



T2D in Children and Adolescents

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T2D Pathophysiology

■ Pediatric vs Adult T2D

The basic pathophysiology of T2D is very similar in pediatric and adult populations. Differences between the two age groups are more in quantitative than qualitative terms





Adults vs Adolescents with T2D

■ **Similarities**

- In both age groups, T2D is characterized by severe insulin resistance and progressive β -cell dysfunction
- In both age groups, T2D disproportionately affects low income, Black and Hispanic patients
- Adolescents with T2D are physically mature and of similar weight and BMI as adults with T2D
- In this case adolescents are like big adults



Adults and Adolescents with T2D

■ Differences

- The pace of deterioration of glucose tolerance from IGT to T2D appears be faster in pediatrics
- A greater proportion of adolescents with T2D from all race and ethnic groups come from low income families
- In pediatrics, there are far fewer T2D than T1D patients



Too Many Trials and Not Enough Patients

- **ClinTrials.Gov:** 16 trials in 10 medications for T2D in pediatrics recruiting ~2000 pts; more coming
- **Pediatric T2D:** An epidemic in relative rather than absolute terms, starting from a base of zero.



Too Many Trials and Not Enough Patients

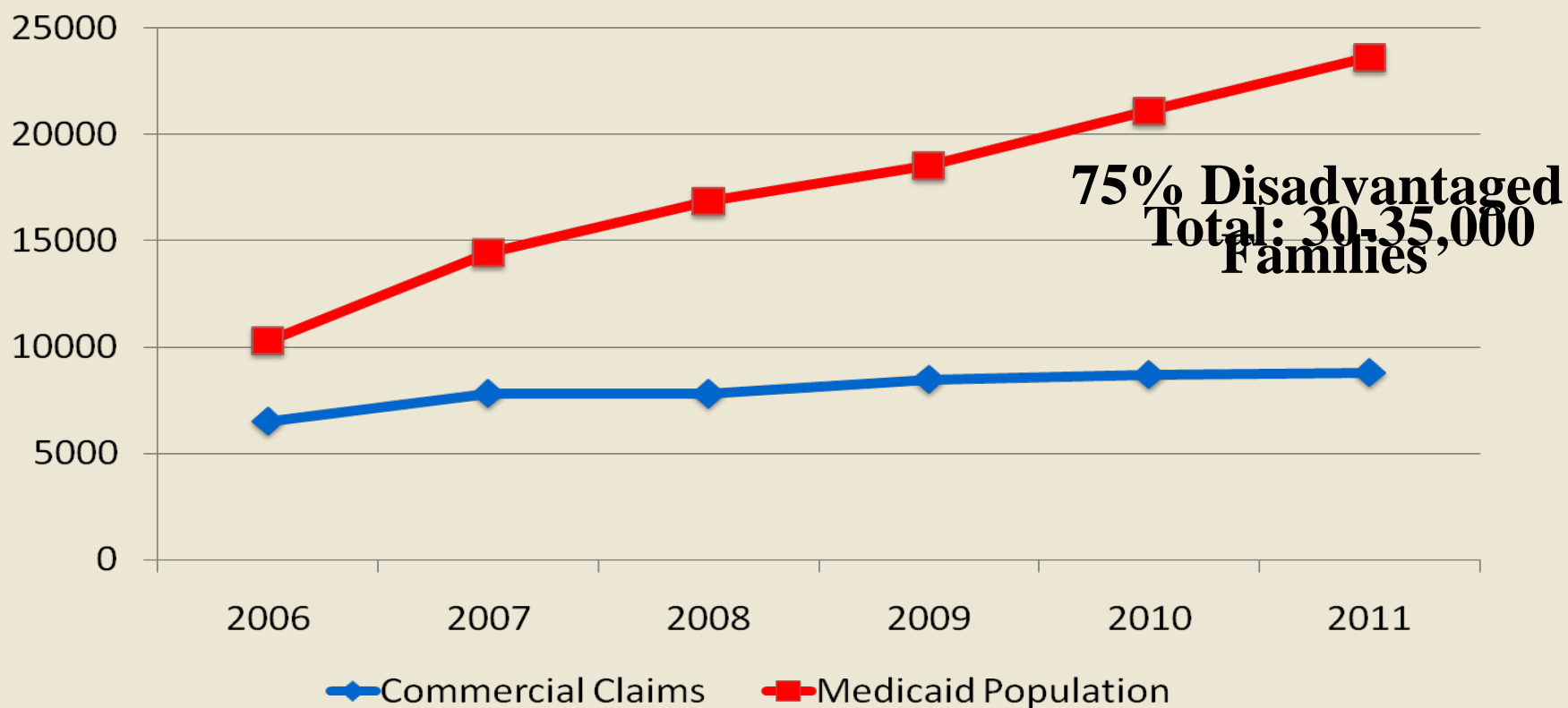
■ **SEARCH Study:**

- At constant incidence over time at 2002 levels
~ 20,000 US youth aged <20 years had T2DM in 2010
- At a yearly 2.3% increase ~ 23,000 US youth aged <20 years had T2DM in 2010





Estimated # of Pediatric T2D from Commercial and Medicaid Claims





Adults and Adolescents with T2D

■ Differences

- Treatment options are much more limited in adolescents than adults with T2D
 - » Metformin, insulin and intensive life-style interventions (ILI) are the only approved therapies in pediatric T2D
 - » Rosiglitazone and glimepiride failed non-inferiority tests vs metformin as monotherapy of T2D in adolescents
 - » Rosiglitazone + metformin was superior to either metformin alone or metformin + ILI in the TODAY Study but TZD's unlikely to be used in pediatrics due to adverse effects of this class of drugs.





Treatment of T2D in Adolescents

■ What about:

- GLP1 agonists?
- DPP4 inhibitors?
- SGLT2 inhibitors?
- Others?

- Adequately powered, randomized clinical trials of the safety and efficacy of these agents in adolescents with T2D have been almost impossible to complete





Difficult Subjects to Recruit and Retain in Studies

- **Adolescent girls:** ~2/3 of the available patient population
- **Cultural and Socio-economic Barriers:** Low-income, inner city Black, Hispanic and White families difficult to recruit for studies, especially Black families who have a lingering distrust of clinical trials as a result of the Tuskegee experience
- **Psycho-social issues:** Behavioral problems, depression and other psychiatric disorders, as well as use of atypical anti-psychotics, are very common.





Study Designs Mandated by Regulatory Authorities have been Major Problems

- **Early randomized clinical trials compared the efficacy and safety of drugs approved for adult T2D with metformin for initial mono-therapy in drug naïve patients with A1c levels > 7.0%**
 - Virtually all pediatric patients with newly diagnosed T2D are immediately treated with insulin and/or metformin
 - An increasing proportion of youth with pre-diabetes are also being treated with metformin.
 - Metformin is well established as initial monotherapy of T2D
 - Unmet need is for second and third line drugs for patients with elevated A1c levels on their current treatment regimen





Metformin vs Experimental Drug as Initial Monotherapy in Drug Naïve Subjects with $A1c \geq 7.0\%$

■ **Treatment Options for Diabetes² in Adolescents and Youth (The Today Study)**

- Study Design: Time to treatment failure in adolescents with T2D who were relatively well controlled on treatment with metformin alone
- Major Eligibility
 - » Age 10-17 years
 - » Duration T2D <2 yrs
 - » $A1c \leq 8.0\%$
- Screening results of >1,000 subjects
 - » Only 13% were receiving no drugs
 - » Their median A1c was 6.1%





Guidelines for Treatment of Newly Diagnosed T2D from the American Academy of Pediatrics

■ Key Recommendations

- Insulin therapy should be initiated in youth with T2D who are:
 - ketotic or in DKA
 - have random BG level ≥ 250 mg/dL or
 - A1c is $>9.0\%$.
- In all other instances, clinicians should start metformin as first-line therapy at the time of diagnosis.



Experimental Drug as Add-on Therapy in Metformin Failures

- **More recent trials examined the safety and efficacy of drugs that have been approved in adults with T2D as add on therapy in patients with elevated A1c levels on metformin but have excluded patients on insulin or other anti-diabetic drugs**
- Treatment regimens of ~1,000 youth with T2D screened for enrollment in the TODAY Study:
 - Metformin alone 45%
 - Insulin alone 13%
 - Insulin+metformin 26%
 - Another drug 3%
 - No drug 13%





Pediatric T2D Study Design Issues: Partial Solutions

■ Efficacy Studies:

- New drugs for the treatment of T2D in pediatrics should be tested against placebo as add on therapy in patients with elevated A1c levels who are being treated with:
 - » metformin and/or insulin and/or any other anti-diabetic drug of a different class

■ Expand the age range to 10-21 years

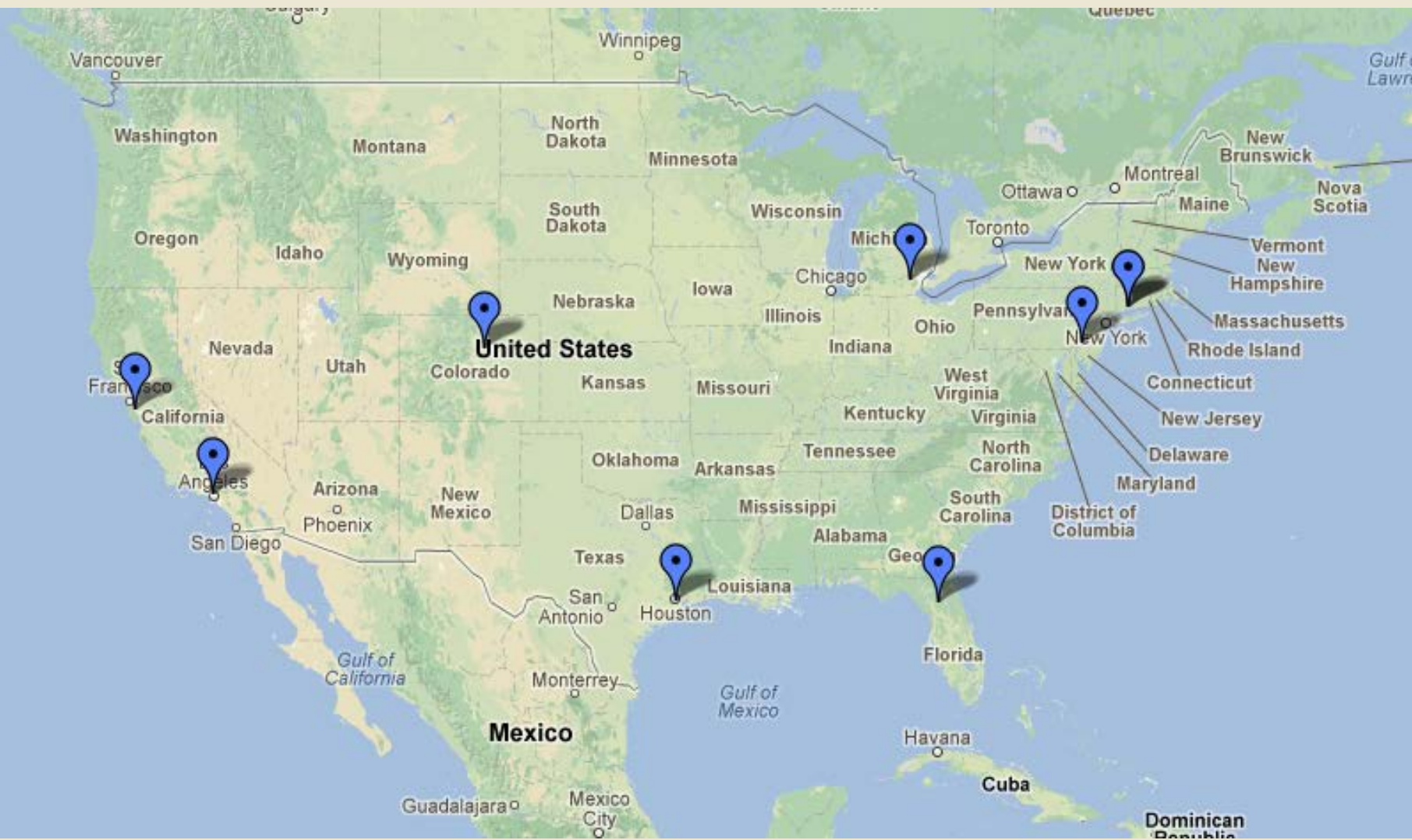




Aren't Metformin and Insulin Enough?

NO







PDC T2D Clinic Registry

- Age 10-18 years
- T2D duration 0-7 years
- ~200 patients with T2D > 1 year enrolled as of 1/1/13
 - Insulin alone (n=58): mean (\pm SD) A1c $9.4 \pm 2.5\%$
 - Insulin + metformin (n=48): A1c $8.9 \pm 2.2\%$
 - Metformin alone (n=46) : A1c $6.1 \pm 2.2\%$



Possible Solution: Extrapolation

■ **Extrapolation (FDA Definition):**

Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another.”





Extrapolation of Adult T2D Data to Pediatric T2D

- **Pediatric and adult T2D have:**
 - Similar presentation and pathophysiology
 - Similar disease progression with metformin monotherapy failing in most patients in the long run
 - Similar efficacy and safety outcome measures
- **Virtually all pediatric T2D patients are in a single, peri-pubertal age range**
 - Not infants or younger children
 - Not little adults



Extrapolation of Adult T2D Data to Pediatric T2D

■ Pathways to Approval

- Similarities in PK/PD characteristics in pediatric and adult T2D patients
- Non-controlled efficacy and safety studies in adolescents
 - » Clinic-based Registries
 - » Post-marketing safety studies

