RESPONSE TO COMMENT ON SO ET AL.

Autoantibody Reversion: Changing Risk Categories in Multiple-Autoantibody–Positive Individuals. Diabetes Care 2020;43:913–917

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We would like to thank Alhamar et al. (1) for their perspective on our article, which included questions regarding the utility of standard autoantibody measures in characterizing preclinical type 1 diabetes and recruitment of prevention trials. To summarize our findings, we reported that 96% of individuals with multiple autoantibodies sustain these autoantibodies over time (2). Further, we found that the 4% of individuals who did not sustain multiple-autoantibody status over time still retained a greater risk of progression to type 1 diabetes than those who never developed multiple autoantibodies. Indeed, decades of research in many population groups and different countries have repeatedly demonstrated that almost all individuals with multiple autoantibodies will eventually develop clinical disease. Additionally, among children at increased genetic risk for type 1 diabetes, those who reverted from a single autoantibody retained an increased risk for clinical diagnosis that was twice as high as autoantibody-negative children (3). We therefore disagree with the assertion of Alhamar et al. that the individuals in our study are entirely healthy and instead argue that they have early-stage type 1 diabetes. Collectively, these data are supportive of current autoantibody measurements to identify and stratify individuals at risk for type 1 diabetes and demonstrate that they are appropriate and sufficiently powerful to serve as entry criteria for clinical trials to slow or stop disease progression (4). Moreover, as recently reported at the American Diabetes Association 79th Scientific Sessions in 2019 and published in *The New England Journal of Medicine*, a single course of anti–T cell therapy using teplizumab slowed progression to type 1 diabetes in individuals with multiple autoantibodies by a median of 2 years, without significant adverse events (5). This important result emphasizes that the use of current autoantibody assays can accurately identify individuals at high risk of disease and that early treatment of those individuals holds significant promise for future clinical translation.

However, heterogeneity in disease progression is a hallmark of type 1 diabetes, and we agree with Alhamar et al. that efforts to parse this heterogeneity are essential. Novel biomarkers that identify those at risk for more rapid progression to clinical disease, or that define treatable disease endotypes (6), are critically needed. Indeed, our work suggests that evaluating changes in biomarkers over time may provide insights into understanding this heterogeneity (2,7). While many novel autoantibody measures, antigen targets, and other immune biomarkers have been described, their relevance in disease prediction must be subjected to the same validation rigor applied to the existing autoantibodies (reviewed in Bonifacio and Achenbach [8]). This iterative and systematic approach will ensure the field continues to build upon the decades of meticulous natural history studies and clinical trial results while still striving for further refinement.

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References

1. Alhamar GE, Strollo R, Pozzilli P. Comment on So et al. Autoantibody reversion: changing risk categories in multiple-autoantibody–positive individuals. Diabetes Care 2020;43:913–917 (Letter). Diabetes Care 2020;43:e102. DOI: 10.2337/dc20-0409
2. So M, O'Rourke C, Bahnson HT, Greenbaum CJ, Speake C. Autoantibody reversion: changing risk categories in multiple-autoantibody–positive individuals. Diabetes Care 2020;43:913–917
3. Vehik K, Lynch KF, Schatz DA, et al.; TEDDY Study Group. Reversion of β-cell autoimmunity changes risk of type 1 diabetes: TEDDY study. Diabetes Care 2016;39:1535–1542
4. Insel RA, Dunne JL, Atkinson MA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care 2015;38:1964–1974
5. Herold KC, Bundy BN, Long SA, et al.; Type 1 Diabetes TrialNet Study Group. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N Engl J Med 2019;381:603–613
6. Battaglia M, Ahmed S, Anderson MS, et al. Introducing the endotype concept to address the challenge of disease heterogeneity in type 1 diabetes. Diabetes Care 2020;43:5–12
7. Speake C, Bahnson HT, Wesley JD, et al. Systematic assessment of immune marker variation in type 1 diabetes: a prospective longitudinal study. Front Immunol 2019;10:2023
8. Bonifacio E, Achenbach P. Birth and coming of age of islet autoantibodies. Clin Exp Immunol 2019;198:294–305