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LETTER

Utility of islet autoantibodies as enrichment biomarkers in type 1 diabetes clinical studies: a viewpoint from the FDA

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Abbreviations

AA Autoantibodies
FDA Food and Drug Administration
T1DC Type 1 Diabetes Consortium

To the Editor: The Center for Drug Evaluation and Research at the US Food and Drug Administration (FDA) recognises both the need for drugs and biologics that can delay or prevent the progression of type 1 diabetes in at-risk individuals and the challenges faced by those developing such products. We believe that strategies to increase trial efficiency are warranted.

Clinical trials designed to demonstrate effectiveness at delaying or preventing type 1 diabetes must enrol individuals who are likely to progress to diagnosis during the trial. Karpen et al [1] describe a consortium-based approach taken to optimise patient selection for type 1 diabetes prevention trials to improve feasibility and efficiency. The authors describe risk factors for type 1 diabetes that have been previously identified, including the presence of islet autoantibodies (AAs) and certain genotypes and clinical characteristics [1]. However, to use a risk factor to optimise sample size and study duration, quantitative predictions of timing to type 1 diabetes diagnosis are required. To this end, the Critical Path Institute's Type 1 Diabetes Consortium (T1DC) obtained and curated data from three longitudinal studies in individuals at risk of developing type 1 diabetes, which were used to generate modelling and validation datasets to quantify the rate of disease progression [1].

The covariates evaluated during the model building process included islet AA combinations (all possible combinations of two, three or four islet AAs), study ID, flag for high-risk HLA subtype, first-degree relative with type 1 diabetes, age, sex, BMI, HbA_{1c} and measurements of blood glucose derived from a 2 h OGTT. The final model was a parametric time-to-event model that used raw or transformed covariates as predictors.

We appreciate the important work of Karpen et al [1] to facilitate the practical use of these biomarkers by constructing a canonical model relating these covariates to a quantitative prediction for time to diagnosis of type 1 diabetes. The covariate selection appears reasonable, including known and potential factors that may affect time to progression of type 1 diabetes. Indeed, categorisation of islet AA status and glycaemic status are the basis for the staged approach to the diagnosis of type 1 diabetes with two or more islet AAs defining stage 1 and 2 disease, with abnormal OGTT defining stage 2 disease. This tool is reasonable to predict the relative impact of patient selection strategies (i.e. enrichment) on the incidence of clinical type 1 diabetes.

We note some limitations to the final model. First, the time a patient spent between detection of two or more AAs and collection of all baseline characteristics (including information from OGTT and HbA_{1c} tests) was ignored by this model. The authors refer to this approach as a 'derived baseline'. In addition, an individual was omitted from the model if all baseline characteristics were not available. As a result, more than half of subjects with two or more AAs were excluded from the analysis due to missingness of a baseline characteristic, and an unreported amount of subject-time was ignored between detection of two or more AAs and meeting derived baseline criteria for included subjects [2]. This approach may limit generalisability of the model, as it is specific to patients who had two or more AAs detected and elected to have an OGTT and HbA_{1c} tested before a type 1 diabetes diagnosis. Furthermore, as voluntary OGTT/HbA_{1c} testing may be

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related to the outcome of interest (e.g. type 1 diabetes diagnosis), and given that subject-time prior to the derived baseline was not accounted for, it is unclear whether the model underestimates time to diagnosis. This underestimation could lead to design of underpowered studies. Modelling approaches that consider all patients and patient-time following emergence of two or more AAs would likely better help inform clinical trial scenarios with broader recruitment (e.g. screening individuals with two or more AAs recently detected, or irrespective of other clinical features) and confidence of the model-based biomarker.

The practical use of the model to predict for populations rather than individuals requires sampling many individuals from a representative population, calculating a prediction for each individual and aggregating such predictions. Understanding the distribution of model covariates in the target population, as well as their relatedness (i.e. correlation) is required for this exercise. Karpen et al [1] discuss the development of a clinical trials simulation (CTS) tool for in silico optimisation of patient selection for type 1 diabetes prevention studies that would allow for drug developers to practically use the model for trial design. We encourage the T1DC's development of this model in discussion with regulators.

Finally, we believe there are opportunities for this work beyond clinical trial enrichment, such as identification of important covariates to include in an efficacy analysis model. We anticipate that the utilisation of these enrichment biomarkers, along with continuing open dialogue regarding the efficient design of clinical trials intended to prevent or delay type 1 diabetes in at-risk individuals, will aid in the development of disease modifying therapeutics that will benefit patients. We encourage stakeholders to continue to improve and expand these model-based biomarkers.

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