A Clinical-Translator's Point-of-View: At the Interface of Patient Care and Basic Science

Diagnosing Diabetes Mellitus in Adults: Type 1, LADA, Type 2: Rationale and Implications of a β-Cell-Centric Classification of Diabetes

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Diagnosing Diabetes Mellitus in Adults:

Type 1, Type 2, LADA

or

Since Confusion Abounds, Isn't it Time for A New Classification Schema for the Diagnosis and Treatment of Diabetes Mellitus (DM)

Get us ready for 'PRECISION MEDICINE'

Presenter Disclosure Information

In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure to the participants:

Stanley Schwartz

Research Support: 0
Employee: 0

Board Member/Advisory Panel: Janssen, Merck, AZ-BMS, BI-Lilly, Salix, Novo, Genesis Biotechnology Group

Stock/Shareholder: Saturn EMR Decision Support APP.

Consultant: NIH RO1 DK085212, Struan Grant PI

Other: Speaker's Bureaus: Janssen, Merck, Novo, Salix, BI-LILLY, Eisai, AZ-Int'l, Amgen

Purely Clinical Answer

Empiric, Pragmatic Approach

It doesn't matter which label is applied ☺

- Insulin-Dependent
  - DKA- ketosis prone : insulin needed for survival
- OR NOT- Everyone else
  - Use 'best clinical guess'; 'label' patient; Independent of age
  - Treat 'as needed' to get glycemic control,
  - (but must work under constraints of current 'definitions' for the classification of T2D- per payors/ governments)

'Diagnosis' Has Many Functions

Need To Be More Than Pragmatic!!

- *To plan patient's care* – MORE tailored patient-centric therapy
- *To prevent* – disease development and progression
- *To predict* – risk of DM
- *To proliferate* – and stimulate new scientific knowledge about DM

AND NEED TO CLASSIFY ACCURATELY

Current DM Classification Failing

(Certainly appropriate with knowledge available when current classification adopted)

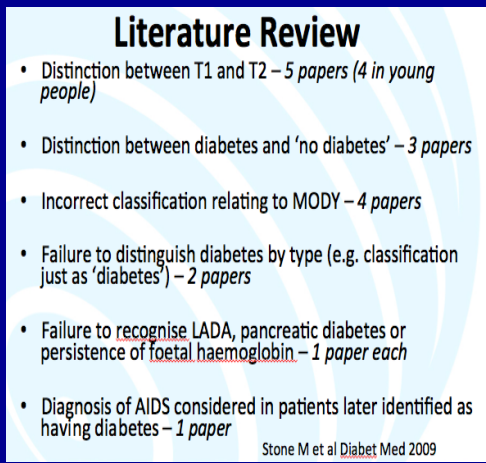
BUT WE'VE LEARNED SO MUCH MORE

- Immune destruction of β-cells / and Insulin Resistance is used as basis of distinction between T1D, and T2D and all other sub-types of DM

- Diagnosis is often *imprecise*
  - *Flatbush DM- present in DKA- 'turn out to be T2DM'*
  - *LADA- Adults who look like 'typical T1DM'*
  - *Antibody positive who look like 'T2DM'*
  - *T1DM with Insulin Resistance (like T2DM)*

Ie: Complicated by extensive *overlap*

yet distinct differences in etiology and phenotype



Definitions: T1D, 'LADA', T2D

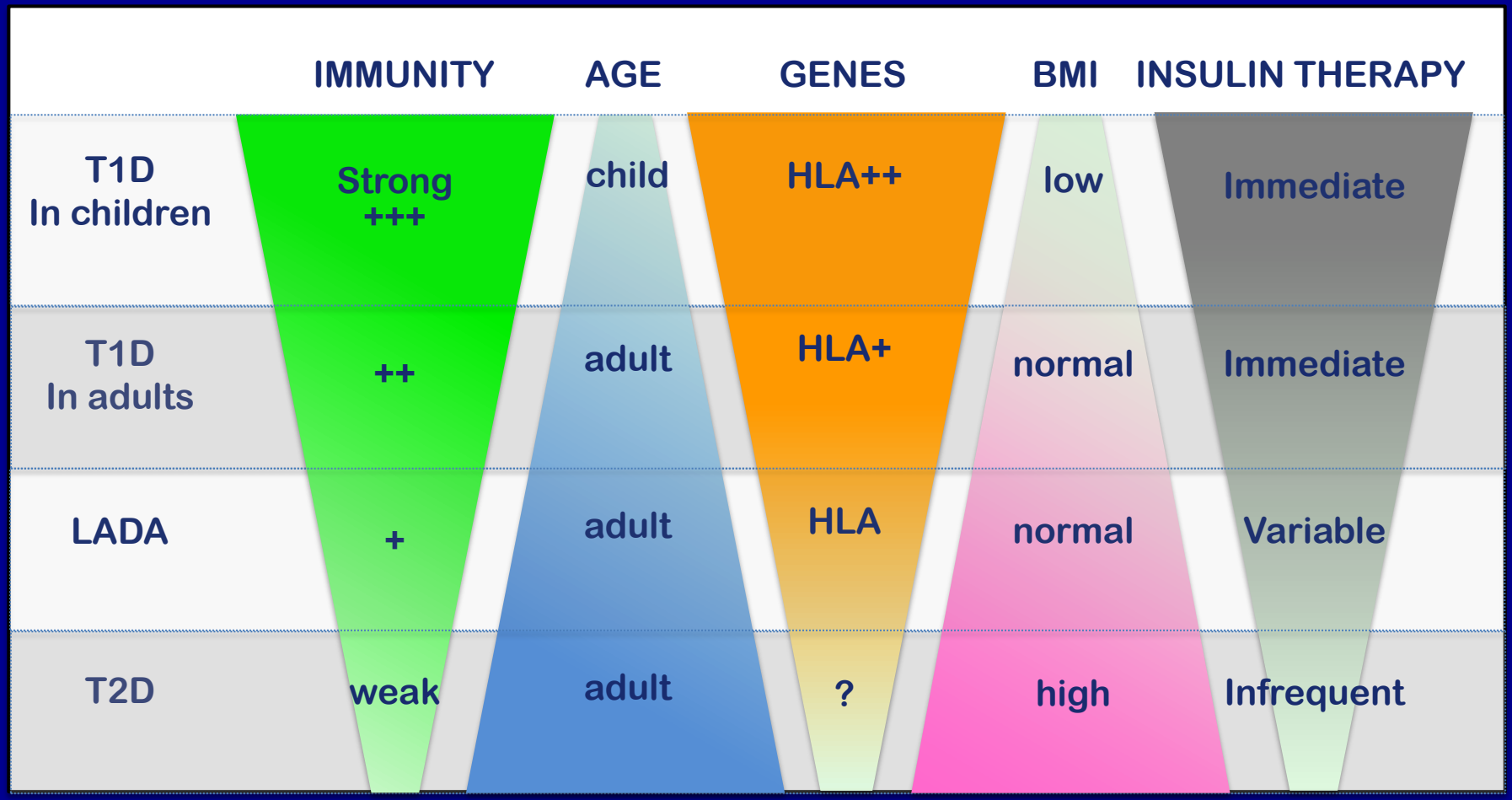
May Seem Precise BUT…, Overlapping Phenotypes

In particular :

'LADA'- Ambiguous classification

- Later age; SPIDDM, 'Slowly progressive T1D
  - 'Slower' destruction of β-cells than T1D
- Antibody positive T2D = 'T1.5D'
  - 'Faster' destruction of β-cells than in T2D
- T-cell abnormal SPIDDM
  - Antibody negative
- Insulin commonly considered the 'go to' drug, even in patients with LADA with retained β-cell function

Comparing Definitions for T1D, 'LADA', T2D



Adapted from Leslie *et al*. Diabetes Metab Res Rev. 2008 Oct;24(7):511-9

Distinct Etiologies and Characteristics

	T1D	'LADA'	T2D	MODY
Typical Age of Onset	All Ages	Usually Age >30	Adults	Usually Age <25
% of all Diabetes	10%	10%	75%	5%
Typical BMI	Mostly Normal or Thin	Mostly Normal or Overweight	Mostly Overweight or Obese	Mostly normal
Ethnicity	All	All	All	All
Progression to insulin Dependence	Fast (Days/Week)	Latent (Months/Years)	Slow (Years)	Depends on MODY type
Insulin Resistance	Mostly no; ~10% ,yes	Some	Yes	Depends on MODY type
Presence of Autoantibodies	Yes (ICA, IA2, GAD65, IAA)	Yes (mostly GAD65), Some not	Some	No
T cell Reponses to islet proteins	Yes	Yes	No	No
Insulin/ C-peptides Level at diagnosis	Undectable or extermely low	Low	Normal to High	Normal
Ketoacidosis	Yes	Yes, many not all	Rare	Rare
* **Insulin Secretion**	Low/null	Varies	Varies	Varies
* **Islet Inflammation**	Chronic Inflammation	Chronic Inflammation	Chronic Inflammation	None
HLA Link	High	Low	None	None
* **TCF7L2 Link**	None	In some pop'n, stronger link than T2D	?5%	None
Other Genes Involved	*PTPN22; INS; CTLA4; CCR5; FOXP3;CLEC16a HNF1A; IL2RA; IL6; ITPR3; OAS1; SUMO4*	*PTPN22; INS*	*PPARG; JAZF1; KCNJ11; NOTCH2; WFS1; IGF2BP2; FTO; SLC30A8; HHEX*	*HNF4A; GCK; HNF1A; IPF1; HNF1B; NEUROD1*
Early Treatment	Insulin required, diet & exercise helpful	Non-Insulin or insulin, diet & exercise helpful	Non-Insulin, diet & increased activity	Gene Specific
Late Treatment	Insulin, diet, exercise	Insulin, pills, diet, exercise	Insulin, pills, diet, exercise	Gene Specific

Distinct Etiologies and Characteristics

	T1D	'LADA'	T2D	MODY
Insulin Secretion	Low/null	Varies	Varies	Varies

	T1D	'LADA'	T2D	MODY
Islet Inflammation	Chronic Inflammation	Chronic Inflammation	Chronic Inflammation	None

	T1D	'LADA'	T2D	MODY
***TCF7L2* Link**	None	Some Pop'n Greater than T2DM	? 5%	None

Diabetes is a Continuum OF β-cell FUNCTION

SO ISSUE IS LESS

'What is LADA?'-

ISSUE IS WHAT ARE MECHANISMS And RATE OF DESTRUCTION OF β-cells In ALL PATIENTS WITH DIABETES-

?Improve therapy!!

Trends in Endocrinology and Metabolism September 2014, Vol. 25, No. 9

Leif Groop, Can genetics improve precision of therapy in diabetes?

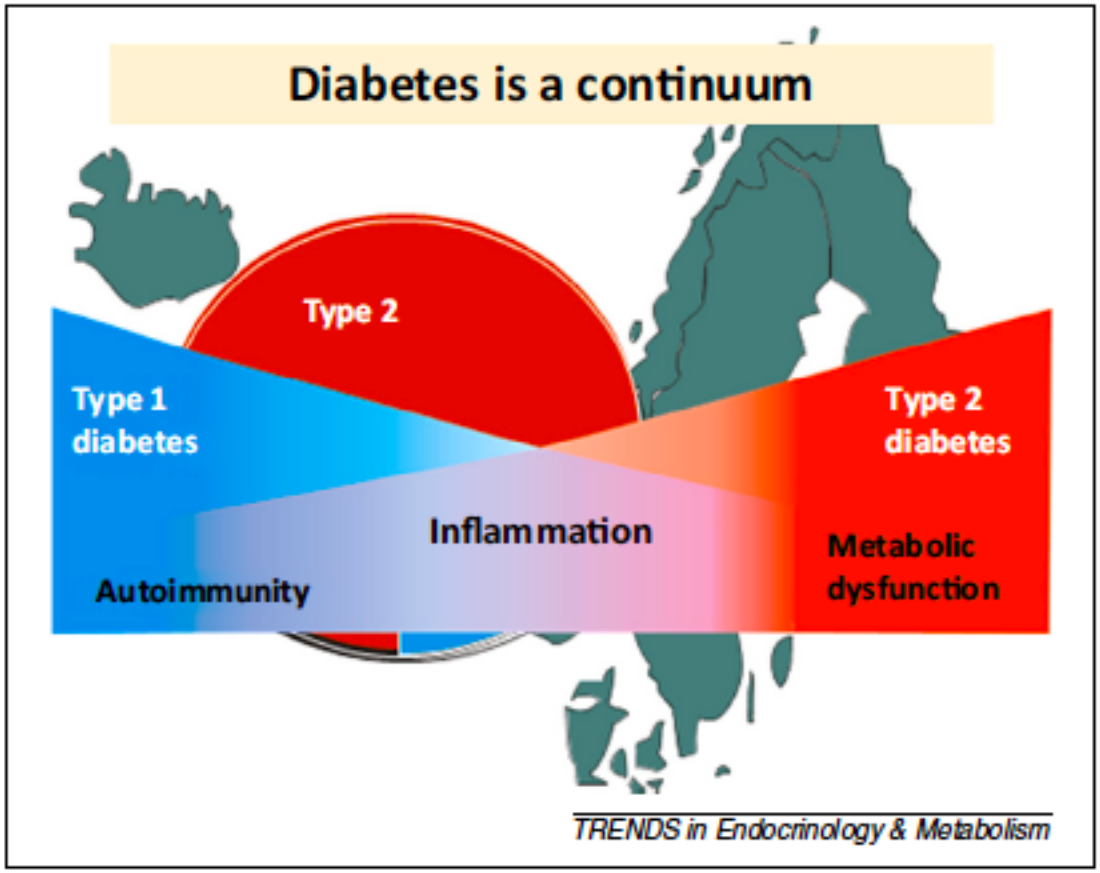


Figure 2. Diabetic disease as a continuum. Type 1 diabetes (T1D) and type 2 diabetes (T2D) most likely represent extremes on a continuum of diabetic subgroups with autoimmunity and T1D to the left and T2D with metabolic syndrome to the right. In between there are latent autoimmune diabetes in adults (LADA) patients and other subgroups that are insufficiently characterized by current diagnostic means.

Summary

- Current definitions are imprecise and ambiguous
  - Complicated by overlapping characteristics (e.g. T1D with T2D parents, or, T2D with antibodies-no insulin)
  - Don't take into account newer understandings of causes of DM/ mechanisms of hyperglycemia

- Need to focus on preservation/ improvement of β-cell function
  Insulin is overused in patients with retained β-cell function

- Multiple mediating pathways of hyperglycemia
  are not taken into account in choice of treatment

- Gov't and payers limit coverage for therapies based on 'diagnosis'

THUS….

Call to Action

- There is a need for a **nomenclature for the classification and diagnosis** of DM that is **in line with up-to-date** knowledge of pathophysiology and newer therapies,
- That supports individualized **(PRECISION)** medicine
- And creates and **targets regimens** that build upon all available treatment options, for the **multiple mediating pathways** of hyperglycemia
- **Forces** , by the logic of the new system, **gov't and insurers to pay** for the logical, effective, safe therapies
- Can **accommodate future** developments

The β-Cell Centric Classification of DM

Intuitively obvious approach…

ANSWERS THE CALL TO ACTION

ALL DM = Hyperglycemia

Classify each patient by the specific cause(s) of the β-cell dysfunction in the clinical presentation of their disease

Prescribe personalized treatment

(patient-centric/ PRECISION MEDICINE)

through targeted therapies

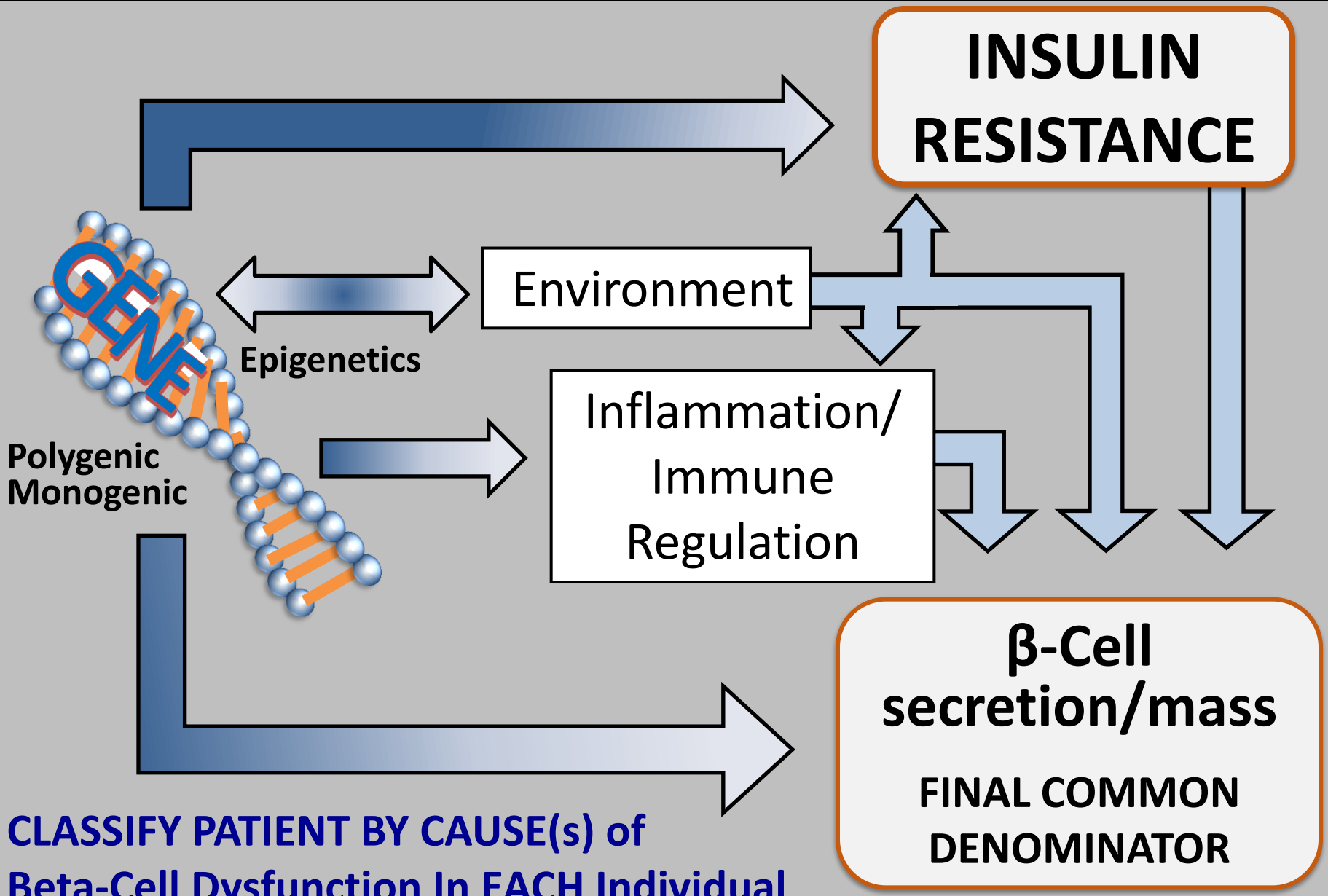
aimed at all possible mediating pathways of hyperglycemia

The 'β-Cell Centric' Classification will help improve diagnosis and treatment,

especially as our knowledge-base expands

β-Cell Centric Classification of Diabetes:

Implications for Classification, Diagnosis, Prevention, Therapy, Research



Pushback

- What about ‘pure’ Insulin Resistance Syndromes?

The β-Cell:
The 'Final Common Denominator'

- Rare Insulin Resistance Syndromes, e.g. leprechaunism, may not have a specific **β-cell** genetic defect, but **β-cells damage may be part of the disease**

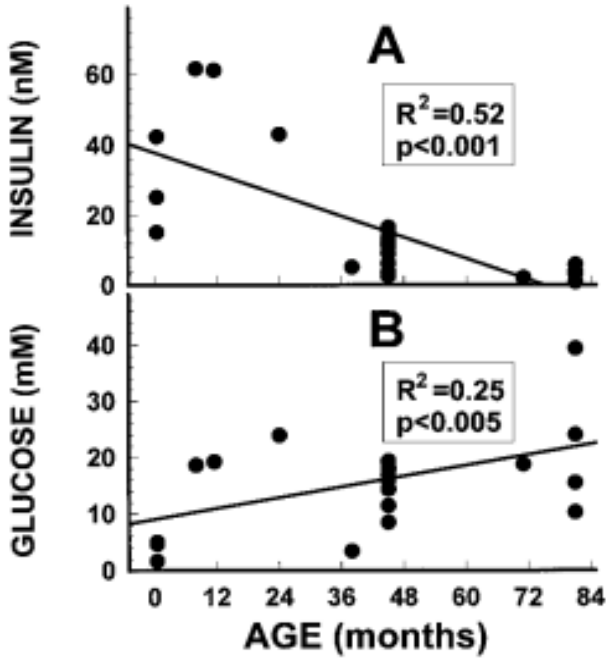


FIG. 2. Age-dependent decrease in insulin (A) and increase in glucos (B) levels in a patient with Rabson-Mendenhall syndrome. Insuli and glucose levels were determined by standard procedures. Dat were analyzed by linear regression, and significance was determine using ANOVA.

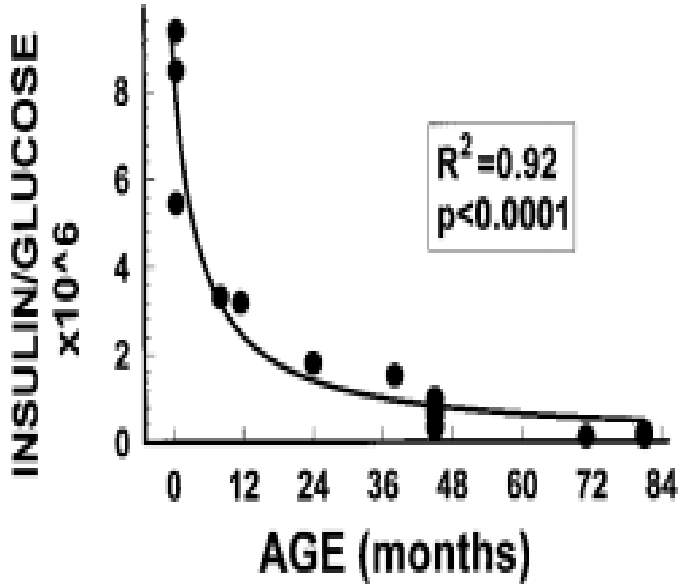


FIG. 4. Exponential decline in the insulin/glucose ratio in Rabson-Mendenhall syndrome. The insulin (nanomoles per L)/glucose (millimoles per L) ratio was plotted as a function of age and fitted to an exponential equation. Significance was determined using ANOVA.

Longo, et al, Progressive decline in insulin levels in Rabson-Mendenhall syndrome. JCEM,1999 Aug;84(8):2623-9.

Pushback-2

(I comment As First Recipient of the Bobby Clarke JDF fellowship☺

Loss of 'T1DM' Designation WILL NOT take away from Focus on 'the CURE'

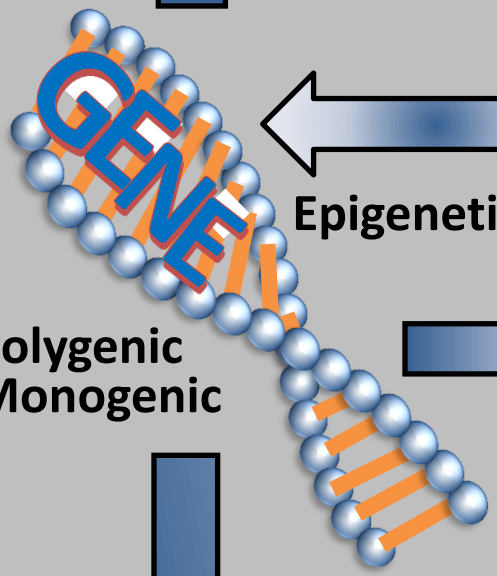
New Classification will FACILITATE SEARCH FOR 'THE CURE"

(focusing on mechanisms that slow the injury/destruction of the b-cell in 'T1-LADA', or speed destruction in 'T2-LADA'etc

Actually , 'Juvenile Diabetes' Fits better, again ☺

β-Cell Centric Classification of Diabetes:

Implications for Classification, Diagnosis, Prevention, Therapy, Research



INSULIN RESISTANCE**

Environment*

Epigenetics

Polygenic
Monogenic

Inflammation/
Immune
Regulation

β-Cell secretion/mass

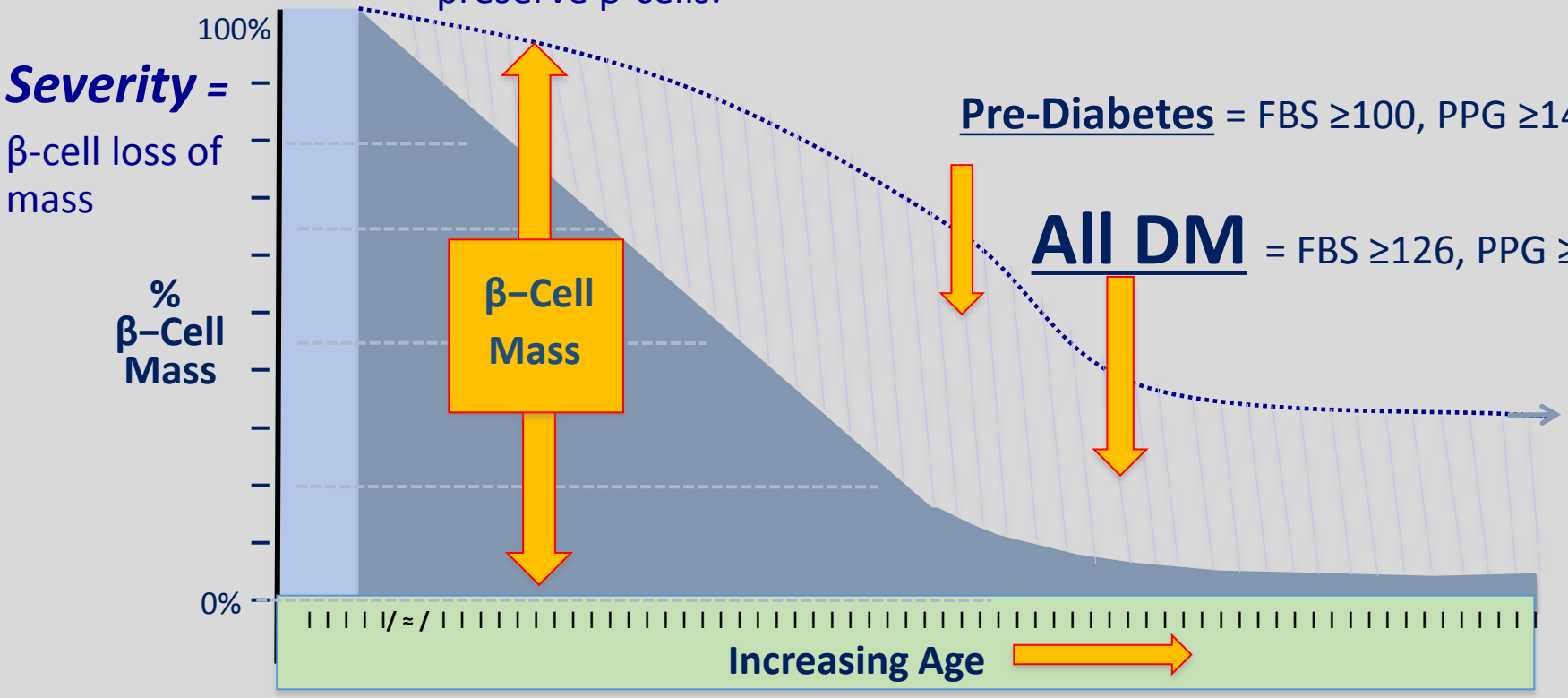
FINAL COMMON DENOMINATOR

*Environment=Genetic suceptibility to
eg: viruses, endocrine disruptors, food AGEs, Gut Biome

**Insulin Resistance= Centrally Induced, Peripheral, Stress Hormones, Gut Biome

Phenotypic Presentation is defined by:

Slope = 'Natural History' over time, i.e.,**RATE OF β-cell LOSS.** Slope is not linear in either T1DM or T2DM, and may be intermittently relapsing, remitting, stabilized, and improved. Complete loss of β-cell mass may never be reached, especially if newer agents better preserve β-cells.



Age at presentation = tipping point when the combined gene effect / environmental trigger is exposed as phenotypic hyperglycemia

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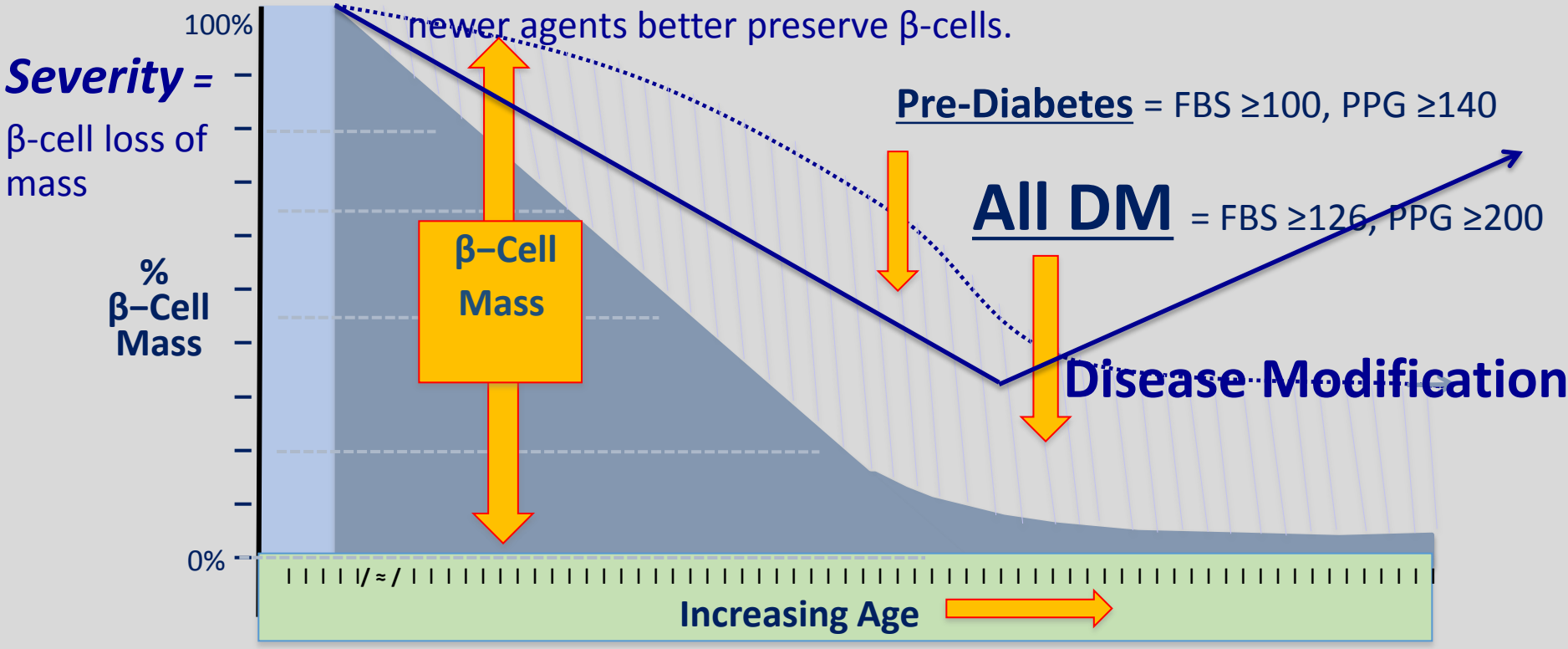
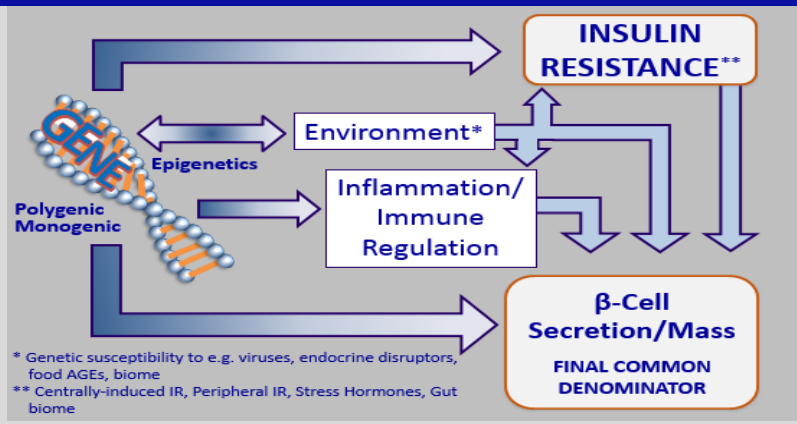


Age at presentation = tipping point when the combined gene effect / environmental trigger is exposed as phenotypic hyperglycemia

β-Cell Centric Classification of DM:

Implications for Classification, Diagnosis, Prevention, Therapy, Research

The β-cell centric classification allows for individualized care



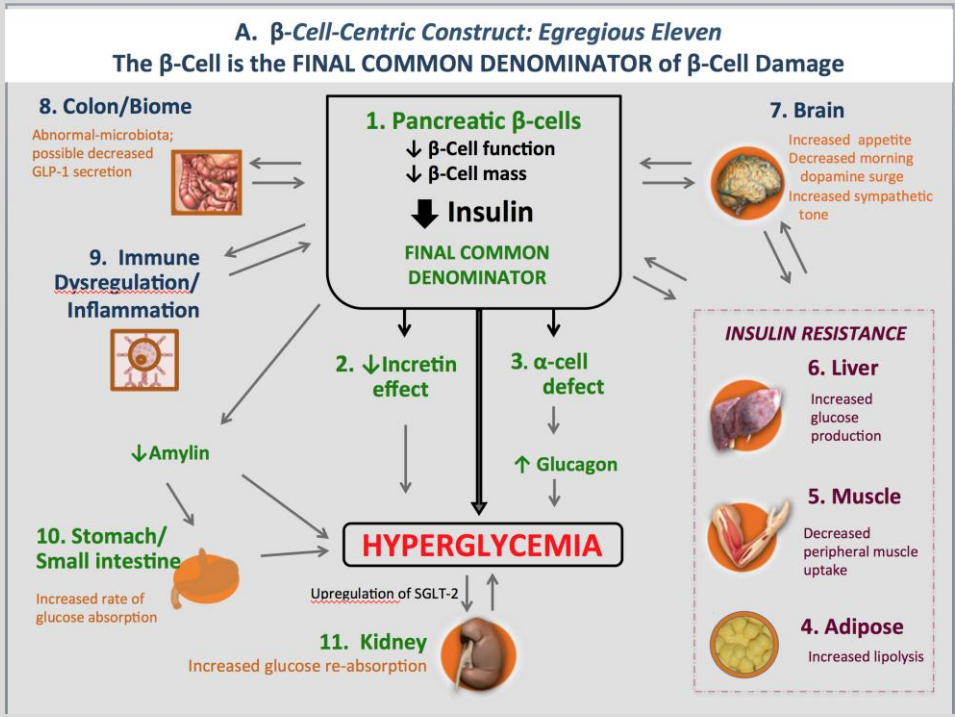
by identifying and treating patient-specific etiologies and mediating pathways of hyperglycemia

EGREGIOUS ELEVEN

1. One CORE Defect- the β-Cell

1. (at least) 6 treatable Causes of β-Cell Damage / HYPERGLYCEMIA

3. 5 treatable mediators of HYPERGLYCEMIA resulting from β-Cell Damage



A. β-*Cell-Centric Construct: Egregious Eleven*

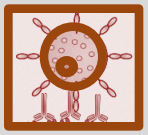
The β-Cell is the FINAL COMMON DENOMINATOR of β-Cell Damage

1. Pancreatic β-cells
↓ β-Cell function
↓ β-Cell mass
⬇ Insulin
FINAL COMMON DENOMINATOR

8. Colon/Biome
Abnormal-microbiota; possible decreased GLP-1 secretion

7. Brain
Increased appetite
Decreased morning dopamine surge
Increased sympathetic tone

9. Immune Dysregulation/ Inflammation



2. ↓Incretin effect

3. α-cell defect
↑ Glucagon

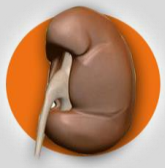
↓Amylin

10. Stomach/ Small intestine
Increased rate of glucose absorption

HYPERGLYCEMIA

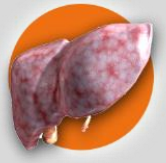
Upregulation of SGLT-2

11. Kidney
Increased glucose re-absorption

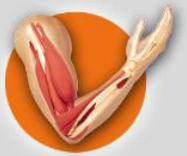


INSULIN RESISTANCE

6. Liver
Increased glucose production



5. Muscle
Decreased peripheral muscle uptake



4. Adipose
Increased lipolysis

Brief Discussions

- Genetics
- Beta-Cell
- Immune Modulation/Inflammation
- Insulin Resistance
- Environment

New β-Cell Centric Construct: *Implications*

Genetics 101 for DM

Phenotype is *DEPENDENT ON*

Genotype:

Number of Genes- which genes- their nature, how many different ones, the 'severity/intensity' of expression!; epigenetics*

i.e: Genes influence:

- B-Cell: Insulin secretory dynamics, sites of susceptibility of β-Cell to destruction by endogenous/ exogenous triggers
- Immune Modulation/Inflammation
- Insulin Resistance
- Environment

(susceptibility to DM COMPLICATIONS)

*Int J Biochem Cell Biol. 2015 May 27. pii: S1357-2725(15)00143-0. doi: 10.1016/j.biocel.2015.05.022. [Epub ahead of print]
Epigenetic dynamics in immunity and autoimmunity. Zhao M1, Wang Z1, Yung S2, Lu Q. ;
Understanding type 2 diabetes: from genetics to epigenetics. Raciti GA, Longo M, Parrillo L, Ciccarelli M, Mirra P, Ungaro P, Formisano P, Miele C, Béguinot F. Acta Diabetol. 2015 Apr 5.

Genotyping

- Genotyping should be used for research (cost ~$100) and later as diagnostic markers on custom chips (even LESS)
- Use for Pharmacogenetics should help guide choice of treatment
- Find Gene action/ Function - Leads to understanding mechanisms
  - e.g.: *TCF7L2;* Potential Therapy re: PARP-1 Inhibitor, other
  - Other Gene/Mechanism/ Therapy
    - low BMR- results in morbid obesity
    - Asian/ Eastern Europeans- store more Visceral Fat at Lower BMI
    - ? PREVENT T2DM-*SLC30A8*
    - Increase RISK- *TBC1D4* (Greenland)

Trends in Endocrinology and Metabolism September 2014, Vol. 25, No. 9

Leif Groop, Can genetics improve precision of therapy in diabetes?

Pharmacogenetics:

Which agents most likely
to be effective
in a given patient

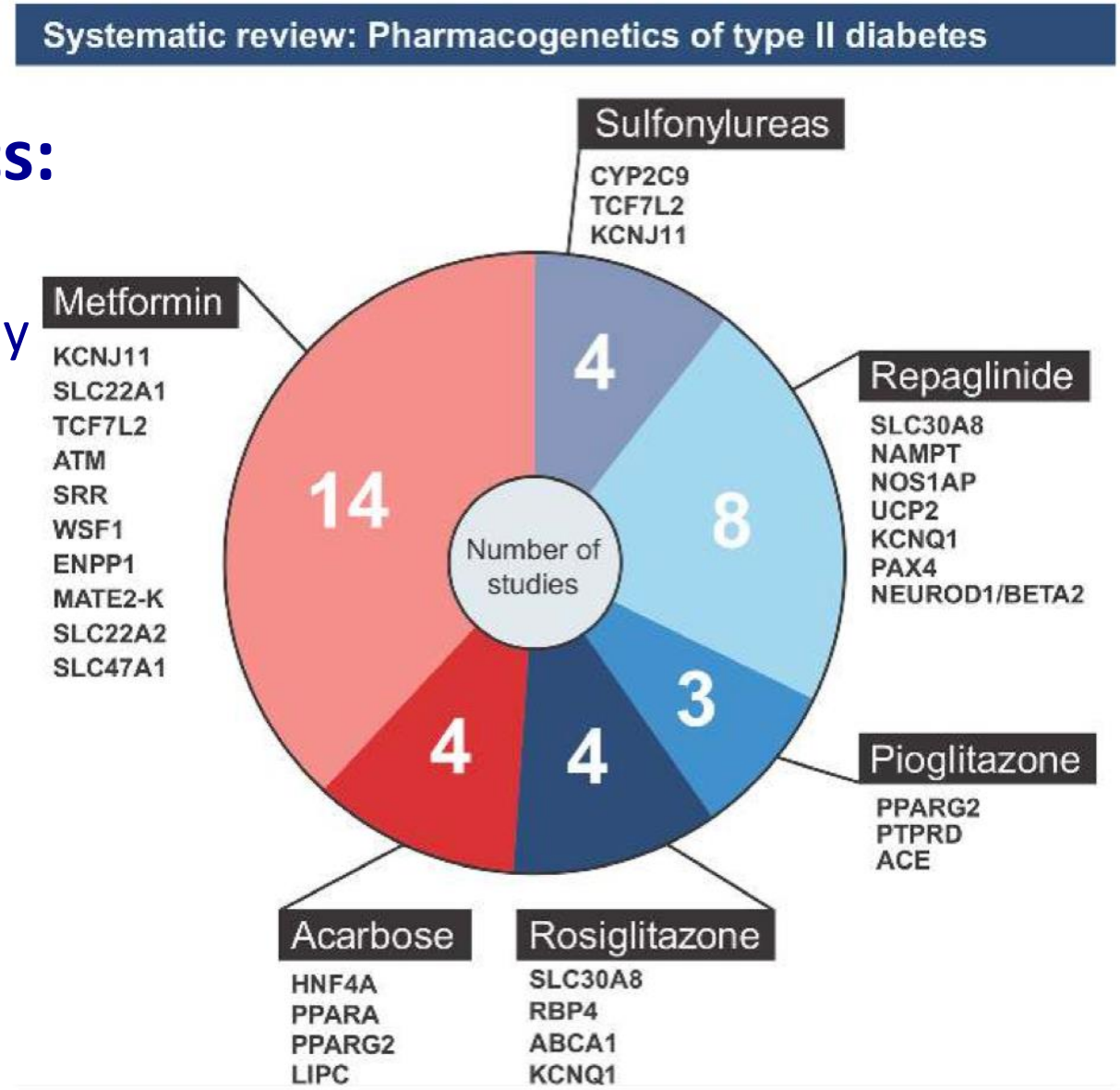
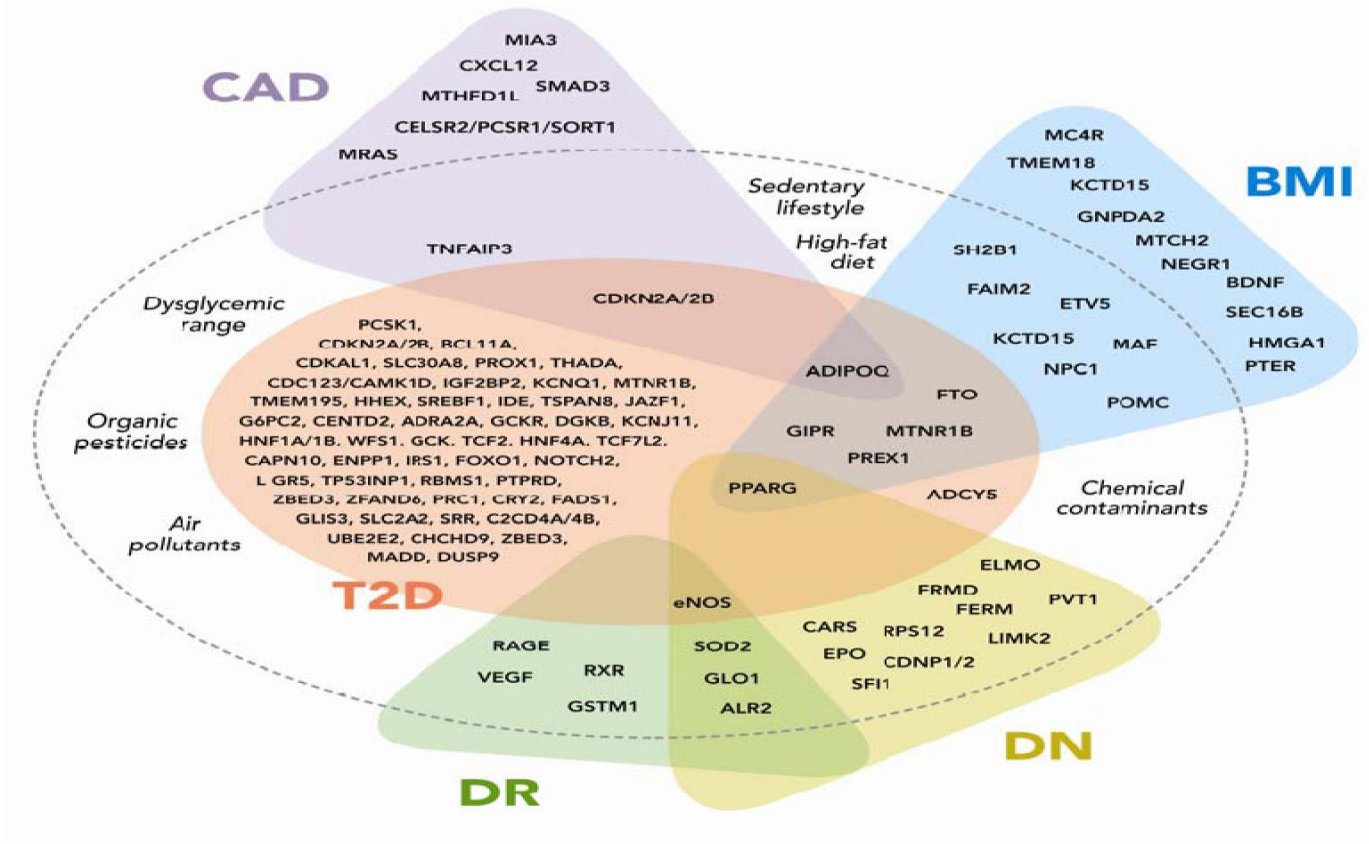


Fig. 1 *Summary of the pharmacokinetic, pharmacodynamic and regulatory genes involved in significant gene–drug interaction in response to antidiabetic medication (adapted from Maruthur et al.* [10]).

Gene/ Environment Interactions with DM and it Complications: some in common to both

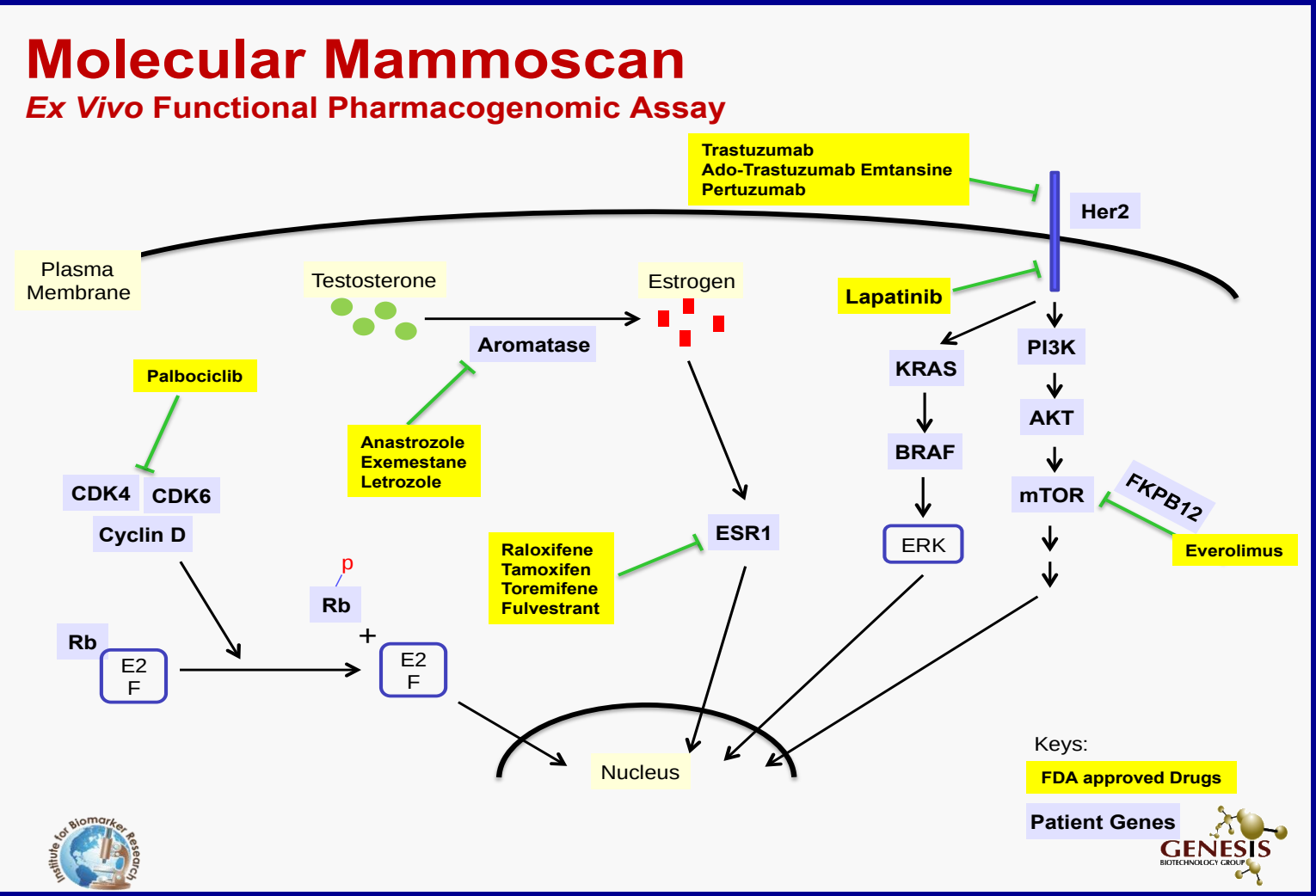


Genes related to b-cells and complication risk may be the Same Or Different

Figure 1. Interplay between genes and environmental/behavioral factors in the development of type 2 diabetes and related vascular complications. Variability in diabetes and obesity-related genes predispose to type 2 diabetes (T2D) and diabetic vascular complications such as coronary artery disease (CAD), diabetic nephropathy (DN), and diabetic retinopathy (DR). Behavioral (e.g., sedentary lifestyle, high-fat diet) and environmental factors (e.g., organic pesticides, chemical exposures, and air pollutants) have complementary effects on the development of type 2 diabetes. Additional genes are associated with CAD and body mass index (BMI) in the general population, without demonstrable effects on the risk of T2D.

Can picture Genomics CHIP for DM as developed for Breast Cancer-

multi-gene assay applied to paraffin-embedded breast cancer tissue, which allows physicians to predict subgroups of hormone-receptor-positive, node-negative patients who may benefit from hormonal therapy alone or require adjuvant chemotherapy to attain the best survival outcome



Could put other ‘ Markers on same chip, eg:

Proteinomics, Metabolomics miRNAs, islet DNA,

IR markers, inflam., Immune markers

As/when validated

Genetics of 'LADA'

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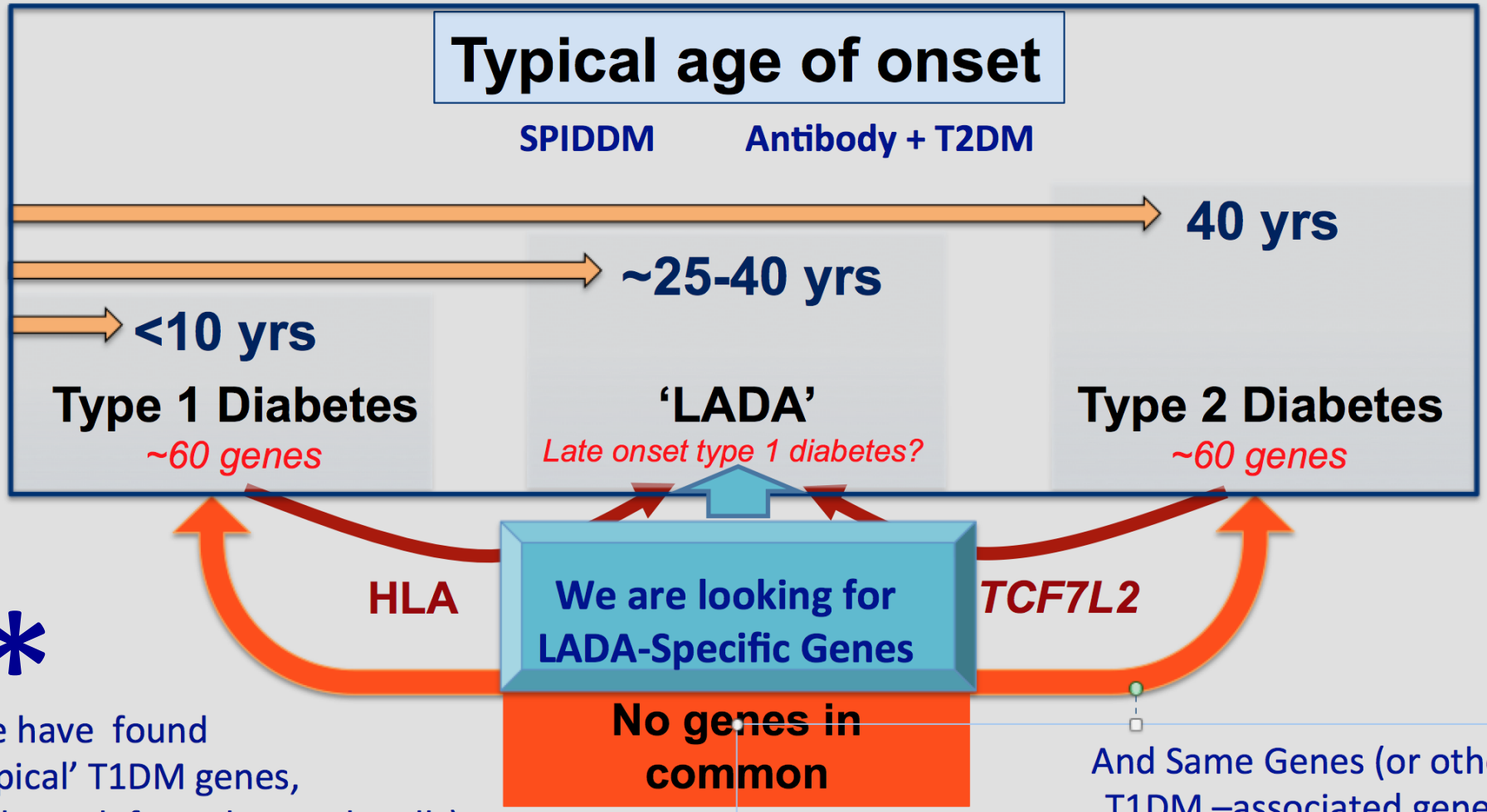


*

We have found 'typical' T1DM genes, (Whose defects destroy b-cells) Whose ABSENSE may result in delay of T1DM, Thus = 'Type 1-Like' LADA

And Same Genes (or other T1DM –associated genes) May be over-represented/ present in 'T2DM- Like' LADA patients

Ex:

Slow Destruction of B-Cells in T1DM-like LADA; Fast Destruction of B-Cells in T2DM-Like LADA

New β-Cell Centric Construct: *Implications*

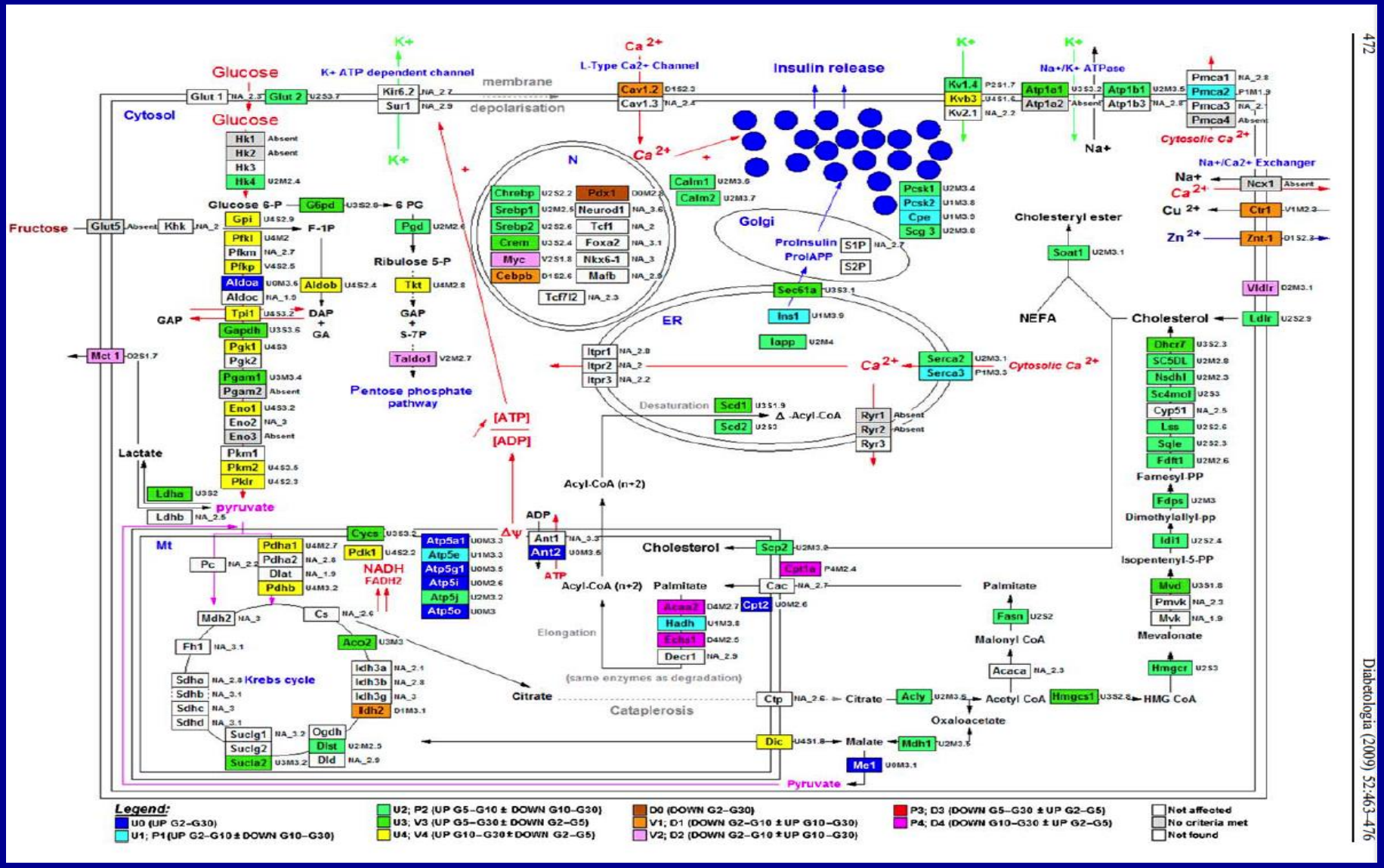
β-cell Issues

- Usual use of Glycemic Criteria- HgA1c, FBS, PPG
- Markers-Usual/Classic= C-Peptide
- New Non-Invasive
  - **β-Cell Mass Measures-**
    Nano-particle labeled exendin imaging
  - **Circulating DNA Markers of β-Cell Destruction**
    Glazer- Hebrew Univ
  - **Circulating mRNAs**
- Try to Determine Mono-Genetic Causes

NO LOGIC FOR USE OF AGENTS THAT MAY CONTRIBUTE TO APOPTOSIS of **β-Cell**

STOP USING SU's, GLINIDES; Minimize INSULIN THERAPY

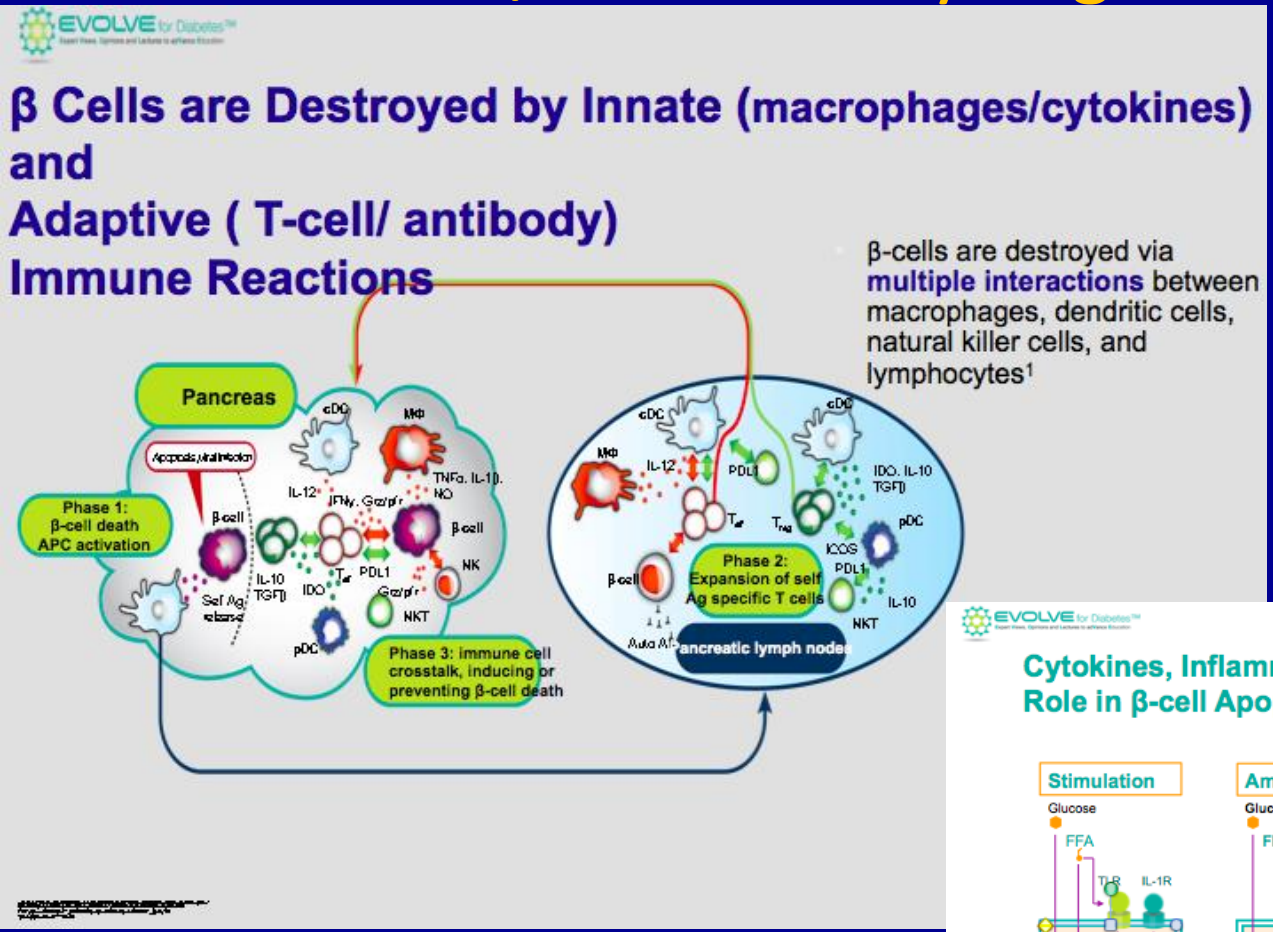
Be aware of all the Secretory Dynamic Pathways involved, AND GENES INVOLVED



472
Diabetologia (2009) 52:463–476

New β-Cell Centric Construct: *Implications*

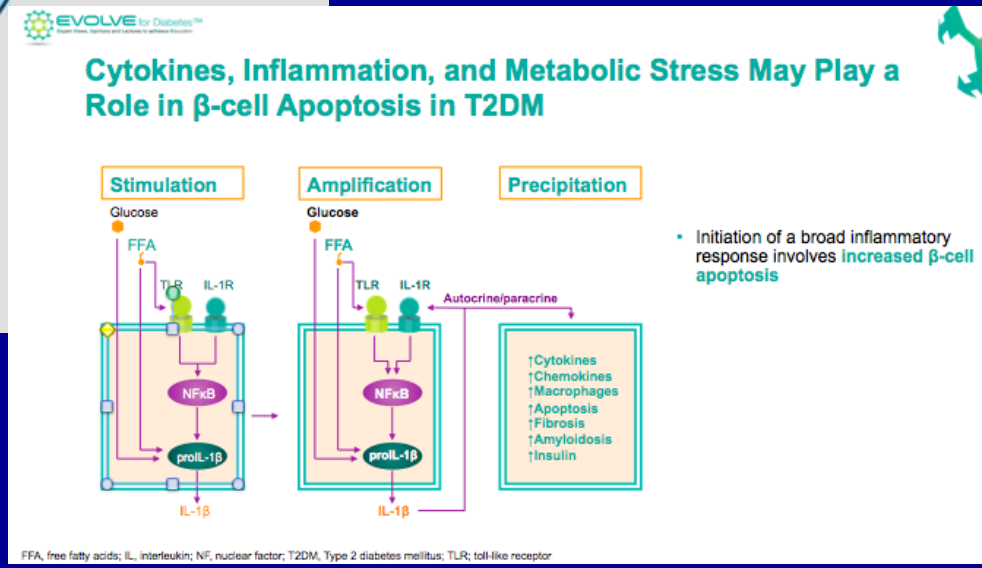
Inflammation/ Immune Dysregulation Issues-ALL DM



Same Processes for T1DM, T2DM

-

Same AND Different Triggers



Yumi Imai1, Anca D. Dobrian2, Margaret A. Morris1,3, and Jerry L. Nadler,Islet inflammation: a unifying target for diabetes treatment? Trends in Endocrinology and Metabolism 2013:1-10 ;
Barbara Brooks-Worrell, Radhika Narla, and Jerry P. Palmer Biomarkers and immune-modulating therapies for Type 2 diabetes Trends in Immunology November 2012, Vol. 33, No. 11; James JohnsonUniversity of British Columbia Vancouver, BC, Canada

Gut Microbiota Trigger Inflammation/ Immune destruction of B-Cell in 'T1DM'

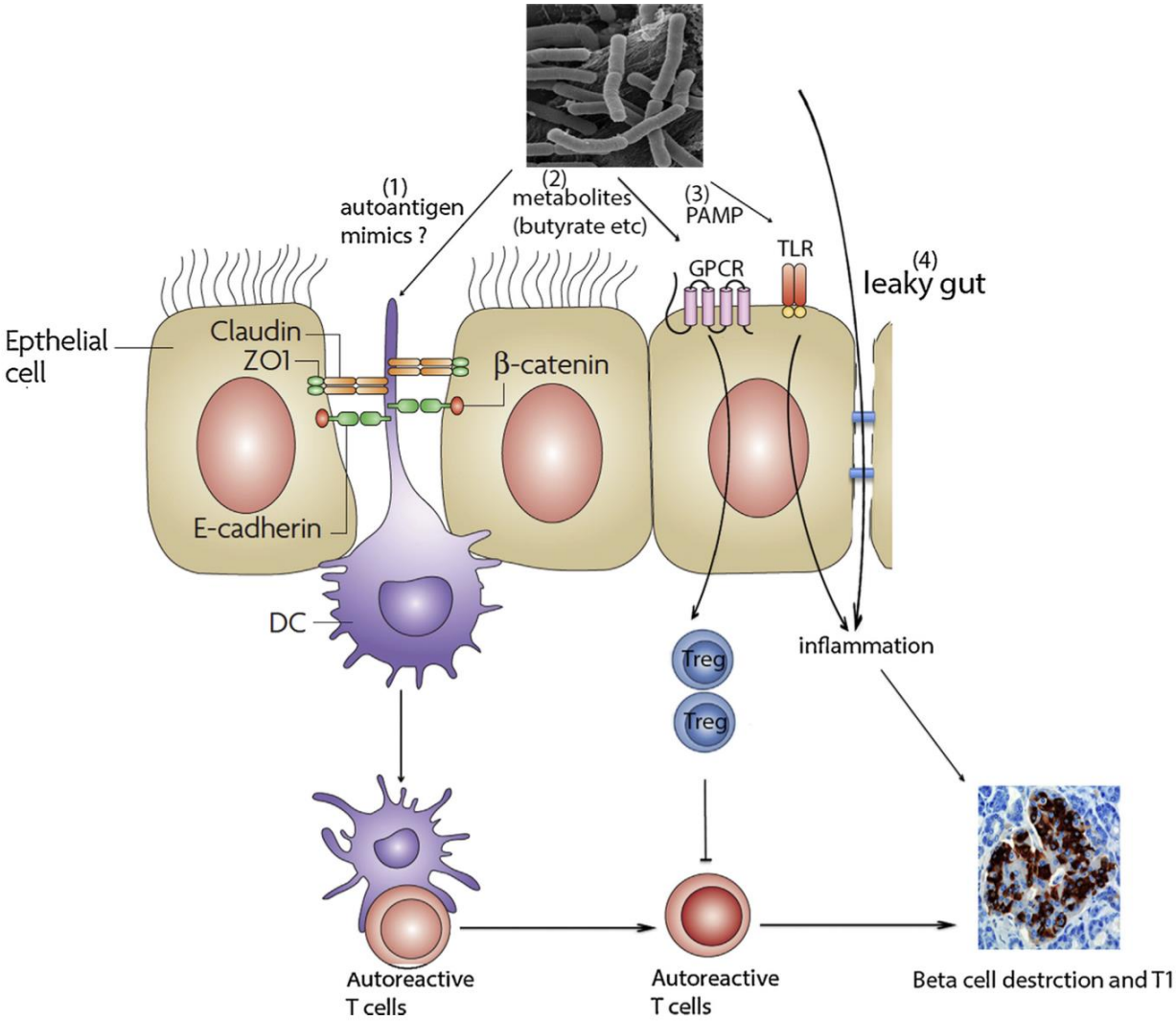
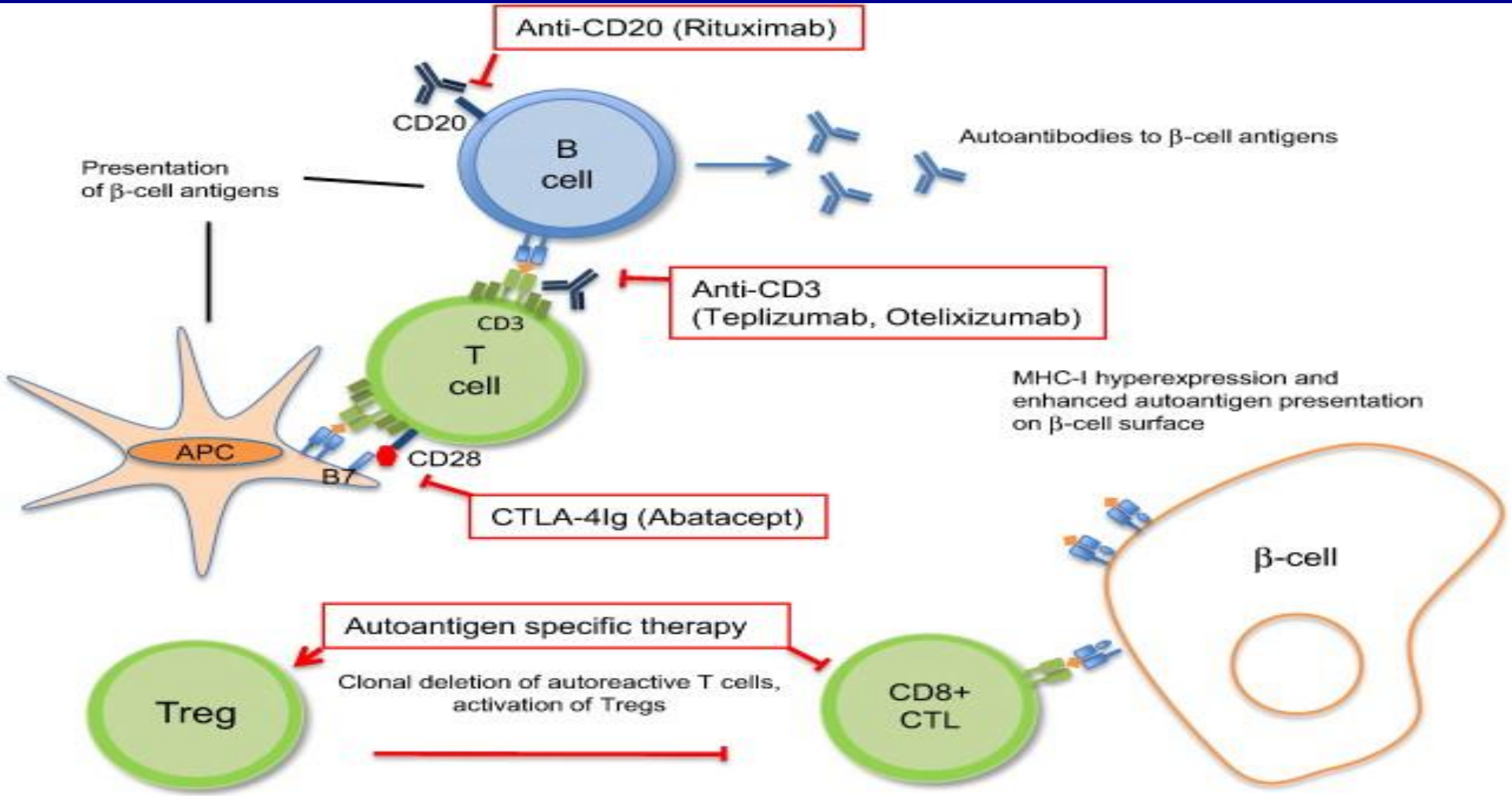


Fig. 1. The role of gut microbiota in the development of T1D. Gut flora can affect islet autoimmunity through mechanisms: (1) expression of autoantigen mimicry to activate autoreactive T cells by antigen-presenting cells to destruct islet beta cells. (2) Generating metabolites, such as acetate, butyrate etc., to induce the differentiation or migration of regulatory T cells to control autoreactivity through GPCR signaling pathway (such as Gpr43). (3) Gut bacteria-derived pathogen-associated molecular patterns (PAMP) activate TLR signaling pathway to initiate the inflammation, which activates autoreactive T cells and/or directly cause injury to beta cells through inflammatory cytokines. (4) Gut bacteria can penetrate the leaky gut and cause inflammation to destruct beta cells.

15) 9–15

Pathogenesis and biological interventions in T1DM- LIKE autoimmune diabetes- Insulitis

The class I MHC molecules are hyperexpressed on the β-cell surface in T1D patients making β-cells more susceptible to cytotoxic lymphocyte (CTL)-mediated destruction.



Novel diagnostic and therapeutic approaches for autoimmune diabetes — A prime time to treat insulitis as a disease

http://dx.doi.org/10.1016/j.clim.2014.11.007 Clinical Immunology, Juha Grönholm , Michael J. Lenardo

Efficacy of Immunotherapy in T1DM: Some Can Delay Decline in C-peptide

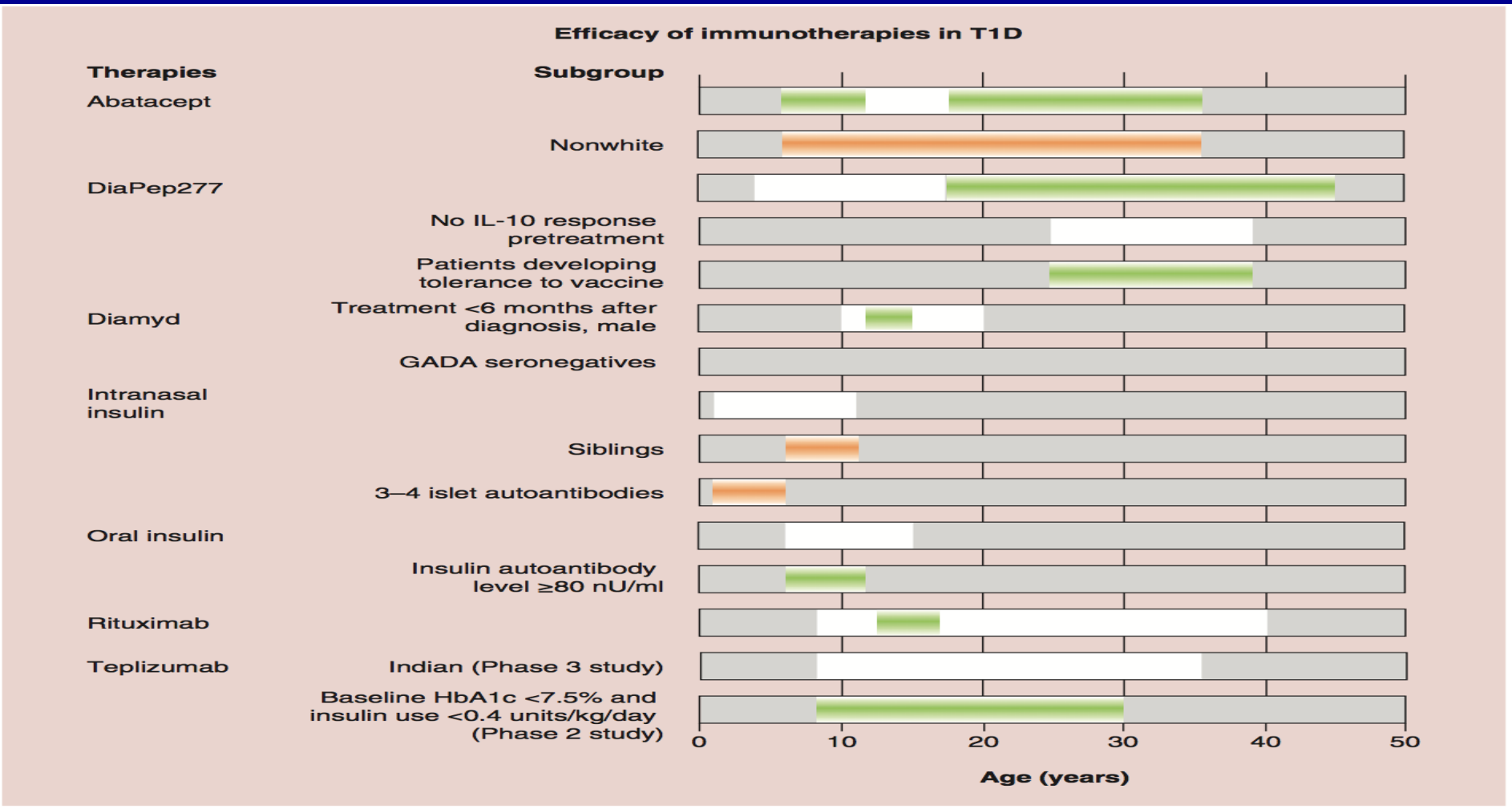


Figure 2. Heterogeneity in efficacy of immunotherapies in Type 1 diabetes. Treatment efficacy is determined by the impact of immunotherapy on decline in stimulated β-cell function as defined by C-peptide production in response to glucose. A positive effect implies delayed decline of C-peptide production upon a given immunotherapy (green). Lack of effect (white) denotes immunotherapy not changing the course of decline in β-cell function compared to placebo-treated subjects, whereas a (tendency of) negative effect implies an accelerated loss in β-cell function in response to intervention therapy (orange).
GADA: Glutamic acid decarboxylase autoantibodies; T1D: Type 1 diabetes.

Wolfflez, Roep,* *Immunotherapy (2015) 7(2), 163–174

Insulin Resistance within the β-Cell Centric Construct

- Insulin Resistance is understood to expose and exacerbate the core β-cell defect
- Genetically- Based
- Exacerbated by Environmental issues: Diet, Activity, Biome
- Includes Multiple Causes of Insulin Resistance

Insulin Resistance Impairs β-Cell Function by:

- Lipo- and gluco-toxicity
- Inflammatory mechanisms
- Adipocytokines effect on β-cell

Insulin Resistance within the β-Cell Centric Construct

- Rare Insulin Resistance Syndromes- eg: leprechaunism may not have a specific **β-Cell** genetic defect, but β-cells may ultimately suffer damage

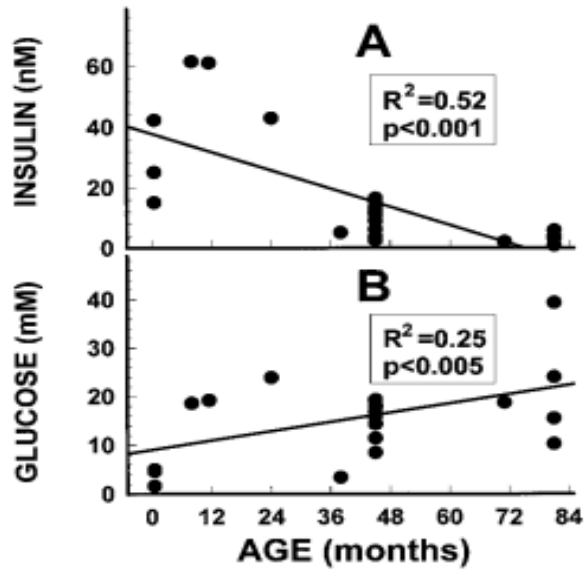


FIG. 2. Age-dependent decrease in insulin (A) and increase in glucose (B) levels in a patient with Rabson-Mendenhall syndrome. Insulin and glucose levels were determined by standard procedures. Data were analyzed by linear regression, and significance was determined using ANOVA.

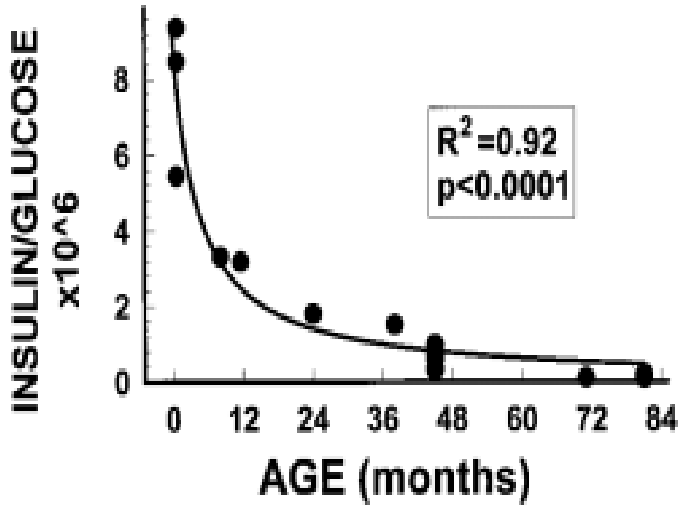


FIG. 4. Exponential decline in the insulin/glucose ratio in Rabson-Mendenhall syndrome. The insulin (nanomoles per L)/glucose (millimoles per L) ratio was plotted as a function of age and fitted to an exponential equation. Significance was determined using ANOVA.

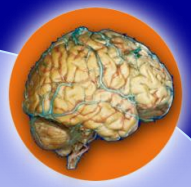
Longo, et al, Progressive decline in insulin levels in Rabson-Mendenhall syndrome. JCEM,1999 Aug;84(8):2623-9.

Potential Causes of Insulin Resistance and Their Interplay

Weight Reduction Agents

Central IR

Loss of dopamine surge in SCN
increased appetite
Increased sympathetic tone



Bromocriptine-QR

Hyperinsulinemia

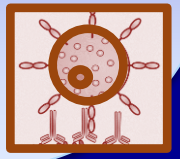
Biome IR

Pro-Biotics,
Pre-Biotics,
Antibiotics

Peripheral IR

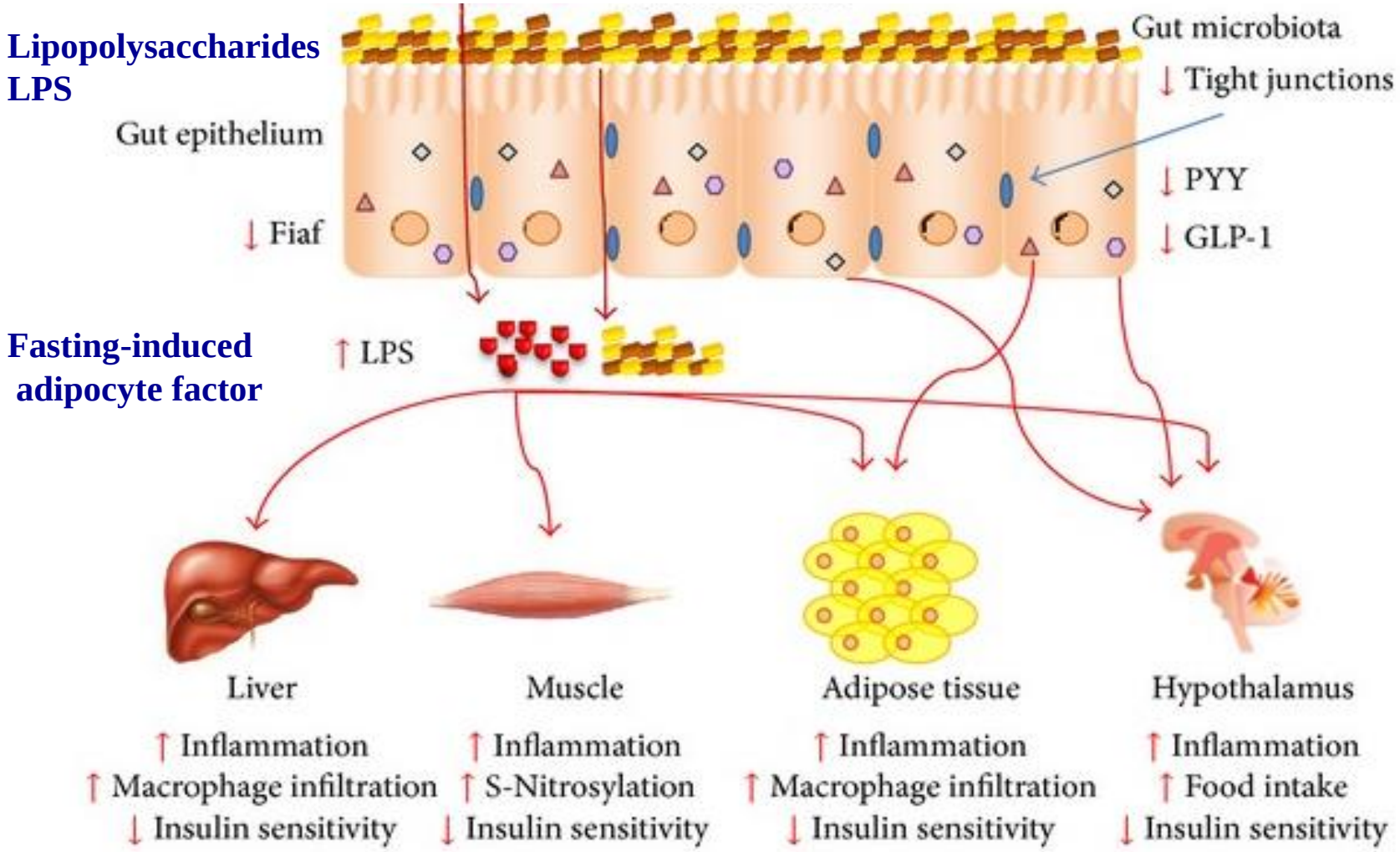
TZD (Pio-) ,
Metformin

Inflammation IR



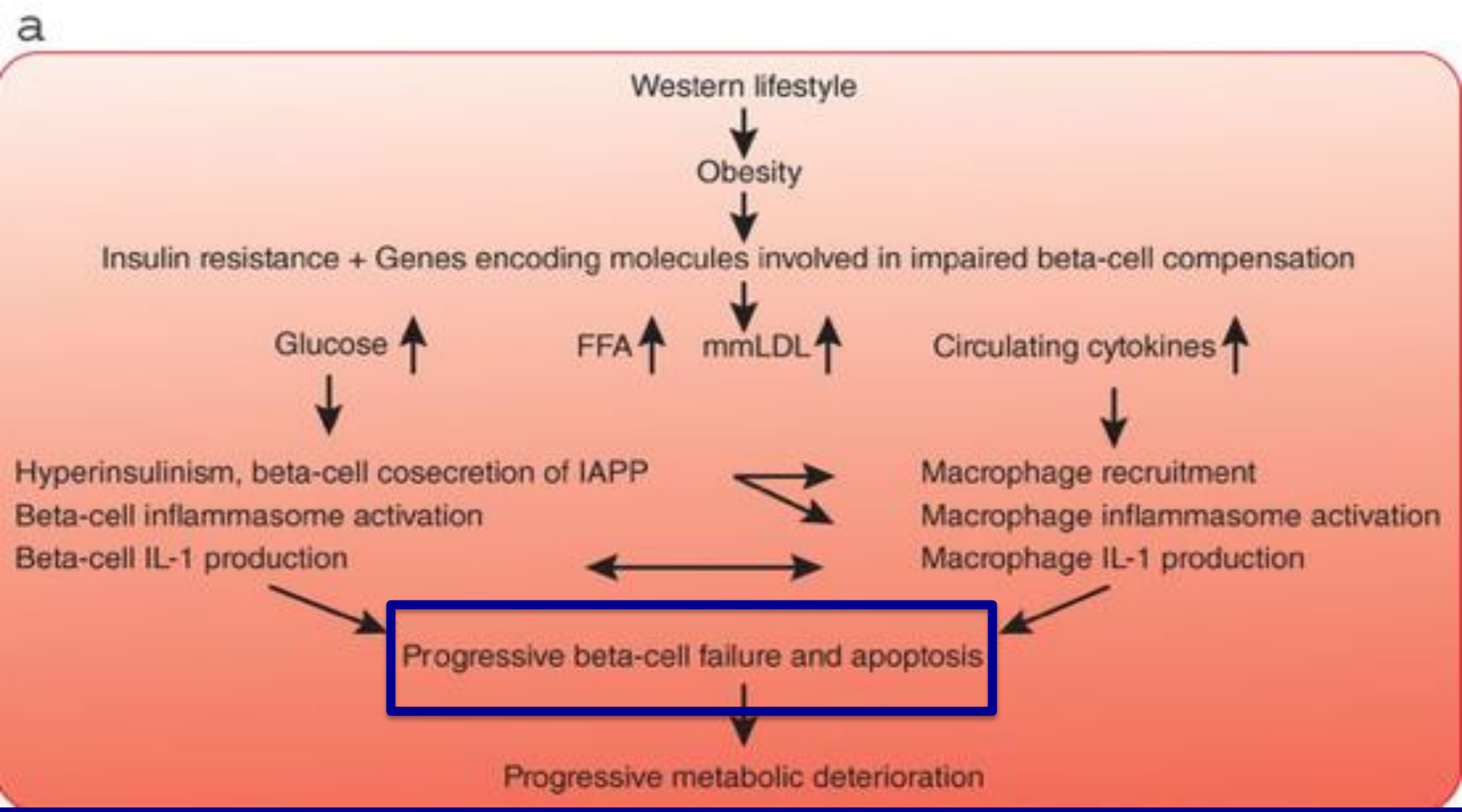
Anti-Inflammatories
Immune modulators

Metabolic Derangement, and Insulin Resistance Associated with Microbiome



Pioglitazone Treats Secondary Adverse Effects of Abnormal Biome

Simplistic Inflammatory and Non-Inflammatory Effects of Insulin Resistance on B-Cell Function



IAPP boosts islet macrophage IL-1 in type 2 diabetes : Nature ...www.nature.com

New β-Cell Centric Construct: *Implications*

Environmental Risk Factors in T1D/T2D, ? 'LADA'

T1D

- Seasonality at diagnosis
- Migrants assume risk of host country
- Risk factors from case-control studies
  - Hormones
  - Stress
  - Improved Hygiene
  - Infant/childhood diet
  - Vitamin D
  - Cow's Milk
  - Gut-microbial Balance – Biome
  - Lack of Physical Activity
  - Viruses – exposures as early as in utero

T2D

- Obesity-Diet
- Lack of Physical Activity
- AGE ingestion

LADA

- Coffee
- More Educated

Can Keep Current Terminology Incorporate the β-Cell Centric Approach with each to determine issues in individual patient or a New Terminology?

	Younger			Older		
				'LADA'		
	T2D	MODY, monogenic	T1D	SPIDDM	Autoimmune T2D	T2D
Genes						
- mono		+,which				
- poly	+,which		+,which	+,which	+,which	+,which
Inflammation	**+/-**	**—**	**+**	**+**	**+**	**+/-**
Resistance	**+/-**		**+/-**	**—**	**+/-**	**+/-**
Environment	+,which		+,which	+,which	+,which	+,which

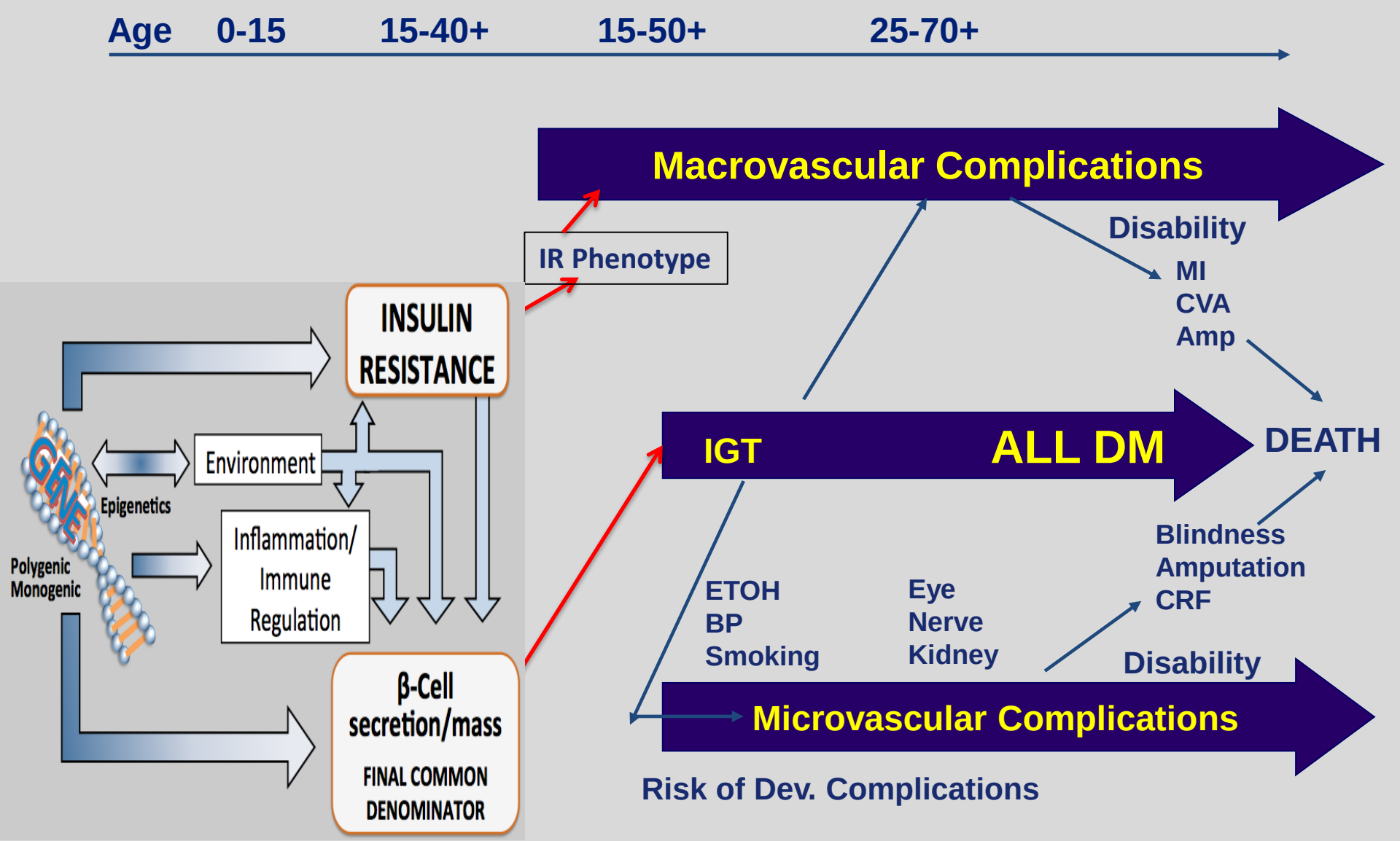
Easier to get buy-in from many different stakeholders, MDs, etc

Or New Terminology Should Reflect the
β-Cell Centric Approach;

Disease = DIABETES; Phenotype= Hyperglycemia		
Genes		
- mono		+,which
- poly	+,which	
Inflammation	**+/-**	
Resistance	**+/-**	
Environment	+,which	

Implications for Therapy: Use whatever logically sensible/necessary based on cause of hyperglycemia in each patient

New approach is Commensurate with Natural History of ALL DM



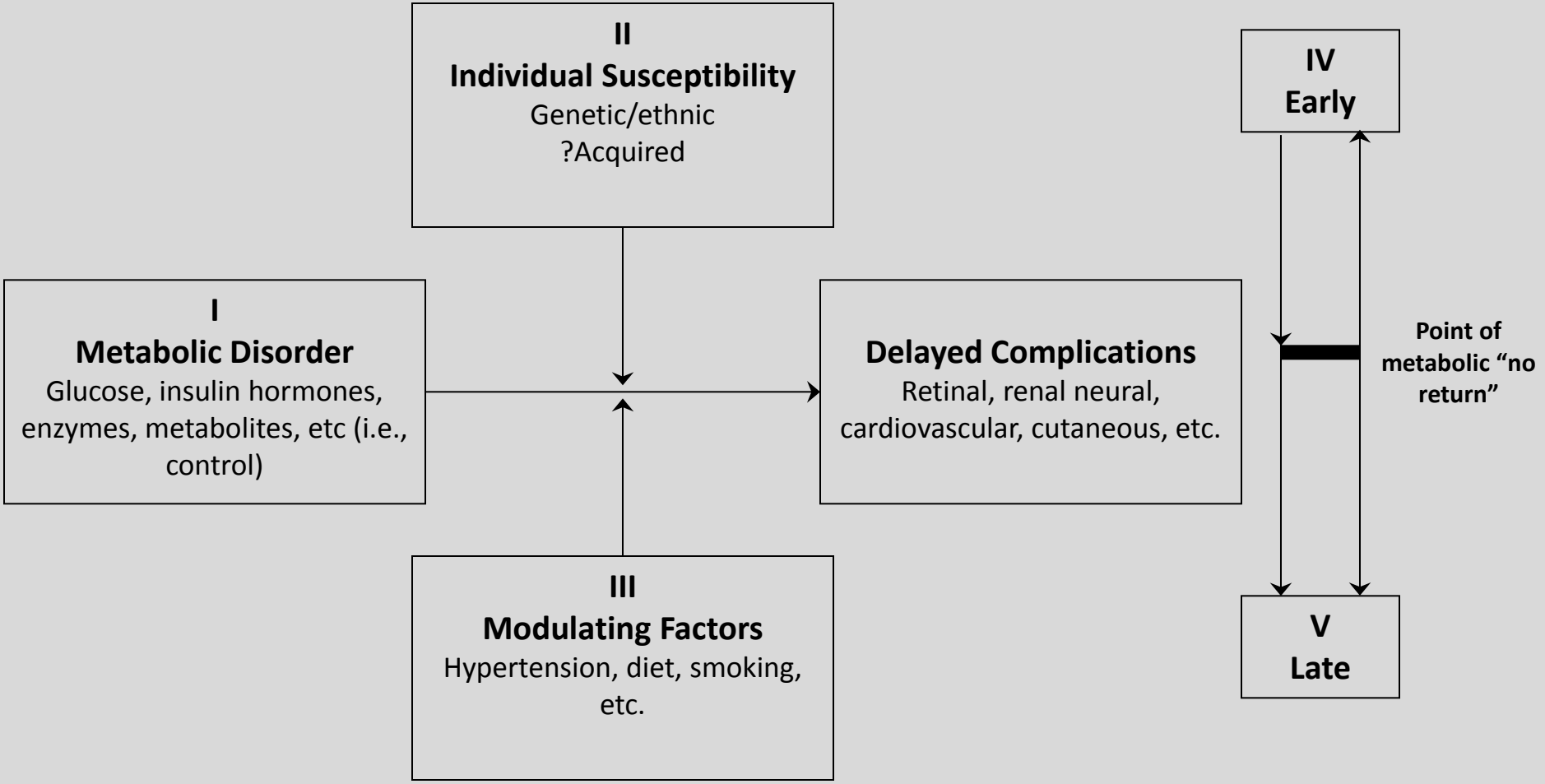
ANOTHER EPIPHANY:

WHAT ABOUT COMPLICATIONS OF DIABETES?

We noticed :

Pathophysiology of Diabetic Complications: Old Conundrum :

why similar HgA1c in different folk give different risks

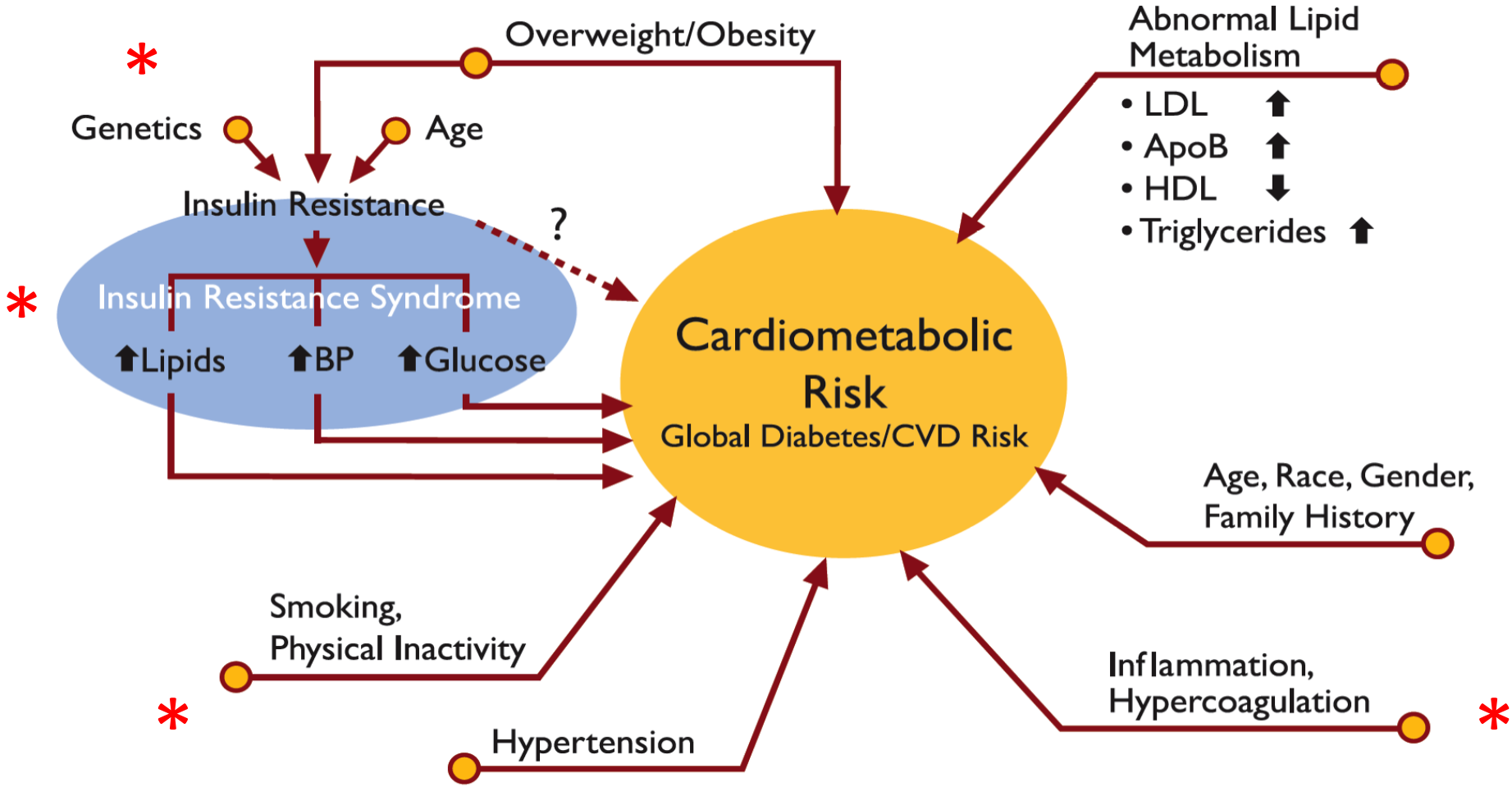


harry keen, chronic complications of diabetes mellitus, chapter 16, in monograph, ed. Galloway et al DM, lilly research labs, 1988

Factors Contributing to Cardiometabolic Risk

American Diabetes Association.
Cure • Care • Commitment®

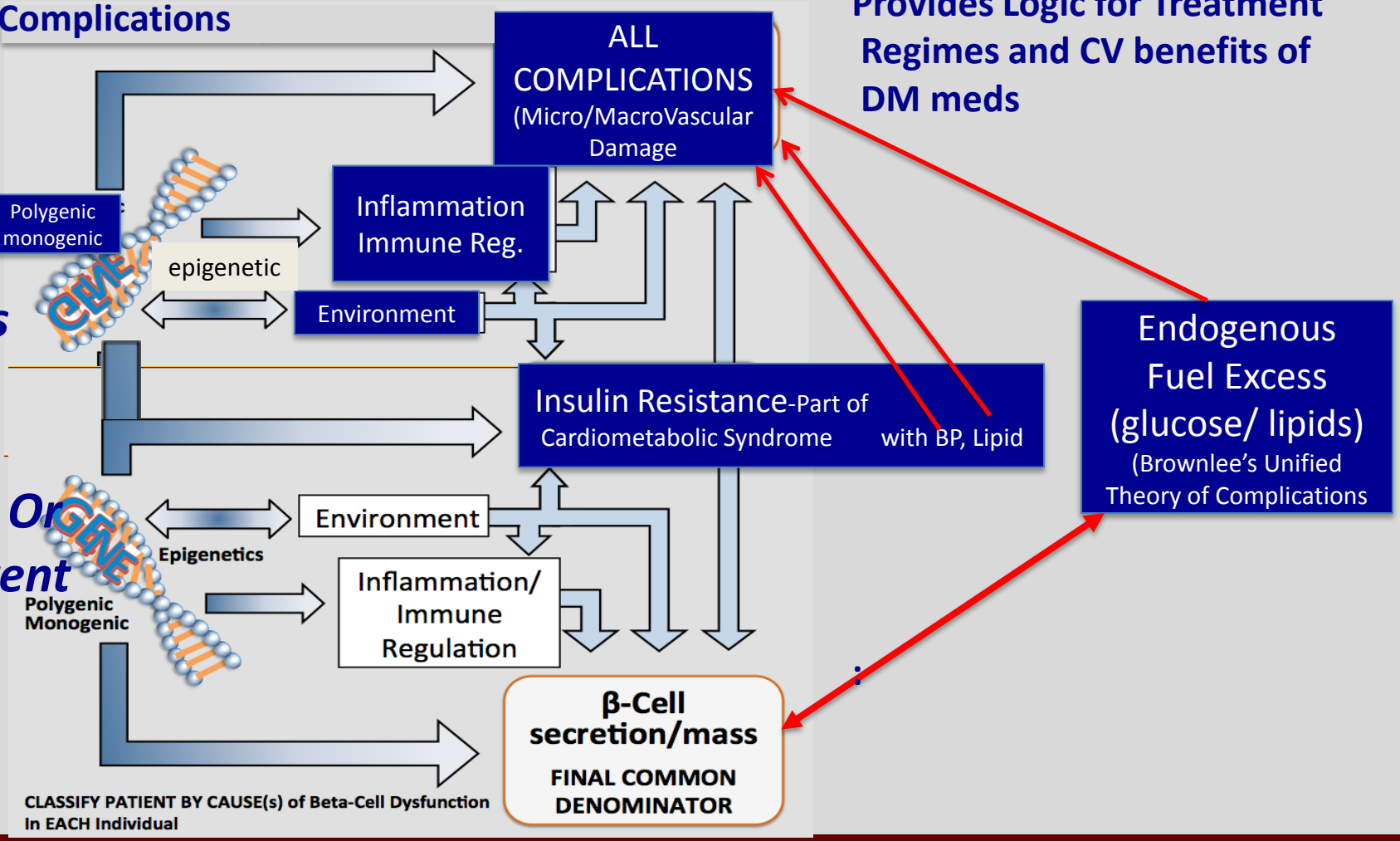
ARE THE SAME AS THOSE THAT DAMAGE THE Beta-Cell



A Unifying Pathophysiologic Approach to The Complications of Diabetes in the Context of the Beta-cell Classification of Diabetes.

MOST MECHANISMS OF B-cell Damage Overlap with Causes of ALL Complications

Provides Logic for Treatment Regimes and CV benefits of DM meds



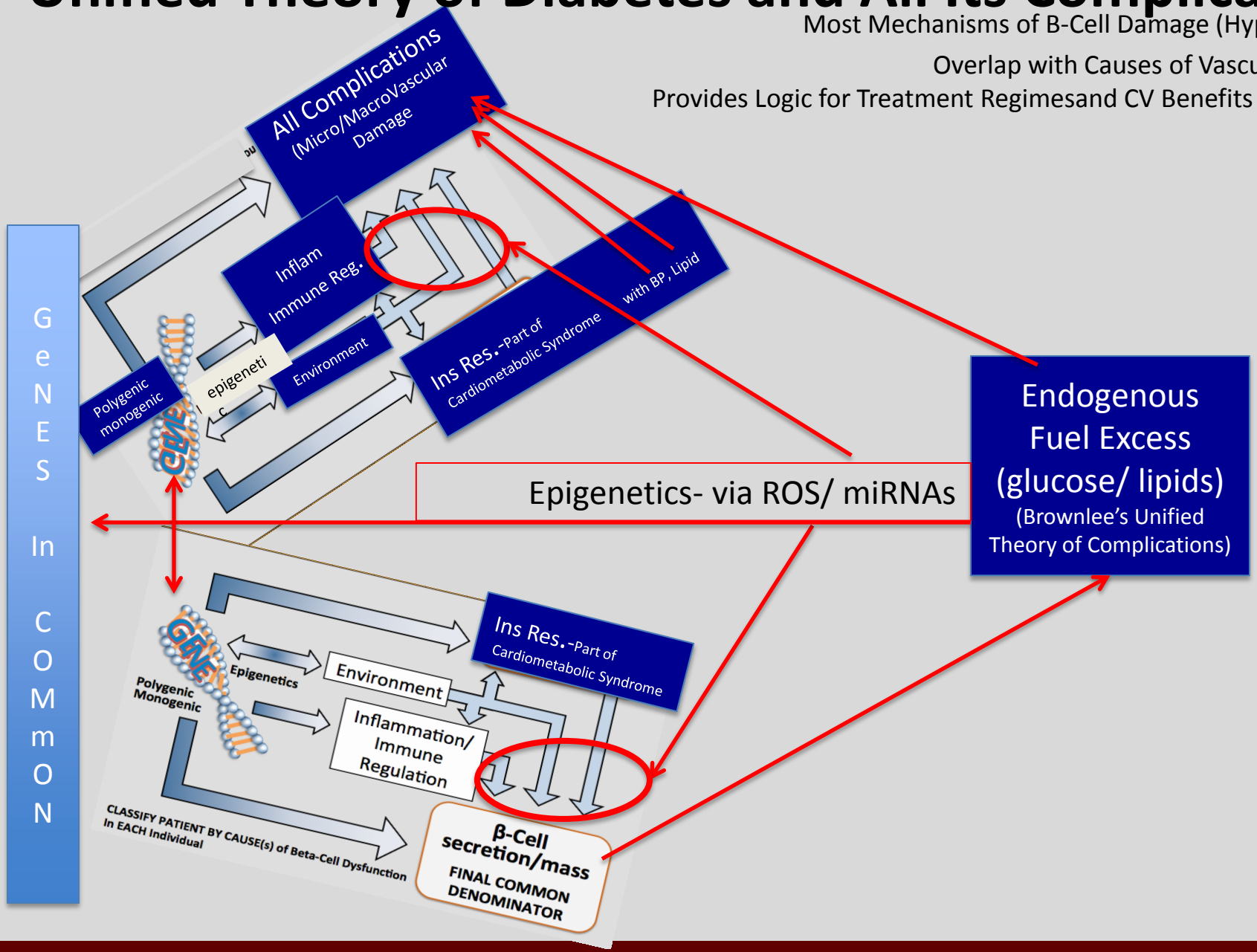
*Environment=Genetic suceptibility to eg: viruses, endocrine disruptors, food AGEs, Gut Biome; **Insulin Resistance= Centrally Induced, Peripheral, Stress Hormones, Gut Biome

Unified Theory of Diabetes and All Its Complications

Most Mechanisms of B-Cell Damage (Hyperglycemia)

Overlap with Causes of Vascular Disease :

Provides Logic for Treatment Regimesand CV Benefits of DM Meds



*Environment=Genetic suceptibility to eg: viruses, endocrine disruptors, food AGEs, Gut Biome; **Insulin Resistance= Centrally Induced, Peripheral, Stress Hormones, Gut Biome

Brownlee's Mechansm's leads to EPIGENETIC EFFECTS

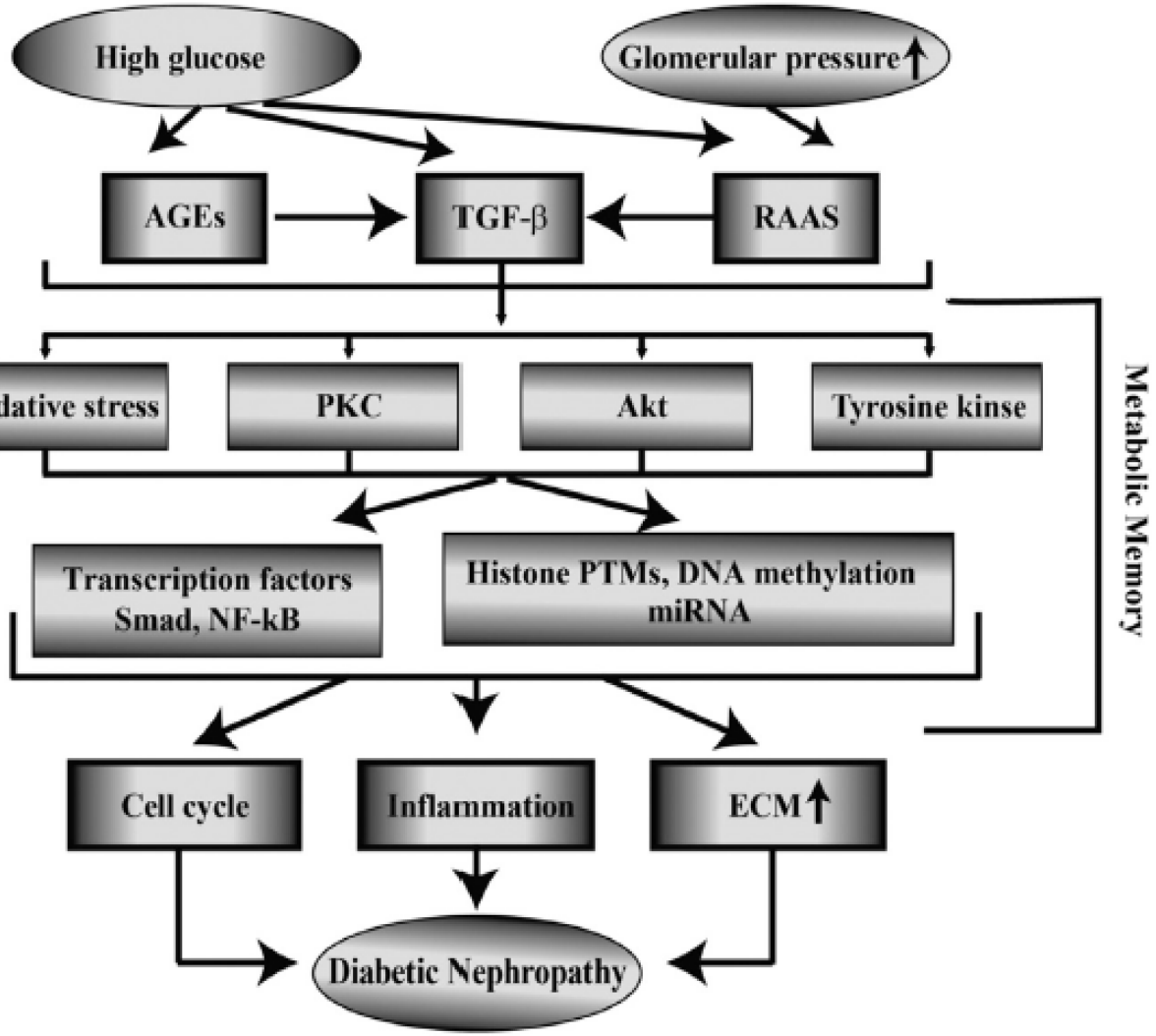
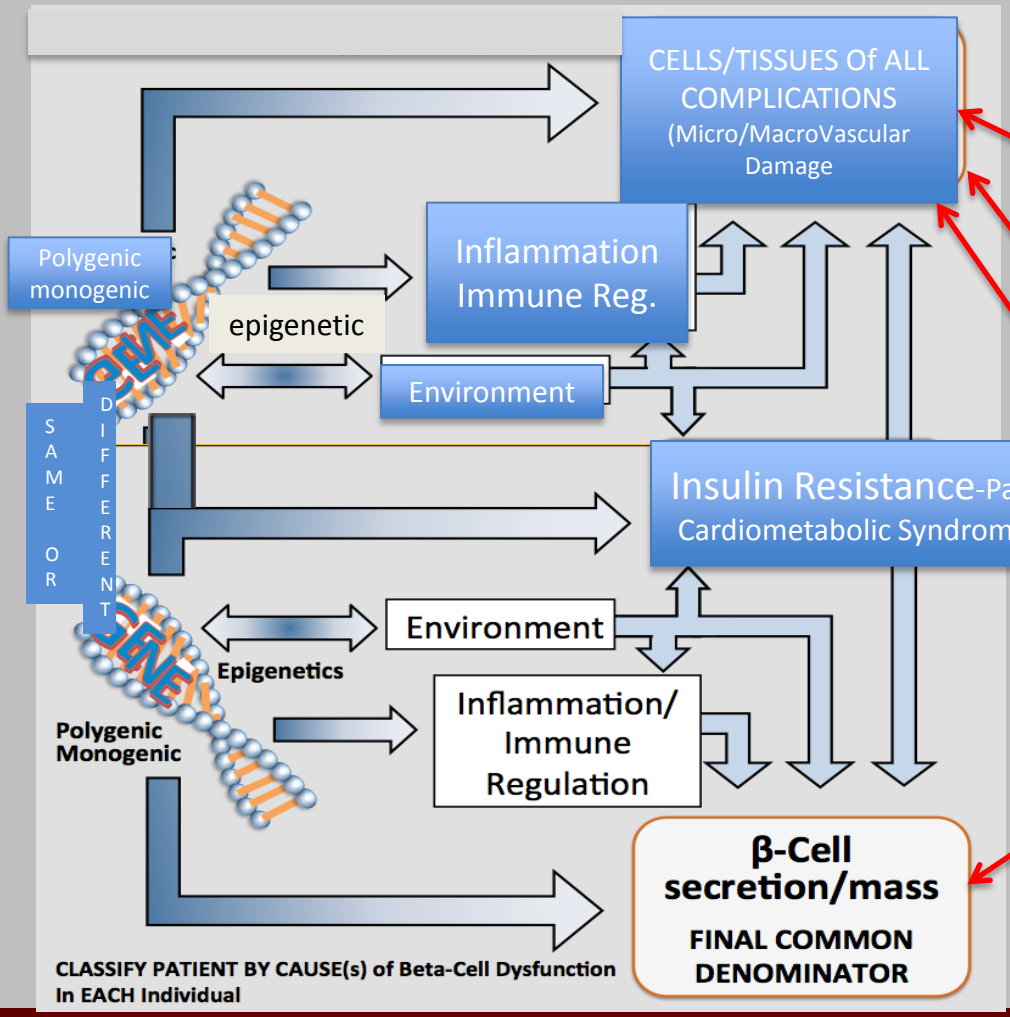


Figure 1. Major pathways involved in the pathophysiology of DN. Complex interactions between metabo hemodynamic factors regulate the pathogenesis of DN. Persistence of HG-mediated damage including epig modifications even after return to normoglycemia can lead to metabolic memory and increased risk for lon complications. PKC, protein kinase C; RAAS, rennin-angiotensin-aldosterone system; AGEs, Advanced gly end products; ECM, Extracellular matrix.

EpigeneticModificationsinthePathogenesisofDiabeticNephropathy
MarpadgaA.Reddy,PhD,JungTakPark,MD,andRamaNatarajan,Seminars inNephrology,
Vol33,No4,July2013,pp341–353

An Integrated Pathophysiologic Approach to The Complications of Diabetes in the Context of the Beta-cell Classification of Diabetes.



Defines Logic for:
Varied Risk of Comp. in Individual Patients with similar HgA1c

Endogenous Fuel Excess (glucose/ lipids)
(Brownlee's Unified Theory of Complications

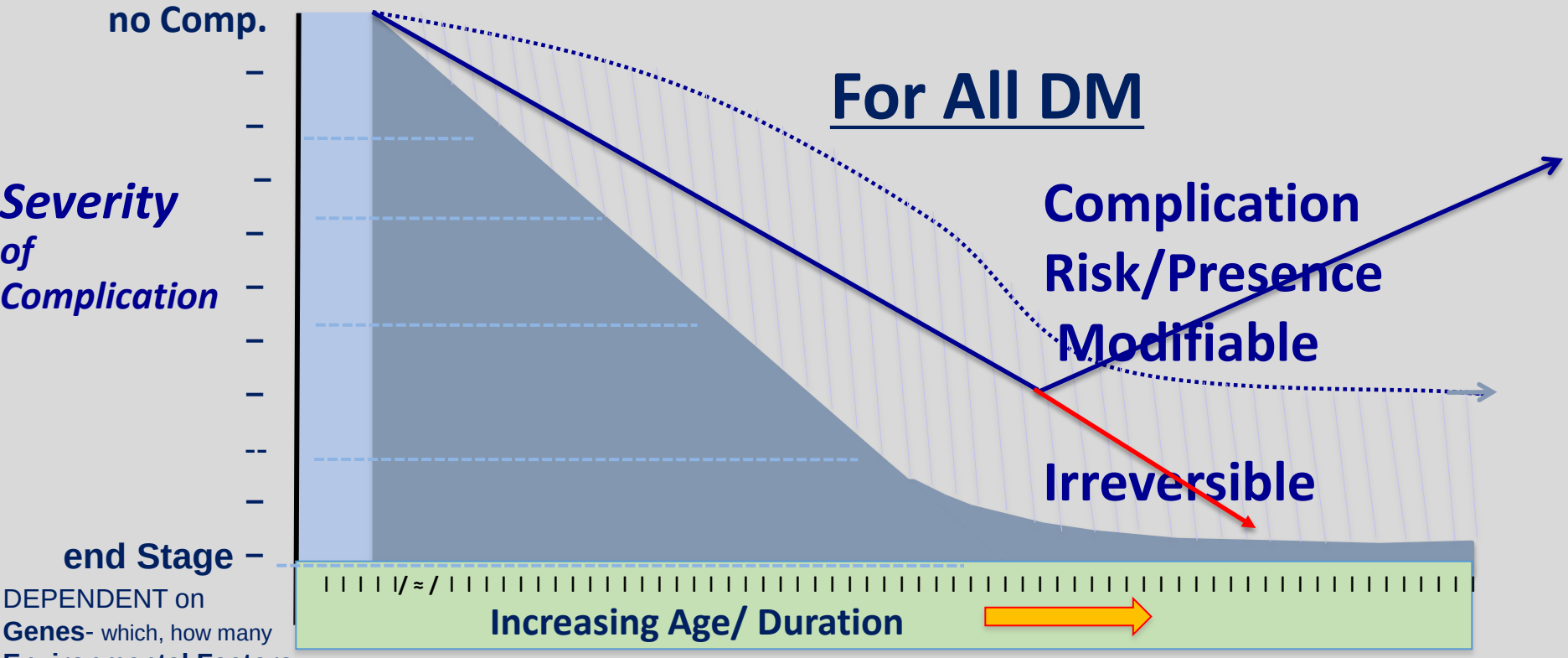
Why some newer meds for DM Decrease Adverse Outcomes without major drops in HgA1c

*Environment=Genetic suceptibility to eg: viruses, endocrine disruptors, food AGEs, Gut Biome; **Insulin Resistance= Centrally Induced, Peripheral, Stress Hormones, Gut Biome

Phenotypic Presentation of Each Complication is defined by:

Slope = 'Natural History' over time,

i.e.= **RATE OF Development of Comp**. Slope is not linear, and may be intermittently relapsing, remitting, stabilized, and improved, until 'point of no return' when presence and damage irreversible



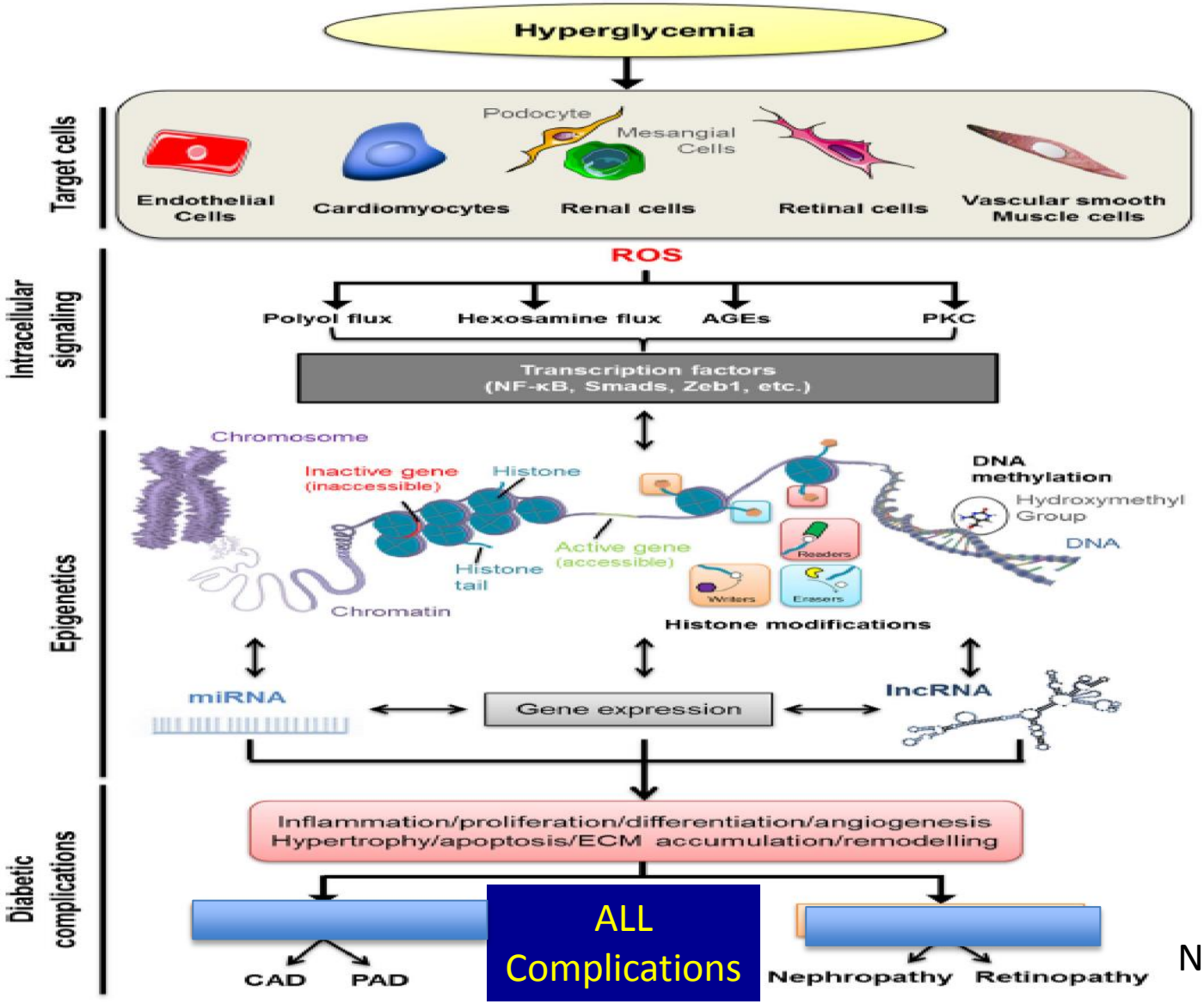
DEPENDENT on
Genes- which, how many
Environmental Factors- which/how many
Inflamatory/ Immune- which factors/ how many
IR/ Cardiometabolic Syndrome

Age/ at presentation = tipping point when the combined pathophysiolocic processes are exposed as phenotypic functional/structural abnormalities

THUS: In Same Context, Need to Change Classification/ Nomenclature of the Complications of Diabetes

- Moreover:
- 'Microvascular/ Macrovascular ' terminology have lost their meaning given new understanding of Causes of Complications-
- it's CELLS/TISSUES affected by the pathophysiologic mechanisms
- Complications of 'T1DM' and T2DM' are the same, not different
- MAJOR CORROLARY: Newer DM medications have been found to reduce complications of Diabetes by the common mechanisms causing DM and DM complications
- Diabetes Medications have become the Cardiologist's Best Friends

Complications are Cellular/Tissue Based: not only 'vascular'



ALL Complications

neurons

Neuropathy

THUS: In Same Context, Need to Change Classification/ Nomenclature of the Complications of Diabetes

- Moreover:
- 'Microvascular/ Macrovascular ' terminology have lost their meaning given new understanding of Causes of Complications-
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- Diabetes Medications have become the Cardiologist's Best Friends

CV Benefits of DM Meds Driven By Other Mechanisms!!

	study	HgA1c drop	eye	nerve	kidney	MACE	CV Mort	MI	CVA	CHF	All Cause Mort	Inferences on Value of Glycemic Control and Other Mechanisms of DM meds in Reducing Complications of Diabetes
Primary	UKPDS	0.9	Reduced	Reduced	Reduced			Reduced			Reduced	Glycemic Hypothesis Proven in Primary
PREV.	DCCT	~2.0	Reduced	Reduced	Reduced	Reduced						Prevention despite 'wrong meds'
SEC	VADT	1.5		–	–	–		–	–	–		Glycemic Benefit could not be proven in face of
OND	ADV.	0.8		↓	↓	↓		–	–	–		Metabolic memory
ARY	ACCORD	1.1		↓	↓	↓	↑	–	–	–		Wrong drugs, wrong process of care
PRE	BROMO-QR	(pts <7.0)				Reduced					↑	Benefits primarily driven
VEN	EMPA-Reg	0.6 early			Reduced	Reduced	Reduced			Reduced		By other mechanisms
TI	IRIS	IR/pre-DM						Reduced	Reduced			Besides glycemia, eg:
ON	LEADER	0.4			Reduced	Reduced	Reduced				Reduced	↓ IR, Arterial Stiffness, Inflam., Symp. Tone

β-Cell (Islet Cell) Classification Model- Implications for Therapy:

Targets for Therapies/ New Guidelines

Medication Choice Based on

1. Glycemic Efficacy

BUT ALSO

2. Number of Targets of Therapy each drug addresses
   (combo therapy efficacy likely depends on number of overlapping mechanisms)

3. Weight loss

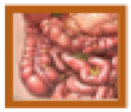
4. Proven Reduction in Risk Factors/ CV outcomes-

Synergies–eg: SGLT-2, (pioglitazone, brompcriptine QR, metformin, GLP-1)

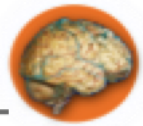
Precision Medicine Approach to DM/ CV Therapy: Algorithms should Assess not only Glycemic benefits of agents/classes but CV/weight benefits

***Implications for New Guidelines

8. Colon/Biome
Probiotics/Prebiotics *
Dpp-4 Inhibitors *
GLP-1 RAs * *WR
Metformin* *

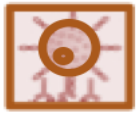


1. *Pancreatic β-cells*
Insulin
FINAL COMMON DENOMINATOR
Dpp-4 Inhibitors *
GLP-1 RAs * *WR
(Ranolazine*)



7. Brain
GLP-1 RAs**WR
Dopamine agonist-QR**
Appetite Suppressants**WR

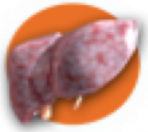
9. Immune Dysregulation/ Inflammation
Dpp-4 Inhibitors *
GLP-1 RAs * *WR
(Anti-Inflammatories
Immune modulators)

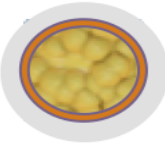


2. ↓Incretin effect
Dpp-4 Inhibitors *
GLP-1 RAs * **WR

3. α-cell defect
↑ Glucagon
Dpp-4 Inhibitors *
GLP-1 RAs * *WR
Pramlintide*

INSULIN RESISTANCE
6. Liver
5. Muscle
4. Adipose





Metformin**
TZDs** *

↓Amylin

10. Stomach/ Small intestine
GLP-1 RAs**WR
Pramlintide*
AGI**

HYPERGLYCEMIA

11. Kidney
SGLT2 inhibitors***WR

* Logic for CV risk/outcome reduction exists
** Supporting Studies Exist
*** Prospective Evidence-Based Data Exists
WR= Weight Reduction

Assessment includes recent prospective trial benefits of SGLT-2 inh, pio, and liraglutide

Sample Triple Therapy: Anticipated Effects

Table III. Proposed optimal triple therapy with the best risk reduction for patients with type 2 diabetes mellitus presenting with established cardiovascular disease.

Variable	Metformin	Pioglitazone	Empagliflozin	Anticipated Effect?
Cardiovascular death	↓	↔	↓↓	↓↓↓
All-cause death	↓	↔	↓↓	↓↓↓
Myocardial infarction	↓	↓	↔	↓↓
Stroke	↓	↓	↔	↓↓
Fluid retention	↔	↑	↓	↔
Heart failure	↔	↑	↓	↔
Weight	↓	↑	↓	↓
Blood pressure	↔	↓	↓	↓↓
HbA_{1c}	↓	↓	↓	↓↓↓
LDL-C	↓	↔	↑	↔
HDL-C	↔	↑	↑	↑↑
Albuminuria	↔	↓	↓	↓↓
Insulin sensitivity	↑	↑↑	↑	↑↑↑

Source: From Schernthaner and Schernthaner.[42]

↓ = lowered; ↑ = elevated; ↔ = unchanged; HbA_{1c} = glycosylated hemoglobin.

An 'Evidence-Based Practice, Patient Centeric' Approach

As a Clinician

Think Inside a Larger Box ☺

Evidence-Based AND Patient Centric:

EVIDENCE-BASED PRACTICE

Mechanism of Disease +

Mechanism of Drug +

Patient Factors =

Right Drug

Clinical Expertise, Expert Opinions

Patient-Based experience

Evidence-Based Medicine

Randomized, prospective trials –(if exists and if patient fits)

Duggal, Evidence-Based Medicine in Practice,, Int' l j. Clinical Practice,65:639-644,2011,Allan D. Sniderman, MD; Kevin J. LaChapelle, MD; Nikodem A. Rachon, MA; and Curt D. Furberg, MD, PhDMayo Clin Proc The Necessity for Clinical Reasoning in the Era of Evidence-Based Medicine October 2013;88(10):1108-1114
Trisha Greenhalgh et al, Evidence based medicine: a movement in crisis? *BMJ* 2014; 348

New β-Cell Centric Construct: *Implications*
Diagnosis Markers

By Virtue of Family History 'DM", Physiogomy, hyperglycemia, in prediabetic and diabetic range *

- Genes
  - Family History
  - Genotype- HLA, *TCF7L2*, etc
- β-Cell
  - FBS, 2hr ppg, HgA1c, ? C-peptide, ?other- β-Cell mass measures
- Inflammation
  - Antibodies, Inflammatory Markers, T-Cell function, ?other
- Insulin Resistance
  - BMI, Adiponectin, Adipocytokines, ? Other

* Individualized and reliant on cost, insurance coverage, formulary, government

Patient-Centric Diagnosis & Process of Care/Therapy

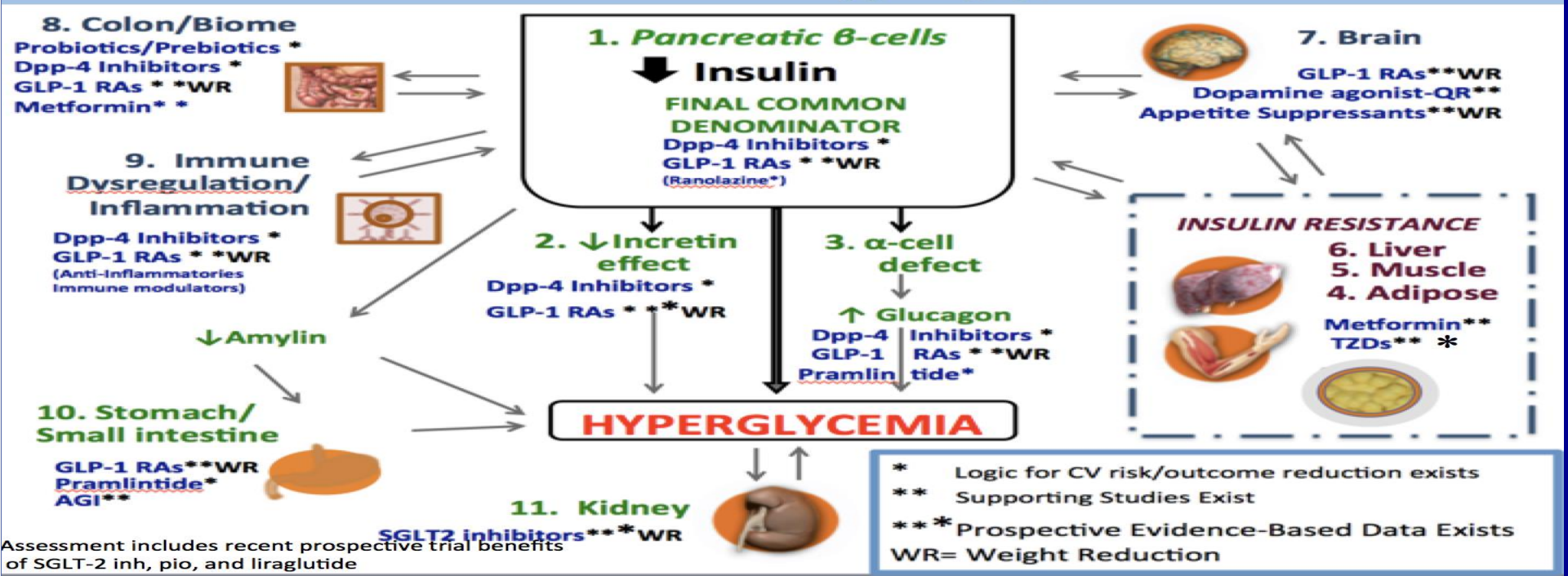
At Risk Individuals

Traditional Labs/Testing
FBS, RBS, HgA1c

Specific Therapy addressing Genotype
Genes

Etiologic Diagnostic Markers:
β-Cell, Insulin resistance, Inflammation, Environment, Genes

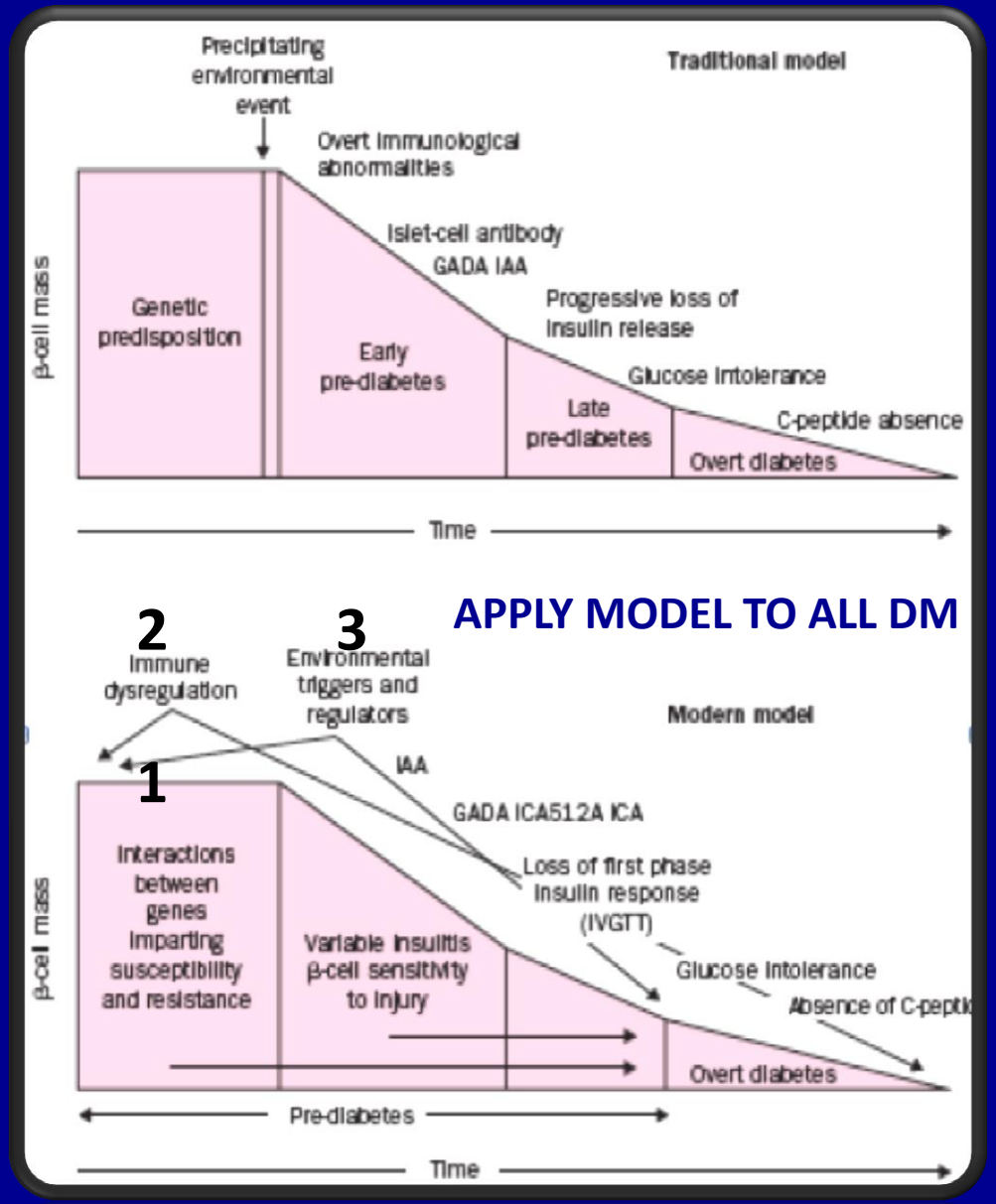
Least Number of Meds that Rx most Number of Mechanisms of Hyperglycemia



Assessment includes recent prospective trial benefits of SGLT-2 inh, pio, and liraglutide

Going Forward: New Focus of Care:
Primary Prevention: ? For All DM in New Classification

- Genetic/antibody screening 1 effort to identify eligible subjects
- Potential Immune Modulators 2
- Environmental Modulation 3
  - Especially as we learn more- vaccination, endocrine disruptors, diet, exercise
- Intervention needs to be extremely safe
- Defining risk factors will facilitate primary prevention studies



Atkinson, Eisenbarth,THE LANCET • Vol 358 • July 21, 2001 225

Choice of Therapy

- Based on
  - Treating Causes of **β-Cell d**ysfunction
  - Treating Abnormalities resulting from **β-Cell dysfunction**
- **No Logic for Agents that Decrease β-Cell dysfunction**

THUS: SELECT AGENTS THAT CAN PRESERVE

β-Cell function/mass

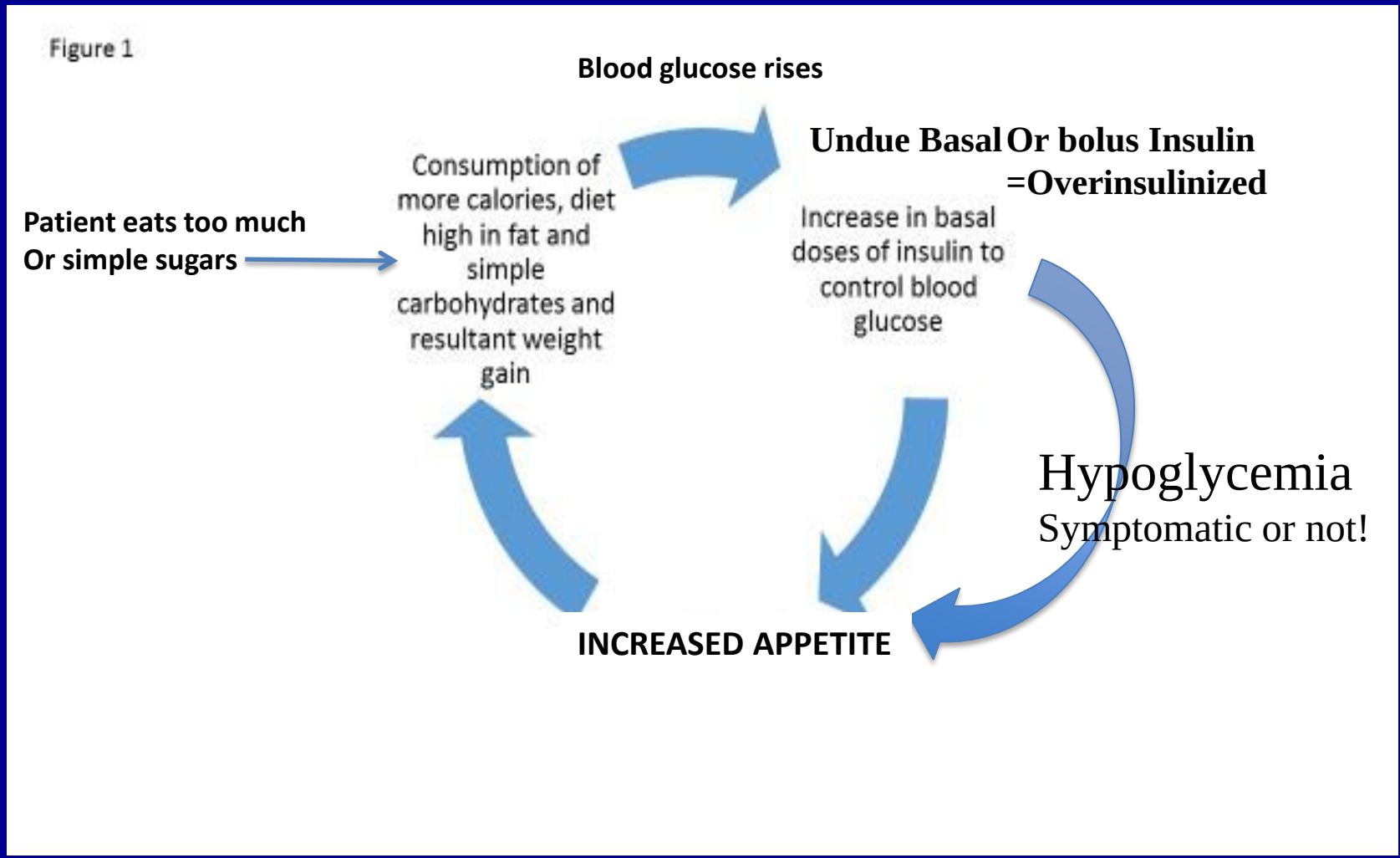
Allows us to Correct a myth

MYTH: "Most Patients with 'T2DM' will eventually progress to insulin because of inexorable **β-Cell loss"**

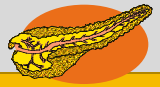
- But data obtained on SU=apoptosis; Hyperinsulinism with weight gain
- **T**hink of bariatric patients –no insulin after 25 years DM/ 20 years insulin
- Most patients dying with DM have > 20% **β-Cell** mass- Butler
- Need to remove >80% pancreas in sub-total pancreatectomies to leave patient with DM post-op

Avoid Early Insulin Therapy (except in Ketosis-prone)

Vicious Circle(s) of Hyperinsulinemia-
Result in Weight Gain and Hypoglycemia



NOTE:
There is NO perfect Exogenous Insulin:
All result in HyperInsulinemia and Potential Hypoglycemia



Endogenous Insulin → **Exquisitely controlled levels of insulin released into the portal vein** → **Fine-tuned, physiologically appropriate insulinemia**

Exogenous Insulin → **'Obligatory' excess peripheral insulin** to get modicum of reduced hepatic glucose production

Hyperinsulin-emia

- **Hypoglycemia**
- **Atherosclerosis**
- **Hypertension**
- **Cancer**
- **Type II Diabetes**
- **Insulin Resistance**
- **Obesity**
- **Weight gain**
- **Dyslipidemia**
- **Chronic Inflammation**

β-cell Dysfunction

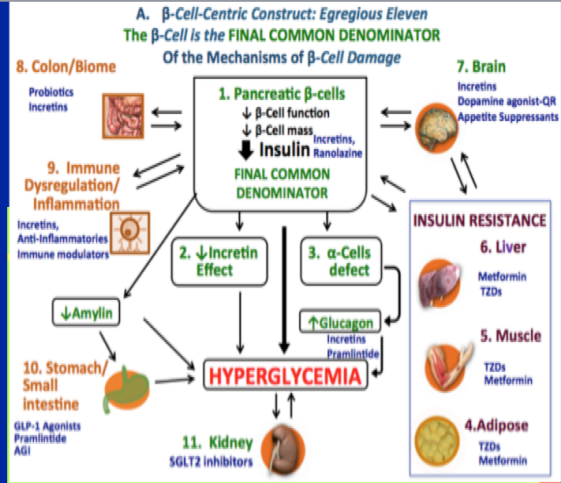
Potential β-cell Exhaustion

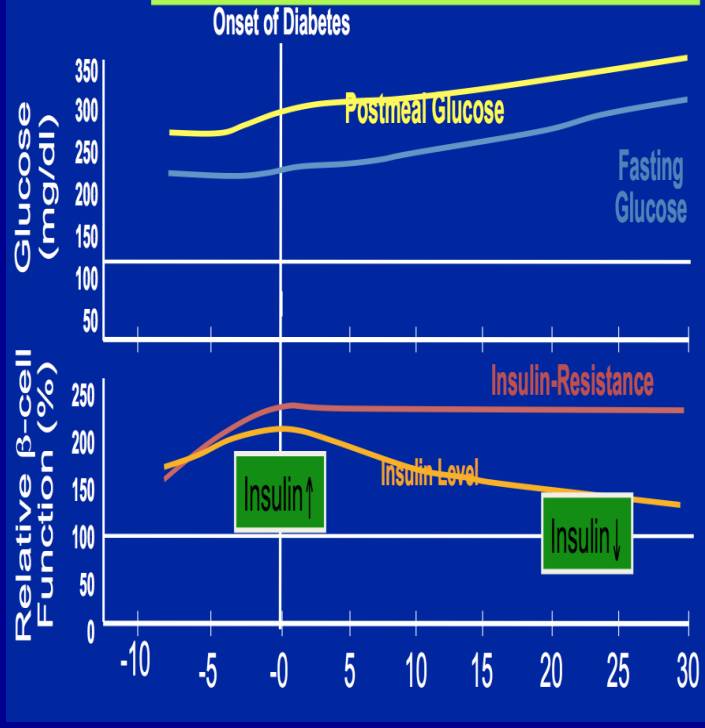
Therapeutic Principles Across Continuum of Care (
Right Drug for Right Patient and vice versa

DETERMINE INSULIN DEPENDENCY-(DKA, c-peptide,?other

DETERMINE Patient Specific Mechanisms of Hyperglycemia

- Treat ? For prevention/ pre-diabetes
- Treat as many of the Egregious 11 Targets as needed,
  least # of agents, lowest sugars/HgA1c as possible
  without undue weight gain or hypoglycemia
- Early Combination Therapy- Patient Centric-
  even 6.5-7.5 HgA1c
  Efficacy, - CV event reduction, Weight Loss
  (Not first-second-third line; Not competition between classes)
- Can Modify therapy after 1m-not 3m-use Fructosamie
- Stabilize, preserve β-cells, the CORE DEFECT
- (NO SU/GLINIDES)-
- Ideally agents will have potential to
  synergistically decrease in CV risk factors / outcomes





Therapeutic Principles Across Continuum of Right Drug for Right Patient and vice versa

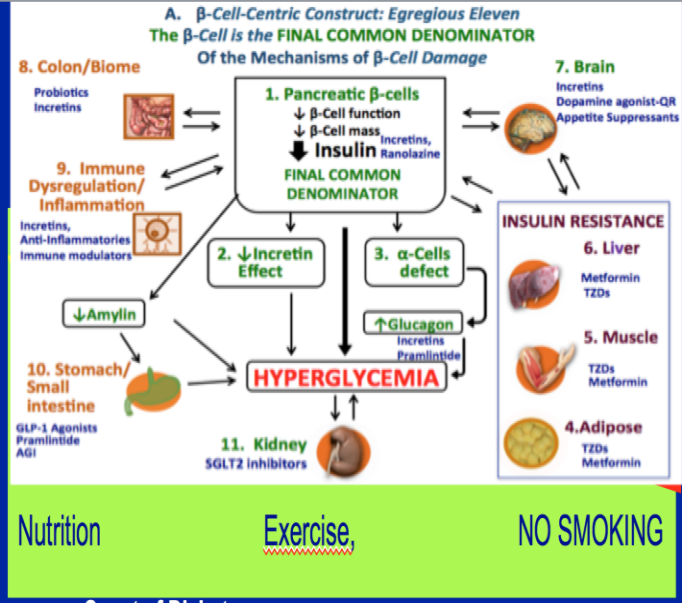
1. Delay Need for Insulin

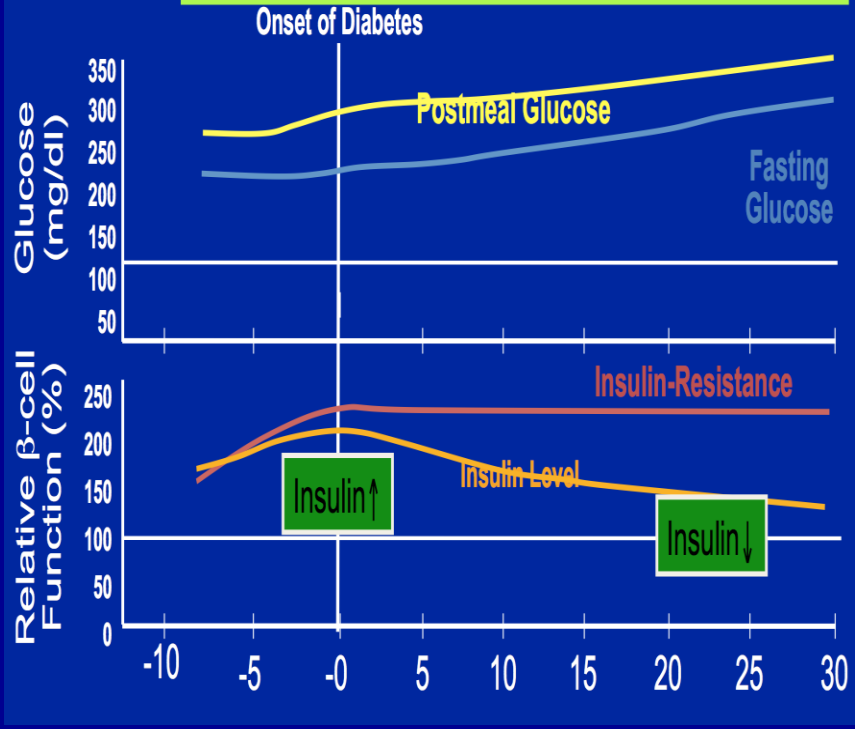
2. No need for Early Insulin

3. If need Insulin, Continue Non-Insulin RX (Avoids need for Meal-Time Insulin-

(Decrease Risk Hypoglycemia 85%- Garber)

4. Get Patients off insulin who had been given early Insulin





Hedge your Bets: Incretins for all patients

DPP4 inhibitors, GLP-1 RAs, [other agents that increase GLP-1 eg: metformin, colsevalam, (TGR-5)]

- T1DM: minimize brittle, dawn, unpredictablity, variability, ? CV benefits, Treat those 'Type 2' Genes', ANTI-INFLAMMATORY
- LADA = SPIDDM/ Autoimmune T2DM. Same as above - Slow , stabilize disease process, ANTI-INFLAMMATORY
- T2DM: Same as above, treats 7 MOA's of DeFronzo's Octet, decreases oxidative stress, β-cell inflammation decreases lipo- and gluco-toxicity, ?preserve mass, decreases appetite, treats IR via wt. loss
- MODY 3- recent report

FOR ALL DM – potential CV benefit (ANTI-INFLAMMATORY)

Reference list for last slide

LADA

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- Kielgast U., et al Treatment of Type 1 Diabetic Patients with GLP-1 and GLP-1 Agonists, Current Diabetes Reviews,2009, 5:266-275

TYPE 2

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- Drucker DJ, Rosen CF. Glucagon-like peptide-1 (GLP-1) receptor agonists, obesity and psoriasis: diabetes meets dermatology. Diabetologia 2011;54:2741–2744
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- Shimoda M, Kanda Y, Hamamoto S, Tawaramoto K, Hashiramoto M, Matsuki M, Kaku K.The human glucagon-like peptide-1 analogue liraglutide preserves pancreatic beta cells via regulation of cell kinetics and suppression of oxidative and endoplasmic reticulum stress in a mouse model of diabetes. Diabetologia. 2011 May;54(5):1098-108. doi: 10.1007/s00125-011-2069-9. Epub 2011 Feb 22.
- Kim JY, Lim DM, Moon CI, Jo KJ, Lee SK, Baik HW, Lee KH, Lee KW, Park KY, Kim BJ.Exendin-4 protects oxidative stress-induced β-cell apoptosis through reduced JNK and GSK3β activity. J Korean Med Sci. 2010 Nov;25(11):1626-32. doi: 10.3346/jkms.2010.25.11.1626. Epub 2010 Oct 26.
- Liu Z, Stanojevic V, Brindamour LJ, Habener GLP1-derived nonapeptide GLP1(28-36)amide protects pancreatic β-cells from glucolipotoxicity. J Endocrinol. 2012 May;213(2):143-54. doi: 10.1530/JOE-11-0328. Epub 2012 Mar 13.
- Glucagon-like peptide 1 analogue therapy directly modulates innate immune-mediated inflammation in individuals with type 2 diabetes mellitus Diabetologia - Clinical and Experimental Diabetes and Metabolism, 03/04/2014

Aggressive medical therapy in diabetes- SUMMARY

SGLT-2 Inh.
Liraglutide
Bromocriptine QR
Pioglitazone
Metformin
Ranolazine
(Incretins)

→ **Hyperglycemia/ Insulin resistance**

ACE inhibitors
ARBs
β-blockers
CCBs
Diuretics

→ **Hypertension**

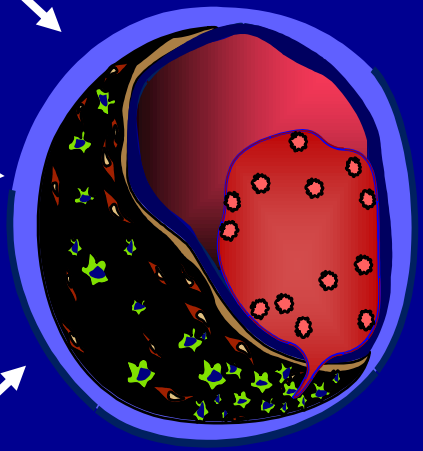
Statins
Fibric acid derivatives
Colsevalam
PCSK-9 Inh

→ **Dyslipidemia**

ASA
Clopidogrel
Ticlopidine

→ **Platelet activation and aggregation**

Atherosclerosis,
CV Outcomes,
CV Risk Factors,
Mortality



DM MEDS MAY BE A
CARDIOLOGIST'S BEST FRIEND

dapted from Beckman JA et al. *JAMA*. 2002;287:2570-81.

Treating the ABCs Reduces Diabetic Complications

Strategy	Complication	Reduction of Complication
Blood glucose control	Heart attack	↓ **37%**[1]
Blood pressure control	Cardiovascular disease	↓ **51%**[2]
	Heart failure	↓ **56%**[3]
	Stroke	↓ **44%**[3]
	Diabetes-related deaths	↓ **32%**[3]
Lipid control	Coronary heart disease mortality	↓**35%**[4]
	Major coronary heart disease event	↓**55%**[5]
	Any atherosclerotic event	↓**37%**[5]
	Cerebrovascular disease event	↓**53%**[4]

[1] UKPDS Study Group (UKPDS 33). *Lancet*. 1998;352:837-853.
[2] Hansson L, et al. *Lancet*. 1998;351:1755-1762.
[3] UKPDS Study Group (UKPDS 38). *BMJ*. 1998;317:703-713.
[4] Grover SA, et al. *Circulation*. 2000;102:722-727.
[5] Pyörälä K, et al. *Diabetes Care*. 1997;20:614-620.

Conclusion

- Current classifications of DM are inadequate:
- new classification schema -the β-cell as THE CORE DEFECT in ALL DM,
- The various mediators of β-cell dysfunction offer key opportunities for Prevention, Therapy, Research and Education
- Same Mechanisms of β-cell dysfunction are responsible for DM complications (explains why some DM meds can decrease CV outcomes)
- Patient care should shift from current classifications that limit therapeutic choices to:
- one that views a given patient's disease and treatment course based on their individual cause(s) of metabolic dysregulation, e.g. genes, inflammation, insulin resistance- (including gut biome, central (brain) mechanisms), environmental factors, etc.

Conclusion-2

- Defining markers, and Processes of Care = patient-centric, Precision Medicine approaches

- In T1D and LADA, in particular, incretins, insulin sensitivity agents, SGLT-2 inhibitors and others are either underutilized in some cases, and under-evaluated in others
- Convene Organizations eg:ADA/EASD/WHO/IDF/AACE / JDF to Revise Classification of DM

- More research always needed, but,
- in an evidence-based PRACTICE approach to care, we can START NOW

Based on 'New' Classification: Recommended Process For Prevention, Diagnosis and Therapy

- Convene ADA/EASD/WHO/AACE Committee: Revise Classification of DM
- Put processes into place. Increase current repositories. JAEB, JDRI to include LADA patients, (but all kinds of hyperglycemic patient types), Large Health Systems (K-P)
- Research into these ideas/approaches
- EDUCATE MDs re :issues

Use Evidence-Based Practice Approaches to DX
Where evidence is incomplete but logic exists,
apply appropriate treatment to improve patient care.

Allan D. Sniderman et al The Necessity for Clinical Reasoning in the Era of Evidence-Based Medicine,Mayo Clin Proc. 2013;88(10):1108-1114