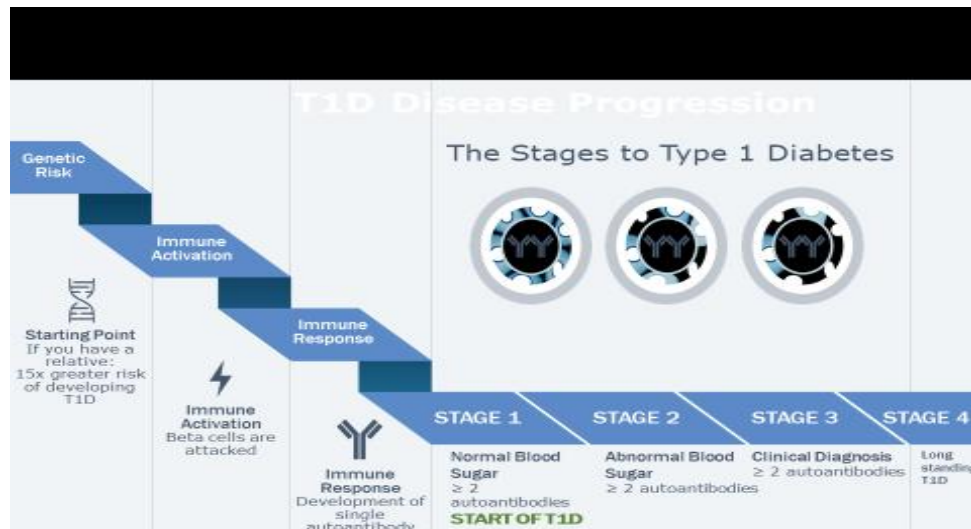


# The Prevention of Type 1 Diabetes



Medical Ground Rounds  
UT Southwestern Medical Center  
Philip Raskin  
July 13, 2018

This is to acknowledge that Philip Raskin, MD has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Raskin will not be discussing off label uses in his presentation.

Philip Raskin, MD

Professor

Division of Endocrinology and Metabolism

Purpose & Overview:

The purpose of this Grand Rounds is to update the efforts to prevent or alter the course of type 1 diabetes. There is considerable interest and research efforts being expended in order to prevent the disease or slow its progression. I plan to discuss the work that is being done in that regard.

Educational Objectives:

1. Understand that the frequency of type 1 diabetes is increasing
2. Understand the new classification of type 1 diabetes and that the disease begins when an individual has two or more diabetes specific immune markers in their blood
3. Understand the effect of age at diagnosis has on the progression of type 1 diabetes
4. Be aware of the studies that attempt to alter the course of type 1 diabetes after a clinical diagnosis has been made
5. Be aware of the studies that attempt to alter the course of type 1 diabetes, before a clinical diagnosis has been made.

Bio Sketch:

Philip Raskin, M.D. received his medical degree from the University of Pittsburgh, School of Medicine and completed a residency in Internal Medicine there. He did a Fellowship in Endocrinology, Diabetes and Metabolism at UT Southwestern Medical Center at Dallas. He is board certified in Internal Medicine and Endocrinology, Diabetes and Metabolism. He is a Fellow of the American College of Physicians and the American College of Endocrinology, and is a Certified Diabetes Educator.

He is presently Professor of Medicine, Department of Internal Medicine and holds the Clifton and Betsy Robinson Chair in Biomedical Research at the University of Texas Southwestern Medical Center at Dallas. He is an Attending Physician in the Diabetes Clinic at Parkland Health and Hospital Systems and the Parkland Memorial Hospital. He is the Principal Investigator in four NIH funded multicenter diabetes trials: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC), TrialNet, The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE Study) and Vitamin D to Prevent Type 2 Diabetes (D2d Study).

Dr. Raskin is a clinical researcher known for his work in diabetes, diabetes complications and diabetes management. He was the Editor of The Journal of Diabetes and Its Complications from 1990 to 2011 and has served as a past Editor of Clinical Diabetes.

He is widely published in such peer reviewed journals, such as the New England Journal of Medicine, The Journal of Clinical Investigation, Diabetes, Diabetes Care, the Annals of Internal Medicine, and The Journal of Diabetes and Its Complications. He has also authored numerous chapters in clinical text books.

## References

- Alhadj Ali M, Liu YF, Arif S, Tatovic D, Shariff H, Gibson VB, Yusuf N, Baptista R, Eichmann M, Petrov N, Heck S, Yang JHM, Tree TIM, Pujol-Autonell I, Yeo L, Baumard LR, Stenson R, Howell A, Clark A, Boulton Z, Powrie J, Adams L, Wong FS, Luzio S, Dunseath G, Green K, O'Keefe A, Bayly G, Thorogood N, Andrews R, Leech N, Joseph F, Nair S, Seal S, Cheung H, Beam C, Hills , Peakman M, Dayan CM. Metabolic And Immune Effects Of Immunotherapy With Proinsulin Peptide In Human New-Onset Type 1 Diabetes. *Sci Transl Med*. 2017 Aug 9;9(402).
- Atkinson, MA, Eisenbarth, GS, Michels, AW. (2014). Type 1 Diabetes. *The Lancet*. January; (383) 69-82.
- Atkinson, MA, Von Herrath M, Powers AC, Clare-Salzler M. (2015) Current Concepts On The Pathogenesis Of Type 1 Diabetes Considerations For Attempts To Prevent and Reverse The Disease. *Diabetes Care*. Jun;38 (6):979-88.
- Atkinson MA, Jeffrey A. Bluestone, George S. Eisenbarth, Matthias Hebrok, Kevan C. Herold, Domenico Accili, Massimo Pietropaolo, Peter R. Arvan, Matthias Von Herrath, Dorene S. Markel, And Christopher J. Rhodes. (2011) How Does Type 1 Diabetes Develop? The Notion Of Homicide Or B-Cell Suicide Revisited. *Diabetes*. May; 60(5): 1370–137.
- Battaglia M, Anderson MS, Buckner JH, Geyer SM, Gottlieb PA, Kay TWH, Lernmark Å, Muller S, Pugliese A, Roep BO Greenbaum CJ, Peakman M. (2017). Understanding And Preventing Type 1 Diabetes Through The Unique Working Model Of Trialnet. *Diabetologia*. Nov;60(11):2139-2147.
- Battaglia M., Atkinson MA., (2015) The Streetlight Effect In Type 1 Diabetes. *Diabetes* Apr; 64(4): 1081-1090.
- Beam CA, MacCallum C, Herold KC, Wherrett DK, Palmer J, Ludvigsson J; Type 1 Diabetes Trialnet Study Group. GAD Vaccine Reduces Insulin Loss In Recently Diagnosed Type 1 Diabetes: Findings From A Bayesian Meta-Analysis. *Diabetologia*. 2017 Jan;60(1):43-49.
- Bollyky JB, Xu P, Butte AJ, Wilson DM, Beam CA, Greenbaum CJ Type 1 Diabetes Trialnet Study Group. (2015). Heterogeneity In Recent-Onset Type 1 Diabetes - A Clinical Trial Perspective. *Diabetes Metab Res Rev*. 2015 Sep;31(6):588-94.
- Censin JC, Nowak C, Cooper N, Bergsten P, Todd JA, Fall T. (2017). Childhood Adiposity And Risk Of Type 1 Diabetes: A Mendelian Randomization Study. *Plos Med*. 2017 Aug 1;14(8):E1002362.
- Chiang JL1, Kirkman MS2, Laffel LM3, Peters AL4; Type 1 Diabetes Sourcebook Authors. (2014). Type 1 Diabetes Through The Life Span: A Position Statement Of The American Diabetes Association. *Diabetes Care*. Jul;37(7):2034-54.

Davis AK, Dubose SN, Haller MJ, Miller KM, Dimeglio LA, Bethin KE, Goland RS, Greenberg EM, Liljenquist DR, Ahmann AJ, Marcovina SM, Peters AL, Beck RW, Greenbaum CJ; T1D Exchange Clinic Network. (2015). Prevalence Of Detectable C-Peptide According To Age At Diagnosis And Duration Of Type 1 Diabetes. *Diabetes Care*. Mar;38(3):476-81.

DIAMOND Project Group. Incidence And Trends Of Childhood Type 1 Diabetes Worldwide 1990-1999. *Diabet Med*. 2006 Aug;23(8):857-66.

Diane K. Wherrett, MD, Brian Bundy, Phd, Linda A. Dimeglio, MD, Stephen E. Gitelman, MD, Robin Goland, MD, Peter A. Gottlieb, MD, Carla J. Greenbaum, MD, Kevan C. Herold, MD, Jennifer B. Marks, MD, Roshanak Monzavi, MD, Antoinette Moran, MD, Tihamer Orban, MD, Jerry P. Palmer, MD, Philip Raskin, MD, Henry Rodriguez, MD, Desmond Schatz, MD, Darrell M. Wilson, MD, Jeffrey P. Krischer, Phd, Skyler, J., MD, And The Type 1 Diabetes Trialnet GAD Study Group. (2011). *Lancet*. Jul 23; 378(9788): 319–327.

Garg Satish K. (2017). Expanding Treatment Options For Improving Health Outcomes In Type 1 Diabetes. Published Online:1 Oct 2017<https://doi.org/10.1089/Dia.2017.1807>.

Herold KC, Usmani-Brown S, Ghazi T, Lebastchi J, Beam CA, Bellin MD, Ledizet M, Sosenko JM, Krischer JP, Palmer JP; Type 1 Diabetes Trialnet Study Group. (2015). B Cell Death And Dysfunction During Type 1 Diabetes Development In At-Risk Individuals. *J Clin Invest*. Mar 2;125(3):1163-73.

Herold KC1, Gitelman SE, Ehlers MR, Gottlieb PA, Greenbaum CJ, Hagopian W, Boyle KD, Keyes-Elstein L, Aggarwal S, Phippard D, Sayre PH, Mcnamara J, Bluestone JA; Abate Study Team. (2013). Teplizumab (Anti-CD3 Mab) Treatment Preserves C-Peptide Responses In Patients With New-Onset Type 1 Diabetes In A Randomized Controlled Trial: Metabolic And Immunologic Features At Baseline Identify A Subgroup Of Responders. *Diabetes*. Nov;62(11):3766-74.

Insel RA, Dunne JL, Atkinson MA, Chiang JL, Dabelea D, Gottlieb PA, Greenbaum CJ, Herold KC, Krischer JP, Lernmark Å, Ratner RE, Rewers MJ, Schatz DA, Skyler JS, Sosenko JM, Ziegler AG. (2015). Staging Presymptomatic Type 1 Diabetes: A Scientific Statement Of JDRF, The Endocrine Society, And The American Diabetes Association. *Diabetes Care*. Oct;38(10):1964-74.

Ismail HM, Xu P, Libman IM, Becker DJ, Marks JB, Skyler JS, Palmer JP, Sosenko JM; Type 1 Diabetes Trialnet Study Group., The Shape Of The Glucose Concentration Curve During An Oral Glucose Tolerance Test Predicts Risk For Type 1 Diabetes. *Diabetologia*. 2018 Jan;61(1):84-92.

Lambert AP, Gillespie KM, Thomson G, Cordell HJ, Todd JA, Gale EA, Bingley PJ. Absolute Risk Of Childhood-Onset Type 1 Diabetes Defined By Human Leukocyte Antigen Class II Genotype: A Population-Based Study In The United Kingdom. *J Clin Endocrinol Metab*. 2004 Aug;89(8):4037-43.

Maahs, David M, MD, Nancy A West, Phd, Jean M. Lawrence, Scd, MPH, MSSA, And Elizabeth J Mayer-Davis, Phd. Epidemiology of Type 1 Diabetes. *Endocrinol Metab Clin North Am.* 2010 Sep; 39(3): 481–497.

Mckenna, Maryn. Diabetes Mystery: Why Are Type 1 Cases Surging? February 1, 2012. <https://www.scientificamerican.com/article/a-diabetes-cliffhanger>

Orban T1, Bundy B, Becker DJ, Dimeglio LA, Gitelman SE, Goland R, Gottlieb PA, Greenbaum CJ, Marks JB, Monzavi R, Moran A, Raskin P, Rodriguez H, Russell WE, Schatz D, Wherrett D, Wilson DM, Krischer JP, Skyler JS; Type 1 Diabetes Trialnet Abatacept Study Group. (2011). *Lancet.* Jul 30;378(9789):412-9

Pescovitz MD, Carla J. Greenbaum, M.D., Heidi Krause-Steinrauf, M.S., Dorothy J. Becker, M.D., Stephen E. Gitelman, M.D., Robin Goland, M.D., Peter A. Gottlieb, M.D., Jennifer B. Marks, M.D., Paula F. Mcgee, M.S., Antoinette M. Moran, M.D., Philip Raskin, M.D., Henry Rodriguez, M.D., Desmond A. Schatz, M.D., Diane Wherrett, M.D., Darrell M. Wilson, M.D., John M. Lachin, Sc.D., And Skyler, J. , M.D., For The Type 1 Diabetes Trialnet Anti-CD20 Study Group. (2009). *New England Journal Of Medicine* November 361(22)2143-52.

Roep BO, Tree T. Immune Modulation In Humans: Implications For Type 1 Diabetes Mellitus. (2014) *Nature Reviews Endocrinology.* April 10 (4):229-42

Sherry N, Hagopian W, Ludvigsson J, Jain SM, Wahlen J, Ferry RJ Jr, Bode B, Aronoff S, Holland C, Carlin D, King KL, Wilder RL, Pillemer S, Bonvini E, Johnson S, Stein KE, Koenig S, Herold KC, Daifotis AG; Protégé Trial Investigators. (2011). Teplizumab For Treatment Of Type 1 Diabetes (Protégé Study): 1-Year Results From A Randomised, Placebo-Controlled Trial. *Lancet.* Aug 6;378(9790):487-97.

Skyler, J., MD, Jeffrey P. Krischer, Phd, Joseph Wolfsdorf, MD, Catherine Cowie, Phd, Jerry P. Palmer, MD, Carla Greenbaum, MD, David, Cuthbertson, MS, Lisa E. Rafkin-Mervis, MS, H. Peter Chase, MD, And Ellen Lescheck, MD. (2005). Effects Of Oral Insulin In Relatives Of Patients With Type 1 Diabetes. *Diabetes Care* 28:1068—1076.

Skyler, J. (2015). Prevention And Reversal Of Type1 Diabetes—Past Challenges And Future Opportunities. *Diabetes Care* June; 38(6): 997-1007.

Skyler, J., Type 1 Diabetes Trialnet Study Group. (2008). Update On Worldwide Efforts To Prevent Type 1 Diabetes. *Ann N Y Acad Sci.* Dec; 1150:190-6.

Taplin CE, Barker JM. (2008). Autoantibodies In Type 1 Diabetes. *Autoimmunity.* 2008 Feb;41(1).

Type 1 Diabetes Trialnet Oral Insulin Study Group, Krischer JP, Schatz DA, Bundy B, Skyler JS, Greenbaum CJ. (2017). Effect of Oral Insulin On Prevention of Diabetes In Relatives Of Patients With Type 1 Diabetes: A Randomized Clinical Trial. *JAMA*. Nov 21;318(19):1891-1902.

Wen-Peng You, Maciej Henneberg. Type 1 Diabetes Prevalence Increasing Globally And Regionally: The Role Of Natural Selection And Life Expectancy At Birth. *BMJ Open Diabetes Res Care*. 2016 Mar 2;4(1).

Wenzlau JM<sup>1</sup>, Juhl K, Yu L, Moua O, Sarkar SA, Gottlieb P, Rewers M, Eisenbarth GS, Jensen J, Davidson HW, Hutton JC. (2007). The Cation Efflux Transporter Znt8 (Slc30A8) Is A Major Autoantigen In Human Type 1 Diabetes. *Proc Natl Acad Sci U S A*. Oct 23;104(43):17040-5.

Wherrett DK, Chiang JL, Delamater AM, Dimeglio LA, Gitelman SE, Gottlieb PA, Herold KC, Lovell DJ, Orchard TJ, Ryan CM, Schatz DA, Wendler DS, Greenbaum CJ; Type 1 Diabetes Trialnet Study Group. (2015) Defining Pathways For Development Of Disease-Modifying Therapies In Children With Type 1 Diabetes: A Consensus Report. *Diabetes Care*. Oct;38(10):1975-85.

Zhao LP, Carlsson A, Larsson HE, Forsander G, Ivarsson SA, Kockum I, Ludvigsson J, Marcus C, Persson M, Samuelsson U, Örtqvist E, Pyo CW, Bolouri H, Zhao M, Nelson WC, Geraghty DE, Lernmark Å; Better Diabetes Diagnosis (BDD) Study Group. Building And Validating A Prediction Model For Paediatric Type 1 Diabetes Risk Using Next Generation Targeted Sequencing Of Class II HLA Genes. *Diabetes Metab Res Rev*. 2017 Nov;33(8).

Ziegler AG<sup>1</sup>, Rewers M, Simell O, Simell T, Lempainen J, Steck A, Winkler C, Ilonen J, Veijola R, Knip M, Bonifacio E, Eisenbarth GS. (2013). Seroconversion To Multiple Islet Autoantibodies And Risk Of Progression To Diabetes In Children. *JAMA*. Jun 19; 309 (23)