101005177 — COVID-RED

COVID-RED

WP1 – Technology and algorithm development and maintenance

D1.7 Updated data capture and transmission strategies

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Abstract

Early discovery of a SARS-CoV-2 infection can reduce transmission of the virus to other susceptible individuals. In particular, identifying changes in physiological signals via wearable devices can serve as an early key infection indicator. In this study, we collected physiological signals to train machine learning algorithms and then used them to identify potential SARS-CoV-2 infections in the study population. To meet our study aims, it was necessary to create the infrastructure for data extraction and analysis. This document describes the steps and infrastructure for extracting users' physiological signals using the Ava wearable bracelet and complementary mobile application (Ava COVID-RED). We describe the four phases undertaken to analyze and adjust the data generating mechanisms including: set up; data collection, cleaning, filtering, storage and transfer; data analysis; and, reporting.

Introduction

Changes in physiological parameters have alerted individuals and medical professionals to a potential infection for a least a century. As early as 1927, researchers have published on the increase in pulse rate associated with fever and illness. [1] Until recently, doctors have relied on highly specialized medical devices, diagnostic tests and personal knowledge to identify illness associated with biophysical symptoms. Wearable sensor technology has catalyzed individualized medicine, enabling for the first time reliable, nearly continuous monitoring of physiological changes. Patients no longer need to rely on single point episodes of arrhythmias, for example, occurring while in person at the doctor's office for accurate diagnosis and treatment. Instead, wearable devices enable individuals to measure, track and record changes in heart rate and other vital signs over time, while engaging in day-to-day activities. Paired with machine learning alogrthims to detect abnormalities from individual baseline parameters, wearable sensor technology can provide real-time feedback about an ongoing or impending health event (e.g., a atrial fibrillation notification on the Apple Watch [2]).Initial studies have demonstrated high levels of accuracy for detecting a range of maladies including Lyme Disease [3], broken bones [4], depression, seizures, diabetes, and obstructive sleep apnea [3][5][6]. In many cases, the wearable device systems have outperformed the current standard of care and diagnosis by doctors, leading European and American regulatory authorities to approve them for use as medical devices [7].

Concurrent with advances in wearable sensor technology, convergent evidence has demonstrated how certain biophysical markers uniquely change in relationship to natural or pathogenic causes. Only within the last five years has ambulatory data gathered daily enabled researchers to document phase-based changes in temperature, breathing rate, and heart rate variability associated with the menstrual cycle, for example, thereby enabling personalized predictions of impending ovulation [7][8][9]. Similarly, wearable sensors tracking changes in resting heart rate and activity levels have identified outbreaks of influenza prior to participant-reported symptom onset [10][11]. A follow-up study has further shown influenza's unique biophysical signature compared to SARS-CoV-2 infections using wearable sensor data [12].

Identifying SARS-CoV-2's effect on physiological parameters represents a significant scientific step towards returning to a pre-pandemic life. The United States' Center for Disease Control and Prevention (CDC) has estimated that more than half of all SARS-CoV-2 transmissions occur due to asymptomatic or pre- symptomatic individuals [13]. Proof-of-concept and pilot studies have shown that algorithms ingesting wearable sensor data could detect COVID-19 in many participants prior to symptom onset [14][15][16][17]. Todate, these studies have applied their algorithms retrospectively; the researchers trained their models on an initial clinical sample before validating them on a holdout set or a new population only after data collection's completion [15][16][18]. Several published protocols have proposed prospectively testing a machine learning algorithm for detecting SARS-CoV-2 infections [19][20][21][22]. As emphasized in our systematic review [23] previous work highlights the need for real-time feedback tohelp individuals determine if they should self-isolate or seek further diagnostic input

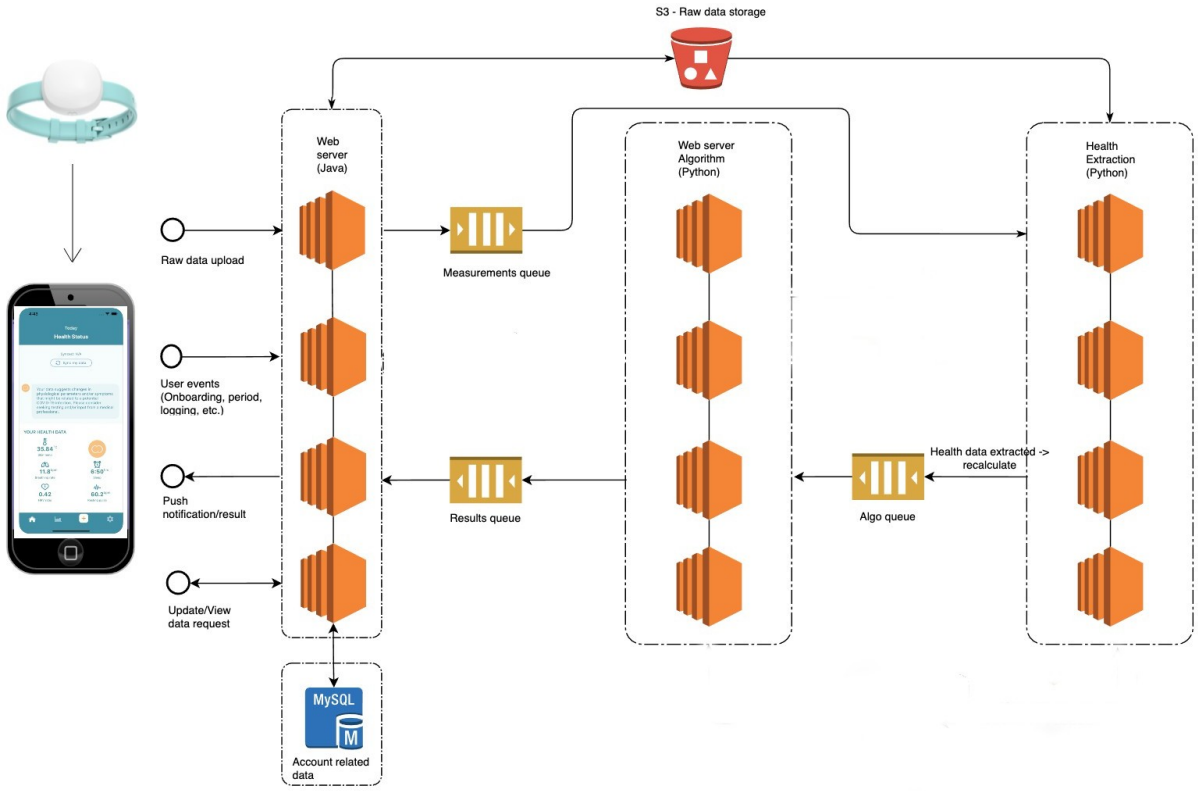
One of the first randomized controlled trials in this space, the “COVID-19 infections – remote early detection” (COVID-RED) study leverages existing wearable sensor technology (the Ava bracelet) and a novel mobile application (Ava COVID-RED) to investigate how a pilot-developed algorithm can accurately detect pre-symptomatic SARS-CoV-2 infection compared to current standard of care. This report outlines the process necessary to update existing wearable sensor data capture and transmission strategies for implementation in COVID-RED. Ensuring the sensor-collected data could be extracted and analyzed in line with the project’s overall objectives required several steps, including: set up; data collection, cleaning, filtering, storage and transfer; data analysis; and, reporting. The following chapters explain each stage in greater detail.

Set up

The system for early COVID-19 detection has three major parts (see Figure 1):

- The wristworn Ava bracelet, used for acquiring physiological signals;
- The Ava COVID-RED mobile application (Android or iOS), used for downloading signal data from thebracelet and syncing it to the backend server;
- The cloud infrastructure, used for storing all physiological signals and generating an algorithm-basedprediction of potential SARS-CoV-2 infection.

Figure 1: System for collection of wearable-measured physiological signals and COVID-19 prediction generation.



The sensor system on the Ava bracelet includes temperature sensors, an accelerometer, and a photoplethysmograph (PPG) sensor (see Figure 2). The temperature sensor measures changes in wrist skin temperature while the accelerometer detects movement and helps determine when the user is asleep. Finally, the PPG sensor detects blood volume variations in the microvascular tissue via a light source that allows photodetectors to detect the reflected light intensity. In addition to wrist skin temperature and sleep data, the Ava bracelet measures breathing rate, heart rate, heart rate variability (HRV), and skin perfusion. The sensors collect data 25 times per second while the user sleeps. Originally designed for fertility tracking, the Ava bracelet has received Food and Drug Administration (FDA) clearance and meets standards for CE-marking as a Class IIA medical device.

The system's second component, its mobile application (app), comprises the user interface, where COVID- RED participants can both input and receive data. In the Daily Diary log (detailed more extensively in Deliverable 1.3), individuals can record COVID-19 symptoms and potential confounds (e.g., antipyretic medication). Additionally, the Ava COVID-RED app interfaces directly with the Ava

bracelet, enabling participants to manually sync the physiological data recorded on the hardware with the backend server. The app also shows algorithm-generated real-time alerts based on device-collected physiological data back to theuser after syncing. In particular, the health status algorithm runs on the third component, the cloud

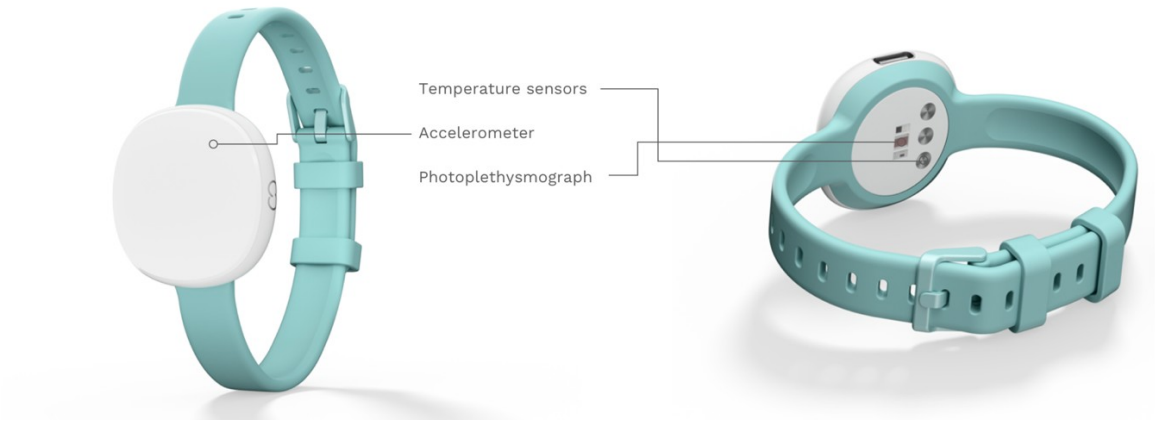


Figure 2: The Ava bracelet and its included sensors.

infrastructure, and then signals to the app to display one of three indicators related to a potential SARS-CoV-2 infection: “No physiological deviations or COVID-19 symptoms detected”; “Some physiological deviations and/or COVID-19 symptoms detected”; or, “Physiological deviations and/or symptoms indicative of a potential COVID-19 infection detected.” For a more detailed description of the algorithm’s development and in-app signal display, please refer to Deliverables 1.4 and 1.3 respectively.

Finally, the cloud-based processes are triggered by user actions such as completing initial onboarding, Daily Diary logging or downloading (syncing) data from the bracelet. All data uploaded by each participant is savedin raw format on an S3 Amazon Web Services (AWS) web server and forwarded for further processing to a proprietary Health Extraction Worker explained further in the chapters below. The wearable device manufacturer abides by General Data Protection Regulation (GDPR) and employs region-specific AWS servers. All participant data is stored anonymously using each person’s COVID-RED assigned clinical ID withpersonally identifiable information (PII) stored separately.

Data collection, cleaning and filtering

The process of collecting physiological parameters from a wristworn device suffers from exposure to environmental artifacts due to normal movements while asleep unrelated to illness-related changes. Thus, thefirst step in data collection involves pre-processing to reduce the risk that these artifacts could jeopardize the signal’s quality. To that end, we strove to make the acquisition process as robust as possible and to exclude potentially inaccurate data points from analysis.

We developed the proprietary Health Extraction Worker with the purpose of cleaning and filtering the raw data collectedby the Ava bracelet. Based on pre-existing knowledge from the Ava Fertility Tracker, we identified scenarios where the data behaves suspiciously and suggests poor quality. In particular, we flagged times when:

- The signal recording was less than 4 hours (defined as the time between the first and last time stamp,without regard to the absolute number of recorded measurements);
- The signal recording included less than 3 hours of sleep (defined as at least 1080 time points);
- A skin temperature reading outside of the 30-42°C range (suggesting a potential error in the temperature sensor);
- An undefined heart rate feature (suggesting a potential error in the PPG sensor); and,

- The Health Extraction Worker process crashed.

The Health Extraction Worker marks a recording as *QUALITY_STOP* if any of the above scenarios occurred.The explicit reason for appearance of *QUALITY_STOP* is not saved in the database, but for debug purposes,it can be reproduced using raw data files stored on an S3 bucket.

There is also a special flag called *QUALITY_ERROR* which occurs when the entire duration of a sleep-event(real time between first and last recording), is missing more than two thirds of the data it should contain. Thistypically occurs due to participant error or a device defect (e.g., the bracelet turns on for a few minutes whilenot being worn).

Before calculating the nightly features for algorithm ingestion, the raw physiological signals are filtered usingmovement data from the accelerometer sensor. The sleep filter identifies only those signals recorded duringsleep and passes them on for data analysis.

Data analysis

After excluding poor quality data, the Health Extraction Worker performs a statistical analysis on the remainingwearable-collected data. It creates feature sets and components by transforming the data into single or multiple values that are representative of a user's physiological state for that night. Depending on the physiological parameter, one or more measurements may be used (e.g., the median versus the mean). Some of the nightly features include:

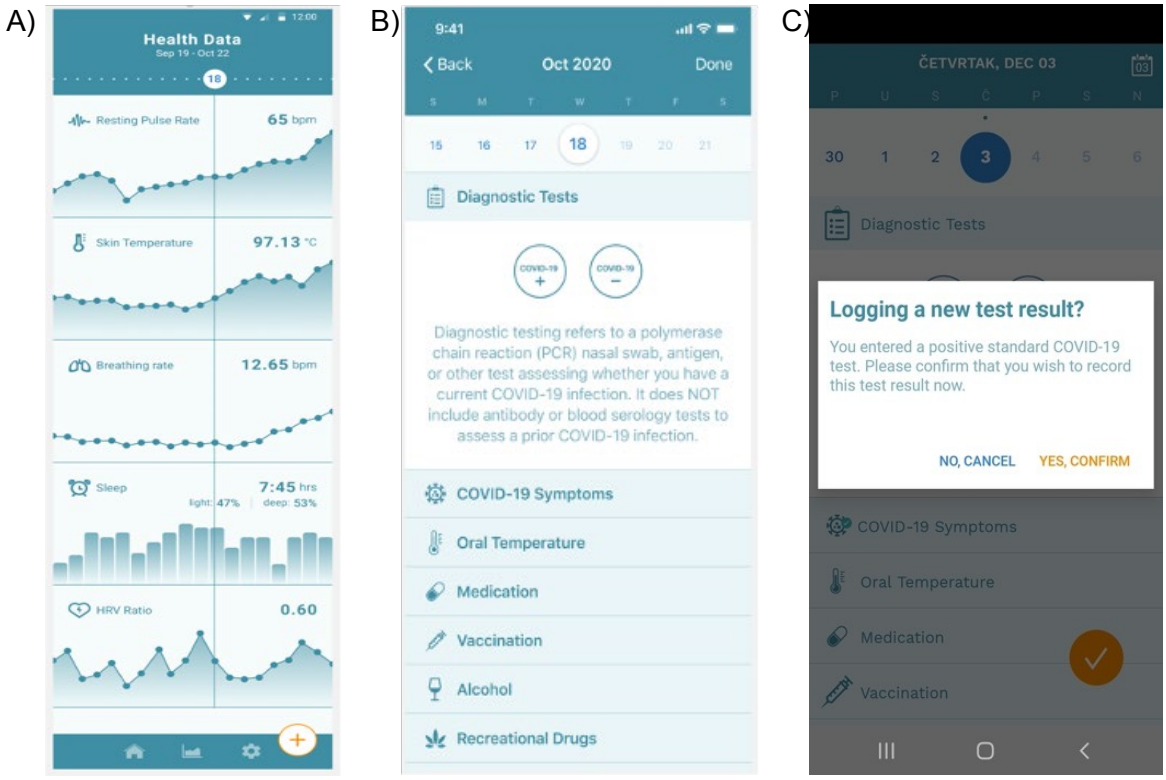
- Skin temperature;
- Breathing rate;
- Heart rate;
- The standard deviation of the N-N interval (SDNN; a measure of HRV);
- Root mean square of successive differences between normal heartbeats (RMSSD; a measure ofHRV);
- HRV Ratio;
- Skin perfusion;
- Last sync date between bracelet and the mobile app;
- Last sync date between the mobile app and the backend server;
- Data quality (*QUALITY_PASS, QUALITY_STOP* or *QUALITY_ERROR*);
- Total sleep (in seconds);
- Percentage of light sleep; and,
- Percentage of deep sleep.

This set of features is generated on a daily basis from signals acquired during sleep and passed to the trainedmachine learning model explained in Deliverable 1.4. A subset of all physiological signals collected by the Avabracelet are then ingested by the algorithm to predict an impending SARS-CoV-2 infection.

Reporting

Through the Ava COVID-RED smartphone application, the COVID-RED participant receives insights about the values of the physiological signals from all nights when the bracelet was worn. Each user can see monthly graphs of their physiological parameters, including resting pulse rate, skin temperature, breathing rate, amount of sleep and HRV ratio (Figure 3a). The participant can toggle each graph on or off based on their personal preference through the Settings menu in the app.

Figure 3: The Ava COVID-RED mobile app is designed to be used in conjunction with the Ava bracelet and provides the user with health charts showing changes in physiological parameters over time (A). COVID-RED participants can also log results from diagnostic tests or COVID-19 symptoms in the Daily Diary (B) which asks them to confirm a positive SARS-CoV-2 test prior to switching to "Confirmed COVID-19" mode (C).



The probability of accurately detecting a SARS-CoV-2 infection increases with additional feedback. To ensure the health status algorithm accounts for expected physiological changes due to alcohol intake or ovulation, COVID-RED participants are asked to record additional information in the Daily Diary survey section of the Ava COVID-RED app. As shown in Figure 3B, an individual can input COVID-19 symptoms, results from a diagnostic COVID-19 test, alcohol and recreational drug use, their oral temperature, medication, and vaccination.

The current machine learning algorithm (v1.0) ingests nightly physiological data and self-reported symptoms to alert participants to a potential SARS-CoV-2 infection in real time. After syncing their bracelet upon waking,the participant may receive one of three messages on their home screen: "No physiological deviations or COVID-19 symptoms detected."; "Some physiological deviations and/or COVID-19 symptoms detected."; or, "Physiological deviations and/or symptoms indicative of a potential COVID-19 infection detected." For more detailed information on the home screen alerts

including screenshots, please see Deliverable 1.3. Over the course of the COVID-RED clinical trial, we will further refine the health status algorithm based on both self-reported and wearable sensor data. Throughout the study, however, participants will have access totheir daily health status and physiological parameters as measured by the Ava bracelet via the Ava COVID-RED mobile app.

Discussion

Recognizing early signs of a SARS-CoV-2 infection can be an essential tool to fight the COVID-19 pandemic by reducing transmission between individuals. A system for early detection of SARS-CoV-2 must fit into a person's every-day life and should not be time consuming or cause additional overhead in order to facilitate its widespread adoption. For that reason, the Ava bracelet, worn only during sleep, and Ava COVID-RED mobileapp constitute an intuitive solution easily adaptable for every person that owns a smartphone.

Repository for primary data

Per Article 29.3 of the COVID-RED Grant Agreement and Article 7.5.4 of the Consortium Agreement, digital research data will be deposited in a research data repository within 30 days of its generation. Special access rights for third parties that need the research data to address the public health emergency will be outlined in the COVID-RED Data Management Plan. However, no special access rights for third parties shall be granted to personal data or data of commercial sensitivity

References

1. Lyon D. M, The Relation of Pulse-rate to Temperature in Febrile Conditions, An International Journal of Medicine, 20(78), 205–218, 1927.
2. Li X, Dunn J, Salins D, Zhou G, Zhou W, Schüssler-Fiorenza Rose S. M. et al, Digital Health: Tracking Physiomes and Activity Using Wearable Biosensors Reveals Useful Health-Related Information, PLoS Biol, 15(1), e2001402, 2017.
3. Dunn J, Runge R, Snyder M, Wearables and the medical revolution, Per Med, 15(5), 429-448, 2018.
4. Choy G, Khalilzadeh O, Michalski M, Do S, Samir A. E, Pianykh O. S, Geis J. R, Pandharipande P. V, Brink J. A, Dreyer K. J, Current Applications and Future Impact of Machine Learning in Radiology, Radiology, 288(2), 318–328, 2018.
5. Ballinger B, Johnson H. et al, DeepHeart: Semi-Supervised Sequence Learning for Cardiovascular Risk Prediction, arXiv:1802.02511v1 [cs.LG], 2018.
6. Wu H, Phenotype-based and Self-learning Inter-individual Sleep Apnea Screening with a Level IV Monitoring System, arXiv:1802.09706v1 [stat.AP], 2018.
7. Goodale B. M, Shilaih M, Falco L, Dammeier F, Hamvas G, Leeners B, Wearable sensors reveal menses-driven changes in physiology and enable prediction of the fertile window: observational study, J Med Internet Res, 21(4), e13404, 2019.
8. Shilaih M, Goodale B. M, Falco L, Kübler F. et al, Modern fertility awareness methods: wrist wearables capture the changes in temperature associated with the menstrual cycle, Biosci Rep, 38(6), BSR20171279, 2018.
9. Shilaih M, Goodale B. M, Falco L, Kübler F, Dammeier F, Leeners B, Capturing the physiological characteristics of early pregnancy using wrist worn wearables, EuropeanSociety of Human Reproduction and Embryology, Barcelona, Spain, 2018.
10. Bradshaw B, Konty K, Ramirez E, Lee W, Signorini A, Foschini L, Influenza surveillance using wearable mobile health devices, Online Journal of Public Health Informatics, 11(1),e249, 2019.
11. Radin J, Wineinger N, Topol E, Steinhubl S, Harnessing wearable device data to improve state-level real-time surveillance of influenza-like illness in the USA: a population-based study, The Lancet Digital Health, 2(2), e85–e93, 2020.
12. Shapiro A, Marinsek N, Clay I, Bradshaw B, Ramirez E, Min J, Trister A, Wang Y, Althoff T, Foschini L, Characterizing COVID-19 and Influenza Illnesses in the Real World via Person-Generated Health Data, Patterns, New York, 2(1), 100188, 2020.

13. Johansson M. A, Quandelacy T. M, Kada S. et al, SARS-CoV-2 Transmission From People Without COVID-19 Symptoms, JAMA Netw open, 4(1), e2035057, 2021.
14. Mishra T, Wang M, Metwally A. A. et al, Pre-symptomatic detection of COVID-19 from smartwatch data, Nat Biomed Eng, 4(12), 1208-1220, 2020.
15. Natarajan A, Su H. W, Heneghan C, Assessment of physiological signs associated with COVID-19 measured using wearable devices, npj Digit Med, 3(1), 2020.
16. Smarr B. L, Aschbacher K, Fisher S. M. et al, Feasibility of continuous fever monitoring using wearable devices, Sci Rep, 10(1), 21640, 2020.
17. Bogu G. K, Snyder M. P, Deep learning-based detection of COVID-19 using wearables data, Published online medRxiv, 01.08.21249474, 2021.
18. Miller D. J, Capodilupo J. V, Lastella M. et al, Analyzing changes in respiratory rate to predict the risk of COVID-19 infection, PLoS One, 15(1), 1-10, 2020.
19. Wong C. K, Ho D. T. Y, Tam A. R. et al, Artificial intelligence mobile health platform for early detection of COVID-19 in quarantine subjects using a wearable biosensor: Protocol for a randomised controlled trial, BMJ Open, 10(7), 1-5, 2020.
20. Xu S, Vital Sensor Monitors for CV19 Detection, Clinical trial https://clinicaltrials.gov/ct2/show/NCT04635787, 2020.
21. Esterl E, Ruybal J, Wearable Diagnostic for Detection of COVID-19 Infection, Clinical trial https://clinicaltrials.gov/ct2/show/NCT04742569, 2021.
22. Koch LM, Jayaraman A, Ryan S, Wearable Sensor to Monitor COVID-19 Like Signs and Symptoms, Clinical trial https://clinicaltrials.gov/ct2/show/NCT04393558, 2020.
23. Mitratza M, Goodale BM, Shagadatova A, Kovacevic V, van de Wijgert J, Brakenhoff TB, Dobson R, et al., The Performance of Wearable Sensors in the Detection of SARS-CoV-2 Infection: A Systematic Review, The Lancet Digital Health, 4(5), e370–83, 2022.

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History of change	