BIOGRAPHICAL SKETCH

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NAME: Hersh Sagreiya, MD

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POSITION TITLE: NCI Fellow

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harvard University (Cambridge, MA)	BA	06/2007	Biochemical Sciences
Stanford University (Stanford, CA)	MD	06/2012	Medicine
University of Pittsburgh (Pittsburgh, PA)	Residency	06/2017	Diagnostic Radiology
Stanford University (Stanford, CA)	Fellowship	06/2019	NCI/Body Fellowship

A. Personal Statement

I am a National Cancer Institute Fellow who is interested in pursuing a career as a physician-scientist. I am board-certified in Diagnostic Radiology. I began a research-intensive fellowship at Stanford in July 2017, mentored by Prof. Daniel Rubin and Prof. Juergen Willmann. I have extensive research experience going back to my undergraduate years when I used Matlab to code visual psychophysics experiments. Subsequently, I worked with Prof. Russ Altman as a medical student and did an additional year of research training under the Howard Hughes Medical Institute Research Training Fellowship. As a result of this work, I became interested in the use of bioinformatics tools to solve questions related to human health and disease, and I gained skills using different programming languages (R, Python, SQL) to perform large-scale data analysis.

As a third and fourth year radiology resident, I collaborated remotely with the laboratories of Dr. Willmann and Dr. Rubin on a study that analyzed quantitative imaging features of human colonic adenocarcinoma in a mouse model using contrast-enhanced ultrasound. I have also analyzed molecular ultrasound data of patients with suspected breast and ovarian cancer using the novel ultrasound imaging agent BR55 and used quantitative imaging features to predict pathological outcome. We plan to expand this approach to the analysis of a larger cohort of mouse data. I am collaborating on a paper that applies a multi-perfusion modelling approach to contrast-enhanced ultrasound in order to make better predictions. I am also collaborating on another paper that uses an unsupervised learning-based approach using curvature learning to predict disease status and treatment effectiveness. I am also applying machine learning to the analysis of ultrasound shear-wave elastography data within kidneys, with the first paper recently submitted. I am also working on multiple projects examining shear-wave elastography in patients with liver disease, including a paper examining patients in cross-section, another paper following patients longitudinally, and another paper taking a computer vision approach.

I am working on a deep learning analysis of head CT data using 3D convolutional neural networks to classify critical disease states, such as hemorrhage. Our first study aims to use an LSTM, a type of recurrent neural network, to assign machine-derived labels based on radiologist reports, to train a network using these labels, and to see how this network performs on radiologist-labeled data. Working with collaborators in the Rubin and Langlotz laboratories has significantly strengthened my knowledge and skills in deep learning, and Stanford has world-class expertise in this field. I have also undergone extensive coursework in machine learning and deep learning, including the Stanford CS 231N course, Convolutional Neural Networks for Visual Perception,

as well as three courses as part of the Coursera Deep Learning specialization. Based on these experiences, I am qualified for my proposed project, which is to analyze a well-curated database of over 3600 ultrasound shear wave elastography examinations using deep learning to automictically grade clinically-significant fibrosis. I received an NVIDIA GPU grant for my research projects. I plan to apply for an NIH K08 grant in early 2019.

B. Positions and Honors

Positions and Employment

2012-2013 Internship, Dept. Internal Medicine, Abington Memorial Hospital, Abington, PA
2013-2017 Residency, Dept. Radiology, University of Pittsburgh, Pittsburgh, PA
2017-2019 Body Imaging Fellowship, Dept. Radiology, Stanford University, Stanford, CA

Honors

2004 Detur Prize, Harvard
2004, 2006 John Harvard Scholarship
2005, 2006 Harvard College Research Program Grants
2006 Harvard Program for Research in Science and Engineering
2007 Magna cum Laude, Harvard
2008-2010 Stanford Medical Scholars Grants (x6)
2009-2010 Howard Hughes Medical Institute Research Training Fellowship
2010 American College of Physicians National Abstract Competition Finalist
2010 American Medical Association Seed Grant Research Program
2010 Stanford Medical Student Research Symposium Award
2017 RSNA Student Travel Award
2017-2018 Stanford Cancer Imaging Training Program (T32)
2017-2019 RSNA Research Fellow Grant
2018 NVIDIA GPU Grant
2018 Society of Abdominal Radiology Power Science Magna Cum Laude Award
2018-2019 Stanford Society of Physician Scholars Grant

C. Contributions to Science

Computer Aided Diagnosis Using Elastography and Machine Learning,* Dept. of Radiology, *Stanford University

Chronic liver disease is a crucial global health problem with rising incidence; in 2013 over 30 million Americans were affected and it was the 12th leading cause of death in the United States. Progressive liver fibrosis stages ranging from no fibrosis (METAVIR stage F0) to cirrhosis (METAVIR stage F4) have been established histologically, and accurate disease staging is paramount for patient management. Liver biopsy has previously been the gold standard for classifying hepatic fibrosis stage; nonetheless, non-invasive diagnosis of liver fibrosis with point shear wave elastography (pSWE), two-dimensional shear wave elastography (2D SWE), and magnetic resonance elastography (MRE) has been shown to be at least as accurate as liver biopsy, albeit with less risks and complications. MRE has been shown to be highly reproducible and accurate for liver stiffness measurement, as has ultrasound elastography, although with somewhat lower accuracy than MRE. Ultrasound elastography is cheaper than MRE and widely used in clinics; nonetheless, it lacks an ideal sensitivity and specificity in grading liver fibrosis, which can negatively influence patient care. Furthermore, ultrasound elastography cut-off values for grading liver fibrosis vary among manufacturers; therefore, results are not interchangeable from one system to another. In addition, studies with the necessary population size to define or improve these cut-off values are becoming harder to conduct due to the lack of a gold standard biopsy.
There is a critical need for robust cut-off values for grading liver fibrosis, which can be applied to all systems and diseases. We have developed a standardized fibrosis staging system and method using machine learning, magnetic resonance elastography (MRE), histopathology, and ultrasound elastography data that performs well regardless of shear wave technique (point vs. 2D). We developed a machine-learning algorithm for fibrosis staging that can accept data from any vendor and shear wave technique and provide a reliable grade that matches MRE and pathology.

a. **Sagreiya, H.,** Akhbardeh, A., Li, D., Sigrist, R., Chung, B., Sonn, G., Tian, L., Rubin, D.L., Willmann, J.K. “Point Shear Wave Elastography Using Machine Learning to Differentiate Renal Cell Carcinoma

and Angiomyolipoma." Submitted.

b. Durot, I., Akhbardeh, A., **Sagreiya, H.,** Loening, A.M., Rubin, D.L. "New Multi-Model Machine Learning Framework to Improve Hepatic Fibrosis Grading Using Ultrasound Elastography Systems from Different Vendors." Submitted.
c. **Sagreiya, H.,** Akhbardeh, A., Li, D., Sigrist, R., Chung, B., Sonn, G., Tian, L., Willmann, J.K. Point Shear Wave Elastography Using Machine Learning to Differentiate Between Renal Cell Carcinoma and Angiomyolipoma. Society of Abdominal Radiology. Scottsdale, Arizona. March 2018. Oral Presentation.

Multi-Model Framework to Estimate Perfusion Parameters Using Contrast-Enhanced Ultrasound Imaging, Dept. of Radiology, Stanford University

In order to diagnose disease in a variety of tissues and monitor treatments effectively, it is important to have an adequate estimation of perfusion parameters, such as peak enhancement, time-to-peak, area-under-the-curve, and mean-transit-time. Different perfusion models are ideal for different types of tissue. However, it is not always clear what is the best perfusion model for a given tissue. Our technique is able to simultaneously evaluate multiple perfusion models and identify the best one, leading to a more precise estimation of blood volume and blood flow. During cancer treatment, there may be minimal change in tumor size, the basis of treatment monitoring using the traditional RECIST criteria. However, there may be underlying changes in perfusion parameters, which can lead to more accurate treatment monitoring. We developed a robust multi-model framework for estimating perfusion parameters to reduce the amount of manual work required to tune the initial parameters and boundary conditions for curve-fitting, saving a substantial amount of time. It allows us apply the proposed perfusion modeling framework to multiple datasets in an automated manner, greatly facilitating the analysis of diverse cases of perfusion data.

a. Akhbardeh, A., **Sagreiya, H.,** El Kaffas, A., Willmann, J.K., Rubin, D.L. (2018). "A Multi-Model Framework to Estimate Perfusion Parameters Using Contrast-Enhanced Ultrasound Imaging." *Medical Physics*. Accepted.
b. El Kaffas, A., Hoogi, A., Tseng, A., Zhou, J., Wang, H., **Sagreiya, H.,** Hristov, D., Rubin, D.L., Willmann, J.K. Volumetric contrast-enhanced ultrasound parametric maps and texture feature extraction for tissue treatment response characterization. *2017 IEEE International Ultrasonics Symposium (IUS)*, Washington, DC, 2017. Conference Paper.
c. El Kaffas, A., **Sagreiya, H.,** Hoogi, A., Zhou, J., Hristov, D., Rubin, D.L., Willmann, J. "3D Contrast-Enhanced Ultrasound Parametric Map Feature Extraction for Cancer Treatment Monitoring." *Radiological Society of North America*. Chicago, IL, Nov. 2016. Abstract.

An Unsupervised Approach for Treatment Effectiveness Monitoring Using Curvature Learning--Stanford University: During cancer treatment, there may be little to no change in tumor size, which is the basis of treatment effectiveness monitoring using the RECIST criteria. However, machine learning could be used to extract additional morphological, textural, and perfusion-related features that improve treatment monitoring. However, supervised machine learning, which is currently widely used, is not always ideal, as it requires an adequate sample size for training and validation, may be prone to over-fitting, and can require manual feature selection and tumor segmentation, which may be time-consuming and expensive for a large dataset. However, an unsupervised learning approach using curvature learning can successfully identify treatment response and diagnose disease using dynamic contrast-enhanced ultrasound. We have developed an unsupervised machine learning technique utilizing curvature learning that can be used for treatment effectiveness monitoring and disease diagnosis using contrast-enhanced ultrasound. With traditional ultrasound, the tumor does not always change in size, which is what the traditional RECIST criteria are based upon. In addition, processing this data is computationally expensive and time-consuming. It is operator dependent due to the need of a region of interest to process the data. There have been some prior attempts to use machine learning, but they have been supervised techniques. This technique does not require any training, and it is a fully unsupervised approach that can dramatically save data processing time. It can also provide a more precise method for quantifying imaging data.

a. Akhbardeh, A., **Sagreiya, H.,** Durot, I., Rubin, D.L., Willmann, J.K. "Unsupervised Approach for Treatment Effectiveness Monitoring Using Curvature Learning." Paper in preparation.

Resident Research, Dept. of Radiology, University of Pittsburgh

I worked with Dr. Alessandro Furlan on a project that involved using radiologic features to predict underlying HCC tumor genetics and another project examining the additional utility of ancillary features in the LI-RADS classification system.

1. Furlan, A., Almusa, O., Yu, R., **Sagreiya, H.,** Borhani, A., Bae, K.T., Marsh, J.W. (2018). A radiogenomic analysis of hepatocellular carcinoma: association between fractional allelic imbalance rate index and tumor features on CT and MR imaging. *British Journal of Radiology*. E-publication ahead of print, doi: 10.1259/bjr.20170962.
2. **Sagreiya, H.,** Iranpour, N., Borhani, A., Cannella, R., Furlan, A. Liver Imaging Reporting and Data System (LI-RADS) v2014: Diagnostic Value of Ancillary Features on MR Imaging**.** *Radiological Society of North America*. Chicago, IL, Nov. 2017. Oral Presentation.

HHMI/Medical Scholars Research, Dept. of Bioengineering, Stanford Medical School

I did research on pharmacogenomics in the lab of Prof. Russ Altman. I wrote the IRB protocol and coordinated a study that involved genotyping 108 patients on warfarin. I also conducted a study that analyzed the STRIDE clinical database and collaborated with other researchers on a dosing algorithm paper and an ethnicity study. To support this work, I received Stanford Medical Scholars (2008-10), HHMI (2009-10) and AMA Foundation (2010-11) grants. I also took a leading role in writing a proposal that Dr. Altman submitted to the NIH NHLBI for sequencing 188 patients, which was successfully funded. I was a reviewer for *BMC Genomics* and *Cureus*. Publications include:

1. International Warfarin Pharmacogenetics Consortium (2009). “Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data.” *New England Journal of Medicine*, 360(8), 753-764.
2. Turcott, R.G., **Sagreiya, H.,** Altman, R.B., Das, A.K (2009). A General Framework for Dose Optimization. *AMIA Annual Symposium Proceedings*, 2009, 656-60.
3. Ashley, E.A., Butte, A.J., Wheeler, M.T., Chen, R., Klein, T.E., Dewey, F.E., Dudley, J.T., Ormond, K.E., Pavlovic, A., Hudgins, L., Gong, L., Hodges, L.M., Berlin, D.B., Thorn, C.F., Sangkuhl, K., Hebert, J.M., Woon, M., **Sagreiya, H.,** Whaley, R., Morgan, A.A., Pushkarev, D., Neff, N.F., Knowles, J.W., Chou, M., Thakuria, J., Rosenbaum, A., Zaranek, A.W., Church, G., Greely, H.T., Quake, S.R., Altman, R.B. (2010). “Clinical evaluation incorporating a personal genome.” *The Lancet*, 375(9725), 1525-1535.
4. **Sagreiya, H.,** & Altman R.B. (2010). “The utility of general purpose versus specialty clinical databases for research: warfarin dose estimation from extracted clinical variables.” *Journal of Biomedical Informatics*, 43(5), 747-51, doi:10.1016/j.jbi.2010.03.014.
5. Owen, R.P., Gong, L., **Sagreiya, H.,** Klein, T.E., & Altman, R.B. (2010). “VKORC1 Pharmacogenomics Summary.” *Pharmacogenetics and Genomics*, 20(10), 642-4.
6. Limdi, N.A., Wadelius, M., Cavallari, L., Eriksson, N., Crawford, D.C., Lee, M.M., Chen, C., Motsinger-Reif, A., **Sagreiya, H.,** Liu, N., Wu, A.H.B, Gage, B.,F., Jorgensen, A., Pirmohamed, M., Shin, J., Suarez-Kurtz, G., Kimmel, S.E., Johnson, J.A., Klein, T.E., Wagner, M.J. (2010). “Warfarin Pharmacogenetics: A single VKORC1 polymorphism is predictive of dose across three racial groups.” *Blood*, 115(18):3827-34.
7. **Sagreiya, H.,** Wen, A., Berube, C., Mir, A., Ramakrishnan, R., Hamilton, A., & Altman, R.B. (2010). “Extending and evaluating a warfarin dosing algorithm that includes CYP4F2 and pooled rare variants of CYP2C9.” *Pharmacogenetics and Genomics*, 20(7), 407-13.
8. Tatonetti, N.P., Dudley, J.T., **Sagreiya, H.,** & Altman, R. B. (2010). “An integrative method for scoring candidate genes from association studies: application to warfarin dosing.” *BMC Bioinformatics,* 11(Suppl 9), S9, doi:10.1186/1471-2105-11-S9-S9.
9. Danese E., Montagnana M., Johnson J.A., Rettie A.E., Zambon C.F., Lubitz S.A., Suarez-Kurtz G., Cavallari L.H., Zhao L., Huang M., Nakamura Y., Mushiroda T., Kringen M.K., Borgiani P., Ciccacci C., Au N.T., Langaee T., Siguret V., Loriot M.A., **Sagreiya H.,** Altman R.B., Shahin M.H., Scott S.A., Khalifa S.I., Chowbay B., Suriapranata I.M., Teichert M., Stricker B.H., Taljaard M., Botton M.R., Zhang J.E., Pirmohamed M., Zhang X., Carlquist J.F., Horne B.D., Lee M.T., Pengo V., Guidi G.C., Minuz P., Fava C. (2012). “Impact of the CYP4F2 p.V433M polymorphism on coumarin dose requirement: systematic review and meta-analysis.” *Clinical Pharmacology and Therapeutics,* 92(6), 746-56.
10. Perera M.A., Cavallari L.H., Limdi N.A., Gamazon E.R., Konkashbaev A., Daneshjou R., Pluzhnikov A., Crawford D.C., Wang J., Liu N., Tatonetti N., Bourgeois S., Takahashi H., Bradford Y., Burkley B.M., Desnick R.J., Halperin J.L., Khalifa S.I., Langaee T.Y., Lubitz S.A., Nutescu E.A., Oetjens M., Shahin M.H., Patel S.R., **Sagreiya H.,** Tector M., Weck K.E., Rieder M.J., Scott S.A., Wu A.H., Burmester J.K.,

Wadelius M., Deloukas P., Wagner M.J., Mushiroda T., Kubo M., Roden D.M., Cox N.J., Altman R.B., Klein T.E., Nakamura Y., Johnson J.A (2013). "Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study." *The Lancet*, 375(9725), 1525-1535.

11. Daneshjou R., Tatonetti N.P., Karczewski K.J., **Sagreiya H.**, Bourgeois S., Drozda K., Burmester J.K., Tsunoda T., Nakamura Y., Kubo M., Tector M., Limdi N.A., Cavallari L.H., Perera M., Johnson J.A., Klein T.E., Altman R.B. (2013). "Pathway analysis of genome-wide data improves warfarin dose prediction." *BMC Genomics*, 2013, 14 Suppl 3, S11.
12. **Sagreiya, H.,** Chen, Y., Kumarasamy, N.A., Ponnusamy, K., Chen, D., Das, A.K. (2017). "Differences in antipsychotic-related adverse events in adult, pediatric, and geriatric populations." *Cureus*, 9(2), e1059, doi:10.7759/cureus.1059.
13. Danese E., Raimondi S., Montagnana M., [and 79 others, including **Sagreiya, H.**]. (2018). The effect of CYP4F2, VKORC1 and CYP2C9 polymorphisms in influencing mean coumarin dose. A single patient data meta-analysis in more than 15,000 individuals. *Clinical Pharmacology and Therapeutics*. Accepted.

Undergraduate Thesis Research, Dept. of Neurobiology, Harvard Medical School
I conducted visual psychophysics experiments in the lab of Prof. Margaret Livingstone. This involved conducting experiments, gathering data, performing statistical analyses in Matlab, and assisting with paper writing. Topics included lightness perception, visual illusions, and speed detection. To support this work, I received undergraduate grants from the Harvard College Research Program (2005, 2006) and the Program for Research in Science and Engineering (2006). Publications include:

1. Howe, P.D.L., Thompson, P.G., Anstis, S.M., **Sagreiya, H.,** Livingstone, M. S. (2006). "Explaining the Footsteps, Bellydancer, Wenceslas, and Kickback Illusions." *Journal of Vision*, 6(12), 1396-1405, http://journalofvision.org/6/12/5/, doi:10.1167/6.12.5.
2. Howe, P.D.L., **Sagreiya, H.,** Curtis, D.L., Zheng, C., Livingstone, M.S. (2007). "The Double-anchoring Theory of Lightness Perception: A Comment on Bressan (2006)." *Psychological Review,* 114(4), 1105-1110.

List of Publications on PubMed:
https://www.ncbi.nlm.nih.gov/pubmed/?term=sagreiya+h

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support
RSNA Fellow Grant 07/01/17-06/30/19
"Quantitative analysis of ovarian cancer with novel molecular ultrasound agent BR55"
Role: PI, Mentors: Prof. Juergen Willmann and Prof. Daniel Rubin
Value $50,000

Completed Research Support
AMA Foundation Seed Grant Research Program 02/24/10-09/25/11
"Complete re-sequencing of genes critical to response to warfarin therapy"
Role: PI, Mentor: Prof. Russ Altman
Value: $2,500

HHMI Research Training Fellowship for Medical Students 06/01/09-05/31/10
"The use of next-generation sequencing and bioinformatics tools to study the pharmacogenomics of warfarin therapy"
Role: PI, Mentor: Prof. Russ Altman
Value: $38,000

Stanford Medical Scholars Research Grants 04/01/08-06/09/10
"Pharmacogenomics of warfarin dosing"
Role: PI, Mentor: Prof. Russ Altman
Value: $72,000