THE FIFTH ANNUAL
EARLY AGE ONSET COLORECTAL CANCER SUMMIT

MAY 2 – 3 | THE TIMES CENTER | NYC

COLON CANCER FOUNDATION

Northwell Health® Cancer Institute

DONALD AND BARBARA ZUCKER SCHOOL of MEDICINE AT HOFSTRA/NORTHWELL

Performing a Knowledge GAP Analysis and Building a Strategic "Action Plan" to Reduce EAO-CRC Incidence and Mortality

Credit Designation: *Northwell Health designates this live activity for a maximum of* ***11 AMA PRA Category 1 Credits™.***

Thursday, May 2, 2019 • 7:00 am – 6:45 pm
Friday, May 3, 2019 • 8:00 am – 12:30 pm
The Times Center • 242 West 41st Street • New York, NY 10018

EAO-CRC

EARLY AGE ONSET COLORECTAL CANCER

SUMMIT 2019

THANK YOU

The Colon Cancer Foundation gratefully acknowledge the exhibit sponsorship provided to support this activity by:

PRESENTING SPONSOR

Northwell Health®
Cancer Institute

EAO-CRC

EARLY AGE ONSET COLORECTAL CANCER

SUMMIT 2019

THANK YOU

The Colon Cancer Foundation gratefully acknowledge the exhibit sponsorship provided to support this activity by:

PLATINUM SPONSOR

LUC WALTER

POSTER SESSION AND RECEPTION SPONSOR

BRACCO

LIFE FROM INSIDE

GOLD SPONSOR

never too young

colorectal cancer alliance

SILVER SPONSORS

EAO-CRC

EARLY AGE ONSET COLORECTAL CANCER

SUMMIT 2019

THANK YOU

The Colon Cancer Foundation gratefully acknowledge the exhibit sponsorship provided to support this activity by:

EXHIBITORS

AliveAndKicking

Boston Scientific

Medtronic

OLYMPUS

COURSE OVERVIEW

This event will bring together leading clinicians, scientists as well as early age onset (EAO) colorectal cancer (CRC) survivors and Caregivers from across the country and internationally. The program will provide extensive opportunities for participants to advance their understanding of the rapidly increasing incidence of rectal and colon cancer among young adults under 50 years of age in the U.S. and abroad.

This groundbreaking program will, for a fifth consecutive year, provide all participants the opportunity to hear from and question leading clinicians and researchers on the life saving potential of timely clinical risk assessment/family cancer health history; earliest possible diagnosis, optimal, fertility preserving clinical care, as well as the latest information regarding national and international EAO CRC incidence trends, pathogenesis, and genetics. In addition, this year's program will present a "Research in Progress" segment featuring currently NCI funded and planned EAO CRC research projects from across America and Europe. Again this year, important Breakout Sessions based on needs-assessments from our survivor community will address challenging issues surrounding Palliative Care, support networks for "Caregivers" and a "Primer" on the "Epigenetics" of EAO CRC specifically requested by our Young Adult CRC Survivor Program Advisory Group.

The course will include lectures, workshops and panel discussions designed to advance the "state-of-the-science" addressing EAO-CRC. Our faculty will once again be world class speakers representing leading academic medical centers with major additional inspiring programmatic contributions from the Early Age Onset Colorectal Cancer Survivor Community of the United States and beyond..

EDUCATIONAL OBJECTIVES

Provide an expert review of the latest published information on the increasing incidence and mortality associated with Early Age Onset Colorectal Cancer in the United States and globally.

Review the State-of-the-Science regarding the known and possible causes of the increasing incidence of EAO-CRC including alterations in our food and water supply, the contribution of novel germline genetic factors and etiologic clues based on the molecular biology of EAO-CRC cancers.

Provide an evidence-based framework for reducing risk, increasing early stage diagnosis and improving treatment and outcomes for young adult colorectal cancer patients.

Define the “Gaps” in our current understanding of Early Age Onset Colorectal Cancer in order to set our clinical and research priorities and develop a strategic plan to reduce EAO-CRC incidence and mortality.

COURSE DIRECTORS

Thomas K. Weber, MD, FACS
COURSE MODERATOR/CHAIR
Director of Surgical Oncology
Northwest Region at Northwell Health
Professor of Surgery Donald and Barbara Zucker School of Medicine at Hofstra/Northwell
Founder and President
Colon Cancer Foundation

Susan K. Peterson, PhD, MPH
COURSE CO-DIRECTOR AND POSTER SESSION CHAIR
Professor of Behavioral Science
The University of Texas MD Anderson Cancer Center

COURSE DIRECTORS

Wasif M. Saif, MD
COURSE CO-DIRECTOR
Deputy Physician-in-Chief and Director of Medical Oncology
Northwell Health Cancer Institute
Professor of Medicine
Donald and Barbara Zucker School of Medicine at Hofstra/Northwell

PLANNING COMMITTEE

Richard Barakat, MD
Physician-in-Chief and Director
Northwell Health Cancer Institute
Professor, Obstetrics and Gynecology,
Donald and Barbara Zucker School of
Medicine at Hofstra/Northwell

Cindy R. Borassi
Executive Director
Colon Cancer Foundation

Northwell health Cancer Institute
Professor of Medical Oncology
Donald and Barbara Zucker School of
Medicine at Hofstra/Northwell

Mary B. Strong, MA
Assistant Vice President, Continuing
Medical Education
Northwell Health

PLANNING COMMITTEE

Heather Hampel, MS, LGC
Associate Director, Division of Human Genetics
Associate Director, Biospecimen Research
Professor, Internal Medicine
Licensed Genetic Counselor
The Ohio State University Comprehensive Cancer Center

Krista Nelson, LCSW OSW-C BCD FAOSW
Oncology Social Worker
Program Manager, Quality & Research, Cancer Support Services & Compassion
Providence Cancer Institute & Providence St Joseph Health

Thomas K. Weber, MD, FACS
Director of Surgical Oncology
Northwest Region at Northwell Health
Professor of Surgery Zucker School of Medicine at Hofstra/Northwell
Founder and President
Colon Cancer Foundation

PLANNING COMMITTEE

Krista Nelson, LCSW OSW-C BCD FAOSW
Oncology Social Worker
Program Manager, Quality & Research,
Cancer Support Services & Compassion
Providence Cancer Institute & Providence
St Joseph Health

Susan K. Peterson, PhD, MPH
Professor of Behavioral Science
The University of Texas MD Anderson
Cancer Center

Wasif M. Saif, MD, MBBS
Deputy Physician-in-Chief and
Director of Medical Oncology

SCHEDULE

This event will be
VIDEO RECORDED

THURSDAY, MAY 2, 2019

7:00 am–8:00 am	**Registration and Breakfast**
8:00 am–8:30 am	**Framing the Conversation: Strategic Challenges in Current Medical Care that Contribute to Young Adult Colorectal Cancer (CRC) Incidence and Mortality. Survivor Testimonials Underscore Opportunities for Improvement in the Prevention and Care of Young Adult Colorectal Cancer** Chelsea Boet,Sarah Debord, Kevin Hays, Kim Newcomer, Susan Pfau, Eric Reddy, Valarie Schlosser, Diana Sloan, Denelle Suranski, Tabitha Trent, Wes Hensel Opening Remarks: Richard R. Barakat, MD, Physician-in-Chief and Director, Northwell Health Cancer Institute How the Survivor Testimonials Framed Today's Program: Thomas K. Weber, MD, FACS, Northwell Health, Colon Cancer Foundation Housekeeping: Cindy R. Borassi, Colon Cancer Foundation

8:30 am–9:35 am	**Session I: The Dimensions of the EAO-CRC Problem: Target Item: Accurate, Regular, Up to Date Measurement of Key Metrics Describing the Early Age Onset Colorectal Cancer Public Health Crisis**
8:30 am–8:40 am	**Overview of United States EAO-CRC Incidence Patterns and Trends** Rebecca L. Siegel, MPH, American Cancer Society
8:40 am–8:50 am	**Overview of Global EAO-CRC Incidence Patterns and Trends** Thomas K. Weber, MD, FACS, Northwell Health, Colon Cancer Foundation
8:50 am–9:00 am	**Utilization of CDC Comparative Effectiveness Research Data to Assess Lynch Syndrome Screening and Surgical Management in Early-Onset Colorectal Cancer** Jordan Karlitz, MD, FACG Tulane University School of Medicine (VIA VIDEO CONFERENCING)
9:00 am–9:10 am	**Overview of European Cancer Registries Data Resources on EAO-CRC** Irit Ben-Aharon, MD, PhD, Rambam Health Care Campus, Haifa, Israel, European Organisation for Research and Treatment of Cancer (EORTC)

9:10 am–9:20 am	**Survey of Young Onset Patients, Survivors, and Caregivers: Self-Reported Clinical, Psychosocial, Financial and Quality of Life Experiences** Ronit Yarden, Ph.D. MHSA, Colorectal Cancer Alliance
9:20 am–9:35 am	**Q&A Panel Discussion–Strategic Plan Development**
9:35 am–9:50 am	**Networking, Coffee, Poster Viewing Break**
9:50 am–11:35 am	**SESSION II: Family History Ascertainment in the U.S. (Addressing Gap 1) What Steps are Needed to Improve the Well Documented Less Than Optimal Status of this Situation? What is Our Best Information on the Documentation of Cancer Family History in Primary Care? What are the Key Elements Required for Success** Moderator: Gregory Feero, MD, PhD, Maine Dartmouth Family Medicine Residency, Augusta, ME; Geisel School of Medicine at Dartmouth, Hanover, NH
9:50 am–10:10 am	**Electronic Health Records (EHR) and Family Cancer History Ascertainment. The Path Forward?** Gregory Feero, MD, PhD, Maine Dartmouth Family Medicine Residency, Augusta, ME; Geisel School of Medicine at Dartmouth, Hanover, NH

10:10 am–10:25 am	**Review of National Colorectal Cancer Roundtable (NCCRT) Family Health History Early Age Onset Colorectal Cancer (EAO-CRC) Task Group Progress and Overview of the NCCRT Risk Assessment and Screening Toolkit to Detect Familial, Hereditary and Early Onset Colorectal Cancer and Next Steps for Dissemination and Implementation** Dennis Ahnen, MD, AGAF, FACG, University of Colorado School of Medicine, Gastroenterology of the Rockies
10:25 am–10:40 am	**Implementation Plan for 2018 American Cancer Society Recommendations (and Rationale) for Screening for the Early Detection of Colorectal Cancer.** Robert A. Smith, PhD, American Cancer Society
10:40 am–10:50 am	**Strategies for Addressing Early Onset CRC: An NCCRT Report** Jan Lowery, Colorado Center for Personalized Medicine
10:50 am–11:00 am	**Detecting Unaffected Individuals with Lynch Syndrome (DUAL)** Sayoni Lahiri, MS, CGC, UT Southwestern Medical Center

11:00 am–11:10 am	**Prevalence of Advanced Colorectal Polyps Among First Degree Relatives of EOCRC Patients** Christine L. Sardo Molmenti, PhD, MPH Feinstein Institute for Medical Research, Northwell Health, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell
11:10 am–11:15 am	**Integrating Education on the Importance of Family Health History Ascertainment and Earliest Possible Diagnosis into the Entire Continuum of Medical and Specialty Education from Medical School Through Board Certification, CME and Recertification** Thomas K. Weber, MD, FACS, Northwell Health, Colon Cancer Foundation
11:15 am–11:30 am	**Q&A Panel Discussion–Strategic Plan Development**
11:30 am–12:15 pm	**LUNCH**
12:15 pm–1:20 pm	**SESSION III: Earliest Possible Diagnosis and Treatment Through Timely Recognition of the Symptoms and Signs of Young Adult CRC (Addressing Gap 2)** Moderator: Whitney Jones, MD, Clinical Professor of Medicine, University of Louisville

12:15 pm–12:25 pm	**A Review of the Published Data Documenting Delays in Diagnosis and the Consequences in Terms of Later Stage Diagnosis and Poorer Outcomes** Whitney F. Jones, MD, Gastro & Endo Associates
12:25 pm–12:35 pm	**Overview of the Continuum of Providers Who Interact with Patients Prior to and Up to A Diagnosis** Chelsea Boet, MD, Spectrum Health Medical Group
12:35 pm–12:45 pm	**Lessons Learned: What Have We Learned from Past Public Health Success Stories?** Jennifer Brown, PhD, NYC Department of Health & Mental Hygiene
12:45 pm–12:55 pm	**Lessons Learned: What Have We Learned from Past Public Health Success Stories?** Tony Foleno, Senior Vice President, Strategy & Evaluation, Ad Council; President, Society for Health Communication

EAO-CRC 2019

12:55 pm–1:05 pm	**Introduction of the EAO-CRC National Clinical Alert and Symptoms and Signs Index** Andrew Albert, MD, MPH, Chicago Gastro LLC. Erin Peterson, Colon Cancer Coalition • Provider Education Outreach Initiatives • Patient Awareness and Advocacy Initiatives
1:05 pm–1:20 pm	**Q&A Panel Discussion–Strategic Plan Development**
1:20 pm–2:45 pm	**SESSION IV: Timely, Effective, Quality of Life & Fertility Preserving State of the Art Treatment (Addressing Gap 3)**
1:20 pm–1:30 pm	**Updates on Current Medical Oncology Approaches to Young-Onset CRC** Andrea Cercek, MD, Memorial Sloan Kettering Cancer Center
1:30 pm–1:40 pm	**Optimal Preservation of Fertility** Nicole Noyes MD, Reproductive Endocrinologist, Northwell Health
1:40 pm–1:50 pm	**Novel Approaches to Metastatic Mismatch Repair (MMR) Deficient and Microsatellite Stable (MSS) Metastatic Colorectal Cancer** Cathy Eng, MD, FACP, FASCO, the University of Texas MD Anderson Cancer Center

1:50 pm–2:00 pm	**From "Bench to Bedside" CRC Experimental Therapeutics and Phase I & II Trials. What's New & What's Next?** Wasif M. Saif, MD, Northwell Health Cancer Institute
2:00 pm–2:10 pm	**GAPS in Providing Palliative Care and the Cost Benefit Ratio for Hospital Systems** James T. D'Olimpio, MD, FACP, FAAHPM, Northwell Health Cancer Institute
2:20 pm–2:35 pm	**Identifying the Key Elements of a Center for Early Age Onset Colorectal Cancer – Panel Discussion** Eric Reddy, Stage IV Colorectal Cancer Survivor Andrea Cercek, MD, Memorial Sloan Kettering Cancer Center Zana Correa, NP, Memorial Sloan Kettering Cancer Center Kimmie Ng, MD, MPH, Dana-Farber Cancer Institute Karen Fasciano, PsyD, Dana-Farber Cancer Institute Christine L. Sardo Molmenti, MPH, PhD Feinstein Institute for Medical Research/ Donald and Barbara Zucker School of Medicine at Hofstra/ Northwell Thomas K. Weber, MD, FACS, Northwell Health, Colon Cancer Foundation Krista Nelson, LCSW OSW-C BCD FAOSW, Providence Cancer Institute, Providence St Joseph Health

3:00 pm–5:35 pm	**SESSION V: How Did this Happen? Investigating the Causes of Early Onset Colorectal Cancers (EAO-CRC) (Addressing Gap 4)**
	The Genetics of Heritable CRC: What's New and Important to Know Regarding the Genetics of EAO-CRC? Noah D. Kauff, MD, Duke Cancer Institute, Duke University Health System Thomas K. Weber, MD, FACS, Northwell Health, Colon Cancer Foundation Susan Wysoki, APR, CRC Advocate
3:10 pm–3:20 pm	**Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients with Early-Onset Colorectal Cancer** Heather Hampel, MS, LGC, the Ohio State University Comprehensive Cancer Center
3:20 pm–3:30 pm	**Molecular Subtype of Colorectal Cancer Associated with Early Age of Onset** Xavier Llor, MD, PhD, Yale University School of Medicine Smilow Cancer Center

3:30 pm–3:40 pm	**Germline Genetic Variants Associated with Young-Onset Colorectal Cancer: the MSKCC Experience** Zsofia K. Stadler, MD Clinical Director, Clinical Genetics Service, Memorial Sloan Kettering Cancer Center
3:40 pm–3:50 pm	**Germline Genetic Features of Young Individuals with Colorectal Cancer** Elena M. Stoffel MD MPH, Director Cancer Genetics Clinic, University of Michigan
3:50 pm–4:00 pm	**Cancer Susceptibility Gene Mutations in Individuals with Colorectal Cancer** Matthew B. Yurgelun MD, Dana-Farber Cancer Institute, Harvard Medical School

What is Driving the Increases in EAO-CRC, 80+% of Which is Not Related to the Named Hereditary CRC Syndromes ?

3:50 pm–4:00 pm	**Obesity, Sedentary Behaviors, and Early-Onset CRC** Yin Cao, MPH, ScD, MPH, Washington University School of Medicine
4:00 pm–4:10 pm	**New Suspects: Diet, Microbiome, Immunology and Cancer Risk** Semir Beyaz, PhD, Cold Spring Harbor Laboratories

4:10 pm–4:20 pm **New Research Information: Current Efforts to Investigate the Causes of Increases in MSS CRC Among Young Adults**

- **The United States**
  - Current NCI Funded Investigations into the Causes of Early Age Onset Colorectal Cancer:
    - ◊ *Colorectal Cancer Risks in People < 50 Years of Age NIH (RO3): Epidemiology, Richard Hayes, DDS, PhD, MPH, the Cancer Institute at NYU Langone*

4:20 pm–4:30 pm

- ◊ *Presentation Early Life Risk Factors and Risk of Colorectal Neoplasia, Kana Wu, MD, PhD, Harvard T.H. Chan School of Public Health, Dana-Farber, Harvard Cancer Center*

4:30 pm–4:40 pm **The European Union: Funded Investigations**

- ◊ *European Organization for Research and Treatment of Cancer (EORTC): Young Onset CRC: Causation, Treatment and Outcomes, Irit Ben-Aharon, MD, PhD, Rambam Health Care Campus, Haifa, Israel European Organisation for Research and Treatment of Cancer*

4:40 pm–4:50 pm

- ◊ *European study of Early-onset Colorectal Cancer (EUREOC): A Collaborative Study of the Biology of Young Onset CRC, Jose Perea, MD, PhD, Fundacion Jimenez Diaz University Hospital, Madrid, Spain*

4:50 pm–5:00 pm	**In Development:** • **CRAYON: ColoRectal Cancer in Adults at Young ONset: New York City Based Prospective Accrual Study of Young Onset Colorectal Cancer** Steven H. Itzkowitz MD, Icahn School of Medicine at Mount Sinai
5:00 pm–5:10 pm	**The Beyond CRC Project** Kimmie Ng, MD, MPH, Dana-Farber Cancer Institute
5:10 pm–5:20 pm	**The Search for Novel Drivers of Young Onset MSS CRC: An Overview of Current NIH, CDC and ACS Efforts** Thomas K. Weber, MD, FACS, Northwell Health
5:20 pm–5:30 pm	**Report Back from Denver EAO CRC Research Meeting** Heather Hampel, the Ohio State University Comprehensive Cancer Center
5:30 pm–5:45 pm	**Discussion and "Next Steps"**
5:45 pm–6:45 pm	**Poster Session and Reception**

FRIDAY, MAY 3, 2019

8:00 am–9:00 am	**REGISTRATION AND BREAKFAST WITH THE EXPERTS, PATIENTS AND THEIR FAMILIES** Krista Nelson, LCSW OSW-C BCD FAOSW Karen Fasciano, PsyD, Dana-Farber Cancer Institute
9:00 am–9:05 am	**WELCOME BACK!** Course Co-Director Wasif M. Saif, MD, MBBS, Northwell Health Cancer Institute
9:00 am–9:05 am	**HOUSEKEEPING** Course Co-Director Susan Peterson, PhD, MPH, The University of Texas MD Anderson Cancer Center

9:05 am–10:05 am	**SESSION VI: Palliative Care: Why Early is Best. (Including Guidance, Support and Resources to Patients and Caregivers During Their Treatment Journey/Continuum of Care (Addressing Gap 5)** James T. D'Olimpio, MD, FACP, FAAHPM, Northwell Health Cancer Institute Sarah Debord, Colon Cancer Coalition Andy Esch, MD, MBA, Palliative Care and Survivorship of Western New York Karen Fasciano, PsyD, Dana-Farber Cancer Institute Susan Pfau, MA, Family Innovations and Wilder Foundation Krista Nelson, LCSW OSW-C BCD FAOSW
10:05 am–10:25 am	**SESSION VI: Epigenetics and its Future Role in the Diagnosis and Treatment of Individuals More Specifically and Accurately** C. Richard Boland, MD, AGAF, UC San Diego

10:25 am–10:45 am	**Networking, Coffee, Poster Viewing Break**
10:45 am–11:20 pm	**STRATEGIC PLANNING SESSION** **(Breakout Groups According to Gap)** 1. **Data, Accurate, Regular to Measurement of Key Metrics** 2. **Family History Ascertainment** 3. **Earliest Possible Stage Diagnosis** 4. **Development of Centers of Excellence Dedicated to the Treatment of EAO CRC Patients and Caregivers** 5. **Research into the Causes of Early Onset Colorectal Cancers**
11:20 am–11:45 pm	**REPORT BACK FROM STRATEGIC ACTION PLAN BREAKOUT GROUPS** **THE EAOCRC PLEDGE**
11:45 pm–12:15 pm	**ABSTRACT POSTER SESSION AWARDS** **CLOSING REMARKS**

FACULTY

DENNIS J. AHNEN, MD

For the last 30 years, Dr. Dennis Ahnen has been an active clinician, educator and investigator in the Gastroenterology Division of the University of Colorado School Of Medicine. His research interests have focused on the biologic understanding and prevention of colorectal cancer. His basic science laboratory has focused on colorectal cancer biology and mechanisms of chemoprevention by non-steroidal anti-inflammatory drugs, his clinical laboratory group has conducted numerous colorectal cancer screening and chemoprevention trials, and his behavioral group has focused on interventions to improve colonoscopic screening in high-risk colorectal cancer families. Clinically, Dr. Ahnen is a Co-Founder of the Hereditary Cancer Clinic at the University of Colorado Hospital and Director of the Genetics Clinic at Gastroenterology of the Rockies. He retired from his Veterans Administration faculty position in October, 2014, and is now Professor Emeritus in the Gastroenterology Division at the University of Colorado School of Medicine. Dr. Ahnen is a member of the Colorado Comprehensive Cancer Center where he continues to work with junior faculty and fellows. He is also working with Gastroenterology of the Rockies to implement a CRC prevention program seamlessly into their practice.

ANDREW ALBERT, MD, MPH

Dr. Andrew Albert is the Medical Director of Digestive Health at Advocate Illinois Masonic Medical Center, Chicago. Dr. Albert received the Grand Prize for the 2017 80% by 2018 National Achievement Awards from the National Colorectal Cancer Roundtable (NCCRT) for his leadership in increasing colorectal cancer screening rates at his institution. Dr. Albert's mission Health System has achieved a greater than 80% screening rate. Realizing that traditional messaging around colon cancer prevention was not enough, Dr. Albert launched the social media campaign, #backoffcoloncancer, in 2017. Within a few weeks, this grass-roots approach became a worldwide movement with thousands of people joining the campaign. He was recently honored for this work as one of 20 Most Inspiring Chicagoans by StreetWise Magazine. Dr. Albert is a leader on the NCCRT Hospital and Health System Advisory Board and leads best practices in colorectal cancer screening across the country. He has published extensively and has presented at numerous conferences, and has collaborated with many colorectal cancer screening advocates across the country. He has also held numerous community and corporate events to bring the messaging to those who need it most. Dr. Albert attended Brandeis University and received his Medical and Masters in Public Health Degrees at the George Washington University Medical Center. He became Chief Resident during his residency at Boston University Medical Center and completed his fellowship in Gastroenterology & Hepatology at Loyola University Medical Center. Dr. Albert has also completed advanced training at the University of Chicago.

RICHARD BARAKAT, MD

Dr. Richard Barakat is an internationally recognized surgeon and clinical investigator who was Chief of the Gynecology Service at Memorial Sloan Kettering from 2001 to 2013 and held the Ronald O. Perelman Chair in Gynecologic Surgery. Dr. Barakat was the lead investigator on several influential research projects at MSK, including a study to compare the benefits of laparoscopic versus standard surgery for patients with endometrial cancer, a study evaluating symptomatic lower-extremity lymphedema in women treated for uterine corpus cancer, and a study testing the efficacy of the Gynecologic Cancer Lymphedema Questionnaire in detecting lower-extremity lymphedema symptoms. Dr. Barakat is author or co-author of more than 340 peer-reviewed articles and numerous textbook chapters and is also an editor of a surgical atlas on gynecologic cancer and of the latest edition of Principles and Practice of Gynecologic Oncology, one of the leading texts in the field.

IRIT BEN-AHARON, MD, PHD

Dr. Irit Ben-Aharon is the Director of the Oncology Division at Rambam Health Care Campus, the largest cancer center in northern Israel, located in Haifa. She is an Associate Professor in the Department of Oncology, Faculty of Medicine, Tel-Aviv University. Dr. Ben-Aharon completed the MD-PhD joint program of Tel-Aviv University and the National Institute of Health's (NIH) and was awarded her PhD in developmental biology in 2004 and her MD at 2005. Dr. Ben-Aharon completed oncology residency at Davidoff Center, Rabin Medical Center in 2011, followed by a fellowship in oncofertility at the Dana-Farber Cancer Center in Boston (2010-2011), and a fellowship at Memorial Sloan Kettering Cancer Center, New York as a Fulbright scholar in 2014-2015 focused on gastrointestinal malignancies and young-onset cancer. Dr. Ben-Aharon returned to Israel in 2015, and led the gastrointestinal oncology at Rabin Medical Center. In 2018, she was appointed as the director of the division of oncology at Rambam Health Care Center.

SEMIR BEYAZ, PHD

Dr. Semir Beyaz' long-term research interests involve the development of a comprehensive understanding of how cancer immune recognition and response pathways are perturbed in response to diet. During his graduate training, Dr. Beyaz developed significant expertise in the assessment of epigenetic, transcriptional and metabolic mechanisms that control cellular fate during cellular differentiation or in response to diet. As a Principal Investigator at Cold Spring Harbor Laboratory, he focused on dissecting the mechanisms of how pro-obesity diets alter immunity in the intestine and impact intestinal tumor initiation, progression, response to therapy, and whether such changes are reversible.

CHELSEA BOET, MD

Dr. Chelsea Boet is an alumnus of Kalamazoo College and Wayne State University School of Medicine. Dr. Boet did her internal medicine and pediatrics residency in Grand Rapids, MI at Spectrum Health and Helen DeVos Children's hospital. Dr. Boet now practices primary care internal medicine and pediatrics in Grandville, MI. She was diagnosed with stage IV colorectal cancer in 2018. She has an incredibly supportive husband, Pete, and 2 beautiful children, Lillian (age 4) and Oliver (age 15 months).

C. RICHARD BOLAND, MD, AGAF

C. Richard (Rick) Boland, MD, AGAF, is a gastroenterologist and Professor of Medicine at the University of California San Diego School of Medicine. He was born and raised in upstate New York, received a B.A. from The University of Notre Dame and an MD from Yale Medical School. He has a career-long research interest in colon cancer, specifically focusing on the genetic causes of colon cancer and familial cancer syndromes.

Dr. Boland started studying familial colorectal cancer as a medical student, and wrote an MD thesis proposing a novel familial aspect of the disease. After clinical training (and two years as a general medical officer in the Indian Health Service), he resumed research with Young S. Kim, MD, at UCSF, studying glycoprotein biochemistry in colorectal cancer. At the University of Michigan, he continued work on cancer-associated glycoprotein alterations, but in 1990, he redirected his focus to the molecular genetics of colorectal cancer following a sabbatical in the Howard Hughes Medical Institute, at which time he resumed work on the hereditary colorectal cancer disease, which he named "Lynch Syndrome." He was among the first gastroenterologists to explore "microsatellite instability" in cancer, and his laboratory developed the first in vitro

Dr. Boland has been an active clinician and teacher. He has been funded continuously by NIH since 1979, has served on multiple NIH (and other) Study Sections and was the chair of the Clinical Integrative Molecular Gastroenterology Study Section from 2014 to 2016, and was on the Multisociety Task for on Colorectal Cancer from 2012-18. He has published about 400 papers, has an H-Index of 89, and has written authoritative chapters for several textbooks of Internal Medicine, Gastroenterology and Genetics. He was elected into the Association of American Physicians in 2001. Dr. Boland was president of the American Gastroenterological Association (AGA) from 2011-2012, was given the AGA Oncology Section Distinguished Mentor Award, the AGA Beaumont Prize for his research in 2015, and the AGA Friedenwald Medal in 2016.

JENNIFER J. BROWN, PHD

As Assistant Director of the Cancer Prevention and Control Program at the New York City Department of Health, Dr. Brown's experience includes public health research, cancer prevention, and publications. As a digital editor and writer, her skills also include communications, health and science journalism, outcomes research, medical education, grant writing, and publication.

A senior editor at EverydayHealth.com, a health site, she sets editorial strategy and managed a team of freelance writers, creating preventive health content to empower readers.

YIN CAO, SCD, MPH

Ms. Yin Cao is a cancer epidemiologist focusing on risk prediction, screening and early detection, and chemoprevention of gastrointestinal malignancies. Her research in colorectal, prostate, and breast cancers have produced over 60 original research papers, including 25 first-/senior-author papers and 2 book chapters.

Her major contributions to cancer risk prediction include the development of the first absolute risk assessment tool for high-risk adenoma that could provide guidance for colorectal cancer (CRC) screening (International Journal of Cancer, 2015). I also developed a user-friendly prediction model of breast cancer for younger women who are not recommended for routine mammography (submitted).

Cancer chemoprevention is Ms. Cao's other focus. Utilizing two large prospective studies, she reported the full constellation of potential benefits of long-term aspirin use in overall cancer prevention (JAMA Oncology, 2016). Her work also provided the first population-based evidence for the role of host immunity in mediating the benefits of aspirin in CRC chemoprevention (Gastroenterology, 2016).

ANDREA CERCEK, MD

Dr. Andrea Cercek is a board-certified medical oncologist who specializes in the treatment of patients with gastrointestinal cancers, particularly colorectal and appendix cancer, and those with peritoneal mesothelioma. She specializes in both systemic chemotherapy and regional

chemotherapy given directly into the liver or the peritoneal cavity. Her research focus is on the development of new therapies for patients, including molecular-based therapies to improve the outcomes for patients with metastatic disease.

ZANA CORREA, NP, BC

Ms. Zana Correa is an American Nurses Credentialing Center board certified nurse practitioner with 17 years of experience in outpatient gastrointestinal oncology in the departments of surgery, medicine, and survivorship at Memorial Sloan-Kettering Cancer Center. As a nurse practitioner with the Colorectal Survivorship Program, Ms. Correa manages an independent practice caring for colon, rectal and anal cancer survivors. She has presented nationally at conferences including the Oncology Nursing Society and American Society of Colorectal Surgeons annual conference. She co-facilities a support group for colorectal cancer survivors and is on the survivors' newsletter committee at Memorial Sloan-Kettering. Ms. Correa serves as an adjunct clinical instructor in the Department of Graduate Nursing at New York University.

SARAH DEBORD

Ms. Sarah DeBord was diagnosed with metastatic colon cancer at age 34. In the 7-plus years since, she has turned her diagnosis into a calling, and become an advocate for other young adults diagnosed with colorectal cancer and parents with young families facing cancer. Ms. DeBord works as a communications and program manager for the Minneapolis-based Colon Cancer Coalition, is a contributing writer for CURE Magazine, volunteers her time with the online patient-led support community COLONTOWN, and blogs about her often adventurous experiences of living with chronic cancer at ColonCancerChick.com.

ANDREW E. ESCH, MD, MBA

Dr. Andrew Esch is a palliative care specialist and consultant focusing on improving the quality of life for patients and their families as they face serious or life-threatening illness through pain and symptom management, coordination of care, and education. Dr. Esch earned his medical degree from the University of Buffalo, where he also earned a combined bachelor of science and master of business administration degree. Currently he is a consultant and faculty member for the Center to Advance Palliative Care (CAPC), and serves as medical director at the Hospice of Orleans in Albion, New York. Prior to joining CAPC, Dr. Esch worked at the Lee Memorial Health System in Fort Myers, Florida, as medical director of palliative care. He has worked in both New York and Florida as a staff physician, a hospice physician, an assistant clinical professor of internal medicine and palliative care.

GREGORY FEERO, MD, PHD

Dr. Gregory Feero attended the University of Pittsburgh School Of Medicine and graduated with an M.D., Ph.D. (Human Genetics) in 1998. He then completed his medical training at the Maine-Dartmouth Family Medicine Residency in Augusta, Maine. After five years on the faculty of the Maine-Dartmouth Family Medicine Residency, he accepted a position at the National Human Genome Research Institute, National Institutes of Health, where he was a senior advisor to the director, and branch chief of the Genomic Healthcare Branch in the Office of Policy, Communication and Education, Office of the Director. In 2009 he returned to Maine. Dr. Feero currently serves as a consultant to the Jackson Laboratory on education issues, is an associate editor for the Journal of the American Medical Association and serves on the National Academies

TONY FOLENO

Mr. Tony Foleno serves as Senior Vice President, Strategy and Evaluation at the Ad Council. In this role, Mr. Foleno advises the strategic planning of more than 35 public service communications campaigns. He also oversees campaign evaluation, establishing key performance indicators and the tools through which they are measured. Mr. Foleno leads cross-campaign analyses designed to optimize Ad Council initiatives, and helps lead Ad Council Edge, a strategic consultancy advising nonprofit and corporate clients. His primary role is to leverage research-based insights into action, helping to ensure that the Ad Council remains a results-driven organization with a single-minded focus on making an impact in people's lives. Prior to joining the Ad Council in 2002, Mr. Foleno managed projects at Public Agenda, a nonpartisan public opinion research organization. He presently serves as 2018-2020 President of the Society for Health Communication, and is an active member of the Advertising Research Foundation, the American Evaluation Association, the 4As, and AAPOR, and serves on the steering committees for Agents of Change, the Market Research Council, and the Fishlinger Center for Public Policy and Research. He is a graduate of Swarthmore College and holds a MA in Sociology from Columbia University.

HEATHER HAMPEL, MS, CGC

Heather Hampel completed her Bachelor of Science degree in Molecular Genetics at the Ohio State University in 1993. She attained her Master's degree in Human Genetics from Sarah Lawrence College in 1995. She received certification from the American Board of Genetic Counseling in 1996. She worked as a cancer genetic counselor at Memorial Sloan- Kettering Cancer Center before moving to The Ohio State University Comprehensive Cancer Center (OSUCCC) in 1997.

Currently, Heather is a Professor in the Department of Internal Medicine and Associate Director of the Division of Human Genetics. She is also the Associate Director of Biospecimen Research for the OSUCCC. She was the study coordinator for the Columbus-area Lynch syndrome study which determined the frequency of Lynch syndrome among newly diagnosed patients with these cancers. This study culminated in first author publications in the New England Journal of Medicine in May of 2005, Cancer Research in August of 2006, and the Journal of Clinical Oncology in December of 2008. She is now the PI of the Ohio Colorectal Cancer Prevention Initiative which is screening colorectal cancer patients from 50 hospitals throughout the state for hereditary cancer syndromes. The first major publication from that study showing that 16% of early-onset colorectal cancers are hereditary was published in 2017 in JAMA Oncology. Heather Hampel was the Region IV Representative on the Board of Directors of the National Society of Genetic Counselors in 2003-4. She was on the Board of Directors for the American Board of Genetic Counseling from 2006-2011, serving as President in 2009 and 2010. She was elected to the Steering Committee member of the National Colorectal Cancer Roundtable in 2016. She has been on the Council of the Collaborative Group of the Americas on Inherited Colorectal Cancer since 2016 and served as President in 2018.

RICHARD B. HAYES, DDS, PHD

Dr. Richard Hayes is a Professor in the Departments of Population Health and Environmental Medicine at New York University School of Medicine. Dr. Hayes has more than 30 years of experience in designing and carrying out epidemiologic investigations on cancer, including the successful execution of case-control and cohort studies in national and international settings. His past research on the etiology of colorectal cancer has involved investigations

of diet, anthropometric factors, and genetics, and, most recently, the human microbiome. His current research involves risk prediction modeling for colorectal cancer, with the purpose determining the appropriate age for beginning colorectal cancer screening, based on genetic and environmental risks. This research also involves identification of differentials for genetic and environmental risk for those younger than age 50 years and older individuals.

WES HENSEL

Mr. Wes Hensel was diagnosed with stage 3 rectal cancer at age 34 during a colonoscopy, after 4 years of being misdiagnosed with hemorrhoids due to rectal bleeding and being "too young" for anything else. After diagnosis, tumor tissue testing on mismatch repair protein expression and subsequent germline genetic testing found that Mr. Hensel had a MLH1 gene mutation for Lynch Syndrome, despite no family history of colorectal cancer. After extensive treatment with radiation and chemotherapy, Mr. Hensel underwent abdominoperitoneal resection with permanent colostomy at MD Anderson Cancer Center, performed by Dr. Nancy You, followed by additional chemotherapy completed in November, 2018. Now age 36, Mr. Hensel was declared "no evidence of disease" in December, 2018. He has a passion for educating others about early-onset colorectal cancer, and for promoting earlier screening, including colonoscopies as a first line of defense when symptoms arise in younger patients. He also is passionate about promoting healthy eating and fitness for cancer prevention and overall health. Mr. Hensel works as a systems engineer in the aerospace industry, and lives with his beautiful wife and 2 lovely children in Tucson, Arizona.

STEVEN H. ITZKOWITZ, MD, FACP, FACG, AGAF

Dr. Steven Itzkowitz is Professor of Medicine and Oncological Sciences, and Director of the GI Fellowship Program at Icahn School of Medicine at Mount Sinai. His research has focused on reducing disparities in colon cancer screening in the general population, developing new non-invasive stool DNA tests to screen for colon cancer, and detecting and preventing colon cancer in inflammatory bowel disease. At the national level, Dr. Itzkowitz is a current member of the Steering Committee of the National Colorectal Cancer Roundtable and a former Chair of the Gastrointestinal Oncology Section of the American Gastroenterological Association. In New York City, he is a former President of the New York Gastroenterological Association and a founder of the New York Crohn's and Colitis Organization (NYCCO). He is immediate past Co-Chair of the New York Citywide Colon Cancer Control Coalition (C5 Coalition) and current Co-Chair of the C5 Coalition Screening Guidelines Committee. At Mount Sinai, since 2000 he has been instrumental in developing and running the institution's colon cancer screening program among minority populations in East Harlem. His team at Mount Sinai was among the first in the nation to demonstrate the effectiveness of patient navigation to enhance screening colonoscopy adherence, proving also that patient navigation is cost effective. He is the founder and Medical Director of the Mount Sinai CO-CARE Registry for patients and their relatives who are at high risk for colon cancer. He is currently organizing a multi-center prospective study of risk factors for Early Onset CRC among several NYC-area academic medical centers.

WHITNEY JONES, MD

Dr. Whitney Jones is a practicing Gastroenterologist, former therapeutic endoscopist and Clinical Professor at the University of Louisville from 1994 until 2017.

In 2003 he founded the Colon Cancer Prevention Project, a state based, nation leading information and advocacy organization. Through the leadership of Colon Cancer Prevention Project and its many partners, Kentucky has more than doubled its screening rates, cut colon cancer mortality by third, and passed into law the lowest barriers for CRC screening of any state.

Since 2016, Dr. Jones has implemented systematic hereditary cancer risk assessment and point of service genetic panels testing in both the office and endoscopy platforms to both prevent and better manage the cancer risks of affected and unaffected patients.

JORDAN KARLITZ, MD

Dr. Jordan Karlitz graduated from the University of California at Berkeley with a degree in molecular biology and genetics. He subsequently attended the McGill University Faculty of Medicine in Montreal where he received his medical degree. He received his internal medicine training at the Columbia University College of Physicians and Surgeons/New York Presbyterian Hospital and completed his fellowship in gastroenterology and hepatology at the Albert Einstein College of Medicine/Montefiore Medical Center.

NOAH D. KAUFF, MD

Dr. Noah Kauff is Director, Clinical Cancer Genetics at Duke Cancer Institute in Durham, North Carolina. Dr. Kauff is a gynecologist and geneticist who specializes in the care of patients who may have an inherited predisposition to cancer. His research interests include: a) analyzing the effect of genetic risk markers on the assessment and treatment of individuals with an inherited predisposition to cancer; b) evaluating methods for incorporating genetic risk assessment into the routine care of oncology patients; c) characterizing the efficacy of risk-reducing strategies

performed for the prevention of inherited cancers; and d) elucidating differences between inherited and sporadic cancers to assist in the development of targeted therapies for hereditary malignancies.

SAYONI LAHIRI, MS, CGC

Ms. Sayoni Lahiri is a board-certified genetic counselor at the University of Texas Southwestern Medical Center in Dallas. Prior to joining UT Southwestern in 2015, Ms. Lahiri completed her Master of Science degree in genetic counseling at Northwestern University and practiced in Orange, California. In addition to providing genetic counseling for patients at risk for hereditary cancer at multiple UT Southwestern clinics, she is also grant coordinator and oversees two of the department's population grants that focus on expanding access to genetic counseling and testing services to the underserved population of north Texas. Ms. Lahiri oversees the implementation of a Cancer Prevention and Research Institute of Texas (CPRIT)- funded population screening program for Lynch syndrome at UT Southwestern and Parkland Hospital, and helped create a CPRIT grant-funded genetic patient navigator role to follow patients with Hereditary Breast and Ovarian Cancer syndrome (HBOC) and Lynch syndrome.

XAVIER LLOR, MD, PHD

Dr. Xavier Lior is Professor of Medicine, Medical Director, Cancer Screening and Prevention Program and Colorectal Cancer Prevention Program, and Co-director, Cancer Genetics and Prevention Program at Yale University School of Medicine. After obtaining his MD degree from the Autonomous University Barcelona, Dr. Llor trained in basic research and Internal Medicine at the University of Chicago and completed his GI fellowship at the University of Illinois at Chicago. He complemented his training with a PhD degree in molecular biology from the University of

JAN LOWERY, PHD, MPH

Dr. Jan Lowery is the Associate Director of Clinical Operations at the Colorado Center for Personalized Medicine. She earned her PhD in Analytical Health Sciences and Epidemiology from the University of Colorado. She is an Adjunct Associate Professor in the Department of Epidemiology at the Colorado School of Public Health.

CHRISTINE MOLMENTI, PHD, MPH

Dr. Christine Molmenti is an Assistant Professor and Cancer Epidemiologist in the Department of Occupational Medicine, Epidemiology and Prevention at the Northwell Health. Her research is focused on the primary and secondary prevention of colorectal cancer through screening/ early detection and lifestyle.

KRISTA NELSON, LCSW OSW-C BCD FAOSW

Krista Nelson is trained as an oncology social worker and works in clinical, research and program management roles within Providence Health and Services. Krista Most recently joined the Compassion team as a Program Manager, and has appreciated bringing her clinical expertise to work on creating supportive infusions of compassion to caregivers.

She provides individual support as well as group support for those affected with cancer and facilitates an online support group for women with metastatic cancer and runs a program for children with a parent with cancer.

Krista defines her role as providing support for people and their families throughout the cancer continuum, and sharing the expertise that she has learned from other patients with cancer. What she loves about working with those affected with cancer, "is being able to witness the grace, courage and life lessons of individuals dealing with cancer and the opportunity to be a part of their journey."

Krista is a past President of the board of directors of the Association of Oncology Social Work and past invited Director of the American Psychosocial Oncology Society. She loves being a part of the national discussion involving the psychosocial care of people with cancer. She has been a speaker at local and national conferences on issues of survivorship, palliative care, distress screening and children who have a parent with cancer. Krista also serves as an Invited Director on the board of directors of the National Accreditation Program for Breast Centers, In 2015, Krista was named as a finalist in the Schwartz Center Compassionate Caregiver of the year award and received and Innovation Award from the Association of Community Cancer Centers as well as was elected to their Board of Trustees in 2016.

Krista also has been a volunteer facilitator at retreats for women with breast cancer and at camps and programs that support grieving children. She also has volunteered annually on medical relief teams to Haiti since 2009.

KIMMIE NG, MD, MPH

Dr. Kimmie Ng has the expertise, training, leadership, and resources necessary to serve as Faculty in this program. She is a board-certified medical oncologist with MD and MPH degrees who specializes in the treatment and investigation of gastrointestinal malignancies. Dr. Ng's research program focuses on the identification of dietary, molecular, and genetic predictors of improved survival in colorectal cancer (CRC) patients. She has published extensively on the relationship between vitamin D status and survival of patients with CRC, and is now translating her findings into randomized clinical trials for patients. She has received multiple grants to support her work, including K07 and R01 awards evaluating vitamin D and inflammation in CRC, and served as Co-Project Leader of Project 2 in the Dana-Farber/Harvard Cancer Center (DF/HCC) SPORE in Gastrointestinal Cancer.

NICOLE NOYES, MD

Dr. Nicole Noyes competed her undergraduate and medical degree at the University of Vermont and then an OB-GYN residency and Reproductive Endocrinology fellowship at Weill-Cornell University School of Medicine. She has participated full-time in academic medicine in New York City ever since, first at Cornell, then at New York University (for 23 years) and now at Northwell Health, where she serves as System Chief for Reproductive Medicine. At NYU, she helped established the University's Fertility Preservation program, one that came to cryopreserve oocytes for more than 4,000 women and produced more than 125 babies using the technology. Dr. Noyes has also frozen oocytes for more than 250 cancer patients. She currently oversees all of Northwell Health's Fertility treatments, including its Fertility Preservation program and will be opening a state-of-the-art Fertility facility on East 64th Street this summer. She remains a consulting fertility preservationist at Memorial Sloan Kettering Cancer Center, has participated in fully-funded NIH research, authored over 60 peer-review manuscripts, given more than 75 guest lectures around the world, is involved with the training of reproductive endocrine fellows, was past chair of the American Society of Reproductive Medicine's Fertility Preservation Special Interest Group and continues to focus her research efforts on fertility preservation, early embryogenesis and human implantation.

JOSE PEREA, MD

Dr. José Perea is a Consultant Colorectal Surgeon and Associate Professor in the Surgery Department at Fundación Jiménez Díaz University Hospital, Madrid, Spain. Dr. Perea's clinical and research interests focus on surgery, gastroenterology and oncology, and in particular, understanding the basis of colorectal cancers with differential phenotypes. He coordinates a multicenter multidisciplinary group within Spain, as well as international collaborations, focused

in general and gastroenterological surgery from the General University Hospital Gregorio Marañón, Madrid, and his PhD (cum laude) from the University of Salamanca. He completed a specialization in clinical research Methodology at the National School of Health, Carlos III Institute, Madrid, and a master of molecular oncology degree from the Spanish National Oncological Research Center (CNIO). Dr. Perea is a member of the scientific committee for the Spanish Society of Coloproctology.

ERIN PETERSON

Ms. Erin Peterson is the Communications Director for the Colon Cancer Coalition where she works to reach the unscreened and underserved with the lifesaving messages of on time colorectal cancer screening. Prior to joining the Colon Cancer Coalition in 2011, Ms. Peterson spent ten years working for a marketing and public relations agency with national brands focusing on building partnerships and reaching consumers through unique marketing approaches.

SUSAN PFAU, MA

Ms. Susan Pfau is a mental health practitioner with Family Innovations and Wilder Foundation. She also serves as a Kid's Support Group facilitator at Gilda's Clubhouse Twin Cities. She earned her MA in Marriage and Family Therapy from Saint Mary's University in Minnesota and her BA in Family Studies from Metropolitan State of Minnesota. Ms. Pfau serves on the advisory board of the Colon Cancer Alliance.

REBECCA SIEGEL, MPH

Ms. Siegel conducts cancer surveillance research across the cancer continuum, from prevention to survivorship, to help inform evidence-based cancer prevention and control in the United States and worldwide. Her primary research interests are emerging trends in cancer occurrence, particularly early-onset colorectal cancer, and cancer disparities based on race, socioeconomic status, and geography.

DIANA SLOAN

Diana Sloan is originally from Chesapeake, Virginia, and is a graduate of James Madison University. She currently lives in Lakeway, Texas, with her husband of nineteen years and their three daughters. Diana was an English teacher until 2012 when she was diagnosed with stage IV colorectal cancer at the age of 38. She is currently incurable and in treatment. Diana now spends her free time making memories with her family and friends and enjoying what her husband aptly named, "The We Don't Wait" tour. She has also found a new passion in advocating for colorectal cancer patients, especially those diagnosed under 50.

ROBERT A. SMITH, PHD

Dr. Robert A. Smith is a cancer epidemiologist and Vice President, Cancer Screening at the National Office of the American Cancer Society (ACS) in Atlanta, Georgia. He also is Adjunct Professor of Epidemiology at the Rollins School of Public Health, Emory University School of Medicine, and an Honorary Professor, Centre for Cancer Prevention, Wolfson Institute of Preventative Medicine at Queen Mary University of London. His primary research interests are cancer epidemiology, evaluation of cancer prevention and early detection programs, quality assurance in the delivery of health services, and cancer rehabilitation and survivorship. He

received his PhD from the State University of New York at Stony Brook in 1983. Prior to joining the staff at the ACS, he held positions with the Boston University School of Public Health, and the Centers for Disease Control. At the ACS he leads the development of cancer screening guidelines, and special research and policy projects focused on cancer prevention and control. He is the author of over 300 peer-reviewed scientific articles, reports, and book chapters, and a frequent lecturer on cancer screening issues. He serves on many international and national government and professional advisory committees and working groups, and in 2017 was a member of the International Agency for Research on Cancer (IARC) Handbooks Working Group for volume 17 on Colorectal Cancer Screening. Dr. Smith was one of the founding members of the National Colorectal Cancer Roundtable, and has served as its Co-Director for 22 years. He also is a founding member of the National Lung Cancer Roundtable and the Principle Investigator of the first 3-year supporting grant. Among his honors, Dr. Smith is an Honorary Fellow of the Society of Breast Imaging; in 2004 he received the Cancer Prevention Laurel for Outstanding National Leadership from the Prevent Cancer Foundation; and in 2011 he received the Medal of Honor from the International Agency for Research on Cancer.

ZSOFIA STADLER, MD

Dr. Zsofia Stadler is a clinical and laboratory investigator with an interest in human cancer genetics with a focus on hereditary and early-onset gastrointestinal cancers. Her research focuses on the use of genomic approaches to improve the identification and characterization of known and novel cancer susceptibility genes for colorectal and pancreas cancers as well as a variety of other inherited cancers. In early-onset, but genetically unexplained cancer patients, her research focuses on the use of whole-genome and exome sequencing to identify novel de

novo or inherited mutations that may account for such early-onset malignancies. With tumor-normal DNA sequencing, her team recently demonstrated that high-frequency microsatellite instability predicts for the presence of germline mutations in the DNA mismatch repair genes, diagnostic of Lynch syndrome, across a broad spectrum of cancers. This suggests that Lynch syndrome is a much more heterogeneous disease than previously thought and any cancer patient harboring a tumor with micorsatellite instability should undergo genetic testing for Lynch syndrome.

ELENA M. STOFFEL, MD, MPH

Dr. Elena Stoffel is an Assistant Professor of Internal Medicine (academic tenure track) and an associate member of the Cancer Epidemiology and Prevention Group of the University of Michigan Comprehensive Cancer Center. Her clinical and research interests are pathogenesis, early detection and prevention of gastrointestinal cancers, with special focus on genetic factors. Her previous work, funded by a K07 Cancer Prevention, Control and Population Sciences Career Development Award from the National Cancer Institute, examined the impact of genetic risk assessment on health behaviors and clinical outcomes of individuals with inherited predisposition to colorectal cancer. In her current position at the University of Michigan, Dr. Stoffel serves as Director of the Cancer Genetics Clinic, and is principal investigator of the University of Michigan Cancer Genetics Registry and the Gastrointestinal Colorectal Biorepository. She has experience as principal investigator in research studies assessing utility of novel endoscopic and non-invasive technologies for early detection of colorectal neoplasia. Dr. Stoffel leads a multidisciplinary team dedicated to diagnosis and management of patients with hereditary cancer syndromes. She is a co-investigator on international collaborative research studies encompassing genetic epidemiology of GI cancers and clinical chemoprevention trials

for individuals with genetic predisposition for colorectal cancer. Dr. Stoffel is a past President of the Collaborative Group of the Americas on Inherited Colorectal Cancer, a member of the American Gastroenterological Association Nominating Committee for Gastrointestinal Oncology, and the American Society of Clinical Oncology (ASCO) Cancer Genetics Committee. She serves on the National Comprehensive Cancer Network Colon and Rectum Guidelines Committee, and the ASCO Gastrointestinal Cancer Advisory Panel (Cancer.net). Dr. Stoffel has led expert review panels on clinical guidelines for management of individuals with hereditary GI cancer syndromes.

MARY B. STRONG, MA,

Ms. Mary Strong is the Assistant Vice President of Continuing Medical Education at Northwell Health. She holds a Bachelor of Science Degree in Community and School Health Education from the Health Sciences Center, State University of New York at Stony Brook. Her Master of Arts Degree in Health Administration was earned from Hofstra University, Hempstead, NY. Mary is currently responsible for the oversight of Northwell Health CME program consisting of medical conferencing, regularly scheduled series, and enduring materials that are designed to accomplish the CME mission of Northwell Health. She has worked in the field of Continuing Medical Education since 1999 when she became Assistant Director of CME for North Shore-LIJ's Department of Professional and Public Health Education. Mary began her professional career as a health educator with the Long Island Diabetes Association where she was involved in community education initiatives. As a health educator for North Shore University Hospital, she planned and developed in-service and health education programs for school administrators, health personnel, faculty, parents and students. Additionally, she was responsible for the organization and implementation of a variety of large scale events, such

as health fairs and community wellness programs. Her years of experience in adult learning, education and program implementation have carried over to her work in continuing medical education. During her tenure as Director, the CME program of the North Shore LIJ Health System (now Northwell Health) achieved, and has maintained, the level of Accreditation with Commendation (2007-2013; 2013-2019), the highest level awarded to CME providers by the Accreditation Council for Continuing Medical Education (ACCME).

DENNELLE SURANSKI

Ms. Denelle Suranski born and raised in Pittsburgh, PA. She is an event coordinator for Allegheny County, Parks and Recreation division and currently enrolled in Carlow University pursuing a degree in Human Resources Management.

She is also stage II rectal cancer survivor diagnosed with Lynch Syndrome, MSH2. Denelle is a 2019 On the Rise model for the Colon Club and delighted to be a 2019 EAOCRC faculty member of Colon Cancer Foundation.

THOMAS K. WEBER, MD, FACS

Dr. Weber is Director of Surgical Oncology, Northwest Region, Northwell Health and Medical Co-Director of Cancer Genetics at Northern Westchester Hospital, Northwell Health. Through 2017, Dr. Weber was Academic Professor of Surgery at the State University of New York at Downstate. As Chief of Surgery at VA New York Harbor Health Care System, Brooklyn Campus Dr. Weber led major initiatives to improve operating room productivity, surgical quality improvement and enhanced multidisciplinary training and care for the surgical patient at the Brooklyn VA Medical Center. In addition, he successfully led multiple new innovations including the establishment of a genetic counseling service, Surgical Telemedicine, implementation of

a surgical simulation center, enhanced postoperative pain control templates and improved communication between surgical teams and waiting family members during extensive surgical procedures. To enhance quality assurance and surgical outcomes he designed an objective analytic analysis of response and completion times of ancillary service response to requests from the surgical service including radiology, cardiology and infectious disease. He also led the full integration of the Manhattan VA Surgical Service into the Brooklyn VA Medical Center following the Hurricane Sandy evacuation of all Manhattan VA patients and staff to the Brooklyn Campus on October 28th, 2012 and their return to Manhattan 6 months later in May 2013.

MATTHEW YURGELUN, MD

Dr. Matthew Yurgelun is a gastrointestinal medical oncologist at the Dana-Farber Cancer Institute affiliated with both the Gastrointestinal Cancer Center and the Cancer Genetics and Prevention Program. He has a longstanding special interest in studying the diagnosis, phenotypes, and management of patients with Lynch syndrome and other hereditary gastrointestinal cancer syndromes. His current research includes studying the benefits and limitations of using widespread multi-gene panel testing – rather than criteria-based targeted genetic testing – in the evaluation of patients at risk for hereditary cancer syndromes.

SESSION V: How Did this Happen? Investigating the Causes of Early Onset Colorectal Cancers (EAO-CRC) (Addressing Gap 4)

The Genetics of Heritable CRC: What's New and Important to Know Regarding the Genetics of EAO-CRC?

Noah D. Kauff, MD, Duke Cancer Institute, Duke University Health System

Thomas K. Weber, MD, FACS, Northwell Health, Colon Cancer Foundation

Susan Wysoki, APR, CRC Advocate

Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients with Early-Onset Colorectal Cancer

Heather Hampel, MS, LGC, the Ohio State University Comprehensive Cancer Center

Molecular Subtype of Colorectal Cancer Associated with Early Age of Onset

Xavier Llor, MD, PhD, Yale University School of Medicine Smilow Cancer Center

Germline Genetic Variants Associated with Young-Onset Colorectal Cancer: the MSKCC Experience

Zsofia K. Stadler, MD Clinical Director, Clinical Genetics Service, Memorial Sloan Kettering Cancer Center

Germline Genetic Features of Young Individuals with Colorectal Cancer

Elena M. Stoffel MD MPH, Director Cancer Genetics Clinic, University of Michigan

Cancer Susceptibility Gene Mutations in Individuals with Colorectal Cancer

Matthew B. Yurgelun MD, Dana-Farber Cancer Institute, Harvard Medical School

What is Driving the Increases in EAO-CRC, 80+% of Which is Not Related to the Named Hereditary CRC Syndromes ?

3:50 pm–4:00 pm **Obesity, Sedentary Behaviors, and Early-Onset CRC**
Yin Cao, MPH, ScD, MPH, Washington University School of Medicine

4:00 pm–4:10 pm **New Suspects: Diet, Microbiome, Immunology and Cancer Risk**
Semir Beyaz, PhD, Cold Spring Harbor Laboratories

4:10 pm–4:20 pm **New Research Information: Current Efforts to Investigate the Causes of Increases in MSS CRC Among Young Adults**

- **The United States**
  - Current NCI Funded Investigations into the Causes of Early Age Onset Colorectal Cancer:
    - ◊ *Colorectal Cancer Risks in People < 50 Years of Age NIH (RO3): Epidemiology, Richard Hayes, DDS, PhD, MPH, the Cancer Institute at NYU Langone*

4:20 pm–4:30 pm
- ◊ *Presentation Early Life Risk Factors and Risk of Colorectal Neoplasia, Kana Wu, MD, PhD, Harvard T.H. Chan School of Public Health, Dana-Farber, Harvard Cancer Center*

4:30 pm–4:40 pm **The European Union: Funded Investigations**
- ◊ *European Organization for Research and Treatment of Cancer (EORTC): Young Onset CRC: Causation, Treatment and Outcomes, Irit Ben-Aharon, MD, PhD, Rambam Health Care Campus, Haifa, Israel European Organisation for Research and Treatment of Cancer*

4:40 pm–4:50 pm
- ◊ *European study of Early-onset Colorectal Cancer (EUREOC): A Collaborative Study of the Biology of Young Onset CRC, Jose Perea, MD, PhD, Fundacion Jimenez Diaz University Hospital, Madrid, Spain*

4:50 pm–5:00 pm **In Development:**
- **CRAYON: ColoRectal Cancer in Adults at Young ONset: New York City Based Prospective Accrual Study of Young Onset Colorectal Cancer**

Steven H. Itzkowitz MD, Icahn School of Medicine at Mount Sinai

5:00 pm–5:10 pm **The Beyond CRC Project**
Kimmie Ng, MD, MPH, Dana-Farber Cancer Institute

5:10 pm–5:20 pm **The Search for Novel Drivers of Young Onset MSS CRC: An Overview of Current NIH, CDC and ACS Efforts**
Thomas K. Weber, MD, FACS, Northwell Health

5:20 pm–5:30 pm **Report Back from Denver EAO CRC Research Meeting**
Heather Hampel, the Ohio State University Comprehensive Cancer Center

“how did this happen?”

Environmental & epigenetic factors

From an evidence based M.D.

“MOM DOCTOR”

2 & 1/2 years of looking for the why

From diagnosis to today


Speedo
AVALON


UNFORTUNATELY JESSICA IS NOT THE ONLY ONE…

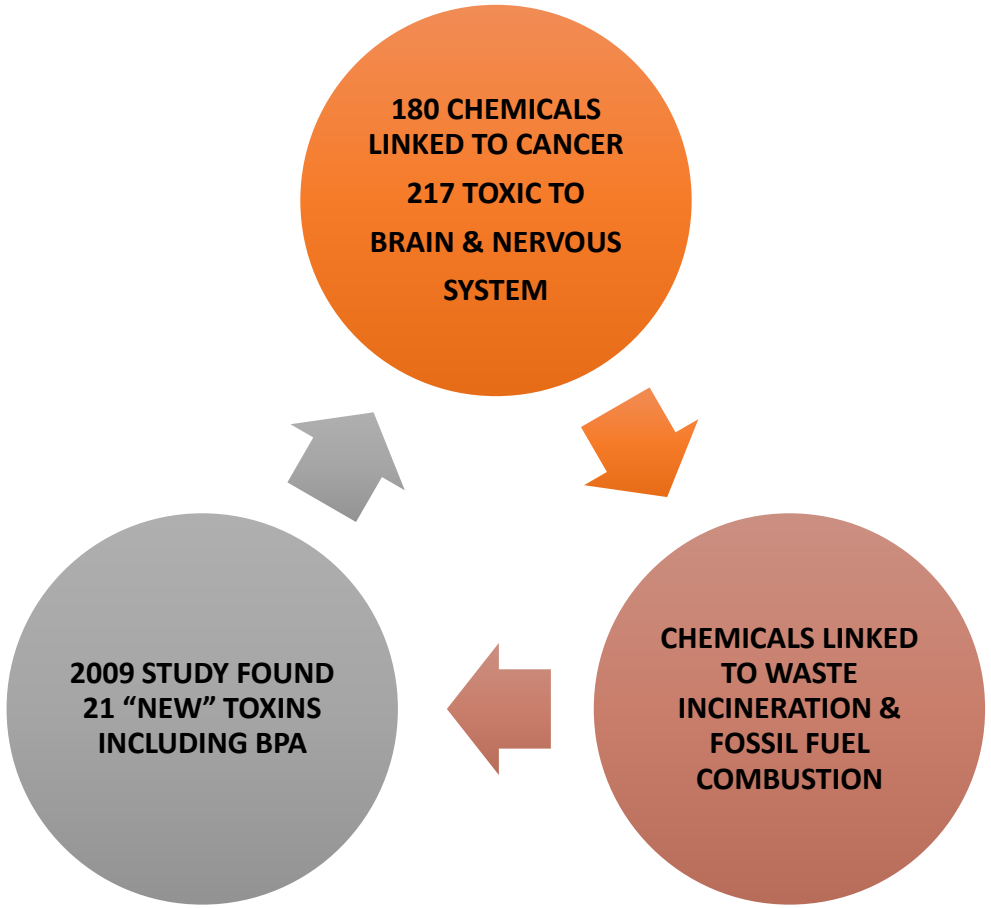
Natal Exposure

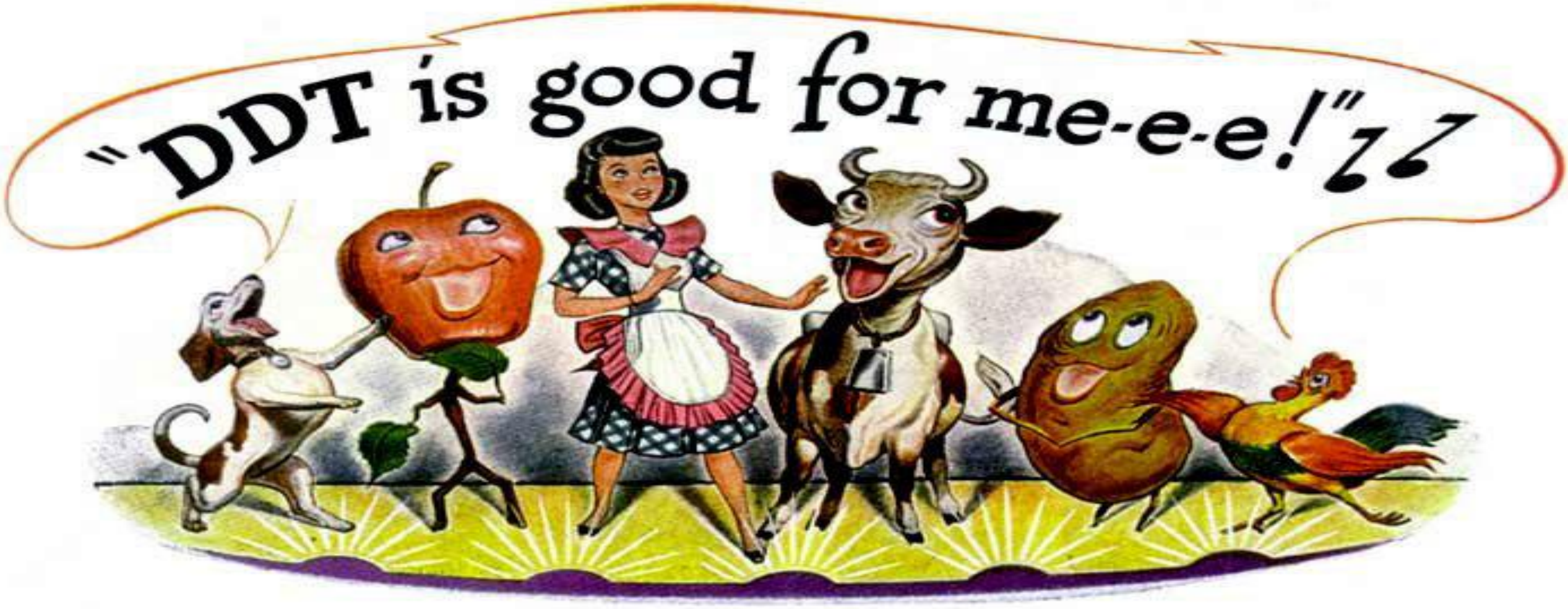
EWG CORD BLOOD STUDY

LEAD
MERCURY
PCB'S

287+
INDUSTRIAL
CHEMICALS

Cord Studies in 2005 &2009





Ddt banned in 1972

Almost 50 years later

CDC Found in 99% of people tested

Guess What? Your veggies still have ddt

- USDA Found DDT Compounds in 42% of Kale Greens & 24% of carrots
- Present in 23 out of 31 common foods everything from yogurt, cheese, peanut butter, and “healthy foods” like sardines and salmon
- Over 30 years over 1.35 billion pounds was sprayed in US alone
- These chemicals are man-made, toxic, bio-accumulate and bio-p

What else was going on?
"Age of Anti-Bacterial"

PROBLEM IS WE ARE BACTERIA!
90% OF OUR CELLS ARE MICROBIAL & 10% HUMAN

Launched in 1997

Anti-Bac is Contrary to HYGIENE HYPOTHESIS

- Early exposure to germs helps child's immune system develop
- Complex gene-environment interactions
- Increases in allergic diseases and inflammatory disorders
- Fine balancing of t-Helper cells (1 &2) and T cell responses
- triggered by altered or missing innate immune cell activation
- Pattern recognition receptors play crucial role in early shaping of immune development of th-2 driven allergic immune responses

“Age of Antibacterial” Triclosan….A Closer Look

- 2010 NRDC SUED THE FDA FOR NOT FINALIZING 1978 BAN ON TRICLOSAN
- IN 2016 FDA BANS TRICLOSAN IN HAND SANITIZER/SOAPS
- BUT IT’S STILL IN THOUSANDS OF PERSONAL CARE PRODUCTS TODAY

How Can Triclosan Be BANNED in Soap But OK in Toothpaste?

colgate.com

Colgate

COLGATE TOTAL® TOOTHPASTE WITH TRICLOSAN

Colgate invented the multi-benefit toothpaste category more than 20 years ago with the introduction of Colgate Total with triclosan. Now we are replacing the formula with **Colgate Total SF** and a different active ingredient that delivers even more benefits.

Learn about the additional benefits offered by new Colgate Total SF

The earlier formula of Colgate Total® toothpaste is uniquely formulated with

Colgate eliminated triclosan from its toothpaste. Could a ban be on the way?

By Corinne Purtill • February 2, 2019

AP PHOTO/CAROLYN KASTER

Now with more flavor, fewer inflammatory compounds.

Colgate-Palmolive's newest product, a toothpaste called Colgate Total SF, rolled out this week with a multimillion-dollar marketing campaign that includes a celebrity-studded commercial that will air during Sunday's Super Bowl.

Latest Featured Obsessions Emails Editions

And By the way…What's Gantrez?

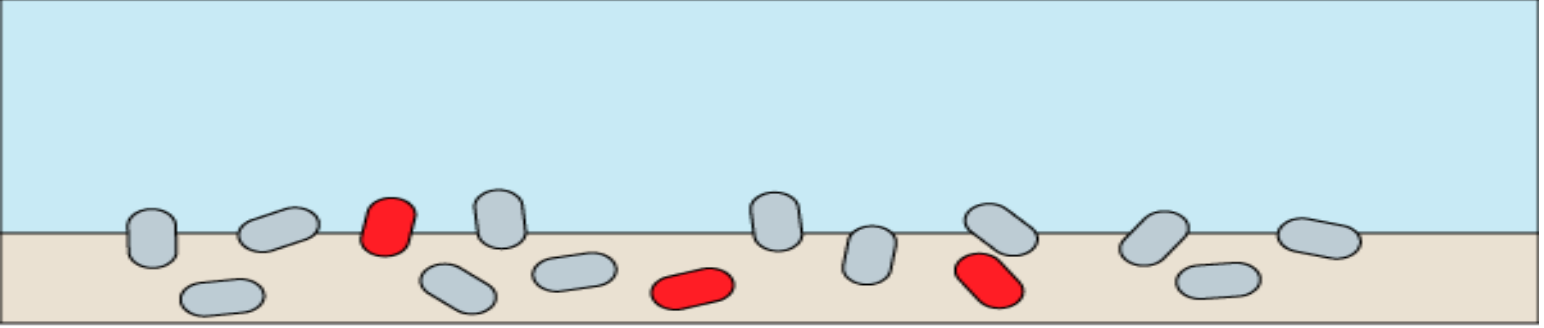
- "The **Colgate Total** formula is so revolutionary it's even patented. Its active ingredient is Triclosan, which is used to help reduce plaque and gum problems. The **Gantrez** copolymer enables Triclosan to continue working in the mouth for 12 hours."
- Genotoxic evaluation of Poly(anhydride) NP's in the Gastrointestinal tract of mice
- High Mucous Permeable Carrier, Able to Reach GI Epithelium
- Significant induction of DNA strand breaks/oxidized bases in duodenum
- Promising nanocarriers as oral drug delivery systems

Tricloslosan…A Closer Look

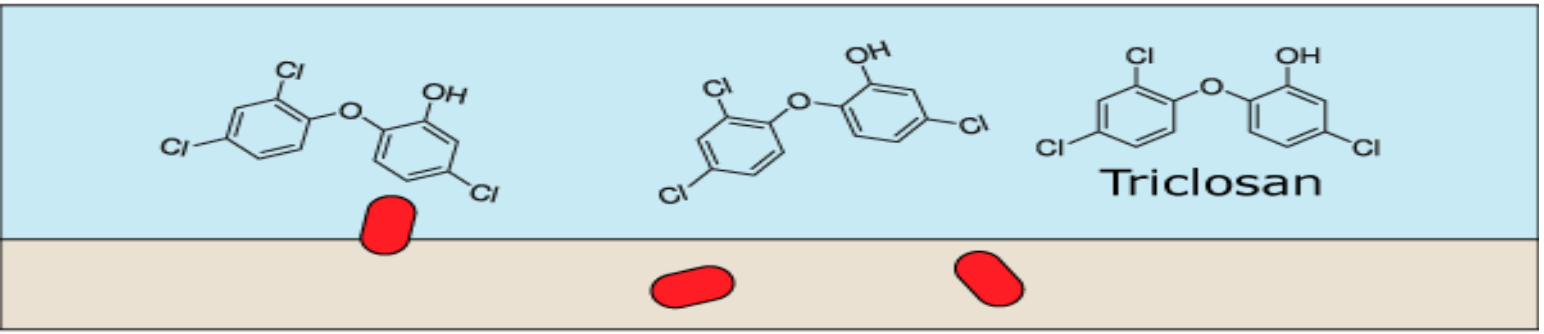
- U-Mass Study/Science & Translation Medicine (May 31, 2018)
- H20 Spiked with Triclosan 3 weeks/Mimic Human Levels
- 100% Gut problems: colon inflammation, rectal bleeding, abdominal pain, reduced lifespan
- Devastated microbiome diversity/Killed off Bifidobacterium
- Transformed intestinal flora into antagonist > Inflammatory response
- Encouraged more aggressive tumor development IN Existing Colon Cancer

TRICLOSAN…A Closer Look

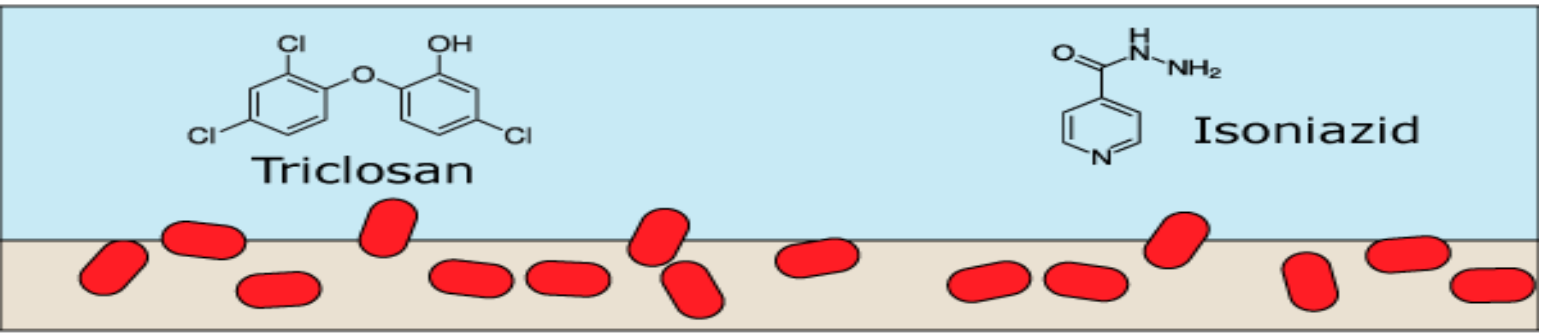
- OVER 4 DECADES AFTER IT WAS KNOWN TO BE UNSAFE (1978-Now)
- Still persistent/no enforcement
- National health & Nutrition examination survey Present 75% of urine samples
- It’s among top 10 biggest pollutants of us rivers
- Mice bred without gut bacteria experienced no inflammation even after exposure to triclosan…which underscores that it’s gut specific
- And it Doesn’t just kill off the good guys….



Normal and mutant bacteria
happily living in the environment



Add triclosan; mutant bacteria survive



The mutant bacteria will reproduce.
Their offspring are immune to many antibiotics.

- Increases Risk of Drug Resistant Bacteria
- Bacteria on your skin become resistant to triclosan itself (TRB)
- TRB has Mutations in Proteins (ENR's) that exacerbate antibacterial resistance

Antibiotics: Most Used in Children

- Antibiotic Use Highest in children u
- 30% of RX antibiotics are unnecessa
- (50 Million RX Year)
- Don’t help with most common issu
- Antibiotic RX is the New “Lollipop”

Antibiotics: the a-bomb

- ONE COURSE WIPES OUT 1/3 OF THE GUT MICROBIOME
- TAKES MONTHS TO YEARS TO GROW BACK
- SOME SPECIES NEVER RETURN

What else was going on?

Age of “whiter & brighter”

Launched in 1998

Eclipse Launched 1999

TITANIUM DIOXIDE

One of the Most Widely Used Pigments in the World

Used in Paper, Paints, Plastics, Coatings, Pharmaceuticals, Sunscreen, Cosmetics, Toothpaste & Food

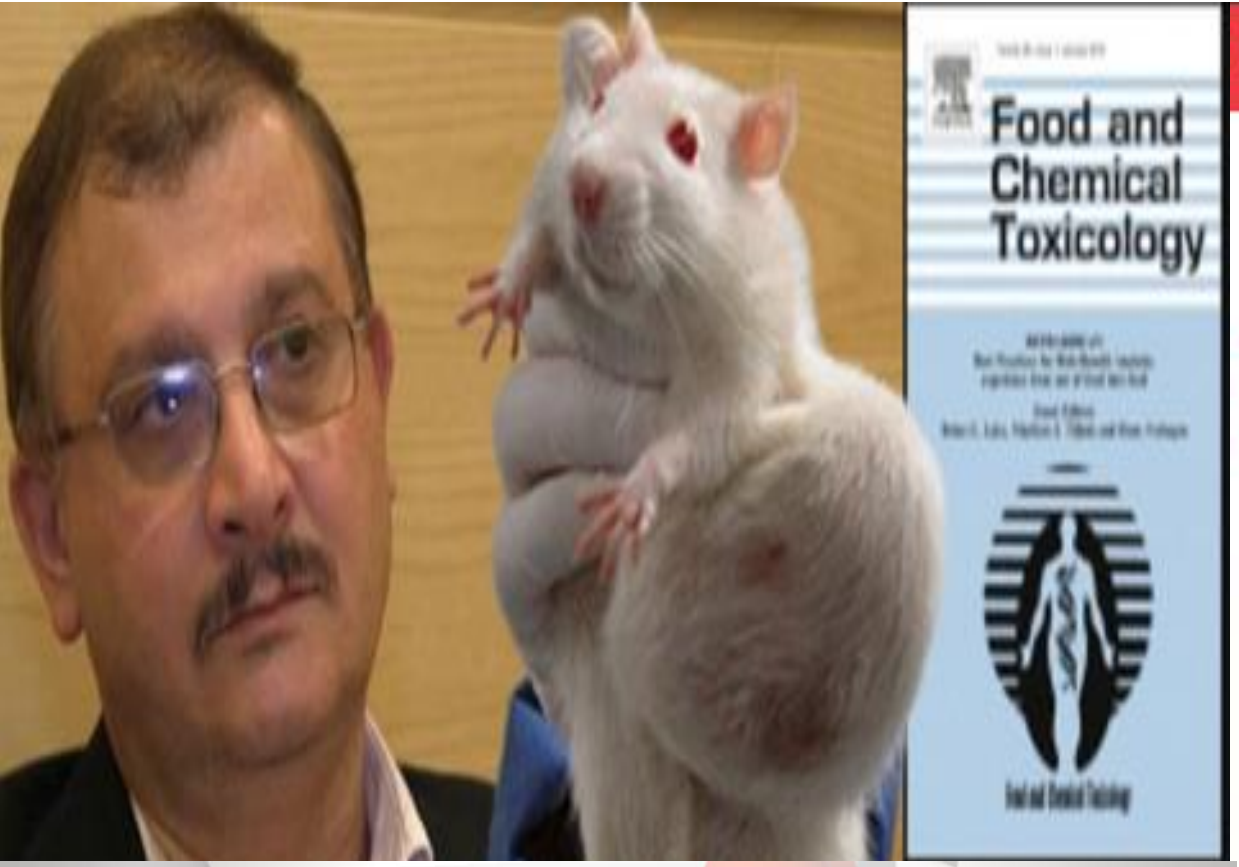
INDEPENDENT

Additive found in toothpaste and food products could cause cancer, say scientists

New study finds titanium dioxide leads to precancerous growths in 40 per cent of rats

Ben Kentish | @BenKentish |
Tuesday 24 January 2017 01:22 GMT |

- E171& TiO2
- FRANCE NATIONAL INSTITUTE FOR AGRICULTURAL RESEARCH
- 90 DAYS IN-VIVO
- FOOD GRADE
- 40% OF RATS DEVELOPED PRECANCEROUS LESIONS ON COLON



c&en

Log In

A Measure Of Titanium Dioxide

Commercial Product Analysis: Because of TiO_2's high levels in candy, children ingest more of the whitener than adults

By **Charlie Schmidt**

Sweet, Sweet Titanium
Candies contain high levels of the whitening compound titanium dioxide.
Credit: Glane23/Wikipedia

Used mainly as a whitening agent, titanium dioxide is a common additive in foods, paints, and personal care products. But scientists know little about how much TiO_2 appears in these products, and that lack of data hinders studies of the chemical's

Transcriptomics analysis reveals new insights in E171-induced molecular alterations in a mouse model of colon cancer.

Proquin H, et al. Sci Rep. 2018.
Show full citation

Abstract

Titanium dioxide as a food additive (E171) has been demonstrated to facilitate growth of chemically induced colorectal tumours in vivo and induce transcriptomic changes suggestive of an immune system impairment and cancer development. The present study aimed to investigate the molecular mechanisms behind the tumour stimulatory effects of E171 in combination with azoxymethane (AOM)/dextran sodium sulphate (DSS) and compare these results to a recent study performed under the same conditions with E171 only. BALB/c mice underwent exposure to 5 mg/kgbw/day of E171 by gavage for 2, 7, 14, and 21 days. Whole genome mRNA microarray analyses on the distal colon were performed. The results show that E171 induced a downregulation of genes involved in the innate and adaptive immune

Effect of microflora and lactose on the absorption of calcium, phosphorus and magnesium in the hindgut of the rat.

Andrieux C, et al. Reprod Nutr Dev. 1983.
Show full citation

Abstract

For 4 weeks, 3-month old germfree (GF) and conventional (CV) rats were given a semi-synthetic diet sterilized by irradiation with or without 10% of lactose. During the 5th week, 0.2% of titanium oxide (TiO2) was added to the diet and the rats were killed at regular intervals throughout the light/dark cycle. The patterns of TiO2 and 45Ca excretion were similar, indicating that TiO2 was a good marker of unabsorbed calcium transit. The apparent absorption coefficient of calcium, magnesium and phosphorus was determined in the ileum, caecum, large intestine and faeces by the mineral/TiO2 ratio. The effects of microflora and lactose varied with the mineral and the digestive tract level studied. --In the small intestine, microflora had no effect on the apparent absorption of calcium and magnesium but did

Food-grade TiO2 impairs intestinal and systemic immune homeostasis, initiates preneoplastic lesions and promotes aberrant crypt development in the rat colon.

Bettini S, et al. Sci Rep. 2017.
Show full citation

Abstract

Food-grade titanium dioxide (TiO2) containing a nanoscale particle fraction (TiO2-NPs) is approved as a white pigment (E171 in Europe) in common foodstuffs, including confectionary. There are growing concerns that daily oral TiO2-NP intake is associated with an increased risk of chronic intestinal inflammation and carcinogenesis. In rats orally exposed for one week to E171 at human relevant levels, titanium was detected in the immune cells of Peyer's patches (PP) as observed with the TiO2-NP model NM-105. Dendritic cell frequency increased in PP regardless of the TiO2 treatment, while regulatory T cells involved in dampening inflammatory responses decreased

Daily Mail .com | Health

France bans 'cancer-causing' food additive that gives chewing gum, white chocolate and packet sauces their colour – but the UK says it's 'not concerned'

By Alexandra Thompson Senior Health Reporter For Mailonline

13:02 EDT 18 Apr 2019, updated 13:06 EDT 18 Apr 2019

Verisk 3E

France Bans Titanium Dioxide (E 171) as Food Additive in Any Food

Back to List

Home / Resource Center / Blog / France Bans Titanium Dioxide (E 171) as Food Additive in Any Food

November 6, 2018 - Sava Kostić

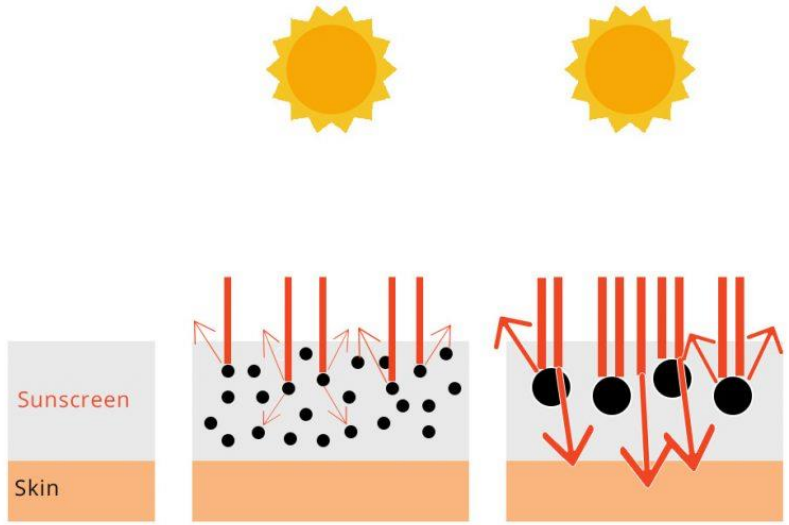
On 1 November 2018 the French Assembly

What we know about Titanium Dioxide on Skin

Not Photostable

It’s in “everything”

IT Is absorbed



- KNOWN CARCINOGEN INHALATION
- NANO Ti02 DISRUPTS FUNCTION OF BACTERIA WITHIN 60 MIN OF EXPOSURE
- TOPICAL USE & INGESTION?
- A PHOTOCALYST TiO2 CAN BE ADDED TO PAINTS, CEMENTS, WINDOWS, AND TILES IN ORDER TO DECOMPOSE ENVIRONMENTAL POLLUTANTS

HOW DO I REGISTER MY COLORBOND ROOFING WARRANTY?

A STEP BY STEP GUIDE

Talk to the EXPERTS
(02) 9970 8359
FREE ADVICE

No.1 Roofing & Building Supplies

EU to opt against health warning for suspected carcinogen

***Decision on titan*ium dioxide follows industry lobbying and could be illegal, critics say**


FDA PROPOSAL ON
UNSAFE SUNSCREEN
CHEMICAL INGREDIENTS
12 commonly used in sunscreen
More research needed before declared safe
FDA'S NEW PROPOSALS ON DRUG STORE SUNSCREEN
SAYS 14 OF THE 16 INGREDIENTS MAY BE UNSAFE
THOSE WHO BROKE THE LAW WHILE BROKERING FINANCIER JEFFREY EPSTEIN


FDA PROPOSAL ON
SAFE SUNSCREEN
MINERAL INGREDIENTS
Zinc oxide
Titanium dioxide
FDA'S NEW PROPOSALS ON DRUG STORE SUNSCREEN
SAYS 14 OF THE 16 INGREDIENTS MAY BE UNSAFE

DOES Natural= safety?

- There are several examples of naturally occurring ELEMENTS minerals and metals that are unsafe
- Aluminum, arsenic, cadmium, chromium, lead, mercury, nickel
- And oh by the way hemlock too...
- Just to name a few…
- We’ve looked at titanium dioxide but what about zinc oxide?
- That must be safe right?...

12. Sunscreens

Most sunscreens contain zinc oxide as a common ingredient. This produces free radicals that can damage the DNA and create room for growth of cancer. Benzophenone-3 is another cancer-causing chemical in sunscreens, which has the tendency to get absorbed in the body.

Photo Credit: iStock

Exposure to ZnO nanoparticles induces oxidative stress and cytotoxicity in human colon carcinoma cells.

De Berardis B, et al. Toxicol Appl Pharmacol. 2010.
Show full citation

Abstract

Engineered nanoparticles offer great promise in many industrial and biomedical applications, however little information is available about gastrointestinal toxicity. The purpose of this study was to assess the cytotoxicity, oxidative stress, apoptosis and proinflammatory mediator release induced by ZnO nanoparticles on human colon carcinoma LoVo cells. The biological activity of these particles was related to their physico-chemical characteristics. The physico-chemical characteristics were evaluated by analytical electron microscopy. The cytotoxicity was determined by growth curves and water-soluble tetrazolium assay. The reactive oxygen species production, cellular glutathione content, changes of mitochondrial membrane potential and

Neurotoxicity induced by zinc oxide nanoparticles: age-related differences and interaction

Lei Tian, Bencheng Lin […] Zhuge Xi

ZnO nanoparticle-induced oxidative stress triggers apoptosis by activating JNK signaling pathway in cultured primary astrocytes

Jieting Wang, Xiaobei Deng, [...], and Wenjun Ding

Additional article information

Zinc Oxide Nanoparticles Induced Oxidative DNA Damage, Inflammation and Apoptosis in Rat's Brain after Oral Exposure

Hala Attia [1,2], Howaida Nounou [3,*] and Manal Shalaby [4]

1 Department of Pharmacology and Toxicology, College of Pharmacy, King Saud University, Riyadh 11495, Saudi Arabia

2 Department of Biochemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt

3 Department of Medical Biochemistry, Faculty of Medicine, Alexandria University, Alexandria 21111, Egypt

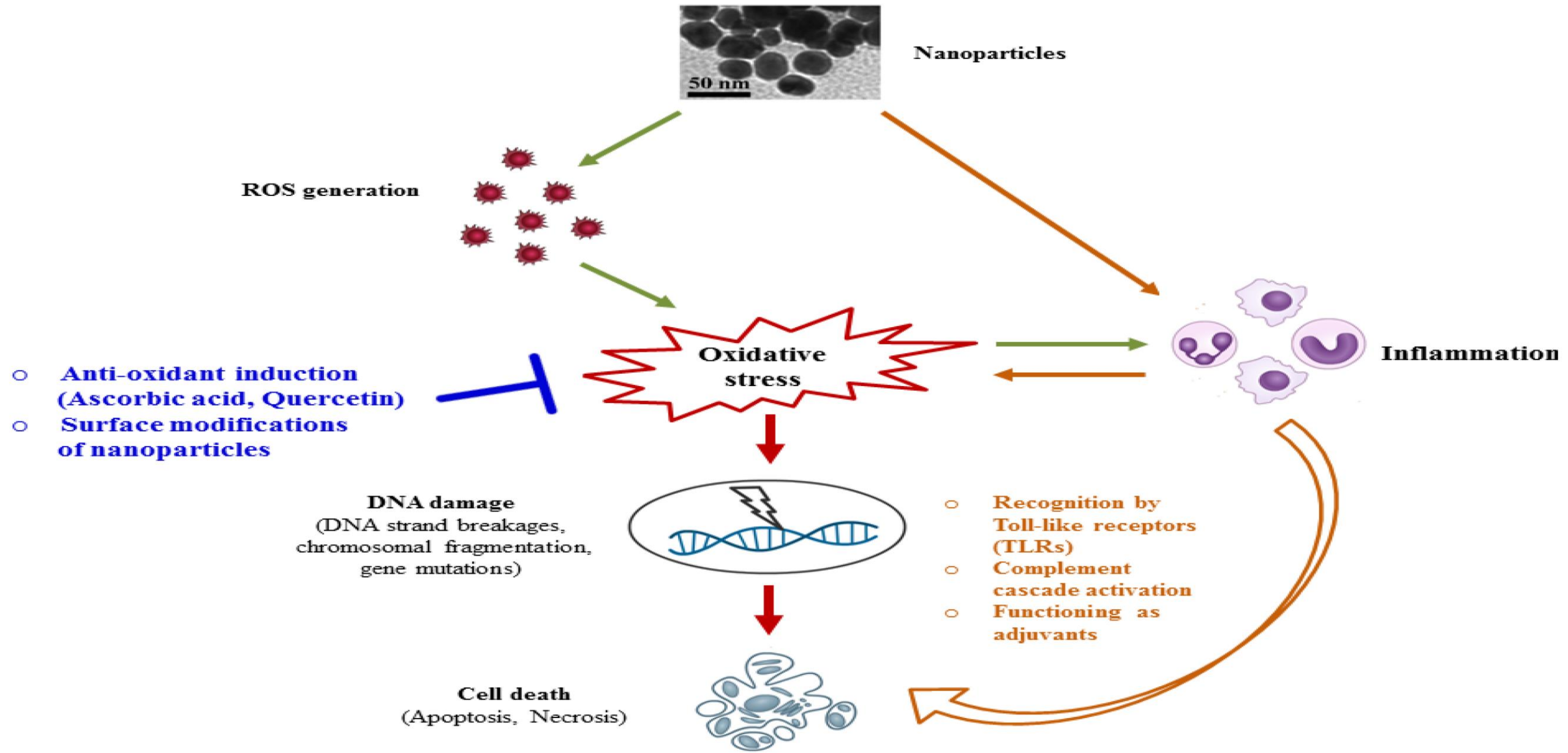
4 Department of Medical Biotechnology, Institute of Genetic Engineering City of Scientific Research and biotechnological applications, Borg El Arab, Alexandria 21111, Egypt

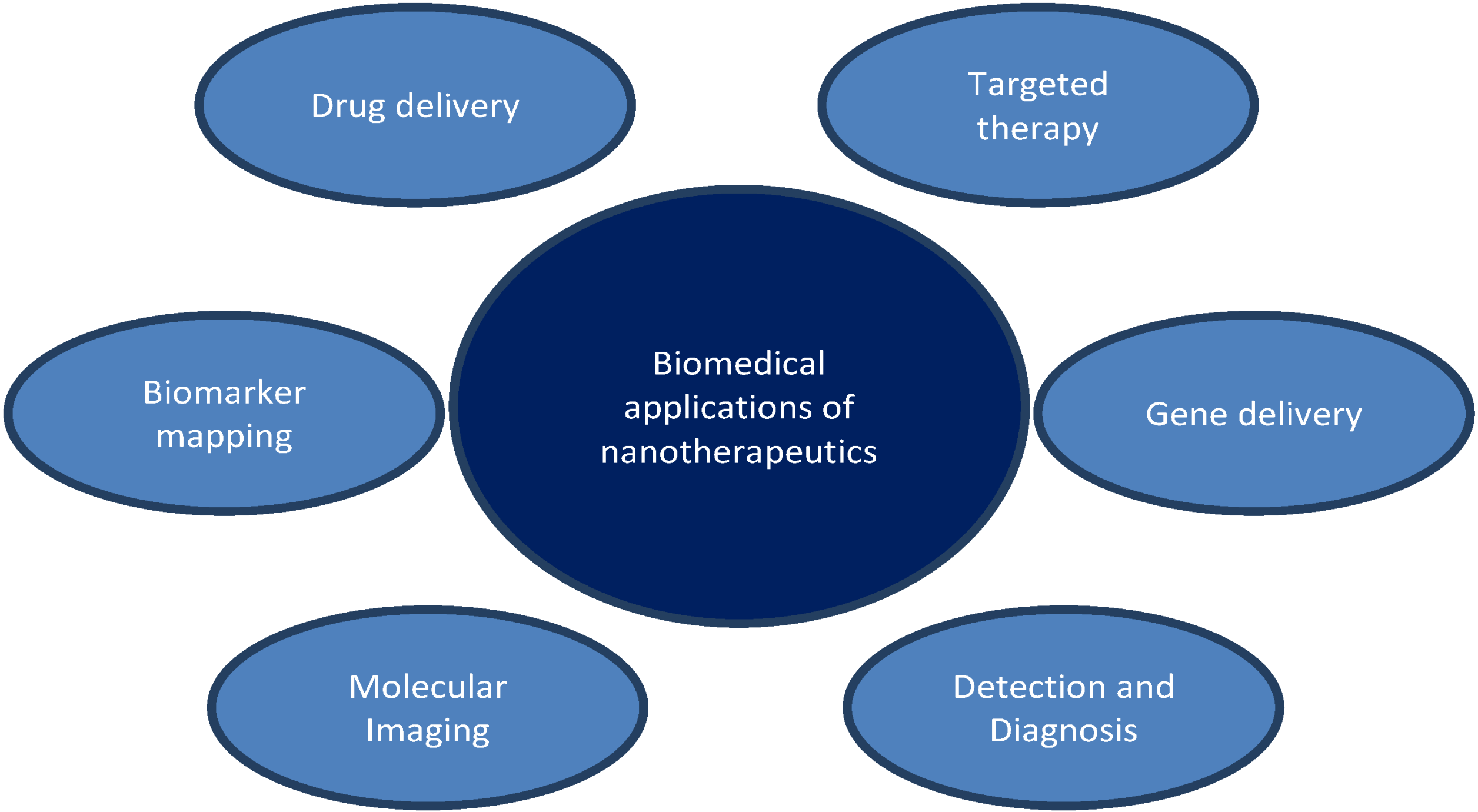
* Author to whom correspondence should be addressed.

Received: 23 April 2018 / Revised: 11 May 2018 / Accepted: 19 May 2018 / Published: 26 May 2018

(This article belongs to the Special Issue Nanoparticles

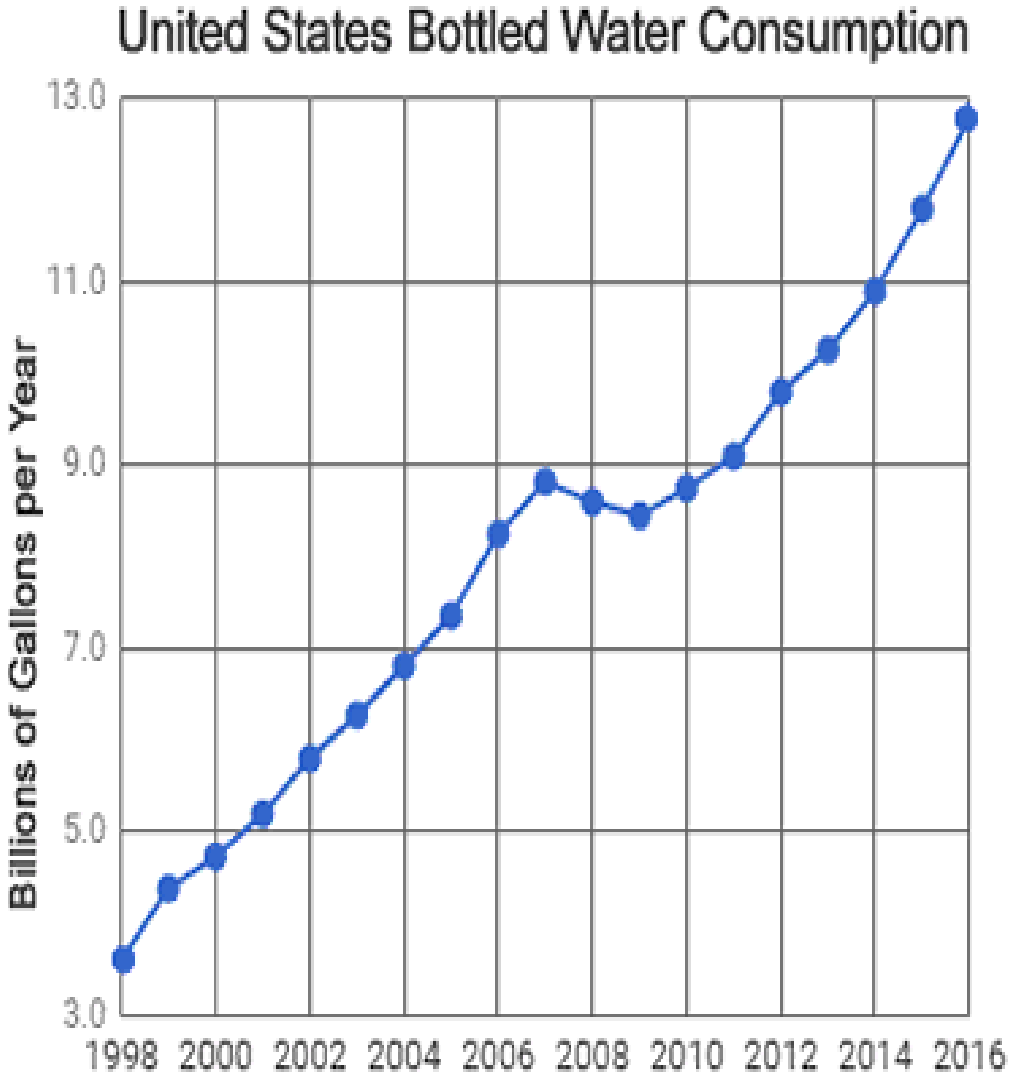
No-NO Nanos


50 nm
Nanoparticles
ROS generation
Oxidative stress
Inflammation
Anti-oxidant induction (Ascorbic acid, Quercetin)
Surface modifications of nanoparticles
DNA damage
(DNA strand breakages, chromosomal fragmentation, gene mutations)
Recognition by Toll-like receptors (TLRs)
Complement cascade activation
Functioning as adjuvants
Cell death
(Apoptosis, Necrosis)


Drug delivery
Targeted therapy
Biomarker mapping
Biomedical applications of nanotherapeutics
Gene delivery
Molecular Imaging
Detection and Diagnosis

What else was going on?

- Water Water Everywhere…
- Bottled Water Boom
- Commercially popular in late 90's
- Dasani launched in 1999



What else was going on?

- Boom of microbeads (PE) in consumer products in everything
- MB Free Waters Act 2015/8 trillion Particles entering aquatic habits daily
- New Study finds Microplastics in Human Stool (Primarily Polypropylene & Polyethylene)
- “This is the first study of its kind and confirms what we have long suspected, that plastics ultimately reach the human gut. Of

What else was going on? Plastics

- Latest study Released this month showed.
- Microplastics (MP's) induce intestinal inflammation and oxidative stress
- Mp's induced significant alterations in the metabolome and microbiome of zebrafish gut
- Significant metabolic and microbial alterations were associated with inflammation and lipid metabolism
- 2nd Study released last month showed Polystyrene/Styrofoam negatively impacted microbiome with changes in glycolipid and energy metabolism

What Else was going on?
Age of “Sippy Cups” BPA

- BPA especially harmful to children
- Surprise It Affects Microbiome
- Sharp Decrease in microbiota Diversity
- Results in altered metabolic profiles
- Not Banned until 2012
- 5 out of 6 sippy Cups labelled

Widespread
Use Late 90’s

Hooray We've Banned "X....sort of"

- One Molecule difference…
- Bpa was replaced with bps
- Brominated tris/chlorinated tris
- Sodium laurel sulfate replaced with sodi  fate
- Ddt was banned in 1972 and then roundup was introduced in 1974
- C8 was banned 10 years ago, 268 variations same chemical

A word about our chemical world

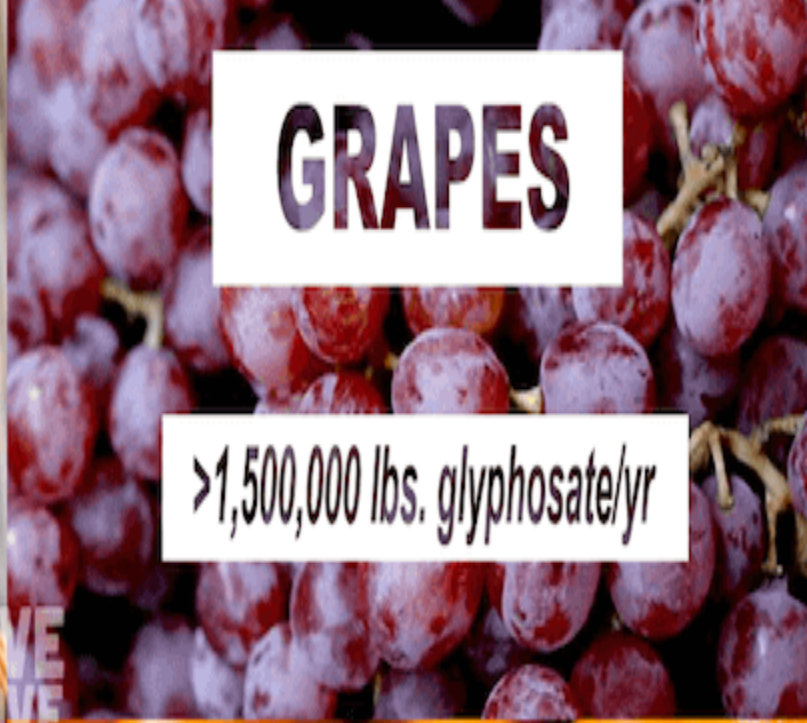
- There are over 80,000 + chemicals in commercial us
- no-pre market testing of chemicals
- CPG & Personal Care companies use loopholes in leg
- “trade Secrets” such as Fragrance/Artificial Flavors
- Chemicals Banned in EU or Other Countries/“GRAS”
- Toothless tiger

What Else was Going On?

- Widespread use of Glyphosate
- Used on over 93% of Soy and Corn Crops
- Used as a Desiccant Wheat/oats/Barley
- 18.9 billion Pounds since 1974
- 75% of that in last decade
- Over 70 crops sprayed

A Word About “BT Corn”

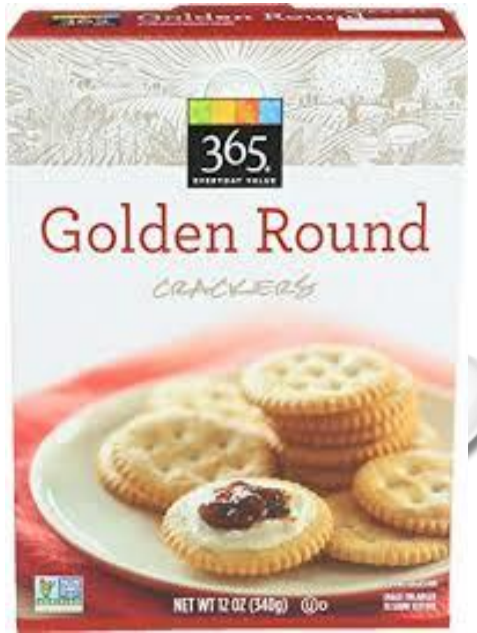
- Bt & Mechanism of Action (to Kill European corn borer)
- Corn crops are sprayed an average of 8x in the field
- BT Has 2 Classes of Toxins 1 of those is Crystal Delta Endotoxins
- Toxic mechanism is for these proteins to bind to receptors in the mid-gut
- Resulting in Rupture of those cells
- So what happens when WE eat ther



LIVE LOVE FRUIT

Glyphosate: How Much are We Eating?

- Not Included in Annual Testing
- EPA Stopped “Special Assessment”
- 1,340 Different Foods



Glyphosate How much are We eating?

- An fda approved food safety testing laboratory found levels in common foods ranging from 290-1,125 PPB
- At only 0.05 ppb roundup resulted in liver/kidney damage and changed the function of more than 4,000 genes
- Levels known to cause organ damage
- U.S. Allows 1.75 mg/kg/bw/day vs. EU 0.3 Mg/k
- Used on >175 Million Acres U.S./440 M Worldw
- Can’t be removed by washing, cooking, baking,


dang
onion chips
Kashi
7 Whole Grain
back to NATURE
Peanut Butter Creme
Cookies
BARBARA'S
Cheese Puffs
Tropicana
SMART BALANCE
LIGHT
plentils
SEA SALT
LENTIL CHIPS
BROWNIE
MIX
PROBURST BITES
not nuts!
SEED Fruit
Soft Baked
CRUNCHY MINIS
Snack Packs
Mini Chips
A Whole New Generation of Toxic Foods
Just arrived at your Natural Grocery
Non-GMO with Glyphosate!

GMO Foods

For more information go to
olmag.co/gmo-foods

Tomato

Tomatoes have been genetically modified, but they are not being grown commerically at thia time

Rice

GMO rice has been approved but is not yet being used commercially

Sweet Corn

More than 70 percent of corn grown in the United States has been genetically engineered

Summer Squash

Farmers don't like GMO squash but some experts say GM squash have blended with wild squash

Salmon

GMO salmon has not been approved by the FDA, but it will be very soon

Canola Oil

87% of canola grown commercially, and 80% of wild canlola is GMO

Yeast

GMO yeast for wine has been approved

Alfalfa

GMO alfalfa is contaminating non GMO alfalfa crops at a rapid rate

Wheat

Unapproved GMO has contaminated wheat fields, and we don't yet know the extent of it

Sugar Beets

90% of Sugar Beets (used to make 50% of our sugar) are GMO

Soy

More than 93% of soybeans the United States produces are genetically modified

Peas

Peas have been genetically modified but are not approved or availlable

Hawaiian Papaya

Most Hawaiian papaya is GMO, even many organic crops are contaminated

Cotton

At least half of cotton grown in the world is GMO

organic lifestyle MAGAZINE

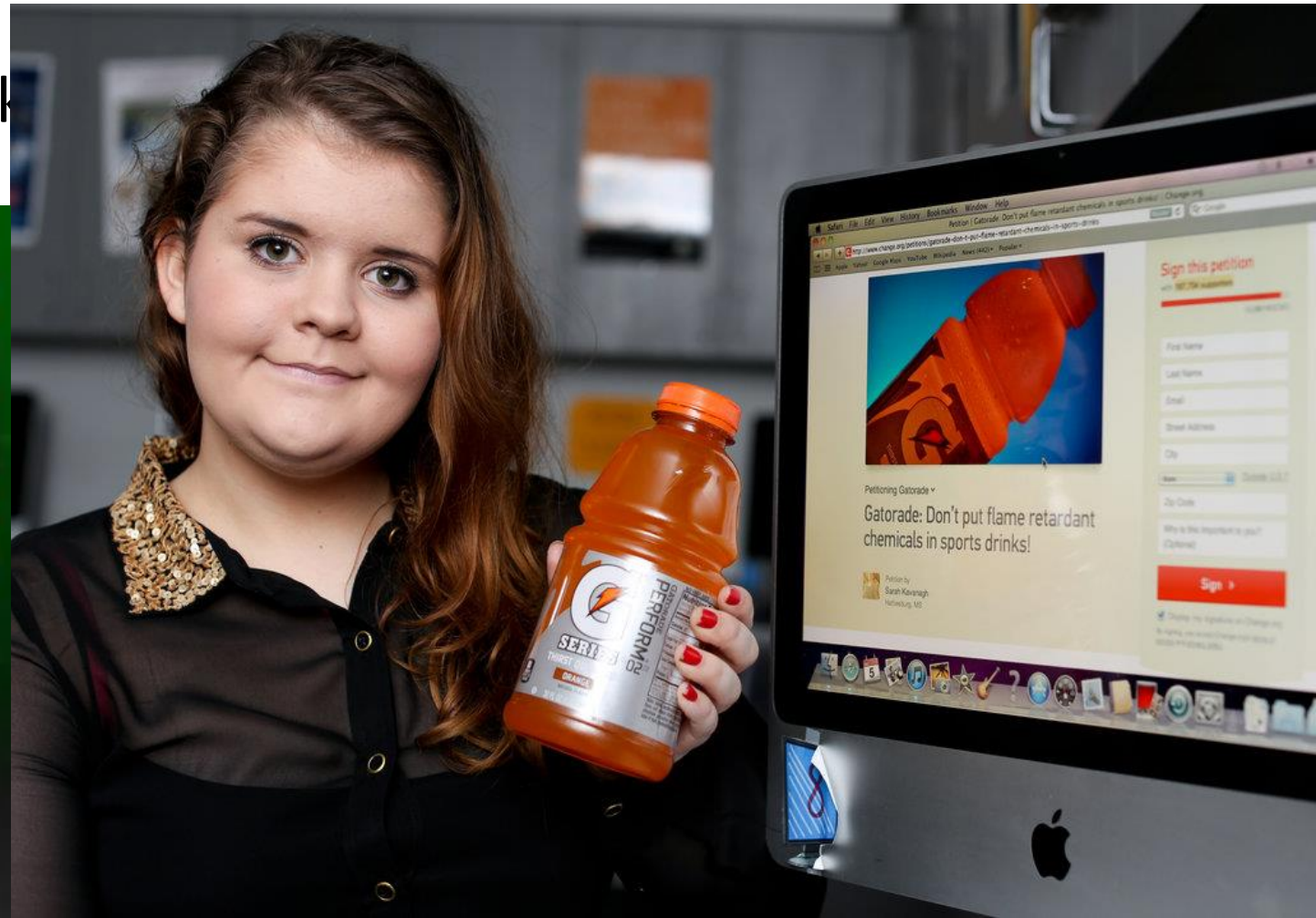
What else was going on?

- Boom of high fructose corn syrup
- Didn't consume sugary cereals
- Fruit drinks or sodas
- We did consume….

A Little “Paint Thinner” in Your Cereal?

A Little “Flame Retardant” in your sports drinks?

- BVO Common In Sports Drink



A word about those “Flame Retardants”

- Studies on the cytotoxicity of oganophosphate F
- show most severe effect on Caco-2 Colon Cance
- Relate directly to the Human Epithelial cell line
- Overproduced Reactive Oxygen species level
- Induced dna lesions & Increased ldh leakage
- Average home has more than 4 pounds
- U.S. babies have highest levels in the world
- Kids have 5x more than their parents

A Little “Cancer” in Your Daily Bread?

- Potassium Bromate Banned (and You were worried about the Gluten & Roundup)
- Class 2 B Carcinogen

A Little “Antifreeze” in Your cake?

- Salad Dressing, Iced Tea, Cake Mixes

A little GMO Fish Antifreeze Protein in your Ice Cream?

- “Anti-Freeze from Fish Blood Keeps Low-Fat Ice Cream Rich and Creamy”

A “Lot” of Emulsifiers Everywhere

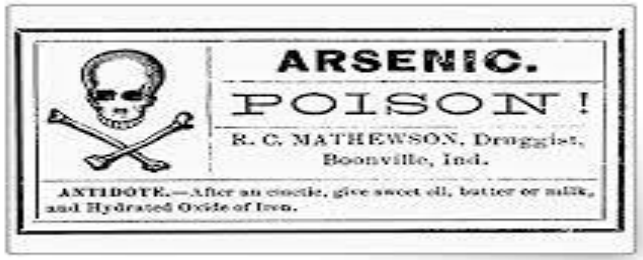
- Dietary emulsifiers directly alter human microbiota composition and gene expression *ex vivo* potentiating intestinal inflammation
- **Food additive alters gut bacteria to cause colorectal cancer**
- **Dietary emulsifier-induced low-grade inflammation promotes colon carcinogenesis**
- Common food additive promotes colon cancer in mice
- Mayonnaise, processed meats, bread, ice cream, peanut Butter, Margarine

There's Something in the Water….

- EWG Database for local Drinking water
- 18 chemicals which exceeded state or federal guidelines
- *Chloroform, hexavalent chromium, barium, Strontium, Radiological contaminants, vanadium, Haloacetic acids, Tricloroacetic acid, Dichloroacetic acid, Dibro
- Chlorate, Fluoride

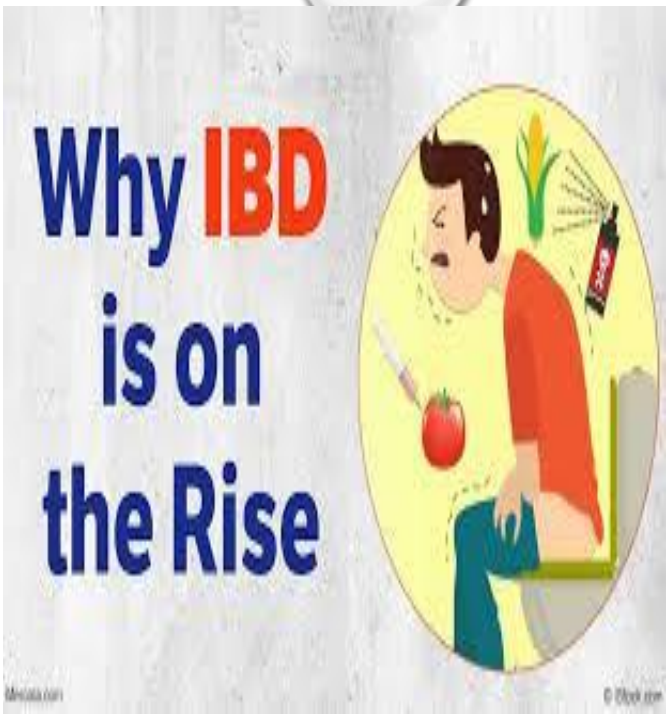
Not your Mother's Flouride

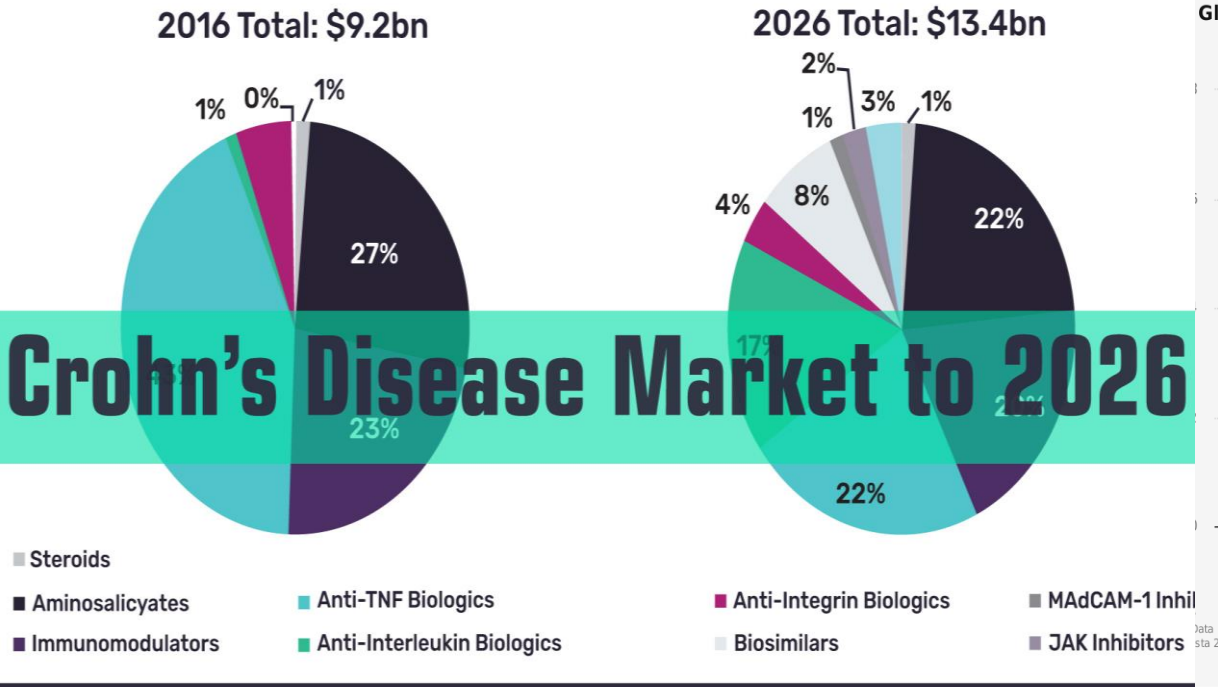
- Municipal H20 Supplies do Not use Natural "fl
- They use Combination of HFSA and SSF
- 100x more arsenic than Alternatives
- HFSA also contains lead/No Exposure Safe

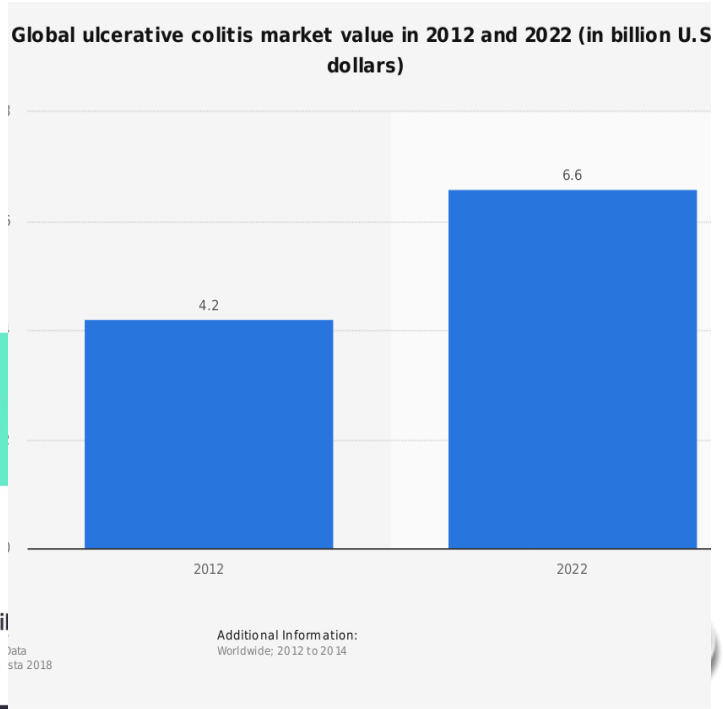


e Writing is on the Wall

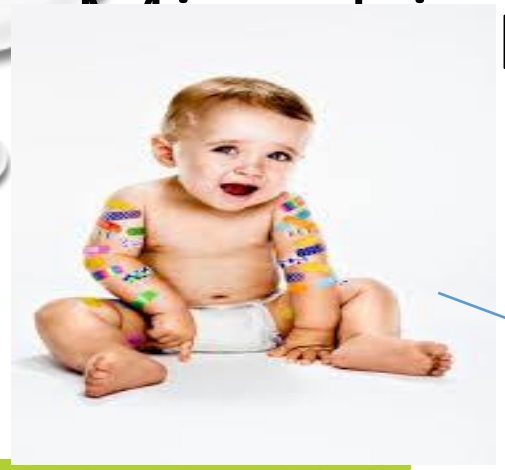
- Increases across all inflammatory bowel conditions
- Ibs, ibd, ulcerative colitis, chron's disease

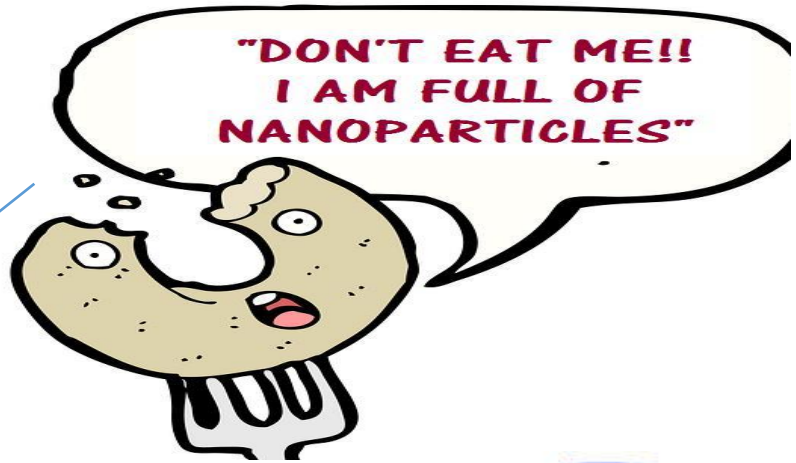


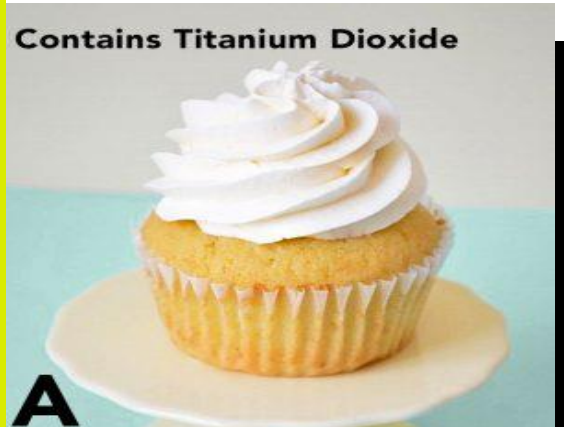


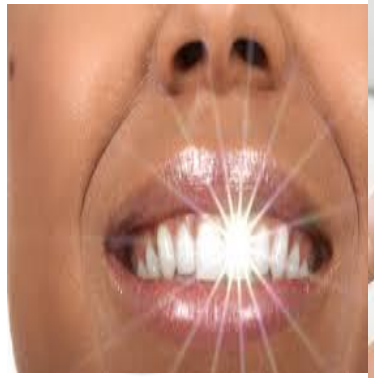


me under attack





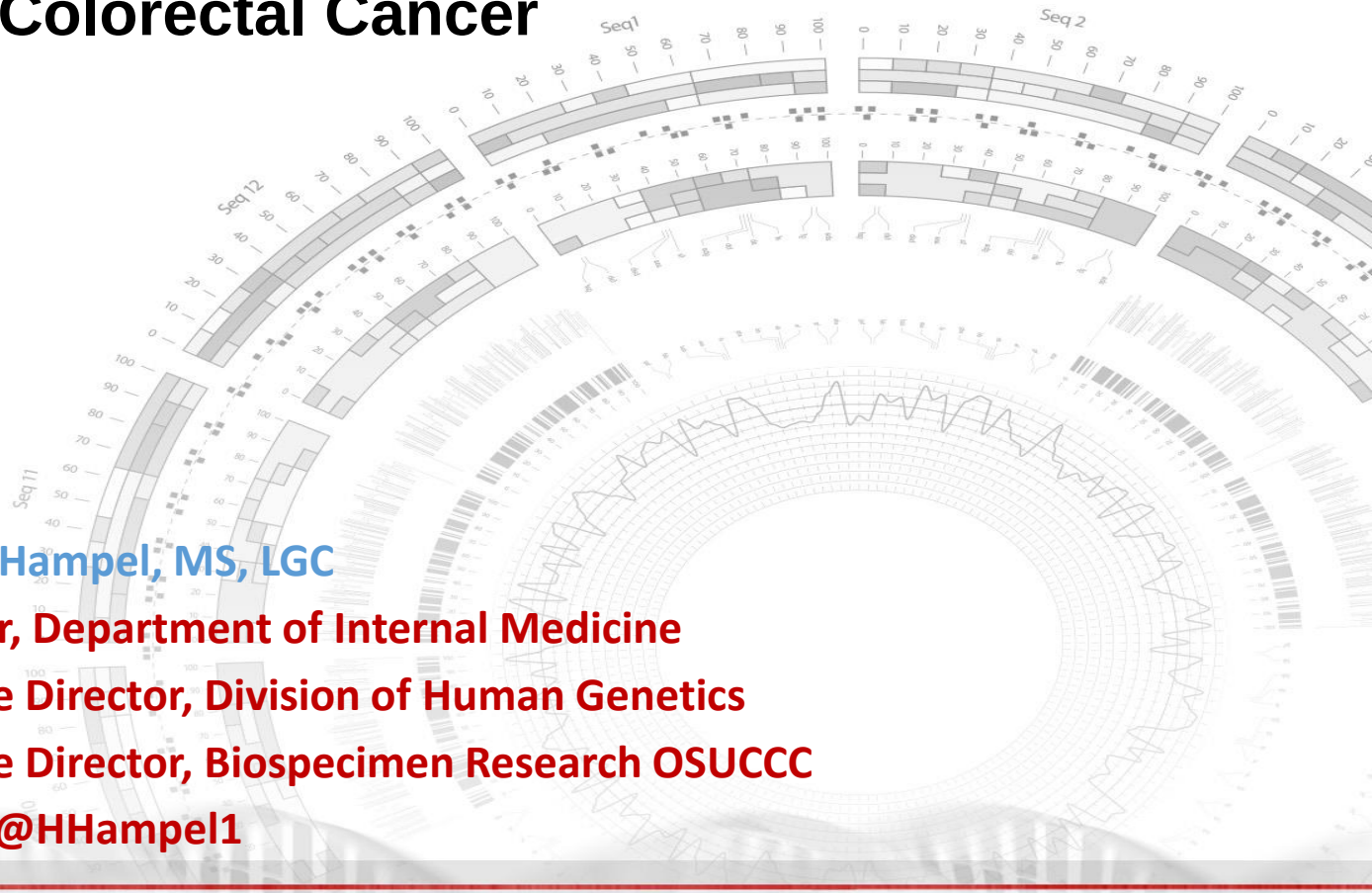




No real answer

- Food
- Air/water
- Environmental exposure
- Chemicals
- Exposure to toxins
- There’s No “good” Answer

Prevalence & Spectrum of Germline Mutations Among Patients with Early Onset Colorectal Cancer



The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

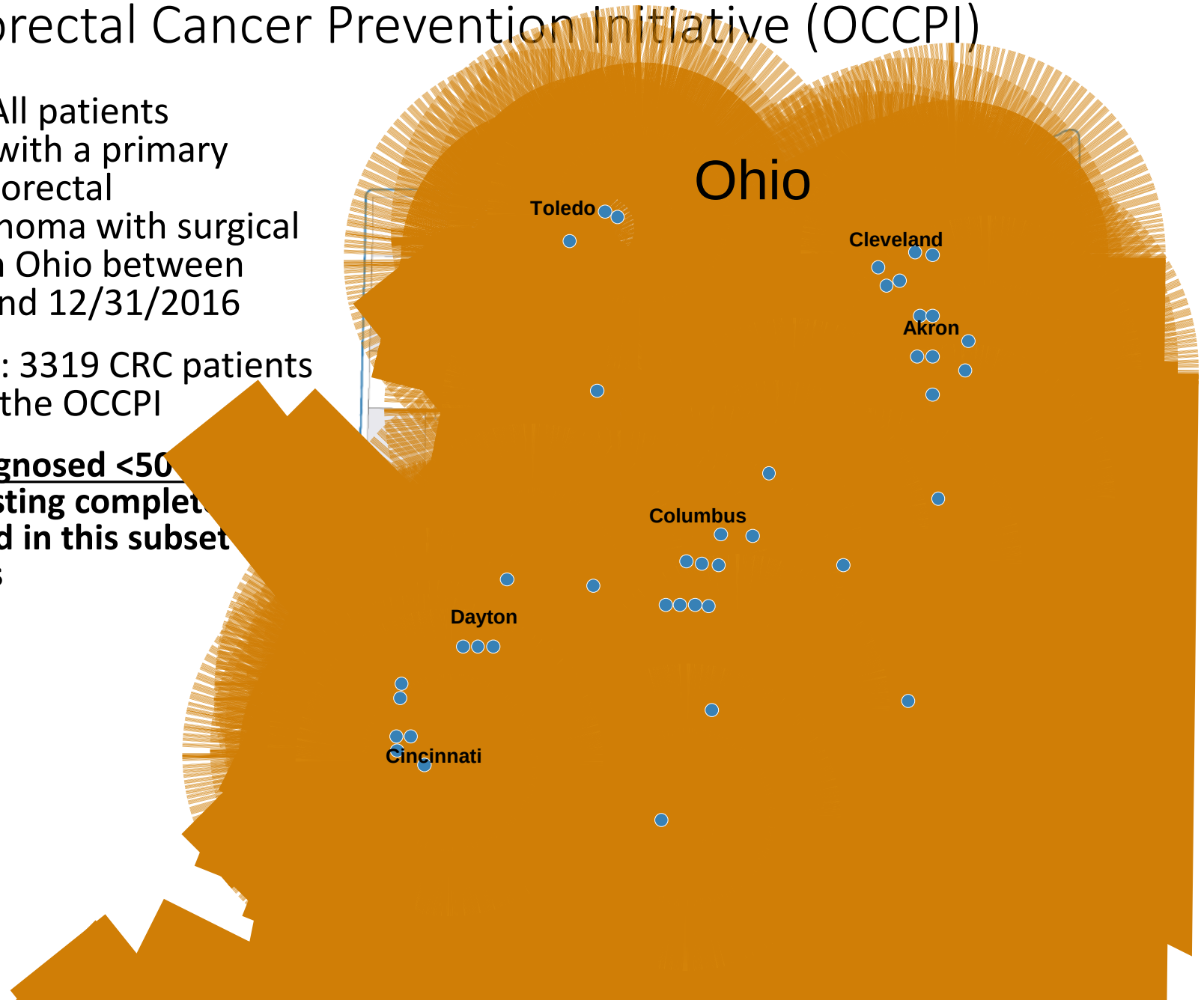
Heather Hampel, MS, LGC
Professor, Department of Internal Medicine
Associate Director, Division of Human Genetics
Associate Director, Biospecimen Research OSUCCC
Twitter: @HHampel1

Disclosures

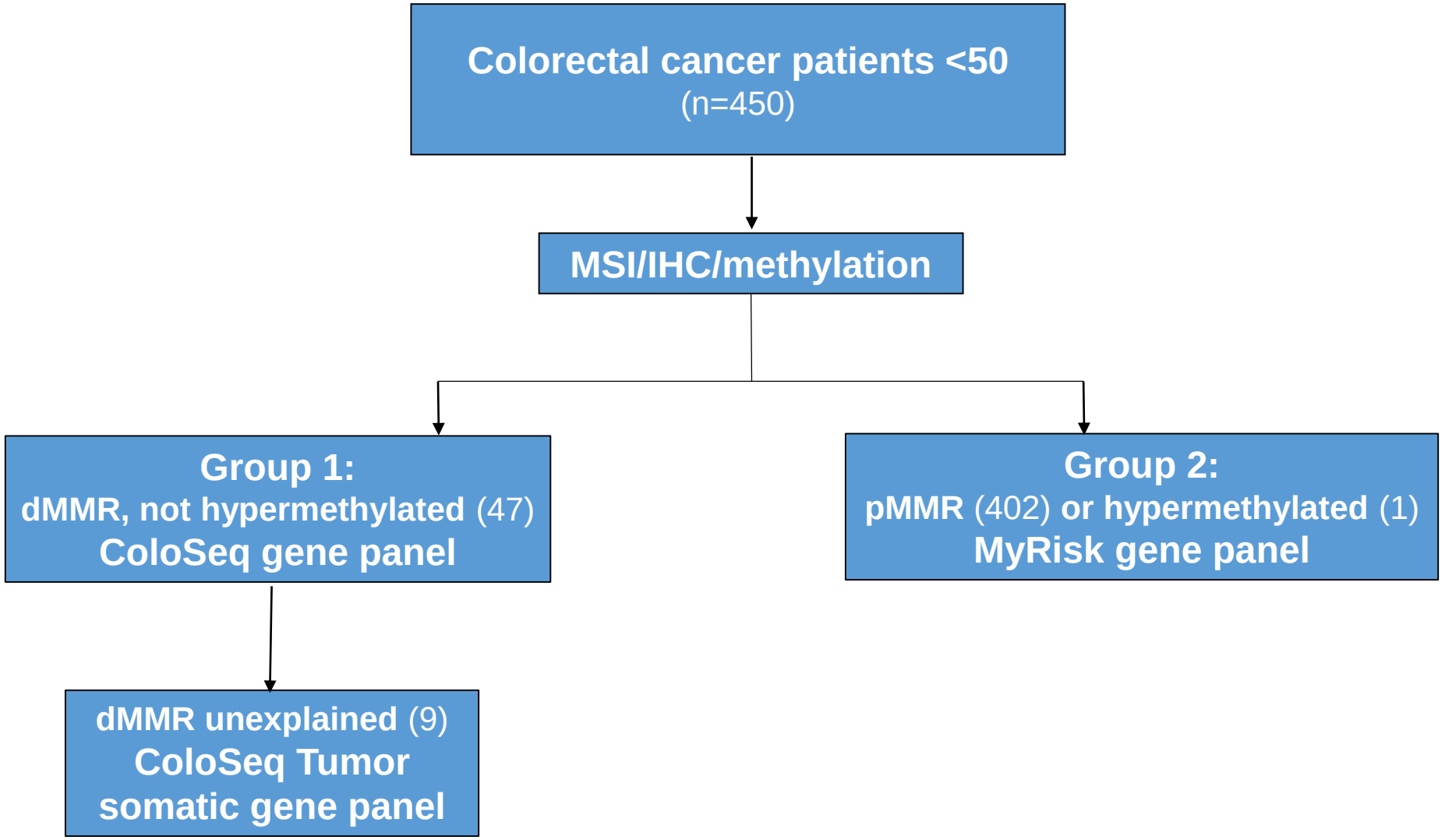
- Collaborative research:
  - Myriad Genetic laboratories
  - Invitae Genetics
  - Ambry Genetics
  - University of Washington Department of Laboratory Medicine
- Scientific advisory boards:
  - InVitae Genetics
  - Genome Medical (includes stock)
  - Promega

Ohio Colorectal Cancer Prevention Initiative (OCCPI)

- **Eligibility**: All patients diagnosed with a primary invasive colorectal adenocarcinoma with surgical resection in Ohio between 1/1/2013 and 12/31/2016
- **Enrollment**: 3319 CRC patients enrolled in the OCCPI
  - **450 diagnosed <50 with testing complet included in this subset analysis**

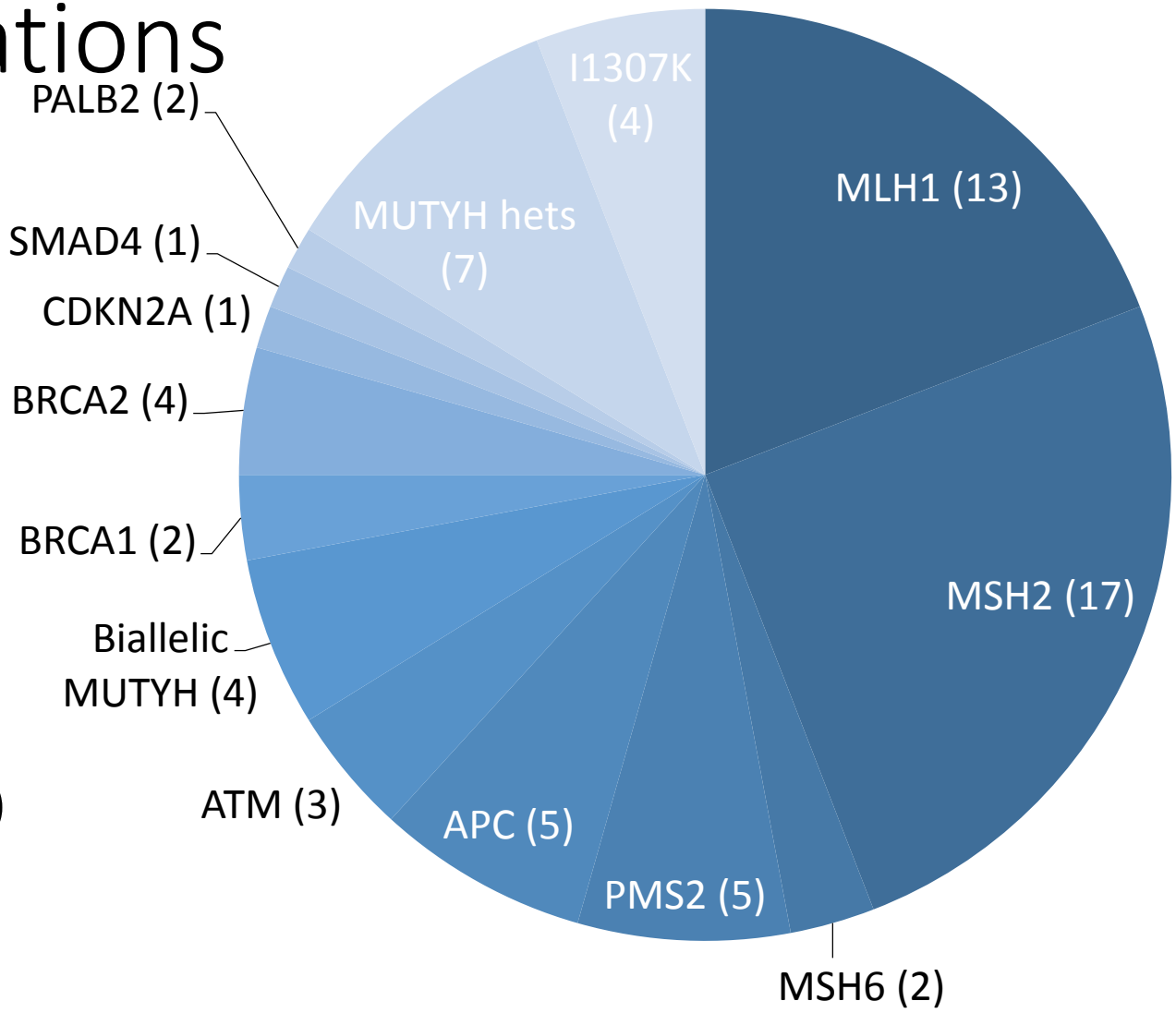


Procedures

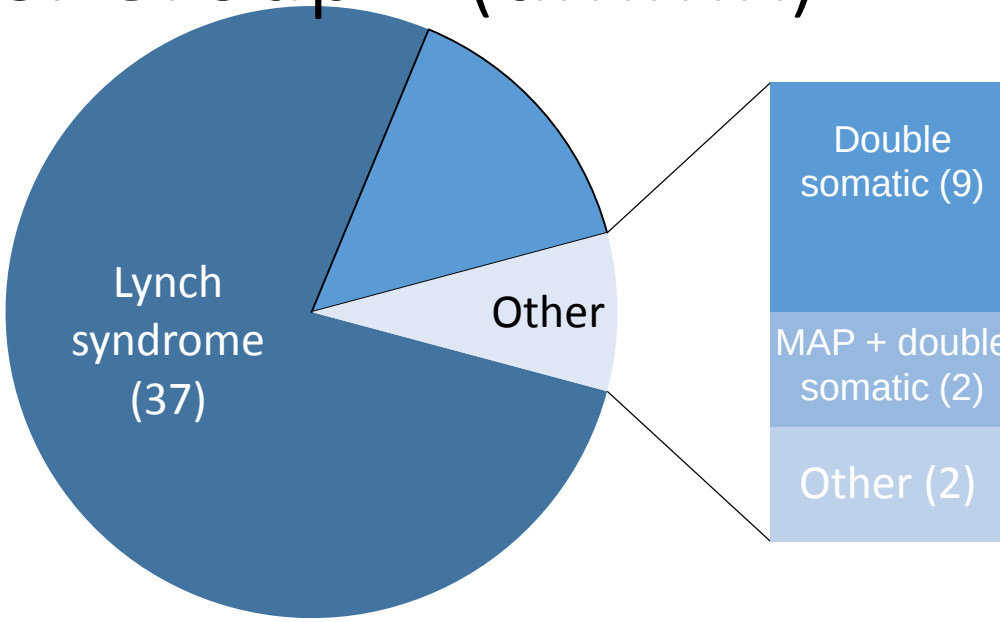

Colorectal cancer patients <50
(n=450)
MSI/IHC/methylation
Group 1:
dMMR, not hypermethylated (47)
ColoSeq gene panel
Group 2:
pMMR (402) or hypermethylated (1)
MyRisk gene panel
dMMR unexplained (9)
ColoSeq Tumor
somatic gene panel

Results: All mutations

- **1 out of 8 (16%)** have at least one hereditary cancer syndrome
- **1 out of 11 (8.4%)** have Lynch syndrome
- **1 out of 15 (7.8%)** have another hereditary cancer syndrome

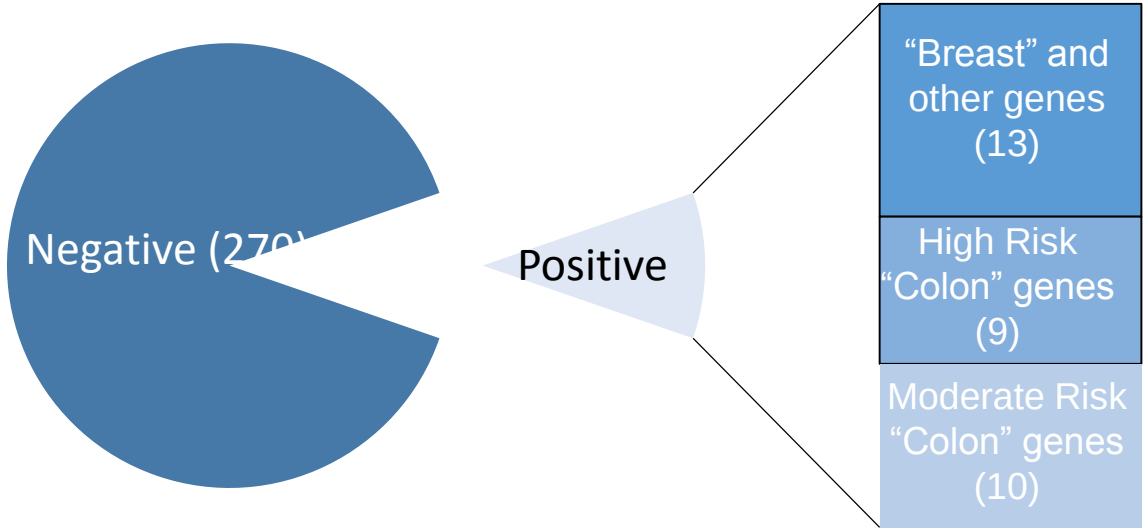


Results: Group 1 (dMMR)



- **37/48** (77%) with a dMMR tumor have LS (13 *MLH1*, 17 *MSH2*, 2 *MSH6*, 5 *PMS2*)
- **2/48** (4%) Other (1 MLH1 methylation & APC I1307K mutation & PMS2 VUS)
- **9/9** with a dMMR tumor and no MMR germline mutation have double somatic mutations
- **2/9** with a dMMR tumor and no MMR germline mutation have biallelic *MUTYH* mutations

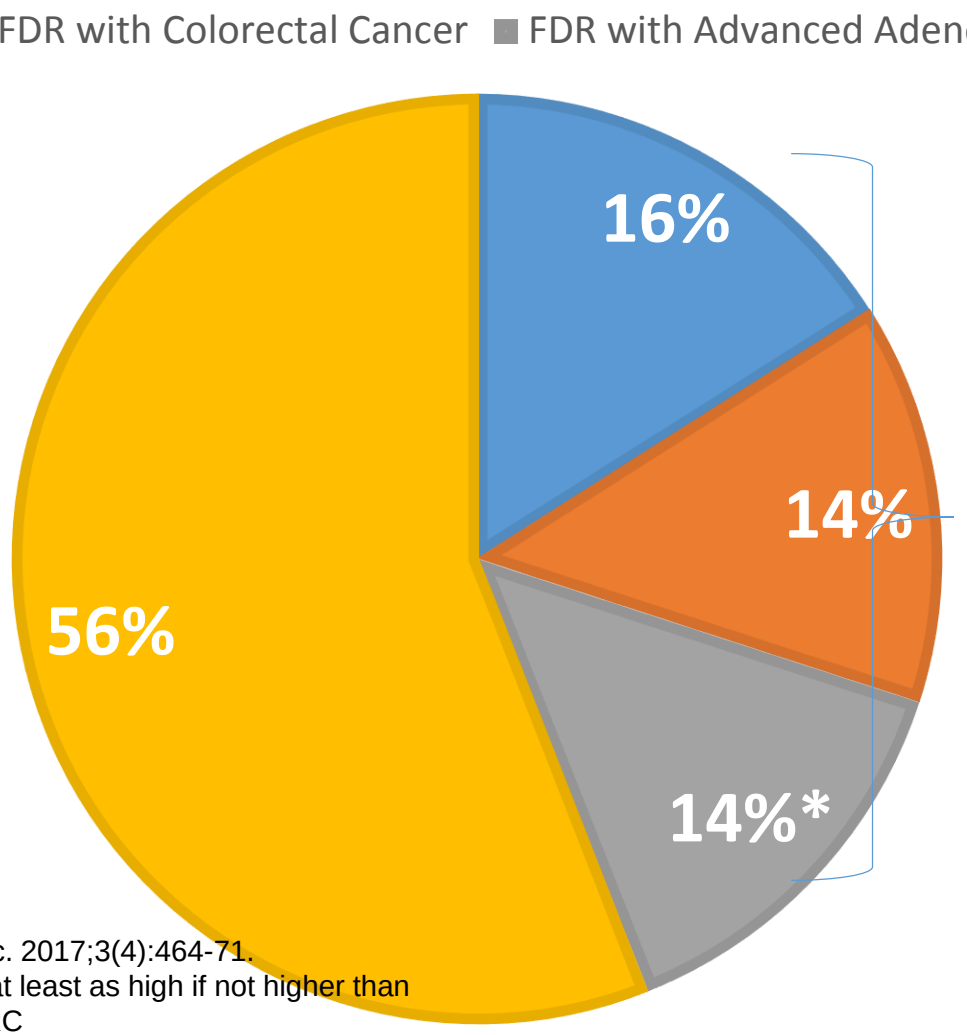
Results: Group 2 (pMMR)



*One patient has mutations in 2 different genes

- **32/402** (8%) with a pMMR tumor have a mutation*
- 9 in genes strongly associated with CRC risk (5 *APC*, 1 *APC/PMS2*, 2 MAP, 1 *SMAD4*)
- 13 in genes not traditionally associated with CRC risk (6 *BRCA1/2*, 3 *ATM*, 1 *ATM/CHEK2*, 2 *PALB2*, 1 *CDKN2A*)
- 10 in low penetrance CRC genes (3 I1307K & 7 *MUTYH* hets)

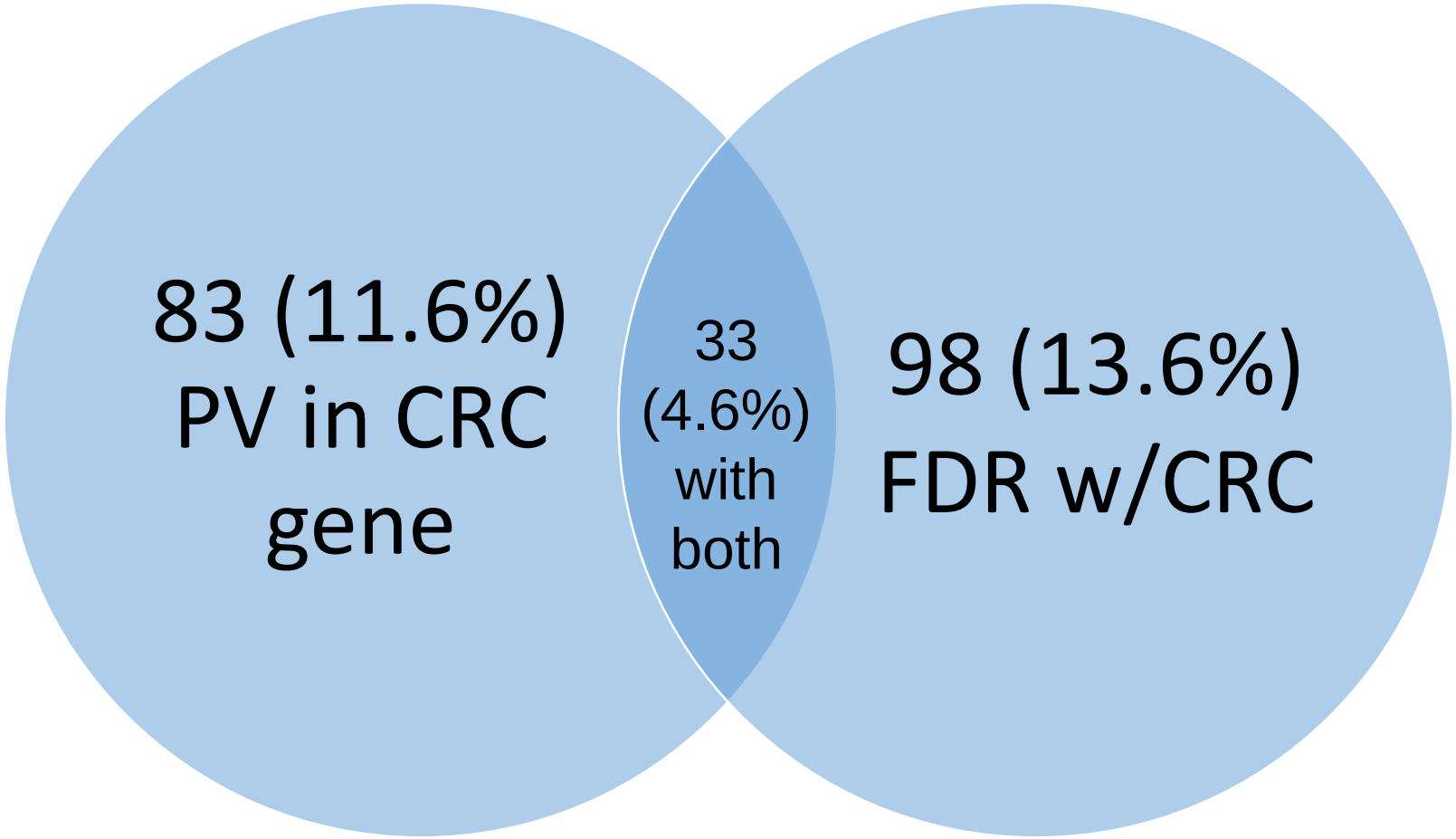
Nearly Half of Early-Onset CRC is Potentially Preventable



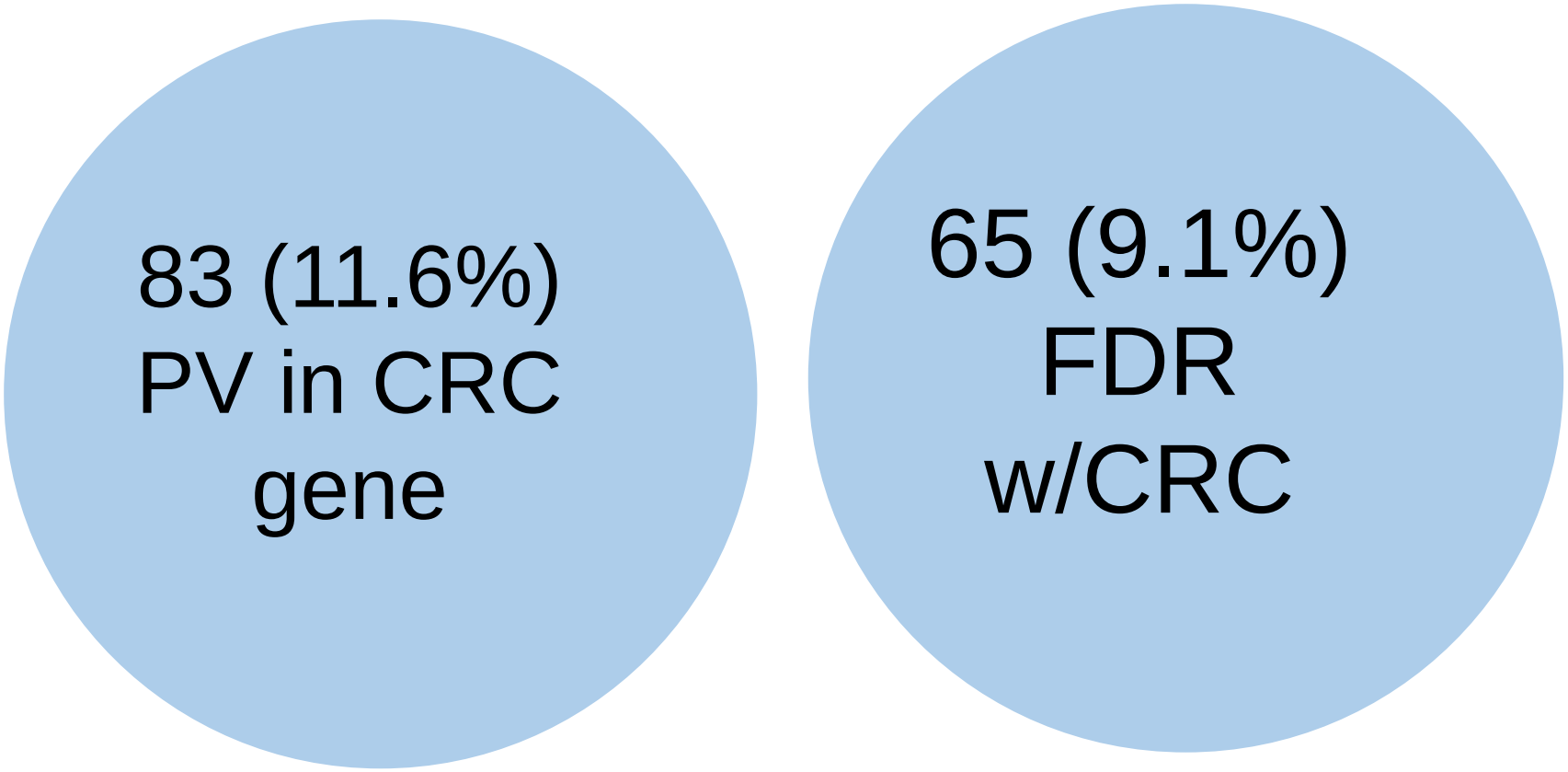
44% of Early-Onset Colorectal Cancer are Preventable by Family History taking and earlier and more frequent

Pearlman R, et al. JAMA Onc. 2017;3(4):464-71.
* Prevalence not known but at least as high if not higher than prevalence of a FDR with CRC

- **718 CRC patients dx <50 with complete testing at end of OCCPI study**
- **148 (20.6%) unique high risk individuals**



For Analysis Purposes

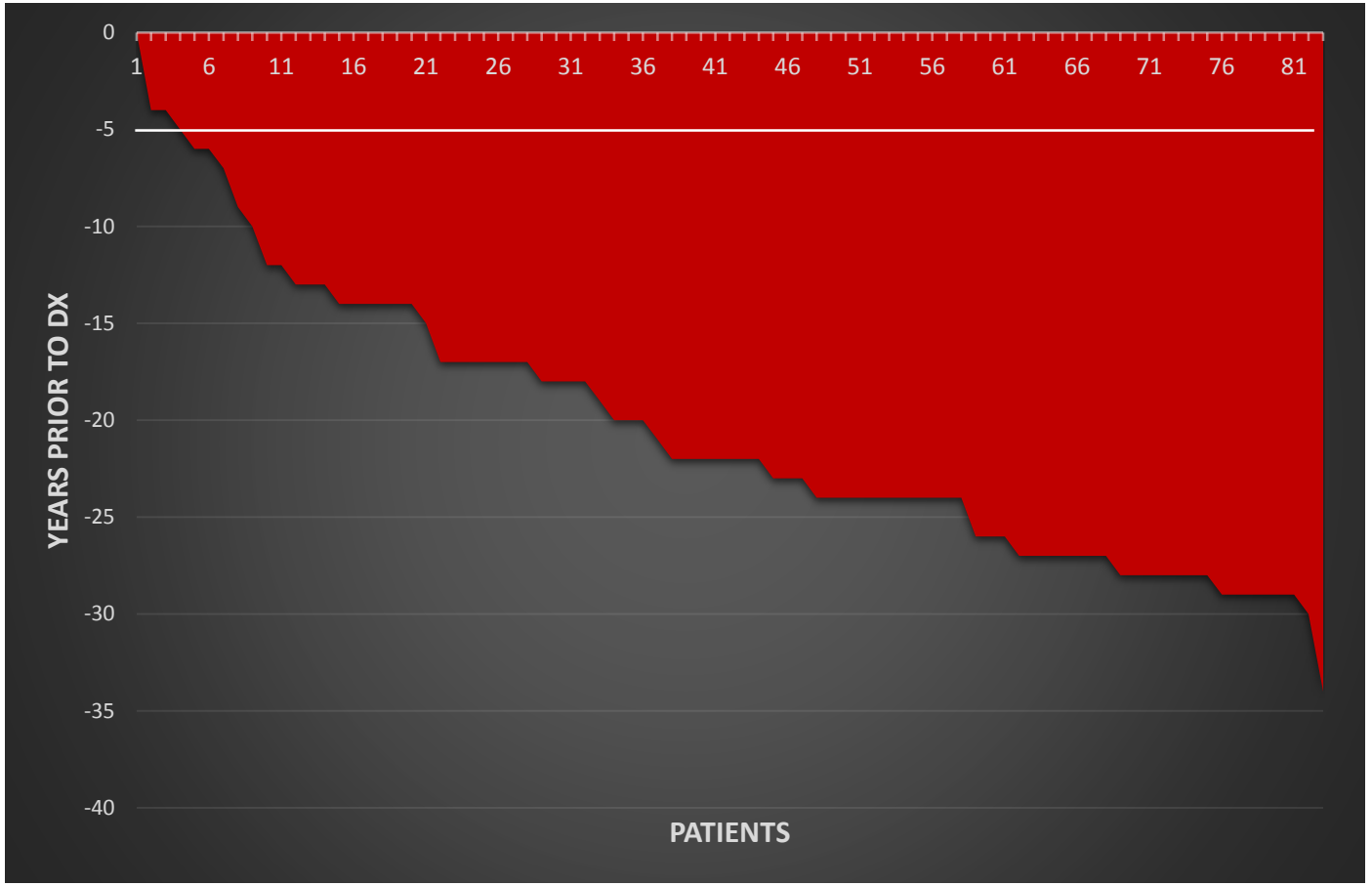


Hereditary CRC Risk Group

- 82 (98.8% of 83) would have initiated surveillance prior to diagnosis
  - 79 (95.2%) would have been potentially prevented (>5 years)
  - 3 (3.6%) would have been potentially downstaged (≤5 years)
    - 1 (1.2%) with stage I CRC (*CHEK2)*
  - 1 (1.2%) neither prevented nor downstaged
    - *MSH2 PV*

Hereditary CRC Risk Group

- Difference between age of onset and first recommended colonoscopy (pathogenic variants with colorectal cancer guidelines)

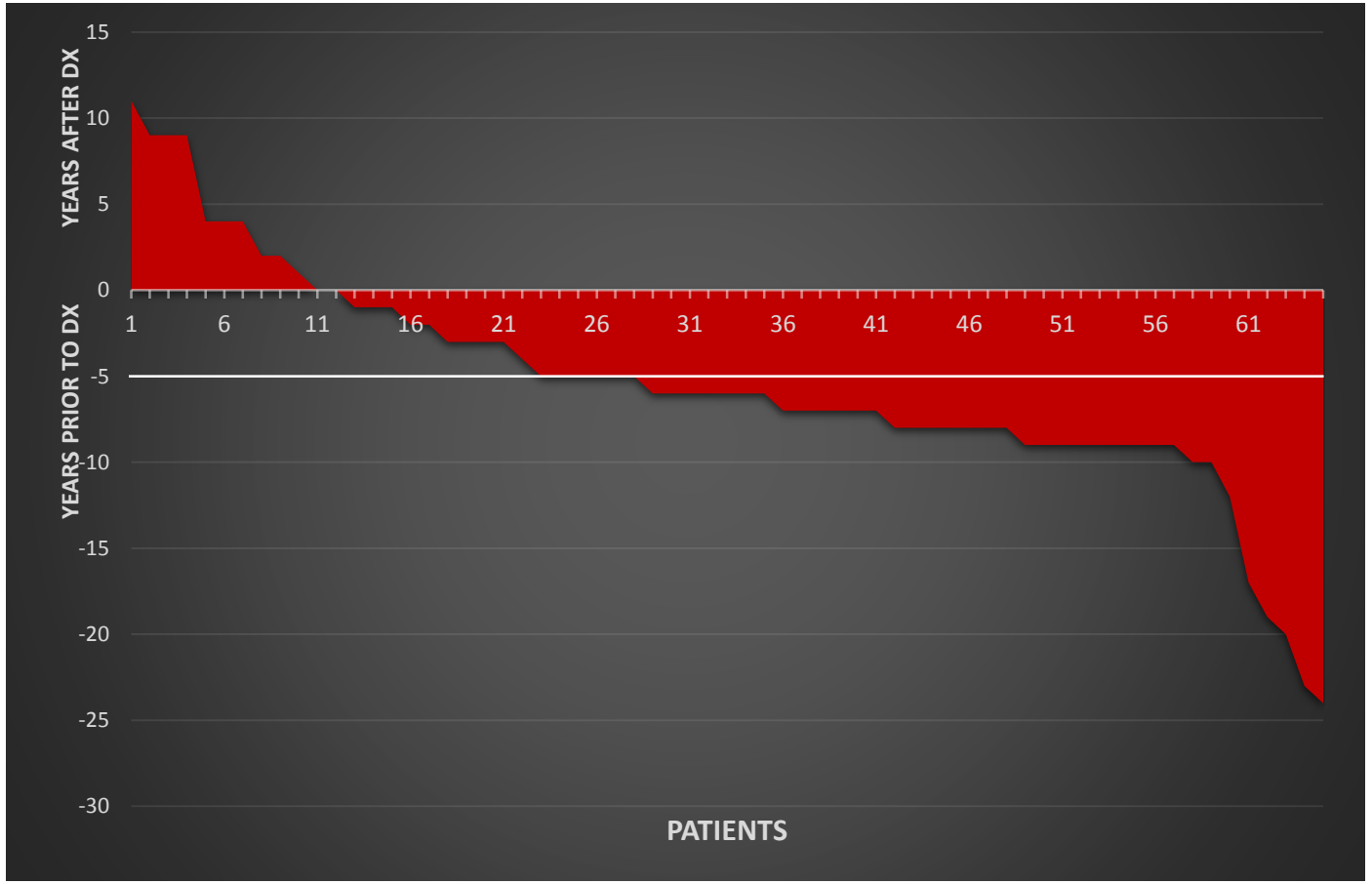


Family History Group

- 53 (81.5%) of 65 would have initiated surveillance prior to diagnosis
  - 37 (56.9%) would have been potentially prevented (>5 years)
  - 16 (24.6%) would have been potentially downstaged (≤5 years)
    - 2 (3.1%) with stage I CRC
  - 12 (18.5%) neither prevented nor downstaged

Family History Group

- Difference between age of onset and first recommended colonoscopy (family history)



Increasing the Yield of Family History

- If family history guidelines were initiated at a maximum age of 35 years compared to 40, the results change:
  - 51 of 65 (78.5%) at age 35 compared to 37 of 65 (56.9%) with current guidelines
  - Also results in 6 (9.2%) beginning surveillance within 5 years of diagnosis
    - 60 (92.3%) could have been prevented or downstaged.

Effects of Adherence to Guidelines

	Colon-oscopy Prior to Diagnosis	CRC Prevented	CRC Downstaged	CRC Not Prevented or Downstaged	Total Patients
Hereditary CRC Risk	82 (98.8%)	79 (95.2%)	3 (3.6%)	1 (1.2%)	83 (100%)
FDR with CRC only	53 (81.5%)	37 (56.9%)	16 (24.6%)	12 (18.5%)	65 (100%)
All High-Risk Patients	135 (91.2%)	116 (78.4%)	19 (12.8%)	13 (8.8%)	148 (100%)

What about the New ACS Screening Guidelines

- All 718 patients diagnosed <50
- None of the cancers would have been prevented since screening would not have started >5 years prior to dx
- 570 without FDR with CRC or PV with CRC guidelines
  - ACS recommendation of colonoscopy at 45
  - 236 (41.4%) potentially downstaged

Overall Results

- 116 of 718 (16.2%) early-onset CRC patients identified through OCCPI would have had their CRC potentially prevented based on FDR with CRC or genetics alone.
- 19 of 718 (2.6%) would have had their CRC potentially downstaged
    - 2 (0.3%) with stage I CRC

Conclusion

- 16% of early-onset CRC patients have a mutation in a cancer susceptibility gene
- 16.2% (116/718) of early-onset CRC potentially preventable.
- Surveillance guidelines for hereditary CRC more effective than those for FDR only (95.2% vs 56.9%).
  - FDR-based guidelines may benefit from adjustment (57.8% current; 80.0% 35)

Acknowledgements

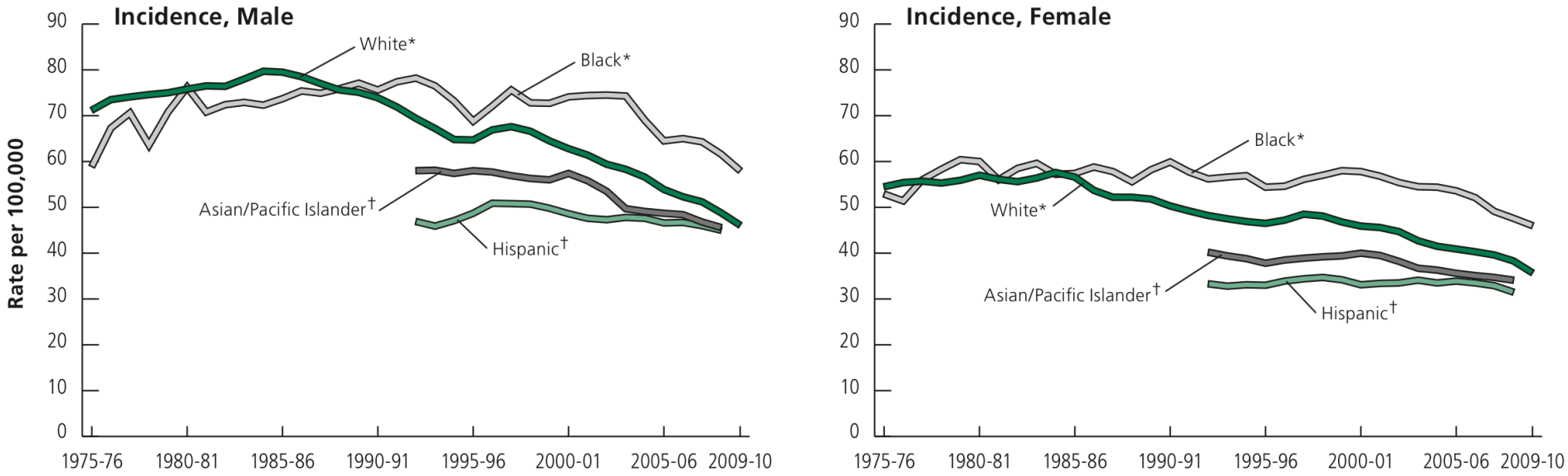
- Rachel Pearlman, MS, LGC
- Peter Stanich, MD
- Keith Pelstring, MS
- Albert de la Chapelle, MD, PhD
- Richard Goldberg, MD
- Wendy Frankel, MD
- Paul Goodfellow, MD
- Weiqiang Zhao, MD
- Ahmet Yilmaz
- Jason Bacher
- Kristin Miller
- Ilene Lattimer, RN, OCN, CCRC
- Christopher Bigley
- Lori Nelsen
- Matthew Kalady, MD
- Brandie Leach, MS, LGC

Molecular subtype of colorectal cancer associated with early age of onset

EAO-CRC fifth annual summit
New York, NY. May 2019

Xavier Llor, M.D., PhD.
Professor of Medicine
Co-Director, Cancer Genetics and Prevention Program
Director, Colorectal Cancer Prevention Program
Yale University and Smilow Cancer Center

Yale SCHOOL OF MEDICINE



Twenty percent higher incidence of CRC among African Americans

Colorectal Cancer Facts and Figures. 2014-16. American Cancer Society

Percentages age adjusted to the 2000 US standard population

	FOBT*	Endoscopy†	Either FOBT or Endoscopy‡
Gender			
Men	9.0	57.4	60.2
Women	8.6	55.6	58.3
Age (years)			
50-64	8.0	52.3	55.2
65+	9.7	61.2	63.7
Race/Ethnicity			
White (non-Hispanic)	9.2	58.5	61.5
Black (non-Hispanic)	8.4	53.0	55.5
Asian§	6.9	44.5	45.9
American Indian/ Alaskan Native¶	6.1	46.5	48.1
Hispanic/Latino	5.6	45.3	47.0

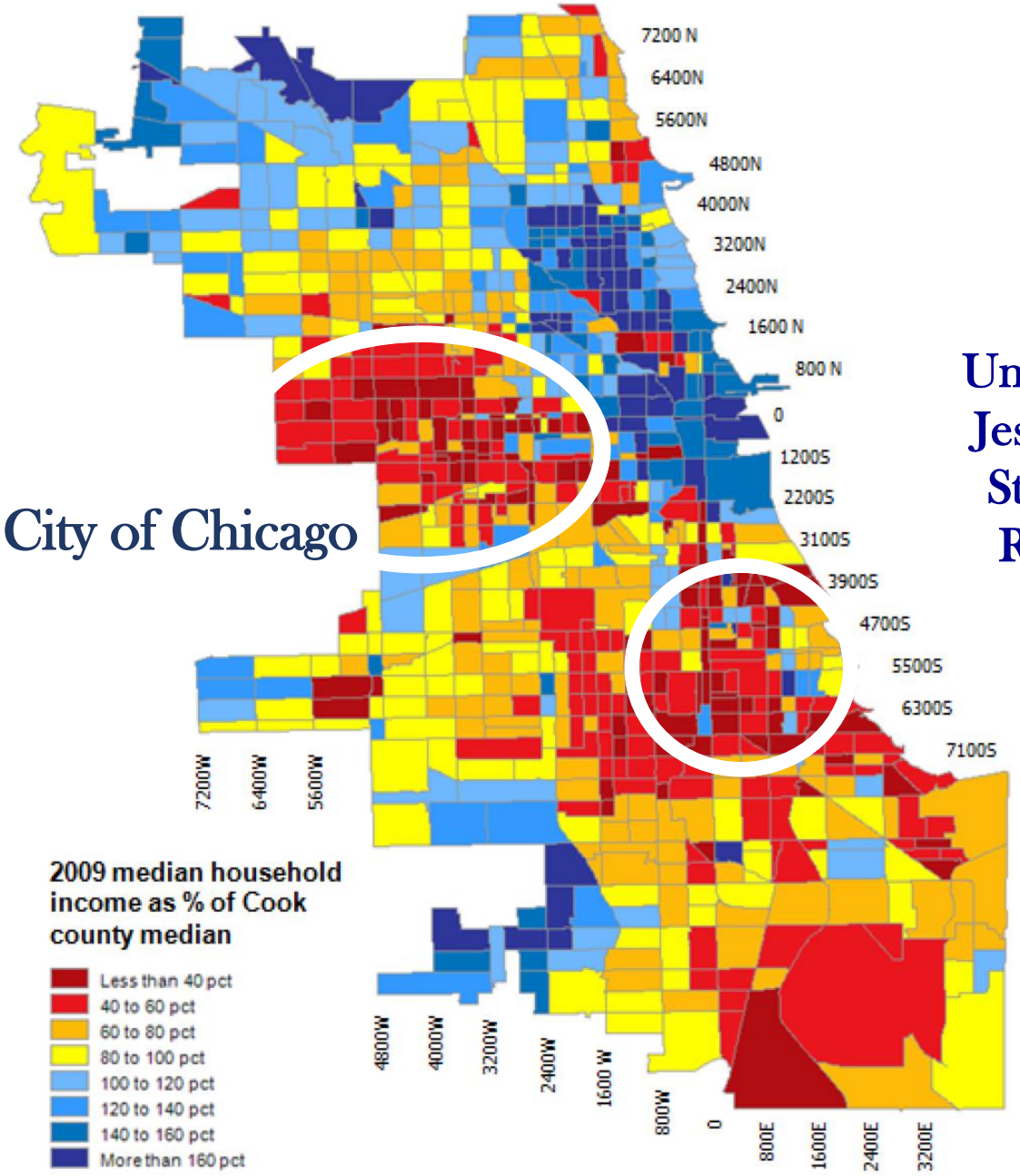
Colorectal Cancer Facts and Figures. 2014-16. ACS

Comprehensive study on colorectal cancer, particular emphasis in addressing disparities

Goals:

a. Establish a large, robust, and well characterized multiethnic database and biological repository of CRCs with a high proportion of AA patients

a. To study molecular and genetic features of CRC, and their interaction with nutritional, behavioral, and toxic exposures



Recruiting hospitals:

University of Illinois at Chicago
Jesse Brown VA
Stroger Hospital of Cook County
Rush University Medical Center

University of Chicago

A. African Americans	Years 2000-2002 %	n=157	Years 2011-2012 %	n=137	p-value
Median age at diagnosis	68		61		<0.01
Individuals diagnosed at age 50 or younger	11%	17/157	22%	30/137	0.01
Cancer stage					0.71
0,I,II	48%	64/132	51%	66/129	
III,IV	52%	68/132	49%	63/129	

B. Non-Hispanic Whites	Years 2000-2002 %	n=102	Years 2011-2012 %	n=69	p-value
Median age at diagnosis	64.5		62		0.04
Individuals diagnosed at age 50 or younger	14%	14/102	15%	10/69	1.00
Cancer stage					0.51
0,I,II	52%	45/87	57%	35/61	
III,IV	48%	42/87	43%	26/61	

SEER (2005-9)

65

70

Xicola, *et al.* Clin Cancer Res. 2014 Sep 15;20(18):4962-70

Age at diagnosis

African Americans		1996-2000		2006-2010	*P*	% Difference
<55	16.7%	594/3,553	19.9%	773/3,878	<0.001	3.2%
55-64	22.3%	791/3,553	25.4%	984/3,878		3.1%
>64	61.0%	2,168/3,553	54.7%	2,121/3,878		-6.3%
Non-Hispanic Whites						
<55	9.6%	988/10,247	13.6%	1,046/7,715	<0.001	4.0%
55-64	14.5%	1,481/10,247	17.7%	1,362/7,715		3.2%
>64	75.9%	7,778/10,247	68.8%	5,307/7,715		-7.1%

Xicola, *et al.* Clin Cancer Res. 2014 Sep 15;20(18):4962-70

Primary analysis

	Proximal location		Distal location		p-value
Median age at diagnosis	64.9		61.8		0.02
Individuals diagnosed at age 50 or younger	15%	25/165	18%	34/189	0.57
Individuals diagnosed at age 55 or younger	25%	42/165	29%	54/189	0.55
Male	60%	98/164	55%	101/185	0.39
Histologic grade					0.08
Low	28%	38/136	22%	33/151	
Moderate	59%	80/136	71%	107/151	
High	13%	18/136	7%	11/151	

Younger patients more commonly associated with distal CRC cancers

Xicola, *et al.* Clin Cancer Res. 2014 Sep 15;20(18):4962-70

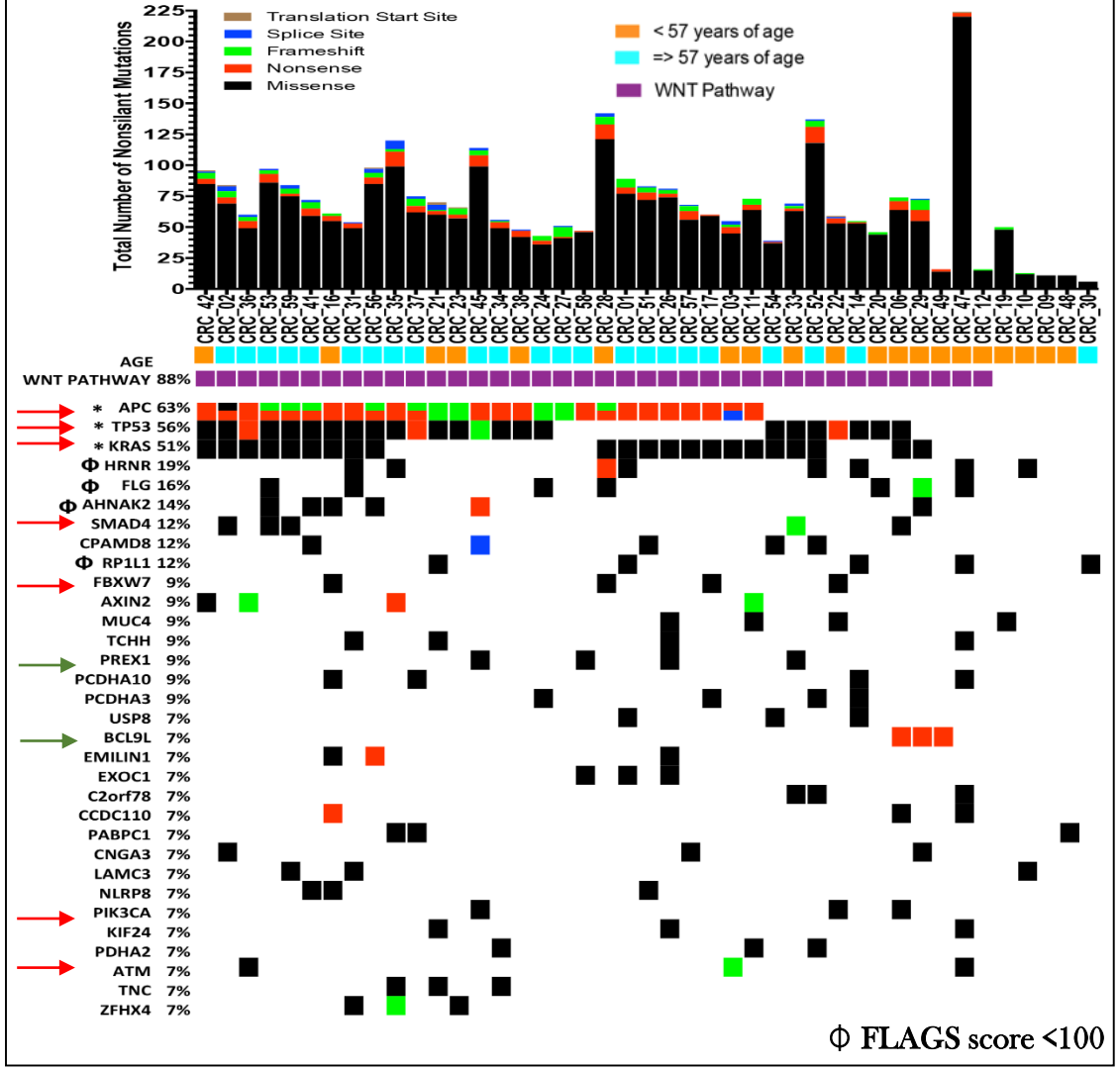
Secondary analysis

	Proximal location		Distal location		p-value
Obese (BMI>30)	21%	13/62	32%	24/74	0.18
Significant exercise	24%	14/59	31%	22/71	0.43
Packs/year >0	49%	26/53	65%	46/71	0.14
Alcohol >0 g/day	20%	11/55	27%	18/67	0.18
Previous colonoscopy	29%	17/58	14%	10/70	0.05
First degree relative with colorectal cancer	9%	5/54	16%	11/69	0.42
Aspirin/NSAIDs	71%	42/57	68%	48/71	0.71
Statins	25%	14/58	32%	23/71	0.43
Cox-2 inhibitors	7%	4/58	4%	3/71	0.70
Presence of lymphocytic infiltrate	44%	26/59	14%	9/66	<0.01
Mucinous phenotype	11%	8/74	8%	8/99	0.77
Cancer Stage					0.28
0,I,II	42%	42/99	50%	63/125	
III,IV	58%	57/99	50%	62/125	
BRAF V600E	0%	0/165	1%	2/190	0.50
KRAS (codons 12,13)	26%	20/76	19%	18/95	0.27

Xicola, *et al.* Clin Cancer Res. 2014 Sep 15;20(18):4962-70

Understand biological differences in CRC among AAs through the analysis of somatic mutational, copy number variation and methylation profiles, and compare features among younger *vs.* older individuals

Mutation analysis



- Somatic mutations generated by Strelka
- Mutation analysis using MutSig (ranked potential driver genes based on q value <0.1)

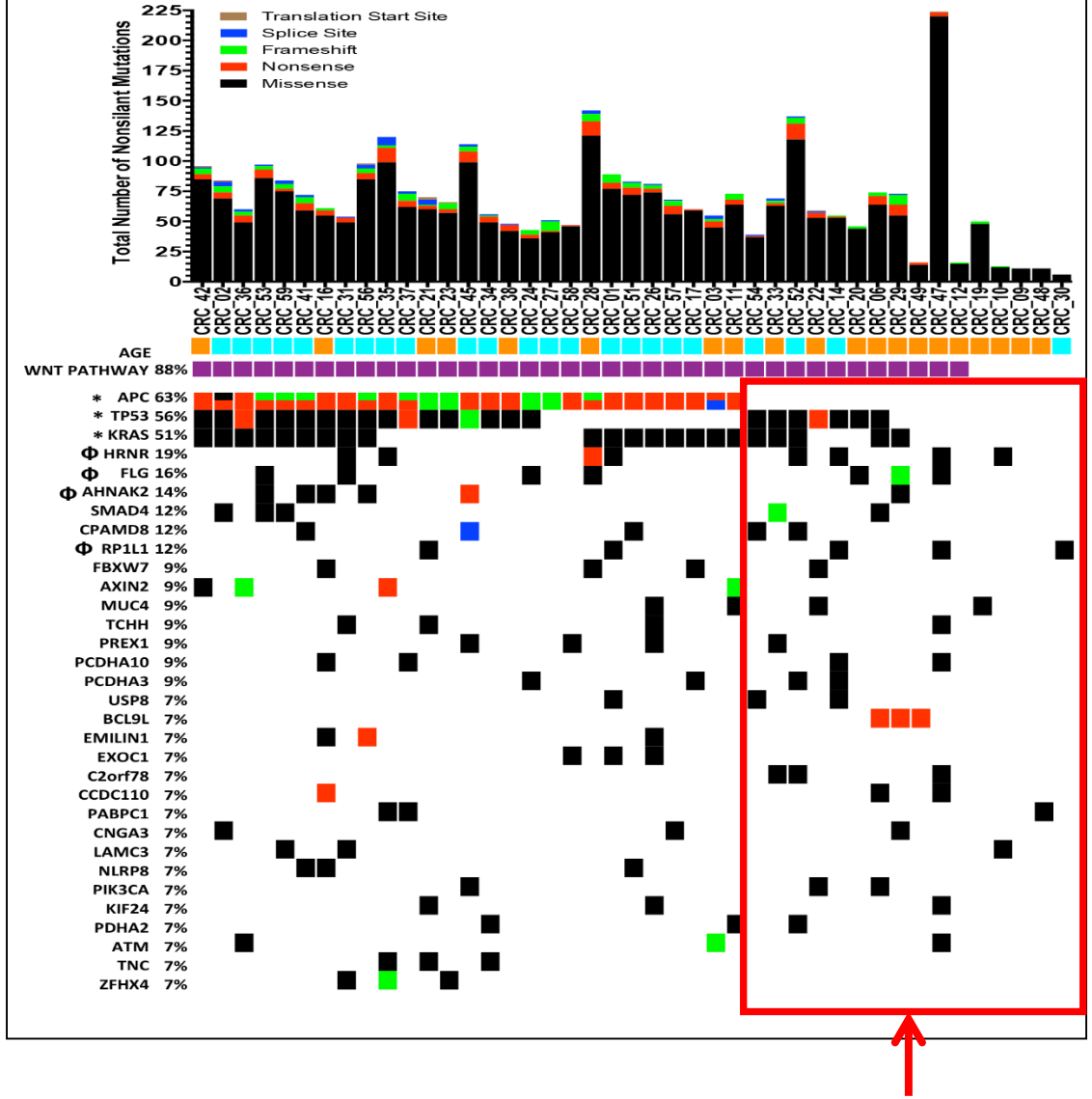
❖ 43 microsatellite stable tumors included
(2 POLE hypermutated excluded)

❖ 32 recurrent mutated genes identified, each of them had at least three non-silent mutations

32 genes: APC, TP53, KRAS, SMAD4, FBXW7, PIK3CA, ATM, well-established CRC driver genes

❖ 2 Novel genes are reasonable drivers: *PREX1* (guanine nucleotide exchange factor for RAC) and *BCL9L* (Wnt signaling)

Xicola, *et al.* Carcinogenesis. 2018, Vol. 39, No. 11: 1331–1341



Lower frequency of *APC* mutations in AA CRCs

- Frequencies of *TP53* and *KRAS* mutations in AA CRCs were not significantly different from those in NHW* CRC
- Frequency of *APC* mutations in AA CRCs (63%) was significantly lower than in NHW* (80%) p=0.03

***APC* mutation-negative CRCs**

*186 non-hypermutated CRCs in NHW from TCGA

Xicola, *et al.* Carcinogenesis. 2018, Vol. 39, No. 11: 1331–1341

APC mutation negative associated with younger age of onset CRC

Feature	APC mutation positive (n=27)	APC mutation negative (n=16)	P value[1]
Clinical-pathological			
Gender, males/females	19/8	7/9	0.11
Age at diagnosis, mean (SD)	62 (12)	51 (11)	0.01
Percent WAA, mean (SD)	80 (20)	73 (13)	0.19
FDR with cancer <60 yo (%)	10 (37)	6 (38)	1
Cases with previous cancer(%)	1 (4)	4 (25)	0.06
Tumor location (R/L)	9/18	6/10	1
TNM stage, 0-II vs III-IV	11/15	9/7	0.52
Grade, Low+Moderate/High	13/10	13/2	0.08

TCGA:

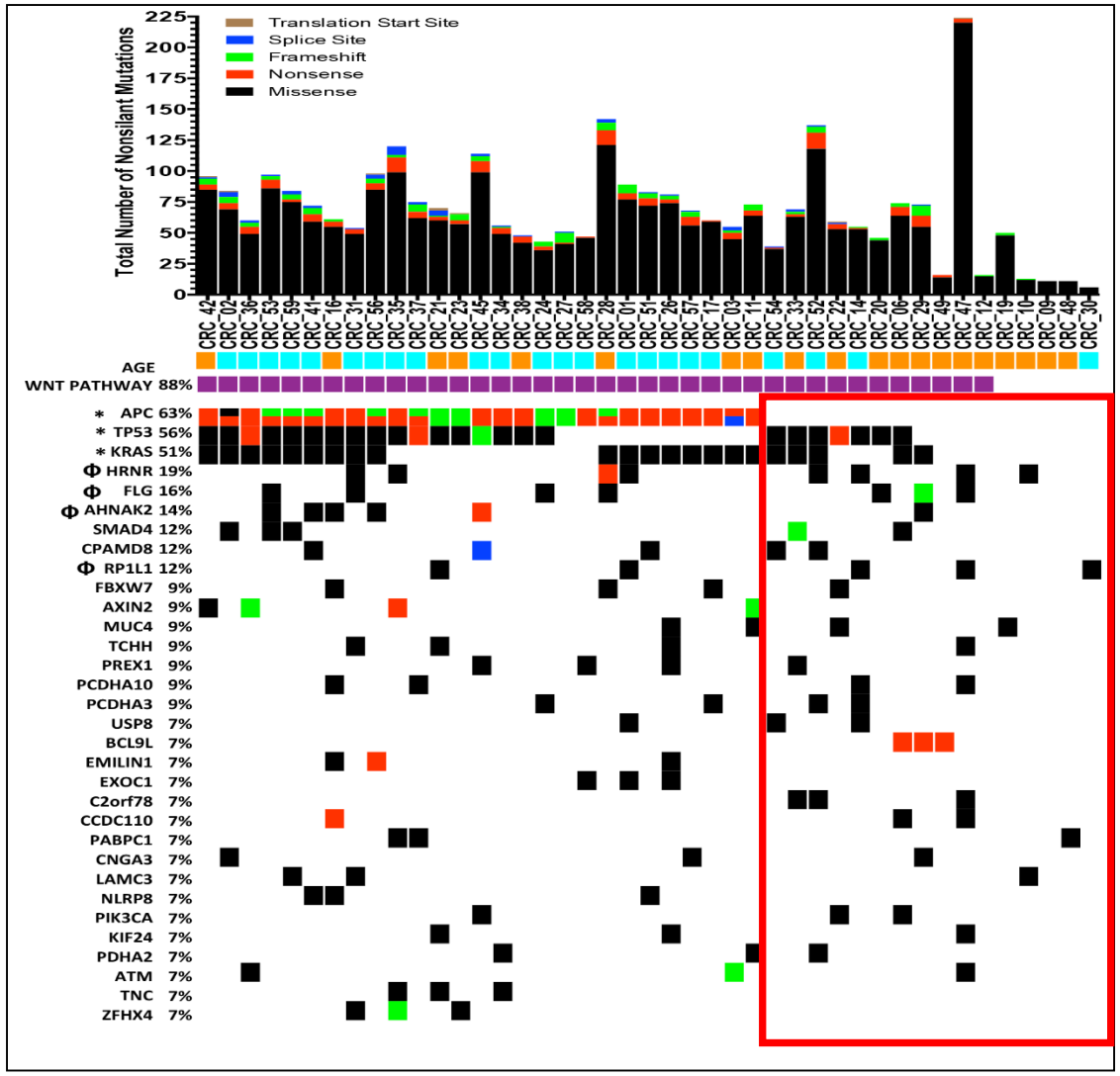
219 NHW non-hypermutated CRC:181 APC mutation +/ 38 APC mutation -

Median age:
APC + : 68.0
APC - : 54.5

Association APC - tumors and early-onset CRC significant ($P < 10^{-5}$)

Xicola, *et al.* Carcinogenesis. 2018, Vol. 39, No. 11: 1331–1341

APC mutation negative have less mutations



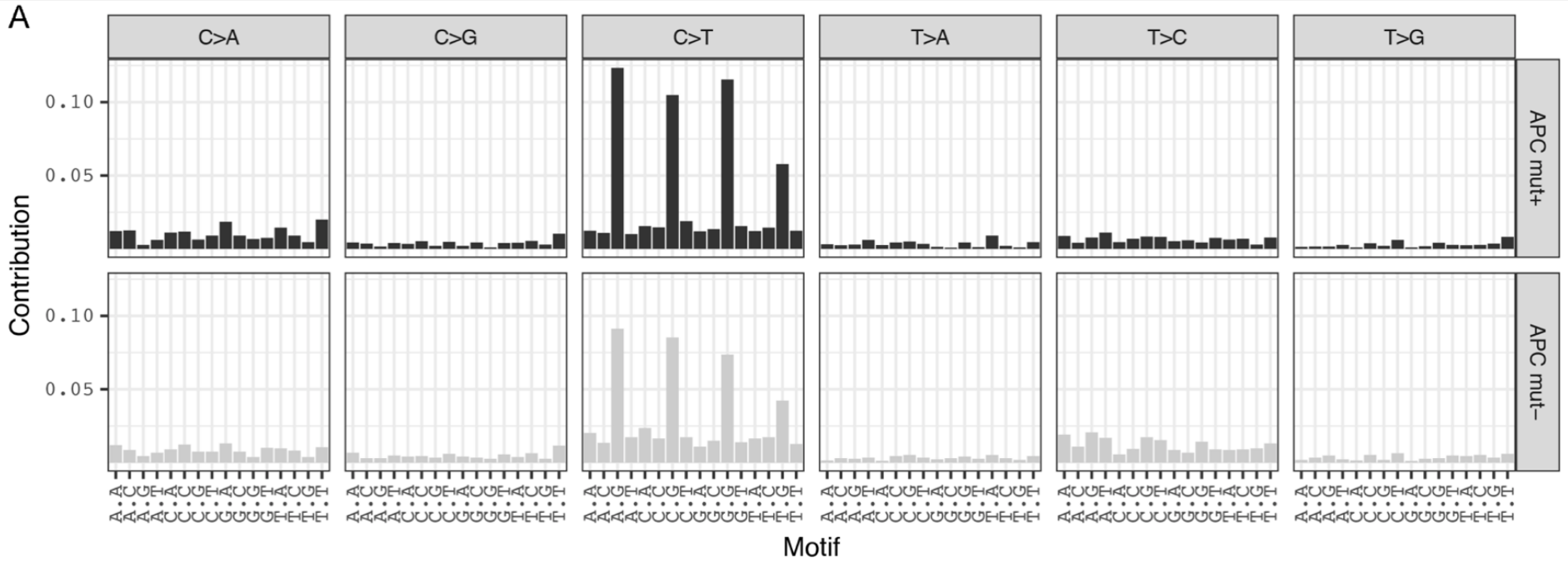
Median mutation frequencies:

- *APC* + : 170
- *APC* - : 107 (P = 0.006, Mann–Whitney test)

***APC* mutation-negative CRCs**

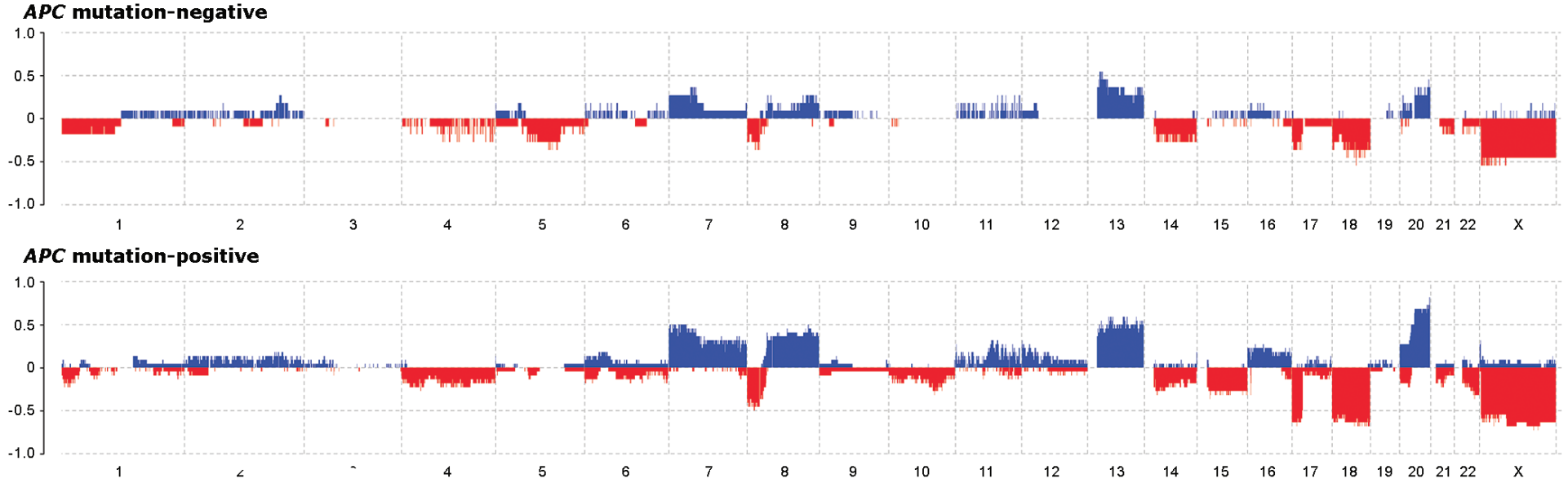
Xicola, *et al.* Carcinogenesis. 2018, Vol. 39, No. 11: 1331–1341

Mutagenesis patterns: equal mutational signatures *APC*+ and *APC*-



- Frequencies of mutant triplets in exome sequencing data
- Predominance of C to T mutations in the CpG dinucleotide (as expected for MSS CRC): reflecting a mutational process dominated by deamination of methylated cytosines
- Equal frequencies of triplets in *APC*+ and *APC*- CRCs

Greater chromosome stability among *APC* mutation negative CRC

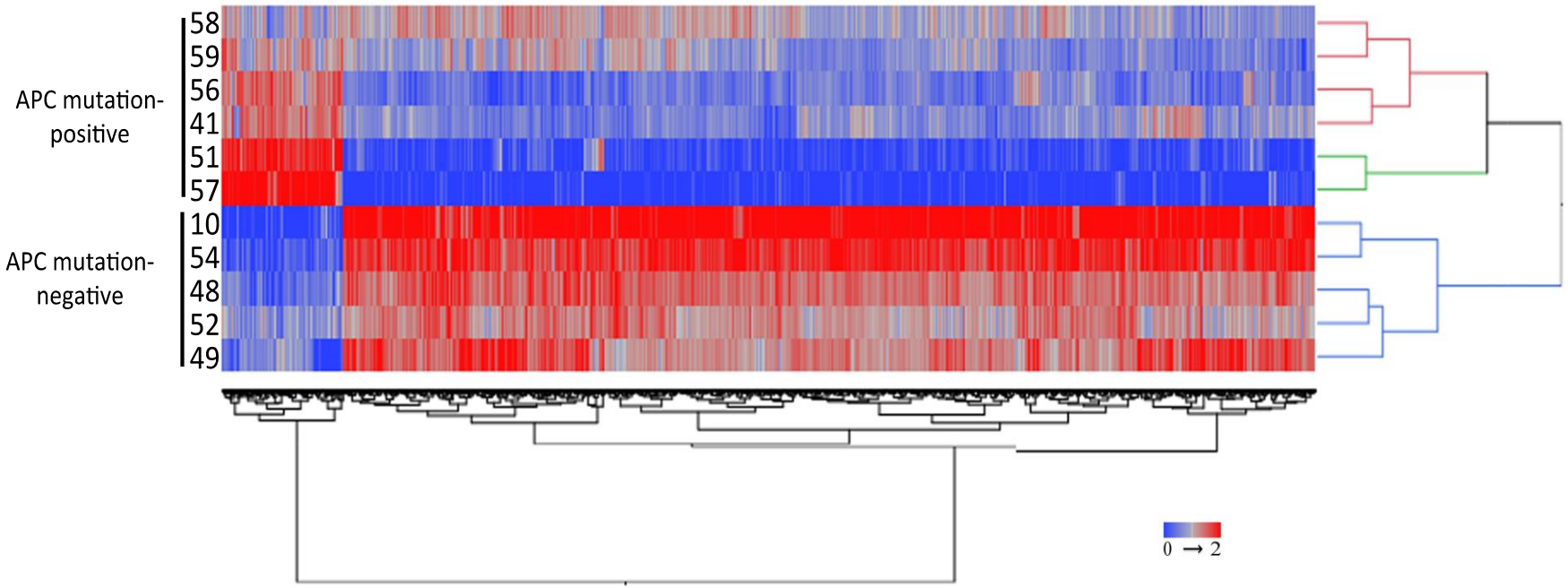


Chromosome-arm gains and losses: substantially lower levels in the *APC*- tumors compared with the *APC*+ tumors (P<0.03; R package Rawcopy)

Xicola, *et al.* Carcinogenesis. 2018, Vol. 39, No. 11: 1331–1341

APC - : genome-wide hypermethylation with focal hypomethylation
APC + : genome-wide hypomethylation with focal hypermethylation

CRC methylation clusters by *APC* mutation status

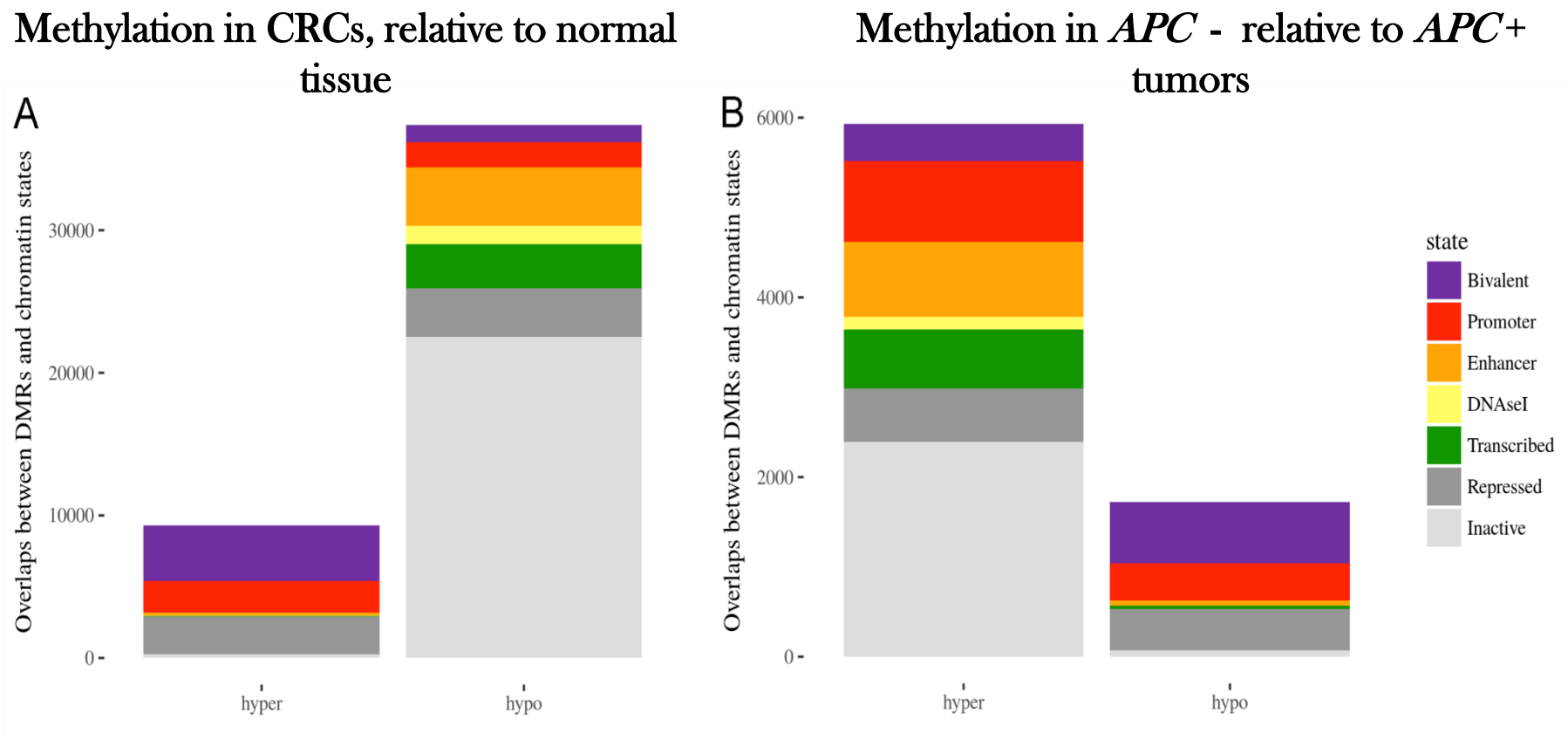


5923 differentially methylated regions (DMR)

Cluster analysis of the 200 most variable DMRs in the TCGA yielded similar results

Xicola, *et al.* Carcinogenesis. 2018, Vol. 39, No. 11: 1331–1341

APC mutation-negative CRCs have hypermethylated regulatory regions



Reference Epigenome Mapping Consortium's chromatin state map for normal colonic mucosa based on ChIP-seq data to annotate differentially methylated regions

Xicola, *et al.* Carcinogenesis. 2018, Vol. 39, No. 11: 1331–1341

APC - specific differentially methylated genes

- Three TCGA-identified cancer driver genes: *SOX9*, *GPC6*, and *KIAA1804*, were hypermethylated in *APC*- tumors whereas the same sites were hypomethylated in *APC*+ tumors.

- Promoter hypermethylation in *APC*- was also observed in key WNT signaling pathway genes including *GATA6*, *TET1*, *FAT1*, and *GLIS1*

Summary

- Younger age of onset CRC associated with *APC* – tumors
- These tumors show fewer somatic mutations and copy number alterations with an increased level of overall hypermethylation than *APC*+ tumors
- *APC*- CRCs are associated with a novel DNA methylation signature: characterized by hypermethylation of select regulatory regions, affecting in particular genes in the WNT signaling pathway
- Methylation of genes in the WNT signaling pathway may allow by-pass of somatic mutation in *APC*

Llor lab
Rosa M Xicola
Julia Clark
Maggie Moran
Tim Carroll
Amy Disharoon
Katie Morrissey
Brian Doyle
Molly Gagnon
Priti Marwaha
Ashley Janoski
Jamie Rawson
Lidiane Gabeira

Ellis lab
Nathan Ellis
Maureen Regan
Archna Krishna
Fabio Pibiri
Mary Yagel

University of Chicago
Sonia Kupfer
Katy Ceryes

Rush University
Josh Melson
Rawan Abassi

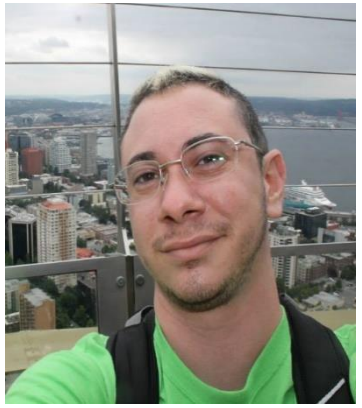
University of Illinois at Chicago
Carol Braunschweig
Cenk Pusatcioglu
Raj Emmadi

Stroger Hospital of Cook County
Vivek Chaudrhy
Victoria Angelova

American Cancer Society®

NATIONAL® CANCER INSTITUTE

Rosa Xicola



Gaius Augustus

Nathan Ellis

Tim Triche Jr

Zarko Manojlovic

John Carpten

Bodour Salhia

American Cancer Society®

NATIONAL CANCER INSTITUTE®

Germline Genetic Variants Associated with Young-Onset Colorectal Cancer: The MSKCC Experience

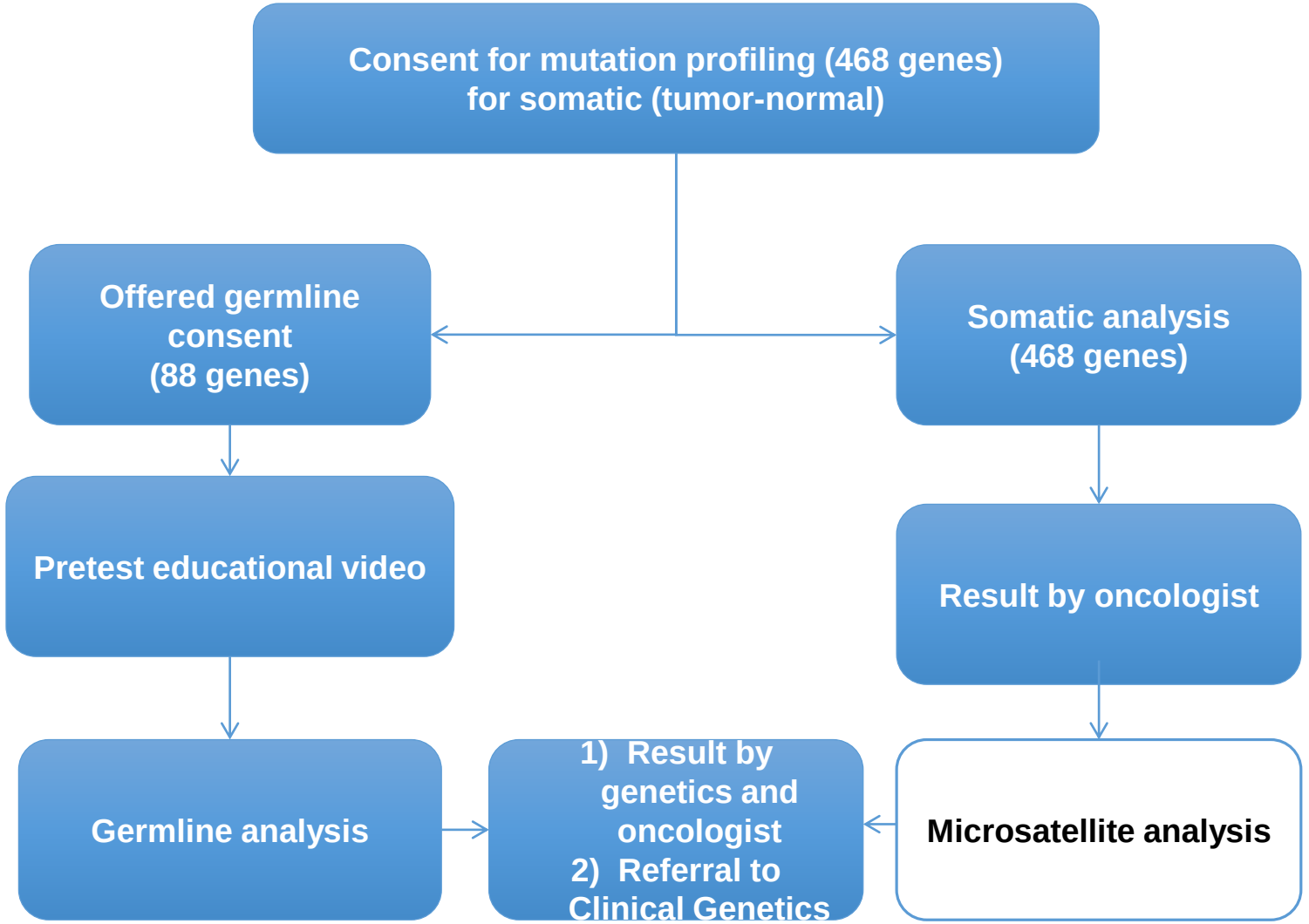
Zsofia K. Stadler, MD
Associate Attending Physician
Clinic Director, Clinical Genetics Service
Lead, Inherited Gastrointestinal Cancer Genetics Program
GI Medical Oncology
Memorial Sloan Kettering Cancer Center

May 2, 2019

Disclosures

- Immediate Family Member, Ophthalmology
  - Consulting/Advisory Role
    - Allergan, Adverum Biotechnologies, Alimera Sciences, Biomarin, Fortress Biotech, Genentech, Novartis, Optos, Regeneron, Regenxbio, Spark Therapeutics

MSK-IMPACT Protocol: Germline Analysis

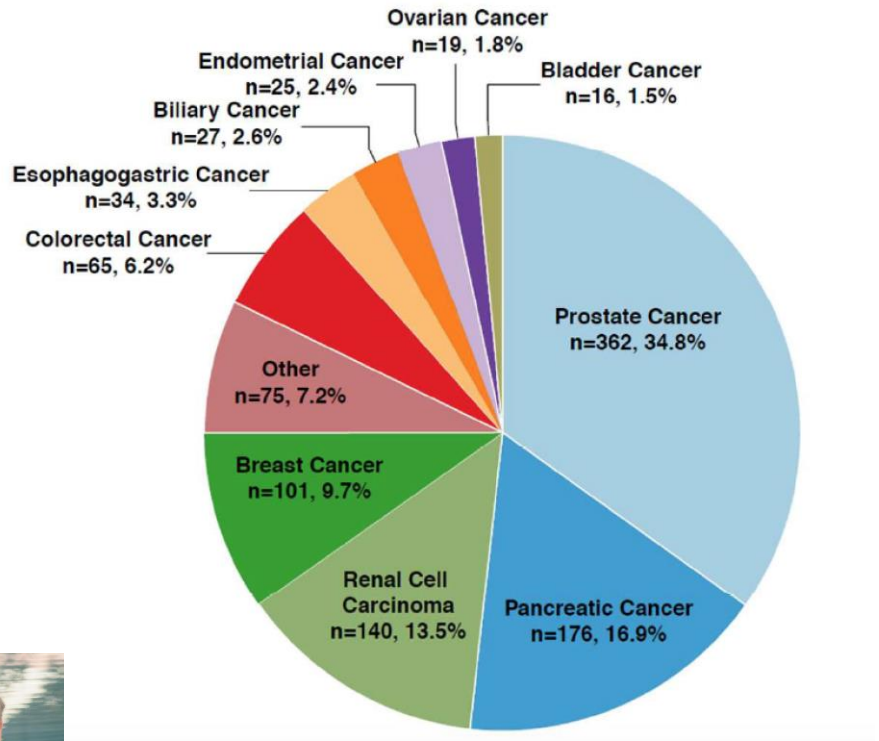


MSK-IMPACT Germline: 88 genes

ABL1	BMPR1A	CRKL	ERBB2	FUBP1	IDH1	MAP2K1	MYOD1	PIK3C3	RAD50	SESN2	TBX3
ACVR1	BRAF	CRLF2	ERBB3	FYN	IDH2	MAP2K2	NBN	PIK3CA	RAD51	SESN3	TCEB1
AGO2	BRCA1	CSDE1	ERBB4	GATA1	IFNGR1	MAP2K4	NCOA3	PIK3CB	RAD51C	SETD2	TCF3
AKT1	BRCA2	CSF1R	ERCC2	GATA2	IGF1	MAP3K1	NCOR1	PIK3CD	RAD51L1	SF3B1	TCF7L2
AKT2	BRD4	CSF3R	ERCC3	GATA3	IGF1R	MAP3K13	NEGR1	PIK3CG	RAD51L3	SH2B3	TEK
AKT3	BRIP1	CTCF	ERCC4	GLI1	IGF2	MAP3K14	NF1	PIK3R1	RAD52	SH2D1A	TERT
ALK	BTK	CTLA4	ERCC5	GNA11	IKBKE	MAPK1	NF2	PIK3R2	RAD54L	SHOC2	TET1
ALOX12B	CALR	CTNNB1	ERF	GNAQ	IKZF1	MAPK3	NFE2L2	PIK3R3	RAF1	SHQ1	TET2
ANKRD11	CARD11	CUL3	ERG	GNAS	IL10	MAPKAP1	NFKBIA	PIM1	RARA	SLX4	TGFBR1
APC	CARM1	CXCR4	ERRFI1	GPS2	IL7R	MAX	NKX2-1	PLCG2	RASA1	SMAD2	TGFBR2
AR	CASP8	CYLD	ESR1	GREM1	INHA	MCL1	NKX3-1	PLK2	RB1	SMAD3	TMEM127
ARAF	CBFB	CYSLTR2	ETV1	GRIN2A	INHBA	MDC1	NOTCH1	PMAIP1	RBM10	SMAD4	TMPRSS2
ARID1A	CBL	DAXX	ETV6	GSK3B	INPP4A	MDM2	NOTCH2	PMS1	RECQL	SMARCA4	TNFAIP3
ARID1B	CCND1	DCUN1D1	EZH1	H3F3A	INPP4B	MDM4	NOTCH3	PMS2	RECQL4	SMARCB1	TNFRSF14
ARID2	CCND2	DDR2	EZH2	H3F3B	INPPL1	MED12	NOTCH4	PNRC1	REL	SMARCD1	TOP1
ARID5B	CCND3	DICER1	FAM123B	H3F3C	INSR	MEF2B	NPM1	POLD1	RET	SMO	TP53
ASXL1	CCNE1	DIS3	FAM175A	HGF	IRF4	MEN1	NRAS	POLE	RFWD2	SMYD3	TP53BP1
ASXL2	CD274	DNAJB1	FAM46C	HIST1H1C	IRS1	MET	NSD1	PPARG	RHEB	SOCS1	TP63
ATM	CD276	DNMT1	FAM58A	HIST1H2BD	IRS2	MGA	NTHL1	PPM1D	RHOA	SOS1	TRAF2
ATR	CD79A	DNMT3A	FANCA	HIST1H3A	JAK1	MITF	NTRK1	PPP2R1A	RICTOR	SOX17	TRAF7
ATRX	CD79B	DNMT3B	FANCC	HIST1H3B	JAK2	MLH1	NTRK2	PPP4R2	RIT1	SOX2	TSC1
AURKA	CDC42	DOT1L	FAT1	HIST1H3C	JAK3	MLL	NTRK3	PPP6C	RNF43	SOX9	TSC2
AURKB	CDC73	DROSHA	FBXW7	HIST1H3D	JUN	MLL2	NUF2	PRDM1	ROS1	SPEN	TSHR
AXIN1	CDH1	DUSP4	FGF19	HIST1H3E	KDM5A	MLL3	NUP93	PRDM14	RPS6KA4	SPOP	U2AF1
AXIN2	CDK12	E2F3	FGF3	HIST1H3F	KDM5C	MPL	PAK1	PREX2	RPS6KB2	SPRED1	UPF1
AXL	CDK4	EED	FGF4	HIST1H3G	KDM6A	MRE11A	PAK7	PRKAR1A	RPTOR	SRC	VEGFA
B2M	CDK6	EGFL7	FGFR1	HIST1H3H	KDR	MSH2	PALB2	PRKCI	RRAGC	SRSF2	VHL
BABAM1	CDK8	EGFR	FGFR2	HIST1H3I	KEAP1	MSH3	PARK2	PRKD1	RRAS	STAG2	VTCN1
BAP1	CDKN1A	EIF1AX	FGFR3	HIST1H3J	KIT	MSH6	PARP1	PTCH1	RRAS2	STAT3	WHSC1
BARD1	CDKN1B	EIF4A2	FGFR4	HIST2H3C	KLF4	MSI1	PAX5	PTEN	RTEL1	STAT5A	WHSC1L1
BBC3	CDKN2A	EIF4E	FH	HIST2H3D	KMT2B	MSI2	PBRM1	PTP4A1	RUNX1	STAT5B	WT1
BCL10	CDKN2B	ELF3	FLCN	HIST3H3	KMT5A	MST1	PDCD1	PTPN11	RXRA	STK11	WWTR1
BCL2	CDKN2C	EP300	FLT1	HLA-A	KNSTRN	MST1R	PDCD1LG2	PTPRD	RYBP	STK19	XIAP
BCL2L1	CEBPA	EPAS1	FLT3	HLA-B	KRAS	MTOR	PDGFRA	PTPRS	SDHA	STK40	XPO1
BCL2L11	CENPA	EPCAM	FLT4	HNF1A	LATS1	MUTYH	PDGFRB	PTPRT	SDHAF2	SUFU	XRCC2
BCL6	CHEK1	EPHA3	FOXA1	HOXB13	LATS2	MYC	PDPK1	RAB35	SDHB	SUZ12	YAP1
BCOR	CHEK2	EPHA5	FOXL2	HRAS	LMO1	MYCL1	PGR	RAC1	SDHC	SYK	YES1
BIRC3	CIC	EPHA7	FOXO1	ICOSLG	LYN	MYCN	PHOX2B	RAC2	SDHD	TAP1	ZFHX3
BLM	CREBBP	EPHB1	FOXP1	ID3	MALT1	MYD88	PIK3C2G	RAD21	SESN1	TAP2	ZRSR2

Prevalence of pathogenic germline variants

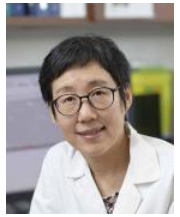
First 1,040 patients prospectively tested by MSK-IMPACT



- **17.5% patients had clinically actionable pathogenic variants conferring cancer susceptibility**
- ***30-55% of these would not have been detected by clinical guidelines-directed testing, depending on case mix, ancestry and stage***

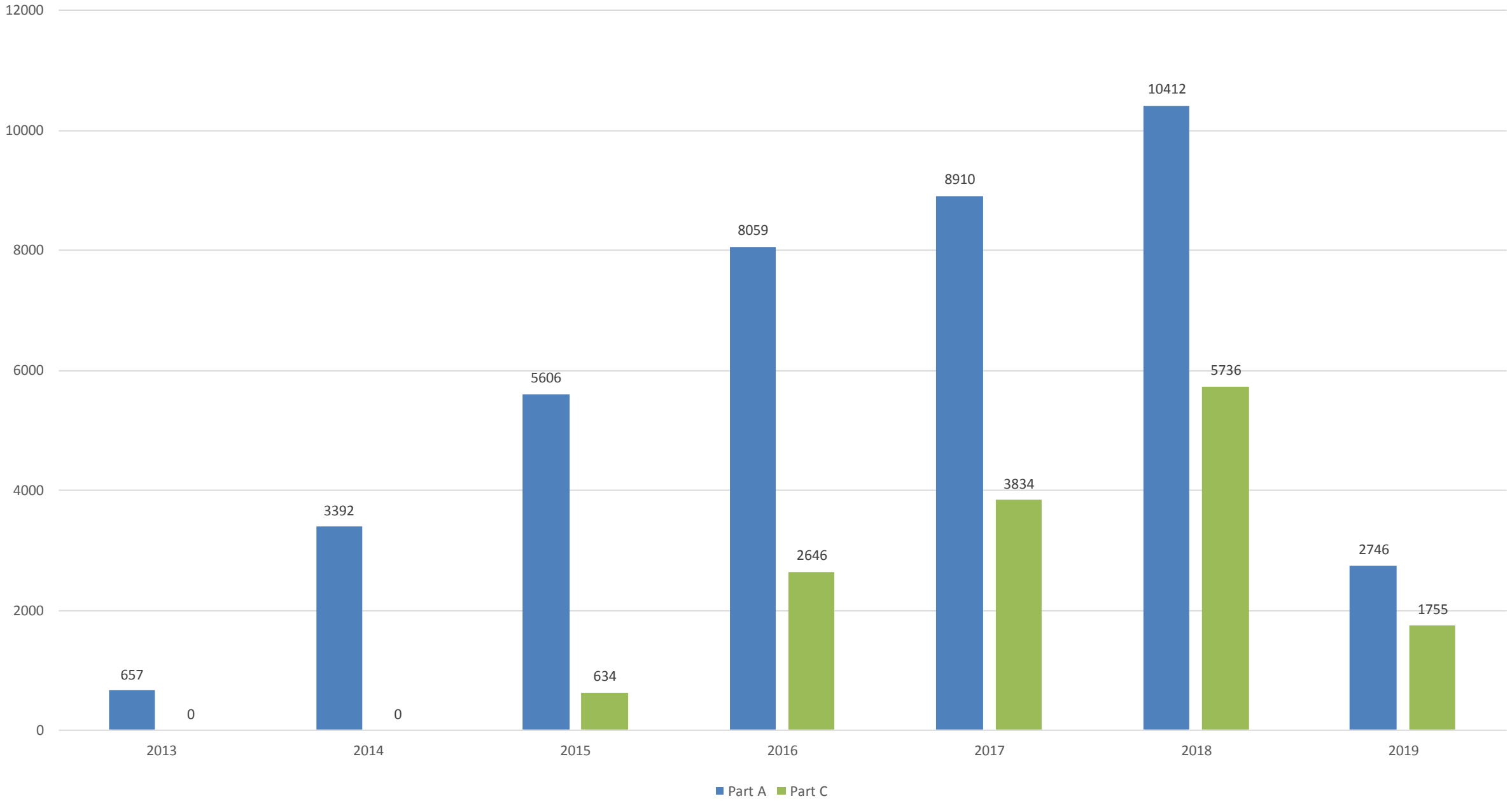






Clinical Genetics: Mark Robson, Kenneth Offit
Diagnostic Molecular Genetics: Diana Mandelker, Ozge Birsoy, Liying Zhang
(Mandelker *et al*., *JAMA* 2017)

Accrual to MSK-IMPACT Somatic and Germline: 2013 – 2019

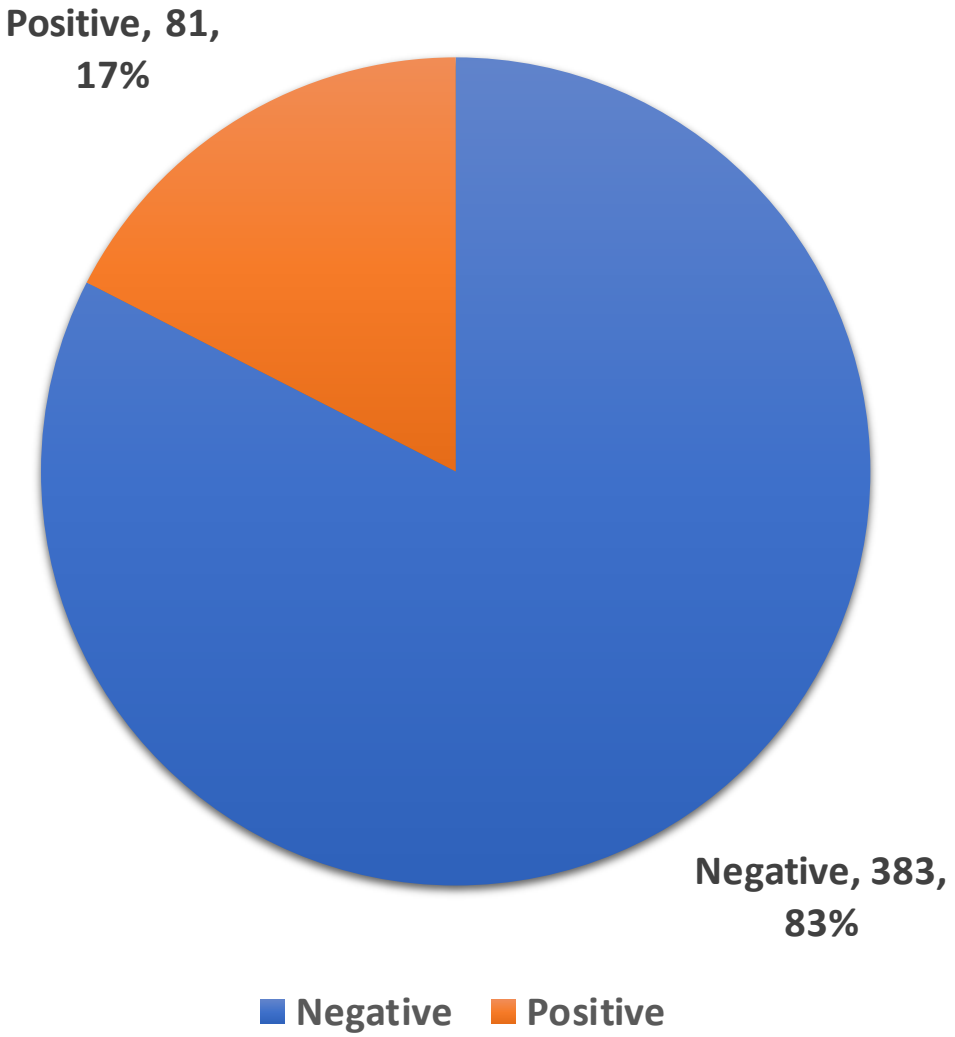


Penetrance	Known CRC Associated Genes
High	*APC, EPCAM, MLH1, MSH2, MSH6, PMS2, MUTYH (biallelic), POLD1, POLE, TP53, SMAD4, BMPR1A, SMAD4, PTEN*
Moderate	*CHEK2*
Low	*APC (1307K)* *MUTYH (heterozygous)*
Recessive/ Uncertain	*MSH3, NTHL1*

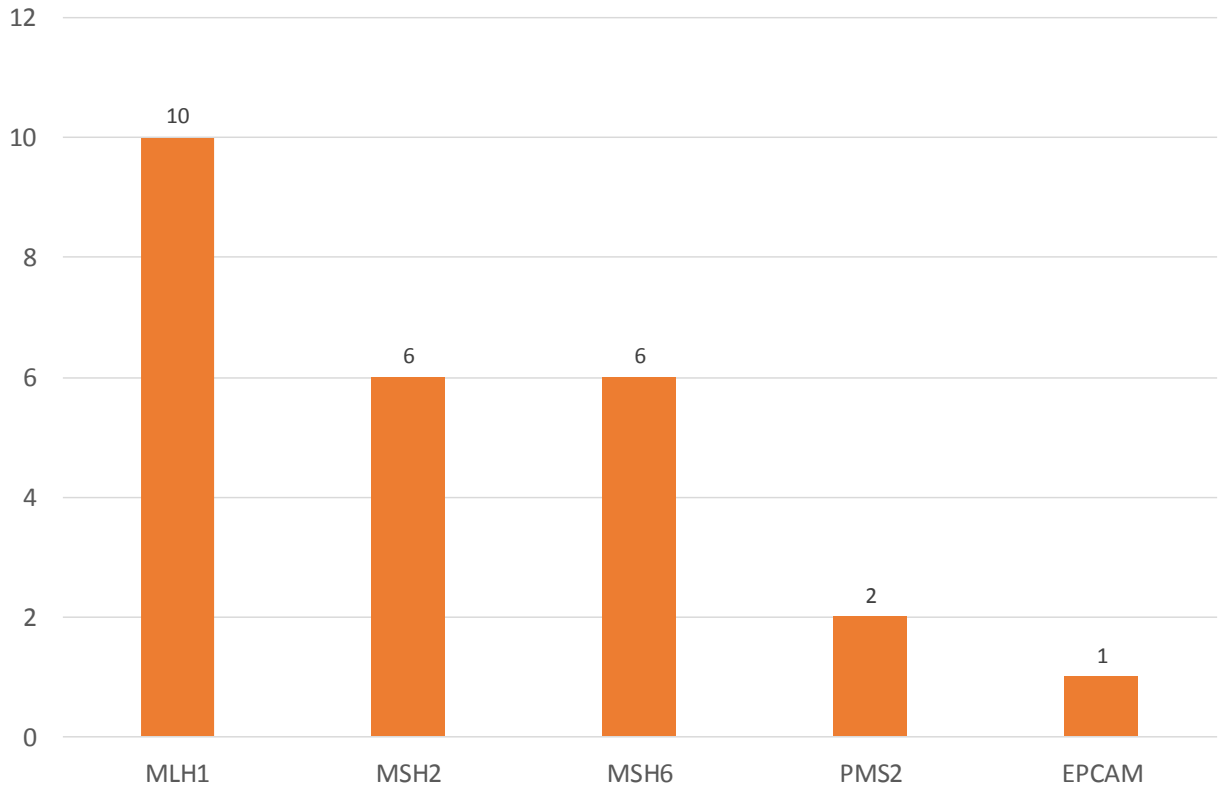
Baseline Characteristics of AYA-CRC (<50 age)

Baseline Characteristics	N=464
Median Age at Diagnosis (range)	42 (14-49)
≤35	114 (24.6%)
>35 but <50	350 (75.4%)
Gender	M: 265 (57%) F: 199 (43%)
Tumor Location	Colon: 290 (62.5%) Rectum: 167 (36%) Unknown: 7 (1.5%)
Other primary cancers	Any other malignancy: 40 (8.6%) Colon: 7 (1.5%) Thyroid: 4 Uterine: 3 Other: 22

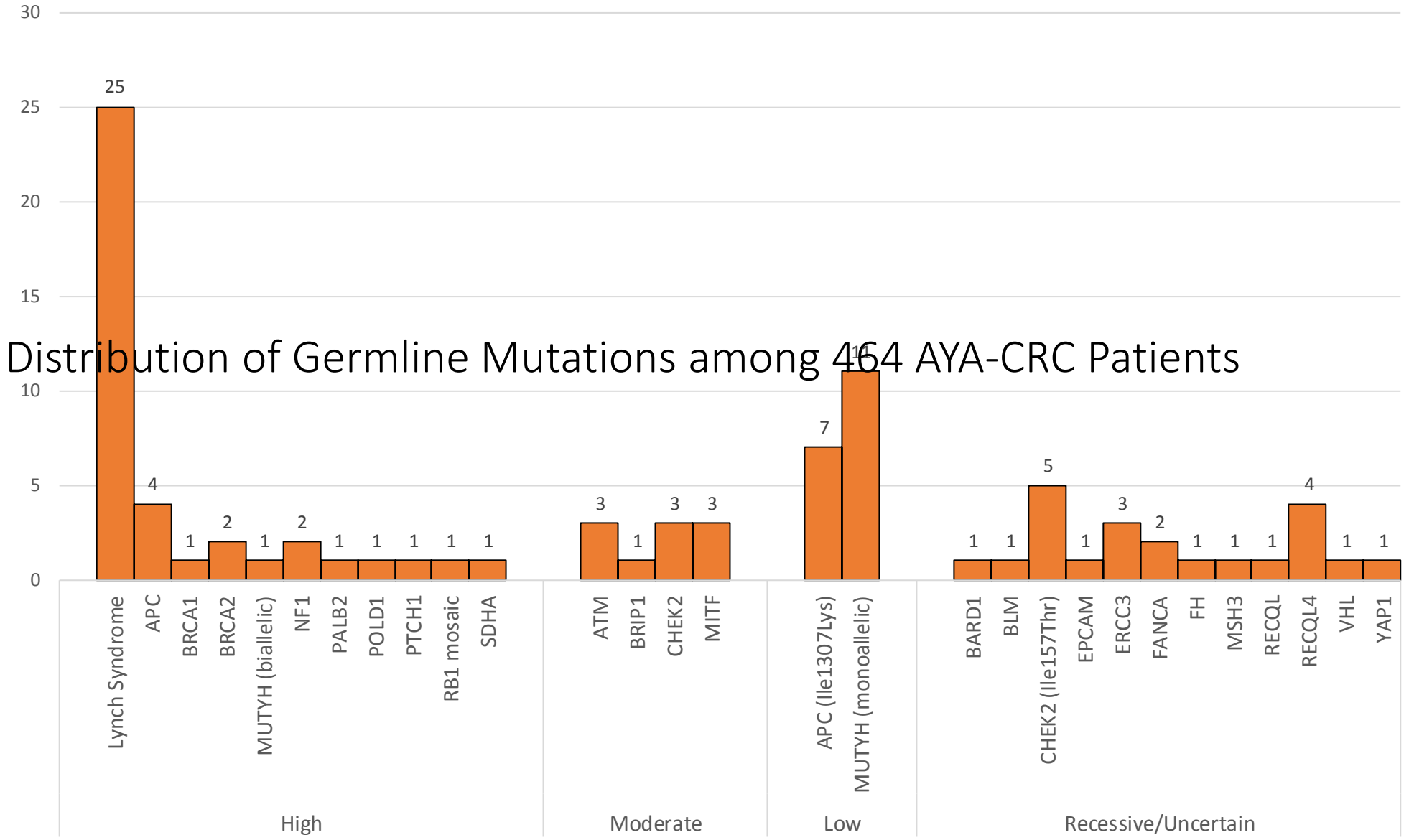
Prevalence of Germline Mutations in CRC patients < age 50 at diagnosis (N=464)



Lynch syndrome:
5.4%
25/464



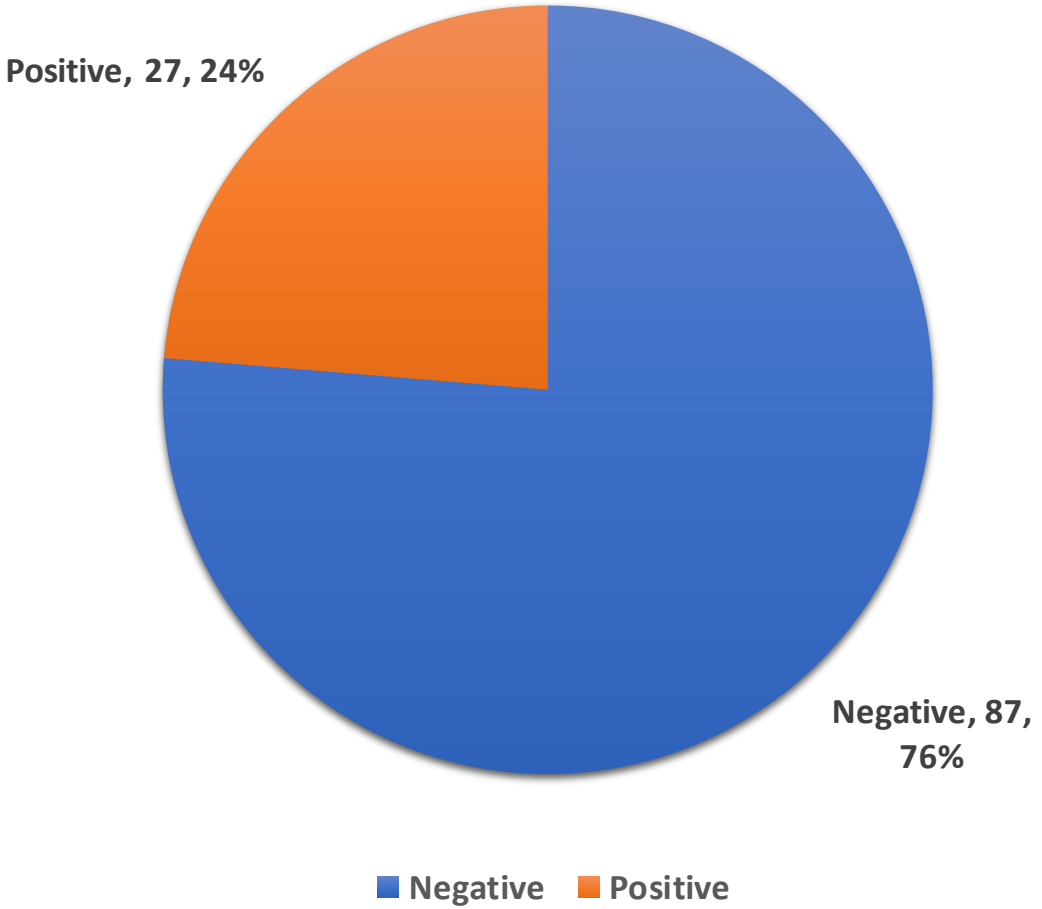
Distribution of Germline Mutations among 464 AYA-CRC Patients



Prevalence of Germline Mutations by Tumor Location

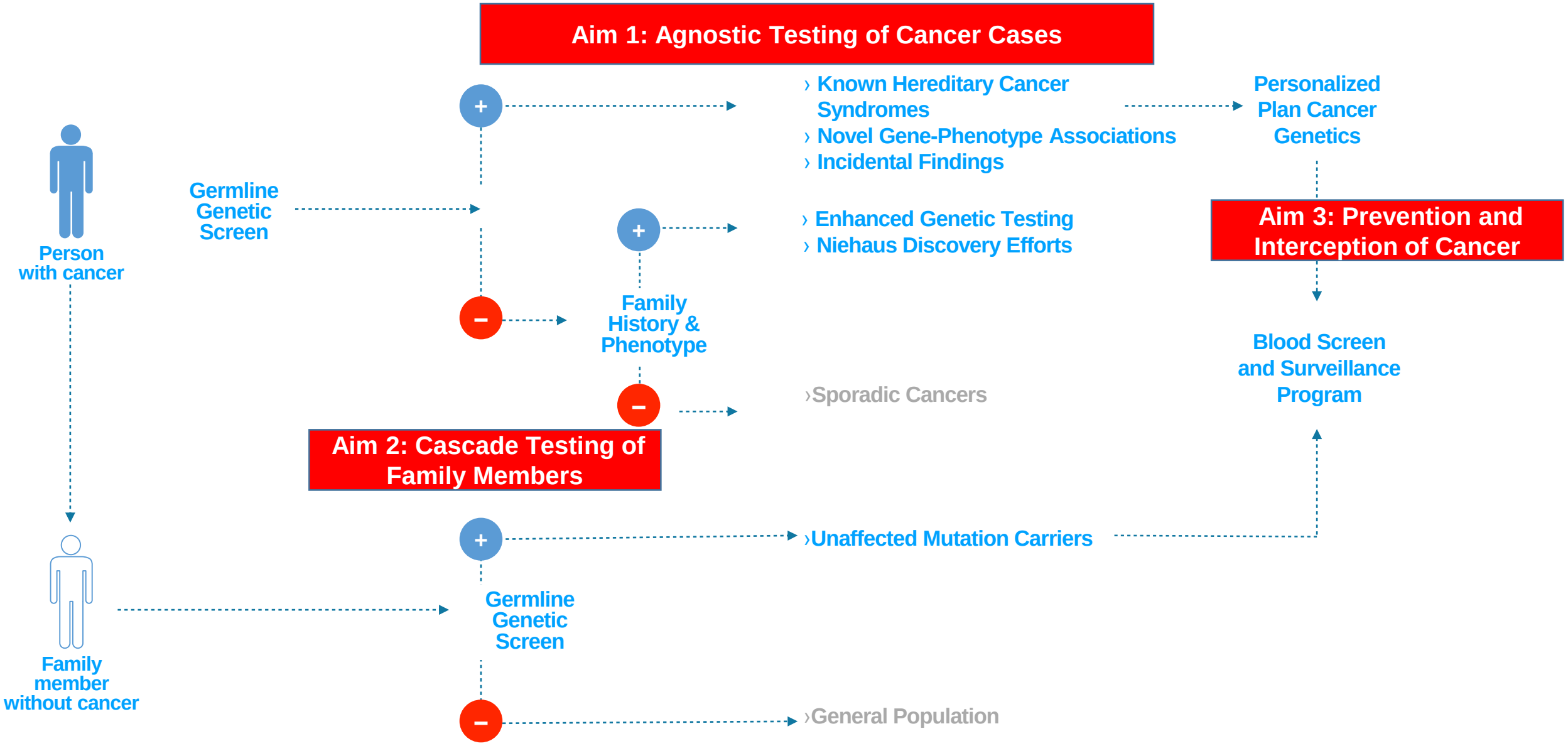
Tumor Location	Penetrance				
	Overall	High	Moderate	Low	Uncertain/ Recessive
Colon (n=290)	18.3% (53)	8.6% (25)	2.1% (6)	3.4% (10)	4.1% (12)
Rectum (n=167)	16.2% (27)	8.4% (14)	1.8% (3)	3% (5)	3% (5)

Prevalence of Germline Mutations in CRC patients age ≤35 at diagnosis (N=114)

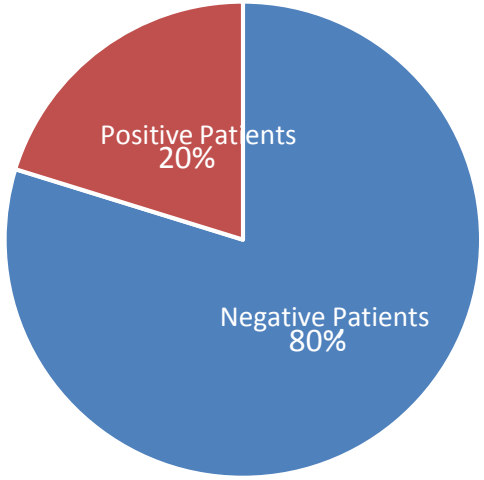


Age	Penetrance				
	Overall	High	Moderate	Low	Uncertain/Recessive
≤35 (n=114)	**23.7% (27)**	12.3% (14)	1.8% (2)	5.3% (6)	4.4% (5)
>35 (n=350)	**15.4% (54)**	7.1% (25)	2% (7)	2.8% (10)	3.4% (12)
All (N=464)	**17.4% (81)**	8.4% (39)	1.9% (9)	3.4% (16)	3.7% (17)

Precision, Interception and Prevention (PIP): Germline Cancer Genetics

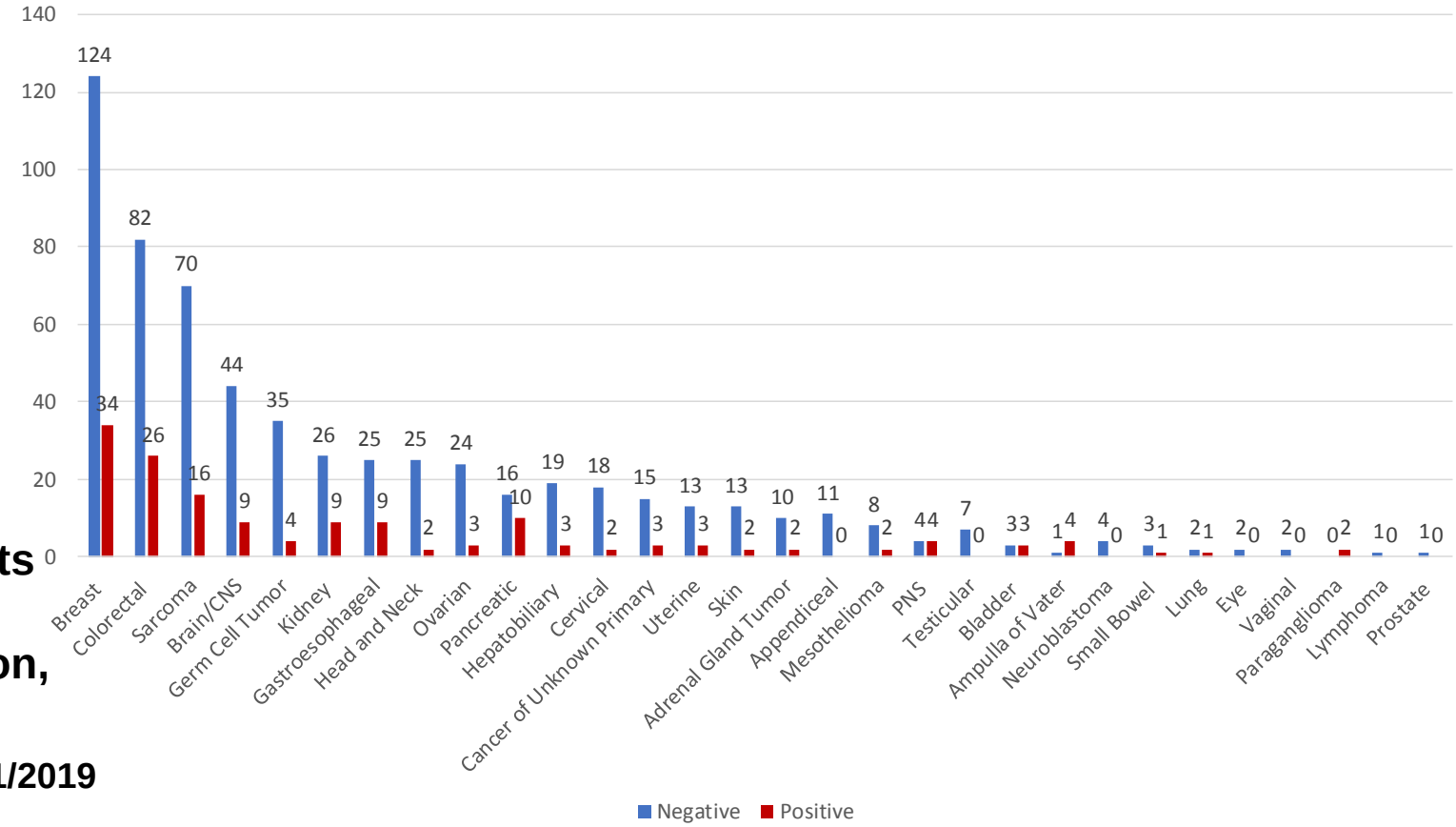


Germline mutations in YOUNG-ADULT cancer patients: Ages 18-35

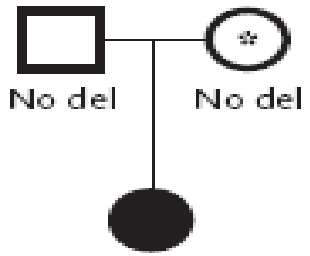


Young-Adult Cancer Patients (age 18-35); N=762
Part of Precision, Interception, Prevention (PIP) effort

Stadler, et al. YA patients as of 2/1/2019



‘Trio’ design



- **10% of TGCT trios with de novo rare copy-number variants (CNVs) (Stadler et al. *AJHG*)**
- **Exome data: 9% of trios with likely gene disrupting, rare, *de novo* mutations**

Genome-Targeted Prevention and Interception Clinic

- Cancer genetics PIP initiatives will result in a substantial increase in the number of individuals with **POSITIVE** germline genetic findings

› **Known Hereditary Cancer Syndromes**
› **Novel Gene-Phenotype Associations**
› **Novel & Incidental Discovery Findings**

› **UNAFFECTED Mutation Carriers**

→

LONGITUDINAL FOLLOW-UP CARE

→

› **Cancer surveillance (breast MRI, mammography, colonoscopy, ultrasonography etc)**
› **Clinical procedures (endometrial biopsy skin biopsy)**
› **Risk-reduction measures: surgical referrals**
› **Direct in-house referral to surgical/medical oncologist**
› **Opportunity for additional research: outcomes, non-invasive prospective screening, cancer prevention trials**

Alicia Latham, MD
in concert with the Survivorship Program, General Medicine Division

Conclusion

YO-CRC has a substantial hereditary component; however, majority of the genetic risk remains unexplained

Identification of germline mutations offers opportunities for early detection, intervention, and prevention

Patient outreach and engagement vital to success of screening and intervention efforts

As part of the Niehaus Center gene discovery efforts, the unexplained rise in young-adult CRC and other cancers will require exome, genome, and possibly transcriptome sequencing and functional genomic studies

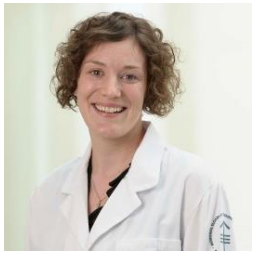
Clinical Genetics Team

Kenneth Offit, MD, MPH

Zsofia Stadler, MD

Mark Robson, MD

Michael Walsh, MD



Karen Cadoo, MD

Maria Carlo, MD

Alicia Latham, MD

Kimberly Amoroso
MS, CGC

Angela Arnold
MS, LCGC

Kelsey Breen
MS, MSc, CGC

Amanda Catchings
MS, CGC

Elise Fiala
MS, CGC

Megan Harlan Fleischut
MS, CGC

Dina Green
MS, CGC

Jennifer Kennedy
MS, CGC

Vanessa Marcell
MS, LCGC

Kelly Morgan
MS, CGC

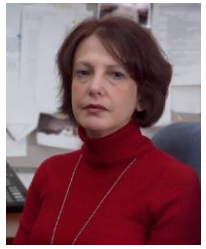
Megha Ranganathan
MS, CGC

Rosalba Sacca
PhD, MS, CGC

Erin Salo-Mullen
MS, MPH, CGC

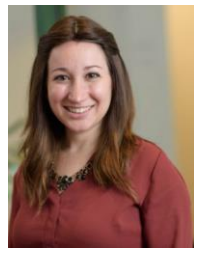
Margaret Sheehan
MS, CGC

Rania Sheikh
MS, CGC



Beth Siegel
MS, CGC

Hetal Vig
MS, CGC



Temima Wildman
MS, CGC

Thank you!

Romeo Milio Lynch Syndrome Foundation
The Fieldstone Family Fund
Niehaus Center for Inherited Genomics
Starr Cancer Consortium
And
Our Patients!

Germline Genetic Features of Young Individuals with CRC

Elena M. Stoffel MD, MPH

Director, Cancer Genetics Clinic

University of Michigan Health System

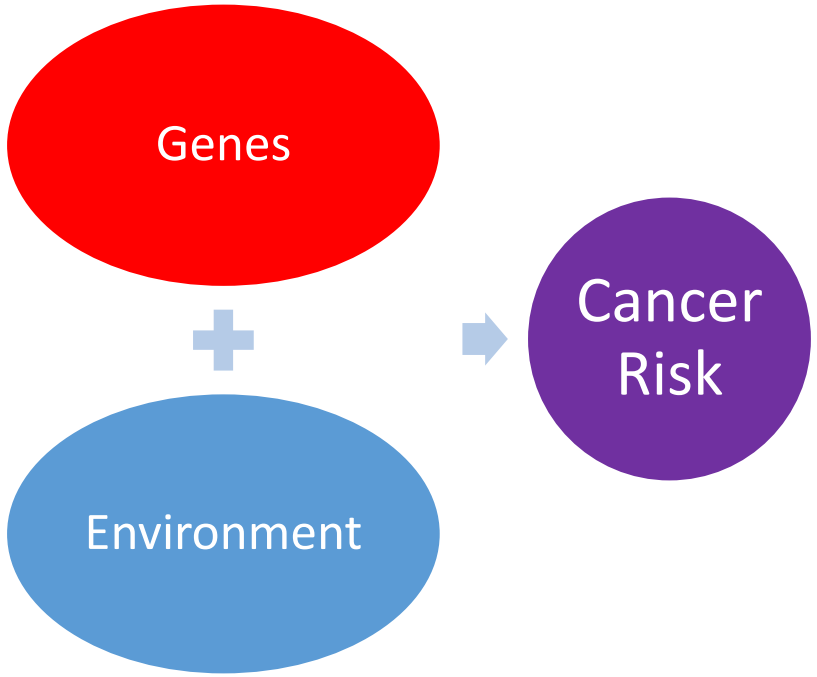
Ann Arbor, MI

CRC Risk Assessment

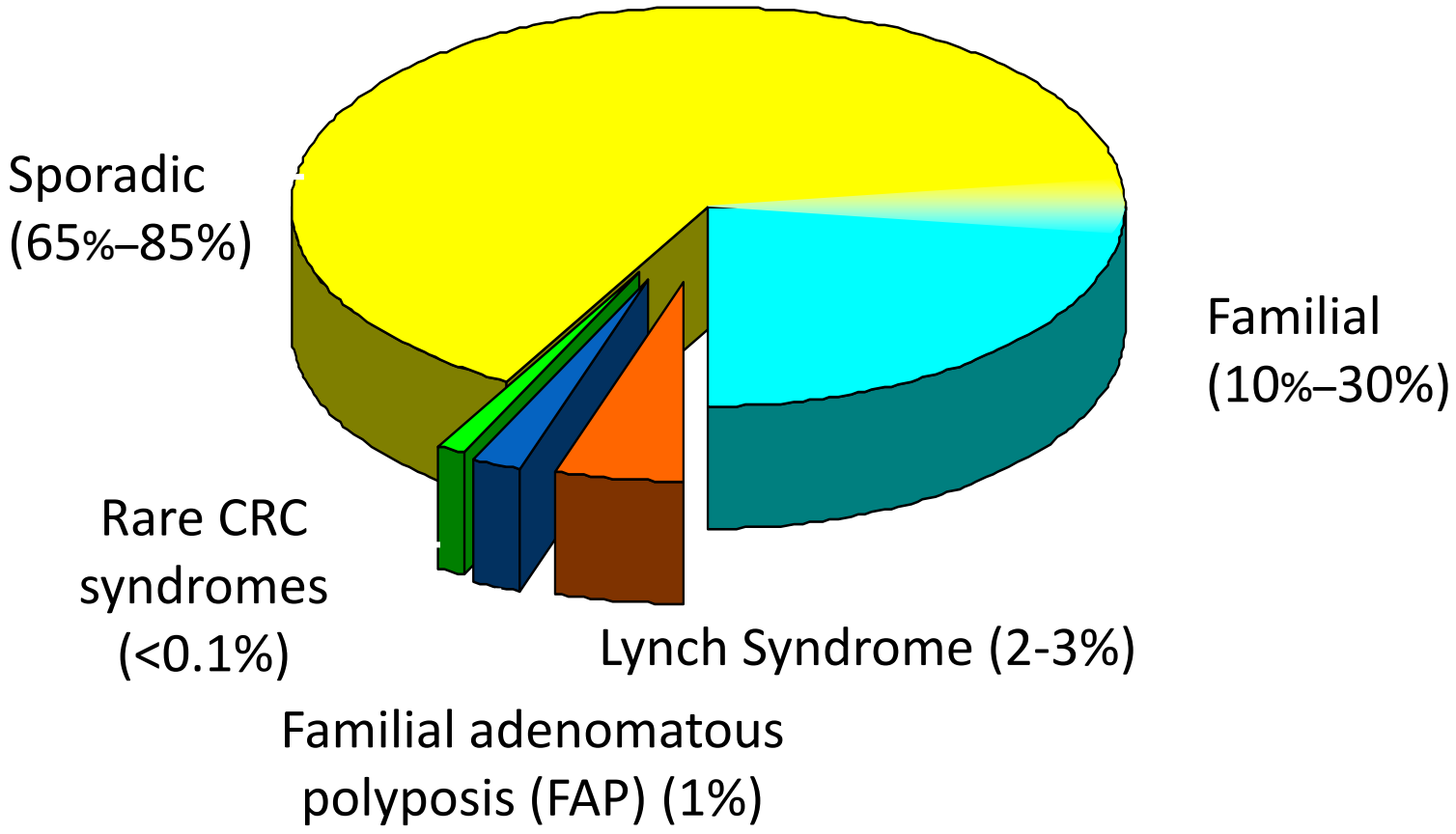
Age>50

Family History
- CRC in first degree relative(s)

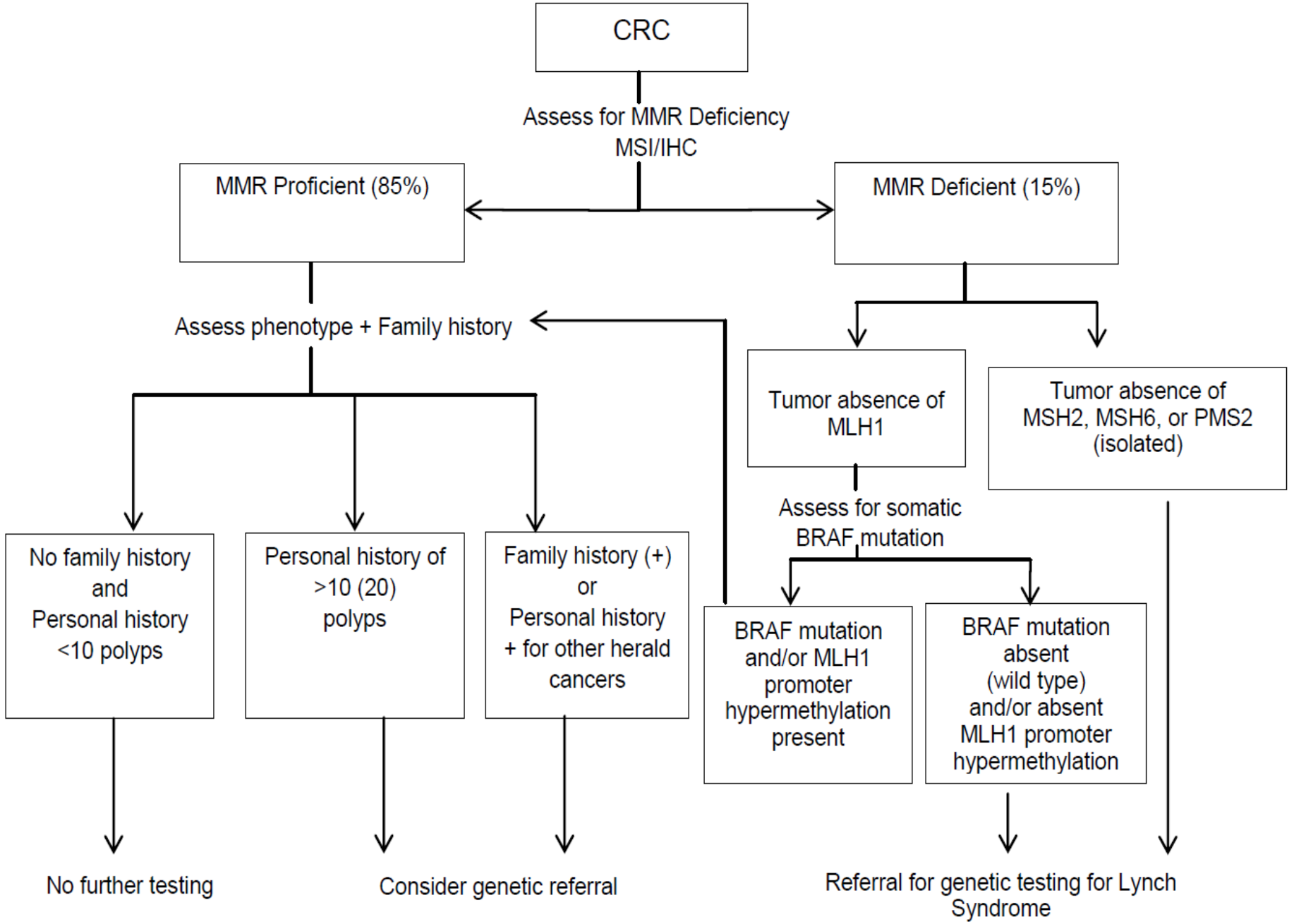
Personal history
- Colorectal adenomas
- Inflammatory Bowel Disease



Genetic Predisposition to CRC ca 1996



Adapted from Burt RW et al. Prevention and Early Detection of CRC, 1996



Stoffel and Boland Gastro 2015

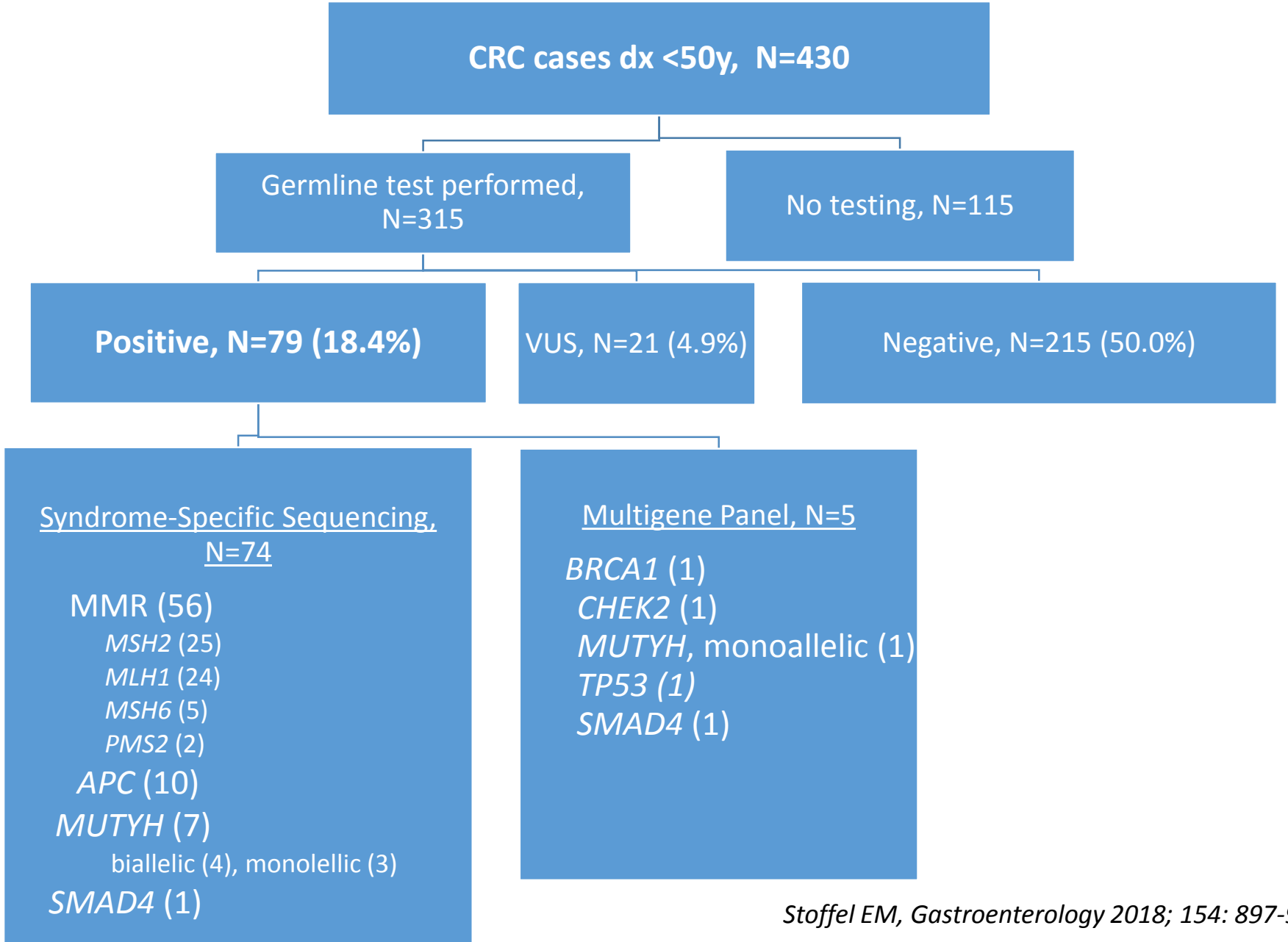
Methods

- Retrospective review of outcomes of clinical genetic evaluation in individuals with CRC age<50
    - 1998-2015

Characteristics of Patients with Young Onset Colorectal Cancer (N=430)	
	Total N=430 (100%)
Female	213 (49.5%)
Mean age dx (range)	40.0 (16-49)
Race	
White	318 (74.0%)
Non-White	31 (13.9%)
MSI-Status*	
MSI-H	41 (9.5%)
MSS	163 (37.9%)
Unknown	226 (52.6%)
Family history*	
FDR with CRC	111 (25.8%)
Tumor stage*	
0-I	54 (12.6%)
II	43 (10.0%)
III-IV	183 (42.6%)
CRC Site*	
Right colon	115 (26.7%)
Left colon	182 (42.3%)
Rectum	72 (16.7%)
Not specified	61 (14.2%)

Stoffel EM, Gastroenterology 2018; 154: 897-905

Outcomes of Clinical Evaluations in Young CRC



Stoffel EM, Gastroenterology 2018; 154: 897-905

Characteristics of Patients with Young Onset Colorectal Cancer (N=430)				
	Total N=430 (100%)	Positive N=79 (18.4%)	No mutation N=215 (50.0%)	VUS N=21 (5%)
Female	213 (49.5%)	41 (51.9%)	103 (47.9%)	13 (61.9%)
Mean age dx (range)	40.0 (16-49)	37.2 (17-49)	41.1 (16-49)	8 (38.1%)
Race				
White	318 (74.0%)	59 (74.7%)	177 (82.3%)	11 (52.4%)
Non-White	31 (13.9%)	4 (13.8%)	11 (5.1%)	6 (28.6%)
MSI-Status*				
MSI-H	41 (9.5%)	17 (21.5%)	20 (9.3%)	1 (4.8%)
MSS	163 (37.9%)	6 (7.6%)	111 (51.6%)	12 (57.1%)
Unknown	226 (52.6%)	56 (70.9%)	84 (39.1%)	8 (38.1%)
Family history*				
FDR with CRC	111 (25.8%)	42 (53.2%)	35 (16.3%)	7 (33.3%)
Tumor stage*				
0-I	54 (12.6%)	20 (25.3%)	23 (10.7%)	3 (14.3%)
II	43 (10.0%)	11 (13.9%)	27 (12.6%)	0 (0.0%)
III-IV	183 (42.6%)	17 (21.5%)	98 (45.6%)	13 (61.9%)
CRC Site*				
Right colon	115 (26.7%)	28 (35.4%)	50 (23.3%)	5 (23.8%)
Left colon	182 (42.3%)	24 (30.4%)	109 (50.7%)	10 (47.6%)
Rectum	72 (16.7%)	6 (7.6%)	47 (21.9%)	5 (23.8%)
Not specified	61 (14.2%)	21 (26.6%)	9 (4.2%)	1 (4.8%)

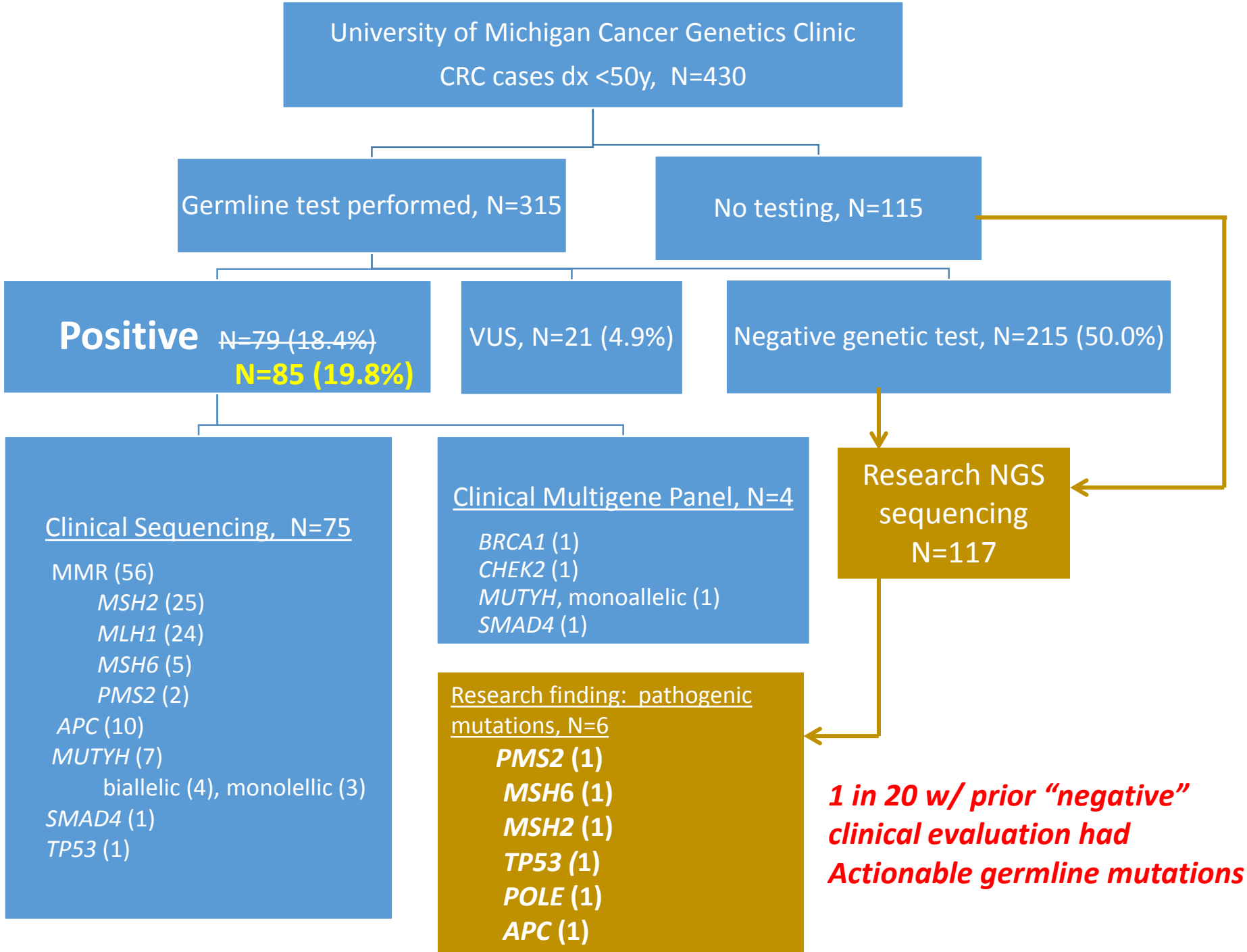
*p<0.05 difference between mutation positive and mutation negative group

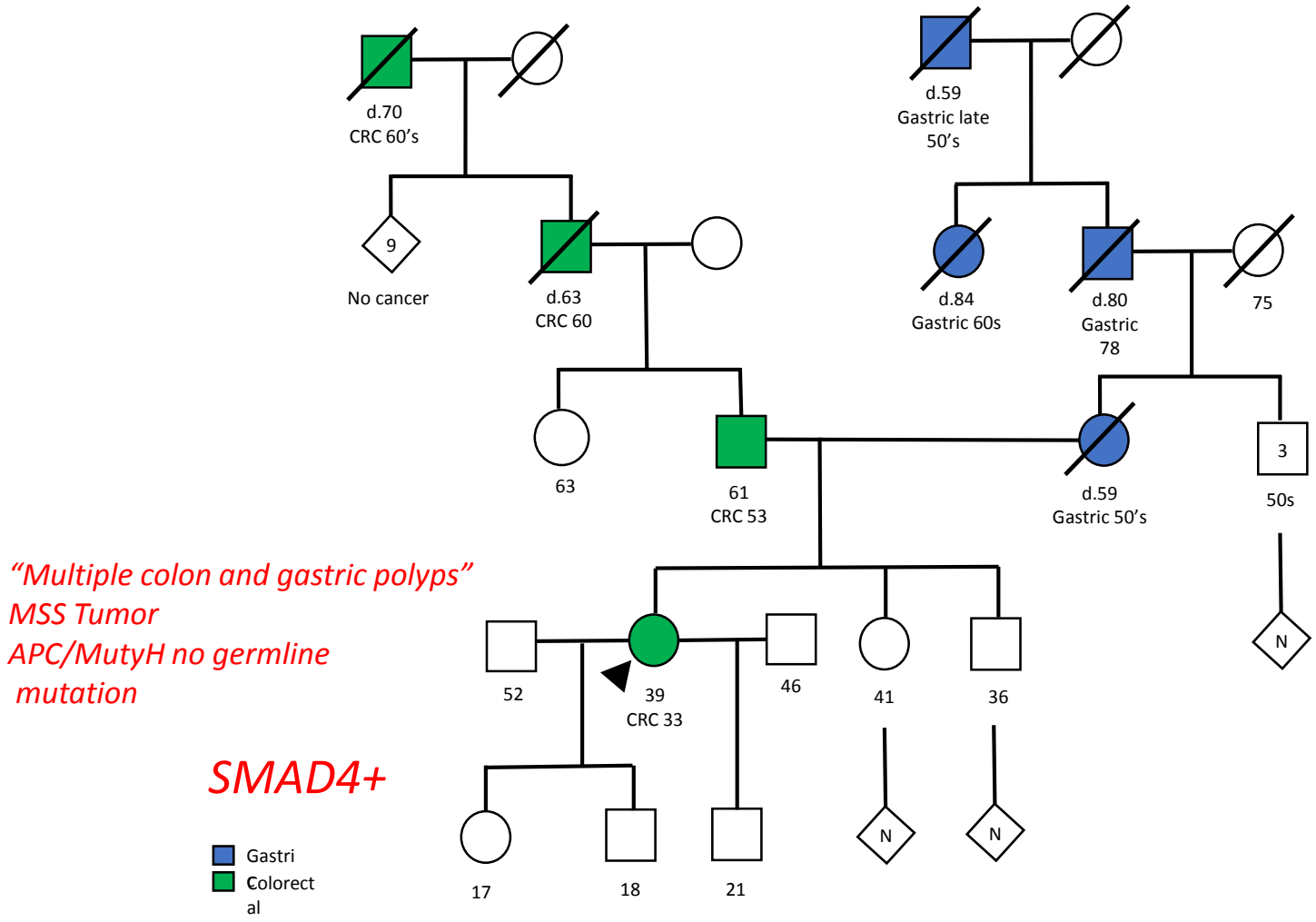
NGS Re-sequencing
(Research-based)

- Patients with CRC dx age<50 with prior "negative" clinical genetics evaluation
  - N=117

- Germline DNA sequenced using NGS sequencing (50x coverage)
  - 124 Cancer Gene Panel (Qiagen GeneRead)

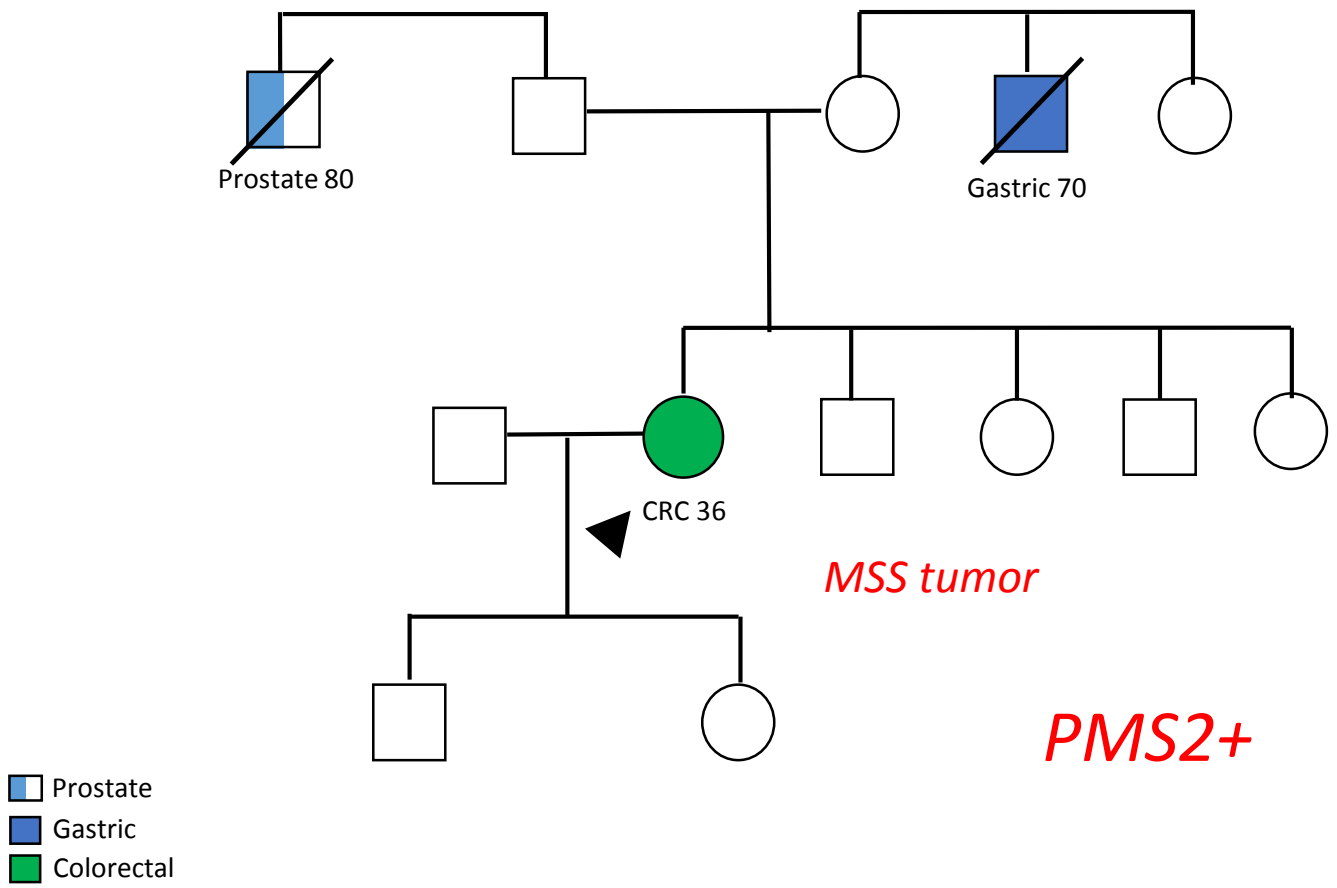
University of Michigan
Health System

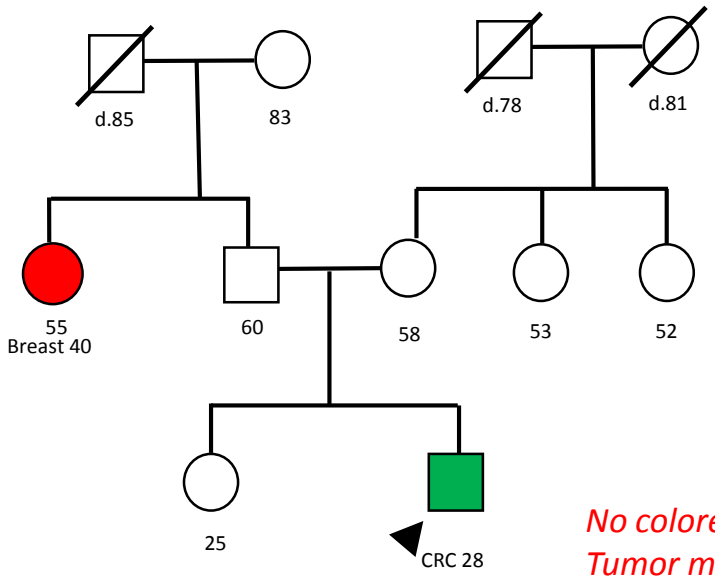

University of Michigan Cancer Genetics Clinic
CRC cases dx <50y, N=430
Germline test performed, N=315
No testing, N=115
Positive ~~N=79 (18.4%)~~ N=85 (19.8%)
VUS, N=21 (4.9%)
Negative genetic test, N=215 (50.0%)
Clinical Sequencing, N=75
MMR (56)
MSH2 (25)
MLH1 (24)
MSH6 (5)
PMS2 (2)
APC (10)
MUTYH (7)
biallelic (4), monolellic (3)
SMAD4 (1)
TP53 (1)
Clinical Multigene Panel, N=4
BRCA1 (1)
CHEK2 (1)
MUTYH, monoallelic (1)
SMAD4 (1)
Research NGS sequencing N=117
Research finding: pathogenic mutations, N=6
PMS2 (1)
MSH6 (1)
MSH2 (1)
TP53 (1)
POLE (1)
APC (1)
1 in 20 w/ prior "negative" clinical evaluation had Actionable germline mutations



"Multiple colon and gastric polyps"
MSS Tumor
APC/MutyH no germline mutation

SMAD4+


Prostate 80
Gastric 70
CRC 36
MSS tumor
PMS2+
Prostate
Gastric
Colorectal



No colorectal polyps
Tumor microsatellite stable

BRCA2 +

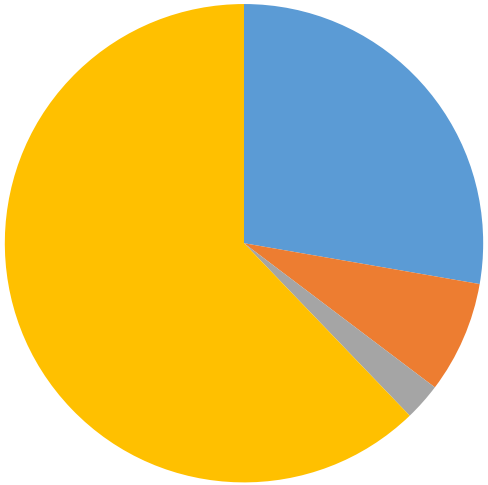
Colorectal
Breast

EO-CRC
Missed Mutation Carriers?

- Family history can vary (48% reported no CRC in FDR)
  - Relatives have not yet developed their cancers
  - Incomplete information
  - Variable penetrance
- Clinical phenotypes can vary
  - Potential overlap in phenotypes of different syndromes
- Tumor testing is not perfect
  - *MSH6* and *PMS2* tumors may be mismatch repair proficient (MSS)

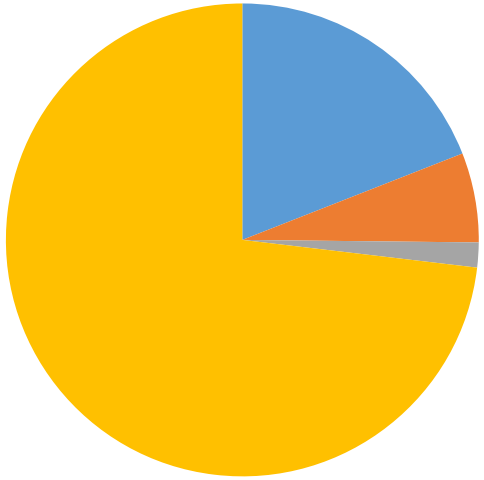
Prevalence of Germline Mutations by CRC Age Group

CRC <35y



Pathogenic Mutation (25.9%)

CRC <50y



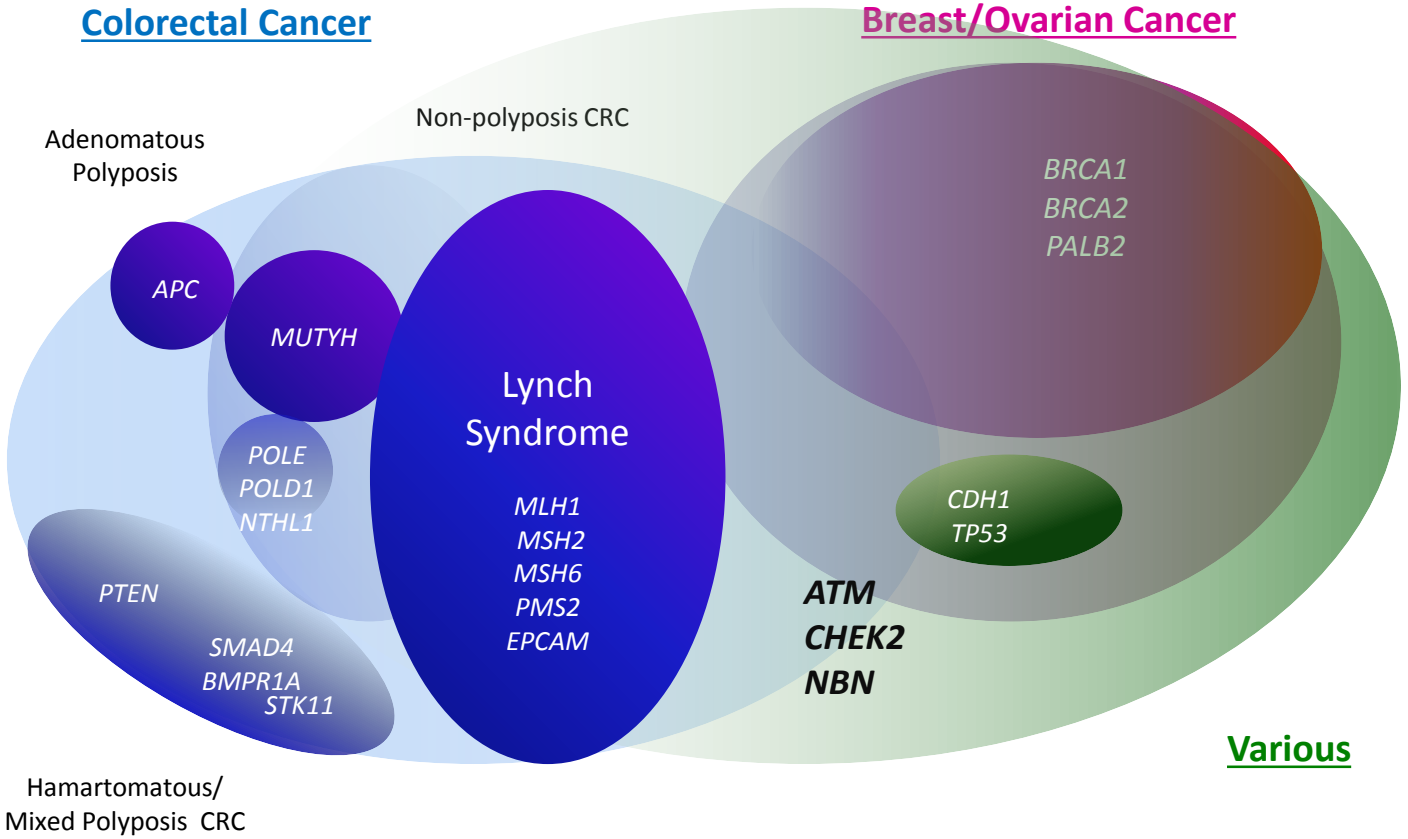
Pathogenic Mutation (19.8%)

Lynch
FAP
Other
No mutation

30% dx<35
(Mork JCO 2015)

16% dx <50
(Pearlman JAMA oncol 2017)

Hereditary Predisposition to Cancer



[a]Darker shading represents higher penetrance
[b]Size approximates population prevalence

Missing Heredity of Complex Diseases

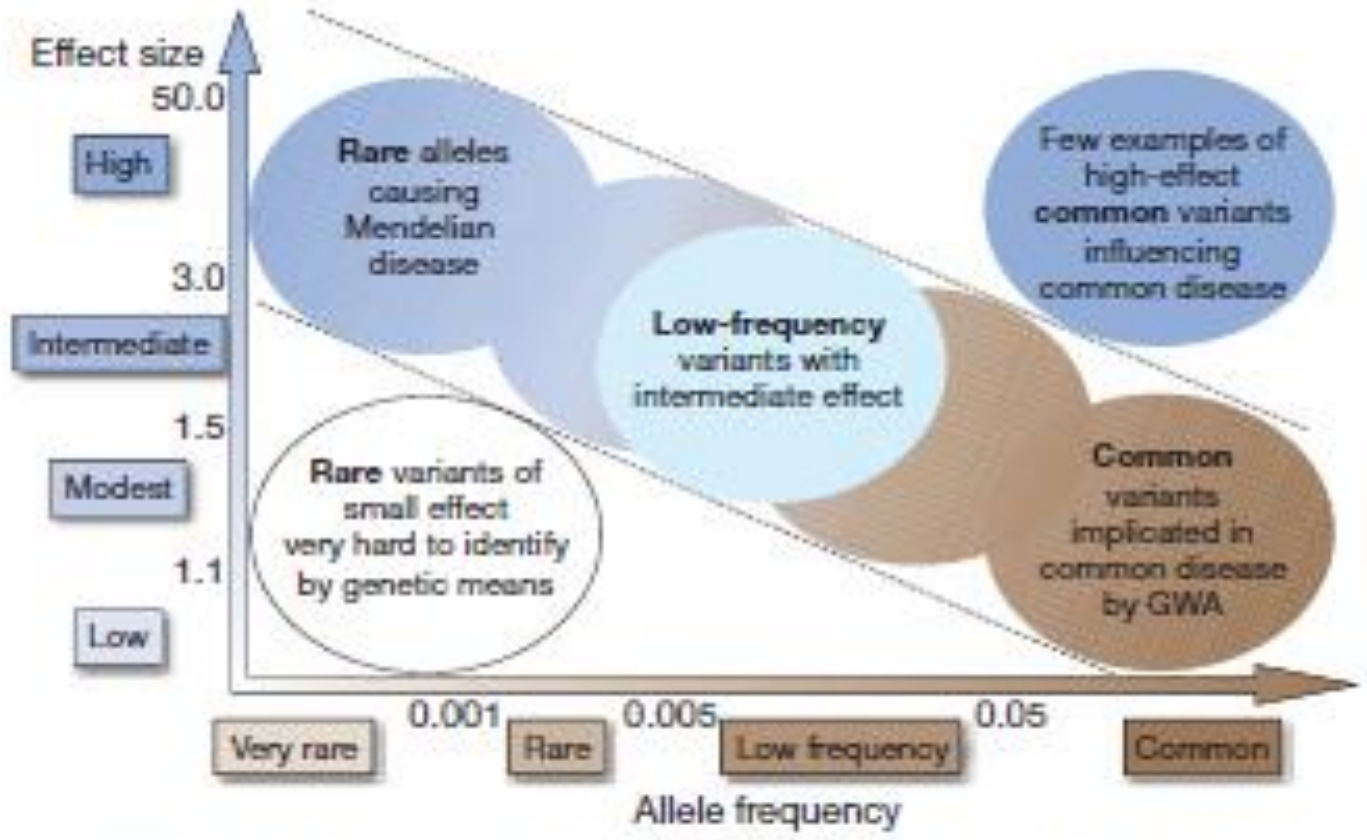


Figure 1 | Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect (odds ratio). Most emphasis and interest lies in identifying associations with characteristics shown within diagonal dotted lines. Adapted from ref. 42.

Manolio et al, Nature 2009

Gastroenterology 2018;154:2152–2164

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

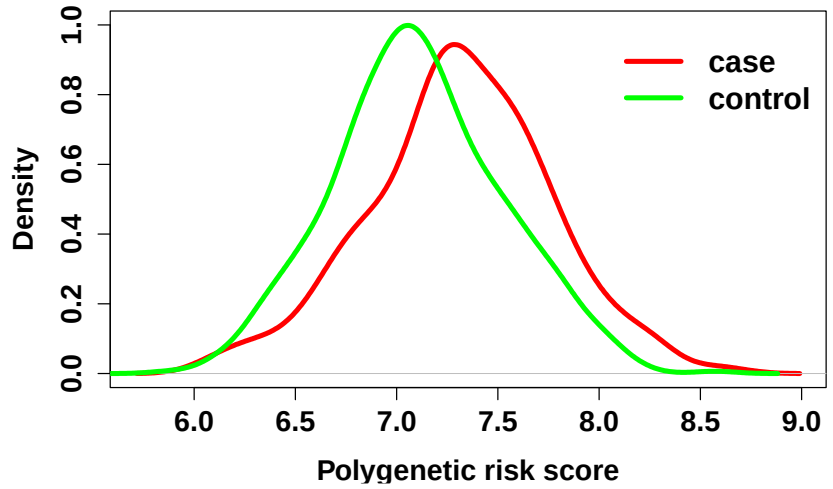
Jihyoun Jeon,[1] Mengmeng Du,[2] Robert E. Schoen,[3] Michael Hoffmeister,[4,5,6] Polly A. Newcomb,[7] Sonja I. Berndt,[8] Bette Caan,[9] Peter T. Campbell,[10] Andrew T. Chan,[11,12,13] Jenny Chang-Claude,[4,5,6] Graham G. Giles,[14] Jian Gong,[7] Tabitha A. Harrison,[7] Jeroen R. Huyghe,[7] Eric J. Jacobs,[10] Li Li,[15] Yi Lin,[7] Loïc Le Marchand,[16] John D. Potter,[7] Conghui Qu,[7] Stephanie A. Bien,[7] Niha Zubair,[7] Robert J. Macinnis,[14] Daniel D. Buchanan,[17,18,19] John L. Hopper,[18,20] Yin Cao,[11,12] Reiko Nishihara,[11] Gad Rennert,[21] Martha L. Slattery,[22] Duncan C. Thomas,[23] Michael O. Woods,[24] Ross L. Prentice,[7] Stephen B. Gruber,[25] Yingye Zheng,[7] Hermann Brenner,[4,5,6] Richard B. Hayes,[26] Emily White,[7] Ulrike Peters,[7] and Li Hsu,[7] on behalf of the Colorectal Transdisciplinary Study and Genetics and Epidemiology of Colorectal Cancer Consortium

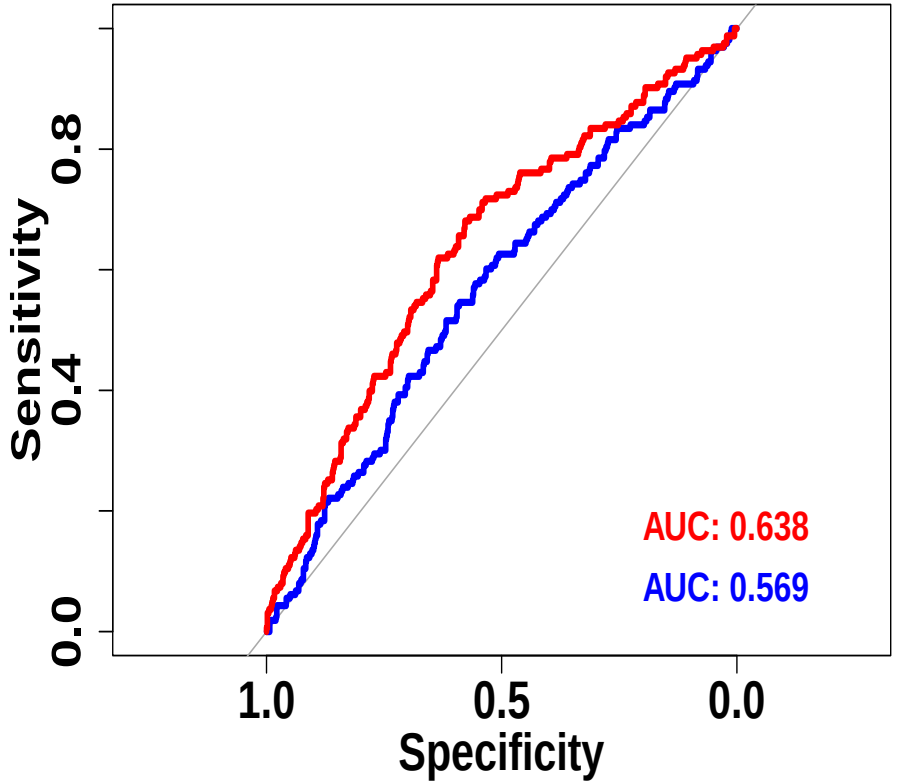
Family History
Genetic (G-score)= 63 SNPs at 49 known CRC loci
Environment (E-score)= BMI
smoking
diet (red meat, fruits/veggies
physical activity
NSAID use

Combined Model AUC: 0.63 (0.62-0.64)
vs 0.53 with family history alone

G-Score Predicts Risk for Early Onset CRC

Cases CRC age<50 N= 163
Controls (Cancer-free) N=600





Polygenic Risk Models
63 SNPs **BLUE**
119 SNPs **RED**

Unpublished

Missing Heredity of Complex Diseases

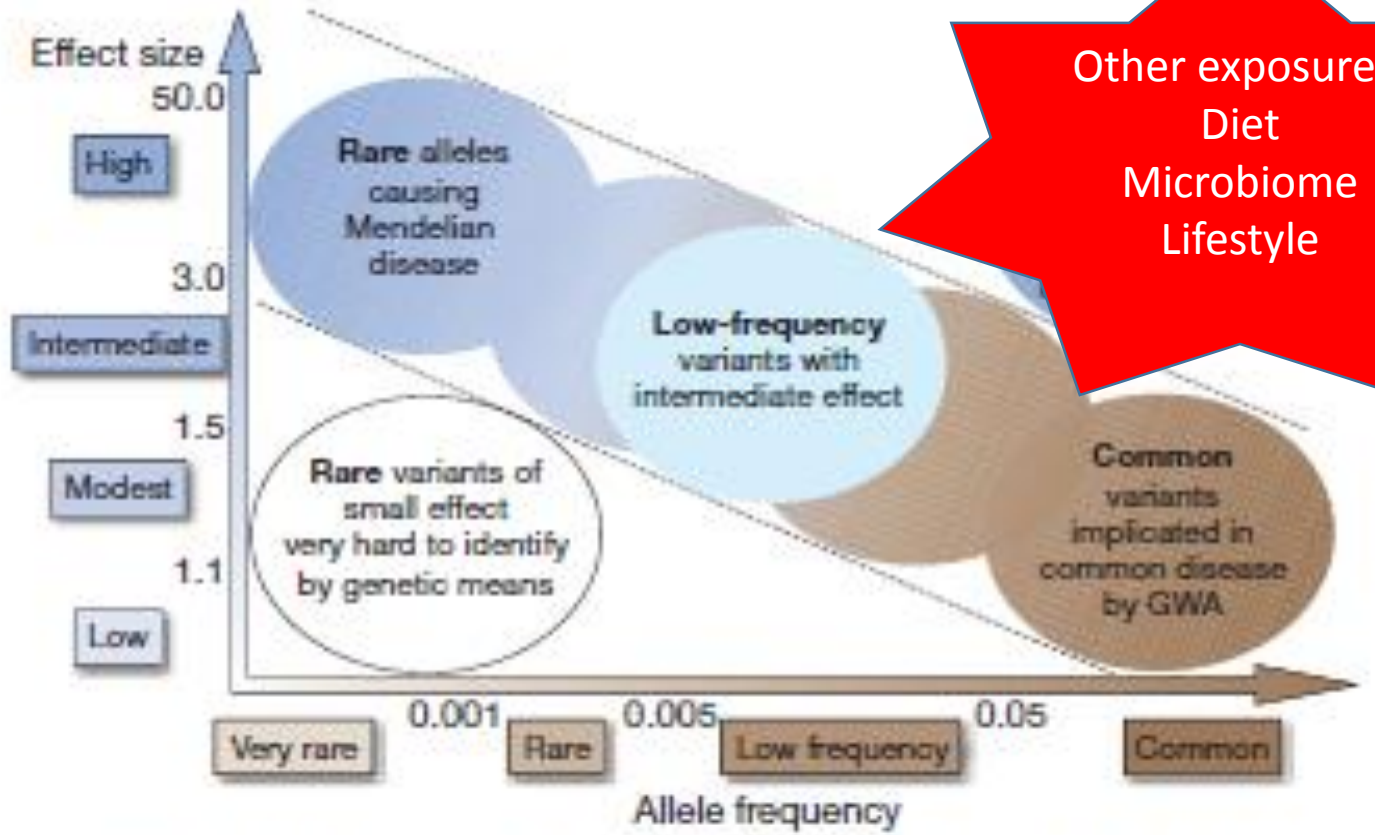


Figure 1 | Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect (odds ratio). Most emphasis and interest lies in identifying associations with characteristics shown within diagonal dotted lines. Adapted from ref. 42.

Other exposures:
Diet
Microbiome
Lifestyle

Manolio et al, Nature 2009

Conclusions: Germline Mutations in Young CRC

- Hereditary Cancer Syndromes diagnosed in 1 in 5 individuals with early onset CRC
- Multigene panel germline testing for all CRC age<50 increases diagnostic yield
- Majority of early onset CRCs are not associated with highly-penetrant hereditary cancer syndromes
  - Utility of genotype and lifestyle data (TBD)
    - CRC risk
    - Pathogenesis

Thank you!

DANA-FARBER
CANCER INSTITUTE

Pathogenic Germline Cancer Susceptibility Gene Variants in Individuals with Colorectal Cancer

Matt Yurgelun, MD

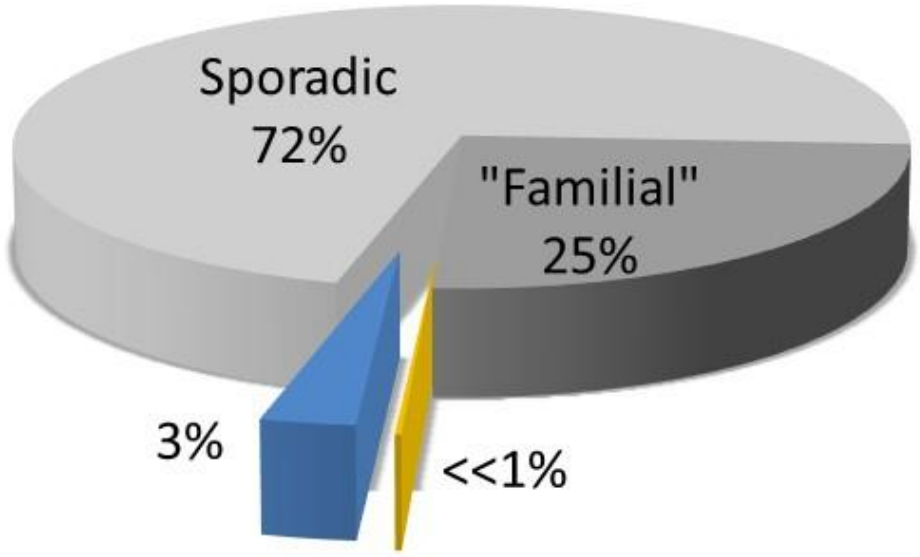
Medical Oncologist, Gastrointestinal Cancer Center
Director, Lynch Syndrome Center
Dana-Farber Cancer Institute

Disclosures

- Work described funded by Myriad Genetic Laboratories, Inc. through a research grant (ended in 2016)

- No other financial disclosures/conflicts of interest

How we used to view hereditary colorectal cancer (circa 2013)



Lynch syndrome
Other rare syndromes

Background

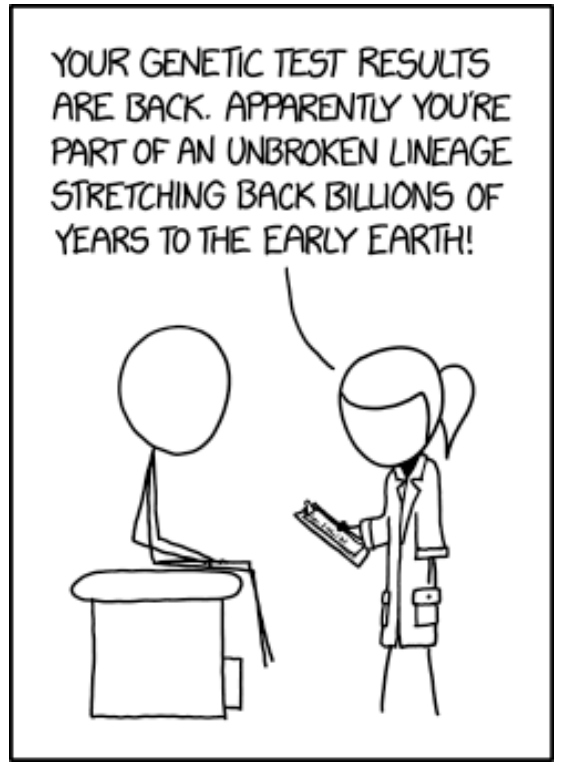
- Hereditary factors play a key role in the etiology and risk of colorectal cancer

- Genetic testing for inherited cancer syndromes has the potential help prevent cancer and cancer-related death
  - Germline risk identified → Specialized risk-reducing interventions
    → At-risk family members tested ("cascade testing")
    → Therapeutic implications for select patients with advanced cancer

- Advances in next-generation sequencing technologies now allow for rapid assessment of numerous genes in parallel
  - Multi-gene panels widely commercially available for hereditary risk assessment
  - Costs rapidly decreasing

Multi-gene germline testing

- Scientific data about the use of such panels is only beginning to emerge
- Ability to perform comprehensive germline evaluation has outpaced our ability to use and interpret such technology
- The more you look, the more you find…



xkcd.com

Multi-gene germline testing

VOLUME 31 · NUMBER 10 · APRIL 1 2013

JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

Multiplex Genetic Testing for Cancer Susceptibility: Out on the High Wire Without a Net?

Susan M. Domchek and Angela Bradbury, *University of Pennsylvania, Philadelphia, PA*
Judy E. Garber, *Dana-Farber Cancer Institute, Boston, MA*
Kenneth Offit and Mark E. Robson, *Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Published Ahead of Print on August 22, 2016 as 10.1200/JCO.2016.68.6725
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2016.68.6725

JOURNAL OF CLINICAL ONCOLOGY | CORRESPONDENCE

Multigene Panels to Evaluate Hereditary Cancer Risk: Reckless or Relevant?

common (approximately 1 in 300) but remains underdiagnosed; and family history reporting is often biased by the proband history and is unreliable in families in which early deaths have occurred, that are small or in which adoption or nonpaternity has occurred, and in which knowledge of family history is poor. One might then argue that the provider who narrowly tests only those genes related to BC in the

Multi-gene germline testing – Colorectal cancer

- Which colorectal cancer patients need multi-gene germline testing?
  - High-risk colorectal cancer cases?
    - Suspected Lynch syndrome
    - Young-onset
  - All individuals with colorectal cancer?
- Aims:
  - To determine whether multi-gene germline testing offers meaningful advantages over syndrome-specific genetic evaluation strategies

Multi-gene germline testing – Suspected Lynch syndrome

- 1260 consecutive individuals referred to a commercial laboratory (Myriad Genetics) for clinical Lynch syndrome testing
  - All with personal history of Lynch-associated cancer and/or polyps
- After completion of clinical Lynch syndrome testing, samples anonymized for research-based testing with 25-gene multiplex panel
- Clinical data obtained from test request forms (completed by clinician ordering testing)
  - Ancestry
  - Personal history of cancer/polyps, including age at diagnosis
  - Family history of cancer

Yurgelun MB, et al. *Gastroenterology* 2015;149:604-13.

25-gene Multiplex Hereditary Cancer Panel

High-penetrance genes

- Lynch syndrome
  - *MLH1, MSH2, MSH6, PMS2, EPCAM*
- ***BRCA1/2***
- Other
  - *APC*
  - *BMPR1A*
  - ***CDH1***
  - ***CDKN2A***
  - ***CDK4***
  - *MUTYH* (biallelic)
  - *PTEN*
  - *SMAD4*
  - *STK11*
  - *TP53*

Low-/moderate-penetrance genes

- ***ATM***
- ***BARD1***
- ***BRIP1***
- ***CHEK2***
- ***NBN***
- ***PALB2***
- ***RAD51C***
- ***RAD51D***

PINK = genes not known to be linked to colorectal cancer risk

Yurgelun MB, et al. *Gastroenterology* 2015;149:604-13.

Multi-gene germline testing – Preliminary Data

- Population: Laboratory-based cohort of 1260 individuals referred for Lynch syndrome genetic testing due to personal history of cancer and/or polyps
- Methods: Multi-gene germline testing with a 25-gene panel. Clinical data obtained from test request form filled out by ordering clinician
- Results: 14.4% mutation prevalence; 39% of all mutations were in non-Lynch genes
  - >1% with *BRCA1/2* mutations; only 33% met NCCN criteria for *BRCA1/2* testing
  - 75% of all mutations found were in "high-penetrance" cancer susceptibility genes
  - 38% of participants had ≥1 VUS
- Conclusions: Clinical criteria for Lynch syndrome testing will identify substantial number of individuals with other forms of hereditary cancer risk
  - Individuals with atypical phenotypes
  - Limiting hereditary risk assessment (MSI/MMR IHC tumor testing and/or germline testing) will fail to identify substantial number of individuals with high-penetrance forms of inherited cancer risk
- Next steps: What about any/all individuals with colorectal cancer?

Yurgelun MB, et al. *Gastroenterology* 2015;149:604-13.

Multi-gene germline testing – All colorectal cancer patients

- Study Population: Clinic-based cohort of 1058 individuals with colorectal cancer (CRC) seen at DFCI and consecutively enrolled in institutional sample registry from 2008-14.
  - No pre-selection for age, personal/family cancer history, MSI/MMR IHC tumor testing

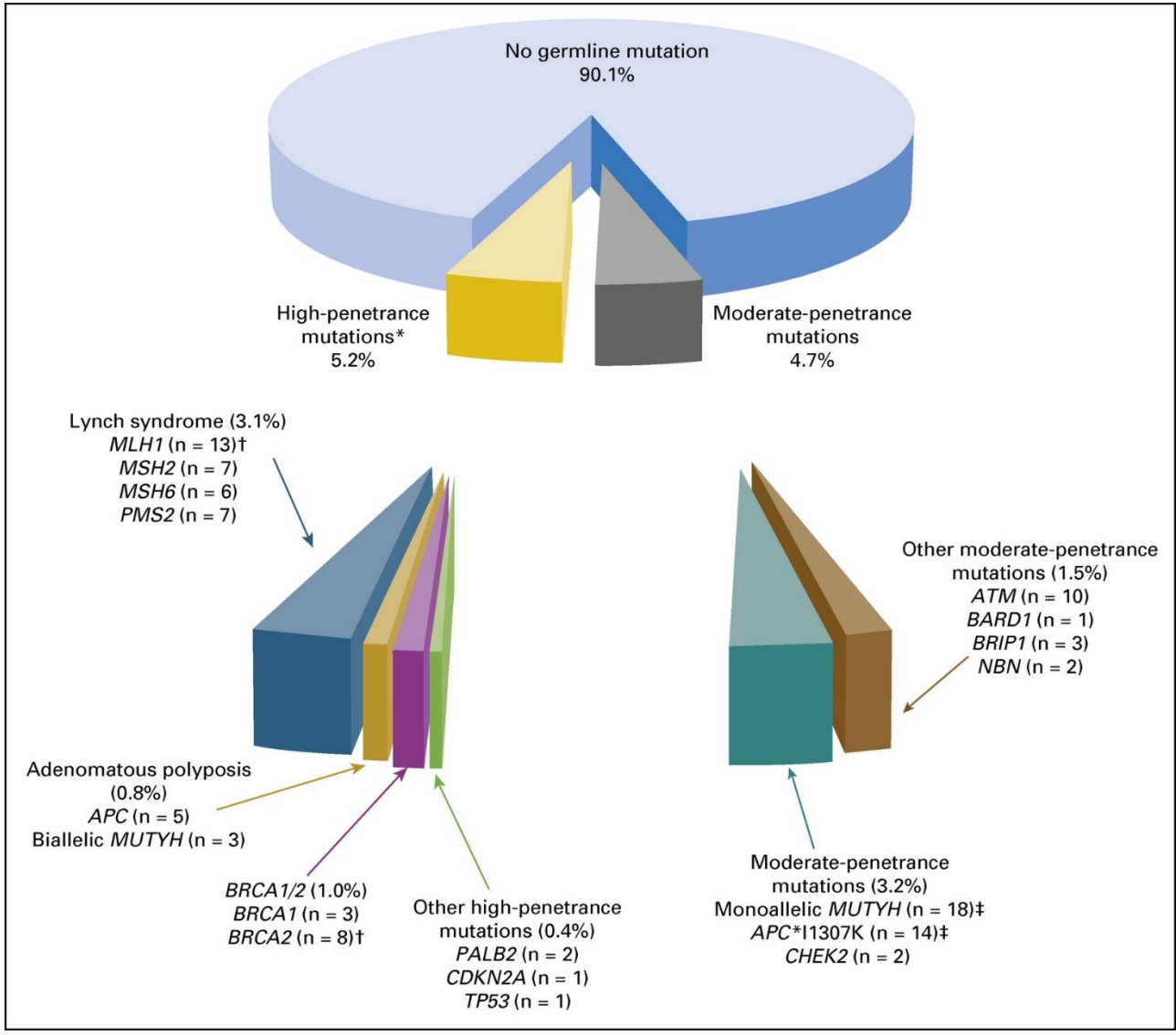
- Methods: Multi-gene germline testing with a 25-gene panel.
  - Pathology and clinical histories (including family history of cancer) verified by medical record review.

Characteristic	N (%)	Characteristic	N (%)
Male/Female	587 (55%) / 471 (45%)	Right-sided CRC	353 (33%)
		Left-sided CRC	362 (34%)
Non-Hispanic white	939 (89%)	Rectal/rectosigmoid CRC	341 (32%)
Non-Hispanic black	50 (5%)		
Hispanic/Latino	27 (3%)	Personal history of >1 CRC	29 (3%)
Asian	22 (2%)	Personal history other non-CRC cancer†	160 (15%)
Mean age at 1st CRC, years	55.7 (SD 12.6) range 21-92	Family history CRC (any)	337 (32%)
Age <50 years	337 (32%)	Family history CRC (1st degree relative)	138 (13%)
		No known family history of cancer†	185 (17%)
Stage 0/I	129 (12%)		
Stage II	202 (19%)		
Stage III	404 (38%)		
Stage IV	321 (30%)		

Yurgelun MB, et al. *J Clin Oncol* 2017;35:1086-95.

Multi-gene germline testing – All colorectal cancer patients

- 105/1058 (9.9%; 95% CI 8.2-11.9%) with ≥1 pathogenic/likely pathogenic germline variant
  - 3.1% with Lynch syndrome
    - 97% with MSI-H and/or MMR-D tumors
    - 97% met clinical criteria for Lynch syndrome testing
  - 7.0% with pathogenic/likely pathogenic germline variants in non-Lynch genes
- 31% of cohort carried ≥1 germline variant of uncertain significance (VUS)



Yurgelun MB, et al. *J Clin Oncol* 2017;35:1086-95.

Multi-gene germline testing – All colorectal cancer patients

- Germline *BRCA1/2* variants
  - Most common high-penetrance non-Lynch finding
    - 1.0% of CRC cohort (1:96)
    - Higher than prevalence in general population (~1:400)

- Only 27% (3/11) *BRCA1/2* probands had clinical histories that fulfilled NCCN criteria for *BRCA1/2* testing
  - 18% (2/11) had personal history of a *BRCA*-associated malignancy (breast cancer and melanoma)

- Nearly half (45%) *BRCA1/2* probands with CRC were diagnosed before age 50 years (range 31-69 years)

Yurgelun MB, et al. *J Clin Oncol* 2017;35:1086-95.

Multi-gene germline testing – All colorectal cancer patients

Factors associated with presence of a non-Lynch mutation (versus non-carriers)

Characteristic	Odds ratio (95% CI)
Age at 1st CRC diagnosis (per 10 yrs)	0.93 (0.76, 1.15)
>1 CRC diagnosis (ref: 1 CRC diagnosis)	**3.70 (1.31, 10.49)**
Personal history of other cancer†	1.76 (0.95, 3.27)
Any 1st degree relatives with CRC	1.22 (0.59, 2.51)
Any 1st degree relatives with breast ca	1.84 (0.99, 3.40)
Any 1st degree relatives with ovarian ca	3.06 (0.97, 9.64)
KRAS mutation status (ref: *KRAS* wild type)	***KRAS* G12C mutation: 4.58 (1.76, 11.92)** Other *KRAS* mutation: 0.79 (0.42, 1.48) Missing *KRAS* status: 0.75 (0.41, 1.39

Yurgelun MB, et al. *J Clin Oncol* 2017;35:1086-95.

Multi-gene germline testing – All colorectal cancer patients

- 9.9% germline mutation prevalence in unselected CRC patients
- 3.1% with Lynch syndrome (97% with MSI-H/MMR-D)
- 7.0% with non-Lynch mutations
  - 0.8% *APC* or biallelic *MUTYH* mutations
  - 1.0% *BRCA1/2* mutations
  - 0.4% with other high-penetrance mutations (*PALB2*, *CDKN2A*, *TP53*)
  - 3.2% low-/moderate-penetrance gene mutations linked to CRC risk
    - monoallelic *MUTYH*, *APC**I1307K, and *CHEK2*

- **65% of high-penetrance (non-Lynch) mutation carriers lacked clinical features of their syndrome**
- Neither age at diagnosis, family history of CRC, nor personal history of other cancer were significant predictors of carrying non-Lynch mutation

Yurgelun MB, et al. *J Clin Oncol* 2017;35:1086-95.

Multi-gene germline testing – early-onset colorectal cancer patients

- 336 individuals (32% of cohort) with diagnosed with CRC prior to age 50
- 47 (14.0%) with ≥1 pathogenic germline variant
  - 21 (6.3% of early-onset) Lynch syndrome
  - 5 (1.5%) polyposis (*APC* or biallelic *MUTYH*)
  - 5 (1.5%) *BRCA1/2*
  - 5 (1.5%) *ATM*
- 290/336 (86%) with normal germline testing
  - Ongoing efforts to examine BMI, tobacco, and other potential risk factors

Characteristic	N (%)
Male/Female	181 (54%) / 155 (46%)
Stage 0/I	31 (9%)
Stage II	64(19%)
Stage III	123 (37%)
Stage IV	117 (35%)
Right-sided CRC	100 (30%)
Left-sided CRC	119 (35%)
Rectal/rectosigmoid CRC	117 (35%)
Family history CRC (any 1st degree relative)	40 (12%)
Family history CRC (multiple 1st degree relatives)	5 (1.5%)

Yurgelun MB, et al. *J Clin Oncol* 2017;35:1086-95.

Conclusions/Summary

- Although universal tumor testing identifies almost all Lynch probands, multigene germline testing identifies an additional 7% of CRC patients with inherited cancer risk
  - Most non-Lynch gene mutations have specific management recommended by NCCN guidelines

- Spectrum of genetic factors in CRC more diverse than traditionally appreciated
  - Classic high-risk features (age, family history) do not effectively identify patients with non-Lynch mutations

- Among early onset (age <50), 14% had pathogenic germline variants, almost half of which were non-classic findings (non-Lynch, non-polyposis)

- Further studies needed to investigate other risk factors in early-onset CRC cases with negative germline testing

What is Driving the Increases in EAO-CRC, 80+% of Which is Not Related to the Named Hereditary CRC Syndromes ?

3:50 pm–4:00 pm **Obesity, Sedentary Behaviors, and Early-Onset CRC**
Yin Cao, MPH, ScD, MPH, Washington University School of Medicine

4:00 pm–4:10 pm **New Suspects: Diet, Microbiome, Immunology and Cancer Risk**
Semir Beyaz, PhD, Cold Spring Harbor Laboratories

4:10 pm–4:20 pm **New Research Information: Current Efforts to Investigate the Causes of Increases in MSS CRC Among Young Adults**

- **The United States**
  - Current NCI Funded Investigations into the Causes of Early Age Onset Colorectal Cancer:
    - ◊ *Colorectal Cancer Risks in People < 50 Years of Age NIH (RO3): Epidemiology, Richard Hayes, DDS, PhD, MPH, the Cancer Institute at NYU Langone*

4:20 pm–4:30 pm
- ◊ *Presentation Early Life Risk Factors and Risk of Colorectal Neoplasia, Kana Wu, MD, PhD, Harvard T.H. Chan School of Public Health, Dana-Farber, Harvard Cancer Center*

4:30 pm–4:40 pm **The European Union: Funded Investigations**
- ◊ *European Organization for Research and Treatment of Cancer (EORTC): Young Onset CRC: Causation, Treatment and Outcomes, Irit Ben-Aharon, MD, PhD, Rambam Health Care Campus, Haifa, Israel European Organisation for Research and Treatment of Cancer*

4:40 pm–4:50 pm
- ◊ *European study of Early-onset Colorectal Cancer (EUREOC): A Collaborative Study of the Biology of Young Onset CRC, Jose Perea, MD, PhD, Fundacion Jimenez Diaz University Hospital, Madrid, Spain*

4:50 pm–5:00 pm **In Development:**
- **CRAYON: ColoRectal Cancer in Adults at Young ONset: New York City Based Prospective Accrual Study of Young Onset Colorectal Cancer**

Steven H. Itzkowitz MD, Icahn School of Medicine at Mount Sinai

5:00 pm–5:10 pm **The Beyond CRC Project**
Kimmie Ng, MD, MPH, Dana-Farber Cancer Institute

5:10 pm–5:20 pm **The Search for Novel Drivers of Young Onset MSS CRC: An Overview of Current NIH, CDC and ACS Efforts**
Thomas K. Weber, MD, FACS, Northwell Health

5:20 pm–5:30 pm **Report Back from Denver EAO CRC Research Meeting**
Heather Hampel, the Ohio State University Comprehensive Cancer Center

Obesity, Sedentary Behaviors, and Early-Onset CRC

Yin Cao, MPH, ScD

Assistant Professor, Division of Public Health Sciences

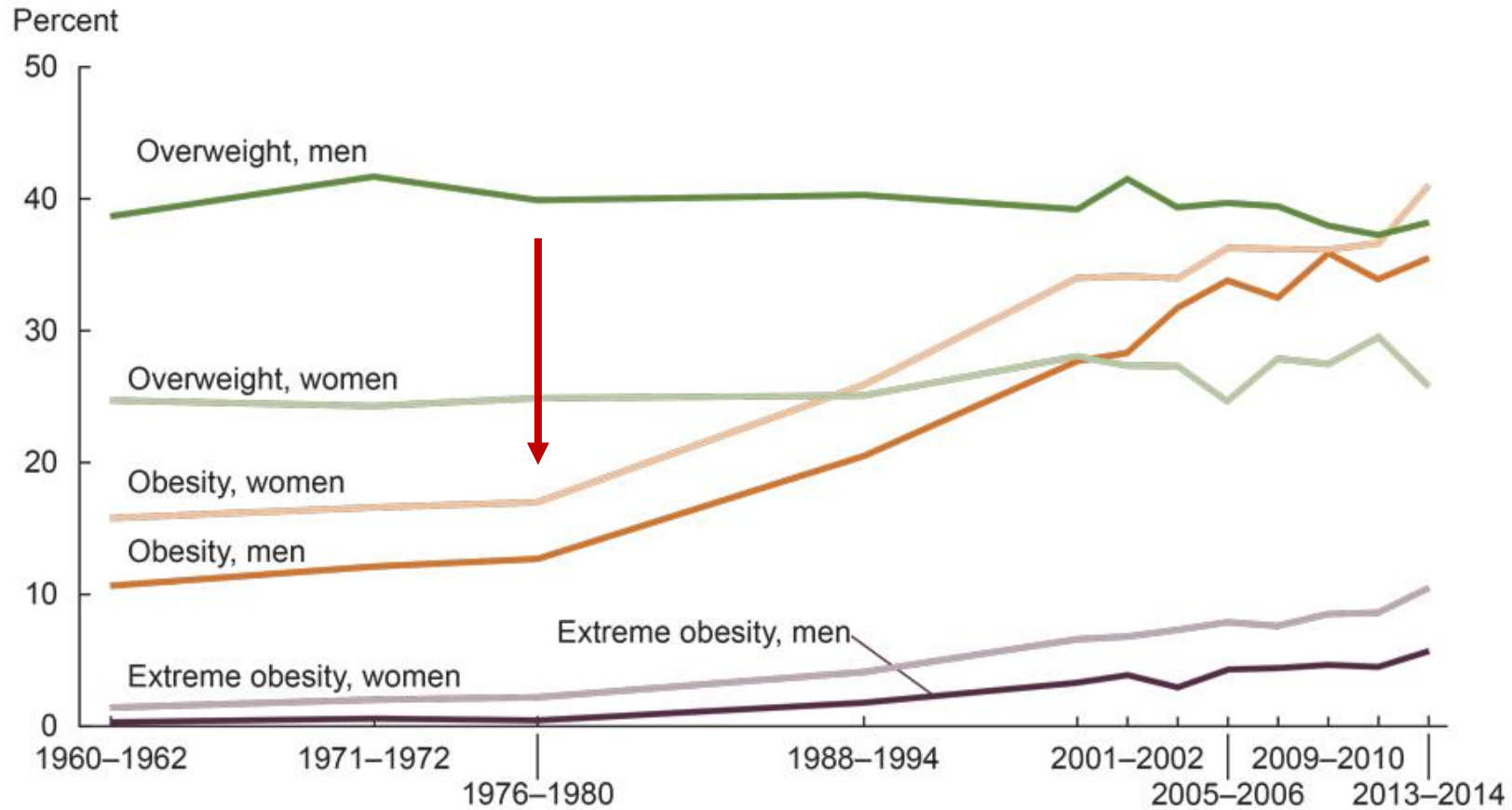
Department of Surgery

Siteman Cancer Center

Washington University in St. Louis

May 2nd, 2019

Trends in adult overweight, obesity, and extreme obesity among men and women aged 20–74: United States, 1960–1962 through 2013–2014



NOTES: Age-adjusted by the direct method to the year 2000 U.S. Census Bureau estimates using age groups 20–39, 40–59, and 60–74. Overweight is body mass index (BMI) of 25 kg/m^2 or greater but less than 30 kg/m^2; obesity is BMI greater than or equal to 30; and extreme obesity is BMI greater than or equal to 40. Pregnant females were excluded from the analysis.
SOURCES: NCHS, National Health Examination Survey and National Health and Nutrition Examination Surveys.

Obesity and risk of CRC

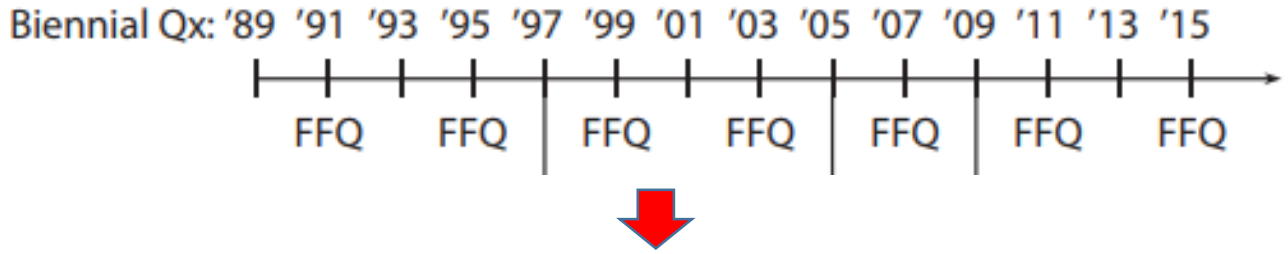
CUP, 2017 (WCRF-AICR)

Type of cancer	RR with BMI per 5 kg/m^2 (95% CI)
Colon (men)	RR 1.10 (1.07–1.13)[1]
Colon (women)	RR 1.04 (1.02–1.06)[1]
Rectal (men)	RR 1.02 (1.01–1.04)[1]
Rectal (women)	RR 1.01 (0.99–1.03)[1]

Murphy *et al*, Nat Rev Gastroenterol Hepatol, 2018

Nurses' Health Study II

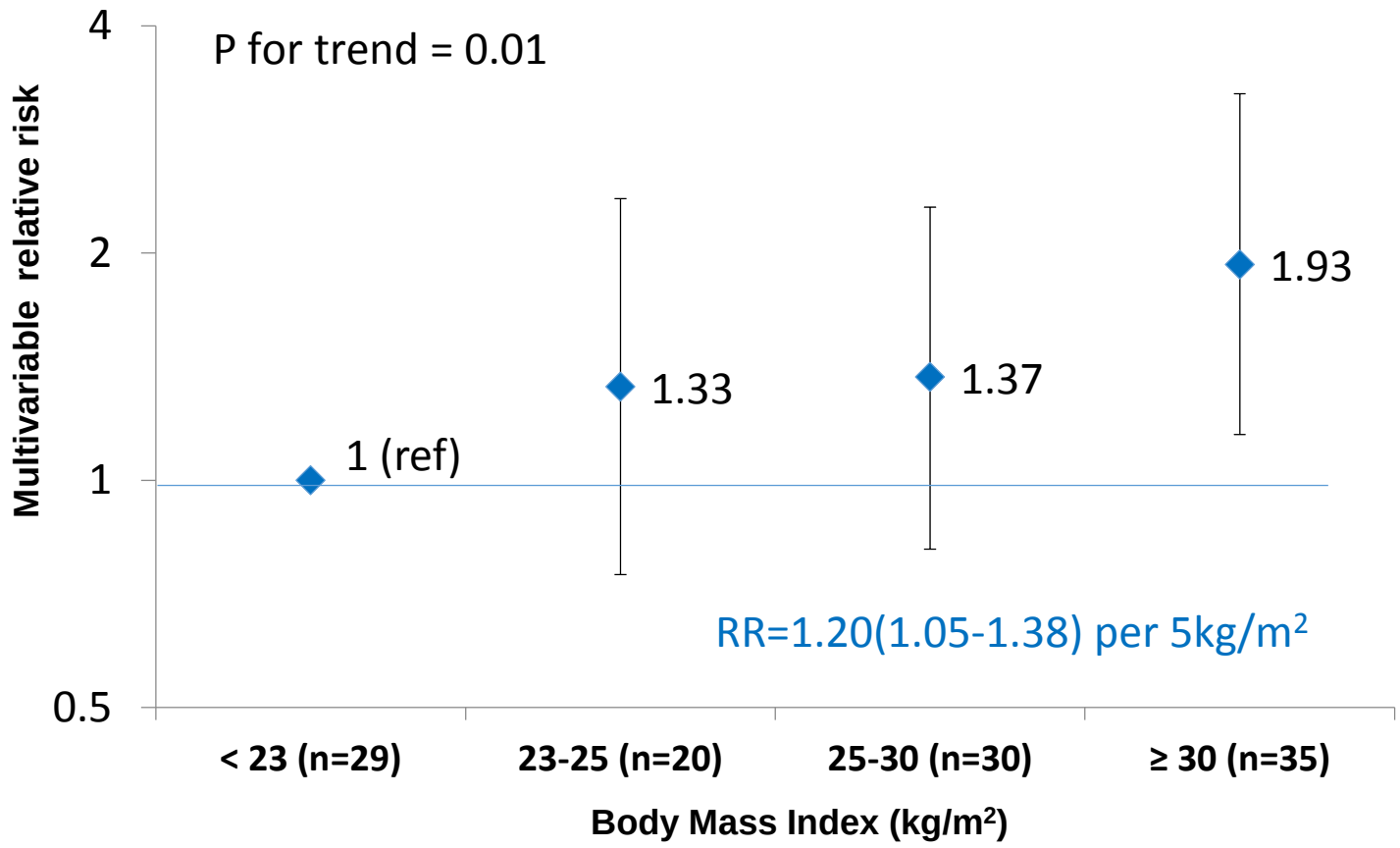
- **Ongoing prospective** follow-up cohort study
- Enrolled in 1989, **116,430 female** nurses **aged from 25 to 42**
- Lifestyle factors, medications, medical diagnoses were updated every 2 years; validated food frequency questionnaire (FFQ) every 4 years



Follow-up rates > 90% in each 2-year cycle for the cohort

Current BMI and risk of early-onset CRC

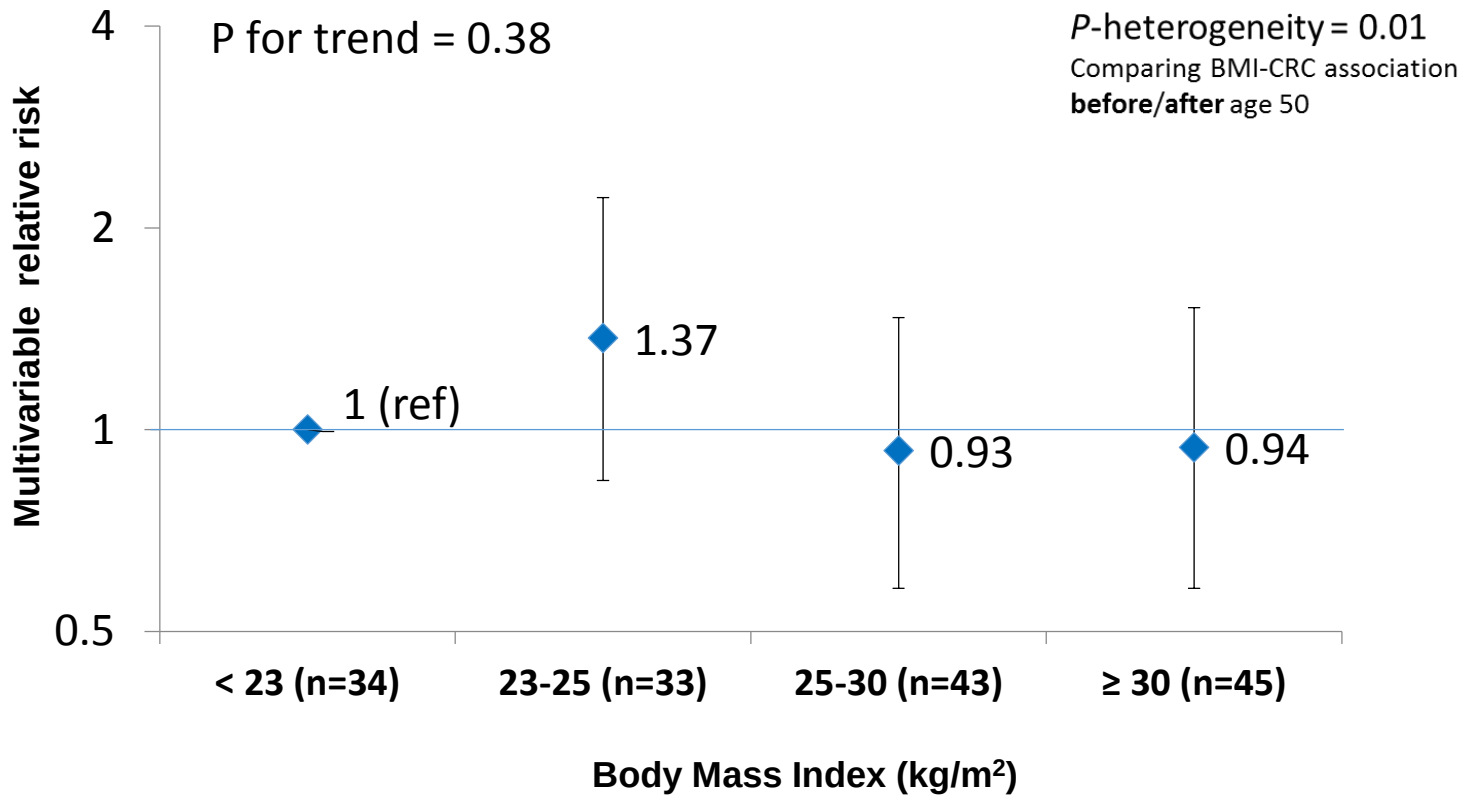
NHS II 1989-2011



Liu *et al*, JAMA Oncology, 2018

Current BMI and risk of CRC diagnosed after age 50

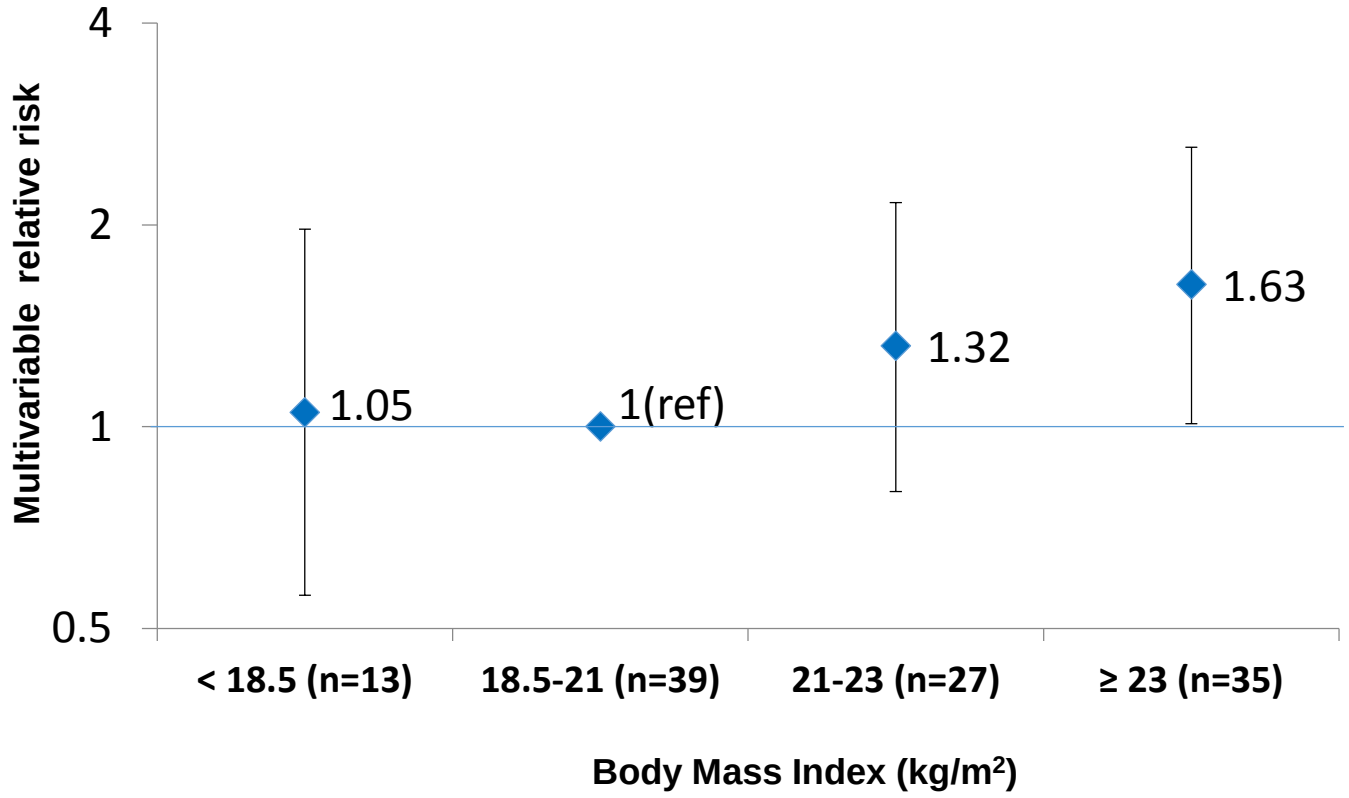
NHS II 1989-2011



Liu *et al*, JAMA Oncology, 2018

BMI at age 18 and risk of early-onset CRC

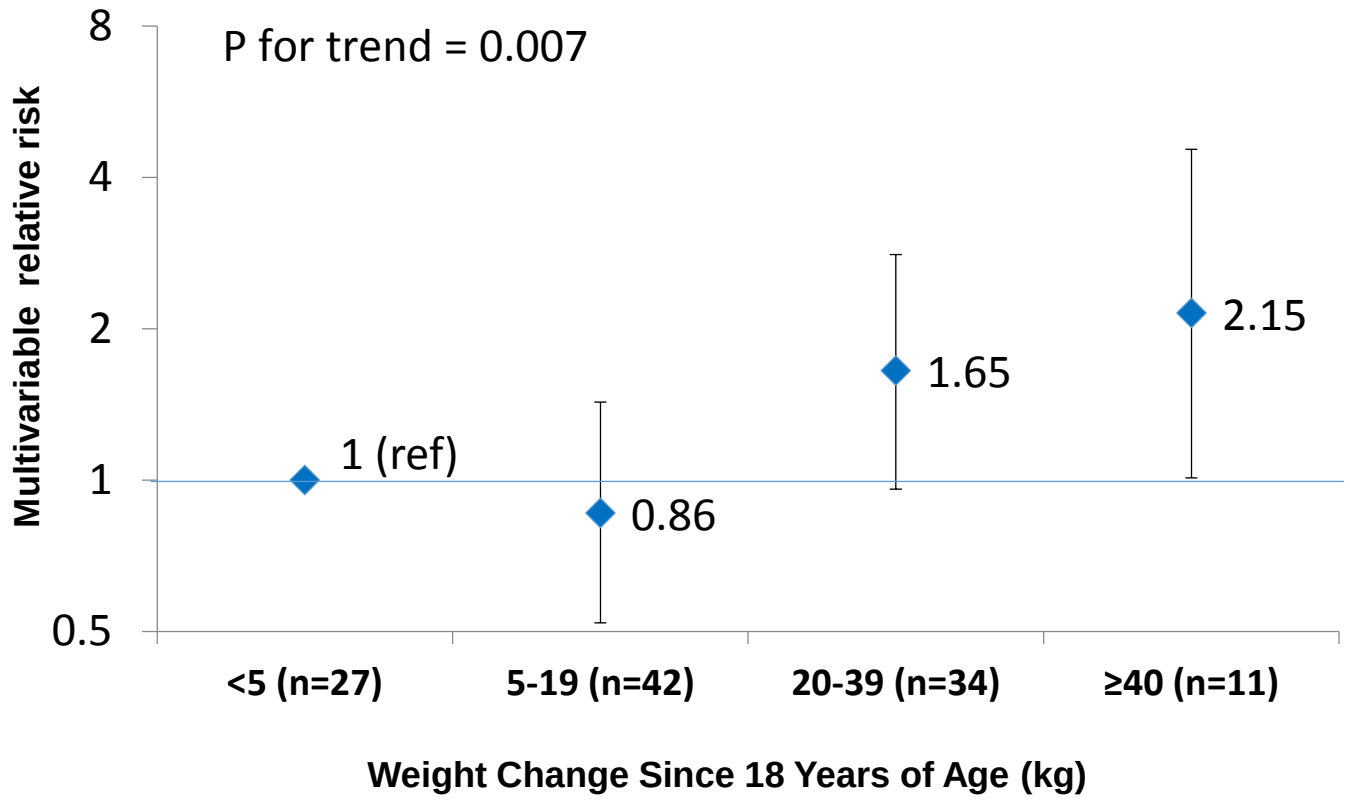
NHS II 1989-2011



Liu *et al*, JAMA Oncology, 2018

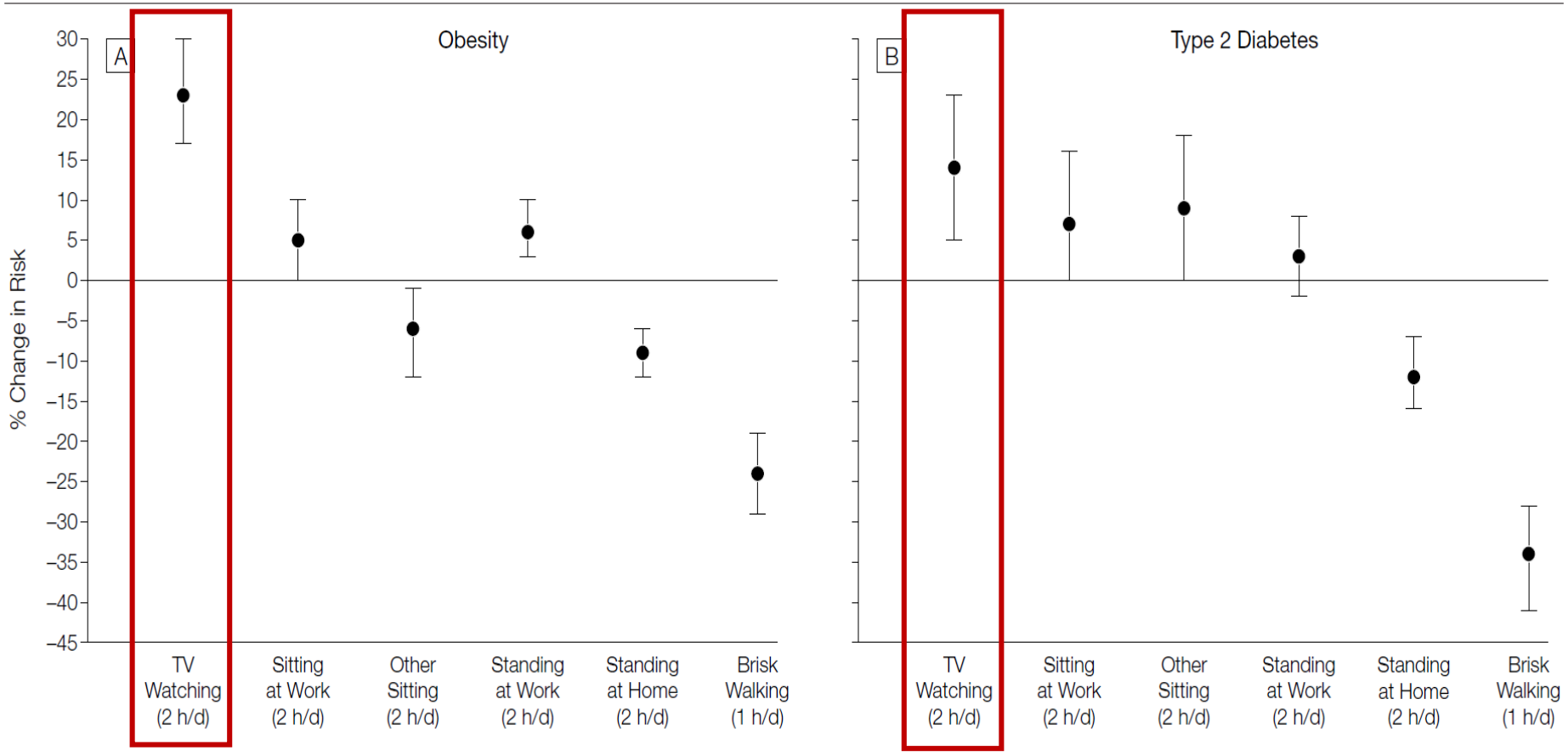
Weight change since 18 and risk of early-onset CRC

NHS II 1989-2011



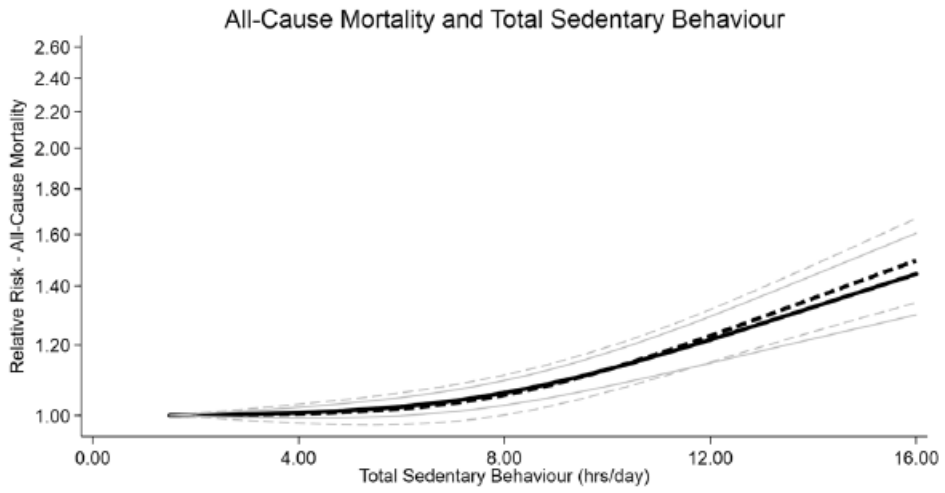
Liu *et al*, JAMA Oncology, 2018

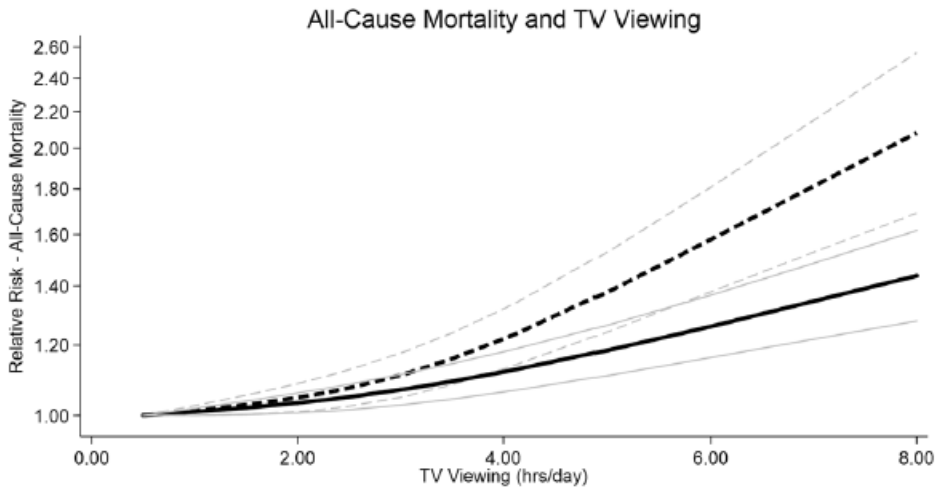
Prolonged sedentary TV watching time increases risk of obesity and type 2 diabetes

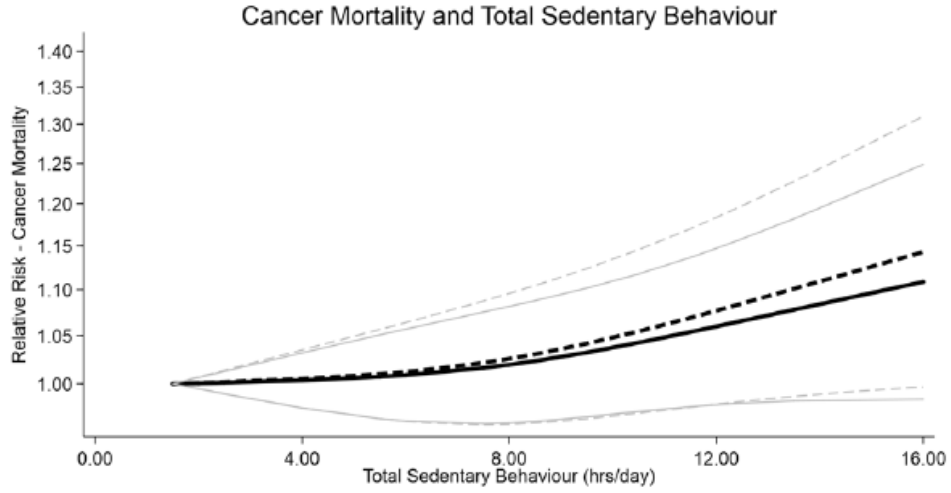


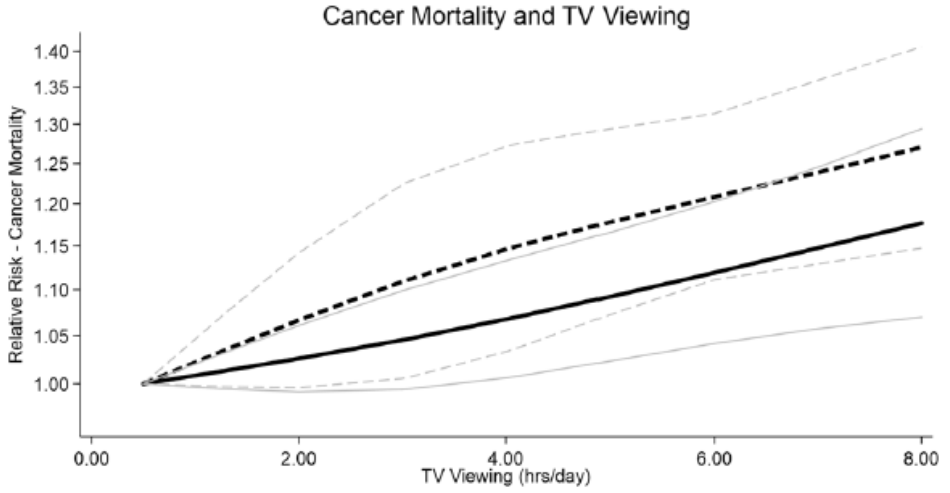
Hu *et al*, JAMA, 2003

Sedentary behaviors and all-cause and cancer-specific mortality



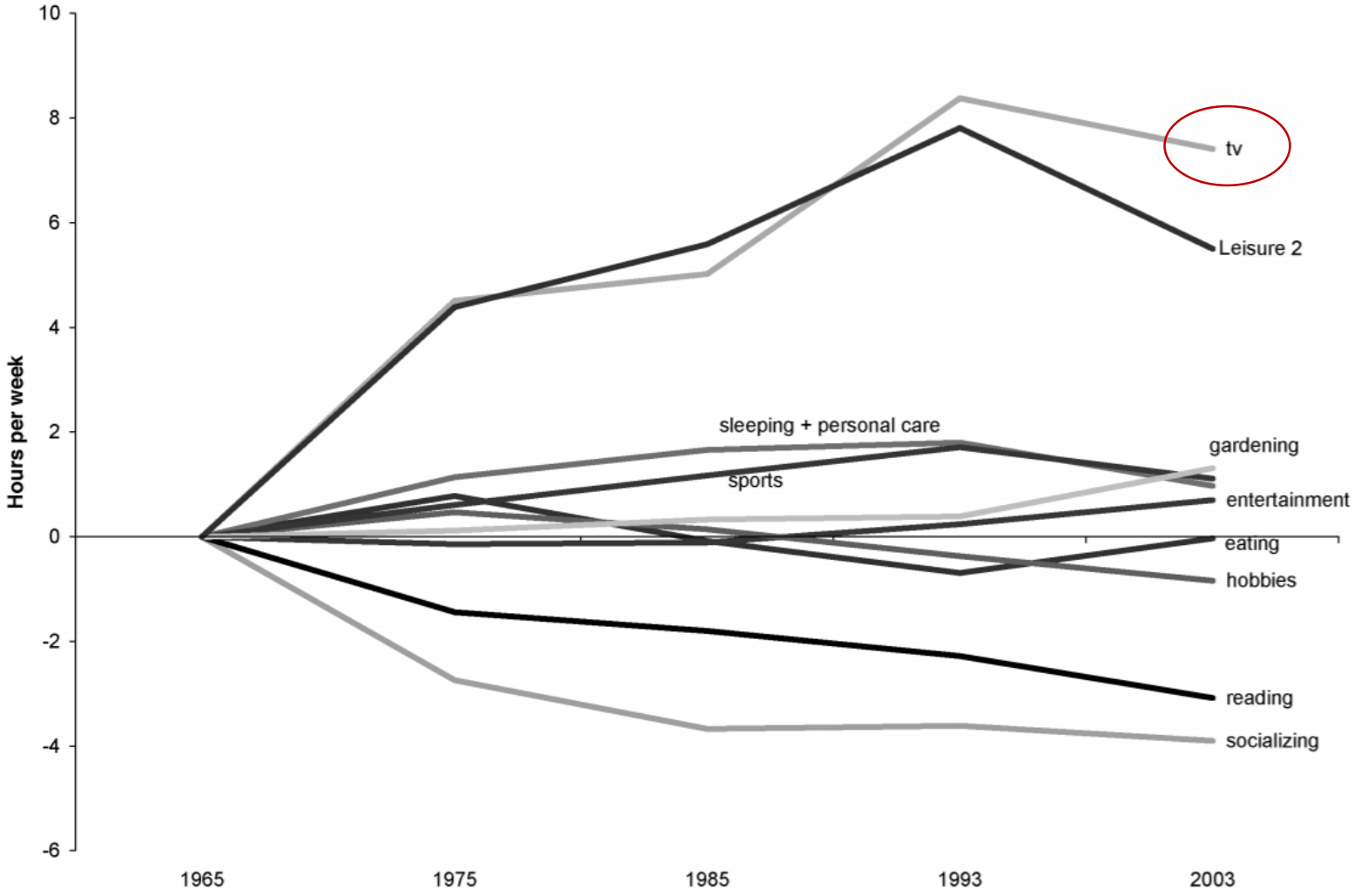






Patterson *et al*, Eur J Epidemiol., 2018

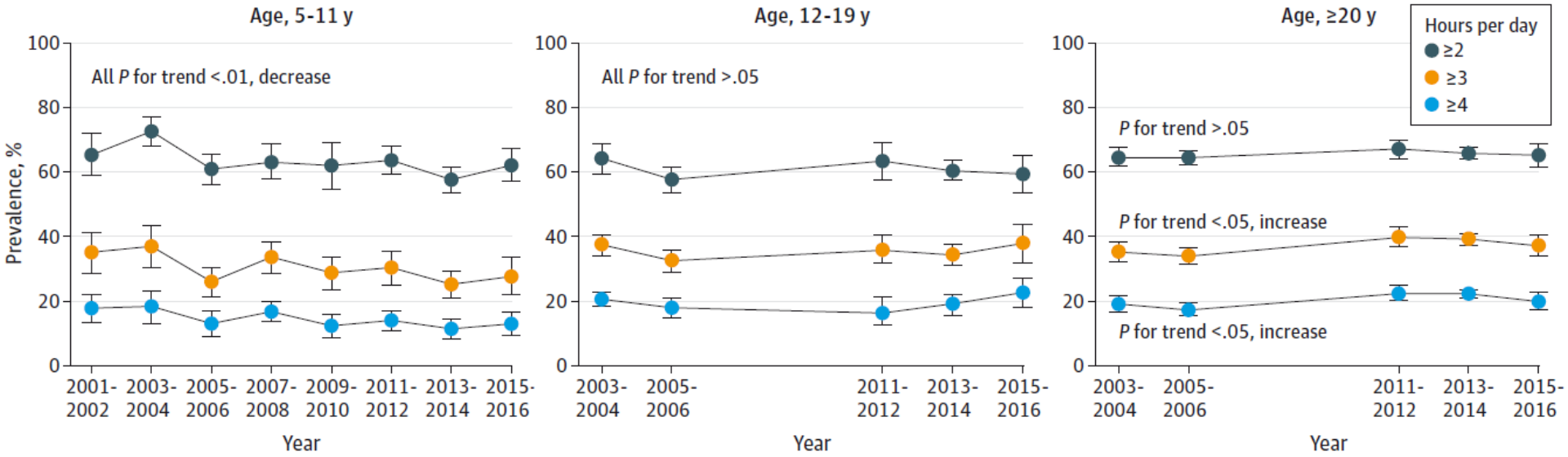
Dramatic increase in TV watching since 1965



Aguiar *et al,* The Quarterly Journal of Economics, 2007

Trends in sitting watching TV/video since 2001

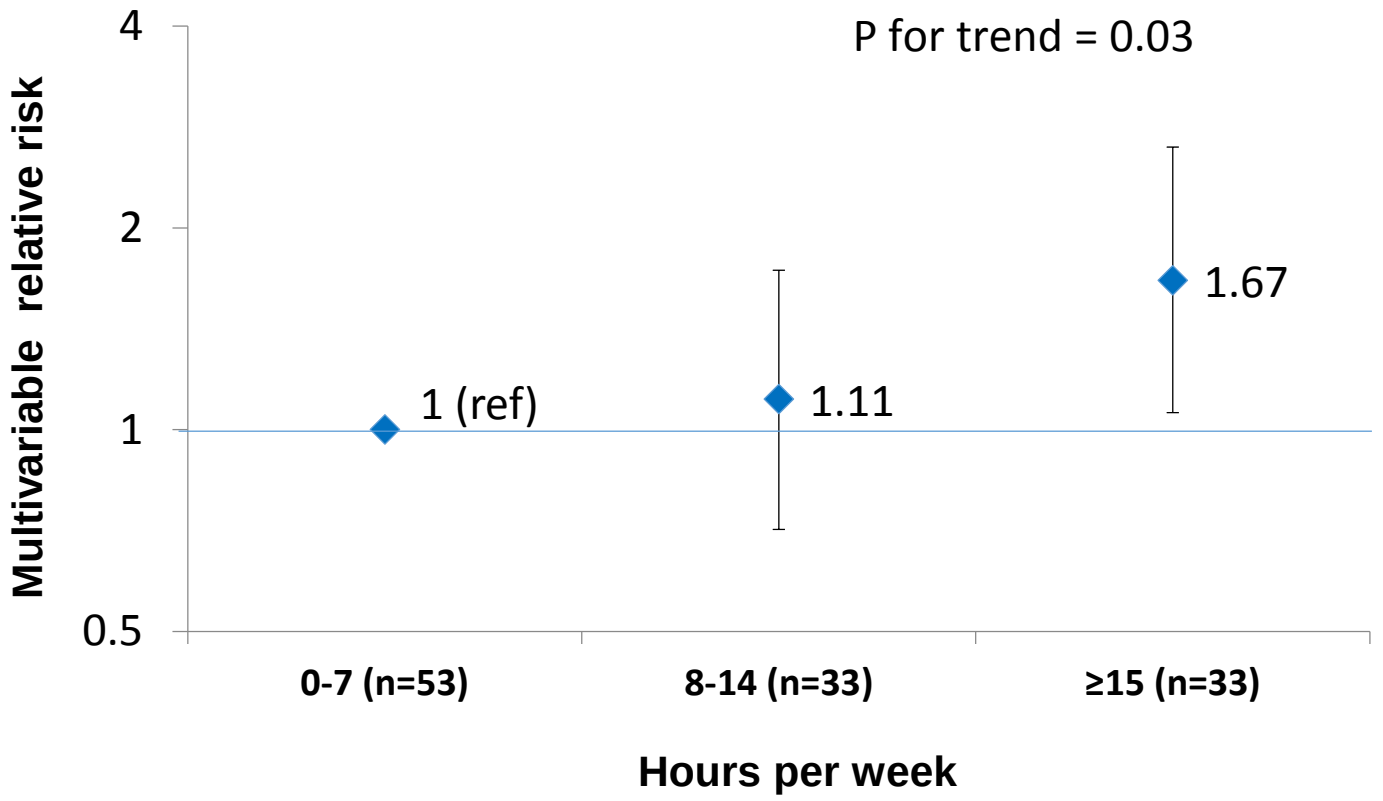
NHANES 2001-2016



Yang *et al*, JAMA, 2019

Sitting watching TV/video and risk of early-onset CRC

NHSII 1991-2011

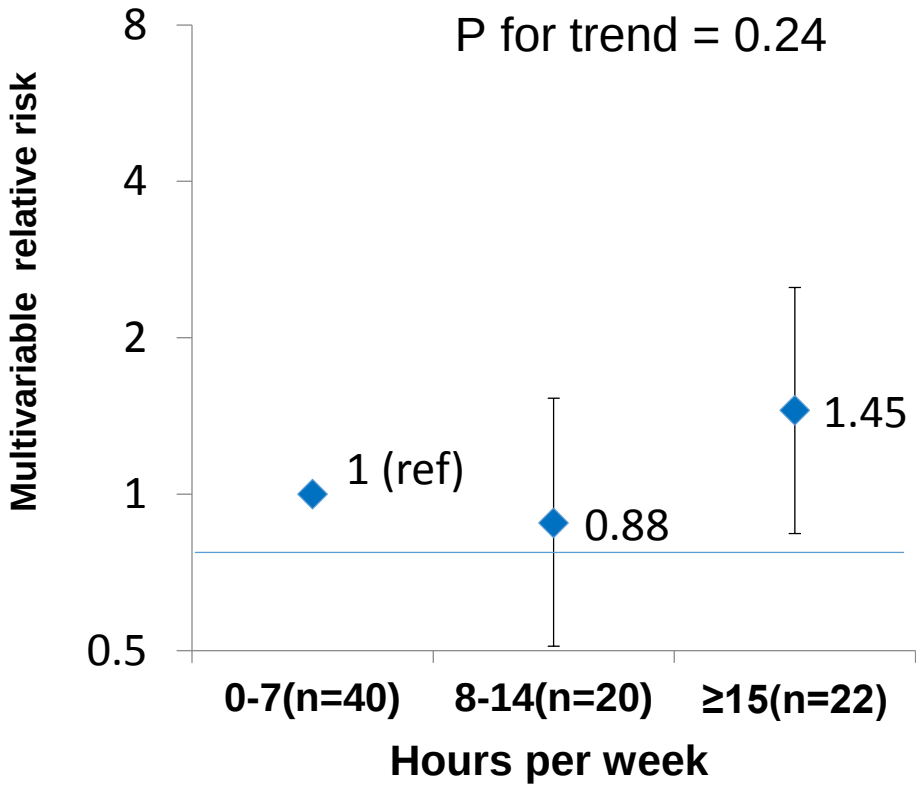


Nguyen *et al*, JNCI Cancer Spectrum, 2018

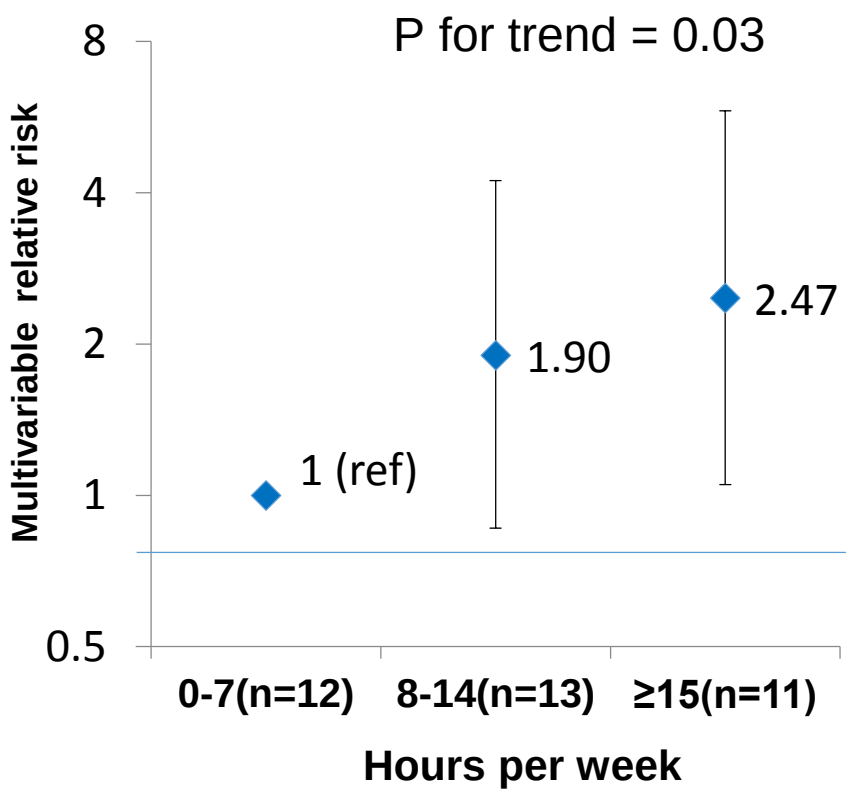
Sitting watching TV/video and risk of early-onset CRC by anatomic site

NHS II 1991-2011

Colon Cancer



Rectal Cancer



Nguyen *et al*, JNCI Cancer Spectrum, 2018

Potential mechanisms linking prolonged sitting and early-onset CRC

- Lower energy use, higher caloric intake, and less healthy diet
- Unbroken sitting in the absence of social or occupational cues
  - Extends exposure to fecal carcinogens, such as secondary bile acids
  - Impairs glucose homeostasis and decreases vitamin D levels
  - Linked to gut dysbiosis and enrichment for cancer associated microbes
  - Occurs in lieu of standing and other light activities that improve blood flow, muscle contraction, glucose regulation, and endothelial function

Summary

- Current obesity, obesity in early adulthood and weight change since early adulthood are associated with increased risk of early-onset CRC
- Prolonged time spent sitting watching TV, is associated with increased risk of early-onset CRC
- Obesity and sedentary behaviors may contribute to the rising burden of early-onset CRC
- Validations are needed

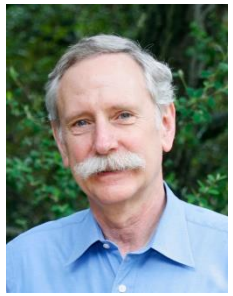
Acknowledgement

Edward Giovannucci, ScD

Professor
epts of Nutrition and Epidemiology
Harvard Chan

Andrew T. Chan, MD

Chief, Clinical and Translational Epidemiology Unit
MGH



Walter Willett, DrPH
Professor
Dept of Nutrition
Harvard Chan

Graham A. Colditz, MD
Chief, Professor
Division of Public Health Sciences,
Wash U

Charles Matthews
Senior investigator
NCI

Curtis Huttenhower, PhD
Professor
Dept of Biostatistics
Harvard Chan

Ulrike Peters, PhD
Research Professor
GECCO Consortium
Fred Hutch

Ann Zauber, PhD

Member
Attending Biostatistician
MSKCC

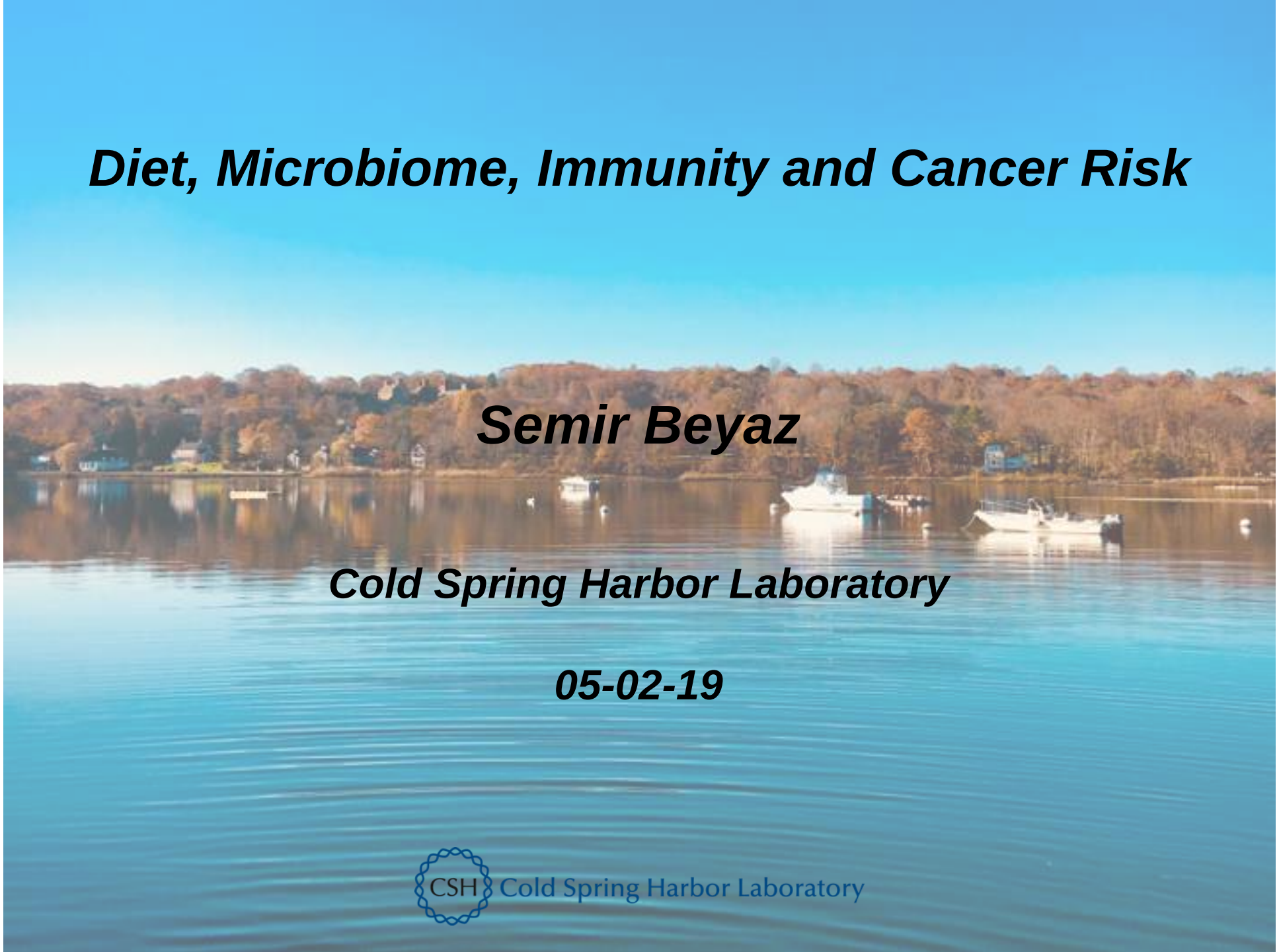
Nicholas O. Davidson
Chief
Professor
Division of Gastroenterology,
Wash U

Li Ding, PhD
Associate Professor
Division of Oncology
McDonnell Genome Institute, **Wash U**

Acknowledgement

- **Cao Lab @ Wash U**
  - Xiaobin Zheng
  - Chao Cao
  - Xiaoyu Zong
  - Cong Wang
  - Alex Kanemaru
  - Hanyu Chen
  - Catherine Shi
  - Xiao Li
- **Clinical & Translational Epi Unit @ MGH GI**
  - Stuart Liu (@southwestern)
  - Long Nguyen
- **Dana Farber**
  - Shuji Ogino
  - Kimmie Ng
- **Harvard Chan**
  - Kana Wu
- **Alberta Health Services**
  - Lin Yang
- **Participants of NHSII**

Diet, Microbiome, Immunity and Cancer Risk



Semir Beyaz

Cold Spring Harbor Laboratory

05-02-19

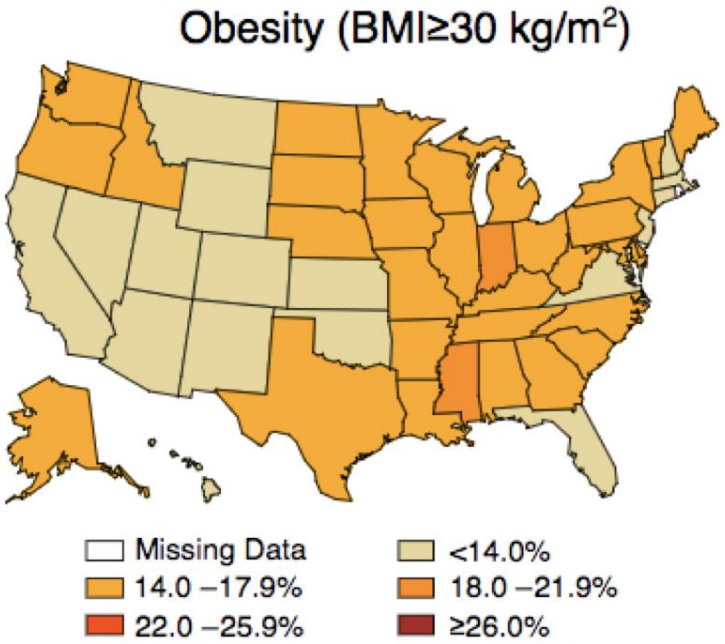
CSH Cold Spring Harbor Laboratory

Are you really what you eat?

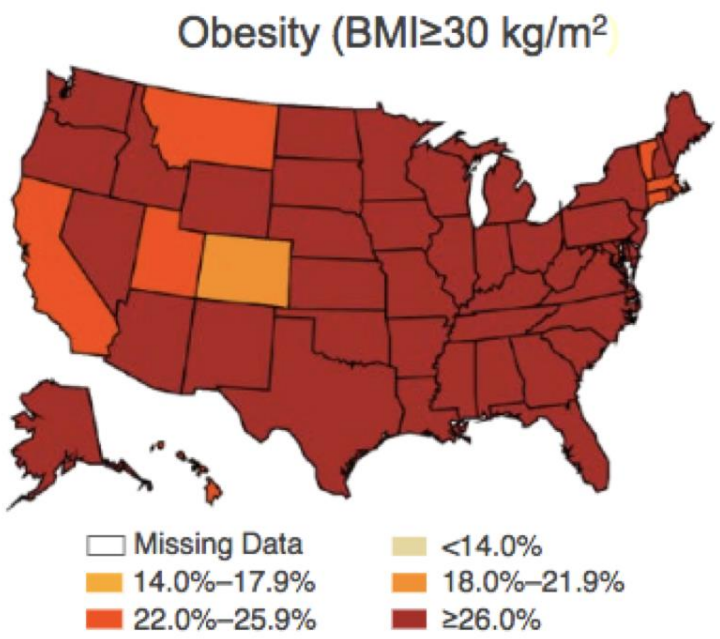
Identify causal molecular and cellular mechanisms that links nutrition to health and disease states such as cancer

Obesity epidemic in the US

1994



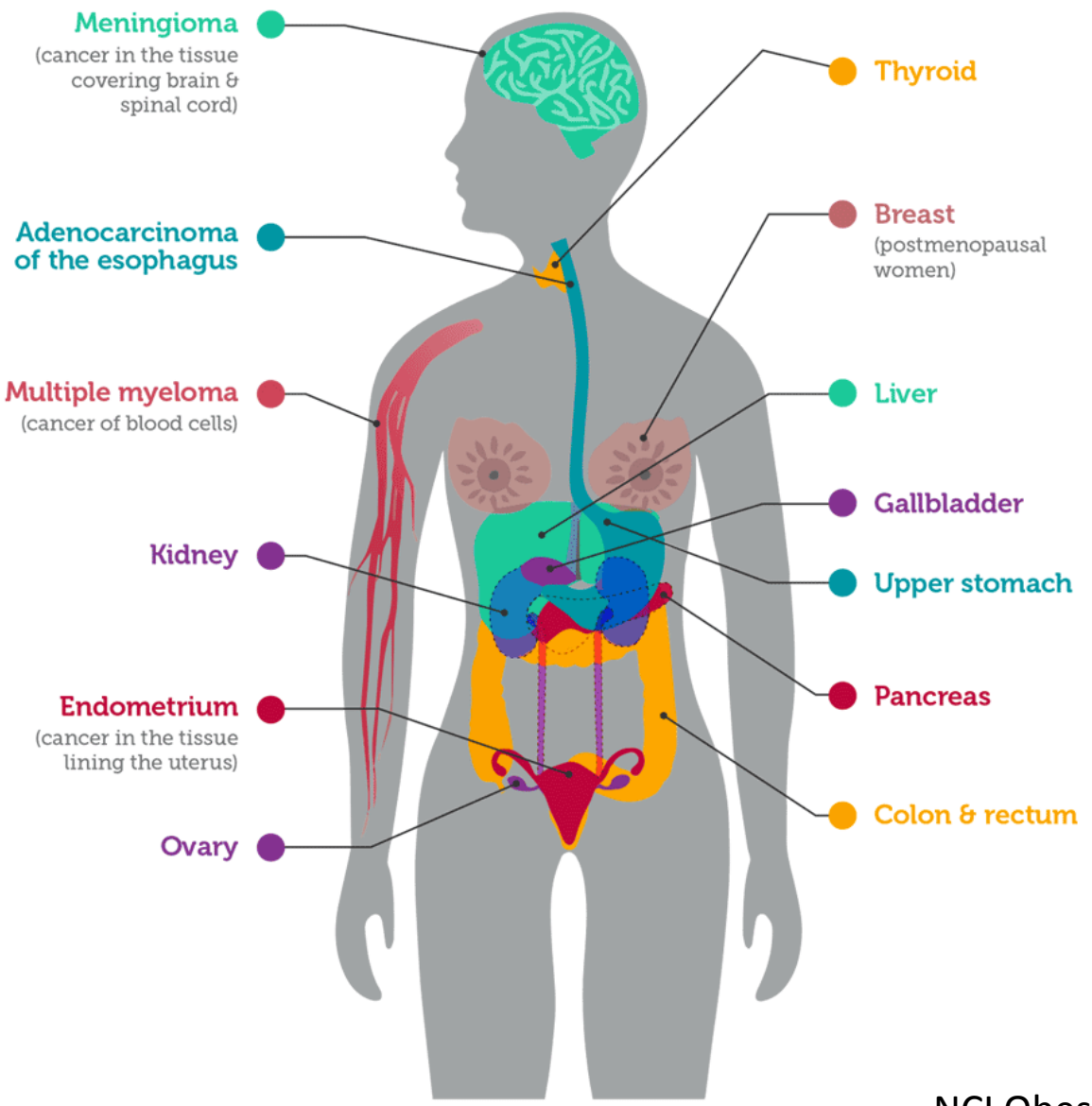
2014



Summary of data collected since 1980s

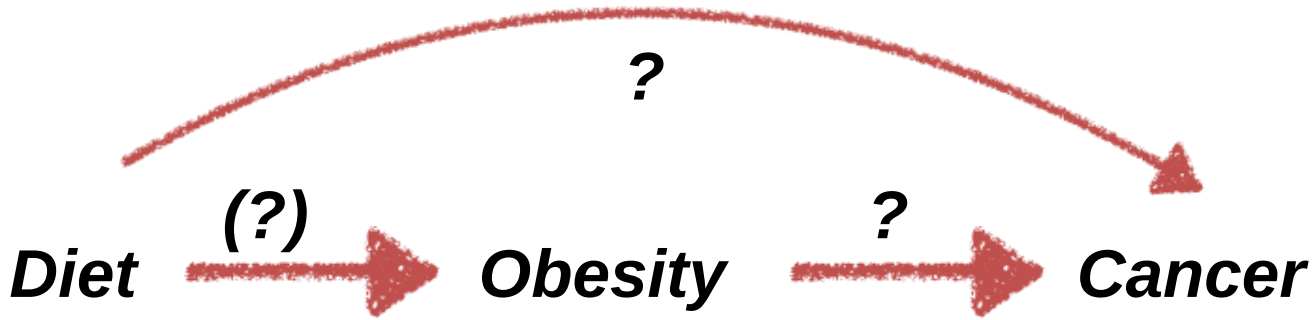
Modified from Center for Disease Control

The link between obesity and cancer risk



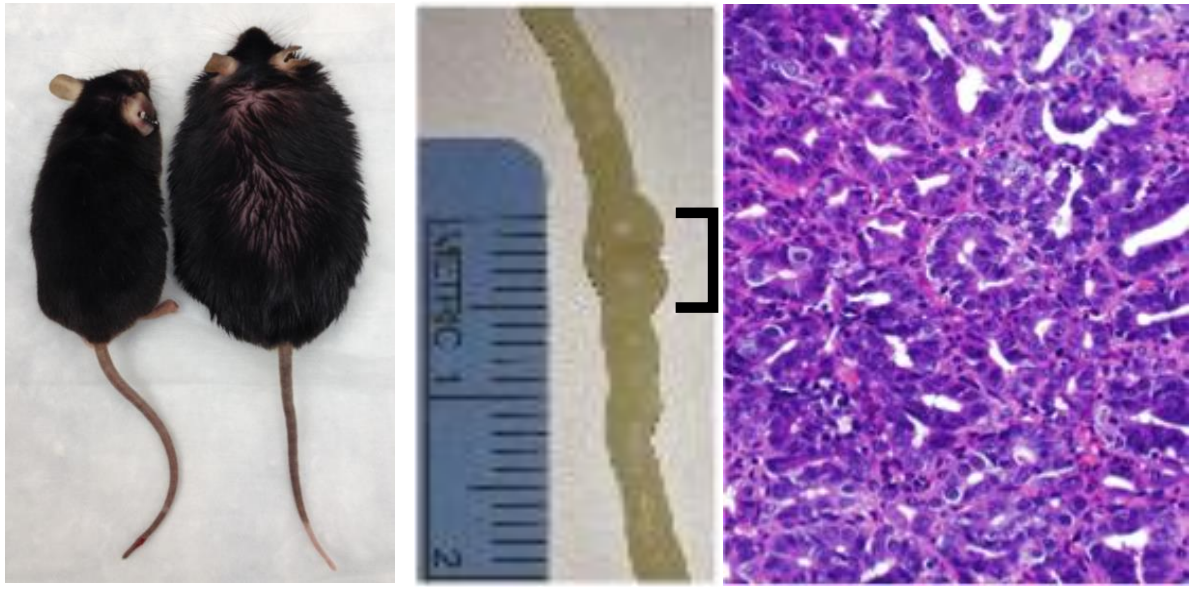
NCI Obesity Fact Sheet

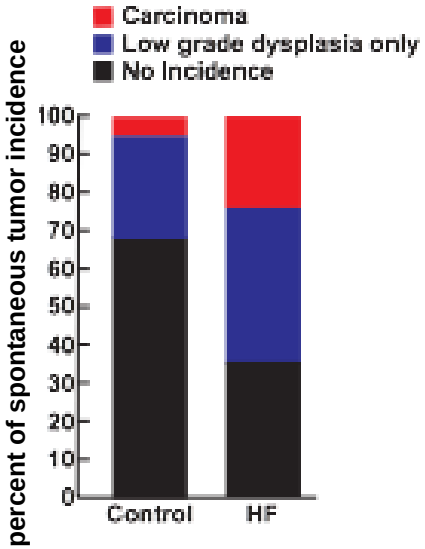
Paradigms for obesity-associated cancers



A complicated problem with lots of variables and lack of causality in associations!

A High Fat Diet (HFD) induced obesity augments spontaneous intestinal carcinoma incidence



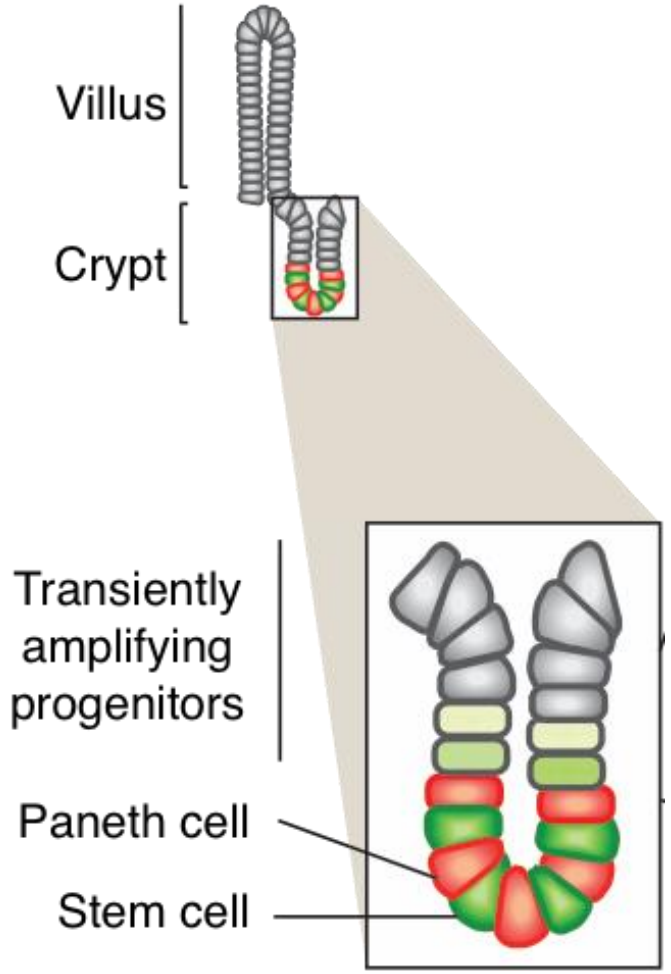


HFD $\xrightarrow{?}$ ↑Tumor

9-12 months long-term lard-based HFD

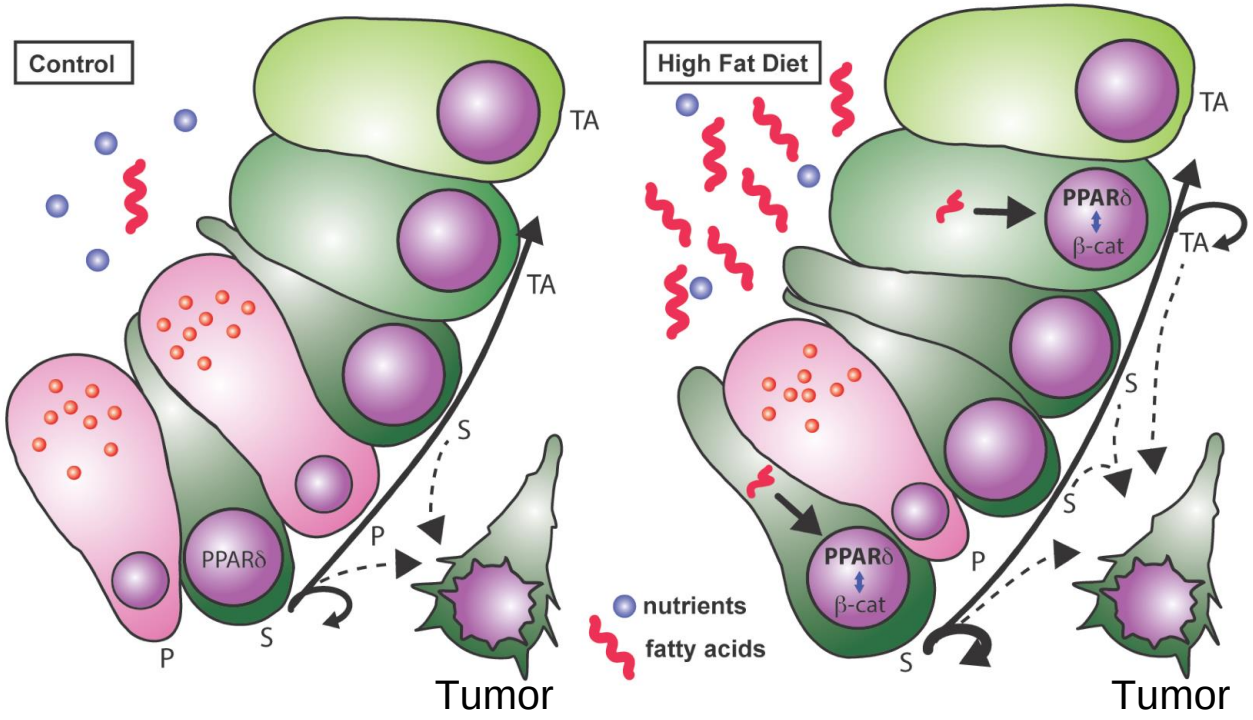
Beyaz *et al*. Nature, 2016

Stem cells maintain the intestinal epithelium and are the cell of origin for intestinal tumors



stem cell activity and increases cancer risk in the intestine

HFD → Fatty acids → ↑ abnormal stem cell activity → ↑ **Tumor**

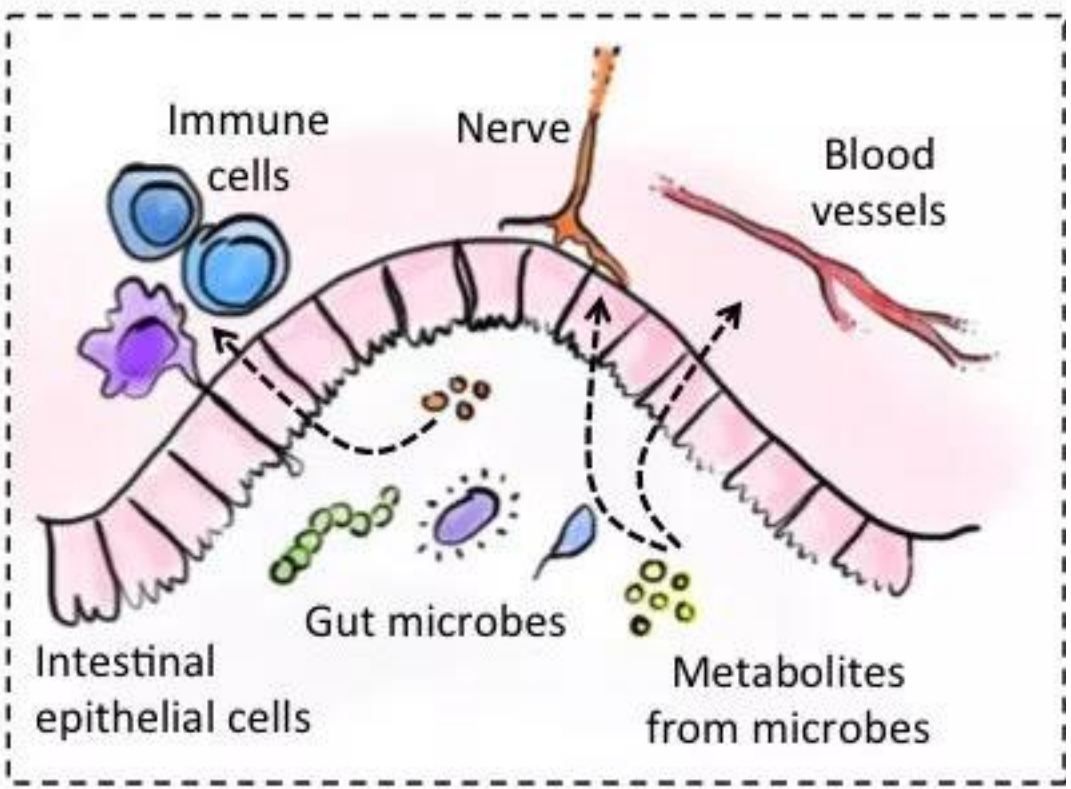


- ***A causal mechanism that links HFD-induced obesity to intestinal cancer***
- ***Targeting PPAR-d for the treatment of obesity associated cancers?***

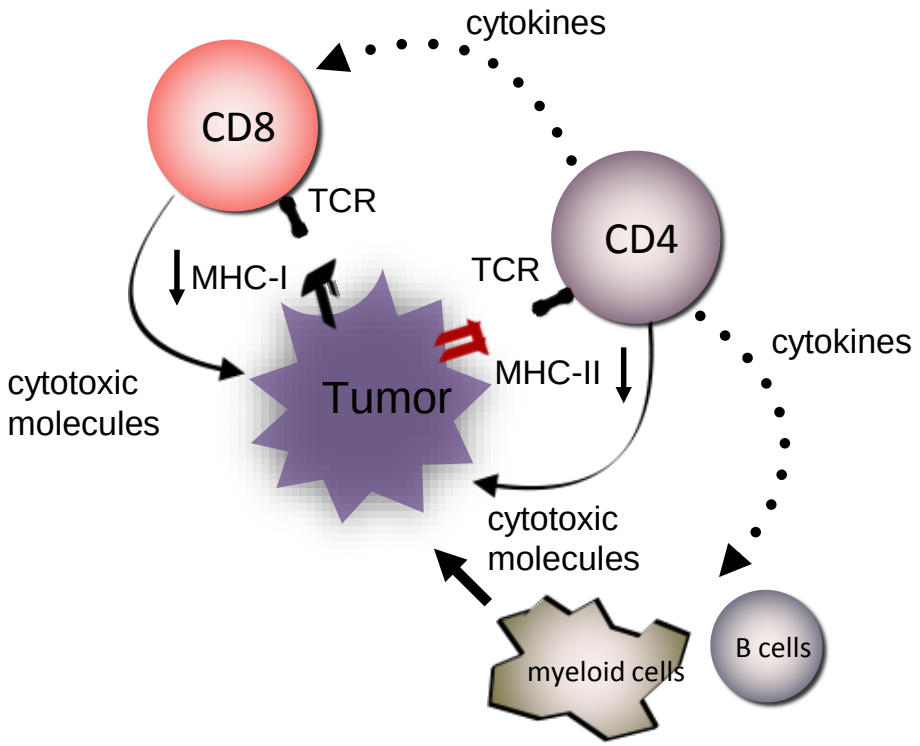
Beyaz *et al*. Nature, 2016

Pascual et al., Nature 2017, Chen et al., Nature Genetics 2018

A step back, a step forward…



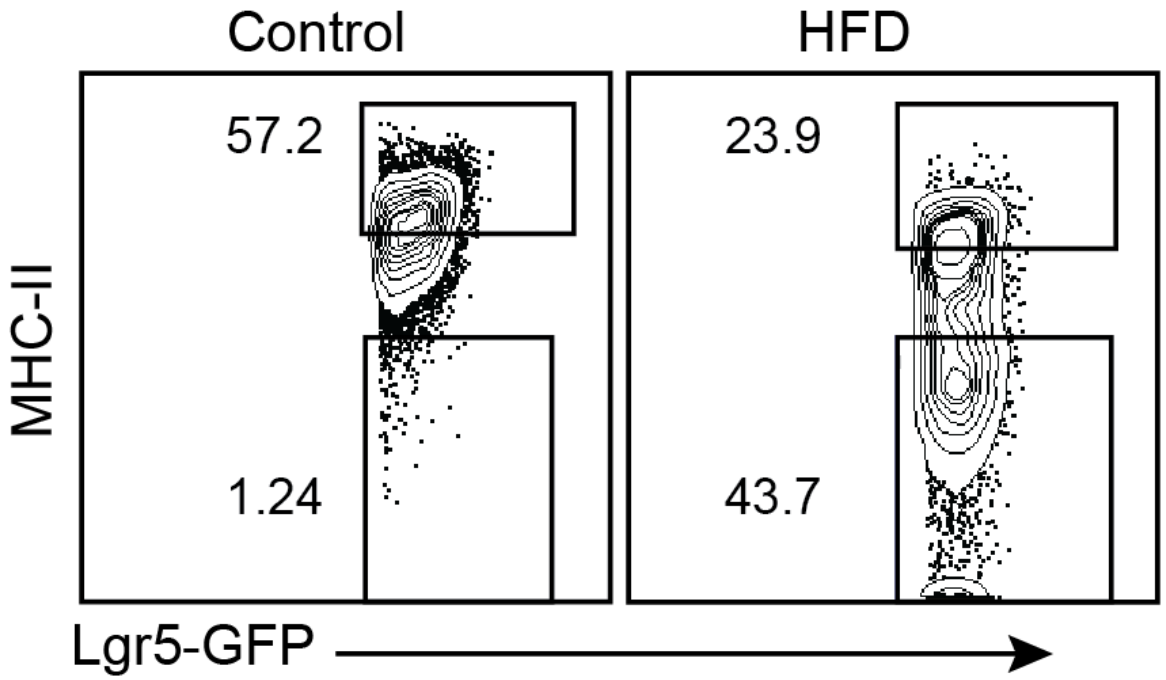
Immune recognition mechanisms that contribute to anti-tumor immunity



Kreiter et al., Nature 2015
Hirschhorn-Cymerman et al., JEM 2012
Haabeth et al., Leukemia 2016
Tarafdar et al., Blood 2017

Tran et al., Science 2014
Spitzer et al., Cell 2017
Hung et al., JEM 1998
Janssen et al., Nature 2003

ISCs express high levels of MHC-II, which is significantly <u>downregulated</u> upon HFD-induced obesity



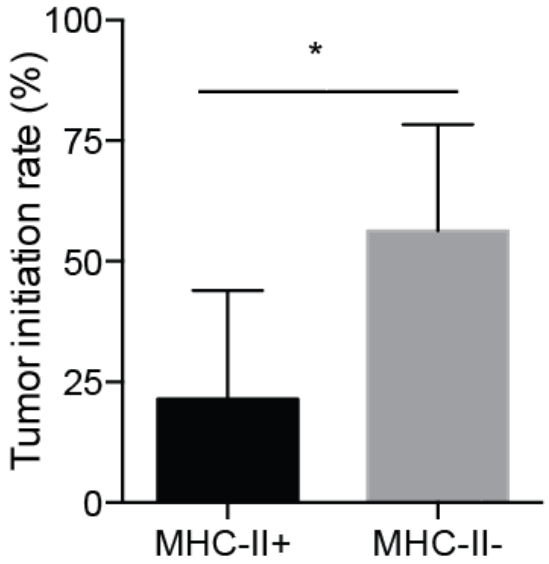
Test whether dampening MHC-II on tumor-initiating cells increase risk of cancer?

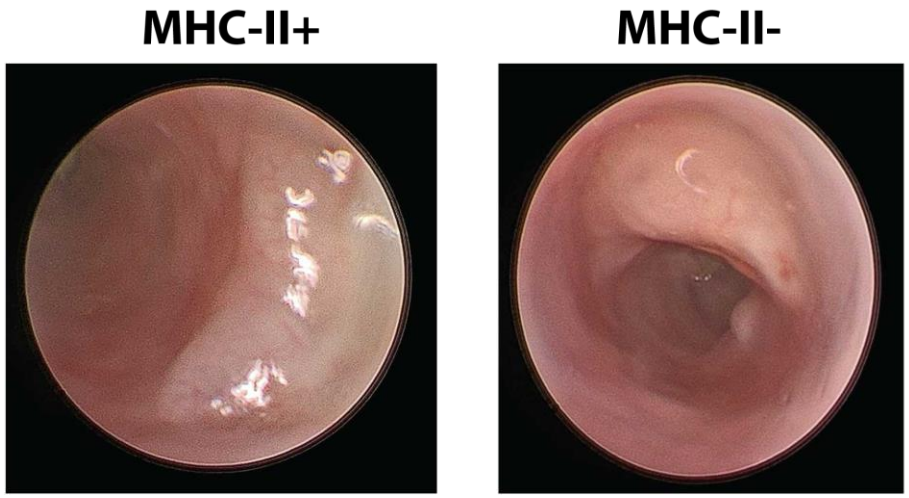
Cerf-Bensussan et al., Journal of Immunology 1984
Hershberg et al., PNAS 1997

Telega et al., Gastroenterology 2000
Biton et al., Cell 2018

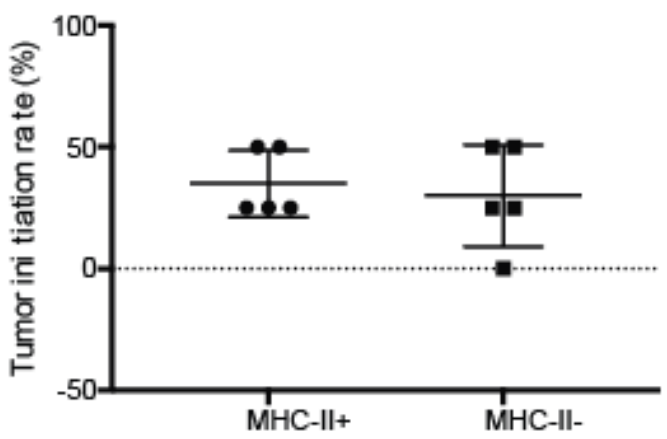
MHC-II- APC-null stem cells give rise to increased numbers of tumors compared to MHC-II+ counterparts in vivo

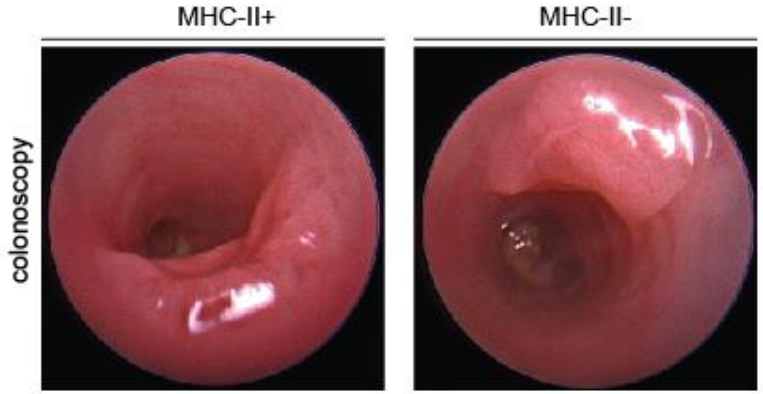
Immune competent hosts



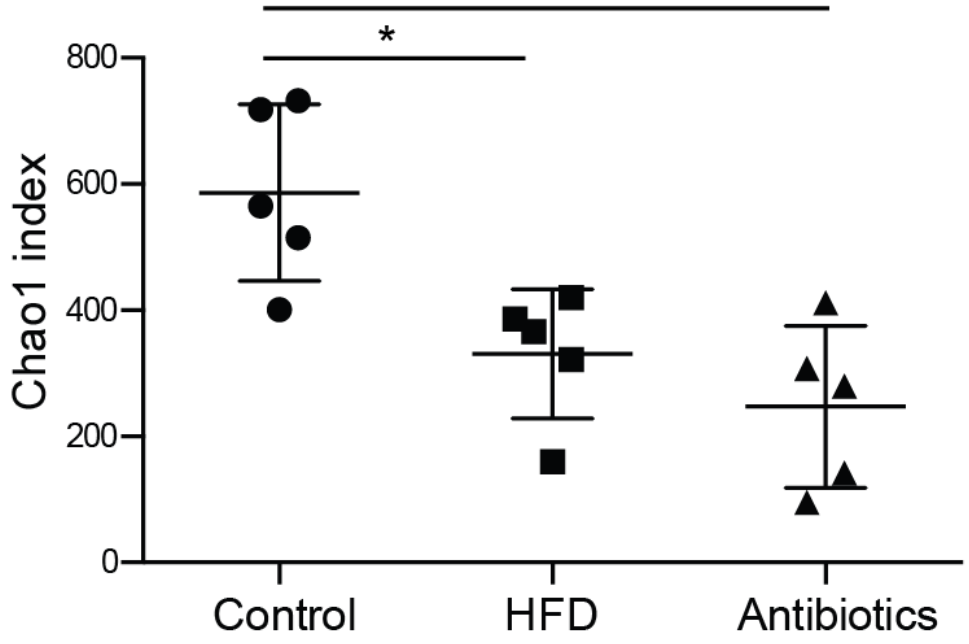


…but not in immune deficient hosts!



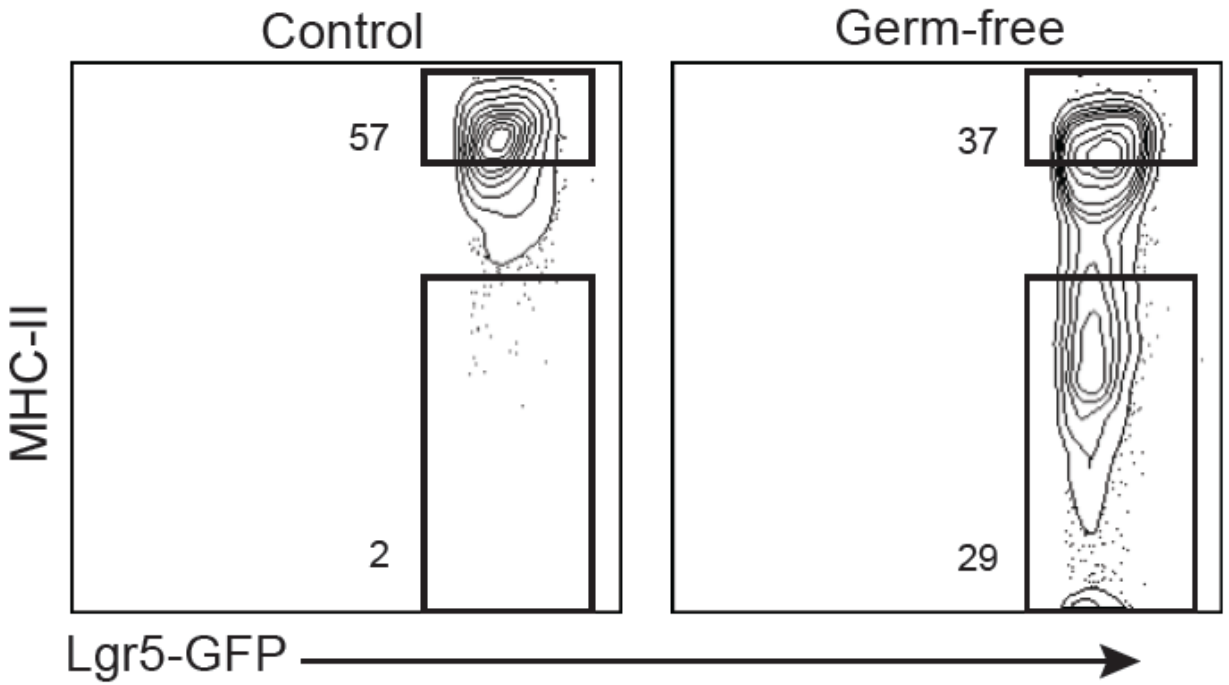


A HFD leads to reduced microbial diversity in the intestine



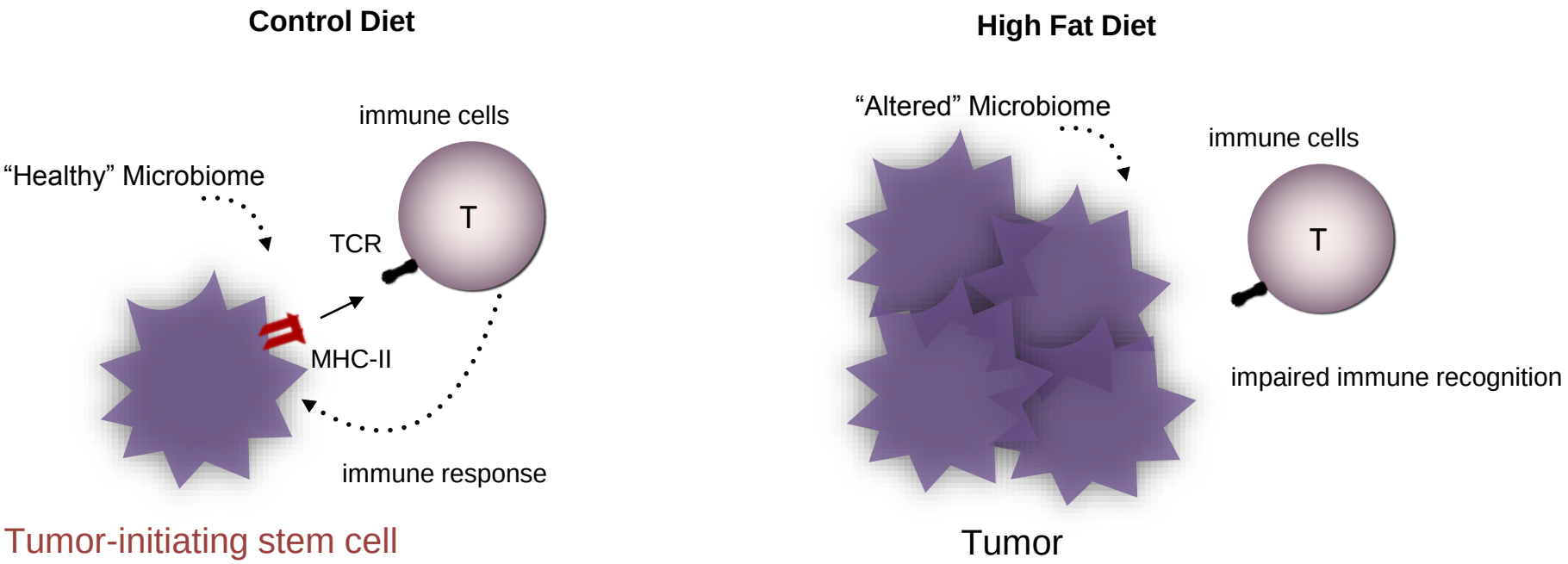
Ley et al. PNAS 2005, Schulz et al. Nature 2014

Germ-free mice exhibit reduced MHC-II expression in ISCs



Bacteria → PRR signaling / Cytokine signaling → **MHC-II expression**

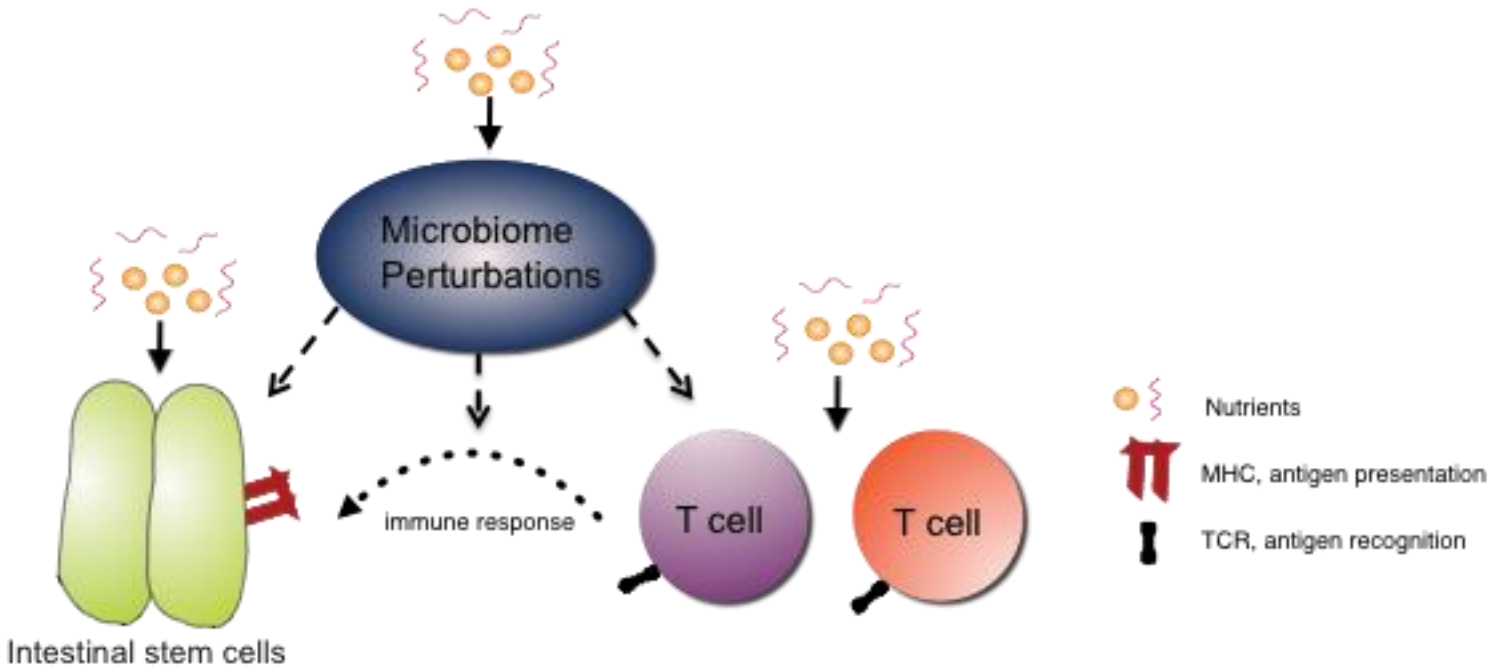
Recognition of tumor cells by the immune system is an important mechanism in controlling intestinal tumorigenicity



HFD → △ Microbiome → ↓ immune recognition → ↑ **Tumor**

Diet-induced alterations in intestinal microbiome regulate immune recognition mechanisms and tumor formation in the intestine

Integrating modules influencing cancer risk



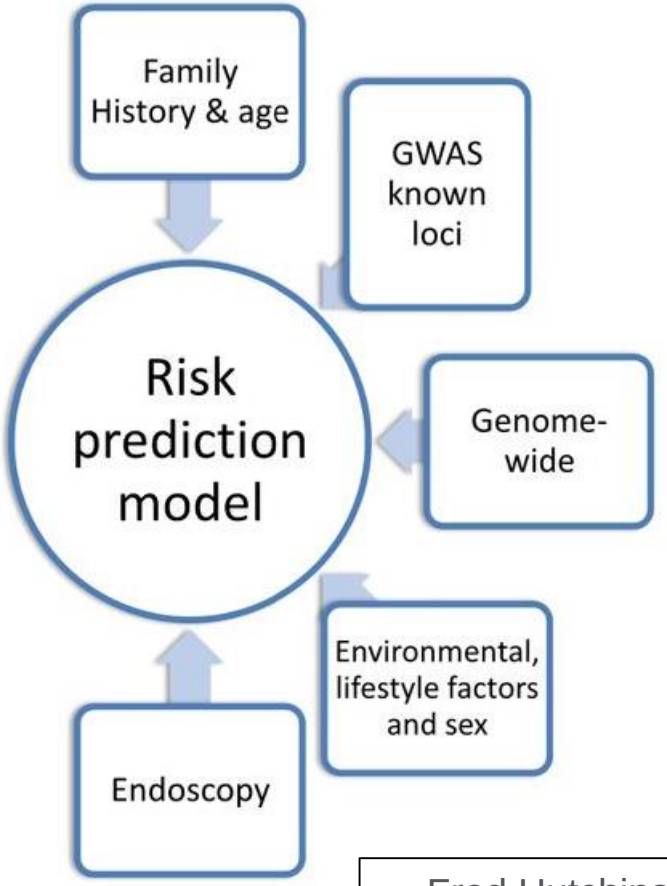
NYU Langone Health

COMMON GENETIC RISK VARIANTS AND SUSCEPTIBILITY TO EARLY-ONSET COLORECTAL CANCER

Richard B. Hayes, DDS, PhD
Department of Population Health, Division of Epidemiology, NYU Langone School of Medicine

GECCO: Comprehensive CRC Risk Prediction to Inform Personalized Screening

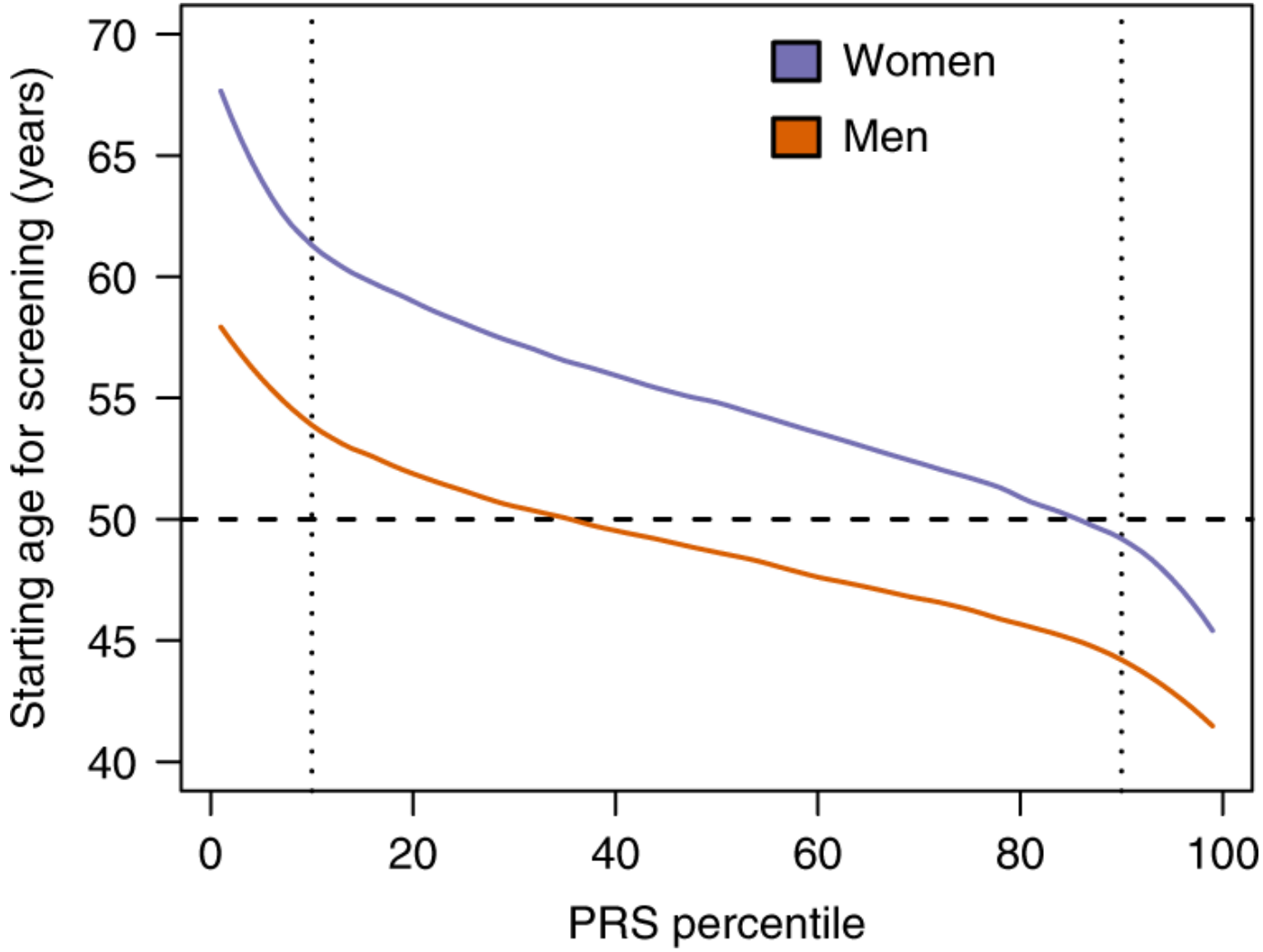
- To build a more comprehensive risk prediction model
  - Improve screening efficiency through risk stratified screening
  - Identify high risk group for targeted preventive intervention
    - *Diet*
    - *Lifestyle*
    - *NSAIDs*



- Fred Hutchinson Cancer Research Center
- Kaiser Permanente Northern California
- NYU Langone Health

R01CA206279, R03CA215775

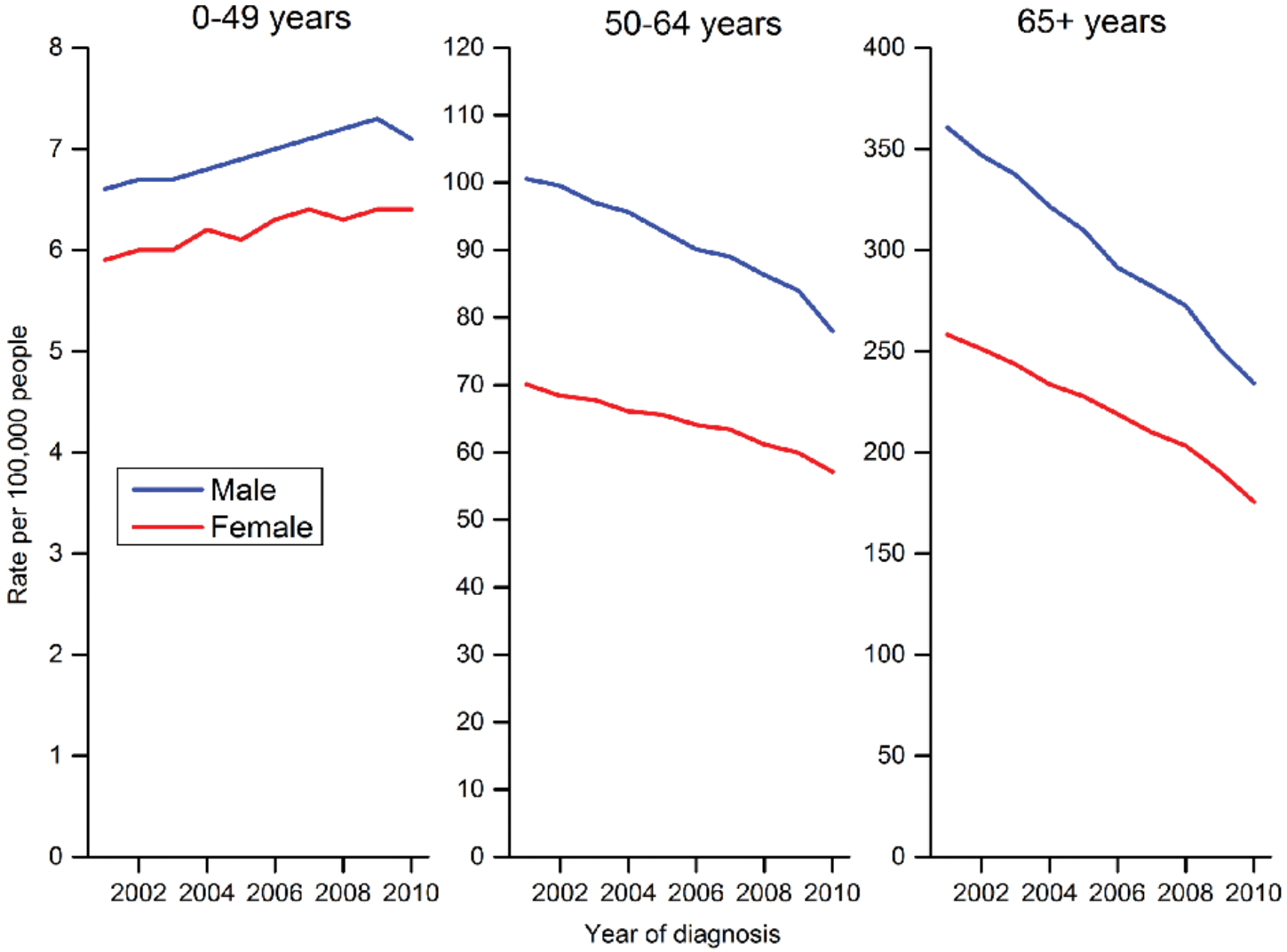
Polygenic risk score and recommended age to start CRC screening



The risk threshold to determine the age for the first screening was set as the average of 10-year CRC risks for a 50-year-old man (1.25%) and woman (0.68%) who have not previously received an endoscopy

Huyghe JR et al., Nature Genetics, 2018

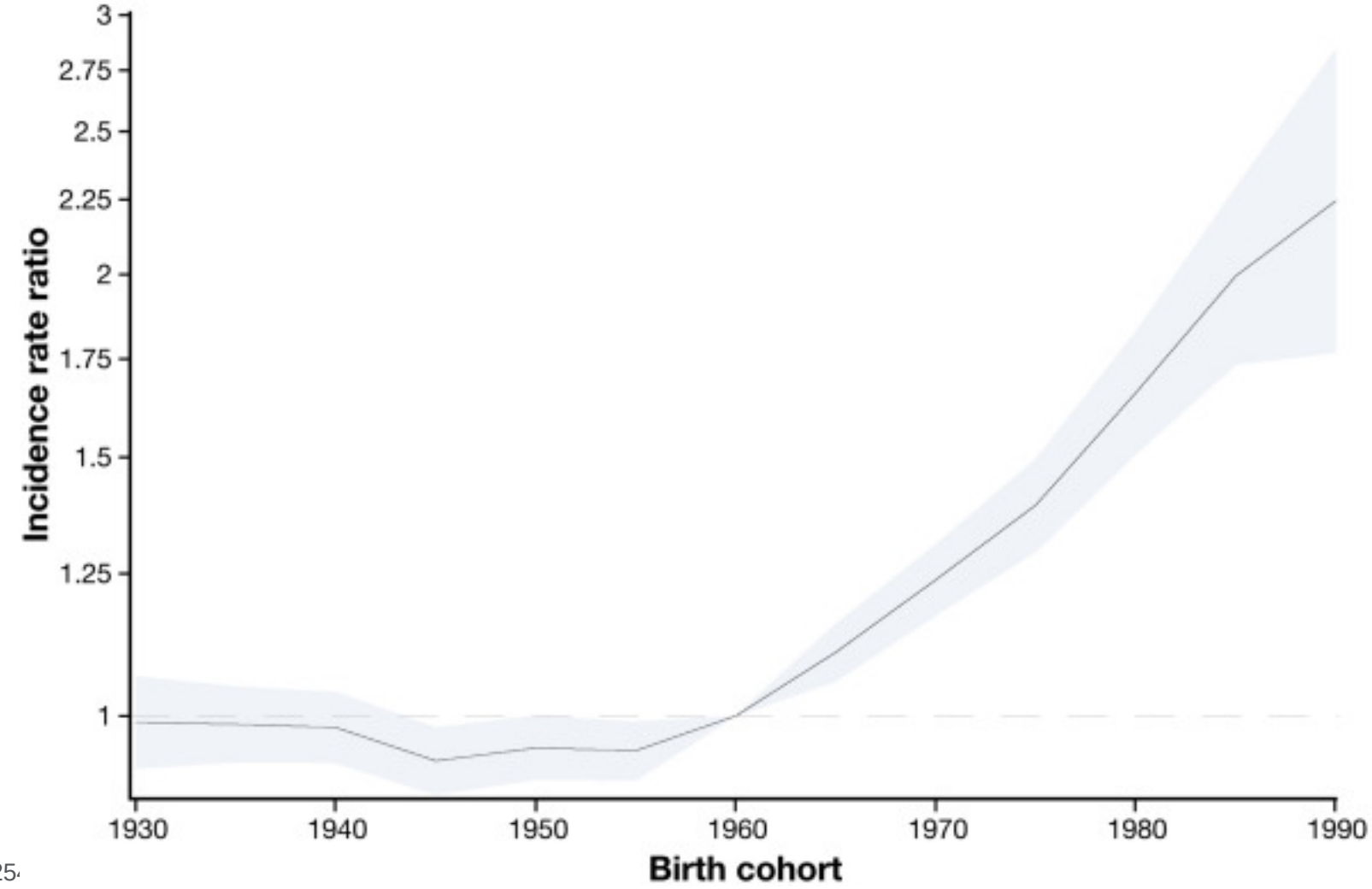
A Second Motivation to Reconsider Age to Start Screening



- Early-onset CRC projected to account for 10% to 25% of newly-diagnosed CRC in the U.S. by 2030
- Presents with:
  - Higher pathologic grade
  - Distant disease
  - Greater incidence of recurrence and metastatic disease
  - Tend toward more disease of the distal colon and rectum

253 Siegel, Rebecca L. et al. “Colorectal cancer statistics, 2014.” *CA: a cancer journal for clinicians* 64 2 (2014): 104-17.

Early-onset CRC, by Birth Cohort, United States, 1930-1990



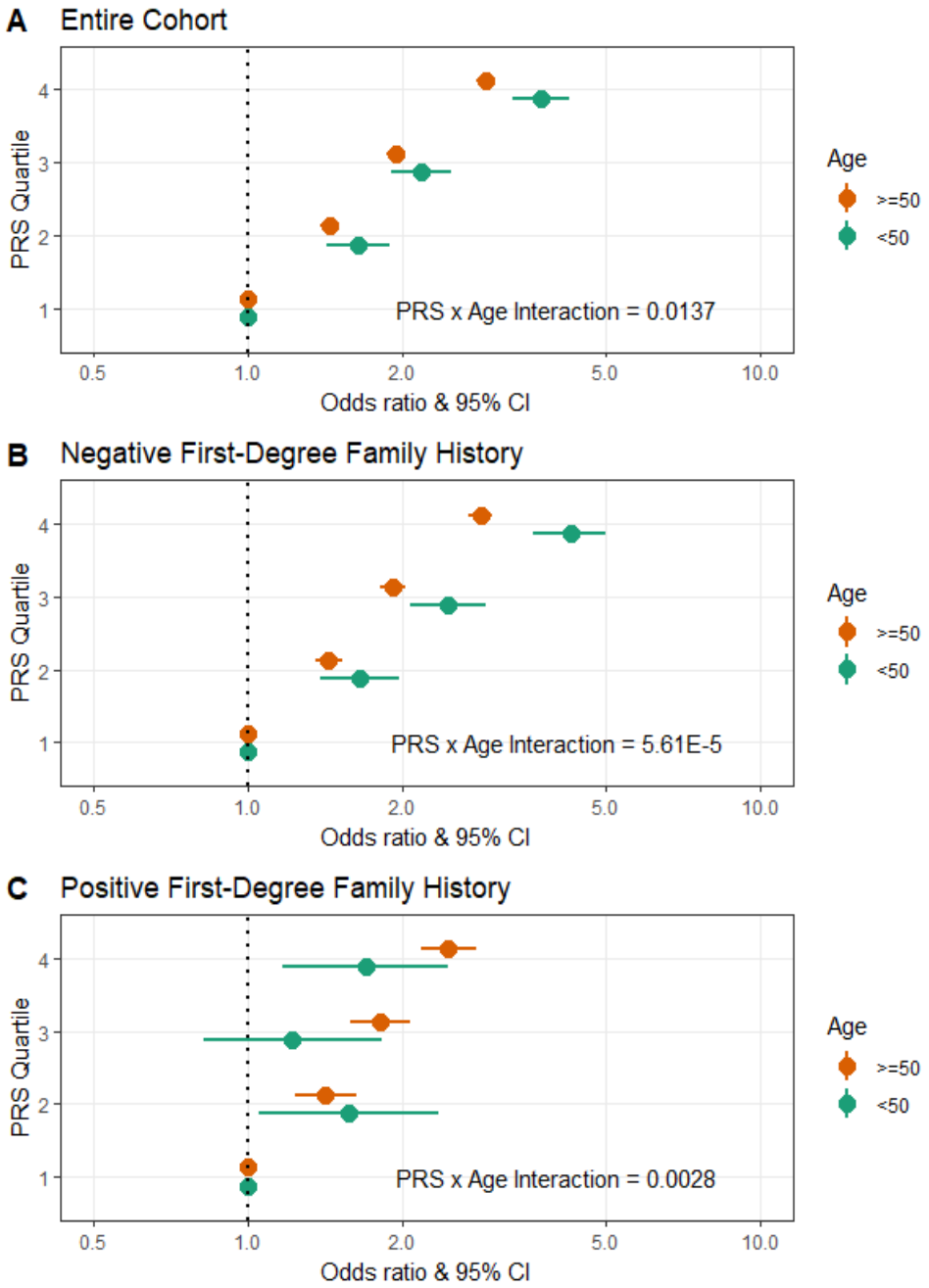
Murphy CC et al., Gatroenterology, 2018

Objective

- Investigate CRC risks associated with a 95 SNP polygenic risk score (PRS) for participants of European ancestry by age (<50, >50) at CRC diagnosis
- Determine whether younger individuals are more susceptible to these risks

Discovery Dataset

- **50,023 CCR Cases and 58,039 Controls**
  - Colon Cancer Family Registry (CCFR)
  - Colorectal Transdisciplinary (CORECT) Study
  - Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO)
- **5,479 CRC and 6,718 Controls, <50 years of age**
- **Limited to European ancestry**
- **First-degree family history** by self-report or interview-administered questionnaire
- **Case-control, cohort and family-based studies**

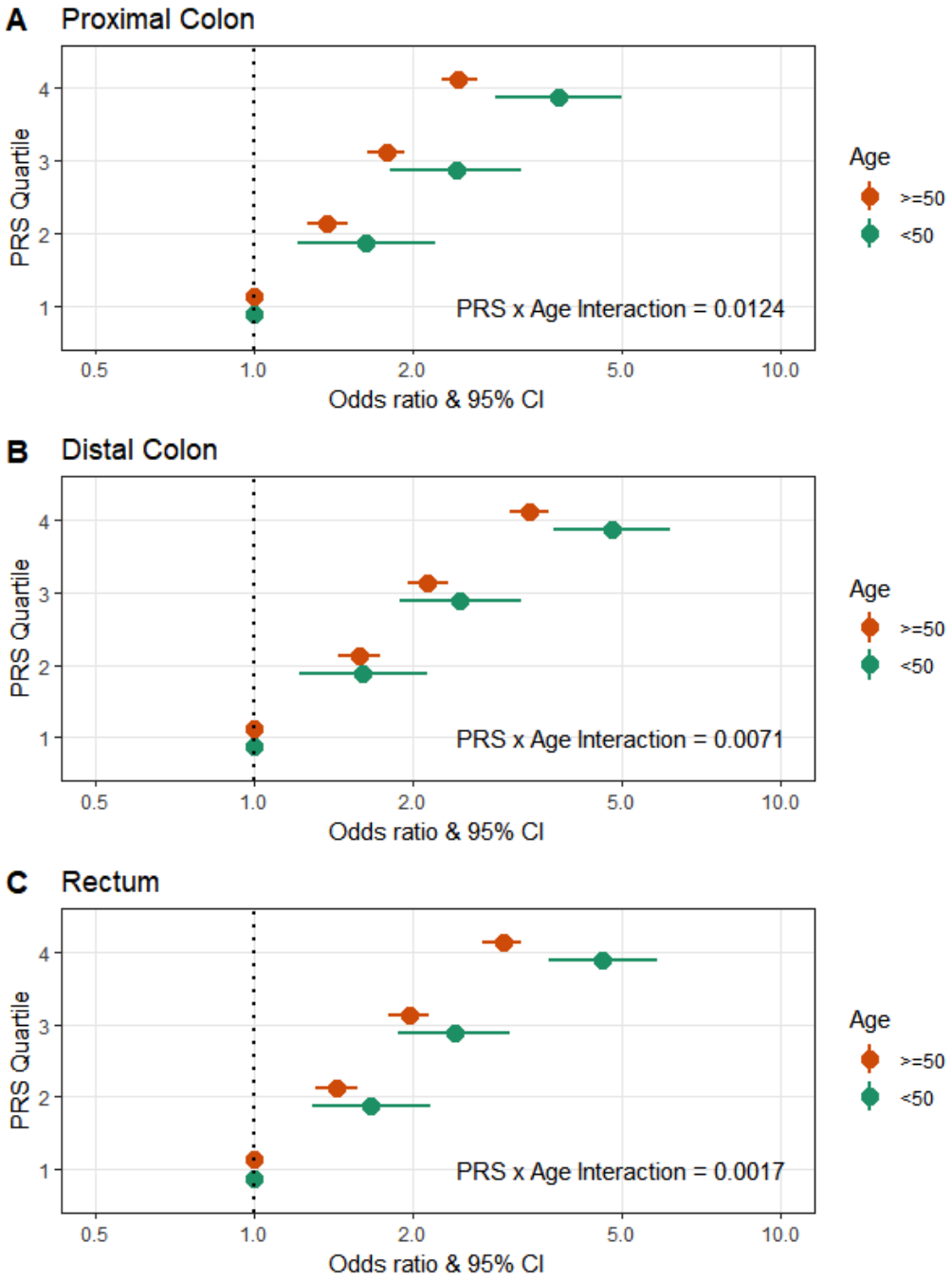


Relative Risk of CRC, by age and First-degree family history of CRC

(A) All participants

(B) Negative for a family history of CRC

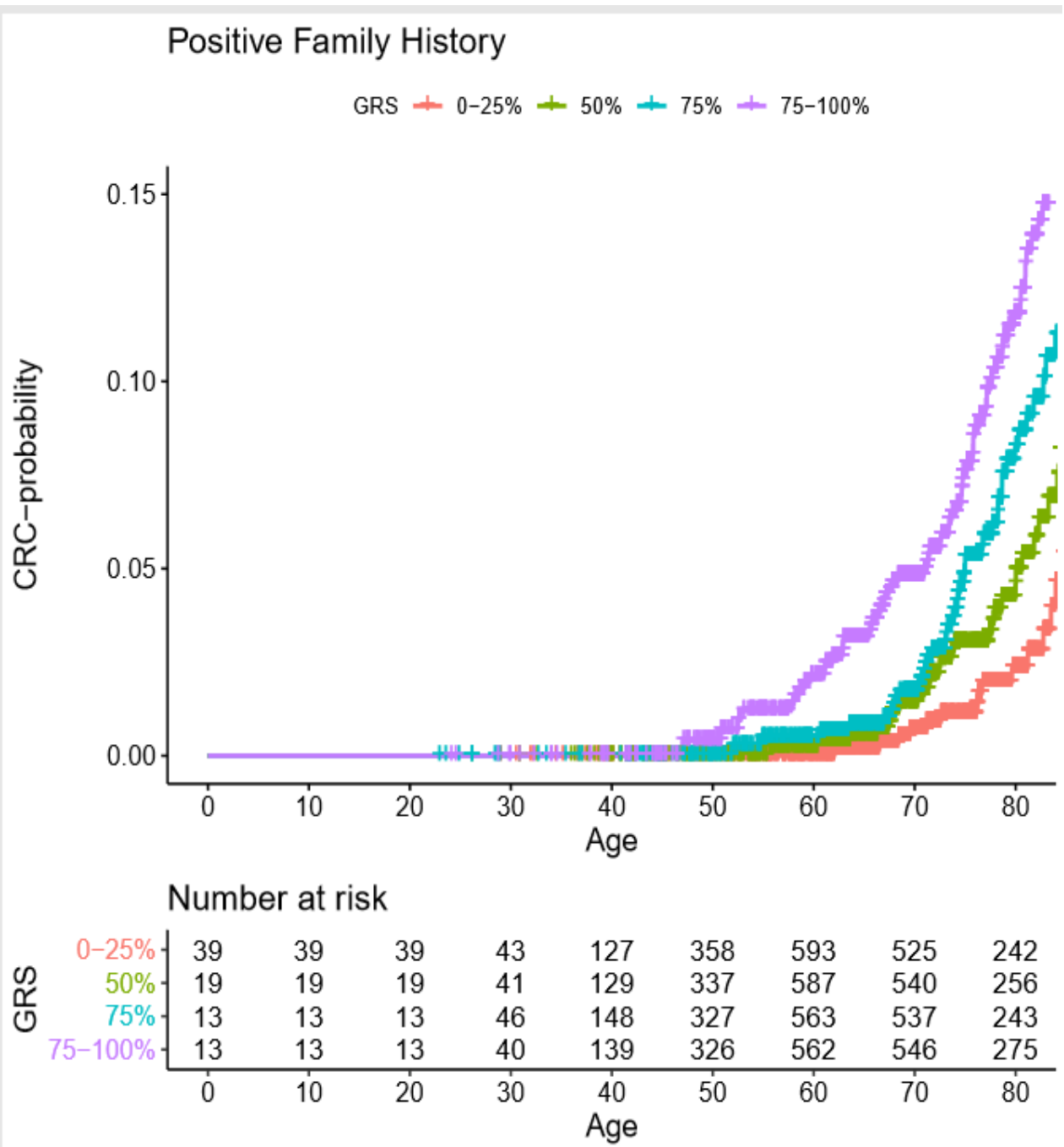
(C) Positive for a family history of CRC

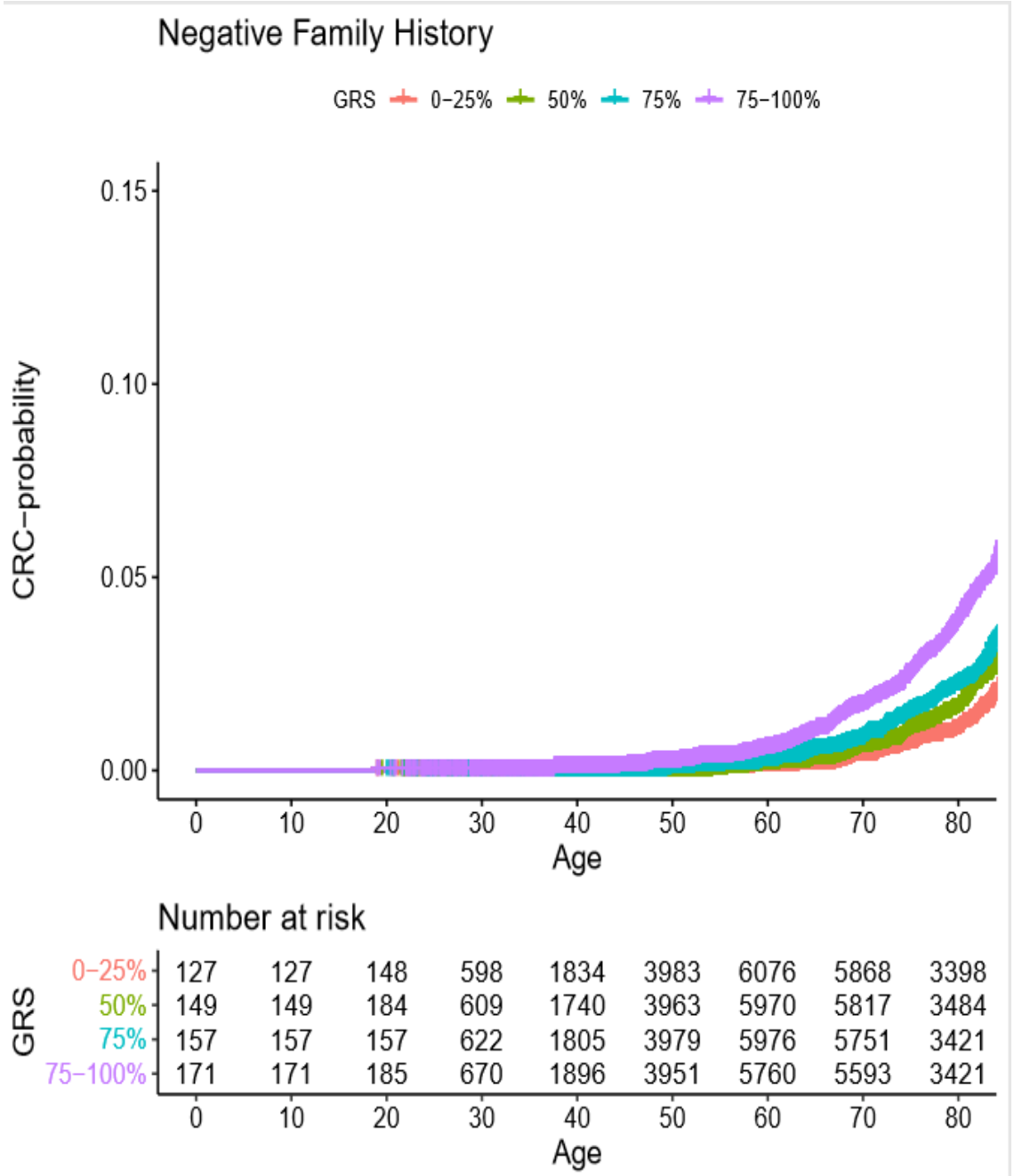


Family History Negative
Relative Risk of CRC, by Disease Site

Replication Dataset

- **72,573 Kaiser Permanente Members participating in the Research Program on Genes, Environment and Health (RPGEH)**
- **Limited to European ancestry (genetically defined)**
- **Cohort linked to the KPNC cancer registry**
- **First-degree family history** by self-report through questionnaire and medical records
- **Cohort Analysis by Kaplan-Meier and Cox regression**


Positive Family History
GRS 0–25% 50% 75% 75–100%
CRC−probability
0.15
0.10
0.05
0.00
0 10 20 30 40 50 60 70 80
Age
Number at risk
GRS
0–25% 39 39 39 43 127 358 593 525 242
50% 19 19 19 41 129 337 587 540 256
75% 13 13 13 46 148 327 563 537 243
75–100% 13 13 13 40 139 326 562 546 275
0 10 20 30 40 50 60 70 80
Age


Negative Family History
GRS 0–25% 50% 75% 75–100%
CRC−probability
0.15
0.10
0.05
0.00
0 10 20 30 40 50 60 70 80
Age
Number at risk
GRS
0–25% 127 127 148 598 1834 3983 6076 5868 3398
50% 149 149 184 609 1740 3963 5970 5817 3484
75% 157 157 157 622 1805 3979 5976 5751 3421
75–100% 171 171 185 670 1896 3951 5760 5593 3421
0 10 20 30 40 50 60 70 80
Age

Further Considerations

- Combining the PRS with environmental/lifestyle risk factors
- 95 SNP PRS was not specific for young-onset CRC
- Assessment was for Europeans only
- We did not take into account Lynch and other rarer syndromes

Classic germline mutations and Early-Onset CRC Ohio, 2013-16

	Germline Mutations			
Early-onset Cases	**MMR only**	**Other CRC**	**None**	
Family History Positive (n=86)				
N	27	6	53	
%	*31.4*	*7.0*	*61.6*	
Family History Negative (n=364)				
N	10	29	325	
%	*2.7*	*7.8*	*89.3*	

Pearlman R. JAMA Oncol. 2017 Apr 1; 3(4): 464–471.

Conclusions

- This is the first study to evaluate an individual's cumulative genetic risk profile for common at-risk alleles and early-onset CRC
- PRS is more strongly associated with early-onset cancer than with late-onset cancer

Thank You!

NYU Langone Health:
Alexi Archambault

Fred Hutchinson Cancer Research Center:
Ulrike Peters
Yu-Ru Su
Minta Thomas
Yi Lin
Li Su
Jeroen R Huyghe

Kaiser Permanente Northern California:
Douglas A Corley
Lori C. Sakoda

University of Michigan:
Jihyoun Jeon

And all the participating studies…

Research Program on Genes, Environment and Health (RPGEH), Kaiser Permanente Northern California (KPNC)
The french Association STudy Evaluating RISK for sporadic colorectal cancer (ASTERISK)
Alpha-Tocopherol, Beta Carotene Cancer Prevention Study (ATBC)
Colon Cancer Family Registry (CCFR)
Hawai'i Colorectal Cancer Studies 2 & 3 (Colo2&3)
ColoCare Consortium (ColoCare)
Colorectal Cancer: Longitudinal Observational study on Nutritional and lifestyle factors that influence colorectal tumor recurrence, survival and quality of life (COLON)
Colorectal Cancer Study of Austria (CORSA)
American Cancer Society Cancer Prevention Study II nested case-control study (CPS-II)
Czech Republic Colorectal Cancer Study (Czech Republic CCS)
Darmkrebs: Chancen der Verhütung durch Screening (DACHS)
Diet, Activity, and Lifestyle Study (DALS3)
Early Detection Research Network (EDRN)
European Prospective Investigation into Cancer and Nutrition (EPIC)
The EPICOLON Consortium (EPICOLON)
Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung, Verlauf der diagnotischen Abklärung bei Krebspatienten (ESTHER-VERDI)
Columbus-area HNPCC study, Ohio Colorectal Cancer Prevention Initiative, and Ohio State University Medical Center (HNPCC, OCCPI, and OSUMC)
Health Professionals Follow-up Study (HPFS)
Kentucky Case-Control Study (Kentucky)
PopGen Biobank (Kiel)
Leeds Colorectal Cancer Study (LCCS)
Melbourne Collaborative Cohort Study (MCCS)
Multiethnic Cohort study (MEC)
Molecular Epidemiology of Colorectal Cancer Study (MECC)
Memorial Sloan Kettering Cancer Center Cohort (MSKCC)
North Carolina Colon Cancer Study-I (NCCCS I)
North Carolina Colon Cancer Study-II (NCCCS II)
Newfoundland Case-Control Study (NFCCR)
Nurses' Health Study (NHS)
Nurses' Health Study (NHS II)
The Northern Sweden Health and Disease Study (NSHDS)
Ontario Familial Colorectal Cancer Registry (OFCCR)
Physicians' Health Study (PHS)
Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)
Postmenopausal Hormones Supplementary Study to the CCFR (PMH-CCFR)
Studies of Epidemiology and Risk Factors in Cancer Heredity (SEARCH)
Swedish Low-Risk Colorectal Cancer Study (SLRCCS)
Swedish Mammography Cohort and Cohort of Swedish Men (SMC and COSM)
The Spanish study (University Hospital of Bellvitge, Hospital of Leon) (Spain)
United Kingdom Biobank (UK Biobank)
Los Angeles County Cancer Surveillance Program (USC-HRT-CRC)
VITamins And Lifestyle (VITAL)
Women's Health Initiative (WHI)

Early life exposures and colorectal neoplasia

Kana Wu, MD, MPH, PhD

Department of Nutrition

Harvard T. H. Chan School of Public Health

World Cancer Research Fund

American Institute for Cancer Research

CUP Continuous Update Project

Analysing research on cancer prevention and survival

2017 DIET, NUTRITION, PHYSICAL ACTIVITY AND COLORECTAL CANCER

		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing	Physical activity[1,2]	Processed meat[3] Alcoholic drinks[4] Body fatness[5] Adult attained height[6]
	Probable	Wholegrains Foods containing dietary fibre[7] Dairy products[8] Calcium supplements[9]	Red meat[10]
LIMITED EVIDENCE	Limited – suggestive	Foods containing vitamin C[11] Fish Vitamin D[12] Multivitamin supplements[13]	Low intakes of non-starchy vegetables[14] Low intakes of fruits[14] Foods containing haem iron[15]
	Limited – no conclusion	Cereals (grains) and their products; potatoes; animal fat; poultry; shellfish and other seafood; fatty acid composition; cholesterol; dietary n-3 fatty acid from fish; legumes; garlic; non-dairy sources of calcium; foods containing added sugars; sugar (sucrose); coffee; tea; caffeine; carbohydrate; total fat; starch; glycaemic load; glycaemic index; folate; vitamin A; vitamin B6; vitamin E; selenium; low fat; methionine; beta-carotene; alpha-carotene; lycopene; retinol; energy intake; meal frequency; dietary pattern	
STRONG EVIDENCE	Substantial effect on risk unlikely		

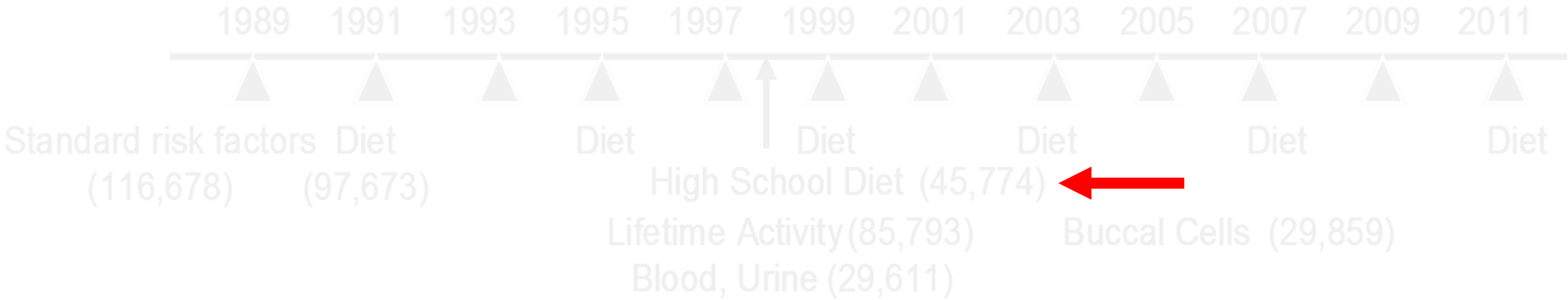
Why study early life exposures and CRC?

- CRC development can take several decades
- By focusing on exposures during adulthood only, etiologically relevant time periods may have been missed
- The recent increase in EOCRC incidence (sporadic) support that early life factors may be involved in development of colorectal cancers
- Except for body fatness data on early life risk factors and colorectal neoplasia are limited

Previous Studies- Early Life Exposures and Colorectal Neoplasia (NHS 2)

Nurses' Health Study 2 (NHS 2)

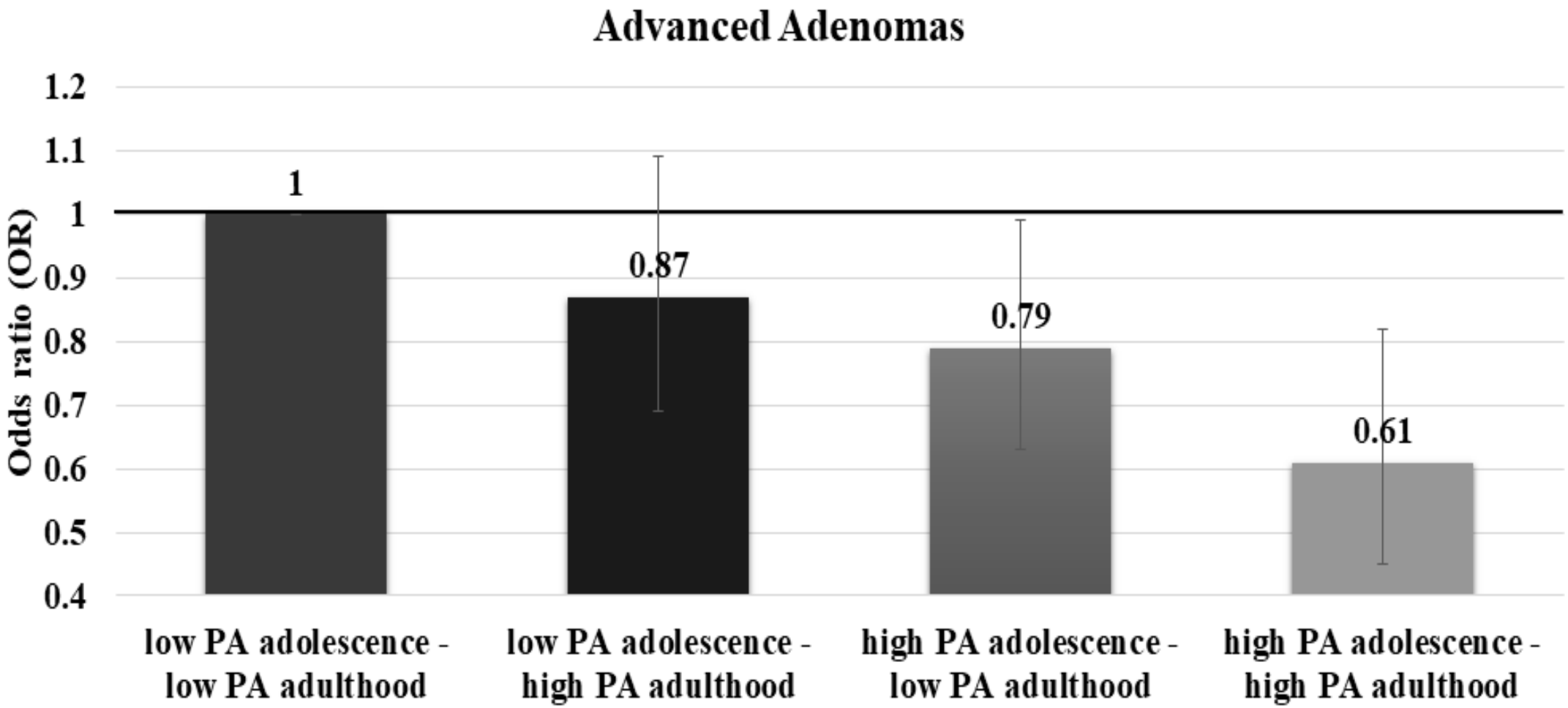
In 1998, 45,774 nurses completed a validated food frequency questionnaire to assess diet during high school (HS-FFQ)



Previous findings in NHS 2 (HS-FFQ)

- Western dietary pattern during adolescence
  - Derived using principal component analysis
    - High intake of desserts and sweets, snack foods, red and processed meat, fries and refined grains
  - Higher risk of **rectal adenoma (adenomatous polyps)**
    - Q5 vs. Q1: **OR 1.78**, 95% CI 1.12-2.85, p-trend 0.005
  - Higher risk of **advanced/high risk adenoma**
    - Q5 vs. Q1: **OR 1.58**, 95% CI 1.07-2.33, p-trend 0.08

Physical activity during adolescence and adulthood and advanced colorectal adenoma (total all age-groups) in NHS 2 (Rezende et al. in press, under embargo, do not cite)



Recently funded NCI grant: EOCRN

- FOA (NCI): Exploratory Grants in Cancer Epidemiology and Genomics Research (R21)

- Principal investigators (MPI): Kana Wu and Shuji Ogino (Brigham and Women's Hospital)

- Title: "*Integrating diet, lifestyle and tumor tissue molecular subtyping to study the role of adolescent calcium intake on the risk of early onset colorectal neoplasia"* (R21 CA230873)

Conclusions

Based on a limited number of studies, there is evidence that diet during adolescence may play a role in development of colorectal neoplasia

(relevant for sporadic EOCRC ?)

Acknowledgements

- Shuji Ogino (MPI on R21)

- Molecular Epidemiology Research Group, Max Delbrück Center for Molecular Medicine (MDC), Berlin, Germany
  - Katharina Nimptsch

Thank you for your attention!

Young Onset CRC: Causation, Treatment and Outcomes

Irit Ben-Aharon MD, PhD

Head, Division of Oncology

Rambam Health Care Campus,

Haifa, Israel

Head, Young-onset Task Force, GI Group, EORTC

RAMBAM
Health Care Campus

EORTC
The future of cancer therapy

Disclosure:

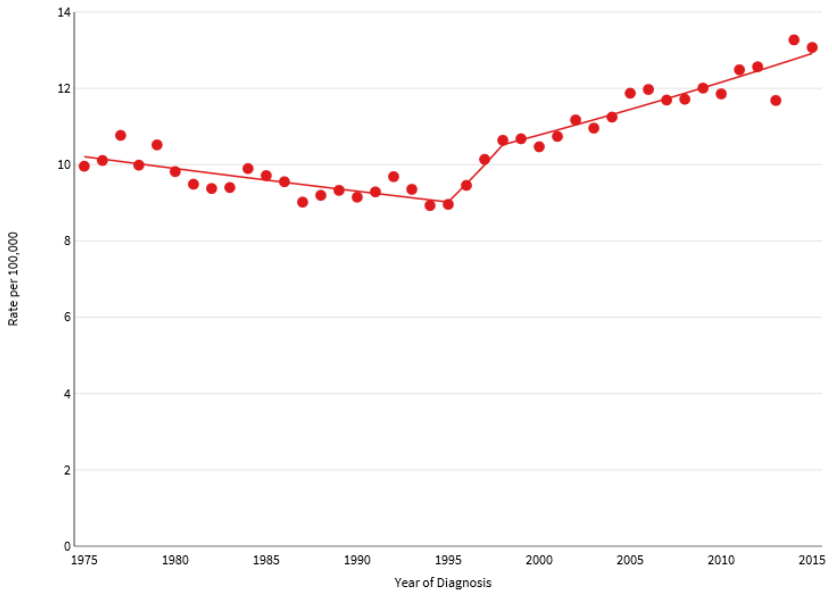
None

RAMBAM
Health Care Campus

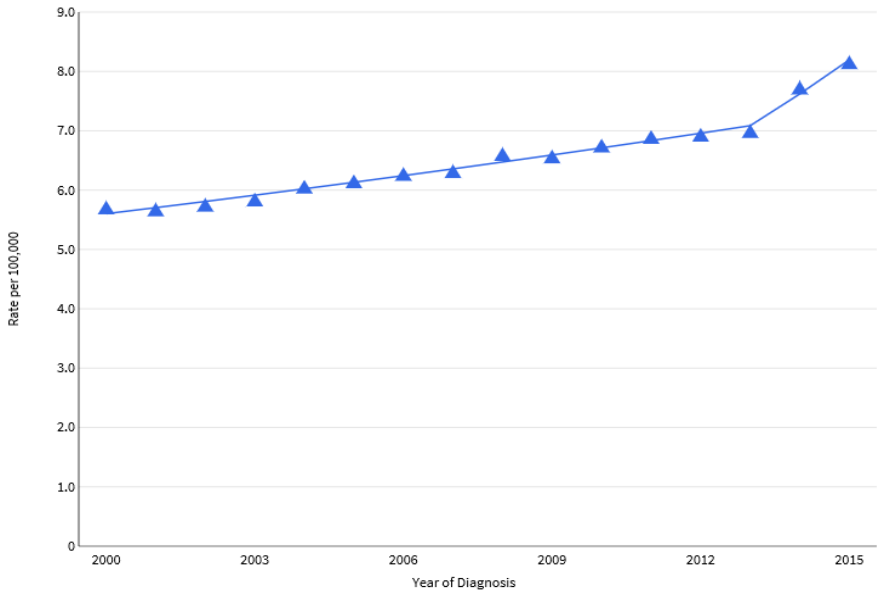
EORTC
The future of cancer therapy

Statistics:

Digestive tract Cancer
Long-Term Trends in SEER
Incidence Rates, 1975-2015
<50y



Colorectal Cancer
Long-Term Trends in SEER
Incidence Rates, 2000-2015
<50y

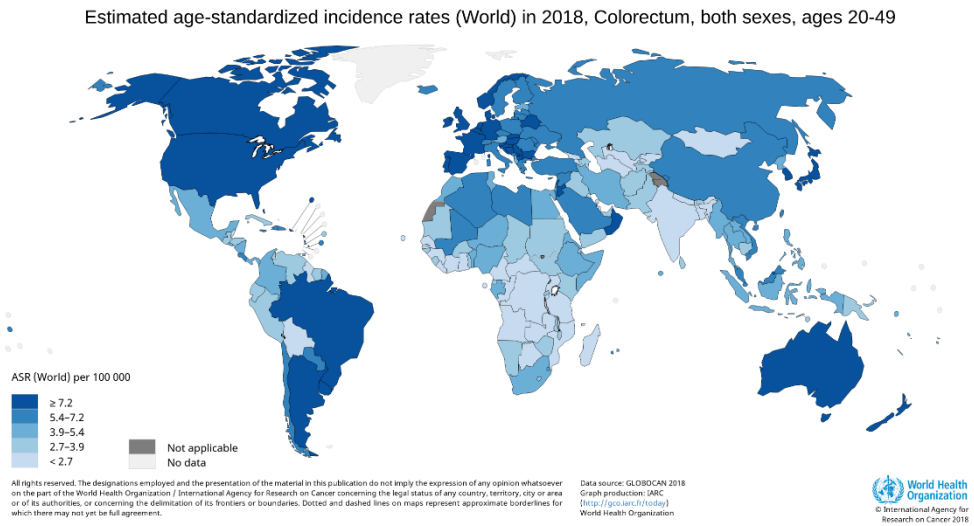


http://seer.cancer.gov/statfacts/html/

Early-Onset CRC across Europe:

The trend observed in Europe is not homogenous:

- Increased incidence in Western Europe
- Mixed trends in Middle Europe
- Stable trend in Mediterranean countries



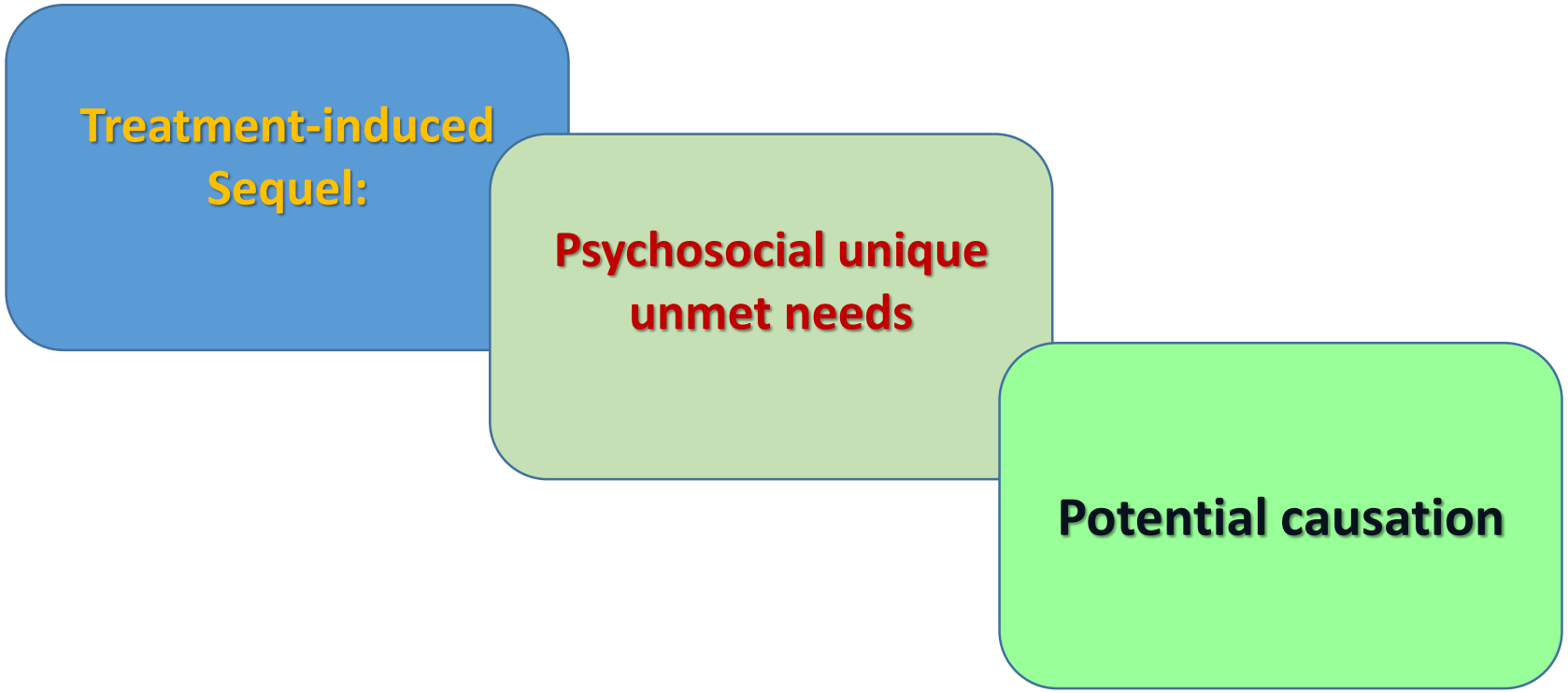
EORTC
The future of cancer therapy

The need for action - EOCRC:

- **Current main areas of AYA -**
  - **Leukemia/Lymphoma, Sarcoma, Breast**
- Lack of evidence for counselling for all young patients groups (relevance of ASCO or ESMO guidelines for FP)
- Registry of reproductive outcomes and cardiovascular morbidity
- Documenting the unmet needs
- Unique environmental factors (microbiome, etc.)
- Efficacy and toxicity of anti-cancer treatment

EORTC
The future of cancer therapy

Relevant issues for young-onset cancer patients



RAMBAM Health Care Campus

EORTC
The future of cancer therapy

Treatment-related toxicities

- Reproductive/Sexual outcomes
- Cardiovascular morbidity
- Secondary cancers

RAMBAM
Health Care Campus

EORTC
The future of cancer therapy

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

New-Onset Cardiovascular Morbidity in Older Adults With Stage I to III Colorectal Cancer

Kelly M. Kenzik, Courtney Balentine, Joshua Richman, Meredith Kilgore, Smita Bhatia, and Grant R. Williams

Chemotherapy-induced vascular toxicity

- The authors evaluated from the SEER-Medicare database patients with stage I-III CRC diagnosed at age > 65 years between 2000-2011 (n = 72,408) and compared these patients with a matched cohort of Medicare patients without cancer (n = 72,408).
- Median age at diagnosis of CRC was 78 years (66-106y), and median follow-up was 8 years.
- The 10-year cumulative incidence of new-onset CVD and CHF were 57.4% and 54.5% compared with 22% and 18% for control, respectively ($P < .001$).
- The authors concluded that **older patients with CRC are at increased risk of developing CVD and CHF.**

No evidence regarding young patients… Can we detect the seed of evil?

Kenzik et al., JCO 2018

JAMA Oncology | Original Investigation

Association of Chemotherapy for Solid Tumors With Development of Therapy-Related Myelodysplastic Syndrome or Acute Myeloid Leukemia in the Modern Era

Lindsay M. Morton, PhD; Graça M. Dores, MD, MPH; Sara J. Schonfeld, PhD, MPH; Martha S. Linet, MD, MPH; Byron S. Sigel, BA; Clara J. K. Lam, PhD; Margaret A. Tucker, MD; Rochelle E. Curtis, MA

Editorial page 303

Supplemental content

IMPORTANCE Therapy-related myelodysplastic syndrome or acute myeloid leukemia (tMDS/AML) is a rare, usually fatal complication of chemotherapy, including certain alkylating agents, topoisomerase II inhibitors, and platinum compounds. With the introduction of new chemotherapeutic agents, expanded indications for established agents, and increased neoadjuvant and adjuvant chemotherapy, tMDS/AML risks in the modern age are poorly understood.

OBJECTIVES To quantify tMDS/AML risk after chemotherapy for solid cancer among United States adults since 2000 and correlate tMDS/AML risk patterns with chemotherapy treatment practices.

RESULTS Based on 1619 tMDS/AML cases in the SEER database (mean [SD] age, 64.3 [12.2] years; 1148 [70.9%] female), tMDS/AML risks were statistically significantly elevated after chemotherapy for 22 of 23 solid cancers (all except colon). Relative risks ranged from 1.5 to greater than 10 and excess absolute risks from 1.4 to greater than 15 cases per 10 000 person-years compared with the general population. Overall survival following tMDS/AML diagnosis was poor (1270 of 1619 patients [78.4%] died; median overall survival, 7 months). For patients treated with chemotherapy at the present time, approximately three-quarters of tMDS/AML cases expected to occur within the next 5 years will be attributable to chemotherapy. In the SEER-Medicare database, use of known leukemogenic agents, particularly platinum compounds, in initial chemotherapy increased substantially since 2000, most notably for gastrointestinal tract cancers (esophagus, stomach, colon, and rectum; 10% in 2000-2001 to 81% during 2012-2013).

Young-Onset Colorectal Cancer Task Force (GITCG)

- Registry with Biobanking / Translational Research
- Quality of life issues
- Causation: Diet, Ethnicity
- Long-term toxicities
- Future design of clinical trials

EORTC
The future of cancer therapy

Study Protocol

CRC patients <50

- **Registry (prevalence + clinical data)**
- **Tissue sample storage**

Curable disease –

- **Non-metastatic**
- **Oligometastatic**

Female patients >43 **Male patients >45**	**Female patients <43** **Male patients <45**
• **Cardiovascular** • **QOL** • **Microbiome** • **Disease outcome** • **Dietary Quest.**	• **Fertility** • **Cardiovascular** • **QOL** • **Microbiome** • **Disease outcome** • **Dietary Quest.**

Late – 5y:
Registry of morbidity
Pregnancies/ART
Disease outcome

Survivorship– 10y:
Registry of morbidity

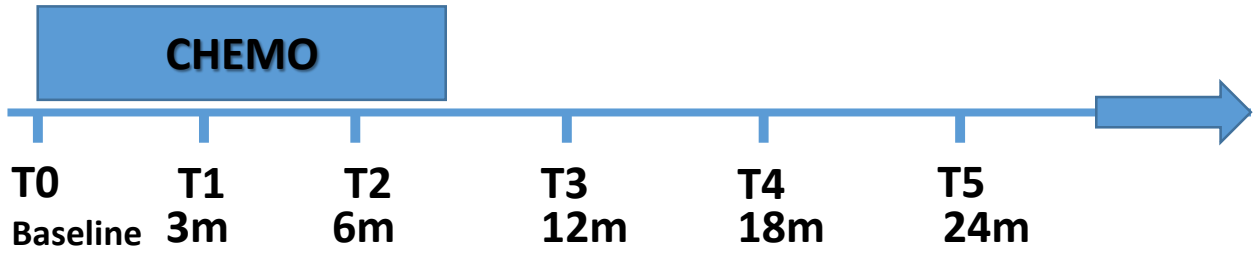
EORTC
The future of cancer therapy

Study design

Inclusion criteria: CRC, age<43y (F) <45 (M)

Early evaluation (0-2y)

- Clinical data
- Menstrual documentation
- Fertility biomarkers
- Vascular biomarkers
- QOL questionnaires (EORTC)
- Toxicity assessment
- Microbiome

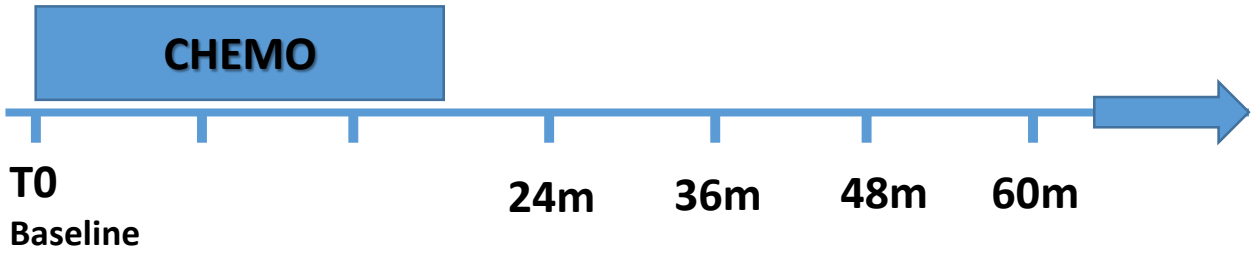


Study design

Inclusion criteria: CRC, age<43y (F) <45 (M)

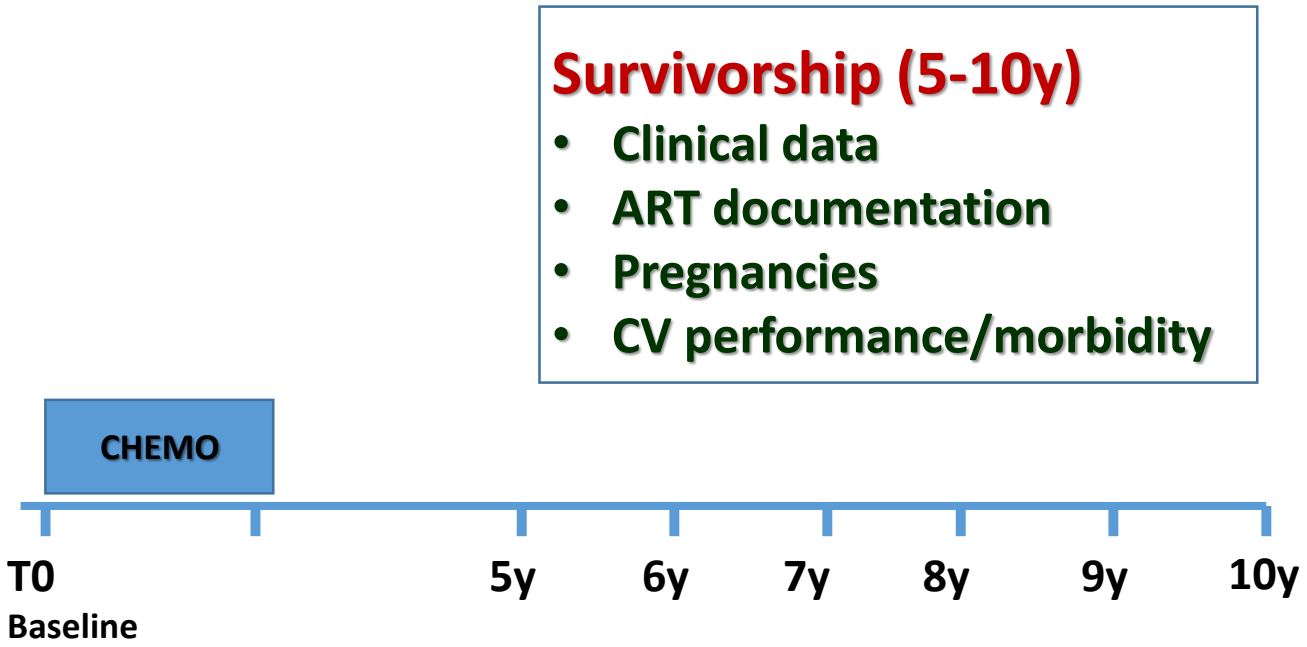
Late evaluation (2-5y)

- **Clinical data**
- **Menstrual documentation**
- **ART documentation**
- **Pregnancies**
- **CV performance/morbidity**



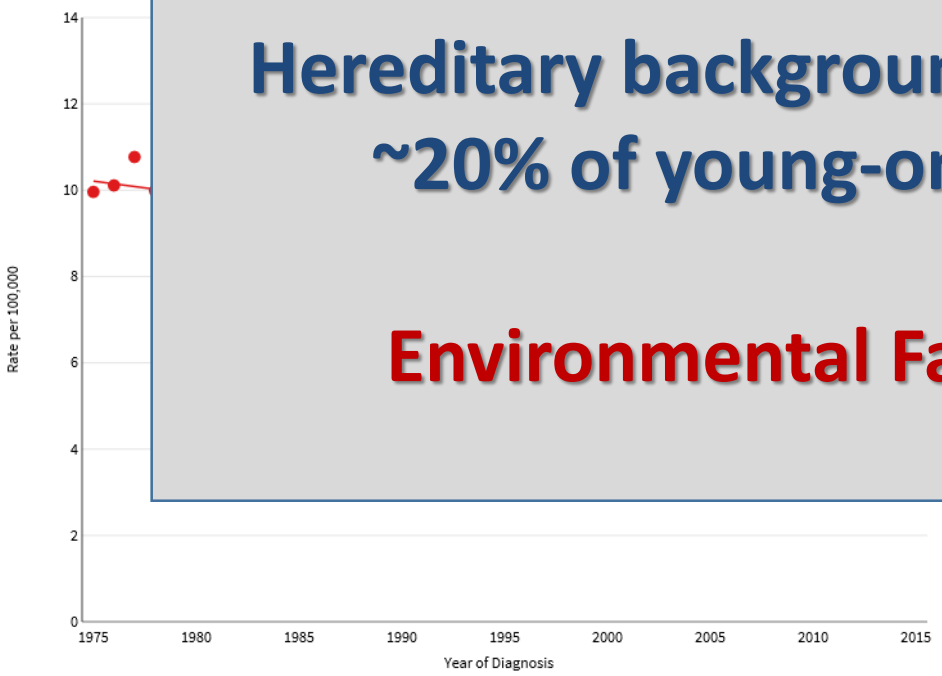
Study design

Inclusion criteria: CRC, age<43y (F) <45 (M)



Statistics:

Digestive tract Cancer
Long-Term Trends in SEER Incidence Rates, 1975-2015
<50y

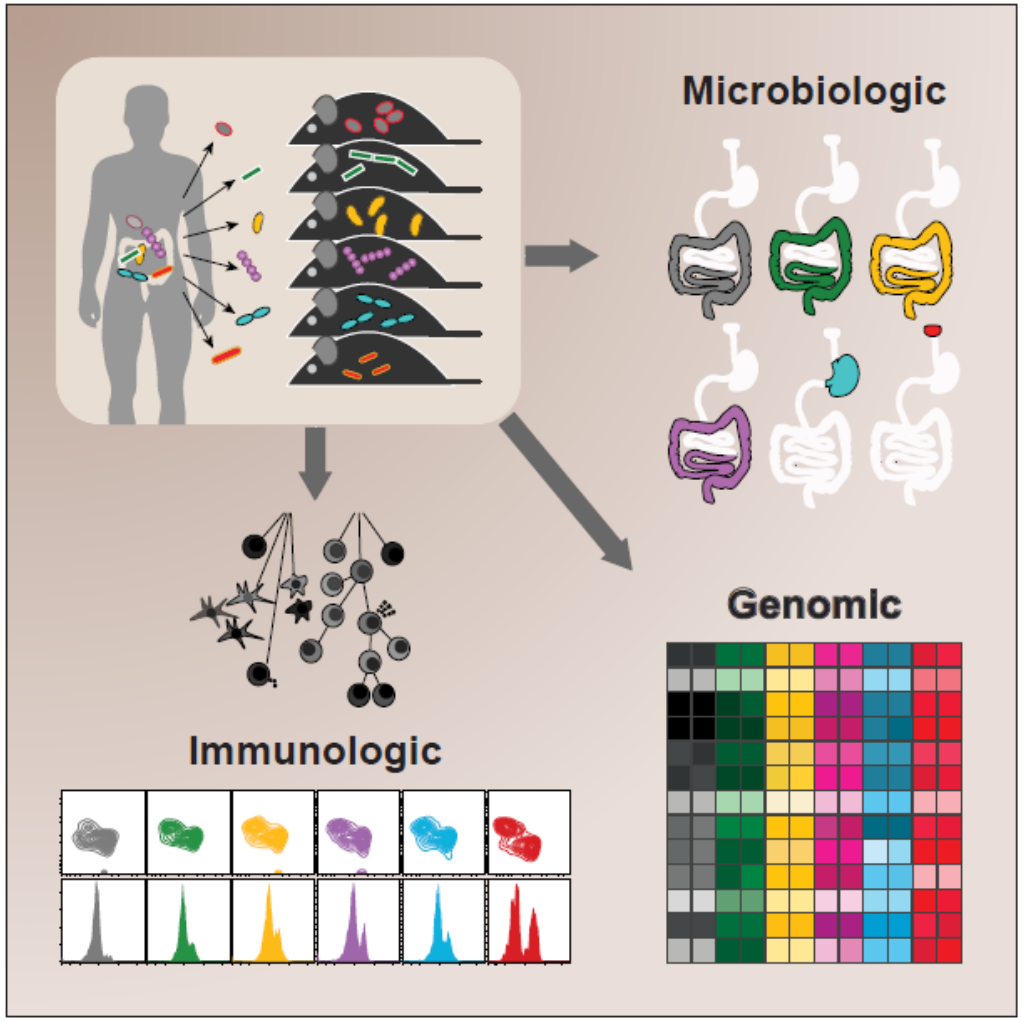


Hereditary background underlies ~20% of young-onset CRC

Environmental Factors??

http://seer.cancer.gov/statfacts/html/

Potential interaction between microbiome and the immune system



Geva-Zatorsky et al., Cell 2017

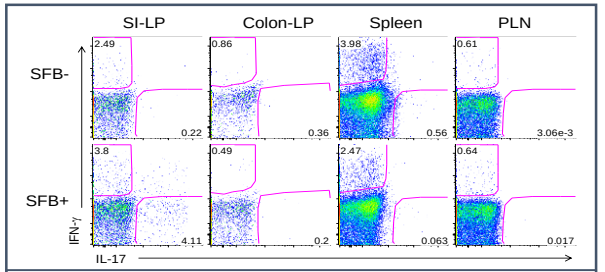
Studying the functional potential of the microbiota

Analysis

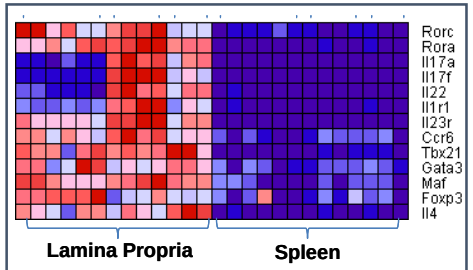
Plasma

Biopsy

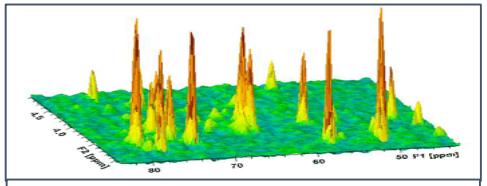
Rectal Swab



Immunologic profiling
- Cell/lineage frequencies, differentiation



Genomic Profiling



Metabolic Profiling (blood)

Geva-Zatorsky et al., Cell 2017

Status (4/2019)

- Protocol was approved for seed funding by GITCG - EORTC
- Initial funding from the GITCG will be used for establishment of collaborative infrastructure – sited were determined
- The protocol is being finalized nowadays - local sites

EORTC
The future of cancer therapy

Pilot prospective study sites – Participating sites

Country	PI
UK	Lizzy Smyth (Cambridge) Jorge Barriuso (Manchester)
Israel	Irit Ben-Aharon
Germany	Maren Knodler (Leipzig) Markus Moehler (Mainz)
Norway	Marianne Goren
Italy	Chiara Cella
Spain	Elena Elez
Czech Republic	Radka Obermannova
Estonia	Anneli Elme
Poland	Lucjan Wyrwicz
Portugal	TBD
Cyprus	Demetris Papamichael
Japan (JCOG)	Mitsumi Terada

EORTC
The future of cancer therapy

Progress Depends on Collaboration

“To go fast,
go alone.

To go far,
go together.”

--African Proverb

European Study of Early-Onset Colorectal Cancer (EUREOC): A Collaborative Study of the Biology of Young Onset CRC

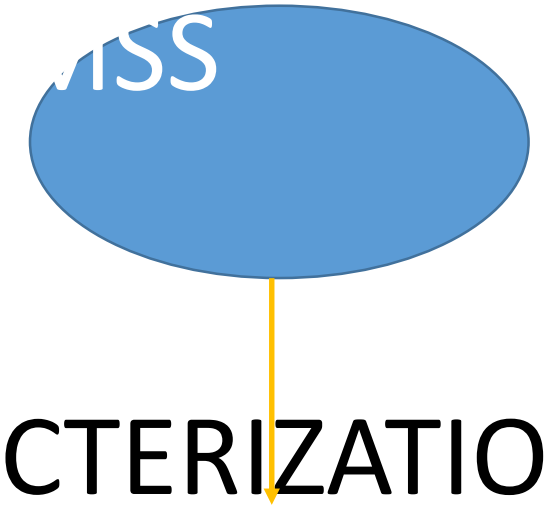
JOSÉ PEREA GARCÍA

Surgery Department. Fundación Jiménez Díaz University Hospital, Madrid. Spain.
Cancer Group. Research Institute FJD.

COLORECTAL CANCER RESEARCH TRASLATIONAL

MULTICENTER GROUP

EOCRC



CHARACTERIZATION:

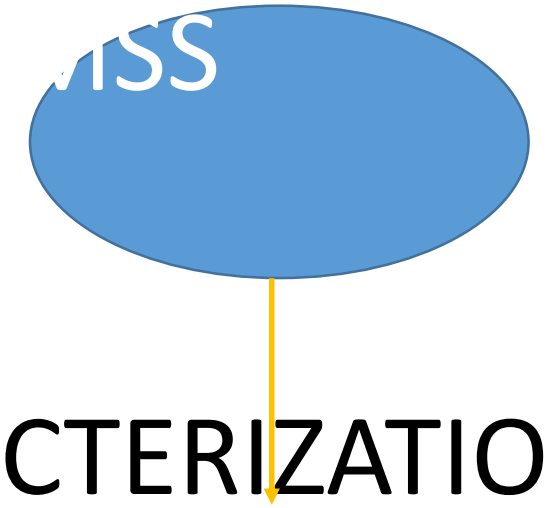
Comparative analysis of carcinogenetic pathways (LOCRC).

Other approaches: Colon locations, etc

aCGH. Identification of possible EOCRC-related genes.

.

EOCRC



CHARACTERIZATION:

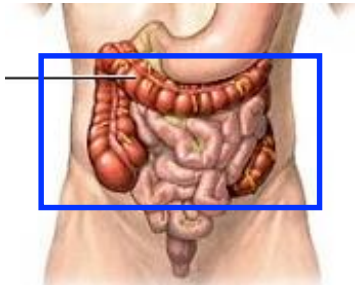
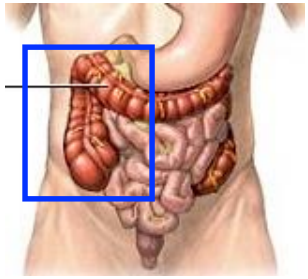
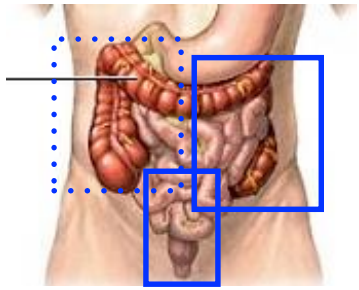
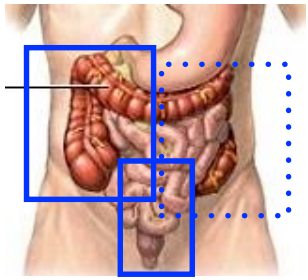
Comparative analysis of carcinogenetic pathways (LOCRC).

Other approaches: Colon locations, etc

aCGH. Identification of possible EOCRC-related genes.

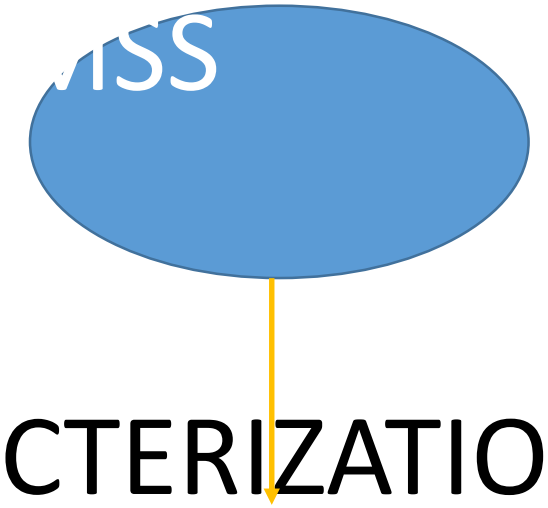
.

EOCRC vs LOCRC. MSI/MSS

MSI EOCRC	MSI LOCRC	MSS EOCRC	MSS LOCRC
MALE	FEMALE	BOTH GENDERS	BOTH GENDERS
			
DUKES A y B	DUKES B	DUKES A, B,C,D	DUKES B,C,D
LS HISTOLOGY	*BRAF MUTATION*	FAMILIAL AGGREGATION AND SPORADIC CRC	SPORADIC CRC
FAMILIAL AGGREGATION LS.			

Perea J et al. J Mol Diagn, 2014

EOCRC



CHARACTERIZATION:

Comparative analysis of carcinogenetic pathways (LOCRC).

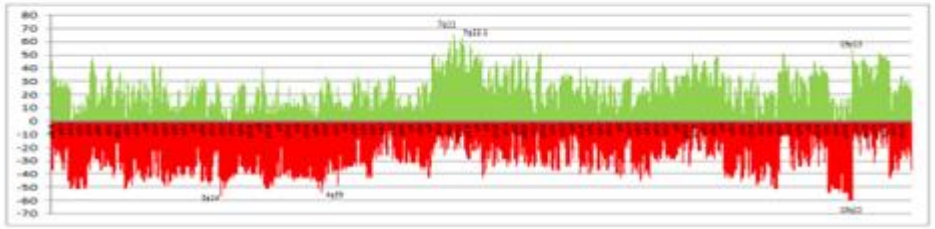
Other approaches: Colon locations, etc

aCGH. Identification of possible EOCRC-related genes.

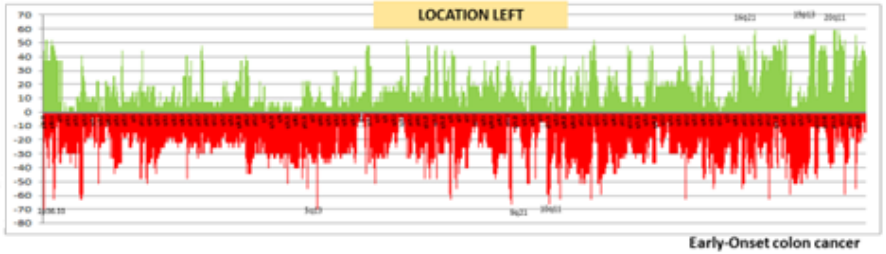
.

Comparative study between EOCRC and LOCRC (R-R; L-L; Rc-Rc)

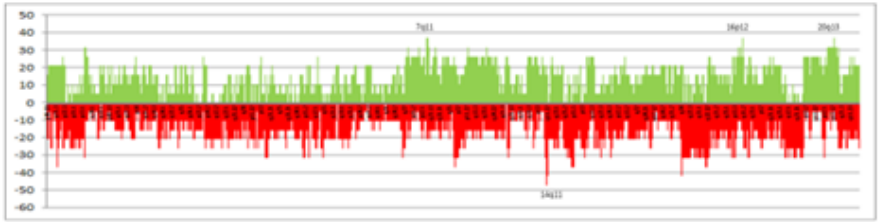
Early-Onset colon cancer



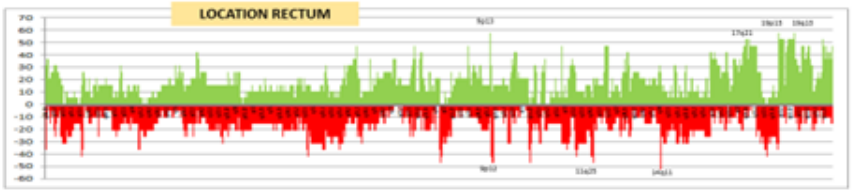
Late-Onset colon cancer



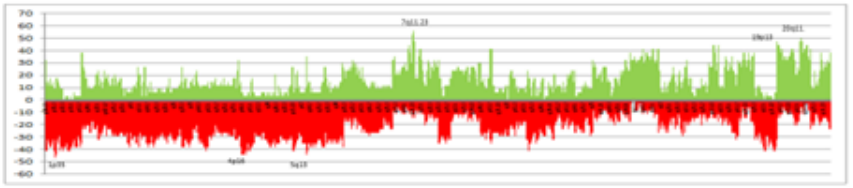
Early-Onset colon cancer



Late-Onset colon cancer



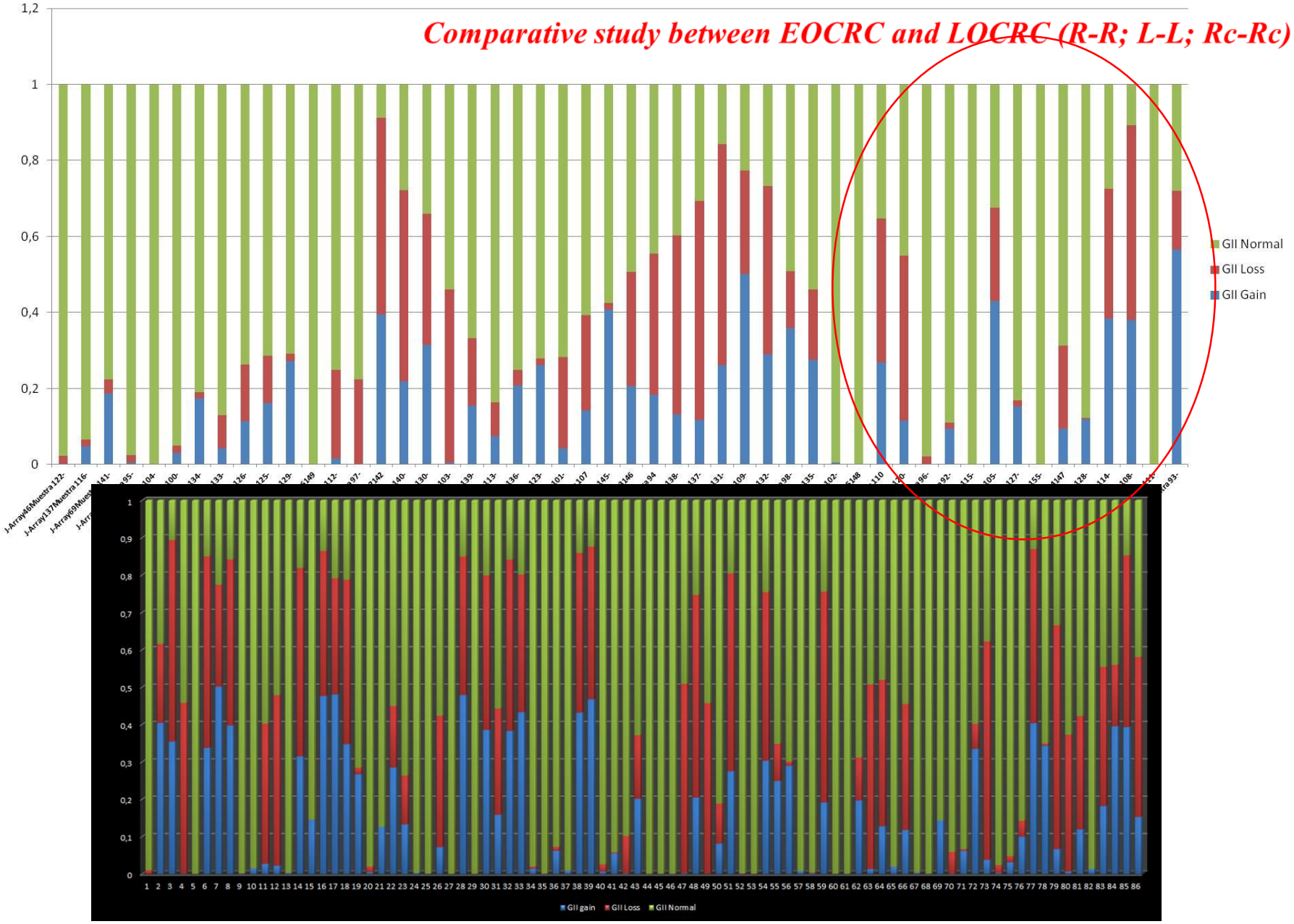
Early-Onset colon cancer



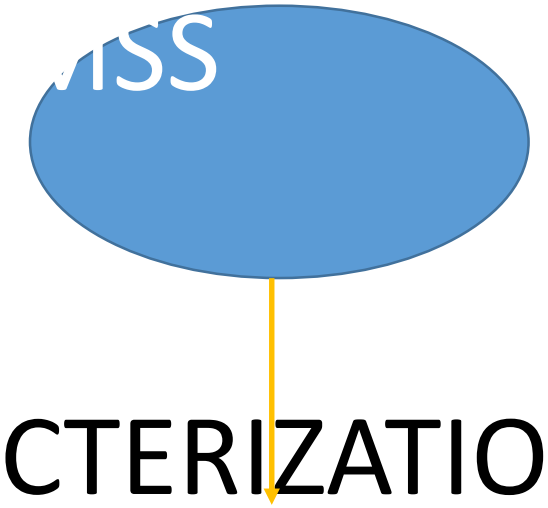
Late-Onset colon cancer

Álvaro E. et al. Int J Mol Sci 2019

Comparative study between EOCRC and LOCRC (R-R; L-L; Rc-Rc)



EOCRC



CHARACTERIZATION:

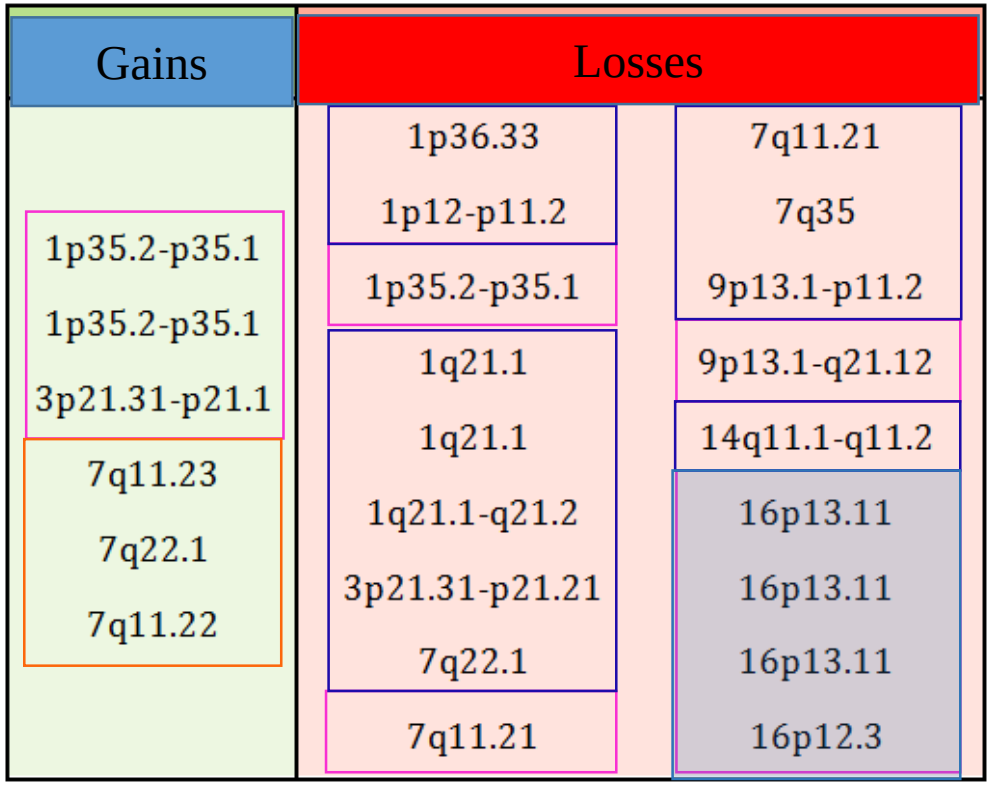
Comparative analysis of carcinogenetic pathways (LOCRC).

Other approaches: Colon locations, etc

aCGH. Identification of possible EOCRC-related genes.

.

- **Common CNVs and/or potentially group-specific**:



p≤0,05
FDR≤0,09

Very frequent within EOCRC and very rare in LOCRC.

More frequent within EOCRC than in LOCRC.

More frequent within LOCRC than in LOCRC.

Arriba M et al. Mol Carcinogen, 2016

EOCRC. *NOMO1* status

- 20 EOCRC of the initial cohort <u>with</u> 16p13.12-p13.11 deletion

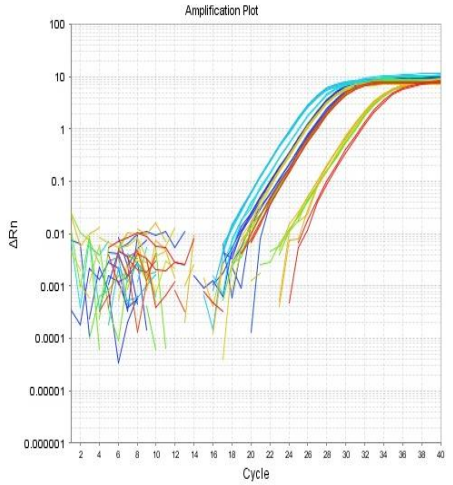
  All of them with *NOMO1* homozygous loss

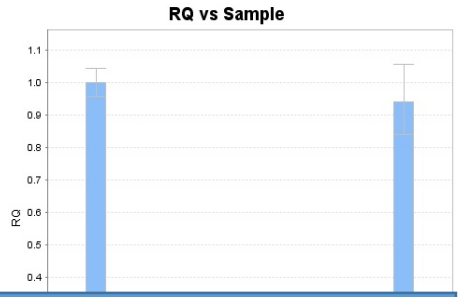
- 14 EOCRC of the initial cohort <u>without</u> 16p13.12-p13.11 deletion

  All of them with *NOMO1* homozygous loss

- 60 additional EOCRC
  - 25 *NOMO1* homozygous loss
  - 9 *NOMO1* heterozygous loss
  - 26 *NOMO1* normal

Total
59 (62.7%) *NOMO1* homozygous loss
9 (9.5%) *NOMO1* heterozygous loss
26 (27.6%) *NOMO1* normal





> 90% MSS

Perea J et al. Oncotarget 2017

16p13.11 REGION

TUMOR SAMPLES

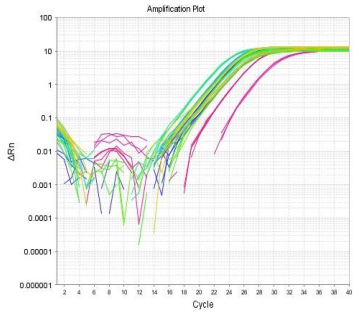
EOCRC: n=94

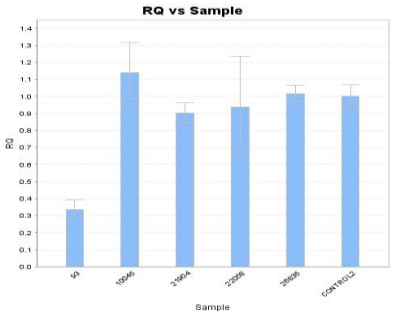
- •Homozygosis: 59 (62.7%)
- •Heterozygosis: 9 (9.5%)
- •Normals: 26 (27.6%)

LOCRC: n=67

- •Homozygosis: 3 (4.5%)
- •Heterozygosis: 9 (13.4%)
- •Normals: 55 (82.1%)

PERYPHERAL BLOOD SAMPLES





Peripheral blood DNA: n=13 (9 somatic homozygotic deletion)

- •Homozygosis: 0
- •Heterozygosis: 0
- •Normals: 13 (100%)

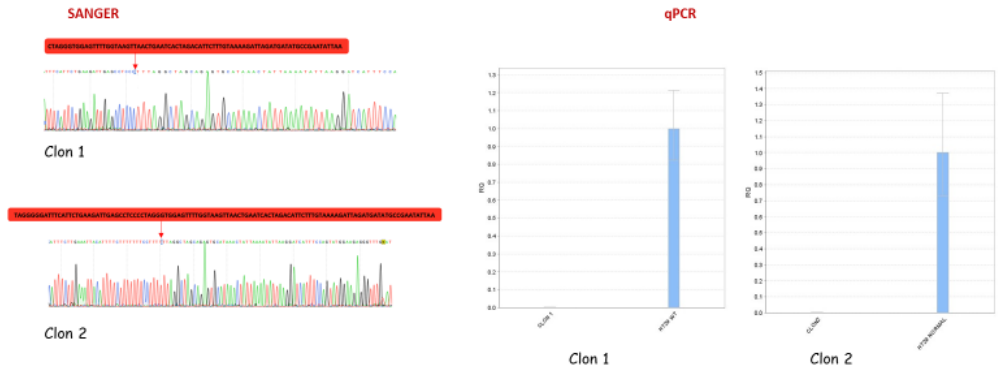
Intermediate: Between 45 and 70 y/o. n=50

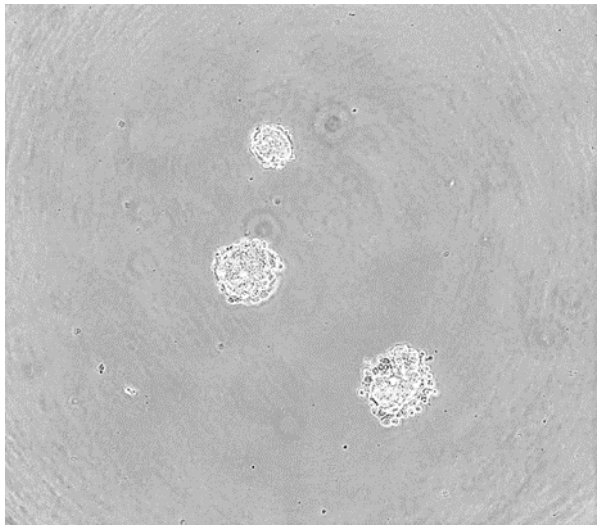
- •Homozygosis: 5 (10%)
- •Heterozygosis: 10 (20%)
- •Normals: 35 (70%)

Perea J et al. Oncotarget 2017

IN-VITRO STUDIES

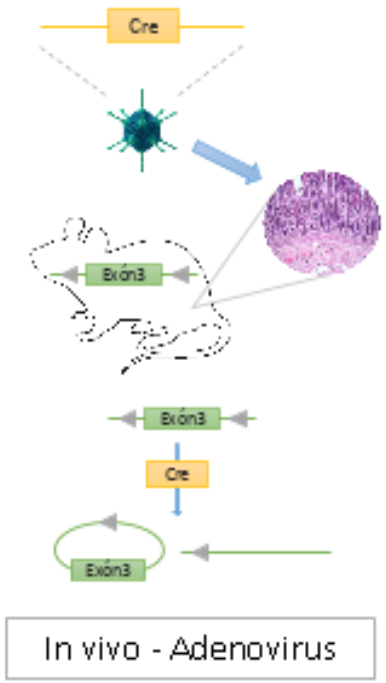
GENERATION OF A KNOCKOUT CELLULAR LINE FOR NOMO THROUGH GENE EDITION TECHNIQUE CRISPR / CAS9

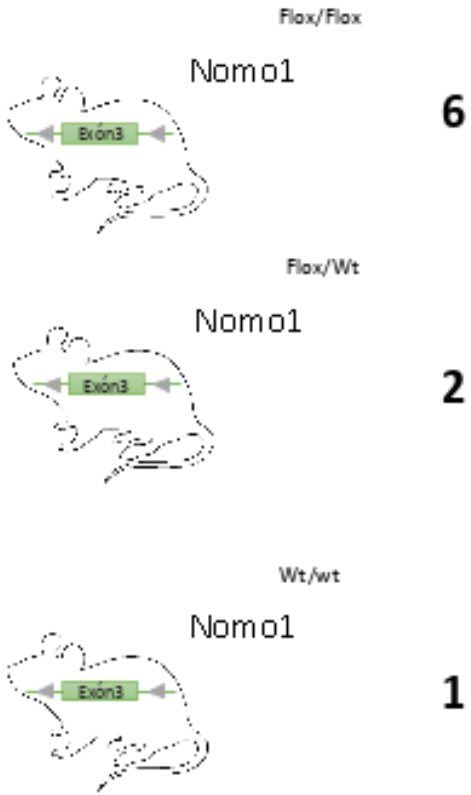




IN-VIVO STUDIES

GENERATION OF CONDITIONAL KNOCKOUT MICE





NEXT STEPS OVER *NOMO1*:

- **Retrospective** study of other populations**:**

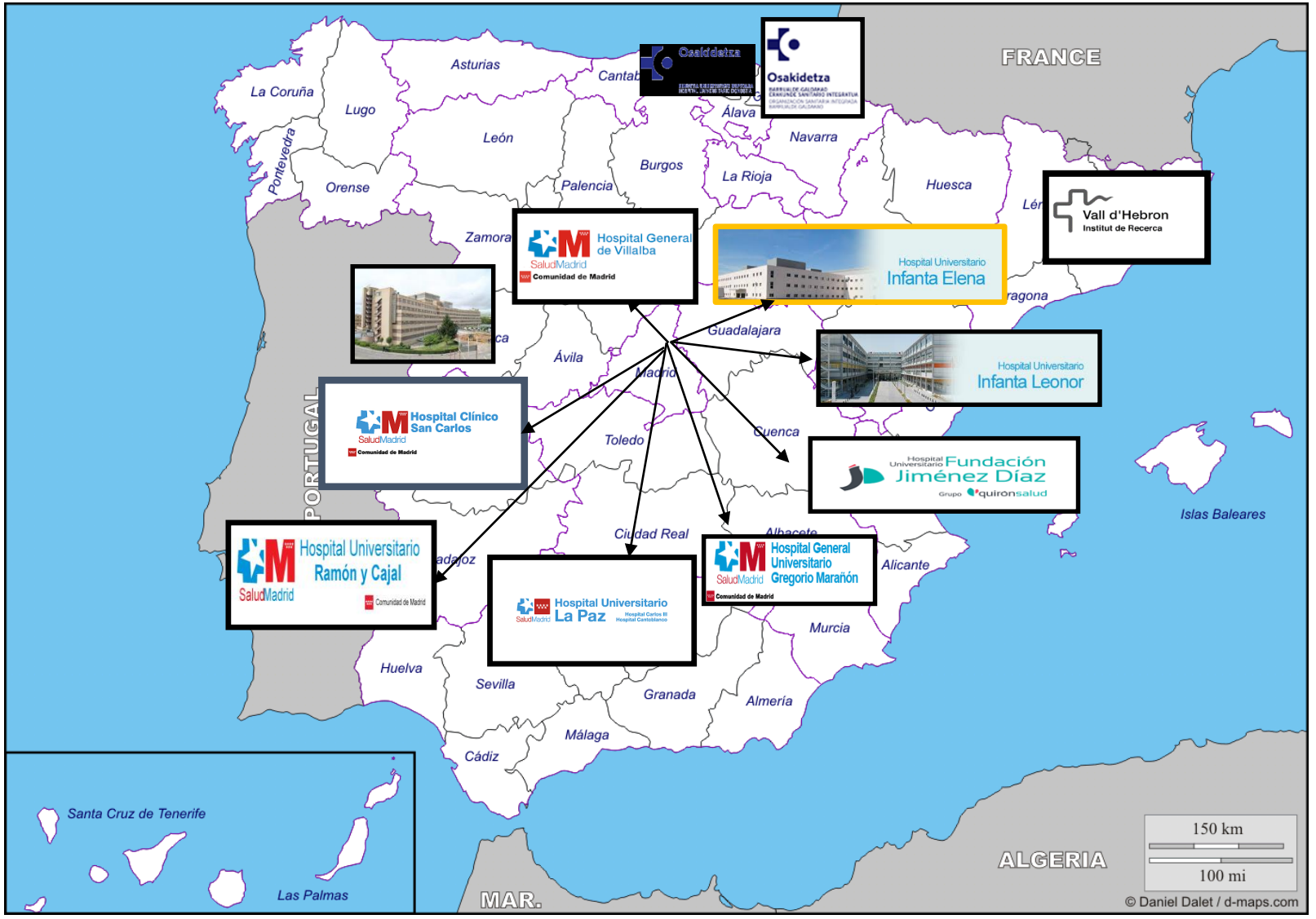
  - Validation sample (EOCRC).
  - Colorectal polyps (<50 y/o).
  - CRC sample without age-of-onset criterion.
  - *NOMO1* status in hepatic metastasis and local recurrence.

- **Prospective** study (EOCRC):

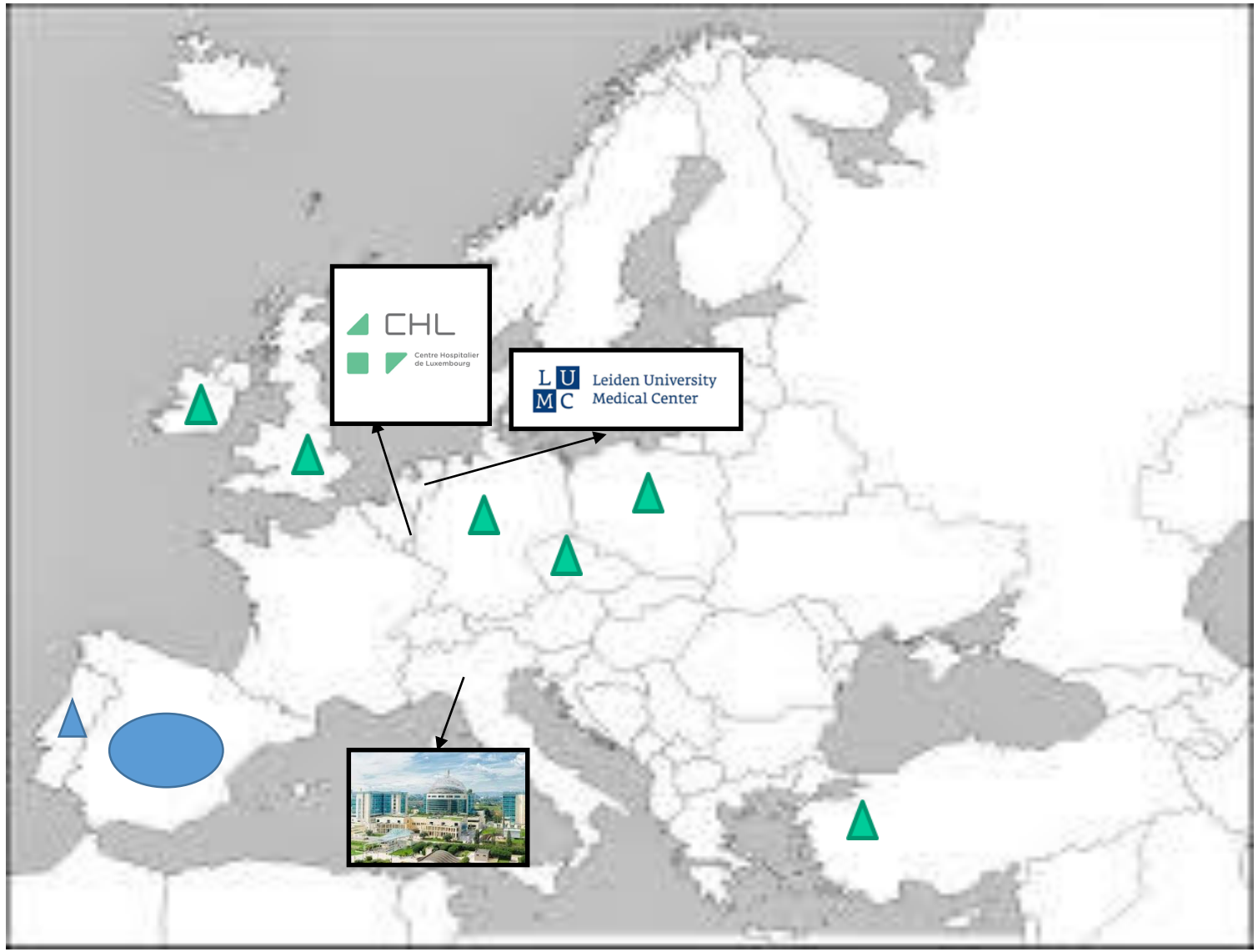
  Liquid biopsy: ~~EARLY DIAGNOSIS / RECURRENCE.~~

  Epidemiological study: ~~enviromental / Microbiome.~~

SPANISH PROSPECTIVE STUDY



EUROPEAN EOCRC STUDY (EUREOC)



WORLDWIDE COLLABORATIONS

SAMPLE COLLECTION

- EOCRC: CRC diagnosed younger than 50 y/o (exclud. IBD)
- Clinical and familial data.
- Epidemilogical questionnaire.

TUMOR AND HEALTHY COLON TISSUE.

STOOL.

PERIPHERAL BLOOD SAMPLES (COMPLETE BLOOD AND PLASMA-SERUM).

EOCRC QUESTIONNAIRE

- Demographic data.
- BMI
- Eating habits
- Other habits: alcohol, smoking and medicines
- Dental history and examination
- Physical activity
- Personal medical history
- Familial medical history

AT THE TIME OF SURGERY: TUMORAL AND HEALTHY TISSUE.
PERIPHERAL BLOOD SAMPLE.

24-48h after surgery, peripheral blood sample (optional).

At the end of the Chemotherapy treatment: SP (optional).

ANNUALLY: BLOOD SAMPLE.
or
RECURRENCE: Tissue and blood sample.

Rectal ADCA: Also, tissue (endoscopy?) and blood sample before neoadjuvant treatment

- **Samples collected and data so far:**

59 EOCRC samples (Spain):

All clinical and familial data. Tumor and normal tissue.
Blood samples (germline and serum/plasma).
5 stool.

47% Rectal; 31% Right; 22% Left.

54 EOCRC samples (Italy)

SOME IMMEDIATE APPROACHES

- Whole exome sequencing.

  APC - / No mutated cases within NGS

- Microbiome-MD2-Obesity and EOCRC.

  Insuline resistance.

- Immunoresponse

APPROACHES OVER *EOCRC*:

SCREENING BASED STRATEGIES.

- Blood-based, **circulating miRNA signature** for the diagnosis-prognosis of patients with EOCRC.
- Defining **risk** populations for EOCRC:

  Obesity/MD2/Insuline resistance.

- **Liquid biopsy:** Early diagnosis and recurrence.

1ST EARLY-ONSET COLORECTAL CANCER

INTERNATIONAL SYMPOSIUM

MADRID
6th JUNE
2019

ColoRectal Cancer in Adults of Young ONset
"CRAYON" Study

Steven Itzkowitz, MD, FACP, FACG, AGAF
Professor of Medicine and Oncological Sciences
Director, GI Fellowship Program
Icahn School of Medicine at Mount Sinai

Mount Sinai

CRAYON Study: Rationale

1. Rates of CRC are increasing among 20-49 yr olds worldwide. Why??
2. Many retrospective studies being performed in USA and abroad.
3. Most experts call for PROSPECTIVE studies to be done.
4. Some prospective studies already being performed (MSKCC, Spain/Europe)
5. Can CRAYON provide more detailed information related to risk factors/causation?

CRAYON Study: Purpose

1. To identify risk factors of Early Onset CRC
2. To use these factors to predict individuals <50 yrs old who are at higher risk of having (current) or developing (future) CRC

CRAYON Study: Why in NYC?

1. NYC GI community: a track record of collaboration

- **C5 Coalition, NYCCO, NYSGE**

2. Density of population conducive to collecting CRC cases and controls in a timely fashion

- **~350 EO-CRC/year (source: NY State Cancer Registry)**

3. Geographic proximity:

- **Relatively shared environmental exposures**
- **Facilitates collaboration, specimen acquisition**
- **Enables patients to be captured even if they change institutions for care**

CRAYON Study: History

October, 2017 NCCRT Summit – initial idea developed

May, 2018 DDW - Imperiale/Itzkowitz

June, 2018 Identify group of interested site PIs

July 24, 2018 First Investigators Meeting

Aug 2018 – Feb 2019 Monthly Conference Calls

Mar 26, 2019 CRAYON Retreat

CRAYON Retreat (Mar 26, 2019)

- **What questions could be answered by CRAYON?**
- **What is the best study design?**
- **Discussion of cases; controls**

CRAYON Investigators

Institution	Investigator	Division/Dept
Mount Sinai	Steven Itzkowitz	GI
	Lina Jandorf	TCI
	Pascale White	GI
	Cristina Villagra	TCI
	Sarah Miller	TCI
	Jamilia Sly	TCI
	Alec Levine	TCI
Columbia	Benjamin Lebwohl	GI
Weill Cornell	Felice Schnoll-Sussman	GI
MSKCC	Robin Mendelsohn	GI
NYU	Peter Liang	GI
Montefiore	Parvathi Myer	GI
Northwell Health	Thomas Weber	Surgery
Indiana University	Thomas Imperiale	GI

CRAYON Retreat: Outside Consultants

Consultant	Institution	Title
Christine Ambrosone	Roswell Park Cancer Institute	Chair, Cancer Prevention & Control
Margaret Du, ScD	MSKCC	Assistant Attending Epidemiologist
Richard Hayes, PhD (unable to attend)	NYU	Professor of Population Health & Environmental Medicine
Elizabeth Kantor, PhD	MSKCC	Assistant Attending Epidemiologist
David Ransohoff, MD	Univ North Carolina	Professor of Medicine; Clinical Prof of Epidemiology
Rebecca Siegel, MPH	American Cancer Society	Strategic Director, Surveillance Information Services
Ann Zauber, PhD	MSKCC	Member, Attending Biostatistician

What questions would you like to see answered by the CRAYON study?

- Is the increasing CRC incidence caused by established risk factors or something novel? What preventable factors exists for EOCRC?
- Is there a target Risk Ratio or Odds Ratio that would be clinically relevant in decision making, and could we reach it with better risk markers?
- Can we capture information regarding early life events, include in utero, early life, and young adult exposure?
- Can we create a registry of all colonoscopies for patients under 50, including both the reason for colonoscopy and the outcome of the colonoscopy?
- To what extent does our population of EOCRC patients have an unknown family history of genetic conditions, such as Lynch Syndrome, that contributes to the development of EOCRC? Can we better educate that sub-population of their risk for EOCRC?

CRAYON: Study Design

- Prospective Case-Control Study
- Cases: individuals age 25-49 with newly diagnosed CRC.
- Controls: individuals age 25-49 from two groups:
  - Colonoscopy-Negative controls (CNC): Underwent colonoscopy for symptoms (change in BM, abd pain, minor bleeding) found to have no neoplasia.
  - Waiting Room Controls: healthy individuals who are escorting patients for colonoscopy and/or colon cancer surgery.
  - ?Friend controls
  - Cases:Controls 1:4 (2 CNC; 2 WRC)
- Eventual Sample size: 400 Cases: 1600 Controls.

CRAYON: Phases of Investigation

Phase	Purpose	Institution	Goal
Phase 1	**Feasibility Study** **(3/19-12/19)**	Mount Sinai	• Enroll cases/controls • Willingness to participate
Phase 2	**Pilot Study** **(10/19-12/20)**	4-5 Sites	• Expand to other sites • Demonstrate collaboration • Refine instruments/bio-specimens
Phase 3	**Main Study** **(Spring 2020 submission)**	All Sites	• Definitive study

CRAYON: Feasibility Study

- To be conducted at Mount Sinai (Funded: The Chemotherapy Foundation)
- Goal: Enroll 10 Cases and 40 Controls
- Conduct interviews to determine willingness to participate in a study that involves an extensive questionnaire, as well as biospecimen collection.
- Interview Questions:
  - Would you be willing to spend 1-2 hours for the initial interview?
  - Would you be willing to complete annual follow-up surveys?
  - We want to learn more about your early childhood experiences. Do you think your parents would be willing to participate? Would you be able to ask them?
  - Would you be willing to provide a blood sample? Stool sample? Saliva sample? Baby teeth (if you/your parents have them)?
  - [For Cases]: Would you be willing to share our flyer and potentially recruit 1-2 friends or family members?

Next Steps

- **Work on Feasibility Study**
- **Prepare for Retreat #2 (Sept 2019)**
- **Develop sites for Pilot phase**
- **Explore funding sources for pilot projects**

CRAYON Study: Rationale

1. Rates of CRC are increasing among 20-49 yr olds worldwide. Why??
2. Many retrospective studies being performed in USA and abroad.
3. Most experts call for PROSPECTIVE studies to be done.
4. Some prospective studies already being performed (MSKCC, Spain/Europe)
5. Can CRAYON provide more detailed information related to risk factors/causation?

CRAYON Study: Purpose

1. To identify risk factors of Early Onset CRC
2. To use these factors to predict individuals <50 yrs old who are at higher risk of having (current) or developing (future) CRC

CRAYON Study: Why in NYC?

1. NYC GI community: a track record of collaboration

- **C5 Coalition, NYCCO, NYSGE**

2. Density of population conducive to collecting CRC cases and controls in a timely fashion

- **~350 EO-CRC/year (source: NY State Cancer Registry)**

3. Geographic proximity:

- **Relatively shared environmental exposures**
- **Facilitates collaboration, specimen acquisition**
- **Enables patients to be captured even if they change institutions for care**

CRAYON Study: History

October, 2017 NCCRT Summit – initial idea developed

May, 2018 DDW - Imperiale/Itzkowitz

June, 2018 Identify group of interested site PIs

July 24, 2018 First Investigators Meeting

Aug 2018 – Feb 2019 Monthly Conference Calls

Mar 26, 2019 CRAYON Retreat

CRAYON Retreat (Mar 26, 2019)

- **What questions could be answered by CRAYON?**
- **What is the best study design?**
- **Discussion of cases; controls**

CRAYON Investigators

Institution	Investigator	Division/Dept
Mount Sinai	Steven Itzkowitz	GI
	Lina Jandorf	TCI
	Pascale White	GI
	Cristina Villagra	TCI
	Sarah Miller	TCI
	Jamilia Sly	TCI
	Alec Levine	TCI
Columbia	Benjamin Lebwohl	GI
Weill Cornell	Felice Schnoll-Sussman	GI
MSKCC	Robin Mendelsohn	GI
NYU	Peter Liang	GI
Montefiore	Parvathi Myer	GI
Northwell Health	Thomas Weber	Surgery
Indiana University	Thomas Imperiale	GI

CRAYON Retreat: Outside Consultants

Consultant	Institution	Title
Christine Ambrosone	Roswell Park Cancer Institute	Chair, Cancer Prevention & Control
Margaret Du, ScD	MSKCC	Assistant Attending Epidemiologist
Richard Hayes, PhD (unable to attend)	NYU	Professor of Population Health & Environmental Medicine
Elizabeth Kantor, PhD	MSKCC	Assistant Attending Epidemiologist
David Ransohoff, MD	Univ North Carolina	Professor of Medicine; Clinical Prof of Epidemiology
Rebecca Siegel, MPH	American Cancer Society	Strategic Director, Surveillance Information Services
Ann Zauber, PhD	MSKCC	Member, Attending Biostatistician

What questions would you like to see answered by the CRAYON study?

- Is the increasing CRC incidence caused by established risk factors or something novel? What preventable factors exists for EOCRC?
- Is there a target Risk Ratio or Odds Ratio that would be clinically relevant in decision making, and could we reach it with better risk markers?
- Can we capture information regarding early life events, include in utero, early life, and young adult exposure?
- Can we create a registry of all colonoscopies for patients under 50, including both the reason for colonoscopy and the outcome of the colonoscopy?
- To what extent does our population of EOCRC patients have an unknown family history of genetic conditions, such as Lynch Syndrome, that contributes to the development of EOCRC? Can we better educate that sub-population of their risk for EOCRC?

CRAYON: Study Design

- Prospective Case-Control Study
- Cases: individuals age 25-49 with newly diagnosed CRC.
- Controls: individuals age 25-49 from two groups:
  - Colonoscopy-Negative controls (CNC): Underwent colonoscopy for symptoms (change in BM, abd pain, minor bleeding) found to have no neoplasia.
  - Waiting Room Controls: healthy individuals who are escorting patients for colonoscopy and/or colon cancer surgery.
  - ?Friend controls
  - Cases:Controls 1:4 (2 CNC; 2 WRC)
- Eventual Sample size: 400 Cases: 1600 Controls.

CRAYON: Phases of Investigation

Phase	Purpose	Institution	Goal
Phase 1	**Feasibility Study** **(3/19-12/19)**	Mount Sinai	• Enroll cases/controls • Willingness to participate
Phase 2	**Pilot Study** **(10/19-12/20)**	4-5 Sites	• Expand to other sites • Demonstrate collaboration • Refine instruments/bio-specimens
Phase 3	**Main Study** **(Spring 2020 submission)**	All Sites	• Definitive study

CRAYON: Feasibility Study

- To be conducted at Mount Sinai (Funded: The Chemotherapy Foundation)
- Goal: Enroll 10 Cases and 40 Controls
- Conduct interviews to determine willingness to participate in a study that involves an extensive questionnaire, as well as biospecimen collection.
- Interview Questions:
  - Would you be willing to spend 1-2 hours for the initial interview?
  - Would you be willing to complete annual follow-up surveys?
  - We want to learn more about your early childhood experiences. Do you think your parents would be willing to participate? Would you be able to ask them?
  - Would you be willing to provide a blood sample? Stool sample? Saliva sample? Baby teeth (if you/your parents have them)?
  - [For Cases]: Would you be willing to share our flyer and potentially recruit 1-2 friends or family members?

Next Steps

- **Work on Feasibility Study**
- **Prepare for Retreat #2 (Sept 2019)**
- **Develop sites for Pilot phase**
- **Explore funding sources for pilot projects**

EAO-CRC

EARLY AGE ONSET COLORECTAL CANCER

SUMMIT 2019

THANK YOU