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Zinc Transporter 8 autoantibodies (ZnT8A) and a Type 1 diabetes-genetic risk score can exclude individuals with type 1 diabetes from inappropriate genetic testing for monogenic diabetes

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We have recently shown that the detection of monogenic diabetes in a population can be improved by excluding individuals with type 1 diabetes identified by having low C-peptide levels and/or the presence of GAD autoantibodies (GADA) or IA-2 autoantibodies (IA-2A) in the UNITED study(1). Since completion of the study, there are now two new tests that also robustly identify T1D; Zinc Transporter 8 autoantibodies (ZnT8A)(2) and the Type 1 Diabetes Genetic Risk Score (T1D-GRS)(3,4). It is not known the extent to which the addition of these new tests will improve the diagnostic s(1). Autoantibodies assessment was performed at recruitment. The median duration of diabetes at recruitment was 7.4 years (IQR 2.5-17.3). GADA and IA-2A were measured as previously described(1). ZnT8A was measured by ELISA (RSR ltd, Cardiff, UK) on a Dynex DS2 ELISA robot (Dynex, Preston, UK). The RSR ZnT8A ELISA is capable of detecting, and quantifying, autoantibodies specific to R325 or to W325, or to residue 325 non-specific variants. We used >99th centile of a control population (n=1559, age range 1-69 years) to define the positivity of ZnT8A (≥126 units for age<30, ≥26 units for age≥30). The T1D-GRS was derived from genotyping 30 common polymorphisms as described previously. We used >50th centile of T1D-GRS, derived from large reference population of T1D from Wellcome Trust Case Control Consortium (n=1963), to define those at high genetic risk of T1D (3,4). All subjects who were GADA and IA-2A negative, had a next-generation targeted panel test for 35 gene causing monogenic diabetes(1). 15/212 individuals were identified with monogenic diabetes. Their mutations and clinical characteristics are described in table 1 of our previous paper (1)

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Author contributions. K.A.P and T.J.M designed the study. K.A.P., B.M.S and M.N.W. researched data and performed statistical analyses. K.A.P. and T.J.M. wrote the first draft of the manuscript, which was modified by all authors. All authors contributed to the discussion and reviewed or edited the manuscript. T.J.M. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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ZnT8A were present in 39/212 (18%) individuals. This increased the number of autoantibody positive individuals from 58 (27%, GAD and/or IA2 positive) to 75 (35%) (p=0.008)(Fig.1). A single autoantibody was found in 44, two in 26 and 5 had all three autoantibodies. .None of the individuals who were positive for the ZnT8A only, had monogenic diabetes.

The T1D-GRS 50th centile cut-off identified 48/212 individuals with probable T1D (those at high genetic risk of T1D). 21 of these were negative for all three autoantibodies (Fig.1). None of these 21 individuals had monogenic diabetes. Thus, addition of the T1D-GRS increased the number of people that can be excluded for genetic testing from 35% with all three autoantibodies to 45% (p=0.003)(Fig.1).

Overall, in individuals with significant endogenous insulin secretion, ZnT8A and T1D-GRS excluded an additional 18% individuals (p<0.001) without missing any monogenic diabetes. These individuals had the similar age of diagnosis, BMI, and UCPCR, from the 27% identified by GADA and IA-2A alone. However, the duration of diabetes was longer in autoantibodies negative T1D individuals who were identified by T1D-GRS compared to autoantibodies positive T1D [3.6 year (IQR 1.2-9.9) vs 14 years (5.8-21.1), p=0.002)]. These two additional tests reduced the number of patients with persistent insulin secretion who needed to be tested for monogenic diabetes from 73% to 55% (p<0.001). The main drawback of these new tests, like GADA and IA-2A antibodies, is that they do not discriminate between type 2 diabetes and monogenic diabetes.

In conclusion two new tests, ZnT8A and the T1D-GRS, helped identify an additional 18% of probable Type 1 diabetes in individuals with significant endogenous insulin secretion excluding the need for monogenic testing. The additional testing is likely to be cost effective as they cost approximately $15 each, which is approximately 1/100th of the cost of a full genetic test.

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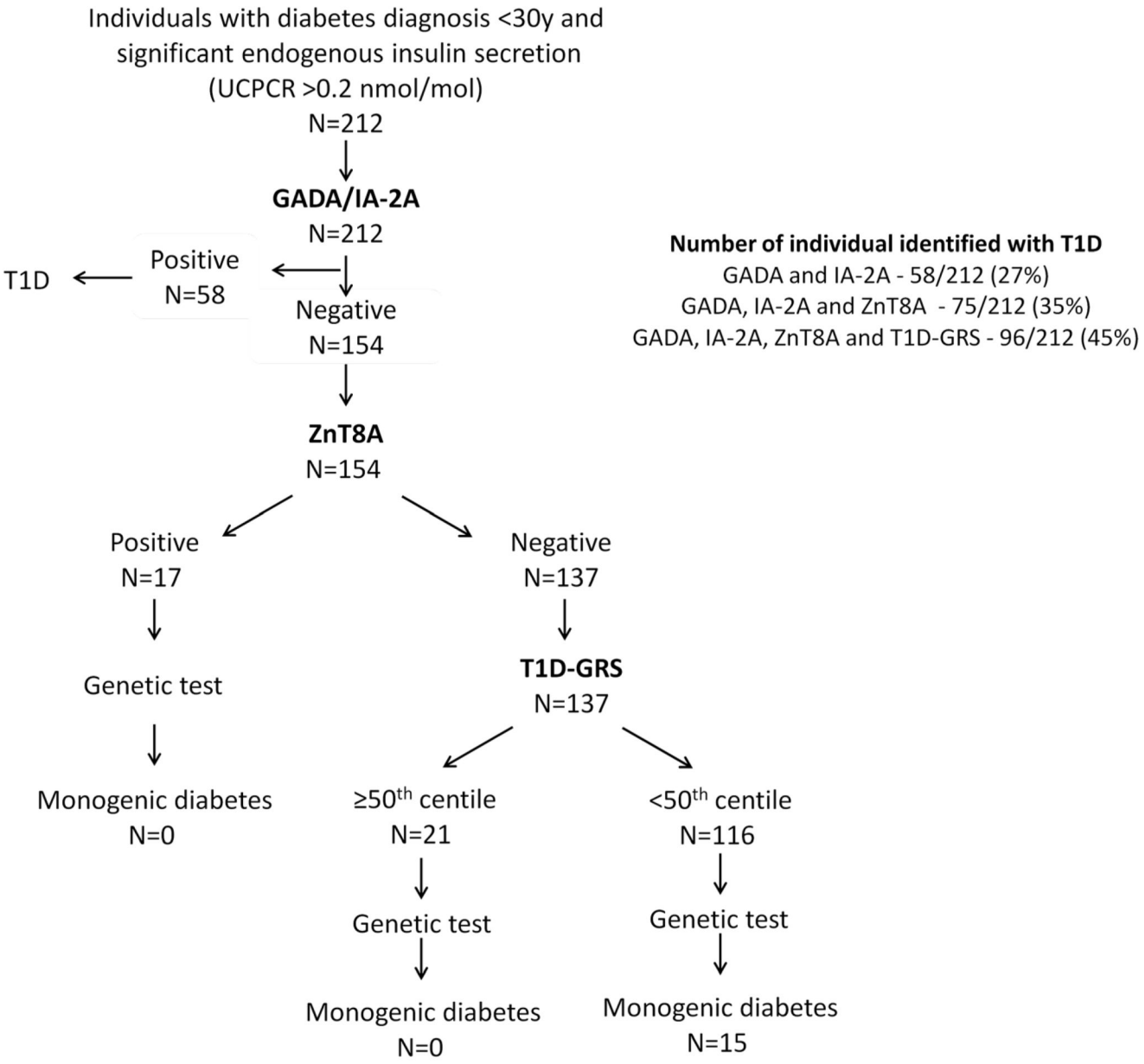

Figure 1.

Benefit of ZnT8A and T1D-GRS in addition to GADA/IA-2A for excluding individuals with T1D from genetic test for monogenic diabetes who have significant endogenous secretion in the UNITED study.