RESEARCH STATEMENT

Anthony Faiola, MFA, PhD

This research statement consists of two parts. Part one is a summary of my research, including three digital health technologies, a brief overview of the science, current projects, and future research. Part two provides a comprehensive overview of all funded project details according to their respective technologies, disease area, and study populations, along with project titles, funding sources, collaborators, etc.

SUMMARY

My research lies at the intersection of biomedical informatics and human-centered computing, where I leverage the medical sciences, the social/cognitive sciences, human factors, and usability science to study, develop, test, and clinically study the effects of digital health solutions with targeted patient populations and clinicians. My formative education, coupled with acquired cross-disciplinary knowledge and research methods, has enabled me to map a progressive line of inquiry with increasing focus and innovation.

Because of the scope of my interdisciplinary background, it is important to briefly clarify my transition to the medical and health sciences. After returning to graduate school to study industrial design, my research interests gradually shifted to the field of human-centered computing and the challenges of complex health systems and human behavior when engaging mobile health applications, biosensor devices, and virtual reality (VR) platforms. Hence, since 2006, the aim of my translational research has been to generate new knowledge and innovative digital health interventions that have a direct impact on the therapeutic treatment of patients with a range of non-communicable diseases. **My current research falls within the broader domain of biomedical informatics, with two foci: (1) Digital Health Solutions and (2) Health Behavior, with considerable emphasis on the former.**

DIGITAL HEALTH

Digital health, as my primary research focus, includes three significantly impactful health information technologies (HIT) with their respective patient populations and interdisciplinary methods. This research includes the assembling of and collaboration with physicians, nurses, biomedical and mechanical engineers, biochemists, biomedical informaticians, and medical researchers who share my passion and focus on several diseases and health conditions. The three HITs include:

HIT #1: VRx-Virtual (Reality) Therapeutics

Overview: The focus of my research that employs immersive VR technology is referred to as VRx therapeutic medicine and is currently revolutionizing non-invasive medicine.[1,2,3] My application of VRx is related to investigating the efficacy of a novel immersive VR training platform to treat mild cognitive impairment (MCI) of cancer (brain and breast), dementia, and stroke patients. The aim is to mitigate cognitive dysfunction and improve synaptic plasticity by increasing sensory engagement through movement/embedded selective attention training exercises. Patients are directed to focus and filter visual/auditory information as they navigate through a 3D immersive game-centered environment.

VR and Neuroscience: By 2020, I observed increasing evidence in the neuroscience literature that VR had the potential of noninvasively improving the cognitive function of cancer survivors. Particularly, by decreasing MCI while mitigating increased downstream cognitive impairment, improving mental health, and the overall quality of life. Studies have demonstrated that brain functional networks are disrupted in post-treatment breast cancer patients.[4,5] In this pathophysiological framework, acute and chronic cognitive impairment result from widespread neural network dysfunction and disruption, cortical network dysconnectivity, and neurotransmitter imbalances associated with acute and chronic widespread brain injury, such as neurotoxicity. Affected areas include all cerebral lobes as well as subcortical areas, which researchers suggest impacts the patients' large-scale distributed neuro-networks.[6,7,8,9,10,11,12] This leads to reduced alertness and pronounced inattention resulting in diffuse cognitive deficits. Hence, MCI may be connected through aberrations in brain functional networks (i.e., the default mode network, salience network, and frontoparietal network).

Based upon this understanding, cognitive non-interventions delivered early in post-treatment to cancer patients may rapidly engage impaired brain neuro-circuitry and promote arousal and attention, providing a novel approach to mitigating MCI. For example, despite the high rates of cognitive disability, a majority of breast cancer survivors do not receive effective post-treatment brain care.[13,14] VRx, as a new form of digital health intervention, has the advanced potential for post-treatment cognitive therapy due to its direct and deep interaction with sensory and attentional networks.[15,16,17,18,19,20,21] VRx produces cognitive stimuli that engage the frontoparietal network (involved in visuospatial processing) and the salience network necessary for selective attention (SA).[22]

Through synergistic effects, VR promotes activity of the locus coeruleus-norepinephrine (LC-NE) system while reducing activity within the default mode network (normally downregulated during tasks requiring focus).[23,24] As LC-NE is a powerful effect on the regulation of multiple memory systems, the hippocampus is responsible for tagging memories with respect to context (time and place).[25] It functions as a reciprocal connection to the rest of the brain through multiple pathways to the neocortex (frontal cortex), including the basal ganglia, thalamus, hypothalamus, and hippocampus. As such, the hippocampus is only one of many memory systems, but one with a special role in storing long-term memories that are contextually meaningful in time and place.[26] Considered together, immersive VR immersive training may aid in the stimulation of time and place neurons, i.e., in the organization of events in different relational dimensions that provide cognitive maps that form episodic memory in space and time. [27,28,29,30]

While VR selection attention exercises are intended to affect the cerebrum (responsible for executive function, attention, memory, mood, and reasoning), the hippocampus and medial entorhinal cortex are targeted for increased spatial learning and memory, which is stimulated when players navigate through the 3D spaces of an immersive VR-based game.[31] Such stimulation provides both spatial input (the where) and non-spatial input (the what), a stimulus effect not seen with 2D interaction with a tablet or computer screen.

In sum, we argue that immersive VR cognitive engagement has the potential to produce pathway integration whenever the player begins to understand his/her global frame of reference from external input about the VR immersive environment through which they are navigating. As such, the VR experience for patients may increase processes that result in numerous receptors releasing neurotransmitters, which could initiate neurogenesis and increased plasticity.

VRx—Phase One: The phase one development of our current VR Cognitive Therapy Platform (built 2021-24) is referred to as: Virtual Reality—Cognitive Rehabilitation Training (**VR-CRT**). As noted, VR-CRT brings scalable innovation for adult cancer, dementia, and stroke patients with MCI. The VR-CRT platform was designed with input from a multidisciplinary team of experts in dementia, physical therapy, neuro-oncology, communication disorders, human-centered computing, and VR game design/programming. Regarding the scalability of VRx, digital solutions for healthcare therapies have recently been approved by the FDA and are now billable items, i.e., reimbursable as health therapies through Medicare/Medicaid.[32] See the Appendix for details.

Due to VR-CRT's ability to engage sensory processing, visuospatial memory, motor behavior, and attentional networks,[33,34,35,36,37,38,39] it has considerable advantages over traditional computerized cognitive training programs. The VRx platform includes an immersive 3D VR environment with 81 embedded attention exercises, offering a unique mechanism of neurotransmitter stimulation. VR-CRT is a scenario goal-driven (game) framework that rewards patients with points and feedback at the end of each module to promote engagement and incentivize use. Backend automated game score tracking encourages aspirational behavior and goal setting with each module completion.

VRx Studies: Outcomes from our recent preliminary pilot one-arm VR-CRT study yielded a small dataset showing a consistent mean improvement in cognitive performance of neuro-oncology (post-treatment) patients after four weeks of daily dosing. Our baseline testing included the Hopkins Verbal Learning Test, Controlled Oral Word Association test, and Trail Making A-B. We observed the greatest improvement with the Controlled Oral Word test with a 40.41% improvement, suggesting increased verbal fluency, executive function, broader cognitive plasticity, and high-order executive abilities. We posit that cognitive gains may be attributed to the VR-CRT training exercises that placed a constant burden on retrieval required for executive control from selective attention switching or cognitive shifting which involves conscious change in attention. Neuro-oncology patients were recruited from the Markey Cancer Center, University of Kentucky.

Our follow-up study with 30 neuro-oncology patients is currently in the final review at PRMC, to begin winter 2025-26, the University of Cincinnati Cancer Center (UCCC). This is an internally UCCC funded study in collaboration with colleagues from neuro-oncology, neurology, and the UC Neuroscience Institute.

We also have an American Cancer Society grant pending for a study with breast cancer survivors with MCI. Additionally, my IU colleagues (Drs. S. Khan and B. Khan) and I are seeking NIH/NIA funding for a feasibility and efficacy study with ICU delirium patients. Our research team is currently preparing for a VR-CRT study that was funded by an internal Indiana University School of Medicine grant. An NIH/NIA Trailblazer Grant and NIH/NIA R01 are anticipated following preliminary data collection. We have a large, well-trained team in place at IU to execute this research.

Additional collaboration with my colleague, Dr. Marco Iosa, is on the way in Rome, Italy at Sapienza University and the Santa Lucia Foundation/Clinic, with data collected slated for winter-spring (2025-26). In our research, we will study the effects of VR-CRT with stroke patients with cognitive impairment. This research will also include the use of a (non-invasive) mobile EEG system to collect data during cognitive training sessions. We will observe and record variations in brain activity in real-time as patients respond to cognitive tasks and other stimuli from within the various geographic locations within the immersive VR environment. This will allow us to more accurately identify the coordinates of cognitive stimuli, load, and emotional responses for future, better targeted, stimuli.

Future Research: AI-Powered VR-CRT–Phase 2: Future research includes a five-year strategic plan based on current funding lines. AI-powered VR-CRT (ai-VR-CRT) will leverage artificial intelligence to enhance the cognitive rehabilitation experience for patients with MCI. Phase two will transition from a simple VR platform with back-end time/action tracking to an AI enhanced training system that challenges player cognition with greater predictive accuracy. ai-VR-CRT holds the potential for greater cognitive stimuli and frontoparietal network engagement. Integration of AI functionality is critical for producing a more intelligent and efficacious approach to MCI therapy.

ai-VR-CRT phase two development is currently on the way, which includes three AI algorithms that allow greater precision in data analysis, real-time player modulation, and tracking of game difficulty and performance, thereby providing increased adaptability for each patient's personalized progress.

AI modeling techniques will be used to push the patient to increase their use of both short-term memory and other executive functions. The system will track/measure patient navigation and interactions (with spaces, objects, and avatars), while anticipating future reactions in real-time. In addition to leveraging AI, we plan to employ greater knowledge of game theory, statistics, eye-tracking, and behavioral theory to better predict individual action and measure patient cognitive health based on movement and reaction time, eye-hand coordination, and accuracy of exercise problem solving. Specifically, **ai-VR-CRT** will employ three AI models: Player Experience Modelling (**PEM**), Non-Playing Character modelling (**NPC**), and Natural Language Processing (**NLP**):

- **PEM** will produce four forms of AI data and analysis: **(1)** Performance and behavioral, e.g. navigational speed/movement, attention exercise scores, spatial orientation, and recognition abilities; **(2)** Input modalities, e.g., speech recognition, written data (intonation, text); **(3)** Adaptation and assessment modeling, a self-adjusting algorithm that analyzes real-time player difficulty. (This AI modeling matches the difficulty of the patients' task to their skill level relative to prior performance. PEM will understand/respond to player performance and modulate difficulty intended to increase patient motivation, while incrementally challenging patient cognitive load—thereby maximizing cognitive stimulation), and **(4)** Predictive cognitive performance, that is, the leveraging of regression-based machine learning algorithms to attain meaningful forecasting about accumulated experience-dependent game improvements and its effect on (decreasing or increasing) cognitive impairment.
- **NPC** will produce intelligent behaviors, including role playing characters' emotion/attitude modeling. This will include sentiment NLP analysis, which supports dialogues with patients, e.g., conversations, giving instructions, or asking questions. NLP-generated insights about how the patient feels and interacts/reacts will be processed in conjunction with PEM to provide game feedback for subsequent game scenarios. Sentiments will also be extracted from the patient's spoken and text messages, allowing believable emotional (natural fluency) responses, thereby deepening the emotional experience through patient-NPC engagement.
- **NLP** will focus on the interpretation and manipulation of human language analysis by NPCs in patient communication, i.e., providing a meaningful automated response by employing sentiment analysis to determine the feelings expressed by the patient. In sum, NLP will greatly enhance the quality of assessing the player's communication in real-time while creating a more immersive real-world experience for the patient player.

New AI VR Partnerships: I recently formed an alliance with the largest funded AI research lab at UC, located in biomedical engineering. The lab's large group of AI students, post-docs, and full-time researchers will allow me to maximize my progress to create another level of therapeutic efficacy for VR-CRT with future funded studies.

HIT #2: Diagnostic Nano-Biosensors

Overview: My team's research with biosensors includes the use of volatile organic compound (VOC) biomarkers and nano-sensor integration, in conjunction with handheld smart sensor systems for accurate and noninvasive detection. Current study populations for this research include patients with prostate cancer and cystic fibrosis, with prior related work with type 1 diabetes (hypoglycemia) patients.[40]

Current Research: This research seeks to determine whether existing VOC detection technology coupled with biometric readouts is sufficiently robust and sensitive to diagnose a multiplicity of diseases by scent. That is, the research seeks to emulate canine disease detection[41,42,43] in a robust and standardized platform that will first be optimized for disease detection accuracy and then be optimized for portability, cost, and speed. Canines detect diseases such as malaria on skin because diseases induce dysregulations of metabolic pathways leading to changes in metabolic byproducts, including VOCs[44] and changes in biometric data (e.g. heart rate, blood pressure).

Our team identified a VOC signature for hypoglycemia[45] in breath, developed selective and sensitive sensors for functional groups associated with this VOC signature,[46,47,48] incorporated the sensors into a prototype array, and developed a smartphone app to deliver the results to end users[49]. Our team additionally has optimized collection and analysis of mouse urine in minute quantities (50 µL)[50,51,52,53] as well as human urine for prostate cancer and remote breath collection for COVID-19.

With this work, we coordinate with our investigators to build data-secure, human-centered, and usability tested interfaces for portable sensors and delivery devices, which includes the translation of biosensor data into usable real-world diagnostics. The research builds on our existing canine-inspired nanosensor technology (funded via NSF 2015-19) that uses VOC biomarkers and smart sensors to detect hypoglycemia from human breath.

The next phase of this technology will have clinical applications in two additional ways with funded research: **First**, VOCs emanating from urine will support screening for patients diagnosed with prostate cancer and will result in a portable GC-MS system to screen and detect prostate cancer in clinical settings and within a patient's home. **Second**, a handheld smart sensor system (integrated with machine learning algorithms) will accurately and noninvasively detect pulmonary exacerbations (PEx) in cystic fibrosis (CF) patients at point-of-care through rapid VOC detection.

HIT #3: Mobile Health (mHealth)

Overview: My work in mHealth includes the design, development, testing, and implementation of mobile apps, web portal dashboards, and backend databases to deliver community-focused, patient/caregiver-centered, and high-quality cancer care. Current study populations for this research include families of cancer patients and underserved cancer patients to improve timely access to a broad range of services and healthcare, besides basic treatment, e.g., chemotherapy. Current and recently completed research includes two projects:

Project #1: This clinical study addresses the mental health disparities of families of cancer patients from rural Kentucky by investigating the efficacy of a newly developed mobile health platform (FamCare+) to reduce anxiety and depression of cancer patient family members by connecting families at home with clinicians at the bedside. The goal is to increase communication and information flow from the bedside (e.g., ICU, cancer treatment, hospice, etc.) to next-of-kin, thereby providing a link with those most responsible for the care of their loved one. FamCare+ provides real-time patient vitals and wellness updates, media tools (texting/video), and convenient access to social/mental health counseling services.[54,55,56] The FamCare+ project began six years ago, passing through multiple iterations of prototyping and testing. A paper is currently being prepared with the findings of this study. (Funding: Markey Cancer Center Community Partnership Planning Grant).[57]

Project #2: The goal of this recently funded project, Comprehensive Connected Cancer Care (C4), is to advance health equity for underserved populations by improving timely access to community-focused, patient-centered, and high-quality cancer care, particularly targeting underserved populations such as rural, low-income uninsured communities. Building on the work of the MyPath platform, C4 improves coordination of care with supportive/ancillary care providers and community services through use of a newly designed, developed, and implemented patient navigation and a digital closed loop referral system. The new patient centered platform will include a dashboard for the navigator and healthcare team and a mobile app for the patients and caregivers to: (1) improve patient-centered communication and engagement in care and (2) increase use of needed psychosocial care and other supportive services through use of the MyPath dashboard and mobile app. (Funding: Merck Foundation Award— *Alliance for Equity in Cancer Care*).

HEALTH BEHAVIOR

Health behavior (Population Health / Disparities) will play a lesser role in forthcoming research. While knowledge gained through several population health and informatics studies has provided both empirical and theoretical grounding for my work in digital health, both time and interest in this area is increasingly limited. My research in health behavior focused on two areas:

1) Population Health: This research focuses on the health disparities of marginalized rural underserved communities throughout the US. These studies focus on self-care behavior, health literacy, and the application of information to support disease prevention and health promotion. This also includes investigating social media cognitive overload associated with information anxiety and avoidance behavior. Our studies have also shown that disparities in health outcomes present difficult challenges to underserved populations in Kentucky, the surrounding states, and globally, in countries like Pakistan and India. As such, these populations often experience a greater burden of disease, with less knowledge of health literacy and disease management. Both mHealth and telehealth have been shown to be vital links to reducing such disparities in rural clinical and home care settings.

2) Health Informatics and Consumer Health Informatics: Work in health informatics focuses on solutions to improve the quality and safety of health care services, building novel data science methods using patient-clinician verbal communication and patient self-reported messages. Specifically, the aim of this work was to identify social media information about adverse drug events and drug effectiveness by linking patient expressions of adverse drug events to medical standard vocabularies. This work also includes text mining algorithms/analysis of patient narrative data of psychiatric antidepressant medication (e.g., Selective Serotonin Reuptake Inhibitors).

My research in consumer health informatics focused on behavior change strategies using mHealth. The most current research in the area targets the wellness needs of parents with children and the elderly. This study evolved out of research related to children's health, while earlier papers focused on mHealth data analytics to support healthy lifestyle management. These position papers on consumer health informatics argue for: 1) empowering the elderly through the use of mobile health to achieve and sustain healthy lifestyle behaviors, 2) developing a sociotechnical system model and the use of mHealth technologies to support the management of noncommunicable diseases such as diabetes, and 3) leveraging health informatics and human factors psychology, through which mHealth and lifestyle management care-team collaboration can significantly support sustainable healthy lifestyle behaviors.

FUNDING

The following list of current and forthcoming funded research outlines the digital health applications used and their respective study populations, with an indication of funding mechanism and status.

VRx-Virtual Therapeutics—

(1) Brain Cancer (Neuro-Oncology)

Funding (Pilot-Phase 1): U of Kentucky Center for Clinical/Translational Science. [Recently Completed Fall 2024] **Title**: A health game intervention for cancer patients suffering from acute cognitive impairment: A clinical study to assess a form of brain stimulation therapy with the potential to improve synaptic plasticity. (*Preliminary Data Collection*) **Collaborators**: Dr. D. Villano, MD (Neuro-Oncology, UK Markey Cancer Center); and Drs. B. Khan & S. Khan, Indiana U., School of Medicine, IU Health, and the Regenstreif Institute.

Funding (Pilot-Phase 2): University of Cincinnati Cancer Center. [Active] Title: Measuring the feasibility, acceptability, and effect of a VR cognitive training intervention for brain cancer survivors with cancer-related cognitive impairment. (*Preliminary Data Collection*) **Collaborators**: Drs. Shatz and Yogendran (Neuro-oncology and Neurology—UC Neuroscience Institute).

(2) Breast Cancer

Funding: American Cancer Society [Pending] **Title**: Measuring the feasibility, acceptability, and fidelity of intervention delivery for a virtual-reality game cognitive training platform for breast cancer patient survivors at risk for mild cognitive impairment. **Collaborators**: Drs. Shatz (neuro-oncology and neurology—UC Neuroscience Institute), Dr. Charif (Oncology) and Dr. Shaughnessy (Survivorship Clinic), College of Medicine.

(3) Alzheimer's / Dementia (*Post-Intensive Care Syndrome*)

Funding: NIH/National Institute of Aging [Forthcoming] **Title**: Measuring the feasibility, acceptability, and fidelity of intervention delivery for virtual-reality cognitive gaming exercise among critically ill older adults at risk for ICU-acquired mild cognitive impairment (Alzheimer's and dementias, including its effect on pain, anxiety, delirium). **Collaborator**: S. Khan, MD, B. Khan, MD, Indiana University School of Medicine and the Regenstreif Institute.

(4) Delirium / Dementia

Funding (Project #1): Indiana University Health Values Grant. [Active] **Title**: Virtual Reality Cognitive

Intervention for Critically Ill Delirium Survivors (VR-Cog). **Collaborators**: S. Khan, MD, B. Khan, MD, Indiana University School of Medicine, and the Regenstreif Institute. (*Preliminary Data Collection*)

Funding (Project #2): U of Cincinnati, Brain Tumor Center, UC Neuroscience Institute. [Forthcoming] **Title**: Measuring the acceptability and effect of a VR cognitive training intervention for dementia patients with mild cognitive impairment. **Collaborator**: Dr. Shatz (Neuro-oncology and Neurology—UC Neuroscience Institute). (*Preliminary Data Collection*)

(5) Stroke
Funding: La Sapienza University, Faculty Research Fellowship [Pending] **Title**: Research: Measuring cognitive performance among post-stroke patients: A pilot study. **Collaborator**: Dr. Marco Iosa, Neuropsychology, Department of Psychology, La Sapienza University, Rome, Italy; and Sr. Researcher, Foundation Santa Lucia (Outpatient Clinic), Rome, Italy

Biosensor Diagnostics—

(1) Prostate Cancer
Funding: American Cancer Society, Grant No. SPA-RFA-Team-1076327. [Active] **Title**: Canine-inspired Identification and Analysis of Volatile Organic Compounds (VOC) Biomarkers of Prostate Cancer using Portable Chromatograph-Mass Spectrometer (GC-MS) and Development of a Hand-held Nanosensor System. **Collaborators**: Co-Pis: Drs. M. Woodlam, PhD, (Indiana U.), M. Agarwal, PhD, (Purdue U.), A. Faiola, PhD.

(2) Cystic Fibrosis
Funding: NIH R01. Collaborators: Co-Pis: Drs. M. Woodlam, PhD, M. Agarwal, PhD, (Indiana U.), A. Faiola, PhD. [Active] **Title**: Development of Canine-Inspired Nanosensor Systems to Detect Pulmonary Exacerbations in Patients with Cystic Fibrosis. **Collaborators**: M. Agarwal, PhD (Contact PI), Indiana U.; PIs: DB. Sanders, MD, S. Cao, MD, M. Woollam, PhD, Indiana U.

Mobile Health—

(1) Cancer—*Psycho-Oncology Patient Support / Health Equity*
Funding: Merck Foundation: *Alliance for Equity in Cancer Care.* [Active] **Title**: Comprehensive Connected Cancer Care (C4) Center. **Collaborators**: Mullett, Hull, Chih, Hesse, CoI: Dr. Faiola, PhD.

(2) Cancer—*Beside-to-Family Communications / Mental Health Support*
Funding: Markey Cancer Center Community Grant, University of Kentucky [Recently Completed Fall 2024] **Title**: Addressing the mental health disparities of families of cancer patients from rural Kentucky: Investigating efficacy to reduce mental trauma using FamCare. **Collaborators**: Drs. Z. Hao, MD; R. Munker, MD. (stem cell / Oncology, UK Markey Cancer Center). (*Preliminary Data Collection*)

APPENDIX

FDA Approval and the Scalability of VRx as Medical Therapeutics

Regarding the scalability of VRx as a digital solution for MCI, healthcare support is steadily growing, with approval for reimbursement for VR therapies.[58] There are several factors that are quickly changing the healthcare paradigm for outpatient treatment using VR therapy. **(1) CPT codes for VR therapy:** Over the last two years the new Category III CPT® code 0770T has been introduced (effective 1/1/23), designed to account for the use of VR technology in therapeutic settings. This code acknowledges the growing role of immersive technology in enhancing therapeutic outcomes. **(2) VR is now considered a billable treatment:** Healthcare system administrators are increasingly integrating VR into multiple types of patient therapies as an adjunct to the base therapy, in conjunction with codes for psychotherapy, speech therapy, health and behavior interventions, therapeutic procedures, and adaptive behavior services,[59] and offering an effective treatment option that is billable. Providers can bill insurance for VR rehab (such as psychotherapy or therapeutic exercises) for reimbursement depending on three (low threshold) requirements: (1) VR must be integrated into the patient's overall treatment plan, (2) Only licensed healthcare professionals, such as therapists, counselors, or medical practitioners, can bill for VR-related services, and (3) Insurance carriers must recognize VR as an effective treatment.[60] According to the American Medical Association, physicians are increasingly incorporating telehealth, VR, and AI into their practices using code **0770T** to report VR-mediated therapy.[61] See note on FDA and Medicare/Medicaid approval for VR therapy.[62]

REFERENCES & NOTES

1 Spiegel BMR, Rizzo A, Persky S, Liran O, Wiederhold B, Woods S, Donovan K, Sarkar K, Xiang H, Joo S, Jotwani R, Lang M, Paul M, Senter-Zapata M, Widmeier K, Zhang H. What Is Medical Extended Reality? A Taxonomy Defining the Current Breadth and Depth of an Evolving Field. J Med Ext Real. 2024 Jan 1;1(1):4-12. doi: 10.1089/jmxr.2023.0012. Epub 2024 Jan 25. PMID: 38505474; PMCID: PMC10945763.

2 Cedars Sinai, Virtual Medicine, https://virtualmedicine.org/

3 Sakhare A, Stradford J, Ravichandran R, Deng R, Ruiz J, Subramanian K, Suh J, Pa J. Erratum: Simultaneous Exercise and Cognitive Training in Virtual Reality Phase 2 Pilot Study: Impact on Brain Health and Cognition in Older Adults. Brain Plast. 2022 Dec 20;8(2):173. doi: 10.3233/BPL-219002. Erratum for: Brain Plast. 7:111. PMID: 36724062; PMCID: PMC9837729.

4 Phillips NS, Rao V, Kmetz L, et al. Changes in Brain Functional and Effective Connectivity After Treatment for Breast Cancer and Implications for Intervention Targets. Brain Connect. May 2022;12(4):385-397. doi:10.1089/brain.2021.0049

5 Hosseini SM, Koovakkattu D, Kesler SR. Altered small-world properties of gray matter networks in breast cancer. BMC Neurol. May 28 2012;12:28. doi:10.1186/1471-2377-12-28

6 Conroy SK, McDonald BC, Smith DJ, et al. Alterations in brain structure and function in breast cancer survivors: effect of post-chemotherapy interval and relation to oxidative DNA damage. Breast Cancer Res Treat. Jan 2013;137(2):493-502. doi:10.1007/s10549-012-2385-x

7 Deprez S, Vandenbulcke M, Peeters R, et al. Longitudinal assessment of chemotherapy-induced alterations in brain activation during multitasking and its relation with cognitive complaints. J Clin Oncol. Jul 1 2014;32(19):2031-8. doi:10.1200/jco.2013.53.6219

8 Lepage C, Smith AM, Moreau J, et al. A prospective study of grey matter and cognitive function alterations in chemotherapy-treated breast cancer patients. Springerplus. 2014;3:444. doi:10.1186/2193-1801-3-444

9 Menning S, de Ruiter MB, Veltman DJ, et al. Changes in brain activation in breast cancer patients depend on cognitive domain and treatment type. PLoS One. 2017;12(3):e0171724. doi:10.1371/journal.pone.0171724

10 Nudelman KN, Wang Y, McDonald BC, et al. Altered cerebral blood flow one month after systemic chemotherapy for breast cancer: a prospective study using pulsed arterial spin labeling MRI perfusion. PLoS One. 2014;9(5):e96713. doi:10.1371/journal.pone.0096713

11 Mo C, Lin H, Fu F, et al. Chemotherapy-induced changes of cerebral activity in resting-state functional magnetic resonance imaging and cerebral white matter in diffusion tensor imaging. Oncotarget. Oct 6 2017;8(46):81273-81284. doi:10.18632/oncotarget.18111

12 Stouten-Kemperman MM, de Ruiter MB, Koppelmans V, Boogerd W, Reneman L, Schagen SB. Neurotoxicity in breast cancer survivors ≥10 years post-treatment is dependent on treatment type. Brain Imaging Behav. Jun 2015;9(2):275-84. doi:10.1007/s11682-014-9305-0

13 Brown SM, Bose S, Banner-Goodspeed V, et al. Approaches to Addressing Post-Intensive Care Syndrome among Intensive Care Unit Survivors. A Narrative Review. Ann Am Thorac Soc. Aug 2019;16(8):947-956. doi:10.1513/AnnalsATS.201812-913FR

14 Jackson JC, Pandharipande PP, Girard TD, et al. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. Lancet Respir Med. May 2014;2(5):369-79. doi:10.1016/s2213-2600(14)70051-7

15 Kang JM, Kim N, Lee SY, et al. Effect of Cognitive Training in Fully Immersive Virtual Reality on Visuospatial Function and Frontal-Occipital Functional Connectivity in Predementia: Randomized Controlled Trial. J Med Internet Res. May 6 2021;23(5):e24526. doi:10.2196/24526

16 Kim H, Kim B-H, Kim M-K, Eom H, Kim J-J. Alteration of resting-state functional connectivity network properties in patients with social anxiety disorder after virtual reality-based self-training. Original Research. Frontiers in Psychiatry. 2022-September-20 2022;13doi:10.3389/fpsyt.2022.959696

17 Moulaei K, Sharifi H, Bahaadinbeigy K, Dinari F. Efficacy of virtual reality-based training programs and games on the improvement of cognitive disorders in patients: a systematic review and meta-analysis. BMC Psychiatry. Feb 12 2024;24(1):116. doi:10.1186/s12888-024-05563-z

18 Riva G, Wiederhold BK, Mantovani F. Neuroscience of Virtual Reality: From Virtual Exposure to Embodied Medicine. Cyberpsychol Behav Soc Netw. Jan 2019;22(1):82-96. doi:10.1089/cyber.2017.29099.gri

19 Shao G, Xu G, Huo C, et al. Effect of the VR-guided grasping task on the brain functional network. Biomed Opt Express. Jan 1 2024;15(1):77-94. doi:10.1364/boe.504669

20 Xu X, Sui L. EEG cortical activities and networks altered by watching 2D/3D virtual reality videos. Journal of Psychophysiology. 2022;36(1):4-12. doi:10.1027/0269-8803/a000278

[21] Zhu S, Sui Y, Shen Y, et al. Effects of Virtual Reality Intervention on Cognition and Motor Function in Older Adults With Mild Cognitive Impairment or Dementia: A Systematic Review and Meta-Analysis. Front Aging Neurosci. 2021;13:586999. doi:10.3389/fnagi.2021.586999

[22] Lorentz L, Müller K, Suchan B. Virtual reality-based attention training in patients with neurological damage: A pilot study. Neuropsychol Rehabil. Jul 19 2023:1-20. doi:10.1080/09602011.2023.2236349

[23] Jordan R, Keller GB. The locus coeruleus broadcasts prediction errors across the cortex to promote sensorimotor plasticity. eLife. 2023/06/07 2023;12:RP85111. doi:10.7554/eLife.85111

[24] Menon V. Salience Network. Brain Mapping. 2015:597-611.

[25] James T, Kula B, Choi S, Khan SS, Bekar LK, Smith NA. Locus coeruleus in memory formation and Alzheimer's disease. Eur J Neurosci. Oct 2021;54(8):6948-6959. doi:10.1111/ejn.15045

[26] James T, Kula B, Choi S, Khan SS, Bekar LK, Smith NA. Locus coeruleus in memory formation and Alzheimer's disease. Eur J Neurosci. Oct 2021;54(8):6948-6959. doi:10.1111/ejn.15045

[27] Lisman J, Buzsáki G, Eichenbaum H, Nadel L, Ranganath C, Redish AD. Viewpoints: how the hippocampus contributes to memory, navigation and cognition. Nat Neurosci. Oct 26 2017;20(11):1434-1447. doi:10.1038/nn.4661

[28] O'Keefe J, Dostrovsky J. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res. Nov 1971;34(1):171-5. doi:10.1016/0006-8993(71)90358-1

[29] Nadel L, MacDonald L. Hippocampus: cognitive map or working memory? Behav Neural Biol. Jul 1980;29(3):405-9. doi:10.1016/s0163-1047(80)90430-6

[30] Maldonado KA, Alsayouri K. Physiology, Brain. StatPearls. StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.; 2024.

[31] Pilly PK, Grossberg S. How do spatial learning and memory occur in the brain? Coordinated learning of entorhinal grid cells and hippocampal place cells. J Cogn Neurosci. May 2012;24(5):1031-54. doi:10.1162/jocn_a_00200

[32] Merhi, L. and Sadarangani, G. (2021). Healthcare Business Today, New Reimbursement Rules Pave the Way for High-Tech Disruption in Physical Therapy, December 24, 2021. Source: https://www.healthcarebusinesstoday.com/new-reimbursement-rules-pave-the-way-for-high-tech-disruption-in-physical-therapy/

[33] Riva G, Wiederhold BK, Mantovani F. Neuroscience of Virtual Reality: From Virtual Exposure to Embodied Medicine. Cyberpsychol Behav Soc Netw. Jan 2019;22(1):82-96. doi:10.1089/cyber.2017.29099.gri

[34] Xu X, Sui L. EEG cortical activities and networks altered by watching 2D/3D virtual reality videos. Journal of Psychophysiology. 2022;36(1):4-12. doi:10.1027/0269-8803/a000278

[35] Shao G, Xu G, Huo C, et al. Effect of the VR-guided grasping task on the brain functional network. Biomed Opt Express. Jan 1 2024;15(1):77-94. doi:10.1364/boe.504669

[36] Kang JM, Kim N, Lee SY, et al. Effect of Cognitive Training in Fully Immersive Virtual Reality on Visuospatial Function and Frontal-Occipital Functional Connectivity in Predementia: Randomized Controlled Trial. J Med Internet Res. May 6 2021;23(5):e24526. doi:10.2196/24526

[37] Kim H, Kim B-H, Kim M-K, Eom H, Kim J-J. Alteration of resting-state functional connectivity network properties in patients with social anxiety disorder after virtual reality-based self-training. Original Research. Frontiers in Psychiatry. 2022-September-20 2022;13doi:10.3389/fpsyt.2022.959696

[38] Moulaei K, Sharifi H, Bahaadinbeigy K, Dinari F. Efficacy of virtual reality-based training programs and games on the improvement of cognitive disorders in patients: a systematic review and meta-analysis. BMC Psychiatry. Feb 12 2024;24(1):116. doi:10.1186/s12888-024-05563-z

[39] Zhu S, Sui Y, Shen Y, et al. Effects of Virtual Reality Intervention on Cognition and Motor Function in Older Adults With Mild Cognitive Impairment or Dementia: A Systematic Review and Meta-Analysis. Front Aging Neurosci. 2021;13:586999. doi:10.3389/fnagi.2021.586999

[40] Woollam M, Siegel AP, Munshi A, Liu S, Tholpady S, Gardner T, Li BY, Yokota H, Agarwal M. Canine-Inspired Chemometric Analysis of Volatile Organic Compounds in Urine Headspace to Distinguish Prostate Cancer in Mice and Men. Cancers (Basel). 2023 Feb 20;15(4):1352. doi: 10.3390/cancers15041352. PMID: 36831694; PMCID: PMC9954105.

[41] Angle, C.; Waggoner, L. P.; Ferrando, A.; Haney, P.; Passler, T., Canine Detection of the Volatilome: A Review of Implications for Pathogen and Disease Detection. 2016, 3 (47).

[42] Dorman, D. C.; Foster, M. L.; Fernhoff, K. E.; Hess, P. R., Canine scent detection of canine cancer: a feasibility study. Vet Med (Auckl) 2017, 8, 69-76.

[43] Jezierski, T.; Walczak, M.; Ligor, T.; Rudnicka, J.; Buszewski, B., Study of the art: canine olfaction used for cancer detection on the basis of breath odour. Perspectives and limitations. Journal of breath research 2015, 9 (2), 027001.

[44] Janfaza, S.; Khorsand, B.; Nikkhah, M.; Zahiri, J., Digging deeper into volatile organic compounds associated with cancer. Biology methods & protocols 2019, 4 (1), bpz014.

[45] Siegel, A. P.; Daneshkhah, A.; Hardin, D. S.; Shrestha, S.; Varahramyan, K.; Agarwal, M., Analyzing breath

samples of hypoglycemic events in type 1 diabetes patients: towards developing an alternative to diabetes alert dogs. Journal of breath research 2017, 11 (2), 026007.

46 Daneshkhah, A.; Shrestha, S.; Agarwal, M.; Varahramyan, K., Poly(vinylidene fluoride-hexafluoropropylene) composite sensors for volatile organic compounds detection in breath. Sensors and Actuators B: Chemical 2015, 221, 635-643.

47 Daneshkhah, A.; Shrestha, S.; Siegel, A.; Varahramyan, K.; Agarwal, M., Cross-Selectivity Enhancement of Poly(vinylidene fluoride-hexafluoropropylene)-Based Sensor Arrays for Detecting Acetone and Ethanol. Sensors (Basel) 2017, 17 (3), 595.

48 Daneshkhah, A.; Vij, S.; Siegel, A. P.; Agarwal, M., Polyetherimide/carbon black composite sensors demonstrate selective detection of medium-chain aldehydes including nonanal. Chemical Engineering Journal 2020, 383, 123104.

49 Faiola, A.; Vatani, H.; Agarwal, M., Hypoglycemic Detection by Human Breath: A Mobile Health App that Alerts Diabetics of Low Blood Glucose. EAI Endorsed Transactions on Ambient Systems 2019, 6 (18).

50 Woollam, M.; Teli, M.; Angarita-Rivera, P.; Liu, S.; Siegel, A. P.; Yokota, H.; Agarwal, M., Detection of Volatile Organic Compounds (VOCs) in Urine via Gas Chromatography-Mass Spectrometry QTOF to Differentiate Between Localized and Metastatic Models of Breast Cancer. Scientific reports 2019, 9 (1), 2526.

51 Wu, D.; Fan, Y.; Liu, S.; Woollam, M. D.; Sun, X.; Murao, E.; Zha, R.; Prakash, R.; Park, C.; Siegel, A. P.; Liu, J.; Agarwal, M.; Li, B. Y.; Yokota, H., Loading-induced antitumor capability of murine and human urine. FASEB J 2020, 34 (6), 7578-7592.

52 Woollam, M.; Wang, L.; Grocki, P.; Liu, S.; Siegel, A. P.; Kalra, M.; Goodpaster, J. V.; Yokota, H.; Agarwal, M., Tracking the Progression of Triple Negative Mammary Tumors over Time by Chemometric Analysis of Urinary Volatile Organic Compounds. 2021, 13 (6), 1462.

53 Woollam, M.; Teli, M.; Liu, S.; Daneshkhah, A.; Siegel, A. P.; Yokota, H.; Agarwal, M., Urinary Volatile Terpenes Analyzed by Gas Chromatography-Mass Spectrometry to Monitor Breast Cancer Treatment Efficacy in Mice. J Proteome Res 2020, 19 (5), 1913-1922.

54 Faiola, A., Abraham, J. & Papautsky, E.L. (2019). Delivering Patient Information and Access to Mental Health Counseling for ICU Families: Towards a Human-Centered Mobile Health System for Room-to-Family Communication. Poster, Extended Abstract and Presentation, *Proceedings from Human Factors and Ergonomics in Health Care, Chicago, IL, March 2019.*

55 Faiola, A. and Abraham, J. (2018). FAMcare: A MICU Room-to-Mobile System—Supporting the Communication Needs of Families, Extended Abstracts, **American Medical Informatics Association, Annual Symposium, San Francisco, CA, November, 2018.** https://symposium2018.zerista.com/event/member/508059

56 Funding: As PI, an AHRQ proposal was recently rejected for funding. This project includes researchers from UIC and Washington University. The ARHQ submission title: "Towards designing an ICU-to-family mHealth for families: Delivering patient information that enhances collaborative communication and supports access to mental health counseling."

57 Collaborators, project titles, and funding amounts are listed in my CV grants section

58 Merhi, L. and Sadarangani, G. (2021). Healthcare Business Today, New Reimbursement Rules Pave the Way for High-Tech Disruption in Physical Therapy, December 24, 2021. Source: https://www.healthcarebusinesstoday.com/new-reimbursement-rules-pave-the-way-for-high-tech-disruption-in-physical-therapy/

59 ABA Coding Coalition. (2023). New CPT® Code Available to Report the Use of Virtual Reality Technology with Therapeutic Services, Source: https://abacodes.org/new-cpt-code-available-to-report-the-use-of-virtual-reality-technology-with-therapeutic-services/

60 Hansei. (2023). Can I Bill for Virtual Reality Rehab? Source: https://hanseisolutions.com/can-i-bill-for-virtual-reality-rehab/

61 Robeznieks, A. (2023). How do AI, VR help doctors deliver care? CPT code tells the tale, American Medical Association. Source: https://www.ama-assn.org/practice-management/cpt/how-do-ai-vr-help-doctors-deliver-care-cpt-code-tells-tale

62 In 2021, AppliedVR, Inc. was granted FDA breakthrough status for the first FDA-authorized immersive VR medical device called RelieVRx for home use for the treatment of chronic low back pain. Centers for Medicare and Medicaid Services (CMS) explains that the device delivers a clinically based multimodal pain self-management program that incorporates evidence-based principles of cognitive behavioral therapy (CBT) and other neuroscience-based behavioral health methods. In 2023, CMS established a Healthcare Common Procedure Coding System Level II code for a VR program for home use. Based on an approval from the FDA, CMS issued the first codes and Medicare benefit category determination for a therapeutic VR Device. In 2024, the first digital mental health solution was approved by the FDA. This decision acknowledges digital mental health therapeutics, with the clearance of DeepWell DTx's. This product marks a significant turning point for the healthcare industry, which connects the reimbursement stream and digital therapeutics. In sum, FDA approval provides recognition of the mental health global crisis and current resource constraints, with new codes proposed by CMS providing monetary incentives for development and adoption by both providers and patients.