RESEARCH ARTICLE

Magnetic Resonance in Medicine

ISMRM Open Science Initiative for Perfusion Imaging (OSIPI): ASL pipeline inventory

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Abstract

Purpose: To create an inventory of image processing pipelines of arterial spin labeling (ASL) and list their main features, and to evaluate the capability, flexibility, and ease of use of publicly available pipelines to guide novice ASL users in selecting their optimal pipeline.

Methods: Developers self-assessed their pipelines using a questionnaire developed by the Task Force 1.1 of the ISMRM Open Science Initiative for Perfusion Imaging. Additionally, each publicly available pipeline was evaluated by two independent testers with basic ASL experience using a scoring system created for this purpose.

Results: The developers of 21 pipelines filled the questionnaire. Most pipelines are free for noncommercial use (n = 18) and work with the standard NIfTI (Neuroimaging Informatics Technology Initiative) data format (n = 15). All pipelines can process standard 3D single postlabeling delay pseudo-continuous ASL images and primarily differ in their support of advanced sequences and features. The publicly available pipelines (n = 9) were included in the independent testing, all of them being free for noncommercial use. The pipelines, in general, provided a trade-off between ease of use and flexibility for configuring advanced processing options.

Conclusion: Although most ASL pipelines can process the common ASL data types, only some (namely, ASLPrep, ASLtbx, BASIL/Quantiphyse, ExploreASL, and MRI-Cloud) are well-documented, publicly available, support multiple ASL types, have a user-friendly interface, and can provide a useful starting point for ASL processing. The choice of an optimal pipeline should be driven by specific data to be processed and user experience, and can be guided by the information provided in this ASL inventory.

KEYWORDS

arterial spin labeling, automated processing pipeline, cerebral blood flow, open science, perfusion

1 | INTRODUCTION

Cerebral blood flow (CBF) is a key physiological parameter for assessing cerebrovascular health in physiological and diseased conditions.[1–3] Arterial spin labeling (ASL) perfusion MRI provides a contrast-agent free acquisition method for the voxel-wise quantification of CBF.[4] Its non-invasive nature and ability to quantify absolute CBF make it ideal in all settings that require repeated acquisitions. ASL has been validated by comparison with other methods that use exogenous contrast agents, such as ^{15}O-H$_2$O-PET and dynamic susceptibility–contrast MRI,[5,6] and has been applied in neurological, neuropsychological, and neuropsychiatric research.[7–9]

Since the inception of ASL, various ASL approaches have been developed and used, which primarily differed in blood labeling,[10,11] readout,[12] use of background suppression,[13] and use of protocols involving multiple labeling times and postlabeling delays (PLDs). A consensus recommendation on acquisition has been formed to facilitate its use in different settings[14]; other ASL protocols are still used based on specific clinical populations, availability, experience in the use of the specific protocol, and compatibility with the MRI scanner. Although basic processing is readily available on the MRI scanner console for the current product sequences, offline processing offers more advanced algorithms, is often required for custom sequences,[15] and can add features such as outlier rejection,[16] quality control,[17] or partial volume correction.[18] Additionally, offline processing is the only option to derive CBF values in different regions of interest or in the template space, as required for statistical analysis.[19] Proper tools are needed for offline processing, ideally with automatic batch mode, which allows processing the entire data set with minimal manual intervention and can easily be scalable to larger data sets without additional manual effort.

For potential users it is often not technically or time-wise feasible to implement their own ASL processing software, particularly for such a wide variety of ASL types. A recent European survey noted that general awareness, technical difficulty, and lack of tools are indeed some of the main hurdles to the more widespread use of ASL and quantitative MRI in general.[20] More than 20 different toolboxes have been released for ASL data processing and analysis[16,19,21-31] from different laboratories that specialize in ASL analysis. The selection of a particular pipeline by a new user can be complicated because of the wide variety of ASL sequences, data formats,[32] and processing methods.[19] Both new and experienced ASL users looking for suitable ASL image processing and quantification software may benefit from a comprehensive and detailed list of ASL image-processing software along with their features to guide their search for a suitable pipeline.

The International Society for Magnetic Resonance in Medicine Open Science Initiative for Perfusion Imaging (ISMRM OSIPI, referred to hereafter as "OSIPI") is an initiative and activity of the ISMRM perfusion study group. Established in May 2020, its mission is to create open-access resources for perfusion imaging research, to improve its reproducibility; speed up the translation into tools for discovery science, drug development, and clinical practice; and eliminate the practice of duplicate development.[33] The activities of OSIPI were divided among task forces. Here, we describe the activities and output of Task Force 1.1 (TF1.1), which is aimed at creating an inventory of the available ASL pipelines, targeting primarily novice ASL users. The inventory summarizes ASL pipeline features that include supported ASL types, type of input and output, and requirements of software and technical expertise as reported by the pipeline developers and independently assessed by task force (TF) volunteers.

2 | METHODS

The development of the ASL pipeline inventory and independent pipeline testing was the goal of TF1.1 for the first 2 years (May 2020–May 2022). Each OSIPI TF has a lead and a co-lead (JP and SD, respectively, for TF1.1), appointed in May 2020 by the OSIPI Strategy Board. TF1.1 also consisted of seven other researchers (HF, UA, CB, VK, LH, HM, and DT) with either technical, biomedical, or clinical backgrounds appointed by the TF leads.

2.1 | Pipeline inventory

The first step of inventory creation entailed compiling a list of pipelines and collecting their basic information, features, and requirements through an online questionnaire developed by the TF and filled by the pipeline developers. The questions broadly focused on:

i information about the developer, method of availability of the software, and license;
ii operating system and other software and hardware requirements;
iii compatibility with the type of input data, MR scanner, and ASL sequence type;
iv details of data processing steps, analysis, and output features;
v software applications in animals or organs other than the brain;

vi availability of batch-mode to automate data processing and flexibility to modify pipeline configuration;

vii the approximate number of ASL studies and ASL scans processed by the pipeline, as self-reported by the developer.

The full questionnaire is provided in the Supporting Information.

The questionnaire and a cover letter explaining the purpose of the inventory were distributed in September 2020 through several channels: (i) Pipeline developers known to the TF members were emailed directly; (ii) the ASL research community was contacted using several mailing lists of perfusion and medical imaging networks (OSIPI,[33] ASL network [https://asl-network.org], GliMR 2.0 COST Action[34] [https://glimr.eu], ISMRM Perfusion study group [https://groups.ismrm.org/perfusion/], Imaging Cerebral Physiology [http://www.icp-network.org], *SPM* [https://www.fil.ion.ucl.ac.uk/spm/support/], and *FSL* [https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Support]). Questionnaires were returned by November 2020.

2.2 | Pipeline testing

The OSIPI TF1.1 also aimed to provide a more objective and independent testing of the capability, flexibility, and ease of use of the pipelines, by running them on a variety of test data sets and scoring the pipelines on a range of features. Between September and November 2021, all pipeline developers were contacted to make their pipelines available for testing (unless already publicly available) and to assist the independent testing by answering questions of the testers if required. Moreover, the ISMRM Perfusion study group, the pipeline developers, and TF members were contacted for volunteers to provide independent testing of the pipelines. All pipelines from the ASL inventory were tested with the following exceptions:

- The developers stated that the pipeline was not ready for independent use without the active support of the developers for one of the following reasons: (i) lack of a comprehensive manual, (ii) requirement of coding expertise or substantial changes in source code to configure a new project, or (iii) being too narrowly focused on a specific goal or a single sequence;

- The software was not publicly available, or it was only accessible under a commercial license and the developers did not grant us a special license.

A unified scoring system was created by TF1.1, which consisted of four categories with a total of 16 criteria as listed subsequently. In addition, a detailed manual for grading was provided for each criterion to allow objective and consistent scoring across testers, including:

- Ease of use

  - Free for noncommercial use or available under a commercial license only. Note that free software can still require or include third-party software with a different license. We recommend commercial users to always check the licenses of all the software used.
  - Ease of installation
  - Ease of data preparation
  - Ease of pipeline configuration
  - Availability of a graphical user interface

- Requirements

  - Requirement of third-party software
  - Instruction for third-party software installation
  - Required programming knowledge for a simple and complex setup
  - Version control of the software

- Flexibility of configuration

  - Availability of batch mode for automated processing
  - For GUIs, batch mode can be saved and reused
  - Flexibility in modifying sequence parameters, support of Brain-Imaging Data Structure format for ASL (ASL-BIDS)
  - Flexibility in modifying quantification parameters
  - Flexibility in modifying processing steps

- Support

  - Availability of a discussion forum, an email, or a hotline for support
  - software under active development

A full list of the criteria and guidance that were given to the testers for the scoring is provided in the Supporting Information "Pipeline Questionnaire."

The independent testing also aimed at assessing the capability of the pipelines to process different types of commonly used ASL data and the flexibility to configure for different types of studies. For this purpose, six ASL data sets were acquired on scanners from the three major vendors (GE, Philips, and Siemens) with various imaging parameters (pulsed ASL or pseudo-continuous ASL [pCASL], 2D/3D acquisition, with/without background suppression, single/multi-PLDs, with/without M_0, with/without high-resolution anatomical reference from

TABLE 1 Summary of the details of the six testing data sets used in the pipeline evaluation. Unless stated otherwise, the data sets were single postlabeling delay with control and label pairs acquired on a single subject in a single session.

Set	Vendor	Type	BSup	M_0	T_1	Relevant details
1	GE	3D spiral pCASL	Yes	Yes	Yes	ASL signal saved as DeltaM; DeltaM and M_0 saved in the same file
2	Siemens	2D-EPI PASL	No	No	Yes	Q2TIPS labeling saturation, M_0 calibration using the control image
3	Siemens	3D-GRASE pCASL	No	Yes	No	One subject scanned in two sessions with two runs per session
4	GE	3D spiral pCASL	Yes	Yes	No	Multi-PLD with seven PLDs and variable labeling duration
5	Philips	2D EPI pCASL	Yes	Yes	No	Time-encoded with Hadamard matrix
6	Siemens	2D	Yes	Yes	Yes	Two subjects acquired with two sequences: (i) EPI FAIR PASL on 7 T; (ii) multiband pCASL on 3 T

Abbreviations: ASL, arterial spin labeling; BSup, background suppression; FAIR, flow-sensitive alternating inversion recovery; GE, GE Healthcare; GRASE, gradient and spin echo; PASL, pulsed ASL; pCASL, pseudo-continuous ASL; PLD, postlabeling delay; Q2TIPS, quantitative imaging of perfusion using a single subtraction II with thin-slice TI_1 periodic saturation.

T_1-weighted scan). The data sets were provided in Neuroimaging Informatics Technology Initiative (NIfTI) format, with corresponding imaging parameters and file and directory structure following the ASL-BIDS definition.[32] PAR/REC, Digital Imaging and Communications in Medicine (DICOM), or ANALYZE formats were provided when the pipeline did not support NIfTI input without penalizing the pipelines. The protocols were detailed in a JSON (JavaScript Object Notation) file according to ASL-BIDS. The details of the data sets are provided in Table 1. Data sets 1 and 2 were GE and Siemens product sequences, which are widely available. Data Set 3 was a repeatability study with two sessions and two runs per session, testing the ability to deal with longitudinal studies with pretask and posttask scans. Data Sets 4 and 5 were advanced multi-PLD acquisitions. Data Set 6 contained a subject scanned at 7 T and at 3 T, testing the ability to incorporate different parameters in the same data set. Note that only the difficulty of pipeline setup, data handling, and the presence of main outputs were assessed. The CBF maps were visually checked for the presence of major processing artifacts and having gray-matter and white-matter CBF values within an expected range. See more information in the Supporting Information "Scoring System."

Each pipeline was randomly assigned to two testers (HF, DA, KB, AC, ZL, TL, JH, BP, and MT), who had no conflicts of interest (no studies with the pipeline developers in the last 2 years) or any previous experience with the pipeline. The testers were junior researchers (predominantly PhD students) with basic ASL experience and diverse backgrounds, including engineering, neuroscience, biomedicine, neurosurgery, and radiology.

Two testers independently scored each pipeline, and the testing coordinator (JP) checked the score agreement between the testers and, in case of significant discrepancy, resolved them by reaching a consensus with the two testers. Testers contacted the developers via official channels when they faced any issue and were unable to solve with instructions in the manual; note that a need for such intervention was part of the scoring system and led to lower scores due to incomplete manuals.

3 | RESULTS

3.1 | Pipeline inventory

We received responses from 21 pipeline developers (Tables 2–5). The results are also published on the OSIPI website (osipi.ismrm.org) and will be updated when new entries are obtained [ref will be provided after the website update].

Most pipelines are free for noncommercial use (n = 18) and easily available (n = 11; Table 2). While most of the pipelines were initially developed as research tools for in-house use, over half of the developers provide a manual or a tutorial (n = 13), publicly available source codes (n = 14), and a graphical user interface (n = 12), making independent external use possible.

Most of the pipelines explicitly declare support for data from the three major vendors (i.e., GE [n = 15], Philips [n = 15], Siemens [n = 16], and all three [n = 12]) (Table 3). Most of the pipelines run on MacOS (n = 13), Windows (n = 14), and Linux (n = 14), whereas one pipeline is an

TABLE 2 Author contact information and affiliation, a link for publication and download, and availability.

				Ease of use		
Pipeline name	Institution	Availability	Author's name	Manual	Source	GUI
ASAP[21]	Erasmus MC	⤓	Virginia Mato Abad	✓		✓
ASL toolbox[22]	University of Pennsylvania	⤓	Ze Wang	✓	✓	✓
ASL-MRICloud[23]	Johns Hopkins School of Medicine	⤓	Yang Li	✓		✓
ASLM	University of Zurich	⤓	Philipp Homan	✓	✓	✓
ASLPrep[31]	University of Pennsylvania	⤓	Azeez Adebimpe	✓	✓	
BASIL	University of Oxford, University of Nottingham	⤓	Michael Chappell	✓	✓	✓
CereFlow	Translational MRI LLC	▤	TransMRI	✓		✓
Clinical ASL-CVR	University Medical Center Utrecht	⤓	Jeroen Siero		✓	
ENABLE	Sunnybrook Research Institute	⧉	Zahra Shirzadi, Brad MacIntosh	✓	✓	
ExploreASL[19]	Amsterdam UMC	⤓	Henk Mutsaerts, Jan Petr	✓	✓	✓
Functional ASL	University of Michigan	⤓	Luis Hernandez-Garcia		✓	✓
Iris pipeline	Erasmus MC	⧉	Esther E. Bron	✓	✓	
LOFT-CBF	LOFT, University of Southern California	⧉	Kay Jann, Danny Wang, Chenyang Zhao		✓	
milxASL[26]	CSIRO	⧉	Amir Fazlollahi			
MJD-ASL	Vanderbilt University Medical Center	⤓	Manus Donahue		✓	✓
nordicICE (nICE)	Oslo University Hospital	⧉	Atle Bjørnerud		✓	✓
Quantiphyse (ASL)	University of Oxford, University of Nottingham	⤓	Michael Chappell	✓		✓
SCRUB-ASL	University of Pennsylvania	⧉	Sudipto Dolui	✓	✓	
Superselective pCASL CBF	UKSH Kiel, UKE Hamburg		Thomas Lindner		✓	
VANDPIRE	Vanderbilt University MC	⤓	Daniel Arteaga, Manus Donahue		✓	✓
Andrea Federspiel	University of Bern		Andrea Federspiel	✓		

Note: On request⧉, a public download is available (commercially available only▤)⤓.

Abbreviations: ASAP, automatic software for ASL processing; ASLPrep, ASL preprocessing; BASIL, Bayesian inference for ASL MRI; CBF, cerebral blood flow; CSIRO, the Commonwealth Scientific and Industrial Research Organization; ENABLE, enhancement of automated blood flow estimate; LOFT, Laboratory of Functional MRI Technology; MC/UMC, University Medical Center; Quantiphyse, visualization and analysis tool for 3D and 4D quantitative and physiological imaging data; VANDPIRE, a novel data-processing pipeline for imaging research.

OS-independent cloud-based tool. Some pipelines use software such as *MATLAB* (n = 13) and *FSL* (n = 10); the former requires a fee for both commercial and academic use, whereas the latter requires a fee only for commercial uses. Other pipelines use free software such as *Python* (n = 3) or *SPM* (n = 8) or parts of it, although noncompiled *SPM* code also requires *MATLAB*. Most pipelines work with the neuroimaging data formats NIfTI (n = 15) and ANALYZE (n = 9), respectively. Less than half of the pipelines support imports from the clinically used DICOM format (n = 9). Only three pipelines support ASL-BIDS,[32] the recently developed ASL extension of the standard for storing image data and acquisition metadata. All pipelines were developed for human brain data, and only a few were reported to be suited also for body imaging in humans (n = 3) and preclinical brain imaging (n = 3).

TABLE 3 Requirements as reported by developers.

Pipeline Name	Supported MR vendors	Operating system	Software requirement	Input data type						Organ, animal
				ANALYZE	DICOM	ENH-DCM	NIfTI	PAR/REC	BIDS	
ASAP				✓	✓		✓			
ASL toolbox				✓			✓			
ASL-MRICloud				✓						
ASLM							✓			
ASLPrep							✓		✓	
BASIL							✓		✓	Mice/rats
CereFlow					✓	✓				
Clinical ASL-CVR				✓	✓	✓	✓	✓		
ENABLE				✓	✓	✓	✓			Monkeys
ExploreASL				✓	✓	✓	✓	✓	✓	
Functional ASL (FASL)				✓	✓		✓	✓		
Iris pipeline				✓	✓	✓	✓	✓		
LOFT-CBF				✓	✓	✓	✓			
milxASL				✓	✓	✓	✓			Prostate
MJD-ASL					✓	✓	✓	✓		Kidney
nordicICE (nICE)				✓	✓		✓			
Quantiphyse (ASL)	N/A				✓		✓			Mice/rats
SCRUB-ASL				✓	✓	✓	✓			
Superselective pCASL CBF								✓		
VANDPIRE					✓	✓		✓		Kidney
Andrea Federspiel							✓			

Note: This table displays the basic requirements on the operating system (MacOS, Linux, Windows, cloud), third-party software (MATLAB, FSL, SPM, Python), data input types, and MR vendors (Agilent, GE Healthcare, Philips Healthcare, Siemens Healthineers, and United Imaging; other vendors might work but were not tested). All pipelines were developed and tested to work with human brain scans; further testing functionality is provided for different organs or for animal use in the last column.

Abbreviations: ASLPrep, ASL preprocessing; BASIL, Bayesian inference for ASL MRI; BIDS, Brain-Imaging Data Structure; CBF, cerebral blood flow; DICOM, Digital Imaging and Communications in Medicine; ENABLE, enhancement of automated blood flow estimate; ENH DCM, enhanced DICOM; NIfTI, Neuroimaging Informatics Technology Initiative.

TABLE 4 Features as reported by developers.

Pipeline name	PASL	pCASL	S-PLD	M-PLD	L-L	T-ENC	VS	fASL	PVC	Output space	Regional evaluation	QC
ASAP		✓	✓						✓			
ASL toolbox	✓	✓	✓	✓				✓	✓			
ASL-MRICloud	✓	✓	✓	✓	✓							✓
ASLM		✓	✓									
ASLPrep	✓	✓	✓						✓			✓
BASIL	✓	✓	✓	✓	✓	✓	✓		✓			
CereFlow	✓	✓	✓	✓								✓
Clinical ASL-CVR		✓	✓	✓	✓				✓			✓
ENABLE	✓	✓	✓	✓					✓			✓
ExploreASL	✓	✓	✓	✓	✓	✓			✓			✓
Functional ASL (FASL)	✓	✓	✓					✓				
Iris pipeline		✓	✓						✓			✓
LOFT-CBF	✓	✓	✓									✓
milxASL	✓	✓	✓						✓			✓
MJD-ASL		✓	✓					✓				✓
nordicICE (nICE)	✓	✓	✓									✓
Quantiphyse (ASL)	✓	✓	✓	✓			✓		✓			✓
SCRUB-ASL	✓	✓	✓	✓		✓			✓			
Superselective pCASL CBF		✓	✓				✓					
VANDPIRE		✓	✓				✓	✓				✓
Andrea Federspiel		✓	✓						✓			

Note: Main features concerning the labeling type (pseudo-continuous ASL [pCASL], pulsed ASL [PASL], single postlabeling delay [s-PLD], multi-PLD [m-PLD], Look-Locker [L-L], time or Hadamard encoded [T-enc]); vessel/superselective (VS), use of partial volume correction (PVC); output space of the resulting maps (ASL space , high-resolution T_1-weighted space , MNI space); output of regional values (whole brain , gray matter , manually provided region of interest , standard atlases); and a presence of a quality control (QC) report or images are provided to facilitate subject exclusion.
Abbreviations: ASAP, automatic software for ASL processing; ASLPrep, ASL preprocessing; BASIL, Bayesian inference for ASL MRI; CBF, cerebral blood flow; VANDPIRE, a novel data-processing pipeline for imaging research.

All the pipelines can process single-PLD pCASL data[14] (Table 4), which is the current clinical ASL standard. Some pipelines can also process the pulsed (n = 13) or multi-PLD (n = 9) ASL data. Only a small number of pipelines support more advanced sequences, such as Look-Locker (n = 4), time-encoded (n = 3), or velocity-selective ASL (n = 3). All pipelines provide the basic processing steps like motion correction and co-registration with structural images. Most pipelines are modular, and either offer a choice of different algorithms or the possibility to add new algorithms. However, more advanced steps, like partial volume correction (available in n = 12) or quality control measures (available n = 14), are not universally available. In general, the pipelines provide a sufficiently wide range of output options, with nearly all providing the individual ASL space output (n = 20) and most providing an output in the MNI and/or T_1 space (n = 13 for both).

Finally, Table 5 lists the number of studies and scans that have been processed by each pipeline as reported by the pipeline developers. Compared with the human brain scans, the number of other organ scans and pre-clinical scans is much smaller, being below 100 for all pipelines.

3.2 | Pipeline testing

Out of 21 pipelines from the ASL inventory, nine pipelines were included in the testing. Nine testers participated. Two had no conflicts of interest or prior experience using any

TABLE 5 Approximate actual use of the pipeline in practice.

Pipeline name	Studies	Human brain scans	Human nonbrain scans	Animal scans
ASAP	10–20	1000–10 000	0	0
ASL toolbox	100+	10 000+	0	0
ASL-MRICloud	N/A	10 000+	0	0
ASLM	5–10	N/A	0	0
ASLPrep	100+	10 000+	0	0
BASIL	50–100	1000–10 000	10–100	10–100
CereFlow	20–50	10 000+	0	0
Clinical ASL-CVR	5–10	100–1000	10–100	0
ENABLE	10–20	1000–10 000	0	0
ExploreASL	50–100	10 000+	0	0
Functional ASL (FASL)	5–10	10–100	0	0
Iris pipeline	5–10	1000–10 000	0	0
LOFT-CBF	10–20	1000–10 000	0	0
milxASL	510	1000–10 000	0	0
MJD-ASL	20–50	100–1000	10–100	0
nordicICE (nICE)	1–5	10–100	0	0
Quantiphyse (ASL)	1–5	10–100	0	1–10
SCRUB-ASL	20–50	10 000+	0	0
Superselective pCASL CBF	1–5	10–100	0	0
VANDPIRE	20–50	100–1000	10–100	0
Andrea Federspiel	10–20	100–1000	0	0

Note: This table lists how many different studies (Column 2) and data sets (Column 3), and how many human brain, nonbrain, and animal scans, were processed by the pipeline. For studies, the developers were able to choose from options 0, 1–5, 5–10, 10–20, 20–50, 50–100, and 100+. For scans, the options were 0, 1–10, 10–100, 100–1000, 1000–10 000, and 10 000+. Note that the numbers were self-assessed by the developers and are approximate estimates only.

Abbreviations: ASAP, automatic software for ASL processing; ASLPrep, ASL preprocessing; BASIL, Bayesian inference for ASL MRI; CBF, cerebral blood flow; ENABLE, enhancement of automated blood flow estimate; LOFT, Laboratory of Functional MRI Technology; pCASL, pseudo-continuous arterial spin labeling; VANDPIRE, a novel data-processing pipeline for imaging research.

tested pipelines; six testers had a single conflict (previous collaboration with specific developers or experience with a specific pipeline); and one tester had two conflicts.

Based on the inventory information provided by the developers, most of the tested pipelines provide GUI for data processing (n = 6), a batch mode for automated processing (n = 7), installation instructions for the required software (n = 8; Table 6), and manuals (n = 8; Table 2). Furthermore, all pipelines provide user support. Only a single pipeline (MRICloud) has a GUI for batch processing; the GUI extension of ExploreASL was not included in this independent testing, as it was not available at the time of testing. Most pipelines (n = 6) support all three operating systems, and one is available as a cloud application. As claimed by the developers (Table 3),

seven tested pipelines supported NIfTI; three supported DICOM; three supported ASL-BIDS; and five supported multi-PLD data.

Figure 1 shows the general scores. All pipelines can be downloaded directly online (n = 5) or after a simple registration (n = 4) (Figure 1A). In most cases, installation (n = 9), data preparation (n = 5), and setup (n = 8) are described in the manual and are easy to follow (Figure 1B). ASAP, MRICloud, BASIL, Quantiphyse, and VANDPIRE have a GUI. ASLPrep and ExploreASL use command-line interfaces but do not require advanced programming skills. ASLtbx and ASLM are recommended only for people with programming skills. Only MRICloud and VANDPIRE have GUIs for batch mode. ASAP, BASIL, and Quantiphyse are more difficult to use in a batch mode than in a single-subject mode (Figure 1C). Only ASLPrep

TABLE 6 Summary results of nonscalar questions in the pipeline assessment.

Pipeline name	GUI					Software					Batch		Support			Version		number
	A	B	C	D	E	🎨	🐍	▦	12	🖵	Yes/No	Save	🗪	✉	🛠	🔔	🗔	number
ASAP	✓	✓				✓		✓	✓	✓	✓			✓		✓	✓	2
ASL toolbox		✓				✓		*	✓	✓	✓j	✓	✓	✓		✓	✓	2.13.0.1
ASL-MRICloud		✓	✓						✓	✓	✓	✓	✓	✓		✓	✓	v5
ASLM						✓			✓	✓	✓			✓		✓		0.1
ASLPrep									✓	✓			✓		✓	✓	✓	v0.2.8
BASIL		✓						✓	✓				✓		✓	✓	✓	6.0.5
ExploreASL						✓		*		✓	✓		✓	✓	✓	✓	✓	1.9.0
Quantiphyse (ASL)		✓		✓		✓	✓			✓			✓	✓	✓	✓	✓	0.9.9
VANDPIRE		✓							✓	✓	✓	✓		✓		✓	✓	1.0

Note: Pictograms: optional (*); instruction of required software installation 🖵; active discussion forum 🗪; email contact ✉; active software development 🛠; notification of currently used version 🔔; all versions available to use 🗔.

Note: A, GUI for a batch data import from DICOM to NIfTI or BIDS; B, GUI for all processing steps on individual subjects; C, GUI for batch processing of multiple subjects; D, GUI for population analysis; E, GUI for results visualization; "Batch Yes/No," mode is available for automated processing; "Save," for GUIs only, the batch-mode configuration can be saved and reused for future study.

Abbreviations: ASAP, automatic software for ASL processing; ASL, arterial spin labeling; DICOM, Digital Imaging and Communications in Medicine; NIfTI, Neuroimaging Informatics Technology Initiative; VANDPIRE, a novel data-processing pipeline for imaging research.

and ExploreASL support ASL-BIDS. ASLtbx can still accept sequence parameters on subject level, but all other pipelines do not allow individual sequence-parameter configuration (Figure 1D).

Figure 2 shows the scores of processing the test data sets, and Figures 3 and 4 show examples of processed Data Sets 3 and 6. Three pipelines (ASAP, ASLM, and MRICloud) required data format conversion from NIfTI to ANALYZE, although that was not penalized in the scoring system. Prior manual splitting of the deltaM and M0 volumes (Data Set 1) or the multi-PLD volumes (Data Set 4) was necessary for ASLtbx, BASIL, and Quantiphyse, leading to rating "consulting needed." Data Set 5 proved difficult to process, as only ASLtbx and ExploreASL have built-in decoding of time-encoded data, although BASIL and Quantiphyse can process the decoded data. VAND-PIRE could only process Data Set 3, as it only works with single-PLD pCASL saved as control-label pairs, although that represents most of the current clinical ASL data. MRICloud could not process Data Set 4 with varying labeling durations, as it can process multi-PLD data only with fixed labeling duration. ASAP and ASLPrep only process ASL images accompanied by T_1-weighted images and hence could not process Data Sets 3 and 4. ASAP and ASLM were given lower scores, primarily because some basic configurations were difficult to set up and important information was missing in the manual, respectively. Although ExploreASL accepted ASL-BIDS, extra processing parameters had to be set for Data Sets 3–5. Only a few

pipelines were able to run the more complex Data Set 3 (n = 5) and Data Set 6 (n = 3) in a batch mode. ASLTbx was not given the highest scores for Data Sets 2–6, because the configuration file was difficult to set up, and some deep-level functions needed to be adjusted to process specific data sets; however, it was able to process all data sets.

4 | DISCUSSION

In this study, we created a comprehensive inventory of available ASL pipelines, summarizing their requirements and features. A subset of these pipelines was evaluated by independent reviewers to assess their ease of use, user requirements, and technical limitations. Although the core functionalities of the pipelines are similar, our findings showed that each pipeline has unique properties that can be useful to different users. Therefore, the inventory and testing results can help users to select a pipeline for their specific needs.

4.1 | ASL pipeline inventory

The ASL pipeline inventory was built on the self-assessment performed by the developers. As it is difficult to fairly assess the flexibility and ease of use of the pipelines by the developers themselves, we have evaluated these by independent reviewers. In addition, most of the
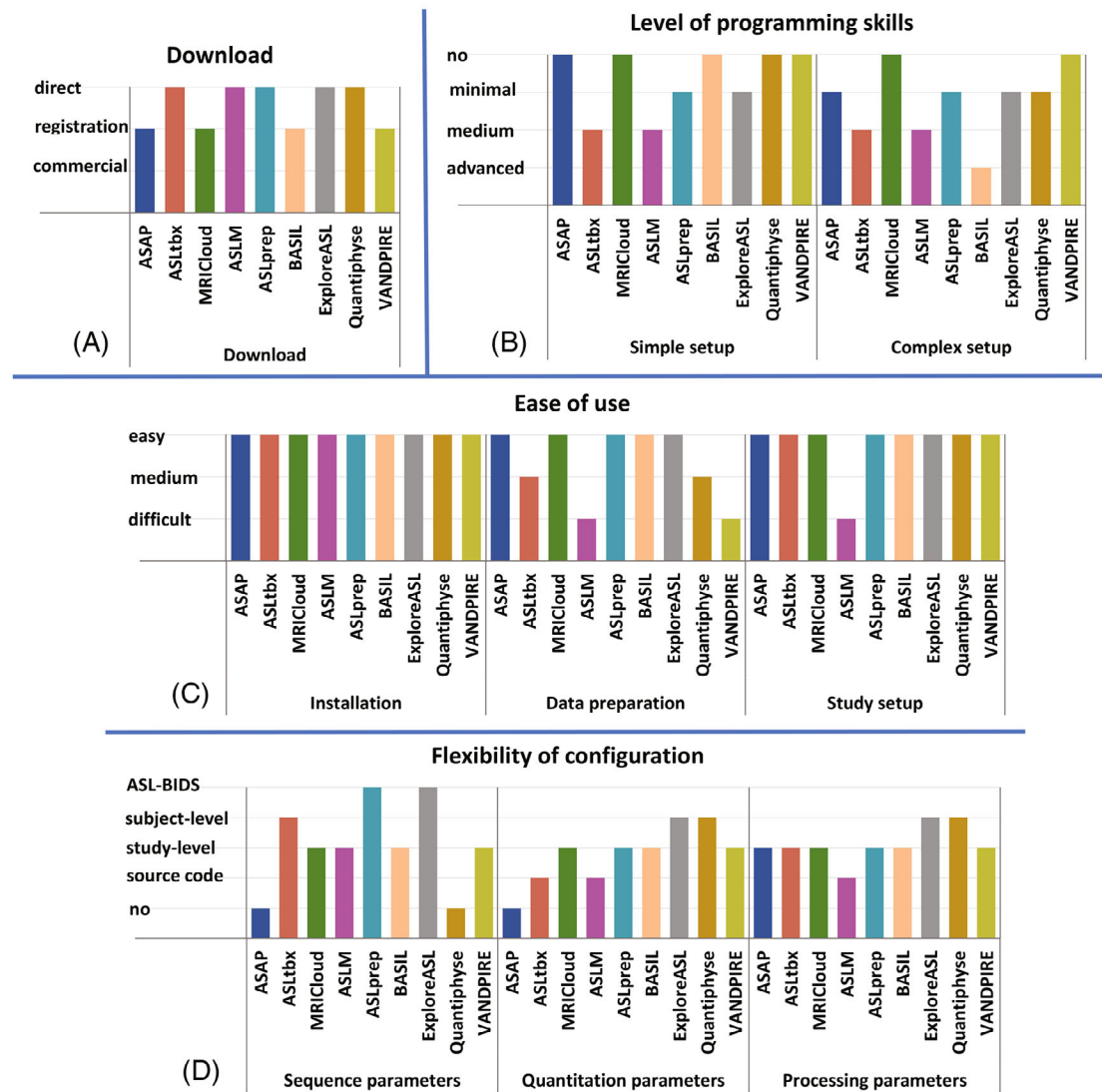
FIGURE 1 Summary of ease of use of pipelines. (A) Download can be done using a direct public link, after registration, or the pipeline has a commercial license. (B) Programming skills are needed to set up a simple study with a single scan or multiple scans of the same type or a complex setup with more than one scan possibly having various sequence types. This requires either no programming knowledge, as a GUI is available; minimal knowledge, as it has simple text-based inputs; medium knowledge of basic scripting; or advanced programming knowledge. (C) Installation, preparation, and setup are either trivial to follow or clearly described in the manual (easy); the description lacks details but is manageable without additional help (medium); or is difficult. (D) The sequence, quantification, and processing parameters in a multisequence study can be configured in Brain-Imaging Data Structure format for ASL (ASL-BIDS) format on the subject level or study level; it has to be changed in the source code or it cannot be changed at all. ASAP, automatic software for ASL processing; ASLPrep, arterial spin labeling preprocessing; BASIL, Bayesian inference for ASL MRI; VANDPIRE, a novel data-processing pipeline for imaging research.

pipelines applied all the relevant steps, such as motion correction, co-registration, and spatial normalization. Therefore, we decided not to report the inclusion of processing steps in the inventory. Finally, the number of scans and studies reported as processed by each pipeline was also self-assessed without strict criteria and should be interpreted with caution. We included it as an approximate assessment of the pipeline maturity, such as the level of effort spent in debugging, validation, and ability to work with different data sets. However, it is difficult to

objectively assess how many studies have been processed with a specific pipeline to date, as pipelines are not always mentioned in the methodological sections of published studies, and some studies might be mentioned in multiple publications. Finally, some pipelines do not even have a publication to reference.

For the inventory, to encourage collaborations, we listed all pipelines whose authors had filled in the questionnaire, regardless of pipeline accessibility. Even in-house pipelines might provide unique specialized
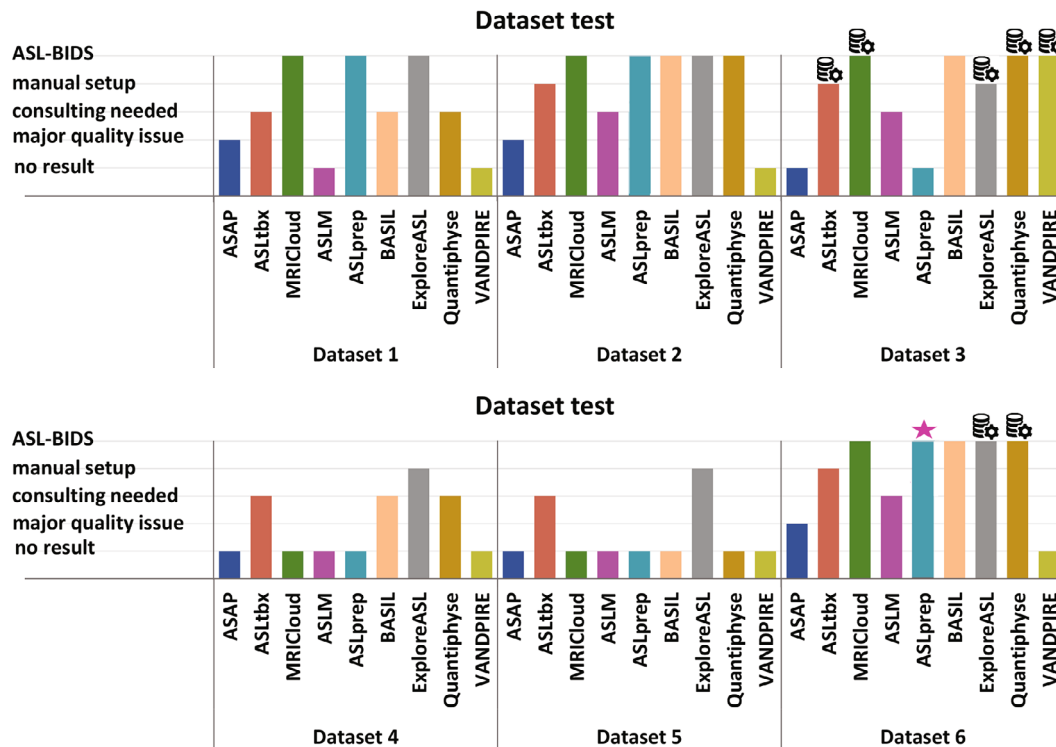
FIGURE 2 Summary of results of six test data sets with five score levels: (i) Brain-Imaging Data Structure format for ASL (ASL-BIDS): Pipeline worked directly with the ASL-BIDS data, or parameters from JSON (JavaScript Object Notation) files were manually filled in the GUI. (ii) Manual setup: Additionally, the data format or internal parameters had to be adapted according to the description in the manual. (iii) Additionally, we had to consult the developers or source code or experiment with different inputs. (iv) Additionally, the pipeline ran into major quality issues with the output. (v) No result: The pipeline did not run, or it crashed, or it was not possible to configure such a data set. Batch mode was tested in Data Sets 3 and 6, and a symbol indicates that the batch mode is available. ASAP, automatic software for ASL processing; ASLPrep, arterial spin labeling preprocessing; BASIL, Bayesian inference for ASL MRI; VANDPIRE, a novel data-processing pipeline for imaging research.

FIGURE 3 Representative axial slice for Data Set 3 for pipelines that processed the data set without major quality issues. The same scale is used for all images. The main differences are in the amount of regularization, noise, cerebral blood flow (CBF) scaling, and processing of the M_0 scan. Gray-matter (GM) masking is applied by default in a novel data-processing pipeline for imaging research (VANDPIRE). BASIL, Bayesian inference for ASL MRI.
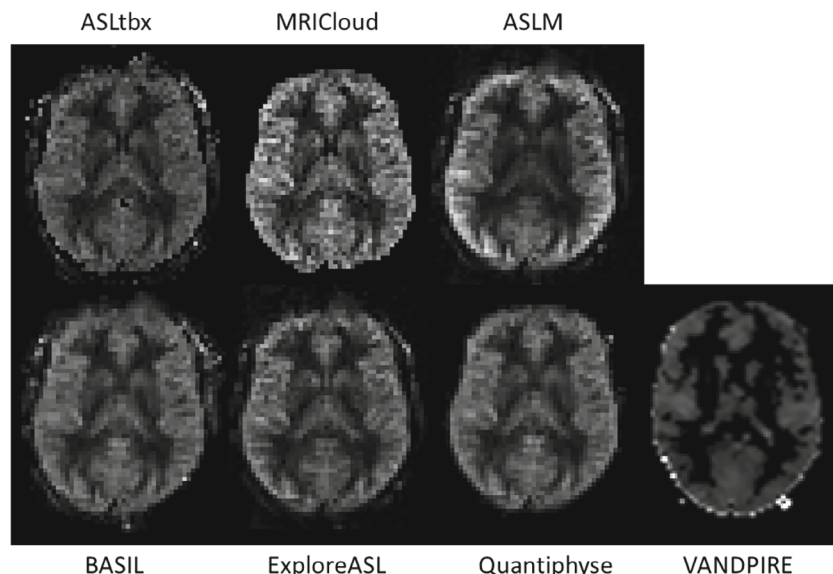
features and can be very valuable for certain research lines with data processed away from the original site. Finally, scanner vendors offer the possibility of quantifying ASL scans directly at the scanner console. Although this can be more useful for clinical use, this often does not include advanced processing and evaluation on the group level.
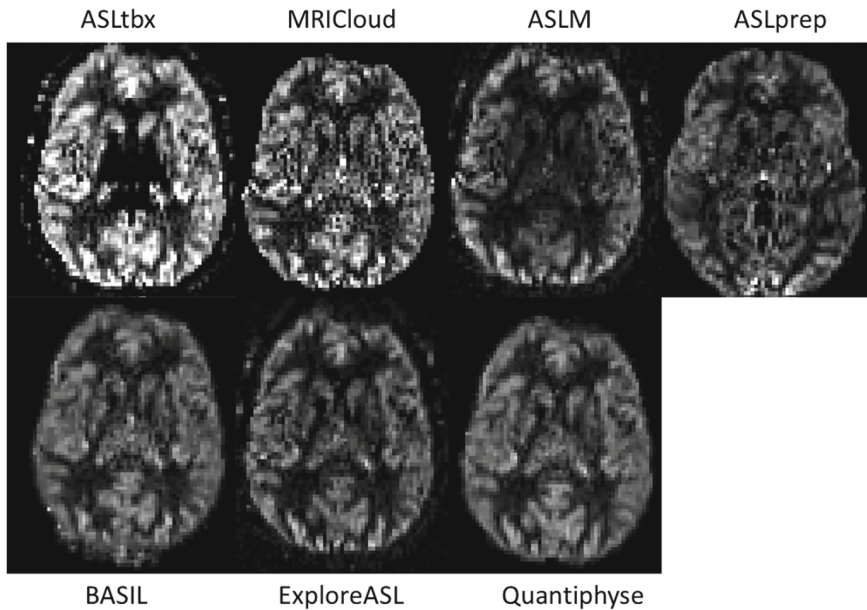
FIGURE 4 A representative axial slice for Data Set 6 for pipelines that processed the data set without major quality issues. The same scale is used for all images. The main differences are in the amount of regularization, noise, cerebral blood flow (CBF) scaling, and use of M_0. Unlike all other data sets, arterial spin labeling preprocessing (ASLPrep) results are shown aligned to the MNI space. BASIL, Bayesian inference for ASL MRI.

Therefore, we have decided not to include MRI vendor pipelines in this inventory.

There are many interactions and dependencies between the 21 listed pipelines due to the thriving collaborations between ASL researchers or the development of research and commercial projects within the same institute. The first publicly available pipeline—ASLtbx—has been widely available for almost two decades, and many other pipelines draw inspiration from it (e.g., SCRUB-ASL uses its motion correction module). Parts of code from the LOFT-CBF pipeline were reused by Andrea Federspiel's pipeline and later ASLM, and were the basis for the commercial spin-off CereFlow. The pipelines MJD-ASL and VANDPIRE were developed in the same institute and share parts of the code. Further pipelines—ASL-MRICloud and nordicICE (nICE)—were developed as an ASL module within a larger software package that is capable of processing structural MRI and other quantitative MRI modalities. Finally, many pipelines, including QUANTIPHYSE, ASL-CVR, ASL-Prep, ENABLE, and ExploreASL, use BASIL to perform the nonlinear fitting for CBF quantification. Despite all these interactions, all pipelines have highly variable input data formats, interfaces, outputs, and settings, making them distinct.

4.2 | Pipeline testing

Most of the testers were junior researchers with a technical or biomedical background and experience in ASL data processing. The testers were asked to assign scores from the perspective of inexperienced and nontechnical users using the scoring protocol, which is expected to provide an objective rating. We believe that this policy provided a fairer assessment than if tested directly by inexperienced users, as the latter group would not have been skilled enough to assess a pipeline's positives and negatives critically. Moreover, it would have required a larger group of inexperienced testers for an accurate assessment.

In the testing, most low scores for test data-set evaluation were related to the difficulty of data preparation due to incomplete manuals. Unlike new ASL users, an experienced user is usually able to prepare the inputs correctly by deriving the correct configuration from the source code, or by splitting and rearranging the NIfTI files. In such cases, we scored the pipelines as "able to process" specific data sets but with "low user-friendliness." Notably, the ASLtbx pipeline was perfectly able to process all data sets, and lower scores for data-set evaluation are only indicating that technical experience is required. ASLtbx is the ASL pipeline with the most years of experience, has high flexibility, has gone through extensive testing by users, has a very active discussion forum, and several other pipelines were partly derived from ASLtbx. Most pipelines provided CBF maps without any significant artifacts, and the CBF values were within a reasonable range for the data sets that we considered, although they varied across pipelines. More challenging and poor-quality data sets can potentially differentiate the pipelines, but such comparison will require extensive data sets of variable quality and is beyond the scope of this manuscript.

ASL-BIDS, introduced in 2021, is the ASL extension of the standard for storing image data and acquiring metadata and should provide standardized tags for

important ASL quantification parameters such as labeling duration or PLD.[32] Currently, only ExploreASL and ASLPrep fully support the use of ASL-BIDS, while several developers are working on implementing it in their pipelines. The commonly used dcm2nii (https://github.com/rordenlab/dcm2niix) is now in the process of fully implementing ASL-BIDS. Support of multiple formats, such as ASL-BIDS, ANALYZE or NIfTI, is also important because they do not contain protected health information, and thus are compatible with Health Insurance Portability and Accountability Act regulations.

Although most pipelines had a batch-processing mode, only a few pipelines were able to batch-process data sets that included various sequences. Although this feature is not required for small studies, it will become increasingly important in the future, given the trend of working with large multisite data sets.

4.2.1 | Discrepancy between ASL pipeline inventory and testing

The testers did not manage to run some pipelines on certain data sets, even though the developers reported support for these specific input formats and sequences. This resulted in some contradictions between the inventory and the pipeline testing. These were due to issues with pipeline configuration or a too-broad definition of the sequence type, rather than incorrect information in the inventory. For example, BASIL and Quantiphyse can process time-encoded data only if the raw data are decoded. Also, MRICloud works for all multi-PLD subtypes except for the sequence with variable labeling durations.

4.3 | Limitations

Both the inventory and pipeline testing have several limitations. First, our inventory is limited by the willingness of the pipeline developers to list their pipelines and the pipeline availability for testing. We anticipate that missing pipelines will be included in our continuously updated online inventory. Also, the inventory contains pipelines for human brain data only, as nobody registered ASL pipelines that would be primarily nonbrain or nonhuman, probably because they are still in an early developmental stage and not widely available. Second, while we tried to design the inventory and testing to answer the important questions from the anticipated user's perspective, it is inevitably incomplete. Also, this inventory is aimed uniquely at pipeline selection and does not provide details or guidance for performing ASL processing. However,

literature is available for ASL beginners for designing studies,[35] acquisition protocol,[14] quantification,[36] processing,[17] and clinical use.[37] Most of the pipelines, however, handle raw data and provide CBF in different regions of interest, which can be used for statistical analysis. Third, there were only two testers per pipeline. Therefore, there is a risk of bias in the evaluation because of a possible difference in ASL processing expertise. However, we anticipate the bias to be minimum as the testers because of the objective nature of the questions. Fourth, we could not perform an extensive comparison between the pipelines in terms of the quality and accuracy of the CBF maps, as the implementation of the processing steps and their configurations often differ. A fair comparison of pipeline performance would need a detailed comparison with different real and synthetic data sets and is out of the scope of this manuscript. A comparison of pipeline performances has been carried out by ISMRM OSIPI TF 6.1 (ASL Challenges). Finally, advanced sequences, such as velocity-selective and vessel-selective ASL, were not included in the testing even though they are increasingly becoming available.

5 | CONCLUSION

We created an inventory of ASL pipelines that we anticipate can serve as a guide to new and experienced ASL users looking for a pipeline that best meets their needs. This should accelerate the adoption of ASL outside of the specialized centers. The inventory also identifies the gaps in the availability of specific processing options, and the test results point out the weak spots in the ease of use of pipelines, both of which provide useful feedback to the developers. This will help to steer future ASL pipeline development, further benefiting the users.

Although it is difficult to recommend a single processing pipeline for all types of ASL data or users, we summarize the features of six pipelines that have an easier installation, more features, or support more ASL types. As a general recommendation, ASLPrep integrates complementary techniques from multiple software packages and uses container technologies that ensure easy installation and reproducibility. However, there is limited flexibility in reconfiguring the pipeline. ASLtbx is a widely available and flexible pipeline with a strong community, although coding expertise might be needed to configure the pipeline for individual studies. MRICloud can process data in the cloud, thus lowering the hardware and user requirement, although it offers lower flexibility in configuration and ASL sequences supported. Both BASIL and QUANTIPHYSE are easy to use and able to process most of the commonly

used ASL variants. Although they offer the most robust quantification of the multi-PLD data, automated processing of larger or heterogeneous data sets might be more cumbersome. ExploreASL provides a reasonably easy-to-use option to process any data with a focus on automated batch processing of heterogeneous studies. ASL-Prep and ExploreASL support the new ASL-BIDS format for easier data sharing.

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CONFLICT OF INTEREST STATEMENT

The authors were involved in the development of the following pipelines or were part of the team developing the pipelines: ASLToolbox (AC), BASIL and Quantiphyse (JH), ExploreASL (HM, VK, BP, JP), ASL-MRICloud (HF, ZL), SCRUB (SD), Super-selective pCASL CBF (TL), and VANDPIRE (DA). These conflicts of interest were considered when assigning pipelines to testers.

DATA AVAILABILITY STATEMENT

For access to testing data sets, contact the corresponding author. The complete questionnaire and scoring guidelines are available in the Supporting Information. The publicly available code of each pipeline was used for the pipeline testing, and links to repositories and the exact version of the software are provided in Table 6.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Data S1: ASL Pipeline Survey

Data S2: General Pipeline Assessment

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