

IMPACT: Our findings suggest that variants related to visual memory and spatial organization are involved in neurodevelopmental and degenerative pathways. This GWAS adds to the growing body of GWAS literature on the genetic basis of cognitive function. Additional analyses are underway to replicate these findings and extend functional annotation.

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Fixing or mixing? Improving small sample size longitudinal microbiome models*

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OBJECTIVES/GOALS: Longitudinal studies capture dynamic host-environment interactions crucial to microbiome research. Commonly used mixed-effects models can struggle with small clinical samples, like many endometrial cancer studies. We will compare them to simpler fixed-effects models, aiming to develop a new fixed-effects differential abundance alternative. **METHODS/STUDY POPULATION:** Starting with simulated data for linear models with a single treatment effect, we will incrementally increase complexity to reflect real-world microbiome data. To observe conditions of misspecification, simulated data of repeated measures will be generated using different distributions, while varying parameters and inter-class correlation. In each condition, linear fixed- and mixed-effects models will be fitted 1000 times to empirically determine p-value, type 1 error rate, and power. We will increase the verisimilitude of our approach by using endometrial cancer data from our lab as a real background, while adding simulated signals. This data will be used to assess extant differential abundance models against our novel fixed-effects model. **RESULTS/ANTICIPATED RESULTS:** Our initial findings indicate that fixed-effects models maintain control over type 1 error rates in small samples, while mixed-effects models do not perform as reliably. We are now exploring the effects of confounders on type 1 error rates and power in linear models, while our next step will evaluate generalized linear models in a differential abundance context. We expect that the fixed-effects models will continue to be as reliable as mixed-effects models, while being less computationally complex. After establishing our theoretical basis, our novel model should perform comparably to mixed-effects models on pseudo-simulated endometrial cancer data and better at small sample sizes. We will finally apply our model to real endometrial cancer data to identify microbial markers of disease predisposition. **DISCUSSION/SIGNIFICANCE OF IMPACT:** By characterizing and improving these statistical tools, we seek to increase the robustness and power of microbiome study results (especially at small sample sizes), ultimately supporting better-informed translational research decisions. This work underscores the importance of statistical methods in advancing microbiome research.

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Leveraging the biodesign process to create impactful medical technologies: A study in neurosurgery

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OBJECTIVES/GOALS: This study demonstrates the utility of the CBID biodesign process for identifying and prioritizing high-impact neurosurgical needs. The research emphasizes the process's role in developing innovative medical technologies that align with the healthcare ecosystem's demands and stakeholder priorities. **METHODS/STUDY POPULATION:** The CBID Spiral Innovation Model, integrating clinical, technical, business, and strategic considerations across clinical challenges in neurosurgery was employed over a 15-week period at a tertiary care center. The process involved three phases: (1) needs identification through 8 weeks of clinical immersion, (2) 7–8 weeks of stakeholder engagement via informational interviews, surveys, and conferences, and (3) iterative refinement based on evidence generation and market value. Stakeholders included over 70 clinicians (neurosurgeons, neurocritical care specialists, neurologists, etc.) across 15 institutions as well as more than 10 payers and hospital administrators. Data collection encompassed direct observation, structured interviews, and comprehensive literature review. **RESULTS/ANTICIPATED RESULTS:** The initial list of 300+ identified neurosurgical needs was reduced to 271 after clinician and market input. High-level market and clinical evidence assessments further reduced this to 74 needs. Finally, through iterative evaluation of evidence generation, market opportunity, and stakeholder feedback, five critical unmet needs in stroke, traumatic brain injury, hydrocephalus, and epilepsy were identified for technological innovation. These needs met the criteria for clinical importance, economic viability, and market accessibility. The findings highlight the effectiveness of the biodesign process in creating a roadmap for innovation that is both clinically relevant and commercially viable. **DISCUSSION/SIGNIFICANCE OF IMPACT:** This study underscores the effectiveness of structured need-finding and prioritization within neurosurgery. Integrating stakeholder perspectives and rigorous analysis, it provides a replicable framework for medical innovation to accelerate the development of impactful solutions across medicine.

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Geographic landscape of US broadband availability from 2017 to 2020

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OBJECTIVES/GOALS: Telehealth is a key solution to improving access to healthcare and disease detection, especially in rural areas. Telehealth access relies on the presence of broadband in an area, which has shifted with the growing importance of internet. We aim to assess the distribution of US county-level broadband availability from 2017 to 2020 overall and by rurality. **METHODS/STUDY POPULATION:** We employed an ecologic study design to examine the distributions of two measures of broadband availability across all US counties from 2017 to 2020. Broadband presence was defined as counties meeting the Federal Communications Commission (FCC) definition of broadband with at least one high-speed internet provider and an average download/upload speed of at least 25/3 megabits per second using 2017–2020 FCC Broadband Deployment Data. Broadband access, or county-year proportion of households with broadband, was defined using 2017–2020 data from the American Community Survey. We used log-binomial and linear regression models and a difference-in-difference analytical approach to estimate the difference in the change in broadband presence and access from 2017 to 2020 between rural and urban counties. **RESULTS/ANTICIPATED RESULTS:** Overall, broadband presence increased

across the study period, where 66.82% of counties had broadband present in 2017 versus 92.57% in 2020. A major jump occurred from 2018 to 2019, where 64.96% of counties had broadband present in 2018 compared to 91.09% in 2019. Broadband access also rose, where the average proportion of households with broadband was 69.43% in 2017 and 78.24% in 2020. The increase in both broadband presence and access from 2017 to 2020 was larger in rural counties compared to urban counties. Specifically, the increase in the probability of having broadband present from 2017 to 2020 was 30% higher in rural compared to urban counties (95% CI: 1.24, 1.38). The increase in the proportion of households with broadband was 1.21% higher from 2017 to 2020 in rural compared to urban counties (95% CI: 0.004, 0.021). **DISCUSSION/SIGNIFICANCE OF IMPACT:** While broadband presence and access both increased from 2017 to 2020, the observed increases were larger in rural compared to urban counties. Improvements in broadband access in the US are continuously needed to increase the use of telehealth and, subsequently, lessen rural/urban disparities in healthcare access and disease detection.

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Defining return to sport in anterior cruciate ligament (ACL) injury recovery with mobile markerless motion capture: A cross-sectional analysis of factors associated with return to activity

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OBJECTIVES/GOALS: Approximately 250,000 anterior cruciate ligament (ACL) tears occur annually in the USA. Symptoms generally improve after ACL reconstruction (ACLR), but 20% of athletes do not return to sport. It is not clear how biomechanical function and mental health impact return to activity, so the purpose of this study is to evaluate their effect on return to activity following ACLR. **METHODS/STUDY POPULATION:** Patients age 18 years and older who have undergone primary ACLR at a single institution who are one year out from their initial procedure will be recruited by email. Patients will be excluded if they had a concomitant or subsequent ligamentous knee injury in the follow-up period since their index procedure. Additionally, patients will be excluded if they do not have access to a mobile phone with video recording capability. The primary outcome will be joint angle kinematics and postural balance metrics derived from patient recorded mobile-phone videos while performing several provocative exercises (sit-to-stand, Star Excursion Balance test). Patients will also be given surveys assessing knee symptoms, psychological readiness for return to sport, mental health, athletic history, and current return to sport level. **RESULTS/ANTICIPATED RESULTS:** We predict that psychological readiness for return to sport following ACL injury and biomechanical postural stability will each be independently associated with return to sport timing following ACLR. Additionally, we anticipate that psychological readiness, as measured by higher ACL-Return to Sport Index scores, will be more strongly associated with return to sport compared to biomechanical movement quality (better gross postural control on skeletal modeling). In other words, higher psychological readiness for return to sport will have a stronger independent association with return to sport level compared to biomechanical movement quality measures. **DISCUSSION/SIGNIFICANCE OF IMPACT:** This study also aims to define return to sport in terms of biomechanics and psychological readiness in an athletically

heterogenous population. Additionally, we will test the feasibility of patient-led, remote, mobile, marker less motion capture for assessment of biomechanical function and distribution of patient-reported outcome measures.

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Predictors of variability in Apple Watch step count data from a 3-year prospective cohort

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OBJECTIVES/GOALS: Physical activity (PA) is a well-documented protective factor against many cardiovascular diseases. PA guidelines to reduce these risks and the impact of variability are unclear, and most studies only examine a 7-day activity window. This study aimed to examine factors related to variability in step counts in a 3-year study of adults aged ≥ 18 years. **METHODS/STUDY POPULATION:** Included were 6,525 participants from the Michigan Predictive Ability and Clinical Trajectories study, a prospective cohort of community-dwelling adults enrolled between 8/14/2018 and 12/19/2019 who received care at Michigan Medicine and were followed for 3 years. Data were collected from Apple Watches provided to participants via the HealthKit. This secondary analysis included those with ≥ 4 valid weeks of data (≥ 4 days with at least 8 hours of wear time). Season was defined as Spring (March 20–June 20), Summer (June 21–September 21), Fall (September 22–December 20), and Winter (December 21–March 19). GEE models against the outcome of variability, defined as weekly standard deviation of step counts, and the predictor of season were adjusted for age, sex, race/ethnicity, weekly average step count, diabetes, and body mass index. **RESULTS/ANTICIPATED RESULTS:** The average (standard deviation (SD)) step counts by season were 7101 (3434) in Spring, 7263 (3354) in Summer, 6863 (3236) in Fall, and 6555 (3211) in Winter. Compared to winter, there was statistically significantly higher variability in all other seasons (p). **DISCUSSION/SIGNIFICANCE OF IMPACT:** In this cohort of community-dwelling adults, we found significant differences in variability of physical activity by season, age, and BMI. Future work will examine how this variability impacts the risk of development of cardiovascular disease, incorporating the impact and recovery trajectories of COVID-19 and other acute respiratory infections.

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The role of bitter taste receptors (T2Rs) in aspirin-exacerbated respiratory disease

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OBJECTIVES/GOALS: Aim 1: Assess the correlation between Tuft cell T2R functionality and Th2 sinonasal inflammation, disease burden, and post-surgical outcomes in AERD patients. Aim 2: Determine if hyperfunctional Tuft cell T2Rs enhance denatonium-stimulated inflammatory responses in nasal epithelial air-liquid interface (ALI) cultures from AERD patients. **METHODS/STUDY POPULATION:** Aim 1: We will conduct a prospective cohort study