Precision Medicine: Where are we with Diabetes?

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Disclosure

- Employee of Corcept therapeutics.

*Ji Hyun Chun (CJ) **does not intend** to discuss the use of any off-label use/unapproved use of drugs or devices

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Objective

- Recognize the limitation of the current diabetes classification
- Describe the newly suggested diabetes classification
- Apply specific therapy for its underlying pathology leading to hyperglycemia and complications

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Stella

- 38yo female referred for new onset diabetes (A1c 10.6%, FPG 290)
- Found during pre-op evaluation for breast nodule that seemed highly suspicious
- Reports polyuria, polydipsia and about 5lbs weight loss in the past 1month
- Reports she's been stress eating (especially sweets) lately due to stress of potential breast cancer

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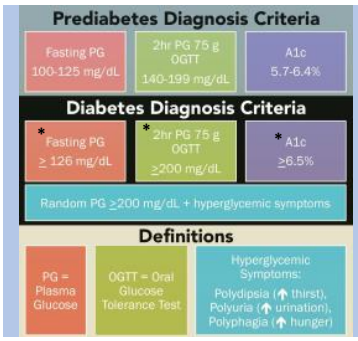

*two (+)tests in same sample or one (+)test in two separate samples

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Classification of DM

- Type 1 (~5%)
- Type 2 (~90%)

→ Which type does Stella have?

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Stella

- History of prediabetes (2-3yrs, A1c 5.7 and 5.9% with IFG), HTN (on lisinopril) and overweight/obesity (BMI 28-30)
- BP 132/78 (on lisinopril), BMI 27
- TC 160, HDL 49, TG 100, LDL 91
- Med list: metformin 1000mg BID (started last week by PCP), lisinopril 10mg/d

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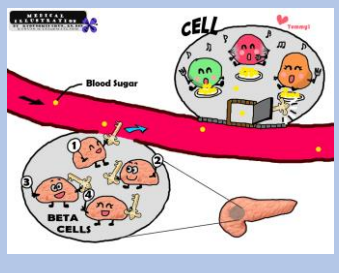
Normal insulin-glucose action



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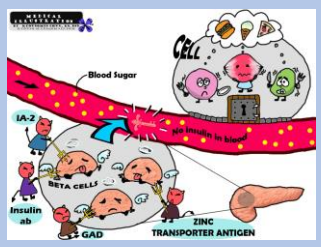
Type 1: due to immune destruction of b-cells (→ insulin deficiency)



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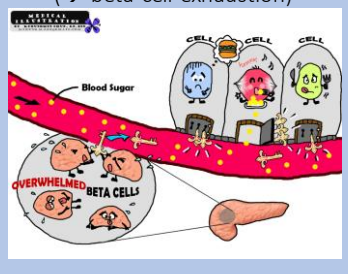
Type 2: insulin resistance (→ beta cell exhaustion)



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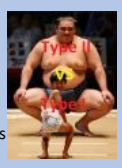
"Classic"

- **DM 1**
  - Early onset (before mid teens)
  - Lean
  - Insulin sensitive
  - Lack of response to noninsulin therapy
  - Symptomatic at diagnosis (DKA, 3Ps)



- **DM 2**
  - Late onset (>50yo)
  - Obese
  - insulin resistance
  - Decent response to noninsulin therapy
  - Asymptomatic at diagnosis

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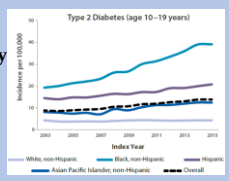
DM 2: Age barrier collapsed

Rise in obesity, including peds obesity



- 1 in 3 new DM in youth (<18yo) is DM2
- Twice the incidence of DM 2 vs DM 1 in high risk youth

doi.org/10.2337/dci22-0046

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Latent Autoimmune Diabetes in Adults (LADA)

- AKA: type 1.5, non-insulin requiring autoimmune diabetes, slowly progressing type 1 diabetes
- "later" onset with (+)antibodies
- 40% of DM 1 diagnosed before 20yo

SEARCH for Diabetes in Youth Study Group et al., 2007

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Latent Autoimmune Diabetes in Adults (LADA)

- UKPDS: frequent (+)autoimmunity in patients who were diagnosed as DM 2
  (34% in 25-34yo and 9% in 55-65yo)
- Faster progression to insulin dependence
- Personal and/or family hx of autoimmune d/o

Desai M, Clark A. Autoimmune diabetes in adults: lessons from the UKPDS.Diabet Med. 2008 Aug;25 Suppl 2:30-4

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When to suspect antibody(+) DM (DM 1 / LADA)

- Younger (< 50yo)
- Leaner (BMI < 25)
- Personal and/or Family hx of autoimmune disorder
- More acute presentation: catabolic state
- Unresponsive to noninsulin therapy
- Rapid progression of insulinopenia requiring insulin therapy.

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Islet cell directed antibodies

	Sensitivity	Specificity
Glutamic acid decarboxylase (GAD65)	70-90%	99%
Insulin (IAA)*	40-70%	99%
Tyrosine phosphatase IA2 (ICA512)**	50-70%	99%
Zinc transporter 8 (ZnT8)	50-70%	99%

*may develop with exogenous insulin treatment even in the absence of autoimmune d/o

** Aka insulinoma-associated antigen (IA-2A)

Table from Gardner D et al. Greenspan's Basic & Clinical Endocrinology, Chapter17. P588

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C-peptide

normal reference: 1.1-4.4ng/mL (measure when fasting glucose < 225)
*supplemental test. Estimates b-cell reserve

Clinical role	Fasting	Stimulated
Absolute insulin deficiency	< 0.24	< 0.6
Likely DM 1 / inability to achieve goal without insulin	< 0.75	< 1.8
Suggests DM 2 or MODY in pts with presumed DM 1 > 3–5y post-dx	> 0.24	> 0.6
Consider MODY/DM 2 in young onset DM at Dx	> 1.2	> 3

Modified from A.G.Jones et al. Diabet. Med. 30, 803-817 (2013)

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Screening for DM 1?

Controversial

high risk (relatives of DM 1) only vs children from gen. population?

Pros:
- Rise in incidence and prevalence of DM 1
- High predictability
- Early recognition → prevent life-threatening DKA

Cons:
- Sporadic > Familial → low cost-effective
- No effective intervention → merely raise anxiety/concerns

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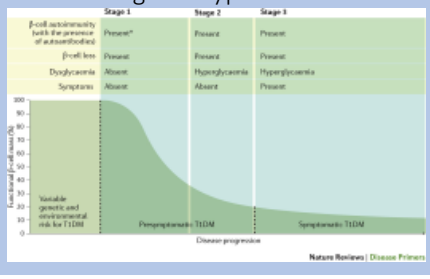
Stages of type 1 DM



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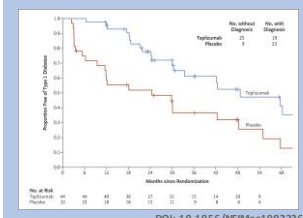
Teplizumab (Tzield)



- Anti-CD3 monoclonal antibody therapy
- Delay progression from stage 2 → stage 3 by 2 years

DOI: 10.1056/NEJMoa1902226

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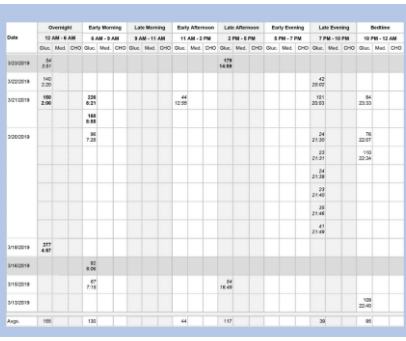

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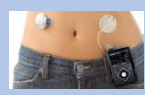
Diabetes Technology Advancements

Insulin delivery device

Glucose monitoring device



Merge



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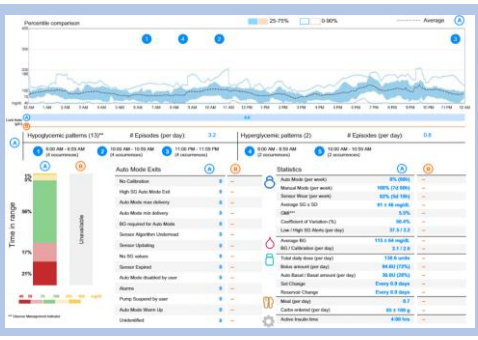

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Stella

- Lifestyle intervention recommendations
- Started on basal insulin 10units and instructed to increase by 3units q2-3days if fasting glucose >150.
- Reports nausea and diarrhea. Changed metformin IR to metformin ER tabs

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Stella

- GAD/insulin ab/ZnT8 (-)
- Glucose 170, C-peptide 2.1

Clinical role	Fasting	Stimulated
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Consider MODY/DM 2 in young onset DM at Dx	> 1.2	> 3

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Classification of DM

- Type 1 (~5%)
  - DM 1a: abs (+)
  - DM 1b: abs (-). Idiopathic.
- Type 2 (~90%)
- Secondary diabetes (~5%)
  → Specific types of diabetes due to other causes

Bullard et al. Prevalence of Diagnosed Diabetes in Adults by Diabetes Type - United States, 2016. MMWR 2018;67:359–361.

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Secondary Diabetes

- Monogenic diabetes
- Disease of exocrine pancreas
- Endocrinopathies
- Drug or chemical-induced
- Infections
- Uncommon forms of immune-mediated diabetes
- Other genetic syndromes associated with diabetes

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Monogenic Diabetes

- Diabetes resulting from a single gene mutation (vs polygenic: DM 1 and 2)
  - Genetic defects of beta cell function
    - Neonatal DM
    - Maturity Onset DM in Youth (MODY)
  - Genetic defects in insulin resistance
    - Primary insulin signaling defects (generalized, partial)
    - Secondary to adipose tissue abnormalities (severe obesity, lipodystrophy)

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Monogenic Diabetes

- 1-2% of DM
- > 80% of MODY not diagnosed
- 7-15% of DM misclassified
  - ~1% of presumed cases of DM 1
  - 4~5% of DM 2 dx < 45yo
- Risk of error high in young adults (20-40yo)
- Often takes 10yrs before diagnosis is made

Carl-Hugo Lachance. Can J Diabetes 40 (2016) 368-375

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MODY

- Maturity Onset of Diabetes in Youth
- Primary defect in b-cell function (insulin secretion or glucose sensing)
- Early onset (usually <25yo)
- Autosomal dominant (off spring 50% chance)

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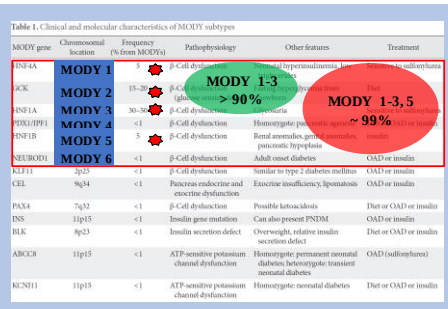

Sung-Hoon Kim. Diabetes Metab J 2015;39:468-477

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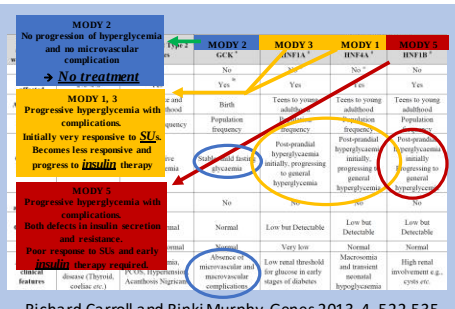

Richard Carroll and Rinki Murphy. Genes 2013, 4, 522-535

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When to suspect?

- DM diagnosed < 6mo of life
- DM without typical features of type 1 or 2 (negative abs, nonobese, other metabolic features, especially with strong FHx)
- Stable/mild fasting hyperglycemia (100-150mg/dL), stable A1c (5.6-7.6%), especially if nonobese

Standards of Medical Care in Diabetes. Diabetes Care 2024

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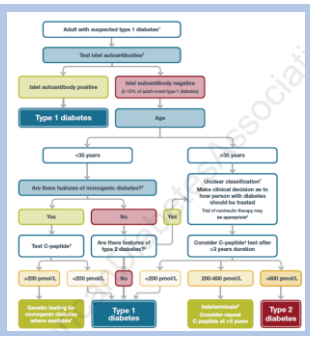

Standards of Medical Care in Diabetes. Diabetes Care 2024

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Importance of correct Dx?

- Optimal treatment strategy
  - Insulin to oral (MODY 1 & 3)
  - No Tx (MODY 2)
  - → improve QoL, glycemic control
- Family member screening
  - → Proper genetic counseling
- Genetic panel is becoming more available/affordable

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Secondary diabetes (other)

- Endocrinopathy
  - Hypercortisolism (Cushing's syndrome)
  - Acromegaly/ Gigantism
  - Hyperaldosteronism
  - Glucagonoma
  - Pheochromocytoma
  - Hyperthyroidism
  - Somatostatinoma
  - - Other
- Exocrine d/o of Pancreas
  - – Pancreatitis
  - – Cystic Fibrosis
  - – Hemochromatosis
  - – Pancreatic cancer

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Hypercortisolism (Cushing's syndrome)

- Prolonged exposure to excessive glucocorticoids
- Cortisol: insulin antagonistic → dysglycemia
- Etiology
  - Exogenous/iatrogenic: most common
  - Endogenous (pituitary, adrenal, ectopic)
- Screening tests (for endogenous)
  - 1mg overnight dexamethasone suppression test
  - Midnight salivary cortisol
  - 24hr urine free cortisol

* **cannot r/o with random cortisol**

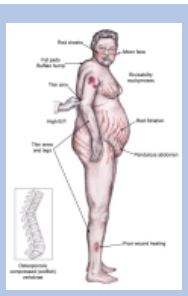

Image accessed 2/10/18 from emedicine.medscape.com/article/2233083-overview

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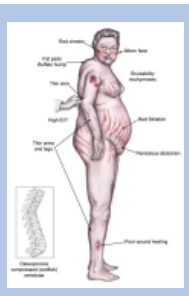
Symptoms	Signs	Overlapping conditions
Features that best discriminate Cushing's syndrome; most do not have a high sensitivity		
	Easy bruising	
	Facial plethora	
	Proximal myopathy (or proximal muscle weakness)	
	Striae (especially if reddish purple and >1 cm wide)	
	In children, weight gain with decreasing growth velocity	
Cushing's syndrome features in the general population that are common and/or less discriminatory		
Depression	Dorsocervical fat pad ("buffalo hump")	Hypertension[2]
Fatigue	Facial fullness	Incidental adrenal mass
Weight gain	Obesity	Vertebral osteoporosis[3]
Back pain	Supraclavicular fullness	Polycystic ovary syndrome
Changes in appetite	Thin skin[1]	Type 2 diabetes[4]
Decreased concentration	Peripheral edema	Hypokalemia
Decreased libido	Acne	Kidney stones
Impaired memory (especially short term)	Hirsutism or female balding	Unusual infections
Insomnia	Poor skin healing	
Irritability		
Menstrual abnormalities		
In children, slow growth	In children, abnormal genital virilization	
	In children, short stature	
	In children, pseudoprecocious puberty or delayed puberty	



Nieman et al. JCEM May 2008, 93(5): 1526-1540

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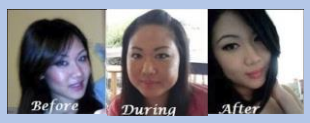
recognition



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Hypercortisolism (Cushing's syndrome)

- 3.4-10% of pts with DM have (hidden) hypercortisolism as underlying cause
- When to suspect/test
  - Premature onset
  - Refractory to treatment
  - Other comorbidities (i.e., HTN, osteoporosis)

Giovanelli et al. J Endocrinol Invest 44, 1581-1596 (2021)

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Hypercortisolism (Cushing's syndrome)

- Screening test
  - 1mg overnight dexamethasone suppression test (ONDST)
    - ***Highest sensitivity*** (r/o if <1.8)
  - Late night salivary cortisol (LNSc)
  - 24hr urine free cortisol (UFC)

***cannot r/o with random cortisol**

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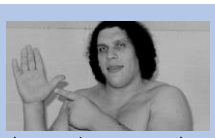
Acromegaly / Gigantism



- Hypersecretion of GH
- GH: insulin antagonist → dysglycemia (Dawn Phenomenon)
- Estimated prevalence of 40/125mil and incidence of 3-4/1mil
- Underdiagnosed?
  - 1,034/1mil when routinely screened IGF-1 in primary care.

Katznelson L, Atkinson J, Cook D, et al. AACE Acromegaly Guidelines, Endocr Pract. 2011;17(Suppl 4)

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Acromegaly / Gigantism

- Most common (99%): pituitary adenoma
- Screening test: IGF-1

*** Cannot r/o with random GH (growth hormone)**

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When to suspect

- 2 or more of the following comorbidities:
  - New onset DM
  - Diffuse arthralgias
  - New onset of refractory hypertension
  - Cardiac disease: biventricular hypertrophy and diastolic/systolic dysfunction
  - Fatigue
  - Headache
  - Carpal tunnel syndrome
  - Sleep apnea syndrome
  - Diaphoresis
  - Loss of vision
  - Colon polyps
  - Progressive jaw malocclusion

Katznelson L, Atkinson J, Cook D, et al. AACE Acromegaly Guidelines, Endocr Pract. 2011;17(Suppl 4)

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recognition

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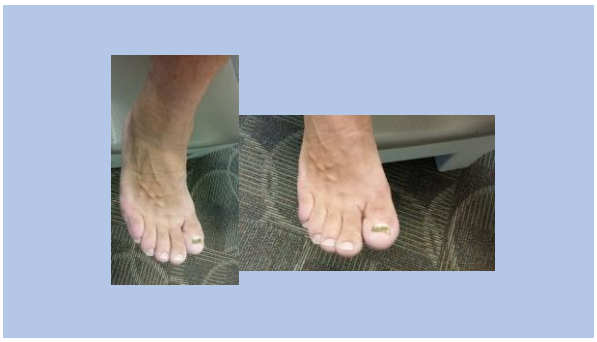

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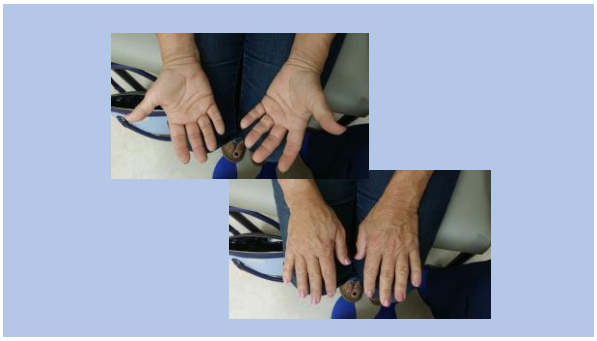

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Secondary diabetes (other)

- Endocrinopathy
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  - Hyperthyroidism
  - Somatostatinoma
  - - Other
- **Exocrine d/o of Pancreas**
  - Pancreatitis
  - Cystic Fibrosis
  - Hemochromatosis
  - Pancreatic cancer

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Hemochromatosis

- Iron overload in parenchymal organs leading to organ toxicity
  - Hereditary
  - Secondary
  - Miscellaneous
- Incidence of hereditary
  - 1 per 200-500, most are of northern European origin

Powell et al. Semin Gastrointest Dis. 2002; 13(2):80-8

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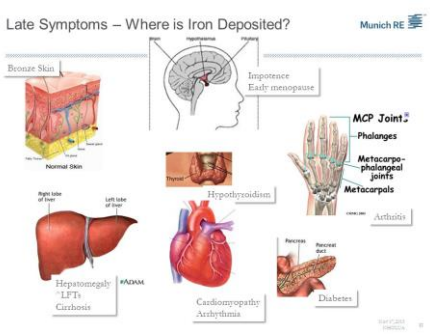

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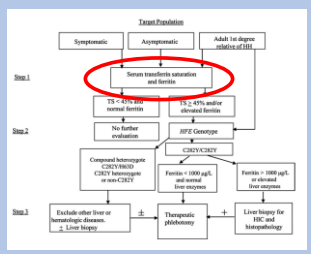
Initial test



Bacon et al. Hepatology, Vol. 54, No 1, 2011

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Clinical conundrum..

- Patient with DM 2
  - Elevated AST/ALT
  - Enlarged heart
  - Hypogonadism
  - Hyperpigmented skin
  - Fatigue
  - Joint pain

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Stella

- Returns following week after insulin initiation.
- Dramatic improvement in glucose (fasting 90-110s, predinner/bedtime 100-130s)
- Doing well with low carb diet. Lost another 7lbs since last visit (week)
- Self d/c basal insulin after 4days due to one time fasting glucose of 73.
- Stays on metformin ER 500mg 2tabs BID
- Still reports nausea and diarrhea.

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Stella

- Advised to lower metformin to 500mg 1tab BID
- Return in 2-3weeks.
- Self d/c metformin after 1 week due to good glycemic control and persistent diarrhea.
- Maintains good glycemic control
- Lost another 10lbs
- Continues to have nausea and diarrhea….

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CT of abdomen

PANCREAS: In the pancreatic head there is a 3.4 x 2.3 x 2.4 cm hypoenhancing an ill-defined mass (series 3 image 35, series 604 image 54). There is tenting of the posterior wall of the SMV suspicious for involvement (series 4 image 55). There also may be a small focus of invasion into a posterior branch in the proximal SMV (image 59 series 4). The celiac artery and branches and SMA do not appear involved. Noted is atrophy of the body and tail the pancreas with mild maintained duct enlargement measuring up to 5 mm.

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Pancreatic cancer

- When to suspect
  - Rapid onset or worsening of diabetes without known cause
  - Abnormal weight loss
  - Abnormal liver/biliary studies
  - Jaundice

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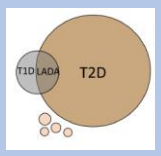
New classification of DM?



SAID: Severe autoimmune DM (6-8%)
SIDD: severe insulin-deficient DM (18-20%)
SIRD: severe insuin-resistant DM (15%)
MOD: mild obesity-related DM (20-25%)
MARD: mild age-related DM (39%)

Towards Improved Precision and a New Classification of DM. doi.org/10.1530/JOE-20-0596

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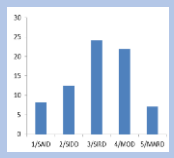
Why?



- Prevalence of MASLD
- Time to CKD
- Time to coronary event

Novel subgroups of adult-onset DM and their association with outcomes: a data-driven cluster analysis of six variables. https://doi.org/10.1016/S2213-8587(18)30051-2

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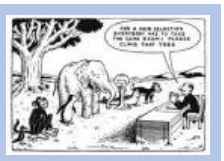
Precision Medicine



- One-size Fits All

vs

- Precision Medicine:
  - approach for disease treatment and prevention based on ***individual variability*** in genes, environment, and lifestyle
  - ***accurately predict*** which treatment and prevention strategies for a particular disease will work in which groups of people

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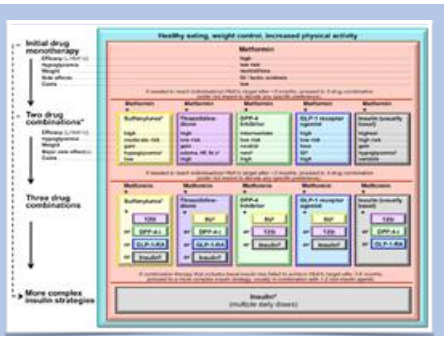
Old Standard



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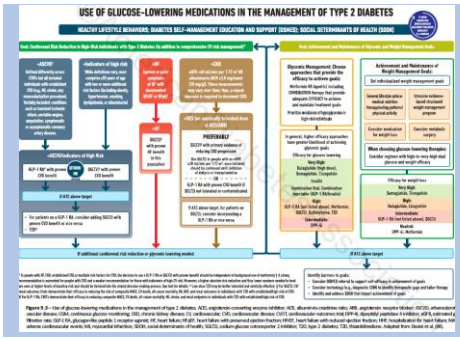

Pharmacologic Approaches to Glycemic Treatment. Diabetes Care. Vol 47, Suppl 1, Jan 2024

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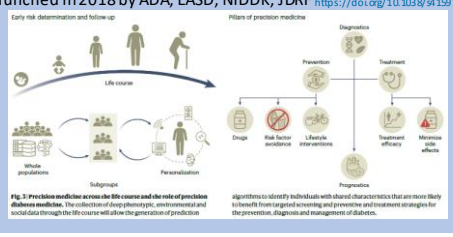
Precision Medicine in Diabetes Initiative (PMDI)

- Launched in 2018 by ADA, EASD, NIDDK, JDRF https://doi.org/10.1038/s41591-023-02502-5



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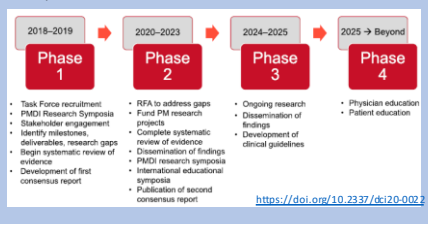
Precision Medicine in Diabetes Initiative (PMDI)

- Road map



https://doi.org/10.2337/dci20-0022

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Summary

- Vast majority of hyperglycemia/diabetes is DM 1 & DM 2 with ~5% being secondary diabetes
- Routine screening for secondary diabetes is not cost effective and need to be considered in patients with high pre-test probability.
  - Unusual features: younger age (<40-50yo), family history, rapid progression of disease, worsening condition despite good adherence to lifestyle and treatment regimen, refractory disease despite polypharmacy
  - Recognition of clinical features (i.e., physical findings, comorbidities)
- Early recognition of these uncommon causes of hyperglycemia can change the course of disease and patient's quality of life

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Q/A

- Thank you!
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