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MS TITLE: Invited Perspective for, "^{18}F-FDG PET derived tumor blood flow changes after one cycle of neoadjuvant chemotherapy predicts outcome in triple-negative breast cancer"

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Running title: FDG derived blood flow predicts outcome

Prior studies have shown that breast cancer patients experienced higher mortality and recurrence risks when their tumors failed to show a decline in blood flow following neoadjuvant therapy, as measured directly from [^{15}O]water PET scans (*1*) or indirectly from dynamic [^{18}F]fluorodeoxyglucose (FDG) PET scans using changes in FDG transport (K1), which can be estimated via kinetic image analyses (*1*, *2*). The gold standard blood flow PET tracer, [^{15}O]water (*3*), is only available at PET imaging centers that have a cyclotron on site due to the short 2 minute half-life of ^{15}O. FDG is a more widely available radiotracer with a half-life that allows regional supply to clinical centers. However, the 60 minute dynamic FDG PET imaging protocol used by Dunnwald et al. that enabled estimates of FDG transport (K1) and metabolic flux (K_i) to predict disease free survival and overall survival (*2*) is impractical in a busy clinical setting (*4*).

New imaging protocols more compatible with typical FDG PET clinical workflows (*4*) might enable routine blood flow or FDG transport measures. In current clinical practice patients are injected with FDG in an uptake room before being brought to the PET/CT room, where the PET scan starts approximately 60 minutes after injection. This workflow allows a busy clinic to average 2 or more FDG PET scans per hour since one patient can undergo image acquisition while other patients are injected with FDG in an uptake room. A dynamic FDG PET scan of 60 minutes is considered disruptive to the clinical workflow because a patient remains on the scanner much longer than the duration of a standard FDG PET whole body scan. The longer required use of the PET/CT room, patients' ability to lie still in the PET scanner for a longer period, specialized equipment, need for technicians trained to conduct more complex image acquisitions, and limited

access to image analysis software and personnel capable of performing kinetic analyses has limited dynamic FDG PET protocols to larger PET imaging centers.

An alternative method for estimating blood flow from FDG PET uses the "first-pass" extraction model of Mullani et al. (*5*) that assumes highly extracted tracers can be used to estimate blood flow using a 1-compartment model during the first-pass of the tracer through the tissue that in practice only requires a 2 minute dynamic PET scan starting simultaneously with injection of FDG (*6-8*). The average first-pass FDG blood flow (first-pass BF) estimates using this method were found to correlate with [^{15}O]water ($R^2 = 0.74$) with first-pass BF estimates being on average 14% below blood flow estimates from [^{15}O]water PET scans (*6*). In this issue of the *Journal of Nuclear Medicine*, Humbert et al. report low overall survival is associated with triple negative breast cancer patients whose tumors experienced a less than 30% drop in tumor first-pass BF following neoadjuvant therapy (*8*). Humbert et al. also found their first-pass BF estimates capable of stratifying between patients with 87% versus 48% overall survival ($p < 0.001$) in women without a pathology complete response (*8*). Humbert et al. results support using first-pass FDG PET scans as an alternative to [^{15}O]water PET scans for estimating blood flow to tumors.

In Humbert et al. results are reported from analyses of a two-part imaging protocol where patients were positioned prone followed by a one bed position FDG 2-minute dynamic PET scan, which was followed by an additional PET scan starting 90 minutes after injection that was completed over prone patients in a region that included first scan's imaging area (*8*). The Humbert et al. two-part image acquisition and analysis method protocol (*8*) is very similar to a two-part protocol previously published by 8

coauthors of Humbert et al. in Cochet et al. (*7*) and it is possible that results from up to 10 patients analyzed by Cochet et al. were included in the Humbert et al. analysis of 46 women with triple-negative breast cancer. The Cochet et al. scan protocol was only performed on women before any treatment (*7*) while the Humbert et al. protocol was completed in patients undergoing neoadjuvant therapy before and after the first course of chemotherapy (*8*). Analyses of the Humbert et al. two-part set of PET images (2 minute dynamic and 90 minute static) yielded estimates of blood flow (first-pass BF from FDG scans) and tumor metabolism (Standardized Uptake Value or SUV) in an analogous manner to kinetic analysis of a single 60 minute dynamic FDG scan yielding estimates of tracer transport (FDG transport or K1) and tumor metabolism (flux or K_i, metabolic rate of FDG or MRFDG, or SUV). A disadvantage of the two-part FDG PET scan image analysis method is the inability to distinguish between free and phosphorylated (i.e. trapped) FDG tracer at later time points, that could lead to overestimation of first-pass BF (*6*) and limitations in the ability to measure change in metabolism with therapy (*9*). An advantage of a 60 minute dynamic FDG PET scan over the Humbert et al. two-part FDG scan protocol is the ability to measure SUV uptake values without PET tracer injection-to-acquisition time variation, which can occur in a busy clinic, since an increase in uptake time variation has been reported to decrease the sensitivity for detecting response in clinical trials using FDG PET endpoints (*10*). On the other hand, the two-part FDG scan protocol proposed by Humbert et al. could have an advantage over a single 60 minute dynamic FDG scan as it may be more compatible with a clinical workflow if the 0 to 2 minute dynamic PET/CT and the second 90 minute static PET/CT scan for one patient can be interleaved with other patient scans to accommodate a busy clinical setting.

However, the Humbert et al. two-part FDG PET/CT scan protocol would have the disadvantage of requiring patients to receive a slightly higher radiation dose due to the requirement for a second, limited field of view CT attenuation scan.

The intriguing results of the study of Humbert et al. (*8*) support FDG first-pass BF estimates as a viable alternative to blood flow estimates from [^{15}O]water PET scans with the major advantage that first-pass BF imaging protocols could be conducted at PET imaging centers without an onsite cyclotron. While the Humbert et al. first-pass 2 minute FDG dynamic PET scan protocol could be implemented in many clinics, it is unclear whether clinics would also accept the logistical complication of adding a second scanning time to the current standard of a single delayed uptake scan. However, innovative PET quantitative methods such as first-pass BF estimation (*5*) and integrated imaging protocols such as proposed by Humbert et al. that allow measurement of orthogonal phenomena such as blood flow and metabolism are important steps forward in translating validated research methods into practical imaging protocols for a busy clinical PET practice.

DISCLOSURE

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