Clinical Research FORUM

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TOP 10 CLINICAL RESEARCH ACHIEVEMENT AWARDS

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CELEBRATING ADVANCEMENTS IN CLINICAL RESEARCH

On behalf of the Clinical Research Forum Board of Directors, thank you for supporting and celebrating the achievements of the 2022 Top Ten Clinical Research Achievement Awardees. This year's award winners provide a great representation of the important and impactful work of clinical researchers across the globe.

Under tremendous pressure, clinical research continues to provide positive impacts on the COVID-19 pandemic through treatment, vaccinations and early detection. Beyond the current pandemic, researchers are developing innovative ways to collaborate with communities, expanding technology and outreach solutions and bringing attention to health issues that can often be overshadowed, but have the potential to improve the lives of millions. I cannot emphasize enough the pride I feel for the amazing work of all our colleagues and for clinical research as a field.

Since 1996, the Clinical Research Forum has put a spotlight on the importance of clinical and translational research, and have advocated for broader support from the federal government. We promote "best practices" that have led to some of the most important treatment breakthroughs of our lifetimes. This is our focus, and we welcome your support with this mission.

I look forward to recognizing accomplishments and achievements from the past year with you tonight.

Harry P. Selker, MD, MSPH

Schedule of Events

Tuesday, April 19
5:00 p.m. – 8:30 p.m. CDT
Hyatt Regency McCormick Place | Chicago, Illinois

Welcome – **Harry Selker, MD, MSPH,** *Chair, Clinical Research Forum; Dean, Tufts Clinical and Translational Science Institute, Tufts University*

Presentation of the Top 10 Awards – **Emma Meagher, MD,** *Board Member, Clinical Research Forum; Vice Dean and Chief Clinical Research Officer; Senior Associate Vice Provost for Human Research; Director, Translational Research Education, Perelman School of Medicine, University of Pennsylvania*

Top 10 Keynote Address

Presentation of the Distinguished Clinical Research Achievement Awards – **Emma Meagher, MD**

Presentation of the Herbert Pardes Clinical Research Excellence Award – **Harry Selker, MD, MSPH**

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Johns Hopkins University School of Medicine

John I. Gallin, MD
CR Forum Liaison to the National Institutes of Health
Associate Director for Clinical Research
Chief Scientific Officer, Clinical Center
National Institutes of Health

William Schuyler Jones, MD

ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness)

Publication: Jones WS, Mulder H, Wruck LM, Pencina MJ, Kripalani S, Muoz D, Crenshaw DL, Effron MB, Re RN, Gupta K, Anderson RD, Pepine CJ, Handberg EM, Manning BR, Jain SK, Girotra S, Riley D, DeWalt DA, Whittle J, Goldberg YH, Roger VL, Hess R, Benziger CP, Farrehi P, Zhou L, Ford DE, Haynes K, VanWormer JJ, Knowlton KU, Kraschnewski JL, Polonsky TS, Fintel DJ, Ahmad FS, McClay JC, Campbell JR, Bell DS, Fonarow GC, Bradley SM, Paranjape A, Roe MT, Robertson HR, Curtis LH, Sharlow AG, Berdan LG, Hammill BG, Harris DF, Qualls LG, Marquis-Gravel G, Modrow MF, Marcus GM, Carton TW, Nauman E, Waitman LR, Kho AN, Shenkman EA, McTigue KM, Kaushal R, Masoudi FA, Antman EM, Davidson DR, Edgley K, Merritt JG, Brown LS, Zemon DN, McCormick TE 3rd, Alikhaani JD, Gregoire KC, Rothman RL, Harrington RA, Hernandez AF; ADAPTABLE Team. Comparative Effectiveness of Aspirin Dosing in Cardiovascular Disease. N Engl J Med. 2021 May 27;384(21):1981-1990. doi: 10.1056/NEJMoa2102137. Epub 2021 May 15. PMID: 33999548

Summary: The ADAPTABLE randomized controlled study evaluated the best dose of aspirin, 81 mg or 325 mg, for people with pre-existing heart disease to prevent death or another heart attack or stroke. The trial took place completely virtually, over the course of six years and enrolled 15,076 participants with heart disease.

ADAPTABLE was the first clincial trial to use PCORnet (The National Patient Centered Clinical Research Network) to enage 40 centers from across the United States to identify participants. Innovative methods were used to follow participants throughout the study. In ADAPTABLE, the role of the patient shifted from participant to partner. Adaptors are patient representatives who were involved in ADAPTABLE from the beginning to improve the research process for participants. Coordinated by the Health eHeart Alliance, the Adaptors provided the patient perspective by asking questions, sharing experiences, and participating in working groups and scientific meetings. Adaptors and researchers created a unique culture of collaboration that helped shape the study experience for participants and created a dynamic environment where participants could ask questions, receive study updates, and share the importance of the research via email, newsletters, and social media. Additionally, researchers also used information from a participants' electronic health records, Medicare claims data, and/or private health plan data to get a more complete picture of their health.

During a 26 month follow-up period, there were no differences in rates of death, hospitalization for heart attack or stroke, and bleeding between participants on either of the two doses. As interest grows for real-world evidence, ADAPTABLE demonstrates that randomized clinical trials can leverage electronic health record data, direct-to-patient methods, and patient-reported outcomes to address important, patient centered questions.

Authors: Jones WS, Mulder H, Wruck LM, Pecina MJ, Munoz D, Kripalani S, Crenshaw D, Effron MB, Re RN, Gupta K, Anderson DR, Pepine CJ, Handberg EM, Manning BR, Jain SK, Girotra S, Riley D, DeWalt DA, Whittle J, Golberg YH, Roger VL, Hess R, Benziger CP, Farrehi P, Zhou L, Ford DE, Haynes K, WanWormer JJ, Knowlton KU, Kraschnewski J, Polonsky TS, Fintel DJ, Ahmad FS, McClay JC, Campbell JR, Bell DS, Fonarow GC, Bradley SM, Paranjape A, Roe MT, Robertson HR, Curtis LH, Sharlow AG, Berdan LG, Hammill BG, Harris DF, Qualls LG, Marquis-Gravel G, Modrow MF, Marcus GM, Carton TW, Nauman E, Waitman LR, Kho AM, Shenkman EA, McTigue KM, Kaushal R, Masoudi FA, Antman EM, Davidson DR, Edgley K, Merritt JG, Brown LS, Cruz HP, Zemon DN, McCormick TE, Alikhaani JD, Gregoire KC, Rothman R, Harrington RA, Hernandez AF

Nominating Institution: Duke University

Funding: PCORI (Patient Centered Outcomes Research Institute)

Robert F. Kushner, MD

Once-Weekly Semaglutide in Adults with Overweight or Obesity

Publication: Wilding, J. P., Batterham, R. L., Calanna, S., Davies, M., Van Gaal, L. F., Lingvay, I., ... & Kushner, R. F. (2021). Once-weekly semaglutide in adults with overweight or obesity. New England Journal of Medicine.

Summary: Obesity is associated with many health complications and decreased life expectancy, thus requiring lifetime management. Current medications for chronic weight management and appetite control induce weight loss by helping people eat less and reduce their caloric intake. Because several barriers limit the use of medication, including a lack of training, a misunderstanding of the biological basis of obesity, and a perceived lack of current medications effectiveness and safety, healthcare providers infrequently consider it a treatment option. Approved by the FDA in 2017 for the treatment of diabetes at doses up to 1 mg, semaglutide mimics a naturally occurring, appetite regulating gut hormone called glucagon-like peptide-1.

In this study, Kushner and his colleagues tested a higher dose of of 2.4 mg in overweight or obese participants. After 68 weeks, individuals who received semaglutide had an average weight loss of 15 percent and one third of participants lost 20 percent of their weight, which is comparable to the results often obtained from undergoing bariatric surgery. This weight loss was also associated with improvements in cardiometabolic risk factors and C-reactive protein (a marker of inflammation), and enhanced participant-reported physical functioning.

The outcome achieved by administering semaglutide is highly significant, since the loss of 15 percent or more body weight can have disease modifying effects in people with type 2 diabetes, hypertension, and obstructive sleep apnea, among other chronic weight-related diseases. Moreover, the excitement generated by Kushner and his colleagues STEP 1 trial sheds new light on a disease that affects 42 percent of American adults and is a major risk factor for increased complications and death from COVID-19. Semaglutide's unparalleled results herald a new generation of emerging hormonally-based receptor agonists, which are far more effective than any other medication approved for chronic weight management, and will reshape how healthcare providers treat patients with obesity.

Authors: Wilding JPH, Batterham R, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF

Nominating Institution: Northwestern University, Feinberg School of Medicine

Funding: The trial was supported by Novo Nordisk

Alicia Agnoli, MD, MPH, MHS

Association of Dose Tapering with Overdose or Mental Health Crisis Among Patients Prescribed Long-Term Opioids

Publication: Agnoli A, Xing G, Tancredi DJ, Magnan E, Jerant A, Fenton JJ. Association of Dose Tapering With Overdose or Mental Health Crisis Among Patients Prescribed Long-term Opioids. JAMA. 2021 Aug 3; 326(5):411-419.

Summary: Many factors have led to a major decrease in opioid prescriptions over the past several years, and many patients who were taking stable doses of opioids for chronic pain have had their doses reduced or tapered. There have been reports of patients becoming suicidal or overdosing on the drug as their doses were reduced.

This study examines the potential risks of dose reduction in patients on stable, long-term opioid therapy in a large, national sample of patients. The study found that opioid tapering was associated with higher rates of both overdose and mental health crises during a one-year follow-up period. These adverse events were especially common in patients who were tapering from higher doses and if the dose was reduced more rapidly. Findings show increased risk of overdose and mental health crisis following dose reduction, suggesting that patients undergoing tapering need significant support to safely reduce or discontinue their opioids. These findings demonstrate that the period of tapering is one of heightened vulnerability for patients on long-term opioid therapy. In efforts to reduce opioid-related harms and improve overall health, clinicians must consider these potential risks associated with tapering and weigh them alongside the risks and benefits of continuing opioid therapy for an individual patient.

The study supports a more cautious and supportive approach to decisions around dose adjustments and should bring pause to practices around rapid and involuntary opioid tapering.

Authors: Agnoli A, Xing G, Tancredi DJ, Magnan E, Jerant A, Fenton JJ

Nominating Institution: University of California, Davis

Funding: This study was supported by a University of California–OptumLabs Research Credit and the Department of Family and Community Medicine, University of California, Davis. Dr Agnoli was supported by the University of California, Davis School of Medicine Dean's Office (Dean's Scholarship inWomen's Health Research).

Lesley A. Inker, MD

New 'Race-Free' Equation to Estimate Kidney Function

Publication: Inker, Lesley A., Nwamaka D. Eneanya, Josef Coresh, Hocine Tighiouart, Dan Wang, Yingying Sang, Deidra C. Crews et al. "New creatinine-and cystatin C "based equations to estimate GFR without race." N Engl J Med 2021; 385:1737-1749, DOI: 10.1056/NEJMoa2102953

Summary: Chronic kidney disease (CKD) is a major public health problem, affecting more than 37 million people in the US. A disproportionate number are Black individuals, who already face unacceptable health disparities and inequities in healthcare delivery. The current standard test is based on blood levels of waste products, most commonly creatinine. Since creatinine levels vary by age and other characteristics, the kidneys' filtration rate is estimated from equations that combine creatinine with a number of adjustment factors, including one for Black race based on findings of higher average creatinine levels among Black individuals compared to nonBlack individuals. The inclusion of the adjustments improves the equation accuracy in all individuals. Recently concerns have arisen that adjustment for race should not be used because race is a social, and not a biological, contrast. However, simply removing the adjustment could lessen accuracy of the equations, which could lead to unintended harm.

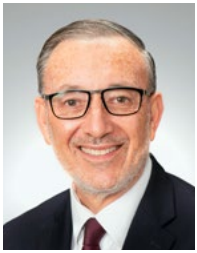
Work done by the Chronic Kidney Disease - Epidemiology Collaboration opens an important path forward by providing new data and racially-neutral options for assessing kidney function. The research team pooled more than 20 diverse populations to develop and test new equations based on creatinine as well as on levels of a different protein, cystatin. Current guidelines recommend first-line estimation of the glomerular filtration rate (GFR) using serum creatinine. The recommended equation includes a coefficient for race (Black versus non-Black) to account for observed differences in creatinine for the same level of measured GFR. As expected, the team found that a new creatinine-based equation that does not include race underestimates measured GFR in Black individuals and overestimates measured GFR in non-Black individuals, but is sufficiently accurate for clinical practice for both groups. The team then developed an eGFR equation incorporating an alternative marker, cystatin C, together with creatinine. It was found to outperform other approaches, yielding eGFR values that are more accurate for both Blacks and non-Blacks, with smaller between-race differences on CKD prevalence.

The study shows their improved creatinine-based estimate offered acceptable accuracy across all populations and that combining creatinine and cystatin yielded the most accurate estimates. All laboratories measure creatinine and nearly all now report estimated GFR whenever a creatinine is ordered, making rapid change feasible. The new equations were recommended for immediate use by a national task force reviewing the inclusion of race in diagnosing kidney diseases.

Authors: Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sand Y, Crews DC, Doria A, Estrella M, Froissart M, Grams ME, Greene T, Grubb A, Gudnason V, Gutierrez OM, Kalil R, Karger AB, Mauer M, Navis G, Nelson RG, Poggio ED, Rodby R, Rossing P, Rule AD, Selvin E, Seegmiller JC, Shlipak MG, Torres VE, Yang W, Ballew SH, Couture SJ, Powe NR, Levey AS

Nominating Institution: Tufts Medical Center, Tufts University School of Medicine

Funding: The measurements and analyses were supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases grant R01DK097020 "Estimating GFR from a Panel of Endogenous Filtration Markers" to Tufts Medical Center



Alejandro Hoberman, MD

Tympanostomy Tubes or Medical Management for Recurrent Acute Otitis Media

Publication: Hoberman A, Preciado D, Paradise JL, Chi DH, Haralam M, Block SL, Kearney DH, Bhatnagar S, Muiz Pujalt GB, Shope TR, Martin JM, Felten DE, Kurs-Lasky M, Liu H, Yahner K, Jeong JH, Cohen NL, Czervionke B, Nagg JP, Dohar JE, Shaikh N. Tympanostomy tubes of medical management for recurrent otitis media. N Engl J Med. 2021;384(19):1789-1799. Doi: 10.1056/NEJMoa2027278.

Summary: After the common cold, ear infection is the most frequently diagnosed illness of children in the United States. Young children who have their first ear infection during their first 12 months of life are susceptible to the development of recurrent acute otitis media, which is attributable to eustachian-tube dysfunction. Recommendations for the management of recurrent acute otitis media have included antimicrobial prophylaxis (no longer favored), tympanostomy-tube placement, and medical management of each episode of acute otitis media. Concerns regarding tympanostomy-tube placement include the risk of anesthesia and surgery, recurrent or persistent otorrhea, and possible scarring or perforation of the tympanic membrane.

This study evaluates best treatment approaches to acute otitis media. The study enrolled 250 children ages 6 to 35 months with documented recurrent ear infections. Children were randomly assigned to receive medical management (oral antibiotics with subsequent ear infections) or surgical insertion of tympanostomy tubes and antibiotic ear drops and followed for 2 years. Overall, there were no differences between children in the two groups regarding rate or severity of ear infections.

Tympanostomy tube placement is the most common operation performed on children after the newborn period. This study shows that episodic antibiotic treatment works as well as surgical placement of tympanostomy tubes and does not increase the risk of bacterial resistance to antibiotics. Physicians can use this data in joint decision making with parents of children with recurrent acute otitis media. With this study, parents can be reassured that medical management can be used without increasing their child's risk to developing antimicrobial resistance with continued antibiotic use.

Authors: Hoberman A, Preciado D, Paradise JL, Chi DH, Haralam M, Block SL, Kearney DH, Bhatnagar S, Mu GB, Shope TR, Martin JM, Felten DE, Lasky MK, Liu H, Yahner K, Jeong JH, Cohen NL, Czervionke B, Nagg JP, Dohar JE, Shaikh N

Nominating Institution: University of Pittsburgh

Funding: Supported by a grant (U01 DC013995-01A1) from the National Institute on Deafness and Other Communication Disorders and by the University of Pittsburgh Clinical and Translational Science Award (UL1RR024153 and UL1TR000005) from the National Center for Research Resources, now at the National Center for Advancing Translational Sciences, National Institutes of Health.

Daniel M. Croymans, MD, MBA, MS

Hengchen Dai, PhD

Silvia Saccardo, PhD

Behavioural Nudges Increase COVID-19 Vaccinations

Publication: Dai H, Saccardo S, Han MA, Roh L, Raja N, Vangala S, Modi H, Pandya S, Sloyan M, Croymans DM. Behavioural nudges increase COVID-19 vaccinations. Nature. 2021 Sep;597(7876):404-409. doi: 10.1038/s41586-021-03843-2. Epub 2021 Aug 2. PMID: 34340242; PMCID: PMC8443442.

Summary: Vaccines have been crucial for eradicating or controlling several deadly infectious diseases. However, enhancing vaccine uptake remains a critical public health challenge admidst the COVID-19 pandemic. Rapid, successful, and sustainable responses to a global pandemic require both cutting-edge mechanistic work in the development of a vaccine or therapeutic combined with cutting-edge behavioral work in rigorously identifying efforts that promote uptake of the vaccine/therapeutic. One without the other can at best have limited impact. Although promoting vaccinations at scale requires a multifaceted approach, this study suggest that behavioural nudges are an important strategy to consider.

Researchers designed text-based reminders that make vaccinations easy to schedule and remember, and delivered them to patients of the UCLA Health healthcare system both one day and eight days after the individual receives notification of vaccine eligibility. The first reminder boosted appointments and vaccination rates within the healthcare system by 6.07 and 3.57 percentage points, respectively; the second reminder increased those outcomes by 1.65 and 1.06 percentage points, respectively. These findings inform the design of behavioral nudges for promoting health decisions, highlighting the value of making vaccination easy and inducing feelings of ownership.

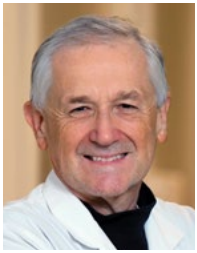
If sent to all 263 million adults in the United States, and assuming the same absolute effect size observed in our first random clinical trial would hold for the 60% of US adults who did not immediately obtain the vaccine, our follow-through reminders could result in 3.31 “5.68 million extra people getting vaccinated within a month of the reminder. Similarly, reminders with the ownership framing would motivate 1.42 “1.74 million extra people to get vaccinated than reminders without such framing.

This research highlights that behavior science insights can increase the rate of COVID-19 vaccinations at close to no marginal cost, and this work has implications for enhancing the uptake of life-saving vaccines across the board, as it highlights the power of making vaccination easy and eliciting feelings of ownership. The findings of this study suggest that behavioral nudges can be an impactful factor to consider in encouraging vaccine uptake. On a large scale, this work could inform strategies to motivate health-related behaviors more broadly, such as scheduling preventive care tests or participating in health-related programs.

Authors: Dai H, Saccardo S, Han M, Roh L, Raja N, Vangala S, Modi H, Pandya S, Slovan M, Croymans DM

Nominating Institution: University of California, Los Angeles

Funding: Funding support for this research was provided by UCLA Health, Anderson School of Management, Anderson Behavioral Lab and Carnegie Mellon University.



Steven Pavletic, MD, MS

Development of Pomalidomide in the Treatment of Chronic Graft-Versus-Host Disease

Publication: Curtis LM, Ostojic A, Venzon DJ, Holtzman NG, Pirsl F, Kuzmina ZJ, Baird K, Rose JJ, Cowen EW, Mays JW, Mitchell SA, Parsons-Wandell L, Joe GO, Comis LE, Berger A, Pusic I, Peer CJ, Figg WD, Cao L, Gale RP, Hakim FT, Pavletic SZ. A randomized phase 2 trial of pomalidomide in subjects failing prior therapy for chronic graft-versus-host disease. Blood. 2021 Feb 18;137(7):896-907. doi: 10.1182/blood.2020006892. PMID: 32976576; PMCID: PMC7918188.

Summary: Allogenic hematopoietic stem cell transplantation is commonly used to treat blood cancers, where a donors blood cells are used to treat a patient's disease. A common side effect of stem cell transplantation is the development of graft-versus-host disease, whereby the donor cells attack healthy tissue in the recipient, leading to disease. In roughly half of cases, this disease progression can be prevented through steroids, however more advanced and disabling Chronic graft-versus-host disease (cGVHD) occurs when steroid treatment is ineffective.

This is a difficult to treat disease that affects roughly 5,000 Americans per year. Dr. Pavletic's team conducted a randomized phase 2 clinical trial at the NIH Clinical Center to determine the safety, efficacy, and preferred dose of pomalidomide in persons with moderate to severe cGVHD who were resistant to previous treatments.

The trial included 34 subjects who were randomized to receive either high or low dose pomalidomide, with a primary endpoint of overall response rate (ORR) at 6 months. Thirty-two patients had severe sclerotic skin and received between two and ten previous therapies. All were partial responses, with no difference in ORR between the cohorts. ORR was 67% in the 24 evaluable subjects at 6 months. Nine subjects had improvement in National Institutes of Health joint/fascia scores. The median change from the baseline in body surface area involvement of skin cGVHD was 27.5%.

Dr. Pavletics team demonstrated that low dose pomalidomide is a safe and effective treatment for advanced chronic graft-versus-host disease (cGVHD). This treatment led to significant improvements in both skin and fascial cGVHD, and promises to become a new treatment for patients with steroid-resistant cGVHD. It also points to potential biologic mechanisms for the future development of new targeted therapies and drug combinations.

Authors: Curtis LM, Ostojic A, Venzon DJ, Holtzman NG, Pirsl F, Kuzmina ZJ, Baird K, Rose JJ, Cowen EW, Mays JW, Mitchell SA, Parsons-Wandell L, Joe GO, Comis LE, Berger A, Pusic I, Peer CJ, Figg WD, Cao L, Gale RP, Hakim FT, Pavletic SZ

Nominating Institution: National Cancer Institute, Center for Cancer Research

Funding: Support for this research was provided by the Center for Cancer Research, National Cancer Institute, National Institutes of Health (NIH) Intramural Research Program, and Celgene Corporation through a Clinical Research Development Agreement (CRADA#02328).

Paul Marasco, PhD

Bionic Arm Restores Natural Behaviors

Publication: Sci Robot. 2021 Sep 8;6(58):eabf3368. doi: 10.1126/scirobotics.abf3368. Epub 2021 Sep 1.

Summary: Lerner Research Institute researchers engineered a first-of-its-kind bionic arm for patients with upper-limb amputations that allows wearers to think, behave and function like a person without an amputation. The team modified a standard-of-care prosthetic with a complex bionic system that combines motor control, touch and grip kinesthesia. It is the first system to test all three sensory and motor functions in a neural-machine interface at once in a prosthetic arm.

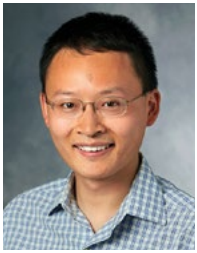
Normally, these brain behaviors are very different between people with and without upper limb prosthetics. For the first time, people with upper-limb amputations are now able to again think like an able-bodied person, which stands to offer prosthesis wearers new levels of seamless reintegration back.

Amputations pose a significant threat to quality of life, and next generation prosthetic limbs can be difficult for the wearer to integrate into their daily lives. Dr. Marasco and colleagues have developed a method to measure sensory and motor features of these limbs, essentially quantifying how much the wearer "feels" like a patient without an amputation. This groundbreaking study will lead to additional improvements in feasibility and usability of these limbs and potentially wearer satisfaction and quality of life.

Authors: Marasco PD, Herbert JS, Sensinger JW, Beckler DT, Thumser ZC, Shehata AW, Williams HE, Wilson KR

Nominating Institution: Cleveland Clinic

Funding: Defense Advanced Research Projects Agency (DARPA) Biological Technologies Office (BTO) under the auspices of D. Weber and A. Emondi through the DARPA Contracts Management Office Grant/Contract No. N66001-15-C-4015. Heather Wilson was supported by the Alberta Innovates Graduate Student Scholarship and the Natural Sciences and Engineering Research Council of Canada (CGS-M)



James Zou, PhD

Evaluating Eligibility Criteria of Oncology Trials Using Real-World Data and AI

Publication: Liu R, Rizzo S, Whipple S, Pal N, Pineda AL, Lu M, Arnieri B, Lu Y, Capra W, Copping R, Zou J. Evaluating eligibility criteria of oncology trials using real-world data and AI. Nature. 2021 Apr;592(7855):629-633. doi: 10.1038/s41586-021-03430-5. Epub 2021 Apr 7. PMID: 33828294.

Summary: Clinical trials are crucial for the development of new therapies that are safe and effective. However, the design of safe and inclusive clinical trial eligibility criteria remains a challenge. Currently, eligibility criteria for clinical trials can be overly restrictive, subjective, and prevent the inclusion of people who could potentially benefit from the trial treatment. The current practices of defining clinical trial eligibility criteria can hinder trial enrollment, participant diversity and the generalizability of results. Dr. Zou and his colleagues built an open-source artificial-intelligence (AI) tool called Trial Pathfinder that uses real-world patient data to guide the design of clinical trial eligibility criteria.

Using EHR data from hundreds of thousands of cancer patients, the study emulated clinical trials under millions of different combinations of eligibility criteria in silico and quantified the impact of each eligibility rule on the treatment efficacy and safety of the real-world patients. Key findings of this innovative approach include:

- Many eligibility criteria that are commonly used to exclude patients from participating in cancer trials could be broadened without affecting patient safety or treatment efficacy. This can make clinical trials more efficient, inclusive and representative.
- Defining eligibility criteria with Trial Pathfinder's data-driven approach increased the eligible pool of trial participants by, on average, 107 percent compared to the eligibility criteria used for the actual trial. In addition to increasing the pool of eligible participants, using data-driven eligibility criteria improved patient survival, suggesting that many patients excluded from trials would have benefitted from trial treatments to a similar or even greater extent than those who participated in the actual trial.
- Using data-driven eligibility criteria expanded the pool of eligible participants to include more minorities, women and individuals over the age of 75 without compromising participant safety.
- The results were consistent for multiple types of cancer, including advanced non-small cell lung cancer, colorectal cancer, advanced melanoma and metastatic breast cancer.

The approach and insights from Dr. Zou's work establish a framework for improving the inclusivity and safety of eligibility criteria for clinical trials. Importantly, Trial Pathfinder is an open source software tool that is widely accessible to the clinical research community. The methodology described in the paper could be widely used by clinical researchers to design clinical trials that are more inclusive, efficient, and safe. While Trial Pathfinder was initially applied to evaluate eligibility criteria for oncology clinical trials, the same approach can be used for diseases beyond cancer, especially as the availability and quality of EHR data increases.

Authors: Liu R, Rizzo S, Whipple S, Pal N, Pineda AL, Lu M, Lu AY, Capra W, Copping R, Zou J

Nominating Institution: Stanford University

Funding: This study was supported by funding from Roche, a NSF CAREER Award and a Chan-Zuckerberg Biohub Investigator Award.

Jean-Laurent Casanova, MD, PhD

The Important Role of Autoantibodies Neutralizing Type I IFNs in COVID-19

Summary: Even though COVID-19 is so recent, no human infectious disease is now better understood in terms of inter-individual variability in the course of infection. Dr. Casanova cracked the enigma of COVID-19, guided by his foundational research into inborn errors of immunity and their autoimmune phenocopies over the last 25 years.

Inspired by his previous work on life-threatening influenza, he discovered the first genetic causes of life-threatening COVID-19 pneumonia, with about 3 percent of the patients enrolled in an international cohort having inborn errors of on certain gene-dependent production and amplification of type I IFNs. Remarkably, he identified adults with certain autosomal recessive traits on gense IRF7 or IFNAR1 deficiency, who had never experienced any severe viral illness prior to their hospitalization for severe COVID-19 pneumonia (Zhang Q. et al. Science 2020). This study pointed to type I IFN immunity as a core mechanism of protective immunity against SARS-CoV-2, and led to the discovery that another 10% of patients with life-threatening COVID-19 pneumonia are sick because of pre-existing neutralizing auto-antibodies to type I IFNs (Bastard P. et al. Science 2020). This breakthrough was made possible by Casanova's previous discovery that auto-antibodies to IFN-γ, IL-6, and IL-17 mimic inborn errors of the corresponding cytokines, underlying mycobacterial, staphylococcal, or fungal infections.

Casanova found that auto-antibodies neutralize lower, more physiological concentrations of IFN-I account for at least 15 percent of cases of critical COVID-19 pneumonia (Bastard et al. Science Immunol 2021). With this landmark paper, Casanova has now provided a convincing explanation for life-threatening COVID-19 pneumonia in at least 20 percent of the patients affected, regardless of ethnicity.

His study of COVID-19 paves the way for the study of many other viral illnesses of the elderly population. Indeed, Casanova recently found that these auto-antibodies can underlie other viral illnesses, such as adverse reactions to the yellow fever live attenuated vaccine virus. The clinical implications of this work are equally important and far-reaching. Patients at risk can be detected by the sequencing of their exomes and the analysis of their plasma. Genetic counseling can be offered to the families and patients can be treated as early as possible in the course of infection.

Authors: Bastard P, Gervais A, Le Voyer T, Rosain J, Philippot Q, Manry J, Michailidis E, Hoffmann HH, Eto S, Garcia-Prat M, Bizien L, Parra-MartÃ-nez A, Yang R, HaljasmÃ¤gi L, Migaud M, SÃ¤rekannu K, Maslovskaja J, de Prost N, Tandjaoui-Lambiotte Y, Luyt CE, Amador-Borrero B, Gaudet A, Poissy J, Morel P, Richard P, Cognasse F, Troya J, TrouilletAssant S, Belot A, Saker K, GarÃ§on P, RiviÃ¨re JG, Lagier JC, Gentile S, Rosen LB, Shaw E, Morio T, Tanaka J, Dalmau D, Tharaux PL, Sene D, Stepanian A, Megarbane B, Triantafyllia V, Fekkar A, Heath JR, Franco JL, Anaya JM, SolÃ©-ViolÃ¡n J, Imberti L, Biondi A, Bonfanti P, Castagnoli R, Delmonte OM, Zhang Y, Snow AL, Holland SM, Biggs C, Moncada-VÃ©lez M, Arias AA, Lorenzo L, Boucherit S, Coulibaly B, Anglicheau D, Planas AM, Haerynck F, Duvlis S, Nussbaum RL, Ozcelik T, Keles S, Bousfiha AA, El Bakkouri J, RamirezSantana C, Paul S, Pan-HammarstrÃ¶m Q, HammarstrÃ¶m L, Dupont A, Kurolap A, Metz CN, Aiuti A, Casari G, Lampasona V, Ciceri F, Barreiros LA, Dominguez-Garrido E, Vidigal M, Zatz M, van de Beek D, Sahanic S, Tancevski I, Stepanovskyy Y, Boyarchuk O, Nukui Y, Tsumura M, Vidaur L, Tangye SG, Burrel S, Duffy D, Quintana-Murci L, Klocperk A, Kann NY, Shcherbina A, Lau YL, Leung D, Coulongeat M, Marlet J, Koning R, Reyes LF, Chauvineau-Grenier A, Venet F, Monneret G, Nussenzweig MC, Arrestier R, Boudhabhay I, Baris-Feldman H, Hagin D, Wauters J, Meyts I, Dyer AH, Kennelly SP, Bourke NM, Halwani R, Sharif-Askari NS, Dorgham K, Sallette J, Sedkaoui SM, AlKhater S, Rigo-Bonnin R, Morandeira F, Roussel L, Vinh DC, Ostrowski SR, Condino-Neto A, Prando C, Bonradenko A, Spaan AN, Gilardin L, Fellay J, Lyonnet S, Bilguvar K, Lifton RP, Mane S

Nominating Institution: The Rockefeller University

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Chi-yuan Hsu, MD, MS

Race, Genetic Ancestry, and Estimating Kidney Function in Chronic Kidney Disease

Summary: The high-profile deaths of a number of Black Americans have triggered considerable public reckoning over the past year and a half regarding race and racism in American society. In medicine, the consideration of race in clinical decision-making has come under intense scrutiny. Perhaps the most high-profile example is the use of race in estimating kidney function (also called the glomerular filtration rate or GFR). Estimated GFR is used in everyday clinical practice to make important decisions ranging from medication usage to whether patients with kidney disease are eligible for transplant. In the past two decades, the vast majority of laboratories in the U.S. have estimated GFR based on equations that consider blood levels of creatinine (a substance produced by muscle and eliminated from the body by the kidneys), age, sex, and race (categorized as Black or non-Black).

The original research that generated the equations concluded that race was important to include because those classified as Black had higher blood creatinine levels than those classified as non-Black at the same level of kidney function, age, and sex. The conventional explanation for this has been racial differences in muscle mass (since creatinine is produced by muscle) but the research studies reporting that have been criticized for numerous scientific shortcomings.

Hsu et al sought to answer three questions leveraging unique data in the Chronic Renal Insufficiency Cohort, including measured GFR, serum creatinine and cystatin C concentrations, genetically-defined ancestry, dietary protein intake, urine creatinine excretion and body composition (by bioelectrical impedance analysis). More than a third of CRIC enrollees self-identified as Black.

First, Hsu et al examined how genetically-defined ancestry compared with self-reported race in the estimation of GFR based on serum creatinine. Second, they evaluated if genetic ancestry or Black race was independently associated with different components of creatinine production, secretion and excretion that may contribute to variations in serum creatinine independent of measured GFR. The authors then assessed whether these non-GFR determinants of serum creatinine could independently or jointly replace the term for Black race or genetic ancestry in GFR estimating equations using serum creatinine. Third, Hsu et al evaluated the potential incremental value of incorporating genetic ancestry or Black race when estimating GFR using serum cystatin C as an alternative filtration marker instead of serum creatinine.

The authors found that when using serum creatinine to estimate GFR, incorporating versus omitting self-reported race yielded better performing estimates. Incorporating genetic ancestry provided estimates of GFR similar to those incorporating self-reported race. Participants who self-identified as Black (or had higher % African ancestry) had greater body mass index, body surface area, height, weight, bioelectrical impedance analysis-quantified phase angle and fat-free muscle mass and 24-hour urine creatinine excretion. This NIH-funded multicenter study shown convincingly that the race coefficient cannot be completely eliminated in GFR estimating equations which rely on creatinine as the filtration marker.

Authors: Hsu CY, Yang W, Parikh RV, Anderson AH, Chen TK, Cohen DL, He J, Mohanty MJ, Lash JP, Mills KT, Muiru AN, Parsa A, Saunders MR, Shafi T, Townsend RR, Waikar SS, Wang J, Wolf M, Tan TC, Feldman HI

Nominating Institution: University of California, San Francisco

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- **COVID-19 Vaccine Acceptance and Hesitancy in Low- and Middle-Income Countries**
  Saad B. Omer, MBBS, MPH, PhD, FIDSA, *Director, Yale Institute for Global Health; Associate Dean, Global Health Research and Professor of Medicine, Infectious Diseases, Yale School of Medicine; Susan Dwight Bliss Professor of Epidemiology of Microbial Diseases, Yale School of Public Health, Yale University School of Medicine*
- **Immune Dysregulation in Common Variable Immunodeficiency**
  Charlotte Cunningham Rundles, MD, MPH, *Assistant Professor, Icahn School of Medicine at Mount Sinai*
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  Charles Coleman Della Santina, MD, PhD, *Professor of Otolaryngology - Head & Neck Surgery and Biomedical Engineering; Director, Johns Hopkins Vestibular Neuro Engineering Lab; Director, Johns Hopkins Cochlear Implant Center, Johns Hopkins School of Medicine*

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