社会、健康、医療に貢献するための学際的公衆衛生学・疫学の未来

Kyoto University School of Public Health (35 min)

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Harvard T.H. Chan School of Public Health
Broad Institute of MIT and Harvard

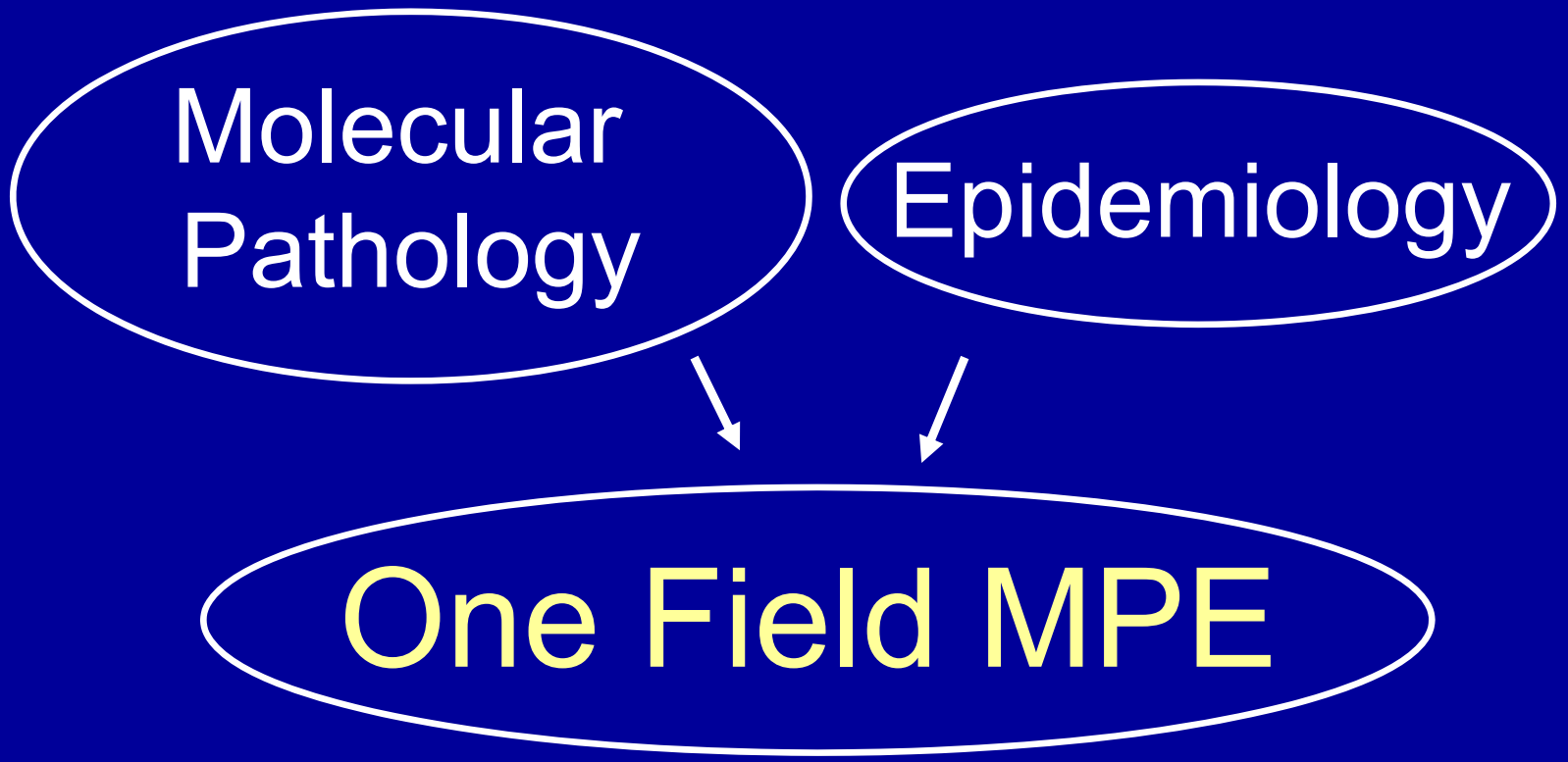
CRC = colorectal cancer

MPE = molecular pathological epidemiology

MSI = microsatellite instability

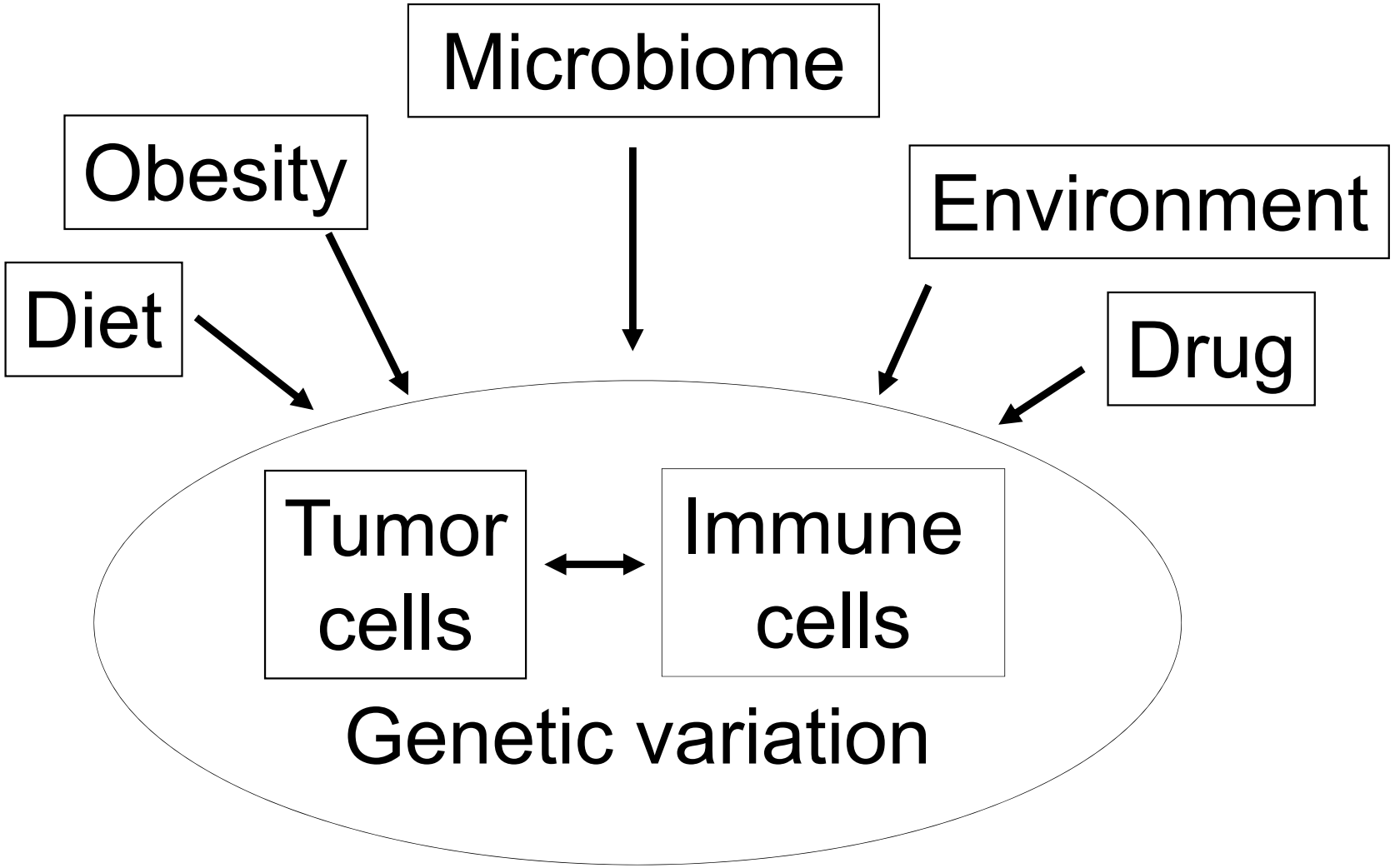
(hypermutator, high neoantigen load)

(Immune checkpoint inhibitor works for MSI-high solid tumors)

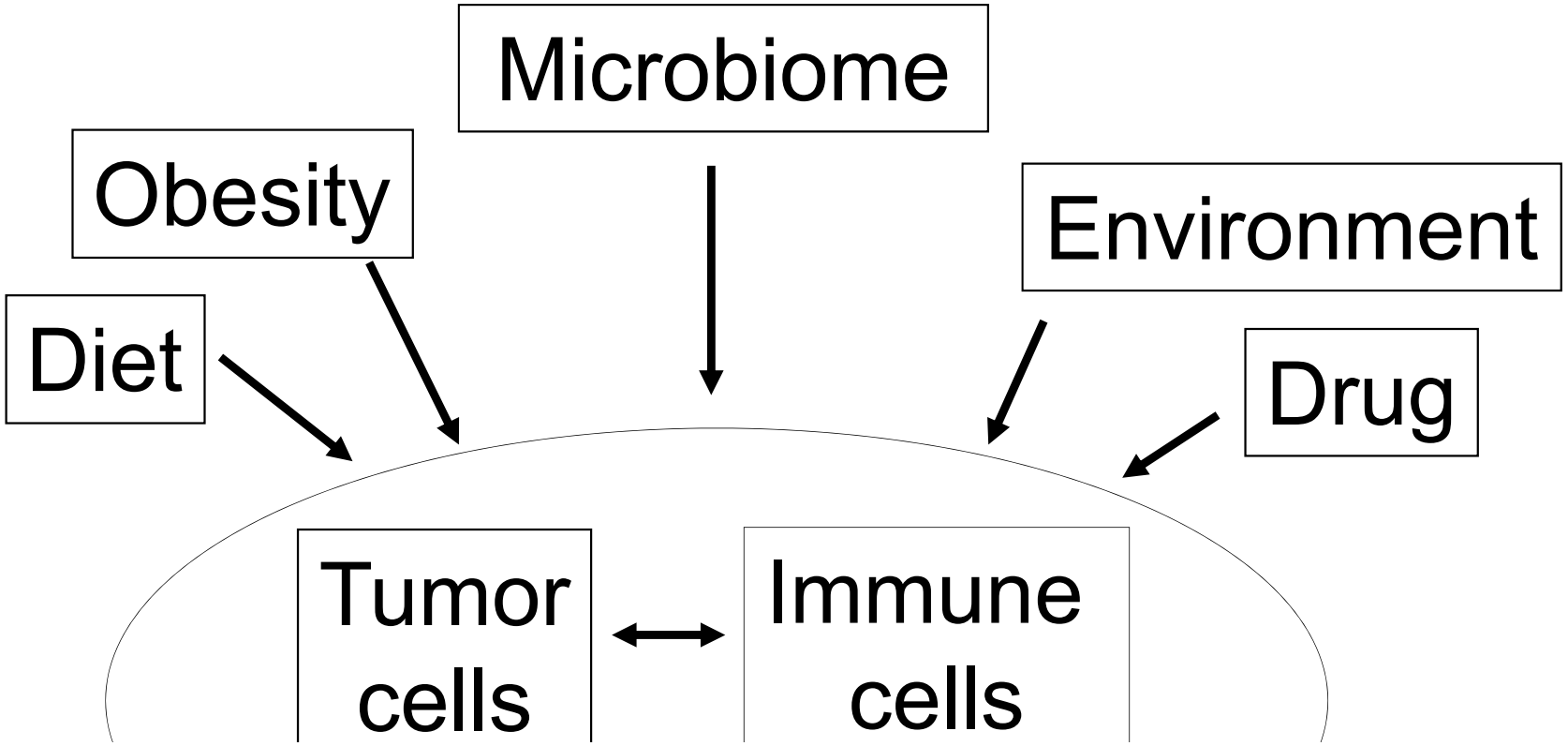


1 + 1 → 100

Big Synergism

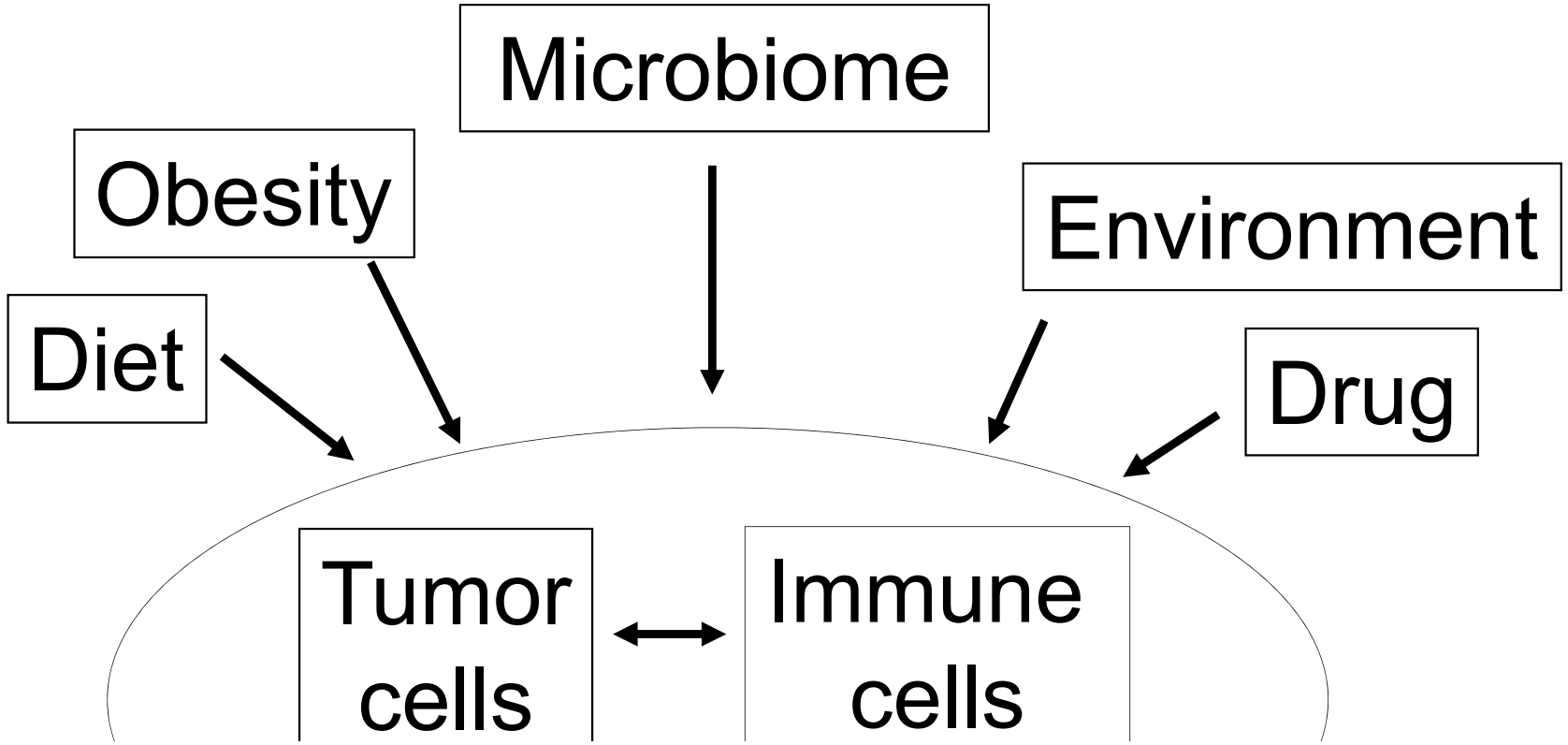


Ogino et al. Gut 2018
Ogino et al. Lancet 2018



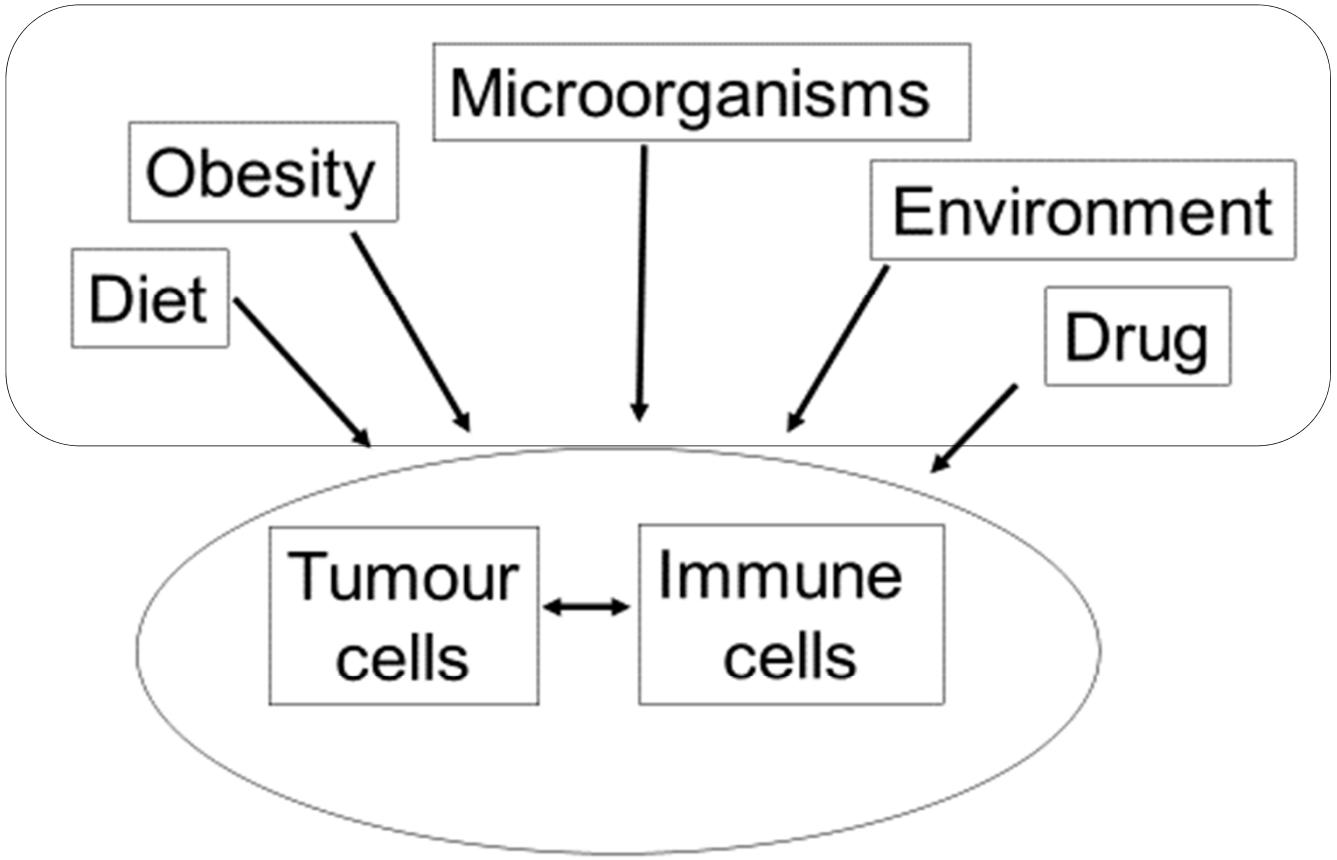
Complex problems necessitate expertise in multiple fields

Ogino et al. Gut 2018
Ogino et al. Lancet 2018



Exposures can easily influence tumor - immune interactions

Ogino et al. Gut 2018
Ogino et al. Lancet 2018

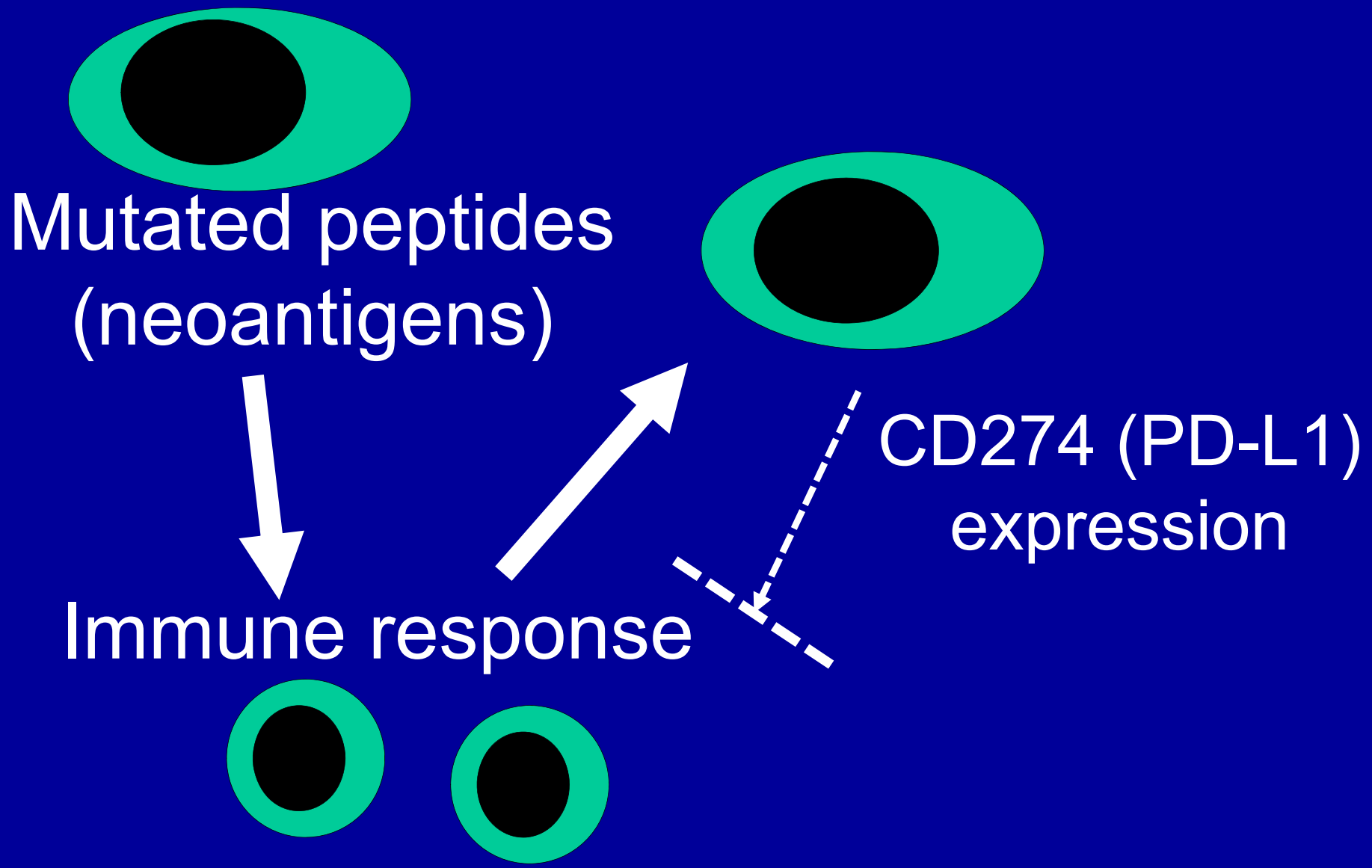


Epidemiology methods

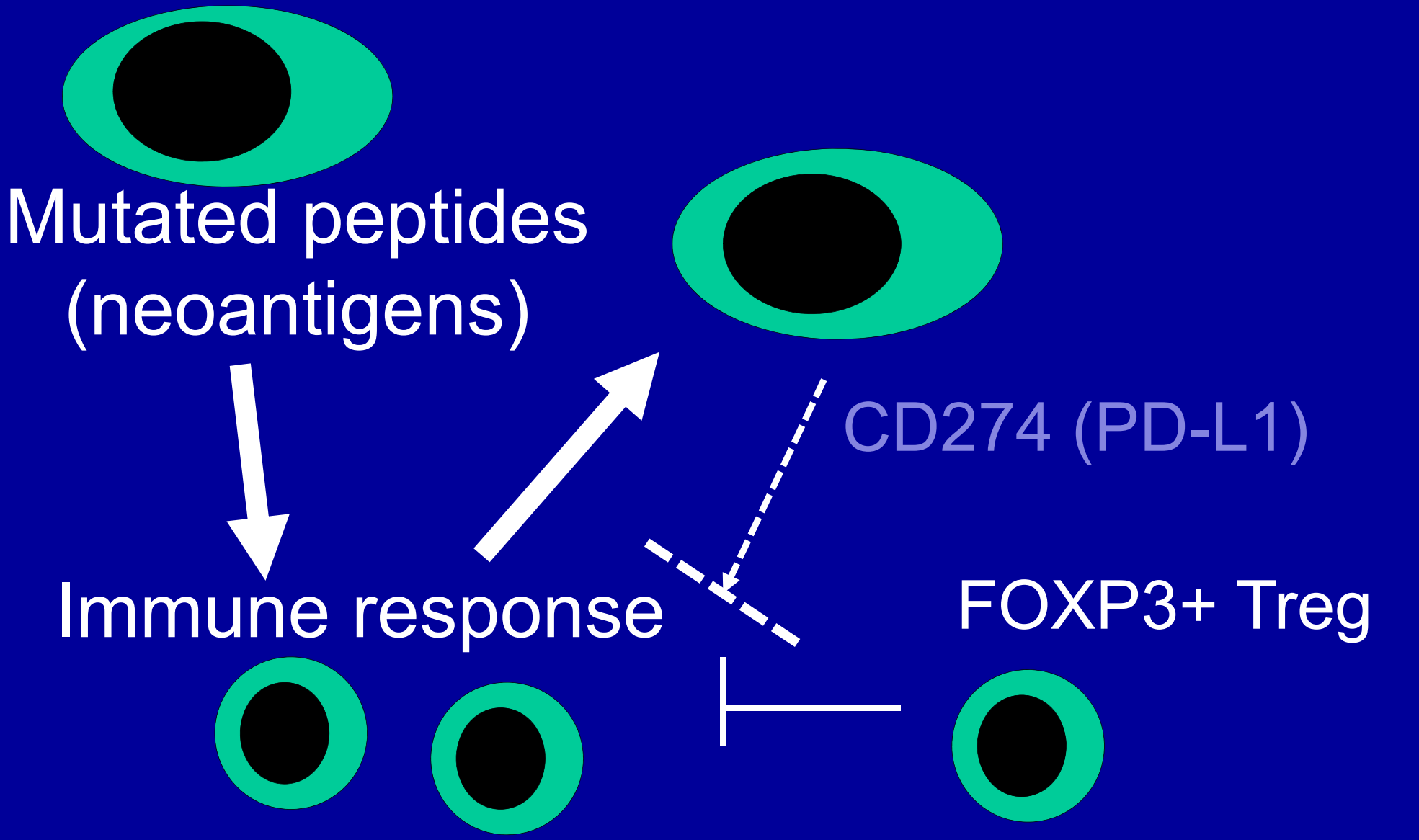
Pathology methods → Integrative MPE

Bioinformatics methods (machine / deep learning)

Tumor - Immune Interactions

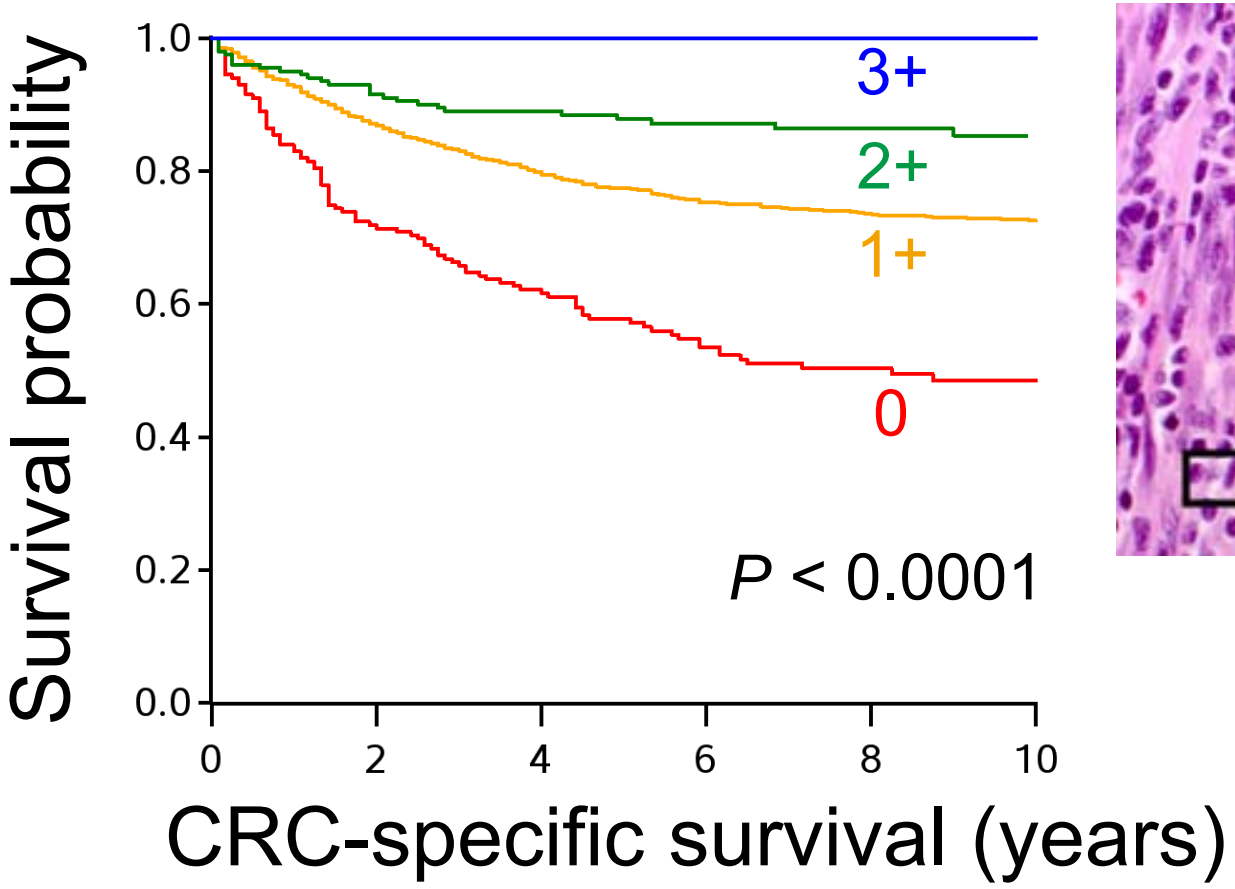


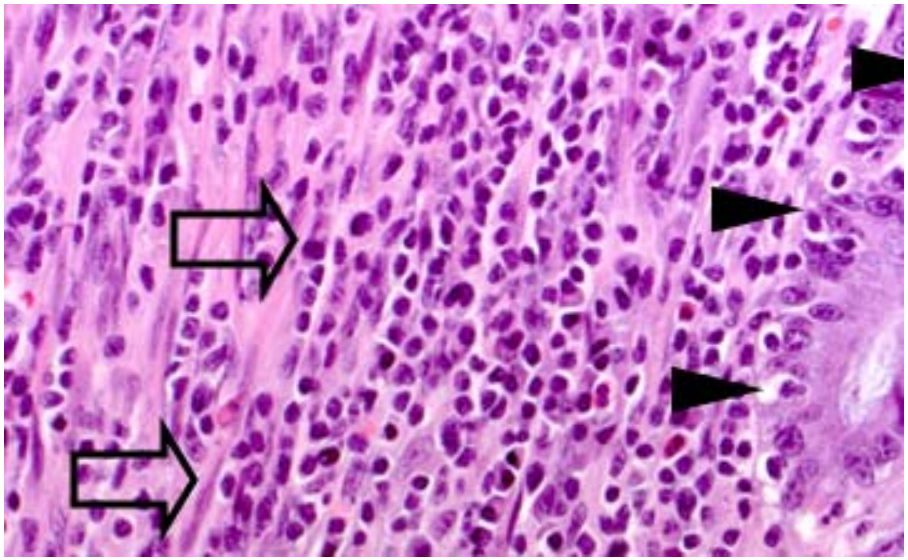
Tumor - Immune Interactions



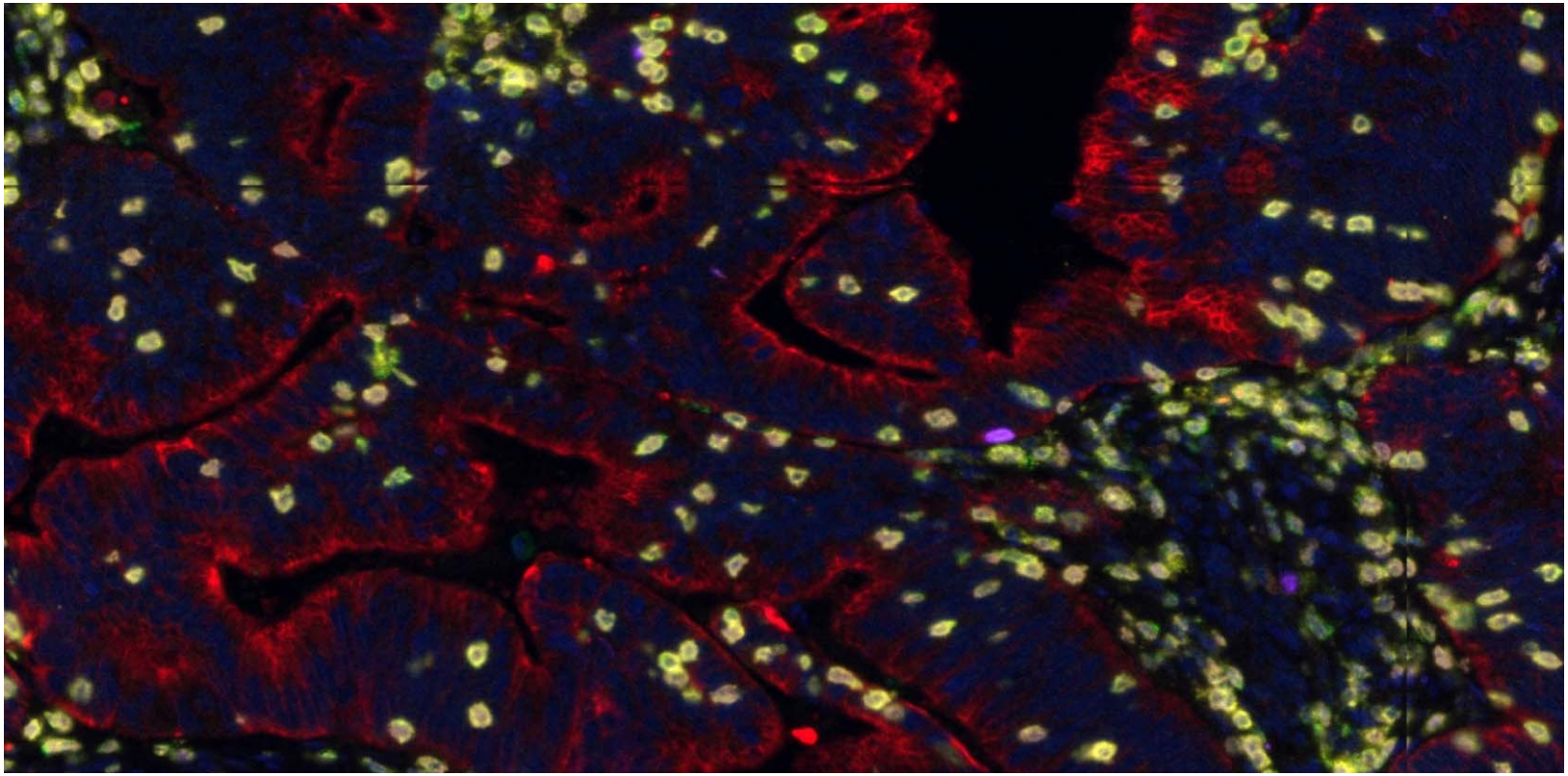
Masugi et al. Gut 2016

Immune cells in tumor microenvironment = best prognostic biomarker (why not clinical decision making?)





Multiplex immunofluorescence



CD3 (brown), CD4 (yellow), CD8 (purple), CD45RO (green), FOXP3 (orange)

Borowsky, et al.

Immunology-MPE Studies

Why are there names of fields (such as “epidemiology”)?

Colon has rich microbiota & immune tissue

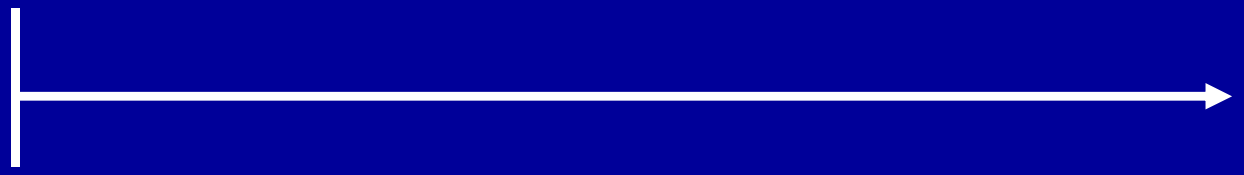
Known risk (or protective) factors

Best model for immunology-MPE

Prospective Cohort Studies

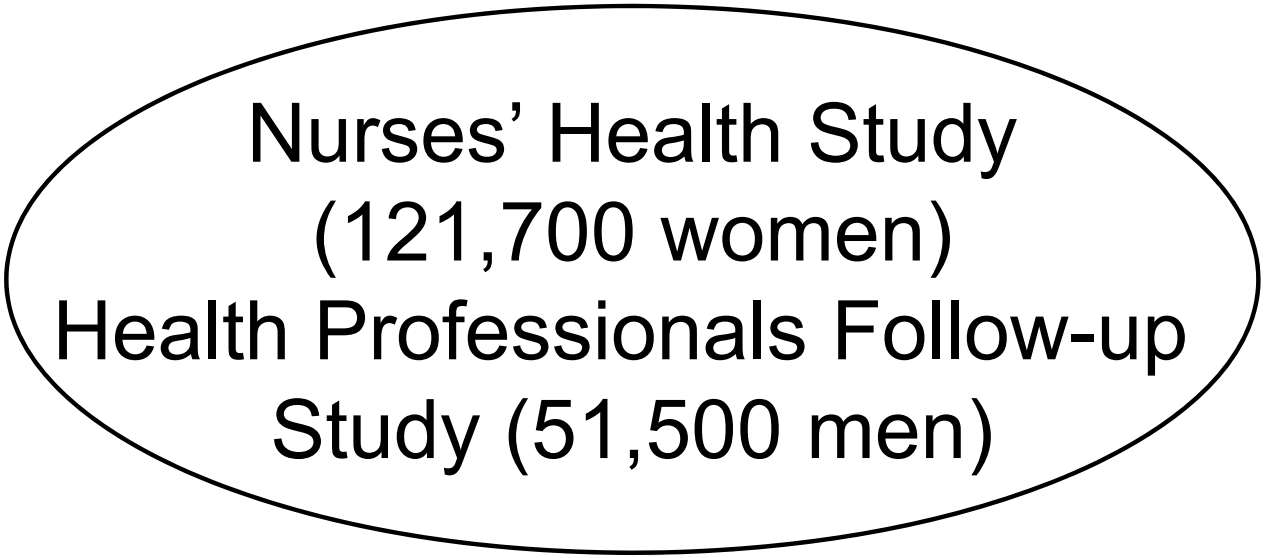
Nurses' Health Study (121,700 women)

1976

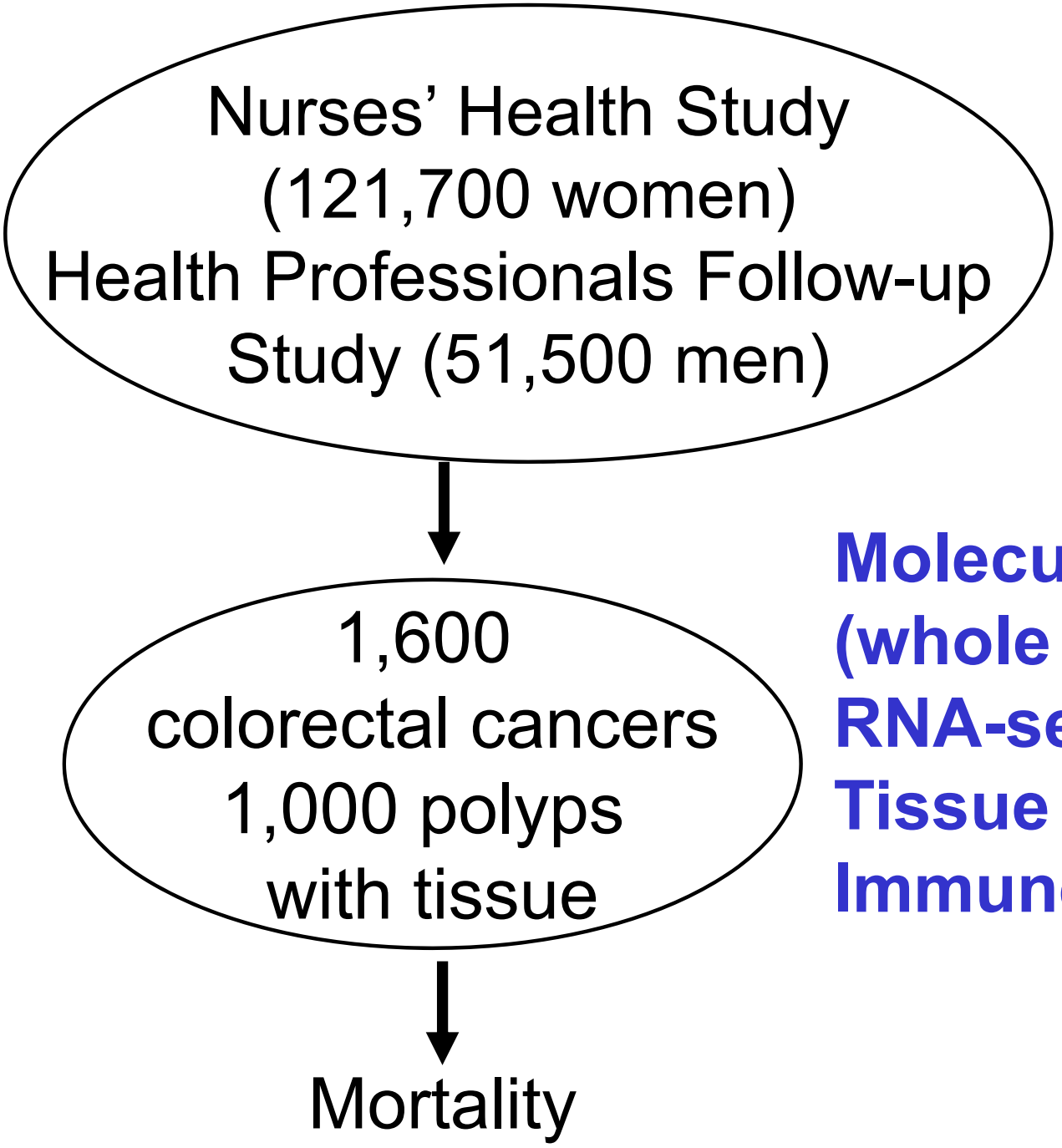


1986

Health Professionals Follow-up Study
(51,500 men)



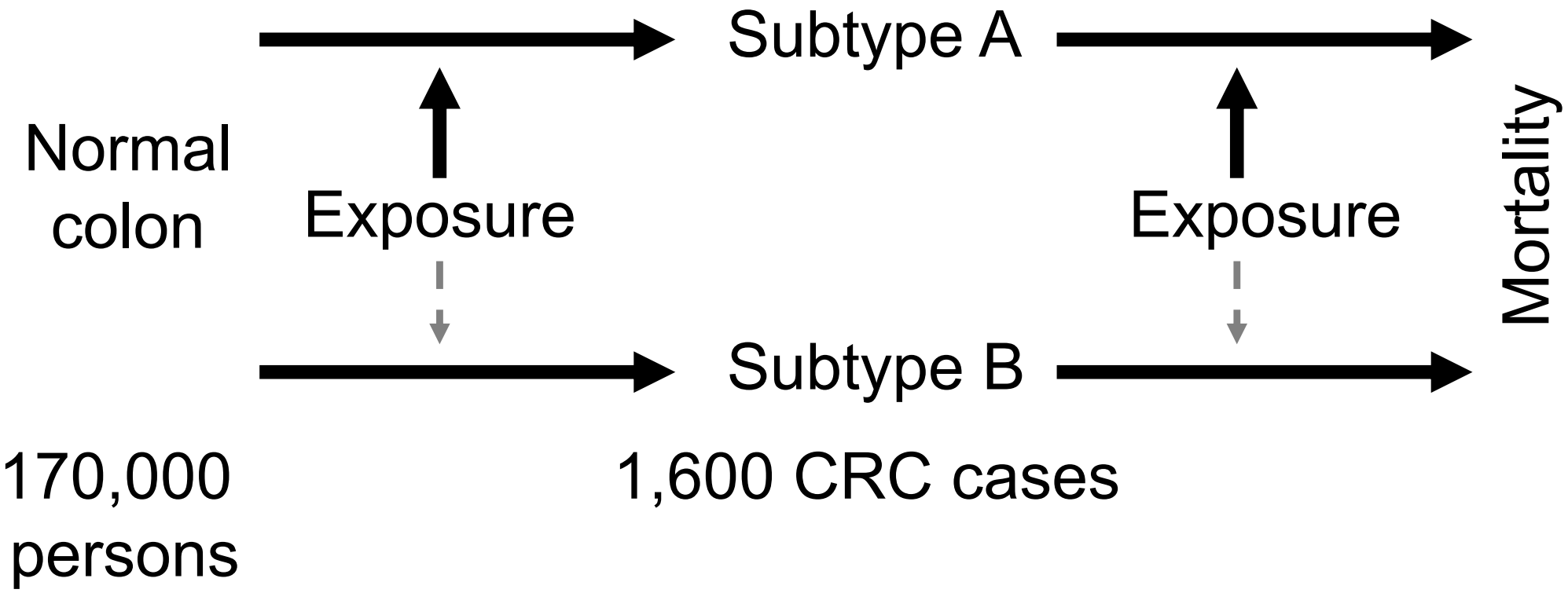
Diet, lifestyle, environment, genetics, plasma metabolomics, etc.

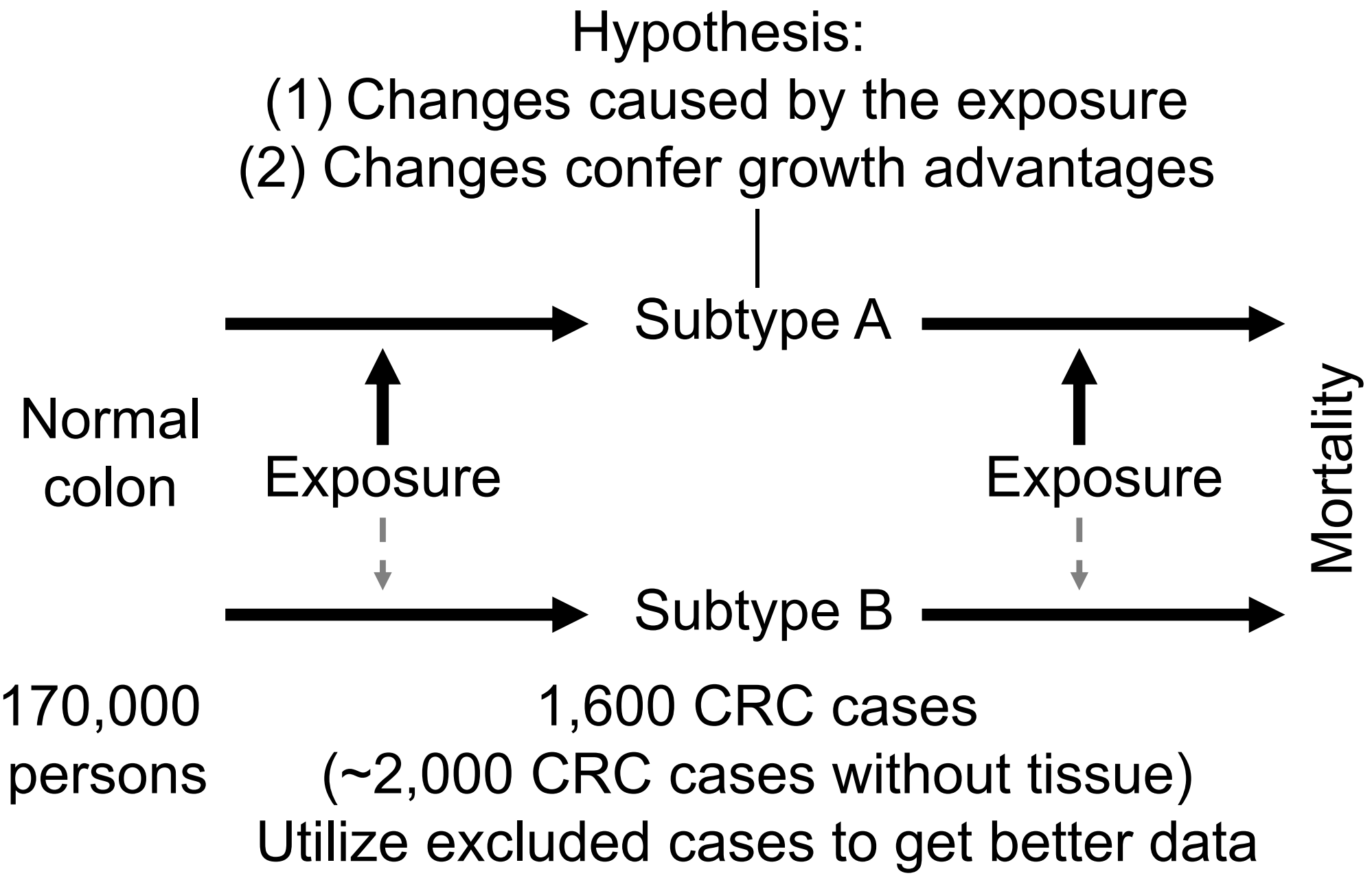


Diet, lifestyle, environment, genetics, plasma metabolomics, etc.

Molecular pathology (whole exome sequencing, RNA-sequencing)
Tissue microbiota
Immune cells

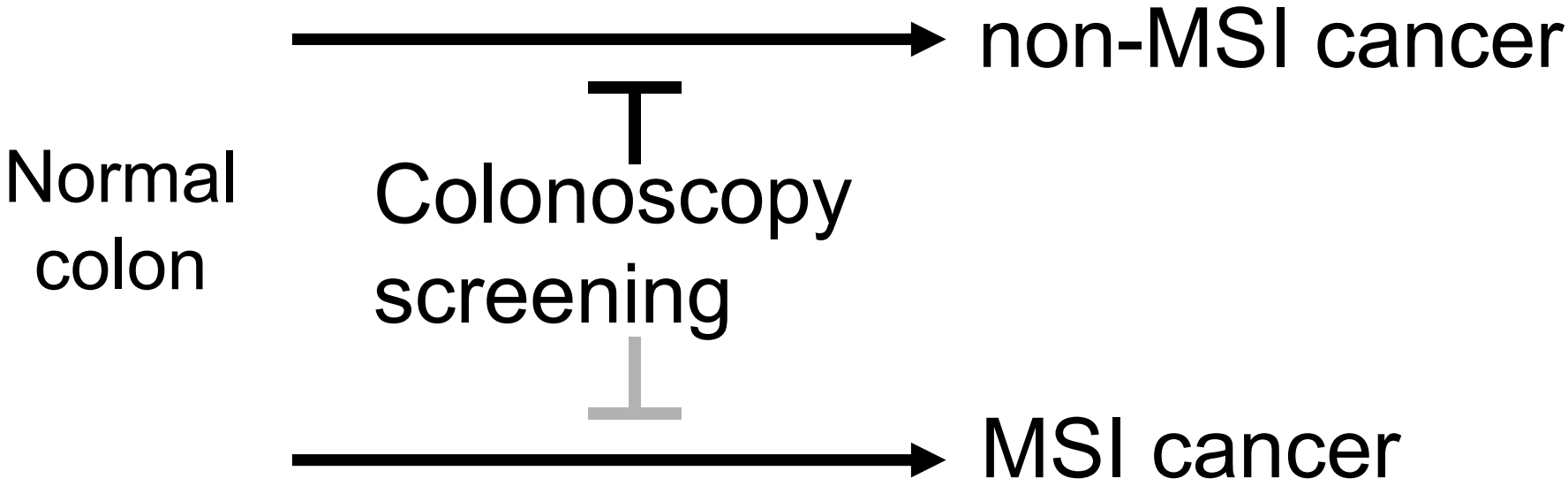
MPE analyses





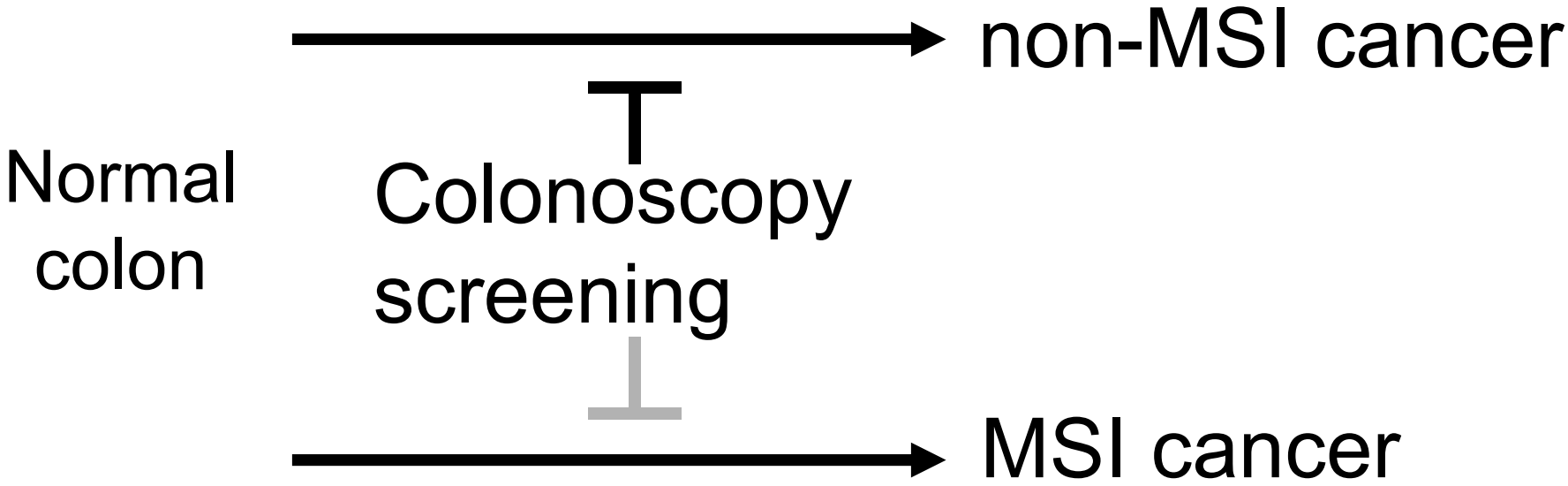
Liu et al. Eur J Epidemiol 2018

Preventive effect of colonoscopy differs by microsatellite instability (MSI) status



Nishihara et al. N Engl J Med 2013

Preventive effect of colonoscopy differs by microsatellite instability (MSI) status

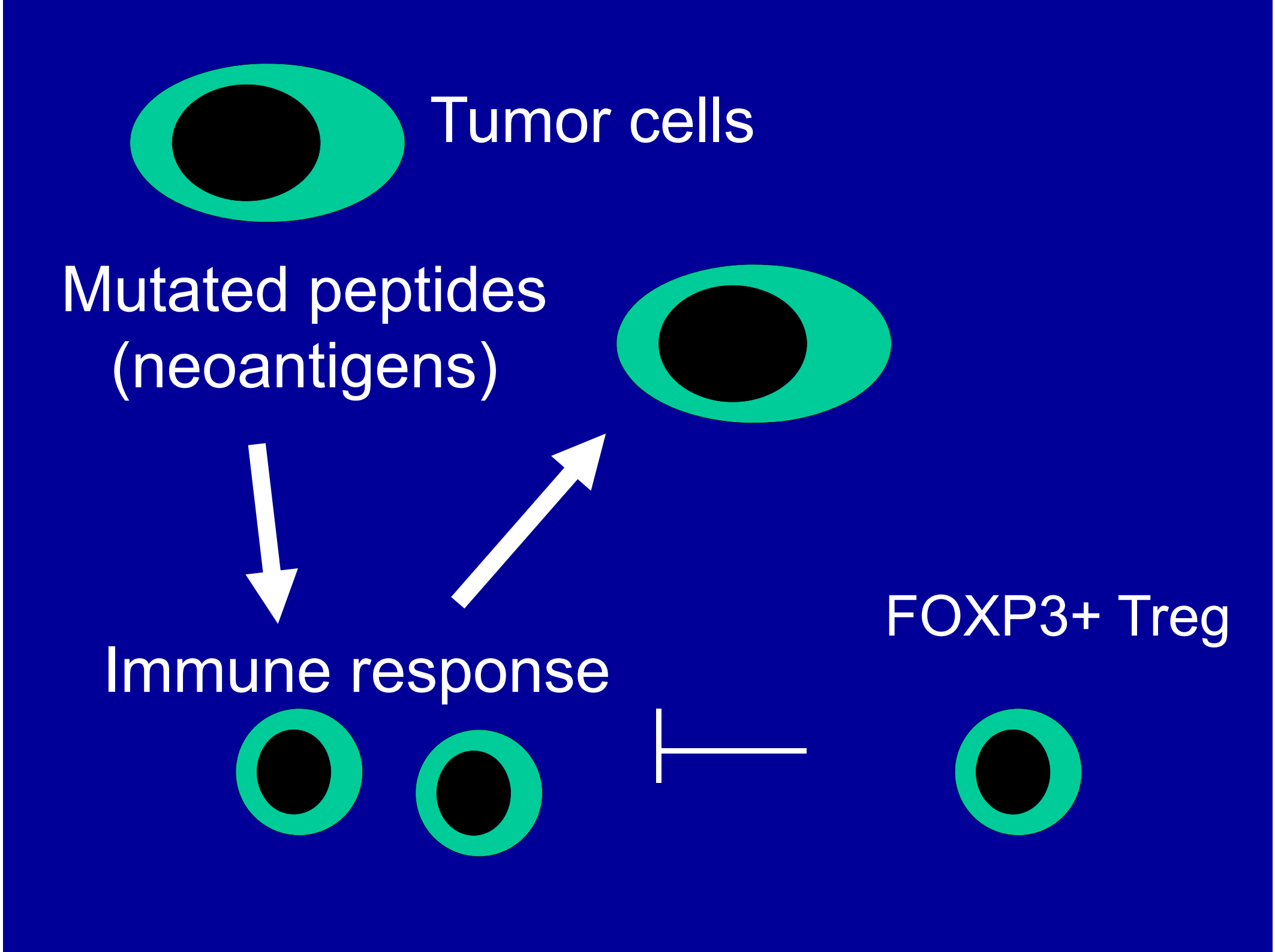


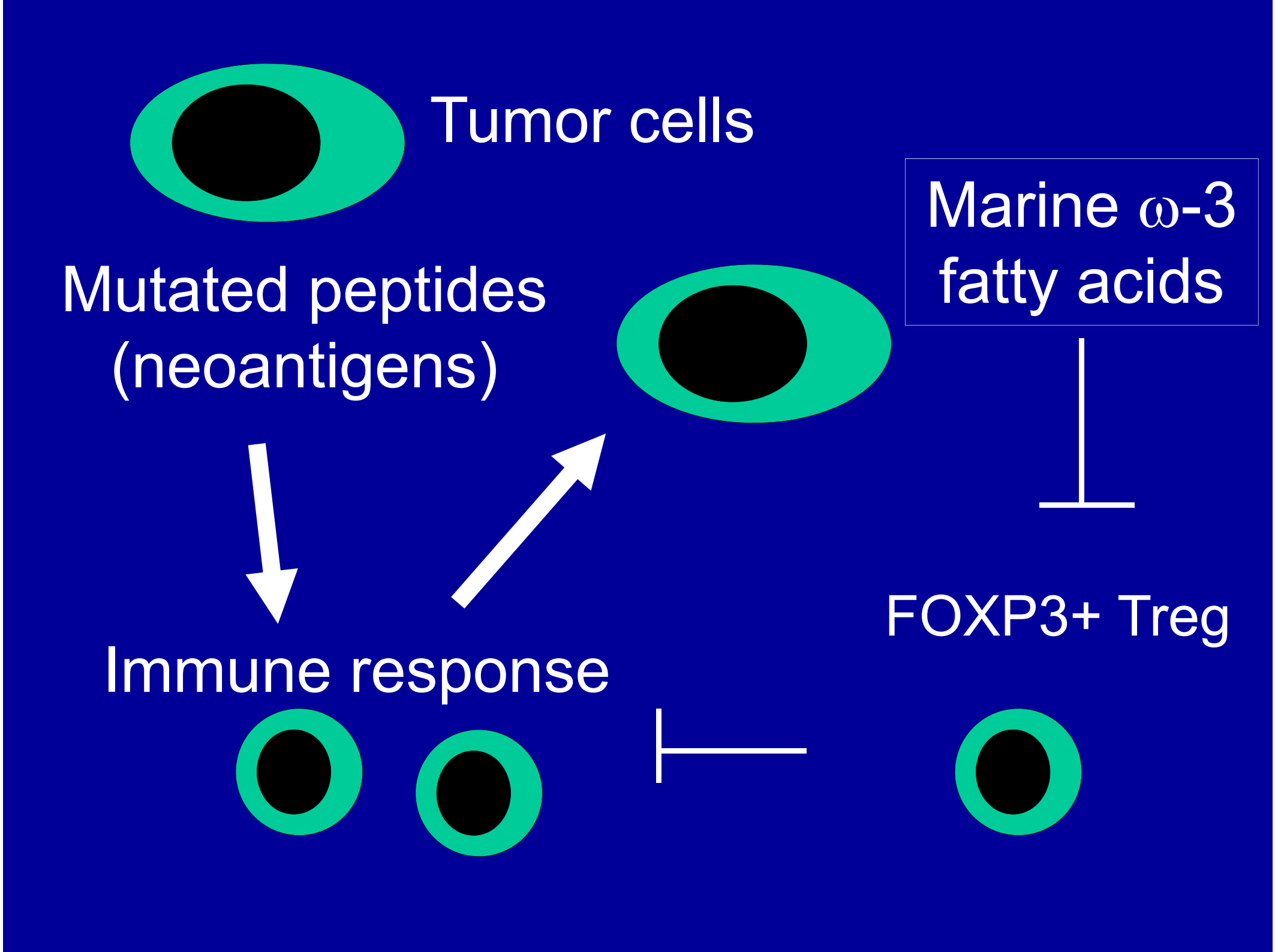
MPE can advance precision prevention (smokers have higher risk for MSI cancer)

Nishihara et al. N Engl J Med 2013

Marine ω-3 polyunsaturated fatty acids (rich in fish oil)

- (?) reduce CRC risk
- Marine ω-3 fatty acids can inhibit regulatory T cells → stimulate effector T cells


Tumor cells
Mutated peptides
(neoantigens)
Immune response
FOXP3+ Treg


Tumor cells
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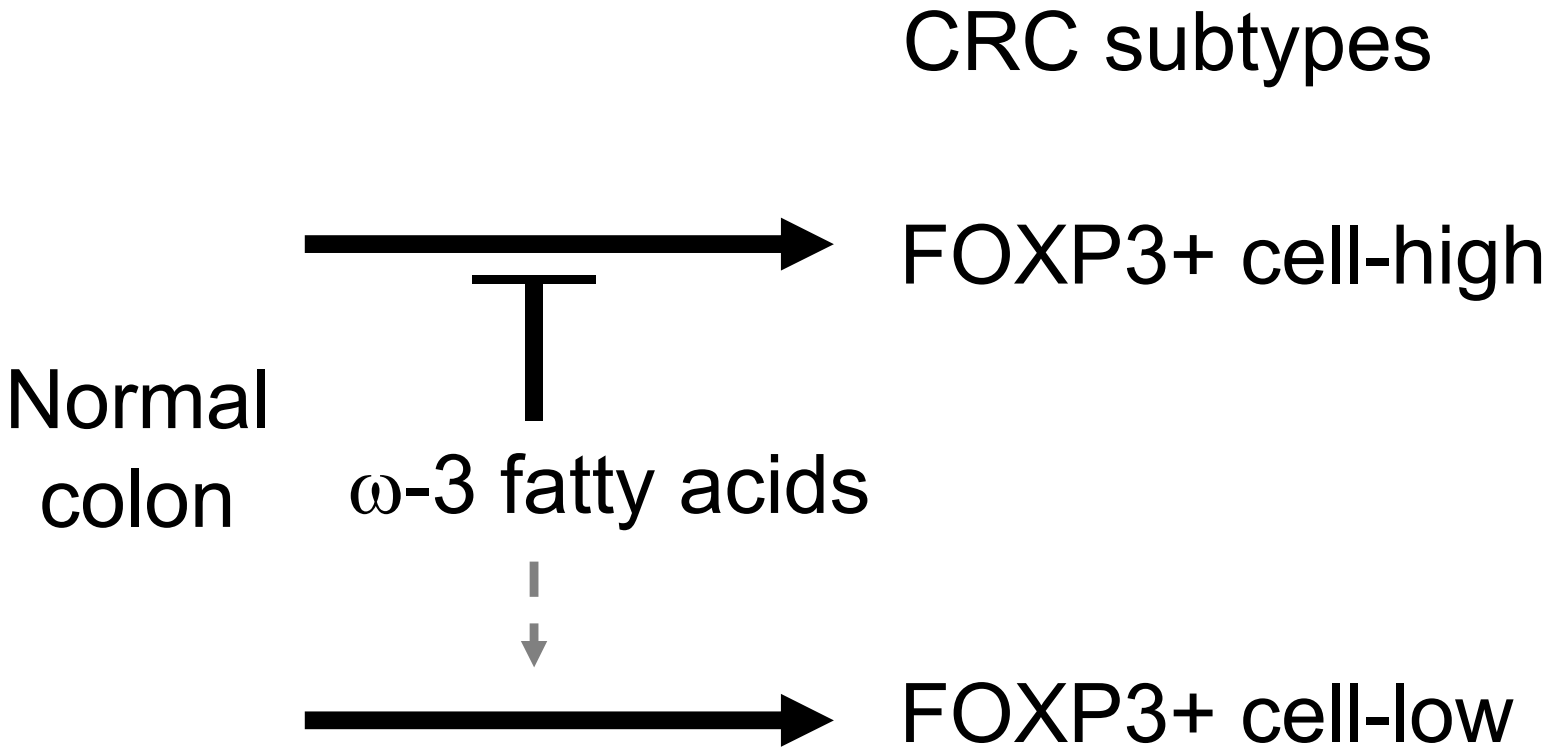
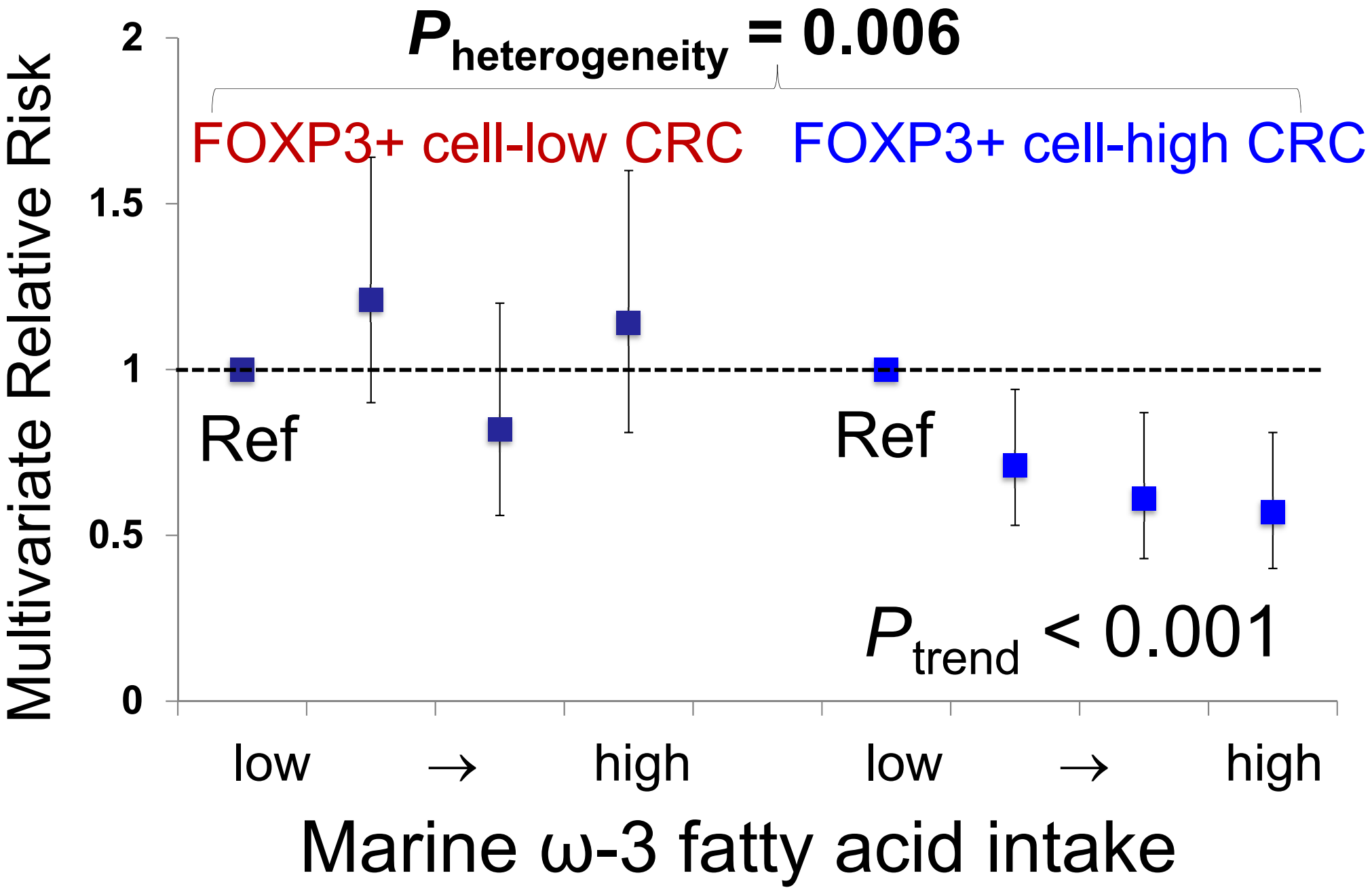
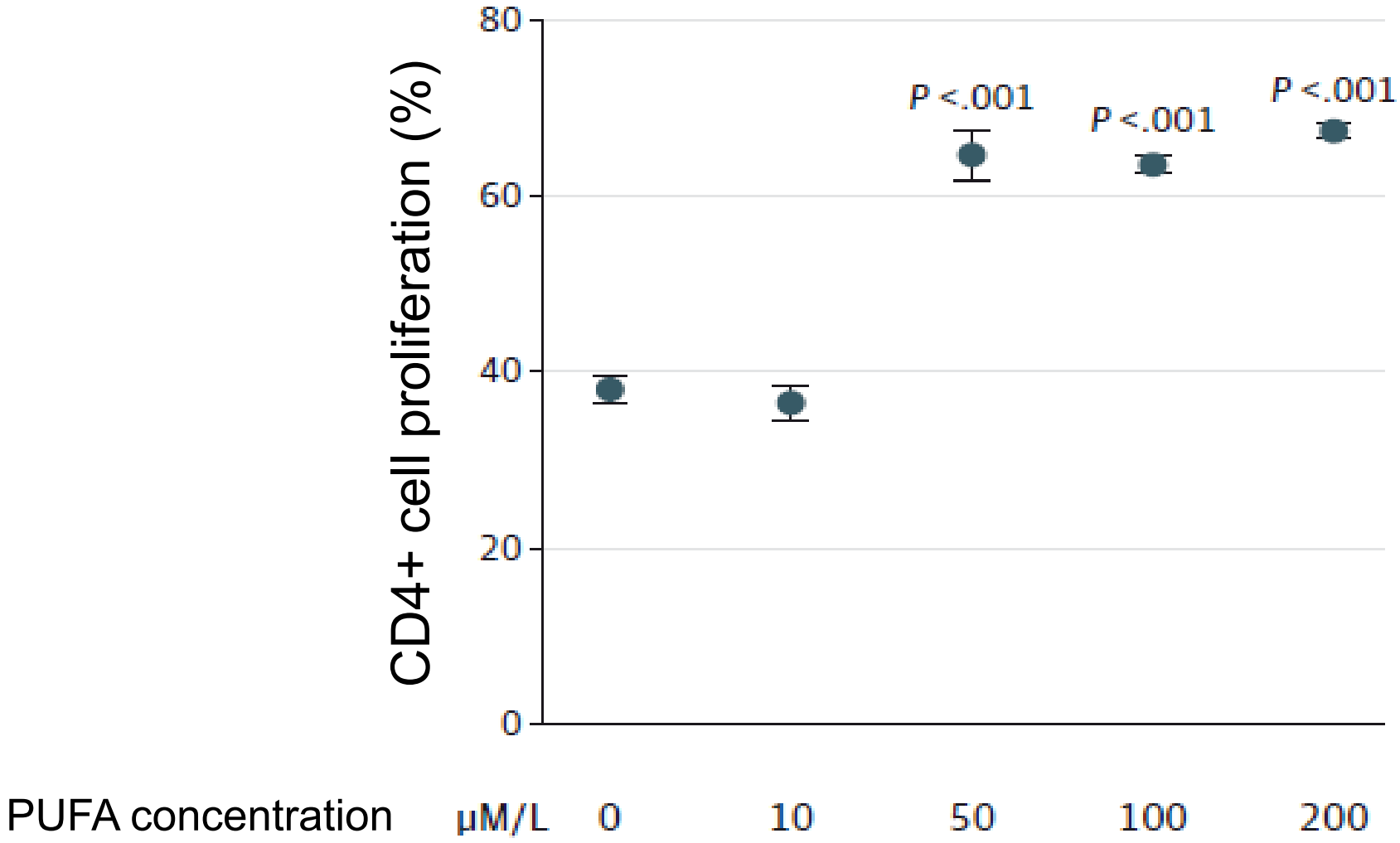

CRC subtypes
FOXP3+ cell-high
Normal colon
ω-3 fatty acids
FOXP3+ cell-low

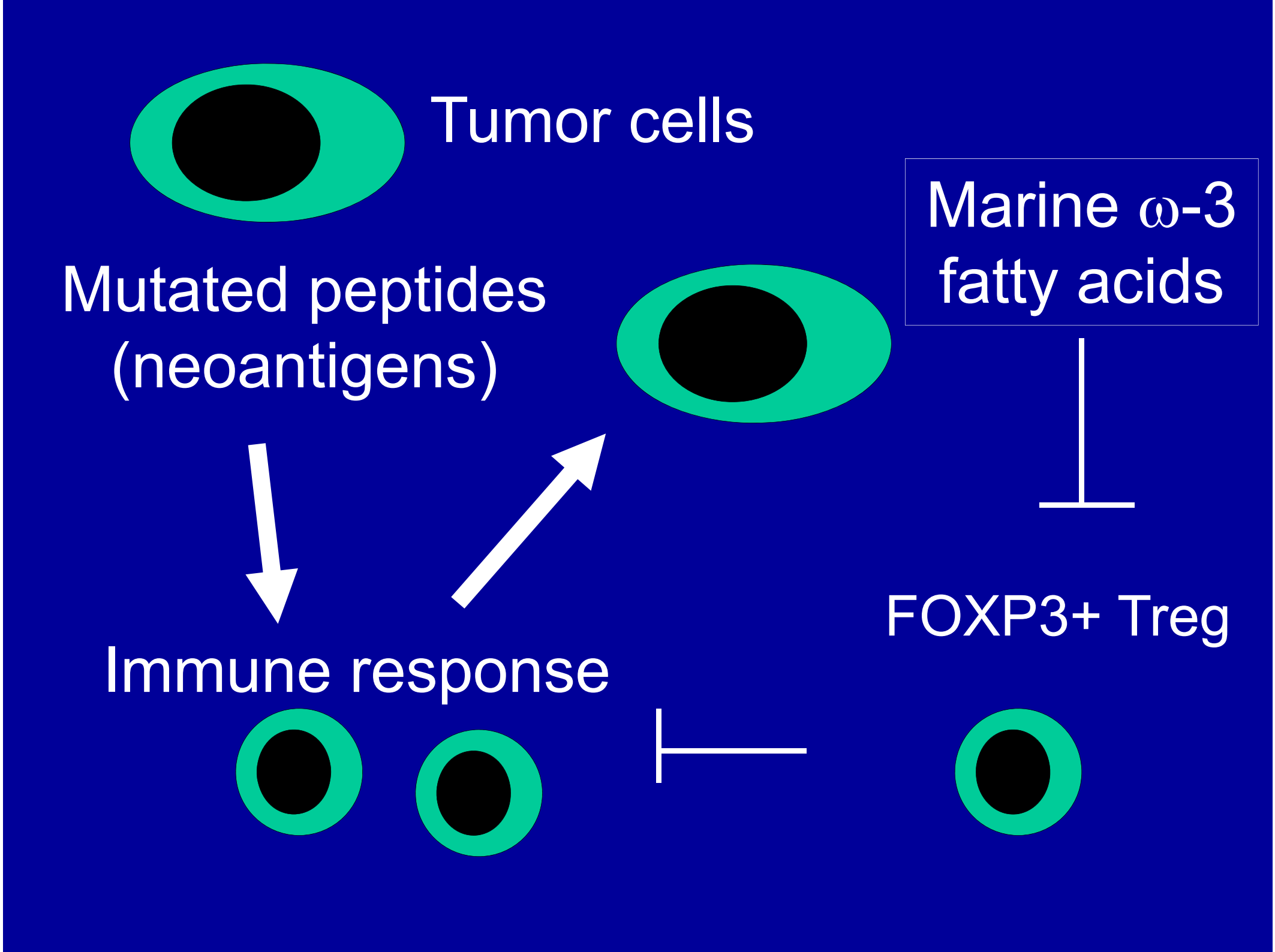


Song et al. JAMA Oncol 2016



PUFA can reduce T-cell suppressive activity of FOXP3+ cell, leading to CD4+ T cell proliferation

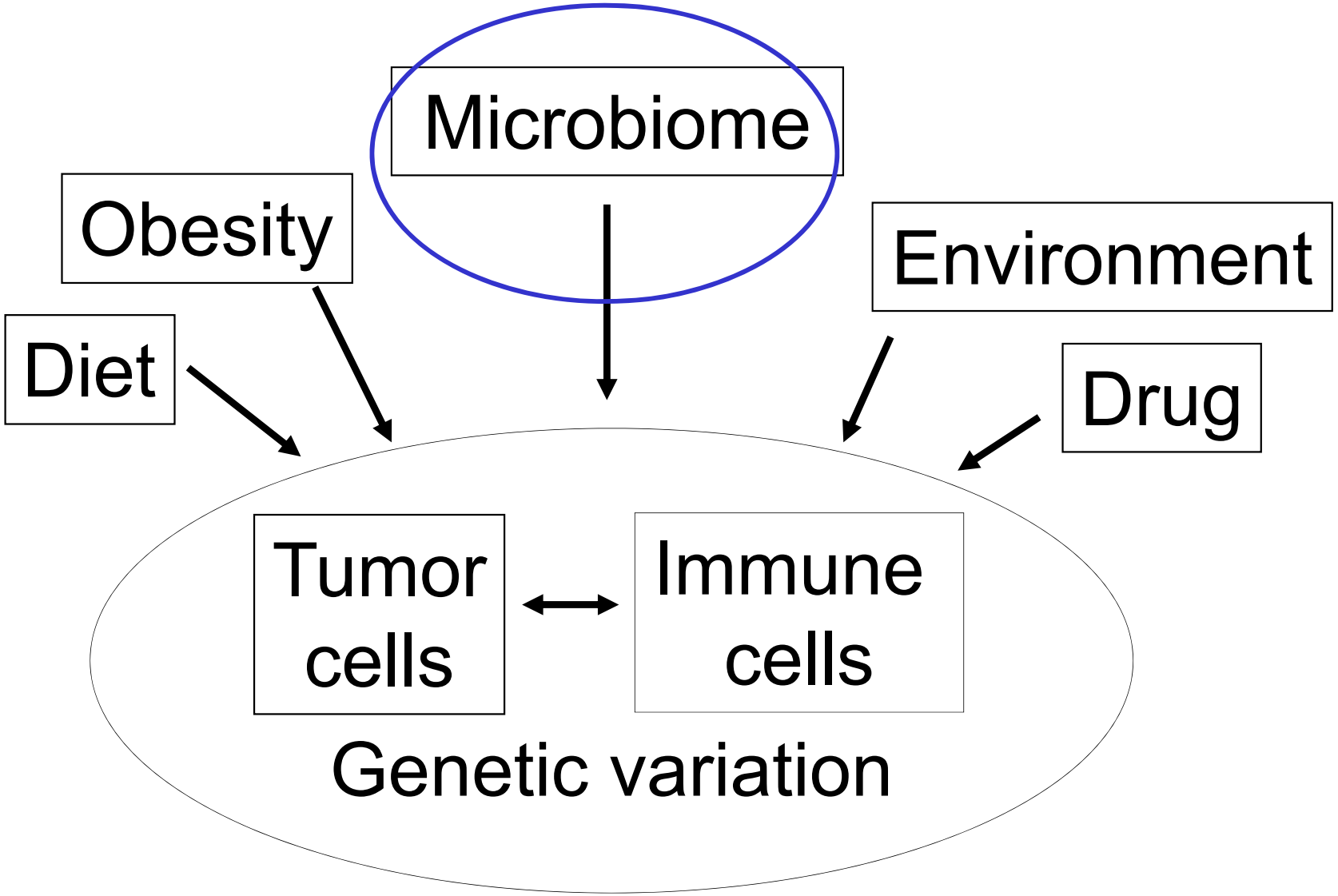
Song et al. JAMA Oncol 2016


Tumor cells
Marine ω-3 fatty acids
Mutated peptides (neoantigens)
FOXP3+ Treg
Immune response

Exposures (or risk factors) influence risk of CRC immune subtype

- Marine ω-3 PUFAs (Song. JAMA Oncol 2016)
- IBD risk SNP (Khalili. Carcinogenesis 2015)
- Vitamin D (Song. Gut 2016)
- Aspirin (Cao. Gastroenterology 2016)
- Inflammatory diet (Liu. Gastroenterology 2018)
- Smoking (Hamada. JNCI 2018)
- Calcium intake (Wang. Cancer Prev Res in press)

Microbiology-MPE (essential for Immunology-MPE)



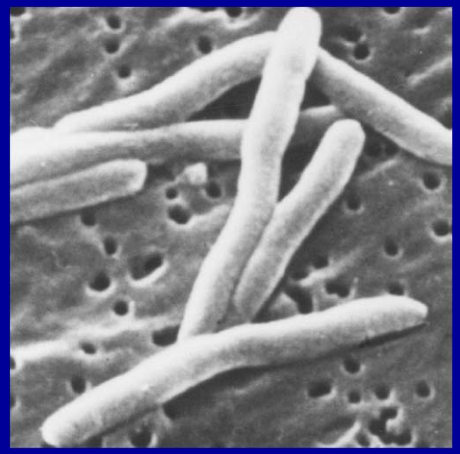
Ogino et al. Nature Rev Clin Oncol 2011
Ogino et al. Gut 2018
Ogino et al. Lancet 2018

Challenges in microbiome research

- Which microorganism causes cancer?
- Experimental models have different microbiome and immune system
- We focus on tumor tissue microbiota

Fusobacterium nucleatum in CRC tissue

Immunosuppressive → lower T cells
Higher stage → shorter survival
MSI-high
Go with metastasis

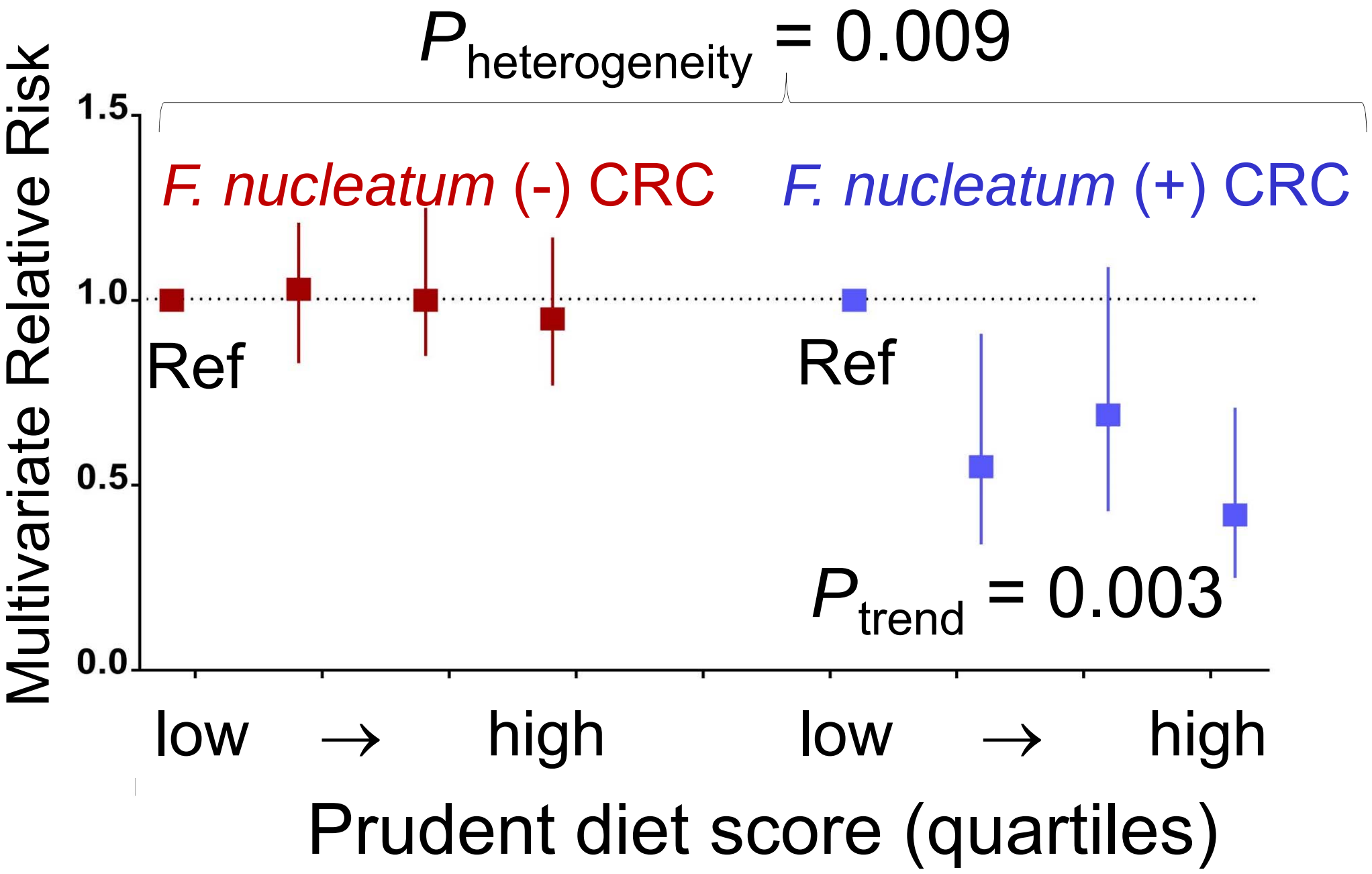


Mima et al. JAMA Oncol 2015
Mima et al. Gut 2016
Bullman et al. Science 2017

Diet ⟶ Gut microbiota ⟶ Cancer

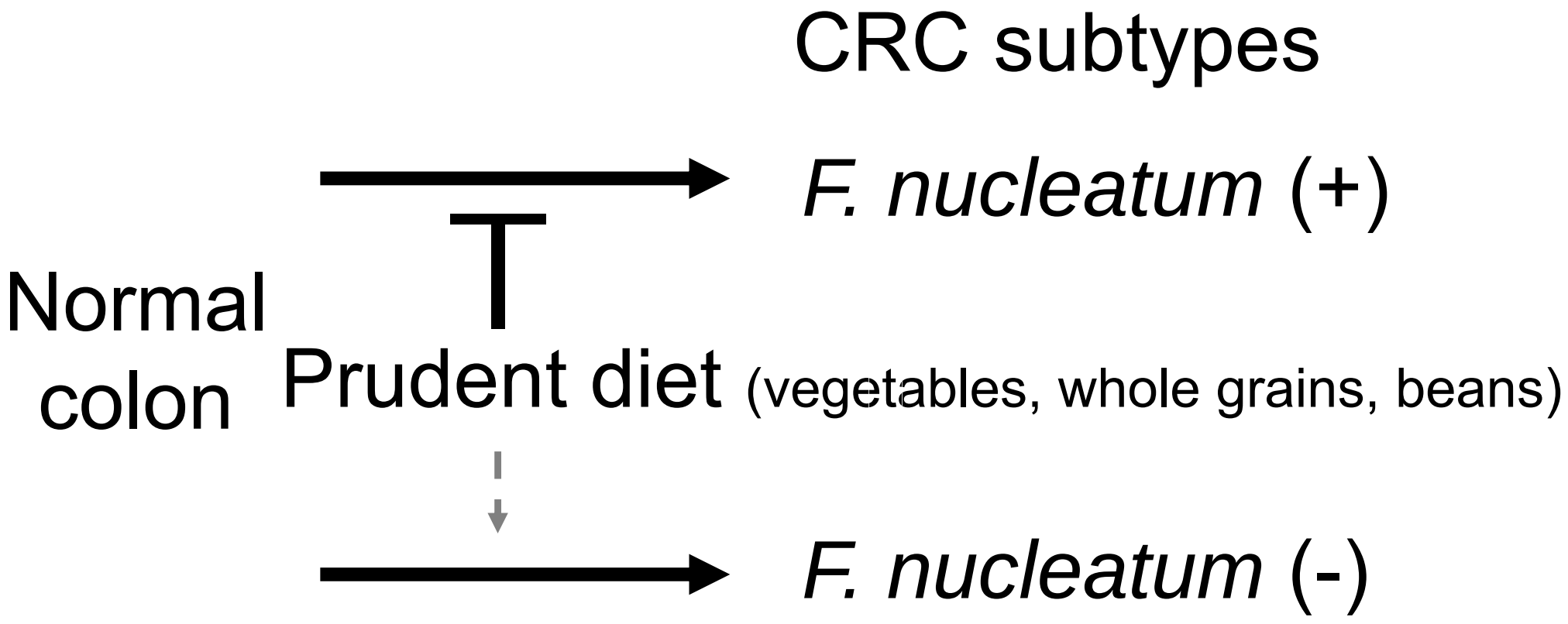
Diet → Gut microbiota → Cancer

Prudent diet (vegetables, whole grains, beans, fiber) → Good microbiota (↓ bad bacteria) ⊣ *Fusobacterium nucleatum*(+) CRC



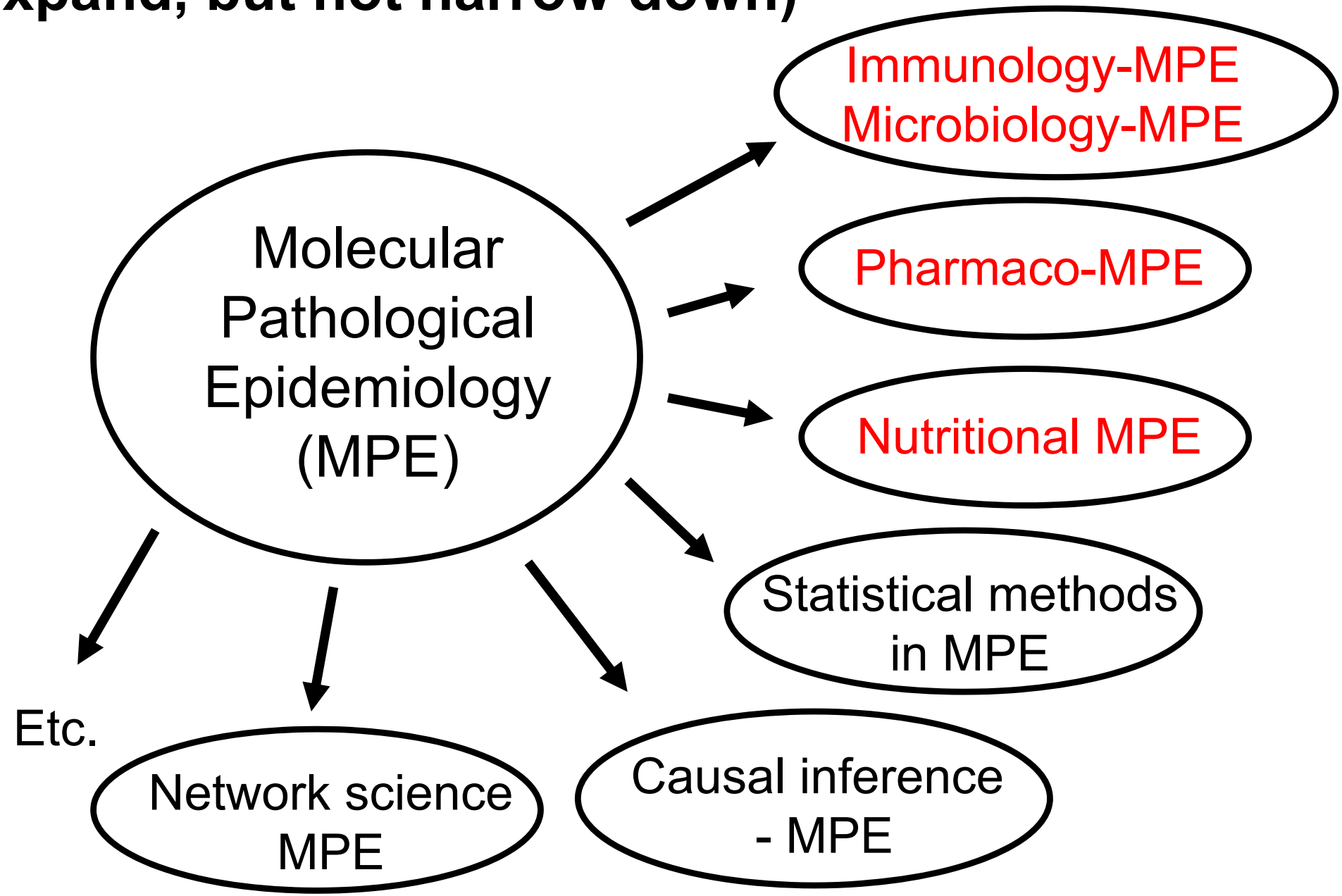
Mehta et al. JAMA Oncol 2017

Prudent diet → microbiota → prevention



Mehta et al. JAMA Oncol 2017

MPE can change our concept on scientific fields (expand, but not narrow down)



Ogino et al. Annu Rev Pathol 2018

THE 5th INTERNATIONAL MOLECULAR PATHOLOGICAL EPIDEMIOLOGY (MPE) MEETING

Discuss Big Data Analysis, and Think Big!

June 2020, Boston, USA

Free registration
Open to public

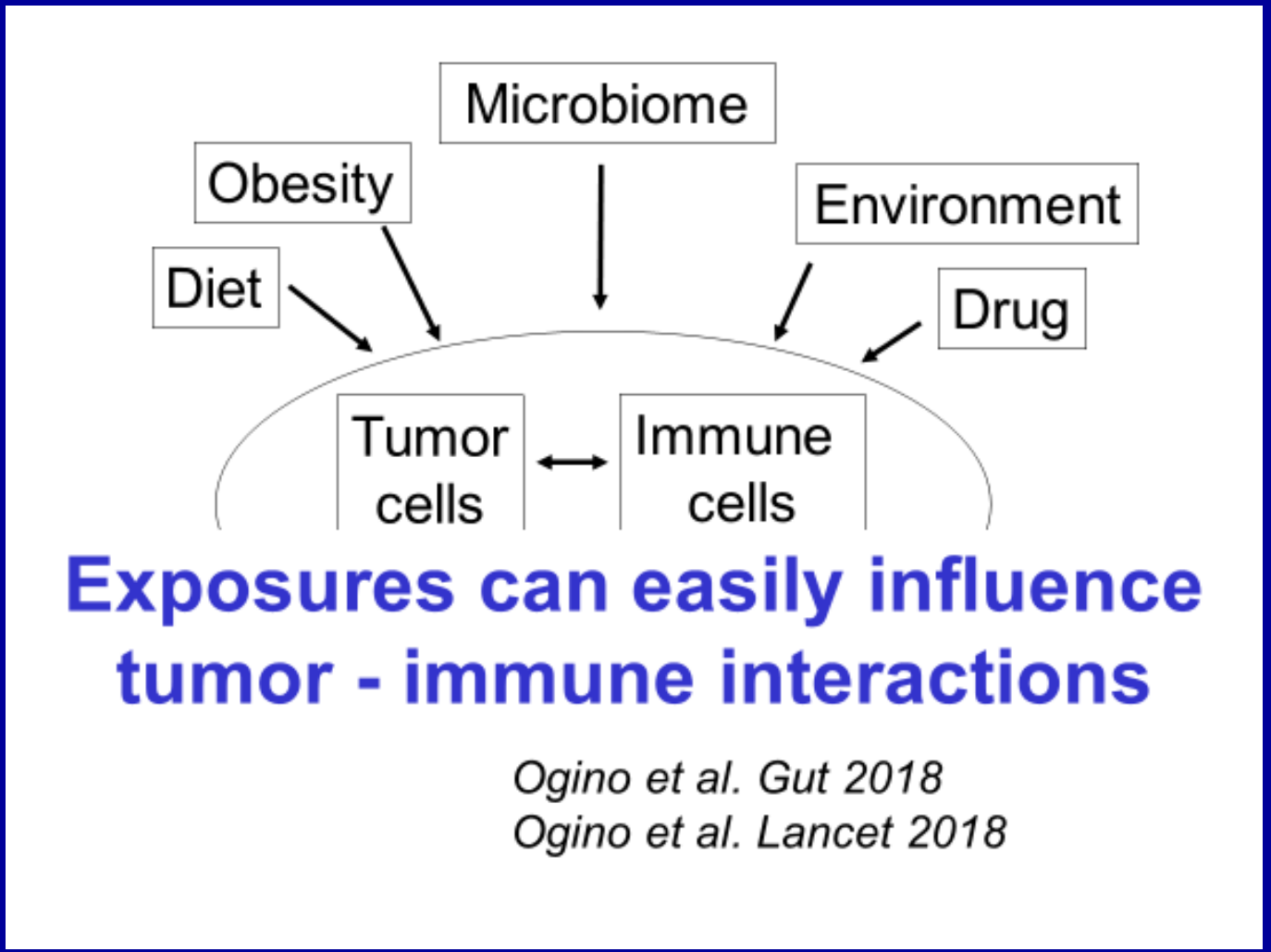
www.mpemeeting.org

Summary

- Immunology-MPE (Molecular Pathological Epidemiology) can provide new insights
  - Exposures can easily influence microbiota–tumor–immune interactions
  - Immunoprevention & therapy (using nutrients & lifestyle)
- Exposures influence immunotherapy
- MPE is making new frontiers
  - There are widely open opportunities!

Summary 2

- Let's do "immunology-MPE" and "microbiology-MPE" studies!



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Acknowledgements #2

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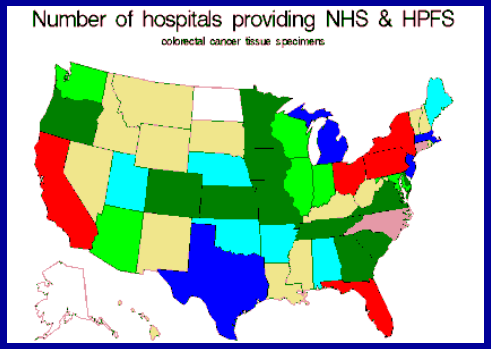
- Various US hospitals/pathology departments for proving medical records and tissue specimens



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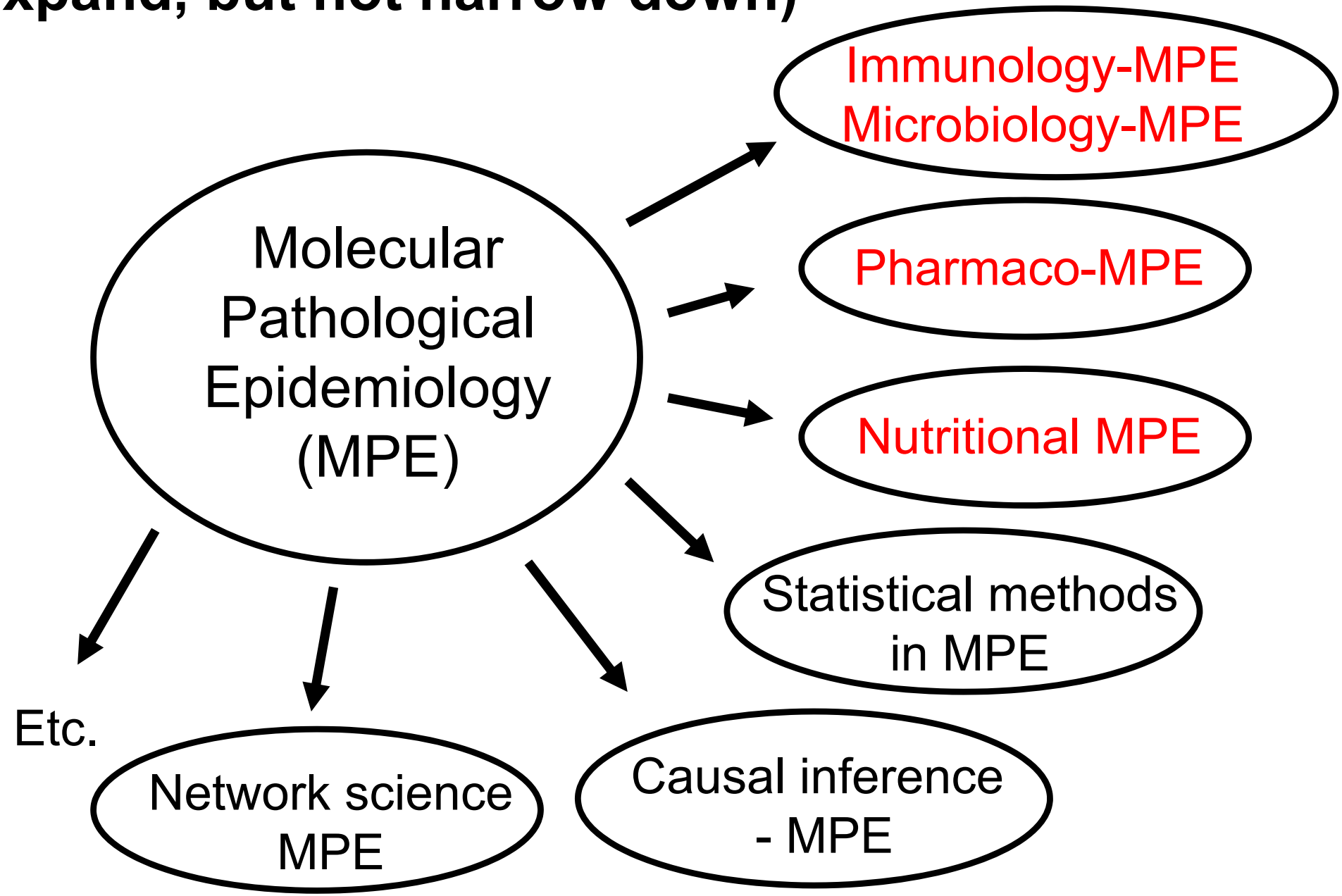
MPE can change our concept on scientific fields (expand, but not narrow down)



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