in school-based screenings and community health programs. These tools aim to be accessible, culturally relevant, and tailored to diverse populations, enhancing early detection, informing personalized interventions, and supporting scalable clinical applications. DISCUSSION/SIGNIFICANCE OF IMPACT: This study explores links between early adversity, biological aging, and mental health, advancing understanding of adolescent depression. Epigenetic biomarkers could improve risk detection and guide tailored interventions in schools and community settings, enhancing access and reducing disparities.

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Universal representation of human diseases using large language models

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OBJECTIVES/GOALS: Understanding the interconnections among over 20,000 human diseases spanning organ systems could inform more precise diagnosis and treatment of diseases. Here, we examine whether the ability of large language models (LLMs) to learn universal representations of concepts can be leveraged to discover complex relationships across human diseases. METHODS/STUDY POPULATION: To address the challenge of computationally representing thousands diseases spanning multiple organ systems, we used internal representations of concepts by LLMs to encode diseases based on their descriptions from standard disease ontologies (ICD10 and Phecodes). To do this, we leveraged application programming interfaces (APIs) of three LLMs-GPT3.5, Mistral and Voyage to encode disease relationships. We then performed unsupervised clustering of the diseases using their encodings (embeddings) from each LLM to determine whether the resulting clusters reflect disease relationships. To enable deeper exploration of disease relationships, we developed interactive plots that provide a system level view of the relationships between thousands of diseases and their association with specific organ systems. RESULTS/ANTICIPATED RESULTS: We found that unsupervised analysis of disease relationships using the LLM encodings reveal high similarities among diseases based on organ systems they affect. All the LLMs clustered diseases into groups largely defined by the organ systems they affect without being trained to specifically classify diseases into their corresponding organ system classification. An exception to this was tumors in which we observed that most tumors cluster together as a group irrespective of the organs they affect. Interestingly, we found that tumors affecting anatomically related organs show higher similarity to each other than to those affecting distantly related organs. In addition to anatomical relationships between diseases, we found that the LLM embeddings capture genetic relationships between diseases. DISCUSSION/SIGNIFICANCE OF IMPACT: Overall, we found that the LLM-derived encodings uphold biologically and clinically significant relationships across organ systems and disease types. These results suggest that LLM encodings could provide a universal framework for representing diseases as computable phenotypes and enable the discovery of complex disease relationships.

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Localization of critical speech areas in glioma-infiltrated brain cortex using local neuronal field potentials via electrocorticography (ECOG)*

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OBJECTIVES/GOALS: The standard care for malignant gliomas includes maximal tumor resection, but challenges arise near functional (speech) areas. Direct cortical stimulation (DCS) identifies functional (nonresectable) cortex. We aim to identify electrophysiologic (via subdural electrode recordings [ECOG]) biomarkers of DCS-positive (functional) areas. METHODS/STUDY POPULATION: Our lab maintains one of the largest datasets of electrophysiology analysis of glioma infiltrated brain cortex in the USA. Recordings of intraoperative brain mapping were analyzed to identify cortical sites that were found to be positive (functional) during DCS. DCS positive and negative (nonfunctional) sites were aligned to corresponding subdural electrodes. Future analysis: We plan to compare the temporal and spectral electrophysiologic variations associated with cortical sites found to be DCS positive versus negative during brain mapping. We plan to train machine learning classifiers that utilize these electrophysiologic biomarkers to discriminate between DCS positive and negative sites. RESULTS/ANTICIPATED RESULTS: In total, our database comprised of 110 resections with brain mapping (DCS) and ECOG, including 4 patients who underwent a second procedure for resection. Eight patients were excluded as their resections were for brain metastases, not glioma. Our final cohort was comprised of 98 glioma resections, including 4 patients who underwent surgery twice for recurrence. During these resections, a total of 1393 sites were mapped via DCS for language function (including picture naming, word reading, and sentence syntax tasks). Of these 1393 sites, 100 sites were found to be DCS positive (7.1% positivity rate). (Currently in the process of conducting analysis comparing electrophysiologic features and biomarkers of DCS positive versus negative sites.) DISCUSSION/SIGNIFICANCE OF IMPACT: This research is ongoing. Identifying electrophysiologic biomarkers of critical DCS-positive regions may provide a durable alternative to stimulation mapping. Due to its resource intensity, DCS has access barriers. Future neurosurgeons may use biomarkers from subdural electrode recordings to plan safer cortical resections.

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Uncovering links between innate immunity, DNA repair, and cognitive health in aging populations

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OBJECTIVES/GOALS: Neurodegenerative diseases involve progressive neuronal loss or dysfunction, often due to accumulated

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damage and impaired repair mechanisms. Our research evaluates the role of innate immune recognition proteins to provide insights into age-related neurodegeneration and cognitive decline. METHODS/STUDY POPULATION: We will utilize transcriptomic data from the Long-Life Family Study (LLFS), a cohort rich in genetic and phenotypic data related to aging and longevity. Our approach includes assessing a set of innate immune recognition proteins, also known as pattern recognition receptors (PRRs) expression across various age groups, focusing on potential correlations with cognitive performance. By analyzing serum transcriptomic profiles, we aim to map changes in expression and DNA repair genes over time, evaluating their connection to cognitive health and neurodegeneration in aging populations. RESULTS/ANTICIPATED RESULTS: We anticipate that the expression of some PRRs will increase with age and correlate with cognitive decline, suggesting a role in age-related neurodegeneration. We also expect a decrease in DNA repair pathway gene expression in older age groups, contrasting with an increase in genes involved in endogenous DNA detection. These results will reveal how PRRs may function as neuroprotective factors and how their expression changes may relate to the decline in DNA repair processes with age, providing a better understanding of innate immune recognition in cognitive health. DISCUSSION/SIGNIFICANCE OF IMPACT: This study will reveal the role of PRRs in aging and neurodegeneration, potentially establishing them as a key player in neuronal protection. Findings may guide future research into therapeutic strategies targeting them for Alzheimer's and other age-related neurodegenerative diseases.

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Precision education and generative AI in surgery utilization study: A framework for global surgical education

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OBJECTIVES/GOALS: Global surgical education is largely driven by high-income countries (HICs), with curricula not tailored to the needs of low- and middle-income countries (LMICs). This study assessed country-specific needs for global surgical curricula and used generative AI to develop tailored curricula. METHODS/STUDY POPULATION: A curriculum framework was developed using expert opinion. Using a focused needs assessment survey, we evaluated international medical students' and trainees' needs for structured global surgery curricula, covering research, education, data and develop tailored curriculum templates for each country, ensuring alignment with the distinct needs of respective LMIC and HIC respondents. The AI-generated curricula were then compared across countries to identify variations in content and focus areas. RESULTS/ANTICIPATED RESULTS: A total of 145 respondents from 18 countries and 6 continents participated, with 94 from LMICs and 51 from HICs. Four countries [Uganda (n = 31), Nigeria (n = 34), the USA (n = 23), and the UK (n = 23)] had more than 10 respondents, with the creation of a country specific global surgery curriculum. Curricula developed by HIC trainees focused on access to resources and infrastructure, future directions of global surgical research, and the role of medical students and early career development with a decreased focus on the history of global surgery. LMIC country-based curriculum focused on introducing the concepts of global surgery, quantifying the burden and epidemiology of surgical disease and had a greater emphasis on case studies and use cases, with decreased focus on resources and collaboration. DISCUSSION/SIGNIFICANCE OF IMPACT: The research introduces a "precision education" approach that could help close the surgical education access gap globally. Further pilot and qualitative studies are necessary to validate the feasibility of AI-generated needs-based curricula.

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Improving risk stratification in kidney transplant outcomes by modeling antigen processing to inform prediction of T-cell epitopes derived from mismatched HLA proteins

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OBJECTIVES/GOALS: We aim to enhance risk prediction in kidney transplantation outcomes by improving models of peptide antigen presentation of mismatched HLA molecules. HLA-derived peptides presented by HLA Class II to T-cells can activate an immune response, ultimately leading to graft failure. We aim to improve peptide prediction by modeling antigen processing. METHODS/STUDY POPULATION: T-cell epitope models for HLA mismatching struggle to predict which peptides are presented because antigen processing by proteases is not well modeled. We model antigen processing of HLA Class II proteins using 3D HLA structures (crystallography data) to create an HLA-specific antigen processing likelihood (APL) model. APL uses conformational stability measurements such as b-factor, COREX, solvent accessible surface area, and sequence entropy to predict cleavage sites from proteolysis. We will

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