Total-Body Parametric ^{18}F-FDG PET of COVID-19

NCT04841707

Protocol 1697954

Protocol Version dated May 24 2021

1) Protocol Title

Title: **Total-Body Parametric ^{18}F-FDG PET of COVID-19**

Protocol Version Date: May 24, 2021

2) Objectives

This is a single-center, pilot study to investigate the organ responses in subjects with COVID-19. We hypothesize that multiparametric imaging with dynamic ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) can monitor the functional changes in patients with COVID-19. The primary objective is to measure the change between COVID-19 patients and normal subjects; the secondary objective is to measure the change in COVID-19 patients between baseline and 4-month follow up. We will primarily assess the pulmonary blood-air barrier (BAB) permeability to glucose but will also evaluate the FDG perfusion-metabolism changes in different organs such as brain, heart, and kidney. All the functional parameters are derived from a single ^{18}F-FDG dynamic PET scan on the EXPLORER total-body PET/CT scanner which is uniquely available in the UC Davis Medical Center.

3) Background

Coronavirus disease 2019 (COVID-19) is a highly infectious respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. The majority of patients who are COVID-19 positive have mild symptoms [2]. However, approximately 20% of the patients can develop acute respiratory distress syndrome (ARDS) [3-6], a common cause of respiratory failure [7] that is associated with a high mortality rate of about 40% in general [7, 8] and even higher in COVID-19 [6, 9]. The complicatedness of COVID-19 is further increased by the fact that "silent hypoxia" exists in many patients [10]. Those patients can breathe normally with a low blood oxygenation level but may be already at a late, very ill stage by the time they are admitted into the hospital.

There is an urgent need for new methods, especially noninvasive imaging methods, to characterize COVID-19 severity and early prediction of ARDS. Existing methods for risk stratification in patients with COVID-19 include clinical exams and laboratory tests which mainly evaluate the body as a whole and do not evaluate the changes specifically in the lungs. Pulmonary function tests are also available. Nevertheless, many patients can have well-preserved lung mechanics while the disease severity keeps worsening, such as in those patients demonstrating silent hypoxia [10]. X-ray imaging, ultrasound, and computed tomography (CT) can image the lungs but focus on anatomical imaging. The anatomical changes may not occur before the disease reaches a late stage. Metabolic imaging with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) only demonstrated mixed results.

Lung blood-air barrier (BAB, a.k.a. alveolar-capillary barrier) is formed by the epithelial cells of the alveolar wall, endothelial cells of the capillaries, and basement membrane [11]. BAB plays a crucial role for normal gas exchange in the lungs for taking in oxygen and releases carbon dioxide [11]. Increased BAB permeability has been well documented as a pathophysiological hallmark of early ARDS [7] and is closely associated with decreased

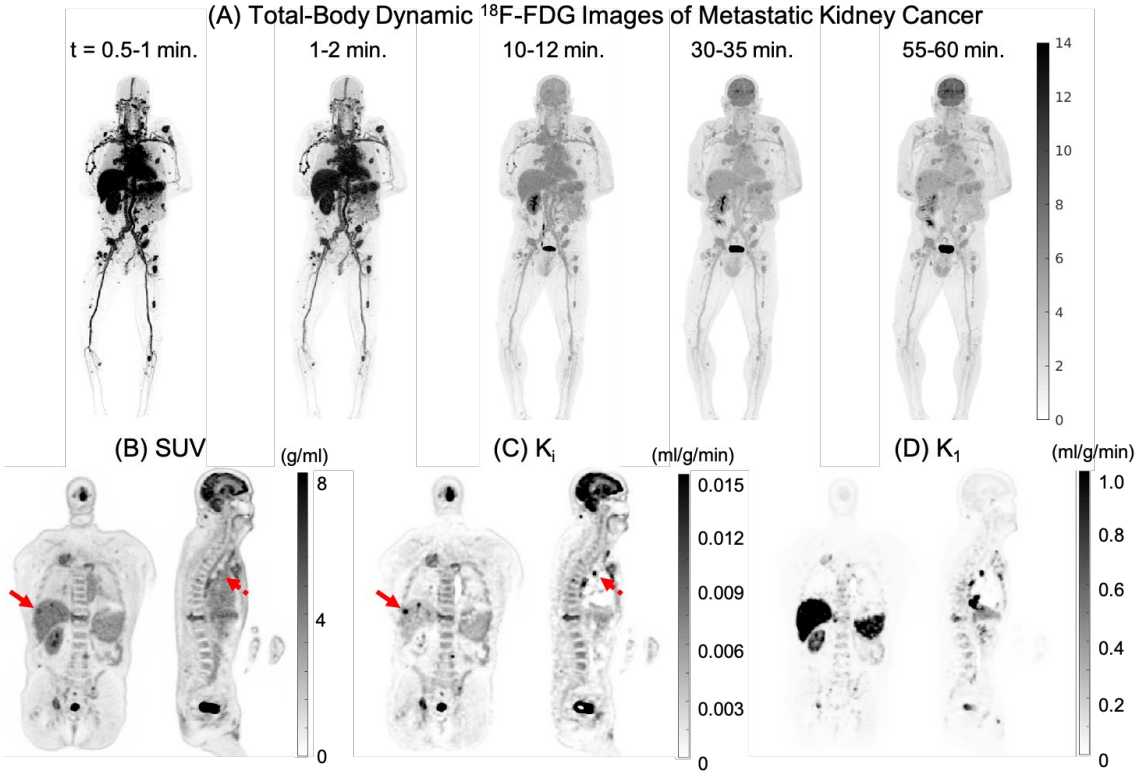

Figure 1 (a-d): Total-body dynamic ^{18}F-FDG PET imaging in a patient with metastatic kidney cancer (A) and enabled multiparametric imaging (B-D). As compared to the clinical standardized uptake value (SUV) image (B), the parametric image of FDG influx rate K_i (C) can achieve higher lesion-to-background (e.g., the liver) contrast. In addition to glucose metabolism imaging by K_i, total-body dynamic PET also enables multiparametric characterization of tumors and organs using additional physiologically important parameters, for example, glucose transport rate K_1 (D), across the entire body.

expression of angiotensin-converting enzyme 2 (ACE2) [12]. In patients with COVID-19, the ACE2 receptor is the entry gate for the SARS-Cov-2 virus to enters the host cells [13, 14]. The virus binding can inhibit the normal role of ACE2 in protecting from lung injury, resulting in increased damage to pulmonary endothelial cells, alveolar epithelial cells, and microangiopathy as confirmed by a very recent autopsy study of COVID-19 patients [15]. These types of injury may increase BAB permeability and lead to protein-rich liquid build-up in the alveoli, which in turn impairs gas exchange [16, 17]. Therefore, the proposed study is aimed at assessing BAB permeability as a biomarker of COVID-19 severity.

However, clinical assessment of BAB permeability is not trivial. Transpulmonary thermodilution can evaluate pulmonary vascular permeability using the ratio of extravascular lung water over pulmonary blood volume [18]. Nevertheless, the method is invasive, associated with complications [19], and affected by the type of ARDS [19]. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) or DCE-CT may be used for imaging vascular permeability but their applications have been mainly limited in brain and tumors [20, 21] with a short axial field of view coverage. In addition, the contrast agents are associated with potential toxicity and injury to the kidney and brain [22-25]. Patients with COVID-19 are at higher risks for contrast toxicity because the virus already attacks multiple organs including the kidney and brain [26-29]. ^{68}Ga-DTPA PET was

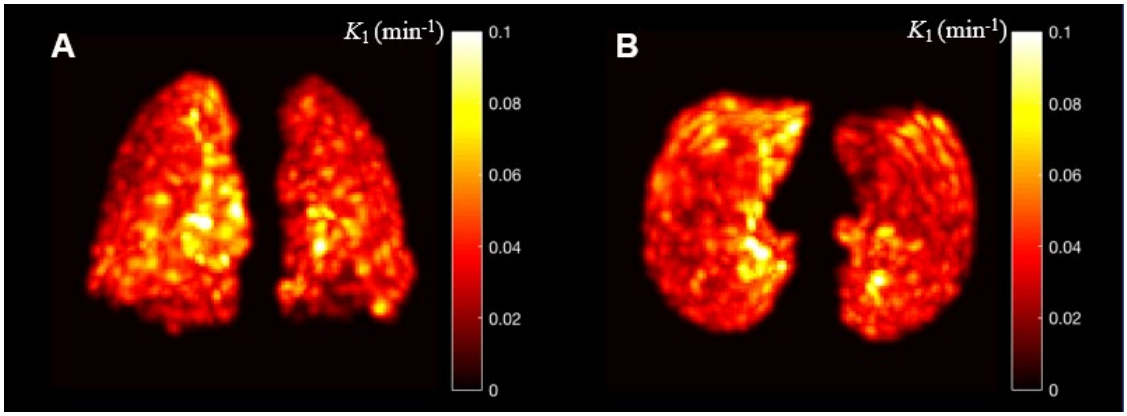

Figure 2. Parametric images of lung FDG K_1 of a healthy subject on the coronal plane (A) and transverse plane (B). Shown are maximum intensity projection images.

utilized for vascular permeability imaging [30-32]. However, the radiotracer is not widely accessible in clinics or would take a long process for clinical translation.

We are developing a single-tracer multiparametric imaging method using PET and the widely available radiotracer ^{18}F-FDG [33-35]. Different from the standard clinical usage of ^{18}F-FDG PET only for metabolic imaging, we exploit dynamic PET imaging and ^{18}F-FDG tracer kinetic modeling to enable simultaneous multiparametric imaging of glucose transport and metabolism. While conventional dynamic PET imaging has been mainly restricted to single-organ imaging because of the limited axial field-of-view (FOV) of traditional PET scanners (15-30 cm), the world's first EXPLORER total-body PET scanner [36, 37] has a long axial FOV of 194 cm with ultrahigh sensitivity and allowing simultaneous dynamic imaging of the entire human body. An example of multiparametric images from a total-body dynamic ^{18}F-FDG PET scan of cancer patients is shown in Figure 1 [38]. In addition to the metabolic imaging as assessed by either the standardized uptake value (SUV) or FDG net influx rate (K_i), the parametric image of FDG K_1 provides an additional dimension of information (glucose blood-to-tissue transport rate) on top of the images of glucose metabolism.

In most organs and tumors, FDG K_1 can be considered as a surrogate of blood flow (perfusion). However, this not the case in the lungs. Our recent theoretical analysis has identified that lung FDG K_1 may represent BAB permeability based on the fact that the extraction of ^{18}F-FDG in lung tissues is small (less than 10%). This is theoretically justified by the classic Renkin-Crone model [39], K_1=FE = F(1-e-$^{PS/F}$) where F represents blood flow, E is the extraction fraction of FDG and PS describes the product of tracer permeability and surface area. When E is small (PS≪F), $K_1 \approx F \times PS/F$

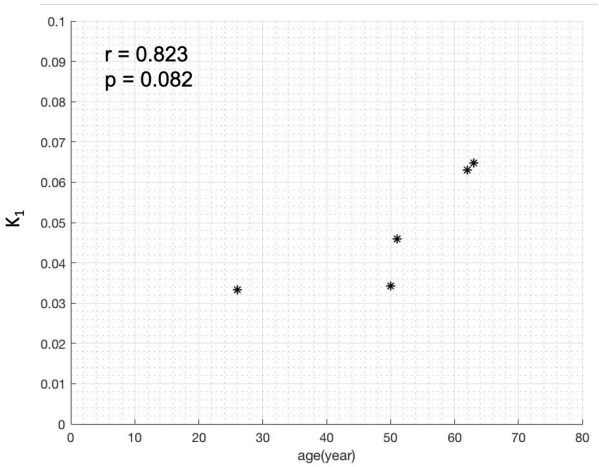

Figure 3. Correlation of lung FDG K_1 (reflecting BAB permeability to glucose) with age.

= PS, thus reflecting permeability, not blood flow. Given the association of BAB permeability with pulmonary ACE2 level [12], our working hypothesis is that lung FDG K_1 correlates with lung injury severity in COVID-19. Specifically, we hypothesize that lung FDG K_1 increases in patients diagnosed with COVID-19 as compared to normal subjects and decreases at 4-month follow-up as compared to its baseline due to more complete recovery. Successful testing of these hypotheses will establish lung FDG K_1 as a noninvasive imaging biomarker of COVID-19 severity, which has the potential to be applied for risk stratification and early assessment of therapeutic response. We have generated the quantification data in 5 healthy subjects. Figure 3 shows lung FDG K_1 versus subject age. While the sample size is small here, the plot shows a trend that increased age is associated with increased lung FDG K_1 and hence increased BAB permeability. This preliminary result is consistent with the observation that elderly is at higher risk of COVID-19, which may be explained by the increased BAB permeability.

From a total-body dynamic FDG-PET scan, we are also able to measure the perfusion-metabolism pattern for other organs. Some of these organs (e.g., brain, kidney, heart) were previously reported of possible damages in patients with COVID-19 [26-29]. We will also study the functional changes in different organs in each of the proposed comparisons.

REFERENCES

[1] W. Guan *et al.*, "Clinical Characteristics of Coronavirus Disease 2019 in China," *New England Journal of Medicine,* vol. 382, no. 18, pp. 1708-1720, Apr 2020, doi: 10.1056/NEJMoa2002032.

[2] Z. Y. Wu and J. M. McGoogan, "Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention," *Jama-Journal of the American Medical Association,* vol. 323, no. 13, pp. 1239-1242, Apr 2020, doi: 10.1001/jama.2020.264810.1001/jama.2020.2648.

[3] D. W. Wang *et al.*, "Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China," *Jama-Journal of the American Medical Association,* vol. 323, no. 11, pp. 1061-1069, Mar 2020, doi: 10.1001/jama.2020.1585.

[4] F. Zhou *et al.*, "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study," *Lancet,* vol. 395, no. 10229, pp. 1054-1062, Mar 2020, doi: 10.1016/s0140-6736(20)30566-3.

[5] Z. Xu *et al.*, "Pathological findings of COVID-19 associated with acute respiratory distress syndrome," *Lancet Respiratory Medicine,* vol. 8, no. 4, pp. 420-422, Apr 2020, doi: 10.1016/s2213-2600(20)30076-x.

[6] C. Wu *et al.*, "Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China," *JAMA Internal Medicine,* 2020, doi: 10.1001/jamainternmed.2020.0994.

[7] M. A. Matthay *et al.*, "Acute respiratory distress syndrome," *Nature Reviews Disease Primers,* vol. 5, Mar 2019, Art no. 18, doi: 10.1038/s41572-019-0069-0.

[8] S. E. Cochi, J. A. Kempker, S. Annangi, M. R. Kramer, and G. S. Martin, "Mortality Trends of Acute Respiratory Distress Syndrome in the United States from 1999 to 2013," *Annals of the American Thoracic Society,* vol. 13, no. 10, pp. 1742-1751, Oct 2016, doi: 10.1513/AnnalsATS.201512-841OC.

[9] P. G. Gibson, L. Qin, and S. Puah, "COVID-19 ARDS: clinical features and differences to “usual” pre-COVID ARDS," *The Medical Journal of Austrilia,* p. Published online: 24 April, 2020.

[10] L. Gattinoni *et al.*, "COVID-19 pneumonia: different respiratory treatments for different phenotypes?," *Intensive Care Medicine*, doi: 10.1007/s00134-020-06033-2.

[11] J. B. West and O. Mathieu-Costello, "Structure, strength, failure, and remodeling of the pulmonary blood-gas barrier," *Annual Review of Physiology,* vol. 61, pp. 543-572, 1999, doi: 10.1146/annurev.physiol.61.1.543.

[12] Y. Imai *et al.*, "Angiotensin-converting enzyme 2 protects from severe acute lung failure," *Nature,* vol. 436, no. 7047, pp. 112-116, Jul 2005, doi: 10.1038/nature03712.

[13] P. Zhou *et al.*, "A pneumonia outbreak associated with a new coronavirus of probable bat origin," *Nature,* vol. 579, no. 7798, pp. 270-+, Mar 2020, doi: 10.1038/s41586-020-2012-7.

[14] M. Hoffmann *et al.*, "SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor," *Cell,* vol. 181, no. 2, pp. 271-+, Apr 2020, doi: 10.1016/j.cell.2020.02.052.

[15] M. Ackermann *et al.*, "Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19," *New England Journal of Medicine,* 2020, doi: 10.1056/NEJMoa2015432.

[16] J. Bhattacharya and M. A. Matthay, "Regulation and Repair of the Alveolar-Capillary Barrier in Acute Lung Injury," *Annual Review of Physiology, Vol 75,* vol. 75, pp. 593-615, 2013, doi: 10.1146/annurev-physiol-030212-183756.

[17] S. Herold, N. M. Gabrielli, and I. Vadasz, "Novel concepts of acute lung injury and alveolar-capillary barrier dysfunction," *American Journal of Physiology-Lung Cellular and Molecular Physiology,* vol. 305, no. 10, pp. L665-L681, Nov 2013, doi: 10.1152/ajplung.00232.2013.

[18] X. Monnet, N. Anguel, D. Osman, O. Hamzaoui, C. Richard, and J. L. Teboul, "Assessing pulmonary permeability by transpulmonary thermodilution allows differentiation of hydrostatic pulmonary edema from ALI/ARDS," *Intensive Care Medicine,* vol. 33, no. 3, pp. 448-453, Mar 2007, doi: 10.1007/s00134-006-0498-6.

[19] X. Monnet and J. L. Teboul, "Transpulmonary thermodilution: advantages and limits," *Critical Care,* vol. 21, Jun 2017, Art no. 147, doi: 10.1186/s13054-017-1739-5.

[20] S. P. Sourbron and D. L. Buckley, "Tracer kinetic modelling in MRI: estimating perfusion and capillary permeability," *Physics in Medicine and Biology,* vol. 57, no. 2, pp. R1-R33, Jan 2012, doi: 10.1088/0031-9155/57/2/r1.

[21] A. Kambadakone *et al.*, "CT Perfusion as an Imaging Biomarker in Monitoring Response to Neoadjuvant Bevacizumab and Radiation in Soft-Tissue Sarcomas: Comparison With Tumor Morphology, Circulating and Tumor Biomarkers, and Gene Expression," *American Journal of Roentgenology,* vol. 204, no. 1, pp. W11-W18, Jan 2015, doi: 10.2214/ajr.13.12412.

[22] M. Rogosnitzky and S. Branch, "Gadolinium-based contrast agent toxicity: a review of known and proposed mechanisms," *Biometals,* vol. 29, no. 3, pp. 365-376, Jun 2016, doi: 10.1007/s10534-016-9931-7.

[23] J. Ramalho, R. C. Semelka, M. Ramalho, R. H. Nunes, M. AlObaidy, and M. Castillo, "Gadolinium-Based Contrast Agent Accumulation and Toxicity: An Update," *American Journal of Neuroradiology,* vol. 37, no. 7, pp. 1192-1198, Jul 2016, doi: 10.3174/ajnr.A4615.

[24] M. S. Davenport, S. Khalatbari, R. H. Cohan, J. R. Dillman, J. D. Myles, and J. H. Ellis, "Contrast Material-induced Nephrotoxicity and Intravenous Low-Osmolality Iodinated Contrast Material: Risk Stratification by Using Estimated Glomerular Filtration Rate," *Radiology,* vol. 268, no. 3, pp. 719-728, Sep 2013, doi: 10.1148/radiol.13122276.

[25] K. M. Hasebroock and N. J. Serkova, "Toxicity of MRI and CT contrast agents," *Expert Opinion on Drug Metabolism & Toxicology,* vol. 5, no. 4, pp. 403-416, Apr 2009, doi: 10.1517/17425250902873796.

[26] T. Chen *et al.*, "Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study," *Bmj-British Medical Journal,* vol. 368, Mar 2020, Art no. m1091, doi: 10.1136/bmj.m1091.

[27] Y. C. Cheng *et al.*, "Kidney disease is associated with in -hospital death of patients with COVID-19," *Kidney International,* vol. 97, no. 5, pp. 829-838, May 2020. [Online]. Available: <Go to ISI>://WOS:000530724500004.

[28] Y. C. Li, W. Z. Bai, and T. Hashikawa, "The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients," *Journal of Medical Virology,* vol. 92, no. 6, pp. 552-555, Jun 2020, doi: 10.1002/jmv.25728.

[29] S. Richardson *et al.*, "Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area," *JAMA,* vol. 323, no. 20, pp. 2052-2059, 2020, doi: 10.1001/jama.2020.6775.

[30] M. A. Mintun, D. R. Dennis, M. J. Welch, C. J. Mathias, and D. P. Schuster, "MEASUREMENTS OF PULMONARY VASCULAR-PERMEABILITY WITH PET AND GA-68 TRANSFERRIN," *Journal of Nuclear Medicine,* vol. 28, no. 11, pp. 1704-1716, Nov 1987. [Online]. Available: <Go to ISI>://WOS:A1987K850000008.

[31] F. S. Calandrino, D. J. Anderson, M. A. Mintun, and D. P. Schuster, "PULMONARY VASCULAR-PERMEABILITY DURING THE ADULT RESPIRATORY-DISTRESS SYNDROME - A POSITRON EMISSION TOMOGRAPHIC STUDY," *American Review of Respiratory Disease,* vol. 138, no. 2, pp. 421-428, Aug 1988, doi: 10.1164/ajrccm/138.2.421.

[32] H. J. Chen *et al.*, "Quantification of Tumor Vascular Permeability and Blood Volume by Positron Emission Tomography," *Theranostics,* vol. 7, no. 9, pp. 2363-2376, 2017, doi: 10.7150/thno.19898.

[33] Y. Zuo, R. Badawi, C. Foster, T. Smith, J. López, and G. Wang, "Multiparametric cardiac 18F-FDG PET in humans: kinetic model selection and identifiability analysis," *arXiv,* p. 2008.05099, 2020.

[34] G. B. Wang, S. Sarkar, E. Kim, and R. D. Badawi, "Time-varying kinetic modeling of high temporal-resolution dynamic 18F-FDG PET data for multiparametric imaging," *J. Nucl. Med.,* vol. 59, no. supplement 1, pp. 503-503, 2018.

[35] G. Wang *et al.*, "Quantification of Glucose Transport Using High Temporal Resolution Dynamic PET Imaging," *J. Nucl. Med.,* vol. 60, no. supplement 1, pp. 521-521, June 22-25 2019.

[36] S. R. Cherry, T. Jones, J. S. Karp, J. Qi, W. W. Moses, and R. D. Badawi, "Total-body PET: Maximizing sensitivity to create new opportunities for clinical research and patient care," *J Nucl Med,* vol. 59, no. 1, pp. 3-12, 2018.

[37] R. D. Badawi *et al.*, "First human imaging studies with the EXPLORER total-body PET scanner," *J Nucl Med,* vol. 60, no. 3, pp. 299-303, 2019.
[38] G. Wang *et al.*, "Total-Body Dynamic PET of Metastatic Cancer: First Patient Results," *J Nucl Med,* vol. 61, no. supplement 1, pp. 208-208, 2020.
[39] R. E. Carson, "Tracer Kinetic Modeling in PET," in *Positron Emission Tomography*, D. L. Bailey, D. W. Townsend, P. E. Valk, and M. N. Maisey Eds. London: Springer, 2005.

4) Inclusion and Exclusion Criteria

We anticipate enrolling participants with a range of infection severity, from those hospitalized, to those who had outpatient treatment.

Inclusion Criteria. Potential participants must meet all of the following criteria to be eligible for study entry.

- COVID-19 positive patients will have a previous positive COVID-19 test and radiologic findings, and/or a positive SARS-CoV-2 antibody test and be in early recovery.
- First PET/CT visit needs to be within 8 weeks of COVID-19 diagnosis.
- Ability to understand and willingness to sign an informed consent form.
- Ability to adhere to the study visit schedule and other protocol requirements.
- All persons ≥18 years of age.

Exclusion Criteria. Potential participants who meet any of the following criteria will be excluded from study entry.

- Pregnant or lactating persons.
- Any condition that would prohibit the understanding or rendering of informed consent.
- Unable to lie supine for 1-hour imaging with PET.
- Prisoners.
- Any comorbidity that, in the opinion of the investigator, could compromise protocol objectives.

5) Study Timelines

We anticipate fifteen participants will be enrolled into this pilot study. We estimate the recruitment period to last 12 months. Medical records of enrolled participants will be followed for one year to determine the clinical outcome. The primary analysis is anticipated to be completed in two years.

6) Study Endpoints

The primary endpoint of this study is to evaluate if there is a significant increase in BAB permeability (as assessed by lung FDG K_1) and changes in organ perfusion-metabolism between subjects diagnosed with COVID-19 and normal subjects (of which the EXPLORER scans are already available through another trial). The secondary endpoint is to evaluate the changes in patients with COVID-19 between baseline and 4-month follow-up in a patient's recovery phase.

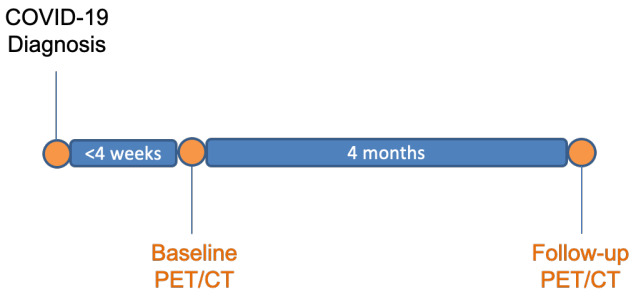

Figure 4: Study protocol.

7) Procedures Involved

COVID-19 Testing: Potential participants with only a previous positive COVID-19 test (viral RNA) lacking radiologic findings, will be asked to undergo a SARS-CoV-2 antibody test prior to enrollment. Prior to the baseline PET/CT scan, each participant must have a negative viral PCR COVID-19 test at least 14 days following their positive COVID-19 test. These tests will be paid by the study.

PET/CT Scans: Each participant will undergo two ^{18}F-FDG PET/CT scans, one at baseline and one at 4-month (+/- 2 weeks) follow-up (Figure 4). A member of the research study team will reach out to the participant prior to the 4-month scan to inquire about the status and date of COVID-19 vaccination. For each scan, participants will be asked to arrive for the study visits at the UC Davis EXPLORER Molecular Imaging Center (3195 Folsom Blvd, Sacramento, CA). A urine pregnancy test will be administered, at no charge, to all participants 18 to 60 years old able to become pregnant, unless documented hysterectomy or bilateral ovarian removal is available. Participants will then have a routine finger stick test for measuring blood sugar level. A technologist will place a thin plastic needle (IV) into a vein at the arm of an eligible participant. The technologist will then instruct the participant to lie supine in the EXPLORER PET/CT scanner. The participant will first undergo an ultra low-dose X-ray CT imaging for attenuation correction purpose. After that, a standard dose of ^{18}F-FDG will be injected into the participant through the IV in a period of 10 seconds. The time when FDG is injected should be recorded. The PET scan commences 10 seconds before the FDG injection and lasts for 60 minutes. After the PET scan, the participant gets off the scanner.

Cognitive Screening: Participants will also undergo screening with the Mini-Cog instrument. The Mini-Cog[1] is a standardized 3-minute instrument utilized to screen for cognitive impairment.

The acquired total-body dynamic PET/CT data will be reconstructed into a sequence of dynamic images. An image-derived input function will be extracted from the dynamic

[1] Borson, Soo, et al. "The mini-cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly." International journal of geriatric psychiatry 15.11 (2000): 1021-1027.

image sequence and kinetic quantification in the lungs and other organs will be performed using the dynamic PET images.

The PET/CT images created for this study are for research and are not meant to evaluate subject health, as they would be if they were part of a clinical (non-research) visit to the doctor or hospital. The images will not receive any routine clinical review by radiologists who interpret PET/CT scans. This means that some findings may be overlooked or misinterpreted. However, if the PET/CT technologists do notice findings that cause concern, they will notify the Study Radiologist. Additionally, if a member of the research team notices any findings that cause concern while conducting image review for study purposes, they will notify the Study Radiologist. The Study Radiologist will conduct a brief review of part of the study images for quality purposes. If the Study Radiologist thinks a clinical problem is present, one of the IRB-approved study physicians will discuss these possible problems with the subject within 8 weeks or immediately upon recognition of any critical finding that requires immediate and/or urgent intervention as described in the Department of Radiology Critical Findings policy (full dataset of images are sometimes not available for review in less than 3 days). Upon written request, we will provide the subject with a copy of a subset of their CT images to take to the physician of their choosing. A subset of PET images may also be shared with the subject unless the images from the study are clinically uninterpretable. In addition, the sponsor may restrict sharing of PET images due to the nature of the research protocol. We will send a standard letter to the designated licensed medical provider identified by the subject, unless one of the study physicians is part of the subject's care. The standard letter will state that (i) the subject's images were acquired exclusively for a research study and incidental findings that may be related to a medical condition were observed by a UC Davis radiologist; (ii) the images did not receive any dedicated routine clinical review and findings may have been overlooked or misinterpreted; (iii) the subject's physician can contact the study doctor at any time if there are any concerns regarding the study or the subject's findings.

8) Data and/or Specimen Management and Confidentiality

All data and images acquired for research purposes will be coded with a research number. Subjects will be assigned sequential ID codes (1-15). Subject identifiers and personal health information (PHI) will be removed from the DICOM header of PET/CT images to protect patient confidentiality

Risk of loss of confidentiality and privacy will be mitigated by hospital EMR and PACS password security and by the protection of consent forms and datasheets with PHI are secured in a locked office and locked file cabinets in the EXPLORER Molecular Imaging Center office. Links in the data to the medical record will be removed before research personnel analyze the data. Access to the code key will be restricted to the investigators and coordinator(s) during the course of the study.

Once informed consent is obtained through a method approved by UC Davis, clinical data will be collected from the electronic medical record, including recent laboratory tests, cardiac function assessment, and imaging variables. Patient's blood pressure, heart rate, and weight will also be obtained for the most recent visit.

9) Data and/or Specimen Banking

N/A

10) Provisions to Monitor the Data to Ensure the Safety of Subjects

This study does NOT involve the administration of therapeutic agents. This study does NOT replace any of the safety monitoring that patients undergo as part of standard clinical care.

^{18}F-FDG PET/CT is routinely used in clinical oncology, cardiology and neurology. Intervention for adverse events that occur during PET/CT scanning will be the responsibility of hospital radiology or nuclear medicine technicians and physician on duty.

11) Withdrawal of Subjects

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigators also have the right to withdraw patients from the study for any of the following reasons:

- Known or suspected pregnancy - this is verified as part of the clinical process since this test is clinically contraindicated on pregnant patients.
- Circumstance(s) deemed by the Nuclear Medicine clinician to be contraindicated for PET/CT
- Patient request

12) Risks to Subjects

Minor and uncommon clinical risks:

- Additional discomfort from lying on the scanner table for 60 additional minutes

Serious and rare risks:

- Loss of privacy or confidentiality

It is worth noting that all the risks listed below are similar to standard-of-care PET/CT test in oncological patients.

Minor and common clinical risks:

- The placement of the intravenous needle in a vein may cause temporary discomfort and a small bruise may form.
- Discomfort due to lying in the PET/CT scanner for 1 hour

Moderate and uncommon clinical risks:

- Infection at the site with the intravenous catheter is placed.

Radiation risks:

- PET/CT involves a radiation exposure that is typical of other diagnostic tests using ionizing radiation
- The amount of radiation exposure received in this study is below the levels that are thought to result in a significant risk of harmful effects.

13) Potential Benefits to Subjects

There are no direct benefits to the study subjects. The result of the study will benefit future patients once the methods are fully developed.

14) Multi-Site Research

This is a single-site study.

15) Community-Based Participatory Research

N/A

16) Sharing of Results with Subjects

The images acquired in this study are experimental and cannot be used by subjects or their clinicians for treatment decision-making. No results will be shared with patients or clinicians.

17) Prior Approvals

Prior approval from the Radiation Use Committee will be obtained before the submission of this protocol for IRB approval.

18) Provisions to Protect the Privacy Interests of Subjects

The rights and welfare of subjects will be protected by the use of subject codes and the removal of all PHI identifiers from the research data and images. The subject code key used to link subject identities to coded data will be kept on a password-protected space to separate it from the clinical data and images. All identifiers, including the code key used to link subjects to coded data, will be destroyed by electronic deletion at the end of the study. Protected health information will not be re-used or disclosed to any other person or entity, expect as required by law or for authorized oversight of the research project.

19) Compensation for Research-Related Injury

The research does not involve more than minimal risk to subjects. If a subject is injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to the subject's insurance company just like any other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury. Subjects do not lose any legal rights by signing the informed consent form.

20) Economic Burden to Subjects

There are no additional expenses either to the study subjects or to the insurers. Study participants will be provided with $100 gift cards after the completion of each scanning visit to compensate for transportation and other trip costs associated with their participation in this study.

21) Drugs or Devices

There are no drugs or devices being tested on this protocol. The EXPLORER total-body PET/CT is FDA approved for routine clinical use.

22) Review Requirements

Are there any contractual obligations or other considerations that require IRB review of this research, or review at intervals other than those required by the Common Rule or FDA? If yes, check box:

☐ Yes

☐ No