Prediabetes in Kids: Screening, Risk Factors, and Treatment Strategies

AAP Webinar

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CME Disclosure

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Outline

- Why preventing type 2 diabetes is critical
- Screening recommendations for prediabetes/type 2 diabetes in youth
- Review definitions of prediabetes vs diabetes
- Natural history of prediabetes in kids
- Potential treatments for prediabetes
- Review DISCOVERY study

Type 2 Diabetes in Children

- Type 2 Diabetes: Combination of insulin resistance and β-cell dysfunction
  - Insulin resistance is more severe than adults
  - β-cell deterioration is more rapid than in adults
- Earlier complications: Macro- and microvascular
- Simulations: Estimated life expectancy will be reduced by ~15 years in youth who develop T2DM

Rhodes et al. Diabet Med 2012

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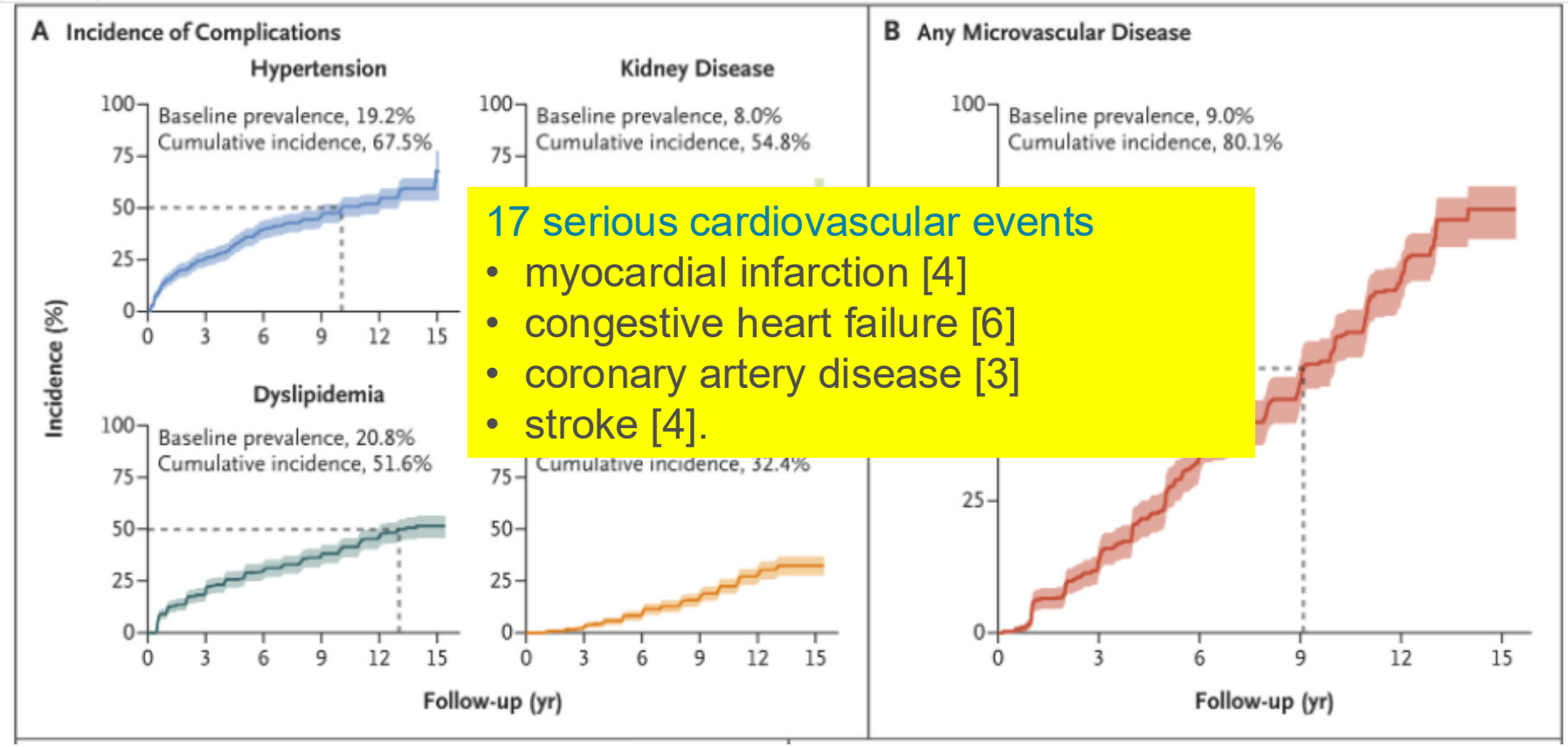
Scary Type 2 Outcomes from TODAY



17 serious cardiovascular events
- myocardial infarction [4]
- congestive heart failure [6]
- coronary artery disease [3]
- stroke [4].

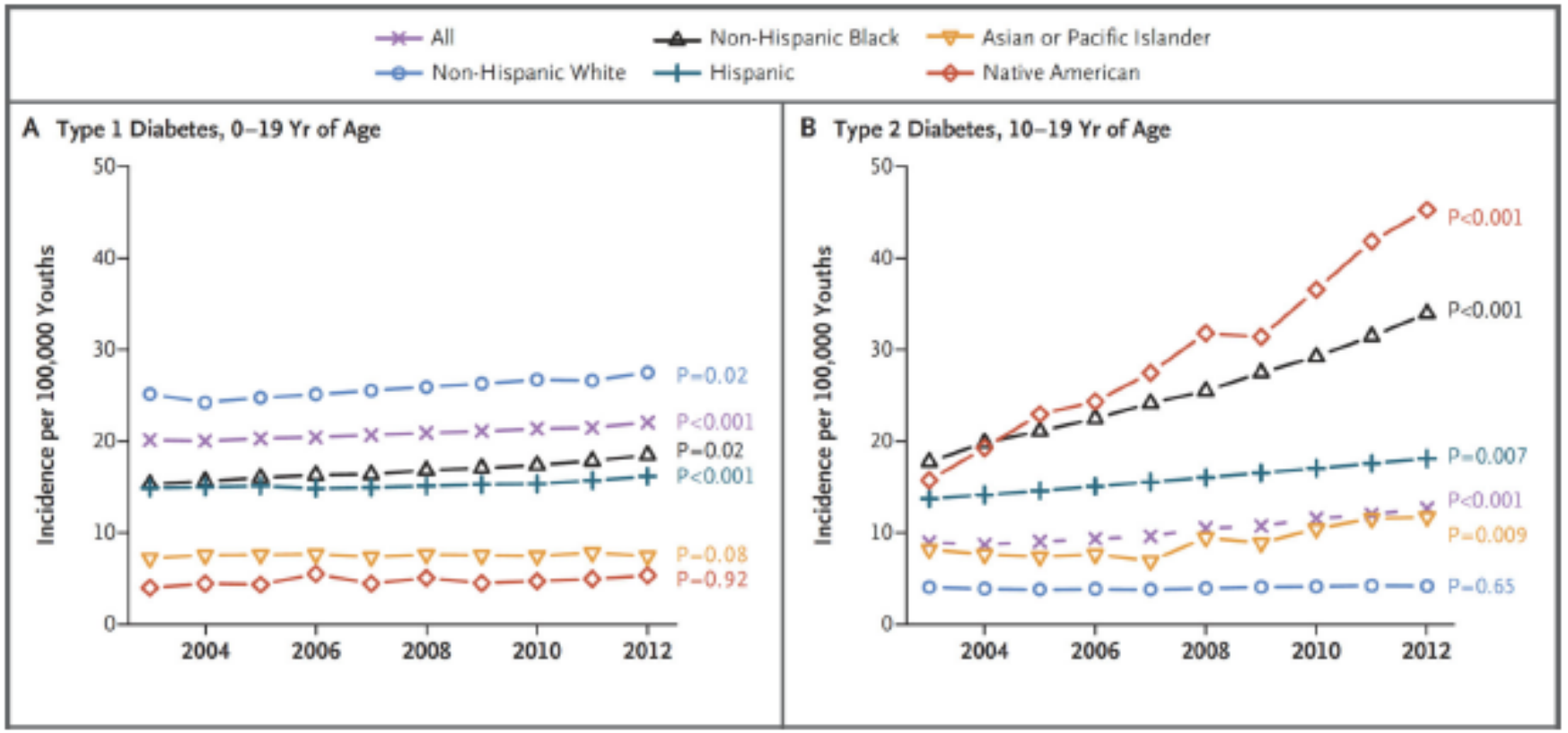
The TODAY study Group N Engl J Med 2021; 385:416-426

*metformin, vs metformin and rosiglitazone, vs metformin and lifestyle

Good News! Better Meds

- Metformin still first line
- GLP-1RAs are now approved in kids (<18 yo)
  - Daily liraglutide (Victoza)
  - Weekly dulaglutide (Trulicity)
  - Weekly exenatide (Bydureon)
- SGLT2 inhibitors are approved in kids
  - Daily empagliflozin (Jardiance)
  - Daily dapagliflozin (Farxiga)
- Try to keep off insulin (or wean off quickly)
  - Do have kids that require full basal bolus insulin by pump or injections
  - Kids that make ketones, presented DKA, Type 1.5 diabetes

Bad News: ALL Diabetes is Increasing



SEARCH study data: Overall prevalence 0.68%

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Screening for Prediabetes/Diabetes

- ADA/ISPAD/AAP: Screen asymptomatic youth ≥10 yo (or onset of puberty, whichever comes first) with overweight or obesity, AND ONE of the following known risk factors:
  - Maternal history of gestational diabetes
  - Family history of T2D in 1st or 2nd degree relative
  - Race/ethnicity: non-white
  - Signs of insulin resistance (includes h/o SGA)
    - NOT insulin level

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What Tests Do I Use to Screen?

- Easiest: fasting glucose and hemoglobin A1C
- OGTT: Recommendation from Endocrine Society for OGTT as "best test", "cost efficient"
  - Studies have shown A1C can be falsely reassuring in children
- Insulin levels no longer recommended on routine screening
  - Assays have a lot of variability
  - Natural insulin resistance during puberty
  - High levels do not correlate well with dysglycemia
  - Useful to determine types of diabetes

Definitions: Diabetes

- A1C ≥6.5%
- Fasting glucose ≥126 mg/dL
- 2-hour on OGTT ≥200 mg/dL
- Random glucose ≥200 mg/dL WITH symptoms

*meds?

*If no symptoms, then need two OR repeated measures

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Real-Life Case

- 15 year old boy with routine screening labs (BMI 33.4 kg/m2), no symptoms
  - Fasting glucose: 126 (H)
  - ALT: 114 (H)
  - AST: 51 (H)
  - GGT: 98 (H)
  - CHOLESTEROL LEVEL: 259 (H)
  - LDL CHOLESTEROL: 154 (H)
  - HDL CHOLESTEROL: 33 (L)
  - TRIGLYCERIDES: 357 (H)
  - HEMOGLOBIN A1C: 6.6 (H)
  - INSULIN: 29.7
  - TSH WITH REFLEX TO T4 FREE, RAPID: 2.652
- Comes to clinic 6 weeks later and A1C was 5.6%, fasting 97 mg/dL

Definitions: Prediabetes

- A1C between 5.7% and 6.4%
- Impaired fasting glucose:
  - Fasting glucose between 100 and 125 mg/dL
- Impaired glucose tolerance:
  - 2 hour on OGTT between 140-199 mg/dL

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Prevalence of Prediabetes

- NHANES: screening by A1c and fasting glucose
  - ~1 in 5 youth ages 12 to 18 (18%)
  - 1 in 4 young adults age 19 to 34 (25%)
- Undiagnosed diabetes was rare (0.3%)
- More common in males
  - Fun fact: Females more likely to get T2DM
- Globally (48 study meta-analysis): 8.4%

Wallace et al. Pediatrics 2020
Han et al. J Diabetes 2022

Hmmm….

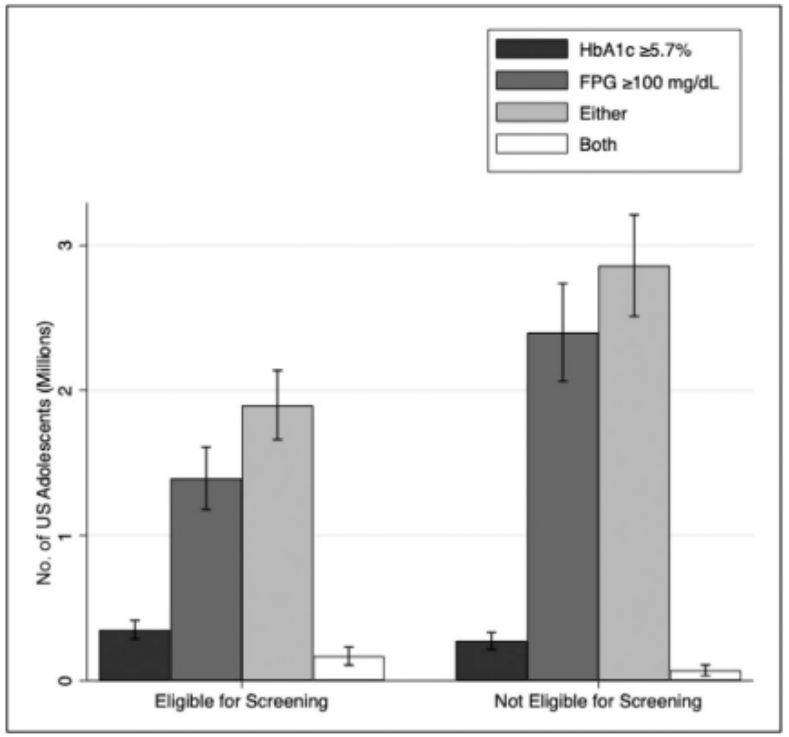

FIGURE 1
Number (in millions) of US adolescents with hyperglycemia (prediabetes or undiagnosed diabetes) in 2016, by diabetes screening eligibility status.

- 3.4% met criteria by A1C
- 15.6% met criteria by fasting glucose
- 1.5% had both
- A1C
  - Sensitivity 55.5%
  - Specificity 76.3%
- FPG
  - Sensitivity 35.8%
  - Specificity 77.1%

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What About IGT?

Table 2. Distribution of Glucose Metabolism Abnormalities in US Adolescents and Young Adults by Age[a]

Characteristic	% (95% CI) Adolescents	Young Adults
Age, y	12-18	19-34
Normal glucose	82.0 (79.9-84.0)	76.0 (73.9-78.1)
IFG only	9.2 (7.8-10.7)	11.4 (9.7-13.4)
IGT only	2.8 (2.0-3.8)	3.2 (2.6-4.0)
Increased HbA_{1c} level only	3.7 (3.0-4.7)	4.6 (3.9-5.4)
IFG + IGT	0.7 (0.3-1.6)	1.3 (0.9-1.9)
IFG + increased HbA_{1c} level	1.0 (0.7-1.6)	2.2 (1.7-2.8)
IGT + increased HbA_{1c} level	0.3 (0.2-0.5)	0.3 (0.2-0.6)
IFG + IGT + increased HbA_{1c} level	0.2 (0.1-0.5)	0.9 (0.5-1.4)
All IFG	11.1 (9.5-13.0)	15.8 (14.0-17.9)
All IGT	4.0 (3.1-5.2)	5.8 (4.9-6.8)
All increased HbA_{1c} level	5.3 (4.3-6.4)	8.0 (7.0-9.2)
Any prediabetes	18.0 (16.0-20.1)	24.0 (21.9-26.1)

- Subset of NHANES had OGTTs
- IF obesity, prediabetes
  - 12.3% by fasting glucose
  - 4.2% by A1C
  - 3.6% by IGT
- IF normal weight, prediabetes
  - 8.2% by fasting glucose
  - 3.8% by A1C
  - 2.8% by IGT

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Physiologic Differences in Parameters

- Impaired fasting glucose
  - Reduced basal insulin secretion
  - Hepatic and renal insulin resistance
  - Are they fasting???
- Impaired glucose tolerance (more of A1C contribution)
  - Impaired post-prandial secretion
  - Increased insulin resistance at the muscle

Conclusions

- Prevalence depends on the metric
- Prediabetes exits in normal weight individuals
  - And in numbers much greater than expected for developing type 1 diabetes
- Rates of T2DM are much much much lower than prediabetes in kids, although the numbers are increasing

So do kids just stay in prediabetes for years?

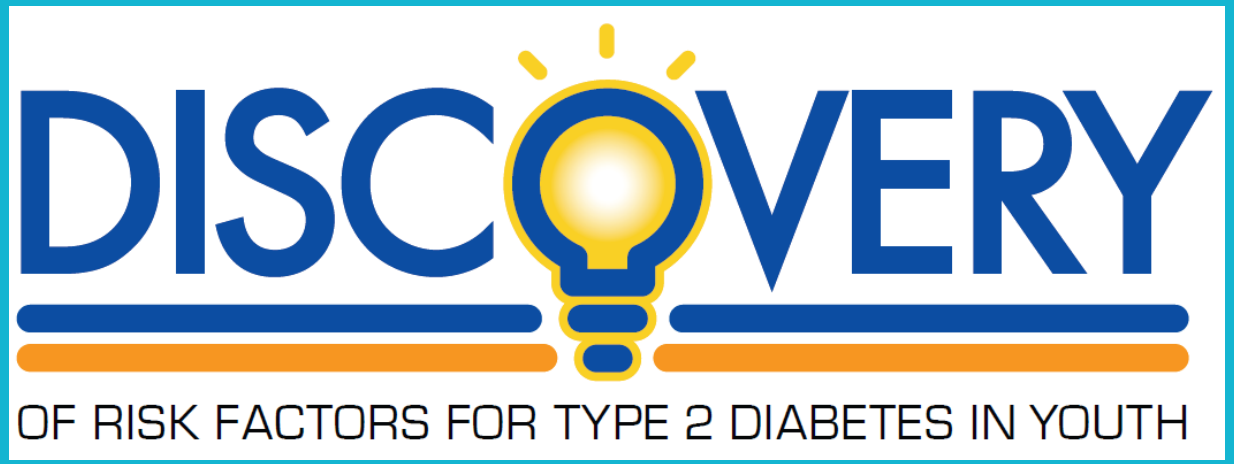
Prediabetes Regresses

- ~70% of youth with prediabetes regress to normoglycemia after puberty
  - Remember natural insulin resistance in puberty
- Studies show a wide range of change
  - 2-25% covert to T2DM
  - 25-30% remain in prediabetes
  - 45-75% revert to normal glucose tolerance

Hoset et al. Ped Endo Metab 2022

SO Which Kids Progress?

- We don't really know
- $$$$
  - Repeat screening
  - Interventions over years
  - Because we don't want to miss those who do tip to T2DM



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Primary Objectives

The primary objectives of DISCOVERY are to:

1. Identify the **physiologic drivers and other determinants of progression to youth-onset T2D** by charting the course of changes in glycemia, β-cell function, insulin sensitivity, psychosocial, behavioral, and social determinants of health during this critical period of maturation.
2. Inform **approaches for precise prediction** of which youth are at highest risk of developing T2D during this period.
3. **Engage local and central stakeholders** to play an active role in the study design and conduct, and provide feedback during follow-up.

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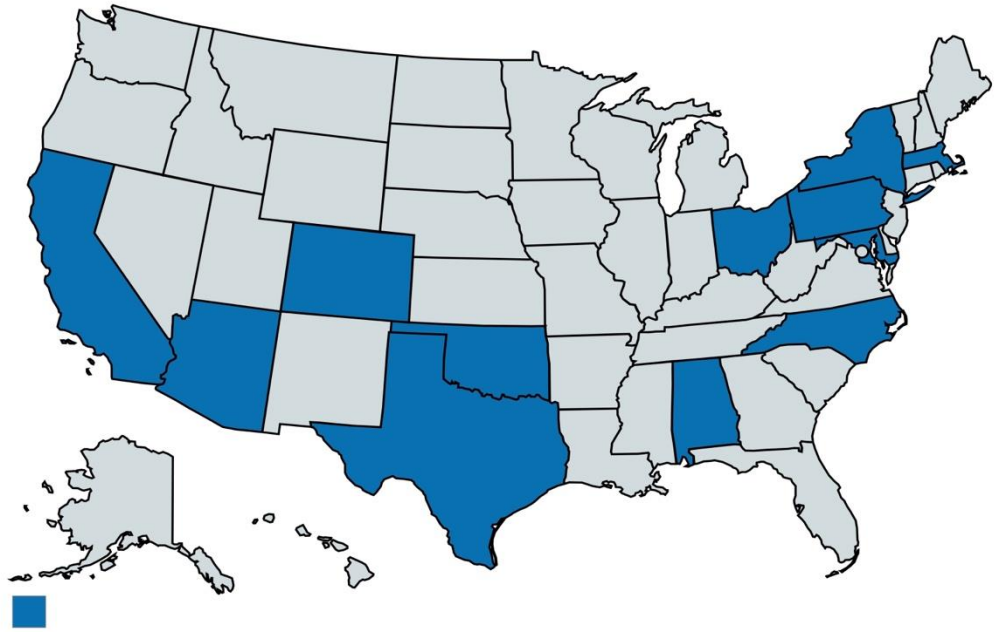
Consortium Sites

ID	Study Site
01	Albert Einstein College of Medicine
02	Arizona State University/ Phoenix Children's
03	Boston Children's/ Joslin Diabetes Center/ Massachusetts General Hospital
04	Children's Hospital of Los Angeles
05	Children's Hospital of Philadelphia
06	Cincinnati Children's Hospital
07	Colorado Navajo
08	Johns Hopkins Hospital
09	Nationwide Children's Hospital
10	NYU Langone Health
11	Texas Children's Hospital/ Baylor College of Medicine
12	University of Alabama at Birmingham
13	University of Colorado
14	University of Oklahoma Health Sciences Center
15	Wake Forest University / Atrium Health



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Study Population: Inclusion Criteria

- 3,600 youth, aged 9-14 years at enrollment, of all genders and race/ethnic groups from 15 clinical centers in the US will be included.
- DISCOVERY participants must have all of the criteria in **Category A**:
  - Overweight or obesity with BMI ≥85th percentile
  - Age 9-13 years for girls, 10-14 years for boys (inclusion younger for girls as puberty tends to start a year earlier in girls)
  - Pubertal Tanner Stage 2 or 3, or Tanner Stage 4 Tanner target distribution: Tanner 2-3: 80%, Tanner 4: 20%.
  - HbA1c 5.5-6.4%
    - HbA1c target distribution: 5.5-5.6%: 25%, 5.7-6.4%: 75%
- Participants who meet all of these categories further need to meet at least one criterion in **Category B**:
  - Family history of T2D in 1st or 2nd degree relative
  - Personal exposure to maternal diabetes (i.e., gestational diabetes mellitus (GDM) or mother with type 1 or type 2 diabetes while pregnant with participant)
  - HbA1c > 6.0%
  - Severe obesity (BMI >99th percentile)
  - Personal history of intrauterine growth restriction (IUGR), small for gestational age (SGA), or low birth weight

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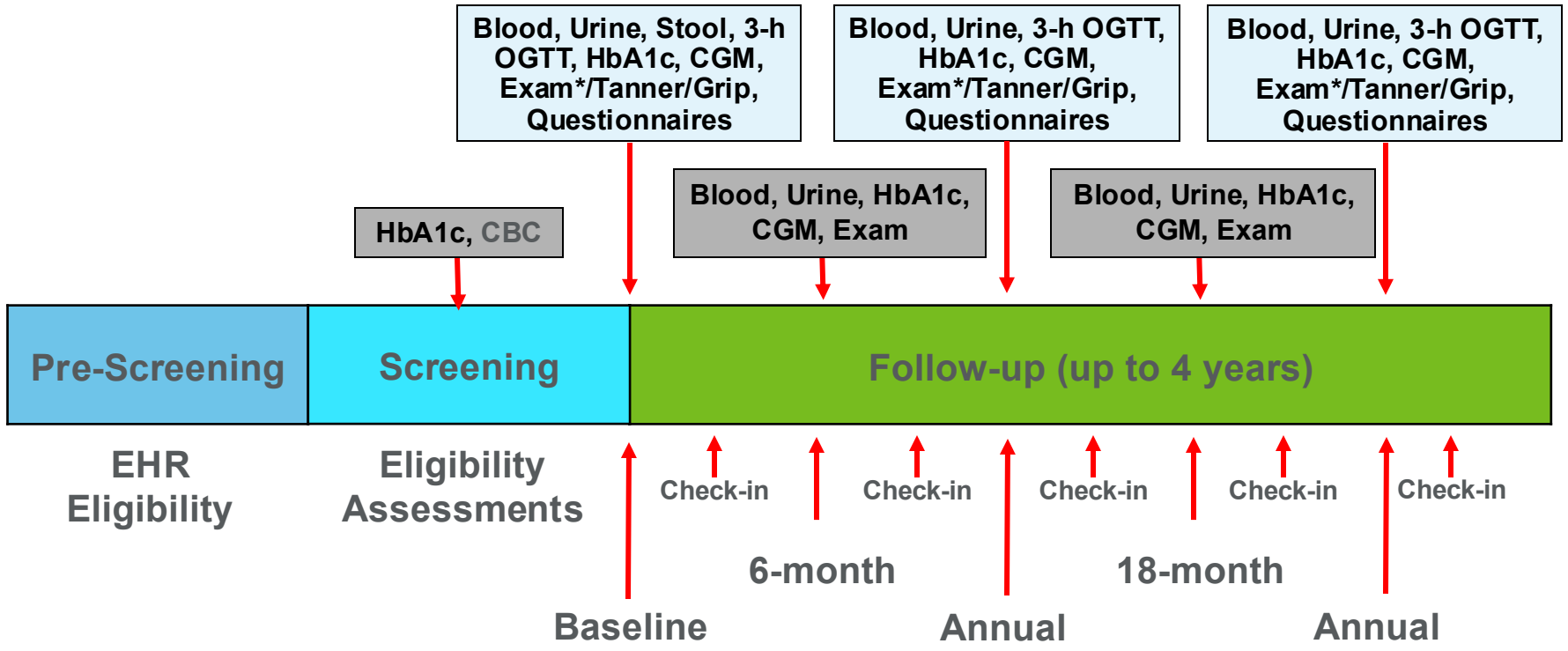
Exclusion Criteria

- No meds that would affect glucose tolerance
- No monogenic obesity (VUSs don't count) or syndromic obesity
- Can't have been diagnosed with diabetes or been on insulin in the past
- No GLP-1 for the last 6 weeks, or plan to start
- No metformin for the last 6 weeks

Study Design



$875 for 2 years

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Questionnaires

- Psychosocial and behavioral questionnaires
  - PHQ9, Peds QL, GAD
- Lifestyle
  - Sleep, dietary
- Social Determinants of Health

STUDY SITE CONTACTS

For more information, please visit
www.DISCOVERYyouthstudy.org
or contact your local study site:

Scan the QR code to
learn more about

DISCOVERY
OF RISK FACTORS FOR TYPE 2 DIABETES IN YOUTH

www.DISCOVERYyouthstudy.org

FIND OUT IF YOUR CHILD IS AT RISK FOR TYPE 2 DIABETES

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Treatments for Prediabetes

There are NO FDA-approved medical therapies for prediabetes

Lifestyle

- Lower carb (low glycemic index) diets
  - no juice/sugar drinks
- Weight reduction through portion reduction, reduced snacking
- Exercise!!!

Healthy diet and exercise IS medicine:

Best chance to keep the kids off meds, prevent progression

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Metformin

- Metformin is still THE first-line therapy for type 2 diabetes in both adults and in kids
  - Safe
    - Used for over 50 years
    - Few contraindications (significant renal disease)
    - Comes in tablet and liquid forms
  - Weight neutral
    - Can even see some minimal weight loss
      - Randomized study in children over 6 months : -1 BMI unit, -3 kg[1]
  - Effective IF diabetes
    - Average A1C reduction as monotherapy across studies= 1.12%
- Some data effective if IGT in kids
  - Metformin appears to slow β-cell decline in adults, but not kids (but no placebo)
- Potential masking of diabetes
  - Ie, A1C goes from 5.7% to 6.3% ON metformin
    - Is this prediabetes or type 2 diabetes, treated?
    - Would have to stop metformin to officially diagnose

1. Yanovski. Diabetes 2011

GLP-1RA

- Approved for weight loss in kids <18 yo
  - semaglutide (Wegovy)
  - liraglutide (Saxenda)
- Has been proven to slow β-cell decline
- Very effective in treating in diabetes
- Overall safe
  - Pancreatitis and gallbladder risk
  - Can't use in MEN (FH of medullary thyroid CA)
- COST (and approval, therefore)

My Approach to Prediabetes

- Really pay attention to family history
  - Autoimmune disease? Could it be developing type 1?
    - Send islet cell autoantibodies
    - This is where fasting insulin/C-peptide can be helpful
    - Now an FDA-approved prevention drug on the market (teplizumab)
  - Strong family history of type 2
    - If only grandparents, have parents been to the doctor recently?
- Other patient labs
  - Evidence of MASLD, dyslipidemia?
  - MASLD: Prediabetes 23.5%, T2DM 6.5%

Newton et al. JAMA Peds 2016

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Approach By the Numbers

- If IFG but normal A1C, I worry less
- Some evidence less regression to normal glucoses is A1C≥6
  - 42% if 5.7 to 5.9% vs 30% if ≥6%
- IGT probably the most worrisome
  - Formal OGTTs are not done often
  - "Unofficial OGTT"—check glucose 2 hours after carb feast
  - Role for continuous glucose monitoring??

Love-Osborne et al. Pediatr Diabetes 2018

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Evaluate for Lifestyle Readiness

- Shared decision making is KEY
- "Assigning" diets and exercise never works well
- Metformin a consideration if significant barriers to lifestyle
- If working hard on lifestyle and weight stalling or glucoses not coming down=GLP-1 meds

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Future Goals

- Who is really at risk of developing diabetes?
  - Can we create a better risk model in children?
  - Targeted interventions

Questions?

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