TrialNet Recommendations for Clinicians

Successful results from an NIH funded Type 1 Diabetes TrialNet study, showing for the first time that progression to clinical type 1 diabetes can be delayed in those with high risk for disease (1), have prompted consideration of broader efforts to identify individuals at risk. To date, autoantibody screening to identify individuals at risk has occurred in the context of research studies, including clinical trials for the prevention of clinical disease. In the light of such progress, some have suggested antibody screening outside of a research study. The intent of this communication is to provide important information for clinicians regarding antibody screening of relatives of probands with type 1 diabetes or individuals from the general population for risk of disease.

1. The presence of two or more different autoantibodies on two occasions in relatives confers a very high probability of progressing to clinical disease (2). Emerging data suggests a similar risk may be present in individuals with multiple antibodies without relatives.
2. The presence of a single antibody confirmed on two occasions in relatives confers ~20% 5-year risk for development of multiple antibodies.
3. Type 1 diabetes risk is modulated by age, family history and genetics. The prevalence of type 1 diabetes in the general population is approximately 1:300. The risk in individuals with a family member is 1:20; thus, the relative risk for development of type 1 diabetes is 15x greater in family members than the risk in the general population. About 5% of relatives and 0.3% without a relative screened for diabetes associated autoantibodies will test positive for at least one; half of these will have two or more autoantibodies.
4. While the presence of multiple antibodies confers high probability of disease progression, it does not indicate when this will occur. The timing of progression can vary from months to many years with younger age associated with more rapid progression.
5. Screening followed by regular monitoring for disease progression among antibody positive individuals markedly reduces diabetic ketoacidosis (DKA) at clinical presentation from >25% with usual care to <4% with screening and monitoring (3,4). There is no evidence that screening for antibodies alone reduces the incidence of DKA.
6. The majority (95%) of relatives of individuals with type 1 diabetes are autoantibody negative at screening. This can be psychologically reassuring. However, there is an impact in individuals who are autoantibody positive. In the context of research programs whereby individuals have access to experts to discuss results and provide ongoing monitoring at no cost to the individual, the initial psychological impacts wane over time (5).
7. At this time there is no therapy approved for clinical use to prevent or delay type 1 diabetes. Multiple trials are ongoing testing agents for the ability to prevent or delay type 1 diabetes. In North America, these trials are being conducted by the NIH funded Type 1 Diabetes TrialNet clinical trials network.

March 2021

Recommendations for Clinicians in North America

1. When asked about whether or not someone should be screened for type 1 diabetes risk,
    a. Explain that an individual's risk for development of type 1 diabetes is greater for those with a relative with type 1 diabetes compared to those without relatives.
    b. Discuss possible risks and benefits of testing, including the current absence of any approved therapy to prevent the development type 1 diabetes.
2. Remember that free expert information, assurance of privacy, testing for antibodies, and ongoing monitoring or enrollment in trials is available through the NIH funded research network TrialNet.
    a. For relatives: TrialNet provides free, confidential antibody testing and ongoing monitoring for relatives who are antibody positive.
    b. For non-relatives: If testing shows that they have one or more antibodies, the test should be confirmed. TrialNet will provide confirmation of positive antibody tests conducted outside of a research study. Antibody positive individuals interested in clinical trials can be referred to TrialNet for a confirmation test whether or not they have a relative with diabetes.
3. When a positive test is confirmed to be positive outside of TrialNet or other research study,
    a. Discuss the results and the implications.
    b. Explain signs and symptoms of diabetes.
    c. Develop a plan for further evaluation of risk and disease progression. Refer to TrialNet for expert advice.
    d. Provide resources for emotional support as appropriate
    e. Discuss the possibility of therapies that may impact progression of disease. Refer to TrialNet for expert advice about available options and risks and benefits of therapies for the individual.

Acknowledgements:

The recommendations were written and edited by TrialNet leadership* (authors provided below). Other NIDDK funded North American Center Directors made suggestions and contributed to the discussion.

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