

# Gastroenterology

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**1617 Development and Validation of a Mucosal Impedance Contour Analysis System to Distinguish Esophageal Disorders**

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*D. A. Patel, T. Higginbotham, J. C. Slaughter, M. Aslam, E. Yuksel, D. Katzka, C. P. Gyawali, M. Mashi, J. Pandolfino, and M. F. Vaezi*

A Novel balloon mucosal impedance catheter is able to differentiate non-GERD from GERD and EoE instantly during routine endoscopy.

**1627 Postprandial Nutrient Handling and Gastrointestinal Hormone Secretion After Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy**

WWW

*M. S. Svane, K. N. Bojsen-Møller, C. Martinussen, C. Dirksen, J. L. Madsen, S. Reitelseder, L. Holm, J. F. Rehfeld, V. B. Kristiansen, G. van Hall, J. J. Holst, and S. Madsbad*

Postprandial nutrient absorption is greatly accelerated after gastric bypass but is only modestly accelerated after SG. Also, gastro-entero-pancreatic hormone secretion differs markedly between the two procedures.

**1642 Effects of Oral Anticoagulants and Aspirin on Performance of Fecal Immunochemical Tests in Colorectal Cancer Screening**

WWW E

*K. R. Randel, E. Botteri, K. M. K. Romstad, S. O. Frigstad, M. Bretthauer, G. Hoff, T. de Lange, and Ø. Holme*

See editorial on page 1553.

In a large colorectal cancer screening cohort in Norway, aspirin and direct-acting oral anticoagulants (DOACs) were associated with less chance of significant finding at colonoscopy after a positive test for blood in stool.

**1650 Effects of Proton Pump Inhibitors on Gastric Emptying and Symptoms: A Systematic Review and Meta-analysis**

WWW E

*P. Vijayvargiya, M. Camilleri, V. Chedid, A. Mandawat, P. J. Erwin, and M. H. Murad*

See editorial on page 1555.

A meta-analysis found a significant association between acceleration of gastric emptying and reduction in upper gastrointestinal symptoms. Proton pump inhibitors are therefore an important component of treatment for gastroparesis.

**1661 Magnitude, Risk Factors, and Factors Associated With Adenoma Miss Rate of Tandem Colonoscopy: A Systematic Review and Meta-analysis**

WWW

*S. Zhao, S. Wang, P. Pan, T. Xia, X. Chang, X. Yang, L. Guo, Q. Meng, F. Yang, W. Qian, Z. Xu, Y. Wang, Z. Wang, L. Gu, R. Wang, F. Jia, J. Yao, Z. Li, and Y. Bai*

The meta-analysis demonstrated higher levels of AMR and advanced AMR than previously thought, and APCC was a better predictor of AMR and advanced AMR than ADR.

**Clinical—Liver**

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**1675 Frailty Associated With Waitlist Mortality Independent of Ascites and Hepatic Encephalopathy in a Multicenter Study***J. C. Lai, R. S. Rahimi, E. C. Verna, M. R. Kappus, M. A. Dunn, M. McAdams-DeMarco, C. E. Haugen, M. L. Volk, A. Duarte-Rojo, D. R. Ganger, J. G. O'Leary, J. L. Dodge, D. Ladner, and D. L. Segev*

Frailty is common in patients with cirrhosis and is associated with death regardless of the presence of ascites or hepatic encephalopathy. Frailty can be objectively be measured in this population using the Liver Frailty Index.

**1683 Direct-Acting Antiviral Therapy Not Associated With Recurrence of Hepatocellular Carcinoma in a Multicenter North American Cohort Study**CME  
WWW  
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A. G. Singal, N. E. Rich, N. Mehta, A. Branch, A. Pillai, M. Hoteit, M. Volk, M. Odewole, S. Scaglione, J. Guy, A. Said, J. J. Feld, B. V. John, C. Frenette, P. Mantry, A. S. Rangnekar, O. Oloruntoba, M. Leise, J. H. Jou, K. R. Bhamidimarri, L. Kulik, T. Tran, H. Samant, R. Dhanasekaran, A. Duarte-Rojo, R. Salgia, S. Eswaran, P. Jalal, A. Flores, S. K. Satapathy, R. Wong, A. Huang, S. Misra, M. Schwartz, R. Mitrani, S. Nakka, W. Noureddine, C. Ho, V. R. Konjeti, A. Dao, K. Nelson, K. Delarosa, U. Rahim, M. Mavuram, J. J. Xie, C. C. Murphy, and N. D. Parikh

See editorial on page 1558.

Direct acting antiviral treatment for hepatitis C virus in patients with a history of treated hepatocellular carcinoma does not increase the risk of hepatocellular carcinoma recurrence.

**1693 Effects of Hypercholesterolemia and Statin Exposure on Survival in a Large National Cohort of Patients With Cirrhosis**

WWW

D. E. Kaplan, M. A. Serper, R. Mehta, R. Fox, B. John, A. Aytaman, M. Baytarian, K. Hunt, J. Albrecht, B. Njei, and T. H. Taddei, for the VOCAL Study Group

Among a large, national sample, each year of exposure to statin therapy was associated with an 8.0%–8.7% reduction of mortality in patients with cirrhosis primarily by reducing hepatic events.

**1707 A Missense Variant in PTPN22 is a Risk Factor for Drug-induced Liver Injury**

WWW

E. T. Cirulli, P. Nicoletti, K. Abramson, R. J. Andrade, E. S. Bjornsson, N. Chalasani, R. J. Fontana, P. Hallberg, Y. J. Li, M. I. Lucena, N. Long, M. Molokhia, M. R. Nelson, J. A. Odin, M. Pirmohamed, T. Rafnar, J. Serrano, K. Stefánsson, A. Stolz, A. K. Daly, G. P. Aithal, and P. B. Watkins, on behalf of Drug-Induced Liver Injury Network (DILIN) investigators and International DILI consortium (iDILIC)

This study identified a new genetic variant that is associated with risk of patients developing liver injury due to drugs and may help understand and ultimately prevent this adverse event.

**1717 Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease**

WWW

P. J. Eddowes, M. Sasso, M. Allison, E. Tsochatzis, Q. M. Anstee, D. Sheridan, I. N. Guha, J. F. Cobbold, J. J. Deeks, V. Paradis, P. Bedossa, and P. N. Newsome

This study provides clinical teams with a better understanding of how to use the Fibroscan device when establishing the severity of injury in the setting of non-alcoholic fatty liver disease.

**1731 Biomarkers Associated With Response to Regorafenib in Patients With Hepatocellular Carcinoma**

WWW

M. Teufel, H. Seidel, K. Köchert, G. Meinhardt, R. S. Finn, J. M. Llovet, and J. Bruix

This analysis identified biomarkers in blood that might be used to identify patients with liver cancer most likely to benefit from treatment with regorafenib.

**Clinical—Pancreas****1742 Phases of Metabolic and Soft Tissue Changes in Months Preceding a Diagnosis of Pancreatic Ductal Adenocarcinoma**WWW  
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R. P. Sah, A. Sharma, S. Nagpal, S. H. Patlolla, A. Sharma, H. Kandlakunta, V. Anani, R. S. Angom, A. K. Kamboj, N. Ahmed, S. Mohapatra, S. Vivekanandhan, K. A. Philbrick, A. Weston, N. Takahashi, J. Kirkland, N. Javeed, A. Matveyenko, M. J. Levy, D. Mukhopadhyay, and S. T. Chari

See editorial on page 1560.

Profound and phased changes in metabolic parameters, body weight, abdominal fat and muscle occur in the 3 years before pancreatic cancer diagnosis, which may provide clues to its early diagnosis.

**1753 Combination of Diclofenac and Sublingual Nitrates Is Superior to Diclofenac Alone in Preventing Pancreatitis After Endoscopic Retrograde Cholangiopancreatography**

*T. Tomoda, H. Kato, T. Ueki, Y. Akimoto, H. Hata, M. Fujii, R. Harada, T. Ogawa, M. Wato, M. Takatani, M. Matsubara, Y. Kawai, and H. Okada*

The combined prophylactic treatment with rectal diclofenac and sublingual isosorbide dinitrate significantly reduced the overall incidence of post-ERCP pancreatitis, when compared with treatment with the diclofenac suppository alone.

**Basic and Translational—Alimentary Tract****1761 Systems Biology Analyses Show Hyperactivation of Transforming Growth Factor- $\beta$  and JNK Signaling Pathways in Esophageal Cancer**

*A. E. Blum, S. Venkitachalam, D. Ravillah, A. K. Chelluboyina, A. M. Kieber-Emmons, L. Ravi, A. Kresak, A. K. Chandar, S. D. Markowitz, M. I. Canto, J. S. Wang, N. J. Shaheen, Y. Guo, Y. Shyr, J. E. Willis, A. Chak, V. Varadan, and K. Guda*

Esophageal adenocarcinoma is a lethal malignancy with limited therapeutic options. TGF $\beta$  and JNK pathways are potential drivers of esophageal adenocarcinoma, uncovering novel therapeutic avenues in this malignancy.

**1775 Correction of Defective T-Regulatory Cells From Patients With Crohn's Disease by Ex Vivo Ligation of Retinoic Acid Receptor- $\alpha$** 

*R. Goldberg, C. Scotta, D. Cooper, E. Nissim-Eliraz, E. Nir, S. Tasker, P. M. Irving, J. Sanderson, P. Lavender, F. Ibrahim, J. Corcoran, T. Prevost, N. Y. Shpigel, F. Marelli-Berg, G. Lombardi, and G. M. Lord*

Patients with Crohn's disease develop intestinal inflammation partly because of an imbalance between inflammatory and anti-inflammatory immune cells. The authors developed a method to expand anti-inflammatory T cells that travel to the gut and correct this imbalance.

**Basic and Translational—Liver****1788 Estrogen Activation of G-Protein-Coupled Estrogen Receptor 1 Regulates Phosphoinositide 3-Kinase and mTOR Signaling to Promote Liver Growth in Zebrafish and Proliferation of Human Hepatocytes**

*S. Chaturantabut, A. Shwartz, K. J. Evason, A. G. Cox, K. Labella, A. G. Schepers, S. Yang, M. Acuña, Y. Houvras, L. Mancio-Silva, S. Romano, D. A. Gorelick, D. E. Cohen, L. I. Zon, S. N. Bhatia, T. E. North, and W. Goessling*

E2 signals via GPER1 to increase embryonic and adult liver size and growth by activation of PI3K signaling to mTOR. E2 signaling via GPER1 contributes to sex-dimorphic adult hepatocyte proliferation and promotes liver cancer formation and progression.

**1805 Hepatitis D Virus-Specific CD8<sup>+</sup> T Cells Have a Memory-Like Phenotype Associated With Viral Immune Escape in Patients With Chronic Hepatitis D Virus Infection**

*H. Kefalakes, C. Koh, J. Sidney, G. Amanakis, A. Sette, T. Heller, and B. Rehermann*

This study identifies targets of HDV-specific CD8<sup>+</sup> T cells in chronic HDV infection and characterizes HDV-specific CD8<sup>+</sup> T cells to provide insight into viral control and disease pathogenesis.

**1820 Mutations in Hepatitis D Virus Allow It to Escape Detection by CD8<sup>+</sup> T Cells and Evolve at the Population Level**

*H. Karimzadeh, M. M. Kiraithe, V. Oberhardt, E. Salimi Alizei, J. Bockmann, J. Schulze zur Wiesch, B. Budeus, D. Hoffmann, H. Wedemeyer, M. Cornberg, A. Krawczyk, J. Rashidi-Alavijeh, F. Rodríguez-Frías, R. Casillas, M. Buti, A. Smedile, S. M. Alavian, A. Heinold, F. Emmerich, M. Panning, E. Gostick, D. A. Price, J. Timm, M. Hofmann, B. Raziourrouh, R. Thimme, U. Protzer, M. Roggendorf, and C. Neumann-Haefelin*

Hepatitis D virus (HDV) mutates to evade immune recognition by CD8<sup>+</sup> T cells. These mutations accumulate at the population level and facilitate viral persistence.

**1834 Polycomb Repressive Complex 2 Proteins EZH1 and EZH2 Regulate Timing of Postnatal Hepatocyte Maturation and Fibrosis by Repressing Genes With Euchromatic Promoters in Mice**

www

*J. M. Grindheim, D. Nicetto, G. Donahue, and K. S. Zaret*

Transcriptional repressor proteins EZH1 and EZH2 are identified as repressing hepatocyte and fibrosis genes with euchromatic promoters to regulate timely postnatal maturation and fibrosis. EZH1/2 loss leads to fibrosis.

**1849 MET Inhibitors Promote Liver Tumor Evasion of the Immune Response by Stabilizing PDL1**

www

*H. Li, C.-W. Li, X. Li, Q. Ding, L. Guo, S. Liu, C. Liu, C.-C. Lai, J.-M. Hsu, Q. Dong, W. Xia, J. L. Hsu, H. Yamaguchi, Y. Du, Y.-J. Lai, X. Sun, P. B. Koller, Q. Ye, and M.-C. Hung***See editorial on page 1563.**

The combination of MET inhibitor and anti-PD1 therapy potently improves the effectiveness of MET inhibitors against HCC.

**1862 Use of Expression Profiles of HBV-DNA Integrated Into Genomes of Hepatocellular Carcinoma Cells to Select T Cells for Immunotherapy**

www

*A. T. Tan, N. Yang, T. Lee Krishnamoorthy, V. Oei, A. Chua, X. Zhao, H. S. Tan, A. Chia, N. Le Bert, D. Low, H. K. Tan, R. Kumar, F. G. Irani, Z. Z. Ho, Q. Zhang, E. Guccione, L.-E. Wai, S. Koh, W. Hwang, W. C. Chow, and A. Bertoletti*

Analysis of hepatitis B virus (HBV) DNA integrated into hepatocellular carcinoma cells can be used to select HBV-specific T-cell receptors for immunotherapy.

**1877 CXCR6 Inhibits Hepatocarcinogenesis by Promoting Natural Killer T- and CD4<sup>+</sup> T-Cell-Dependent Control of Senescence**

www

*J. C. Mossanen, M. Kohlhepp, A. Wehr, O. Krenkel, A. Liepelt, A. A. Roeth, D. Möckel, F. Heymann, T. Lammers, N. Gassler, J. Hermann, J. Jankowski, U. P. Neumann, T. Luedde, C. Trautwein, and F. Tacke***See editorial on page 1565.**

Inflammation may promote liver cancer, but can also have antitumoral effects. The chemokine receptor CXCR6, which is related to inflammatory lymphocyte recruitment in liver diseases, suppresses hepatocarcinogenesis by promoting NKT- and CD4<sup>+</sup> T cell-dependent senescence control.

**1890 Plasma Cell Polarization to the Immunoglobulin G Phenotype in Hepatocellular Carcinomas Involves Epigenetic Alterations and Promotes Hepatoma Progression in Mice**

www

*Y. Wei, X.-M. Lao, X. Xiao, X.-Y. Wang, Z.-J. Wu, Q.-H. Zeng, C.-Y. Wu, R.-Q. Wu, Z.-X. Chen, L. Zheng, B. Li, and D.-M. Kuang*

B cell-macrophage interaction induces sequential IgG<sup>+</sup> plasma cell differentiation, protumorigenic macrophage polarization, effector T cell suppression, and hepatoma progression.

**Basic and Translational—Pancreas****1905 Prevalence of Germline Mutations Associated With Cancer Risk in Patients With Intraductal Papillary Mucinous Neoplasms**

www

*M. Skaro, N. Nanda, C. Gauthier, M. Felsenstein, Z. Jiang, M. Qiu, K. Shindo, J. Yu, D. Hutchings, A. A. Javed, R. Beckman, J. He, C. L. Wolfgang, E. Thompson, R. H. Hruban, A. P. Klein, M. Goggins, L. D. Wood, and N. J. Roberts*

Sequencing of 94 genes associated with cancer risk in patients with surgically resected intraductal papillary mucinous neoplasms identified frequent deleterious germline mutations.

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*F. Kanwal*

**BRIEF COMMUNICATIONS**

- 1919 **Prevalence of Pathogenic Variants of *FAN1* in More Than 5000 Patients Assessed for Genetic Predisposition to Colorectal, Breast, Ovarian, or Other Cancers**  
*A. Fievet, E. Mouret-Fourme, C. Colas, A. de Pauw, D. Stoppa-Lyonnet, and B. Buecher*
- 1921 **Long-term Outcomes of Fecal Microbiota Transplantation in Patients With Cirrhosis**  
*J. S. Bajaj, A. Fagan, E. A. Gavis, Z. Kassam, M. Sikaroodi, and P. M. Gillevet*
- 1924 **RNA Analysis Identifies Pathogenic Duplications in *MSH2* in Patients With Lynch Syndrome**  
*B. R. Conner, F. Hernandez, B. Souders, T. Landrith, C. R. Boland, and R. Karam*

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- 1926 **Gut Microbes Drive T-Cell Infiltration into Colorectal Cancers And Influence Prognosis**  
*J. P. Thomas, D. Divekar, J. Brooks, and A. J. M. Watson*
- 1928 **How Deep Are the Roots of Barrett's Esophagus?**  
*K. Nowicki-Osuch and M. Di Pietro*
- 1930 **Lights and Shadows on Fibrates as Second-Line Therapy of Primary Biliary Cholangitis**  
*M. Colombo, A. Lleo, and A. Lleo*

**CORRESPONDENCE**

- 1932 **Circulating Epithelial Cells in Patients With Liver Disease**  
*J. Wang, R. Dong, and S. Zheng*
- 1932 **Reply to "Detection and Analysis of Circulating Epithelial Cells in Liquid Biopsies from Patients with Liver Disease": Implications for Transplant Chimerism**  
*F. J. M. Roos, J. N. M. Ijzermans, and L. J. W. van der Laan*
- 1933 **Reply**  
*I. Bhan, M. Aryee, and D. T. Ting*

- 1934 Predict, Resect, Identify and Discard Strategy with Full-field Optical Coherence Tomography: Two Steps Forward, One Step Back**  
*F. Yang, D. Ma, and Z. Li*
- 1935 Reply**  
*F. Prat, F. Beuvon, and M. Camus*
- 1936 Correction**

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