

Henry Ford Health System Publication List – May 2016

This bibliography aims to recognize the scholarly activity and provide ease of access to journal articles, meeting abstracts, book chapters, books and other works published by Henry Ford Health System personnel. Searches were conducted in PubMed, Embase, Web of Science, and Google Scholar during June, and then imported into EndNote for formatting. There are 125 unique citations listed this month. Because of various limitations, this does not represent an exhaustive list of all published works by Henry Ford Health System authors.

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Behavioral Health

Miller-Matero LR, Bryce K, Hyde-Nolan ME, Dykhuis KE, Eshelman A, and Abouljoud M. Health literacy status affects outcomes for patients referred for transplant *Psychosomatics* 2016;PMID: 27231187. [Full Text](#)

Behavioral Health, Henry Ford Health System, Detroit, MI. Electronic address: Lmatero1@hfhs.org.
Behavioral Health, Henry Ford Health System, Detroit, MI; Transplant Institute, Henry Ford Health System, Detroit, MI.
Behavioral Health, Henry Ford Health System, Detroit, MI.
Transplant Institute, Henry Ford Health System, Detroit, MI.

BACKGROUND: It is hypothesized that limited health literacy affects outcomes for patients referred for transplant; however, research has not examined this for all types of end-stage organ disease. **OBJECTIVE:** The purpose of this study was to determine whether health literacy and cognitive impairment were related to listing for transplant and posttransplant outcomes. **METHODS:** Chart reviews were conducted on 398 patients who completed a required psychiatric evaluation before transplant listing. Information gathered from these evaluations included reading ability, math ability, and cognitive functioning. Variables before transplant and 6 months after transplantation were also collected. **RESULTS:** Patients with limited reading ability were less likely to be listed for transplant ($p = .018$) and were more likely to be removed from listing ($p = .042$), to miss appointments prelisting ($p = .021$), and to experience graft failure ($p = .015$). Patients with limited math ability were less likely to be listed ($p = .010$) and receive a transplant ($p = 0.031$), and more likely to be readmitted posttransplant ($p = .029$). Patients with cognitive impairment were less likely to be listed ($p = .043$) and to receive a transplant ($p = .010$). **CONCLUSIONS:** To achieve superior transplant access and outcomes, transplant providers should regularly screen patients for limited health literacy and cognitive impairment. Future studies should evaluate whether interventions result in better outcomes for these patients.

Behavioral Health

Miller-Matero LR, Chipungu K, Martinez S, Eshelman A, and Eisenstein D. How do I cope with pain? Let me count the ways: awareness of pain coping behaviors and relationships with depression and anxiety *Psychol Health Med* 2016:1-9. PMID: 27221277. [Article Request Form](#)

a Behavioral Health , Henry Ford Health System , Detroit , MI , USA.
b Obstetrics & Gynecology , Henry Ford Health System , Detroit , MI , USA.

Patients with chronic pain are often undertreated with medications alone and need alternative ways of coping. Identifying pain coping skills patients use may be beneficial; however, no research has investigated whether patients are aware of their coping skills. The purpose of this study was to determine whether patients are aware of their pain coping skills, whether certain patient characteristics were related to using coping strategies, and whether coping strategies were related to psychiatric symptoms. Chart reviews were conducted on seventy-eight chronic pain patients who completed a semi-structured psychological interview. Patients endorsed using more coping strategies on the measure compared to the verbal self-report. Identifying with certain patient demographics was related to higher use of some coping strategies. Symptoms of anxiety and depression were also related to the use of some coping strategies. Anxiety was negatively related to ignoring the pain and using self-talk coping statements and positively related to catastrophizing. Depression was negatively related to the use of distraction, ignoring the pain,

and using self-talk coping statements. Depression and pain severity were both positively related to catastrophizing and prayer. Results suggest that clinicians may need to help patients become aware of adaptive coping strategies they already use and that the use of certain coping strategies is related to lower levels of depression and anxiety.

Cardiology

Al-Mallah MH, Juraschek SP, Whelton S, Dardari ZA, **Ehrman JK**, Michos ED, Blumenthal RS, Nasir K, Qureshi WT, **Brawner CA**, **Keteyian SJ**, and Blaha MJ. Sex differences in cardiorespiratory fitness and all-cause mortality: The Henry Ford exercise testing (fit) project *Mayo Clin Proc* 2016; 91(6):755-762. PMID: 27161032. [Full Text](#)

Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI; King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, King Abdulaziz Cardiac Center, Ministry of National Guard, Health Affairs, Riyadh, Saudi Arabia. Electronic address: mouaz74@gmail.com.

The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, MD.

Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI.

Cardiovascular Medicine, Wake Forest University School of Medicine, Winston-Salem, NC.

OBJECTIVE: To determine whether sex modifies the relationship between fitness and mortality. **PATIENTS AND METHODS:** We included 57,284 patients without coronary artery disease or heart failure who completed a routine treadmill exercise test between 1991 and 2009. We determined metabolic equivalent tasks (METs) and linked patient records with mortality data via the Social Security Death Index. Multivariable Cox regression was used to determine the association between sex, fitness, and all-cause mortality. **RESULTS:** There were 29,470 men (51.4%) and 27,814 women (48.6%) with mean ages of 53 and 54 years, respectively. Overall, men achieved 1.7 METs higher than women ($P < .001$). During median follow-up of 10 years, there were 6402 deaths. The mortality rate for men in each MET group was similar to that for women, who achieved an average of 2.6 METs lower ($P = .004$). Fitness was inversely associated with mortality in both men (hazard ratio [HR], 0.84 per 1 MET; 95% CI, 0.83-0.85) and women (HR, 0.83 per 1 MET; 95% CI, 0.81-0.84). This relationship did not plateau at high or low MET values. **CONCLUSION:** Although men demonstrated 1.7 METs higher than women, their survival was equivalent to that of women demonstrating 2.6 METs lower. Furthermore, higher MET values were associated with lower mortality for both men and women across the range of MET values. These findings are useful for tailoring prognostic information and lifestyle guidance to men and women undergoing stress testing.

Cardiology

Atkinson TM, Ohman EM, **O'Neill WW**, Rab T, and Cigarroa JE. A practical approach to mechanical circulatory support in patients undergoing percutaneous coronary intervention: An interventional perspective *JACC Cardiovasc Interv* 2016; 9(9):871-883. PMID: 27151604. [Full Text](#)

Knight Cardiovascular Institute, Oregon Health and Science University, Portland, Oregon.

Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina.

Division of Cardiology, Henry Ford Hospital, Detroit, Michigan.

Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia.

Knight Cardiovascular Institute, Oregon Health and Science University, Portland, Oregon. Electronic address: cigarroa@ohsu.edu.

Percutaneous mechanical circulatory support has been used to stabilize patients in cardiogenic shock and provide hemodynamic support during high-risk percutaneous coronary interventions for several decades. The goal of this paper is to provide a practical approach to percutaneous mechanical circulatory support in patients undergoing percutaneous coronary intervention with cardiogenic shock and/or high risk features to aid in decision making for interventional cardiologists.

Cardiology

Collins SP, Levy PD, Martindale JL, Dunlap ME, Storrow AB, Pang PS, Albert NM, Felker GM, Fermann GJ, Fonarow GC, Givertz MM, Hollander JE, **Lanfear DJ**, Lenihan DJ, Lindenfeld JM, Peacock WF, Sawyer DB, Teerlink JR, and Butler J. Clinical and research considerations for patients with hypertensive acute heart failure: A consensus statement from the society of academic emergency medicine and the heart failure society of america acute heart failure working group *J Card Fail* 2016; PMID: 27262665. [Full Text](#)

Department of Emergency Medicine, Vanderbilt University, Nashville, Tennessee. Electronic address: sean.collins@vanderbilt.edu.

Department of Emergency Medicine, Wayne State University, Detroit, Michigan.

Department of Emergency Medicine, SUNY Downstate, New York, New York.
Department of Medicine, Case Western University, Cleveland, Ohio.
Department of Emergency Medicine, Vanderbilt University, Nashville, Tennessee.
Department of Emergency Medicine, Indiana University, Indianapolis, Indiana.
Department of Medicine, Cleveland Clinic, Cleveland, Ohio.
Department of Medicine, Duke University, Raleigh-Durham, North Carolina.
Department of Emergency Medicine, University of Cincinnati, Cincinnati, Ohio.
Department of Medicine, University of California, Los Angeles, California.
Department of Medicine, Harvard Medical School, Boston, Massachusetts.
Department of Emergency Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania.
Department of Medicine, Henry Ford Health System, Detroit, Michigan.
Department of Medicine, Vanderbilt University, Nashville, Tennessee.
Department of Emergency Medicine, Baylor College of Medicine, Houston, Texas.
Department of Medicine, Maine Medical Center, Portland, Maine.
Department of Medicine, San Francisco VA Medical Center, San Francisco, California.
Department of Medicine, Stony Brook University, Long Island, New York.

Management approaches for patients in the emergency department (ED) who present with acute heart failure (AHF) have largely focused on intravenous diuretics. Yet, the primary pathophysiologic derangement underlying AHF in many patients is not solely volume overload. Patients with hypertensive AHF (H-AHF) represent a clinical phenotype with distinct pathophysiologic mechanisms that result in elevated ventricular filling pressures. To optimize treatment response and minimize adverse events in this subgroup, we propose that clinical management be tailored to a conceptual model of disease based on these mechanisms. This consensus statement reviews the relevant pathophysiology, clinical characteristics, approach to therapy, and considerations for clinical trials in ED patients with H-AHF.

Cardiology

Eirin A, Ebrahimi B, Kwon SH, Fiala JA, Williams BJ, Woollard JR, He Q, **Gupta RC, Sabbah HN**, Prakash YS, Textor SC, Lerman A, and Lerman LO. Restoration of mitochondrial cardiolipin attenuates cardiac damage in swine renovascular hypertension *J Am Heart Assoc* 2016; 5(6)PMID: 27247333. [Full Text](#)

Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.
Diabetes and Obesity Research Center, Sanford-Burnham Medical Research Institute, Orlando, FL.
Division of Cardiovascular Medicine, Henry Ford Health System, Detroit, MI.
Department of Anesthesiology, Mayo Clinic, Rochester, MN.
Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN.
Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN lerman.lilach@mayo.edu.

BACKGROUND: Renovascular hypertension (RVH) impairs cardiac structure and left ventricular (LV) function, but whether mitochondrial injury is implicated in RVH-induced myocardial damage and dysfunction has not been defined. We hypothesized that cardiac remodeling in swine RVH is partly attributable to cardiac mitochondrial injury. **METHODS AND RESULTS:** After 12 weeks of hypercholesterolemic (HC)-RVH or control (n=14 each), pigs were treated for another 4 weeks with vehicle or with the mitochondrial-targeted peptide (MTP), Bendavia (0.1 mg/kg subcutaneously, 5 days/week), which stabilizes mitochondrial inner-membrane cardiolipin (n=7 each). Cardiac function was subsequently assessed by multidetector-computed tomography and oxygenation by blood-oxygen-level-dependent magnetic resonance imaging. Cardiolipin content, mitochondrial biogenesis, as well as sarcoplasmic-reticulum calcium cycling, myocardial tissue injury, and coronary endothelial function were assessed ex vivo. Additionally, mitochondrial cardiolipin content, oxidative stress, and bioenergetics were assessed in rat cardiomyocytes incubated with tert-butyl hydroperoxide (tBHP) untreated or treated with MTP. Chronic mitoprotection in vivo restored cardiolipin content and mitochondrial biogenesis. Thapsigargin-sensitive sarcoplasmic reticulum Ca(2+)-ATPase activity that declined in HC-RVH normalized in MTP-treated pigs. Mitoprotection also improved LV relaxation (E/A ratio) and ameliorated cardiac hypertrophy, without affecting blood pressure or systolic function. Myocardial remodeling and coronary endothelial function improved only in MTP-treated pigs. In tBHP-treated cardiomyocytes, mitochondrial targeting attenuated a fall in cardiolipin content and bioenergetics. **CONCLUSIONS:** Chronic mitoprotection blunted myocardial hypertrophy, improved LV relaxation, and attenuated myocardial cellular and microvascular remodeling, despite sustained HC-RVH, suggesting that mitochondrial injury partly contributes to hypertensive cardiomyopathy.

Cardiology

Gheorghide M, Larson CJ, Shah SJ, Greene SJ, Cleland JG, Colucci WS, Dunnmon P, Epstein SE, Kim RJ, Parsey RV, Stockbridge N, Carr J, Dinh W, Krahn T, Kramer F, Wahlander K, Deckelbaum LI, Crandall D, Okada S, Senni M, Sikora S, **Sabbah HN**, and Butler J. Developing new treatments for heart failure: Focus on the heart *Circ Heart Fail* 2016; 9(5)PMID: 27166246. [Full Text](#)

From the Center for Cardiovascular Innovation (M.G.) and Division of Cardiology (S.J.S.), Northwestern Feinberg School of Medicine, Northwestern University, Chicago, IL; Cardiovascular & Metabolic Diseases Drug Discovery Unit, Takeda Pharmaceuticals, Chicago, IL (C.J.L., S.O.); Division of Cardiology, Duke University Medical Center, Durham, NC (S.J.G., R.J.K.); National Heart & Lung Institute, Imperial College, London, United Kingdom (J.G.F.C.); Cardiovascular Medicine Section, Boston University School of Medicine and Boston Medical Center, MA (W.S.C.); Division of Cardiovascular and Renal Products, the United States Food and Drug Administration, Silver Spring, MD (P.D., N.S.); MedStar Heart and Vascular Institute, MedStar Washington Hospital Center, Washington DC (S.E.E.); Psychiatry Department (R.V.P.) and Cardiology Division (J.B.), Stony Brook University, NY; Stealth Bio Therapeutics, Philadelphia, PA (J.C.); Global Drug Discovery, Bayer HealthCare AG, Wuppertal, Germany (W.D., T.K., F.K.); Department of Cardiology, Witten University, Witten, Germany (W.D.); Astra Zeneca Research and Development, Gothenburg, Sweden (K.W.); CSL Behring, Philadelphia, PA (L.I.D.); Sunovion Pharmaceuticals Inc, Marlborough, MA (D.C.); Dipartimento Cardiovascolare, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy (M.S.); Cardiocell Inc, San Diego, CA (S.S.); and Cardiology Division, Henry Ford Hospital, Detroit, MI (H.N.S.). m-gheorghide@northwestern.edu.

From the Center for Cardiovascular Innovation (M.G.) and Division of Cardiology (S.J.S.), Northwestern Feinberg School of Medicine, Northwestern University, Chicago, IL; Cardiovascular & Metabolic Diseases Drug Discovery Unit, Takeda Pharmaceuticals, Chicago, IL (C.J.L., S.O.); Division of Cardiology, Duke University Medical Center, Durham, NC (S.J.G., R.J.K.); National Heart & Lung Institute, Imperial College, London, United Kingdom (J.G.F.C.); Cardiovascular Medicine Section, Boston University School of Medicine and Boston Medical Center, MA (W.S.C.); Division of Cardiovascular and Renal Products, the United States Food and Drug Administration, Silver Spring, MD (P.D., N.S.); MedStar Heart and Vascular Institute, MedStar Washington Hospital Center, Washington DC (S.E.E.); Psychiatry Department (R.V.P.) and Cardiology Division (J.B.), Stony Brook University, NY; Stealth Bio Therapeutics, Philadelphia, PA (J.C.); Global Drug Discovery, Bayer HealthCare AG, Wuppertal, Germany (W.D., T.K., F.K.); Department of Cardiology, Witten University, Witten, Germany (W.D.); Astra Zeneca Research and Development, Gothenburg, Sweden (K.W.); CSL Behring, Philadelphia, PA (L.I.D.); Sunovion Pharmaceuticals Inc, Marlborough, MA (D.C.); Dipartimento Cardiovascolare, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy (M.S.); Cardiocell Inc, San Diego, CA (S.S.); and Cardiology Division, Henry Ford Hospital, Detroit, MI (H.N.S.).

Compared with heart failure (HF) care 20 to 30 years ago, there has been tremendous advancement in therapy for ambulatory HF with reduced ejection fraction with the use of agents that block maladaptive neurohormonal pathways. However, during the past decade, with few notable exceptions, the frequency of successful drug development programs has fallen as most novel therapies have failed to offer incremental benefit or raised safety concerns (ie, hypotension). Moreover, no therapy has been approved specifically for HF with preserved ejection fraction or for worsening chronic HF (including acutely decompensated HF). Across the spectrum of HF, preliminary results from many phase II trials have been promising but are frequently followed by unsuccessful phase III studies, highlighting a disconnect in the translational process between basic science discovery, early drug development, and definitive clinical testing in pivotal trials. A major unmet need in HF drug development is the ability to identify homogeneous subsets of patients whose underlying disease is driven by a specific mechanism that can be targeted using a new therapeutic agent. Drug development strategies should increasingly consider therapies that facilitate reverse remodeling by directly targeting the heart itself rather than strictly focusing on agents that unload the heart or target systemic neurohormones. Advancements in cardiac imaging may allow for more focused and direct assessment of drug effects on the heart early in the drug development process. To better understand and address the array of challenges facing current HF drug development, so that future efforts may have a better chance for success, the Food and Drug Administration facilitated a meeting on February 17, 2015, which was attended by clinicians, researchers, regulators, and industry representatives. The following discussion summarizes the key takeaway dialogue from this meeting.

Cardiology

Jain T, Nowak R, Hudson M, Frisoli T, Jacobsen G, and McCord J. Short- and long-term prognostic utility of the HEART score in patients evaluated in the emergency department for possible acute coronary syndrome *Crit Pathw Cardiol* 2016; 15(2):40-45. PMID: 27183252. [Full Text](#)

From the *Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan; daggerDepartment of Emergency Medicine, Henry Ford Hospital, Detroit, Michigan; double daggerHenry Ford Heart and Vascular Institute, Detroit, Michigan; and section signDepartment of Biostatistics, Henry Ford Hospital, Detroit, Michigan.

INTRODUCTION: The HEART score is a risk-stratification tool that was developed and validated for patients evaluated for possible acute coronary syndrome (ACS) in the emergency department (ED). We sought to determine the short-term and long-term prognostic utility of the HEART score. **METHODS:** A retrospective single-center analysis of 947 patients evaluated for possible ACS in the ED in 1999 was conducted. Patients were followed for major adverse cardiac events (MACEs) at 30 days: death, acute myocardial infarction, or revascularization procedure. All-cause mortality was assessed at 5 years. The HEART score was compared with the Thrombolysis in Myocardial Infarction (TIMI) score. **RESULTS:** At 30 days, 14% (135/947) of patients had an MACE: 48 deaths (5%), 84 acute myocardial infarctions (9%), and 48 (5%) revascularization procedures. The MACE rate in patients with HEART score ≤ 3 was 0.6% (1/175) involving a revascularization procedure, 9.5% (53/557) in patients with HEART score between 4 and 6, and 38% (81/215) with HEART score ≥ 7 . The C-statistic for the HEART score was 0.82 and 0.68 for the TIMI score for predicting 30-day MACE ($P < 0.05$). Patients with HEART score ≤ 3 had lower 5-year mortality rate compared with those with TIMI score of 0 (10.6% vs. 20.5%, $P = 0.02$). **CONCLUSIONS:** The HEART score is a valuable risk-stratification tool in predicting not only short-term MACE but also long-term mortality in patients evaluated for possible ACS in the ED. The HEART score had a superior prognostic value compared with the TIMI score.

Cardiology

Karatasakis A, Tarar MN, Karmaliotis D, **Alaswad K**, Yeh RW, Jaffer FA, Wyman RM, Lombardi WL, Grantham JA, Kandzari DE, Lembo NJ, Moses JW, Kirtane AJ, Parikh M, Garcia S, Doing A, Pershad A, Shah A, Patel M, Bahadorani J, Shoultz CA, Jr., Danek BA, Thompson CA, Banerjee S, and Brilakis ES. Guidewire and microcatheter utilization patterns during antegrade wire escalation in chronic total occlusion percutaneous coronary intervention: Insights from a contemporary multicenter registry *Catheter Cardiovasc Interv* 2016;PMID: 27184465. [Full Text](#)

VA North Texas Healthcare System and University of Texas Southwestern Medical Center, Dallas, Texas.

Columbia University, New York, New York.

Henry Ford Hospital, Detroit, Michigan.

Beth Israel Deaconess Medical Center, Boston, Massachusetts.

Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.

Torrance Memorial Medical Center, Torrance, California.

PeaceHealth St. Joseph Medical Center, Bellingham, Washington.

Mid America Heart Institute, Kansas City, Missouri.

Piedmont Heart Institute, Atlanta, Georgia.

Minneapolis VA Healthcare System and University of Minnesota, Minneapolis, Minnesota.

Medical Center of the Rockies, Loveland, Colorado.

Banner Good Samaritan Cavanagh Heart Clinic, Phoenix, Arizona.

Methodist Hospital, Houston, Texas.

VA San Diego Healthcare System and University of California San Diego, San Diego, California.

Providence Health Center, Waco, Texas.

Boston Scientific, Natick, Massachusetts.

OBJECTIVES: We sought to describe contemporary guidewire and microcatheter utilization for antegrade wire escalation (AWE) during chronic total occlusion (CTO) percutaneous coronary intervention (PCI). **BACKGROUND:** Equipment utilization for AWE has been variable and evolving over time. **METHODS:** We examined device utilization during 694 AWE attempts in 679 patients performed at 15 experienced US centers between May 2012 and April 2015. **RESULTS:** Mean age was 65.6 \pm 9.7 years, and 85% of the patients were men. Successful wiring occurred in 436 AWE attempts (63%). Final technical and procedural success was 91% and 89%, respectively. The mean number of guidewire types used for AWE was 2.2 \pm 1.4. The most frequently used guidewire types were the Pilot 200 (Abbott Vascular, 56% of AWE procedures), Fielder XT (Asahi Intecc, 45%), and the Confianza Pro 12 (Asahi Intecc, 28%). The same guidewires were the ones that most commonly crossed the occlusion: Pilot 200 (36% of successful AWE crossings), Fielder XT (20%), and Confianza Pro 12 (11%). A microcatheter or over-the-wire balloon was used for 81% of AWE attempts; the Corsair microcatheter (Asahi Intecc) was the most commonly used (44%). No significant association was found between guidewire type and incidence of major adverse cardiac events (MACE). **CONCLUSIONS:** Our contemporary, multicenter CTO PCI registry demonstrates that the most commonly used wires for AWE are polymer-jacketed guidewires. "Stiff" and polymer-jacketed guidewires appear to provide high crossing rates without an increase in MACE or perforation, and may thus be considered for upfront use. (c) 2016 Wiley Periodicals, Inc.

Cardiology

Kim J, **Al-Mallah M**, Juraschek SP, **Brawner C**, **Keteyian SJ**, Nasir K, Dardari ZA, Blumenthal RS, and Blaha MJ. The association of clinical indication for exercise stress testing with all-cause mortality: the FIT Project *Arch Med Sci* 2016; 12(2):303-309. PMID: 27186173. [Full Text](#)

Division of Cardiology, Department of Medicine, University of Cincinnati College of Medicine, Cincinnati, OH, USA; Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, MD, USA. Henry Ford Health System, Detroit, MI, USA; King Abdul-Aziz Cardiac Center, Riyadh, Saudi Arabia. Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, MD, USA. Henry Ford Health System, Detroit, MI, USA.

INTRODUCTION: We hypothesized that the indication for stress testing provided by the referring physician would be an independent predictor of all-cause mortality. **MATERIAL AND METHODS:** We studied 48,914 patients from The Henry Ford Exercise Testing Project (The FIT Project) without known congestive heart failure who were referred for a clinical treadmill stress test and followed for 11 +/-4.7 years. The reason for stress test referral was abstracted from the clinical test order, and should be considered the primary concerning symptom or indication as stated by the ordering clinician. Hierarchical multivariable Cox proportional hazards regression was performed, after controlling for potential confounders including demographics, risk factors, and medication use as well as additional adjustment for exercise capacity in the final model. **RESULTS:** A total of 67% of the patients were referred for chest pain, 12% for shortness of breath (SOB), 4% for palpitations, 3% for pre-operative evaluation, 6% for abnormal prior testing, and 7% for risk factors only. There were 6,211 total deaths during follow-up. Compared to chest pain, those referred for palpitations (HR = 0.72, 95% CI: 0.60-0.86) and risk factors only (HR = 0.72, 95% CI: 0.63-0.82) had a lower risk of all-cause mortality, whereas those referred for SOB (HR = 1.15, 95% CI: 1.07-1.23) and pre-operative evaluation (HR = 2.11, 95% CI: 1.94-2.30) had an increased risk. In subgroup analysis, referral for palpitations was protective only in those without coronary artery disease (CAD) (HR = 0.75, 95% CI: 0.62-0.90), while SOB increased mortality risk only in those with established CAD (HR = 1.25, 95% CI: 1.10-1.44). **CONCLUSIONS:** The indication for stress testing is an independent predictor of mortality, showing an interaction with CAD status. Importantly, SOB may be associated with higher mortality risk than chest pain, particularly in patients with CAD.

Cardiology

Kutyifa V, Daubert JP, **Schuger C**, Goldenberg I, Klein H, Aktas MK, McNitt S, Stockburger M, Merkely B, Zareba W, and Moss AJ. Novel ICD Programming and Inappropriate ICD Therapy in CRT-D Versus ICD Patients: A MADIT-RIT Sub-Study *Circ Arrhythm Electrophysiol* 2016; 9(1):e001965. PMID: 26743237. [Full Text](#)

From the University of Rochester Medical Center, Heart Research Follow-Up Program, Rochester, NY (V.K., I.G., H.K., M.K.A., S.M., W.Z., A.J.M.); Duke University Medical Center, Division of Cardiology, Durham, NC (J.P.D.); Henry Ford Hospital, Detroit, MI (C.S.); Experimental and Clinical Research Center, a Joint Cooperation between the Charite Medical Faculty and the Max-Delbrueck Center for Molecular Medicine, Berlin, Germany (M.S.); and Semmelweis University, Heart and Vascular Center, Budapest, Hungary (B.M.).
Valentina.Kutyifa@heart.rochester.edu.

From the University of Rochester Medical Center, Heart Research Follow-Up Program, Rochester, NY (V.K., I.G., H.K., M.K.A., S.M., W.Z., A.J.M.); Duke University Medical Center, Division of Cardiology, Durham, NC (J.P.D.); Henry Ford Hospital, Detroit, MI (C.S.); Experimental and Clinical Research Center, a Joint Cooperation between the Charite Medical Faculty and the Max-Delbrueck Center for Molecular Medicine, Berlin, Germany (M.S.); and Semmelweis University, Heart and Vascular Center, Budapest, Hungary (B.M.).

BACKGROUND: The Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate therapy (MADIT-RIT) trial showed a significant reduction in inappropriate implantable cardioverter defibrillator (ICD) therapy in patients programmed to high-rate cut-off (Arm B) or delayed ventricular tachycardia therapy (Arm C), compared with conventional programming (Arm A). There is limited data on the effect of cardiac resynchronization therapy with a cardioverter defibrillator (CRT-D) on the effect of ICD programming. We aimed to elucidate the effect of CRT-D on ICD programming to reduce inappropriate ICD therapy in patients implanted with CRT-D or an ICD, enrolled in MADIT-RIT. **METHODS AND RESULTS:** The primary end point of this study was the first inappropriate ICD therapy. Secondary end points were inappropriate anti-tachycardia pacing and inappropriate ICD shock. The study enrolled 742 (49%) patients with an ICD and 757 (51%) patients with a CRT-D. Patients implanted with a CRT-D had 62% lower risk of inappropriate ICD therapy than those with an ICD only (hazard ratio [HR] =0.38, 95% confidence interval: 0.25-0.57; P<0.001). High-rate cut-off or delayed ventricular tachycardia therapy programming significantly reduced the risk of inappropriate ICD therapy compared with conventional ICD programming in ICD (HR=0.14 [B versus A]; HR=0.21 [C versus A]) and CRT-D patients (HR=0.15 [B versus A]; HR=0.23 [C versus A]; P<0.001 for all). There was a significant reduction in inappropriate anti-tachycardia pacings in both group and a significant reduction in inappropriate ICD shock in CRT-D patients. **CONCLUSIONS:** Patients implanted with a CRT-D have lower risk of

inappropriate ICD therapy than those with an ICD. Innovative ICD programming significantly reduces the risk of inappropriate ICD therapy in both ICD and CRT-D patients. CLINICAL TRIAL REGISTRATION: <http://clinicaltrials.gov>; Unique identifier: NCT00947310.

Cardiology

McAuley PA, Blaha MJ, **Keteyian SJ, Brawner CA**, Al Rifai M, Dardari ZA, Ehrman JK, and **Al-Mallah MH**. Fitness, fatness, and mortality: The FIT (henry ford exercise testing) project *Am J Med* 2016;PMID: 27154778. [Full Text](#)

Department of Health, Physical Education, and Sport Studies, Winston Salem State University, 141B Anderson, 601 S Martin Luther King Jr Drive, Winston Salem, NC 27110. Electronic address: mcauleypa@wssu.edu.
Ciccarone Center for the Prevention of Heart Disease, Johns Hopkins School of Medicine, 1830 E. Monument Street, Baltimore, MD 21287.

Division of Cardiovascular Medicine, Henry Ford Hospital, 6525 Second Avenue, Detroit, MI 48202.

Division of Cardiovascular Medicine, Henry Ford Hospital, 6525 Second Avenue, Detroit, MI 48202; King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, King Abdul Aziz Cardiac Center, Ministry of National Guard Health Affairs, Riyadh, Kingdom of Saudi Arabia.

BACKGROUND: The combined influence of fitness and fatness on mortality risk in diverse populations has not been adequately explored. Our aim was to assess the relative impact of exercise capacity and body mass index (BMI) on all-cause mortality. **METHODS:** We included 29,257 men and women (mean age 53 years; 27% African-American) from The Henry Ford Exercise Testing (FIT) Project without cardiovascular disease and diabetes mellitus at baseline. All patients completed a symptom-limited maximal treadmill stress test between 1991 and 2009. Patients were grouped for analysis by exercise capacity (≥ 10 METs and < 10 METs) and obesity status (≥ 30 kg/m² and < 30 kg/m²) forming four subgroups. Independent and joint associations of BMI and exercise capacity with all-cause mortality were assessed using Cox proportional hazard models. **RESULTS:** During a mean follow-up of 10.8 years, 1,898 (6.5%) patients died. We observed a strong inverse association between exercise capacity (per 1 MET unit) and all-cause mortality (HR [95% CI], 0.86 [0.85-0.88]). BMI (per 1 BMI unit) was inversely related to mortality (HR [95% CI], 0.98 [0.97-0.99]). In joint analysis, the highest mortality risk was in the < 10 METs/ < 30 kg/m² subgroup. **CONCLUSIONS:** Reduced exercise capacity was a strong independent risk factor for all-cause mortality in this racially diverse population. Given the comparatively limited impact of BMI, more emphasis should be placed on measuring exercise capacity, and developing strategies for its improvement, in cardiovascular disease prevention programs.

Cardiology

Morgan JA, Go PH, Xuereb L, Kaur B, Akrawe S, Nemeh HW, Borgi J, Lanfear DE, Williams CT, and Paone G. Outcomes on continuous flow left ventricular assist devices: A single institutional 9-year experience *Ann Thorac Surg* 2016;PMID: 27173072. [Full Text](#)

Division of Cardiothoracic Surgery, Henry Ford Hospital, Heart and Vascular Institute, Detroit, Michigan. Electronic address: jamorganmd@hotmail.com.

Division of Cardiothoracic Surgery, Henry Ford Hospital, Heart and Vascular Institute, Detroit, Michigan.

BACKGROUND: Continuous-flow left ventricular assist devices (LVADs) have become the standard of care for patients with advanced heart failure. The goal of this study was to review our 9-year institutional experience. **METHODS:** From March 2006 through May 2015, 231 patients underwent implantation of 240 CF LVADs, HeartMate II LVAD (Thoratec Corp., Pleasanton, CA; n = 205) or HVAD (HeartWare Inc., Framingham, MA; n = 35). Of these, 127 devices (52.9%) were implanted as bridge to transplantation (BTT) and 113 (47.1%) as destination therapy (DT). **RESULTS:** Mean age was 51.2 \pm 11.9 years for BTT patients and 58.2 \pm 11.4 years for DT patients (p < 0.001). There was a higher incidence of preoperative diabetes, renal insufficiency, peripheral vascular disease, and previous cardiac operation in DT patients (p < 0.05). Survival was higher for BTT patients, with 1-, 6-, 12-, and 24-month survivals of 91.0%, 90.0%, 88.5%, and 72.1%, respectively, versus 85.3%, 81.1%, 75.6%, and 59.0%, respectively, for DT patients (p = 0.038). Gastrointestinal bleeding was the most common complication (29.6%), followed by right ventricular failure (22.5%) and stroke (15.0%), with a similar incidence for BTT and DT patients. Preoperative liver biopsy (hazard ratio [HR] 2.27, p = 0.036), mechanical support (HR 1.82, p = 0.025), aspartate transaminase (HR 1.07, p = 0.001), and alanine aminotransferase (HR 0.95, p = 0.024) were severe independent predictors of survival in multivariate analysis. **CONCLUSIONS:** These data indicate excellent survival for BTT and DT patients on long-term LVAD support. However, for LVAD therapy to become a plausible alternative to heart transplantation, we need to further decrease the incidence of postoperative complications.

Cardiology

O'Neill BP, Wheatley G, Bashir R, Edmundowicz D, O'Murchu B, **O'Neill WW**, Patil P, Chen A, Forfia P, and Cohen HA. Study design and rationale of the heterotopic implantation of the Edwards-Sapien XT transcatheter valve in the inferior Vena cava for the treatment of severe tricuspid regurgitation (HOVER) trial *Catheter Cardiovasc Interv* 2016;PMID: 27122473. [Full Text](#)

Temple Heart and Vascular Institute, Philadelphia, Pennsylvania.
Henry Ford Health System, Detroit, Michigan.

BACKGROUND: Tricuspid regurgitation (TR) is an under treated disease. Although surgery for TR remains an effective therapy, many patients are considered to be at a high risk or otherwise inoperable. Caval valve implant (CAVI) offers an alternative to surgery in these patients. Trials assessing the safety and efficacy of caval valve implant are lacking. **METHODS:** The Heterotopic Implantation Of the Edwards-Sapien XT Transcatheter Valve in the Inferior Vena cava for the treatment of severe Tricuspid Regurgitation (HOVER) trial is an FDA approved, physician initiated, prospective, non-blinded (open label), non-randomized safety and feasibility study to determine the safety and efficacy of the heterotopic implantation of the Edwards-Sapien XT valve in the inferior vena cava for the treatment of severe TR in patients who are at high risk or inoperable. Patients with severe TR in the absence of severe pulmonary hypertension will be recruited. They will be evaluated by a multi-disciplinary team who will agree by consensus that the patients' symptoms are from TR. They will undergo imaging to assess the size of the inferior vena cava (IVC) to determine feasibility of the procedure. If patients meet the inclusion criteria and are free from exclusion criteria, after informed consent they will be eligible for enrollment in the study. A total of 30 patients will be enrolled. The primary objective of the study will be to demonstrate procedural success at 30-days and patient success at 1-year. **CONCLUSION:** Caval valve implant may present an alternative for patients who are at high risk or inoperable for tricuspid valve surgery (TVS) for TR. (c) 2016 Wiley Periodicals, Inc.

Cardiology

Wang DD, Eng M, Greenbaum A, Myers E, Forbes M, Pantelic M, Song T, Nelson C, Divine G, Taylor A, Wyman J, Guerrero M, Lederman RJ, Paone G, and O'Neill W. Predicting LVOT Obstruction After TMVR *JACC Cardiovasc Imaging* 2016;PMID: 27209112. [Full Text](#)

Division of Cardiology, Center for Structural Heart Disease, Henry Ford Health System, Detroit, Michigan. Electronic address: dwang2@hfhs.org.

Division of Cardiology, Center for Structural Heart Disease, Henry Ford Health System, Detroit, Michigan.

Henry Ford Innovation Institute, Henry Ford Health System, Detroit, Michigan.

Division of Radiology, Henry Ford Health System, Detroit, Michigan.

Division of Cardiology, Center for Structural Heart Disease, Henry Ford Health System, Detroit, Michigan; Division of Cardiology, Evanston Hospital/NorthShore University Health System, Evanston, Illinois.

Cardiovascular and Pulmonary Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Center for Health Policy and Health Services Research

Abid Z, Oh SS, Hu D, Sen S, Huntsman S, Eng C, Farber HJ, Rodriguez-Cintron W, Rodriguez-Santana JR, Serebrisky D, Avila PC, Thyne SM, Kim KA, Borrell LN, **Keoki Williams L**, Seibold MA, Burchard EG, and Kumar R. Maternal age and asthma in Latino populations *Clin Exp Allergy* 2016;PMID: 27238356. [Full Text](#)

Division of Allergy-Immunology, Department of Medicine, Northwestern University, Chicago, IL.

Department of Medicine, University of California, San Francisco, CA.

Department of Biostatistics, University of California, San Francisco, CA.

Department of Pediatrics, Section of Pulmonology, Baylor College of Medicine, Houston, Texas Children's Hospital.

Veterans Caribbean Health Care System, San Juan, PR.

Centro de Neumología Pediátrica, CSP, San Juan, PR.

Pediatric Pulmonary Division, Jacobi Medical Center, Bronx, NY.

Department of Pediatrics, University of California, San Francisco, CA.

Department of Preventive Medicine, Northwestern University, Chicago, IL.

Department of Health Sciences, , Lehman College, CUNY, NY.

Department of Internal Medicine, Henry Ford Health System, Detroit, MI.

Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, MI.

Center for Genes, Environment and Health, National Jewish Health, Denver, CO.

Division of Allergy-Immunology, Department of Pediatrics, Northwestern University, Chicago, IL.

The Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL.

BACKGROUND: Younger maternal age at birth is associated with increased risk of asthma in offspring in European descent populations, but has not been studied in Latino populations. **OBJECTIVES:** We sought to examine the relationship between maternal age at birth and prevalence of asthma in a nationwide study of Latino children. **METHODS:** We included 3473 Latino children aged 8-21 years (1696 subjects with physician-diagnosed asthma and 1777 healthy controls) from five U.S. centers and Puerto Rico recruited from July 2008 through November 2011. We used multiple logistic regression to examine the effect of maternal age at birth on asthma in offspring overall, and in analyses stratified by ethnic subgroup (Mexican American, Puerto Rican, and Other Latino). Secondary analyses evaluated the effects of siblings, acculturation, and income on this relationship. **RESULTS:** Maternal age <20 years was significantly associated with a decreased odds of asthma in offspring, independent of other risk factors (OR = 0.73, 95% CI: 0.57-0.93). In subgroup analyses, the protective effect of younger maternal age was observed only in Mexican Americans (OR = 0.53, 95% CI: 0.36, 0.79). In Puerto Ricans, older maternal age was associated with a decreased odds of asthma (OR = 0.65, 95% CI: 0.44-0.97). In further stratified models, the protective effect of younger maternal age in Mexican Americans was seen only in children without older siblings (OR = 0.44, 95% CI: 0.23-0.81). **CONCLUSION AND CLINICAL RELEVANCE:** In contrast to European descent populations, younger maternal age was associated with a decreased odds of asthma in offspring in Mexican American women. Asthma is common in urban minority populations but the factors underlying the varying prevalence among different Latino ethnicities in the U.S. is not well understood. Maternal age represents one factor which may help explain this variability. This article is protected by copyright. All rights reserved.

Center for Health Policy and Health Services Research

Ali R, Schwalb JM, Nerenz DR, Antoine HJ, and Rubinfeld I. Use of the modified frailty index to predict 30-day morbidity and mortality from spine surgery *J Neurosurg Spine* 2016:1-5. PMID: 27153143. [Full Text](#)

Department of Neurosurgery, Henry Ford Hospital;
Neuroscience Institute and the Center for Health Policy and Health Services Research, Henry Ford Health System;
and

Department of Surgery, Henry Ford Hospital, Detroit, Michigan.

OBJECTIVE Limited tools exist to stratify perioperative risk in patients undergoing spinal procedures. The modified frailty index (mFI) based on the Canadian Study of Health and Aging Frailty Index (CSHA-FI), constructed from standard demographic variables, has been applied to various other surgical populations for risk stratification. The authors hypothesized that it would be predictive of postoperative morbidity and mortality in patients undergoing spine surgery. **METHODS** The 2006-2010 National Surgical Quality Improvement Program (NSQIP) data set was accessed for patients undergoing spine surgeries based on Current Procedural Terminology (CPT) codes. Sixteen preoperative clinical NSQIP variables were matched to 11 CSHA-FI variables (changes in daily activities, gastrointestinal problems, respiratory problems, clouding or delirium, hypertension, coronary artery and peripheral vascular disease, congestive heart failure, and so on). The outcomes assessed were 30-day occurrences of adverse events. These were then summarized in groups: any infection, wound-related complication, Clavien IV complications (life-threatening, requiring ICU admission), and mortality. **RESULTS** A total of 18,294 patients were identified. In 8.1% of patients with an mFI of 0 there was at least one morbid complication, compared with 24.3% of patients with an mFI of ≥ 0.27 ($p < 0.001$). An mFI of 0 was associated with a mortality rate of 0.1%, compared with 2.3% for an mFI of ≥ 0.27 ($p < 0.001$). Patients with an mFI of 0 had a 1.7% rate of surgical site infections and a 0.8% rate of Clavien IV complications, whereas patients with an mFI of ≥ 0.27 had rates of 4.1% and 7.1% for surgical site infections and Clavien IV complications, respectively ($p < 0.001$ for both). Multivariate analysis showed that the preoperative mFI and American Society of Anesthesiologists classification of \geq III had a significantly increased risk of leading to Clavien IV complications and death. **CONCLUSIONS** A higher mFI was associated with a higher risk of postoperative morbidity and mortality, providing an additional tool to improve perioperative risk stratification.

Center for Health Policy and Health Services Research

Buu A, **Williams LK**, and Yang JJ. An efficient genome-wide association test for mixed binary and continuous phenotypes with applications to substance abuse research *Stat Methods Med Res* 2016; PMID: 27215414. [Full Text](#)

Department of Health Behavior and Biological Sciences, University of Michigan, USA.
Department of Internal Medicine, Henry Ford Health System, USA
The Center for Health Policy and Health Services Research, Henry Ford Health System, USA.
School of Nursing, University of Michigan, USA jjyang@umich.edu.

We propose a new genome-wide association test for mixed binary and continuous phenotypes that uses an efficient numerical method to estimate the empirical distribution of the Fisher's combination statistic under the null hypothesis.

Our simulation study shows that the proposed method controls the type I error rate and also maintains its power at the level of the permutation method. More importantly, the computational efficiency of the proposed method is much higher than the one of the permutation method. The simulation results also indicate that the power of the test increases when the genetic effect increases, the minor allele frequency increases, and the correlation between responses decreases. The statistical analysis on the database of the Study of Addiction: Genetics and Environment demonstrates that the proposed method combining multiple phenotypes can increase the power of identifying markers that may not be, otherwise, chosen using marginal tests.

Center for Health Policy and Health Services Research

Fishbein AB, Lee TA, Cai M, Oh SS, Eng C, Hu D, Huntsman S, Farber HJ, Serebrisky D, Silverberg J, **Williams LK**, Seibold MA, Sen S, Borrell LN, Avila P, Rodriguez-Cintrón W, Rodriguez-Santana JR, Burchard EG, and Kumar R. Sensitization to mouse and cockroach allergens and asthma morbidity in urban minority youth: Genes-environments and admixture in latino american (gala-ii) and study of african-americans, asthma, genes, and environments (SAGE-II) *Ann Allergy Asthma Immunol* 2016;PMID: 27238578. [Full Text](#)

Northwestern University Lurie Children's Hospital, Chicago, Illinois. Electronic address: afishbein@luriechildrens.org.
University of Illinois at Chicago, Chicago, Illinois.
Northwestern University Lurie Children's Hospital, Chicago, Illinois.
University of California San Francisco, San Francisco, California.
Baylor College of Medicine, Houston, Texas.
Jacobi Medical Center, New York, New York.
Department of Internal Medicine, Henry Ford Health System, Detroit, Michigan.
Integrated Center for Genes, Environment, and Health, National Jewish Health, Denver, Colorado.
City University of New York, Bronx, New York.
Veterans Caribbean Health Care System, San Juan, Puerto Rico.
Centro de Neumología Pediátrica, San Juan, Puerto Rico.

BACKGROUND: Pest allergen sensitization is associated with asthma morbidity in urban youth but minimally explored in Latino populations. Specifically, the effect of mouse sensitization on the risk of asthma exacerbation has been unexplored in Latino subgroups. **OBJECTIVE:** To evaluate whether pest allergen sensitization is a predictor of asthma exacerbations and poor asthma control in urban minority children with asthma. **METHODS:** Latino and African American children (8-21 years old) with asthma were recruited from 4 sites across the United States. Logistic regression models evaluated the association of mouse or cockroach sensitization with asthma-related acute care visits or hospitalizations. **RESULTS:** A total of 1,992 children with asthma in the Genes-environments and Admixture in Latino American (GALA-II) and Study of African-Americans, Asthma, Genes, and Environments (SAGE-II) cohorts were studied. Asthmatic children from New York had the highest rate of pest allergen sensitization (42% mouse, 56% cockroach), with the lowest rate in San Francisco (4% mouse, 8% cockroach). Mouse sensitization, more than cockroach, was associated with increased odds of acute care visits (adjusted odds ratio [aOR], 1.47; 95% CI, 1.07-2.03) or hospitalizations (aOR, 3.07; 95% CI, 1.81-5.18), even after controlling for self-reported race and site of recruitment. In stratified analyses, Mexican youth sensitized to mouse allergen did not have higher odds of asthma exacerbation. Other Latino and Puerto Rican youth sensitized to mouse had higher odds of hospitalization for asthma (aORs, 4.57 [95% CI, 1.86-11.22] and 10.01 [95% CI, 1.77-56.6], respectively) but not emergency department visits. **CONCLUSION:** Pest allergen sensitization is associated with a higher odds of asthma exacerbations in urban minority youth. Puerto Rican and Other Latino youth sensitized to mouse were more likely to have asthma-related hospitalizations than Mexican youth.

Center for Health Policy and Health Services Research

Mitchell S, Roso S, Samuel M, and **Pladevall-Vila M**. Unmet need in the hyperlipidaemia population with high risk of cardiovascular disease: a targeted literature review of observational studies *BMC Cardiovasc Disord* 2016; 16(1):74. PMID: 27114245. [Full Text](#)

RTI Health Solutions, The Pavilion, Towers Business Park, Wilmslow Road, Didsbury, Manchester, M20 2LS, UK. semitchell@rti.org.
Pfizer Ltd., Walton Oaks, Dorking Road, Walton-on-the-Hill, Tadworth, Surrey, KT20 7NS, UK.
NUS Yong Loo Lin School of Medicine, NUHS Tower Block, Level 11, 1E Kent Ridge Road, Singapore, 119228, Singapore.
RTI Health Solutions, Trav. Gracia 56 Atico 1 08006, Barcelona, Spain.
The Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, MI, USA.

BACKGROUND: The aim of this study was to examine recommended target levels of low-density lipoprotein cholesterol (LDL-C) for hyperlipidaemia patients at high risk (i.e., with two or more risk factors or coronary heart disease or its risk equivalents) for cardiovascular disease (CVD); to determine LDL-C targets recommended by guidelines, and to examine the proportions of patients who do not achieve targeted LDL-C levels in real-world studies. **METHODS:** Electronic databases were searched: Medline, Medline In-Process, Embase, BIOSIS, and the Cochrane Library (1 January 2005 to 31 December 2013). Guideline searches were limited to publications in the last 5 years. There were no geographical or language restrictions. **RESULTS:** Seventeen guidelines and 42 observational studies that reported on high-risk hyperlipidaemia patients were identified. The National Cholesterol Education Program-Adult Treatment Panel III's LDL-C target levels were the most common guidelines used for patients with very high hyperlipidaemia. However, between 68 and 96 % of patients in the studies did not achieve an LDL-C goal <70 mg/dL, except in one study conducted in China (16.9 %). In high-risk patients, 61.8 to 93.8 % did not achieve a target of <100 mg/dL. Regarding common comorbidities, patients with concomitant CVD or diabetes were least likely to reach their target LDL-C goals. **CONCLUSION:** In patients with high risk for CVD, the majority of patients do not attain recommended LDL-C goals, highlighting worldwide suboptimal hyperlipidaemia management and missed opportunities for reduction of the patients CVD risk. Lipid-modifying management strategies need to be intensified.

Center for Health Policy and Health Services Research

Moorman AC, Tong X, Spradling PR, **Rupp LB, Gordon SC, Lu M**, Teshale EH, Boscarino JA, Trinacty CM, Schmidt MA, Xu F, and Holmberg SD. Prevalence of renal impairment and associated conditions among hcv-infected persons in the chronic hepatitis cohort study (CHeCS) *Dig Dis Sci* 2016; PMID: 27216163. [Full Text](#)

Division of Viral Hepatitis, CDC, Mailstop G-37, Atlanta, GA, 30329, USA. Amoorman@cdc.gov.

Division of Viral Hepatitis, CDC, Mailstop G-37, Atlanta, GA, 30329, USA.

Henry Ford Health System, 2799 West Grand Blvd., Detroit, MI, USA.

Geisinger Center for Health Research, Geisinger Health System, 100 N. Academy Avenue, Danville, PA, 17822, USA.

Kaiser Permanente-Center for Health Research, Kaiser Permanente Hawaii, 501 Alakawa Street, Suite 201, Honolulu, HI, 96817, USA.

Center for Health Research Northwest, Kaiser Permanente Northwest, 3800 N. Interstate Avenue, Portland, OR, 97227-1098, USA.

BACKGROUND: Guidelines for the treatment of HCV-infected persons were updated in August 2015 with new recommendations for patients with renal impairment. Treatment is imperative for patients with severe, renal-associated extrahepatic manifestations of HCV infection. **AIMS:** We sought to describe the prevalence of these conditions among current HCV-infected patients in a population-based prospective, observational cohort study at four large US health systems. **METHODS:** Data from cohort patients with chronic HCV infection during 2012 were analyzed for the period from 2006 to 2013. We determined the prevalence of mild to moderately impaired renal function defined as having the most recent estimated glomerular filtration rate [eGFR] ≤ 80 ml/min/1.73 m², with severe impairment defined as eGFR < 30 ml/min/1.73 m², based on the treatment guidelines. Prevalence of extrahepatic conditions was ascertained using ICD9-codes. **RESULTS:** Among 5772 persons, the prevalence of eGFR ≤ 80 was 33 % and eGFR < 30 was 2 %, including among patients with hepatic fibrosis. Diagnosed extrahepatic renal manifestations were rare: vasculitis- 0.2 %, nephrotic syndrome- 0.3 %, and cryoglobulinemia- 0.9 %. **CONCLUSIONS:** While the prevalence of severe renal impairment and diagnosed extrahepatic manifestations was low, mild-to-moderate renal impairment was common in HCV patients, including those with advanced liver fibrosis for whom the need for treatment is urgent.

Center for Health Policy and Health Services Research

Teshale EH, Xing J, Moorman A, Holmberg SD, Spradling PR, **Gordon SC, Rupp LB, Lu M**, Boscarino JA, Trinacty CM, Schmidt MA, and Xu F. Higher all-cause hospitalization among patients with chronic hepatitis C: the Chronic Hepatitis Cohort Study (CHeCS), 2006-2013 *J Viral Hepat* 2016; PMID: 27186944. [Full Text](#)

Division of Viral Hepatitis, CDC, Atlanta, GA, USA.

Henry Ford Hospital, Detroit, MI, USA.

Geisinger Health System, Danville, PA, USA.

Kaiser Permanente Hawaii, Honolulu, HI, USA.

Kaiser Permanente Northwest, Portland, OR, USA.

In the United States, hospitalization among patients with chronic hepatitis C virus (HCV) infection is high. The healthcare burden associated with hospitalization is not clearly known. We analysed data from the Chronic Hepatitis Cohort Study, an observational cohort of patients receiving care at four integrated healthcare systems, collected from

2006 to 2013 to determine all-cause hospitalization rates of patients with chronic HCV infection and the other health system patients. To compare the hospitalization rates, we selected two health system patients for each chronic HCV patient using their propensity score (PS). Propensity score matching was conducted by site, gender, race, age and household income to minimize differences attributable to these characteristics. We also compared primary reason for hospitalization between chronic HCV patients and the other health system patients. Overall, 10 131 patients with chronic HCV infection and 20 262 health system patients were selected from the 1 867 802 health system patients and were matched by PS. All-cause hospitalization rates were 27.4 (27.0-27.8) and 7.4 (7.2-7.5) per 100 persons-year (PY) for chronic HCV patients and for the other health system patients, respectively. Compared to health system patients, hospitalization rates were significantly higher by site, gender, age group, race and household income among chronic HCV patients ($P < 0.001$). Compared to health system patients, chronic HCV patients were more likely to be hospitalized from liver-related conditions ($RR = 24.8$, $P < 0.001$). Hence, patients with chronic HCV infection had approximately 3.7-fold higher all-cause hospitalization rate than other health system patients. These findings highlight the incremental costs and healthcare burden of patients with chronic HCV infection associated with hospitalization.

Dermatology

Cheng C, **Ozog D**, Chaffins M, Ginsberg D, and Krakowski A. Ablative fractional resurfacing for treatment of focal dermal hypoplasia in a pediatric patient with goltz syndrome *Lasers Surg Med* 2016; 48(4):428-428. PMID: Not assigned. Abstract

Henry Ford Hosp, Detroit, MI 48202 USA. Rady Childrens Hosp, San Diego, CA USA.

Dermatology

Foley P, **Stein-Gold L**, Kircik L, Fowler J, Jackson M, Tan J, Draleos Z, Fleischer A, Appell M, Steinhoff M, Lynde C, Hong L, and Jacovella J. Ivermectin 1% Cream, an effective and safe topical treatment of inflammatory lesions of papulopustular rosacea *Australas J Dermatol* 2016; 57:32-32. PMID: Not assigned. Abstract

[Foley, P.] St Vincents Hosp, Dept Dermatol, Melbourne, Vic, Australia. [Foley, P.] Skin & Canc Fdn Inc, Melbourne, Vic, Australia. [Stein-Gold, L.] Henry Ford Med Ctr, Dept Dermatol, Detroit, MI USA. [Kircik, L.] Derm Res PLLC, Louisville, KY USA. [Fowler, J.; Jackson, M.] Dermatol Specialists Res, Louisville, KY USA. [Tan, J.] Univ Western Ontario, Windsor, ON, Canada. [Tan, J.] Windsor Clin Res Inc, Windsor, ON, Canada. [Draleos, Z.] Duke Univ, Sch Med, Durham, NC USA. [Fleischer, A.] Wake Forest Univ Hlth Sci, Salem, NC USA. [Appell, M.] Total Skin & Beauty Dermatol Ctr, Birmingham, AL USA. [Steinhoff, M.] Univ Coll Dublin, UCD Charles Inst Dermatol, Dublin 2, Ireland. [Lynde, C.] Lynderm Clin Res Inc, Markham, ON, Canada. [Hong, L.] Galderma R&D, Princeton, NJ USA. [Jacovella, J.] Galderma R&D SNC, Sophia Antipolis, France.

Dermatology

Hanifin JM, Ellis CN, Frieden IJ, Folster-Holst R, **Stein Gold LF**, Secci A, Smith AJ, Zhao C, Kornyeveva E, and Eichenfield LF. OPA-15406, a novel, topical, nonsteroidal, selective phosphodiesterase-4 (PDE4) inhibitor, in the treatment of adult and adolescent patients with mild to moderate atopic dermatitis (AD): A phase-II randomized, double-blind, placebo-controlled study *J Am Acad Dermatol* 2016; PMID: 27189825. [Full Text](#)

Oregon Health and Science University, Portland, Oregon.

Department of Dermatology, University of Michigan Medical School, Ann Arbor, Michigan.

University of California, San Francisco School of Medicine, San Francisco, California.

University Clinics of Schleswig-Holstein, Campus Kiel, Germany.

Henry Ford Health Systems, Detroit, Michigan.

Otsuka Pharmaceutical Development and Commercialization Inc, Princeton, New Jersey.

Otsuka Pharmaceutical Development and Commercialization Inc, Princeton, New Jersey. Electronic address: elena.kornyeveva@otsuka-us.com.

University of California, San Diego School of Medicine and Rady Children's Hospital, San Diego, California.

BACKGROUND: Peripheral leukocytes in patients with atopic dermatitis (AD) have elevated phosphodiesterase-4 activity, which is associated with production of proinflammatory mediators. OPA-15406 is a phosphodiesterase-4 inhibitor with high selectivity for phosphodiesterase-4-B. **OBJECTIVES:** We sought to assess effectiveness and tolerability of topical OPA-15406 in patients with AD. **METHODS:** This was a randomized, double-blind, vehicle-controlled, phase-II study. Patients 10 to 70 years of age with mild or moderate AD received topical OPA-15406 0.3% ($n = 41$), OPA-15406 1% ($n = 43$), or vehicle ($n = 37$) twice daily for 8 weeks. **RESULTS:** The primary end point, Investigator Global Assessment of Disease Severity score of 0 or 1 with greater than or equal to 2-grade reduction, was met at week 4 in the OPA-15406 1% group ($P = .0165$ vs vehicle). Mean percentage improvement from baseline

Eczema Area and Severity Index score for OPA-15406 1% was notable in week 1 (31.4% vs 6.0% for vehicle; P = .0005), even larger in week 2 (39.0% vs 3.0%; P = .0001), and persisted for 8 weeks. Visual analog scale pruritus scores improved from moderate to mild within the first week in the OPA-15406 1% group (36.4% mean change; P = .0011). OPA-15406 levels in blood were negligible. Incidence of adverse events was low, with most events mild in intensity. LIMITATIONS: Further confirmatory phase-III studies are required. CONCLUSION: OPA-15406 ointment may provide an effective therapeutic modality for patients with mild to moderate AD.

Dermatology

O'Brien R, **Porto DA**, **Friedman BJ**, and **Douglass MC**. Elderly female with swelling of the right breast *Ann Emerg Med* 2016; 67(6):e25-26. PMID: 27217142. [Full Text](#)

Wayne State University School of Medicine, Detroit, MI.
Department of Dermatology, Henry Ford Hospital, Detroit, MI.

Dermatology

Taieb A, **Stein Gold L**, Feldman SR, Dansk V, and Bertranou E. Cost-effectiveness of ivermectin 1% cream in adults with papulopustular rosacea in the United States *J Manag Care Spec Pharm* 2016; 22(6):654-665. PMID: 27231793. [Full Text](#)

- 1 Hopital Saint-Andre, Service de Dermatologie et Dermatologie Pediatrique, Bordeaux Cedex, France.
- 2 Department of Dermatology, Henry Ford Medical Center, Detroit, Michigan, United States.
- 3 Department of Dermatology, Center for Dermatology Research, Wake Forest School of Medicine, Winston-Salem, North Carolina, United States.
- 4 PAREXEL Access Consulting, PAREXEL International, London, England.

BACKGROUND: Papulopustular rosacea is a chronic skin disease involving central facial erythema in combination with papules and pustules. Papulopustular rosacea is treated with topical, systemic, or a combination of topical and systemic therapies. Currently approved topical therapies include azelaic acid gel/cream/foam twice daily (BID) and metronidazole cream/gel/lotion BID. Ivermectin 1% cream once daily (QD) is a new topical agent for the treatment of papulopustular rosacea that has been approved for the management of inflammatory lesions of rosacea and offers an alternative to current treatments. **OBJECTIVE:** To evaluate the cost-effectiveness of ivermectin 1% cream QD compared with current topical treatments in order to understand the cost of adding ivermectin as a treatment option that would bring additional clinical benefit for adults with papulopustular rosacea in the United States. **METHODS:** The cost-effectiveness of ivermectin 1% cream QD was compared with metronidazole 0.75% cream BID and azelaic acid 15% gel BID for adults in the United States with moderate-to-severe papulopustular rosacea using a Markov cohort state transition structure with 2 mutually exclusive health states (rosacea and no rosacea) and 5 phases. Patients could succeed or fail to respond to treatment and experience a relapse after treatment success. The model took a health care payer perspective (direct medical costs of topical and/or systemic therapy plus health care costs for physician and specialist visits) and used a 3-year time horizon. The model was run for a cohort of 1,000 patients. Costs (2014 U.S. dollars) and benefits (disease-free days and quality-adjusted life-years [QALYs]) were discounted at a rate of 3% per annum. Cost-effectiveness was determined by the incremental cost-effectiveness ratio (ICER) and measured in terms of incremental cost per QALY gained (estimated from health state utilities for patients with and without rosacea). Univariate and probabilistic sensitivity analyses (PSA) were conducted to assess the robustness of model outcomes. **RESULTS:** Compared with metronidazole 0.75% cream BID, ivermectin 1% cream QD was associated with higher costs but provided greater clinical benefit, with an ICER of \$13,211 per QALY gained. For a cohort of 1,000 patients, ivermectin 1% cream QD provided an additional 72,922 disease-free days (200 years) over a 3-year period compared with metronidazole 0.75% cream BID, leading to a lower cost per disease-free day for ivermectin 1% cream QD (\$4.54) compared with metronidazole 0.75% cream BID (\$4.85). Ivermectin 1% cream QD was associated with lower total costs and greater clinical benefit compared with azelaic acid 15% gel BID at year 3 and dominated this treatment. After 3 years, ivermectin 1% cream QD was associated with the lowest health care costs (\$62,767 compared with \$73,284 for metronidazole 0.75% cream BID and \$77,208 for azelaic acid 15% gel BID), reflecting a 15% reduction in physician visit costs, when compared with metronidazole 0.75% cream BID, and almost a 20% reduction, when compared with azelaic acid 15% gel BID. The univariate sensitivity analyses indicated that the results are sensitive to the time horizon selected: the longer the time horizon, the more beneficial the results for ivermectin 1% cream QD relative to the comparators, although even at 1 year, ivermectin 1% cream QD dominated azelaic acid 15% gel BID. The PSA suggested that ivermectin 1% cream QD was the most likely treatment to be cost-effective at a willingness-to-pay threshold of \$15,000 and above. **CONCLUSIONS:** Ivermectin 1% cream QD had favorable incremental cost-effectiveness when compared with metronidazole 0.75% cream BID and dominated azelaic acid 15% gel BID in the treatment of papulopustular rosacea in the United States. Therefore, ivermectin 1% cream QD may be a good first-line treatment for papulopustular rosacea, providing additional clinical

benefit at no or low additional cost. **DISCLOSURES:** This study was sponsored by Galderma Laboratories. The sponsor was involved in the design of the model structure but not in the collection of the data used to populate the model. Manuscript preparation was also funded by Galderma. Taieb is an investigator and advisor for Galderma. Gold is an investigator for Galderma. Feldman is a consultant and speaker for Galderma and has received grants from Galderma. Dansk and Bertranou received a research grant from Galderma to conduct this study. Dansk and Bertranou contributed to the design of the model structure, the sourcing and inputting of the data, and the interpretation of the results. Taieb, Feldman, and Gold contributed to the interpretation of the results. All authors reviewed draft versions of the manuscript and gave permission for the submission of the final version.

Dermatology

Yan C, Gao N, Sun H, Yin J, Lee P, **Zhou L**, Fan X, and Yu FS. Targeting imbalance between il-1beta and il-1 receptor antagonist ameliorates delayed epithelium wound healing in diabetic mouse corneas *Am J Pathol* 2016; 186(6):1466-1480. PMID: 27109611. [Full Text](#)

Department of Ophthalmology, Graduate Program, Shanghai Ninth Peoples' Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; Department of Ophthalmology, Kresge Eye Institute, and the Department of Anatomy and Cell Biology, Wayne State University School of Medicine, Detroit, Michigan.

Department of Ophthalmology, Kresge Eye Institute, and the Department of Anatomy and Cell Biology, Wayne State University School of Medicine, Detroit, Michigan.

Department of Dermatology, Henry Ford Immunology Program, Henry Ford Health System, Detroit, Michigan.

Department of Ophthalmology, Graduate Program, Shanghai Ninth Peoples' Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. Electronic address: fanxq@sh163.net.

Department of Ophthalmology, Kresge Eye Institute, and the Department of Anatomy and Cell Biology, Wayne State University School of Medicine, Detroit, Michigan. Electronic address: fyu@med.wayne.edu.

Patients with diabetes mellitus often develop corneal complications and delayed wound healing. How diabetes might alter acute inflammatory responses to tissue injury, leading to delayed wound healing, remains mostly elusive. Using a streptozotocin-induced type I diabetes mellitus mice and corneal epithelium-debridement wound model, we discovered that although wounding induced marked expression of IL-1beta and the secreted form of IL-1 receptor antagonist (sIL-1Ra), diabetes suppressed the expressions of sIL-1Ra but not IL-1beta in healing epithelia and both in whole cornea. In normoglycemic mice, IL-1beta or sIL-1Ra blockade delayed wound healing and influenced each other's expression. In diabetic mice, in addition to delayed reepithelization, diabetes weakened phosphatidylinositol 3-kinase-Akt signaling, caused cell apoptosis, diminished cell proliferation, suppressed neutrophil and natural killer cell infiltrations, and impaired sensory nerve reinnervation in healing mouse corneas. Local administration of recombinant IL-1Ra partially, but significantly, reversed these pathological changes in the diabetic corneas. CXCL10 was a downstream chemokine of IL-1beta-IL-1Ra, and exogenous CXCL10 alleviated delayed wound healing in the diabetic, but attenuated it in the normal corneas. In conclusion, the suppressed early innate/inflammatory responses instigated by the imbalance between IL-1beta and IL-1Ra is an underlying cause for delayed wound healing in the diabetic corneas. Local application of IL-1Ra accelerates reepithelialization and may be used to treat chronic corneal and potential skin wounds of diabetic patients.

Dermatology

Yin C, Weiland M, Miao ZM, Li C, **Zhou L**, and **Mi QS**. Deletion of microRNA miR-146a does not prevent streptozotocin-induced murine autoimmune type 1 diabetes *Diabetes Metab* 2016; PMID: 27133137. [Full Text](#)

Shandong Provincial Key Laboratory of Metabolic Disease, the Affiliated Hospital of Qingdao University, 16 Jiangsu Road, Qingdao 266003, China; Henry Ford Immunology Program, Departments of Dermatology and Internal Medicine, Henry Ford Health System, 1, Ford Place, 48202 Detroit, MI, United States; Department of Dermatology, Henry Ford Health System, 48202 Detroit, MI, United States.

Henry Ford Immunology Program, Departments of Dermatology and Internal Medicine, Henry Ford Health System, 1, Ford Place, 48202 Detroit, MI, United States; Department of Dermatology, Henry Ford Health System, 48202 Detroit, MI, United States.

Shandong Provincial Key Laboratory of Metabolic Disease, the Affiliated Hospital of Qingdao University, 16 Jiangsu Road, Qingdao 266003, China.

Henry Ford Immunology Program, Departments of Dermatology and Internal Medicine, Henry Ford Health System, 1, Ford Place, 48202 Detroit, MI, United States; Department of Dermatology, Henry Ford Health System, 48202 Detroit, MI, United States; Department of Internal Medicine, Henry Ford Health System, 48202 Detroit, MI, United States.

Henry Ford Immunology Program, Departments of Dermatology and Internal Medicine, Henry Ford Health System, 1, Ford Place, 48202 Detroit, MI, United States; Department of Dermatology, Henry Ford Health System, 48202 Detroit,

MI, United States; Department of Internal Medicine, Henry Ford Health System, 48202 Detroit, MI, United States.
Electronic address: qmi1@hfhs.org.

Dermatology

Zhang X, Liu Q, Wang J, Li G, Weiland M, Yu FS, Mi QS, Gu J, and Zhou L. TIM-4 is differentially expressed in the distinct subsets of dendritic cells in skin and skin-draining lymph nodes and controls skin langerhans cell homeostasis *Oncotarget* 2016;PMID: 27224924. [Full Text](#)

Department of Dermatology, Second Military Medical University Changhai Hospital, Shanghai, China.

Henry Ford Immunology Program, Henry Ford Health System, Detroit, MI, United States of America.

Department of Dermatology, Henry Ford Health System, Detroit, MI, United States of America.

Department of Anatomy and Cell Biology, Wayne State University School of Medicine, Detroit, MI, United States of America.

Department of Internal Medicine, Henry Ford Health System, Detroit, MI, United States of America.

T cell immunoglobulin and mucin-4 (TIM-4), mainly expressed on dendritic cells (DC) and macrophages, plays an essential role in regulating immune responses. Langerhans cells (LC), which are the sole DC subpopulation residing at the epidermis, are potent mediators of immune surveillance and tolerance. However, the significance of TIM-4 on epidermal LCs, along with other cutaneous DCs, remains totally unexplored. For the first time, we discovered that epidermal LCs expressed TIM-4 and displayed an increased level of TIM-4 expression upon migration. We also found that dermal CD207+ DCs and lymph node (LN) resident CD207-CD4+ DCs highly expressed TIM-4, while dermal CD207- DCs and LN CD207-CD4- DCs had limited TIM-4 expressions. Using TIM-4-deficient mice, we further demonstrated that loss of TIM-4 significantly upregulated the frequencies of epidermal LCs and LN resident CD207-CD4+ DCs. In spite of this, the epidermal LCs of TIM-4-deficient mice displayed normal phagocytic and migratory abilities, comparable maturation status upon the stimulation as well as normal repopulation under the inflamed state. Moreover, lack of TIM-4 did not affect dinitrofluorobenzene-induced contact hypersensitivity response. In conclusion, our results indicated that TIM-4 was differentially expressed in the distinct subsets of DCs in skin and skin-draining LNs, and specifically regulated epidermal LC and LN CD207-CD4+ DC homeostasis.

Diagnostic Radiology

Shah BA, Sever A, and Cressman S. Breast imaging BINGO: an educational game to supplement the traditional assessment style *Med Sci Educ* 2016;1-5. PMID: Not assigned. [Article Request Form](#)

Breast Imaging Bingo (BIB) follows the traditional bingo game format. Multiple choice questions were created by one of the authors, a breast imaging fellowship trained radiologist with 14 years of experience, and every bingo ball was associated with a multiple choice question. A session of BIB was conducted at the 2015 American Osteopathic College of Radiology (AOOCR) Breast Imaging Innovations Conference, where 125 radiologists were in attendance. Reception to BIB was positive. Participants found the game enjoyable (89 %) and would use an educational gaming format like BIB to supplement the traditional series of case conferences or didactic lectures (91 %).

Emergency Medicine

Body R, Mueller C, Giannitsis E, Christ M, Ordonez-Llanos J, de Filippi CR, **Nowak R**, Panteghini M, Jernberg T, Plebani M, Verschuren F, French JK, Christenson R, Weiser S, Bendig G, Dilba P, and Lindahl B. The use of very low concentrations of high sensitivity troponin T to rule out acute myocardial infarction using a single blood test *Acad Emerg Med* 2016;PMID: 27178492. [Full Text](#)

Emergency Department, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, United Kingdom.

Cardiovascular Sciences Research Group, University of Manchester, Oxford Road, Manchester, United Kingdom.

Universitatsspital Basel, Department of Cardiology, Petersgraben 4, 4031, Basel, Switzerland.

Medizinische Universitatsklinik (Kreihl-Linik) Abteilung Innere Medizin III Kardiologie, Angiologie und Pneumologie Im Neuenheimer Feld 410, 69120, Heidelberg, Germany.

Klinikum Nurnberg Nord, Klinik fur Notfallmedizin und Internistische Intensivmedizin, Prof.-Ernst-Nathan-Str.1, 90419, Nurnberg, Germany.

IIB-Hospital de la Santa Creu i Sant Pau and Universitat Autònoma, Sant Quinti, 89, 08041, Barcelona, Spain.

University of Maryland, Division of Cardiology, 22, South Greene St., Baltimore, MD, 21212, USA.

Henry Ford West Bloomfield Hospital, 6777, West Maple Road, West Bloomfield, MI 48322, USA.

Azienda Ospedaliera Luigi Sacco Laboratorio Analisi Chimico Cliniche, Via G.B. Grassi 74, 20157, Milan, Italy.

Karolinska University Hospital, Department of Cardiology, Huddinge, 14186, Stockholm, Sweden.
Servizio Medicina di Laboratorio Azienda Ospedaliera, Università di Padova Via Giustiniano, 35128, Padova, Italy.
Department of Acute Medicine, Cliniques Universitaires St-Luc, Université Catholique de Louvain, Brussels, Belgium.
Department of Cardiology, Liverpool Hospital, Elizabeth Street, Liverpool, New South Wales, 2170, Australia.
University of Maryland School of Medicine, 685, W Baltimore St #480, Baltimore, MD 21201, USA.
Roche Diagnostics Germany, Nonnenwald 2, 82377, Penzberg, Germany.
Department of Medical Sciences and Uppsala Clinical Research Center, Uppsala University, 75185, Uppsala, Sweden.

BACKGROUND: Recent single center and retrospective studies suggest that acute myocardial infarction (AMI) could be immediately excluded without serial sampling in patients with initial high sensitivity troponin T (hs-cTnT) levels below the limit of detection (LoD) of the assay and no ECG ischemia. **OBJECTIVE:** We aimed to determine the external validity of those findings in a multi-center study at 12 sites in 9 countries. **METHODS:** TRAPID-AMI was a prospective diagnostic cohort study including patients with suspected cardiac chest pain within 6h of peak symptoms. Blood drawn on arrival was centrally tested for hs-cTnT (Roche, 99th percentile 14ng/L, LoD 5ng/L). All patients underwent serial troponin sampling over 4-14h. The primary outcome, prevalent AMI, was adjudicated based on sensitive troponin I (Siemens Ultra) levels. Major adverse cardiac events (MACE) including AMI, death or rehospitalisation for acute coronary syndrome with coronary revascularization were determined after 30 days. **RESULTS:** We included 1,282 patients, of whom 213 (16.6%) had AMI and 231 (18.0%) developed MACE. Of 560 (43.7%) patients with initial hs-cTnT levels below the LoD, 4 (0.7%) had AMI. In total, 471 (36.7%) patients had both initial hs-cTnT levels below the LoD and no ECG ischemia. These patients had a 0.4% (n=2) probability of AMI, giving 99.1% (95% CI 96.7-99.9%) sensitivity and 99.6% (95% CI 98.5-100.0%) negative predictive value. The incidence of MACE in this group was 1.3% (95% CI 0.5-2.8%). **CONCLUSIONS:** In the absence of ECG ischemia, the detection of very low concentrations of hs-cTnT at admission seems to allow rapid, safe exclusion of AMI in one-third of patients without serial sampling. This could be used alongside careful clinical assessment to help reduce unnecessary hospital admissions.

Emergency Medicine

Goyal N, Taylor AR, and Rivers EP. Relationship between central and peripheral venous oxygen saturation and lactate levels: A prospective study *J Emerg Med* 2016; PMID: 27210904. [Full Text](#)

Department of Emergency Medicine, Henry Ford Health System, Detroit, Michigan; Department of Internal Medicine, Henry Ford Health System, Detroit, Michigan.

Department of Public Health Science, Division of Biostatistics, Henry Ford Health System, Detroit, Michigan.

Department of Emergency Medicine, Henry Ford Health System, Detroit, Michigan; Department of Surgery, Henry Ford Health System, Detroit, Michigan.

BACKGROUND: Optimization of tissue oxygen delivery to meet consumption demands is important in the resuscitation of critically ill patients. Central venous oxygen saturation (ScvO₂) and lactate levels are often used to guide resuscitation; however, invasive monitoring is required for the former. Clinicians searching for less invasive alternatives may consider using peripheral venous oxygen saturation (SpvO₂) and lactate levels as a substitute. **OBJECTIVES:** To determine the relationship between SpvO₂ and ScvO₂ and peripheral and central lactate levels. **METHODS:** All patients with a central venous catheter in an academic emergency department and intensive care unit were eligible for the study. Blood was obtained simultaneously from a central and peripheral vein and measured for oxygen saturation and lactate levels. Results were analyzed using intraclass correlation coefficient (ICC), Bland-Altman plots, and receiver operating characteristic curves. **RESULTS:** Seventy-nine paired blood samples were analyzed. SpvO₂ and ScvO₂ have moderate agreement: ICC = 0.53 (95% confidence interval [CI] 0.35-0.67). A Bland-Altman plot revealed substantial bias (-4.47; limits of agreement -38.6, 29.6). SpvO₂ \geq 85% was 90% specific for ScvO₂ \geq 70%, and SpvO₂ of \leq 55% had a 94% sensitivity for ScvO₂ $<$ 70%. Central and peripheral venous lactate levels showed almost perfect agreement: ICC = 0.92 (95% CI 0.87-0.95), bias of 0.46 (limits of agreement -1.78-2.70). **CONCLUSION:** SpvO₂ and ScvO₂ have moderate agreement. There was excellent agreement between peripheral and central lactate levels, making them interchangeable. The clinical implications of these substitutions in real-time patient management require further study.

Emergency Medicine

Jain T, Nowak R, Hudson M, Frisoli T, Jacobsen G, and McCord J. Short- and long-term prognostic utility of the HEART score in patients evaluated in the emergency department for possible acute coronary syndrome *Crit Pathw Cardiol* 2016; 15(2):40-45. PMID: 27183252. [Full Text](#)

From the *Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan; daggerDepartment of Emergency Medicine, Henry Ford Hospital, Detroit, Michigan; double daggerHenry Ford Heart and Vascular Institute, Detroit, Michigan; and section signDepartment of Biostatistics, Henry Ford Hospital, Detroit, Michigan.

INTRODUCTION: The HEART score is a risk-stratification tool that was developed and validated for patients evaluated for possible acute coronary syndrome (ACS) in the emergency department (ED). We sought to determine the short-term and long-term prognostic utility of the HEART score. **METHODS:** A retrospective single-center analysis of 947 patients evaluated for possible ACS in the ED in 1999 was conducted. Patients were followed for major adverse cardiac events (MACEs) at 30 days: death, acute myocardial infarction, or revascularization procedure. All-cause mortality was assessed at 5 years. The HEART score was compared with the Thrombolysis in Myocardial Infarction (TIMI) score. **RESULTS:** At 30 days, 14% (135/947) of patients had an MACE: 48 deaths (5%), 84 acute myocardial infarctions (9%), and 48 (5%) revascularization procedures. The MACE rate in patients with HEART score ≤ 3 was 0.6% (1/175) involving a revascularization procedure, 9.5% (53/557) in patients with HEART score between 4 and 6, and 38% (81/215) with HEART score ≥ 7 . The C-statistic for the HEART score was 0.82 and 0.68 for the TIMI score for predicting 30-day MACE ($P < 0.05$). Patients with HEART score ≤ 3 had lower 5-year mortality rate compared with those with TIMI score of 0 (10.6% vs. 20.5%, $P = 0.02$). **CONCLUSIONS:** The HEART score is a valuable risk-stratification tool in predicting not only short-term MACE but also long-term mortality in patients evaluated for possible ACS in the ED. The HEART score had a superior prognostic value compared with the TIMI score.

Emergency Medicine

Miller JB, Kinni H, Amer A, and Levy PD. Therapies to reduce blood pressure acutely *Curr Hypertens Rep* 2016; 18(6):43. PMID: 27125389. [Full Text](#)

Department of Emergency Medicine, Henry Ford Hospital, Detroit, MI, USA. jmiller6@hfhs.org.

Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, USA. jmiller6@hfhs.org.

Wayne State University, Detroit, MI, USA. jmiller6@hfhs.org.

Department of Emergency Medicine, Henry Ford Hospital, Detroit, MI, USA.

Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, USA.

Wayne State University, Detroit, MI, USA.

Department of Emergency Medicine, Wayne State University, Detroit, MI, USA.

Clinicians make frequent treatment decisions regarding acute blood pressure reduction for the critically ill. Key to the decision making process is a balance between reducing arterial wall stress and maintaining perfusion to vital organs. In this article, we review the physiological considerations underlying acute blood pressure management, including the concept of cerebral autoregulation and its adaptations to chronic hypertension. We then discuss available pharmacological interventions suited for reducing blood pressure acutely. We also discuss specific blood pressure targets in common critical illnesses and consider future directions in this therapeutic area.

Emergency Medicine

Nagarwala J, Dev S, and Markin A. The vomiting patient: Small bowel obstruction, cyclic vomiting, and gastroparesis *Emerg Med Clin North Am* 2016; 34(2):271-291. PMID: 27133244. [Full Text](#)

Department of Emergency Medicine, Henry Ford Hospital, 2799 West Grand Boulevard, CFP-258, Detroit, MI 48202, USA; Department of Emergency Medicine, Wayne State University School of Medicine, Detroit, MI, USA. Electronic address: jnagarw1@hfhs.org.

Departments of Emergency Medicine and Internal Medicine, University of Michigan, Ann Arbor, MI, USA.

Department of Emergency Medicine, Henry Ford Hospital, 2799 West Grand Boulevard, CFP-258, Detroit, MI 48202, USA; Department of Internal Medicine, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202, USA.

Vomiting and abdominal pain are common in patients in the emergency department. This article focuses on small bowel obstruction (SBO), cyclic vomiting, and gastroparesis. Through early diagnosis and appropriate management, the morbidity and mortality associated with SBOs can be significantly reduced. Management of SBOs involves correction of physiologic and electrolyte disturbances, bowel rest and removing the source of the obstruction. Treatment of acute cyclic vomiting is primarily directed at symptom control, volume and electrolyte repletion, and appropriate specialist follow-up. The mainstay of therapy for gastroparesis is metoclopramide.

Emergency Medicine

Sachwani GR, Jaehne AK, Jayaprakash N, Kuzich M, Onkoba V, Blyden D, and Rivers EP. The association between blood glucose levels and matrix-metalloproteinase-9 in early severe sepsis and septic shock *J Inflamm (Lond)* 2016; 13:13. PMID: 27110221. [Full Text](#)

Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202 USA.

BACKGROUND: Hyperglycemia is a frequent and important metabolic derangement that accompanies severe sepsis and septic shock. Matrix-Metalloproteinase 9 (MMP-9) has been shown to be elevated in acute stress hyperglycemia, chronic hyperglycemia, and in patient with sepsis. The objective of this study was to examine the clinical and pathogenic link between MMP-9 and blood glucose (BG) levels in patients with early severe sepsis and septic shock. **METHODS:** We prospectively examined 230 patients with severe sepsis and septic shock immediately upon hospital presentation and before any treatment including insulin administration. Clinical and laboratory data were obtained along with blood samples for the purpose of this study. Univariate tests for mean and median distribution using Spearman correlation and analysis of variance (ANOVA) were performed. A p value ≤ 0.05 was considered statistically significant. **RESULTS:** Patients were grouped based on their presenting BG level (mg/dL): BG <80 (n = 32), 80-120 (n = 53), 121-150 (n = 38), 151-200 (n = 23), and > 201 (n = 84). Rising MMP-9 levels were significantly associated with rising BG levels (p = 0.043). A corresponding increase in the prevalence of diabetes for each glucose grouping from 6.3 to 54.1 % (p = 0.0001) was also found. As MMP-9 levels increased a significantly (p < 0.001) decreases in IL-8 (pg/mL) and ICAM-1 (ng/mL) were noted. **CONCLUSION:** This is the first study in humans demonstrating a significant and early association between MMP-9 and BG levels in in patients with severe sepsis and septic shock. Neutrophil affecting biomarkers such as IL-8 and ICAM-1 are noted to decrease as MMP-9 levels increase. Clinical risk stratification using MMP-9 levels could potentially help determine which patients would benefit from intensive versus conventional insulin therapy. In addition, antagonizing the up-regulation of MMP-9 could serve as a potential treatment option in severe sepsis or septic shock patients.

Family Medicine

Park B, and Choo SH. The burden of prostatic calculi is more important than the presence *Asian J Androl* 2016; PMID: 27184549. [Full Text](#)

Department of Urology, Kangnam General Hospital, Yongin, Korea; Department of Family Medicine, Henry Ford Hospital, Wayne State University School of Medicine, Detroit, MI, United States.
Department of Urology, Ajou University School of Medicine, Suwon, Korea.

Prostatic calculi are a common finding on transrectal prostate ultrasound. However, it remains unclear whether they are significantly associated with lower urinary tract symptoms (LUTS). Our objective was to evaluate the association between prostatic calculi and LUTS with a focus on "calculi burden" because no studies have investigated prostatic calculi using "calculi burden" as an indicator. A total of 606 participants who received transrectal prostate ultrasound were divided into two groups according to the presence of prostatic calculi. "Calculi burden" was defined as the sum of the transverse diameters of all visible calculi within the prostate. The International Prostatic Symptom Score (IPSS) and a quality of life (QoL) score were collected. Both groups were compared, and a multivariate analysis was performed to predict moderate/severe LUTS. Linear correlation was evaluated between calculi burden and IPSS in the calculi group. No differences in total IPSS, voiding IPSS, or QoL score were detected between the two groups, but storage IPSS was significantly higher in the calculi group than that of controls. The multivariate analysis showed that the presence of prostatic calculi was not an independent predictor of moderate/severe LUTS. A positive linear correlation was detected between calculi burden and storage IPSS in calculi group (r = 0.148). However, no correlation was found between calculi burden and total IPSS, voiding IPSS, or QoL score. Our results showed that the presence of prostatic calculi was not a significant factor predicting moderate/severe LUTS. However, an increased calculi burden may be associated with aggravating storage symptoms.

Gastroenterology

Lok AS, Pan CQ, Han SB, Trinh HN, Fessel WJ, Rodell T, Massetto B, Lin L, Gaggar A, Subramanian GM, McHutchison JG, Ferrari C, Lee H, Gordon SC, and Gane EJ. Randomized phase II study of GS-4774 as a therapeutic vaccine in virally suppressed patients with chronic hepatitis B *J Hepatol* 2016; PMID: 27210427. [Full Text](#)

Division of Gastroenterology and Hepatology, University of Michigan Health System, Ann Arbor, MI, USA. Electronic address: aslok@med.umich.edu.

Department of Medicine, New York University Langone Medical Center, New York University School of Medicine, NY, USA.

Department of Medicine, Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA.

San Jose Gastroenterology, San Jose, CA, USA.
Department of Medicine, Kaiser Permanente, San Francisco, CA, USA.
GlobelImmune, Louisville, CO, USA.
Gilead Sciences, Inc., Foster City, CA, USA.
Department of Infectious Diseases, University of Parma, Italy.
Division of Gastroenterology and Hepatology, Tufts Medical Center, Boston, MA, USA.
Division of Gastroenterology, Henry Ford Hospital, Detroit, MI, USA.
Auckland City Hospital, Auckland, New Zealand.

BACKGROUND & AIMS: GS-4774 is a heat-inactivated, yeast-based, T-cell vaccine designed to elicit hepatitis B virus (HBV)-specific T-cell responses. We evaluated the safety, tolerability and efficacy of GS-4774 in patients with chronic HBV infection. **METHODS:** In this phase II study, 178 patients with chronic HBV infection and no cirrhosis who were virally suppressed on an oral antiviral (OAV) for 1 year were randomized (1:2:2:2) to continue OAV alone or receive OAV plus GS-4774 2, 10, or 40 yeast units (YU) subcutaneously every 4 weeks until week 20. OAV was continued for the remainder of the study. Efficacy was measured by decline in serum hepatitis B surface antigen (HBsAg) from baseline to week 24. **RESULTS:** Baseline characteristics were similar across groups (mean age, 45-50 years; male, 62-74%; Asian, 68-80%; hepatitis B e antigen (HBeAg)-positive, 24-26%; mean HBsAg, 2.5-3.1 log₁₀ IU/ml). There were no significant differences between groups in mean HBsAg declines from baseline to week 24 or 48. Five HBeAg-positive patients receiving GS-4774 experienced HBeAg loss vs. none in the control group. Three GS-4774 40 YU-treated patients had HBsAg declines 0.5 log₁₀ IU/ml, but no patient experienced loss of serum HBsAg. No virologic breakthrough occurred. Injection site reactions were the most frequent adverse event (AE), and there were no treatment discontinuations. **CONCLUSIONS:** GS-4774 was well tolerated, but did not provide significant reductions in serum HBsAg in virally suppressed patients with chronic hepatitis B. Efficacy of GS-4774 in treatment naive patients remains to be determined. **LAY SUMMARY:** GS-4774 is a therapeutic vaccine designed to improve the immune response against hepatitis B virus (HBV) in patients who already have chronic infection with HBV. In this study, GS-4774 was safe and well tolerated in patients with chronic HBV infection receiving oral antiviral therapy, but did not result in a clinical benefit. Combination approaches with other agents, and evaluation in other populations of patients with HBV are ongoing to determine if GS-4774 might have a therapeutic benefit.

Gastroenterology

Moorman AC, Tong X, Spradling PR, **Rupp LB, Gordon SC, Lu M**, Teshale EH, Boscarino JA, Trinacty CM, Schmidt MA, Xu F, and Holmberg SD. Prevalence of renal impairment and associated conditions among hcv-infected persons in the chronic hepatitis cohort study (CHeCS) *Dig Dis Sci* 2016; PMID: 27216163. [Full Text](#)

Division of Viral Hepatitis, CDC, Mailstop G-37, Atlanta, GA, 30329, USA. Amoorman@cdc.gov.
Division of Viral Hepatitis, CDC, Mailstop G-37, Atlanta, GA, 30329, USA.
Henry Ford Health System, 2799 West Grand Blvd., Detroit, MI, USA.
Geisinger Center for Health Research, Geisinger Health System, 100 N. Academy Avenue, Danville, PA, 17822, USA.
Kaiser Permanente-Center for Health Research, Kaiser Permanente Hawaii, 501 Alakawa Street, Suite 201, Honolulu, HI, 96817, USA.
Center for Health Research Northwest, Kaiser Permanente Northwest, 3800 N. Interstate Avenue, Portland, OR, 97227-1098, USA.

BACKGROUND: Guidelines for the treatment of HCV-infected persons were updated in August 2015 with new recommendations for patients with renal impairment. Treatment is imperative for patients with severe, renal-associated extrahepatic manifestations of HCV infection. **AIMS:** We sought to describe the prevalence of these conditions among current HCV-infected patients in a population-based prospective, observational cohort study at four large US health systems. **METHODS:** Data from cohort patients with chronic HCV infection during 2012 were analyzed for the period from 2006 to 2013. We determined the prevalence of mild to moderately impaired renal function defined as having the most recent estimated glomerular filtration rate [eGFR] \leq 80 ml/min/1.73 m², with severe impairment defined as eGFR < 30 ml/min/1.73 m², based on the treatment guidelines. Prevalence of extrahepatic conditions was ascertained using ICD9-codes. **RESULTS:** Among 5772 persons, the prevalence of eGFR \leq 80 was 33 % and eGFR < 30 was 2 %, including among patients with hepatic fibrosis. Diagnosed extrahepatic renal manifestations were rare: vasculitis- 0.2 %, nephrotic syndrome- 0.3 %, and cryoglobulinemia- 0.9 %. **CONCLUSIONS:** While the prevalence of severe renal impairment and diagnosed extrahepatic manifestations was low, mild-to-moderate renal impairment was common in HCV patients, including those with advanced liver fibrosis for whom the need for treatment is urgent.

Gastroenterology

Parekh R, Kazimi M, Skorupski S, Fagoaga O, Jafri S, and Segovia MC. Intestine transplantation across a positive crossmatch with preformed donor-specific antibodies *Transplant Proc* 2016; 48(2):489-491. PMID: 27109984.

[Full Text](#)

Department of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan.

Department of Transplant Surgery, Henry Ford Hospital, Detroit, Michigan.

Department of Pathology, Henry Ford Hospital, Detroit, Michigan.

Department of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan. Electronic address: msegovi3@hfhs.org.

BACKGROUND: We describe our experience using a modified protocol for immunosuppression for intestine transplantation across a positive crossmatch. Patients who underwent transplantation in 2013 were evaluated over a 12-month period for rejection and infectious events with comparison to procedure-matched controls on our standard protocol of immunosuppression. **PATIENTS AND METHODS:** We used a modified protocol for intestine and multivisceral transplantation for patients with a positive flow crossmatch. In addition to our standard protocol, patients with positive crossmatch were given rituximab and intravenous immunoglobulin (IVIg) preoperatively. DSA was sent for clinical evaluation at monthly intervals. Patients were screened for rejection by endoscopic evaluation. **RESULTS:** Four patients underwent transplantation within a single year across a positive crossmatch. Two received isolated intestine transplants and 2 had multivisceral transplantation (MVT). During the 12-month follow-up, 1 patients had an episode of severe acute cellular rejection, which was managed with increased immunosuppression. None of the patients had episodes of cytomegalovirus infection. One patient developed major infection and 3 patients developed minor bacterial infections. Among procedure-matched controls with negative final crossmatch on standard management (no preoperative rituximab or IVIg), 2 developed mild acute cellular rejection and 2 developed minor infections. One developed cytomegalovirus viremia with invasion to the colonic mucosa. **CONCLUSIONS:** We report our protocol for immunosuppression for IT and MVT across a positive crossmatch. This allowed transplantation despite the presence of a positive crossmatch, with low rejection rates but potentially increased risk for major infections compared to the negative crossmatch controls on our standard protocol.

Gastroenterology

Rao B, Jafri SM, Kazimi M, Mullins K, Raoufi M, and Segovia MC. A case report of acute cellular rejection following intestinal transplantation managed with adalimumab *Transplant Proc* 2016; 48(2):536-538. PMID: 27109995. [Full Text](#)

Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan.

Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan.

Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, Michigan.

Department of Pathology, Henry Ford Hospital, Detroit, Michigan.

Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan. Electronic address: msegovi3@hfhs.org.

There is a higher incidence of acute cellular rejection (ACR) in small bowel transplantation (SBT) compared with transplantation of other solid organs. Although there are reports on the use of infliximab to successfully treat ACR refractory to other treatments, there are no reports, to our knowledge, regarding the use of adalimumab. We present a case of a female patient with a history of Crohn's disease who underwent an isolated SBT and developed an episode of severe ACR. She was initially treated with methylprednisolone, thymoglobulin, basiliximab, and a dosage adjustment of tacrolimus. Results of repeat endoscopies and biopsies revealed no significant improvement. The patient initiated treatment with adalimumab every 2 weeks for a total of 6 months, in addition to maintenance treatment with prednisone and tacrolimus. Subsequent evaluations showed gradual improvement to normal mucosa and villi without ulceration. A regimen that incorporates adalimumab can thus be used to treat ACR after intestinal transplantation. Larger multicenter studies are needed to show the full efficacy of this therapeutic regimen.

Gastroenterology

Rao B, Segovia MC, Kazimi M, Parekh R, Raoufi M, and Jafri SM. Use of everolimus after multivisceral transplantation: A report of two cases *Transplant Proc* 2016; 48(2):485-488. PMID: 27109983. [Full Text](#)

Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan.

Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan. Electronic address: msegovi3@hfhs.org.

Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, Michigan.

Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan.
Department of Pathology, Henry Ford Hospital, Detroit, Michigan.

Inhibitors of mechanistic target of rapamycin are used in solid organ transplant procedures to avoid calcineurin inhibitor complications, including nephrotoxicity and malignancy. We present 2 cases of multivisceral transplantation for neuroendocrine tumor (NET) for which everolimus was implemented for its potential to prevent NET recurrence as well as preserve renal function. The first case was complicated by NET recurrence in the liver before initiation of everolimus. After initiation of everolimus, the patient developed a ventral hernia and elevated aminotransferase levels with nonspecific biopsy findings. The second case was complicated by cytomegalovirus infection with elevated everolimus trough levels as well as acute cellular rejection. Everolimus was reinitiated in both cases in addition to decreasing the dosage of tacrolimus, and there were no further complications. Everolimus was beneficial in stabilizing renal function in both patients and has the theoretical potential to prevent recurrence of NET.

Gastroenterology

Teshale EH, Xing J, Moorman A, Holmberg SD, Spradling PR, **Gordon SC, Rupp LB, Lu M**, Boscarino JA, Trinacity CM, Schmidt MA, and Xu F. Higher all-cause hospitalization among patients with chronic hepatitis C: the Chronic Hepatitis Cohort Study (CHeCS), 2006-2013 *J Viral Hepat* 2016; PMID: 27186944. [Full Text](#)

Division of Viral Hepatitis, CDC, Atlanta, GA, USA.
Henry Ford Hospital, Detroit, MI, USA.
Geisinger Health System, Danville, PA, USA.
Kaiser Permanente Hawaii, Honolulu, HI, USA.
Kaiser Permanente Northwest, Portland, OR, USA.

In the United States, hospitalization among patients with chronic hepatitis C virus (HCV) infection is high. The healthcare burden associated with hospitalization is not clearly known. We analysed data from the Chronic Hepatitis Cohort Study, an observational cohort of patients receiving care at four integrated healthcare systems, collected from 2006 to 2013 to determine all-cause hospitalization rates of patients with chronic HCV infection and the other health system patients. To compare the hospitalization rates, we selected two health system patients for each chronic HCV patient using their propensity score (PS). Propensity score matching was conducted by site, gender, race, age and household income to minimize differences attributable to these characteristics. We also compared primary reason for hospitalization between chronic HCV patients and the other health system patients. Overall, 10 131 patients with chronic HCV infection and 20 262 health system patients were selected from the 1 867 802 health system patients and were matched by PS. All-cause hospitalization rates were 27.4 (27.0-27.8) and 7.4 (7.2-7.5) per 100 persons-year (PY) for chronic HCV patients and for the other health system patients, respectively. Compared to health system patients, hospitalization rates were significantly higher by site, gender, age group, race and household income among chronic HCV patients ($P < 0.001$). Compared to health system patients, chronic HCV patients were more likely to be hospitalized from liver-related conditions ($RR = 24.8$, $P < 0.001$). Hence, patients with chronic HCV infection had approximately 3.7-fold higher all-cause hospitalization rate than other health system patients. These findings highlight the incremental costs and healthcare burden of patients with chronic HCV infection associated with hospitalization.

Hematology, Oncology and the Josephine Ford Cancer Institute

Alkhatib Y, Albashaireh D, Al-Aqtash T, and **Awdish R**. The role of tyrosine kinase inhibitor "Lapatinib" in pulmonary hypertension *Pulm Pharmacol Ther* 2016; 37:81-84. PMID: 26965087. [Full Text](#)

Division of Hematology/Oncology, Henry Ford Hospital/Wayne State University, USA. Electronic address: Yalkhat1@hfhs.org.
Division of Cardiology, Tulane University, USA.
Division of Pulmonary and Critical Care, Deaconess Health System, USA.
Division of Pulmonary and Critical Care, Henry Ford Hospital/Wayne State University, USA.

INTRODUCTION: Pulmonary Arterial Hypertension (PAH) and cancer share growth factor and protein kinase signaling pathways that result in smooth muscle cell proliferation and vasculopathy. There is little known about the impact of Lapatinib on the pulmonary vasculature. After reporting a case of Lapatinib-induced PAH we investigated the association of Lapatinib with the development of PAH in our institution. **METHODS:** We reviewed charts for all patients treated with Lapatinib at our institution between 2008 and 2013. Patients who had undergone 2D-echocardiogram both prior to and after treatment were included in the analysis. Increase in Pulmonary artery systolic pressure (PASP) was assessed. Patients were also evaluated in terms of risk factors for non-Group 1 PAH. **RESULTS:** A total of 27 patients were found to have 2-D echo done before and after starting treatment with Lapatinib. Six patients were found to have significant increase in their PASP after starting treatment. Right heart catheterization

before and after stopping the medication was available in three patient, confirming the diagnosis of PAH with complete resolution after stopping the medication. The median pre-treatment and post treatment PASP in those 6 patients was 29 mmHg and 65.5 mmHg respectively (N = 6; p = 0.027). CONCLUSION: Lapatinib might be associated with the development of PAH. PASP should be evaluated in patients who become short of breath while on treatment, and stopping the drug in cases where no other reasons are identified could be associated with reversibility of the elevated pulmonary artery pressure.

Hematology, Oncology and the Josephine Ford Cancer Institute

Alkhatib Y, and Guo Y. Lymphadenopathy in a patient with chronic myeloid leukaemia *Br J Haematol* 2016; PMID: 27174048. [Full Text](#)

Hematology/Oncology Division, Henry Ford Hospital, Detroit, MI, USA. Yalkhat1@hfhs.org.

Hematology, Oncology and the Josephine Ford Cancer Institute

Farhan S, Peres E, and Janakiraman N. Choice of unmanipulated t cell replete graft for haploidentical stem cell transplant and posttransplant cyclophosphamide in hematologic malignancies in adults: Peripheral blood or bone marrow-review of published literature *Adv Hematol* 2016; 2016:6950346. PMID: 27118973. [Full Text](#)

Stem Cell Transplant Program, Henry Ford Hospital, Detroit, MI 48202, USA.

Allogeneic hematopoietic stem cell transplantation (SCT) is often the only curative option for many patients with malignant and benign hematological stem cell disorders. However, some issues are still of concern regarding finding a donor like shrinking family sizes in many societies, underrepresentation of the ethnic minorities in the registries, genetic variability for some races, and significant delays in obtaining stem cells after starting the search. So there is a considerable need to develop alternate donor stem cell sources. The rapid and near universal availability of the haploidentical donor is an advantage of the haploidentical SCT and an opportunity that is being explored currently in many centers especially using T cell replete graft and posttransplant cyclophosphamide. This is probably because it does not require expertise in graft manipulation and because of the lower costs. However, there are still lots of unanswered questions, like the effect of use of bone marrow versus peripheral blood as the source of stem cells on graft-versus-host disease, graft versus tumor, overall survival, immune reconstitution, and quality of life. Here we review the available publications on bone marrow and peripheral blood experience in the haploidentical SCT setting.

Hematology, Oncology and the Josephine Ford Cancer Institute

Geng Z, Xu F, and **Zhang Y.** MiR-129-5p-mediated Beclin-1 suppression inhibits endothelial cell autophagy in atherosclerosis *Am J Transl Res* 2016; 8(4):1886-1894. PMID: 27186312. [Full Text](#)

Institute of Cardiovascular Diseases of PLA, Xinqiao Hospital, Third Military Medical University Chongqing 400037, China.

Oncology Radiotherapy Center of PLA 302 Hospital Beijing 100039, China.

Josephine Ford Cancer Center, Department of Internal Medicine, Henry Ford Health System Detroit, MI 48202, USA.

Endothelial cell injury and subsequent death play an essential role in the pathogenesis of atherosclerosis. Autophagy of endothelial cells antagonizes the development of atherosclerosis, whereas the underlying molecular mechanisms are unclear. MicroRNA-129-5p (miR-129-5p) is a well-defined tumor suppressor in some types of cancer, while it is unknown whether miR-129-5p may also play a role in the development of atherosclerosis. Here, we addressed this question in the current study. We examined the levels of endothelial cell autophagy in ApoE (-/-) mice supplied with high-fat diet (HFD), a mouse model for atherosclerosis (simplified as HFD mice). We analyzed the levels of Beclin-1 and the levels of miR-129-5p in the purified CD31+ endothelial cells from mouse aorta. Prediction of the binding between miR-129-5p and 3'-UTR of Beclin-1 mRNA was performed by bioinformatics analyses and confirmed by a dual luciferase reporter assay. The effects of miR-129-5p were further analyzed in an in vitro model using oxidized low-density lipoprotein (ox-LDL)-treated human aortic endothelial cells (HAECs). We found that HFD mice developed atherosclerosis in 12 weeks, while the control ApoE (-/-) mice that had received normal diet (simplified as CTL mice) did not. Compared to CTL mice, HFD mice had significantly lower levels of endothelial cell autophagy, resulting from decreases in Beclin-1 protein, but not mRNA. The decreases in Beclin-1 in endothelial cells were due to HFD-induced increases in miR-129-5p, which suppressed the translation of Beclin-1 mRNA via 3'-UTR binding. These in vivo findings were reproduced in vitro on ox-LDL-treated HAECs. Together, these data suggest that upregulation of miR-129-5p by HFD may impair the protective effects of endothelial cell autophagy against development of atherosclerosis through suppressing protein translation of Beclin-1.

Hematology, Oncology and the Josephine Ford Cancer Institute

Hung J, **Taylor AR**, **Divine GW**, Hafron JM, and **Hwang C**. The effect of time to castration resistance on outcomes with abiraterone and enzalutamide in metastatic prostate cancer *Clin Genitourin Cancer* 2016; PMID: 27157640.

[Full Text](#)

Department of Urology, Oakland University William Beaumont School of Medicine, Rochester, MI.
Department of Public Health Sciences, Josephine Ford Cancer Institute, Henry Ford Health System, Detroit, MI.
Department of Hematology/Oncology, Josephine Ford Cancer Institute, Henry Ford Health System, Detroit, MI.
Electronic address: chwang2@hfhs.org.

BACKGROUND: Abiraterone and enzalutamide are 2 novel androgen receptor (AR)-targeting therapies that improve survival in patients with metastatic castration-resistant prostate cancer. The factors that predict abiraterone and enzalutamide response are lacking. The objective of the present study was to determine whether the outcomes from primary androgen deprivation therapy (ADT) could predict the outcomes with subsequent novel AR-targeting therapies. **MATERIALS AND METHODS:** We identified 80 consecutive patients with metastatic castration-resistant prostate cancer treated with abiraterone or enzalutamide. Cox regression models were used to analyze the relationships between the primary ADT response and the primary outcome of progression-free survival (PFS) after initiating novel hormonal therapy. The secondary outcomes included prostate-specific antigen decline and overall survival. The survival probabilities were plotted using the Kaplan-Meier method, and the differences assessed with the log-rank test. **RESULTS:** The time to castration resistance with primary ADT showed a significant association with both PFS and overall survival after initiating novel hormone therapy ($P = .032$ and $P = .028$, respectively). Patients with progression during primary ADT before 1 year had a median PFS of 3.4 months compared with a median PFS of 7.6 and 8.1 months for patients whose time to castration resistance was ≥ 1 and ≤ 5 years ($P = .008$) and > 5 years ($P = .026$), respectively. However, the time to castration resistance was not an independent predictor of survival or the PSA response with novel AR-targeting therapy on multivariate analysis. **CONCLUSION:** A rapid time to progression during primary ADT was associated with poor outcomes but was not an independent predictor of the response to enzalutamide or abiraterone.

Hemophilia and Thrombosis Treatment Center

Witkop ML, McLaughlin JM, Anderson TL, Munn JE, **Lambing A**, and Tortella B. Predictors of non-adherence to prescribed prophylactic clotting-factor treatment regimens among adolescent and young adults with a bleeding disorder *Haemophilia* 2016; PMID: 27216992. [Full Text](#)

Northern Regional Bleeding Disorders Center, Traverse City, MI, USA.
Pfizer Inc, US Medical Affairs, Collegeville, PA, USA.
University of Michigan Haemophilia Treatment Center, Ann Arbor, MI, USA.
Henry Ford Adult Haemophilia & Thrombosis Treatment Center, Detroit, MI, USA.

INTRODUCTION: Adherence to clotting-factor treatment regimens, especially among adolescents and young adults (AYAs), is under-researched. **AIM:** We determined factors associated with better adherence to prophylaxis. **METHODS:** From April through December 2012, a convenience sample of AYA (aged 13-25 years) persons with haemophilia or von Willebrand disease (VWD) completed an online survey that assessed adherence to prescribed prophylactic treatment regimens [Validated Haemophilia Regimen Treatment Adherence Scale (VERITAS)-Pro]. Logistic regression analysis assessed demographic and clinical factors related to non-adherence (VERITAS-Pro ≥ 57). **RESULTS:** Seventy-three prophylactically treating AYAs participated. Of which, 88%, 8% and 4% had haemophilia A, B and VWD respectively. Almost all (90%) had severe disease and 58% had never developed an inhibitor. Most were aged 13-17 years (56%), white (78%), non-Hispanic (88%), never married (94%) and had some type of health insurance (96%). Median VERITAS-Pro score was 48 (range = 25-78) and 22 (30%) participants were non-adherent to prophylaxis (VERITAS-Pro ≥ 57). Final logistic regression modelling suggested that, compared to those aged 13-17 years, participants aged 18-25 years were 6.2 (95% CI: 1.8-21.0; $P < 0.01$) times more likely to be non-adherent. Compared to respondents whose mother had at least a Bachelor's degree, respondents whose mother did not were 3.8 (95% CI: 1.0-14.3; $P = 0.05$) times more likely to be non-adherent. **CONCLUSIONS:** Results suggest that adherence efforts should be especially targeted to young adults as they transition from adolescence (i.e. parental supervision) and assume primary responsibility for their bleeding disorder care. Healthcare providers should be mindful of AYAs whose mothers have less formal education and ensure that adequate time and resources are dedicated to family adherence education.

Hypertension and Vascular Research

Kumar N, Astegno A, Chen J, Giorgetti A, and Dominici P. Residues in the distal heme pocket of arabidopsis non-symbiotic hemoglobins: Implication for nitrite reductase activity *Int J Mol Sci* 2016; 17(5)PMID: 27136534. [Full Text](#)

Hypertension & Vascular Research Division, Department of Internal Medicine, Henry Ford Hospital, Detroit, MI 48202, USA. nkumar3@hfhs.org.

Department of Biotechnology, University of Verona, Strada Le Grazie 15, 37134 Verona, Italy. nkumar3@hfhs.org.

Department of Biotechnology, University of Verona, Strada Le Grazie 15, 37134 Verona, Italy.

alessandra.astegno@univr.it.

Department of Biotechnology, University of Verona, Strada Le Grazie 15, 37134 Verona, Italy.

jianchen0722@gmail.com.

Department of Biotechnology, University of Verona, Strada Le Grazie 15, 37134 Verona, Italy.

alejandro.giorgetti@univr.it.

Department of Biotechnology, University of Verona, Strada Le Grazie 15, 37134 Verona, Italy.

paola.dominici@univr.it.

It is well-established that plant hemoglobins (Hbs) are involved in nitric oxide (NO) metabolism via NO dioxygenase and/or nitrite reductase activity. The ferrous-deoxy Arabidopsis Hb1 and Hb2 (AHb1 and AHb2) have been shown to reduce nitrite to NO under hypoxia. Here, to test the hypothesis that a six- to five-coordinate heme iron transition might mediate the control of the nitrite reduction rate, we examined distal pocket mutants of AHb1 and AHb2 for nitrite reductase activity, NO production and spectroscopic features. Absorption spectra of AHbs distal histidine mutants showed that AHb1 mutant (H69L) is a stable pentacoordinate high-spin species in both ferrous and ferric states, whereas heme iron in AHb2 mutant (H66L) is hexacoordinated low-spin with Lys69 as the sixth ligand. The bimolecular rate constants for nitrite reduction to NO were 13.3 +/- 0.40, 7.3 +/- 0.5, 10.6 +/- 0.8 and 171.90 +/- 9.00 M⁽⁻¹⁾.s⁽⁻¹⁾ for AHb1, AHb2, AHb1 H69L and AHb2 H66L, respectively, at pH 7.4 and 25 degrees C. Consistent with the reductase activity, the amount of NO detected by chemiluminescence was significantly higher in the AHb2 H66L mutant. Our data indicate that nitrite reductase activity is determined not only by heme coordination, but also by a unique distal heme pocket in each AHb.

Infectious Diseases

Isseh IN, Bourgi K, Nakhle A, Ali M, and Zervos MJ. False-positive cerebrospinal fluid cryptococcus antigen in Libman-Sacks endocarditis *Infection* 2016;PMID: 27246719. [Full Text](#)

Department of Internal Medicine, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI, 48202, USA.

iisseh1@hfhs.org.

Department of Internal Medicine, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI, 48202, USA.

Division of Infectious Diseases, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI, 48202, USA.

BACKGROUND: Cryptococcus meningoencephalitis is a serious opportunistic infection associated with high morbidity and mortality in immunocompromised hosts, particularly patients with advanced AIDS disease. The diagnosis is established through cerebrospinal fluid (CSF) cryptococcus antigen detection and cultures. Cryptococcus antigen testing is usually the initial test of choice due its high sensitivity and specificity along with the quick availability of the results. **CASE REPORT:** We hereby report a case of a false-positive CSF cryptococcus antigen assay in a patient with systemic lupus erythematosus presenting with acute confusion. While initial CSF evaluation revealed a positive cryptococcus antigen assay, the patient's symptoms were inconsistent with cryptococcus meningoencephalitis. A repeat CSF evaluation, done 3 days later, revealed a negative CSF cryptococcus antigen assay. **CONCLUSION:** Given the patient's active lupus disease and the elevated antinuclear antibody titers, we believe that the initial positive result was a false positive caused by interference from autoantibodies.

Infectious Diseases

Suleyman G, Perri M, Vager D, Samuel L, Zervos MJ, Alangaden G, and Tibbetts RJ. Characterization of Salmonella Isangi possessing a CTX-M15 ESBL associated with an outbreak in a US Hospital *Diagn Microbiol Infect Dis* 2016;PMID: 27130476. [Full Text](#)

Department of Infectious Disease, Henry Ford Health System, Detroit, MI 48202.

Infectious Disease Research Laboratory, Henry Ford Health System, Detroit, MI 48202.

Department of Pathology, Henry Ford Health System, Detroit, MI 48202.

Department of Pathology, Henry Ford Health System, Detroit, MI 48202. Electronic address: rtibbet1@hfhs.org.

Over an approximately 50-day period in 2015, an outbreak of CTX-M-15 extended spectrum beta-lactamase-(ESBL)-possessing *Salmonella* Isangi occurred among 19 adult surgical patients and one healthcare worker (HCW) at a large urban tertiary care hospital in the United States. A total of 45 *S. Isangi* isolates were isolated from stool (35), blood (4), urine (3), respiratory (2), and wound (1) cultures. Phenotypically, all but three isolates demonstrated resistance to ampicillin, ampicillin/sulbactam, ceftriaxone, and cefepime, and one isolate was resistant to ertapenem. Genotypically, a single CTX-M-15 ESBL was identified in all but three isolates by real-time PCR. Interestingly, two of the CTX-M-15 negative, susceptible isolates were isolated from a single patient who initially had a CTX-M positive, resistant strain. Isolates were clonally related, including both resistant and susceptible strains, as confirmed by pulse field gel electrophoresis (PFGE). This is the first case of a novel *Salmonella* outbreak at this hospital, and we believe it to be the first case of an *S. Isangi* serotype outbreak in the United States.

Infectious Diseases

Suleyman G, Tibbetts R, Perri MB, Vager D, Xin Y, Reyes K, Samuel L, Chami E, Starr P, Pietsch J, Zervos MJ, and Alangaden G. Nosocomial Outbreak of a Novel Extended-Spectrum beta-Lactamase *Salmonella enterica* Serotype Isangi Among Surgical Patients *Infect Control Hosp Epidemiol* 2016;1-8. PMID: 27108715.

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1Department of Infectious Disease, Henry Ford Hospital, Detroit, Michigan.

2Department of Pathology, Henry Ford Hospital, Detroit, Michigan.

3Research Laboratory, Henry Ford Hospital, Detroit, Michigan.

4Public Health Sciences, Henry Ford Hospital, Detroit, Michigan.

5Infection Control, Henry Ford Hospital, Detroit, Michigan.

OBJECTIVE Nosocomial outbreaks caused by *Salmonella* are rare. We describe the investigation and control of a cluster of novel extended-spectrum beta-lactamase (ESBL) *Salmonella enterica* serotype Isangi in a hospital in southeastern Michigan. **METHODS** An epidemiologic investigation, including case-control study, assessment of infection control practices and environmental cultures, was performed to identify modes of transmission. Healthcare workers (HCWs) exposed to case patients were screened. Strain relatedness was determined using pulsed-field gel electrophoresis (PFGE); ESBL confirmation was conducted using real-time PCR. Control measures were implemented to prevent further transmission. **RESULTS** Between September 2 and October 22, 2015, 19 surgical patients, including 10 organ transplant recipients and 1 HCW, had positive *S. Isangi* cultures. Of these case patients and HCW, 13 had gastroenteritis, 2 had bacteremia, 1 had surgical-site infection, and 4 were asymptomatic. Pulsed-field gel electrophoresis (PFGE) showed 89.5% similarity among the isolates in these cases. Isolates with resistant-phenotypes possessed plasmid-mediated CTX-M15 ESBL. A total of 19 case patients were compared with 57 control participants. Case patients had significantly higher odds of exposure to an intraoperative transesophageal (TEE) probe (adjusted odds ratio 9.0; 95% confidence interval, 1.12-72.60; $P=.02$). Possible cross-transmission occurred in the HCW and 2 patients. Cultures of TEE probes and the environment were negative. The outbreak ended after removal of TEE probes, modification of reprocessing procedures, implementation of strict infection control practices, and enhanced environmental cleaning. **CONCLUSIONS** We report the first nosocomial ESBL *S. Isangi* outbreak in the United States. Multiple control measures were necessary to interrupt transmission of this gastrointestinal pathogen. Exposure to possibly contaminated TEE probes was associated with transmission. Periodic monitoring of reprocessing procedures of TEE probes may be required to ensure optimal disinfection. *Infect Control Hosp Epidemiol* 2016;1-8.

Internal Medicine

Fernandez DC, Machicado J, and Davogusto G. Gastrointestinal stromal tumor arising from a gastric duplication cyst *ACG Case Rep J* 2016; 3(3):175-177. PMID: 27144196. [Full Text](#)

Division of Internal Medicine Henry Ford Hospital/Wayne State University, Detroit, MI.

Division of Gastroenterology, University of Pittsburgh, Pittsburgh, PA.

Division of Internal Medicine, University of Texas, Houston, TX.

Gastric duplication cysts (GDC) are rarely diagnosed in adults, but previous cases have been associated with malignancy. We present a case of gastrointestinal stromal tumor (GIST) arising from a GDC in a 71-year-old woman who presented with 3 years of early satiety, anorexia, abdominal distention, and weight loss. Abdominal CT showed a 9.3 x 5.2 x 9.5-cm well-circumscribed cystic mass arising 3 cm above the gastroduodenal junction. The cyst was resected, and histopathology was consistent with GDC. Future studies are needed to clarify the malignant potential of GDC and the molecular pathways for its development.

Internal Medicine

Francis MD, Julian KA, Winger DA, **Drake S**, Bollman K, Nabors C, Pereira A, Rosenblum M, Zelenski AB, Sweet D, Thomas K, Varney A, Warm E, and Francis ML. Continuity clinic model and diabetic outcomes in internal medicine residencies: Findings of the educational innovations project ambulatory collaborative *J Grad Med Educ* 2016; 8(1):27-32. PMID: 26913099. [Full Text](#)

BACKGROUND: Efforts to improve diabetes care in residency programs are ongoing and in the midst of continuity clinic redesign at many institutions. While there appears to be a link between resident continuity and improvement in glycemic control for diabetic patients, it is uncertain whether clinic structure affects quality measures and patient outcomes. **METHODS:** This multi-institutional, cross-sectional study included 12 internal medicine programs. Three outcomes (glycemic control, blood pressure control, and achievement of target low-density lipoprotein [LDL]) and 2 process measures (A1C and LDL measurement) were reported for diabetic patients. Traditional, block, and combination clinic models were compared using analysis of covariance (ANCOVA). Analysis was adjusted for continuity, utilization, workload, and panel size. **RESULTS:** No significant differences were found in glycemic control across clinic models ($P = .06$). The percentage of diabetic patients with LDL < 100 mg/dL was 60% in block, compared to 54.9% and 55% in traditional and combination models ($P = .006$). The percentage of diabetic patients with blood pressure < 130/80 mmHg was 48.4% in block, compared to 36.7% and 36.9% in other models ($P < .001$). The percentage of diabetic patients with HbA1C measured was 92.1% in block compared to 75.2% and 82.1% in other models ($P < .001$). Also, the percentage of diabetic patients with LDL measured was significantly different across all groups, with 91.2% in traditional, 70.4% in combination, and 83.3% in block model programs ($P < .001$). **CONCLUSIONS:** While high scores on diabetic quality measures are achievable in any clinic model, the block model design was associated with better performance.

Internal Medicine

Goyal N, Taylor AR, and Rivers EP. Relationship between central and peripheral venous oxygen saturation and lactate levels: A prospective study *J Emerg Med* 2016; PMID: 27210904. [Full Text](#)

Department of Emergency Medicine, Henry Ford Health System, Detroit, Michigan; Department of Internal Medicine, Henry Ford Health System, Detroit, Michigan.

Department of Public Health Science, Division of Biostatistics, Henry Ford Health System, Detroit, Michigan.

Department of Emergency Medicine, Henry Ford Health System, Detroit, Michigan; Department of Surgery, Henry Ford Health System, Detroit, Michigan.

BACKGROUND: Optimization of tissue oxygen delivery to meet consumption demands is important in the resuscitation of critically ill patients. Central venous oxygen saturation (ScvO₂) and lactate levels are often used to guide resuscitation; however, invasive monitoring is required for the former. Clinicians searching for less invasive alternatives may consider using peripheral venous oxygen saturation (SpvO₂) and lactate levels as a substitute. **OBJECTIVES:** To determine the relationship between SpvO₂ and ScvO₂ and peripheral and central lactate levels. **METHODS:** All patients with a central venous catheter in an academic emergency department and intensive care unit were eligible for the study. Blood was obtained simultaneously from a central and peripheral vein and measured for oxygen saturation and lactate levels. Results were analyzed using intraclass correlation coefficient (ICC), Bland-Altman plots, and receiver operating characteristic curves. **RESULTS:** Seventy-nine paired blood samples were analyzed. SpvO₂ and ScvO₂ have moderate agreement: ICC = 0.53 (95% confidence interval [CI] 0.35-0.67). A Bland-Altman plot revealed substantial bias (-4.47; limits of agreement -38.6, 29.6). SpvO₂ \geq 85% was 90% specific for ScvO₂ \geq 70%, and SpvO₂ of \leq 55% had a 94% sensitivity for ScvO₂ < 70%. Central and peripheral venous lactate levels showed almost perfect agreement: ICC = 0.92 (95% CI 0.87-0.95), bias of 0.46 (limits of agreement -1.78-2.70). **CONCLUSION:** SpvO₂ and ScvO₂ have moderate agreement. There was excellent agreement between peripheral and central lactate levels, making them interchangeable. The clinical implications of these substitutions in real-time patient management require further study.

Internal Medicine

Guzman Rojas P, Gallegos Lopez R, Ciliotta Chehade A, Scavino Y, **Morales A**, and Tagle M. [Autoimmune hepatitis induced by isotretinone] Article in Spanish *Rev Gastroenterol Peru* 2016; 36(1):86-89. PMID: 27131947.

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Universidad Peruana Cayetano Heredia. Lima, Peru.

Universidad Nacional Mayor de San Marcos. Lima, Peru.

Clinica Anglo Americana. Lima, Peru.

Egredao de Henry Ford Hospital, EEUU.

Clinica Anglo Americana. Lima, Peru; Facultad de Medicina de la Universidad Peruana Cayetano Heredia. Lima, Peru.

We describe a case of a teenage patient with the diagnosis of drug induced autoimmune hepatitis. The patient is a 16 years old female, with the past medical history of Hashimotoeaeuros hypothyroidism controlled with levothyroxine, who started treatment with Isotretionin (A(R)Accutane) 20 mg q/12 hours for a total of 3 months for the treatment of severe acne. The physical examination was within normal limits and the results of the laboratory exams are: Baseline values of ALT 28 U/L, AST 28 U/L. Three months later: AST 756 U/L, ALT 1199U/L, alkaline phosphatase 114 U/L, with normal bilirubin levels throughout the process. The serology studies were negative for all viral hepatitis; ANA titers were positive (1/160) and igG levels were also elevated. A liver biopsy was performed, and was compatible with the diagnosis of autoimmune hepatitis. Corticosteroid therapy was started with Prednisone 40 mg per day one week after stopping the treatment with isotretionin, observing an improvement in the laboratory values. We describe this case and review the world literature since there are no reported cases of Isotretinoin-induced autoimmune hepatitis.

Internal Medicine

Isseh IN, Bourgi K, Nakhle A, Ali M, and Zervos MJ. False-positive cerebrospinal fluid cryptococcus antigen in Libman-Sacks endocarditis *Infection* 2016; PMID: 27246719. [Full Text](#)

Department of Internal Medicine, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI, 48202, USA.
iisseh1@hfhs.org.

Department of Internal Medicine, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI, 48202, USA.
Division of Infectious Diseases, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI, 48202, USA.

BACKGROUND: Cryptococcus meningoencephalitis is a serious opportunistic infection associated with high morbidity and mortality in immunocompromised hosts, particularly patients with advanced AIDS disease. The diagnosis is established through cerebrospinal fluid (CSF) cryptococcus antigen detection and cultures. Cryptococcus antigen testing is usually the initial test of choice due its high sensitivity and specificity along with the quick availability of the results. **CASE REPORT:** We hereby report a case of a false-positive CSF cryptococcus antigen assay in a patient with systemic lupus erythematosus presenting with acute confusion. While initial CSF evaluation revealed a positive cryptococcus antigen assay, the patient's symptoms were inconsistent with cryptococcus meningoencephalitis. A repeat CSF evaluation, done 3 days later, revealed a negative CSF cryptococcus antigen assay. **CONCLUSION:** Given the patient's active lupus disease and the elevated antinuclear antibody titers, we believe that the initial positive result was a false positive caused by interference from autoantibodies.

Internal Medicine

Jain T, Nowak R, Hudson M, Frisoli T, Jacobsen G, and McCord J. Short- and long-term prognostic utility of the HEART score in patients evaluated in the emergency department for possible acute coronary syndrome *Crit Pathw Cardiol* 2016; 15(2):40-45. PMID: 27183252. [Full Text](#)

From the *Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan; daggerDepartment of Emergency Medicine, Henry Ford Hospital, Detroit, Michigan; double daggerHenry Ford Heart and Vascular Institute, Detroit, Michigan; and section signDepartment of Biostatistics, Henry Ford Hospital, Detroit, Michigan.

INTRODUCTION: The HEART score is a risk-stratification tool that was developed and validated for patients evaluated for possible acute coronary syndrome (ACS) in the emergency department (ED). We sought to determine the short-term and long-term prognostic utility of the HEART score. **METHODS:** A retrospective single-center analysis of 947 patients evaluated for possible ACS in the ED in 1999 was conducted. Patients were followed for major adverse cardiac events (MACEs) at 30 days: death, acute myocardial infarction, or revascularization procedure. All-cause mortality was assessed at 5 years. The HEART score was compared with the Thrombolysis in Myocardial Infarction (TIMI) score. **RESULTS:** At 30 days, 14% (135/947) of patients had an MACE: 48 deaths (5%), 84 acute myocardial infarctions (9%), and 48 (5%) revascularization procedures. The MACE rate in patients with HEART score ≤ 3 was 0.6% (1/175) involving a revascularization procedure, 9.5% (53/557) in patients with HEART score between 4 and 6, and 38% (81/215) with HEART score ≥ 7 . The C-statistic for the HEART score was 0.82 and 0.68 for the TIMI score for predicting 30-day MACE ($P < 0.05$). Patients with HEART score ≤ 3 had lower 5-year mortality rate compared with those with TIMI score of 0 (10.6% vs. 20.5%, $P = 0.02$). **CONCLUSIONS:** The HEART score is a valuable risk-stratification tool in predicting not only short-term MACE but also long-term mortality in patients evaluated for possible ACS in the ED. The HEART score had a superior prognostic value compared with the TIMI score.

Internal Medicine

Miller JB, Kinni H, Amer A, and Levy PD. Therapies to reduce blood pressure acutely *Curr Hypertens Rep* 2016; 18(6):43. PMID: 27125389. [Full Text](#)

Department of Emergency Medicine, Henry Ford Hospital, Detroit, MI, USA. jmiller6@hfhs.org.

Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, USA. jmiller6@hfhs.org.

Wayne State University, Detroit, MI, USA. jmiller6@hfhs.org.

Department of Emergency Medicine, Henry Ford Hospital, Detroit, MI, USA.

Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, USA.

Wayne State University, Detroit, MI, USA.

Department of Emergency Medicine, Wayne State University, Detroit, MI, USA.

Clinicians make frequent treatment decisions regarding acute blood pressure reduction for the critically ill. Key to the decision making process is a balance between reducing arterial wall stress and maintaining perfusion to vital organs. In this article, we review the physiological considerations underlying acute blood pressure management, including the concept of cerebral autoregulation and its adaptations to chronic hypertension. We then discuss available pharmacological interventions suited for reducing blood pressure acutely. We also discuss specific blood pressure targets in common critical illnesses and consider future directions in this therapeutic area.

Internal Medicine

Minhas AS, Jiang Q, Gu X, Haymart B, Kline-Rogers E, Almany S, Kozlowski J, **Krol GD**, Kaatz S, Froehlich JB, and Barnes GD. Renal function in atrial fibrillation patients switched from warfarin to a direct oral anticoagulant *J Thromb Thrombolysis* 2016;PMID: 27217043. [Full Text](#)

Department of Internal Medicine, University of Michigan Medical Center, 2F208 UH , 1500 E. Medical Center Dr., SPC 5052, Ann Arbor, MI, 48109-5052, USA. aminhas@umich.edu.

Frankel Cardiovascular Center, University of Michigan Medical Center, Ann Arbor, MI, USA.

Oakland University/Beaumont Hospital, Royal Oak, MI, USA.

Huron Valley Sinai Hospital, Commerce Township, MI, USA.

Henry Ford Hospital, Detroit, MI, USA.

Hurley Medical Center, Flint, MI, USA.

Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, MI, USA.

All available direct oral anticoagulants (DOACs) are at least partially eliminated by the kidneys. These agents are increasingly being used as alternatives to warfarin for stroke prevention in patients with atrial fibrillation. The aim of this study was to identify changes in renal function and associated DOAC dosing implications in a multicenter cohort of atrial fibrillation patients switched from warfarin to DOAC treatment. We included all patients in the Michigan Anticoagulation Quality Improvement Initiative cohort who switched from warfarin to a DOAC with atrial fibrillation as their anticoagulant indication between 2009 and 2014, and who had at least two creatinine values. Compliance with FDA-recommended dosing based on renal function was assessed. Of the 189 patients switched from warfarin to a DOAC, 34 (18.0 %) had a baseline creatinine clearance <50 mL/min and 23 (12.2 %) experienced important fluctuations in renal function. Of these 23 patients, 6 (26.1 %) should have impacted the DOAC dosing, but only 1 patient actually received an appropriate dose adjustment. Additionally, 15 (7.9 %) of patients on DOACs had a dose change performed, but only one patient demonstrated a change in renal function to justify the dose adjustment. Most atrial fibrillation patients who switched from warfarin to a DOAC had stable renal function. However, the majority of patients who had a change in renal function did not receive the indicated dose change. As the use of DOACs expands, monitoring of renal function and appropriate dose adjustments are critical.

Internal Medicine

Rao B, Jafri SM, Kazimi M, Mullins K, Raoufi M, and Segovia MC. A case report of acute cellular rejection following intestinal transplantation managed with adalimumab *Transplant Proc* 2016; 48(2):536-538. PMID: 27109995. [Full Text](#)

Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan.

Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan.

Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, Michigan.

Department of Pathology, Henry Ford Hospital, Detroit, Michigan.

Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan. Electronic address: msegovi3@hfhs.org.

There is a higher incidence of acute cellular rejection (ACR) in small bowel transplantation (SBT) compared with transplantation of other solid organs. Although there are reports on the use of infliximab to successfully treat ACR refractory to other treatments, there are no reports, to our knowledge, regarding the use of adalimumab. We present a case of a female patient with a history of Crohn's disease who underwent an isolated SBT and developed an episode of severe ACR. She was initially treated with methylprednisolone, thymoglobulin, basiliximab, and a dosage adjustment of tacrolimus. Results of repeat endoscopies and biopsies revealed no significant improvement. The patient initiated treatment with adalimumab every 2 weeks for a total of 6 months, in addition to maintenance treatment with prednisone and tacrolimus. Subsequent evaluations showed gradual improvement to normal mucosa and villi without ulceration. A regimen that incorporates adalimumab can thus be used to treat ACR after intestinal transplantation. Larger multicenter studies are needed to show the full efficacy of this therapeutic regimen.

Internal Medicine

Rao B, Segovia MC, Kazimi M, Parekh R, Raoufi M, and Jafri SM. Use of everolimus after multivisceral transplantation: A report of two cases *Transplant Proc* 2016; 48(2):485-488. PMID: 27109983. [Full Text](#)

Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan.
Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan. Electronic address: msegovi3@hfhs.org.
Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, Michigan.
Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan.
Department of Pathology, Henry Ford Hospital, Detroit, Michigan.

Inhibitors of mechanistic target of rapamycin are used in solid organ transplant procedures to avoid calcineurin inhibitor complications, including nephrotoxicity and malignancy. We present 2 cases of multivisceral transplantation for neuroendocrine tumor (NET) for which everolimus was implemented for its potential to prevent NET recurrence as well as preserve renal function. The first case was complicated by NET recurrence in the liver before initiation of everolimus. After initiation of everolimus, the patient developed a ventral hernia and elevated aminotransferase levels with nonspecific biopsy findings. The second case was complicated by cytomegalovirus infection with elevated everolimus trough levels as well as acute cellular rejection. Everolimus was reinitiated in both cases in addition to decreasing the dosage of tacrolimus, and there were no further complications. Everolimus was beneficial in stabilizing renal function in both patients and has the theoretical potential to prevent recurrence of NET.

Internal Medicine

Yin C, Weiland M, Miao ZM, Li C, **Zhou L,** and **Mi QS.** Deletion of microRNA miR-146a does not prevent streptozotocin-induced murine autoimmune type 1 diabetes *Diabetes Metab* 2016; PMID: 27133137. [Full Text](#)

Shandong Provincial Key Laboratory of Metabolic Disease, the Affiliated Hospital of Qingdao University, 16 Jiangsu Road, Qingdao 266003, China; Henry Ford Immunology Program, Departments of Dermatology and Internal Medicine, Henry Ford Health System, 1, Ford Place, 48202 Detroit, MI, United States; Department of Dermatology, Henry Ford Health System, 48202 Detroit, MI, United States.
Henry Ford Immunology Program, Departments of Dermatology and Internal Medicine, Henry Ford Health System, 1, Ford Place, 48202 Detroit, MI, United States; Department of Dermatology, Henry Ford Health System, 48202 Detroit, MI, United States.
Shandong Provincial Key Laboratory of Metabolic Disease, the Affiliated Hospital of Qingdao University, 16 Jiangsu Road, Qingdao 266003, China.
Henry Ford Immunology Program, Departments of Dermatology and Internal Medicine, Henry Ford Health System, 1, Ford Place, 48202 Detroit, MI, United States; Department of Dermatology, Henry Ford Health System, 48202 Detroit, MI, United States; Department of Internal Medicine, Henry Ford Health System, 48202 Detroit, MI, United States.
Henry Ford Immunology Program, Departments of Dermatology and Internal Medicine, Henry Ford Health System, 1, Ford Place, 48202 Detroit, MI, United States; Department of Dermatology, Henry Ford Health System, 48202 Detroit, MI, United States; Department of Internal Medicine, Henry Ford Health System, 48202 Detroit, MI, United States.
Electronic address: qmi1@hfhs.org.

Internal Medicine

Zhang X, Liu Q, Wang J, Li G, Weiland M, Yu FS, **Mi QS,** Gu J, and **Zhou L.** TIM-4 is differentially expressed in the distinct subsets of dendritic cells in skin and skin-draining lymph nodes and controls skin langerhans cell homeostasis *Oncotarget* 2016; PMID: 27224924. [Full Text](#)

Department of Dermatology, Second Military Medical University Changhai Hospital, Shanghai, China.

Henry Ford Immunology Program, Henry Ford Health System, Detroit, MI, United States of America.
Department of Dermatology, Henry Ford Health System, Detroit, MI, United States of America.
Department of Anatomy and Cell Biology, Wayne State University School of Medicine, Detroit, MI, United States of America.
Department of Internal Medicine, Henry Ford Health System, Detroit, MI, United States of America.

T cell immunoglobulin and mucin-4 (TIM-4), mainly expressed on dendritic cells (DC) and macrophages, plays an essential role in regulating immune responses. Langerhans cells (LC), which are the sole DC subpopulation residing at the epidermis, are potent mediators of immune surveillance and tolerance. However, the significance of TIM-4 on epidermal LCs, along with other cutaneous DCs, remains totally unexplored. For the first time, we discovered that epidermal LCs expressed TIM-4 and displayed an increased level of TIM-4 expression upon migration. We also found that dermal CD207+ DCs and lymph node (LN) resident CD207-CD4+ DCs highly expressed TIM-4, while dermal CD207- DCs and LN CD207-CD4- DCs had limited TIM-4 expressions. Using TIM-4-deficient mice, we further demonstrated that loss of TIM-4 significantly upregulated the frequencies of epidermal LCs and LN resident CD207-CD4+ DCs. In spite of this, the epidermal LCs of TIM-4-deficient mice displayed normal phagocytic and migratory abilities, comparable maturation status upon the stimulation as well as normal repopulation under the inflamed state. Moreover, lack of TIM-4 did not affect dinitrofluorobenzene-induced contact hypersensitivity response. In conclusion, our results indicated that TIM-4 was differentially expressed in the distinct subsets of DCs in skin and skin-draining LNs, and specifically regulated epidermal LC and LN CD207-CD4+ DC homeostasis.

Medical Education

Sanford B, **Whitehouse S**, and **Kokas M**. Do acgme physician-patient communication milestones align with hcchps patient satisfaction measures for doctor communication? *Am J Med Qual* 2016; PMID: 27259872. [Full Text](#)

Wayne State University School of Medicine, Detroit, MI bsanford@med.wayne.edu.
Henry Ford Hospital, Detroit, MI.

Nephrology

Desai T, **Yee J**, and **Soman S**. Smartphone apps: A patient's new best friend? *Clin J Am Soc Nephrol* 2016; PMID: 27173170. [Full Text](#)

Division of Nephrology, W.G. (Bill) Hefner VA Medical Center, Salisbury, North Carolina;
Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, Michigan.
Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, Michigan SSoman1@hfhs.org.

Nephrology

Locatelli F, Mazzaferro S, and **Yee J**. Iron therapy challenges for the treatment of nondialysis CKD patients *Clin J Am Soc Nephrol* 2016; PMID: 27185524. [Full Text](#)

Department of Nephrology, Dialysis and Transplantation, Alessandro Manzoni Hospital, Lecco, Italy; f.locatelli@ospedale.lecco.it.
Department of Cardiovascular, Respiratory, Nephrologic and Geriatric Sciences, Sapienza University, Rome, Italy; and.
Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, Michigan.

The clinical consequences of untreated, severe anemia in patients with nondialysis CKD can be significant, but disparities exist in the anemia treatment guidelines and position papers issued from working groups and associations across the world. These differ in hemoglobin target and iron levels and their emphasis on various iron markers and other clinical outcomes. Not surprisingly, disparities are observed in anemia treatment strategies among patients with nondialysis CKD across different areas of the world. Over the past decade, the prescription and dosage of both iron therapies and erythropoiesis-stimulating agents have shifted, with notable regional differences observed. Moreover, there is ongoing debate regarding oral versus intravenous administration of iron. Compared with oral iron therapy, which often leads to gastrointestinal adverse events, low patient adherence, and low efficacy, intravenous iron administration has been associated with potential serious adverse events, such as anaphylaxis. New iron-based compounds and drugs currently under development are reviewed to describe their potential benefits in the treatment of anemia in patients with CKD. New oral compounds, including iron-based phosphate binders, heme iron polypeptide, and liposomal iron, show different rates of absorption with possibly different efficacy and improved tolerability. These new potential therapies offer health care providers additional anemia treatment options for their

patients with CKD; however, the management of anemia in the CKD population continues to present challenges that require prospective studies to identify the optimal iron therapy for patients.

Nephrology

Singasani R, Goggins M, Patel A, and Venkat K. Liver transplant alone or simultaneous liver kidney transplantation? Case report illustrating dilemmas in patient selection for dual transplantation *Am J Kidney Dis* 2016; 67(5):A101-A101. PMID: Not assigned. Abstract

[Singasani, Reddy; Goggins, Mariella; Patel, Anita; Venkat, K.] Henry Ford Hosp, Detroit, MI 48202 USA.

The inferior outcomes of liver transplantation alone in end-stage liver disease (ESLD) associated with significant renal dysfunction can be improved by simultaneous liver kidney transplantation (SLK). However, excessively liberal dual organ transplantation decreases availability of kidneys for transplantation in end-stage renal disease (ESRD) patients. A recent patient of ours illustrates the potential decision-making dilemmas encountered in this setting. A 63-year-old man awaiting liver transplantation for ESLD secondary to Hepatitis-C developed acute kidney injury (AKI) with serum creatinine (SCr) increasing from 2.0 to 3.1 mg/dl over 1 week. Dysmorphic RBCs and RBC casts in the urine sediment, increase in urine protein/creatinine ratio from 0.13 g/g to 2.85 g/g, low C3/C4 complements, and positive rheumatoid factor and IgG/IgM cryoglobulins suggested hepatitis-C-associated cryoglobulinemic glomerulonephritis. Pre-transplant kidney biopsy was precluded by ESLD-associated coagulopathy. We suggested rituximab and/or methylprednisolone bolus therapy to see if AKI can be reversed and kidney transplantation avoided. However, the liver transplant team did not want to use pre-transplant immunosuppression in this very ill patient prone to opportunistic infections, which might delay/preclude life-saving liver transplantation. Further increase in SCr over next 10 days to 4.9 mg/dl led to acceptance for SLK, performed 3 weeks post-AKI development. Intraoperative native kidney biopsy revealed cryoglobulinemic glomerulonephritis. Three weeks post-transplantation, SCr was 0.8-1.0 mg/dl, with normal urinalysis and serum complement levels. It is possible that improvement of renal status was at least in part due to reversal of native glomerulonephritis by post-transplant immunosuppression. Although current guidelines recommend 4 weeks of severe AKI or >3 months of advanced chronic kidney disease (eGFR < 40 ml/min/1.73m²) as indications for SLK, patients such as ours do not clearly fit into either category and present major challenges in determining the need for dual organ transplantation

Nephrology

Singasani R, Ngansop T, Kumbar L, Li J, Yee J, and Yessayan L. Renal sparing in levamisole/cocaine induced systemic vasculitis *Am J Kidney Dis* 2016; 67(5):A101-A101. PMID: Not assigned. Abstract

[Singasani, Reddy; Ngansop, Thierry; Kumbar, Lalathaksha; Li, Jian; Yee, Jerry; Yessayan, Lenart] Henry Ford Hosp, Detroit, MI 48202 USA.

circulating autoantibodies. Pregnant patients with lupus or myasthenia gravis can deliver babies with corresponding disease in the neonate.^{1,2} Neonatal membranous nephropathy (MN) not associated with congenital infection was first described in 1990 and attributed to the passive transfer of maternal antibodies to putative renal antigens.³ More than a decade later, Debiec et al⁴ identified the first antigen involved in such cases as neutral endopeptidase (NEP), a metalloprotease present on the surface of the podocyte and involved in the proteolytic regulation of vasoactive peptides. Debiec et al described a mother with a mutation preventing NEP expression who had formed anti-NEP antibodies due to fetomaternal alloimmunization from a previous miscarriage; these antibodies were to cross the placenta and cause subepithelial deposits in the fetal kidney of a subsequent pregnancy. M-type phospholipase A2 receptor (PLA2R) was later identified as the major autoantigen for primary MN in adults.⁵ Little literature exists about pregnancy outcomes in patients with nephrotic syndrome due to primary MN, with no data available about pregnancy in PLA2R-associated disease. We present what we believe to be the first known case of pregnancy in a patient with PLA2R-associated MN who was seropositive for anti-PLA2R autoantib.

Nephrology

Soi V, Moore CL, Kumbar L, and Yee J. Prevention of catheter-related bloodstream infections in patients on hemodialysis: challenges and management strategies *Int J Nephrol Renovasc Dis* 2016; 9:95-103. PMID: 27143948. [Full Text](#)

Division of Nephrology and Hypertension, Henry Ford Health System, Detroit, MI, USA.

Catheter-related bloodstream infections are a significant source of morbidity and mortality in the end-stage renal disease population. Although alternative accesses to undergoing renal replacement therapy exist, many patients begin hemodialysis with a dialysis catheter due to logistic and physiologic factors involved in arteriovenous fistula creation and maturation. Colonization of catheters via skin flora leads to the production of biofilm, which acts as a reservoir for virulent bacteria. Preventative therapies center on appropriate catheter maintenance, infection control measures, and early removal of devices as patients transition to other access. Despite best efforts, when conservative measures fail to prevent infections in a high-risk population, antimicrobial lock therapy should be considered as an option to combat catheter-related bloodstream infections.

Nephrology

Szamosfalvi B, Westover A, Buffington D, Yevzlin A, and Humes HD. Immunomodulatory device promotes a shift of circulating monocytes to a less inflammatory phenotype in chronic hemodialysis patients *Asaio j* 2016;PMID: 27258222. [Full Text](#)

*Department of Internal Medicine, University of Michigan Medical School, 4520C MSRB I, SPC 5651, 1150 W. Medical Center Dr., Ann Arbor, MI 48109 daggerInnovative BioTherapies, Inc., 650 Avis Drive, Suite 300, Ann Arbor, MI 48108 #CytoPherx, Inc., 401 W. Morgan Rd., Ann Arbor, MI 48108 +Henry Ford Health System, 2799 West Grand Blvd., Detroit, MI 48202.

Patients with end stage renal disease (ESRD) on chronic hemodialysis (HD) suffer accelerated morbidity and mortality rates due to cardiovascular disease and infections. Chronic inflammation plays a critical role in these poor outcomes. The activated monocyte (MO), has become a prime therapeutic target to modulate this inflammatory process. A selective cytopheretic device (SCD) was evaluated to assess its effects on the circulating MO pool. A pilot trial was undertaken in 15 ESRD patients on HD with c-reactive protein (CRP) levels greater than 5 mg/dl. An excellent safety profile was observed with no decline in leukocyte (LE) or platelet counts. The effect of SCD therapy on MO phenotypes in these patients was determined on peripheral blood MO utilizing flow cytometry. SCD therapy promoted a shift in MO phenotype from predominantly CD14 expressing MO at baseline/pre-SCD therapy to CD14 expressing MO post-SCD therapy. A significant shift in MO population phenotype afforded by a single SCD therapy session was observed ($p < 0.013$). In a subset of patients ($n=7$) presenting with type 2 diabetes mellitus (T2D), this persistent decline in MO CD14 expression was sustained as long as 2 weeks post therapy. These results demonstrate SCD therapy has the potential to modulate the chronic pro-inflammatory state in ESRD patients.

Nephrology

Umeukeje EM, Merighi JR, Browne T, Wild M, **Almaan H**, **Umanath K**, Lewis JB, Wallston KA, and Cavanaugh KL. Health care providers' support of patients' autonomy, phosphate medication adherence, race and gender in end stage renal disease *J Behav Med* 2016;PMID: 27167227. [Full Text](#)

Division of Nephrology and Hypertension, Vanderbilt University Medical Center, 1161 21st Avenue MCN S-3223, Nashville, TN, 37232, USA.

Vanderbilt Center for Kidney Disease, Nashville, TN, USA.

School of Social Work, University of Minnesota, Saint Paul, MN, USA.

College of Social Work, University of South Carolina, Columbia, SC, USA.

Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, MI, USA.

Vanderbilt University School of Nursing, Nashville, TN, USA.

Division of Nephrology and Hypertension, Vanderbilt University Medical Center, 1161 21st Avenue MCN S-3223, Nashville, TN, 37232, USA. kerri.cavanaugh@vanderbilt.edu.

Vanderbilt Center for Kidney Disease, Nashville, TN, USA. kerri.cavanaugh@vanderbilt.edu.

This study was designed to assess dialysis subjects' perceived autonomy support association with phosphate binder medication adherence, race and gender. A multi-site cross-sectional study was conducted among 377 dialysis subjects. The Health Care Climate (HCC) Questionnaire assessed subjects' perception of their providers' autonomy support for phosphate binder use, and adherence was assessed by the self-reported Morisky Medication Adherence Scale. Serum phosphorus was obtained from the medical record. Regression models were used to examine independent factors of medication adherence, serum phosphorus, and differences by race and gender. Non-white HCC scores were consistently lower compared with white subjects' scores. No differences were observed by gender. Reported phosphate binder adherence was associated with HCC score, and also with phosphorus control. No significant association was found between HCC score and serum phosphorus. Autonomy support, especially in non-white end stage renal disease subjects, may be an appropriate target for culturally informed strategies to optimize mineral bone health.

Nephrology

Yee J. Intensive care unit renal replacement therapy: Less is more (or better) *Adv Chronic Kidney Dis* 2016; 23(3):131-133. PMID: 27113686. [Full Text](#)

Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, MI.

Nephrology

Yessayan L, Yee J, Frinak S, and Szamosfalvi B. Continuous renal replacement therapy for the management of acid-base and electrolyte imbalances in acute kidney injury *Adv Chronic Kidney Dis* 2016; 23(3):203-210. PMID: 27113697. [Full Text](#)

Division of Nephrology and Hypertension, Department of Internal Medicine, Henry Ford Hospital, Detroit, MI; and Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Henry Ford Hospital, Detroit, MI. Electronic address: Lyessay1@hfhs.org.

Division of Nephrology and Hypertension, Department of Internal Medicine, Henry Ford Hospital, Detroit, MI; and Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Henry Ford Hospital, Detroit, MI.

Continuous renal replacement therapy (CRRT) is used to manage electrolyte and acid-base imbalances in critically ill patients with acute kidney injury. Although a standard solution and prescription is acceptable in most clinical circumstances, specific disorders may require a tailored approach such as adjusting fluid composition, regulating CRRT dose, and using separate intravenous infusions to mitigate and correct these disturbances. Errors in fluid prescription, compounding, or delivery can be rapidly fatal. This article provides an overview of the principles of acid-base and electrolyte management using CRRT.

Neurology

Affan M, Schultz L, Cerghet M, and Elias S. Clinical and radiological presentation of neurosarcoidosis: Single center cohort study of 107 cases (p6.114) *Neurology* 2016; 86(16 Supplement) PMID: Not assigned. Abstract

Objective: To describe clinical, radiologic manifestations and treatment outcomes in 107 patients with neurosarcoidosis. **Background:** Neurosarcoidosis (NS) is reported in less than 5[percent] of patients with systemic sarcoidosis while isolated NS without systemic involvement represents 17[percent] of NS. A definitive diagnosis requires histologic confirmation, which rarely is obtained in NS. Our current knowledge for diagnosis and treatment relies on case reports. **Methods:** The study setting was a large, integrated health care system serving southeastern Michigan. 107 patients seen from 1995-2015 were found to meet the criteria for definitive, probable or possible NS (Zajicek, 1999). Neurological symptoms, sociodemographic, laboratory, radiographic and treatment data were collected. Descriptive statistics and chi-square tests were conducted using SAS version 9.4. **Results:** Of 107 patients, 58[percent] were male and 74[percent] African American. Average age of presentation was 49.1 year. Brain was the most common site involved (50[percent]), followed by cranial nerves (39[percent]), spine (29[percent]). Majority (81[percent]) had multisystem sarcoidosis with lung most commonly involved (56[percent]). For those with complete workup, blood ACE was elevated in half of patients and only a third had elevated CSF ACE (29[percent]). Significantly higher rates of elevated blood ACE were seen in patients with multisystem involvement ($p=0.005$). Abnormal laboratory tests seen frequently were elevated CSF WBC (65[percent]), elevated CSF protein (53[percent]) and elevated serum C-reactive protein (75[percent]). Most common clinical presentations were headache (20[percent]), optic neuritis (13[percent]), myelitis (13[percent]) and Bell's palsy (8[percent]). Prednisone was used as initial treatment (93[percent]) while methotrexate was the most common used long term immunosuppressant (35[percent]). **Conclusion:** We present the largest described case series of NS. Clinical presentation was diverse with multi-system involvement in most cases. We found that certain laboratory tests may be useful tools for diagnosis. Further epidemiological analysis is needed to develop prediction models and better screening programs for early detection. **Disclosure:** Dr. Affan has nothing to disclose. Dr. Schultz has nothing to disclose. Dr. Cerghet has nothing to disclose. Dr. Elias has nothing to disclose.

Neurology

Ekanger LA, Mills DR, **Ali MM**, Polin LA, Shen Y, Haacke EM, and Allen MJ. Spectroscopic characterization of the 3+ and 2+ oxidation states of europium in a macrocyclic tetraglycinate complex *Inorg Chem* 2016; PMID: 27244124.

[Article Request Form](#)

Department of Chemistry, Wayne State University, 5101 Cass Avenue, Detroit, Michigan 48202, United States.
Department of Neurology, Henry Ford Hospital, 1 Ford Place, Detroit, Michigan 48202, United States.

Department of Oncology, Wayne State University School of Medicine , 110 East Warren Avenue, Detroit, Michigan 48201, United States.
Barbara Ann Karmanos Cancer Institute , 4100 John R Street, Detroit, Michigan 48201, United States.
Department of Radiology, Wayne State University School of Medicine , 3990 John R Street, Detroit, Michigan 48201, United States.

The 3+ and 2+ oxidation states of europium have drastically different magnetic and spectroscopic properties. Electrochemical measurements are often used to probe EuIII/II oxidation state changes, but a full suite of spectroscopic characterization is necessary to demonstrate conversion between these two oxidation states in solution. Here, we report the facile conversion of an europium(III) tetraglycinate complex into its EuII analogue. We present electrochemical, luminescence, electron paramagnetic resonance, UV-visible, and NMR spectroscopic data demonstrating complete reversibility from the reduction and oxidation of the 3+ and 2+ oxidation states, respectively. The EuII-containing analogue has kinetic stability within the range of clinically approved GdIII-containing complexes using an acid-catalyzed dissociation experiment. Additionally, we demonstrate that the 3+ and 2+ oxidation states provide redox-responsive behavior through chemical-exchange saturation transfer or proton relaxation, respectively. These results will be applicable to a wide range of redox-responsive contrast agents and Eu-containing complexes.

Neurology

Jia L, Wang L, Chopp M, Zhang Y, Szalad A, and Zhang ZG. MicroRNA 146a locally mediates distal axonal growth of dorsal root ganglia neurons under high glucose and sildenafil conditions *Neuroscience* 2016; 329:43-53. PMID: 27167084. [Full Text](#)

Department of Neurology, Henry Ford Hospital, 2799 W. Grand Boulevard, Detroit, MI 48202, United States.
Department of Neurology, Henry Ford Hospital, 2799 W. Grand Boulevard, Detroit, MI 48202, United States;
Department of Physics Oakland University, Rochester, MI 48309, United States.
Department of Neurology, Henry Ford Hospital, 2799 W. Grand Boulevard, Detroit, MI 48202, United States.
Electronic address: zhazh@neuro.hfh.edu.

Axonal loss contributes to induction of diabetic peripheral neuropathy. Sildenafil, a phosphodiesterase type 5 inhibitor, ameliorates neurological dysfunction in diabetic peripheral neuropathy. However, the direct effect of high glucose and sildenafil on axonal growth has not been extensively investigated. Using rat primary dorsal root ganglia (DRG) neurons cultured in a microfluidic chamber, we investigated the effect of axonal application of high glucose and sildenafil on distal axonal growth. We found that axonal, but not cell body, application of high glucose locally inhibited distal axonal growth. However, axonal application of sildenafil overcame high glucose-reduced axonal growth. Quantitative real-time RT-PCR (qRT-PCR) and Western blot analysis of distal axonal samples revealed that high glucose reduced axonal miR-146a levels and substantially increased miR-146a target genes, IRAK1 and TRAF6 in the axon. In contrast, sildenafil significantly reversed high glucose-reduced miR-146a levels and high glucose-increased IRAK1 and TRAF6. Gain- and loss-of function of miR-146a in DRG neurons revealed that miR-146a mediated the local effect of high glucose on the distal axonal growth. These in vitro data provide new insights into molecular mechanisms of diabetic peripheral neuropathy.

Neurology

Kumar A, **Giri S**, and Kumar A. AICAR-mediated AMPK activation induces protective innate responses in bacterial endophthalmitis *Cell Microbiol* 2016;PMID: 27264993. [Full Text](#)

Department of Ophthalmology/Kresge Eye Institute, Wayne State University, Detroit, MI, USA.
Department of Neurology, Henry Ford Health System, Detroit, MI, USA.
Department of Anatomy and Cell Biology, Wayne State University, Detroit, MI, USA.
Department of Immunology and Microbiology, Wayne State University, Detroit, MI, USA.

The retina is considered to be the most metabolically active tissue in the body. However, the link between energy metabolism and retinal inflammation, as incited by microbial infection such as endophthalmitis remains unexplored. In this study, using a mouse model of *Staphylococcus aureus* (SA) endophthalmitis, we demonstrate that the activity (phosphorylation) of AMP-activated protein kinase alpha (AMPKalpha), a cellular energy sensor, and its endogenous substrate; acetyl-CoA carboxylase (ACC) is downregulated in the SA-infected retina. Intravitreal administration of an AMPK activator, 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) restored AMPKalpha and ACC phosphorylation. AICAR treatment reduced both the bacterial burden and intraocular inflammation in SA-infected eyes by inhibiting NF- κ B and MAP kinases (p38 and JNK) signaling. The anti-inflammatory effects of AICAR were diminished in eyes pretreated with AMPK inhibitor, Compound C. The bioenergetics (Seahorse) analysis of SA-infected microglia and bone marrow-derived macrophages (BMDM) revealed an increase in glycolysis, which was

reinstated by AICAR treatment. AICAR also reduced the expression of SA-induced glycolytic genes, including hexokinase 2 (HK2), and glucose transporter 1 (Glut1) in microglia, BMDM, and the mouse retina. Interestingly, AICAR treatment enhanced the bacterial phagocytic and intracellular killing activities of cultured microglia, macrophages, and neutrophils. Furthermore, AMPK α 1 global knockout mice exhibited increased susceptibility towards SA endophthalmitis, as evidenced by increased inflammatory mediators and bacterial burden and reduced retinal function. Together, these findings provide the first evidence that AMPK activation promotes retinal innate defense in endophthalmitis by modulating energy metabolism, and that it can be targeted therapeutically to treat ocular infections.

Neurology

Lewis A, **Varelas P**, and Greer D. Pregnancy and brain death: Lack of guidance in U.S. hospital policies *Am J Perinatol* 2016;PMID: 27159202. [Article Request Form](#)

Division of Neurocritical Care, Departments of Neurology and Neurosurgery, NYU Langone Medical Center, New York, New York.

Departments of Neurology and Neurosurgery, Henry Ford Hospital, Detroit, Michigan.

Department of Neurology, Yale University School of Medicine, New Haven, Connecticut.

Objective The death of Marlise Munoz, a pregnant woman who suffered an anoxic brain injury in November 2013, highlights the social, ethical, legal, and medical controversies associated with brain death in pregnancy. We sought to evaluate whether institutions in the United States have policies in place for situations in which a pregnant woman is declared brain dead. **Study Design** Institutional brain-death protocols from hospitals in the United States were obtained in cooperation with local and regional organ procurement agencies. Each protocol was reviewed to determine if and how it addressed brain death in pregnancy. **Results** We reviewed 317 unique brain-death protocols. In eight protocols (2.5%), it was noted that a pregnant patient could not be evaluated for brain death if the fetus could be preserved. Of the protocols that permitted brain-death evaluation, 289 (93.8%) did not include guidance about fetal management after maternal brain death and 305 (99%) did not indicate who was responsible for making decisions for the fetus. **Conclusion** Very few institutional brain-death policies address the issue of pregnancy. The creation of guidelines on management of the social and ethical challenges associated with brain death in pregnancy may be helpful.

Neurology

Mahajan A, Balakrishnan P, Patel A, Konstantinidis I, Nistal D, Annapureddy N, Poojary P, Nadkarni GN, and **Sidiropoulos C**. Epidemiology of inpatient stay in parkinson's disease in the united states: Insights from the nationwide inpatient sample *J Clin Neurosci* 2016;PMID: 27242063. [Full Text](#)

Department of Neurology, Henry Ford Health System, 2799 W. Grand Boulevard, K-11, Detroit, MI 48202, USA; Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA. Electronic address: amahaja1@hfhs.org.

Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA.

Division of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

Division of Rheumatology, Vanderbilt University Medical Center, Nashville, TN, USA.

Department of Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

Department of Neurology, Henry Ford Health System, 2799 W. Grand Boulevard, K-11, Detroit, MI 48202, USA.

The total number of people living with Parkinson's disease (PD) worldwide is expected to double by 2030. The risk factors for emergency department visits in PD patients have been described before, however, there is limited data on inpatient hospitalizations of PD patients. We derived our study cohort from the Nationwide Inpatient Sample (NIS) database from 2002-2011. The NIS is a stratified 20% sample of discharges from all U.S. hospitals. We extracted causes of hospitalization using International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes and calculated inpatient mortality, length of stay and cost. Further, the significance of trends over 10 years was assessed. A total of 3,015,645 (weighted) admissions of PD patients were documented from 2002-2011. Pneumonia, urinary tract infection (UTI), septicemia and aspiration pneumonitis were the most common causes of admission, of which incidence of sepsis and UTI was trending up. Of all causes, 3.9% of the admissions resulted in inpatient mortality. Inpatient mortality for PD patients decreased from 4.9% in 2002 to 3.3% in 2011 ($p < 0.001$). The median length of stay has also steadily declined from 3.6 days in 2002 to 2.3 days in 2011. However, the inflation-adjusted cost of care has been steadily rising, from \$22,250 per hospitalization in 2002 to \$37,942 in 2011. We conclude that the epidemiology of inpatient admissions in PD has changed significantly over the last decade. Our study

underscores the need for future, in-depth prospective studies to explore this changing disease spectrum to design preventive measures and targeted interventions.

Neurology

Sidiropoulos C, Rammo R, Merker B, Mahajan A, LeWitt P, Kaminski P, Womble M, Zec A, Taylor D, Wall J, and Schwab JM. Intraoperative MRI for deep brain stimulation lead placement in Parkinson's disease: 1 year motor and neuropsychological outcomes *J Neurol* 2016; 263(6):1226-1231. PMID: 27126457. [Full Text](#)

Parkinson's Disease and Movement Disorders Program, Henry Ford Hospital, 6777 West Maple Road, West Bloomfield, MI, 48322, USA. csidiro1@hfhs.org.

Department of Neurosurgery, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.

Division of Neuropsychology, Henry Ford Health System, 1 Ford Place, Suite 1E, Detroit, MI, 48202, USA.

Department of Neurology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.

Parkinson's Disease and Movement Disorders Program, Henry Ford Hospital, 6777 West Maple Road, West Bloomfield, MI, 48322, USA.

William Beaumont Health System, 3601 W 13 Mile Rd, Royal Oak, MI, 48073, USA.

Traditional deep brain stimulation requires intraoperative neurophysiological confirmation of electrode placement. Recently, purely image guided methods are being evaluated as to their clinical efficacy in comparison to surgery using microelectrode recordings. We used the ClearPoint(R) system to place electrodes in both the subthalamic nucleus and globus pallidus internus in patients with advanced Parkinson's disease. Off medication UPDRS scores were assessed before and 1 year after surgery as well as pre- and 1 year post-operative neuropsychological outcomes. Targeting precision was also assessed. Patients implanted in the subthalamic nucleus improved by 46.2 % in their UPDRS scores post-operatively ($p = 0.03$) whereas the globus pallidus group improved by 41 % ($p = 0.06$). There were no significant adverse neuropsychological outcomes in either group of patients. Mean radial error for the STN group was 1.2 +/- 0.7 mm and for the GPi group 0.8 mm +/- 0.3 mm. Image guided DBS using the ClearPoint(R) system has high targeting precision with robust clinical outcomes. Our data are in accord with recent studies using the same or similar technologies and provide a rationale for a large comparative study of image-guided versus microelectrode guided DBS.

Neurology

Zhang Y, Zhang ZG, Chopp M, Meng Y, Zhang L, Mahmood A, and Xiong Y. Treatment of traumatic brain injury in rats with N-acetyl-seryl-aspartyl-lysyl-proline *J Neurosurg* 2016:1-14. PMID: 27203137. [Full Text](#)

Departments of 1 Neurosurgery and.

Neurology, Henry Ford Hospital, Detroit; and.

Department of Physics, Oakland University, Rochester, Michigan.

OBJECTIVE The authors' previous studies have suggested that thymosin beta 4 (Tbeta4), a major actin-sequestering protein, improves functional recovery after neural injury. N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) is an active peptide fragment of Tbeta4. Its effect as a treatment of traumatic brain injury (TBI) has not been investigated. Thus, this study was designed to determine whether AcSDKP treatment improves functional recovery in rats after TBI. **METHODS** Young adult male Wistar rats were randomly divided into the following groups: 1) sham group (no injury); 2) TBI + vehicle group (0.01 N acetic acid); and 3) TBI + AcSDKP (0.8 mg/kg/day). TBI was induced by controlled cortical impact over the left parietal cortex. AcSDKP or vehicle was administered subcutaneously starting 1 hour postinjury and continuously for 3 days using an osmotic minipump. Sensorimotor function and spatial learning were assessed using a modified Neurological Severity Score and Morris water maze tests, respectively. Some of the animals were euthanized 1 day after injury, and their brains were processed for measurement of fibrin accumulation and neuroinflammation signaling pathways. The remaining animals were euthanized 35 days after injury, and brain sections were processed for measurement of lesion volume, hippocampal cell loss, angiogenesis, neurogenesis, and dendritic spine remodeling. **RESULTS** Compared with vehicle treatment, AcSDKP treatment initiated 1 hour postinjury significantly improved sensorimotor functional recovery (Days 7-35, $p < 0.05$) and spatial learning (Days 33-35, $p < 0.05$), reduced cortical lesion volume, and hippocampal neuronal cell loss, reduced fibrin accumulation and activation of microglia/macrophages, enhanced angiogenesis and neurogenesis, and increased the number of dendritic spines in the injured brain ($p < 0.05$). AcSDKP treatment also significantly inhibited the transforming growth factor-beta1/nuclear factor-kappaB signaling pathway. **CONCLUSIONS** AcSDKP treatment initiated 1 hour postinjury provides neuroprotection and neurorestoration after TBI, indicating that this small tetrapeptide has promising therapeutic potential for treatment of TBI. Further investigation of the optimal dose and therapeutic window of AcSDKP treatment for TBI and the associated underlying mechanisms is therefore warranted.

Neuropsychology

Sidiropoulos C, Rammo R, Merker B, Mahajan A, LeWitt P, Kaminski P, Womble M, Zec A, Taylor D, Wall J, and Schwab JM. Intraoperative MRI for deep brain stimulation lead placement in Parkinson's disease: 1 year motor and neuropsychological outcomes *J Neurol* 2016; 263(6):1226-1231. PMID: 27126457. [Full Text](#)

Parkinson's Disease and Movement Disorders Program, Henry Ford Hospital, 6777 West Maple Road, West Bloomfield, MI, 48322, USA. csidiro1@hfhs.org.

Department of Neurosurgery, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.

Division of Neuropsychology, Henry Ford Health System, 1 Ford Place, Suite 1E, Detroit, MI, 48202, USA.

Department of Neurology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.

Parkinson's Disease and Movement Disorders Program, Henry Ford Hospital, 6777 West Maple Road, West Bloomfield, MI, 48322, USA.

William Beaumont Health System, 3601 W 13 Mile Rd, Royal Oak, MI, 48073, USA.

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Neurosurgery

Ali R, Schwab JM, Nerenz DR, Antoine HJ, and Rubinfeld I. Use of the modified frailty index to predict 30-day morbidity and mortality from spine surgery *J Neurosurg Spine* 2016:1-5. PMID: 27153143. [Full Text](#)

Department of Neurosurgery, Henry Ford Hospital;

Neuroscience Institute and the Center for Health Policy and Health Services Research, Henry Ford Health System; and

Department of Surgery, Henry Ford Hospital, Detroit, Michigan.

OBJECTIVE Limited tools exist to stratify perioperative risk in patients undergoing spinal procedures. The modified frailty index (mFI) based on the Canadian Study of Health and Aging Frailty Index (CSHA-FI), constructed from standard demographic variables, has been applied to various other surgical populations for risk stratification. The authors hypothesized that it would be predictive of postoperative morbidity and mortality in patients undergoing spine surgery. **METHODS** The 2006-2010 National Surgical Quality Improvement Program (NSQIP) data set was accessed for patients undergoing spine surgeries based on Current Procedural Terminology (CPT) codes. Sixteen preoperative clinical NSQIP variables were matched to 11 CSHA-FI variables (changes in daily activities, gastrointestinal problems, respiratory problems, clouding or delirium, hypertension, coronary artery and peripheral vascular disease, congestive heart failure, and so on). The outcomes assessed were 30-day occurrences of adverse events. These were then summarized in groups: any infection, wound-related complication, Clavien IV complications (life-threatening, requiring ICU admission), and mortality. **RESULTS** A total of 18,294 patients were identified. In 8.1% of patients with an mFI of 0 there was at least one morbid complication, compared with 24.3% of patients with an mFI of ≥ 0.27 ($p < 0.001$). An mFI of 0 was associated with a mortality rate of 0.1%, compared with 2.3% for an mFI of ≥ 0.27 ($p < 0.001$). Patients with an mFI of 0 had a 1.7% rate of surgical site infections and a 0.8% rate of Clavien IV complications, whereas patients with an mFI of ≥ 0.27 had rates of 4.1% and 7.1% for surgical site infections and Clavien IV complications, respectively ($p < 0.001$ for both). Multivariate analysis showed that the preoperative mFI and American Society of Anesthesiologists classification of \geq III had a significantly increased risk of leading to Clavien IV complications and death. **CONCLUSIONS** A higher mFI was associated with a higher risk of postoperative morbidity and mortality, providing an additional tool to improve perioperative risk stratification.

Neurosurgery

Cloughesy TF, Landolfi J, Hogan DJ, Bloomfield S, Carter B, Chen CC, Elder JB, **Kalkanis SN**, Kesari S, Lai A, **Lee IY**, Liau LM, **Mikkelsen T**, Nghiemphu PL, Piccioni D, **Walbert T**, Chu A, Das A, Diago OR, Gammon D, Gruber HE, Hanna M, Jolly DJ, Kasahara N, McCarthy D, Mitchell L, Ostertag D, Robbins JM, Rodriguez-Aguirre M, and

Vogelbaum MA. Phase 1 trial of vocimagene amiretrorepvec and 5-fluorocytosine for recurrent high-grade glioma *Sci Transl Med* 2016; 8(341):341ra375. PMID: 27252174. [Article Request Form](#)

Department of Neuro-Oncology and Department of Neurosurgery, 710 Westwood Plaza, University of California, Los Angeles, Los Angeles, CA 90095, USA.

New Jersey Neuroscience Institute, John F. Kennedy Medical Center, 65 James Street, Edison, NJ 08820, USA.
Tocagen Inc., 3030 Bunker Hill Street, San Diego, CA 92109, USA.

Moore Cancer Center, Department of Neurosciences, University of California, San Diego, 3855 Health Sciences Drive, La Jolla, CA 92093, USA.

Ohio State University Wexner Medical Center, 410 West 10th Avenue, Columbus, OH 43210, USA.

Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202, USA.

Ribomed Biotechnologies Inc., 3030 Bunker Hill Street, San Diego, CA 92109, USA. University of Arizona Cancer Center, 1515 North Campbell Avenue, Tucson, AZ 85724, USA.

Department of Cell Biology and Sylvester Comprehensive Cancer Center, Miller School of Medicine, University of Miami, Miami, FL 33136, USA.

Ribomed Biotechnologies Inc., 3030 Bunker Hill Street, San Diego, CA 92109, USA.

Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA. vogelbm@ccf.org.

Toca 511 (vocimagene amiretrorepvec) is an investigational nonlytic, retroviral replicating vector (RRV) that delivers a yeast cytosine deaminase, which converts subsequently administered courses of the investigational prodrug Toca FC (extended-release 5-fluorocytosine) into the antimetabolite 5-fluorouracil. Forty-five subjects with recurrent or progressive high-grade glioma were treated. The end points of this phase 1, open-label, ascending dose, multicenter trial included safety, efficacy, and molecular profiling; survival was compared to a matching subgroup from an external control. Overall survival for recurrent high-grade glioma was 13.6 months (95% confidence interval, 10.8 to 20.0) and was statistically improved relative to an external control (hazard ratio, 0.45; $P = 0.003$). Tumor samples from subjects surviving more than 52 weeks after Toca 511 delivery disproportionately displayed a survival-related mRNA expression signature, identifying a potential molecular signature that may correlate with treatment-related survival rather than being prognostic. Toca 511 and Toca FC show excellent tolerability, with RRV persisting in the tumor and RRV control systemically. The favorable assessment of Toca 511 and Toca FC supports confirmation in a randomized phase 2/3 trial (NCT02414165).

Neurosurgery

Hodges TR, Ferguson SD, Caruso HG, Kohanbash G, Zhou S, Cloughesy TF, Berger MS, Poste GH, Khasraw M, Ba S, Jiang T, **Mikkelsen T**, Yung WKA, de Groot JF, Fine H, Cantley LC, Mellingshoff IK, Mitchell DA, Okada H, and Heimberger AB. Prioritization schema for immunotherapy clinical trials in glioblastoma *Oncol Immunology* 2016; PMID: Not assigned. [Article Request Form](#)

A.B. Heimberger, Department of Neurosurgery, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Background: Emerging immunotherapeutic strategies for the treatment of glioblastoma (GBM) such as dendritic cell (DC) vaccines, heat shock proteins, peptide vaccines, and adoptive T-cell therapeutics, to name a few, have transitioned from the bench to clinical trials. With upcoming strategies and developing therapeutics, it is challenging to critically evaluate the practical, clinical potential of individual approaches and to advise patients on the most promising clinical trials. Methods: The authors propose a system to prioritize such therapies in an organized and data-driven fashion. This schema is based on four categories of factors: antigenic target robustness, immune-activation and -effector responses, preclinical vetting, and early evidence of clinical response. Each of these categories is subdivided to focus on the most salient elements for developing a successful immunotherapeutic approach for GBM, and a numerical score is generated. Results: The Score Card reveals therapeutics that have the most robust data to support their use, provides a reference prioritization score, and can be applied in a reiterative fashion with emerging data. Conclusions: The authors hope that this schema will give physicians an evidence-based and rational framework to make the best referral decisions to better guide and serve this patient population.

Neurosurgery

Lewis A, **Varelas P**, and Greer D. Pregnancy and brain death: Lack of guidance in U.S. hospital policies *Am J Perinatol* 2016; PMID: 27159202. [Article Request Form](#)

Division of Neurocritical Care, Departments of Neurology and Neurosurgery, NYU Langone Medical Center, New York, New York.

Departments of Neurology and Neurosurgery, Henry Ford Hospital, Detroit, Michigan.

Department of Neurology, Yale University School of Medicine, New Haven, Connecticut.

Objective The death of Marlise Munoz, a pregnant woman who suffered an anoxic brain injury in November 2013, highlights the social, ethical, legal, and medical controversies associated with brain death in pregnancy. We sought to evaluate whether institutions in the United States have policies in place for situations in which a pregnant woman is declared brain dead. **Study Design** Institutional brain-death protocols from hospitals in the United States were obtained in cooperation with local and regional organ procurement agencies. Each protocol was reviewed to determine if and how it addressed brain death in pregnancy. **Results** We reviewed 317 unique brain-death protocols. In eight protocols (2.5%), it was noted that a pregnant patient could not be evaluated for brain death if the fetus could be preserved. Of the protocols that permitted brain-death evaluation, 289 (93.8%) did not include guidance about fetal management after maternal brain death and 305 (99%) did not indicate who was responsible for making decisions for the fetus. **Conclusion** Very few institutional brain-death policies address the issue of pregnancy. The creation of guidelines on management of the social and ethical challenges associated with brain death in pregnancy may be helpful.

Neurosurgery

Pabaney AH, Ali R, Kole M, and Malik GM. Arteriovenous malformations of the corpus callosum: Pooled analysis and systematic review of literature *Surg Neurol Int* 2016; 7(Suppl 9):S228-236. PMID: 27127713. [Full Text](#)

Department of Neurological Surgery, Henry Ford Hospital, 2799 W. Grand Blvd, Detroit, MI 48202, USA.

BACKGROUND: Arteriovenous malformations (AVMs) of the corpus callosum (CC) are rare entities. We performed a systematic review of the available literature to better define the natural history, patient characteristics, and treatment options for these lesions. **METHODS:** A MEDLINE, Google Scholar, and The Cochrane Library search were performed for studies published through June 2015. Data from all eligible studies were used to examine epidemiology, natural history, clinical features, treatment strategies, and outcomes of patients with CC-AVMs. A systematic review and pooled analysis of the literature were performed. **RESULTS:** Our search yielded 37 reports and 230 patients. Mean age at presentation was 26.8 years (+/-13.12 years). AVMs were most commonly located in the splenium (43%), followed by the body (31%), and then the genu (23%) of the CC. A Spetzler-Martin grade of III was the most common (37%). One hundred eighty-seven (81.3%) patients presented with hemorrhage, 91 (40%) underwent microsurgical excision, and 87 (38%) underwent endovascular embolization. Radiosurgery was performed on 57 (25%) patients. Complete obliteration of the AVM was achieved in 102 (48.1%) patients and approximately twice as often when microsurgery was performed alone or in combination with other treatment modalities (94% vs. 49%; $P < 0.001$). Mean modified Rankin Scale (mRS) at presentation was 1.54 and mean mRS at last follow-up was 1.31. This difference was not statistically significant ($P = 0.35$). **CONCLUSION:** We present an analysis of the pooled data in the form of a systematic review focusing on management of CC-AVMs. This review aims to provide a valuable tool to aid in decision making when dealing with this particular subtype of AVM.

Neurosurgery

Sidiropoulos C, Rammo R, Merker B, Mahajan A, LeWitt P, Kaminski P, Womble M, Zec A, Taylor D, Wall J, and Schwab JM. Intraoperative MRI for deep brain stimulation lead placement in Parkinson's disease: 1 year motor and neuropsychological outcomes *J Neurol* 2016; 263(6):1226-1231. PMID: 27126457. [Full Text](#)

Parkinson's Disease and Movement Disorders Program, Henry Ford Hospital, 6777 West Maple Road, West Bloomfield, MI, 48322, USA. csidiro1@hfhs.org.

Department of Neurosurgery, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.

Division of Neuropsychology, Henry Ford Health System, 1 Ford Place, Suite 1E, Detroit, MI, 48202, USA.

Department of Neurology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.

Parkinson's Disease and Movement Disorders Program, Henry Ford Hospital, 6777 West Maple Road, West Bloomfield, MI, 48322, USA.

William Beaumont Health System, 3601 W 13 Mile Rd, Royal Oak, MI, 48073, USA.

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Neurosurgery

Zhang Y, Zhang ZG, Chopp M, Meng Y, Zhang L, Mahmood A, and Xiong Y. Treatment of traumatic brain injury in rats with N-acetyl-seryl-aspartyl-lysyl-proline *J Neurosurg* 2016;1-14. PMID: 27203137. [Full Text](#)

Departments of 1 Neurosurgery and
Neurology, Henry Ford Hospital, Detroit; and
Department of Physics, Oakland University, Rochester, Michigan.

OBJECTIVE The authors' previous studies have suggested that thymosin beta 4 (Tbeta4), a major actin-sequestering protein, improves functional recovery after neural injury. N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) is an active peptide fragment of Tbeta4. Its effect as a treatment of traumatic brain injury (TBI) has not been investigated. Thus, this study was designed to determine whether AcSDKP treatment improves functional recovery in rats after TBI. **METHODS** Young adult male Wistar rats were randomly divided into the following groups: 1) sham group (no injury); 2) TBI + vehicle group (0.01 N acetic acid); and 3) TBI + AcSDKP (0.8 mg/kg/day). TBI was induced by controlled cortical impact over the left parietal cortex. AcSDKP or vehicle was administered subcutaneously starting 1 hour postinjury and continuously for 3 days using an osmotic minipump. Sensorimotor function and spatial learning were assessed using a modified Neurological Severity Score and Morris water maze tests, respectively. Some of the animals were euthanized 1 day after injury, and their brains were processed for measurement of fibrin accumulation and neuroinflammation signaling pathways. The remaining animals were euthanized 35 days after injury, and brain sections were processed for measurement of lesion volume, hippocampal cell loss, angiogenesis, neurogenesis, and dendritic spine remodeling. **RESULTS** Compared with vehicle treatment, AcSDKP treatment initiated 1 hour postinjury significantly improved sensorimotor functional recovery (Days 7-35, $p < 0.05$) and spatial learning (Days 33-35, $p < 0.05$), reduced cortical lesion volume, and hippocampal neuronal cell loss, reduced fibrin accumulation and activation of microglia/macrophages, enhanced angiogenesis and neurogenesis, and increased the number of dendritic spines in the injured brain ($p < 0.05$). AcSDKP treatment also significantly inhibited the transforming growth factor-beta1/nuclear factor-kappaB signaling pathway. **CONCLUSIONS** AcSDKP treatment initiated 1 hour postinjury provides neuroprotection and neurorestoration after TBI, indicating that this small tetrapeptide has promising therapeutic potential for treatment of TBI. Further investigation of the optimal dose and therapeutic window of AcSDKP treatment for TBI and the associated underlying mechanisms is therefore warranted.

Obstetrics, Gynecology and Women's Health Services

Miller-Matero LR, Chipungu K, Martinez S, Eshelman A, and Eisenstein D. How do I cope with pain? Let me count the ways: awareness of pain coping behaviors and relationships with depression and anxiety *Psychol Health Med* 2016;1-9. PMID: 27221277. [Article Request Form](#)

a Behavioral Health , Henry Ford Health System , Detroit , MI , USA.
b Obstetrics & Gynecology , Henry Ford Health System , Detroit , MI , USA.

Patients with chronic pain are often undertreated with medications alone and need alternative ways of coping. Identifying pain coping skills patients use may be beneficial; however, no research has investigated whether patients are aware of their coping skills. The purpose of this study was to determine whether patients are aware of their pain coping skills, whether certain patient characteristics were related to using coping strategies, and whether coping strategies were related to psychiatric symptoms. Chart reviews were conducted on seventy-eight chronic pain patients who completed a semi-structured psychological interview. Patients endorsed using more coping strategies on the measure compared to the verbal self-report. Identifying with certain patient demographics was related to higher use of some coping strategies. Symptoms of anxiety and depression were also related to the use of some coping strategies. Anxiety was negatively related to ignoring the pain and using self-talk coping statements and positively related to catastrophizing. Depression was negatively related to the use of distraction, ignoring the pain, and using self-talk coping statements. Depression and pain severity were both positively related to catastrophizing and prayer. Results suggest that clinicians may need to help patients become aware of adaptive coping strategies they already use and that the use of certain coping strategies is related to lower levels of depression and anxiety.

Obstetrics, Gynecology and Women's Health Services

Randall TC, Goodman A, Schmeler K, Durfee J, Pareja R, **Munkarah A**, Rulisa S, Ghebre R, Trimble EL, and Chuang L. Cancer and the world's poor: What's a gynecologic cancer specialist to do? *Gynecol Oncol* 2016;PMID: 27210817. [Full Text](#)

Women in low- and middle-income countries (LMICs) face a drastically increased burden of cervical cancer and the same burden of other gynecologic cancers as do women in high-income countries, yet there are few resources or specialists to meet their needs. 85% of deaths from cervical cancer occur in LMICs. As the population of these regions age, and as death from infectious diseases decrease, this burden will increase further without strong intervention. There are few cancer specialists in LMICs and training in gynecologic cancer care is rare. Gynecologic cancer specialists are uniquely positioned to meet this challenge as advocates, educators and experts. On behalf of the SGO International Committee, we call on our colleagues to meet this historic challenge.

Obstetrics, Gynecology and Women's Health Services

Wang W, Kryczek I, Dostal L, Lin H, Tan L, Zhao L, Lu F, Wei S, Maj T, Peng D, He G, Vatan L, Szeliga W, Kuick R, Kotarski J, Tarkowski R, Dou Y, **Rattan R**, **Munkarah A**, Liu JR, and Zou W. Effector T cells abrogate stroma-mediated chemoresistance in ovarian cancer *Cell* 2016; 165(5):1092-1105. PMID: 27133165. [Article Request Form](#)

Department of Obstetrics and Gynecology, University of Michigan School of Medicine, Ann Arbor, MI 48109, USA;
Department of Surgery, University of Michigan School of Medicine, Ann Arbor, MI 48109, USA.
Department of Surgery, University of Michigan School of Medicine, Ann Arbor, MI 48109, USA.
Department of Chemistry, University of Michigan, Ann Arbor, MI 48109, USA.
Department of Obstetrics and Gynecology, University of Michigan School of Medicine, Ann Arbor, MI 48109, USA.
Department of Biostatistics, University of Michigan School of Medicine, Ann Arbor, MI 48109, USA.
The First Department of Gynecologic Oncology and Gynecology, Medical University in Lublin, Lublin 20-081, Poland.
Department of Pathology, University of Michigan School of Medicine, Ann Arbor, MI 48109, USA.
Department of Women's Health Services, Henry Ford Health System, Detroit, MI 48202, USA.
Department of Obstetrics and Gynecology, University of Michigan School of Medicine, Ann Arbor, MI 48109, USA;
The University of Michigan Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI 48109, USA.
Electronic address: rliu@med.umich.edu.
Department of Surgery, University of Michigan School of Medicine, Ann Arbor, MI 48109, USA; The University of Michigan Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI 48109, USA; Graduate Programs in Immunology and Tumor Biology, University of Michigan, Ann Arbor, MI 48109, USA. Electronic address: wzou@med.umich.edu.

Effector T cells and fibroblasts are major components in the tumor microenvironment. The means through which these cellular interactions affect chemoresistance is unclear. Here, we show that fibroblasts diminish nuclear accumulation of platinum in ovarian cancer cells, resulting in resistance to platinum-based chemotherapy. We demonstrate that glutathione and cysteine released by fibroblasts contribute to this resistance. CD8(+) T cells abolish the resistance by altering glutathione and cysteine metabolism in fibroblasts. CD8(+) T-cell-derived interferon (IFN)γ controls fibroblast glutathione and cysteine through upregulation of gamma-glutamyltransferases and transcriptional repression of system xc(-) cystine and glutamate antiporter via the JAK/STAT1 pathway. The presence of stromal fibroblasts and CD8(+) T cells is negatively and positively associated with ovarian cancer patient survival, respectively. Thus, our work uncovers a mode of action for effector T cells: they abrogate stromal-mediated chemoresistance. Capitalizing upon the interplay between chemotherapy and immunotherapy holds high potential for cancer treatment.

Obstetrics, Gynecology and Women's Health Services

Xu Y, Burmeister C, Hanna RK, Munkarah A, and Elshaikh MA. Predictors of survival after recurrence in women with early-stage endometrial carcinoma *Int J Gynecol Cancer* 2016;PMID: 27206283. [Full Text](#)

Department of *Radiation Oncology and daggerPublic Health Science, double daggerDivision of Gynecologic Oncology, Department of Women's Health Services, Henry Ford Hospital, Detroit, MI.

OBJECTIVE: Factors predictive of survival after recurrent early-stage endometrial carcinoma have not been thoroughly investigated. The purpose of this study was to explore factors that impact disease-specific survival (DSS) and overall survival (OS) after recurrence in women with early-stage endometrial carcinoma. MATERIALS AND METHODS: After institutional review board approval, we identified 104 women with 2009 International Federation of Gynecology and Obstetrics stage I to II uterine endometrioid carcinoma who developed disease recurrence between January 1990 and December 2014. The Kaplan-Meier approach and Cox regression analysis were used to assess

DSS and OS after recurrence and to determine factors influencing these survival end points. RESULTS: Median age of the study cohort was 65 years with a median follow-up time of 42.8 months after hysterectomy. Median time to recurrence was 15.8 months. Recurrences were diagnosed in 60 patients (57.7%) who were originally managed with observation after hysterectomy and in 44 patients (42.3%) who were initially managed with adjuvant radiation treatment. Fifty-six patients (54%) had pelvic recurrence (vaginal and/or pelvic), whereas 48 (46%) had extrapelvic recurrence. Five-year DSS and OS for the entire study population was 44% and 37%, respectively. Five-year DSS and OS were longer for patients with pelvic recurrence compared with patients with extrapelvic recurrence (66% vs 18% and 55% vs 17%, $P < 0.0001$). Five-year DSS was also longer for radiation-naïve patients than for radiation-treated patients (51% vs 34%, $P = 0.023$). On multivariate analysis of DSS and OS, pelvic recurrence ($P < 0.001$) was the only significant predictor of longer DSS and OS. CONCLUSIONS: In women with recurrent early-stage endometrioid carcinoma, our study suggests that site of recurrence (pelvic vs extra pelvic) is the only predictor of survival. In addition, we found that radiation naïveté and pelvic recurrence correlated with longer DSS and OS.

Ophthalmology and Eye Care Services

Cheung AY, David JA, and **Ober MD**. Spontaneous bilateral hemorrhagic choroidal detachments associated with malignant hypertension *Retin Cases Brief Rep* 2016; PMID: 27177073. [Full Text](#)

*Department of Ophthalmology, Beaumont Health System, Oakland University William Beaumont School of Medicine, Royal Oak, Michigan; daggerOakland University William Beaumont School of Medicine, Rochester, Michigan; double daggerRetina Consultants of Michigan, Southfield, Michigan; and section signDepartment of Ophthalmology, Henry Ford Hospital, Detroit, Michigan.

PURPOSE: To report the details of a patient with bilateral spontaneous suprachoroidal hemorrhages related to malignant hypertension. METHODS: Observational case report with review of relevant literature. RESULTS: A 62-year-old man with a history of hypertension was referred secondary to bilateral temporal scotomas and persistent headache for 3 days. Symptoms began during an inpatient admission for malignant hypertension. Examination revealed bilateral 360 degrees hemorrhagic choroidal detachments without retinal hemorrhage or detachment. Choroidal hemorrhages underwent prompt resolution with blood pressure control. CONCLUSION: Spontaneous suprachoroidal hemorrhage is a rare event and should prompt a focused systemic workup including the evaluation of blood pressure.

Ophthalmology and Eye Care Services

Tse SM, Farley ND, Tomasko KR, and Amin SR. Intraoperative LASIK Complications *Int Ophthalmol Clin* 2016; 56(2):47-57. PMID: 26938337. [Full Text](#)

Orthopaedics

Feist C, Holden P, and **Fitzgerald J**. Novel compound heterozygous mutations in inositol polyphosphate phosphatase-like 1 in a family with severe opsismodysplasia *Clin Dysmorphol* 2016; PMID: 27233067. [Full Text](#)

Departments of aPerinatology bOrthopaedics and Rehabilitation, Oregon Health and Science University, Portland, Oregon cDepartment of Orthopaedic Surgery, Bone and Joint Center, Henry Ford Hospital System, Detroit, Michigan, USA.

This study aimed to identify the genetic basis of a severe skeletal lethal dysplasia. The main clinical features of two affected fetuses included short limbs with flared metaphyses, bowed radii, femora and tibiae, irregular ossification of hands and feet, and marked platyspondyly. Affected and nonaffected family members were subjected to whole-exome sequencing, followed by immunoblot analysis on amniocytes isolated from one of the affected individuals. Unique compound heterozygous variants in the inositol polyphosphate phosphatase-like 1 (INPPL1) gene encoding the SHIP2 protein were identified in both affected individuals. One variant was inherited from each unaffected parent. Both allelic variants, c.(2327-1G>C);(1150_1151delGA), are predicted to result in premature stop codons leading to nonsense-mediated mRNA decay of the mutant alleles and no production of SHIP2. The absence of SHIP2 was confirmed by immunoblot analysis of proband amniocytes. This skeletal disorder is caused by the complete absence of the SHIP2 protein. INPPL1 mutations have been reported in opsismodysplasia, an autosomal recessive skeletal dysplasias with significant delayed bone formation. Our finding highlights the critical role that INPPL1/SHIP2 plays in skeletal development.

Orthopaedics

Fitzgerald J. New insights into articular cartilage regeneration *Semin Cell Dev Biol* 2016;PMID: 27130635.

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Bone and Joint Center, Department of Orthopedic Surgery, Henry Ford Hospital System, Detroit, MI 48202, USA.
Electronic address: jfitzge2@hfhs.org.

Adult articular cartilage has a poor capacity to undergo intrinsic repair. Current strategies for the repair of large cartilage defects are generally unsatisfactory because the restored cartilage does not have the same resistance to biomechanical loading as authentic articular cartilage and degrades over time. Recently, a new research direction, focused on intrinsic cartilage regeneration rather than fibrous repair by external means, has emerged. This review explores the new developments in this rapidly moving field as they relate to regenerative articular cartilage healing.

Orthopaedics

Makhni EC, Saltzman BM, Meyer MA, **Moutzouros V**, Cole BJ, Romeo AA, and Verma NN. Outcomes after shoulder and elbow injury in baseball players: are we reporting what matters? *Am J Sports Med* 2016;PMID: 27159299.

[Full Text](#)

Division of Sports Medicine, Rush University Medical Center, Chicago, Illinois, USA ericmakhnimd@gmail.com.
Division of Sports Medicine, Rush University Medical Center, Chicago, Illinois, USA.
Department of Orthopaedic Surgery, Henry Ford Hospital, Detroit, Michigan, USA.

BACKGROUND: Return to play, as well as time to return to play, are the most important metrics considered by athletes when attempting to make treatment decisions after injury. However, the consistency of reporting of these metrics in the scientific literature is unknown. **PURPOSE:** To investigate patterns of outcomes reporting in the medical literature of shoulder and elbow injuries in active baseball players. **STUDY DESIGN:** Systematic review. **METHODS:** A systematic review of literature published within the past 10 years was performed to identify all recent clinical studies focusing on shoulder and elbow injuries in baseball players across all levels. Review articles, case reports, and laboratory/biomechanical studies were all excluded. **RESULTS:** A total of 49 studies were included for review. The majority of studies were either level 3 or level 4 evidence (96%). In total, 71% of studies reported on rates of return to preinjury level of play, whereas 31% of studies reported on time to return to preinjury level of play. Only 47% of studies reported on both rate and time of return to preinjury level of play. A minority of studies (8%) reported patient satisfaction rates. Finally, 27 different subjective and patient-reported outcomes were reported, and none of these appeared in more than 14% of all studies. **CONCLUSION:** Time to return to preinjury level of play is inadequately reported in studies of shoulder and elbow injury in baseball players. Similarly, satisfaction rates and scores are underreported. Finally, the significant variability of subjective and patient-reported outcomes utilized may undermine the ability of clinicians to accurately compare results from different studies.

Otolaryngology – Head and Neck Surgery

Craig JR, Petrov D, Khalili S, Brooks SG, Lee JY, Adappa ND, and Palmer JN. The nasofrontal beak: A consistent landmark for superior septectomy during Draf III drill out *Am J Rhinol Allergy* 2016; 30(3):230-234. PMID: 27216356.

[Article Request Form](#)

Department of Otolaryngology, Henry Ford Hospital, Detroit, Michigan, USA.

INTRODUCTION: Cerebrospinal fluid (CSF) leak occurs in 1-11% of endoscopic Draf III, or endoscopic modified Lothrop, procedures. CSF leak can occur during surgery during a superior nasal septectomy. This study investigated whether the posterior edge of the nasofrontal beak (NFB) at the level of the internal frontal ostium is a safe landmark to use to avoid skull base injury when beginning the superior septectomy. **METHODS:** Preoperative computed tomography maxillofacial scans were reviewed from 100 patients from the University of Pennsylvania sinus surgery data base. The narrowest anteroposterior distance between the posterior edge of the NFB and the anterior aspect of the olfactory fossa (OF) at the level of the internal frontal ostium was measured in each patient. Measurements were taken in the midline and to the left and right of midline. Six fresh cadaver heads were also dissected to evaluate these relationships. **RESULTS:** On computed tomography analysis, the NFB was anterior to the OF on the left and right of the midline in 100% of the patients, with mean distances of 6.04 and 6.41 mm, respectively. The NFB was anterior to the OF in the midline in 98% of patients, with a mean distance of 9.02 mm. In all six cadavers, the posterior edge of the NFB was anterior to the OF in the midline and to the left and right of midline at the level of the internal frontal ostia. **CONCLUSIONS:** During Draf III, the posterior edge of the NFB was a reliable landmark for avoiding iatrogenic CSF leak during the superior septectomy.

Otolaryngology – Head and Neck Surgery

Noyek S, **Yaremchuk K**, and Rotenberg B. Does melatonin have a meaningful role as a sleep aid for jet lag recovery? *Laryngoscope* 2016; PMID: 27238501. [Full Text](#)

Department of Otolaryngology-Head & Neck Surgery, University of Western Ontario, London, Ontario, Canada.
Department of Otolaryngology-Head & Neck Surgery, Henry Ford Health System, Detroit, Michigan, U.S.A.

Pathology

Gomez-Gelvez JC, Salama ME, Perkins SL, Leavitt M, and **Inamdar KV**. Prognostic impact of tumor microenvironment in diffuse large b-cell lymphoma uniformly treated with r-chop chemotherapy *Am J Clin Pathol* 2016; 145(4):514-523. PMID: 27124945. [Full Text](#)

From the Department of Pathology, Henry Ford Hospital, Detroit, MI Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY.

Department of Pathology, University of Utah and ARUP Institute for Experimental Pathology, Salt Lake City, UT.
Department of Pathology, Intermountain Health System, Salt Lake City, UT.

From the Department of Pathology, Henry Ford Hospital, Detroit, MI kinamda1@hfhs.org.

OBJECTIVES: We evaluated the prognostic impact of cell-of-origin classification as well as intratumoral regulatory T cells (Tregs), macrophages, and microvessel density (MVD) on 115 patients (74 in the training set and 41 in the validation set) diagnosed with de novo diffuse large B-cell lymphoma (DLBCL) and uniformly treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy. **METHODS:** The prognostic impact of Tregs, macrophages, and MVD was evaluated using FOXP3, CD68, and CD34 immunohistochemical stains, respectively. In addition, we designed a scoring system where 1 point was awarded per each adverse prognostic factor, including non-germinal center B-cell-like subtype, FOXP3 17% or more, CD68 less than 2%, and MVD less than 800 vessels/mm². **RESULTS:** Although only MVD was statistically significant on multivariate analysis, the scoring system significantly segregated patients into low- and high-risk groups. Patients having two or more adverse prognostic factors (high-risk group) demonstrated significantly worse event-free and progression-free survivals in the training set and event-free survival in the validation set. **CONCLUSIONS:** The concomitant evaluation of cell of origin along with tumor microenvironment components identifies patients with DLBCL treated with R-CHOP chemotherapy portraying a worse prognosis.

Pathology

Parekh R, Kazimi M, Skorupski S, Fagoaga O, Jafri S, and Segovia MC. Intestine transplantation across a positive crossmatch with preformed donor-specific antibodies *Transplant Proc* 2016; 48(2):489-491. PMID: 27109984.

[Full Text](#)

Department of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan.

Department of Transplant Surgery, Henry Ford Hospital, Detroit, Michigan.

Department of Pathology, Henry Ford Hospital, Detroit, Michigan.

Department of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan. Electronic address: msegovi3@hfhs.org.

BACKGROUND: We describe our experience using a modified protocol for immunosuppression for intestine transplantation across a positive crossmatch. Patients who underwent transplantation in 2013 were evaluated over a 12-month period for rejection and infectious events with comparison to procedure-matched controls on our standard protocol of immunosuppression. **PATIENTS AND METHODS:** We used a modified protocol for intestine and multivisceral transplantation for patients with a positive flow crossmatch. In addition to our standard protocol, patients with positive crossmatch were given rituximab and intravenous immunoglobulin (IVIg) preoperatively. DSA was sent for clinical evaluation at monthly intervals. Patients were screened for rejection by endoscopic evaluation. **RESULTS:** Four patients underwent transplantation within a single year across a positive crossmatch. Two received isolated intestine transplants and 2 had multivisceral transplantation (MVT). During the 12-month follow-up, 1 patients had an episode of severe acute cellular rejection, which was managed with increased immunosuppression. None of the patients had episodes of cytomegalovirus infection. One patient developed major infection and 3 patients developed minor bacterial infections. Among procedure-matched controls with negative final crossmatch on standard management (no preoperative rituximab or IVIg), 2 developed mild acute cellular rejection and 2 developed minor infections. One developed cytomegalovirus viremia with invasion to the colonic mucosa. **CONCLUSIONS:** We report our protocol for immunosuppression for IT and MVT across a positive crossmatch. This allowed transplantation despite the presence of a positive crossmatch, with low rejection rates but potentially increased risk for major infections compared to the negative crossmatch controls on our standard protocol.

Pathology

Rao B, Jafri SM, Kazimi M, Mullins K, Raoufi M, and Segovia MC. A case report of acute cellular rejection following intestinal transplantation managed with adalimumab *Transplant Proc* 2016; 48(2):536-538. PMID: 27109995. [Full Text](#)

Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan.
Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan.
Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, Michigan.
Department of Pathology, Henry Ford Hospital, Detroit, Michigan.
Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan. Electronic address: msegovi3@hfhs.org.

There is a higher incidence of acute cellular rejection (ACR) in small bowel transplantation (SBT) compared with transplantation of other solid organs. Although there are reports on the use of infliximab to successfully treat ACR refractory to other treatments, there are no reports, to our knowledge, regarding the use of adalimumab. We present a case of a female patient with a history of Crohn's disease who underwent an isolated SBT and developed an episode of severe ACR. She was initially treated with methylprednisolone, thymoglobulin, basiliximab, and a dosage adjustment of tacrolimus. Results of repeat endoscopies and biopsies revealed no significant improvement. The patient initiated treatment with adalimumab every 2 weeks for a total of 6 months, in addition to maintenance treatment with prednisone and tacrolimus. Subsequent evaluations showed gradual improvement to normal mucosa and villi without ulceration. A regimen that incorporates adalimumab can thus be used to treat ACR after intestinal transplantation. Larger multicenter studies are needed to show the full efficacy of this therapeutic regimen.

Pathology

Rao B, Segovia MC, Kazimi M, Parekh R, Raoufi M, and Jafri SM. Use of everolimus after multivisceral transplantation: A report of two cases *Transplant Proc* 2016; 48(2):485-488. PMID: 27109983. [Full Text](#)

Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan.
Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan. Electronic address: msegovi3@hfhs.org.
Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, Michigan.
Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan.
Department of Pathology, Henry Ford Hospital, Detroit, Michigan.

Inhibitors of mechanistic target of rapamycin are used in solid organ transplant procedures to avoid calcineurin inhibitor complications, including nephrotoxicity and malignancy. We present 2 cases of multivisceral transplantation for neuroendocrine tumor (NET) for which everolimus was implemented for its potential to prevent NET recurrence as well as preserve renal function. The first case was complicated by NET recurrence in the liver before initiation of everolimus. After initiation of everolimus, the patient developed a ventral hernia and elevated aminotransferase levels with nonspecific biopsy findings. The second case was complicated by cytomegalovirus infection with elevated everolimus trough levels as well as acute cellular rejection. Everolimus was reinitiated in both cases in addition to decreasing the dosage of tacrolimus, and there were no further complications. Everolimus was beneficial in stabilizing renal function in both patients and has the theoretical potential to prevent recurrence of NET.

Pathology

Rayson D, Lupichuk S, Potvin K, Dent S, Shenkier T, Dhesy-Thind S, Ellard SL, Prady C, Salim M, Farmer P, **Allo G**, Tsao MS, Allan A, Ludkovski O, Bonomi M, Tu D, Hagerman L, Goodwin R, Eisenhauer E, and Bradbury P. Canadian Cancer Trials Group IND197: a phase II study of foretinib in patients with estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2-negative recurrent or metastatic breast cancer *Breast Cancer Res Treat* 2016; 157(1):109-116. PMID: 27116183. [Full Text](#)

Division of Medical Oncology, Queen Elizabeth II Health Sciences Centre, Room 457A, 1276 South Park Street, Bethune Building, Halifax, NS, B3H 2Y9, Canada. daniel.rayson@nshealth.ca.
Tom Baker Cancer Centre, Calgary, AB, Canada.
London Regional Cancer Program, London, ON, UK.
Ottawa Hospital Research Institute, Ottawa, ON, Canada.
BCCA-Vancouver Cancer Centre, Vancouver, BC, Canada.
Juravinski Cancer Centre at Hamilton Health Sciences, Hamilton, ON, Canada.
BCCA-Cancer Centre for the Southern Interior, Kelowna, BC, Canada.
Hopital Charles LeMoine, Greenfield Park, QC, Canada.

Allan Blair Cancer Centre, Regina, SK, Canada.
Queen's University, Kingston General Hospital, Kingston, ON, Canada.
Henry Ford Health System, Detroit, MI, USA.
University Health Network-OCI/Princess Margaret Hospital, Toronto, ON, Canada.
Canadian Cancer Trials Group (CCTG), Queen's University, Kingston, CA, Canada.

In murine models, overexpression of the MET receptor transgene induces tumors with human basal gene expression characteristics supporting MET inhibition as a treatment strategy for triple-negative breast cancer (TNBC). Foretinib is an oral multi-kinase inhibitor of MET, RON, AXL, TIE-2, and VEGF receptors with anti-tumor activity in advanced HCC and papillary renal cell cancer. Patients with centrally reviewed primary TNBC and 0-1 prior regimens for metastatic disease received daily foretinib 60 mg po in a 2-stage single-arm trial. Primary endpoints were objective response and early progression rates per RECIST 1.1. In stage 2, correlative studies of MET, PTEN, EGFR, and p53 on archival and fresh tumor specimens were performed along with enumeration of CTCs. 45 patients were enrolled with 37 patients having response evaluable and centrally confirmed primary TNBC (cTNBC). There were 2 partial responses (ITT 4.7 % response evaluable cTNBC 5.4 %) with a median duration of 4.4 months (range 3.7-5 m) and 15 patients had stable disease (ITT 33 %, response evaluable cTNBC 40.5 %) with a median duration of 5.4 months (range 2.3-9.7 m). The most common toxicities (all grades/grade 3) were nausea (64/4 %), fatigue (60/4 %), hypertension (58/49 %), and diarrhea (40/7 %). Six serious adverse events were considered possibly related to foretinib and 4 patients went off study due to adverse events. There was no correlation between MET positivity and response nor between response and PTEN, EGFR, p53, or MET expression in CTCs. Although CCTG IND 197 did not meet its primary endpoint, the observation of a clinical benefit rate of 46 % in this cTNBC population suggests that foretinib may have clinical activity as a single, non-cytotoxic agent in TNBC (ClinicalTrials.gov number, NCT01147484).

Pathology

Suleyman G, Perri M, Vager D, Samuel L, Zervos MJ, Alangaden G, and Tibbetts RJ. Characterization of *Salmonella* Isangi possessing a CTX-M15 ESBL associated with an outbreak in a US Hospital *Diagn Microbiol Infect Dis* 2016; PMID: 27130476. [Full Text](#)

Department of Infectious Disease, Henry Ford Health System, Detroit, MI 48202.
Infectious Disease Research Laboratory, Henry Ford Health System, Detroit, MI 48202.
Department of Pathology, Henry Ford Health System, Detroit, MI 48202.
Department of Pathology, Henry Ford Health System, Detroit, MI 48202. Electronic address: rtibbet1@hfhs.org.

Over an approximately 50-day period in 2015, an outbreak of CTX-M-15 extended spectrum beta-lactamase-(ESBL)-possessing *Salmonella* Isangi occurred among 19 adult surgical patients and one healthcare worker (HCW) at a large urban tertiary care hospital in the United States. A total of 45 *S. Isangi* isolates were isolated from stool (35), blood (4), urine (3), respiratory (2), and wound (1) cultures. Phenotypically, all but three isolates demonstrated resistance to ampicillin, ampicillin/sulbactam, ceftriaxone, and cefepime, and one isolate was resistant to ertapenem. Genotypically, a single CTX-M-15 ESBL was identified in all but three isolates by real-time PCR. Interestingly, two of the CTX-M-15 negative, susceptible isolates were isolated from a single patient who initially had a CTX-M positive, resistant strain. Isolates were clonally related, including both resistant and susceptible strains, as confirmed by pulse field gel electrophoresis (PFGE). This is the first case of a novel *Salmonella* outbreak at this hospital, and we believe it to be the first case of an *S. Isangi* serotype outbreak in the United States.

Pathology

Suleyman G, Tibbetts R, Perri MB, Vager D, Xin Y, Reyes K, Samuel L, Chami E, Starr P, Pietsch J, Zervos MJ, and Alangaden G. Nosocomial Outbreak of a Novel Extended-Spectrum beta-Lactamase *Salmonella enterica* Serotype Isangi Among Surgical Patients *Infect Control Hosp Epidemiol* 2016:1-8. PMID: 27108715.

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1Department of Infectious Disease, Henry Ford Hospital, Detroit, Michigan.
2Department of Pathology, Henry Ford Hospital, Detroit, Michigan.
3Research Laboratory, Henry Ford Hospital, Detroit, Michigan.
4Public Health Sciences, Henry Ford Hospital, Detroit, Michigan.
5Infection Control, Henry Ford Hospital, Detroit, Michigan.

OBJECTIVE Nosocomial outbreaks caused by *Salmonella* are rare. We describe the investigation and control of a cluster of novel extended-spectrum beta-lactamase (ESBL) *Salmonella enterica* serotype Isangi in a hospital in southeastern Michigan. **METHODS** An epidemiologic investigation, including case-control study, assessment of

infection control practices and environmental cultures, was performed to identify modes of transmission. Healthcare workers (HCWs) exposed to case patients were screened. Strain relatedness was determined using pulsed-field gel electrophoresis (PFGE); ESBL confirmation was conducted using real-time PCR. Control measures were implemented to prevent further transmission. RESULTS Between September 2 and October 22, 2015, 19 surgical patients, including 10 organ transplant recipients and 1 HCW, had positive *S. Isangi* cultures. Of these case patients and HCW, 13 had gastroenteritis, 2 had bacteremia, 1 had surgical-site infection, and 4 were asymptomatic. Pulsed-field gel electrophoresis (PFGE) showed 89.5% similarity among the isolates in these cases. Isolates with resistant-phenotypes possessed plasmid-mediated CTX-M15 ESBL. A total of 19 case patients were compared with 57 control participants. Case patients had significantly higher odds of exposure to an intraoperative transesophageal (TEE) probe (adjusted odds ratio 9.0; 95% confidence interval, 1.12-72.60; P=.02). Possible cross-transmission occurred in the HCW and 2 patients. Cultures of TEE probes and the environment were negative. The outbreak ended after removal of TEE probes, modification of reprocessing procedures, implementation of strict infection control practices, and enhanced environmental cleaning. CONCLUSIONS We report the first nosocomial ESBL *S. Isangi* outbreak in the United States. Multiple control measures were necessary to interrupt transmission of this gastrointestinal pathogen. Exposure to possibly contaminated TEE probes was associated with transmission. Periodic monitoring of reprocessing procedures of TEE probes may be required to ensure optimal disinfection. *Infect Control Hosp Epidemiol* 2016;1-8.

Pathology

Williamson SR. Renal oncocytoma with perinephric fat invasion *Int J Surg Pathol* 2016; PMID: 27170678. [Full Text](#)

Henry Ford Health System, Detroit, MI, USA Wayne State University School of Medicine, Detroit, MI, USA
seanwill@temple.edu.

Pharmacy

Veve MP, Wagner JL, Kenney RM, Grunwald JL, and Davis SL. Comparison of fosfomycin to ertapenem for outpatient or step-down therapy of extended-spectrum beta-lactamase urinary tract infections *Int J Antimicrob Agents* 2016; PMID: 27234673. [Full Text](#)

Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI, USA; Henry Ford Hospital, Detroit, MI, USA.
Henry Ford Hospital, Detroit, MI, USA.

Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI, USA; Henry Ford Hospital, Detroit, MI, USA. Electronic address: sldavis@wayne.edu.

Extended-spectrum beta-lactamase (ESBL) enzymes cause resistance to common beta-lactam antibiotics and are associated with poor outcomes. Management of ESBL urinary tract infections (UTIs) is challenging given the limited treatment options available outside the hospital setting. In this study, the primary endpoint of UTI-related 30-day hospital re-admission or emergency department/clinic revisit rates was compared for fosfomycin and ertapenem outpatient ESBL UTI treatments. A retrospective cohort study was performed on patients with ESBL UTIs treated with outpatient fosfomycin or ertapenem from January 2010 to February 2015. Inclusion criteria were age ≥ 18 years, outpatient treatment with fosfomycin or ertapenem for symptomatic ESBL UTI, and positive urine cultures with microbiologically proven ESBL-producing bacteria. A non-inferiority margin of 0.15 was selected to detect a difference in the primary endpoint. Patient and infection characteristics were compared. A sensitivity analysis with propensity score matching was performed. In total, 178 patients were included (89 fosfomycin-treated and 89 ertapenem-treated). Ertapenem-treated patients received longer outpatient antibiotic treatment (10 days vs. 6 days; $P < 0.001$). ESBL isolates identified were 149 *Escherichia coli* (83.7%), 26 *Klebsiella* spp. (14.6%) and 3 other (1.7%). Common dosage regimens were oral dose of 3 g fosfomycin every 72 h (62%), oral dose of 3 g fosfomycin every 48 h (23%) and intravenous dose of 1 g ertapenem daily (76%). The thirty-day re-admission/revisit rates for fosfomycin and ertapenem were 14.6% vs. 13.5% (1.1% difference; 97.5% CI, -0.11 to 0.13). Fosfomycin was non-inferior to ertapenem for treating outpatient ESBL UTIs and should be considered as appropriate step-down therapy for these infections.

Psychiatry

Paulson D, Shah M, Miller-Matero LR, Eshelman A, and Abouljoud M. Cognition predicts quality of life among patients with end-stage liver disease *Psychosomatics* 2016; PMID: 27184728. [Full Text](#)

Department of Psychology, University of Central Florida, Orlando, FL; Consultation/Liaison Psychiatry, Henry Ford Health System, Detroit, MI.

Department of Psychology, University of Central Florida, Orlando, FL. Electronic address: mshah@knights.ucf.edu.
Consultation/Liaison Psychiatry, Henry Ford Health System, Detroit, MI.
Transplant Institute, Henry Ford Health System, Detroit, MI.

BACKGROUND: Impaired cognitive functioning and poor quality of life (QoL) are both common among patients with end-stage liver disease; however, it is unclear how these are related. **OBJECTIVE:** This study examines how specific cognitive domains predict QoL among liver transplant candidates by replicating Stewart and colleagues' (2010) 3-factor model of cognitive functioning, and determining how variability in these cognitive domains predicts mental health and physical QoL. **METHODS:** The sample included 246 patients with end-stage liver disease who were candidates for liver transplant at a large, Midwestern health care center. Measures, including the Repeatable Battery for the Assessment of Neuropsychological Status, Trail Making Test, Shipley Institute of Living Scale, Short-Form Health Survey-36 Version 2, and Hospital Anxiety and Depression Scale, comprised latent variables representing global intellectual functioning, psychomotor speed, and learning and memory functioning. **RESULTS:** Confirmatory factor analysis results indicate that the 3-factor solution model comprised of global intellectual functioning, psychomotor speed, and learning and memory functioning fit the data well. Addition of physical and mental health QoL latent factors resulted in a structural model also with good fit. Results related physical QoL to global intellectual functioning, and mental health QoL to global intellectual functioning and psychomotor functioning. **CONCLUSIONS:** Findings elucidate a relationship between cognition and QoL and support the use of routine neuropsychological screening with end-stage liver disease patients, specifically examining the cognitive domains of global intellectual, psychomotor, and learning and memory functioning. Subsequently, screening results may inform implementation of targeted interventions to improve QoL.

Public Health Sciences

Affan M, Schultz L, Cerghet M, and Elias S. Clinical and radiological presentation of neurosarcoidosis: Single center cohort study of 107 cases (p6.114) *Neurology* 2016; 86(16 Supplement) PMID: Not assigned. Abstract

Objective: To describe clinical, radiologic manifestations and treatment outcomes in 107 patients with neurosarcoidosis. **Background:** Neurosarcoidosis (NS) is reported in less than 5[percent] of patients with systemic sarcoidosis while isolated NS without systemic involvement represents 17[percent] of NS. A definitive diagnosis requires histologic confirmation, which rarely is obtained in NS. Our current knowledge for diagnosis and treatment relies on case reports. **Methods:** The study setting was a large, integrated health care system serving southeastern Michigan. 107 patients seen from 1995-2015 were found to meet the criteria for definitive, probable or possible NS (Zajicek, 1999). Neurological symptoms, sociodemographic, laboratory, radiographic and treatment data were collected. Descriptive statistics and chi-square tests were conducted using SAS version 9.4. **Results:** Of 107 patients, 58[percent] were male and 74[percent] African American. Average age of presentation was 49.1 year. Brain was the most common site involved (50[percent]), followed by cranial nerves (39[percent]), spine (29[percent]). Majority (81[percent]) had multisystem sarcoidosis with lung most commonly involved (56[percent]). For those with complete workup, blood ACE was elevated in half of patients and only a third had elevated CSF ACE (29[percent]). Significantly higher rates of elevated blood ACE were seen in patients with multisystem involvement ($p=0.005$). Abnormal laboratory tests seen frequently were elevated CSF WBC (65[percent]), elevated CSF protein (53[percent]) and elevated serum C-reactive protein (75[percent]). Most common clinical presentations were headache (20[percent]), optic neuritis (13[percent]), myelitis (13[percent]) and Bell's palsy (8[percent]). Prednisone was used as initial treatment (93[percent]) while methotrexate was the most common used long term immunosuppressant (35[percent]). **Conclusion:** We present the largest described case series of NS. Clinical presentation was diverse with multi-system involvement in most cases. We found that certain laboratory tests may be useful tools for diagnosis. Further epidemiological analysis is needed to develop prediction models and better screening programs for early detection. **Disclosure:** Dr. Affan has nothing to disclose. Dr. Schultz has nothing to disclose. Dr. Cerghet has nothing to disclose. Dr. Elias has nothing to disclose.

Public Health Sciences

Goyal N, Taylor AR, and Rivers EP. Relationship between central and peripheral venous oxygen saturation and lactate levels: A prospective study *J Emerg Med* 2016; PMID: 27210904. [Full Text](#)

Department of Emergency Medicine, Henry Ford Health System, Detroit, Michigan; Department of Internal Medicine, Henry Ford Health System, Detroit, Michigan.
Department of Public Health Science, Division of Biostatistics, Henry Ford Health System, Detroit, Michigan.
Department of Emergency Medicine, Henry Ford Health System, Detroit, Michigan; Department of Surgery, Henry Ford Health System, Detroit, Michigan.

BACKGROUND: Optimization of tissue oxygen delivery to meet consumption demands is important in the resuscitation of critically ill patients. Central venous oxygen saturation (ScvO₂) and lactate levels are often used to guide resuscitation; however, invasive monitoring is required for the former. Clinicians searching for less invasive alternatives may consider using peripheral venous oxygen saturation (SpvO₂) and lactate levels as a substitute. **OBJECTIVES:** To determine the relationship between SpvO₂ and ScvO₂ and peripheral and central lactate levels. **METHODS:** All patients with a central venous catheter in an academic emergency department and intensive care unit were eligible for the study. Blood was obtained simultaneously from a central and peripheral vein and measured for oxygen saturation and lactate levels. Results were analyzed using intraclass correlation coefficient (ICC), Bland-Altman plots, and receiver operating characteristic curves. **RESULTS:** Seventy-nine paired blood samples were analyzed. SpvO₂ and ScvO₂ have moderate agreement: ICC = 0.53 (95% confidence interval [CI] 0.35-0.67). A Bland-Altman plot revealed substantial bias (-4.47; limits of agreement -38.6, 29.6). SpvO₂ \geq 85% was 90% specific for ScvO₂ \geq 70%, and SpvO₂ of \leq 55% had a 94% sensitivity for ScvO₂ $<$ 70%. Central and peripheral venous lactate levels showed almost perfect agreement: ICC = 0.92 (95% CI 0.87-0.95), bias of 0.46 (limits of agreement -1.78-2.70). **CONCLUSION:** SpvO₂ and ScvO₂ have moderate agreement. There was excellent agreement between peripheral and central lactate levels, making them interchangeable. The clinical implications of these substitutions in real-time patient management require further study.

Public Health Sciences

Greenlee H, Neugut AI, Falci L, Hillyer GC, Buono D, Mandelblatt JS, Roh JM, Ergas IJ, Kwan ML, Lee M, Tsai WY, Shi Z, **Lamerato L**, Kushi LH, and Hershman DL. Association between complementary and alternative medicine use and breast cancer chemotherapy initiation: The breast cancer quality of care (bqual) study *JAMA Oncol* 2016;PMID: 27243607. [Full Text](#)

Mailman School of Public Health, Columbia University, New York, New York²Herbert Irving Comprehensive Cancer Center, Columbia University, New York, New York.

Mailman School of Public Health, Columbia University, New York, New York²Herbert Irving Comprehensive Cancer Center, Columbia University, New York, New York³College of Physicians and Surgeons, Columbia University, New York, New York.

Mailman School of Public Health, Columbia University, New York, New York.

Lombardi Comprehensive Cancer Center, Department of Oncology, Georgetown University Medical Center, Washington, DC.

Division of Research, Kaiser Permanente Northern California, Oakland.

Department of Epidemiology and Biostatistics, University of California-San Francisco, San Francisco.

Henry Ford Health System, Detroit, Michigan.

Importance: Not all women initiate clinically indicated breast cancer adjuvant treatment. It is important for clinicians to identify women at risk for noninitiation. **Objective:** To determine whether complementary and alternative medicine (CAM) use is associated with decreased breast cancer chemotherapy initiation. **Design, Setting, and Participants:** In this multisite prospective cohort study (the Breast Cancer Quality of Care [BQUAL] study) designed to examine predictors of breast cancer treatment initiation and adherence, 685 women younger than 70 years with nonmetastatic invasive breast cancer were recruited from Columbia University Medical Center, Kaiser Permanente Northern California, and Henry Ford Health System and enrolled between May 2006 and July 31, 2010. Overall, 306 patients (45%) were clinically indicated to receive chemotherapy per National Comprehensive Cancer Network guidelines. Participants were followed for up to 12 months. **Exposures:** Baseline interviews assessed current use of 5 CAM modalities (vitamins and/or minerals, herbs and/or botanicals, other natural products, mind-body self-practice, mind-body practitioner-based practice). CAM use definitions included any use, dietary supplement use, mind-body use, and a CAM index summing the 5 modalities. **Main Outcomes and Measures:** Chemotherapy initiation was assessed via self-report up to 12 months after baseline. Multivariable logistic regression models examined a priori hypotheses testing whether CAM use was associated with chemotherapy initiation, adjusting for demographic and clinical covariates, and delineating groups by age and chemotherapy indication. **Results:** A cohort of 685 women younger than 70 years (mean age, 59 years; median age, 59 years) with nonmetastatic invasive breast cancer were recruited and followed for up to 12 months to examine predictors of breast cancer treatment initiation. Baseline CAM use was reported by 598 women (87%). Chemotherapy was initiated by 272 women (89%) for whom chemotherapy was indicated, compared with 135 women (36%) for whom chemotherapy was discretionary. Among women for whom chemotherapy was indicated, dietary supplement users and women with high CAM index scores were less likely than nonusers to initiate chemotherapy (odds ratio [OR], 0.16; 95% CI, 0.03-0.51; and OR per unit, 0.64; 95% CI, 0.46-0.87, respectively). Use of mind-body practices was not related to chemotherapy initiation (OR, 1.45; 95% CI, 0.57-3.59). There was no association between CAM use and chemotherapy initiation among women for whom chemotherapy was discretionary. **Conclusions and Relevance:** CAM use was high among patients with early-stage breast cancer enrolled in a multisite prospective cohort study. Current dietary supplement use and higher number of CAM modalities used but not mind-body practices were associated with decreased initiation of clinically indicated

chemotherapy. Oncologists should consider discussing CAM with their patients during the chemotherapy decision-making process.

Public Health Sciences

Hung J, **Taylor AR, Divine GW**, Hafron JM, and **Hwang C**. The effect of time to castration resistance on outcomes with abiraterone and enzalutamide in metastatic prostate cancer *Clin Genitourin Cancer* 2016; PMID: 27157640.

[Full Text](#)

Department of Urology, Oakland University William Beaumont School of Medicine, Rochester, MI.
Department of Public Health Sciences, Josephine Ford Cancer Institute, Henry Ford Health System, Detroit, MI.
Department of Hematology/Oncology, Josephine Ford Cancer Institute, Henry Ford Health System, Detroit, MI.
Electronic address: chwang2@hfhs.org.

BACKGROUND: Abiraterone and enzalutamide are 2 novel androgen receptor (AR)-targeting therapies that improve survival in patients with metastatic castration-resistant prostate cancer. The factors that predict abiraterone and enzalutamide response are lacking. The objective of the present study was to determine whether the outcomes from primary androgen deprivation therapy (ADT) could predict the outcomes with subsequent novel AR-targeting therapies. **MATERIALS AND METHODS:** We identified 80 consecutive patients with metastatic castration-resistant prostate cancer treated with abiraterone or enzalutamide. Cox regression models were used to analyze the relationships between the primary ADT response and the primary outcome of progression-free survival (PFS) after initiating novel hormonal therapy. The secondary outcomes included prostate-specific antigen decline and overall survival. The survival probabilities were plotted using the Kaplan-Meier method, and the differences assessed with the log-rank test. **RESULTS:** The time to castration resistance with primary ADT showed a significant association with both PFS and overall survival after initiating novel hormone therapy ($P = .032$ and $P = .028$, respectively). Patients with progression during primary ADT before 1 year had a median PFS of 3.4 months compared with a median PFS of 7.6 and 8.1 months for patients whose time to castration resistance was ≥ 1 and ≤ 5 years ($P = .008$) and > 5 years ($P = .026$), respectively. However, the time to castration resistance was not an independent predictor of survival or the PSA response with novel AR-targeting therapy on multivariate analysis. **CONCLUSION:** A rapid time to progression during primary ADT was associated with poor outcomes but was not an independent predictor of the response to enzalutamide or abiraterone.

Public Health Sciences

Jain T, Nowak R, Hudson M, Frisoli T, Jacobsen G, and **McCord J**. Short- and long-term prognostic utility of the HEART score in patients evaluated in the emergency department for possible acute coronary syndrome *Crit Pathw Cardiol* 2016; 15(2):40-45. PMID: 27183252. [Full Text](#)

From the *Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan; daggerDepartment of Emergency Medicine, Henry Ford Hospital, Detroit, Michigan; double daggerHenry Ford Heart and Vascular Institute, Detroit, Michigan; and section signDepartment of Biostatistics, Henry Ford Hospital, Detroit, Michigan.

INTRODUCTION: The HEART score is a risk-stratification tool that was developed and validated for patients evaluated for possible acute coronary syndrome (ACS) in the emergency department (ED). We sought to determine the short-term and long-term prognostic utility of the HEART score. **METHODS:** A retrospective single-center analysis of 947 patients evaluated for possible ACS in the ED in 1999 was conducted. Patients were followed for major adverse cardiac events (MACEs) at 30 days: death, acute myocardial infarction, or revascularization procedure. All-cause mortality was assessed at 5 years. The HEART score was compared with the Thrombolysis in Myocardial Infarction (TIMI) score. **RESULTS:** At 30 days, 14% (135/947) of patients had an MACE: 48 deaths (5%), 84 acute myocardial infarctions (9%), and 48 (5%) revascularization procedures. The MACE rate in patients with HEART score ≤ 3 was 0.6% (1/175) involving a revascularization procedure, 9.5% (53/557) in patients with HEART score between 4 and 6, and 38% (81/215) with HEART score ≥ 7 . The C-statistic for the HEART score was 0.82 and 0.68 for the TIMI score for predicting 30-day MACE ($P < 0.05$). Patients with HEART score ≤ 3 had lower 5-year mortality rate compared with those with TIMI score of 0 (10.6% vs. 20.5%, $P = 0.02$). **CONCLUSIONS:** The HEART score is a valuable risk-stratification tool in predicting not only short-term MACE but also long-term mortality in patients evaluated for possible ACS in the ED. The HEART score had a superior prognostic value compared with the TIMI score.

Public Health Sciences

Suleyman G, Tibbetts R, Perri MB, Vager D, Xin Y, Reyes K, Samuel L, Chami E, Starr P, Pietsch J, Zervos MJ, and Alangaden G. Nosocomial Outbreak of a Novel Extended-Spectrum beta-Lactamase Salmonella enterica Serotype Isangi Among Surgical Patients *Infect Control Hosp Epidemiol* 2016;1-8. PMID: 27108715.

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1Department of Infectious Disease, Henry Ford Hospital, Detroit, Michigan.

2Department of Pathology, Henry Ford Hospital, Detroit, Michigan.

3Research Laboratory, Henry Ford Hospital, Detroit, Michigan.

4Public Health Sciences, Henry Ford Hospital, Detroit, Michigan.

5Infection Control, Henry Ford Hospital, Detroit, Michigan.

OBJECTIVE Nosocomial outbreaks caused by Salmonella are rare. We describe the investigation and control of a cluster of novel extended-spectrum beta-lactamase (ESBL) Salmonella enterica serotype Isangi in a hospital in southeastern Michigan. **METHODS** An epidemiologic investigation, including case-control study, assessment of infection control practices and environmental cultures, was performed to identify modes of transmission. Healthcare workers (HCWs) exposed to case patients were screened. Strain relatedness was determined using pulsed-field gel electrophoresis (PFGE); ESBL confirmation was conducted using real-time PCR. Control measures were implemented to prevent further transmission. **RESULTS** Between September 2 and October 22, 2015, 19 surgical patients, including 10 organ transplant recipients and 1 HCW, had positive S. Isangi cultures. Of these case patients and HCW, 13 had gastroenteritis, 2 had bacteremia, 1 had surgical-site infection, and 4 were asymptomatic. Pulsed-field gel electrophoresis (PFGE) showed 89.5% similarity among the isolates in these cases. Isolates with resistant-phenotypes possessed plasmid-mediated CTX-M15 ESBL. A total of 19 case patients were compared with 57 control participants. Case patients had significantly higher odds of exposure to an intraoperative transesophageal (TEE) probe (adjusted odds ratio 9.0; 95% confidence interval, 1.12-72.60; P=.02). Possible cross-transmission occurred in the HCW and 2 patients. Cultures of TEE probes and the environment were negative. The outbreak ended after removal of TEE probes, modification of reprocessing procedures, implementation of strict infection control practices, and enhanced environmental cleaning. **CONCLUSIONS** We report the first nosocomial ESBL S. Isangi outbreak in the United States. Multiple control measures were necessary to interrupt transmission of this gastrointestinal pathogen. Exposure to possibly contaminated TEE probes was associated with transmission. Periodic monitoring of reprocessing procedures of TEE probes may be required to ensure optimal disinfection. *Infect Control Hosp Epidemiol* 2016;1-8.

Public Health Sciences

Teshale EH, Xing J, Moorman A, Holmberg SD, Spradling PR, **Gordon SC, Rupp LB, Lu M**, Boscarino JA, Trinacry CM, Schmidt MA, and Xu F. Higher all-cause hospitalization among patients with chronic hepatitis C: the Chronic Hepatitis Cohort Study (CHeCS), 2006-2013 *J Viral Hepat* 2016; PMID: 27186944. [Full Text](#)

Division of Viral Hepatitis, CDC, Atlanta, GA, USA.

Henry Ford Hospital, Detroit, MI, USA.

Geisinger Health System, Danville, PA, USA.

Kaiser Permanente Hawaii, Honolulu, HI, USA.

Kaiser Permanente Northwest, Portland, OR, USA.

In the United States, hospitalization among patients with chronic hepatitis C virus (HCV) infection is high. The healthcare burden associated with hospitalization is not clearly known. We analysed data from the Chronic Hepatitis Cohort Study, an observational cohort of patients receiving care at four integrated healthcare systems, collected from 2006 to 2013 to determine all-cause hospitalization rates of patients with chronic HCV infection and the other health system patients. To compare the hospitalization rates, we selected two health system patients for each chronic HCV patient using their propensity score (PS). Propensity score matching was conducted by site, gender, race, age and household income to minimize differences attributable to these characteristics. We also compared primary reason for hospitalization between chronic HCV patients and the other health system patients. Overall, 10 131 patients with chronic HCV infection and 20 262 health system patients were selected from the 1 867 802 health system patients and were matched by PS. All-cause hospitalization rates were 27.4 (27.0-27.8) and 7.4 (7.2-7.5) per 100 persons-year (PY) for chronic HCV patients and for the other health system patients, respectively. Compared to health system patients, hospitalization rates were significantly higher by site, gender, age group, race and household income among chronic HCV patients (P < 0.001). Compared to health system patients, chronic HCV patients were more likely to be hospitalized from liver-related conditions (RR = 24.8, P < 0.001). Hence, patients with chronic HCV infection had approximately 3.7-fold higher all-cause hospitalization rate than other health system patients. These findings highlight the incremental costs and healthcare burden of patients with chronic HCV infection associated with hospitalization.

Public Health Sciences

Xu Y, Burmeister C, Hanna RK, Munkarah A, and Elshaikh MA. Predictors of survival after recurrence in women with early-stage endometrial carcinoma *Int J Gynecol Cancer* 2016; PMID: 27206283. [Full Text](#)

Department of *Radiation Oncology and daggerPublic Health Science, double daggerDivision of Gynecologic Oncology, Department of Women's Health Services, Henry Ford Hospital, Detroit, MI.

OBJECTIVE: Factors predictive of survival after recurrent early-stage endometrial carcinoma have not been thoroughly investigated. The purpose of this study was to explore factors that impact disease-specific survival (DSS) and overall survival (OS) after recurrence in women with early-stage endometrial carcinoma. **MATERIALS AND METHODS:** After institutional review board approval, we identified 104 women with 2009 International Federation of Gynecology and Obstetrics stage I to II uterine endometrioid carcinoma who developed disease recurrence between January 1990 and December 2014. The Kaplan-Meier approach and Cox regression analysis were used to assess DSS and OS after recurrence and to determine factors influencing these survival end points. **RESULTS:** Median age of the study cohort was 65 years with a median follow-up time of 42.8 months after hysterectomy. Median time to recurrence was 15.8 months. Recurrences were diagnosed in 60 patients (57.7%) who were originally managed with observation after hysterectomy and in 44 patients (42.3%) who were initially managed with adjuvant radiation treatment. Fifty-six patients (54%) had pelvic recurrence (vaginal and/or pelvic), whereas 48 (46%) had extrapelvic recurrence. Five-year DSS and OS for the entire study population was 44% and 37%, respectively. Five-year DSS and OS were longer for patients with pelvic recurrence compared with patients with extrapelvic recurrence (66% vs 18% and 55% vs 17%, $P < 0.0001$). Five-year DSS was also longer for radiation-naïve patients than for radiation-treated patients (51% vs 34%, $P = 0.023$). On multivariate analysis of DSS and OS, pelvic recurrence ($P < 0.001$) was the only significant predictor of longer DSS and OS. **CONCLUSIONS:** In women with recurrent early-stage endometrioid carcinoma, our study suggests that site of recurrence (pelvic vs extra pelvic) is the only predictor of survival. In addition, we found that radiation naïvete and pelvic recurrence correlated with longer DSS and OS.

Pulmonary

Alkhatib Y, Albashaireh D, Al-Aqtash T, and Awdish R. The role of tyrosine kinase inhibitor "Lapatinib" in pulmonary hypertension *Pulm Pharmacol Ther* 2016; 37:81-84. PMID: 26965087. [Full Text](#)

Division of Hematology/Oncology, Henry Ford Hospital/Wayne State University, USA. Electronic address: Yalkhat1@hfhs.org.

Division of Cardiology, Tulane University, USA.

Division of Pulmonary and Critical Care, Deaconess Health System, USA.

Division of Pulmonary and Critical Care, Henry Ford Hospital/Wayne State University, USA.

INTRODUCTION: Pulmonary Arterial Hypertension (PAH) and cancer share growth factor and protein kinase signaling pathways that result in smooth muscle cell proliferation and vasculopathy. There is little known about the impact of Lapatinib on the pulmonary vasculature. After reporting a case of Lapatinib-induced PAH we investigated the association of Lapatinib with the development of PAH in our institution. **METHODS:** We reviewed charts for all patients treated with Lapatinib at our institution between 2008 and 2013. Patients who had undergone 2D-echocardiogram both prior to and after treatment were included in the analysis. Increase in Pulmonary artery systolic pressure (PASP) was assessed. Patients were also evaluated in terms of risk factors for non-Group 1 PAH. **RESULTS:** A total of 27 patients were found to have 2-D echo done before and after starting treatment with Lapatinib. Six patients were found to have significant increase in their PASP after starting treatment. Right heart catheterization before and after stopping the medication was available in three patient, confirming the diagnosis of PAH with complete resolution after stopping the medication. The median pre-treatment and post treatment PASP in those 6 patients was 29 mmHg and 65.5 mmHg respectively ($N = 6$; $p = 0.027$). **CONCLUSION:** Lapatinib might be associated with the development of PAH. PASP should be evaluated in patients who become short of breath while on treatment, and stopping the drug in cases where no other reasons are identified could be associated with reversibility of the elevated pulmonary artery pressure.

Pulmonary

Diekemper RL, Patel S, Mette SA, Ornelas J, Ouellette DR, and Casey KR. Making the GRADE: CHEST updates its methodology *Chest* 2016; PMID: 27142185. [Full Text](#)

Doctor Evidence, Santa Monica, CA.

CHEST, Glenview, IL. Electronic address: spatel@chestnet.org.

University of Arkansas for Medical Sciences, Little Rock, AR.

CHEST, Glenview, IL.

Henry Ford Hospital, Detroit, MI.
University of Wisconsin School of Medicine and Public Health, Madison, WI.

BACKGROUND: The American College of Chest Physicians (CHEST) has been at the forefront of evidence-based clinical practice guideline development for more than two decades. In 2006, CHEST adopted a modified system of GRADE (Grading of Recommendations Assessment, Development and Evaluation) to support their rigorous guideline development methodology. The evolution of CHEST's Living Guidelines Model as well as their collaborative efforts with other organizations has necessitated improvements in their guideline development methodology. **METHODS:** CHEST has made the decision to transition to the standard GRADE method for rating the certainty of evidence and grading recommendations in their evidence-based clinical practice guidelines, a deviation from the "modified" approach that was adapted in 2006. **RESULTS:** A standard GRADE approach will be used to grade recommendations in all CHEST guidelines, including updates to previously published guidelines. **CONCLUSION:** CHEST's adoption of a standard GRADE approach will ensure that its guideline development methodology is more consistent with that used by other organizations, better align evidence synthesis methods, and result in more explicit and easy to understand recommendations.

Radiation Oncology

Freytag SO, Movsas B, and Stricker H. Clinical trials of oncolytic adenovirus-mediated gene therapy *Mol Ther* 2016; 24:S205-S205. PMID: Not assigned. Abstract

[Freytag, Svend O.; Movsas, Benjamin] Henry Ford Hlth Syst, Radiat Oncol, Detroit, MI USA. [Stricker, Hans] Henry Ford Hlth Syst, Urol, Detroit, MI USA.

Radiation Oncology

Gordon JJ. On the feasibility of extracting dose-response curves from clinical DVH data using correlation and regression analysis *Biomedical Physics and Engineering Express* 2016; 2(1) PMID: [Article Request Form](#)

J.J. Gordon, Department of Radiation Oncology, Henry Ford Health System, Detroit, United States

Purpose: To quantify the ability of correlation and regression analysis to extract the normal lung dose-response function from dose volume histogram (DVH) and radiation pneumonitis (RP) data. **Methods:** A local injury model is adopted, in which radiation-induced damage (functional loss) is the integral of the DVH with function $R(D)$. R is Priskis $H(G)$ where $H()$ is the sigmoid cumulative distribution of functional reserve. RP incidence is a Bernoulli function of risk. A homogeneous patient cohort is assumed, allowing non-dose-related factors to be ignored. Clinically realistic DVHs are combined with the injury model to simulate RP data. **Results:** Correlation analysis is often used to identify a subset of predictor variables that are significantly correlated with outcome, for inclusion in a predictive model. In the local injury model, all DVH metrics VD contribute to damage through the integral with $R(D)$. Correlation analysis therefore has limited value. The subset of VD that are most significantly correlated with incidence varies randomly from trial to trial as a result of random variations in the DVH set, and does not necessarily reveal anything useful about the patient cohort or the underlying biological dose-response relationship. Regression or matrix analysis has the potential to extract $R(D)$ from damage or risk data, provided smoothness regularization is employed. Extraction of $R(D)$ from incidence data was not successful, due to its higher level of statistical variability. **Conclusions:** To the authors' knowledge, smoothness regularization has not been applied to this problem, so represents a novel approach. Dose-response functions can be successfully extracted from measurements of integral (as opposed to regional) lung damage G , suggesting value in re-visiting available measurements of ventilation, perfusion and radiographic damage. The techniques developed here can potentially be used to extract the dose-response functions of different tissues from multiple types of quantitative volumetric imaging data.

Radiation Oncology

Price RG, Kim JP, Zheng W, Chetty IJ, and Glide-Hurst C. Image guided radiation therapy using synthetic computed tomography images in brain cancer *Int J Radiat Oncol Biol Phys* 2016; PMID: 27209500. [Full Text](#)

Department of Radiation Oncology, Henry Ford Health System, Detroit, Michigan; Department of Radiation Oncology, Wayne State University School of Medicine, Detroit, Michigan.

Department of Radiation Oncology, Henry Ford Health System, Detroit, Michigan.

Department of Radiation Oncology, Henry Ford Health System, Detroit, Michigan; Department of Radiation Oncology, Wayne State University School of Medicine, Detroit, Michigan. Electronic address: churst2@hfhs.org.

PURPOSE: The development of synthetic computed tomography (CT) (synCT) derived from magnetic resonance (MR) images supports MR-only treatment planning. We evaluated the accuracy of synCT and synCT-generated digitally reconstructed radiographs (DRRs) relative to CT and determined their performance for image guided radiation therapy (IGRT). **METHODS AND MATERIALS:** Magnetic resonance simulation (MR-SIM) and CT simulation (CT-SIM) images were acquired of an anthropomorphic skull phantom and 12 patient brain cancer cases. SynCTs were generated using fluid attenuation inversion recovery, ultrashort echo time, and Dixon data sets through a voxel-based weighted summation of 5 tissue classifications. The DRRs were generated from the phantom synCT, and geometric fidelity was assessed relative to CT-generated DRRs through bounding box and landmark analysis. An offline retrospective analysis was conducted to register cone beam CTs (n=34) to synCTs and CTs using automated rigid registration in the treatment planning system. Planar MV and KV images (n=37) were rigidly registered to synCT and CT DRRs using an in-house script. Planar and volumetric registration reproducibility was assessed and margin differences were characterized by the van Herk formalism. **RESULTS:** Bounding box and landmark analysis of phantom synCT DRRs were within 1 mm of CT DRRs. Absolute planar registration shift differences ranged from 0.0 to 0.7 mm for phantom DRRs on all treatment platforms and from 0.0 to 0.4 mm for volumetric registrations. For patient planar registrations, the mean shift differences were 0.4 +/- 0.5 mm (range, -0.6 to 1.6 mm), 0.0 +/- 0.5 mm (range, -0.9 to 1.2 mm), and 0.1 +/- 0.3 mm (range, -0.7 to 0.6 mm) for the superior-inferior (S-I), left-right (L-R), and anterior-posterior (A-P) axes, respectively. The mean shift differences in volumetric registrations were 0.6 +/- 0.4 mm (range, -0.2 to 1.6 mm), 0.2 +/- 0.4 mm (range, -0.3 to 1.2 mm), and 0.2 +/- 0.3 mm (range, -0.2 to 1.2 mm) for the S-I, L-R, and A-P axes, respectively. The CT-SIM and synCT derived margins were <0.3 mm different. **CONCLUSION:** DRRs generated by synCT were in close agreement with CT-SIM. Planar and volumetric image registrations to synCT-derived targets were comparable with CT for phantom and patients. This validation is the next step toward MR-only planning for the brain.

Radiation Oncology

Saba NF, Salama JK, Beitler JJ, Busse PM, Cooper JS, Jones CU, Koyfman S, Quon H, Ridge JA, **Siddiqui F**, Worden F, Yao M, and Yom SS. ACR Appropriateness criteria(R) for nasopharyngeal carcinoma *Head Neck* 2016;PMID: 27131050. [Full Text](#)

Emory University, Atlanta, Georgia, American Society of Clinical Oncology.
Duke University, Durham, North Carolina.
Emory University School of Medicine, Atlanta, Georgia.
Massachusetts General Hospital, Boston, Massachusetts.
Maimonides Cancer Center, Brooklyn, New York.
Radiological Associates of Sacramento, Sacramento, California.
Cleveland Clinic, Cleveland, Ohio.
Johns Hopkins University, Baltimore, Maryland.
Fox Chase Cancer Center, Philadelphia, Pennsylvania, American College of Surgeons.
Henry Ford Health System, Detroit, Michigan.
University of Michigan, Ann Arbor, Michigan, American Society of Clinical Oncology.
University Hospitals Case Medical Center, Cleveland, Ohio.
University of California San Francisco, San Francisco, California.

BACKGROUND: Nasopharyngeal carcinoma (NPC) presents mostly with locally advanced disease and is treated with multimodal therapy; however, consensus is lacking for different clinical scenarios. **METHODS:** The American College of Radiology (ACR) Appropriateness Criteria(R) are evidence-based guidelines for specific clinical conditions that are reviewed every 3 years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of current medical literature from peer-reviewed journals and the application of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures by the panel. In those instances in which evidence is lacking or not definitive, expert opinion may be used to recommend imaging or treatment. **RESULTS:** The ACR Expert Panel on Radiation Oncology - Head and Neck Cancer developed consensus recommendations for guiding management of nasopharyngeal carcinoma. **CONCLUSION:** Multidisciplinary evaluation is essential to guiding the optimal use of surgery, radiation, and systemic therapy in this disease. (c) 2015 American College of Radiology Head Neck, 2015.

Radiation Oncology

To DT, **Kim JP**, **Price RG**, **Chetty IJ**, and **Glide-Hurst CK**. Impact of incorporating visual biofeedback in 4D MRI *J Appl Clin Med Phys* 2016; 17(3):6017. PMID: 27167270. [Article Request Form](#)

Henry Ford Health System. DTO1@hfhs.org.

Precise radiation therapy (RT) for abdominal lesions is complicated by respiratory motion and suboptimal soft tissue contrast in 4D CT. 4D MRI offers improved contrast although long scan times and irregular breathing patterns can be limiting. To address this, visual biofeedback (VBF) was introduced into 4D MRI. Ten volunteers were consented to an IRB-approved protocol. Prospective respiratory-triggered, T2-weighted, coronal 4D MRIs were acquired on an open 1.0T MR-SIM. VBF was integrated using an MR-compatible interactive breath-hold control system. Subjects visually monitored their breathing patterns to stay within predetermined tolerances. 4D MRIs were acquired with and without VBF for 2- and 8-phase acquisitions. Normalized respiratory waveforms were evaluated for scan time, duty cycle (programmed/acquisition time), breathing period, and breathing regularity (end-inhale coefficient of variation, EI-COV). Three reviewers performed image quality assessment to compare artifacts with and without VBF. Respiration-induced liver motion was calculated via centroid difference analysis of end-exhale (EE) and EI liver contours. Incorporating VBF reduced 2-phase acquisition time (4.7 +/- 1.0 and 5.4 +/- 1.5 min with and without VBF, respectively) while reducing EI-COV by 43.8% +/- 16.6%. For 8-phase acquisitions, VBF reduced acquisition time by 1.9 +/- 1.6 min and EI-COVs by 38.8% +/- 25.7% despite breathing rate remaining similar (11.1 +/- 3.8 breaths/min with vs. 10.5 +/- 2.9 without). Using VBF yielded higher duty cycles than unguided free breathing (34.4% +/- 5.8% vs. 28.1% +/- 6.6%, respectively). Image grading showed that out of 40 paired evaluations, 20 cases had equivalent and 17 had improved image quality scores with VBF, particularly for mid-exhale and EI. Increased liver excursion was observed with VBF, where superior-inferior, anterior-posterior, and left-right EE-EI displacements were 14.1 +/- 5.8, 4.9 +/- 2.1, and 1.5 +/- 1.0 mm, respectively, with VBF compared to 11.9 +/- 4.5, 3.7 +/- 2.1, and 1.2 +/- 1.4 mm without. Incorporating VBF into 4D MRI substantially reduced acquisition time, breathing irregularity, and image artifacts. However, differences in excursion were observed, thus implementation will be required throughout the RT workflow.

Radiation Oncology

Wen N, Snyder KC, Scheib SG, Schmelzer P, Qin Y, Li H, Siddiqui MS, and Chetty IJ. Technical Note: Evaluation of the systematic accuracy of a frameless, multiple image modality guided, linear accelerator based stereotactic radiosurgery system *Med Phys* 2016; 43(5):2527. PMID: 27147363. [Full Text](#)

Department of Radiation Oncology, Henry Ford Health System, 2799 West Brand Boulevard, Detroit, Michigan 48202.

Varian Medical System, Tafernstrasse 7, Dattwil AG 5405, Switzerland.

PURPOSE: To evaluate the total systematic accuracy of a frameless, image guided stereotactic radiosurgery system. **METHODS:** The localization accuracy and intermodality difference was determined by delivering radiation to an end-to-end prototype phantom, in which the targets were localized using optical surface monitoring system (OSMS), electromagnetic beacon-based tracking (Calypso(R)), cone-beam CT, "snap-shot" planar x-ray imaging, and a robotic couch. Six IMRT plans with jaw tracking and a flattening filter free beam were used to study the dosimetric accuracy for intracranial and spinal stereotactic radiosurgery treatment. **RESULTS:** End-to-end localization accuracy of the system evaluated with the end-to-end phantom was 0.5 +/- 0.2 mm with a maximum deviation of 0.9 mm over 90 measurements (including jaw, MLC, and cone measurements for both auto and manual fusion) for single isocenter, single target treatment, 0.6 +/- 0.4 mm for multitarget treatment with shared isocenter. Residual setup errors were within 0.1 mm for OSMS, and 0.3 mm for Calypso. Dosimetric evaluation based on absolute film dosimetry showed greater than 90% pass rate for all cases using a gamma criteria of 3%/1 mm. **CONCLUSIONS:** The authors' experience demonstrates that the localization accuracy of the frameless image-guided system is comparable to robotic or invasive frame based radiosurgery systems.

Radiation Oncology

Xu Y, Burmeister C, Hanna RK, Munkarah A, and Elshaikh MA. Predictors of survival after recurrence in women with early-stage endometrial carcinoma *Int J Gynecol Cancer* 2016; PMID: 27206283. [Full Text](#)

Department of *Radiation Oncology and daggerPublic Health Science, double daggerDivision of Gynecologic Oncology, Department of Women's Health Services, Henry Ford Hospital, Detroit, MI.

OBJECTIVE: Factors predictive of survival after recurrent early-stage endometrial carcinoma have not been thoroughly investigated. The purpose of this study was to explore factors that impact disease-specific survival (DSS) and overall survival (OS) after recurrence in women with early-stage endometrial carcinoma. **MATERIALS AND METHODS:** After institutional review board approval, we identified 104 women with 2009 International Federation of Gynecology and Obstetrics stage I to II uterine endometrioid carcinoma who developed disease recurrence between January 1990 and December 2014. The Kaplan-Meier approach and Cox regression analysis were used to assess DSS and OS after recurrence and to determine factors influencing these survival end points. **RESULTS:** Median age of the study cohort was 65 years with a median follow-up time of 42.8 months after hysterectomy. Median time to

recurrence was 15.8 months. Recurrences were diagnosed in 60 patients (57.7%) who were originally managed with observation after hysterectomy and in 44 patients (42.3%) who were initially managed with adjuvant radiation treatment. Fifty-six patients (54%) had pelvic recurrence (vaginal and/or pelvic), whereas 48 (46%) had extrapelvic recurrence. Five-year DSS and OS for the entire study population was 44% and 37%, respectively. Five-year DSS and OS were longer for patients with pelvic recurrence compared with patients with extrapelvic recurrence (66% vs 18% and 55% vs 17%, $P < 0.0001$). Five-year DSS was also longer for radiation-naive patients than for radiation-treated patients (51% vs 34%, $P = 0.023$). On multivariate analysis of DSS and OS, pelvic recurrence ($P < 0.001$) was the only significant predictor of longer DSS and OS. CONCLUSIONS: In women with recurrent early-stage endometrioid carcinoma, our study suggests that site of recurrence (pelvic vs extra pelvic) is the only predictor of survival. In addition, we found that radiation naivete and pelvic recurrence correlated with longer DSS and OS.

Radiation Oncology

Zhong H, Adams J, **Glide-Hurst C**, Zhang H, **Li H**, and **Chetty IJ**. Development of a deformable dosimetric phantom to verify dose accumulation algorithms for adaptive radiotherapy *J Med Phys* 2016; 41(2):106-114. PMID: 27217622.

[Full Text](#)

Department of Radiation Oncology, Henry Ford Health System, Detroit, MI, USA.

Department of Radiation Oncology, Wayne State University, Detroit, MI, USA.

Department of Radiation Oncology, Northwestern University, Chicago, IL, USA.

Adaptive radiotherapy may improve treatment outcomes for lung cancer patients. Because of the lack of an effective tool for quality assurance, this therapeutic modality is not yet accepted in clinic. The purpose of this study is to develop a deformable physical phantom for validation of dose accumulation algorithms in regions with heterogeneous mass. A three-dimensional (3D) deformable phantom was developed containing a tissue-equivalent tumor and heterogeneous sponge inserts. Thermoluminescent dosimeters (TLDs) were placed at multiple locations in the phantom each time before dose measurement. Doses were measured with the phantom in both the static and deformed cases. The deformation of the phantom was actuated by a motor driven piston. 4D computed tomography images were acquired to calculate 3D doses at each phase using Pinnacle and EGSnrc/DOSXYZnrc. These images were registered using two registration software packages: VelocityAI and Elastix. With the resultant displacement vector fields (DVF), the calculated 3D doses were accumulated using a mass-and energy congruent mapping method and compared to those measured by the TLDs at four typical locations. In the static case, TLD measurements agreed with all the algorithms by 1.8% at the center of the tumor volume and by 4.0% in the penumbra. In the deformable case, the phantom's deformation was reproduced within 1.1 mm. For the 3D dose calculated by Pinnacle, the total dose accumulated with the Elastix DVF agreed well to the TLD measurements with their differences <2.5% at four measured locations. When the VelocityAI DVF was used, their difference increased up to 11.8%. For the 3D dose calculated by EGSnrc/DOSXYZnrc, the total doses accumulated with the two DVFs were within 5.7% of the TLD measurements which are slightly over the rate of 5% for clinical acceptance. The detector-embedded deformable phantom allows radiation dose to be measured in a dynamic environment, similar to deforming lung tissues, supporting the validation of dose mapping and accumulation operations in regions with heterogeneous mass, and dose distributions.

Radiology

Becker MD, Butler PF, Bhargavan-Chatfield M, **Harkness BA**, Metter D, MacFarlane CR, Ghesani M, Wilcox P, and Oates ME. Adult gamma camera myocardial perfusion imaging: Diagnostic reference levels and achievable administered activities derived from ACR accreditation data *J Am Coll Radiol* 2016; 13(6):688-695. PMID: 27131619.

[Full Text](#)

Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey; University Radiology, East Brunswick, New Jersey. Electronic address: mbecker@univrad.com.

American College of Radiology, Reston, Virginia.

Department of Radiology, Henry Ford Health System, Detroit, Michigan.

Department of Radiology, University of Texas Health Science Center, San Antonio, Texas.

Department of Radiology, New York University School of Medicine, New York, New York.

Department of Radiology and Medicine, University of Kentucky College of Medicine and UK HealthCare, Lexington, Kentucky.

PURPOSE: The aim of this study was to glean from accreditation surveys of US nuclear medicine facilities the in-practice radiopharmaceutical diagnostic reference levels (DRLs) and achievable administered activities (AAAs) for adult gamma camera myocardial perfusion imaging (MPI). METHODS: Data were collected from the ACR Nuclear Medicine Accreditation Program during one three-year accreditation cycle from May 1, 2012, to April 30, 2015. Data

elements included radiopharmaceutical, administered activity, examination protocol, interpreting physician specialty, practice type, and facility annual examination volume. Facility demographics, DRLs, and AAAs were tabulated for analysis. RESULTS: The calculated DRLs and AAAs are consistent with previously published surveys, and they adhere to national societal guidelines. Facilities seeking ACR accreditation are nearly evenly split between hospital based with multiple gamma cameras and office based with single gamma cameras. The majority of facilities use single-day, low-dosage/high-dosage (99m)Tc-based protocols; a small minority use (201)TlCl protocols. Administered activities show a consistency across facilities, likely reflecting adoption of standard MPI protocols. CONCLUSIONS: This practice-based analysis provides DRL and AAA benchmarks that nuclear medicine facilities may use to refine gamma camera MPI protocols. In general, the protocols submitted for ACR accreditation are consistent with national societal guidelines. The results suggest that there may be opportunities to further reduce patient radiation exposure by using modified examination protocols and newer gamma camera software and hardware technologies.

Radiology

Wang DD, Eng M, Greenbaum A, Myers E, Forbes M, Pantelic M, Song T, Nelson C, Divine G, Taylor A, Wyman J, Guerrero M, Lederman RJ, Paone G, and O'Neill W. Predicting LVOT Obstruction After TMVR *JACC Cardiovasc Imaging* 2016;PMID: 27209112. [Full Text](#)

Division of Cardiology, Center for Structural Heart Disease, Henry Ford Health System, Detroit, Michigan. Electronic address: dwang2@hfhs.org.

Division of Cardiology, Center for Structural Heart Disease, Henry Ford Health System, Detroit, Michigan. Henry Ford Innovation Institute, Henry Ford Health System, Detroit, Michigan.

Division of Radiology, Henry Ford Health System, Detroit, Michigan.

Division of Cardiology, Center for Structural Heart Disease, Henry Ford Health System, Detroit, Michigan; Division of Cardiology, Evanston Hospital/NorthShore University Health System, Evanston, Illinois.

Cardiovascular and Pulmonary Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Rheumatology

Coit P, Dozmorov MG, Merrill JT, McCune WJ, **Maksimowicz-McKinnon K**, Wren JD, and Sawalha AH. Epigenetic reprogramming in naive CD4+ T cells favoring T cell activation and non-Th1 effector T cell immune response as an early event in lupus flares *Arthritis Rheumatol* 2016;PMID: 27111767. [Full Text](#)

Division of Rheumatology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA.

Department of Biostatistics, Virginia Commonwealth University, Richmond, Virginia, USA.

Clinical Pharmacology Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, USA.

Division of Rheumatology, Henry Ford Health System, Detroit, Michigan, USA.

Arthritis and Clinical Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, USA.

Department of Biochemistry and Molecular Biology, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA.

Center for Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, Michigan, USA.

OBJECTIVE: Systemic lupus erythematosus is a relapsing autoimmune disease that affects multiple organ systems. T cells play an important role in the pathogenesis of lupus, however, early T cell events triggering disease flares are incompletely understood. We studied DNA methylation in naive CD4+ T cells from lupus patients to determine if epigenetic remodeling in CD4+ T cells is an early event in lupus flares. METHODS: A total of 74 lupus patients with disease activity ranging from 0-18 as measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) were included in this study. Naive CD4+ T cells were isolated from peripheral blood samples and DNA extracted for genome-wide methylation assessment. RNA was also extracted from a subset of patients to determine the relationship between epigenetic changes and transcriptional activity using RNA sequencing and microRNA arrays. RESULTS: We demonstrate that naive CD4+ T cells in lupus undergo an epigenetic pro-inflammatory shift implicating effector T cell responses in lupus flare. This epigenetic landscape change occurs without expression changes of corresponding genes, and poises naive CD4+ T cells for Th2, Th17, and Tfh immune responses, and opposes inhibitory TGF-beta signaling. Bioinformatics analyses indicate that the epigenetic modulator EZH2 might be playing an important role in shifting the epigenetic landscape with increased disease activity in lupus naive CD4+ T cells. Further, the expression of miR26a which is sensitive to glucose availability and which targets EZH2 was negatively correlated with disease activity in lupus patients. CONCLUSION: An epigenetic landscape shift in naive CD4+ T cells that favors T cell activation and non-Th1 immune responses predates transcriptional activity and correlates with lupus activity. A role for EZH2 dysregulation in triggering lupus flares warrants further investigation. This article is protected by copyright. All rights reserved

Sleep Medicine

Espie CA, Luik AI, Cape J, **Drake CL**, Siriwardena AN, Ong JC, Gordon C, Bostock S, Hames P, Nisbet M, Sheaves B, R GF, Freeman D, Costa-Font J, Emsley R, and Kyle SD. Digital Cognitive Behavioural Therapy for Insomnia versus sleep hygiene education: the impact of improved sleep on functional health, quality of life and psychological well-being. Study protocol for a randomised controlled trial *Trials* 2016; 17(1):257. PMID: 27216112. [Full Text](#)

Sleep and Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences, University of Oxford, Sir William Dunn School of Pathology, Oxford, UK. colin.espie@ndcn.ox.ac.uk.

Big Health Ltd., London, UK. colin.espie@ndcn.ox.ac.uk.

Sleep and Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences, University of Oxford, Sir William Dunn School of Pathology, Oxford, UK.

Big Health Ltd., London, UK.

Division of Psychology and Language Sciences, Faculty of Brain Sciences, University College London, London, UK.

Department of Sleep Disorders and Research Center, Henry Ford Health System, Detroit, MI, USA.

School of Health and Social Care, University of Lincoln, Lincoln, UK.

Rush University Medical Center, Chicago, IL, USA.

CIRUS Centre for Integrated Research and Understanding of Sleep, Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia.

Sleep and Circadian Neuroscience Institute, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK.

The London School of Economics and Political Science, London, UK.

Centre for Biostatistics, Institute of Population Health, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK.

BACKGROUND: Previous research has demonstrated that digital CBT (dCBT), delivered via the Internet, is a scalable and effective intervention for treating insomnia in otherwise healthy adults and leads to significant improvements in primary outcomes relating to sleep. The majority of people with insomnia, however, seek help because of the functional impact and daytime consequences of poor sleep, not because of sleep discontinuity per se. Although some secondary analyses suggest that dCBT may have wider health benefits, no adequately powered study has investigated these as a primary endpoint. This study specifically aims to investigate the impact of dCBT for insomnia upon health and well-being, and will investigate sleep-related changes as mediating factors.

METHODS/DESIGN: We propose a pragmatic, parallel-group, randomised controlled trial of 1000 community participants meeting criteria for insomnia disorder. In the DIALS trial (Digital Insomnia therapy to Assist your Life as well as your Sleep), participants will be randomised to dCBT delivered using web and/or mobile channels (in addition to treatment as usual (TAU)) or to sleep hygiene education (SHE), comprising a website plus a downloadable booklet (in addition to TAU). Online assessments will take place at 0 (baseline), 4 (mid-treatment), 8 (post-treatment), and 24 (follow-up) weeks. At week 25 all participants allocated to SHE will be offered dCBT, at which point the controlled element of the trial will be complete. Naturalistic follow-up will be invited at weeks 36 and 48. Primary outcomes are functional health and well-being at 8 weeks. Secondary outcomes are mood, fatigue, sleepiness, cognitive function, productivity and social functioning. All main analyses will be carried out at the end of the final controlled follow-up assessments and will be based on the intention-to-treat principle. Further analyses will determine whether observed changes in functional health and well-being are mediated by changes in sleep. The trial is funded by Big Health Ltd.

DISCUSSION: This study will be the first large-scale, specifically designed investigation of the health and well-being benefits of CBT for insomnia, and the first examination of the association between CBT-mediated sleep improvement and health status. **TRIAL REGISTRATION:** ISRCTN60530898 .

Sleep Medicine

Palagini L, Bruno RM, **Cheng P**, Mauri M, Taddei S, **Ghiadoni L**, **Drake CL**, and Morin CM. Relationship between insomnia symptoms, perceived stress and coping strategies in subjects with arterial hypertension: psychological factors may play a modulating role *Sleep Med* 2016; 19:108-115. PMID: 27198955. [Full Text](#)

Department of Clinical Experimental Medicine, Psychiatric Unit, University of Pisa, Pisa, Italy. Electronic address: lpalagini@tiscali.it.

Institute of Clinical Physiology - CNR, Pisa, Italy.

Sleep Disorders Center Henry Ford Health System, Novi, MI, USA.

Department of Clinical Experimental Medicine, Psychiatric Unit, University of Pisa, Pisa, Italy.

Department of Clinical Experimental Medicine, Hypertension Unit, University of Pisa, Pisa, Italy.

Sleep Disorders Center Henry Ford Health System, Novi, MI, USA; Department of Clinical Experimental Medicine, Hypertension Unit, University of Pisa, Pisa, Italy.

Ecole de Psychologie, Université Laval, Québec City, Québec, Canada.

OBJECTIVE: The aim of the study was to evaluate perceived stress and coping strategies in people with hypertension, according to the presence of insomnia symptoms and by using a set of variables that included anxiety and depressive symptoms evaluation. **METHODS:** A total of 371 hypertensive patients were enrolled during their first visit to the Hypertension Outpatient Unit. The Perceived Stress Scale (PSS), Brief-COPE, Insomnia Severity Index (ISI), Beck Depression Inventory (BDI), Self-rating Anxiety Scale (SAS), and State-Trait Anxiety Inventory (STAI) were administered. Patients with other sleep disorders or with incomplete data (n = 41) were excluded. **RESULTS:** Data from 330 hypertensive patients were analyzed (males 51%, mean age 57 +/- 13 years). Those with insomnia symptoms (n = 70, 21%) were older (p = 0.02), more frequently females (p = 0.01), and presented with higher PSS (p < 0.001), BDI (p < 0.0001), SAS (p = 0.0003), and STAI (p < 0.0001) scores than those without insomnia symptoms. In a linear regression trait, anxiety (p < 0.0001) and depressive symptoms (p < 0.05) were independent predictors of high PSS. Patients with insomnia symptoms showed lower scores in coping strategies, such as positive reframing (p = 0.03) and emotional support (p = 0.04), and an increased score in behavioral disengagement (p = 0.03). Trait anxiety and insomnia severity were independent predictors of less effective coping strategies. **CONCLUSIONS:** People with hypertension and insomnia symptoms showed higher perceived stress and less effective coping strategies than non-insomniacs; psychological factors such as trait anxiety and depressive symptoms may play a modulating role in these relationships. Prevention and treatment of insomnia symptoms and psychological factors should receive high attention for people with hypertension.

Surgery

Ali R, Schwab JM, Nerenz DR, Antoine HJ, and Rubinfeld I. Use of the modified frailty index to predict 30-day morbidity and mortality from spine surgery *J Neurosurg Spine* 2016;1-5. PMID: 27153143. [Full Text](#)

Department of Neurosurgery, Henry Ford Hospital;
Neuroscience Institute and the Center for Health Policy and Health Services Research, Henry Ford Health System;
and.
Department of Surgery, Henry Ford Hospital, Detroit, Michigan.

OBJECTIVE Limited tools exist to stratify perioperative risk in patients undergoing spinal procedures. The modified frailty index (mFI) based on the Canadian Study of Health and Aging Frailty Index (CSHA-FI), constructed from standard demographic variables, has been applied to various other surgical populations for risk stratification. The authors hypothesized that it would be predictive of postoperative morbidity and mortality in patients undergoing spine surgery. **METHODS** The 2006-2010 National Surgical Quality Improvement Program (NSQIP) data set was accessed for patients undergoing spine surgeries based on Current Procedural Terminology (CPT) codes. Sixteen preoperative clinical NSQIP variables were matched to 11 CSHA-FI variables (changes in daily activities, gastrointestinal problems, respiratory problems, clouding or delirium, hypertension, coronary artery and peripheral vascular disease, congestive heart failure, and so on). The outcomes assessed were 30-day occurrences of adverse events. These were then summarized in groups: any infection, wound-related complication, Clavien IV complications (life-threatening, requiring ICU admission), and mortality. **RESULTS** A total of 18,294 patients were identified. In 8.1% of patients with an mFI of 0 there was at least one morbid complication, compared with 24.3% of patients with an mFI of ≥ 0.27 (p < 0.001). An mFI of 0 was associated with a mortality rate of 0.1%, compared with 2.3% for an mFI of ≥ 0.27 (p < 0.001). Patients with an mFI of 0 had a 1.7% rate of surgical site infections and a 0.8% rate of Clavien IV complications, whereas patients with an mFI of ≥ 0.27 had rates of 4.1% and 7.1% for surgical site infections and Clavien IV complications, respectively (p < 0.001 for both). Multivariate analysis showed that the preoperative mFI and American Society of Anesthesiologists classification of \geq III had a significantly increased risk of leading to Clavien IV complications and death. **CONCLUSIONS** A higher mFI was associated with a higher risk of postoperative morbidity and mortality, providing an additional tool to improve perioperative risk stratification.

Surgery

Gardner AK, Nepomnayshy D, **Reickert C**, Gee DW, Brydges R, Korndorffer JR, Jr., Scott DJ, and Sachdeva AK. The value proposition of simulation *Surgery* 2016;PMID: 27206331. [Full Text](#)

University of Texas Southwestern Medical Center, Dallas, TX. Electronic address:
aimee.gardner@utsouthwestern.edu.
Lahey Hospital and Medical Center, Burlington, MA.
Henry Ford Hospital, Detroit, MI.
Massachusetts General Hospital, Boston, MA.
University of Toronto, Toronto, ON, Canada.
Canada Tulane University School of Medicine, New Orleans, LA.
University of Texas Southwestern Medical Center, Dallas, TX.
American College of Surgeons, Chicago, IL.

BACKGROUND: Simulation has been shown to improve trainee performance at the bedside and in the operating room. As the use of simulation-based training is expanded to address a host of health care challenges, its added value needs to be clearly demonstrated. Demonstrable improvements will support the expansion of infrastructure, staff, and programs within existing simulation facilities as well as the establishment of new facilities to meet growing needs and demands. Thus, organizational and institutional leaders, faculty members, and other stakeholders can be assured of the best use of existing resources and can be persuaded to make greater investments in simulation-based training for the future. **METHODS:** A multidisciplinary panel was convened during the 8th Annual Meeting of the Consortium of the American College of Surgeons-Accredited Education Institutes (Simulation Centers) in March 2015 to discuss the added value of simulation-based training. Panelists shared the ways in which the value of simulation was demonstrated at their institutions. **CONCLUSION:** The value of simulation-based training was considered and described in terms of educational impact, patient care outcomes, and costs.

Surgery

Goyal N, Taylor AR, and Rivers EP. Relationship between central and peripheral venous oxygen saturation and lactate levels: A prospective study *J Emerg Med* 2016; PMID: 27210904. [Full Text](#)

Department of Emergency Medicine, Henry Ford Health System, Detroit, Michigan; Department of Internal Medicine, Henry Ford Health System, Detroit, Michigan.

Department of Public Health Science, Division of Biostatistics, Henry Ford Health System, Detroit, Michigan.

Department of Emergency Medicine, Henry Ford Health System, Detroit, Michigan; Department of Surgery, Henry Ford Health System, Detroit, Michigan.

BACKGROUND: Optimization of tissue oxygen delivery to meet consumption demands is important in the resuscitation of critically ill patients. Central venous oxygen saturation (ScvO₂) and lactate levels are often used to guide resuscitation; however, invasive monitoring is required for the former. Clinicians searching for less invasive alternatives may consider using peripheral venous oxygen saturation (SpvO₂) and lactate levels as a substitute. **OBJECTIVES:** To determine the relationship between SpvO₂ and ScvO₂ and peripheral and central lactate levels. **METHODS:** All patients with a central venous catheter in an academic emergency department and intensive care unit were eligible for the study. Blood was obtained simultaneously from a central and peripheral vein and measured for oxygen saturation and lactate levels. Results were analyzed using intraclass correlation coefficient (ICC), Bland-Altman plots, and receiver operating characteristic curves. **RESULTS:** Seventy-nine paired blood samples were analyzed. SpvO₂ and ScvO₂ have moderate agreement: ICC = 0.53 (95% confidence interval [CI] 0.35-0.67). A Bland-Altman plot revealed substantial bias (-4.47; limits of agreement -38.6, 29.6). SpvO₂ \geq 85% was 90% specific for ScvO₂ \geq 70%, and SpvO₂ of \leq 55% had a 94% sensitivity for ScvO₂ $<$ 70%. Central and peripheral venous lactate levels showed almost perfect agreement: ICC = 0.92 (95% CI 0.87-0.95), bias of 0.46 (limits of agreement -1.78-2.70). **CONCLUSION:** SpvO₂ and ScvO₂ have moderate agreement. There was excellent agreement between peripheral and central lactate levels, making them interchangeable. The clinical implications of these substitutions in real-time patient management require further study.

Surgery

Healy MA, McCahill LE, Chung M, Berri R, Ito H, Obi SH, Wong SL, Hendren S, and **Kwon D.** Intraoperative fluid resuscitation strategies in pancreatectomy: Results from 38 hospitals in michigan *Ann Surg Oncol* 2016; PMID: 27116681. [Full Text](#)

Department of Surgery, Center for Healthcare Outcomes & Policy, University of Michigan, Ann Arbor, MI, USA. healym@umich.edu.

Metro Health Hospital, Wyoming, MI, USA.

Spectrum Health Medical Group, Grand Rapids, MI, USA.

St. John Providence Hospitals, Grosse Pointe Woods, MI, USA.

Michigan State University, Lansing, MI, USA.

Allegiance Health, Jackson, MI, USA.

Dartmouth Geisel School of Medicine, Hanover, NH, USA.

Department of Surgery, Center for Healthcare Outcomes & Policy, University of Michigan, Ann Arbor, MI, USA.

Department of Surgery, Henry Ford Health System, Detroit, MI, USA.

BACKGROUND: Fluid administration practices may affect complication rates in some abdominal surgeries, but effects in patients undergoing pancreatectomy are not understood well. We sought to determine whether amount of intraoperative fluid administered to patients undergoing pancreatectomy is associated with postoperative complication rates and to determine whether hospitals vary in their fluid administration practices. **METHODS:** Data for 504 patients

undergoing pancreatectomy at 38 hospitals between 2012 and 2015 were evaluated. The main exposure was intraoperative fluid administration (≤ 10 , 10-15, > 15 mL/kg/h). Mortality, complications, and length of stay were the main outcomes of interest. Patient-level associations between exposure and outcome were tested, with adjustment for potentially confounding patient and surgical factors, using random intercept, mixed-effects linear or logistic regression models. Hospitals were then categorized as having a restrictive, intermediate, or liberal resuscitation practice, and adjusted outcomes were compared. RESULTS: A total of 167 (33.1 %), 185 (36.7 %) and 152 (30.2 %) patients received restrictive, intermediate, or liberal fluid administration, respectively. Hospitals with more restrictive practices had significantly lower adjusted 30-day mortality than those with more liberal practices (2.7 vs. 6.6 %; $P < 0.001$). Hospitals with more restrictive practices had the lowest rates of severe (Grade 2 and 3) complications (15.4 % restrictive vs. 25.3 % intermediate vs. 44.3 % liberal; $P < 0.001$). More restrictive hospitals had decreased adjusted mean length of stay (9.5 days vs. 12.7 days intermediate vs. 11.6 days liberal; $P < 0.001$). CONCLUSIONS: More restrictive intraoperative resuscitation practices in pancreatectomy are associated with decreased hospital-level mortality, severe complications, and length of stay.

Surgery

Miller-Matero LR, Bryce K, Hyde-Nolan ME, Dykhuis KE, Eshelman A, and Abouljoud M. Health literacy status affects outcomes for patients referred for transplant *Psychosomatics* 2016;PMID: 27231187. [Full Text](#)

Behavioral Health, Henry Ford Health System, Detroit, MI. Electronic address: Lmatero1@hfhs.org.
Behavioral Health, Henry Ford Health System, Detroit, MI; Transplant Institute, Henry Ford Health System, Detroit, MI.
Behavioral Health, Henry Ford Health System, Detroit, MI.
Transplant Institute, Henry Ford Health System, Detroit, MI.

BACKGROUND: It is hypothesized that limited health literacy affects outcomes for patients referred for transplant; however, research has not examined this for all types of end-stage organ disease. OBJECTIVE: The purpose of this study was to determine whether health literacy and cognitive impairment were related to listing for transplant and posttransplant outcomes. METHODS: Chart reviews were conducted on 398 patients who completed a required psychiatric evaluation before transplant listing. Information gathered from these evaluations included reading ability, math ability, and cognitive functioning. Variables before transplant and 6 months after transplantation were also collected. RESULTS: Patients with limited reading ability were less likely to be listed for transplant ($p = .018$) and were more likely to be removed from listing ($p = .042$), to miss appointments prelisting ($p = .021$), and to experience graft failure ($p = .015$). Patients with limited math ability were less likely to be listed ($p = .010$) and receive a transplant ($p = 0.031$), and more likely to be readmitted posttransplant ($p = .029$). Patients with cognitive impairment were less likely to be listed ($p = .043$) and to receive a transplant ($p = .010$). CONCLUSIONS: To achieve superior transplant access and outcomes, transplant providers should regularly screen patients for limited health literacy and cognitive impairment. Future studies should evaluate whether interventions result in better outcomes for these patients.

Surgery

Morgan JA, Go PH, Xuereb L, Kaur B, Akrawe S, Nemeh HW, Borgi J, Lanfear DE, Williams CT, and Paone G. Outcomes on continuous flow left ventricular assist devices: A single institutional 9-year experience *Ann Thorac Surg* 2016;PMID: 27173072. [Full Text](#)

Division of Cardiothoracic Surgery, Henry Ford Hospital, Heart and Vascular Institute, Detroit, Michigan. Electronic address: jamorganmd@hotmail.com.
Division of Cardiothoracic Surgery, Henry Ford Hospital, Heart and Vascular Institute, Detroit, Michigan.

BACKGROUND: Continuous-flow left ventricular assist devices (LVADs) have become the standard of care for patients with advanced heart failure. The goal of this study was to review our 9-year institutional experience. METHODS: From March 2006 through May 2015, 231 patients underwent implantation of 240 CF LVADs, HeartMate II LVAD (Thoratec Corp., Pleasanton, CA; $n = 205$) or HVAD (HeartWare Inc., Framingham, MA; $n = 35$). Of these, 127 devices (52.9%) were implanted as bridge to transplantation (BTT) and 113 (47.1%) as destination therapy (DT). RESULTS: Mean age was 51.2 \pm 11.9 years for BTT patients and 58.2 \pm 11.4 years for DT patients ($p < 0.001$). There was a higher incidence of preoperative diabetes, renal insufficiency, peripheral vascular disease, and previous cardiac operation in DT patients ($p < 0.05$). Survival was higher for BTT patients, with 1-, 6-, 12-, and 24-month survivals of 91.0%, 90.0%, 88.5%, and 72.1%, respectively, versus 85.3%, 81.1%, 75.6%, and 59.0%, respectively, for DT patients ($p = 0.038$). Gastrointestinal bleeding was the most common complication (29.6%), followed by right ventricular failure (22.5%) and stroke (15.0%), with a similar incidence for BTT and DT patients. Preoperative liver biopsy (hazard ratio [HR] 2.27, $p = 0.036$), mechanical support (HR 1.82, $p = 0.025$), aspartate transaminase (HR 1.07, $p = 0.001$), and alanine aminotransferase (HR 0.95, $p = 0.024$) were severe independent predictors of survival

in multivariate analysis. CONCLUSIONS: These data indicate excellent survival for BTT and DT patients on long-term LVAD support. However, for LVAD therapy to become a plausible alternative to heart transplantation, we need to further decrease the incidence of postoperative complications.

Surgery

Parekh R, Kazimi M, Skorupski S, Fagoaga O, Jafri S, and Segovia MC. Intestine transplantation across a positive crossmatch with preformed donor-specific antibodies *Transplant Proc* 2016; 48(2):489-491. PMID: 27109984.

[Full Text](#)

Department of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan.

Department of Transplant Surgery, Henry Ford Hospital, Detroit, Michigan.

Department of Pathology, Henry Ford Hospital, Detroit, Michigan.

Department of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan. Electronic address: msegovi3@hfhs.org.

BACKGROUND: We describe our experience using a modified protocol for immunosuppression for intestine transplantation across a positive crossmatch. Patients who underwent transplantation in 2013 were evaluated over a 12-month period for rejection and infectious events with comparison to procedure-matched controls on our standard protocol of immunosuppression. **PATIENTS AND METHODS:** We used a modified protocol for intestine and multivisceral transplantation for patients with a positive flow crossmatch. In addition to our standard protocol, patients with positive crossmatch were given rituximab and intravenous immunoglobulin (IVIg) preoperatively. DSA was sent for clinical evaluation at monthly intervals. Patients were screened for rejection by endoscopic evaluation. **RESULTS:** Four patients underwent transplantation within a single year across a positive crossmatch. Two received isolated intestine transplants and 2 had multivisceral transplantation (MVT). During the 12-month follow-up, 1 patients had an episode of severe acute cellular rejection, which was managed with increased immunosuppression. None of the patients had episodes of cytomegalovirus infection. One patient developed major infection and 3 patients developed minor bacterial infections. Among procedure-matched controls with negative final crossmatch on standard management (no preoperative rituximab or IVIg), 2 developed mild acute cellular rejection and 2 developed minor infections. One developed cytomegalovirus viremia with invasion to the colonic mucosa. **CONCLUSIONS:** We report our protocol for immunosuppression for IT and MVT across a positive crossmatch. This allowed transplantation despite the presence of a positive crossmatch, with low rejection rates but potentially increased risk for major infections compared to the negative crossmatch controls on our standard protocol.

Surgery

Park KU, Rubinfeld I, Hodari A, and Hammoud Z. Prolonged length of stay after esophageal resection: Identifying drivers of increased length of stay using the nsqip database *J Am Coll Surg* 2016; PMID: 27118713. [Full Text](#)

Department of Surgery, Henry Ford Health System, Detroit, MI.

Department of Cardiac and Thoracic Surgery, Henry Ford Health System, Detroit, MI. Electronic address: Zhammou1@hfhs.org.

BACKGROUND: Although influence of technical complications in association to hospital length of stay has been studied extensively in esophageal resection, nontechnical factors responsible for prolonged length of stay have not been reported. Using the NSQIP dataset, we hypothesized that we would be able to identify factors associated with prolonged length of stay after esophagectomy. **STUDY DESIGN:** National Surgical Quality Improvement Program data from 2005 to 2012 were reviewed for CPT codes for esophagectomy. Outlier status for length of stay was defined as >75th percentile. Logistic regression was used to predict outlier status and linear regression to discern factors contributing to longer lengths of stay. **RESULTS:** A total of 3,538 cases were reviewed. The 75th percentile for length of stay was 17 days. Preoperative predictors of hospital stay outliers include emergency surgery and frailty index (odds ratios = 3.7 and 3.6; $p < 0.001$). Deep organ space infection and progressive renal insufficiency had the highest likelihood of prolonged length of stay (odds ratios = 5.2 and 5.1; $p < 0.001$). Failure to wean off of ventilator in 48 hours, urinary tract infection, and pneumonia were associated with length of stay outlier (odds ratios = 3.7, 2.7, and 2.7; all $p < 0.001$). **CONCLUSIONS:** Urinary tract infection and pneumonia after esophagectomy are associated with longer hospital stays. Although meticulous surgical technique remains paramount, our study demonstrates that postoperative nontechnical complications factor into prolonged hospital stays. Focus on such factors can lead to reductions in hospital stays.

Surgery

Patel HJ, Herbert MA, **Paone G**, Heiser JC, Shannon FL, Theurer PF, Bell GF, and Prager RL. The midterm impact of transcatheter aortic valve replacement on surgical aortic valve replacement in michigan *Ann Thorac Surg* 2016;PMID: 27154157. [Full Text](#)

University of Michigan Cardiovascular Center, Ann Arbor, Michigan. Electronic address: hjpatel@med.umich.edu.
Southwest Data Consultants, Dallas, Texas.

Division of Cardiac Surgery, Henry Ford Hospital, Detroit, Michigan.

Division of Cardiac and Thoracic Surgery, Spectrum Health, Grand Rapids, Michigan.

Division of Cardiovascular and Thoracic Surgery, William Beaumont Hospital, Royal Oak, Michigan.

The Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative, Ann Arbor, Michigan.

University of Michigan Cardiovascular Center, Ann Arbor, Michigan.

BACKGROUND: We characterized the midterm impact of transcatheter aortic valve replacement (TAVR) on surgical aortic valve replacement (SAVR) volume, patient profiles, and outcomes in Michigan. **METHODS:** We analyzed data obtained after SAVR (n = 15,288) and TAVR (n = 1,783) using the Michigan Society of Thoracic and Cardiovascular Surgery Quality Collaborative from 2006 to 2015. During this period, 17 of 33 hospitals developed TAVR programs. **RESULTS:** Annual SAVR volume increased by 38.1% at TAVR hospitals and by 20.4% at non-TAVR hospitals, (p trend < 0.001). In TAVR hospitals, the Society of Thoracic Surgeons (STS) Predicted Risk of Mortality (PROM) decreased before (4.7% +/- 5.1%) and after (3.5% +/- 3.6%) initiation of TAVR (p < 0.001). Rates of 30-day mortality (pre-TAVR, 3.9% vs post-TAVR, 2.7%; p < 0.001) and renal failure (pre-TAVR, 5.2% vs post-TAVR, 3.3%; p < 0.001) but not stroke (pre-TAVR, 1.9% vs post-TAVR, 1.7%; p = 0.47) were lower after TAVR implementation. Length of stay decreased from 9.0 to 8.5 days (p < 0.001). When analyzing high-risk patients undergoing SAVR (ie, PROM >8%), neither mortality, stroke, nor renal failure was different (all p > 0.15). Despite a reduction in the STS-PROM, non-TAVR hospitals did not display changes in mortality, stroke, or renal failure for either the entire or the high-risk SAVR cohorts after initiation of TAVR in Michigan. **CONCLUSIONS:** TAVR implementation in Michigan has dramatically increased overall SAVR volume. This phenomenon has occurred with a concomitant decrease in preoperative risk profile and has improved early SAVR outcomes, particularly at TAVR hospitals, but surprisingly not in patients considered at high preoperative risk. As TAVR use increases, these issues may be further clarified and elucidated.

Surgery

Paulson D, Shah M, **Miller-Matero LR**, **Eshelman A**, and **Abouljoud M**. Cognition predicts quality of life among patients with end-stage liver disease *Psychosomatics* 2016;PMID: 27184728. [Full Text](#)

Department of Psychology, University of Central Florida, Orlando, FL; Consultation/Liaison Psychiatry, Henry Ford Health System, Detroit, MI.

Department of Psychology, University of Central Florida, Orlando, FL. Electronic address: mshah@knights.ucf.edu.

Consultation/Liaison Psychiatry, Henry Ford Health System, Detroit, MI.

Transplant Institute, Henry Ford Health System, Detroit, MI.

BACKGROUND: Impaired cognitive functioning and poor quality of life (QoL) are both common among patients with end-stage liver disease; however, it is unclear how these are related. **OBJECTIVE:** This study examines how specific cognitive domains predict QoL among liver transplant candidates by replicating Stewart and colleagues' (2010) 3-factor model of cognitive functioning, and determining how variability in these cognitive domains predicts mental health and physical QoL. **METHODS:** The sample included 246 patients with end-stage liver disease who were candidates for liver transplant at a large, Midwestern health care center. Measures, including the Repeatable Battery for the Assessment of Neuropsychological Status, Trail Making Test, Shipley Institute of Living Scale, Short-Form Health Survey-36 Version 2, and Hospital Anxiety and Depression Scale, comprised latent variables representing global intellectual functioning, psychomotor speed, and learning and memory functioning. **RESULTS:** Confirmatory factor analysis results indicate that the 3-factor solution model comprised of global intellectual functioning, psychomotor speed, and learning and memory functioning fit the data well. Addition of physical and mental health QoL latent factors resulted in a structural model also with good fit. Results related physical QoL to global intellectual functioning, and mental health QoL to global intellectual functioning and psychomotor functioning. **CONCLUSIONS:** Findings elucidate a relationship between cognition and QoL and support the use of routine neuropsychological screening with end-stage liver disease patients, specifically examining the cognitive domains of global intellectual, psychomotor, and learning and memory functioning. Subsequently, screening results may inform implementation of targeted interventions to improve QoL.

Surgery

Rao B, Jafri SM, Kazimi M, Mullins K, Raoufi M, and Segovia MC. A case report of acute cellular rejection following intestinal transplantation managed with adalimumab *Transplant Proc* 2016; 48(2):536-538. PMID: 27109995. [Full Text](#)

Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan.
Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan.
Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, Michigan.
Department of Pathology, Henry Ford Hospital, Detroit, Michigan.
Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan. Electronic address: msegovi3@hfhs.org.

There is a higher incidence of acute cellular rejection (ACR) in small bowel transplantation (SBT) compared with transplantation of other solid organs. Although there are reports on the use of infliximab to successfully treat ACR refractory to other treatments, there are no reports, to our knowledge, regarding the use of adalimumab. We present a case of a female patient with a history of Crohn's disease who underwent an isolated SBT and developed an episode of severe ACR. She was initially treated with methylprednisolone, thymoglobulin, basiliximab, and a dosage adjustment of tacrolimus. Results of repeat endoscopies and biopsies revealed no significant improvement. The patient initiated treatment with adalimumab every 2 weeks for a total of 6 months, in addition to maintenance treatment with prednisone and tacrolimus. Subsequent evaluations showed gradual improvement to normal mucosa and villi without ulceration. A regimen that incorporates adalimumab can thus be used to treat ACR after intestinal transplantation. Larger multicenter studies are needed to show the full efficacy of this therapeutic regimen.

Surgery

Rao B, Segovia MC, Kazimi M, Parekh R, Raoufi M, and Jafri SM. Use of everolimus after multivisceral transplantation: A report of two cases *Transplant Proc* 2016; 48(2):485-488. PMID: 27109983. [Full Text](#)

Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan.
Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan. Electronic address: msegovi3@hfhs.org.
Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, Michigan.
Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan.
Department of Pathology, Henry Ford Hospital, Detroit, Michigan.

Inhibitors of mechanistic target of rapamycin are used in solid organ transplant procedures to avoid calcineurin inhibitor complications, including nephrotoxicity and malignancy. We present 2 cases of multivisceral transplantation for neuroendocrine tumor (NET) for which everolimus was implemented for its potential to prevent NET recurrence as well as preserve renal function. The first case was complicated by NET recurrence in the liver before initiation of everolimus. After initiation of everolimus, the patient developed a ventral hernia and elevated aminotransferase levels with nonspecific biopsy findings. The second case was complicated by cytomegalovirus infection with elevated everolimus trough levels as well as acute cellular rejection. Everolimus was reinitiated in both cases in addition to decreasing the dosage of tacrolimus, and there were no further complications. Everolimus was beneficial in stabilizing renal function in both patients and has the theoretical potential to prevent recurrence of NET.

Surgery

Ruggero JM, and Prakash SN. Symptomatic lymphoepithelial cyst of the pancreas: successful treatment without pancreatic resection *J Surg Case Rep* 2016; 2016(4) PMID: 27141046. [Full Text](#)

Department of General Surgery, Henry Ford Macomb Hospital, 15855 19 Mile Rd. Clinton Township, MI 48038, USA
Jrugg2@hfhs.org.
Department of General Surgery, Henry Ford Macomb Hospital, 15855 19 Mile Rd. Clinton Township, MI 48038, USA.

Lymphoepithelial cysts (LECs) of the pancreas are rare benign lesions with unknown pathogenesis. LECs are true cysts that mimic pseudocysts and cystic neoplasms making diagnosis challenging. We report a case of a symptomatic LEC of the pancreas in a 67-year-old man who had severe epigastric pain. Workup including computed tomography and endoscopic ultrasound were non-diagnostic. The patient underwent attempted surgical resection; however, the mass was unresectable. The mass was enucleated and drained, and pathology returned LEC. The patient underwent a normal postoperative course and remained symptom free. Most LECs are diagnosed after an extensive pancreatic resection for suspicious cystic masses. The aim of this report is to show that operative management of LECs should not be limited to pancreatic resections. Excision and enucleation of LEC of the

pancreas is a better alternative than an extensive pancreatic resection. Preoperative diagnosis of LECs appears to be the limiting factor.

Surgery

Schmoekel NH, O'Connor JV, and Scalea TM. Nonoperative damage control: The use of extracorporeal membrane oxygenation in traumatic bronchial avulsion as a bridge to definitive operation *Ann Thorac Surg* 2016; 101(6):2384-2386. PMID: 27211954. [Full Text](#)

Henry Ford Hospital, Detroit, Michigan.

University of Maryland School of Medicine, R. Adams Cowley Shock Trauma Center, Baltimore, Maryland. Electronic address: jconnor@umm.edu.

University of Maryland School of Medicine, R. Adams Cowley Shock Trauma Center, Baltimore, Maryland.

The conventional treatment for an avulsed bronchus is emergent thoracotomy and repair or lobectomy. The principles of damage control thoracic operations include initial hemorrhage control with delayed definite repair after physiologic resuscitation. We report a multiply injured patient with avulsion of the left lower lobe bronchus. Profound acidosis, hypercarbia, and hypoxia precluded an emergent operation, and venovenous extracorporeal membrane oxygenation (V-V ECMO) was used for organ support during physiologic resuscitation. After the achievement of physiologic repletion, a thoracotomy and lobectomy were performed while the patient was supported by V-V ECMO.

Surgery

Simmons RM, Ballman KV, Cox C, Carp N, Sabol J, Hwang RF, Attai D, Sabel M, **Nathanson D**, Kenler A, Gold L, Kaufman C, Han L, Bleznak A, Stanley Smith J, Holmes D, Fornage B, Le-Petross C, Hoda S, McCall L, and Hunt KK. A phase II trial exploring the success of cryoablation therapy in the treatment of invasive breast carcinoma: Results from ACOSOG (Alliance) Z1072 *Ann Surg Oncol* 2016; PMID: 27221361. [Full Text](#)

Department of Surgery, Iris Cantor Women's Health Center, The New York Presbyterian Hospital, Joan and Sanford Weill Medical College of Cornell University, New York, NY, USA. rms2002@med.cornell.edu.

Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN, USA.

Department of Surgery, University of South Florida, Tampa, FL, USA.

Department of Surgery, Lankenau Medical Center, Wynnewood, PA, USA.

Department of Breast Surgical Oncology, MD Anderson Cancer Center, Houston, TX, USA.

Department of Surgery, Providence Saint Joseph Medical Center, Burbank, CA, USA.

Department of Surgery, University of Michigan Hospital, Ann Arbor, MI, USA.

Department of Surgery, Henry Ford Hospital, Detroit, MI, USA.

Department of Surgery, Bridgeport Hospital, Bridgeport, CT, USA.

Department of Surgery, Genesys Regional Medical Center, Grand Blanc, MI, USA.

Department of Surgery, Bellingham Breast Center, Bellingham, WA, USA.

Department of Surgery, Indiana University Hospital, Indianapolis, IN, USA.

Department of Surgery, Lehigh Valley Hospital, Allentown, PA, USA.

Department of Surgery, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA.

Department of Surgery, University of Southern California, Los Angeles, CA, USA.

Department of Diagnostic Radiology, MD Anderson Cancer Center, Houston, TX, USA.

Department of Pathology, Weill Cornell Medical College, New York, NY, USA.

Alliance Statistics and Data Center, Duke University, Durham, NC, USA.

BACKGROUND: Cryoablation is a well-established technique to treat fibroadenomas. Pilot studies suggest this could be an effective non-surgical treatment for breast cancer. American College of Surgeons Oncology Group Z1072 is a phase II trial exploring the effectiveness of cryoablation in the treatment of breast cancers. **METHODS:** The primary endpoint of Z1072 was the rate of complete tumor ablation, defined as no remaining invasive breast cancer (IBC) or ductal carcinoma in situ (DCIS) on pathologic examination of the targeted lesion. A secondary objective was to evaluate the negative predictive value of magnetic resonance imaging (MRI) to determine residual IBC or DCIS. Eligible patients included those with unifocal invasive ductal breast cancer ≤ 2 cm, with <25 % intraductal component and tumor enhancement on MRI. A total of 19 centers contributed 99 patients, of which 86 patients (87 breast cancers) were evaluable for data analysis. **RESULTS:** Final pathology results, regardless of whether residual IBC/DCIS was in the targeted ablation zone or elsewhere in the breast, showed successful ablation in 66/87 (75.9 %) cancers. The 90 % confidence interval for the estimate of successful cryoablation was 67.1-83.2, with the one-sided lower-sided 90 % CI of 69.0. The negative predictive value of MRI was 81.2 % (90 % CI 71.4-88.8). When multifocal disease outside of the targeted cryoablation zone was not defined as an ablation failure, 80/87 (92 %) of the treated

cancers had a successful cryoablation. CONCLUSION: Further studies with modifications on the Z1072 protocol could be considered to evaluate the role for cryoablation as a non-surgical treatment of early-stage breast cancer.

Surgery

Strobel RJ, Liang Q, Zhang M, Wu X, Rogers MA, Theurer PF, Fishstrom AB, **Harrington SD**, DeLucia A, 3rd, **Paone G**, Patel HJ, Prager RL, and Likosky DS. A preoperative risk model for postoperative pneumonia after coronary artery bypass grafting *Ann Thorac Surg* 2016;PMID: 27261082. [Full Text](#)

Medical School, University of Michigan, Ann Arbor, Michigan.

Department of Biostatistics, University of Michigan, Ann Arbor, Michigan.

Department of Cardiac Surgery, University of Michigan, Ann Arbor, Michigan.

Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan.

Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative, Ann Arbor, Michigan.

Heart and Vascular Institute, Henry Ford Macomb Hospitals, Clinton Township, Michigan.

Department of Cardiac Surgery, Bronson Methodist Hospital, Kalamazoo, Michigan.

Division of Cardiac Surgery, Henry Ford Hospital, Detroit, Michigan.

Department of Cardiac Surgery, University of Michigan, Ann Arbor, Michigan; Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative, Ann Arbor, Michigan.

Department of Cardiac Surgery, University of Michigan, Ann Arbor, Michigan; Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative, Ann Arbor, Michigan. Electronic address: likosky@umich.edu.

BACKGROUND: Postoperative pneumonia is the most prevalent of all hospital-acquired infections after isolated coronary artery bypass graft surgery (CABG). Accurate prediction of a patient's risk of this morbid complication is hindered by its low relative incidence. In an effort to support clinical decision making and quality improvement, we developed a preoperative prediction model for postoperative pneumonia after CABG. **METHODS:** We undertook an observational study of 16,084 patients undergoing CABG between the third quarter of 2011 and the second quarter of 2014 across 33 institutions participating in the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative. Variables related to patient demographics, medical history, admission status, comorbid disease, cardiac anatomy, and the institution performing the procedure were investigated. Logistic regression through forward stepwise selection ($p < 0.05$ threshold) was utilized to develop a risk prediction model for estimating the occurrence of pneumonia. Traditional methods were used to assess the model's performance. **RESULTS:** Postoperative pneumonia occurred in 3.30% of patients. Multivariable analysis identified 17 preoperative factors, including demographics, laboratory values, comorbid disease, pulmonary and cardiac function, and operative status. The final model significantly predicted the occurrence of pneumonia, and performed well (C-statistic: 0.74). These findings were confirmed through sensitivity analyses by center and clinically important subgroups. **CONCLUSIONS:** We identified 17 readily obtainable preoperative variables associated with postoperative pneumonia. This model may be used to provide individualized risk estimation and to identify opportunities to reduce a patient's preoperative risk of pneumonia through prehabilitation.

Surgery

Wang DD, Eng M, Greenbaum A, Myers E, Forbes M, Pantelic M, Song T, Nelson C, Divine G, Taylor A, Wyman J, Guerrero M, Lederman RJ, Paone G, and O'Neill W. Predicting LVOT Obstruction After TMVR *JACC Cardiovasc Imaging* 2016;PMID: 27209112. [Full Text](#)

Division of Cardiology, Center for Structural Heart Disease, Henry Ford Health System, Detroit, Michigan. Electronic address: dwang2@hfhs.org.

Division of Cardiology, Center for Structural Heart Disease, Henry Ford Health System, Detroit, Michigan.

Henry Ford Innovation Institute, Henry Ford Health System, Detroit, Michigan.

Division of Radiology, Henry Ford Health System, Detroit, Michigan.

Division of Cardiology, Center for Structural Heart Disease, Henry Ford Health System, Detroit, Michigan; Division of Cardiology, Evanston Hospital/NorthShore University Health System, Evanston, Illinois.

Cardiovascular and Pulmonary Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Urology

Abdollah F, Ye Z, Miller DC, Linsell SM, Montie JE, Peabody JO, and Ghani KR. Understanding the use of prostate biopsy among men with limited life expectancy in a statewide quality improvement collaborative *Eur Urol* 2016;PMID: 27113032. [Full Text](#)

Vattikuti Urology Institute and VUI Center for Outcomes Research Analytics and Evaluation, Henry Ford Hospital, Detroit, MI, USA.
Department of Urology, University of Michigan, Ann Arbor, MI, USA.
Department of Urology, University of Michigan, Ann Arbor, MI, USA. Electronic address: kghani@med.umich.edu.

BACKGROUND: The potential harms of a prostate cancer (PCa) diagnosis may outweigh its benefits in elderly men. **OBJECTIVE:** To assess the use of prostate biopsy in men with limited life expectancy (LE) within the practices comprising the Michigan Urological Surgery Improvement Collaborative (MUSIC). **DESIGN, SETTING, AND PARTICIPANTS:** MUSIC is a consortium of 42 practices and nearly 85% of the urologists in Michigan. From July 2013 to October 2014, clinical data were collected prospectively for all men undergoing prostate biopsy. **OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS:** We calculated comorbidity-adjusted LE in men aged ≥ 66 yr and identified men with < 10 yr LE (limited LE) undergoing a first biopsy. Our LE calculator was not designed for men aged < 66 yr; thus these men were excluded. Multivariable models estimated the proportion of all biopsies performed for men with limited LE in each MUSIC practice, adjusting for differences in patient characteristics. We also evaluated what treatments, if any, these patients received. **RESULTS AND LIMITATIONS:** Among 3035 men aged ≥ 66 yr undergoing initial prostate biopsy, 60% had none of the measured comorbidities. Overall, 547 men (18%) had limited LE. Compared with men with a longer LE, these men had significantly higher prostate-specific antigen levels and abnormal digital rectal examination findings. The adjusted proportion of biopsies performed for men with limited LE ranged from 3.8% to 39% across MUSIC practices ($p < 0.001$). PCa was diagnosed in 69% of men with limited LE; among this group, 74% received any active treatment. Of these men, 46% had high-grade cancer (Gleason score 8-10). **CONCLUSIONS:** Among a large and diverse group of urology practices, nearly 20% of prostate biopsies are performed in men with limited LE. These data provide useful context for quality improvement efforts aimed at optimizing patient selection for prostate biopsy. **PATIENT SUMMARY:** In this report, nearly 2 of every 10 men undergoing prostate biopsy had a life expectancy (LE) < 10 yr. Implementing LE calculators in clinical practice may help refine patient selection for prostate biopsy.

Urology

Chao GF, Krishna N, Aizer AA, **Dalela D**, Hanske J, Li H, Meyer CP, Kim SP, Mahal BA, Reznor G, Schmid M, Choueiri TK, Nguyen PL, M OL, and Trinh QD. Asian Americans and prostate cancer: A nationwide population-based analysis *Urol Oncol* 2016; 34(5):233.e237-233.e215. PMID: 26725248. [Full Text](#)

Department of Medicine, Harvard Medical School, Boston, MA.
Division of Urologic Surgery and Center for Surgery and Public Health, Brigham and Womens Hospital, Harvard Medical School, Boston, MA.
Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Womens Hospital, Harvard Medical School, Boston, MA.
Center for Outcomes Research, Analytics and Evaluation, Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI.
Urology Institute, University Hospitals Case Medical Center, Case Western Reserve University School of Medicine, Cleveland, OH.
Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA.
Division of Urologic Surgery and Center for Surgery and Public Health, Brigham and Womens Hospital, Harvard Medical School, Boston, MA. Electronic address: trnh.qd@gmail.com.

INTRODUCTION: It remains largely unknown if there are racial disparities in outcomes of prostate cancer (PCa) for Asian American and Pacific Islanders (PIs) (AAPIs). We examined differences in diagnosis, management, and survival of AAPI ethnic groups, relative to their non-Hispanic White (NHW) counterparts. **METHODS:** Patients ($n = 891,100$) with PCa diagnosed between 1988 and 2010 within the surveillance, epidemiology, and end results database were extracted and stratified by ethnic group: Chinese, Japanese, Filipino, Hawaiian, Korean, Vietnamese, Asian Indian/Pakistani, PI, and Other Asian. The effect of ethnic group on stage at presentation, rates of definitive treatment, and PCa-specific mortality was assessed. The severity at diagnosis was defined as: localized (TxNOM0), regional (TxN1M0), or metastatic (TxNxM1). **RESULTS:** Relative to NHWs, Asian Indian/Pakistani, Filipino, Hawaiian, and PI men had significantly worse outcomes. Filipino (odds ratio [OR] = 1.38, 95% CI: 1.27-1.51), Hawaiian, (OR = 1.70, 95% CI: 1.41-2.04), Asian Indian/Pakistani (OR = 1.37, 95% CI: 1.15-1.64), and PI men (OR = 1.90, 95% CI: 1.46-2.49) were more likely to present with metastatic PCa ($P < 0.001$). In patients with localized PCa, Filipino men were less likely to receive definitive treatment (OR = 0.91; 95% CI: 0.84-0.97; $P = 0.005$). Most AAPI groups had lower rates of PCa death except for Hawaiian (hazard ratio = 1.52; 95% CI: 1.30-1.77; $P < 0.0001$) and PI men (hazard ratio = 1.43; 95% CI: 1.12-1.82; $P < 0.0001$). **CONCLUSIONS:** Compared with NHWs, AAPI groups were more likely to present with advanced PCa but had better cancer-specific survival. Conversely, Hawaiian and PI men were at greater risk for PCa-specific mortality. Given the different cancer profiles, our results show that there is a need for disaggregation of AAPI data.

Urology

Dalela D, Loppenberg B, Sood A, Sammon J, and Abdollah F. Contemporary role of the decipher(r) test in prostate cancer management: Current practice and future perspectives *Rev Urol* 2016; 18(1):1-9. PMID: 27162506. [Full Text](#)

VUI Center for Outcomes, Research, Analytics and Evaluation, Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI.

We performed a systematic literature search to identify original articles and editorials about the Decipher((R)) Prostate Cancer Test (GenomeDx Biosciences, San Diego, CA) to provide an overview of the current literature and its present role in urologic clinical practice. The Decipher test, which uses the expression of 22 selected RNA markers (from a total of over 1.4 million), showed a very high discrimination in predicting clinical metastasis (0.75-0.83) and cancer-specific mortality (0.78) in external validation studies, outperforming all routinely available clinicopathologic characteristics. Further, the timing of postoperative radiotherapy (adjuvant vs salvage) may be guided based on Decipher scores. The Decipher test was also the only independent predictor of clinical metastasis in patients with biochemical recurrence after surgery. The Decipher Genomic Resource Information Database (GRID) is a novel research tool that captures 1.4 million marker expressions per patient and may facilitate precision-guided, individualized care to patients with prostate cancer. In this era of precision medicine, Decipher, along with the Decipher GRID platform, is a promising genomic tool that may aid in managing prostate cancer patients throughout the continuum of care and delivering appropriate treatment at an individualized level.

Urology

Freytag SO, Movsas B, and Stricker H. Clinical trials of oncolytic adenovirus-mediated gene therapy *Mol Ther* 2016; 24:S205-S205. PMID: Not assigned. Abstract

[Freytag, Svend O.; Movsas, Benjamin] Henry Ford Hlth Syst, Radiat Oncol, Detroit, MI USA. [Stricker, Hans] Henry Ford Hlth Syst, Urol, Detroit, MI USA.

Urology

Griffin MA, Janosek-Albright KJ, Diaz-Insua M, Elshatanoufy S, and Atiemo HO. Quality of life outcomes in peri-urethral calcium hydroxylapatite injection *Int Urogynecol J* 2016; PMID: 27250833. [Full Text](#)

Urogynecology Division, Department of Obstetrics and Gynecology, Henry Ford Hospital, K-9 Urology, 2799 West Grand Blvd, Detroit, MI, 48202, USA. mgriffi3@hfhs.org.

Henry Ford Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI, USA.

Urogynecology Division, Department of Obstetrics and Gynecology, Henry Ford Hospital, K-9 Urology, 2799 West Grand Blvd, Detroit, MI, 48202, USA.

INTRODUCTION AND HYPOTHESIS: Peri-urethral calcium hydroxylapatite injection is an established treatment for patients with stress urinary incontinence. Information is limited regarding calcium hydroxylapatite treatment and quality of life (QOL) outcomes. We hypothesize that patients might improve QOL after peri-urethral calcium hydroxylapatite injection, which was reflected in validated questionnaires. **METHODS:** The peri-urethral calcium hydroxylapatite injection billing code was used to identify patients who underwent injection from 2011-2013. Female patients who completed the American Urological Association Symptom Score (AUASS), the AUASS QOL and Michigan Incontinence Symptom Index (M-ISI), and the bother score (M-ISI bother), or pad count at baseline and follow-up were included. Change in questionnaire scores and pads were assessed using the paired t test. **RESULTS:** Sixty patients underwent 1 (30), 2 (63) or 3 (7 %) peri-urethral calcium hydroxylapatite injections performed by a single surgeon. Thirty-seven patients provided questionnaires and 38 provided pad counts, all with a mean age of 75 years. The overall AUASS, AUASS QOL, and overall M-ISI scores improved in 67.6, 54.8, and 61.3 % respectively (4.5 +/- 7.9, 1.3 +/- 1.7 and 5.5 +/- 8.6 respectively). The M-ISI bother score improved in 44.8 % with a mean improvement of 0.5 +/- 2.9, but did not reach significance. There was a 1.7 +/- 3.7 decrease in the mean number of pads used daily after the procedure (p = 0.006) and 19 % experienced transient urinary retention. **CONCLUSIONS:** Peri-urethral calcium hydroxylapatite injections can improve urinary QOL scores in patients with initial and recurrent stress urinary incontinence. This short-term retrospective analysis suggests that larger long-term studies focusing on QOL outcomes are needed to evaluate the effect of peri-urethral calcium hydroxylapatite has on incontinence-specific QOL.

Urology

Hanske J, Meyer CP, **Sammon JD**, Choueiri TK, **Menon M**, Lipsitz SR, Noldus J, Nguyen PL, Sun M, and Trinh QD. The influence of marital status on the use of breast, cervical, and colorectal cancer screening *Prev Med* 2016; PMID: 27215758. [Full Text](#)

Center for Surgery and Public Health and Division of Urologic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; Department of Urology, Marien Hospital, Ruhr-University Bochum, Herne, Germany.

Center for Surgery and Public Health and Division of Urologic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Center for Outcomes Research, Analytics and Evaluation, Vattikuti Urology Institute, Henry Ford Health System, Detroit, Michigan, USA.

Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA.

Center for Surgery and Public Health and Division of Urologic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

Department of Urology, Marien Hospital, Ruhr-University Bochum, Herne, Germany.

Department of Radiation Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA.

Center for Surgery and Public Health and Division of Urologic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA. Electronic address: qtrinh@bwh.harvard.edu.

PURPOSE: To examine the impact of marital status on the use of screening for breast, cervical, and colorectal cancer. **METHODS:** We relied on 2012 Behavioral Risk Factor Surveillance System Survey age-appropriate screening cohorts. Appropriate screening for breast, cervical, and colorectal cancer was determined according to United States Preventive Services Task Force recommendations in effect at the time of the 2012 survey. Complex samples logistic regression models were performed to examine the effect of marital status on cancer screening. **RESULTS:** Overall, 81.6, 83.9, and 68.9% of married participants underwent breast, cervical, and colorectal cancer, respectively, relative to 74.2, 75.1, and 60.9% for divorced/widowed/separated, individuals, and 74.7, 78.7, and 53.4% for never married individuals. Marital status (married vs. never married) was an independent predictor of screening for all cancers examined: breast cancer, odds ratio (OR): 1.42 (95% confidence interval [CI]: 1.25-1.61); cervical cancer, OR: 1.29 (95% CI: 1.16-1.43); colorectal cancer, OR: 1.63 (95%CI: 1.51-1.77). Gender-specific subgroup analyses for colorectal cancer suggests that marital status may exert a greater effect in men, relative to women (married men: OR 1.75, 95%CI: 1.56-1.96; married women: OR: 1.52, 95%CI: 1.35-1.70). **CONCLUSION:** Being married is associated with increased utilization of breast, cervical, and colorectal cancer screening. The influence of marital status was greater in men relative to women eligible for colorectal cancer screening. Our results emphasize the importance of social determinants of health-seeking behaviors.

Urology

Lieberman L, **Barod R**, Tapper A, **Kumar R**, and **Rogers C**. Robotic nephrectomy for central renal tumors with intraoperative evaluation of tumor histology *J Robot Surg* 2016; PMID: 27146858. [Full Text](#)

Wayne State University School of Medicine, 540 E. Canfield Rd, Detroit, MI, USA.

Vattikuti Urology Institute, Henry Ford Health Systems, 2799 W. Grand Blvd, Detroit, MI, USA.

Vattikuti Urology Institute, Henry Ford Health Systems, 2799 W. Grand Blvd, Detroit, MI, USA. crogers2@hfhs.org.

Patients undergoing nephrectomy for central renal tumors suspicious for renal cell carcinoma (RCC) may carry a small risk of having transitional cell carcinoma (TCC) on final pathology, even in the absence of filling defects or abnormal cytology. We describe outcomes in such patients undergoing robotic nephrectomy for suspected RCC, with intraoperative specimen assessment to guide completion ureterectomy if TCC is present. Between September 2010 and August 2015, ten patients had central renal masses suspicious for RCC, which were not amenable to nephron-sparing surgery. Patients underwent a four-arm robotic nephrectomy technique using a GelPOINT(R) access port. Following hilar ligation, the ureter was divided between adjacent hem-o-lok clips, placed in an endocatch bag, and extracted through the GelPOINT incision for the frozen section analysis. If intraoperative assessment confirmed TCC, a robotic completion ureterectomy and a bladder cuff excision were performed. Of the ten patients with central tumors who underwent robotic nephrectomy for suspected RCC, four (40 %) had TCC on the frozen section analysis and underwent completion ureterectomy. Five patients had RCC, and one patient had an oncocytoma. Mean age was 63.1 years (49-76) and mean tumor size was 4.0 cm (1.9-7.6). Mean operating time was 246 min (135-328). All patients had negative margins. Mean length of stay was 2.5 days. No recurrences were documented at median 8.5

months follow-up. For patients undergoing robotic nephrectomy for central renal tumors, intraoperative specimen evaluation can help determine the need for minimally invasive completion ureterectomy.

Urology

Loppenberg B, Dalela D, Karabon P, Sood A, Sammon JD, Meyer CP, Sun M, Noldus J, Peabody JO, Trinh QD, Menon M, and Abdollah F. The impact of local treatment on overall survival in patients with metastatic prostate cancer on diagnosis: a national cancer data base analysis *Eur Urol* 2016; PMID: 27174537. [Full Text](#)

VUI Center for Outcomes Research, Analytics, and Evaluation, Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI, USA; Department of Urology, Marien Hospital Herne, Ruhr-University Bochum, Herne, Germany.

VUI Center for Outcomes Research, Analytics, and Evaluation, Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI, USA.

VUI Center for Outcomes Research, Analytics, and Evaluation, Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI, USA; Henry Ford Health System, Public Health Sciences, Detroit, MI, USA.

Division of Urology, Center for Surgery and Public Health, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

Department of Urology, Marien Hospital Herne, Ruhr-University Bochum, Herne, Germany.

VUI Center for Outcomes Research, Analytics, and Evaluation, Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI, USA. Electronic address: firmas.abdollah@gmail.com.

BACKGROUND: The role of local treatment (LT) in patients with metastatic prostate cancer (mPCa) at diagnosis is controversial. **OBJECTIVE:** We set to evaluate the potential impact of LT on overall mortality (OM) in men with mPCa, and how this impact is influenced by tumor and patient characteristics. **DESIGN, SETTINGS, AND PARTICIPANTS:** A total of 15 501 patients with mPCa were identified in the National Cancer Data Base (2004-2012) and categorized in LT (radical prostatectomy or radiation therapy targeted to prostate) versus nonlocal treatment (NLT; all other patients). **OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS:** The two arms (LT vs NLT) were matched using propensity scores to minimize selection bias. To evaluate LT impact on OM in relation to baseline characteristics, first multivariable Cox regression analysis was used to predict OM in patients treated with NLT, then interaction between predicted OM risk and LT status was tested. **RESULTS AND LIMITATIONS:** Overall, 9.5% (n=1470) of patients received LT. In the postpropensity matched cohorts, 3-yr OM-free survival was higher in the LT group versus the NLT group (69% vs 54%; p<0.001). In multivariable Cox regression, the NLT group, age, and Charlson comorbidity index were predictors of OM (all p<=0.03). This model was used to predict the 3-yr OM risk. The interaction between predicted OM and LT status was significant (p<0.001). The benefit of LT on OM decreased progressively as predicted OM risk increased. Specifically, the 3-yr absolute improvement in OM-free survival was 15.7%, for patients with predicted OM risk <=20% versus 0% for those with predicted OM risk >=72%. **CONCLUSIONS:** Men with mPCa at diagnosis benefit from LT in terms of OM. This is largely affected by baseline characteristics. Specifically, patients with a relatively low tumor risk and good general health status appear to benefit the most. **PATIENT SUMMARY:** We used a large hospital-based database to evaluate which patients might benefit from local therapy when metastasized prostate cancer was present at diagnosis. Local therapy is associated with a survival benefit in men with less aggressive tumors and good general health.

Urology

Meyer CP, Hansen J, Boehm K, Tilki D, **Abdollah F**, Trinh QD, Fisch M, Sauter G, Graefen M, Huland H, Chun FK, and Ahyai SA. Tumor volume improves the long-term prediction of biochemical recurrence-free survival after radical prostatectomy for localized prostate cancer with positive surgical margins *World J Urol* 2016; PMID: 27260503.

[Full Text](#)

Department of Urology, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246, Hamburg, Germany. Christian.p.meyer@gmail.com.

Division of Urology, Brigham and Women's Hospital, Boston, MA, USA. Christian.p.meyer@gmail.com.

Department of Urology, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246, Hamburg, Germany.

Martini Clinic Prostate Cancer Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI, USA.

Division of Urology, Brigham and Women's Hospital, Boston, MA, USA.

Department of Pathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

PURPOSE: To develop a novel application evaluating the effect of tumor volume (TV) and percentage of high-grade tumor volume (%HGTV) on long-term biochemical recurrence-free survival rate (BCRFS) after radical prostatectomy (RP) in patients with pT2 PCa. **METHODS:** Retrospective analysis of 903 men with pT2 PCa between 1992 and 2004 at a single European tertiary care center was performed. Cox regression models identified risk factors for BCR. A

nomogram was developed to predict the BCRFS at 5, 10 and 15 years after RP. Decision curve analyses were performed to identify the net increase in cases identified by the full model. RESULTS: BCR-free survival rates at 5, 10 and 15 years were 94, 90 and 86 %. In Cox regression analyses, TV, %HGTV and positive surgical margin status (SM) were independent predictors of BCR. Predictive accuracies (PA) at 5, 10 and 15 years of the base model (PSA, Gleason score, SM) were 76.8 % (95 % CI 67.9-78.2 %), 70.5 % (95 % CI 64.9-75.0 %) and 68.1 % (95 % CI 60.6-73.5 %). The full model, including TV and %HGTV, achieved 76.9, 72.4 and 70.7 %. These PA differences were statistically significant at 10 and 15 years ($p < 0.001$). CONCLUSIONS: TV and %HGTV could potentially serve as valuable measures to stratify patients at high risk of BCR. The use of our nomogram should be considered to counsel patients with pT2 disease and SM and to design appropriate follow-up or treatment regimens.

Urology

Ross AE, Den RB, Yousefi K, Trock BJ, Tosoian J, Davicioni E, Thompson DJ, Choeung V, Haddad Z, Tran PT, Trabulsi EJ, Gomella LG, Lallas CD, **Abdollah F**, Feng FY, Klein EA, Dicker AP, Freedland SJ, Karnes RJ, and Schaeffer EM. Efficacy of post-operative radiation in a prostatectomy cohort adjusted for clinical and genomic risk *Prostate Cancer Prostatic Dis* 2016; PMID: 27136742. [Article Request Form](#)

James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, MD, USA.

Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA.

GenomeDx Biosciences, Vancouver, BC, Canada.

EMMES Canada, Burnaby, BC, Canada.

Department of Radiation Oncology, Johns Hopkins Hospital, Baltimore, MD, USA.

Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI, USA.

Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA.

Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA.

Department of Surgery, Division of Urology, Center for Integrated Research on Cancer and Lifestyle, Samuel Oschin Comprehensive Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA.

Surgery section, Durham Veteran Affairs Medical Center, Durham, NC, USA.

Department of Urology, Mayo Clinic, Rochester, MN, USA.

Department of Urology, Northwestern University, Evanston, IL, USA.

BACKGROUND: To date, there have been no published trials examining the impact of salvage radiation therapy (SRT) in the post-operative setting for prostate cancer (PCa). We conducted a retrospective, comparative study of post-operative radiation following radical prostatectomy (RP) for men with pT3 disease or positive margins (adverse pathological features, APF). METHODS: 422 PCa men treated at four institutions with RP and having APF were analyzed with a primary end point of metastasis. Adjuvant radiation treatment (ART, $n=111$), minimal residual disease (MRD) SRT ($n=70$) and SRT ($n=83$) were defined by PSA levels of <0.2 , $0.2-0.49$ and 0.5 ng ml $^{-1}$, respectively, before radiation therapy (RT) initiation. Remaining 157 men who did not receive additional therapy before metastasis formed the no RT arm. Clinical-genomic risk was assessed by Cancer of the Prostate Risk Assessment Post-Surgical (CAPRA-S) and Decipher. Cox regression was used to evaluate the impact of treatment on outcome. RESULTS: During the study follow-up, 37 men developed metastasis with a median follow-up of 8 years. Both CAPRA-S and Decipher had independent predictive value on multivariable analysis for metastasis ($P<0.05$). Adjusting for clinical-genomic risk, SRT and no RT had hazard ratios of 4.31 (95% confidence interval, 1.20-15.47) and 5.42 (95% confidence interval, 1.59-18.44) for metastasis compared with ART, respectively. No significant difference was observed between MRD-SRT and ART ($P=0.28$). Men with low-to-intermediate CAPRA-S and low Decipher value have a low rate of metastatic events regardless of treatment selection. In contrast, men with high CAPRA-S and Decipher benefit from ART, however the cumulative incidence of metastasis remains high. CONCLUSIONS: The decision as to the timing and need for additional local therapy following RP is nuanced and requires providers and patients to balance risks of morbidity with improved oncological outcomes. Post-RP treatment can be safely avoided for men who are low risk by clinical-genomic risk, whereas those at high risk should favor enrollment in clinical trials. *Prostate Cancer and Prostatic Diseases* advance online publication, 3 May 2016; doi:10.1038/pcan.2016.15.

Urology

Sood A, Hemal AK, Assimos DG, **Peabody JO**, **Menon M**, and Ghani KR. Robotic anastrophic nephrolithotomy utilizing near infrared fluorescence image-guidance: Idea, development, exploration, assessment, long-term monitoring (ideal) stage 0 animal model study *Urology* 2016; PMID: 27210569. [Full Text](#)

Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI. Electronic address: asood1@hfhs.org.

Department of Urology, Wake Forest Baptist Medical Center, Winston-Salem, NC.

Department of Urology, University of Alabama at Birmingham, Birmingham, AL.

Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI.

Department of Urology, University of Michigan, Ann Arbor, MI.

OBJECTIVES: To test the feasibility of robotic anatomic nephrolithotomy (RANL) using near infrared fluorescence (NIRF) image-guidance for treating staghorn stones, in an in vivo stone surgery model. **METHODS:** We developed a novel technique of RANL in a preclinical setting following guidelines on safe surgical innovation from the IDEAL collaborative. We performed two RANL procedures on two live Yorkshire porcine females (IDEAL stage 0 study). The robot was docked in the flank position and a mini-GelPOINT™ was placed periumbilically as an assistant port. A model staghorn 'stone' was created in vivo by injecting low viscosity DenMat™ precision material into the renal pelvis. NIRF image-guidance, following clamping of the posterior renal artery, was used to determine if an anatomic plane could be identified. One procedure was assessed under cold ischemia, with ice-slush injected onto the renal surface via the mini-GelPOINT™. **RESULTS:** Both porcine subjects underwent RANL successfully. Replica staghorn models could be created reliably (mean size 5.1 cm; solidification time 2-3 minutes). NIRF image-guidance afforded clear vascular demarcation for precise scoring of an anatomic plane in both kidneys. The staghorn models were removed in toto through the anatomic incision in both subjects. Mean blood loss was 160 cc. Mean console and ischemia times were 114 and 34.5 minutes, respectively; ice-slush hypothermia led to a renal surface temperature of 15.4 degrees C. **CONCLUSIONS:** In this IDEAL stage 0 preclinical study, we demonstrated that NIRF image-guidance is able to accurately identify the renal avascular plane, thus permitting an anatomic approach for robotic excision of staghorn stones.

Urology

Sood A, Klett DE, Abdollah F, Sammon JD, Pucheril D, Menon M, Jeong W, and Peabody JO. Robot-assisted partial cystectomy with intraoperative frozen section examination: Evolution and evaluation of a novel technique *Investig Clin Urol* 2016; 57(3):221-228. PMID: 27195322. [Full Text](#)

Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI, USA.

PURPOSE: To describe a novel modification to robot-assisted partial cystectomy (RAPC) that allows for intraoperative surgical margin assessment by bimanual-examination and frozen-section analysis. **MATERIALS AND METHODS:** A total of 7 patients underwent RAPC at a single tertiary-care institution between 2008 and 2013. The technique evolved over the study-period and permitted real-time intraoperative surgical margin evaluation in the last 5 patients via bimanual-examination and frozen-section analysis, utilizing the GelPOINT platform (a hand-assist device). The GelPOINT platform was placed through a 4- to 5-cm vertical supraumbilical incision and allowed for rapid retrieval of the bladder specimen without compromising the pneumoperitoneum or prolonging the operative time. Perioperative, oncological and functional outcomes were evaluated; all patients had a minimum 12-month follow-up. At the time of last follow-up, a cross-sectional survey of patients was performed to evaluate regret/satisfaction utilizing validated questionnaires. **RESULTS:** The mean age was 72.5 years; 71.4% of the patients were men (n=5). All patients underwent RAPC for a malignant indication. The mean operative and console times were 291 and 217 minutes, respectively. No patient had a positive surgical margin. Mean length-of-stay was 1.7 days. At a median follow-up of 38.9 months, 1 patient experienced a local recurrence 6 months postsurgery. The only mortality was secondary to Lewy-body disease, in the same patient, 1 year postoperatively. Patient assessment of regret and satisfaction indicated 0% regret and 0% dissatisfaction. **CONCLUSIONS:** The 'modified' technique of RAPC is technically feasible, safe, and reproducible; further, RAPC leads to favorable oncological, functional and quality-of-life outcomes in patients eligible for partial cystectomy.

Urology

Thamilselvan V, Menon M, and Thamilselvan S. Combination of carmustine and selenite effectively inhibits tumor growth by targeting androgen receptor, androgen receptor-variants and Akt in preclinical models: New hope for patients with prostate cancer *Int J Cancer* 2016; PMID: 27198552. [Full Text](#)

Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI, 48202, USA.

Despite established androgen receptor (AR) antagonists, AR/AR-variants signaling remain a major obstacle for the successful treatment of castration resistant prostate cancer (CRPC). In addition, CRPC cells adapt to survive via AR-independent pathways to escape next generation therapies. Therefore, there is an urgent need for drugs that can target these signaling pathways in CRPC. In the present study, we sought to determine whether carmustine and selenite in combination could induce apoptosis and inhibit growth of CRPC in-vitro and in-vivo. CRPC (22Rv1, VCaP and PC-3) cell culture and xenograft mouse model were used. Combination of carmustine and selenite treatment significantly increased reactive oxygen species, apoptosis and growth inhibition in CRPC cells with down regulation of anti-apoptotic (Bcl-2 and Mcl-1) and proliferative proteins (c-Myc and cyclin-D1). This effect was associated with complete reduction of AR/AR-variants, AR-V7, PSA and significant induction of p27Kip1. Combination treatment

substantially abolished phospho-Akt, phospho-GSK-3 β and anchorage-independent growth in AR-positive and AR-negative cells. Consistent with in-vitro results, combination treatment effectively induced apoptosis and completely inhibited xenograft tumor growth and markedly reduced AR/AR-variants, AR-V7, PSA, and Bcl-2 in xenograft tumors without causing genotoxicity in host mice. Individual agent treatment showed only partial effect. The combination treatment showed a significant synergistic effect. The present study is the first to demonstrate that the combination of carmustine and selenite treatment completely suppressed CRPC tumor growth by reducing AR/AR-variants and Akt signaling. Our findings suggest that the combination of carmustine and selenite could constitute a promising next-generation therapy for successful treatment of patients with CRPC. This article is protected by copyright. All rights reserved.

Urology

Yoon HJ, Shanker A, Wang Y, Kozminsky M, Jin Q, **Palanisamy N**, Burness ML, Azizi E, Simeone DM, Wicha MS, Kim J, and Nagrath S. Tunable thermal-sensitive polymer-graphene oxide composite for efficient capture and release of viable circulating tumor cells *Adv Mater* 2016;PMID: 27115557. [Article Request Form](#)

Department of Chemical Engineering, University of Michigan, 2300 Hayward Street, Ann Arbor, MI 48109, USA.
Department of Electrical Engineering and Computer Science, South Dakota State University, Brookings, SD 57007, USA.

Biointerfaces Institute, University of Michigan, 2800 Plymouth Road, Ann Arbor, MI 48109, USA.

Translational Oncology Program, University of Michigan Health System, 1600 Huron Pkwy, Ann Arbor, MI 48109, USA.

Macromolecular Science and Engineering, University of Michigan, 2300 Hayward Street, Ann Arbor, MI 48109, USA.
Henry Ford Health System, 1 Ford Place, Detroit, MI 48202, USA.

Department of Internal Medicine, University of Michigan Comprehensive Cancer Center, 1500 E. Medical Center Drive, Ann Arbor, MI 48109, USA.

Department of Material Science and Engineering, Department of Biomedical Engineering, Department of Chemistry, University of Michigan, 2300 Hayward Street, Ann Arbor, MI 48109, USA.

This study presents a highly sensitive microfluidic system to capture circulating tumor cells from the whole blood of cancer patients. The device incorporates graphene oxide into a thermoresponsive polymer film to serve as the first step of an antibody functionalization chemistry. By decreasing the temperature, captured cells may be released for subsequent analysis.