Institution: University College London		
Unit of Assessment: 4 - Psychology, Psychiatry and Neuroscience		
Title of case study: Transforming the use of Arterial Spin Labelling for clinical practice globally		
Period when the underpinning research was undertaken: 2011 - 2015		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Xavier Golay	Professor	2008 - Present
Period when the claimed impact occurred: 2015 - 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Arterial Spin Labelling (ASL) is a non-invasive MRI technique for measuring cerebral blood flow, a key indicator of common, debilitating neurological diseases. Despite being easily implemented, cheaper and safer than existing alternatives, ASL remained underused due to a lack of harmonization in the MRI technology. Research led by Professor Golay at UCL produced harmonised guidelines on the use of ASL in clinical settings. The methodology has been adopted by the manufacturers of >90% of the world's MRI scanners, dramatically increasing adoption of the technique by clinicians globally, changing practice, improving patient outcomes and generating significant market growth in the commercial sector.

2. Underpinning research

Arterial Spin Labelling (ASL) is a technique first invented in the 1990s to measure brain perfusion (i.e., the rate of delivery of blood to the tissues). This measurement is important in almost all neurological diseases (dementias, tumours, strokes, multiple sclerosis) giving very early indications of the physiological state of the brain. It can be used to diagnose conditions (often earlier than other technologies) and accurately monitor disease progression. ASL has major advantages over all alternative techniques, being fully non-invasive (and therefore lower risk), and easily added to an existing MRI scan at minimal additional costs. Golay has been researching ASL since its discovery. Since moving to UCL in 2008, he has continued to work on developing ASL for several diseases in clinical settings [**R1**]. By the early 2010s, the technique was able to provide useful images in human subjects, but uncoordinated academic development globally had produced a profusion of different methods adopted by MRI manufacturers. The differences were significant enough to make the comparison of data from different MRI scanners impossible, preventing the adoption of ASL despite its advantages.

Golay's almost unique research experience as an MRI physicist specialising in brain perfusion made him one of the first to identify the need for harmonization of the methodology to allow its endorsement by the worldwide community. At UCL, he established a pan--European network of collaborators to this end, leading a successful bid for an EU COST Action networking grant (COST BM1103 Arterial Spin Labelling in Dementia, or 'AID').

The AID action (2011-2015) achieved its five core research objectives:

1. To harmonise and compare all existing ASL acquisition methods and to shortlist and further develop a number of techniques based on a selection of quantitative parameters.

2. To develop automatic image processing software to offer the best possible precision and reproducibility when comparing quantitative perfusion parameters.
3. To establish clinical trials to compare results obtained from ASL to FDG-PET across several European countries.
4. To validate use of ASL as a biomarker of disease onset and progression, and a possible trial outcome measure.
5. To establish a pan-European ASL network, which would become the reference sites for all aspects related to ASL in research and clinical routine.

As the COST Action network Chair, Golay established and co-ordinated the programme of research that delivered further developments in the field, and co-authored several studies involving many groups throughout Europe. The body of research includes work on advanced image processing techniques to improve estimation of various parameters [**R3, R6**]; careful comparison studies to highlight the major issues when using data acquired on scanners from various manufacturers [**R4**]; and providing in depth theoretical and practical insights into common ASL MRI methods [**R5**]. Golay also set up and co-ordinated conferences, workshops, training sessions and the exchange of students between labs to share technology. These activities jointly led to the publication of a set of recommendations in the form of a 'White Paper' [**R2**] contributed to, and endorsed by, 245 scientists as well as both the American Society of Neuroradiology and the American Society of Functional Neuroradiology, with impact confirmed by over 1,100 citations on Google Scholar.

3. References to the research

[R1] Paling, D., Thade Petersen, E., Tozer, D., Altmann, D. R., Wheeler-Kingshott, C. A., Kapoor, R., Miller, D. H., et al. (2014). Cerebral arterial bolus arrival time is prolonged in multiple sclerosis and associated with disability. *Journal of Cerebral Blood Flow and Metabolism*, *34(1*), 34-42. doi: 10.1038/jcbfm.2013.161

[R2] Alsop, D. C., Detre, J. A., Golay, X., Günther, M., Hendrikse, J., Hernandez-Garcia, L., Lu, H., MacIntosh, B. J., Parkes, L. M., Smits, M., van Osch, M. J. P., Wang, D. J. J., Wong, E.C., & Zaharchuk, G. (2015). Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: a consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. *Magnetic Resonance in Medicine, 73(1*), 102-116. doi: 10.1002/mrm.25197

[R3] Castellaro, M., Peruzzo, D., Mehndiratta, A., Pillonetto, G., Petersen, E. T., Golay, X., Chappell, M. A., & Bertoldo, A. (2015). Estimation of arterial arrival time and cerebral blood flow from QUASAR arterial spin labeling using stable spline. *Magnetic Resonance in Medicine, 74(6*), 1758-1767. doi: 10.1002/mrm.25525

[R4] Mutsaerts, H. J., van Osch, M. J., Zelaya, F. O., Wang, D. J. , Nordhøy, W., Wang, Y., Wastling, S., Fernandez-Seara, M. A., Petersen, E. T., Pizzini, F. B., Fallatah, S., Hendrikse, J., Geier, O., Günther, M., Golay, X., Nederveen, A. J., Bjørnerud A., & Groote, I. R., (2015). Multi-vendor reliability of arterial spin labeling perfusion MRI using a near-identical sequence: implications for multi-center studies, *Neuroimage*, *113*, 143-52. doi: 10.1016/j.neuroimage.2015.03.043.

[R5] De Vita E., Günther, M., Golay, X., & Thomas, D. L. (2012). Magnetisation transfer effects of Q2TIPS pulses in ASL. *Magnetic Resonance Materials in Physics, Biology and Medicine, 25(*2),113-126. doi: 10.1007/s10334-011-0298-z.

[R6] Chappell, M. A., Woolrich, M. W., Petersen, E. T., Golay, X. and Payne, S. J. (2013). Comparing model-based and model-free analysis methods for QUASAR arterial spin labeling perfusion quantification. *Magnetic Resonance in Medicine*, *69(5*), 1466-1475. doi: 10.1002/mrm.24372

4. Details of the impact

The Arterial Spin Labelling In Dementia (AID) programme has changed the MRI industry's approach to ASL. Outcomes were disseminated through publications, press releases and at

international conferences to members of the community as well as professionals working for the main Original Equipment Manufacturers (OEMs). Manufacturers welcomed the standardised approach laid out in the white paper [**R2**], recognising its potential to increase uptake of an underused technology. Four manufacturers accounting for over 90% of MRI sales worldwide (Siemens Healthineers, GE Healthcare, Philips Healthcare, Canon Medical Systems) have all aligned their products with the harmonised guidelines during this REF period. All ASL software purchased from these manufacturers now uses the methodology defined by the project led by Golay, and all customers subscribing to an MRI package (hospitals, research centres, etc.) will have had the option of updating their ASL software automatically.

The harmonisation of ASL products resulting from the White Paper's adoption by these three key companies has led to:

- An increase in the uptake and use of ASL around the world, with more and more clinicians buying the technology.
- The pioneering use of ASL in clinical trials, both as a biomarker for patient recruitment and/or as an early biomarker of response to therapy.

Commercial impact: Sales of harmonised ASL clinical software packages worldwide have seen a notable increase since the publication of the White Paper (released online in December 2014), from USD37,910,000 in 2014 to USD48,550,000 in 2019; this represents a near-trebling of the compound annual growth rate (CAGR) for this market compared to the period 2010-14 **[S1]**.

Representatives of the market-leading manufacturer in this space (Siemens Healthineers' Magnetic Resonance division) confirm the importance of *"the work led by [Golay] and the COST Action BM1103 on 'ASL in Dementia', and particularly the publication of the White Paper on ASL."* and recognise that his "*constant efforts on the development of more robust technologies, as well as on the continuous education of radiologists, clearly helped develop the market linked particularly to this MRI application."* They note the increase in demand for ASL in the clinical practice and research community following publication of the White Paper and its impact on the Siemens product line: "*To meet this demand, we implemented this technique and extensively tested it with our clinical collaboration community. Eventually, we brought the technique into our product for scanners of our new software baseline and we also see a steady increase of ASL installations over the years, indicating that ASL is accepted by the market. Currently, we see on average more than 30 research institutes each year being interested in participating in the assessment and application of prototypical 3D ASL imaging techniques"* **[S2].**

The Director of MR Clinical Science at Philips Healthcare has also recognised the importance of the work of Golay and his UCL colleagues: *"You were the main applicant of the EU COST Action BM1103 (Arterial spin labelling initiative in Dementia), which resulted in many collaborations in the field of ASL MRI in Europe and beyond. The impact and influence of the work performed in these initiatives on Philips and its MR business has been substantial."* Referring to the White Paper, he observes: *"This consensus paper gives very clear and actionable recommendations on how ASL sequences should be implemented on a clinical scanner to be performed successfully in clinical practice. Philips implemented an ASL product according to these consensus guidelines. It's important to realise that without these guidelines, it would have been far more difficult for Philips to bring a product to market; without clinical scientific consensus, it would have been very difficult to decide on the best implementation. ASL is an important part of our clinical MR offering. To illustrate its importance, roughly half of the new clinical MRI scanners are equipped with ASL functionality"* **[S3].**

In the REF period, Gold Standard Phantoms (a company spun out by Golay at UCL in 2015) has sold 15 units of the QASPER phantom based on Professor Golay's ASL research to customers in Australia, USA, UK, Netherlands, Belgium, Czech Republic, Singapore, China

and Japan. QASPER generated sales of GBP370,000 for the company (approximately 50% of total sales) in that period **[S4]**.

Canon Medical Systems Corporation is using the spinout's ASL phantom to optimise product development and acquire data to submit to the FDA and has found the product and the work of Golay and COST extremely useful, "*currently using [it] to optimize the development of our product sequence, according to the specifications of your reference paper, and acquire the necessary data we wish to use for submission to the FDA. For manufacturers like Canon, it is often difficult to establish what is the best sequence to implement in a field as crowded as ASL…your work and that of the COST Action [network] on identifying the best implementation has been very useful to establish the main direction used to develop our own product*" **[S5].**

Finally, GE Healthcare also praised the work from the COST Action network and explained that '*GE Healthcare's product implementation of Arterial Spin Labeling constitutes a 3D-based acquisition following a pseudo-continuous ASL labelling scheme. The recommendations subsequently put forward by the […] seminal consensus paper aligned well with that technical strategy. The reference paper […] has been instrumental in providing a framework for sites newly adopting ASL. We have observed a growing interest in non-contrast perfusion as a way of reducing cost and simplifying clinical workflow and an increase in the adoption of ASL in routine clinical imaging of the brain"* **[S6]**.

Impact on patients and practice:
Although the overall increase in sales since 2015 [**S1**] reflects an increase in the use of ASL, uptake of the technique worldwide varies by region and healthcare model. In the US, which accounts for almost half the global ASL market, private practices will use ASL as standard during neurological MRIs. In addition, Golay has been chairing the Quantitative Imaging Biomarkers Alliance (QIBA) Committee of the Radiological Society of North America (RSNA) responsible for writing the 'profile' (essentially a 'how to' guide) for the use of ASL as a biomarker in clinical trials.

A practicing neuroradiologist at University of California San Diego, formerly of Massachusetts General Hospital summarises its impact on care: *"The ASL white paper has been critical in making ASL a vitally important tool in clinical practice and research at two large academic institutions with high patient volumes. It has unquestionably improved patient care and ushered a new and exciting era of clinical ASL research".*

More specifically: "*The guidance provided by the white paper has allowed us to standardize our approach and implement an ASL protocol that is useful across a wide variety of neuropathology. At UCSD, for example, ASL is now performed in >90% of routine brain MRI protocols, compared to <5% just five years ago in 2015. ASL is used in 100% of our primary brain tumor protocols to i) distinguish between progressive tumor and post-radiation change and ii) identify areas of aggressive, high grade tumor. ASL is also a core component of our rapid stroke protocol (one of just four sequences) and can approximate regions of at-risk tissue in acute stroke. These ASL-based assessments in both brain tumor and stroke are typically not possible with conventional MR sequences and result in improved diagnosis and treatment of our patients. These are just two of the many areas in which ASL has changed our clinical neuroradiology practice, and this would not have been possible without the set of universal ASL guidelines provided by the white paper"* **[S7]**.

In Europe, the number and variety of key users and clinicians involved in the COST project **[S8]** has ensured widespread take-up of the findings. A clinician at the University of Geneva/Uppsala University observes: "*In my personal practice, ASL has become a routine practice and I use it every day"* [**S9**]. A neuroradiologist at Erasmus University Medical Center (the Netherlands) confirms: "*I use ASL for several indications in patients with neurological disease in my clinical practice, particularly in the assessment of cognitive disorders and neuro-oncology (brain tumours). ASL is routinely performed in every brain scan done for the assessment of cognitive disorders, which is approximately 100 scans per year. In patients with brain tumours, we use ASL in selected cases, amounting to about 100-150 cases per year"* **[S9]**.

She also notes the importance of ASL's higher diagnostic accuracy: "*It is my experience that for brain tumour patients ASL overcomes several limitations of the more commonly used DSC perfusion MRI technique. In a retrospective assessment of 29 patients who both underwent ASL and DSC perfusion, ASL provided additional information in 8, i.e. >25% of cases.*" [**S9**]

The increased use of ASL via MRI instead of other methods of measurement has a variety of benefits depending on the disease. Since it does not require a gadolinium (Gd) injection, clinicians find ASL of particular interest in those conditions in which in general Gd injection is not performed (e.g., dementia/neurodegenerative disorders) or if use of Gd injection is limited (e.g., renal insufficiency, allergy, children, pregnancy) **[S9].** In dementia, the main alternative involves invasive use of potentially toxic contrast agents associated with medical risks and higher costs. In some cases in Europe, fluorodeoxyglucose uptake is measured using a PET scan, but this is expensive and involves radiation. The standard of care for brain tumours also involves contrast agents. Replacing these methods with ASL is less invasive and less risky to patients. As a neurologist notes: "*this also has a potential financial benefit, by reducing the cost for contrast agent*" **[S9].**

Impact on clinical trials:
There are currently no drugs for the treatment of dementia, and clinical trials have historically been very expensive in the absence of an accurate and easily measured biomarkers. Subtle changes in perfusion are clear and appear before the first symptoms of reduced brain function, so ASL can accurately identify more patients at an earlier stage for recruitment to clinical trials. The number of new trials using ASL has doubled (according to clinicaltrials.gov) since the white paper, from an average of 15 per annum between 2010 and 2014 (with only a few uses recorded prior to 2010) to 30 per annum since 2015 **[S10]** demonstrating a clear impact on the way ASL enhances ability to undertake trials.

ASL allows a greater number of patients to be diagnosed and monitored during clinical study. Consequently, the search for effective drugs to treat disease including dementia is shortened. Gold Standard Phantoms' perfusion phantoms are key in this process ensuring that MRIs are calibrated and provide accurate and reproducible results.

5. Sources to corroborate the impact

[S1] Market report: *Global 3D ASL Market, 2010-2019*, published by Eon Market Research, December 2020.
[S2] Letter of support from VP Digital, Magnetic Resonance & VP Research & Clinical Translation, Magnetic Resonance, Siemens Healthineers.
[S3] Letter of support from the Director, MR Clinical Science, Phillips Healthcare.
[S4] Letter from Gold Standard Phantoms.
[S5] Letter from Canon.
[S6] Letter from GE.
[S7] Email from clinician at the University of California, San Diego.
[S8] Excel sheet incorporating the list of all scientists endorsing the publication.
[S9] Emails from clinicians at Universities in Switzerland, Sweden and the Netherlands using the technique.
[S10] Excel sheets from ClinicalTrials.gov.