

# Gastroenterology

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**(CME) (E) (WWW)** *P. Wieszczyn, E. Waldmann, M. Løberg, J. Regula, M. Rupinski, M. Bugajski, K. Gray, M. Kalager, M. Ferlitsch, M. F. Kaminski, and M. Bretthauer*

**See editorial on page 1007.**

Alongside adenoma characteristics, colonoscopists performance may be an important factor guiding timing of follow-up surveillance colonoscopies.

**1075 Artificial Intelligence System to Determine Risk of T1 Colorectal Cancer Metastasis to Lymph Node**

**(WWW)** *S.-e. Kudo, K. Ichimasa, B. Villard, Y. Mori, M. Misawa, S. Saito, K. Hotta, Y. Saito, T. Matsuda, K. Yamada, T. Mitani, K. Ohtsuka, A. Chino, D. Ide, K. Imai, Y. Kishida, K. Nakamura, Y. Saiki, M. Tanaka, S. Hoteya, S. Yamashita, Y. Kinugasa, M. Fukuda, T. Kudo, H. Miyachi, F. Ishida, H. Itoh, M. Oda, and K. Mori*

This study identified patient and clinical factors that can be used in an algorithm to identify patients with T1 colorectal cancer who are at greatest risk for lymph node metastases and should therefore undergo additional treatment.

**1085 Colorectal Cancer Screening With Repeated Fecal Immunochemical Test Versus Sigmoidoscopy: Baseline Results From a Randomized Trial**

**(E) (WWW)** *K. R. Randel, A. L. Schult, E. Botteri, G. Hoff, M. Bretthauer, G. Ursin, E. Natvig, P. Berstad, A. Jørgensen, P. K. Sandvei, M. E. Olsen, S. O. Frigstad, O. Darre-Næss, E. R. Norvard, N. Bolstad, H. Kørner, A. Wibe, K.-A. Wensaas, T. de Lange, and Ø. Holme*

**See editorial on page 1009.**

In this randomized trial, the participation was higher and more colorectal cancers and advanced adenomas were detected after three rounds of fecal immunochemical testing, compared to sigmoidoscopy screening.

**1097 Participation in Competing Strategies for Colorectal Cancer Screening: A Randomized Health Services Study (PICCOLINO Study)***N. D. Pilonis, M. Bugajski, P. Wieszczyn, M. Rupinski, M. Pisera, E. Pawlak, J. Regula, and M. F. Kaminski*

Offering a combination of fecal test (FIT) and primary colonoscopy increased participation in colorectal cancer screening compared to colonoscopy alone. Increased participation in combined strategies did not increase detection of target lesions.

**1106 The Colombian Chemoprevention Trial: 20-Year Follow-Up of a Cohort of Patients With Gastric Precancerous Lesions***M. B. Piazuelo, L. E. Bravo, R. M. Mera, M. C. Camargo, J. C. Bravo, A. G. Delgado, M. K. Washington, A. Rosero, L. S. Garcia, J. L. Realpe, S. P. Cifuentes, D. R. Morgan, R. M. Peek Jr, P. Correa, and K. T. Wilson*

In a Hispanic population, *H pylori* eradication reduced the progression of gastric precancerous lesions during a 20-year follow-up period. Incomplete-type intestinal metaplasia is a high-risk factor for gastric cancer development.

**1118 Longitudinal Changes in Fecal Calprotectin Levels Among Pregnant Women With and Without Inflammatory Bowel Disease and Their Babies***E. S. Kim, L. Tarassishin, C. Eisele, A. Barre, N. Nair, A. Rendon, K. Hawkins, A. Debebe, S. White, A. Thjømøe, E. Mørk, M. Bento-Miranda, H. Panchal, M. Agrawal, A. Patel, C.-L. Chen, A. Kornbluth, J. George, P. Legnani, E. Maser, H. Loudon, M.-T. Mella, J. Stone, M. Dubinsky, J. Sabino, J. Torres, J.-F. Colombel, I. Peter, J. Hu, and The Mount Sinai Road to Prevention Study Group*

Pregnancy decreases inflammatory activity in mothers with IBD but babies born to IBD mothers have higher fecal calprotectin levels up to 3 years of life. Certain microbial features strongly correlated with maternal and infant fecal calprotectin levels.

**1131 Pregnancy and Neonatal Outcomes After Fetal Exposure to Biologics and Thiopurines Among Women With Inflammatory Bowel Disease***U. Mahadevan, M. D. Long, S. V. Kane, A. Roy, M. C. Dubinsky, B. E. Sands, R. D. Cohen, C. D. Chambers, and W. J. Sandborn, Crohn's Colitis Foundation Clinical Research Alliance*

Among 1491 pregnant women with IBD, there was no increase in harm to the pregnancy or the infants by drug exposure (biologics, thiopurines or both in combination).

**Clinical—Liver****1140 County Differences in Liver Mortality in the United States: Impact of Sociodemographics, Disease Risk Factors, and Access to Care***D. Goldberg, K. Ross-Driscoll, and R. Lynch*

There are significant county-level differences in liver disease-related mortality, even in the same state; this variation is largely explained by demographics (eg, race), risk factors (eg, alcohol use), and access to specialty liver care (ie, distance needed to travel).

**1151 Protective Role of Tacrolimus, Deleterious Role of Age and Comorbidities in Liver Transplant Recipients With Covid-19: Results From the ELITA/ELTR Multi-center European Study***L. S. Belli, C. Fondevila, P. A. Cortesi, S. Conti, V. Karam, R. Adam, A. Coilly, B. G. Ericzon, C. Loinaz, V. Cuervas-Mons, M. Zambelli, L. Llado, F. Diaz-Fontenla, F. Invernizzi, D. Patrono, F. Faitot, S. Bhoori, J. Pirenne, G. Perricone, G. Magini, L. Castells, O. Detry, P. M. Cruchaga, J. Colmenero, F. Berrevoet, G. Rodriguez, D. Ysebaert, S. Radenne, H. Metselaar, C. Morelli, L. G. De Carlis, W. G. Polak, and C. Duvoux, for all of the centers contributing to the ELITA-ELTR COVID-19 Registry*

**See editorial on page 1012.**

In liver transplant recipients with Covid-19, tacrolimus use had a positive independent effect on survival. This novel finding should encourage clinicians to keep Tacrolimus at the usual dose as it may be beneficial when treating COVID-19.

## Basic and Translational—Alimentary Tract

**1164 Identifying Novel Susceptibility Genes for Colorectal Cancer Risk From a Transcriptome-Wide Association Study of 125,478 Subjects**

www

X. Guo, W. Lin, W. Wen, J. Huyghe, S. Bien, Q. Cai, T. Harrison, Z. Chen, C. Qu, J. Bao, J. Long, Y. Yuan, F. Wang, M. Bai, G. R. Abecasis, D. Albanes, S. I. Berndt, S. Bézieau, D. T. Bishop, H. Brenner, S. Buch, A. Burnett-Hartman, P. T. Campbell, S. Castellví-Bel, A. T. Chan, J. Chang-Claude, S. J. Chanock, S. H. Cho, D. V. Conti, A. d. I. Chapelle, E. J. M. Feskens, S. J. Gallinger, G. G. Giles, P. J. Goodman, A. Gsur, M. Guinter, M. J. Gunter, J. Hampe, H. Hampel, R. B. Hayes, M. Hoffmeister, E. Kampman, H. M. Kang, T. O. Keku, H. R. Kim, L. Le Marchand, S. C. Lee, C. I. Li, L. Li, A. Lindblom, N. Lindor, R. L. Milne, V. Moreno, N. Murphy, P. A. Newcomb, D. A. Nickerson, K. Offit, R. Pearlman, P. D. P. Pharoah, E. A. Platz, J. D. Potter, G. Rennert, L. C. Sakoda, C. Schafmayer, S. L. Schmit, R. E. Schoen, F. R. Schumacher, M. L. Slattery, Y.-R. Su, C. M. Tangen, C. M. Ulrich, F. J. B. van Duijnhoven, B. Van Guelpen, K. Visvanathan, P. Vodicka, L. Vodickova, V. Vymetalkova, X. Wang, E. White, A. Wolk, M. O. Woods, G. Casey, L. Hsu, M. A. Jenkins, S. B. Gruber, U. Peters, and W. Zheng

This large-scale transcriptome-wide association study (TWAS) has revealed 25 putative susceptibility genes, including five in novel loci and an additional nine in GWAS loci that have not been previously reported.

**1179 *Streptococcus thermophilus* Inhibits Colorectal Tumorigenesis Through Secreting  $\beta$ -Galactosidase**

www COV

Q. Li, W. Hu, W.-X. Liu, L.-Y. Zhao, D. Huang, X.-D. Liu, H. Chan, Y. Zhang, J.-D. Zeng, O. O. Coker, W. Kang, S. S. M. Ng, L. Zhang, S. H. Wong, T. Gin, M. T. V. Chan, J.-L. Wu, J. Yu, and W. K. K. Wu

The bacteria *S thermophilus* has a potential for preventing colorectal cancer.

**1194 Reduction of Squalene Epoxidase by Cholesterol Accumulation Accelerates Colorectal Cancer Progression and Metastasis**

www

S. Y. Jun, A. J. Brown, N. K. Chua, J.-Y. Yoon, J.-J. Lee, J. O. Yang, I. Jang, S.-J. Jeon, T.-I. Choi, C.-H. Kim, and N.-S. Kim

Cholesterol has long been linked to how deadly colorectal cancer (CRC) is. Our study provides a link between cholesterol and CRC, identifying a key cholesterol enzyme (SQLE) as an important player in CRC aggressiveness and a promising prognostic tool for predicting this cancer.

**1208 Sympathetic Input to Multiple Cell Types in Mouse and Human Colon Produces Region-Specific Responses**

www

K. M. Smith-Edwards, B. S. Edwards, C. M. Wright, S. Schneider, K. A. Meerschaert, L. L. Ejoh, S. A. Najjar, M. J. Howard, K. M. Albers, R. O. Heuckeroth, and B. M. Davis

Sympathetic neuron activity produces region-specific responses in diverse cell types in the colon to differentially regulate motility and other functions in proximal and distal colon.

**1224 The Balance of Stromal BMP Signaling Mediated by *GREM1* and *ISLR* Drives Colorectal Carcinogenesis**

www

H. Kobayashi, K. A. Gieniec, J. A. Wright, T. Wang, N. Asai, Y. Mizutani, T. Lida, R. Ando, N. Suzuki, T. R. M. Lannagan, J. Q. Ng, A. Hara, Y. Shiraki, S. Mii, M. Ichinose, L. Vrbanac, M. J. Lawrence, T. Sammour, K. Uehara, G. Davies, L. Lisowski, I. E. Alexander, Y. Hayakawa, L. M. Butler, A. C. W. Zannettino, M. O. Din, J. Hasty, A. D. Burt, S. J. Leedham, A. K. Rustgi, S. Mukherjee, T. C. Wang, A. Enomoto, M. Takahashi, D. L. Worthley, and S. L. Woods

BMP signaling regulated by two CAF-specific factors, *GREM1* and *ISLR*, defines CAF biology, contributes to CRC progression, and can be therapeutically targeted using a novel hepatocyte-directed AAV gene therapy.

**1240 A Novel Role of *SLC26A3* in the Maintenance of Intestinal Epithelial Barrier Integrity**

www

A. Kumar, S. Priyamvada, Y. Ge, D. Jayawardena, M. Singhal, A. N. Anbazhagan, I. Chatterjee, A. Dayal, M. Patel, K. Zadeh, S. Saksena, W. A. Alrefai, R. K. Gill, M. Zadeh, N. Zhao, M. Mohamadzadeh, and P. K. Dudeja

We demonstrate that DRA (key chloride transporter) plays an important role in maintaining gut barrier function as loss of the DRA gene promotes leaky gut implicated in development of IBD.

- 1256 Dicarbonyl Electrophiles Mediate Inflammation-Induced Gastrointestinal Carcinogenesis**  
 A. P. Gobert, O. Boutaud, M. Asim, I. A. Zagol-Ikapitte, A. G. Delgado, Y. L. Latour, J. L. Finley, K. Singh, T. G. Verriere, M. M. Allaman, D. P. Barry, K. M. McNamara, J. C. Sierra, V. Amarnath, M. N. Tantawy, D. Bimczok, M. B. Piazuelo, M. K. Washington, S. Zhao, L. A. Coburn, and K. T. Wilson

We have shown that potent oxidative molecules, called dicarbonyl electrophiles, are generated during inflammation of the gastrointestinal tract. Blocking these molecules reduces the development of gastric and colon cancer.

- 1269 Paneth Cell Alertness to Pathogens Maintained by Vitamin D Receptors**  
 R. Lu, Y.-g. Zhang, Y. Xia, J. Zhang, A. Kaser, R. Blumberg, and J. Sun

Vitamin D receptor (VDR) maintains the Paneth cell alertness to pathogens in intestinal disorders. Genetically and environmentally regulated VDR in the Paneth cells may set the threshold for the development of chronic inflammation.

- 1284 RNA N<sup>6</sup>-Methyladenosine Methyltransferase METTL3 Facilitates Colorectal Cancer by Activating the m<sup>6</sup>A-GLUT1-mTORC1 Axis and Is a Therapeutic Target**  
 H. Chen, S. Gao, W. Liu, C.-C. Wong, J. Wu, J. Wu, D. Liu, H. Gou, W. Kang, J. Zhai, C. Li, H. Su, S. Wang, F. Soares, J. Han, H. H. He, and J. Yu

METTL3 promotes CRC by activating m<sup>6</sup>A-GLUT1-mTORC1 axis. METTL3 is a promising therapeutic target for the treatment of CRC.

- 1301 *Fusobacterium nucleatum* Adheres to *Clostridioides difficile* via the Radd Adhesin to Enhance Biofilm Formation in Intestinal Mucus**  
 M. A. Engevik, H. A. Danhof, J. Auchtung, B. T. Endres, W. Ruan, E. Bassères, A. C. Engevik, Q. Wu, M. Nicholson, R. A. Luna, K. W. Garey, S. E. Crawford, M. K. Estes, R. Lux, M. B. Yacyshyn, B. Yacyshyn, T. Savidge, R. A. Britton, and J. Versalovic

Our work shows that the pathogen *Clostridium difficile* chemotaxes, aggregates and forms resilient biofilms with another pathogen *Fusobacterium nucleatum* in the intestinal mucus layer.

## Basic and Translational—Liver

- 1315 Enhanced Meningeal Lymphatic Drainage Ameliorates Neuroinflammation and Hepatic Encephalopathy in Cirrhotic Rats**  
 S.-J. Hsu, C. Zhang, J. Jeong, S.-i. Lee, M. McConnell, T. Utsumi, and Y. Iwakiri

Our study has revealed that enhanced meningeal lymphatic drainage is a novel therapeutic approach for the treatment of hepatic encephalopathy, a serious complication of liver disease.

## Basic and Translational—Pancreas

- 1330 Single-Nucleus and In Situ RNA-Sequencing Reveal Cell Topographies in the Human Pancreas**  
 L. Tosti, Y. Hang, O. Debnath, S. Tiesmeyer, T. Trefzer, K. Steiger, F. W. Ten, S. Lukassen, S. Ballke, A. A. Kühl, S. Spieckermann, R. Bottino, N. Ishaque, W. Weichert, S. K. Kim, R. Eils, and C. Conrad

See editorial on page 1014.

This study generated the first comprehensive human pancreas cell atlas and revealed the existence of novel cell types and states in this organ.

- 1345 Extracellular Vesicle Analysis Allows for Identification of Invasive IPMN**  
 K. S. Yang, D. Ciprani, A. O'Shea, A. S. Liss, R. Yang, S. Fletcher-Mercaldo, M. Mino-Kenudson, C. Fernández-del Castillo, and R. Weissleder

See editorial on page 1016.

Blood based analysis of circulating vesicles expressing MUC5AC enables the detection of invasive IPMNs.

- 1359 Cadherin 11 Promotes Immunosuppression and Extracellular Matrix Deposition to Support Growth of Pancreatic Tumors and Resistance to Gemcitabine in Mice**  
 I. Peran, S. Dakshanamurthy, M. D. McCoy, A. Mavropoulos, B. Allo, A. Sebastian, N. R. Hum, S. C. Sprague, K. A. Martin, M. J. Pishvaian, E. E. Vietsch, A. Wellstein, M. B. Atkins, L. M. Weiner, A. A. Quong, G. G. Loots, S. S. Yoo, S. Assefnia, and S. W. Byers

The authors found that loss or inhibition of a protein found in pancreatic tumors but not healthy pancreas extends survival of mice with pancreatic tumors by promoting an anti-tumor immunity and increasing the response to chemotherapy.

**1373 Lead-Time Trajectory of CA19-9 as an Anchor Marker for Pancreatic Cancer Early Detection**

**E** **www** J. F. Fahrman, C. M. Schmidt, X. Mao, E. Irajizad, M. Loftus, J. Zhang, N. Patel, J. Vykoukal, J. B. Dennison, J. P. Long, K.-A. Do, J. Zhang, J. A. Chabot, M. D. Kluger, F. Kastrinos, L. Brais, A. Babic, K. Jajoo, L. S. Lee, T. E. Clancy, K. Ng, A. Bullock, J. Genkinger, M. T. Yip-Schneider, A. Maitra, B. M. Wolpin, and S. Hanash

See editorial on page 1019.

CA19-9 can serve as an anchor marker for pancreatic cancer early detection. Inclusion of additional markers such as LRG1 and TIMP1 may have value for identifying cases missed by CA19-9 alone.

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M. Dougan, Y. Wang, A. Rubio-Tapia, and J. K. Lim

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**E** **www** A. Bui, L. Yang, A. Myint, and F. P. May

See editorial on page 1022.

**1397 Colonoscopy With Polypectomy Reduces Long-Term Incidence of Colorectal Cancer in Both Men and Women: Extended Results From the Minnesota Colon Cancer Control Study**

**www** A. Shaikat, M. Shyne, J. S. Mandel, D. Snover, and T. R. Church

**1400 Estimating the Backlog of Colonoscopy due to Coronavirus Disease 2019 and Comparing Strategies to Recover in Ontario, Canada**

**www** J. Tinmouth, S. Dong, C. Stogios, L. Rabeneck, M. Rey, and C. Dubé, on behalf of the ColonCancerCheck/Gastrointestinal Endoscopy COVID Working Group

**1403 Low Incidence of Severe Gastrointestinal Complications in COVID-19 Patients Admitted to the Intensive Care Unit: A Large, Multicenter Study**

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**1406 Socioeconomic Factors Contribute to the Higher Risk of COVID-19 in Racial and Ethnic Minorities With Chronic Liver Diseases**

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- 1417 Association Between Preadmission Acid Suppressive Medication Exposure and Severity of Illness in Patients Hospitalized With COVID-19**  
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- 1433 Corrections**

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