APPENDIX 1: SUGGESTED ROADMAP

a. Key Mover

Identification of key research questions (**targets**), projects (**trials**), and participants (**teams**) necessary to change standard practice currently confined to considering the degree of stenosis and symptomatic status of the patient. This begins by examination of existing evidence that is valuable for identifying knowledge gaps through **systematic reviews**. Results of these reviews can then be used to **formulate key research priorities** for guiding development of RCTs.

There are several key questions and projects to be addressed in this period and these include:

"Imaging: how to define the carotid plaque and what features should be explored?"

The carotid plaque morphology and composition can be analyzed using different techniques: MRI, CTA, US.

MRI: The use of dedicated carotid surface coils and multiple MR contrasts has been the mainstay of carotid plaque characterization. There are now commercially available carotid surface coils and MRI pulse sequences (3D T1W, CE-T1W, T2W, TOF, MPRAGE) similar to those used for research in academic centers. There are multiple commercially available post-processing platforms for analysis of the carotid plaque. Despite all of this, multi-contrast carotid plaque MRI is mostly performed at academic centers limiting its generalizability.

To drive the adoption of carotid plaque imaging into everyday practice, there is an urgent need to investigate and test the utility of carotid plaque imaging using standard neck coils that are already in standard use for MR angiography of the neck vessels. A 4-minute 3D MPRAGE sequence is commercially available and can be employed for large FOV imaging using commercially available

neurovascular coils[1]. Single-contrast carotid plaque MRI is therefore readily available for use outside of research/academic centers. However, image resolution is compromised if dedicated carotid coils are not applied.

US : US (especially with 3D methods) assessment of TPA,TPV, and identification of ulcerations has been well documented. In addition, the ability to assess the effects of statins has revealed a sub-population not responding to guideline-based statin therapy. While commercially available 3D US units exist, the current limitations in superior-inferior coverage and software to measure TPA/TPV/ulcerations outside the research/academic institution are lacking. Correlation of the findings on ultrasound-based plaque imaging with MRI and CT plaque imaging has not been established.

CT Carotid CTA is widely available and the cross-sectional CT images of the arterial wall acquired during the angiography sequences can also be used to visualize plaque. This was the first plaque imaging modality to undergo the RSNA Quantitative Imaging Biomarker Alliance (QIBA) certification process. When complete, carotid plaque CT using QIBA compliant CT scanners, imaging protocols and analysis software generate highly reproducible plaque analysis in the routine clinical environment. There are multiple commercially available software platforms that can analyze carotid plaques on CTA with one program also demonstrating histological correlation. The detection of the outer wall of the carotid plaque is currently a semi-automated technique which will require dedicated CT technologist/radiologist time to complete. The greatest limitation with carotid plaque CT is the lack of natural history studies and/or drug treatment RCTs to support its use in this situation. An increasing number of studies are being reported on the clinical value of CTA[2].

In summary, the best modality to image carotid plaque may depend on local expertise and preference. A combination of plaque components (LRNC, IPH, thin/ruptured FC) along with plaque volume are

likely to be the best features for identifying high risk plaque and for measuring the effectiveness of lipid-lowering therapy over time.

Best practices for accurate quantitation

In this phase, accurate and reproducible quantitation would be addressed by application of the RSNA QIBA Profile for Atherosclerotic Biomarkers. QIBA is a multi-disciplinary consortium sponsored by the RSNA with the purpose of defining processes that enable the implementation and advancement of quantitative imaging methods. These methods are described in a QIBA Profile document that outlines the process for reliable and accurate measurement. The goal of a QIBA Profile is to achieve a useful level of performance for a given biomarker and to lead to acceptance of quantitative imaging biomarkers by the imaging community, clinical trial industry, and regulatory agencies. A large number of stakeholders have participated in the drafting of the "Atherosclerosis Biomarkers by (C)CTA – 2020" which has reached the Consensus Stage, having passed public comment with clinical, medical physics, and regulatory agency participation (http://qibawiki.rsna.org/images /8/87/QIBA_CTA_Profile_as_of_2020-Mar-10.pdf).

Also, the economic impact and the indications of different organizations should be taken into account in order to identify an optimal balancing in terms of diagnostic stratification of the risk and economic impact of the process. On August 4th 2020 the recently issued U.S. Preventive Services Task Force (USPSTF) document recommended against screening the general adult population for asymptomatic carotid artery stenosis (https://uspreventiveservicestaskforce.org/uspstf/draft-recommendation/carotid-artery-stenosis-screening-2021) and it concludes "with moderate certainty that screening for asymptomatic carotid artery stenosis in the general population has no benefit and may be harmful". This type of consideration that requires dedicated economic and outcome analysis should be addressed in dedicated future manuscripts.

PILOT TRIAL definition

After the definition of the frameshift information an effort to design multi-centre prospective trials would be necessary in order to define the role of imaging in the choice of the therapy. Agreement among neurologists, radiologists, vascular surgeons, and the other physicians who play a role in the stroke prevention work-up would be fundamental. Under this scenario the simplest choice would be to change the parameter used in selecting the therapeutic option. For example, rather than the presence of the degree of stenosis, plaque features based on evidence should be applied taking into account:

- Evidence(s) of increased risk of plaque's rupture
- Technology threshold allowing wide adoption

In the trial-phase definition, all this information would be obtained and analyzed by the use of questionnaire.

In this phase it would be possible to apply for temporary or emerging reimbursement codes and policy based on systematic review of currently available study data meeting a relatively modest evidentiary standard (with justification being to encourage sufficient use to build the larger evidence base).

b. Early

The aim would be to introduce plaque morphology into existing medical workflows while comparing its benefits against the established economic and clinical value of the established standards. Undertake early development of local reimbursement codes/policies in readiness for larger body of evidence of efficacy and patient benefit. This phase is targeted to two main objectives:

1) collecting a larger evidence base mainly through individual patient meta-analysis (methodologically more rigorous than the systematic review used in the previous phase), to combine the results of studies and perform sub-ancillary analysis.

2) initiate an RCT according to the shared view of the phase

In this phase, the aim is to successively introduce plaque morphology into existing medical workflows with established economic and clinical value, but without a new reimbursement codes or policies during the period when the temporary codes and policies are being considered by health and payer systems based on the applications having been filed in the prior phase.

c. Mainstream

Establish a multi-centre multivendor track record of techniques and patient outcomes toward permanent guidelines and policy changes. Collaborative central database construction for rapid, large data collection and analysis would accelerate this process. Standardised imaging protocols would allow accrual from both clinical (eligible retrospective and prospective studies) and ongoing research imaging, with capture of standardized patient clinical data ideally with follow up, requiring appropriate patient consent. In this phase the results from ongoing prospective trials (MESA[3], ARIC[4], SCAPIS[5], CAPIAS[6], PARISK[7], CAIN[8], Rotterdam Scan Study[9], CARE-II[10], HeCES2[11], ECST-2[12]) aimed to assess the value of plaque imaging in stroke risk stratification or outcome (SmartRisk, NCT00860184; CREST-2, NCT02240862; ACST-2, ISRCTN21144362) will be released. This will provide information on biomarkers of plaque vulnerability and their role on clinical decision making on outcomes. In the meantime, the preliminary results from RCTs with plaque imaging to inform clinical management will provide efficacy in the short-term follow up timeframe.

Temporary reimbursement codes or policy recommendations will be in place, for the purpose of enabling and incentivizing the collection of increasing data and establishing efficacy enabling permanent guideline and policy changes.

d. Full

Results from RCTs will address the outcome differences between best medical treatment compared to interventional treatment (CEA/CAS), and treatment selection randomized to the current standards

(degree of stenosis) versus plaque imaging as the new inclusion criteria. Change in clinical practice would lead to update of policies, guidelines, and billing codes. The new standards of practice will be confirmed to improve outcomes. This phase will permanently change codes, policies, and guidelines that are then set in place by jurisdiction.

APPENDIX 2: REPRODUCIBILITY OF IMAGING TECHNIQUES

MRI reproducibility: MRI-based tissue quantification is consistently accurate and reproducible when compared with histological evaluation of CEA specimens. Carotid bifurcation plaque characterization compared across three different MRI vendors showed interclass correlation (ICC) for intra-platform reproducibility to be very good with intra- and inter-reader reproducibility ranging from 0.83 to 0.99, respectively, for the lumen, wall, and total vessel areas, indicating strong agreement for repeated measurements[13]. Another study showed the intra-observer and interobserver reproducibility for quantitative area measurements of vessel lumen, plaque, lipid-rich necrotic core (LRNC), and fibrous components was overall high with sub-optimal results for the LRNC [14]. The status of the fibrous cap can be evaluated qualitatively (i.e.: thick, thin or ruptured) or quantitatively but with less reproducibility: measuring cap thickness remains challenging due to spatial resolution exacerbated by the patient motion[15]. In summary, quantification of vessel wall volume and the ratio of the wall to the wall and lumen thickness is the most reproducible MRI feature and the best to use in the evaluation of drug therapy over time, although a larger percent volume change in LRNC can also be detected[16].

Ultrasound reproducibility: The reproducibility of ultrasound in the plaque volume is very good with an intra-observer and inter-observer measurement reliability of 94% and 93.2%, respectively[17]. Echo-lucent plaques with heterogeneous content and irregular surface, are considered unstable and a cause of thromboembolic ischemic events. The number of ulcers depicted by 3D ultrasound was reliably detected ($\kappa = 0.83$) with interobserver reliability of $\kappa = 0.78$[18].

CT reproducibility: CT-based tissue quantification utilizing recently available image processing software[19] demonstrated a high correlation and low bias with ex-vivo histopathological quantitative

measures of atherosclerotic plaque tissue characteristics[19]. Intrareader variability was low and the repeatability coefficient ranged from 1.50 mm^2 to 1.83 mm^2. Inter-reader variability was also low with repeatability coefficients ranged from 2.09 mm^2 to 4.43 mm^2. Additional performance testing of the software program analysis of carotid CTA from a wide variety of CT manufacturers at multiple centers was also performed[2,20].

References

1. Saba L, Yuan C, Hatsukami TS, et al. Carotid Artery Wall Imaging: Perspective and Guidelines from the ASNR Vessel Wall Imaging Study Group and Expert Consensus Recommendations of the American Society of Neuroradiology. *AJNR Am J Neuroradiol* https://doi.org/10.3174/ajnr.A5488.
2. Zhu G, Li Y, Ding V, et al. Semiautomated Characterization of Carotid Artery Plaque Features From Computed Tomography Angiography to Predict Atherosclerotic Cardiovascular Disease Risk Score. *J Comput Assist Tomogr* 2019;43:452–9.
3. Zavodni AEH, Wasserman BA, McClelland RL, et al. Carotid artery plaque morphology and composition in relation to incident cardiovascular events: the Multi-Ethnic Study of Atherosclerosis (MESA). *Radiology* 2014;271:381–9.
4. Bijari PB, Wasserman BA, Steinman DA. Carotid Bifurcation Geometry Is an Independent Predictor of Early Wall Thickening at the Carotid Bulb. *Stroke* 2014;45:473–8.
5. Bergström G, Berglund G, Blomberg A, et al. The Swedish CArdioPulmonary BioImage Study: objectives and design. *J Intern Med* 2015;278:645–59.
6. Bayer-Karpinska A, Schwarz F, Wollenweber FA, et al. The carotid plaque imaging in acute stroke (CAPIAS) study: protocol and initial baseline data. *BMC Neurol* 2013;13:201.
7. Truijman MTB, Kooi ME, van Dijk AC, et al. Plaque At RISK (PARISK): prospective multicenter study to improve diagnosis of high-risk carotid plaques. *Int J Stroke* 2014;9:747–54.
8. Tardif J-C, Spence JD, Heinonen TM, et al. Atherosclerosis imaging and the Canadian Atherosclerosis Imaging Network. *Can J Cardiol* 2013;29:297–303.
9. Ikram MA, van der Lugt A, Niessen WJ, et al. The Rotterdam Scan Study: design update 2016 and main findings. *Eur J Epidemiol* 2015;30:1299–315.
10. Zhao X, Li R, Hippe DS, et al. Chinese Atherosclerosis Risk Evaluation (CARE II) study: a novel cross-sectional, multicentre study of the prevalence of high-risk atherosclerotic carotid plaque in Chinese patients with ischaemic cerebrovascular events-design and rationale. *Stroke Vasc Neurol* 2017;2:15–20.
11. Nuotio K, Ijäs P, Heikkilä HM, et al. Morphology and histology of silent and symptom-causing atherosclerotic carotid plaques - Rationale and design of the Helsinki Carotid Endarterectomy Study 2 (the HeCES2). *Ann Med* 2018;50:501–10.
12. Mortimer R, Nachiappan S, Howlett DC. Carotid artery stenosis screening: where are we now? *Br J Radiol* 2018;91:20170380.
13. Saam T, Hatsukami TS, Yarnykh VL, et al. Reader and platform reproducibility for quantitative assessment of carotid atherosclerotic plaque using 1.5T Siemens, Philips, and General Electric scanners. *J Magn Reson Imaging* 2007;26:344–52.
14. Takaya N, Cai J, Ferguson MS, et al. Intra- and interreader reproducibility of magnetic resonance imaging for quantifying the lipid-rich necrotic core is improved with gadolinium contrast enhancement. *J Magn Reson Imaging* 2006;24:203–10.
15. Makris GC, Teng Z, Patterson AJ, et al. Advances in MRI for the evaluation of carotid atherosclerosis. *Br J Radiol* 2015;88.
16. Saam T, Kerwin WS, Chu B, et al. Sample size calculation for clinical trials using magnetic resonance imaging for the quantitative assessment of carotid atherosclerosis. *J Cardiovasc Magn Reson* 2005;7:799–808.
17. Russell DA, Wijeyaratne SM, Gough MJ. Relationship of carotid plaque echomorphology to presenting symptom. *Eur J Vasc Endovasc Surg* 2010;39:134–8.
18. Madani A, Beletsky V, Tamayo A, et al. High-risk asymptomatic carotid stenosis: ulceration on 3D ultrasound vs TCD microemboli. *Neurology* 2011;77:744–50.
19. Sheahan M, Ma X, Paik D, et al. Atherosclerotic Plaque Tissue: Noninvasive Quantitative Assessment of Characteristics with Software-aided Measurements from Conventional CT

Angiography. *Radiology* 2018;286:622–31.

20. Chrencik MT, Khan AA, Luther L, et al. Quantitative assessment of carotid plaque morphology (geometry and tissue composition) using computed tomography angiography. *J Vasc Surg* 2019;70:858–68.