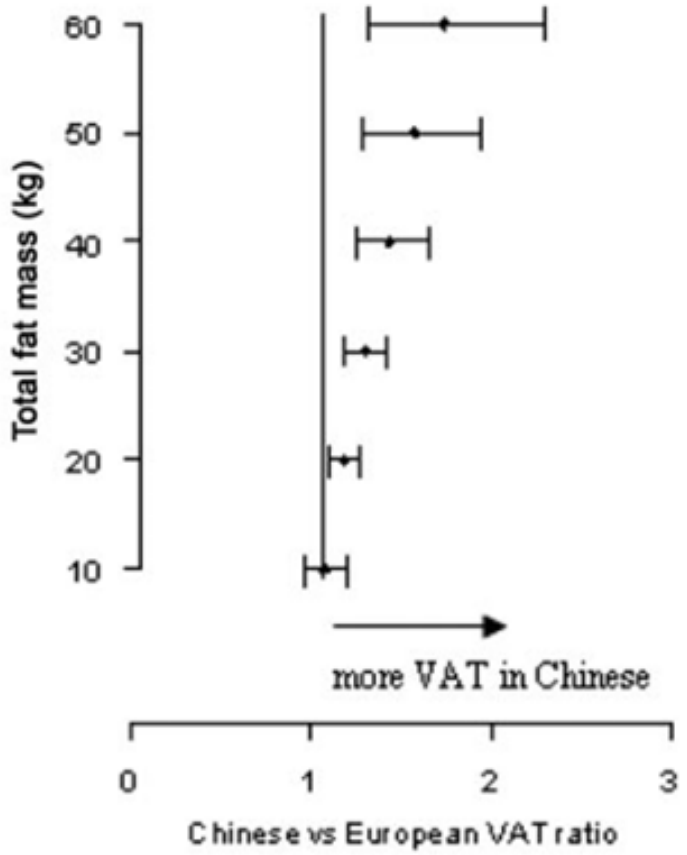
Can T2D partitioned polygenic scores inform on phenotypic heterogeneity across populations?

BMI-related T2D risk differs across populations



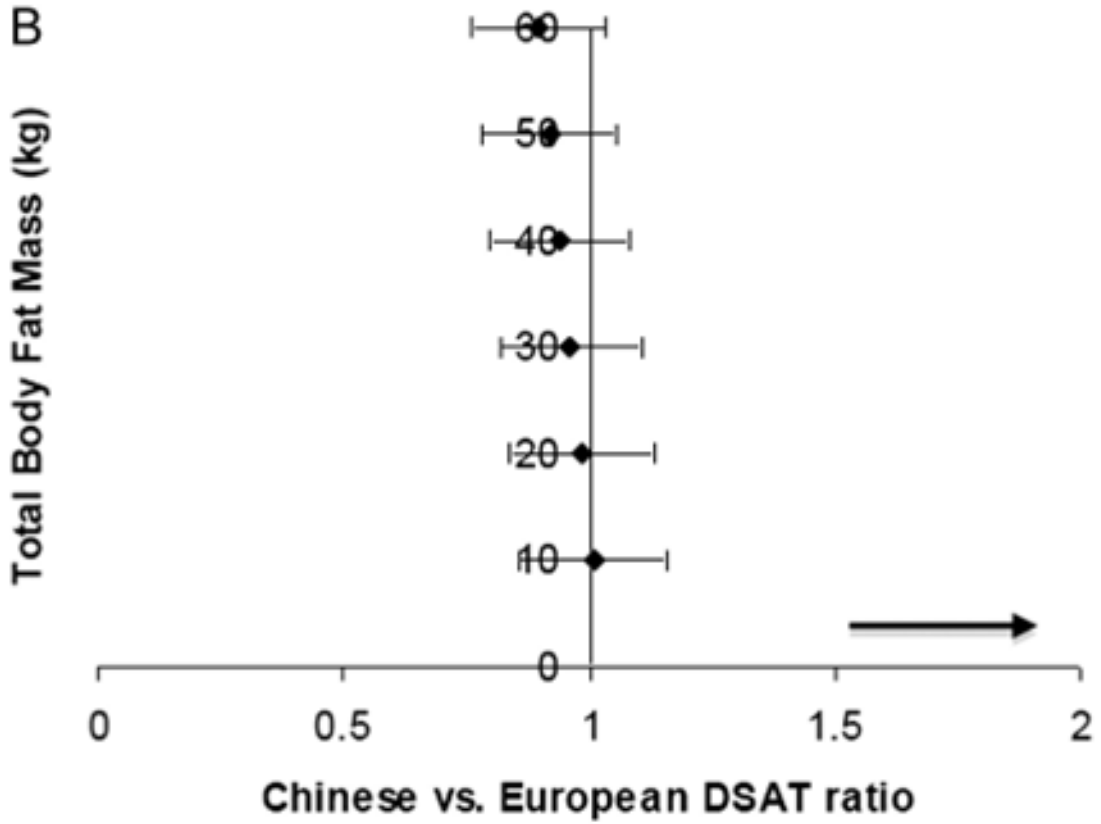
Ma, Annals of the NYAS, 2013

With increasing total fat mass (kg), Chinese individuals have more VAT, but less SAT than European individuals



Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT)[1–3]

Scott A Lear, Karin H Humphries, Simi Kohli, Arun Chockalingam, Jiri J Frohlich, and C Laird Birmingham



Original Article
OBESITY BIOLOGY AND INTEGRATED PHYSIOLOGY

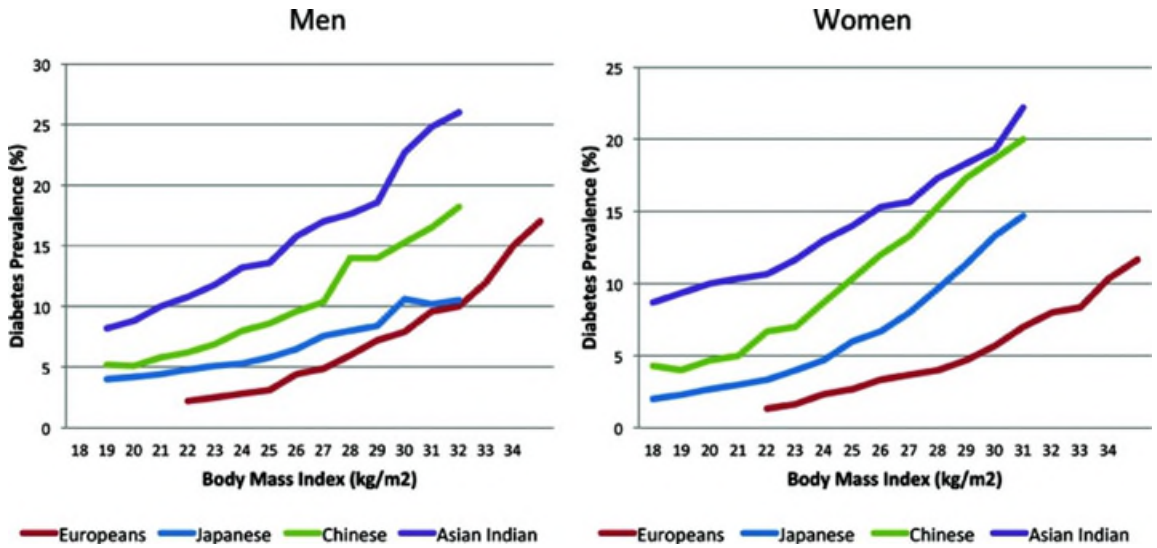
Obesity

Differences in Subcutaneous Abdominal Adiposity Regions in Four Ethnic Groups

Simi Kohli[1] and Scott A. Lear[1,2,3]

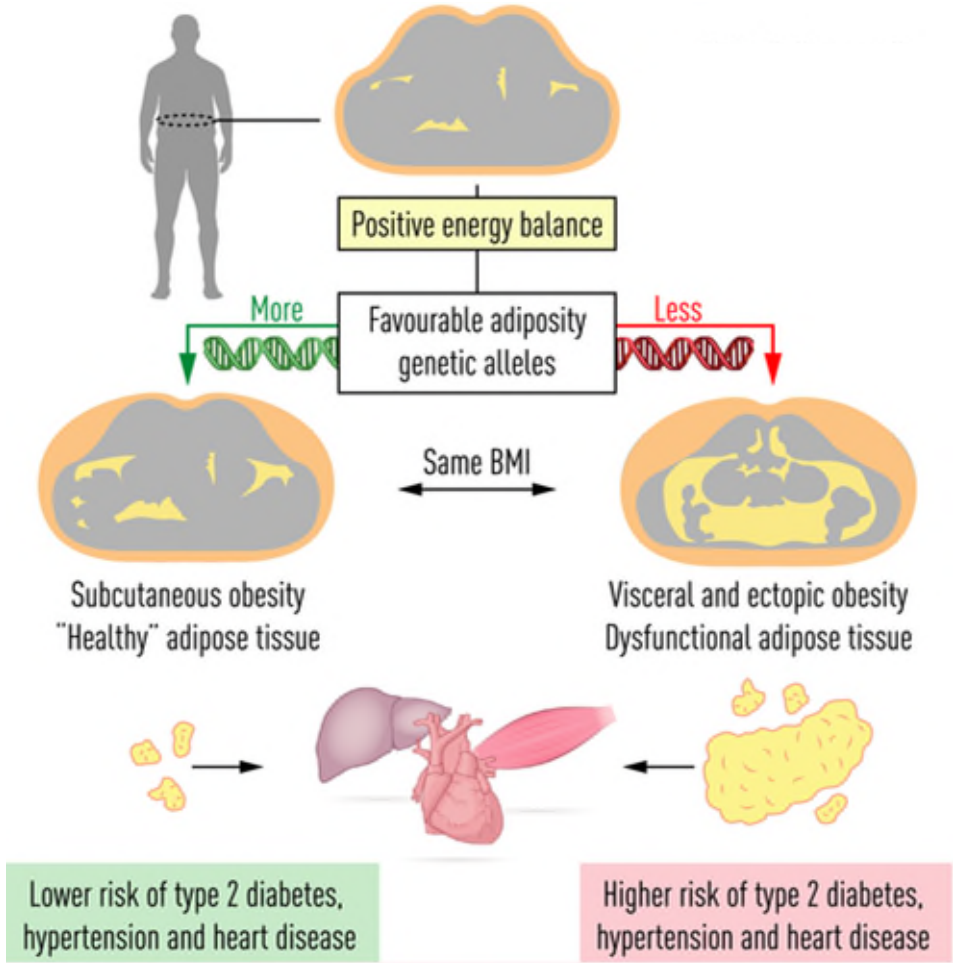
Can T2D partitioned polygenic scores inform on phenotypic heterogeneity across populations?

T2D risk at the same BMI differs across populations



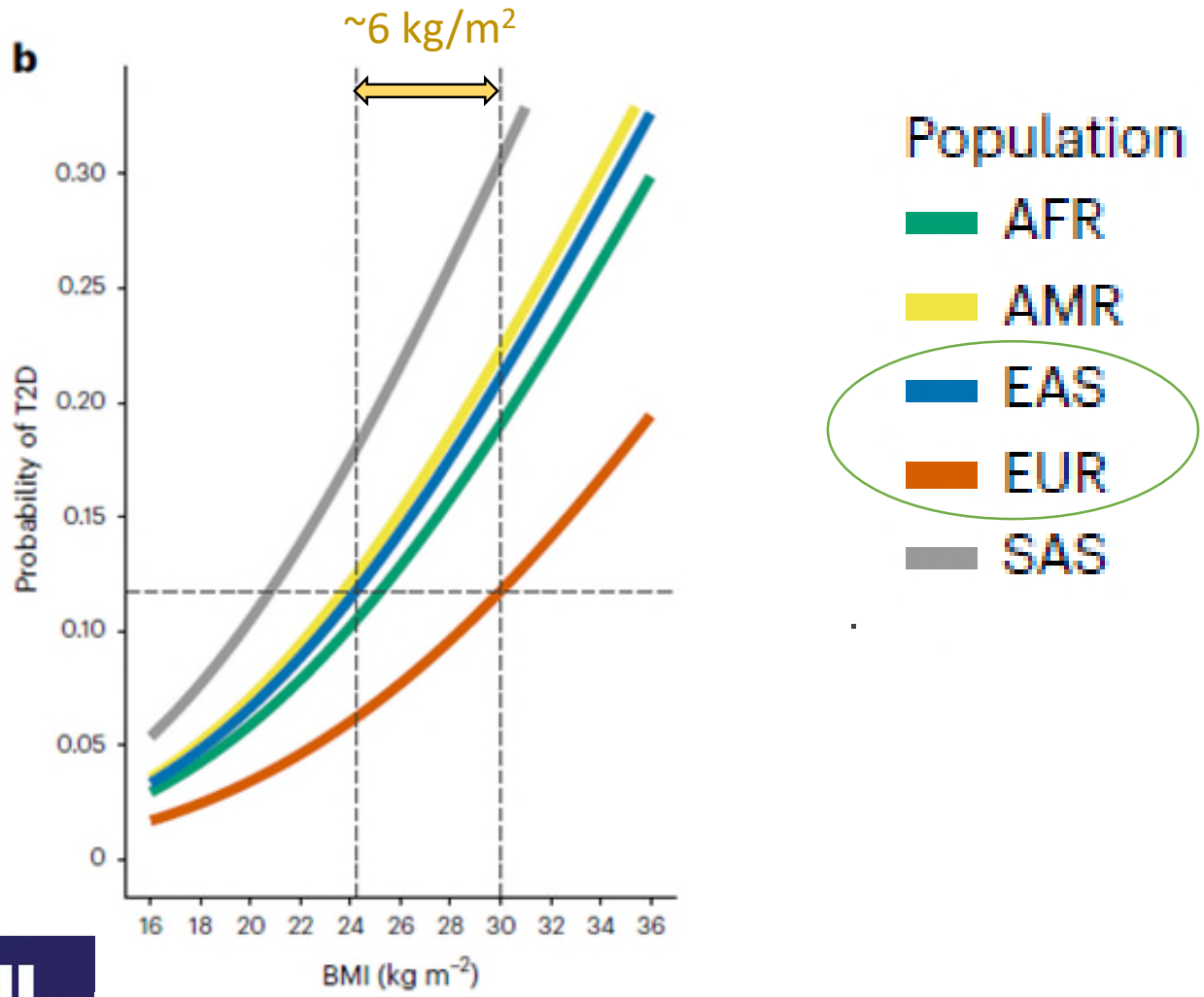
Ma, Annals of the NYAS, 2013

Could this be explained by a T2D genetic risk related to fat storage?



Yaghootkar, Journal of Internal Medicine, 2020

T2D Lipodystrophy-like polygenic scores inform on T2D heterogeneity across ancestry groups



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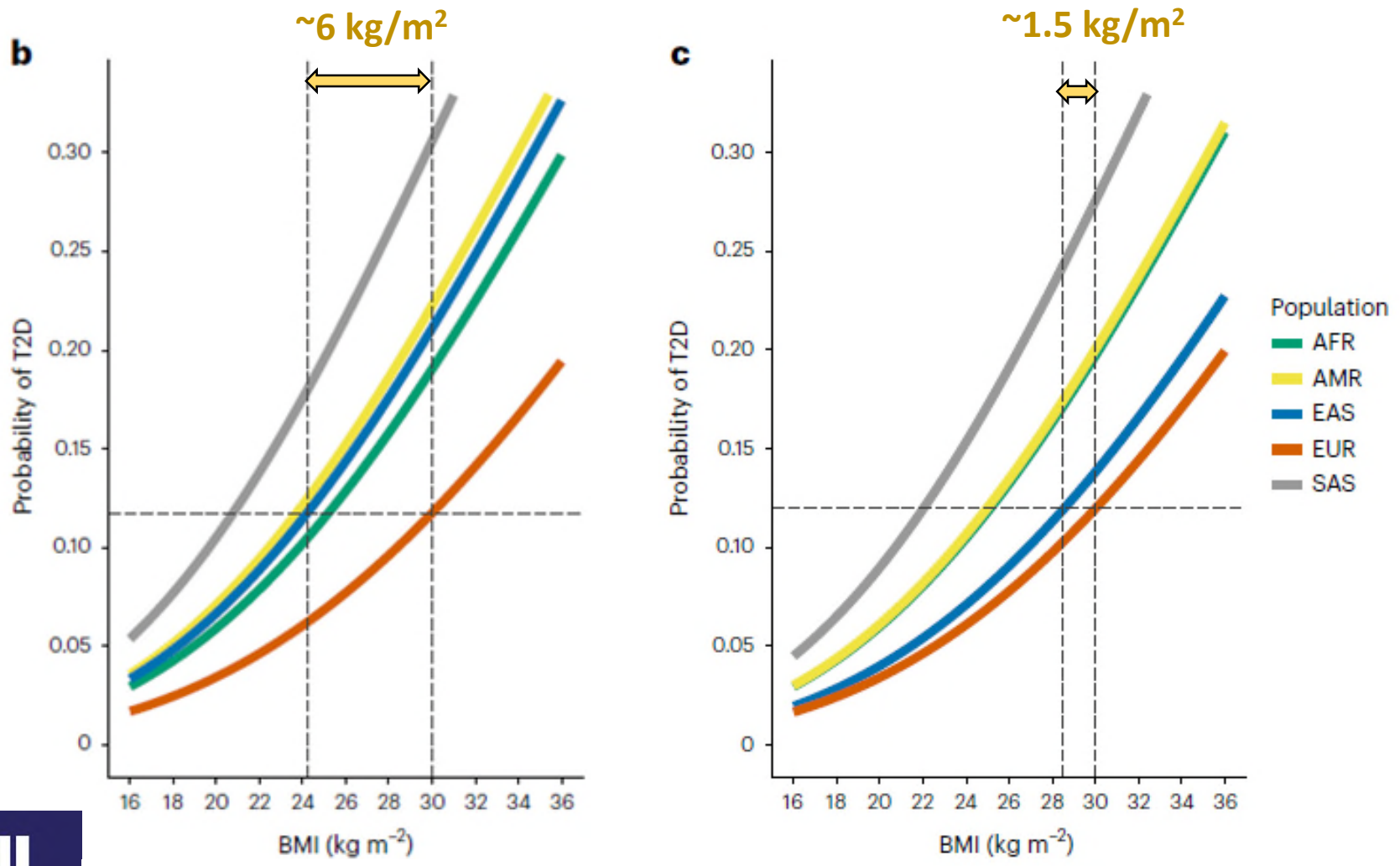
Mass General Brigham

Smith, Deutsch et al Nature Medicine 2024

T2D Lipodystrophy-like polygenic scores inform on T2D heterogeneity across ancestry groups

Adjusted for "Lipodystrophy" polygenic scores



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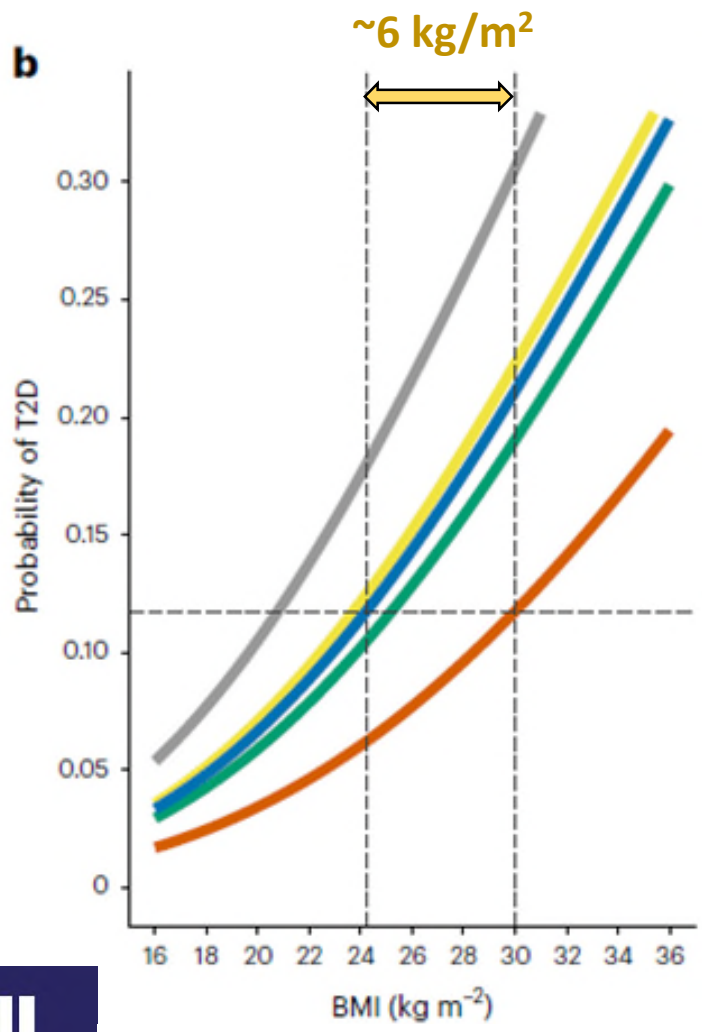
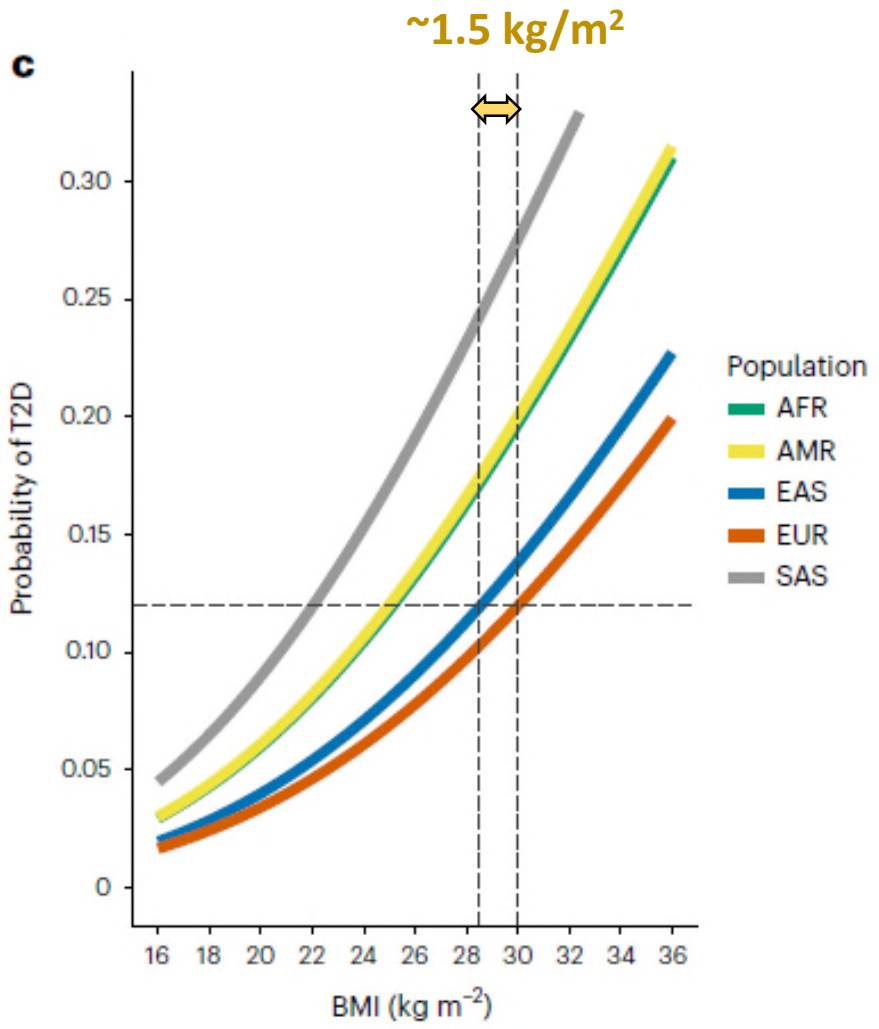
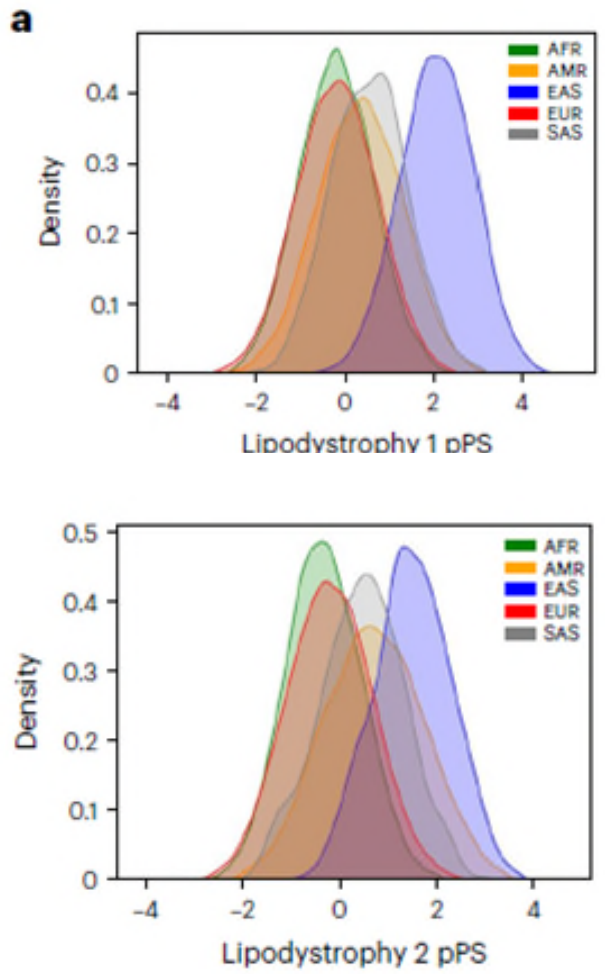
T2D Lipodystrophy-like polygenic scores inform on T2D heterogeneity across ancestry groups

Adjusted for "Lipodystrophy" polygenic scores







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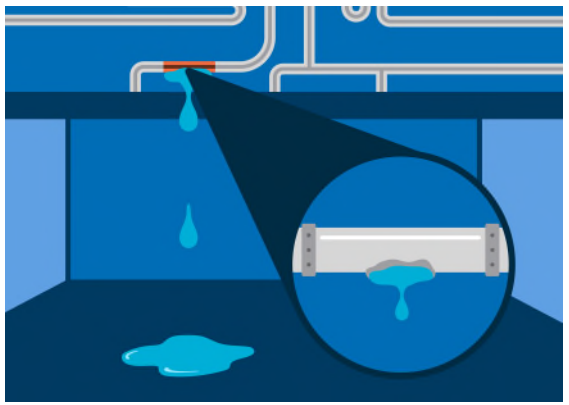
Smith, Deutsch et al Nature Medicine 2024

Summary: Genetic Insight into T2D Heterogeneity

- **For precision medicine in diabetes, we need better understanding of underlying disease mechanisms to inform patient heterogeneity.**
  - Genetics can help us improve understanding of disease pathogenesis.

- **Monogenic diabetes** is caused by rare variants, represents clear endotypes with treatment implications.

- **Type 2 diabetes** is polygenic with robust polygenetic disease processes:
  - Some shared with monogenic disease
  - Dissect patient clinical heterogeneity in aggregate (not individual-level)
  - Connect processes to tissues/cells
  - Define human cellular phenotypes
  - Inform on clinical T2D differences across populations



Thank you!

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- Caitlin Ellis
- Steven Gage
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- Sarah Hsu
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- Alisa Manning
- Melina Claussnitzer
- Hesam Dashti
- Jason Flannick
- Alicia Huerta
- Kenny Westerman
- Ravi Mandla
- Philip Schroeder
- Vicky Kaur
- Samantha Laber
- Sophie Strobel

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- Josée Dupuis
- James Meigs
- Jerry Rotter
- Liana Billings