SUMMARY: Porksen et al have detailed the natural history of 261 children with a new diagnosis of type 1 diabetes, with regard to glycemic control, beta cell functional reserve and evolution of beta cell autoantibodies. They have also investigated a monogenic basis for beta cell dysfunction or destruction among the children lacking beta cell autoantibodies. Beta cell reserve was measured by serial C-peptide responses to a mixed meal, the autoantibodies measured are those directed against ICA, GAD65 an IA-2, and the genes investigated by sequencing are HNF-1a and HNF-4a in those with a family history of diabetes and KCNJ11, ABCC8 and INS in those without a family history of diabetes.

The investigators find that about 9% of the patients are autoantibody-negative (although two become positive 6 and 12 months after diagnosis). The Ab- patients at all time points measured have better beta cell reserve than the Ab+ patients (as measured by C-peptide responses, proinsulin levels and insulin requirement) as well as better glycemic control (as measured by responses to oral glucose challenge and insulin dose-adjusted HbA1c).

Finally, the investigators identify a single Ab- patient with a novel ABCC8 mutation that could affect SUR1 function with respect to insulin secretion; in vitro this mutation interferes with K-ATP channel function in a manner that is reversible with sulfonylurea; however, treatment of the patient with glibenclamide is not successful and this is attributed to the fact that this patient with a HLA class II risk allele converted to Ab+ status 6 months later and hence probably had co-existing autoimmunity leading to complete beta cell destruction.

MAJOR COMPULSORY REVISIONS:

1. A major concern in regard to establishing the frequency of the “Ab-” phenotype in this cohort is lack of measurement of the ZnT8 autoantibody. Inclusion of ZnT8 autoantibody data would make this paper much stronger since it could well shift several of the Ab- pts into the Ab+ category. This in turn could affect some of the conclusions in regard to the sustained preservation of beta cell function in Ab- patients. It could actually heighten the difference in regard to this outcome between Ab+ and Ab- groups, although it would make the latter group smaller. At any rate, it has to be done, since by now ZnT8 is now quite well established as a bona fide disease-relevant beta cell autoantibody. In fact, in table 1B, there is a blank column and a mysterious entry in the legend that suggests that this blank
column had been created for ZnT8 Ab data. Are the authors choosing not to present this data for some reason? If so, this should be stated and discussed.

2. The study is described as a “multicenter … investigation with 18 participating centers from … countries in Europe and Japan”. However, there are no authors from the Japanese center(s). I raise this issue because the non-Caucasian ethnicities are not described. What ethnic groups comprised the 16% who were non-Caucasian? This is of relevance to understanding why ethnic frequencies were not different between the Ab+ and Ab- groups.

3. Somewhat related to my comment #2, it is surprising that there were no differences in HLA risk group frequencies between the Ab+ and Ab- groups. The authors should discuss the potential implications of this lack of difference. For example, could it be in part because of “occult” ZnT8 Ab+ patients in the Ab-group? In other studies comparing patients with Ab+ to Ab- phenotypes of insulinopenic diabetes (e.g., in adults with A+B- compared to A-B- forms of ketosis-prone diabetes: Nalini et al, Diabetes Care 31(6):1195-1200, 2008) there are distinct differences in the frequencies of high-risk HLA class II alleles.

4. It is stated (p. 7) that 6 of the 22 Ab- patients had first-degree relatives with diabetes, and that apparently was the basis for investigating only these subjects for the two MODY genes. What were the phenotypes of diabetes in these relatives, and how was the information obtained so as to be reasonably sure that such relatives were absent in those without a “family history of diabetes”. The authors should provide more details about the relatives’ phenotypes (at least some details of their ages of onset, potential for being type 1 or type 2, etc).

5. It is reasonable as well as useful to suppose that an Ab- group of new onset type 1 diabetic children might be enriched in monogenic forms of the illness, but why restrict the MODY gene candidates to HNF1a and HNF4a? Why not GCK, PDX and others?

6. More information is needed regarding the cutoff values for GADA. What was the basis for the cutoff of 10 units/ml? Was it set at the 99th percentile of a control group (as for the IA-2 Ab measurement)? If so, what were key characteristics of the control group? Ethnicity of the control group can affect background titers and percentile cutoffs for GADA, and thus the frequency of GADA positivity in the study group.

7. Given the lack of information about the non-Caucasian ethnicities, the small numbers of non-Caucasian subjects, and point #6 above, it appears unjustified to conclude (page 9) that ethnicity has a minor role in Ab- T1D in childhood.

MINOR ESSENTIAL REVISIONS:

1. On page 7, the reader is referred to figure 1 to demonstrate that the Ab-patients had lower “blood glucose fluctuations” than the Ab+ group. The term “fluctuations” is misleading, as it suggests that data were obtained from something along the lines of continuous glucose monitoring. In fact, I believe figure 1C shows change over two time points after a glucose challenge – at least, I think so; this figure needs a clear legend.

2. It would be helpful if ethnicity data were provided in Table 1A.
3. On page 7, it is stated that Ab- patients had 0.65% lower HbA1c than Ab+ patients – after what duration of time post-diagnosis?

4. Spelling is inconsistent, e.g. “sulphonylureas” (p. 10) vs. “sulfonylureas”.

5. The word “apparent” is unnecessary at the bottom of page 3.

6. The construction “…magnitude of immunological markers..” (page 3) is awkward. Are the authors referring to the number of autoantibodies?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.