RESEARCH STATEMENT
Anthony Faiola

My research lies at the intersection of Biomedical Informatics and Health Behavior, focusing on the development of three emerging digital health technologies (DHT) and their corresponding patient populations. DHT include AI-driven virtual reality (VR) therapeutic medicine, Volatile organic compound (VOC) biomarkers biosensors, and Mobile health (mHealth/Telehealth). This work includes my lead of interdisciplinary teams—collaborating with clinicians, engineers, medical researchers, and computer scientists—to develop these interventions, focusing on optimizing care for patient populations in the areas of cancer, Alzheimer's disease (mild cognitive impairment), and cystic fibrosis.

BIOMEDICAL INFORMATICS

1: AI-Driven VR Therapeutic Medicine (VRx)

Background: The focus of my research that employs immersive AI-driven VR therapeutic medicine (VRx) technology is currently revolutionizing non-invasive healthcare, as observed by leading researchers nationwide. My research investigates the efficacy of our novel VRx training platform designed to treat mild cognitive impairment (MCI) in patients with Alzheimer's disease, related dementias (ADRD) and cancer-related cognitive impairment. By engaging patients in a cognitive training (game-centered) VR environment, this DHT increases sensory engagement through embedded selective attention exercises to mitigate cognitive dysfunction and enhance synaptic plasticity.[1,2,3,4,5] Considerable clinical effort has aimed to ameliorate MCI in patients with ADRD through interventions such as physical exercise, mindfulness, and digital cognitive training. While pharmacotherapy manages certain cognitive symptoms, these approaches often yield conflicting outcomes and present significant side effects. Furthermore, a critical lack of scalable, accessible cognitive rehabilitation services hinders effective management. Consequently, ADRD progresses, leading to severe inattention and diffuse deficits within the frontoparietal, cingulo-opercular, and salience networks. Therefore, there is a pressing need for innovative, sustainable, and scalable treatment models to mitigate further functional decline.[6,7,8,9,10,11,12,13,14,15,16] Emerging neuroscience literature indicates that VR offers a non-invasive approach to enhancing cognitive function in cancer survivors. By mitigating downstream cognitive impairment, VR therapy can improve mental health and quality of life. For instance, studies confirm that post-treatment (chemotherapy and radiation) breast cancer patients frequently experience disrupted functional brain networks, including the default mode network, salience network, and frontoparietal network. This pathophysiological framework results in diffuse cognitive deficits, including reduced alertness, memory loss, and severe inattention, which are often left untreated. To address this, early intervention with immersive VRx can directly engage impaired neural circuits, promoting arousal and attention. Specifically, VRx produces tailored stimuli that target the frontoparietal neuro-network for visuospatial processing and the salience network for selective attention, offering a promising, novel digital therapeutic approach for enhancing MCI patient cognitive recovery.[17,18,19,20]

Hypothesis: I posit that the synergetic effects between VR immersion and embedded selective attention exercises within our VRx platform activates the locus coeruleus-norepinephrine (LC-NE) system while downregulating the default mode network. Given the LC-NE system's critical role in memory regulation, this activation enables the hippocampus to more effectively tag memories within the complexity of time and place. Furthermore, the hippocampus maintains reciprocal connections to the neocortex through multiple pathways, acting as a functional hub for the basal ganglia, thalamus, and hypothalamus. While it is one of many memory systems, the hippocampus plays a critical role in storing long-term memories that are contextually meaningful in time and place. This role is especially relevant to immersive VRx training, which simulates time and place neurons to foster cognitive mapping, life-navigation, and the recall of personal events. Consequently, VRx may aid in the organization of episodic memories, particularly for ADRD patients, whose hippocampal integrity is among the first affected.[21,22,23,24] Immersive VR selective attention exercises target the cerebrum to facilitate executive function, memory, and mood, while simultaneously engaging the hippocampus and medial entorhinal cortex to boost spatial learning. Because this high-level stimulus surpasses traditional 2D or analog programs, we argue that VRx—as a non-invasive, immersive tool—strengthens neural pathways and enhances memory processes, ultimately increasing neurotransmission and promoting cognitive plasticity.[25]

VR-CRT Preliminary Data: In a recently completed single-arm study (11/15/2023 to 8/1/2024) in collaboration with John Villano, MD PhD, Neuro-Oncology Division, Markey Cancer Center, University of Kentucky, demonstrated cognitive improvement using the **VR-CRT 1.0 platform** with 6 brain cancer survivors. Project title: *Investigating the Usability, Feasibility, and Effect of a Virtual Reality Cognitive Training System on Brain Cancer Patients with Mild Cognitive Impairment: A Quasi-Experimental (Single-Arm) Pilot Study*. VR-CRT daily dosing occurred for 4 weeks, at 15 minutes per day for week 1, adding 5 minutes per week. Three standardized neuropsychology scales were administered at baseline and post intervention, including the Hopkins Verbal Learning Test (HVLT), Controlled Oral Word Association test (COWA), and Trail Making A and B test (TMT).[26]

The Intervention, **VR-CRT 1.0,** was developed between 2021 and 2024, our Virtual Reality Cognitive Rehabilitation Training (VR-CRT) platform delivers scalable, innovative care for adults with MCI, specifically targeting cancer and ADRD. Created by a multidisciplinary team of neuro-oncology, physical therapy, and gaming experts, VR-CRT ensures high user engagement. By stimulating sensory processing, visuospatial memory, and attentional networks, VR-CRT offers significant advantages over traditional 2D computerized training. The immersive platform features 81 scenario-driven, gamified exercises that boost engagement through real-time feedback, while automated backend tracking encourages continuous, goal-oriented progress.[27,28,29,30,31,32]

Preliminary findings met our feasibility criteria of >80%. All SUS and NASA scores were in the higher index, suggesting a high degree of usability, with low workload demand. For effect, the COWA findings showed a significant improvement (41.38%), with a paired sample T-Test confirming that the participants' COWA scores improved significantly from pre- to post-intervention ($p = 0.03$), indicating enhanced verbal fluency and executive functioning after intervention. HVLT (combined) showed improvements of 18.75% for Form A and 11.32% for Form B, which also showed a significant improvement ($p = .04$) in the retention discrimination index from pre- to post-test. The TM-A/B test showed an improvement (25.97%), suggesting that the participants spent less time completing both parts A and B, but was not statistically significant.[33]

This study demonstrates that VR-CRT offers modest to significant cognitive improvements for patients with Mild Cognitive Impairment (MCI). Despite a small sample size, these formative findings suggest that home-based VR platforms, featuring diverse, targeted exercises and navigation tasks, hold promise for MCI rehabilitation. Our findings support the hypothesis that VR immersion, combined with embedded selective attention exercises, stimulates neural pathways to improve executive function, working memory, and cognitive plasticity. Although the small sample size—limited by strict inclusion criteria and patient health severity—is a limitation, the preliminary success of VR-CRT 1.0 supports further investigation. We anticipant greater validation of these outcomes from three studies running concurrently using the same VR-CRT 1.0 intervention, VR-CRT 2.0 studies forthcoming. See details below.

AI-Driven VR-CRT 2.0: While my basic VR-CRT 1.0 platform effectively provides cognitive stimuli and engages the frontoparietal network, the AI-driven VR-CRT 2.0 will significantly enhance therapeutic and diagnostic endpoints. The new iteration integrates two foundational AI models to deliver three core improvements: (1) precise tracking, prediction, and personalization of MCI patient cognitive performance; (2) real-time cognitive monitoring through intelligent, interactive non-player characters (NPCs); and (3) expanded, diverse VR environments. Furthermore, VR-CRT 2.0 will recognize and modulate patient performance by introducing an assortment of new brain training games, such as fast-paced decision-making and strategic games that require quick thinking, reflexes, and coordination. The following foundational and generative AI models will be employed.

Player Experience Modelling (PEM) will deliver two key outcomes: (1) data analysis of game performance, focusing on metrics like navigation speed, attention, and spatial orientation; and (2) predictive cognitive modeling, which uses regression-based machine learning to forecast a patient's experience-dependent progress. By analyzing real-time performance against historical data, these self-adjusting algorithms modulate game difficulty to match skill level, incrementally increasing cognitive load by directing MCI patients to new, more challenging environments.[34,35] In sum, PEM will assist in maximizing cognitive stimulation while increasing neuroplasticity.

Non-Playing Character (NPC) modeling will produce intelligent, role-playing behaviors to support NPC-patient dialogues. These NPCs will employ sentiment (Natural Language Processing) analysis to allow for emotionally accurate responses (voice intonation analysis) and deeper dialogue engagement. Technically, this involves pre-training and fine-tuning Vision-Language Models (VLM) using alignment strategies tailored for patient emotional responses. Behind these engagements, AI agents will perform autonomous reasoning and planning, utilizing Retrieval-Augmented Generation (RAG) to transform unstructured conversational text into computable, auditable evidence. The central aim of using intelligent NCP is to move beyond simple chatbots to

agents that can plan and reason (i.e., understand a complex, multi-step VR personal history. AI-driven NLP-patient conversations will strategically introduce the use of the Patient-Reported Outcomes Measurement Information System (PROMIS), Cognitive Function: Short Form 8a 2.0 questions (8 questions) to track patient cognitive function throughout the length of the study. NLP-patient generated insights about how the patient is progressing will be collected in real-time in the cloud for analysis in conjunction with PEM data to provide performance feedback for integration into subsequent game scenarios.

In sum, our intelligent NPC system leverages advanced role-playing capabilities to support deep, empathetic patient dialogues that utilize sentiment analysis to deliver emotionally accurate, healthcare-tailored conversations.[36,37] See Figure 1 for an illustration of the VR-CRT 2.0 VR environment and backend AI-driven NPC-Patient avatar communication.

Illustration of VR environment with intelligent NPC engaging in conversation with MCI patient avatar. Botton-half graphics outline AI infrastructure with AI-driven smart NPC backend integration modeling and user interaction on the left and data analytic processing framework on the right side.

VR-CRT Scalability: VR-CRT revolutionizes cognitive training for patient with MCI by delivering personalized therapeutic experiences, dramatically enhancing scalability while ensuring patient privacy, accessibility, and convenience. While conventional cognitive rehabilitation struggles with scalability, VR-CRT enhances reach and efficacy through AI-driven, real-time tracking of performance metrics and session metrics. By automating adaptive difficulty adjustments based on individual performance, VR-CRT maintains optimal cognitive challenges to promote neuroplasticity. Ultimately, this AI-integrated, immersive platform significantly improves both assessment quality and real-world rehabilitation outcomes. The pathway to widespread adoption is strengthened by three factors: increasing FDA authorizations for home-use immersive devices, the implementation of CPT 0770T for billable VR therapeutics, and a rapidly maturing consumer VR marketplace. With FDA clearances for digital mental health tools expanding rapidly as of 2024, the infrastructure for remote care is established. Furthermore, with an estimated 65.9 million U.S. VR users by 2026 and over 171 million globally, the market is primed for widespread adoption of VR-based cognitive rehabilitation.[38,39,40]

VR-CRT 1.0 Current Studies: Three current studies involving the VRx VR-CRT 1.0 platform focus on neuro-oncology, ADRD, and delirium patients with MCI, conducted with their respective collaborators:

1. **Co-PI: Dr. Lalanthica Yogendran (Neuro-Oncology),** University of Cincinnati, Cancer Center, College of Medicine, ClinicalTrials.gov, NCT#: NCT07313709
2. **Co-PI: Dr. Rhonna Shatz (Neurology),** University of Cincinnati, Gardner Neuroscience Institute, College of Medicine. Intervention: VR-CRT 2.0.
3. **Co-PIs: Drs. Sikandar Khan and Babar Khan, (ICU: Pulmonary Medicine),** Indiana University, Methodist Hospital the Center for Aging, and the Regenstrief Institute, Indianapolis, IN, School of Medicine, ClinicalTrials.gov, NCT#: NCT07496255.

VR-CRT Forthcoming Studies: Two studies with patient populations that include stroke and older adults with MCI, conducted with their respective collaborators:

1. **Co-PI, Drs. Marco Iosa and Claudia Salera, La Sapienza University, Psychology, Div. of Neuropsychology,** and Santa Lucia Foundation, Neurorehabilitation Inpatient Hospital, Rome, Italy.

Project Title: *Measuring cognitive performance among post-stroke patients: A pilot study. Lectures: Digital health solution methods and innovation*. Intervention: VR-CRT 1.0 translated into Italian.

2. **Co-PIs, Dr. Yonas Geda, Barrow Neurological Institute (Phoenix, AZ), (Neuropsychiatry) and Dr. Tesfaye Mersha Pulmonary Medicine (Biomedical Informatics) Indiana University School of Medicine**.
    - This is a current multi-PI R01 submission designed to test an integrated multimodal lifestyle intervention on plasma p-Tau217 levels and cognitive performance in patients with mild cognitive impairment (MCI). This work will apply VR-CRT 2.0 (VR cognitive training platform) to pre-ADRD patients, while tracking patient cognitive performance with enhanced therapeutic and diagnostic precision. **Project Title:** *Multimodal Lifestyle Intervention: Virtual Reality and AI assisted Cognitive Training, Physical Activity, and Time Restricted Eating in Mild Cognitive Impairment*.

2: VOC Biomarker Biosensors

Our research leverages volatile organic compounds (VOC) biomarkers and nano-sensor integration within handheld, smart systems to enable accurate, noninvasive disease detection of prostate cancer and cystic fibrosis diagnostics.[41] This research aims to determine if VOC detection technology, coupled with biometric readouts, can robustly diagnose multiple diseases via scent, emulating the capability of canine detection in a standardized, high-accuracy platform. Following optimization for accuracy, the platform will be refined for portability, cost, and speed. Recognizing that diseases induce metabolic changes (e.g., changes in VOCs, heart rate, and blood pressure), this project advances our previous NSF-funded canine-inspired nanosensor technology (2015-19), which successfully identified breath-based VOC signatures to detect hypoglycemia via a prototype smartphone-linked sensor array.[42,43,44,45,46,47] Our current funded research focuses on two innovative, human-centered clinical VOC-driven nano-sensor applications:

Project #1: We are currently optimizing the detection of VOCs from minute (50 µL) mouse and human urine samples, enabling a portable GC-MS system for non-invasive prostate cancer screening in both clinical and home settings. (Funding: American Cancer Society)

- **Project Title:** *Canine-inspired Identification and Analysis of Volatile Organic Biomarkers of Prostate Cancer using Portable GC-MS & Develop, of a Hand-held Nanosensor System*.
- **Collaborators**:
    - **Mangilal Agarwal, PhD**, Professor, Biomedical Engineering and Informatics, Luddy School of Informatics, Computing, & Engineering
    - **Mark Woollam, PhD**, Sr. Research Scientist, Biochemistry, Integrated Nanosystems Development Institute, Indiana University School of Science
    - **Thomas Gardner, MD**, Department of Urology, IU School of Medicine
    - **Alberto Martini, MD**, Assistant Professor, Department of Urology and Clinical Oncology, College of Medicine, University of Cincinnati

Project #2: We are currently deploying a handheld, machine-learning-driven smart sensor for real-time detection of pulmonary exacerbations (PEx) in cystic fibrosis patients at the point-of-care. Both projects involve close collaboration with investigators to ensure secure, usability-tested interfaces, translating advanced biosensor data into actionable real-world diagnostics.[48,49]

- **Project Title:** *Hand-held Smart Sensor for Detecting Cystic Fibrosis Pulmonary Exacerbations*
- **Collaborators**:
    - **Mangilal Agarwal, PhD**, Professor, Biomedical Engineering and Informatics, Luddy School of Informatics, Computing, & Engineering
    - **Mark Woollam, PhD**, Sr. Research Scientist, Biochemistry, Integrated Nanosystems Development Institute, Indiana University School of Science
    - **Don Sanders, MD**, Professor of Pediatrics and Pulmonary Medicine, Indiana University School of Medicine

3: mHealth/Telehealth

My work in telehealth (mHealth) spans the design, development, and clinical testing of digital health tools—including applications, web dashboards, and backend databases—to deliver community-focused, patient-centered cancer care. My research focuses on improving access to holistic care beyond clinical treatment (e.g., chemotherapy) for underserved cancer patients and their families. Two studies focusing on optimizing patient-provider communication include:

Project #1: To address mental health disparities among rural Kentucky families of cancer patients, this study evaluated FamCare+, a novel mHealth platform designed to reduce anxiety and depression by connecting remote families with bedside clinicians. The platform facilitates enhanced communication and information flow from ICU or senior care settings to families at home. FamCare+ provides real-time patient vitals, wellness updates, secure multimedia tools (text/video), and direct access to social and mental health services. Following six years of development, the project has undergone multiple, rigorous iterations of prototyping and testing.[50] (Funding: Markey Cancer Center Community Partnership Planning Grant).[51,52,53]

- **Project Title:** *Addressing the mental health disparities of families of cancer patients from rural Kentucky: Investigating the efficacy to reduce mental trauma using FamCare*.
- **Collaborators**:
  - **Zhonglin Hao, MD,** Medical oncologist, Thoracic Oncology Program, Markey Cancer Center, College of Medicine, University of Kentucky
  - **Reinhold Munker, MD,** Hematology/Blood & Marrow Transplantation, Markey Cancer Center, College of Medicine, University of Kentucky

Project #2: The funded Comprehensive Connected Cancer Care (C4) project aims to advance health equity for underserved populations, particularly rural and low-income uninsured communities, by providing timely, high-quality, and community-focused cancer care. Building on the MyPath platform, C4 enhances care coordination through a new patient navigation model and a digital, closed-loop referral system. This platform will empower patients and clinicians via a dedicated dashboard for navigation teams and a mobile app for patients and caregivers, directly resulting in (1) improved patient-centered communication and (2) increased utilization of psychosocial care and supportive services. (Funding: Merck Foundation Award— *Alliance for Equity in Cancer Care*).[54]

- **Project Title:** *Comprehensive Connected Cancer Care*.
- **Collaborators**:
  - **Timothy W. Mullett, MD**, Medical Director, Markey Cancer Center Network Development, College of Medicine, University of Kentucky
  - **Pamela Hull, PhD**, Associate Professor of Behavioral Science, Associate Director of Population Science and Community Impact, Markey Cancer Center, College of Medicine, University of Kentucky
  - **Ming Chih, PhD**, Associate Professor, College of Health Sciences, University of Kentucky

HEALTH BEHAVIOR

Prior research in population health and health informatics has indirectly aligned with my primary work in biomedical informatics. The scope of this work includes two specialized areas:

1) Population Health: Our research addresses health disparities in marginalized, rural, and underserved communities, focusing on self-care, health literacy, and information application for disease prevention. We investigate the impact of social media cognitive overload on health information anxiety and avoidance behavior. Our findings highlight that underserved populations in Kentucky, neighboring states, and international settings—including India and Pakistan—face significant challenges, resulting in higher disease burdens and limited access to care. Our empirical work emphasizes that mHealth and telehealth are vital tools in reducing these disparities in both clinical and home settings.[55,56,57,58]

2) Health/Consumer Informatics: My research in health informatics leverages novel data science methods to improve the quality and safety of care by analyzing patient-clinician conversations and self-reported messages.

Specifically, this project aims to identify, adverse drug events and treatment effectiveness by mapping patient narratives to medical standard vocabularies. Furthermore, it involves developing text-mining algorithms to analyze patient experiences with psychiatric medications, such as Selective Serotonin Reuptake Inhibitors (SSRIs).[59,60,61]

My research in consumer health informatics focuses on behavior change strategies via mHealth, specifically targeting wellness for parents and the elderly. Building on previous work in data analytics for lifestyle management, the focus was on three key areas: 1) empowering elderly populations to sustain healthy habits via mobile tools, 2) developing sociotechnical, mHealth-driven models for managing noncommunicable diseases (e.g., diabetes), and 3) integrating human factors psychology to enhance care-team collaboration for sustainable health.[62,63,64]

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[40] 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.

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