

# Gastroenterology

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## ORIGINAL RESEARCH

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**2060 Loss of Chromatin-Remodeling Proteins and/or CDKN2A Associates With Metastasis of Pancreatic Neuroendocrine Tumors and Reduced Patient Survival Times**  
*S. Roy, W. A. LaFramboise, T.-C. Liu, D. Cao, A. Luvison, C. Miller, M. A. Lyons, R. J. O'Sullivan, A. H. Zureikat, M. E. Hogg, A. Tsung, K. K. Lee, N. Bahary, R. E. Brand, J. S. Chennat, K. E. Fasanella, K. McGrath, M. N. Nikiforova, G. I. Papachristou, A. Slivka, H. J. Zeh, and A. D. Singhi*

Through whole-exome sequencing of distant metastatic pancreatic neuroendocrine tumors (PanNETs), recurrent genomic alterations were identified in *DAXX*, *ATRX*, *SETD2*, *ARID1A* and *CDKN2A*, and may represent prognostic markers of poor patient outcome.

## 2064 Methotrexate Reduces DNA Integrity in Sperm From Men With Inflammatory Bowel Disease

*D. Ley, J. Jones, J. Parrish, S. Salih, F. Caldera, E. Tirado, B. Leader, and S. Saha*

This study showed that men with IBD taking methotrexate have significant deficits in sperm integrity despite having normal basic semen analyses, suggesting that their fertility is compromised by methotrexate use.

### Full Reports

#### Clinical—Alimentary Tract

## 2068 The Effect of Endoscopic Surveillance in Patients With Barrett's Esophagus: A Systematic Review and Meta-analysis

*D. C. Codipilly, A. K. Chandar, S. Singh, S. Wani, N. J. Shaheen, J. M. Inadomi, A. Chak, and P. G. Iyer*

A meta-analysis of studies assessing the impact of surveillance endoscopy in Barrett's esophagus appears to show an improvement in cancer mortality and earlier lesion detection, but these results are limited by a lack of randomized controlled trials and lead/length time bias.

## 2087 Dietary Patterns After the Weaning and Lactation Period Are Associated With Celiac Disease Autoimmunity in Children

*M. Barroso, S. A. Beth, T. Voortman, V. W. V. Jaddoe, M. C. van Zelm, H. A. Moll, and J. C. Kiefte-de Jong*

Higher adherence to a Prudent dietary pattern characterized by high intake of vegetables, vegetable oils, pasta, and grains, was associated with lower odds of having celiac disease autoimmunity at 6 years of age.

## 2097 Clinical and Genomic Correlates of Neutrophil Reactive Oxygen Species Production in Pediatric Patients With Crohn's Disease

*L. A. Denson, I. Jurickova, R. Karns, K. A. Shaw, D. J. Cutler, D. T. Okou, A. Dodd, K. Quinn, K. Mondal, B. J. Aronow, Y. Haberman, A. Linn, A. Price, R. Bezold, K. Lake, K. Jackson, T. D. Walters, A. Griffiths, R. N. Baldassano, J. D. Noe, J. S. Hyams, W. V. Crandall, B. S. Kirschner, M. B. Heyman, S. Snapper, S. L. Guthery, M. C. Dubinsky, N. S. Leleiko, A. R. Otley, R. J. Xavier, C. Stevens, M. J. Daly, M. E. Zwick, and S. Kugathasan*

A subset of pediatric Crohn's Disease patients exhibit mutations in genes which encode NADPH oxidases, which are in turn associated with reduced production of neutrophil reactive oxygen species and a more aggressive clinical course.

#### Clinical—Liver

## 2111 Baseline Factors Associated With Improvements in Decompensated Cirrhosis After Direct-Acting Antiviral Therapy for Hepatitis C Virus Infection

*O. El-Sherif, Z. G. Jiang, E. B. Tapper, K. C. Huang, A. Zhong, A. Osinusi, M. Charlton, M. Manns, N. H. Afdhal, K. Mukamal, J. McHutchison, D. M. Brainard, N. Terrault, and M. P. Curry*

A new scoring system may help clinicians predict which patients with liver failure are likely to benefit the most from treatment with direct-acting antiviral therapy.

#### Basic and Translational—Alimentary Tract

## 2122 Change in Populations of Macrophages Promotes Development of Delayed Gastric Emptying in Mice

*G. Cipriani, S. J. Gibbons, K. E. Miller, D. S. Yang, M. L. Terhaar, S. T. Eisenman, T. Ördög, D. R. Linden, G. B. Gajdos, J. H. Szurszewski, and G. Farrugia*

Diabetic gastroparesis is a serious complication of diabetes with few effective treatments. In a mouse model of disease, the authors identified targets in immune cells for treatment of diabetic gastroparesis.

**2137 Super-Enhancer-Driven Long Non-Coding RNA LINC01503, Regulated by TP63, Is Over-Expressed and Oncogenic in Squamous Cell Carcinoma**

J.-J. Xie, Y.-Y. Jiang, Y. Jiang, C.-Q. Li, M.-C. Lim, O. An, A. Mayakonda, L.-W. Ding, L. Long, C. Sun, L.-H. Lin, L. Chen, J.-Y. Wu, Z.-Y. Wu, Q. Cao, W.-K. Fang, W. Yang, H. Soukiasian, S. J. Meltzer, H. Yang, M. Fullwood, L.-Y. Xu, E.-M. Li, D.-C. Lin, and H. P. Koeffler

LINC01503 is a novel super-enhancer-driven lncRNA that is up-regulated in squamous cell carcinoma (SCC). Considering its association with poor patient survival and its oncogenic functions, LINC01503 represents a potential biomarker and therapeutic target for this malignancy.

**2152 Determining Risk of Colorectal Cancer and Starting Age of Screening Based on Lifestyle, Environmental, and Genetic Factors**

J. Jeon, M. Du, R. E. Schoen, M. Hoffmeister, P. A. Newcomb, S. I. Berndt, B. Caan, P. T. Campbell, A. T. Chan, J. Chang-Claude, G. G. Giles, J. Gong, T. A. Harrison, J. R. Huyghe, E. J. Jacobs, L. Li, Y. Lin, L. Le Marchand, J. D. Potter, C. Qu, S. A. Bien, N. Zubair, R. J. Macinnis, D. D. Buchanan, J. L. Hopper, Y. Cao, R. Nishihara, G. Rennert, M. L. Slattery, D. C. Thomas, M. O. Woods, R. L. Prentice, S. B. Gruber, Y. Zheng, H. Brenner, R. B. Hayes, E. White, U. Peters, and L. Hsu, on behalf of the Colorectal Transdisciplinary Study and Genetics and Epidemiology of Colorectal Cancer Consortium

Both environmental/lifestyle and genetic risk factors inform a person's risk for colorectal cancer and could be used for devising individually tailored prevention strategies.

**2165 Analysis of Genes Associated With Monogenic Primary Immunodeficiency Identifies Rare Variants in XIAP in Patients With Crohn's Disease**

L. Amininejad, B. Charlotiaux, E. Theatre, C. Liefferinckx, J. Dmitrieva, P. Hayard, V. Muls, J.-M. Maisin, M. Schapira, J.-M. Ghislain, P. Closset, M. Talib, M. Abramowicz, Y. Momozawa, V. Deffontaine, F. Crins, M. Mni, L. Karim, N. Cambisano, S. Ornemese, A. Zucchi, C. Minsart, J. Deviere, J.-P. Hugot, M. De vos, E. Louis, S. Vermeire, A. Van Gossum, W. Coppieters, J.-C. Twizere, M. Georges, and D. Franchimont, and The International IBD Genetics Consortium

See editorial on page 2022.

Genes associated with monogenic primary immunodeficiencies may also harbor mutations involved in inflammatory bowel disease. Systematic evaluation of these genes led to the identification of such genetic variation in the gene encoding XIAP.

## Basic and Translational—Liver

**2178 Alterations in Intestinal Microbiota Lead to Production of Interleukin 17 by Intrahepatic  $\gamma\delta$  T-Cell Receptor-Positive Cells and Pathogenesis of Cholestatic Liver Disease**

D. Tedesco, M. Thapa, C. Y. Chin, Y. Ge, M. Gong, J. Li, S. Gumber, P. Speck, E. J. Elrod, E. M. Burd, W. H. Kitchens, J. F. Magliocca, A. B. Adams, D. S. Weiss, M. Mohamadzadeh, and A. Grakoui

These results suggest that a particular genetic disease can resculpture the microbiota with far-reaching immunological and pathological consequences.

**2194 HCV Genotype 6a Escape From and Resistance to Velpatasvir, Pibrentasvir, and Sofosbuvir in Robust Infectious Cell Culture Models**

L. V. Pham, S. Ramirez, J. M. Gottwein, U. Fahnøe, Y.-P. Li, J. Pedersen, and J. Bukh

Clinical strains of HCV genotype 6a can be adapted to propagate in cultured cells, permitting mechanistic studies of the complete life cycle for this important genotype.

**2209 P300 Acetyltransferase Mediates Stiffness-Induced Activation of Hepatic Stellate Cells Into Tumor-Promoting Myofibroblasts**

C. Dou, Z. Liu, K. Tu, H. Zhang, C. Chen, U. Yaqoob, Y. Wang, J. Wen, J. van Deursen, D. Sicard, D. Tschumperlin, H. Zou, W.-C. Huang, R. Urrutia, V. H. Shah, and N. Kang

See editorial on page 2025.

Cancer cells recruit hepatic stellate cells to form a stiff stroma and the stromal stiffness, in return, activates RHOA-AKT-p300 mechanosignaling of hepatic stellate cells to promote tumor growth in the liver.

**2222 Dysregulated Response of Follicular Helper T Cells to Hepatitis B Surface Antigen Promotes HBV Persistence in Mice and Associates With Outcomes of Patients**  
*X. Wang, Q. Dong, Q. Li, Y. Li, D. Zhao, J. Sun, J. Fu, F. Meng, H. Lin, J. Luan, B. Liu, M. Wang, F.-S. Wang, F. He, and L. Tang*

This study demonstrated that attenuation of FOXP3+ T-regulatory cell suppressive function by CTLA4 blockade restores the follicular helper T cell-dependent anti-HBs response and promotes HBV clearance in HBV-persistent mice.

**2237 Secretion of Hepatitis C Virus Replication Intermediates Reduces Activation of Toll-Like Receptor 3 in Hepatocytes**  
*O. Grünvogel, O. Colasanti, J.-Y. Lee, V. Klöss, S. Belouzard, A. Reustle, K. Esser-Nobis, J. Hesebeck-Brinckmann, P. Mutz, K. Hoffmann, A. Mehrabi, R. Koschny, F. W. R. Vondran, D. Gotthardt, P. Schnitzler, C. Neumann-Haefelin, R. Thimme, M. Binder, R. Bartenschlager, J. Dubuisson, A. H. Dalpke, and V. Lohmann*

The authors identified a novel viral immune evasion mechanism based on secretion of viral double stranded RNA from infected cells within extracellular vesicles. Through this process, Hepatitis C virus (HCV) is less efficiently recognized, helping to maintain persistence.

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**2252 Neuronal Transforming Growth Factor beta Signaling via SMAD3 Contributes to Pain in Animal Models of Chronic Pancreatitis**  
*L. Liu, Y. Zhu, M. Noë, Q. Li, and P. J. Pasricha*

Transforming growth factor beta in pancreatic tissue acts directly on pancreatic sensory neurons to increase pain sensitivity in chronic pancreatitis.

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