Integrating Omics into Functional Biomarkers of Type 1 Diabetes

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Biomarkers are critical to the staging and diagnosis of type 1 diabetes (T1D). Functional biomarkers offer insights into T1D immunopathogenesis and are often revealed using "omics" approaches that integrate multiple measures to identify involved pathways and functions. Application of the omics biomarker discovery may enable personalized medicine approaches to circumvent the more recently appreciated heterogeneity of T1D progression and treatment. Use of omics to define functional biomarkers is still in its early years, yet findings to date emphasize the role of cytokine signaling and adaptive immunity in biomarkers of progression and response to therapy. Here, we share examples of the use of omics to define functional biomarkers focusing on two signatures, T-cell exhaustion and T-cell help, which have been associated with outcomes in both the natural history and treatment contexts.

We live in an era defined by the intersection of three powerful trends in medicine. One trend is the evolution of personalized medicine, which seeks to match the right drugs to the right patients at the right doses and times. Personalized medicine has been most successful where a therapeutic agent is clearly linked to the genetic basis or cause of the disease. So far, personalized medicine has been less successful with genetically complex diseases like type 1 diabetes (T1D), which is caused by the autoimmune destruction of pancreatic β cells. Another powerful trend in the current era is the explosive growth of the identification and use of biomarkers for a host of different purposes during the disease process, including risk of disease, diagnosis, prognosis and course, as well as prediction, safety, and response of therapeutic intervention. Yet a third trend is the development over the past two decades of multiple "omics" technologies, which make simultaneous parallel measurements on tens of thousands of individual analytes (e.g., proteins, DNA, RNA, metabolites, etc.). These measurements are then analyzed using powerful statistical techniques to provide unbiased insights into disease mechanisms, drug targets, and biomarkers. While progress in these three trends has perhaps been less rapid than initially hoped, they have established themselves in the mainstream and there remains a great deal of excitement about their potential (Quezada et al. 2017; Chen et al. 2023; Lim et al. 2024).

In this review, we highlight recent developments that illustrate the value and future

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prospects of omics technologies for discovering and applying functional immune biomarkers in T1D to better understand disease mechanisms and guide precision medicine. As examples, we focus on exhausted CD8 T cells induced by T-cell reduction therapies and alterations in helper T cells induced by T-cell costimulation blockade.

BIOMARKERS IN T1D

A biomarker is defined by the U.S. Food and Drug Administration (FDA) as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions" (FDA-NIH Biomarker Working Group 2016). Biomarker measurements may be functional or physiological, biochemical, or molecular in nature (IPCS INCHEM 1993). There are multiple types of biomarkers, including those to assess disease susceptibility or risk, diagnosis, prognosis and course, prediction, and the safety and response of therapeutic intervention (Table 1). Several recent reviews have covered biomarkers for disease susceptibility, diagnosis, prognosis, and course of T1D (Brenu et al. 2023; Fyvie and Gillespie 2023; Sarkar et al. 2023), so we will focus here on emerging biomarkers of prediction and response to therapy aided by omics technologies.

A pharmacodynamic (PD) biomarker that "indicates biologic activity of a medical product or environmental agent" (FDA-NIH Biomarker Working Group 2016) is one type of measure indicating response to therapy. During drug development, PD biomarkers are used to measure drug activity for dose selection or to ensure that a drug is acting as predicted. The relevance of PD biomarkers for T1D therapy is indicated by analysis of samples from multiple clinical studies in T1D including studies with rituximab (Linsley et al. 2018a), abatacept (Linsley et al. 2019b), and teplizumab (Linsley et al. 2021b). Overall, these analyses showed evidence for nonuniform PD activity, with better response to therapy occurring in subjects with higher PD activity as discussed below.

Individual variation in drug response can be partly exploited in the context of drug development (Polasek et al. 2018). However, the clinical study of many different doses in many different patients is impractical and expensive, so drug developers generally use a more practical one-dose-fits-all model. In addition, regulatory agencies usually require safe and effective doses for a population, not the best dose for each individual patient. Moreover, since clinical trials usually have tight inclusion criteria and focus on relatively homogenous populations, increased inter-individual variation in optimal dosing is to be expected when trial results are extrapolated to larger populations after approval.

Another factor affecting the linkage between drug PD activity and therapeutic benefit in T1D is the common practice of treating younger patients using dosing primarily determined in adults. Typically, drugs, including biologics such as monoclonal antibodies and fusion proteins (Liu et al. 2019), are approved with more extensive dosing information available for adults than children. Approved doses are oftentimes "weight tiered," and it may be unclear how best to extrapolate doses determined in adults to children. Thus, while desirable, the concept of "precision dosing" (Polasek et al. 2018) is difficult to

Table 1. Examples of biomarkers in type 1 diabetes (T1D)

Biomarker type	Example	Stage of development
Susceptibility or risk	AAb number	In clinical use
Diagnosis and course	HbA1c, C-peptide	In clinical use
Susceptibility or risk	PRS	Development and validation
Prediction	Insufficient data	Discovery
Safety and response to therapy	Insufficient data	Discovery

(PRS) polygenic risk score, (AAb) autoantibody.

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achieve in practice, especially in a disease such as T1D, which affects children.

One way to achieve more optimal dosing is to use treat-to-target (T2T) strategies (Garber 2014). T2T is a medical strategy that sets a goal of altering target disease activity values to reach targeted values for each individual patient. Activity values may be derived from measurements made with biomarkers, laboratory tests, or clinical examination. If target values are not reached, types or doses of medications may be adjusted according to a predefined protocol. The process may be iterated until the target values are achieved. T2T strategies have been explored in investigations of medications and dosing in T1D (Mathieu et al. 2016; Russell-Jones et al. 2023), T2D (Mathieu et al. 2023; Philis-Tsimikas et al. 2023), and other autoimmune disease (van Vollenhoven 2019; Garcia et al. 2022; Parra Sánchez et al. 2022). While T2T strategies typically use disease biomarkers, a potentially powerful approach for the future would be to incorporate PD biomarkers that are functional in nature and capable of measuring drug responses across time and age (Kearns and Artman 2015) that may inform when to initiate treatment, repeat dosing, or change therapies.

APPLICATION OF OMICS IN T1D

Since the sequencing of the human genome, developments in several technologies have facilitated the simultaneous and parallel measurement of biological molecules at genome-wide scales (National Research Council (US) Committee on a Framework for Developing a New Taxonomy of Disease 2011; Dzau et al. 2017). The vast amounts of data obtained using these technologies have enabled unbiased examination of biological processes at a previously unobtainable scale and have provided numerous candidate biomarkers. Collectively, the scientific technologies associated with measuring such biological molecules in a high-throughput way are termed "omics" (National Guideline Centre (UK) 2018). The technologies used in these studies include "proteomics, transcriptomics, genomics, metabolomics, lipidomics, and epigenomics, which correspond to global analyses of proteins, RNA, genes, metabolites, lipids, and methylated DNA or modified histone proteins in chromosomes, respectively" (National Guideline Centre (UK) 2018). In oncology, the use of omics for biomarker discovery has advanced to such a degree that there now are multiple commercially available transcriptomic-based tests for prognosis, prediction of metastasis probability, and treatment recommendations for several cancer types (Tsakiroglou et al. 2023). While there also has been considerable effort with omics-based studies in T1D (Fig. 1), in contrast to cancer, none of these studies have yet progressed to the extent of generating commercial products in widespread use.

Some T1D studies have used genomics data to reveal risk and prognostic biomarkers, useful as measures of susceptibility but not rate of progression. The decreased costs of generating genomics data and the increased availability of genetic data have facilitated the development of polygenic scores that aggregate risk variants from multiple loci into a single genetic or polygenic risk score (GRS or PRS, respectively). The current status of GRS studies was recently reviewed (Luckett et al. 2023). GRSs are being tested in several studies of disease risk in the general population (Sims et al. 2022). A factor limiting the use of GRS is that most early studies of T1D genetics have been conducted in European ancestry populations (Luckett et al. 2023). European-based GRSs are a powerful tool that will be improved upon with future large case-control studies from non-European populations, which will increase the accuracy of GRSs across diverse ancestries (Luckett et al. 2023).

There is a long history of transcriptomic studies in T1D, with studies dating back decades, largely focusing on the ability to predict or determine risk for T1D (Maas et al. 2002; Liu et al. 2006). Most transcriptomic studies in humans have focused on peripheral blood, which has the advantage of being easily accessed but the disadvantage of being collected distal to the primary site of disease (the pancreas). The majority of early transcriptomic studies with peripheral blood were investigator-driven and involved small cohorts and have not led to consensus diagnostic T1D signatures. However, there are several more recent studies involving larger and

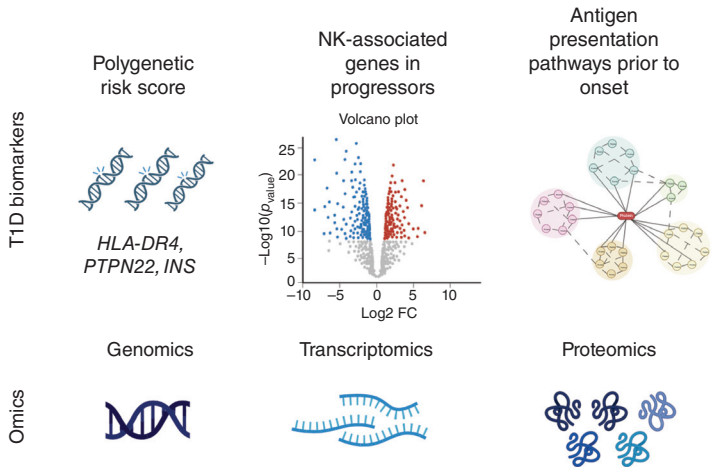

Figure 1. Examples of omics integration into functional biomarkers in type 1 diabetes (T1D). Omics technologies have been used to define functional biomarkers in many genetic diseases. Application to complex diseases like T1D is in its early stages, with some examples shown.

more highly powered cohorts that may overcome some of the limitations of earlier studies that focus on predicting disease progression and onset even when limited to peripheral blood samples. Measurement of β-cell death using cell-free DNA (cfDNA) in sera is a new and evolving field. Elevations of cfDNA levels can be measured in the periphery in the transplant setting (Ventura-Aguiar et al. 2022; Foda et al. 2023). Another approach being investigated is to measure changes in methylation patterns (methylone) (Spector et al. 2023). Methylation changes in cfDNA in T1D have been reported (Voss et al. 2021; Abdel-Karim et al. 2024; Drawshy et al. 2024), but these have not yet been robustly distinguished from chronic inflammation. Yet another evolving omics field in T1D is the microbiome. Early studies have suggested a role for the microbiome in T1D, glycemic control, and disease-related complications (van Heck et al. 2022).

The Environmental Determinants of Diabetes in the Young (TEDDY) consortium is a prospective cohort study aimed at determining the genetic and environmental interactions causing T1D (TEDDY Study Group 2008). A recent transcriptomic study with the TEDDY cohort analyzed longitudinal blood transcriptomes of 2013 samples from 400 individuals before the development of both T1D and islet autoimmunity (Xhonneux et al. 2021). These investigators identified age-associated changes in gene expression in healthy infancy and age-independent changes tracking with progression to islet autoimmunity and T1D. A model developed from these data to predict individual risk of T1D onset and the association of a natural killer (NK) cell signature with progression was validated with an independent cohort.

Another approach to transcriptomic studies was demonstrated by a meta-analysis of multiple previously published investigator-generated transcriptomic data sets (Ochsner et al. 2022) with the aim of generating testable hypotheses around signaling pathway dysfunction in T1D. These investigators repurposed and combined 17 data sets from the Gene Expression Omnibus (GEO) database to interrogate gene expression differences between T1D and normoglycemic controls. Genes that were preferentially induced or repressed in T1D immune cells were identified and validated against community benchmarks. They then used these genes to infer and validate signaling node networks regulating the expression of these gene sets. They further developed use cases demonstrating how informed integration of these networks with complementary digital resources can be useful. The entire data matrix was made available for unrestricted access and reuse by the research community.

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Proteomics research presents technological challenges that have led the field, in general, to lag behind transcriptomics research. Despite these limitations, the TEDDY consortium recently described a proteomics study that perhaps came closer to developing usable progression biomarkers than any transcriptomic study to date (Nakayasu et al. 2023). This study used untargeted proteomics of 2252 samples from 184 individuals to identify 376 proteins regulated even before autoimmunity. Additionally, they found that extracellular matrix and antigen presentation proteins were differentially regulated in individuals who progressed to T1D compared with those that remained in autoimmunity. Using targeted proteomics measurements, the investigators identified 167 proteins in 6426 samples from 990 individuals and validated 83 of these biomarkers. Machine learning analysis of these biomarkers accurately predicted whether individuals would remain in autoimmunity or develop T1D 6 months before autoantibody appearance.

BIOLOGY LEARNED FROM OMICS STUDIES IN T1D

Omics data can provide prognostic and response biomarker signatures from which biological function is beginning to be inferred. These biological findings from single omics data can then be verified using more focused and functional techniques. In this manner, some early clues about the immunopathogenesis of T1D have been revealed using omics in an unbiased manner (Fig. 2). For example, a signature enriched for B-cell-specific transcripts is present upon autoantibody conversion indicative of initiation of autoimmunity (Xhonneux et al. 2021). In a reciprocal manner, B-cell signatures have also been associated with kidney transplant tolerance (Newell et al. 2010). Further studies are required to better understand the functional role of B cells in these settings. Concomitant with this T1D B-cell signature are features that are associated with the rate of disease progression. NK and memory CD4 T-cell signatures increased preferentially in HLA DR4 individuals who developed autoantibodies to insulin first and early in life. By comparison, an early TNF-enriched monocyte signature marked HLA DR3 individuals who developed early autoantibodies to GADA first. Single-cell studies measuring a more limited number of features confirmed changes in cytokine signaling, B-cell subsets, and NK function with disease progression (for review, see Long and Buckner 2022) offering evidence for genetics, cytokine-, and cell-specific influence on T1D

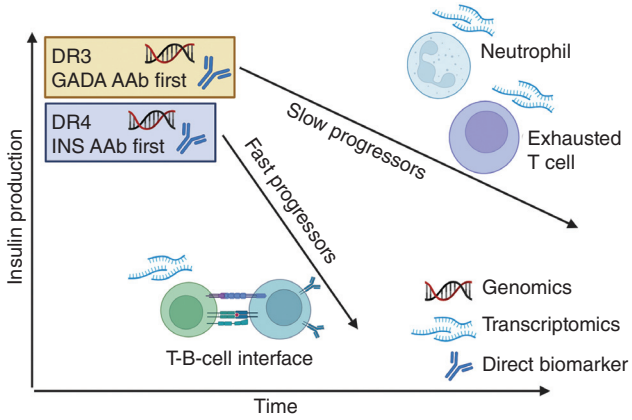

Figure 2. Examples of omics used to predict outcome in type 1 diabetes (T1D). Stable (boxes) and dynamic (arrows) features are associated with slow or fast loss of insulin production over time. Shown are examples of functional biomarkers identified using omics. INS and GADA AAb (autoantibody) first refer to the initial AAb in islet autoimmunity.

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severity. In a related example, higher levels of a neutrophil transcriptomic signature and lower levels of a B-cell transcriptomic signature were associated with slower progression in two complementary studies comparing a large number of placebo subjects from clinical trials (Dufort et al. 2019; Suomi et al. 2023). Together these individual studies demonstrate the potential of omics discovery combined with focused studies, to identify immune biomarkers that predict the rate of disease progression.

Exploratory omics studies of T1D-associated T-cell receptor (TCR) sequences have also underscored the integral role of T cells in T1D pathogenesis. The TCR is comprised most commonly of an α and β chain that both contain regions of high sequence variability (complementarity determining regions or CDRs). Sequence differences within the most variable of these regions (CDR3) can serve as biomarkers for T-cell clonality and have been most commonly studied across TCR β chains (Jacobsen et al. 2017). TCRs may be unique to one individual (private) or shared across multiple individuals, either in the general population or with T1D (public). Since public TCRs are found in a larger segment of the population, they are more suitable for therapeutic targets and biomarker studies. More than 30 public TCRs have been identified to date in the pancreas and peripheral blood of individuals with T1D. Shared TCR β chains from these public TCRs are increased in individuals with earlier disease onset T1D (Mitchell et al. 2022, 2023), offering candidate genomic biomarkers of disease progression with the caveat that these initial studies were performed in genetically similar cohorts.

Beyond these advances with TCR β-chain sequencing, much remains to be determined about TCR biology and its application as a predictive or prognostic biomarker. The specificities of most sequenced public TCRs remain undefined, many of which may also be useful for biomarker studies. The usefulness of TCR α chains is also poorly understood with the exception of recent studies that provide insight into common islet reactivity of shared TCR sequences (Linsley et al. 2021a, 2023). In another study, TCRs reactive to preproinsulin, a precursor of secreted insulin, were found at a higher proportion in T1D as compared to HLA-matched healthy controls (Anderson et al. 2021). Thus, while in its infancy, TCR genomics is beginning to offer clues about the specificity of a finite number of shared T1D-associated TCR sequences and, with additional studies and deeper sampling, has the potential to be used to predict early disease onset and severity.

Omics studies of PD biomarkers in the context of immunotherapy offer clues as to how and why a treatment may work better in one individual than another and the underlying immunopathology, but this variability has also limited the discovery of robust biomarkers common to all T1D individuals. A recent review of treatment PD biomarkers (Linsley et al. 2021b) emphasized the potential use of PD biomarkers in personalized medicine. In general, the signature and timing of PD biomarkers are specific to the treatment. However, when looking across treatments, collectively, PD biomarkers of better response indicate a role for cytokine and cell-type-specific inflammation with adaptive cells playing a prominent role. Yet, a challenge of these studies is that few associations with response have been validated given the requirement to perform additional clinical trials. Two notable exceptions are signatures of T-cell exhaustion and T-cell help that are associated with response in multiple contexts discussed here in detail.

EXHAUSTED CD8 T CELLS AS A FUNCTIONAL BIOMARKER OF BETTER OUTCOME IN T1D

Common features across autoimmune diseases may limit disease progression, consistent with a finite number of mechanisms of immune tolerance. Epigenetic and transcriptional signatures define exhausted CD8 T cells (Tex) (Blank et al. 2019). In a hallmark study across multiple diseases, a gene signature with features of Tex was associated with slower autoimmune disease progression (McKinney et al. 2010, 2015). This finding laid the conceptual foundation for the discovery of signatures of Tex associated with better outcomes in T1D.

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CD8 T-cell exhaustion is a unique lineage that develops in a setting of chronic antigen stimulation such as cancer and chronic viral infection, and more recently appreciated in autoimmunity (McLane et al. 2019). In T1D, a whole blood transcriptomic signature with features of Tex was increased in responders to anti-CD3 therapy (Long et al. 2016). This increase was confirmed in additional trials using the T1D Tex-associated EOMES, TIGIT, and KLRG1 cellular phenotype (Herold et al. 2019; Mathieu et al. 2024). Given that Tex were not originally characterized in T1D, follow-up studies were performed to confirm the tolerance-promoting function of these cells. The CD8 T-cell signature was marked by transcription factors and inhibitory receptors common to Tex. Progressive loss of proinflammatory cytokine production is a feature of Tex and this hyporesponsiveness was augmented following therapy (Sims et al. 2021) and in vitro upon inhibitory receptor ligation (Long et al. 2016). Thus, across multiple studies, transcriptomics facilitated the discovery and functional definition of Tex in the context of anti-CD3 treatment in T1D.

Tex association with better outcome in T1D is not restricted to anti-CD3 therapy. Higher levels of a whole blood and CD8 T-cell transcriptional signature of Tex following treatment with LFA3-Ig, a fusion protein that binds CD2, also associated with better response to therapy (Diggins et al. 2021). As in the anti-CD3 studies, the LFA3-Ig Tex-associated signature was confirmed to mark hyporesponsive cells expressing multiple inhibitory receptors indicative of Tex. Beyond the therapeutic setting, higher frequencies of CD8 Tex were associated with slower progression (McKinney et al. 2010, 2015; Wiedeman et al. 2020) and autoreactive T cells have been shown to be restrained by increased exhaustion-associated inhibitory receptors (Wiedeman et al. 2020; Grebinoski et al. 2022). While not as well understood, CD4 T cells expressing multiple inhibitory receptors are also increased with T-cell therapy (Rigby et al. 2015; Jacobsen et al. 2023), although their function has not been well defined. Taken together, these omics and functional studies suggest that higher levels of T1D-associated Tex are linked to better response to T-cell reduction therapies in T1D.

FOLLICULAR HELPER T CELLS AS A FUNCTIONAL BIOMARKER OF WORSE OUTCOME IN T1D

Follicular helper T (TfH) cells are a specialized subset of CD4 T cells that are essential for providing help to B cells (Song and Craft 2024). A peripheral blood counterpart of TfH, termed circulating TfH (cTfH), are found in the peripheral blood and share many features of TfH making them a tractable biomarker in T1D. cTfH, defined by a transcriptional signature and cytometry, were increased in at-risk and T1D subjects as compared to healthy controls (Shao et al. 2020), and higher levels of activated cTfH associated with faster disease progression (Habib et al. 2019; Long and Buckner 2022). The primary role of TfH is to interact with B cells and aberrations in B cells are also associated with faster disease progression (Smith et al. 2020). Thus, the TfH B-cell axis may be critical in driving more severe disease. CTLA4Ig treatment blocks the TfH B cells interaction, and TpH levels at the time of treatment were found to predict beneficial response to therapy in recent-onset T1D individuals (Edner et al. 2020). In contrast, the expansion of B cells following therapy marks poor response to CTLA4Ig (Linsley et al. 2019b). This is consistent with TfH being increased early in the disease and associated with more severe autoimmunity in general (Walker 2022). Thus, TfH cells have a unique signature that associates with worse outcome in T1D and autoimmunity more broadly.

CD8 Tex and TfH have opposing associations with outcome in T1D, yet they share several features (Fig. 3). Both Tex and TfH development are multistage processes (Walker 2022). These processes lead to appreciable heterogeneity with the potential for multiple factors to influence Tex and TfH-cell subsets over the course of T1D. Beyond T1D, both cell subsets have been associated with outcome in cancer. However, in contrast to autoimmunity, TfH are beneficial in cancer (Cui et al. 2023) while increased Tex are associated with worse tumor clearance (McLane et al. 2019). This dichotomy in Tex and Tfh function in T1D is also exemplified with cancer therapy. Many cancers can be successfully treated with

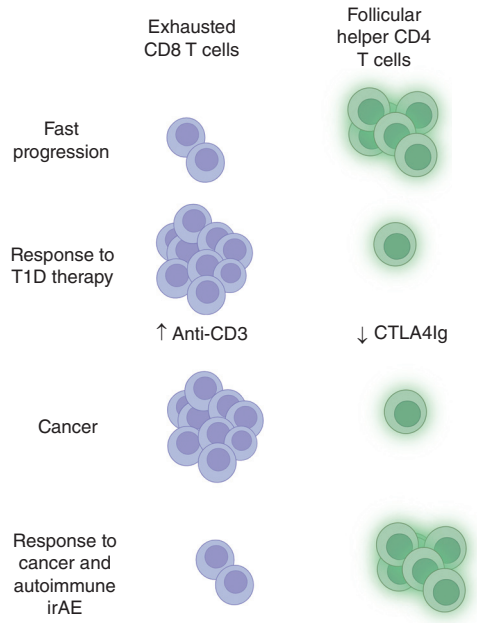

Figure 3. Multipronged identification of T-cell subsets associated with dichotomous type 1 diabetes (T1D) outcome. Reciprocal levels of exhausted T cells and follicular helper T cells, discovered using transcriptomics and cytometry, are associated with outcome in T1D natural progression, response to therapy, and immune response adverse event (irAE) in cancer therapy.

inhibitory checkpoint blockade (ICB) thought to deplete or antagonize Tex. However, autoimmunity may occur as an immune-related adverse event (irAE) of ICB treatment, sometimes including T1D (Dougan and Pietropaolo 2020) and TfH (Lechner et al. 2023). Thus, multipronged evidence supports the interpretation that CD8 Tex and CD4 TfH are associated with outcome in T1D, cancer, and irAEs, but in a reciprocal manner. With additional validation, changes in the abundance of these cell types may serve as biomarkers of disease progression and response.

CONCLUDING REMARKS

Direct autoantibody and serum biomarkers linked to insulin production are the foundation of disease staging of T1D (Insel et al. 2015). This staging ultimately led to the first FDA-approved therapy for the prevention of T1D (Hirsch 2023). Functional biomarkers differ from direct biomarkers in that they provide insight into the immunopathology of T1D. Translation of functional biomarkers is in its infancy, but it holds promise to determine who will progress more quickly and who will respond to what treatment. Functional biomarkers identified to date in T1D have primarily been transcriptional. However, new single-cell technologies using a range of omics and improved computational analyses are already beginning to expand the number and type of functional biomarkers in T1D including new multimodal approaches. These approaches will be further advanced with the integration of current and future large data sets and the use of artificial intelligence (AI)-driven analyses. Given the speed of advances in omics techniques and analyses and increased collaborative efforts in the field of T1D, the hope is that omics will enable personalized medicine for complex diseases like T1D in the near future.

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