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ORIGINAL RESEARCH

Full Reports

GI Cancer

- 1136 Ceramides Increase Fatty Acid Utilization in Intestinal Progenitors to Enhance Stemness and Increase Tumor Risk**

Y. Li, B. Chaurasia, M. M. Rahman, V. Kaddai, J. A. Maschek, J. A. Berg, J. L. Wilkerson, Z. S. Mahmassani, J. Cox, P. Wei, P. J. Meikle, D. Atkinson, L. Wang, A. M. Poss, M. C. Playdon, T. S. Tippetts, E. M. Mousa, K. Nittayaboon, P. V. Anandh Babu, M. J. Drummond, H. Clevers, J. A. Shayman, Y. Hirabayashi, W. L. Holland, J. Rutter, B. A. Edgar, and S. A. Summers

These studies demonstrate that ceramides, which are products of fat and protein metabolism, may link unhealthy diets to the formation of intestinal polyps that seed cancer.

- 1151 Genetic Control of Alternative Splicing and its Distinct Role in Colorectal Cancer Mechanisms**
M. Zhang, C. Chen, Z. Lu, Y. Cai, Y. Li, F. Zhang, Y. Liu, S. Chen, H. Zhang, S. Yang, H. Gen, Y. Jiang, C. Ning, J. Huang, W. Wang, L. Fan, Y. Zhang, M. Jin, J. Han, Z. Xiong, M. Cai, J. Liu, C. Huang, X. Yang, B. Xu, H. Li, B. Li, X. Zhu, Y. Wei, Y. Zhu, J. Tian, and X. Miao

The comprehensive splicing quantitative trait loci resource highlighted the distinct power of splicing quantitative trait loci signals to uncover the molecular mechanisms of cancer and demonstrated that splicing quantitative trait loci rs61746794 contributed to increased risk of colorectal cancer by promoting the splicing of *PRMT7* exon 16, presenting a novel lead for a biologically interpretable paradigm for cancer risk.

- 1168 The Tissue Systems Pathology Test Outperforms Pathology Review in Risk Stratifying Patients With Low-Grade Dysplasia**

A. M. Khoshiwal, N. F. Frei, R. E. Pouw, TissueCypher SURF LGD Study Pathologists Consortium, C. Smolko, M. Arora, J. J. Siegel, L. C. Duits, R. J. Critchley-Thorne, and J. J. G. H. M. Bergman

See editorial on page 1106.

A study in the screening cohort of a randomized controlled trial demonstrated that the tissue systems pathology test (TSP-9) objectively risk-stratified patients with Barrett's esophagus and community-based low-grade dysplasia, whereas a panel of expert and generalist pathologists demonstrated significant interobserver variability. The TSP-9 test outperformed pathology review in predicting neoplastic progression and detected 80.4% of progressors when used as an adjunct to pathology review of low-grade dysplasia. The results of the study indicate that the TSP-9 test provides an objective solution to subjective and variable pathology review and can improve outcomes for patients with an initial diagnosis of low-grade dysplasia by maximizing the identification and early treatment of progressors with eradication therapy and downstaging the management of low-risk patients to a surveillance-only approach.

Inflammatory Bowel Disease

1180 **Strictureing Crohn's Disease Single-Cell RNA Sequencing Reveals Fibroblast Heterogeneity and Intercellular Interactions**

www

P. K. Mukherjee, Q. T. Nguyen, J. Li, S. Zhao, S. M. Christensen, G. A. West, J. Chandra, I. O. Gordon, S. Lin, J. Wang, R. Mao, D. Czarnecki, C. Rayan, I. Goren, S. Banerjee, P. Kotak, T. Plesec, S. Lal, T. Fabre, S. Asano, K. Bound, K. Hart, C. Park, R. Martinez, K. Dower, T. A. Wynn, S. Hu, N. Naydenov, M. Decaris, S. Turner, S. D. Holubar, S. R. Steele, C. Fiocchi, A. I. Ivanov, K. M. Kravarik, and F. Rieder

This work creates an understanding of which cell types are present in Crohn's disease strictures and control tissues and how they interact with each other to cause disease. These findings were used to identify a potential novel treatment target.

1197 **Incidence, Prevalence, and Racial and Ethnic Distribution of Inflammatory Bowel Disease in the United States**

www

J. D. Lewis, L. E. Parlett, M. L. Jonsson Funk, C. Brensinger, V. Pate, Q. Wu, G. K. Dawwas, A. Weiss, B. D. Constant, M. McCauley, K. Haynes, J. Y. Yang, D. E. Schaubel, A. Hurtado-Lorenzo, and M. D. Kappelman

Approximately 2.4 to 2.7 million Americans are diagnosed with inflammatory bowel diseases. The prevalence of inflammatory bowel diseases was highest among non-Hispanic Whites and residents of the Northeast.

Functional GI Disease

1206 **Efficacy of Probiotics in Irritable Bowel Syndrome: Systematic Review and Meta-analysis**

CME www

V. C. Goodoory, M. Khasawneh, C. J. Black, E. M. M. Quigley, P. Moayyedi, and A. C. Ford

We studied the efficacy of probiotics for irritable bowel syndrome. There was some evidence of efficacy, but the quality of the trials included makes it hard to draw definitive conclusions. Future trials should be more rigorous and could focus on potentially effective strains or species from this meta-analysis.

Pancreas

1219 **CLDN18.2 BiTE Engages Effector and Regulatory T Cells for Antitumor Immune Response in Preclinical Models of Pancreatic Cancer**

www

Y. Xu, J. Fu, M. Henderson, F. Lee, N. Jurcak, A. Henn, J. Wahl, Y. Shao, J. Wang, M. Lyman, V. Funes, B. Espinoza, R. Zhang, I. Washington, S. Y. Chen, H. Zlomke, J. Wang, N. Niu, P. Li, F. Meng, W. Burns, M. Friedrich, S. Stienen, J. M. Bailis, and L. Zheng

This study, by using clinically relevant mouse models, shows that the Claudin 18.2 bispecific T-cell engager treatment can engage antitumor effector T cells and also convert regulatory T cells from an immunosuppressive T-cell subtype to an antitumor T-cell subtype for treating pancreatic cancer and gastric cancer.

Hepatobiliary

1233 **T Cell CEACAM1-TIM-3 Crosstalk Alleviates Liver Transplant Injury in Mice and Humans**

www COV

H. Kojima, K. Kadono, H. Hirao, K. J. Dery, T. Torgerson, S. Yao, F. M. Kaldas, D. G. Farmer, R. S. Blumberg, and J. W. Kupiec-Weglinski

Recipient-derived T cell carcinoembryonic antigen-related cell adhesion molecule 1 signaling alleviates liver transplant injury by promoting T cell immunoglobulin domain and mucin domain-containing protein 3, which by interacting with hepatic carcinoembryonic antigen-related cell adhesion molecule 1 suppresses nuclear factor- κ B activation in Kupffer cells.

1249 Endoscopic Ultrasound-Guided Biliary Drainage of First Intent With a Lumen-Apposing Metal Stent vs Endoscopic Retrograde Cholangiopancreatography in Malignant Distal Biliary Obstruction: A Multicenter Randomized Controlled Study (ELEMENT Trial)

Y.-I. Chen, A. Sahai, G. Donatelli, E. Lam, N. Forbes, J. Mosko, S. C. Paquin, F. Donnellan, A. Chatterjee, J. Telford, C. Miller, E. Desilets, G. Sandha, S. Kenshil, R. Mohamed, G. May, I. Gan, J. Barkun, N. Calo, A. Nawawi, G. Friedman, A. Cohen, T. Maniere, P. Chaudhury, P. Metrakos, G. Zogopoulos, A. Bessissow, J. A. Khalil, V. Baffis, K. Waschke, J. Parent, C. Soulellis, M. Khashab, R. Kunda, O. Geraci, M. Martel, K. Schwartzman, J. F. Fiore Jr, E. Rahme, and A. Barkun

See editorial on page 1108.

The study compared 2 different procedures for treating blockages in the bile duct from certain types of cancer. The newer modality—endoscopic ultrasound-guided choledochoduodenostomy—had no major differences from the other procedure—endoscopic retrograde cholangiopancreatography with metal stenting—meaning that the former is a viable and safe alternative for patients with this condition, providing more treatment options for physicians and patients.

Artificial Intelligence

1262 Deep Learning-Enabled Diagnosis of Liver Adenocarcinoma

T. Albrecht, A. Rossberg, J. D. Albrecht, J. P. Nicolay, B. K. Straub, T. S. Gerber, M. Albrecht, F. Brinkmann, A. Charbel, C. Schwab, J. Schreck, A. Brobeil, C. Flechtenmacher, M. von Winterfeld, B. C. Köhler, C. Springfield, A. Mehrabi, S. Singer, M. N. Vogel, O. Neumann, A. Stenzinger, P. Schirmacher, C.-A. Weis, S. Roessler, J. N. Kather, and B. Goepfert

An innovative artificial intelligence algorithm predicts major forms of hepatic adenocarcinoma using conventional histopathologic slides with clinical grade performance, supporting pathologists in diagnosis making with explainable model decision.

RESEARCH LETTER

1276 Germline Determinants of Esophageal Adenocarcinoma

M. Lee, G. Eng, A. Handte-Reinecker, MGH-MIT Gastrointestinal Cohorts Working Group, V. S. Deshpande, O. H. Yilmaz, and M. K. Gala

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R. B. Issaka, A. T. Chan, and S. Gupta

1292 AGA Clinical Practice Update on the Epidemiology, Evaluation, and Management of Exocrine Pancreatic Insufficiency: Expert Review

D. C. Whitcomb, A. M. Buchner, and C. E. Forsmark

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