Table 2: Overview of the imaging techniques dedicated to brain hemodynamics (adapted from Wintermark et al. [27]).

	PET	SPECT	DSC	ASL	fMRI
Age range	Adults (and children for static exams)	Adults (and children)	Adults (and children)	Adults + children	Adults (and children)
Contrast material	$^{15}O_2$, C $^{15}O_2$, $H_2{}^{15}O$	^{99}Tc-HMPAO, ^{99}Tc-ECD, ^{133}Xe, ^{123}I-IMP (diffusible)	Gadolinium chelate (nondiffusible)	None (endogenous contrast)	None
Radiation/study	0.5–2 mSv	3.5–12 mSv	None	None	None
Data acquisition	5–9 min	10–15 min	1 min	5–10 min	
Data processing	5–10 min	5 min	5 min	5 min	
Assessed parameters	CBV, CBF, rOEF, glucose metabolism	CBF	CBF, CBV, MTT, TTP, permeability map	CBF	BOLD signal
Quantitative accuracy	Yes	Yes for ^{133}Xe and ^{123}I-IMP	Not in daily practice	Yes	
Including for low perfused areas	Yes	Not applicable	Not applicable	Not below 10 mL/min/100 g	Yes
Reproducibility	5%	10%	10–15%	10%	
Spatial resolution	4–6 mm	1 cm	2 mm	2 mm	
Minimal time interval between 2 successive exams	10 min	10 min	25 min	0 min	
Applications in neurodegenerative disorders	Yes	Yes	No	Yes	Yes

the ASL techniques measure CBF, with the advantage of not requiring contrast injection. Many researchers are now migrating towards the use of ASL, since it poses less risk for the patients than DSC and nuclear medicine techniques.

A variety of studies in both animal models and human subjects have demonstrated that regional CBF maps can be accurately depicted by ASL [48–50], and the results obtained with ASL are consistent with those obtained from PET studies [51], since CBF and metabolic consumption are markers of cerebral dysfunction [50].

In clinical studies of AD and MCI, metabolic imaging with FDG-PET [52, 53] and SPECT [54, 55] have highlighted loss of activity in temporal, parietal, and frontal association cortex, along with PCC and precuneus. Additionally, a study using a covariance ^{15}O-PET pattern [56] acquired during rest showed increased flow in the insula, cuneus, pulvinar, lingual, fusiform, superior occipital, and parahippocampal gyri, whereas decreased flow was found in cingulate, inferior parietal lobe, middle and inferior frontal, and supramarginal and precentral gyri. These results are in agreement with the findings reported in ASL studies.

In AD, medial temporal lobe is characterized by severe atrophy, so the detection of metabolism changes or subtle flow disturbances are difficult to evaluate with nuclear medicine techniques [57–59], since PET or SPECT studies do not correct for atrophy. Thus, one important advantage of combining ASL with structural MRI is the possibility of quantifying perfusion changes per cc of tissue in the same setting, allowing structure-function correlations within a single modality. Additionally, PET studies are prone to underestimate flow in regions with high blood flow, whereas ASL is less affected by water permeability due to the timescales of imaging and tracers decay [60]. Finally, SPECT can also suffer from saturation effects in the uptake of the tracer [61], and it has a low spatial resolution.

6. What Can ASL Add to the Diagnosis Flow of Patients with AD in the Amyloid-PET Era?

CSF studies and amyloid-PET imaging are considered molecular biomarkers of the disease, demonstrating the presence of the pathogenic protein "in vivo." Its detection, in one way or another, is becoming increasingly important for establishing the diagnosis of probable AD [62]. However, recent evidence shows "positive" amyloid-PET studies in cognitively healthy individuals; thus these findings should be interpreted with caution [63]. Furthermore, it involves significant costs beyond the reach of most centers. On the other hand, ASL should be considered as functional or indirect biomarker, such as FDG-PET, showing focal abnormalities in perfusion within specific brain areas due to an underlying neurodegenerative process disrupting the neurovascular coupling [24]. Thus, amyloid-PET and ASL provide different but complementary information, which ideally might be integrated together in the diagnosis process of patients with cognitive decline. However, amyloid-PET requires great economic investment, which cannot often be carried out.