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LETTER TO THE EDITOR

Letter to the editor regarding 'perspective: diagnostic laboratories should urgently develop T cell assays for SARS-CoV-2 infection'

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In 'Perspective: Diagnostic laboratories should urgently develop T-cell assays for SARS-CoV-2 infection,' Ameratunga and colleagues present the case for urgent development of T-cell assays for diagnosis of past severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1]. We agree with the authors' assessment that there is a need for rigorously validated T-cell–based assays and that these assays have clinical utility for identifying past SARS-CoV-2 infection, particularly for patients with borderline or undetectable results using RT-PCR or serology tests. T-cell assays may have value for identifying prior SARS-CoV-2 infection in the following groups: convalescent patients with waning antibody titers; individuals with a history of asymptomatic or mild infection who may have a poor or diminished antibody response; patients with unexplained myocarditis, pulmonary fibrosis, thrombotic events, or psychiatric morbidity long after initial infection; individuals who may mount a T-cell response without an antibody response; and patients receiving donor blood products that may contain SARS-CoV-2–specific antibodies [1–6].

Although the authors correctly noted a lack of commercially available assays at the time of submission [1], we would like to report the development and validation of a highly sensitive and standardized T-cell–based assay (T-Detect™ COVID, available from Adaptive Biotechnologies, Seattle, Washington, USA) that received Emergency Use Authorization (EUA) from the US Food and Drug Administration (FDA) on 5 March 2021 for identification of prior SARS-CoV-2 infection from blood samples [7]. T-Detect COVID relies on next-generation sequencing of the T-cell receptor (TCR) repertoire to identify sequences associated with clonal expansion of SARS-CoV-2–specific T-cells [8]. The assay is run on standard whole blood specimens, supporting its utility as a high-throughput diagnostic that can be performed at scale.

Clinical validation studies of T-Detect COVID revealed that the assay exhibits ≥95% positive agreement and ~100% negative agreement in identifying prior exposure/infection with SARS-CoV-2 [8]. Determination of recent or past SARS-CoV-2 infection is based on application of a statistical classifier developed from 4,470 SARS-CoV-2–associated public TCR sequences ascertained by comparing TCR repertoires from more than 1,500 coronavirus disease 2019 (COVID-19)-positive patients and 3,500 controls [8,9]. The classifier considers both clonal breadth, a reflection of the number of distinct T-cell clonal lineages in a repertoire that are SARS-CoV-2 specific, and clonal depth, defined as the relative frequency of SARS-CoV-2–specific T-cell clones in the repertoire [9]. The classifier is robust to confounders (e.g., age, sex) and demonstrated a lack of cross-reactivity with other viruses and respiratory pathogens [8]. Analysis of clinical samples in real-world studies revealed that the depth and breadth of SARS-CoV-2–specific T-cell responses correlate with neutralizing antibody (nAb) titers, supporting a role for TCR repertoire sequencing as a surrogate for SARS-CoV-2 protective immunity. Further correlational analyses demonstrate that class II-associated TCRs targeting the spike and nucleocapsid viral proteins are the primary drivers of the association with nAb titers, highlighting the importance of CD4 + T-cell responses in the development of functional humoral immunity [10]. These findings also suggest that the results of TCR repertoire sequencing reflect both humoral and T-cell compartments and can provide a potential means to distinguish between patients who have contracted COVID-19 and those with protective immunity due to vaccines that selectively target the spike protein.

Despite its utility for identifying past SARS-CoV-2 infection and exposure, potential limitations of NGS-based T-cell testing may include lack of universal access, delivery of dichotomous (positive/negative) results, and provision of limited information on mechanistic aspects of the T-cell response to SARS-CoV-2. Due to the sophisticated equipment required for high-throughput NGS, access to NGS-based T-cell testing may be limited to commercial laboratories and expert academic centers. Currently, T-Detect COVID is the only available NGS-based T-cell assay for evaluating past SARS-CoV-2 infection and is offered only in the United States. Similar to the ELISpot and interferon-γ release assays described by Ameratunga and colleagues [1], the

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T-Detect COVID assay is designed to provide a binary response indicating evidence of prior SARS-CoV-2 infection. However, unlike functional T-cell assays, supporting quantitative results are not provided with the T-Detect COVID report, and in the absence of this additional information (e.g. a score) a negative result provides no additional interpretation and may be less informative for research purposes. While TCR repertoire sequencing can provide evidence of a proliferative T-cell response specific to SARS-CoV-2 antigens, this approach alone cannot provide other mechanistic insights into T-cell function, such as cytokine profiles and enumeration of specific T-cell subsets. However, data from nondiagnostic, research-based applications of the TCRβ repertoire profiling platform, in combination with other data sources, have enabled additional insights into the T-cell response to specific antigens, such as identification of specific TCR/antigen pairings and assignment of class I/II HLA restriction [11]. These data are available for a subset of TCR sequences through Adaptive's research-focused NGS platform, immunoSEQ T-MAP COVID (https://www.immunoseq.com/tmap-covid/), which allows researchers to access sequence, patient, and population-level data found in the freely available ImmuneCODE™ database (https://immunerace.adaptivebiotech.com/data/).

Despite these limitations, evaluation of clinical samples using TCR repertoire sequencing supports the clinical utility of T-cell–based assays in many of the settings outlined by Ameratunga and colleagues. TCR sequencing was shown to have equivalent or greater sensitivity for detecting past SARS-CoV-2 infection compared with commercial antibody serology testing [8,10,12], which was most apparent among patients with milder symptoms and those with samples collected >150 days after diagnosis [10]. TCR repertoire sequencing successfully diagnosed prior infection in 68% of SARS-CoV-2–positive samples testing negative for nAb titers and in 37% of SARS-CoV-2–positive samples categorized as negative by nAb as well as 2 different serological assays; most of these samples were from non-hospitalized individuals [10]. In addition, the depth and breadth of the T-cell response were associated with clinical correlates of more severe disease, including older age, male sex, hospitalization, difficulty breathing, and fever [10,12]. These data are consistent with reports showing elevated T-cell responses in symptomatic individuals that can persist months after SARS-CoV-2 infection [13]. Also, the data align with the proposed clinical value of T-cell testing in patients who may have reduced antibody levels, such as convalescent patients long after infection and individuals with asymptomatic or mild infections [1,10], as well as those who experience long-term complications or inflammatory sequelae, such as multisystem inflammatory syndrome in children (MIS-C) and in adults (MIS-A) [5,14,15]. These observations, as well as other rapidly accumulating data, support the role of T-cell repertoire testing in providing critical insights on the SARS-CoV-2 immune response, which is relevant for evaluating natural as well as vaccine-induced immunity.

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Declaration of Interests

S Dalai discloses employment and equity interest in Adaptive Biotechnologies. L Baldo discloses leadership, employment, and equity interest in Adaptive Biotechnologies. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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