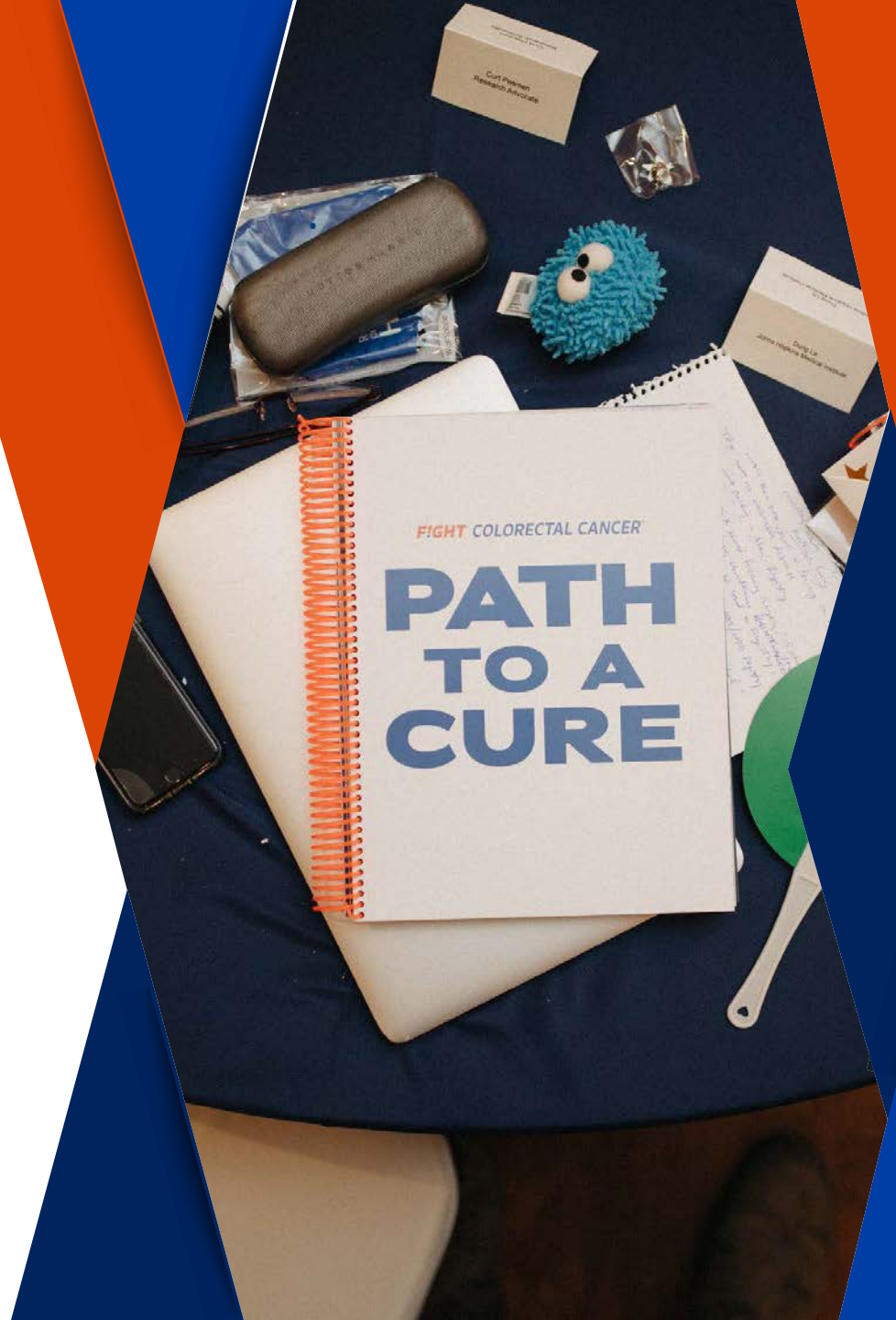
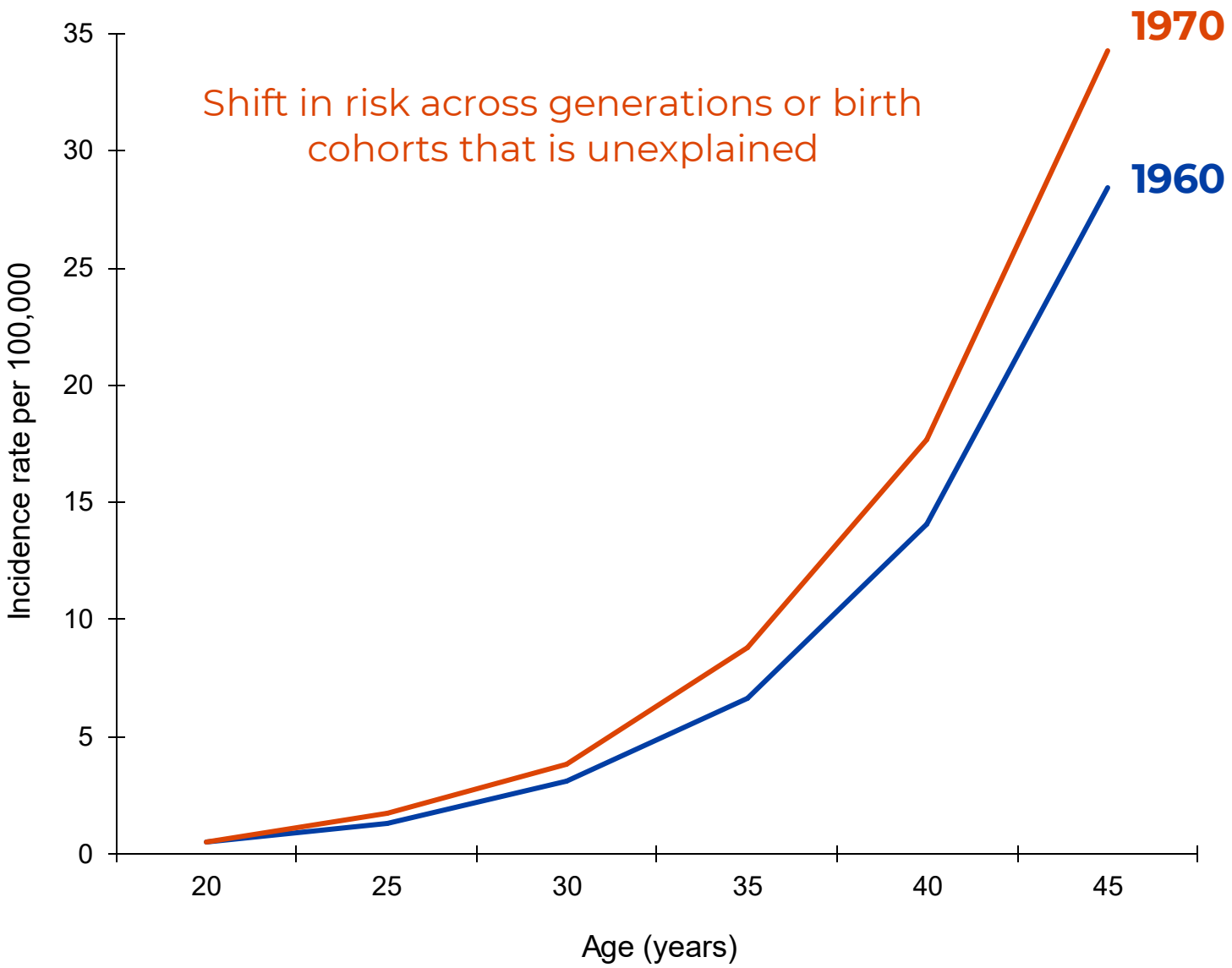
2023 EAO-CRC Think Tank
Breakout Session

Research Opportunities for Biology and Etiology



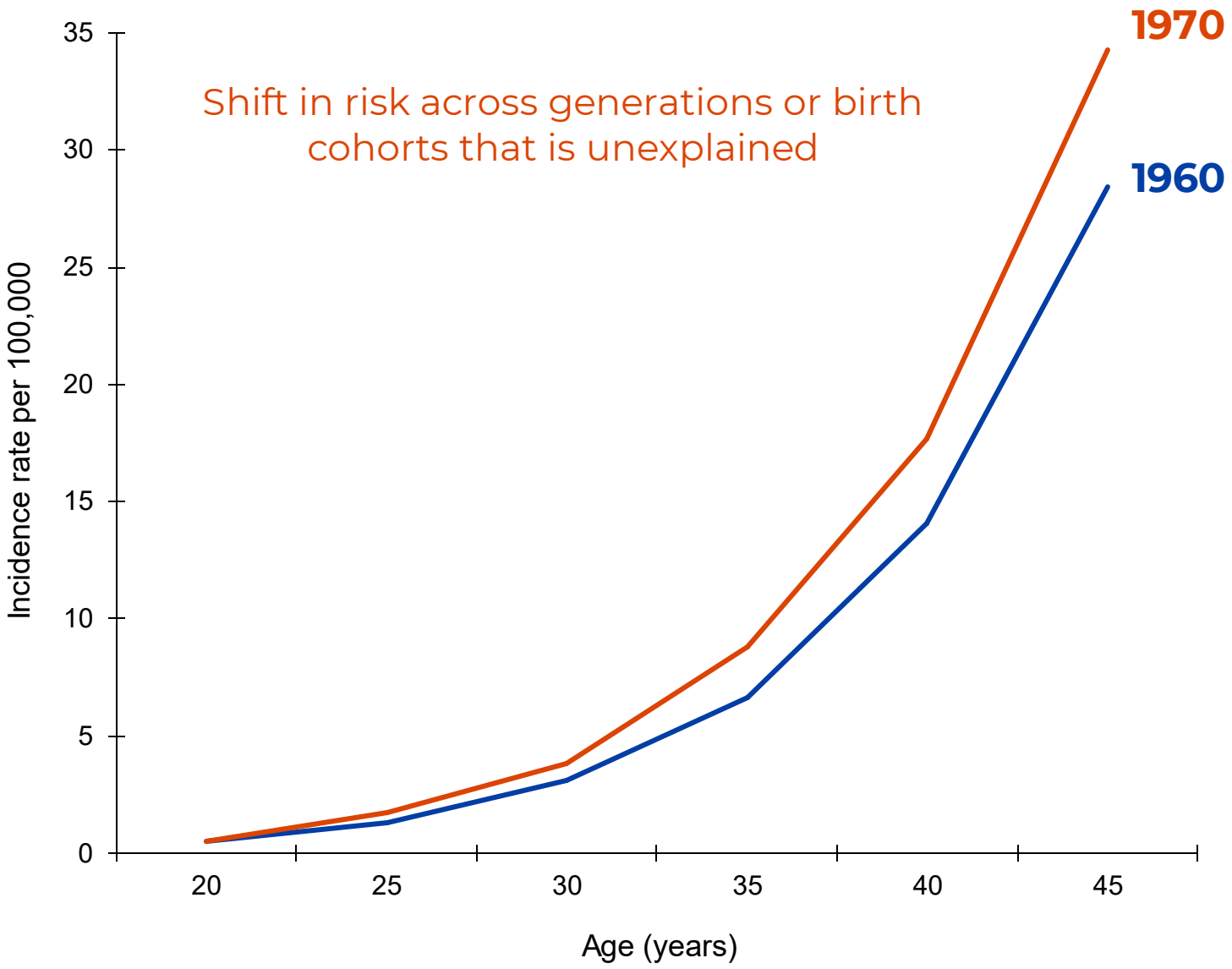
FIGHT COLORECTAL CANCER™

Part II: Biology and Etiology



Data source: SEER 9, 1975 – 2021, Ages 20 – 49 years

Part II: Biology and Etiology



Increases cannot be explained by germline genetics

Environment is a key suspect

Data source: SEER 9, 1975 – 2021, Ages 20 – 49 years

Moderators

Cathy Eng, MD, FACP, FASCO

MODERATOR

SPEAKER

Vanderbilt-Ingram Comprehensive Cancer Center

Caitlin Murphy, PhD, MPH

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UTHealth Houston School of Public Health

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Dean Jones, PhD

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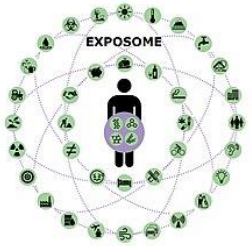
Emory University School of Medicine



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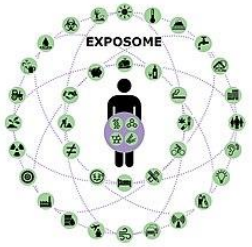
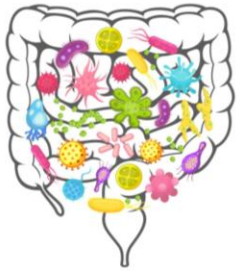


Mariana Byndloss, DVM, PhD

SPEAKER

Vanderbilt-Ingram Comprehensive Cancer Center



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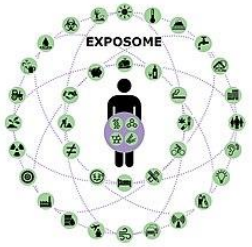

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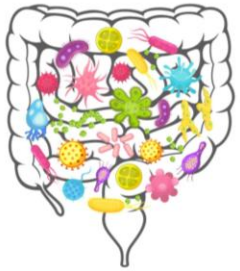

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SPEAKER

Johns Hopkins University School of Medicine

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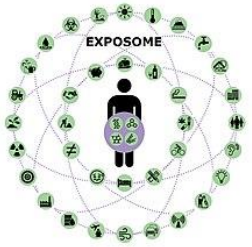

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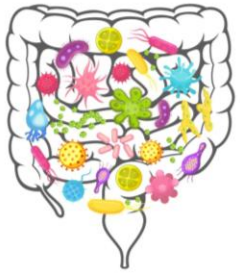

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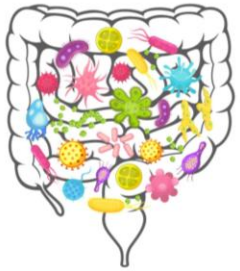

Kit Curtius, BS, PhD

SPEAKER

UC San Diego Moores Comprehensive Cancer Center

Environmental & Occupational Exposures: Key Considerations for Exposome Research

Understanding the exposome as a complement to the genome can be a tool for predicting risk and possibly preventing disease in the future.

Dean Jones, PhD

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Emory University School of Medicine

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The Causes of Cancer: Quantitative Estimates of Avoidable Risks of Cancer in the United States Today

Text section No.	Factor or class of factors	Percent of all cancer deaths	
		Best estimate	Range of acceptable estimates
5.1	Tobacco	30	25–40
5.2	Alcohol	3	2–4
5.3	Diet	35	10–70
5.4	Food additives	<1	–5[a]–2
5.5	Reproductive[b] and sexual behaviour	7	1–13
5.6	Occupation	4	2–8
5.7	Pollution	2	<1–5
5.8	Industrial products	<1	<1–2
5.9	Medicines and medical procedures	1	0.5–3
5.10	Geophysical factors[c]	3	2–4
5.11	Infection	10 ?	1–?
5.12	Unknown	?	?

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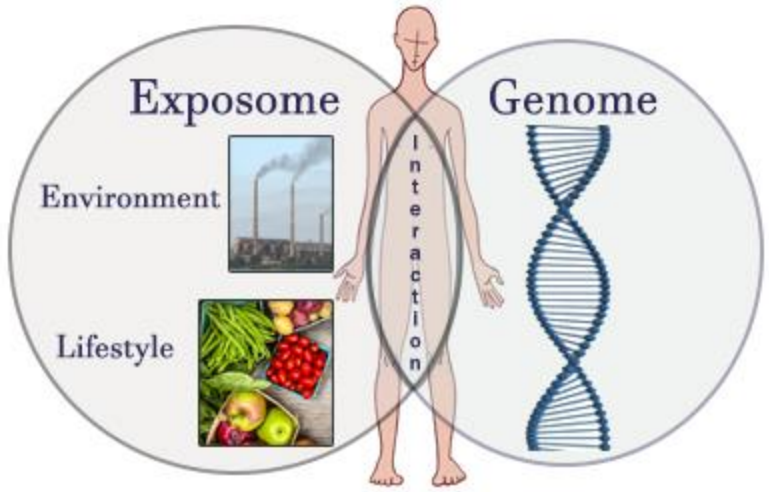
Editorial

Complementing the Genome with an "Exposome": The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology

Christopher Paul Wild

Molecular Epidemiology Unit, Centre for Epidemiology and Biostatistics, Leeds Institute of Genetics, Health and Therapeutics, Faculty of Medicine and Health, University of Leeds, Leeds, United Kingdom



Environmental & Occupational Exposures: Key Considerations for Exposome Research

Dean Jones, PhD

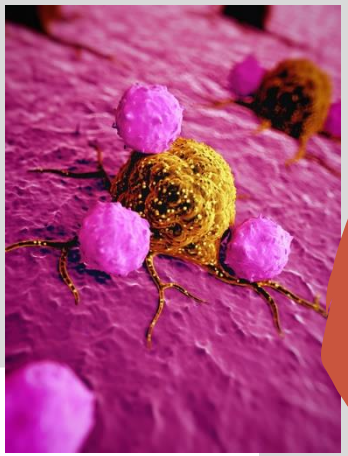
SPEAKER

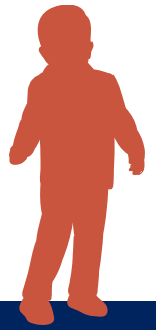
Emory University School of Medicine

Exposure

Biologic response

Health outcomes





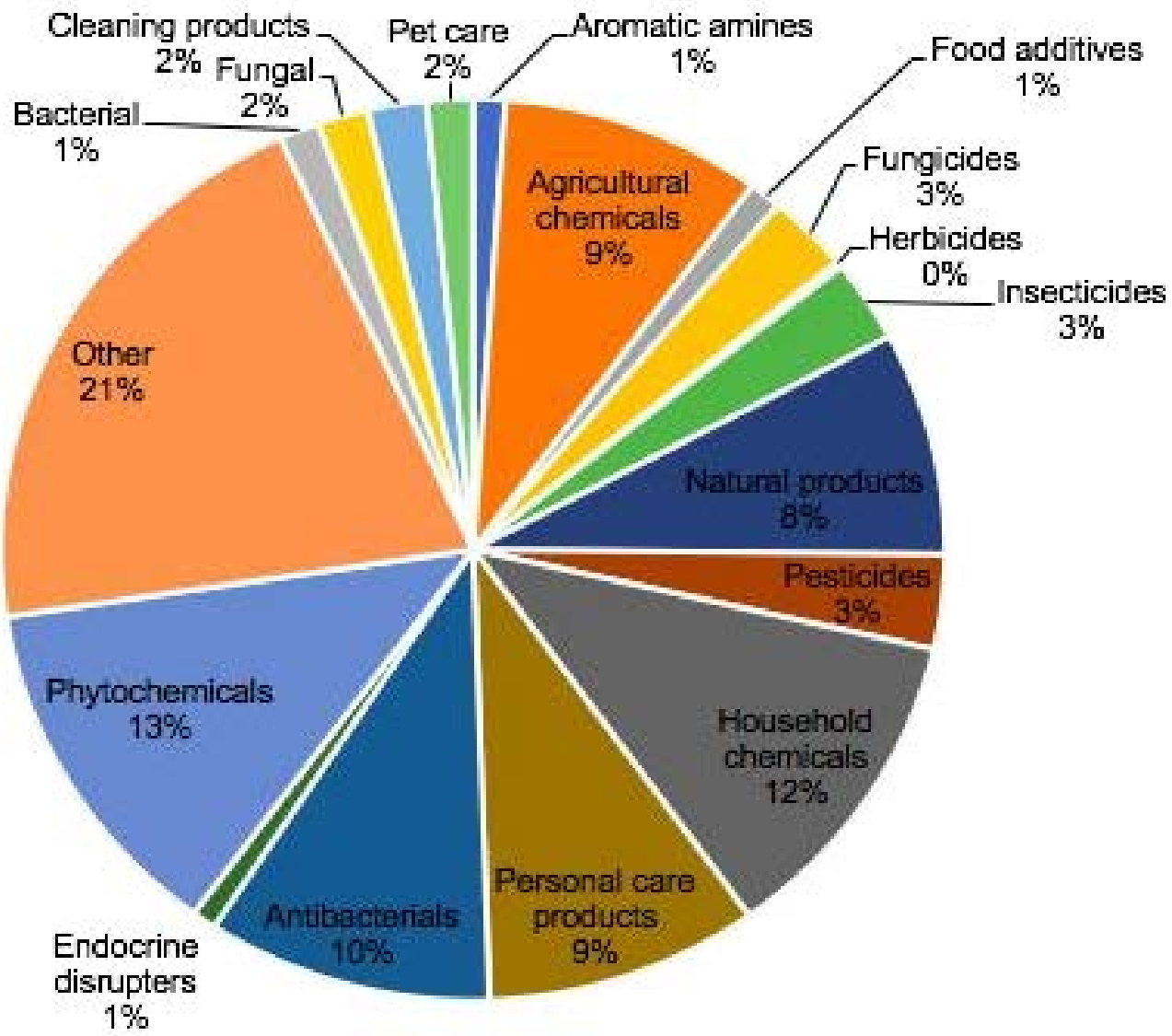
In utero | Birth | Childhood | Adolescence | Adulthood

New Tools to Measure the Exposome

Dean Jones, PhD

SPEAKER

Emory University School of Medicine



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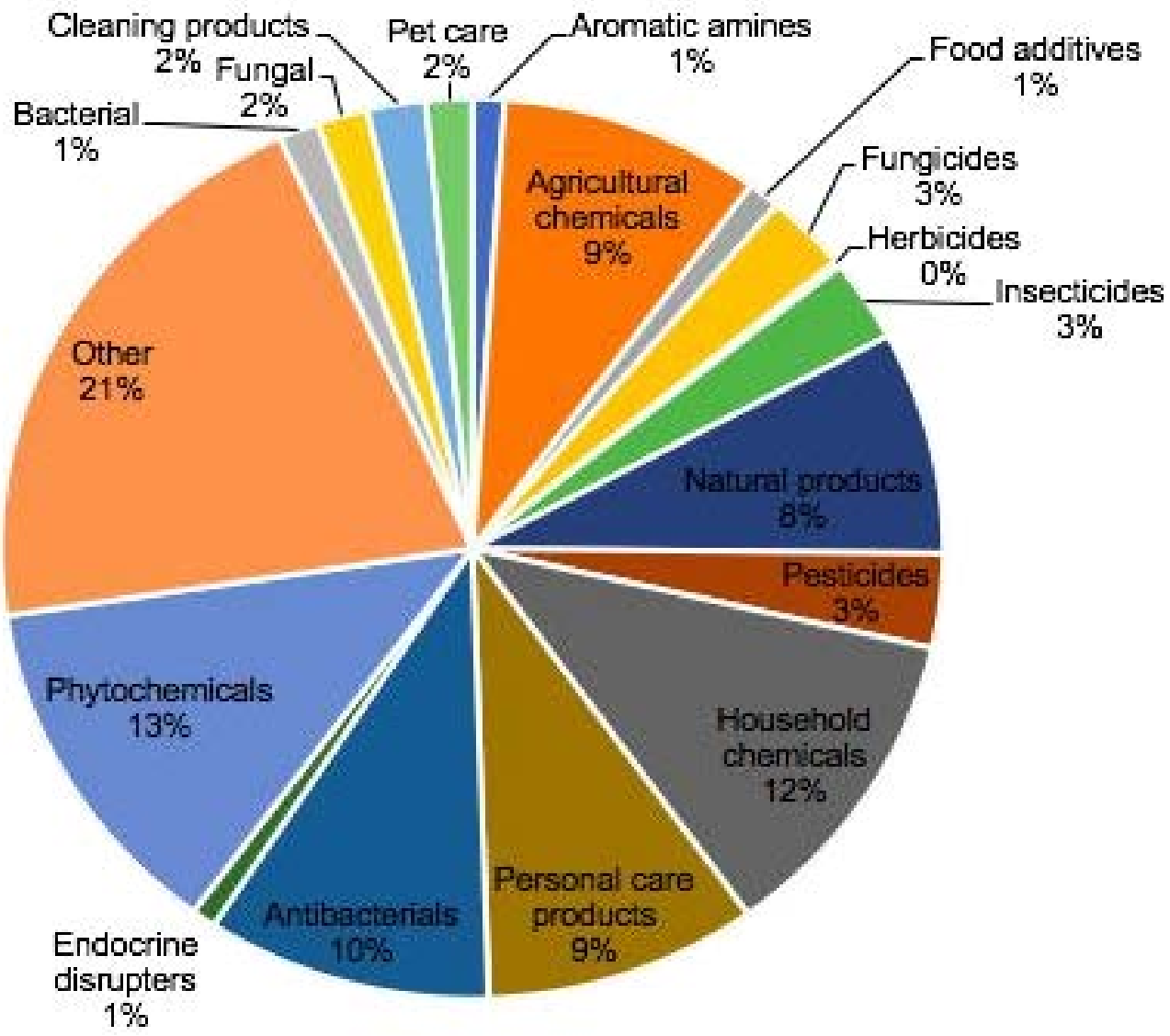


Apply high-resolution mass spectrometry methods to archival samples

↓

Select signals positively associated with outcome

↓

Annotate signals as metabolites or environmental chemicals

↓

Use network analysis to find metabolome-exposome networks

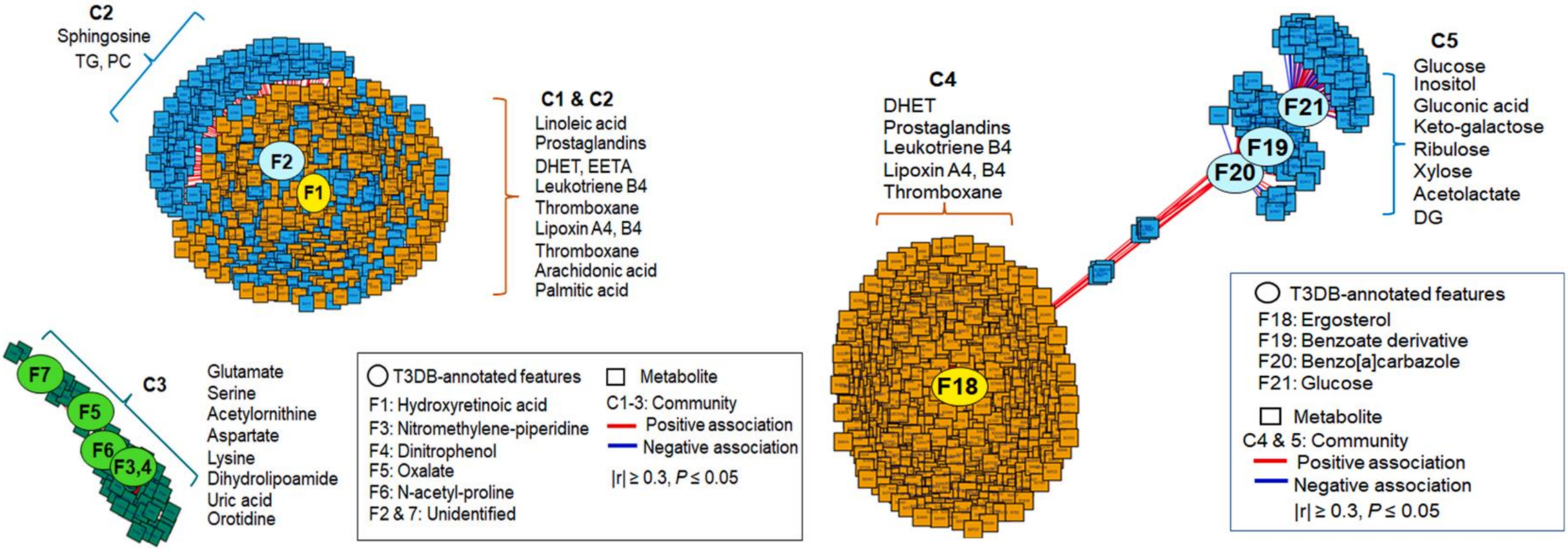
“Exposome Detective Work” Lessons Learned from Breast Cancer

Dean Jones, PhD

SPEAKER

Emory University School of Medicine

Breast cancer is linked to environmental chemicals associated with changes in amino acids known to impact nutrient sensing and cell survival pathways in breast cancer

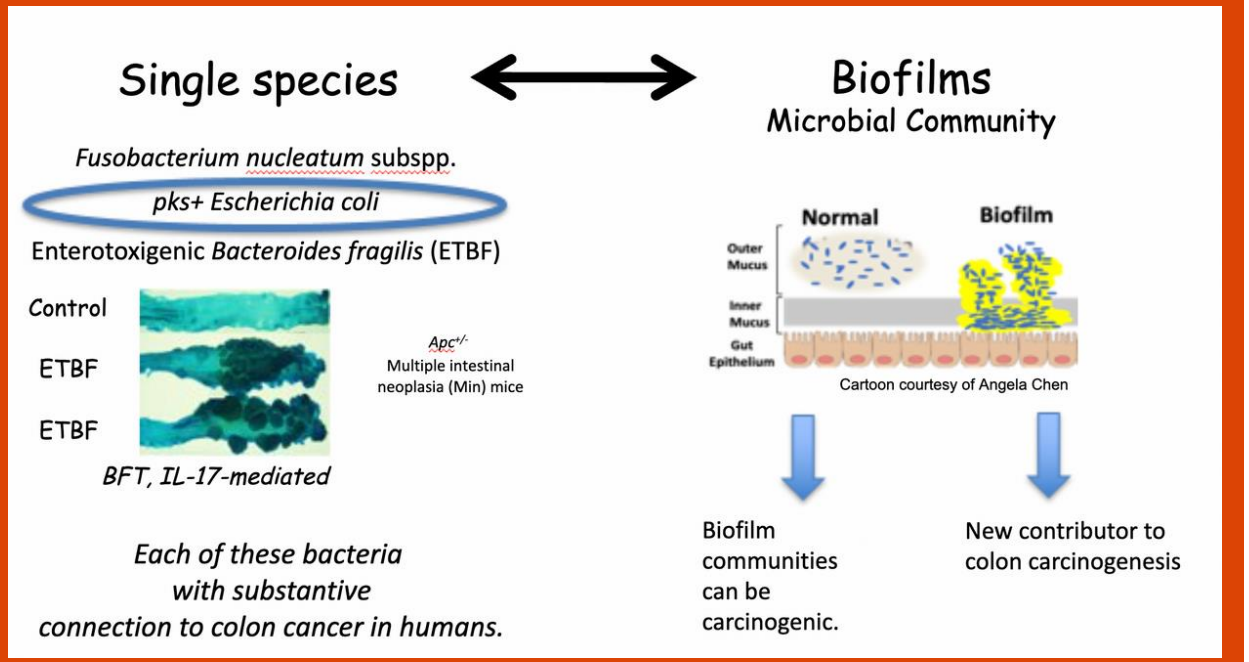


Microbes and Colon Cancer: Where are We?

Cynthia Sears, MD
SPEAKER
Johns Hopkins University School of Medicine

Progress to prevention of CRC requires that we can discern the strains, host contexts and/or identify biomarkers in which colonization with these bacteria pose an oncogenic risk to the individual.

- Two paradigms: single species and biofilm communities.
- Biofilms are newly understood to be contributors to colon carcinogenesis.
- pks+ E. coli are considered a prime candidate for initiating colon tumor development.
- Various studies show associations betweens pks & E.coli colonized individuals and polyp formation, biofilms and polyp formation; and C. difficile initiating colon tumor formation in germ-free mice.



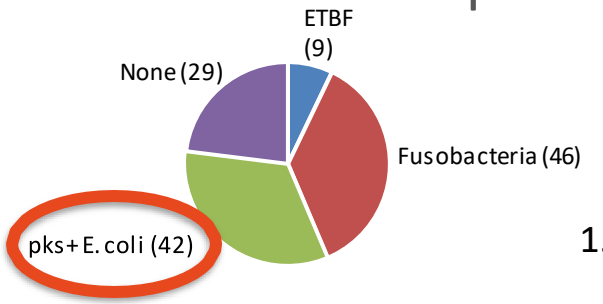
Epidemiology of oncogenic bacteria in those at risk for CRC

ETBF
Fn
pks+ E. coli

Team:
OPTIMISTICC

UK-CRUK
Grand
Challenges

Question:
How often are oncogenic bacteria detected in screening colonoscopy patients & is there an association with polyp formation?



N=98 individuals

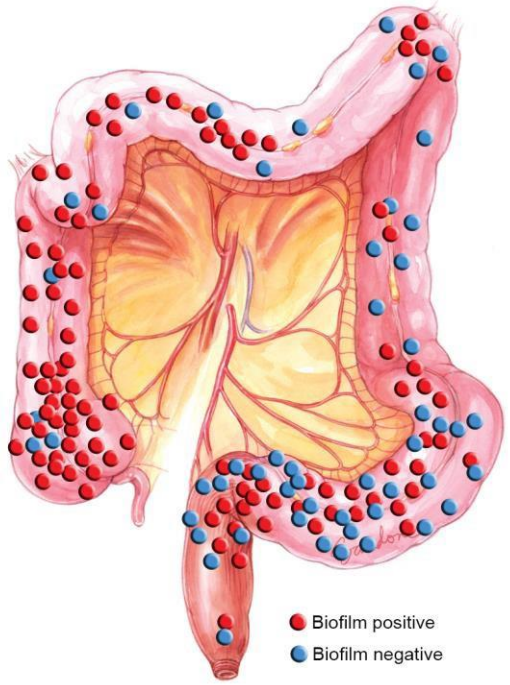
--Fusobacteria common; *F. nucleatum* rare (N=2)
--9 patients (9%), multiple oncogenic bacteria

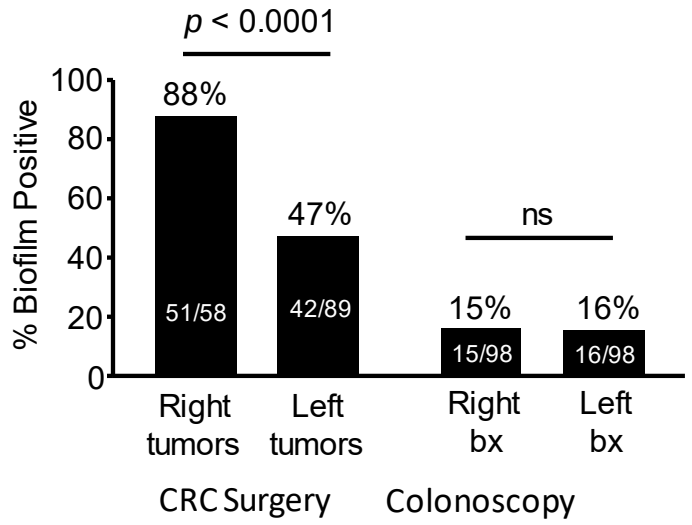
Key Takeaway:
polyps were only more common in *pks+ E. coli*-colonized individuals (unadjusted odds ratios: 3.06 pks Ec colonization alone, 1.32 pks Ec colonization with one or more oncogenic bacteria)

Campódonico V, Geis A et al, unpublished
Martha Shrubsole, VUMC

Biofilms are prevalent in sporadic CRC, particularly in the right colon
(US & Malaysia)

Surgically removed US & MAL tumors





Human

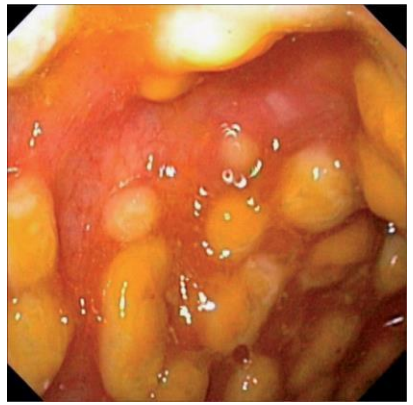
Biofilm+ human colon tissues are pro-carcinogenic:

- Decreased barrier function
- Activation of carcinogenic mucosal & CEC pathways (IL-6, Stat3)
- CEC proliferation
- Tumor induction in Min mice (*Apc*$^{+/-}$) (using 5 CRCs)

CEC, colonic epithelial cell
Min, multiple intestinal neoplasia

Dejea et al, *PNAS* 2014
Johnson et al, *Cell Metab* 2015
Drewes et al, *NPJ Biofilms Microbiomes* 2017
Domingue et al, *Mucosal Immunology* 2020
Tomkovich 2019
JCI

Clostridioides difficile Infection (CDI)
A disease precipitated by antibiotic exposure & microbiota disruption

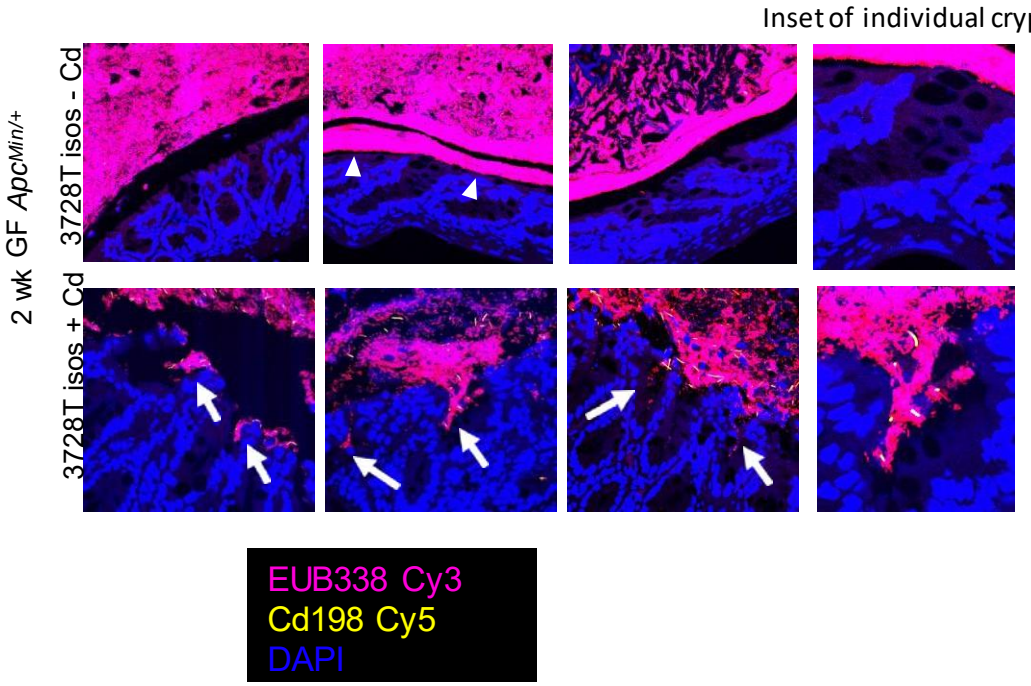


Lancet 371:1486, 2008

Gram-positive, spore-forming obligate anaerobe
Produces two potent toxins: TxA, TxB
Most common health care-associated infection, USA
Leading cause of gastroenteritis death, USA
Data on persistence and impact on human colon over time absent

C. difficile promotes biofilm invasion deep into colonic crypts in distal colons of mice at 2 wk p.i. dependent on TxB

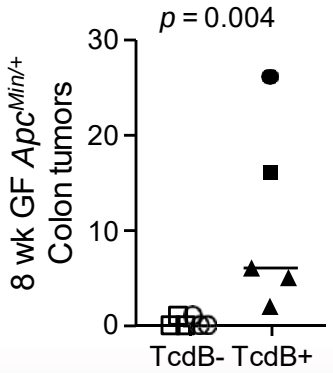
Julia Drewes
Asst Prof, JHU



Normal mucus bi-layer with some regions of direct contact (arrowheads) but no crypt invasion

Deep crypt invasion of biofilms (*C. difficile* and other bacteria)

C. difficile-positive community induces tumors driven by a single virulence gene of *C. difficile*: TxB



Drewes J, Chen A et al, Cancer Discovery, 6/22

M7404 strains courtesy of Dena Lyras, Borden Lacy

Could disruption of microbiota and intestinal epithelium interactions metabolic interactions drive early-onset colorectal cancer?

Mariana Byndloss, DVM, PhD
SPEAKER
Vanderbilt-Ingram Comprehensive Cancer Center

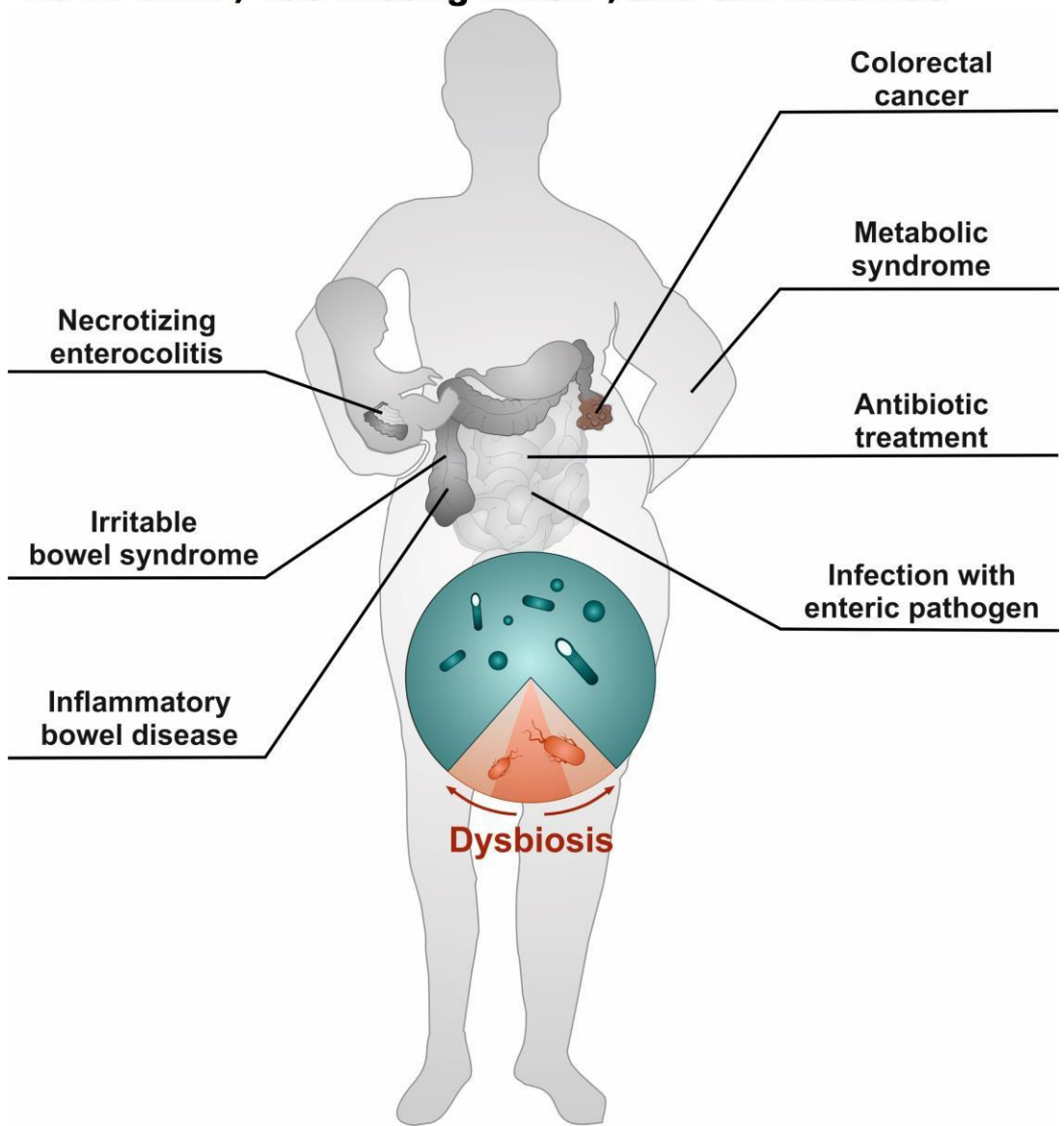
Research is being done to understand the complex interplay of microbiota, genetics, and environmental factors as it relates to disease development, especially early-age onset CRC.

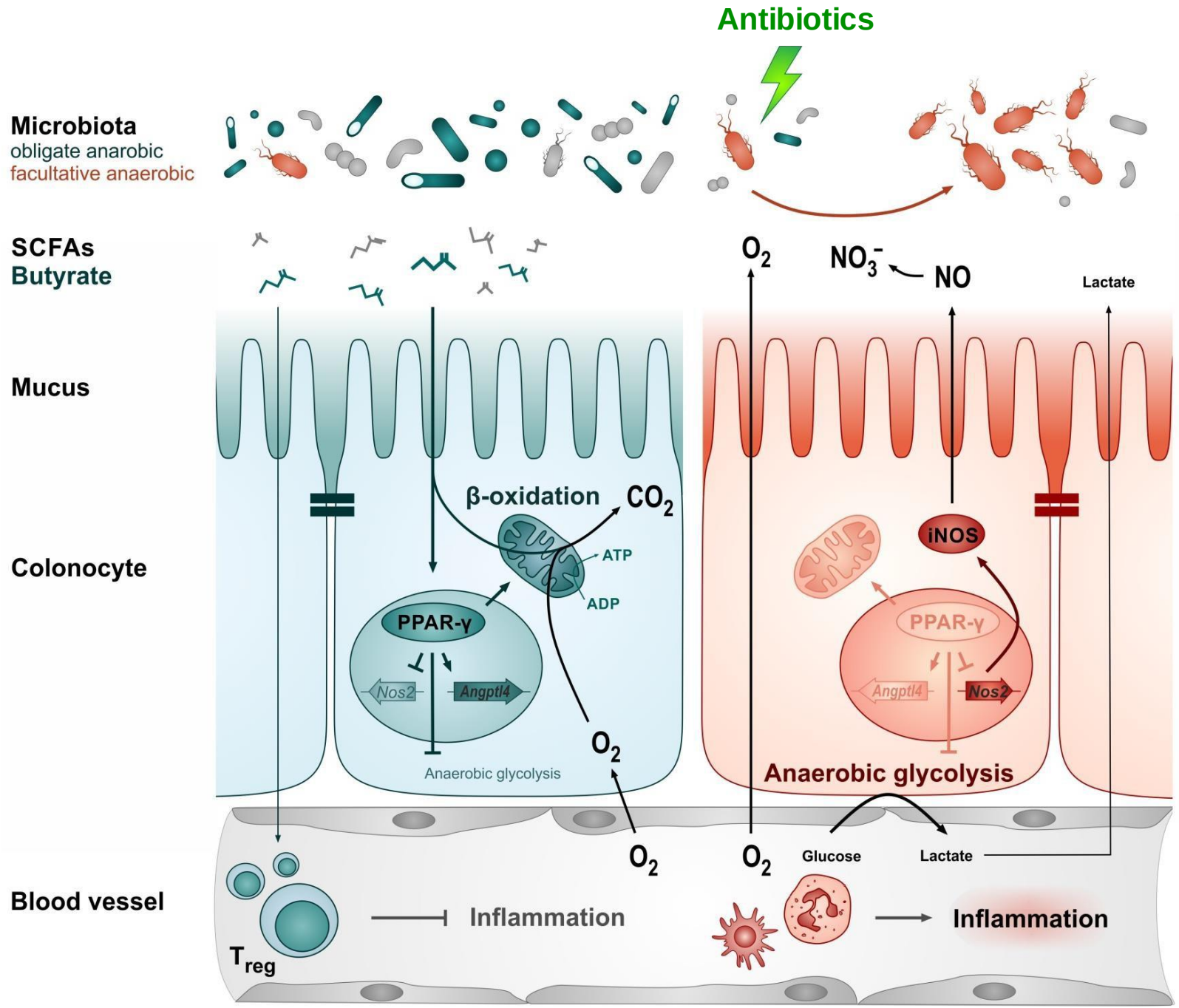
Environmental exposures including high fat diets and antibiotics, can lead to dysbiosis which promotes angiogenesis, loss of apoptosis and cell proliferation.

Early-life exposures might contribute to disease later in life and affect host health due to the impact on microbial metabolites and subsequent host inflammation.

Proteobacteria: microbial signature of dysbiosis in gut microbiota

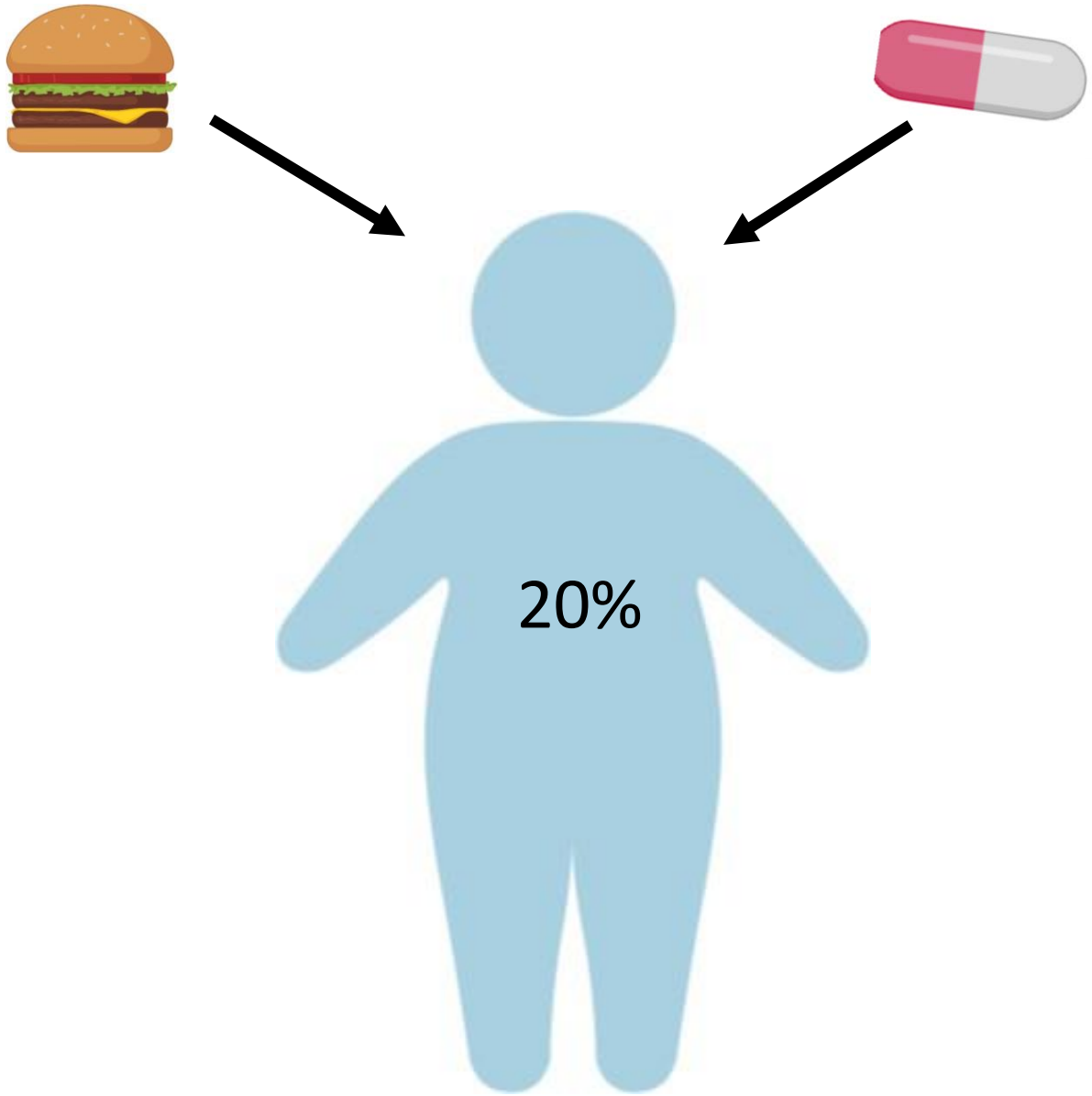
Na-Ri Shin*, Tae Woong Whon*, and Jin-Woo Bae

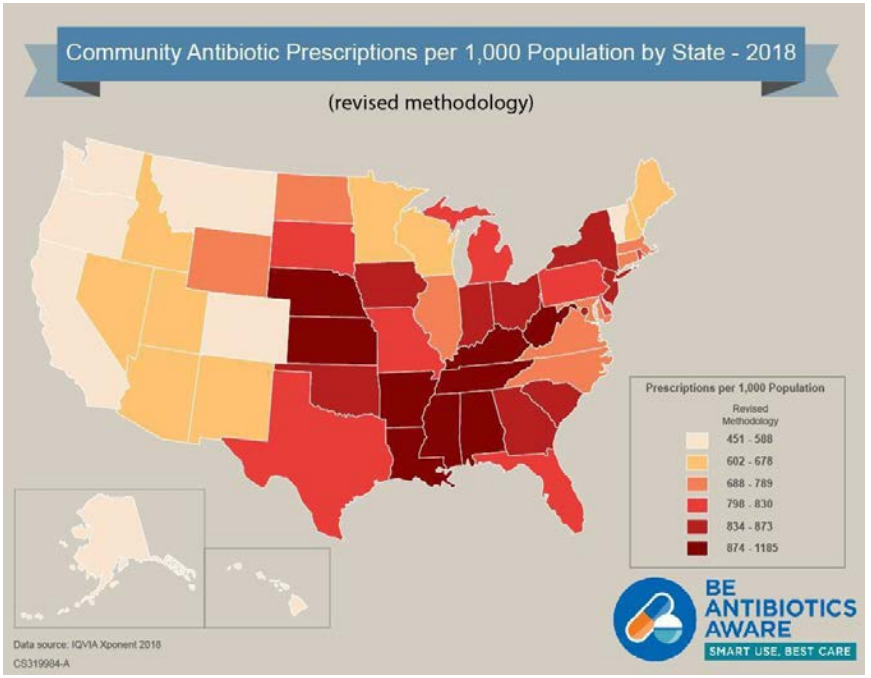




Byndloss et al., Science, 2017

What if we could study concurrent exposure to risk factors?





Aging Markers and Early-Onset Colorectal Cancer

Kit Curtius, BS, PhD
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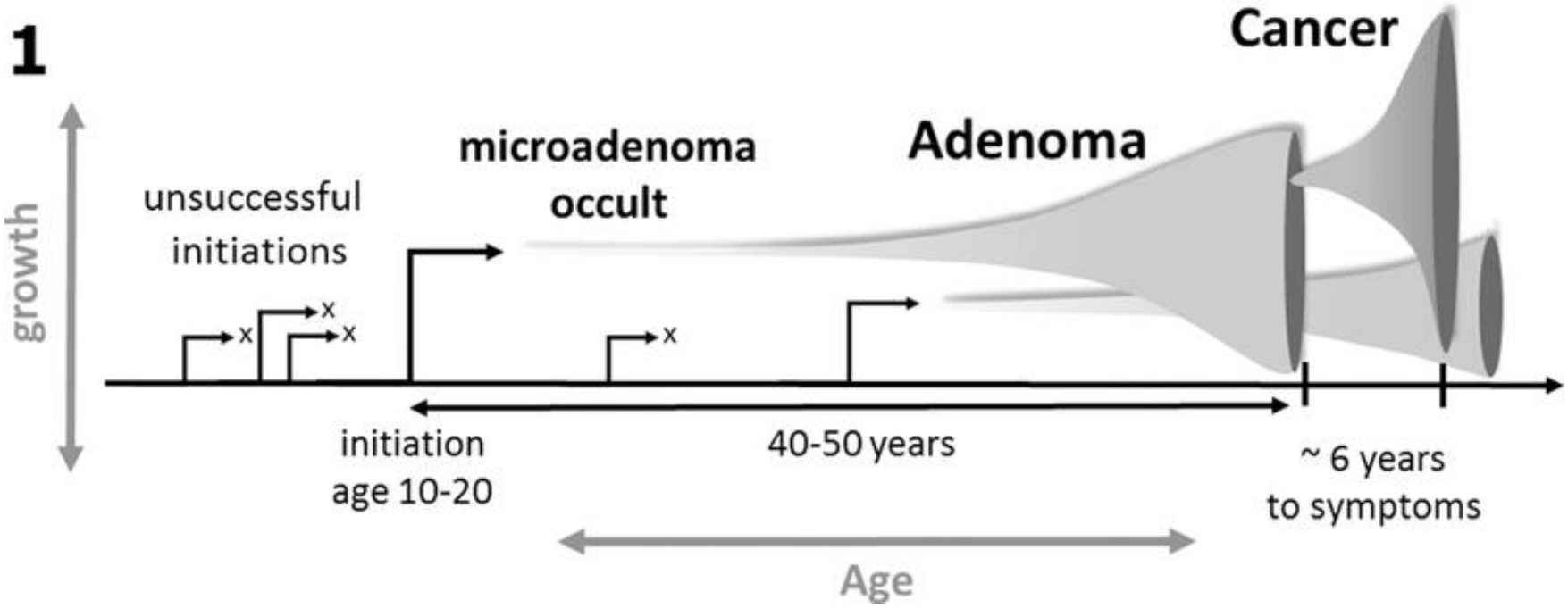
UC San Diego Moores Comprehensive Cancer Center

Epigenetic drift or “aging” provides a measure of time from initiation to invasive cancer and may be used as biomarker of risk



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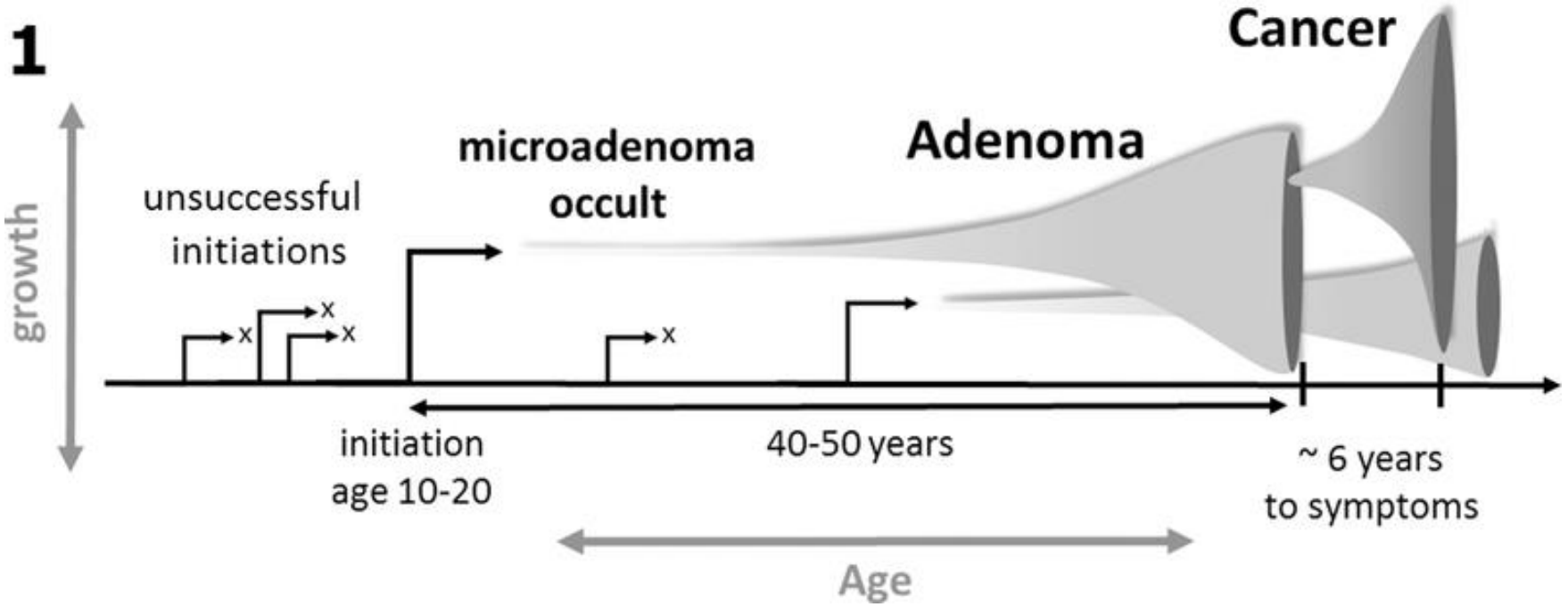

Can we intervene earlier by identifying those who age at an accelerated rate?

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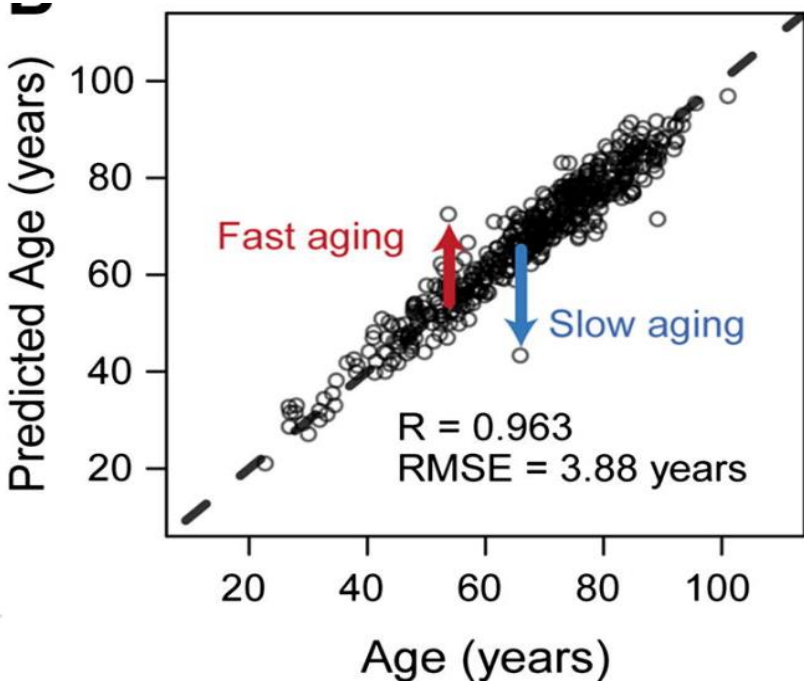

Mathematical models can classify "fast aging" and "slow aging" using epigenome-wide data

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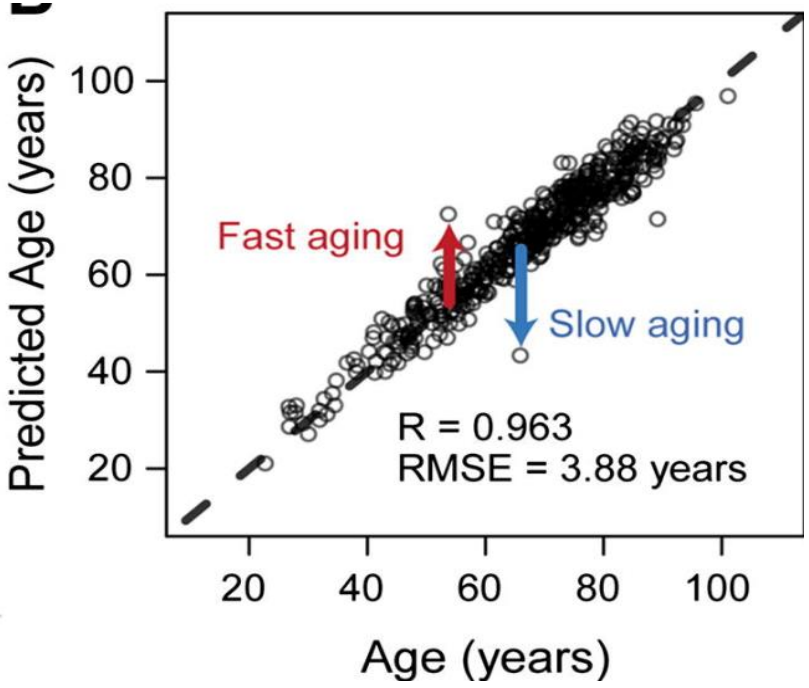

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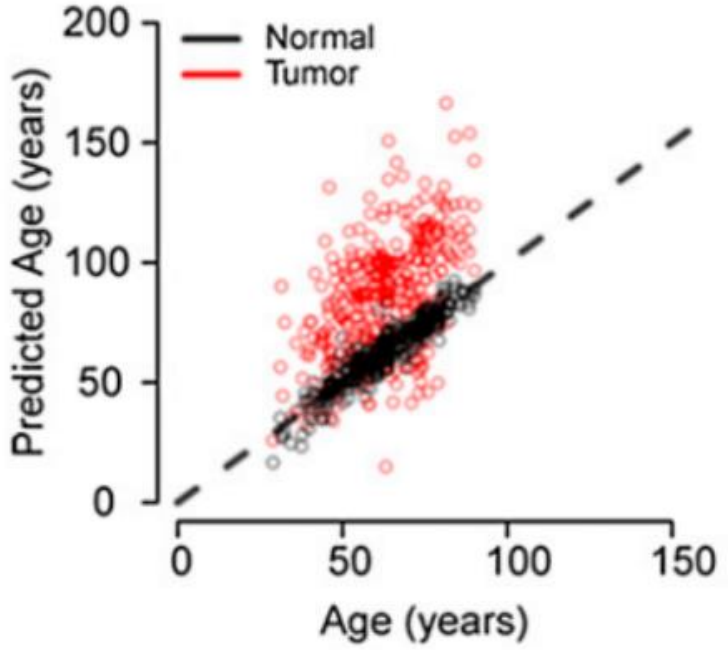

Tumor tissue is epigenetically "older" than normal tissue

Aging Markers and Early-Onset Colorectal Cancer

Kit Curtius, BS, PhD
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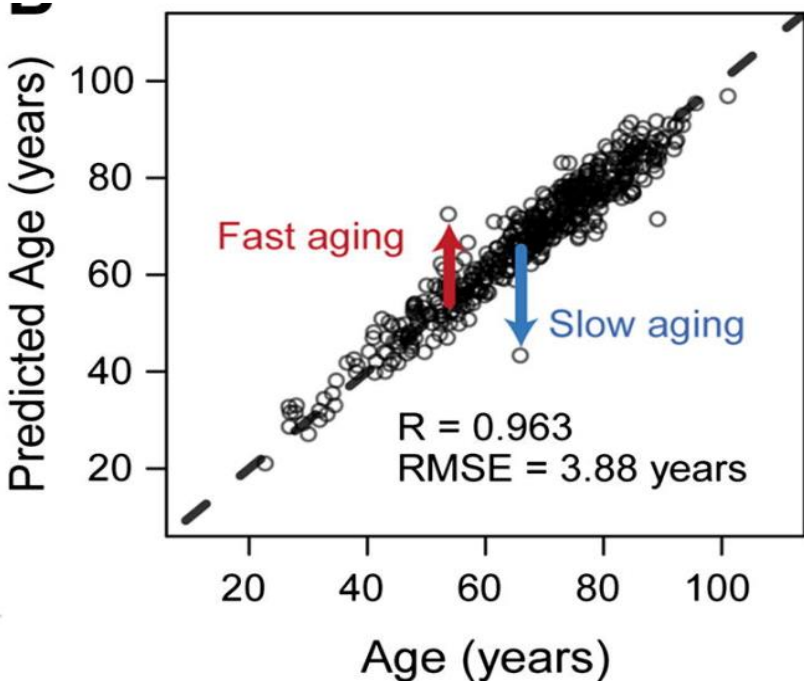

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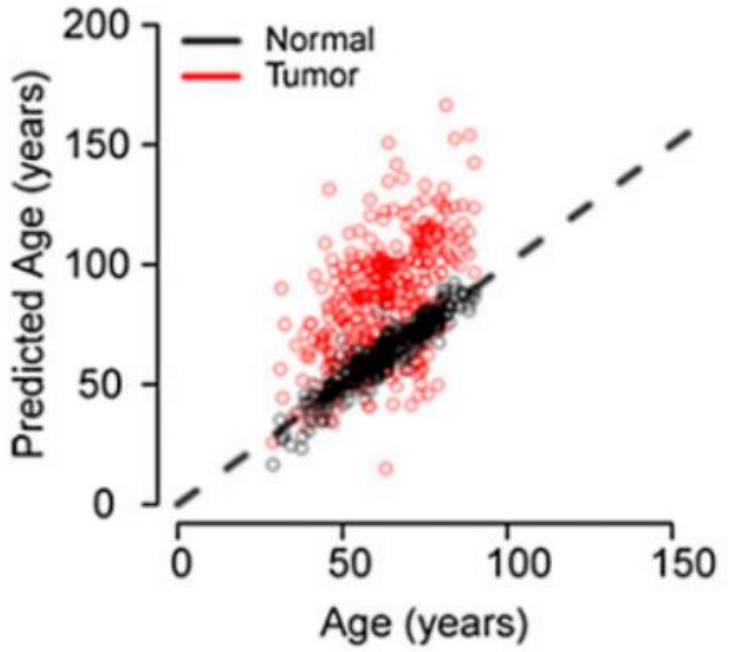

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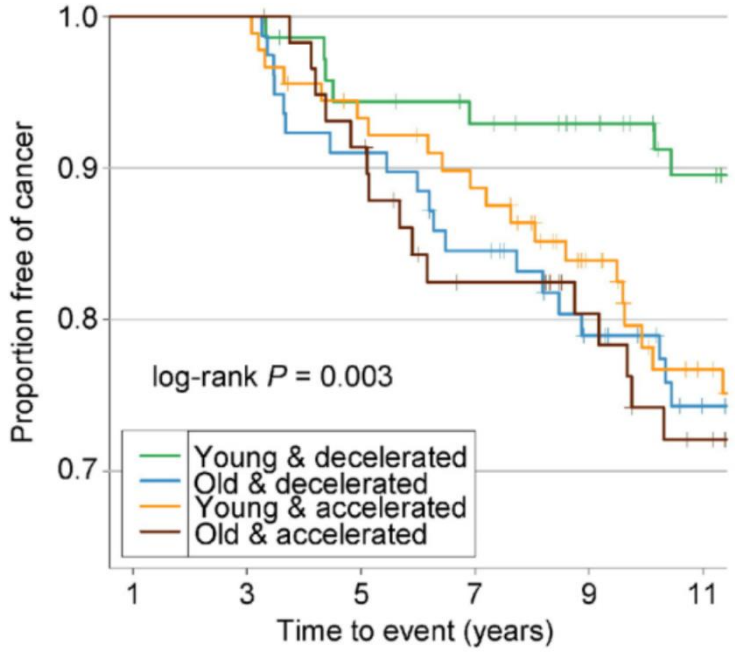
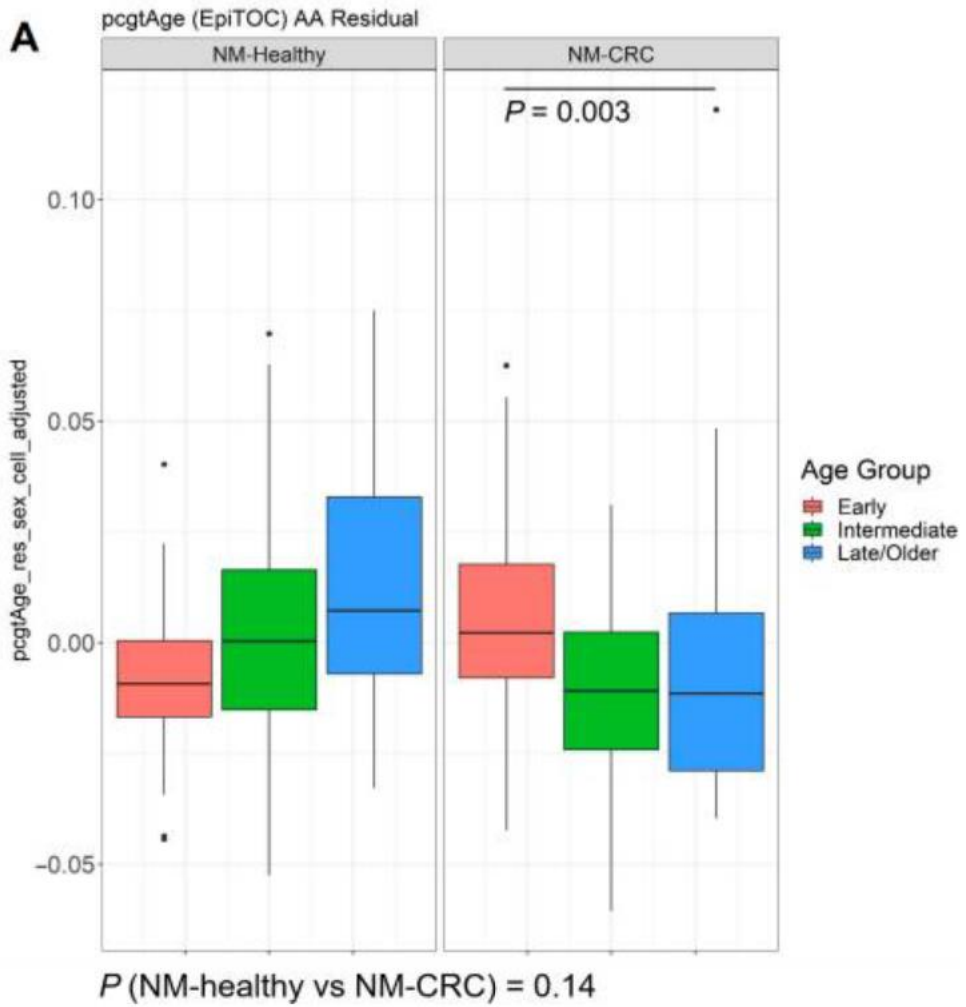
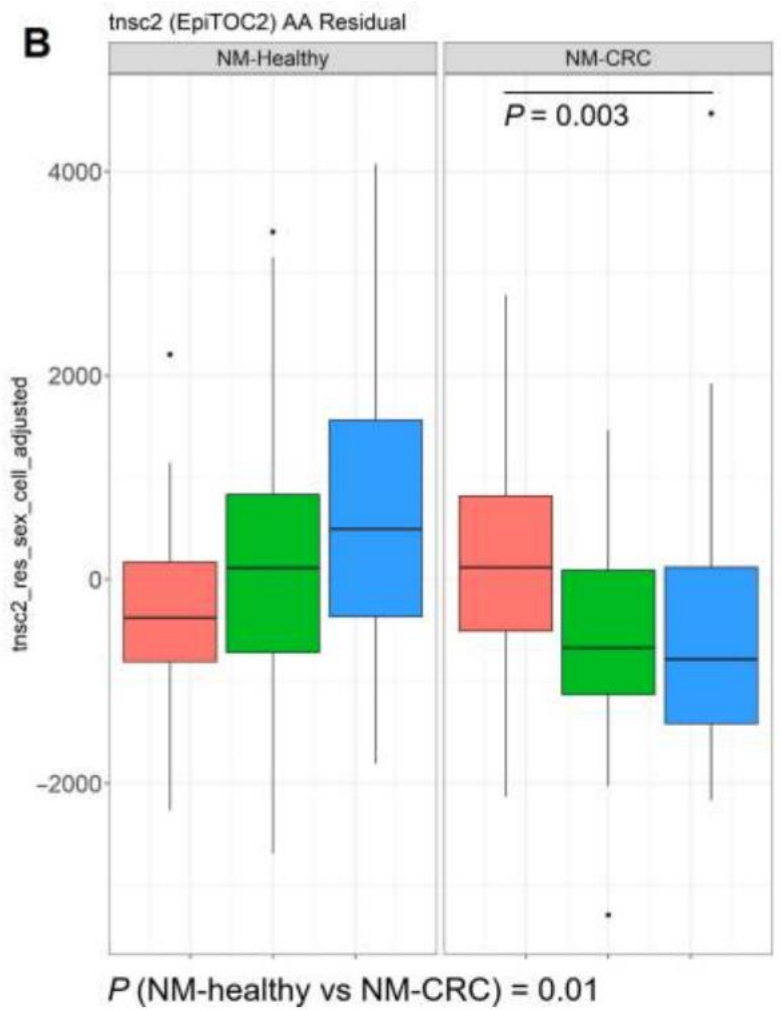


Epigenetic age measured in blood predicts cancer incidence and mortality

Accelerated Aging as a Biomarker for Early-onset Colorectal Cancer

Kit Curtius, BS, PhD
SPEAKER
UC San Diego Moores Comprehensive Cancer Center

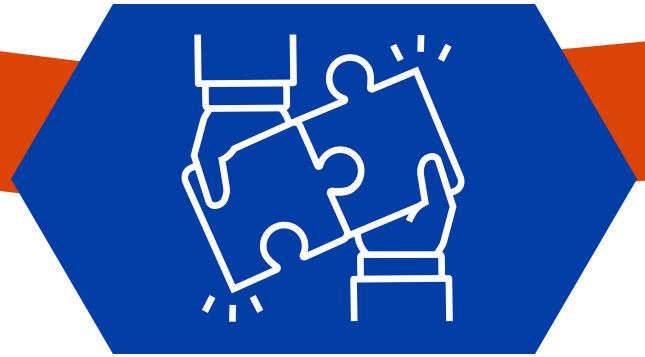




Accelerated aging is increased in paired normal tissue of persons with early- vs. later-onset colorectal cancer

Recurring Themes Across Tracks

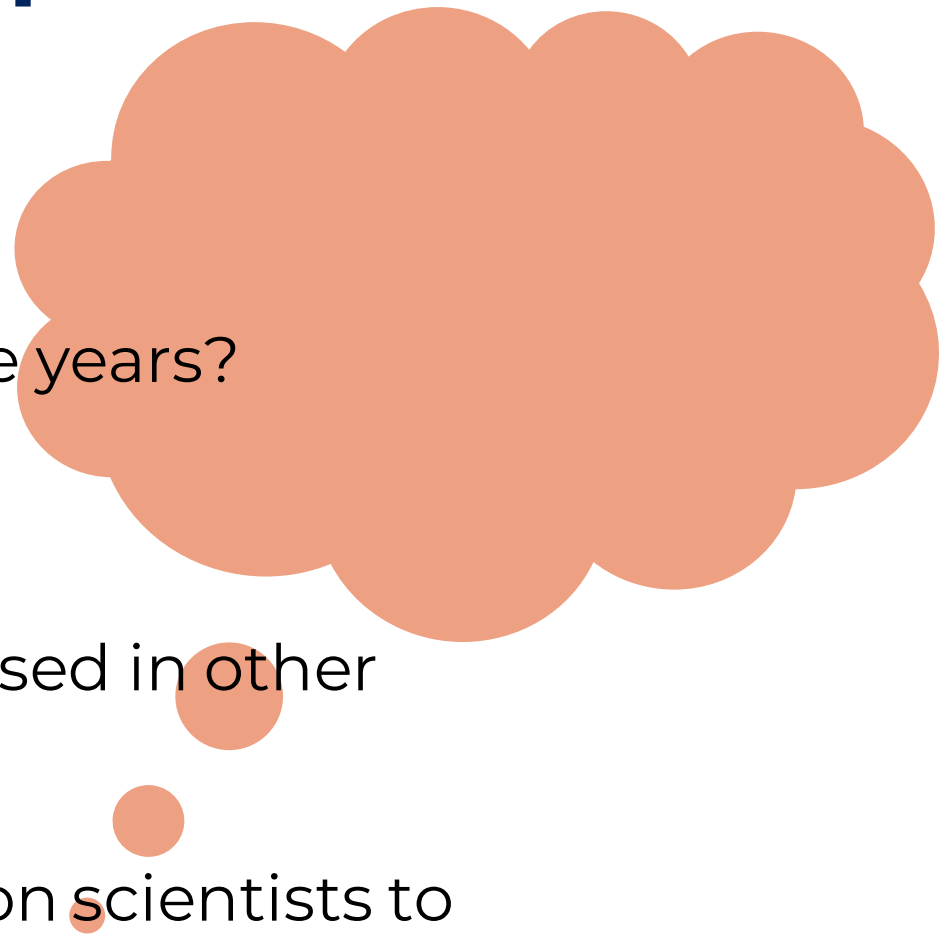
Multi-dimensional approaches are required to understand EAO-CRC, with consideration for the exposome, metabolome, microbiome, methylome, and genome.



Each panel emphasized need for collaboration including sharing data and samples, as well as deeper communication among researchers, clinicians, and patient advocates.

Future interventions will likely be tailored to individuals based on “omics” and not one-size-fits-all

Key Questions for Discussion



What do we know? What do we **not** know?

What do we hope to discover in the next five years?

How do we integrate “omics” measures?

Are there opportunities to adapt methods used in other fields for our purpose?

Can we better connect bench and population scientists to lead this work?

How do we do involve patients and advocates?