


ORIGINAL ARTICLE

Assessment of humoral and cellular immune responses to SARS CoV-2 vaccination (BNT162b2) in immunocompromised renal allograft recipients

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Abstract

Background: Assessing the composition of immune responses to SARS-CoV-2 vaccines is critical for our understanding of protective immunity, especially for immune compromised patients. The Pfizer (BNT162b2) vaccination showed >90% efficacy in protecting individuals from infection. However, these studies did not examine responses in immunocompromised kidney transplant patients (KT). Subsequent reports in KT have shown severe deficiencies in Spike-specific immunoglobulin G (IgG) responses prompting booster vaccinations, but a broader understanding of T-cell immunity to vaccinating is lacking.

Methods: We examined SARS-CoV-2 Spike IgG and CD4+/CD8+ Spike-specific T-cell responses in 61 KT patients maintained on different immunosuppressive protocols (ISP) (Tac + mycophenolate mofetil + prednisone) versus (belatacept + MMF + prednisone) and compared to 41 healthy controls. We also examined cytomegalovirus-cytotoxic T-cell responses (CMV-Tc) in both groups to assess T-cell memory.

Results: Our data confirmed poor Spike IgG responses in vaccinated KT patients with both ISP (21% demonstrating Spike IgG 1M post-second dose of BNT162b2 vs. 93% in controls). However, 35% of Spike IgG (-) patients demonstrated CD4+ and/or CD8+ T-cell responses. All but one CMV-IgG+ patient demonstrated good CMV-Tc responses. No differences in T-cell immunity by ISP were seen.

Conclusion: Immunocompromised KT recipients showed severe defects in humoral and T-cell immune response after vaccination. No differences in immune responses to SARS-CoV-2 Spike peptides were observed in KT patients by ISP post-vaccination. The detection of Spike-specific T-cell immunity in the absence of Spike IgG suggests that vaccination in immunocompromised KT patients may provide partial immunity, although not preventing infection, T-cell immunity may limit its severity.

KEYWORDS

belatacept, kidney transplant, SARS-CoV-2, tacrolimus, vaccine



1 | INTRODUCTION

The SARS-CoV-2 pandemic is a continuing source of morbidity and mortality worldwide. To date, there have been 278 085 905 documented cases and 5 398 444 deaths reported.¹ The human suffering and devastation to our economies brought on by SARS-CoV-2 and variants of concern (VOCs) is persistent. Therapeutic efforts aimed at treating established SARS-CoV-2 infections show limited efficacy, at best. To this end, the last best hope is vaccination to establish a broad based immunity to protect individuals and limit evolution of VOCs likely to express resistance to SARS-CoV-2 vaccines.

The Pfizer BNT162b2 mRNA vaccine demonstrated excellent efficacy for prevention of SARS-CoV-2 infection in clinical trials with >90% efficacy for protection against ancestral SARS-CoV-2 infection.² Importantly, this did not include an assessment of efficacy in immunocompromised individuals, including kidney transplant patients. Sahin et al.³ demonstrated that mRNA vaccines elicit both humoral and T-cell immunity in non-immunocompromised individuals. Recent data also demonstrated that immunocompromised transplant recipients had increased mortality after SARS-CoV-2 infection which makes the efforts for development of effective vaccine strategies more prescient.⁴⁻⁸ This is in concert with recent data generated from multiple investigators demonstrating a major impairment of humoral immune responses in immunocompromised kidney transplant patients that generally show improved responses to a third booster vaccine.⁹⁻¹⁵ Despite these observations, there are still a large number of immunocompromised individuals who fail to demonstrate humoral immune responses to the third booster vaccine. Thus, despite multiple manuscripts evaluating primarily SARS-CoV-2 Spike immunoglobulin G (IgG) responses, there is little correlative information regarding the presence or absence of T-cell responses in immunocompromised patients after vaccination.

In addition, the evolution of humoral and T-cell immune responses to SARS-CoV-2 vaccination in kidney transplant patients is not well understood, including the impact of different immunosuppressive protocols. Here, we report on an assessment of humoral (Spike-specific IgG) and CD4+/CD8+ T-cell responses to SARS-CoV-2 mRNA vaccination (BNT162b2) in immunocompromised kidney transplant patients compared to non-immunocompromised individuals. In addition, we analyzed the impact of immunosuppressive regimens on immune responses to BNT162b2 vaccination assessing patients on tacrolimus + mycophenolate + prednisone (Tac+) versus patients maintained on belatacept + mycophenolate + prednisone (Bela+). We also examined T-cell immune responses to cytomegalovirus (CMV) peptides in immunocompromised individuals as a measure of immunologic memory and compared them to SARS-CoV-2 T-cell responses.

2 | MATERIALS AND METHODS

2.1 | Study participants

All participants signed consent forms prior to study initiation. This study was approved by the institutional review board at Cedars-Sinai

Medical Center (protocol IRB number: 000 42267). The study was conducted in accordance with the ethical guideline based on federal regulations and the common rule.

Kidney transplant recipients who were greater than 1 month post-second dose of the Pfizer BNT162b2 mRNA vaccine had determinations of Spike-receptor binding domain (RBD)-specific IgG levels and analysis of Spike-specific CD4+/CD8+ T-cell immune responses. Responses were compared to healthy individuals (non-immunocompromised) enrolled as controls (Table 1). Fresh whole blood was collected in sodium heparinized tubes for T-cell stimulation assay. Plasma obtained was stored at -80°C for SARS-CoV-2 Spike-RBD-IgG analysis.

2.2 | SARS-CoV-2 Spike-specific T-cell assay

The SARS-CoV-2 Spike-specific T-cell assay was developed in our laboratory and was fully validated.¹⁶ Briefly, whole blood was incubated with 1 µg/ml SARS CoV-2 Spike glycoprotein (JPT Peptide Technologies GmbH, Berlin, Germany) in the presence of brefeldin A and anti-CD28/CD49d (BD Biosciences, San Jose, CA, USA) for 9 h at 37°C. The activated CD4+ (interleukin-2 (IL-2)/tumor necrosis factor alpha (TNF-α))⁺ cells and CD8+ (TNF-α/interferon (IFN)-γ)⁺ were enumerated and defined as CoV-2-specific T cells after deducting the background levels in blood only conditions. Dual cytokines (%) in CD4+ or CD8+ cells ≥0.05% were considered positive. Negative and positive controls included cells not incubated with peptides and those stimulated with phytohemagglutinin (PHA).

2.3 | CMV-specific T-cell assay

CMV-specific T cells were detected by cytokine flow cytometry developed in our laboratory as described earlier.¹⁷ Briefly, whole blood was incubated with 1.75 µg/ml CMV protein pp65 peptides pool together with brefeldin A and anti-CD28/CD49d for 6 h at 37°C. The IFNγ+ cell% in CD8+ cells were enumerated and defined as CMV-specific cytotoxic T cells (CMV-Tc). CMV-Tc ≥0.20% were considered positive.

2.4 | Cytokine flow cytometry analysis

Cultured cells were stained with fluorochrome-conjugated antibodies to CD3+ (FITC), CD4+ (PerCP Cy5.5), CD8+ (V450), CD45+ (V500), and CD56+ (PE-CF594) (BD Biosciences). After erythrocytes were lysed by permeabilization, intracellular cytokines were stained with fluorochrome-conjugated antibodies to IL-2 (APC), IFN-γ (PE), and TNF-α (PE-Cy7) (BD Biosciences).

2.5 | Measurement of SARS-CoV-2 Spike-RBD-specific IgG in plasma

The levels of SARS-CoV-2 Spike IgG were measured by using CoVS1-RBD ELISA kit (Ray Biotech, GA, USA) as per the manufacturer's manual.

TABLE 1 Characteristics of transplant (Tx) patients and healthy controls (HC)

Variable	HC (n = 41)	Tx (n = 61)	p-Value ^a
Age (years), median, IQR	28-75 (52, 18)	26-78 (66, 14)	<.001
Gender (%)			
Male	41 (17/41)	59 (36/61)	.106
Female	58 (24/41)	41 (25/61)	
Month post-transplant		4-317 (median = 27, IQR = 66)	
Prior transplant		12	

Abbreviation: IQR, interquartile range.

^aComparison of Tx versus HC (Fisher's exact test). Bold text indicates statistically significant differences.

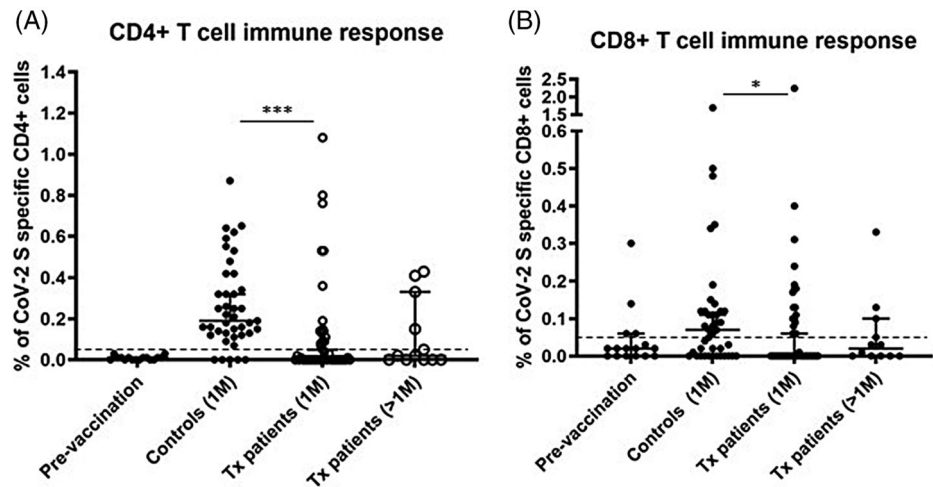


FIGURE 1 Deficient CoV-2 T cells in vaccinated renal transplant patients. Fresh whole blood was stimulated with SARS-CoV-2 Spike peptides overnight. CoV-2-specific CD4+ (A) and CD8+ (B) were enumerated in healthy controls and transplant recipients (Tx) ≥ 1 month post-second dose of BNT162b2 vaccine. The dotted line represents the cutoff level (0.05%) for positive CoV-2 T cells. * $p < .05$, *** $p < .001$

Briefly, the 96-well plates coated with the SARS-CoV-2 S1 RBD protein were incubated with plasma followed by biotinylated anti-human IgG. After washing, Horse Radish Peroxidase (HRP)-conjugated streptavidin was added, and Spike-specific IgG was quantitated by Optical Density (OD) 450 nm reading.

2.6 | Statistical analysis

Data were congregated in GraphPad Prism for statistical analysis. Mann-Whitney *U* test and Fisher's exact test were used for analyzing the statistical difference between two groups. *p*-Value less than .05 was considered significant.

3 | RESULTS

3.1 | Evaluation of SARS-CoV-2 Spike-specific T-cell responses

To determine the impact of immunosuppression on vaccine responses, we analyzed Spike-specific T-cell immunity in 16 pre-vaccinated

healthy individuals, 41 vaccinated healthy controls (1 month post-second dose of vaccine), and 61 vaccinated kidney transplant recipients (49 at 1 month and 12 at 2–3 months post-second dose of vaccine). T-cell immune responses to SARS-CoV-2 Spike peptides were not determined prior to vaccination in kidney transplant patients. Data are summarized in Figure 1A,B. Briefly, no healthy controls showed CD4+ T-cell reactivity to Spike proteins prior to vaccination (pre-vaccination). However, there was a significant response to vaccination detected at 1 month post-vaccination. This contrasted with poor SARS-CoV-2 Spike-specific CD4+ T-cell responses seen in transplant recipients 1 month post-second dose of the BNT162b2 vaccination, 88% (36 of 41) positive in healthy controls versus 37% (18 of 49) positive in Tx recipients ($p < .0001$). Repeat analysis performed 2–3 months post-second vaccination demonstrated that ~42% of transplant recipients developed positive CD4+ T-cell responses (five of 12, >1 month). CD8+ Spike-specific T cells were detected in 56% (23 of 41) healthy controls and 37% (18 of 49) kidney transplant recipients 1 month post-second dose of the BNT162b2 vaccination ($p = \text{NS}$) (Figure 1B). CoV-2-specific CD8+ Spike-specific T-cell responses remained low in transplant recipients when analyzed 2–3 months post-vaccination (33%, four of 12). Our data suggest that CD4+/CD8+ T-cell responses to Spike proteins

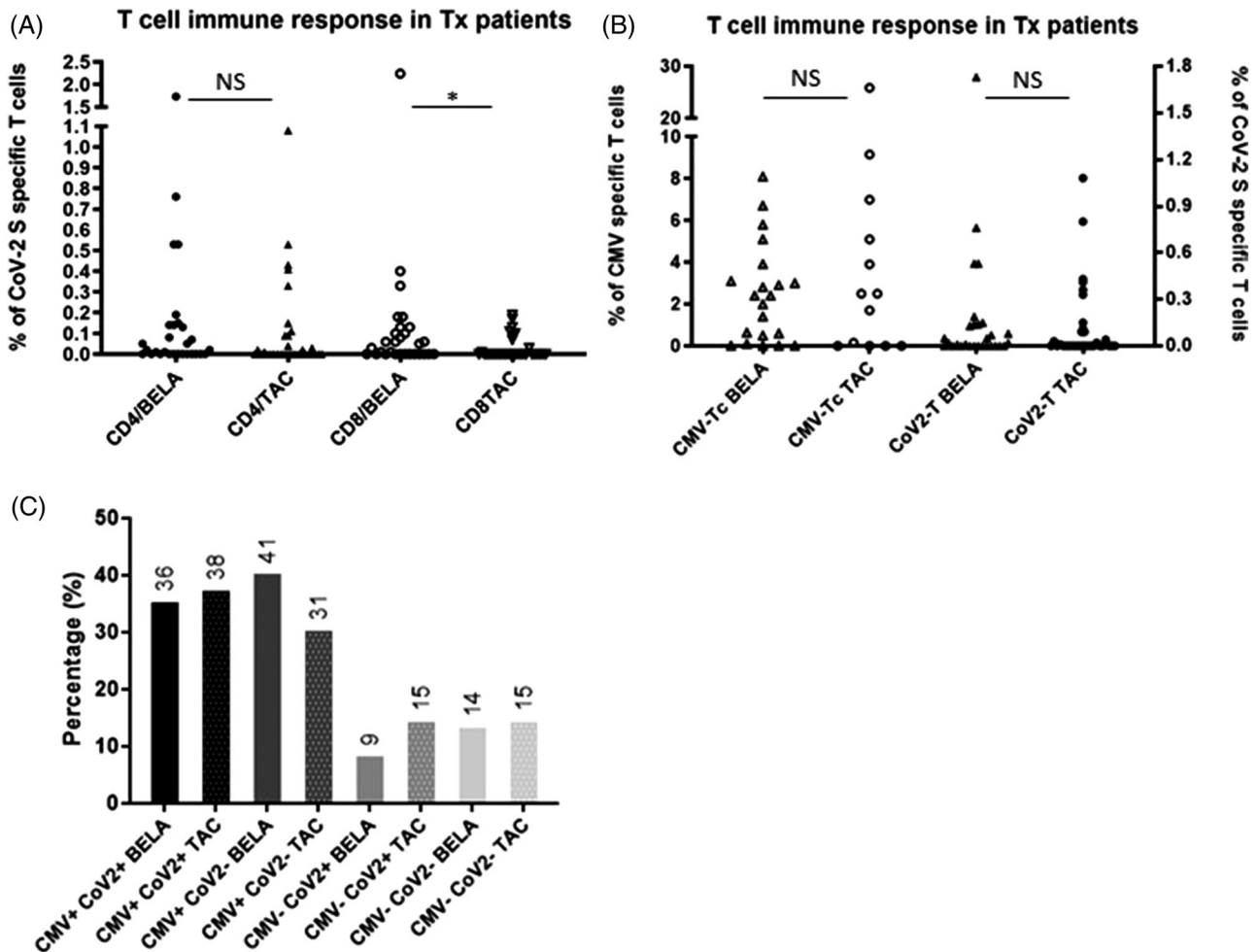


FIGURE 2 Effect of immunosuppression on T-cell responses in vaccinated transplant recipients. (A) Transplant recipients were divided into two groups based on immunosuppression: belatacept + mycophenolate + prednisone (Bela) versus tacrolimus + mycophenolate + prednisone (Tac). CoV-2 Spike-specific CD4⁺ and CD8⁺ T cells were compared 1 month post-second dose of BNT162b2 vaccine. (B) Similar to (A), cytomegalovirus-specific cytotoxic T cells (CMV-Tc) responses were compared between Bela and Tac treated transplant recipients. (C) The percentages of Bela and Tac recipients with CMV-Tc (CMV) and/or SARS-CoV-2-specific T-cell responses (CoV-2T) (CoV2) were analyzed. NS: not significant ($p > .05$), $*p < .05$

in transplant recipients was significantly lower than those seen in non-immunocompromised individuals.

3.2 | Impact of immunosuppressive agents on T-cell immune responses after BNT162b2 vaccination

Kidney transplant patients evaluated in this study were maintained on tacrolimus + MMF + steroids (Tac, 52%, 32 of 61) or belatacept + MMF + steroids (Bela, 48%, 29 of 61). Our analysis of SARS-CoV-2 Spike-specific CD4⁺ T-cell responses in the Tac versus Bela groups, showed no significant differences, but better CD8⁺ T-cell response in Bela group ($p = .022$, power = 0.33) (Figure 2A). These observations suggest that selected patients receiving belatacept can develop de novo immune responses to Spike peptides at the T-cell level. This contrasts with previous reports of poor Spike IgG and T-cell responses to vaccination in patients treated with belatacept therapy.¹⁴ Reasons for this

are not readily apparent except for the possible impact of assay differences used.

3.3 | Analysis of CMV-specific T-cell immune responses in BNT162b2 vaccinated immunocompromised patients

CMV is the most common viral infection in transplant patients and CMV-specific T-cell immune responses could be dampened by immunosuppression post transplantation. To better understand T-cell immunity in immunocompromised kidney transplant recipients, we compared the SARS-CoV-2-specific T-cell responses (CoV-2T) to CMV-Tc (Figure 2B,C). Here, CMV-Tc represents a memory response and all CMV-Tc+ patients were also CMV-IgG+. For the CMV-Tc negative patients ($n = 10$), all but one was CMV-IgG negative. This is consistent with no previous exposure to CMV. However, from



TABLE 3 Humoral and cellular immunity to SARS-CoV-2 in vaccinated transplant patients

Immunity	No. of patients (%)
CD4+/CD8+/IgG+	2 (5%)
CD4+/CD8+/IgG-	3 (8%)
CD4+/CD8-/IgG+	3 (8%)
CD4+/CD8-/IgG-	4 (11%)
CD4-/CD8+/IgG+	1 (3%)
CD4-/CD8+/IgG-	6 (16%)
CD4-/CD8-/IgG+	2 (5%)
CD4-/CD8-/IgG-	17 (45%)

Abbreviation: IgG, immunoglobulin G.

transient in nature and do not reflect the likely presence of memory B cells, T cells, and plasma cells. Assays of T-cell responses (CD4+/CD8+) are emerging and may aid in identifying a more durable immunity aimed at eliminating infected cells (CD8+) and initiating CD4+ T cells which are critical to coordinating adaptive immunity toward the virus and generating long-lasting immunologic memory.²⁰

Recent reports have demonstrated poor IgG and T-cell immunity in patients receiving belatacept-based immunosuppression.^{14,15} However, our analysis of Spike-RBD-IgG and CD4+/CD8+ Spike-specific T-cell responses in renal transplant patients vaccinated with BNT162b2 showed no significant differences in either Spike-RBD-IgG or CD4+/CD8+ T-cell responses. In this regard, we were suspicious of the effect of MMF in both groups.²¹ Our analysis of Spike-RBD-IgG showed only 21% with positive responses in transplant patients. However, analysis of CD4+/CD8+ Spike-specific T cells showed that 35% of patients had a positive T-cell response (CD4+ and/or CD8+). Cucchiari et al.²² reported that 70% of kidney transplant recipients had no IgG/IgM seroconversion after mRNA-1273 SARS-CoV-2 vaccination, in which 50% showed positive T cells against Spike proteins. This indicates that despite the absence of SARS-CoV-2 Spike-RBD-IgG, T-cell immunity is present in one-third of those vaccinated. We have recently reported on divergent immune responses to SARS-CoV-2 vaccines in immunocompromised patients receiving B-cell depletion. Here, we saw no SARS-CoV-2 Spike-RBD-IgG, but were able to detect vigorous CD4+/CD8+ T-cell responses in all patients. Revaccination in two patients resulted in a significant expansion of T cells specific for SARS-CoV-2 Spike peptides, but Spike-RBD-IgG remained negative.²³

Reports of the efficacy of a third BNT162b2 booster vaccine resulted in FDA recommendations for the broad application of booster vaccinations in immunocompromised individuals.^{12,13,15} However, these findings contrast with data from Chavarot et al.¹⁵ who examined Spike IgG responses in transplant patients maintained on belatacept therapy. Here, only 6.4% of patients showed Spike IgG after the third BNT162b2 vaccine. Of importance, 12 patients developed COVID 19 infections with 50% mortality. These authors also identified

poor T-cell immunity to SARS-CoV-2 peptides in belatacept treated patients. There were no confirmed cases of COVID 19 infection in our transplant patients studied here. However, there were two patient deaths from SARS-CoV-2 in vaccinated (x2 BNT162b2) patients in whom we did not have the opportunity to assess Spike IgG or T-cell immunity.

Although our study is limited by low statistical power primarily due to low sample size, we feel the observations are still important. Overall, our study showed that 45% of our kidney transplant patient cohort failed to demonstrate Spike IgG and CD4+/CD8+ T-cell responses. This patient group is likely at high risk for SARS-CoV-2 infection and are unlikely to respond to repeated vaccination, thus should be considered for passive immunotherapy with monoclonal antibodies to SARS-CoV-2 Spike protein.

The essential question here regards the importance and possible protective capacity of CD4+/CD8+ T cells in patients who fail to demonstrate SARS-CoV-2 Spike-RBD-IgG responses. Recent data have elucidated this question in patients who recovered from SARS-CoV-2 infection. Peng et al.²⁴ demonstrated robust CD4+/CD8+ T-cell responses to SARS-CoV-2 after infection which also included a demonstration of diverse T-cell responses that likely extended beyond the persistence of Spike-IgG. Here, understanding the function of both humoral and cellular responses to SARS-CoV-2 and vaccines is critical in defining the composition of an effective immune response. Spike IgG responses are essential for mediation of sterilizing immunity. Here, Spike IgG would bind to and eliminate virus before infection can occur. The critical difference between cellular and humoral immunity is that T cells cannot prevent infection since antigen presentation is required before T-cell activation can occur. With this, SARS-CoV-2 Spike-specific CD4+/CD8+ T cells can be rapidly activated within hours of Spike-RBD exposure, as was shown in our studies, and initiate deployment of SARS-CoV-2 immunity. Since infection is required for T-cell activity, patients would likely have mild to moderate symptoms, but are unlikely to develop severe disease.^{25,26} In this regard, Oberhardt et al.²⁷ recently showed that vaccine-induced CD8+ T cells are the primary mediators of protection after vaccination as they emerged prior to detection of neutralizing antibody and expand after booster vaccination. Thus, detection of CD4+/CD8+ T-cell immunity to SARS-CoV-2 in patients failing to generate Spike-IgG likely infers an important component of protective immunity allowing us to no longer consider these patients “unvaccinated” based on assessment of Spike IgG alone.

Another important aspect of analysis of T-cell immune responses is the ability to detect immune responses to VOCs. We have recently reported on CD4+/CD8+ T-cells reactivity with SARS-CoV-2 (ancestral Spike) and VOCs. Here, equivalent reactivity to alpha and delta Spike peptides was seen. Thus T-cell immunity confers a diverse and broadly reactive immune responses to ancestral and emerging VOCs.¹⁷

In summary, our study demonstrates that vaccination with BNT162b2 vaccination can result in SARS-CoV-2-specific T-cell immunity in immunosuppressive patients who show no SARS-CoV-2 Spike IgG responses. Although T-cell responses alone are not able to

prevent SARS-CoV-2 infection, they would likely emerge rapidly killing infected cells and result in decreased length and severity of illness.

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AUTHOR CONTRIBUTIONS

Ruan Zhang participated in the research design, data analysis, data interpretation, and the writing of the paper. Bong-Ha Shin participated in the research design, assay performance, data analysis, and the writing of the paper. Terry-Ann M. Gadsden participated in the performance of the research. Anna Petrosyan participated in the performance of the research. Ashley Vo participated in the performance of the research. Noriko Ammerman participated in the performance of the research. Supreet Sethi participated in the performance of research. Edmund Huang participated in the performance of the research. Alice Peng participated in the performance of the research. Reiad Najjar participated in the performance of the research. Janet Atienza participated in the performance of the research. Irene Kim participated in the performance of the research. Stanley C. Jordan participated in the research design, data interpretation, and the writing of the paper.

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