

## Contents

### ON THE COVER

Gastroenterology

Please see Jung et al on page 36 for more information.



### COVERING THE COVER

1 A. T. Chan and C. S. Williams

### COMMENTARY

4 A Curmudgeon Reflects on Half a Century of Gastrointestinal Pathology  
H. D. Appelman

### MENTORING, EDUCATION, AND TRAINING CORNER

7 How to Prepare for and Write a Grant: Personal Perspectives  
N. O. Davidson and H. B. El-Serag

### EDITORIALS

12 "New" Cancer Genes and Inherited Colorectal Cancer Risk: Caveat Emptor  
M. B. Yurgelun and C. R. Boland

See Broderick P et al on page 75.

14 Inflammatory Bowel Disease: A Global Disease That Needs a Broader Ensemble of Populations  
A. Franke

See Brant SR et al on page 206.

16 Isthmus Time Is Here: Runx1 Identifies Mucosal Stem Cells in the Gastric Corpus  
J. R. Goldenring and J. C. Mills

See Matsuo J et al on page 218.

19 Genetic Optimization of Liver Cancer Therapy: A Patient-Derived Primary Cancer Cell-Based Model

P. Munoz-Garrido and J. B. Andersen

See Gao Q et al on page 232.

Video Related article in CGH

CME quiz Editorial accompanies this article Additional online content available Cover

Publisher: *Gastroenterology* (ISSN 0016-5085) is published monthly (semi monthly in January and May) in two indexed volumes by Elsevier Inc, 230 Park Avenue, New York, NY 10169. Periodicals postage paid at New York, NY and additional mailing offices. POSTMASTER: Send address changes to GASTROENTEROLOGY, Elsevier Health Sciences Division, Subscription Customer Service, 3251 Riverport Lane, Maryland Heights, MO 63043. 2017 US subscription rates: Individual, \$684.00; student and resident, \$261.00. Outside of the U.S. and possessions: Individual, \$968.00; student and resident, \$562.00; surface delivery, no additional charge; air mail delivery, add \$78.00. Prices subject to change without notice.

- 21 **SMAD About Hepatitis C Virus Cell Entry and Liver Disease**  
*C. C. Colpitts and T. F. Baumert*  
See Zhang F et al on page 257.

## GASTROENTEROLOGY IN MOTION

- 24 **Breath Testing for Barrett's Esophagus Using Exhaled Volatile Organic Compound Profiling With an Electronic Nose Device**  
*D. K. Chan, L. Zakko, K. H. Visrodia, C. L. Leggett, L. S. Lutzke, M. A. Clemens, J. D. Allen, M. A. Anderson, and K. K. Wang*

## CLINICAL CHALLENGES AND IMAGES IN GI

- 27 **Abdominopelvic CT in a Patient With Seizure, Anemia, and Hypocalcemia**  
*N. Zamani, H. Hassanian-Moghaddam, and M. Latifi*
- 29 **A Rare Cause of Painful Skin Rash in Crohn's Disease**  
*C. Umapathy, N. Seth, and S. Ganesh*
- 31 **A Rare Cause of Generalized Edema**  
*J.-W. Chou, K.-S. Cheng, and C.-P. Lin*
- 34 **Unusual Colonic Obstruction**  
*Y.-Y. Chen, C.-C. Chen, and C.-Y. Chen*

## ELECTRONIC CLINICAL CHALLENGES AND IMAGES IN GI

For a full list, please see the table of contents online at [www.gastrojournal.org](http://www.gastrojournal.org).

## REVIEWS AND PERSPECTIVES

### Reviews in Basic and Clinical Gastroenterology and Hepatology

- 36 **Transforming Growth Factor  $\beta$  Superfamily Signaling in Development of Colorectal Cancer**  
*B. Jung, J. J. Staudacher, and D. Beauchamp*
- 53 **Using Big Data to Discover Diagnostics and Therapeutics for Gastrointestinal and Liver Diseases**  
*B. Wooden, N. Goossens, Y. Hoshida, and S. L. Friedman*

## ORIGINAL RESEARCH

### Brief Reports

- 68 **Hypermutation In Pancreatic Cancer**  
*J. L. Humphris, A.-M. Patch, K. Nones, P. J. Bailey, A. L. Johns, S. McKay, D. K. Chang, D. K. Miller, M. Pajic, K. S. Kassahn, M. C. J. Quinn, T. J. C. Bruxner, A. N. Christ, I. Harliwong, S. Idrisoglu, S. Manning, C. Nourse, E. Nourbakhsh, A. Stone, P. J. Wilson, M. Anderson, J. L. Fink, O. Holmes, S. Kazakoff, C. Leonard, F. Newell, N. Waddell, S. Wood, R. S. Mead, Q. Xu, J. Wu, M. Pinese, M. J. Cowley, M. D. Jones, A. M. Nagrial, V. T. Chin, L. A. Chantrill, A. Mawson, A. Chou, C. J. Scarlett, A. V. Pinho, I. Rooman, M. Giry-Laterriere, J. S. Samra, J. G. Kench, N. D. Merrett, C. W. Toon, K. Epari, N. Q. Nguyen, A. Barbour, N. Zeps, N. B. Jamieson, C. J. McKay, C. R. Carter, E. J. Dickson, J. S. Graham, F. Duthie, K. Oien, J. Hair, J. P. Morton, O. J. Sansom, R. Grützmann, R. H. Hruban, A. Maitra, C. A. Iacobuzio-Donahue, R. D. Schulick, C. L. Wolfgang, R. A. Morgan, R. T. Lawlor, B. Rusev, V. Corbo, R. Salvia, I. Cataldo, G. Tortora, M. A. Tempero, Australian Pancreatic Cancer Genome Initiative, O. Hofmann, J. R. Eshleman, C. Pilarsky, A. Scarpa, E. A. Musgrove, A. J. Gill, J. V. Pearson, S. M. Grimmond, N. Waddell, and A. V. Biankin*

Defining mutation loads and optimal assays may inform precision therapies and better clinical trials for immunotherapy in pancreatic cancer.

**75 Validation of Recently Proposed Colorectal Cancer Susceptibility Gene Variants in an Analysis of Families and Patients—a Systematic Review**

*P. Broderick, S. E. Dobbins, D. Chubb, B. Kinnersley, M. G. Dunlop, I. Tomlinson, and R. S. Houlston*

See editorial on page 12.

Published evidence supports an association between variants in NTHL1 and RPS20 with colorectal cancer (CRC), but not for other recently reported CRC susceptibility variants.

**78 A System for In Vivo Imaging of Hepatic Free Fatty Acid Uptake**

*H. M. Park, K. A. Russo, G. Karateev, M. Park, E. Dubikovskaya, L. J. Kriegsfeld, and A. Stahl*

A bioluminescence imaging system with a free fatty acid (FFA) probe may be useful for studying the changes in hepatic FFA flux in models of liver disease.

**Full Reports**

**Clinical—Alimentary Tract**

**82 Effectiveness of Pelvic Physiotherapy in Children With Functional Constipation Compared With Standard Medical Care**

*M. L. van Engelenburg-van Lonkhuyzen, E. M. J. Bols, M. A. Benninga, W. A. Verwijs, and R. A. de Bie*

Pelvic physiotherapy is a likely effective treatment option for functional constipation in children.

**92 Lifestyle Risk Factors for Serrated Colorectal Polyps: A Systematic Review and Meta-analysis**

*L. Bailie, M. B. Loughrey, and H. G. Coleman*

Several changeable lifestyle factors, most notably smoking and alcohol, are associated with risk for serrated colorectal polyps.

**105 Similar Efficacy of Proton-Pump Inhibitors vs H2-Receptor Antagonists in Reducing Risk of Upper Gastrointestinal Bleeding or Ulcers in High-Risk Users of Low-Dose Aspirin**

*F. K. L. Chan, M. Kyaw, T. Tanigawa, K. Higuchi, K. Fujimoto, P. K. Cheong, V. Lee, Y. Kinoshita, Y. Naito, T. Watanabe, J. Y. L. Ching, K. Lam, A. Lo, H. Chan, R. Lui, R. S. Y. Tang, Y. Sakata, Y. K. Tse, T. Takeuchi, O. Handa, H. Nebiki, J. C. Y. Wu, T. Abe, T. Mishiro, S. C. Ng, and T. Arakawa*

PPIs and H2RAs were similarly effective against long-term upper GI bleeding in high-risk aspirin users.

**111 Identification of an Intestinal Microbiota Signature Associated With Severity of Irritable Bowel Syndrome**

*J. Tap, M. Derrien, H. Törnblom, R. Brazeilles, S. Cools-Portier, J. Doré, S. Störsrud, B. Le Nevé, L. Öhman, and M. Simrén*

An intestinal microbiota profile was associated with severity of IBS symptoms. This microbiota signature can be used to explore relevant features in future IBS studies.

**124 Colon Hypersensitivity to Distension, Rather Than Excessive Gas Production, Produces Carbohydrate-Related Symptoms in Individuals With Irritable Bowel Syndrome**

*G. Major, S. Pritchard, K. Murray, J. P. Alappadan, C. L. Hoad, L. Marciani, P. Gowland, and R. Spiller*

Visceral hypersensitivity rather than excess gas, was associated with symptoms among IBS patients eating FODMAP-containing foods.

**Clinical—Liver**

**134 Proton Pump Inhibitors Increase Risk for Hepatic Encephalopathy in Patients With Cirrhosis in A Population Study**

*C.-F. Tsai, M.-H. Chen, Y.-P. Wang, C.-J. Chu, Y.-H. Huang, H.-C. Lin, M.-C. Hou, F.-Y. Lee, T.-P. Su, and C.-L. Lu*

PPI use among patients with cirrhosis was associated with an increased risk for hepatic encephalopathy.

- 142** **Eradication of Hepatitis C Virus Infection in Patients With Cirrhosis Reduces Risk of Liver and Non-Liver Complications**  
*P. Nahon, V. Bourcier, R. Layese, E. Audureau, C. Cagnot, P. Marcellin, D. Guyader, H. Fontaine, D. Larrey, V. De Ledinghen, D. Ouzan, F. Zoulim, D. Roulot, A. Tran, J.-P. Bronowicki, J.-P. Zarski, V. Leroy, G. Riachi, P. Calès, J.-M. Péron, L. Alric, M. Bourlière, P. Mathurin, S. Dharancy, J.-F. Blanc, A. Abergel, L. Serfaty, A. Mallat, J.-D. Grangé, P. Attali, Y. Bacq, C. Wartelle, T. Dao, Y. Benhamou, C. Pilette, C. Silvain, C. Christidis, D. Capron, B. Bernard-Chabert, D. Zucman, V. Di Martino, V. Thibaut, D. Salmon, M. Ziol, A. Sutton, S. Pol, and F. Roudot-Thoraval, for the ANRS CO12 CirVir Group*

Successful treatment of hepatitis C was associated with a reduced overall mortality and risk of death from liver-related and non-liver-related causes.

- 157** **Transjugular Intrahepatic Portosystemic Shunts With Covered Stents Increase Transplant-Free Survival of Patients With Cirrhosis and Recurrent Ascites**  
*C. Bureau, D. Thabut, F. Oberti, S. Dharancy, N. Carbonell, A. Bouvier, P. Mathurin, P. Ota, P. Cabarrou, J. M. Péron, and J. P. Vinel*

TIPS with covered stents were associated with improved transplant-free survival among cirrhotic patients with ascites.

- 164** **Effectiveness of Elbasvir and Grazoprevir Combination, With or Without Ribavirin, for Treatment-Experienced Patients With Chronic Hepatitis C Infection**  
*P. Kwo, E. J. Gane, C.-Y. Peng, B. Pearlman, J. M. Vierling, L. Serfaty, M. Buti, S. Shafran, P. Stryszak, L. Lin, J. Gress, S. Black, F. J. Dutko, M. Robertson, J. Wahl, L. Lupinacci, E. Barr, and B. Haber*

The combination tablet of elbasvir and grazoprevir, with or without ribavirin, effectively induced sustained virologic response 12 weeks after treatment in patients with HCV genotype 1, 4, or 6 infection failed by previous treatment with peginterferon and ribavirin.

## Basic and Translational—Alimentary Tract

- 176** **Rectal Delivery of a DNzyme That Specifically Blocks the Transcription Factor GATA3 and Reduces Colitis in Mice**  
*V. Popp, K. Gerlach, S. Mott, A. Turowska, H. Garn, R. Atreya, H.-A. Lehr, I.-C. Ho, H. Renz, B. Weigmann, and M. F. Neurath*

GATA3 levels are increased in patients with ulcerative colitis and correlate with production of inflammatory cytokines in mice and humans. A DNzyme that prevents expression of GATA3 reduces colitis in mice and cytokine levels in the colon.

- 193** **Fucosylation Deficiency in Mice Leads to Colitis and Adenocarcinoma**  
*Y. Wang, D. Huang, K.-Y. Chen, M. Cui, W. Wang, X. Huang, A. Awadallah, Q. Li, A. Friedman, W. W. Xin, L. Di Martino, F. Cominelli, A. Miron, R. Chan, J. G. Fox, Y. Xu, X. Shen, M. F. Kalady, S. Markowitz, I. Maillard, J. B. Lowe, W. Xin, and L. Zhou*

Carcinogenesis in a subset of colon cancer was found to result from a molecular mechanism driven by fucosylation deficiency and/or HES1-loss.

- 206** **Genome-Wide Association Study Identifies African-Specific Susceptibility Loci in African Americans With Inflammatory Bowel Disease**  
*S. R. Brant, D. T. Okou, C. L. Simpson, D. J. Cutler, T. Haritunians, J. P. Bradfield, P. Chopra, J. Prince, F. Begum, A. Kumar, C. Huang, S. Venkateswaran, L. W. Datta, Z. Wei, K. Thomas, L. J. Herrinton, J.-M. A. Klapproth, A. J. Quiros, J. Seminerio, Z. Liu, J. S. Alexander, R. N. Baldassano, S. Dudley-Brown, R. K. Cross, T. Dassopoulos, L. A. Denson, T. A. Dhere, G. W. Dryden, J. S. Hanson, J. K. Hou, S. Z. Hussain, J. S. Hyams, K. L. Isaacs, H. Kader, M. D. Kappelman, J. Katz, R. Kellermayer, B. S. Kirschner, J. F. Kuemmerle, J. H. Kwon, M. Lazarev, E. Li, D. Mack, P. Mannon, D. E. Moulton, R. D. Newberry, B. O. Osuntokun, A. S. Patel, S. A. Saeed, S. R. Targan, J. F. Valentine, M.-H. Wang, M. Zonca, J. D. Rioux, R. H. Duerr, M. S. Silverberg, J. H. Cho, H. Hakonarson, M. E. Zwick, D. P. B. McGovern, and S. Kugathasan*

**See editorial on page 14.**

Susceptibility loci associated with Crohn's disease and ulcerative colitis were found exclusively in an African American population.

- 218 Identification of Stem Cells in the Epithelium of the Stomach Corpus and Antrum of Mice**  
 J. Matsuo, S. Kimura, A. Yamamura, C. P. Koh, M. Z. Hossain, D. L. Heng, K. Kohu, D. C.-C. Voon, H. Hiai, M. Unno, J. B. Y. So, F. Zhu, S. Srivastava, M. Teh, K. G. Yeoh, M. Osato, and Y. Ito

See editorial on page 16.

A Runx1 enhancer element, eR1, was used to express oncogenic mutations in gastric stem cells, proving a new model for studies of gastric carcinogenesis.

## Basic and Translational—Liver

- 232 Cell Culture System for Analysis of Genetic Heterogeneity Within Hepatocellular Carcinomas and Response to Pharmacologic Agents**

Q. Gao, Z.-C. Wang, M. Duan, Y.-H. Lin, X.-Y. Zhou, D. L. Worthley, X.-Y. Wang, G. Niu, Y. Xia, M. Deng, L.-Z. Liu, J.-Y. Shi, L.-X. Yang, S. Zhang, Z.-B. Ding, J. Zhou, C.-M. Liang, Y. Cao, L. Xiong, R. Xi, Y.-Y. Shi, and J. Fan

See editorial on page 19.

A patient-derived cell line-based model, integrating genetic and pharmacologic data from multiregional cancer samples, provides a platform to elucidate how intratumor heterogeneity affects sensitivity to different therapeutic agents.

- 243 Estrogen Signals Through Peroxisome Proliferator-Activated Receptor- $\gamma$  Coactivator 1 $\alpha$  to Reduce Oxidative Damage Associated With Diet-Induced Fatty Liver Disease**

A. Besse-Patin, M. Léveillé, D. Oropeza, B. N. Nguyen, A. Prat, and J. L. Estall

In mice, loss of estrogen signaling contributes to oxidative damage caused by low levels of PGC1A in liver, exacerbating steatohepatitis associated with diets high in fructose and fat.

- 257 Infection of Hepatocytes With HCV Increases Cell Surface Levels of Heparan Sulfate Proteoglycans, Uptake of Cholesterol and Lipoprotein, and Virus Entry by Up-regulating SMAD6 and SMAD7**

F. Zhang, C. Sodroski, H. Cha, Q. Li, and T. J. Liang

See editorial on page 21.

A complex mechanism of HCV entry may link inflammation, immune regulation, and metabolic dysfunction.

## CONTINUING MEDICAL EDUCATION (CME)/MOC ACTIVITIES

- e15 Exam 1: Breath Testing for Barrett's Esophagus Using Exhaled Volatile Organic Compound Profiling With an Electronic Nose Device**
- e17 Exam 2: Lifestyle Risk Factors for Serrated Colorectal Polyps: A Systematic Review and Meta-analysis**
- e18 Exam 3: American Gastroenterological Association Institute Guideline on the Management of Crohn's Disease After Surgical Resection**

## AGA SECTION

- 271 American Gastroenterological Association Institute Guideline on the Management of Crohn's Disease After Surgical Resection**

G. C. Nguyen, E. V. Loftus Jr, I. Hirano, Y. Falck-Ytter, S. Singh, S. Sultan, and the AGA Institute Clinical Guidelines Committee

- 276 American Gastroenterological Association Institute Guideline on the Management of Crohn's Disease After Surgical Resection: Clinical Decision Support Tool**

American Gastroenterological Association Institute

- 277 American Gastroenterological Association Institute Technical Review on the Management of Crohn's Disease After Surgical Resection**

M. Regueiro, F. Velayos, J. B. Greer, C. Bougatsos, R. Chou, S. Sultan, and S. Singh

296 **Managing Crohn's Disease After Surgery: A Patient Guide**  
*American Gastroenterological Association Institute*

**SELECTED SUMMARIES**

298 **Endoscopic Findings in Eosinophilic Esophagitis and Esophageal Distensibility: A Proxy for Transmural Modeling?**  
*B. Kochar and E. S. Dellon*

**CORRESPONDENCE**

- 300 **Sofosbuvir and Daclatasvir Anti-Viral Therapy Fails to Clear HEV Viremia and Restore Reactive T Cells in a HEV/HCV Co-Infected Liver Transplant Recipient**  
*M. C. Donnelly, S. N. Imlach, F. Abravanel, S. Ramalingam, I. Johannessen, J. Petrik, A. R. Fraser, J. D. M. Campbell, P. Bramley, H. R. Dalton, P. C. Hayes, N. Kamar, and K. J. Simpson*
- 301 **Bismuth and Non-bismuth Quadruple Therapy for *Helicobacter pylori* Eradication: Time to Make the Switch in Clinical Practice?**  
*J.-M. Liou, J.-T. Lin, and M.-S. Wu*
- 303 **The Toronto *Helicobacter pylori* Consensus in Context**  
*Y. Niv*
- 303 **Reply**  
*C. A. Fallone, J. P. Gisbert, N. Chiba, S. Veldhuyzen van Zanten, L. Fischbach, R. H. Hunt, N. L. Jones, C. Render, G. I. Leontiadis, P. Moayyedi, and J. K. Marshall*
- 304 **No Excess Cancer Recurrence After Immunosuppressive Drugs in a Meta-analysis of Cohorts of Patients With Immune-mediated Diseases: A Mirage Related to Propensity Bias?**  
*L. Beaugerie and L. Peyrin-Biroulet*
- 306 **Reply**  
*E. Shelton and A. N. Ananthakrishnan*
- 306 **Indomethacin to Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis: When and How?**  
*J. George, A. K. Saluja, and J. S. Barkin*
- 307 **Reply**  
*N. R. Thiruvengadam, K. A. Forde, V. Chandrasekhara, and M. L. Kochman*

**Access to the full content of Gastroenterology Online is available to all subscribers!**

AGA members have seamless access to full Gastroenterology content from the AGA Web site. Simply sign in to <http://www.gastro.org>, visit the Publications section of the Web site, and click on Gastroenterology. You will be directed to the Journal Web site and will have full access to all content without having to supply a different username and password. Members can also visit <http://www.gastrojournal.org> directly and click on "Activate Online Access." Nonmember subscribers must create an online user account and activate their subscription to access the full text of articles on Gastroenterology Online. To activate your individual online subscription, please visit <http://www.gastrojournal.org> and click on "Activate Online Access." To activate your account, you

will need your subscriber account or member number, which you can find on your mailing label. (AGA members must use their 10-digit member number, including leading zeros). If you have any questions regarding your online subscription please call Elsevier Customer Service at (800) 654-2452.

Institutional access to Gastroenterology Online will be allowed only by limited site licensing. Further instructions will be available online. Personal subscriptions to Gastroenterology Online are for individual use only and may not be transferred. Use of Gastroenterology Online is subject to agreement to the terms and conditions of use as indicated online.

**AGA Member Number**

**Your Account Number**

Sample mailing label

GAST0000101864  
 JANE DOE  
 531 MAIN ST  
 CENTER CITY, NY 10001-001

1GAST V91-4 1234567-8  
 JANE DOE  
 531 MAIN ST  
 CENTER CITY, NY 10001-001