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PRACTICAL TEACHING CASE**1703 "Doc, I Can't Walk"—A Classic Presentation of a Rare Disease**CME *A. R. Sondhi, E. J. Wamsteker, and M. S. Piper***REVIEWS AND PERSPECTIVES****Brief Review****1706 Roles for Interleukin 17 and Adaptive Immunity in Pathogenesis of Colorectal Cancer***C. G. Hurtado, F. Wan, F. Housseau, and C. L. Sears***ORIGINAL RESEARCH****Brief Report****1716 Decrease in Incidence of Young-Onset Colorectal Cancer Before Recent Increase**WWW *C. C. Murphy, A. G. Singal, J. A. Baron, and R. S. Sandler*

The incidence of colorectal cancer is increasing in younger (age <50 years) adults. In contrast, a clear pattern of declining incidence rates from 1975 through 1990 was found.

Full Reports**Clinical—Alimentary Tract****1720 Identification of Prognostic Phenotypes of Esophageal Adenocarcinoma in 2 Independent Cohorts**CME WWW *T. Sawas, S. Killcoyne, P. G. Iyer, K. K. Wang, T. C. Smyrk, J. B. Kisiel, Y. Qin, D. A. Ahlquist, A. K. Rustgi, R. J. Costa, M. Gerstung, R. C. Fitzgerald, and D. A. Katzka, for the OCCAMS Consortium*

There are two potential types of esophageal adenocarcinoma based on the presence or absence of Barrett's esophagus in the background that determine prognosis with improved survival in Barrett's patients.

1729 Model to Select On-Therapy vs Off-Therapy Tests for Patients With Refractory Esophageal or Extraesophageal SymptomsWWW *D. A. Patel, R. Sharda, Y. A. Choksi, J. C. Slaughter, T. Higginbotham, C. G. Garrett, D. O. Francis, K. Ravi, S. Hasak, D. Katzka, C. P. Gyawali, and M. F. Vaezi*

An externally validated clinical model estimated pre-test probability of abnormal pH in patients who have failed PPI therapy, which can help clinicians determine diagnostic testing strategies for these patients.

1741 FXR-Dependent Modulation of the Human Small Intestinal Microbiome by the Bile Acid Derivative Obeticholic AcidWWW *E. S. Friedman, Y. Li, T.-C. D. Shen, J. Jiang, L. Chau, L. Adorini, F. Babakhani, J. Edwards, D. Shapiro, C. Zhao, R. M. Carr, K. Bittinger, H. Li, and G. D. Wu*

FXR-dependent suppression of bile acids in humans leads to a reversible induction of bacteria inhibited by bile acids, found in the small intestine, and are components of the diet.

1753 Efficacy of Secretagogues in Patients With Irritable Bowel Syndrome With Constipation: Systematic Review and Network Meta-analysisE WWW *C. J. Black, N. E. Burr, E. M. M. Quigley, P. Moayyedi, L. A. Houghton, and A. C. Ford*

See editorial on page 1677.

In a network meta-analysis comparing 15 trials of secretagogues, containing 8462 patients with IBS-C, Linaclotide 290 mcg once-daily was ranked first for efficacy for almost all endpoints.

1764 Identification of Menopausal and Reproductive Risk Factors for Microscopic Colitis—Results From the Nurses' Health Study**E** **www***K. E. Burke, A. N. Ananthakrishnan, P. Lochhead, P.-H. Liu, O. Olen, J. F. Ludvigsson, J. M. Richter, S. S. Tworoger, A. T. Chan, and H. Khalili***See editorial on page 1679.**

In two large cohorts of US women, exogenous hormone use in the form of oral contraceptives and menopausal hormone therapy is associated with increased risk of developing microscopic colitis.

1776 Prevalence of Advanced, Precancerous Colorectal Neoplasms in Black and White Populations: A Systematic Review and Meta-analysis**www***T. F. Imperiale, P. R. Abhyankar, T. E. Stump, and T. W. Emmett*

A systematic review and meta-analysis of studies comparing prevalence of advanced adenomatous polyps / advanced neoplasia in average-risk Black and White patients undergoing screening colonoscopy found no difference in prevalence.

1787 Mortality From Postscreening (Interval) Colorectal Cancers Is Comparable to That From Cancer in Unscreened Patients—A Randomized Sigmoidoscopy Trial**www***H. C. Jodal, M. Løberg, Ø. Holme, H.-O. Adami, M. Bretthauer, L. Emilsson, D. F. Ransohoff, G. Hoff, and M. Kalager*

In this randomized sigmoidoscopy screening trial including 98,684 individuals with follow-up median 14.8 years, mortality did not differ significantly between individuals with interval CRCs and unscreened patients with clinically detected CRCs.

1795 Efficacy and Safety of Budesonide, vs Mesalazine or Placebo, as Induction Therapy for Lymphocytic Colitis**www***S. Mielhke, D. Aust, E. Mihaly, P. Armerding, G. Böhm, O. Bonderup, F. Fernández-Bañares, J. Kupcinskas, L. K. Munck, K.-U. Rehbehn, T. Nacak, R. Greinwald, and A. Münch, on behalf of the BUG-1/LMC Study Group*

Treatment with budesonide for 8 weeks achieves clinical remission in approximately 80% of patients with active lymphocytic colitis. Mesalazine was not significantly more effective than placebo.

1805 Healthy Lifestyle Factors Associated With Lower Risk of Colorectal Cancer Irrespective of Genetic Risk**www***P. R. Carr, K. Weigl, L. Jansen, V. Walter, V. Erben, J. Chang-Claude, H. Brenner, and M. Hoffmeister*

In a large population-based case-control study, a healthier lifestyle appears to reduce the risk of CRC, regardless of the patient's genetic profile.

Clinical—Liver**1816 Effects of Long-term Norfloxacin Therapy in Patients With Advanced Cirrhosis****www***R. Moreau, L. Elkrief, C. Bureau, J.-M. Perarnau, T. Thévenot, F. Saliba, A. Louvet, P. Nahon, A. Lannes, R. Anty, S. Hillaire, B. Pasquet, V. Ozenne, M. Rudler, I. Ollivier-Hourmand, M. A. Robic, L. d'Alteroche, V. Di Martino, M.-P. Ripault, A. Pauwels, J.-D. Grangé, N. Carbonell, J.-P. Bronowicki, A. Payancé, P.-E. Rautou, D. Valla, N. Gault, and D. Lebrec, for the NORFLOCIR Trial Investigators*

Long-term oral norfloxacin therapy decreased 6-month mortality in advanced cirrhosis patients with ascites fluid protein concentrations of less than 15 g/L but not in those with ascites fluid protein concentrations of 15 g/L or more.

1828 Risk of Hepatocellular Cancer in Patients With Non-Alcoholic Fatty Liver Disease

CME **WWW** *F. Kanwal, J. R. Kramer, S. Mapakshi, Y. Natarajan, M. Chayanupatkul, P. A. Richardson, L. Li, R. Desiderio, A. P. Thrift, S. M. Asch, J. Chu, and H. B. El-Serag*

The risk of hepatocellular cancer was higher in patients with NAFLD than that observed in general clinical populations. The risk of hepatocellular cancer in patients with cirrhosis was higher than currently accepted thresholds for starting surveillance.

1838 Evidence of Chronic Allograft Injury in Liver Biopsies From Long-term Pediatric Recipients of Liver Transplants

WWW *S. Feng, J. C. Bucuvalas, A. J. Demetris, B. E. Burrell, K. M. Spain, S. Kanaparthi, J. C. Magee, D. Ikle, A. Lesniak, J. J. Lozano, E. M. Alonso, R. A. Bray, N. E. Bridges, E. Doo, H. M. Gebel, N. A. Gupta, R. W. Himes, A. M. Jackson, S. J. Lobritto, G. V. Mazariegos, V. L. Ng, E. B. Rand, A. H. Sherker, S. Sundaram, Y. P. Turmelle, and A. Sanchez-Fueyo*

Analysis of liver biopsies from clinically ideal pediatric liver transplant recipients identifies 3 distinct clusters. The cluster characterized by interface activity exhibits a tissue gene expression profile characteristic of rejection.

Basic and Translational—Alimentary Tract**1852 Loss of Tight Junction Protein Claudin 18 Promotes Progressive Neoplasia Development in Mouse Stomach**

WWW *S. J. Hagen, L.-H. Ang, Y. Zheng, S. N. Karahan, J. Wu, Y. E. Wang, T. J. Caron, A. P. Gad, S. Muthupalani, and J. G. Fox*

The loss of claudin 18, a tight junction protein, occurs early in the development of human gastric cancer, and results in pre-malignant changes that drive neoplastic transformation of the stomach mucosa in mice.

1868 Combined Inactivation of TP53 and MIR34A Promotes Colorectal Cancer Development and Progression in Mice Via Increasing Levels of IL6R and PAI1

WWW *M. G. Öner, M. Rokavec, M. Kaller, N. Bouznad, D. Horst, T. Kirchner, and H. Hermeking*

The inhibition of up-regulated Mir34a-targets, exemplarily demonstrated here for IL-6R and Pai-1, may represent an attractive therapeutic intervention for late stage CRCs with combined inactivation of *MIR34a* and *TP53*.

1883 Loss of MYO5B Leads to Reductions in Na⁺ Absorption With Maintenance of CFTR-Dependent Cl⁻ Secretion in Enterocytes

WWW **COV** *A. C. Engevik, I. Kaji, M. A. Engevik, A. R. Meyer, V. G. Weis, A. Goldstein, M. W. Hess, T. Müller, H. Koepsell, P. K. Dudeja, M. Tyska, L. A. Huber, M. D. Shub, N. Ameen, and J. R. Goldenring*

Mice with deletion of Myosin Vb (MYO5B) were studied as a model of Microvillus Inclusion Disease. Diarrhea was due to the combination of an inability to absorb sodium and fluid with the continued secretion of chloride.

1898 Human Monoclonal Antibodies That Neutralize Pandemic GII.4 Noroviruses

WWW *G. Alvarado, K. Ettayebi, R. L. Atmar, R. G. Bombardi, N. Kose, M. K. Estes, and J. E. Crowe Jr.*

This study identifies the first panel of human IgA and IgG monoclonal antibodies that neutralize human norovirus GII.4 Sydney 2012.

1908 Identification of Genes Associated With Hirschsprung Disease, Based on Whole-Genome Sequence Analysis, and Potential Effects on Enteric Nervous System Development

E **WWW** *C. S.-m. Tang, P. Li, F. P.-L. Lai, A. X. Fu, S.-T. Lau, M. T. So, K. N.-C. Lui, Z. Li, X. Zhuang, M. Yu, X. Liu, N. D. Ngo, X. Miao, X. Zhang, B. Yi, S. Tang, X. Sun, F. Zhang, H. Liu, Q. Liu, R. Zhang, H. Wang, L. Huang, X. Dong, J. Tou, K. S.-E. Cheah, W. Yang, Z. Yuan, K. Y.-I. Yip, P.-C. Sham, P. K.-H. Tam, M.-M. Garcia-Barcelo, and E. S.-W. Ngan*

See editorial on page 1681.

The authors established an experimental paradigm by jointly analyzing rare and common genetic variants and integrating genetics with the human iPSC-based model to decode the oligogenic etiology of HSCR.

Basic and Translational—Liver**1923 TM6SF2 Promotes Lipidation and Secretion of Hepatitis C Virus in Infected Hepatocytes**

www

A. Boyer, S. B. Park, Y. S. de Boer, Q. Li, and T. J. Liang

This study reveals an important human gene and its function that is responsible for the production of infectious HCV. This finding provides important knowledge about how HCV infects humans and causes disease.

1936 Association Between Expression Level of PD1 by Tumor-Infiltrating CD8⁺ T Cells and Features of Hepatocellular Carcinoma

E www

H.-D. Kim, G.-W. Song, S. Park, M. K. Jung, M. H. Kim, H. J. Kang, C. Yoo, K. Yi, K. H. Kim, S. Eo, D.-B. Moon, S.-M. Hong, Y. S. Ju, E.-C. Shin, S. Hwang, and S.-H. Park

See editorial on page 1684.

According to the presence or absence of a discrete PD1-high tumor-infiltrating CD8⁺ T-cell population, two distinct subgroups of HCC patients with distinct biological and clinical implications were identified.

1951 microRNA 193a-5p Regulates Levels of Nucleolar- and Spindle-Associated Protein 1 to Suppress Hepatocarcinogenesis

www

S. Roy, G. J. Hooiveld, M. Seehawer, S. Caruso, F. Heinzmann, A. T. Schneider, A. K. Frank, D. V. Cardenas, R. Sonntag, M. Luedde, C. Trautwein, I. Stein, E. Pikarsky, S. Loosen, F. Tacke, M. Ringelhan, S. K. Avsaroglu, A. Goga, M.-A. Buendia, M. Vucur, M. Heikenwalder, J. Zucman-Rossi, L. Zender, C. Roderburg, and T. Luedde

MIR193A-5p-dependent downregulation of NUSAP1 represents a model-independent mechanism controlling tumor cell proliferation, survival and invasion and represents a potential therapeutic target in human HCC.

1967 Rapid Disruption of Genes Specifically in Livers of Mice Using Multiplex CRISPR/Cas9 Editing

www

F. P. Pankowicz, M. Barzi, K. H. Kim, X. Legras, C. S. Martins, C. R. Wooton-Kee, W. R. Lagor, J. C. Marini, S. H. Elsea, B. Bissig-Choisat, D. D. Moore, and K.-D. Bissig

The authors developed a new technique (SLiK) where genes can be disrupted in the livers of mice and thereby create a rapid liver specific knockout model.

1971 Expression of STING Is Increased in Liver Tissues From Patients With NAFLD and Promotes Macrophage-Mediated Hepatic Inflammation and Fibrosis in Mice

E www

X. Luo, H. Li, L. Ma, J. Zhou, X. Guo, S.-L. Woo, Y. Pei, L. R. Knight, M. Deveau, Y. Chen, X. Qian, X. Xiao, Q. Li, X. Chen, Y. Huo, K. McDaniel, H. Francis, S. Glaser, F. Meng, G. Alpini, and C. Wu

See editorial on page 1687.

The present study provides compelling evidence supporting a deleterious role for stimulator of interferon genes in development and progression of non-alcoholic fatty liver disease.

Basic and Translational—Pancreas**1985 An Inhibitor of GSK3B and HDACs Kills Pancreatic Cancer Cells and Slows Pancreatic Tumor Growth and Metastasis in Mice**

www

M. Edderkaoui, C. Chheda, B. Soufi, F. Zayou, R. W. Hu, V. K. Ramanujan, X. Pan, L. G. Boros, J. Tajbakhsh, A. Madhav, N. A. Bhowmick, Q. Wang, M. Lewis, R. Tuli, A. Habtezion, R. Murali, and S. J. Pandol

Researchers designed, synthesized and tested a novel molecule, Metavert, to treat pancreatic cancer. Metavert prevented metastasis, drug resistance, improved mice survival and changed glucose metabolism in the cancer.

1999 Stratification of Pancreatic Ductal Adenocarcinomas Based on Tumor and Microenvironment

Features

F. Puleo, R. Nicolle, Y. Blum, J. Cros, L. Marisa, P. Demetter, E. Quertinmont, M. Svrcek, N. Elarouci, J. Iovanna, D. Franchimont, L. Verset, M. G. Galdon, J. Devière, A. de Reyniès, P. Laurent-Puig, J.-L. Van Laethem, J.-B. Bachet, and R. Maréchal

See editorial on page 1689.

An integrated tumor/microenvironment classification system is proposed for pancreatic adenocarcinoma based on 309 formalin-fixed paraffine embedded samples. This stratification has major prognostic implications and implies potential subtype-specific therapeutic opportunities.

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- e17 CME Exam 2: Identification of Prognostic Phenotypes of Esophageal Adenocarcinoma in 2 Independent Cohorts**
- e18 CME Exam 3: Risk of Hepatocellular Cancer in Patients With Non-Alcoholic Fatty Liver Disease**

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- 2014 Fellow Education Improved Through Mobile Clinical Decision Support Application: A Multi-Center Approach Involving Peri-Procedural Antithrombotic Use**
A. T. Strauss, T. W. James, and S. C. Mathews
- 2016 Detection and Analysis of Circulating Epithelial Cells in Liquid Biopsies From Patients With Liver Disease**
I. Bhan, K. Mosesso, L. Goyal, J. Philipp, M. Kalinich, J. W. Franses, M. Choz, R. Oklu, M. Toner, S. Maheswaran, D. A. Haber, A. X. Zhu, R. T. Chung, M. Aryee, and D. T. Ting

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- 2019 Probiotics for Treating Irritable Bowel Syndrome: Are Bugs the Best Drugs?**
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- 2021 Is Liver Injury an Affordable Risk of Immune Checkpoint Inhibitor Therapy for Cancer?**
M. Colombo and A. Lleo
- 2023 Crohn’s Disease and Ulcerative Colitis: From Epidemiology and Immunobiology to a Rational Diagnostic Approach**
R. K. Cross

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- 2024 Intending to Treat Patients With Irritable Bowel Syndrome With Cognitive–Behavioral Therapy**
A. C. Ford

2024 Reply
J. Lackner and J. Jaccard

2025 Innate Immune Cells Regulate Oncoimmunity and Cancer Development
A.-P. Bai and Y. Guo

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