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Letter

High-frequency temperature monitoring for early detection of febrile adverse events in patients with cancer

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Fever is an important early sign of serious treatment-related adverse events such as cytokine release syndrome (CRS) caused by chimeric antigen receptor T cell (CAR-T) immunotherapy and such as infection related to chemotherapy-induced neutropenia (Oved, Barrett and Teachey, 2019; Freifeld et al., 2011), both events that are commonly experienced by patients with cancer. The standard approach for detecting fever in hospitalized patients is intermittent temperature monitoring, typically every 4–8 h; this could lead to inherent delays in diagnosis of febrile adverse events.

The availability of non-invasive, wireless, wearable sensors to continuously monitor body temperature raises the possibility of earlier detection and diagnosis of fever and its associated adverse events. Some studies have begun to investigate this possibility (Jordan et al., 2017; Sampson et al., 2019; Liu et al., 2020; Smarr et al., 2020), yet a systematic investigation in patients with cancer performed with FDA-approved devices and compared to standard-of-care (SOC) monitoring is needed. Furthermore, the large volume of high-frequency temperature data that can be obtained from a wearable sensor opens the possibility of carrying out computational analysis to identify signals for anticipating fever before it occurs.

To investigate these possibilities, we conducted a prospective study in 68 patients receiving hematopoietic stem cell transplant (HCT) or CAR-T therapy in the inpatient setting (Figure S1A). After providing institutional review board (IRB)-approved informed consent, patients were asked to wear a self-administered, non-invasive, and FDA-approved wearable sensor (TempTraq®, BlueSpark Technologies), applied as an axillary skin patch according to manufacturer's instructions, to capture high-frequency temperature measurements (HFTM) every 2 min; data were wirelessly transmitted in real time to a cloud-based server (Sampson et al., 2019). HFTM data from 62 patients (n = 39 HCT, n = 23 CAR-T) were available for analysis to compare timing of fever detection with SOC temperature measurements, which are typically taken every 4–8 h by nursing staff as part of routine clinical care. During the monitoring period, we collected a total of 585 days of HFTM data across all 62 participants with a median data capture of 8.5 days per patient. When patients were wearing an HFTM patch, we collected ~90-fold more data points with HFTM (n = 421,367) than with SOC (n = 4,816).

First, we evaluated the timing of SOC- and HFTM-detected fevers and found that HFTM detected 89% (24/27) of these fevers a median 5.5 h (h) earlier than SOC did (Figure S1B). For the three fevers detected earlier by SOC, the median time was 1.9 h earlier. Overall (n = 27 fever events analyzed), HFTM showed a median 4.9 h earlier detection time than SOC showed.

As expected, most fevers detected in patients who had received CAR-T therapy were related to CRS; whereas in patients who had received HCT, infection-related fevers were more common (Figure S1C). Interestingly, we found that fevers caused by infections were detected by HFTM significantly earlier (median = 18.5 h) than by CRS (median = 4.4 h; $p = 0.012$, two-tailed t test); examples are shown in Figures S1D–F.

We further investigated whether we could computationally identify potentially predictive signals that precede fever (i.e., before an HFTM-detected temperature rise to 38°C). We hypothesized that subtle perturbations in temperature dynamics may be discernible prior to fever and may manifest in circadian modeling analysis as deviations from baseline circadian pattern. To test our hypothesis, we fit a circadian profile based on 24 h of preceding data for every data point leading up to independent HFTM fever events that had sufficient data for circadian modeling (Figure S1G). This approach allowed for real-time updating of the circadian profile (magenta curves) with an average temperature measurement (green lines), and amplitude and phase (the time of the minimum of the circadian profile) estimates.

From the circadian fit, we computed circadian residuals (Figure S1H, blue dots), which are defined as the difference between the circadian fit and the data point recorded. To incorporate changes

in average temperature that may have occurred across larger timescales, we also computed a standardized residual of the average temperature (orange dots). Finally, for our subsequent analysis, we computed a total residual, which is defined as the sum of the circadian and average temperature residuals (red dots). We separated the total residuals into two groups based on periods of time: pre-fever day residuals (i.e., residuals from 24 h immediately prior to fever, red shaded region) and a patient-specific baseline (i.e., residuals calculated prior to the pre-fever day, blue shaded region).

We then projected the patient-specific baseline residuals onto the pre-fever day, matching the phase estimates for each data point to the phase of the pre-fever day to account for specific measurement bias at certain times of the circadian cycle. We computed the residual difference (Figure S1I) between the pre-fever day and the patient-specific baseline period and predicted 95% confidence intervals after sampling with replacement 1,000 times. In general, the residuals in the pre-fever day began to deviate positively from those of the patient-specific baseline ~12 h prior to fever. Moreover, this deviation was sustained and statistically significant from ~3.5 h pre-fever up to fever onset, with additional discrete spikes of statistical significance ~5–6 h and 8 h before fever onset; this data collectively demonstrates signals in HFTM data that presaged the occurrence of fever.

Taken together, our results demonstrate the potential of an HFTM approach using wearable sensors to provide considerable lead time (4.9 h earlier than SOC) for early detection of febrile adverse events. This approach has the potential to add 3.5 h or more lead time via circadian modeling. This duration of lead time is clinically significant for patients with cancer, who are commonly immunocompromised and at risk for infection, because time-to-first antibiotics can play an important role in subsequent mortality in neutropenic fevers and sepsis (Mullen et al., 2000; Wingard, Hsu, and Hiemenz, 2011), especially in the setting of septic shock, where mortality increases with every hour of delay in antibiotic administration (Kumar et al., 2006). Our inpatient study provides a foundation for investigation in the outpatient setting. In particular, the impact of early detection of infection may be seen on a larger scale among outpatients with cancer who are receiving chemotherapy and who are at risk for febrile neutropenia. Our data were collected using an FDA-approved wearable sensor suitable for home use, making this technique readily implementable.

Furthermore, the lead time provided by HFTM is also clinically relevant to the monitoring of patients treated with CAR-T. It can enable earlier intervention in CRS through escalation of care, including earlier administration of anti-cytokine therapies (e.g., tocilizumab [an IL-6R antagonist]) (Oved, Barrett and Teachey, 2019), and this may reduce life-threatening morbidity and mortality associated with CRS. This lead time could also facilitate the transition of extremely expensive inpatient CAR-T care to the outpatient setting because the lead time could provide sufficient time for the patient to return to the hospital in a case of impending CRS.

We hope that our results will spur more in-depth investigation of the HFTM approach in patients with cancer, ultimately through prospective clinical trials. Elements to be investigated in future work include: optimizing patient education and support to minimize missing data; developing computational algorithms to probabilistically identify the cause and clinical actionability of a fever from temperature dynamics and additional clinical data; and increasingly individualizing prediction and detection of febrile adverse events by using a patient's own baseline temperature pattern as a reference, rather than a one-size-fits-all 38°C threshold approach.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2021.07.019.

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DECLARATION OF INTERESTS

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