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
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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Papers of special note have been highlighted as either of interest (•) or of considerable interest (+++) to readers.

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