



Precision Medicine in the Prevention of Type 2 Diabetes

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Disclosure to Participants

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 - Please refer to learning goals and objectives
 - Learners must attend the full activity and complete the evaluation in order to claim continuing education credit/hours
- Conflict of Interest (COI) and Financial Relationship Disclosures:
 - Presenter: Brenda Montgomery, RN, MSHS, CDE, Clinical Science Liaison for AstraZeneca
 - Presenter: Erika Gebel Berg, PhD– No COI/Financial Relationship to disclose
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Learning Objectives

- Identify subpopulations of people with prediabetes that will benefit from particular diabetes prevention interventions
- Review genetic factors that may affect the selection of diabetes prevention interventions
- Learn about the evaluation of various pharmacologic agents in the prevention of diabetes

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Outline

1. Precision Medicine: Definition
2. Prediabetes
 - Urgency of Prevention
 - Natural History
3. Lessons from the Diabetes Prevention Program
 - Patient Factors (Phenotype)
 - Genetics (Genotype)
4. Prevention Beyond Lifestyle and Metformin

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What is Precision Medicine?

“an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.” --NIH

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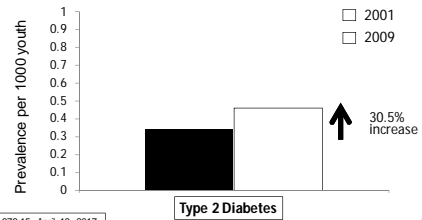
The Urgency of Prevention

- An estimated 84.1 million Americans have prediabetes
- Every year, 1.5 million are diagnosed with type 2 diabetes

Centers for Disease Control and Prevention. *National Diabetes Statistics Report, 2017*

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SEARCH for Diabetes in Youth Study



N England J MED, 376:15, April 13, 2017

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The Urgency of Prevention

Understanding how to prevent or delay T2DM and when to intervene, with the goal of reducing long-term morbidity and mortality in a cost-effective manner, is perhaps *the most important public health question in diabetes.*

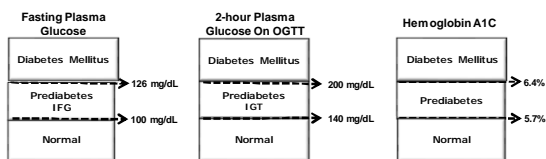
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We Need Your Help

Diabetes self-management education and support programs may be appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the development of diabetes. **B**

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What is Prediabetes?



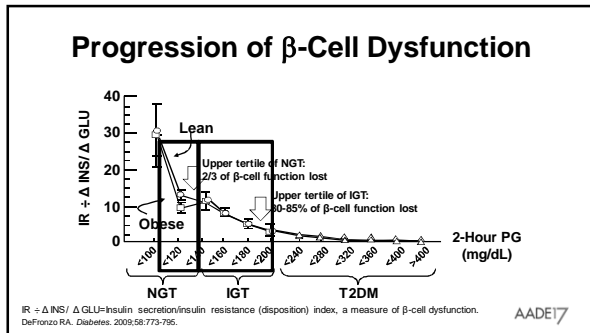
American Diabetes Association. *Diabetes Care*. 2017;40 Suppl 1:S11-24

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Natural History of Prediabetes

Beta-cell failure occurs much earlier in the natural history of type 2 diabetes and is more severe than previously appreciated

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The Staging of Type 2 Diabetes

Goal: Identify distinct genotypes and phenotypes of subtypes of diabetes to facilitate individualized treatment

- Disease Duration/Complications
- Pathophysiology
- Genetics

Skylar et al., Diabetes 66:241-255, 2017. AADE17

We Can Change the Natural History of Type 2 Diabetes

- Find prediabetes early through effective screening
- Management aimed at near-normal glucose without hypoglycemia
 - And without weight gain
- Benefit is sustained

Phillips et al. Diabetes Care. 37: 2668-2676. AADE17

We Can Change the Natural History of Type 2 Diabetes

“If we found prediabetes and early diabetes when they first presented and treated them more effectively, we could prevent or delay the progression of hyperglycemia and the development of complications.”

Phillips et al. Diabetes Care. 37: 2668-2676. AADE17

ARE YOU AT RISK FOR TYPE 2 DIABETES?

Diabetes Risk Test

1. How old are you? (18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90-99)

2. How many times have you been told you have prediabetes or diabetes? (None, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10)

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Trials to Prevent/Delay Progression from Prediabetes to Type 2 Diabetes

Lifestyle Changes

- Malmö Study
- Da Qing Study
- Finnish Diabetes Prevention Study
- Diabetes Prevention Program

Other

- Metabolic Surgery

Medications

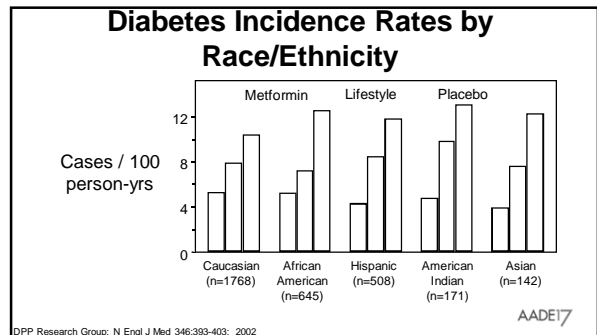
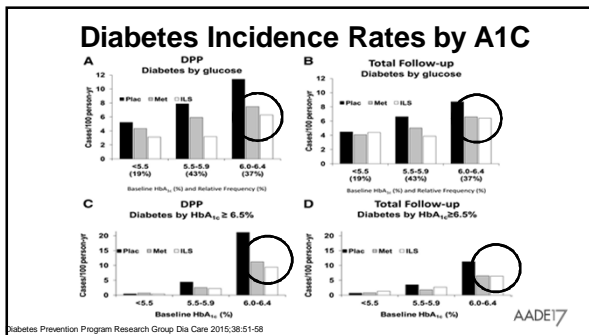
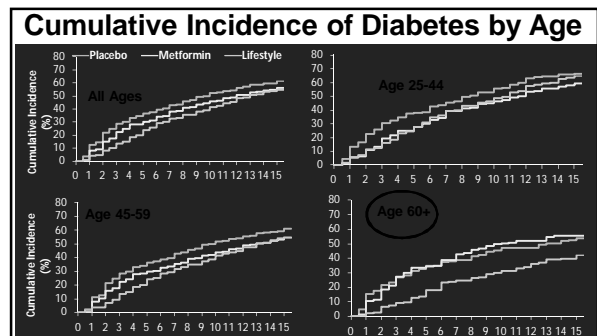
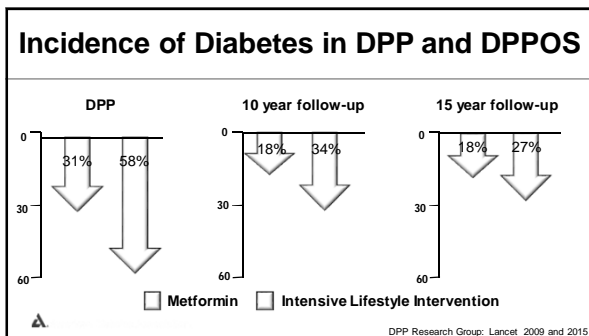
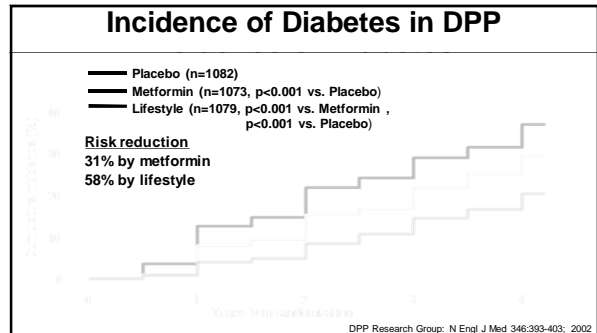
- Diabetes Prevention Program: metformin, (troglitazone)
- TRIPOD: troglitazone
- STOP-NIDDM: acarbose
- NAVIGATOR: nateglinide and valsartan
- DREAM: rosiglitazone and ramipril
- XENDOS: orlistat
- ORIGIN: glargine insulin
- ACT NOW: pioglitazone
- CANOE: rosi/metformin
- SCALE: liraglutide

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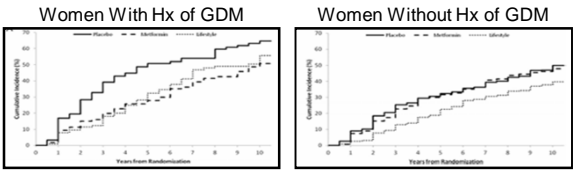
Lessons from DPP: Phenotype

- Age
- A1C
- Race/Ethnicity
- Medical History
- BMI

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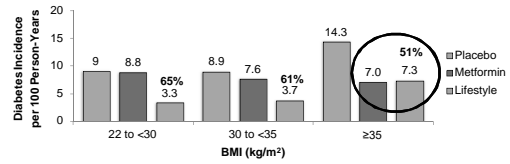
Diabetes Incidence in Women With and Without a History of Gestational Diabetes



Arora VR et al. J Clin Endocrinol Metab. 100:1646-1653. 2015

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Diabetes Incidence by BMI



DPP Research Group. N Engl J Med. 2002;346:393-403.

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DPP: Diabetes Incidence Rates by Age, BMI, History of GDM, and A1C

	Placebo	Lifestyle	Metformin
Cases per 100 Patient Years			
Age (years)	25-44	11.6	
	45-59	10.8	4.7, 7.6
	≥60	10.8	
BMI (kg/m²)	22 to <30	9	
	30 to <35	8.9	3.7, 7.6
	≥35	14.3	
GDM	No	8.6	4.4, 7.4
	Yes	12.8	
A1C	<5.5%	~1	~1
	5.5-5.9%	4	2.5, 2.4
	6.0-6.4	21	

DPP Research Group. N Engl J Med. 2002;346:393-403. 2002; Rafter RE et al. J Clin Endocrinol Metab. 93:4774-4779. 2006

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Precision Medicine in ADA's Standards of Care

Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI ≥ 35 kg/m², those aged <60 years, women with prior gestational diabetes mellitus, and/or those with rising A1C despite lifestyle intervention. **A**

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Call To Action: Metformin

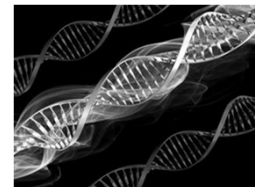
- Only 3.7% of patients with prediabetes were prescribed metformin over three years in a national sample of 17,352 working-age adults between 2010-2012.
- Low prescription rates may be due to lack of indication
- Ideally, metformin would be approved as a treatment for prevention: ADA, AACE, Endocrine Society, and DPP Researchers are petitioning the FDA. Stay tuned...

Moin et al. Annals of Internal Medicine. 2002;346:393-403. 2015 Apr 21;162(8):542-8

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Lessons from DPP: Genotype

How do certain genetic factors influence diabetes risk by modifying the protective effects of DPP interventions?



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MC4R

- Encodes melanocortin 4 receptor and is associated with feeding behavior
- *MC4R* point mutations are associated with human obesity and have a prevalence of 1.0-2.5% in people with BMI greater than 30.
- In people with a particular *MC4R* point mutation (rs17066866), metformin worked better than lifestyle management in overall weight loss at 6 months and two years.
- In participants with another *MC4R* point mutation (rs17066829), lifestyle management worked better at preventing diabetes than for those without this variant (HR: 0.80)

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Farooqi and O'Rahilly, *Endocr Rev*. 2006 Dec;27(7):710-18; Flores, *PLoS Med* 13(7): e1002102

SLC47A1

- Encodes the metformin transporter MATE1
- Point mutations with CT or TT have increased responsiveness to metformin:
 - **Metformin vs Placebo** HR 0.58 (0.46-0.73), $P < 0.001$
 - Effect not seen for CC
 - **Metformin vs Placebo** HR 1.07 (0.77-1.50), $P = 0.68$

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Becker, et al. *Diabetes*. 2009;58(3):745-749.

Overall Genetic Risk from 34 Point Mutations

- Point mutations associated with T2D at genome-wide significance levels
- Weighted genotype risk score (GRS), including 34 point mutations
- No significant interaction between GRS and treatment arms

Lifestyle intervention was effective regardless of genetic risk

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Hivert, *Diabetes*. 2011 Apr; 60(4): 1340-1348.

Beyond Metformin and Lifestyle

- Current options
 - Lifestyle intervention
 - Metformin
- Limited choice
- Where do we go from here?
- What is the evidence?

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Medical and Surgical Interventions Shown to Delay or Prevent T2D

Intervention	Follow-up Period	Reduction in Risk of T2D (P value vs placebo)
Antihyperglycemic agents		
Metformin ¹	2.8 years	31% (P<0.001)
Acarbose ²	3.3 years	25% (P=0.0015)
Pioglitazone ³	2.4 years	72% (P<0.001)
Rosiglitazone ⁴	3.0 years	60% (P<0.0001)
Weight loss interventions		
Orlistat ⁵	4 years	37% (P=0.0032)
Phentermine/topiramate ⁶	2 years	79% (P<0.05)
Liraglutide 3 mg/day	3 years	80% (P<0.01)
Bariatric surgery ⁷	10 years	75% (P<0.001)

¹ DPP Research Group. *N Engl J Med*. 2002;346:977-986. ² Sirtori CR, et al. *Diabetes Care*. 2002;25:1023-1029. ³ Nathan DM, et al. *Diabetes Care*. 2005;28:1070-1076. ⁴ Nathan DM, et al. *Diabetes Care*. 2005;28:1077-1083. ⁵ Sirtori CR, et al. *Diabetes Care*. 2002;25:1030-1036. ⁶ Sirtori CR, et al. *Diabetes Care*. 2002;25:1037-1043. ⁷ Sirtori CR, et al. *Diabetes Care*. 2002;25:1044-1050.

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Effect of Pioglitazone on Development of T2D in Patients with Prediabetes

ACT NOW

Annual Incidence rates:

- Pioglitazone: 2.1%
- Placebo: 7.6%

Conversion to Normoglycemia:

- Pioglitazone: 48%
- Placebo: 38%

No. at Risk	0	6	12	18	24	30	36	42	48
Placebo	299	259	228	204	191	134	83	17	
Pioglitazone	303	262	244	228	216	140	87	24	

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ACT NOW: Actos Now for the Prevention of Diabetes (T2D) in Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT) Type 2 Diabetes Mellitus. Nathan DM, et al. *N Engl J Med*. 2011;364:1104-1115.

Balancing Benefits and Risk

- Treatment with Pioglitazone in patients with impaired glucose tolerance reduced the risk of progression to diabetes by 72%
- For every 18 people treated with Pioglitazone for 1 year, one case of diabetes will be prevented
- This benefit comes with significant weight gain and edema

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Effect of Rosiglitazone on New-Onset Diabetes or Death in Patients with Prediabetes

Increased likelihood of Regression to Normoglycemia By 70-80 %

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Balancing Benefits and Risk

- For every 1000 people treated with Rosiglitazone for 3 years, about 144 cases of diabetes will be prevented...
- With an excess of 4 to 5 cases of congestive heart failure

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Trials to Reduce Progression of Prediabetes to Type 2 Diabetes

Lifestyle	Non-thiazolidinedione						Thiazolidinediones						
Di-Ging, DPP4s, DPP, DPP4	DPP4, DPP4, DPP4	STGR, Met, Met	XEN, Met, Met	NNMIS, Met, Met	DRY, Met, Met	GAP, Met, Met	TRIPDD, Met, Met	DPP, Met, Met	DREAM, Met, Met	ACT, Met, Met	NDM, Met, Met		
42%*	58%*	58%†	29%†	31%†	26%*	25%†	37%†	37%†	28%†	55%†	62%†	75%†	72%†

*vs control †vs placebo

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Effects of Liraglutide in Obese Patients with Prediabetes

SCALE Obesity and Prediabetes (N=3731)

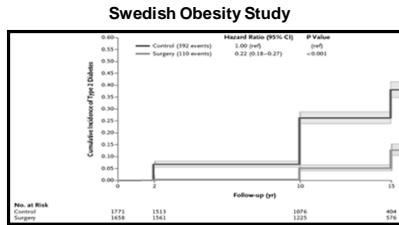
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Balancing Benefits and Risk

- Gastrointestinal side effects (nausea/vomiting/diarrhea)
- Increased heart rate
- ? Acute pancreatitis ?
- C-cell hyperplasia/medullary thyroid tumors in animals
- Injectable
- Training requirements
- Cost

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Effect of Bariatric/Metabolic Surgery on Incidence of Type 2 Diabetes



Carlsson LM, et al. *N Engl J Med*. 2012;367:685-704.

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Balancing Benefits and Risk

- Risk associated with surgery
- Dumping syndrome (nausea, colic, diarrhea), vitamin and mineral deficiencies, anemia, osteoporosis, and, rarely, severe hypoglycemia from insulin hypersecretion
- Increased risk for substance use
- Cost

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NIDDK Guidelines

Bariatric surgery may be an option for adults who have a BMI of 40 or more

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Summary and Conclusions

- Prediabetes is a big problem and precision medicine offers strategies for targeting interventions to those individuals most likely to benefit
- We are at the dawn of using genetics to guide treatment in diabetes and prediabetes, but more is likely to come
- Lifestyle intervention and metformin have the strongest evidence base in prediabetes, but there may be benefits of going beyond these interventions for particular patients

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Thank You!

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