Peritoneal Surface Malignancy

Relaunching OHSU's HIPEC Program

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Disclosures

- None

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Agenda

- Overview of Peritoneal Surface Malignancies and HIPEC
- MythBusters – PSM Edition
- Active Areas of Investigation
- OHSU's PSM/HIPEC Program

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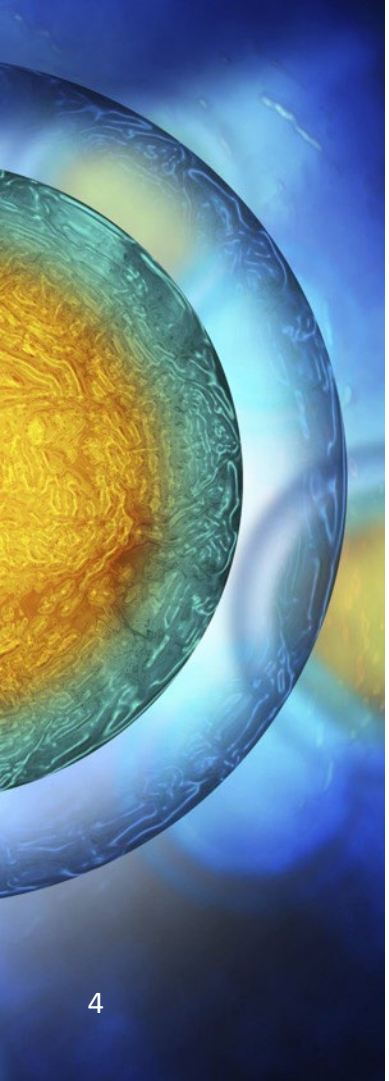

Peritoneal Surface Malignancy

- Broad and heterogenous group of diseases
- Pathophysiology complex and not fully understood
  - Mesothelial transformation (primary)
  - Shedding and implantation (secondary)
- Diagnosis is challenging, often requires direct visualization (laparoscopy/laparotomy)

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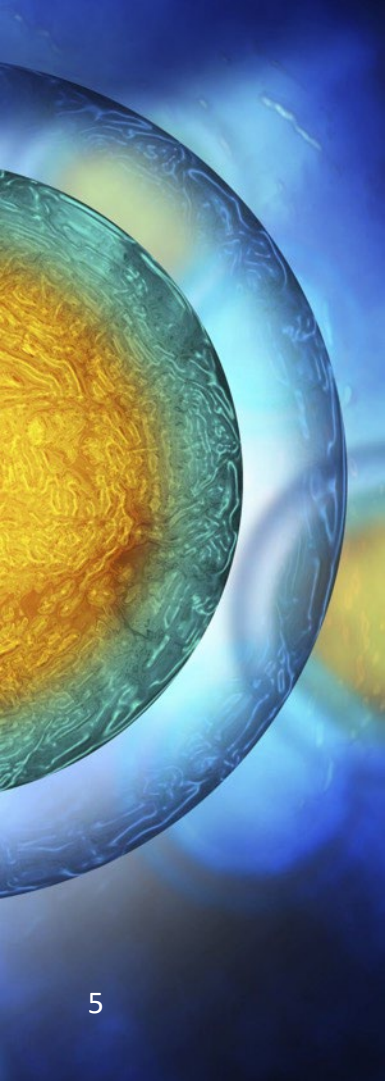

Intraperitoneal Therapies

(with or without Cytoreduction)

- HIPEC: Hyperthermic Intraperitoneal Chemotherapy
- NIPS: Neoadjuvant Intraperitoneal and Systemic Chemotherapy
- PIPAC: Pressurizd Intraperitoneal Aerosol Chemotherapy
- EPIC: Early Postoperative Intraperitoneal Chemotherapy

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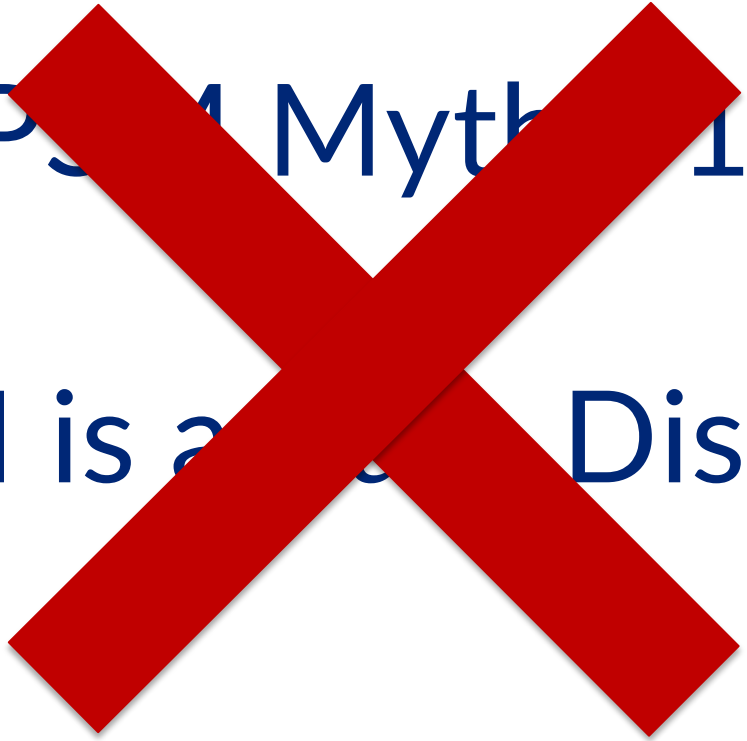
MYTHBUSTERS

PSM Myth 1:

PSM is a Disease



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Epidemiology

- GLOBOCAN Registry does not designate PSM: don't have an exact incidence of PSM
  - Most data comes from western/high income cohort samples
- Labeled an orphan disease – limits funding
- Actually incredibly common
  - Autopsy studies suggest upwards of 20% of solid organ cancer patients dying with peritoneal metastases present (despite NCCN single digit incidences)
  - Colorectal cancer is 2nd most cancer: 5-8% synchronous, another 5-12% metachronous PSM
  - Ovarian cancer: 60-70% develop PSM
- Long list of other cancers

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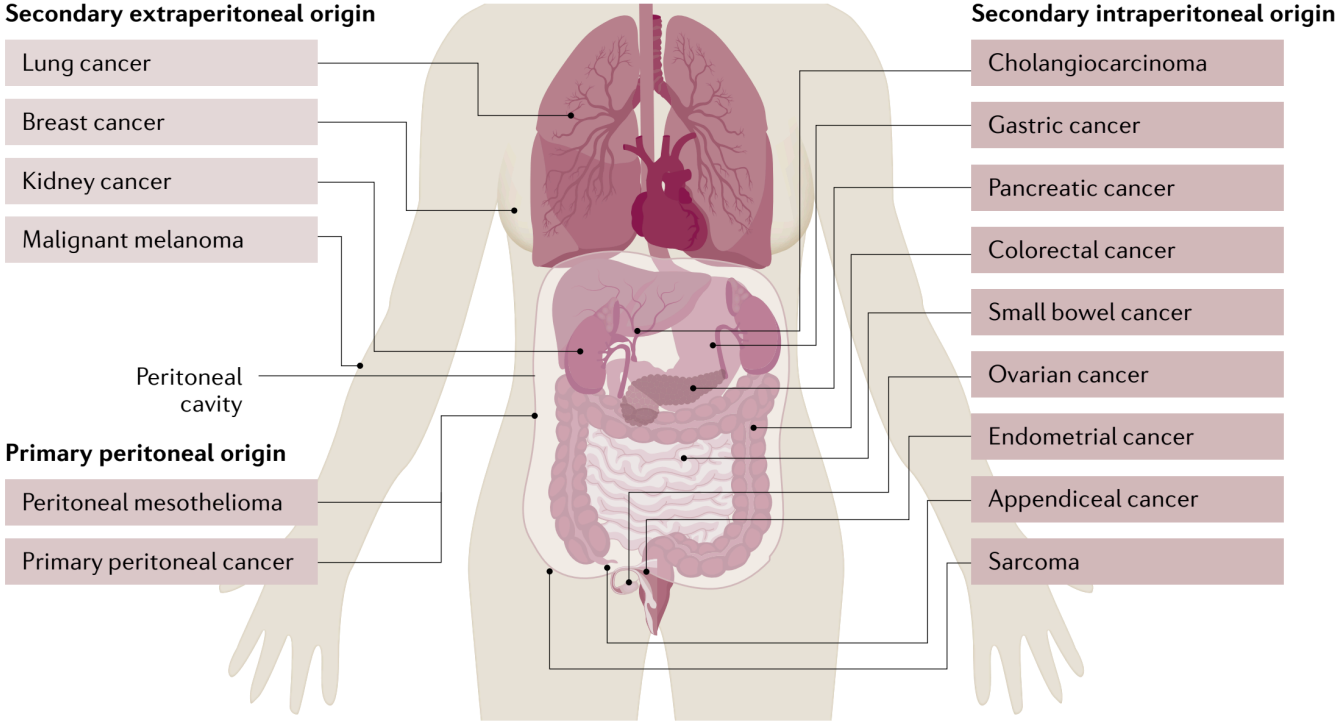
Epidemiology



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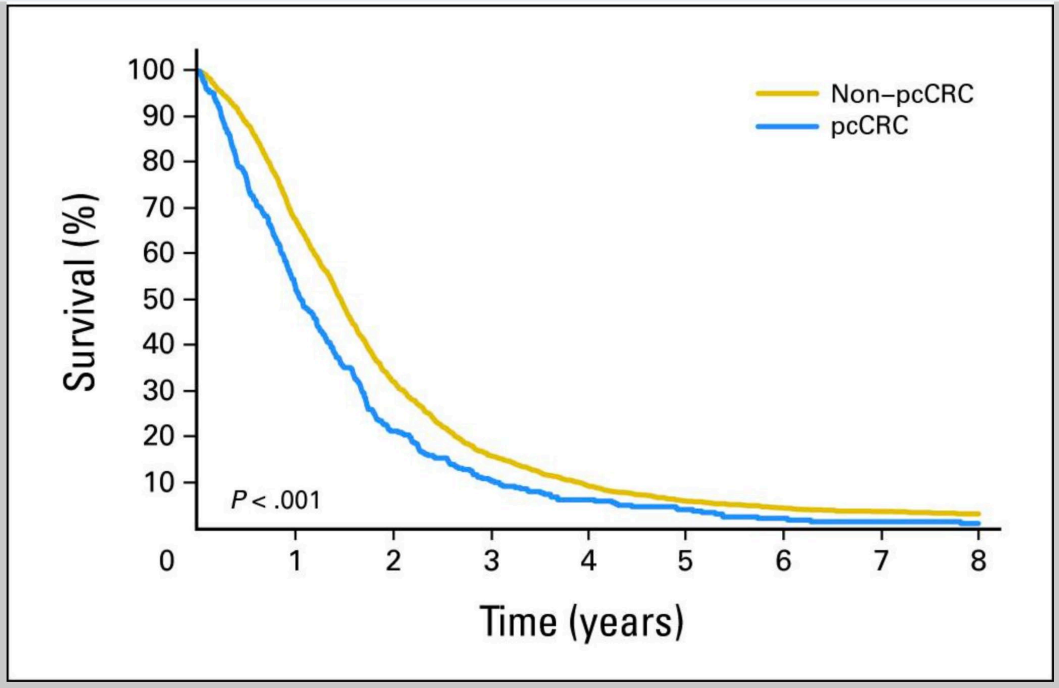
Stigma and Nihilism



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Long Term Survival

- Subset of patients in almost every disease site

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Long Term Survival

- CRC
  - Median survival with CRS/HIPEC 40-60 months
  - 16% 10-year survival; increased to 40% if PCI<10
- Ovarian
  - Median survival 40-70 months
- Appendiceal Adenocarcinoma
  - 3-10 years median survival
  - >20 year for LAMN

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Long Term Survival

- Those who get complete cytoreduction do better (refer early!)
- Long-term survival is an appropriate goal of care and a valid endpoint for clinical trials

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PSM Myth 3:

Systemic therapy is Standard of Care

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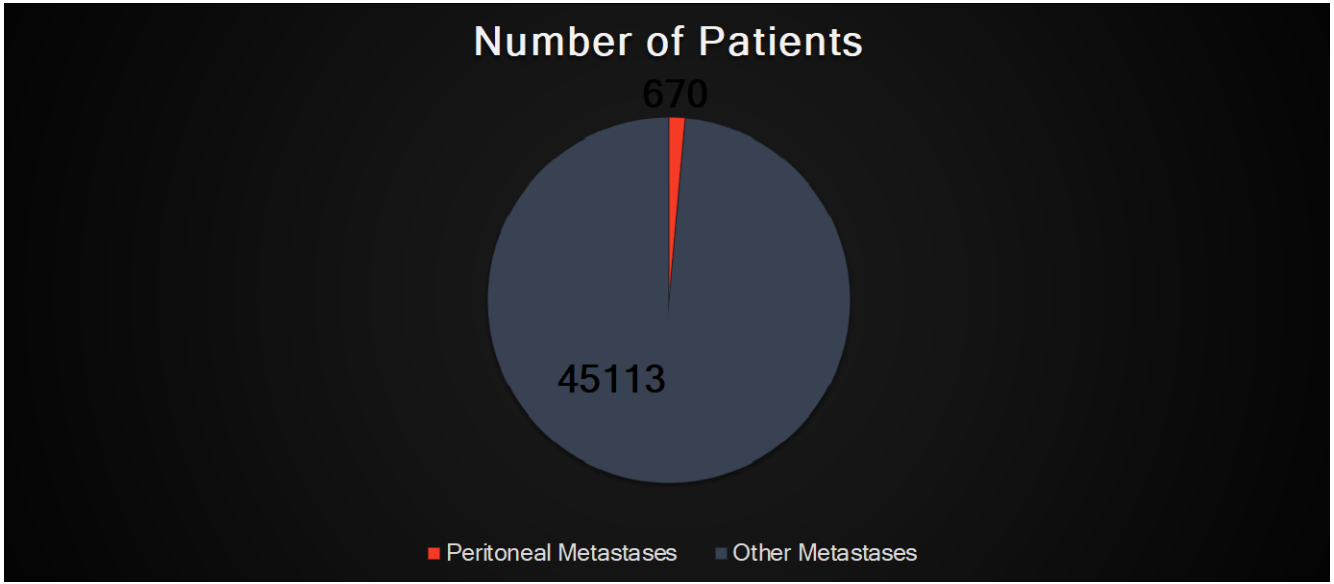
Systematic Exclusion from Clinical Trials



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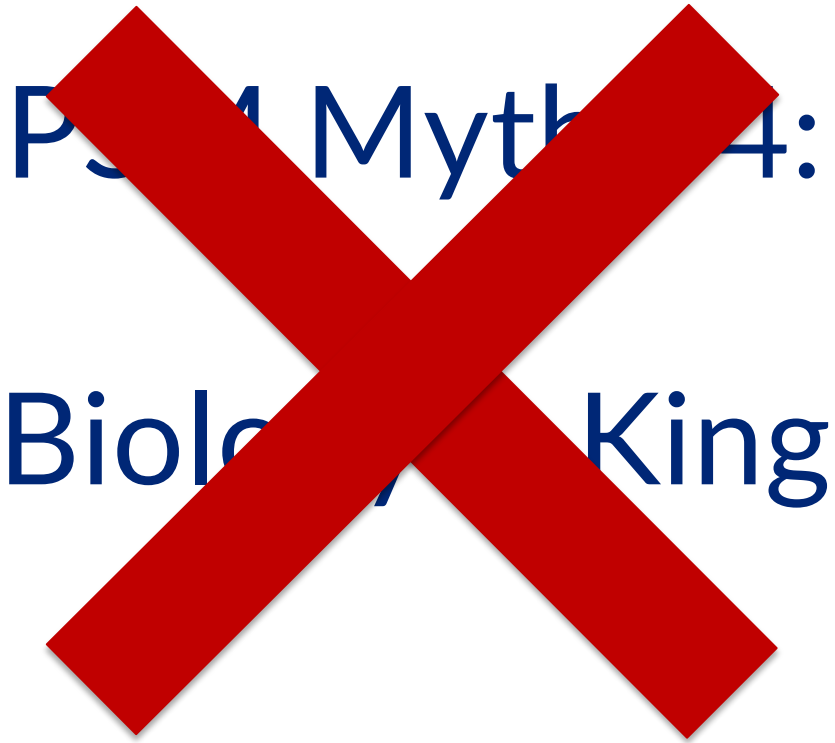
Standard of Care for PSM?

- Upfront CRS for CRC is standard in several countries
- Mixed in the US (Chicago Consensus Guidelines gives options of CRS/HIPEC alone, before, or after chemotherapy)
- Median survival 16 months on systemic vs >40 months after complete CRS/HIPEC…refer early!
  - CAIRO6 first to study systemic chemo in this population



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Candidacy for Oligometastatic Approach

1. Performance status/tolerability of surgery
2. Burden of disease/PCI/resectability
3. Tumor biology…but what does this mean in PSM?
   - Site of primary
   - LAMN vs adenocarcinoma
   - Grade/differentiation
   - High risk path features (LVI, PNI, LN+, signet rings, goblet cells, etc)

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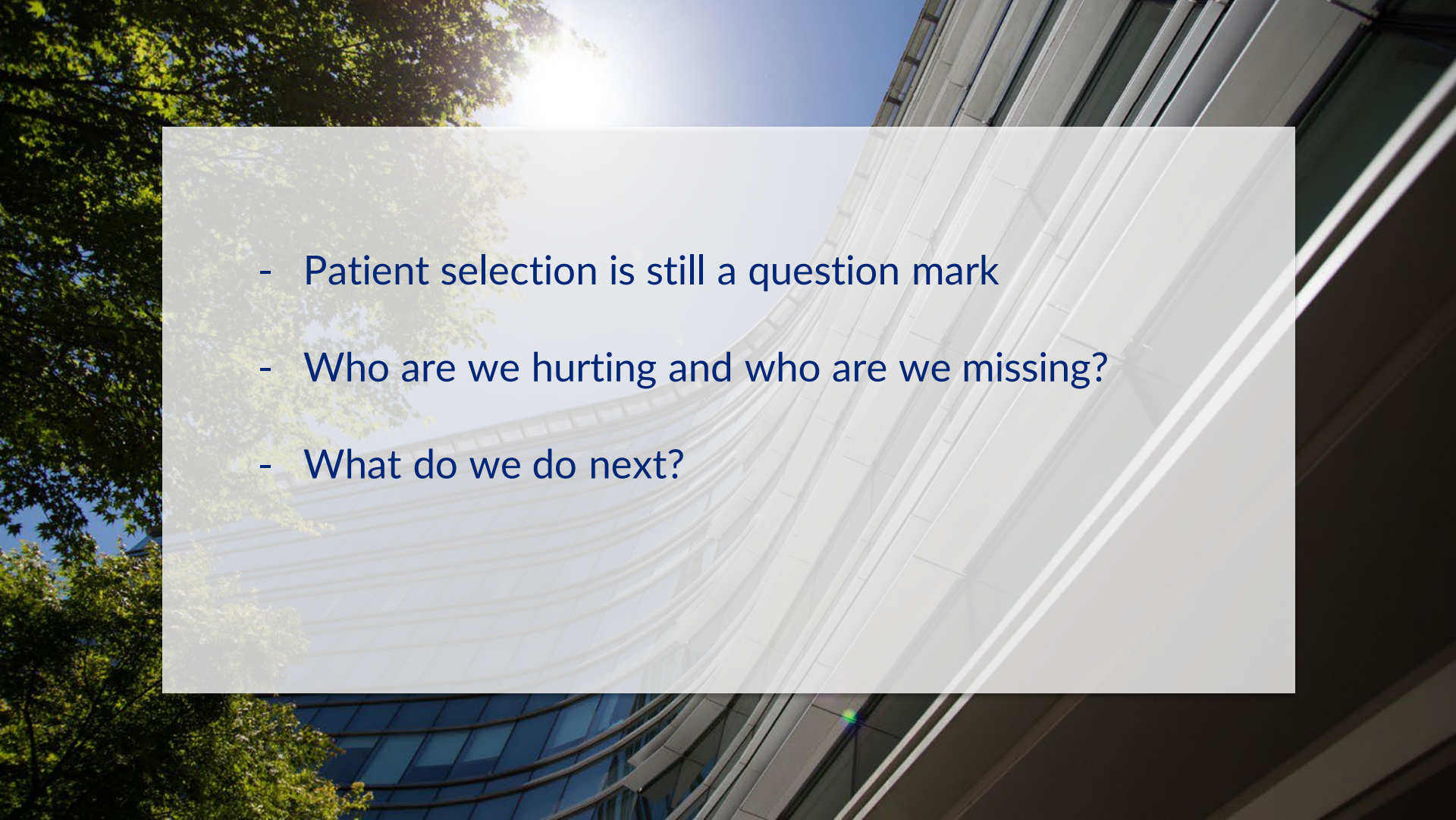
36 year old woman
LAMN with PMP
62 year old man
Pancreatic adenocarcinoma



- Patient selection is still a question mark
- Who are we hurting and who are we missing?
- What do we do next?

Active Areas of Research

- Microbiome and diet/metabolomics
- Precision oncology
- Detection and surveillance
- Quality of life
- Surgical clinical trials

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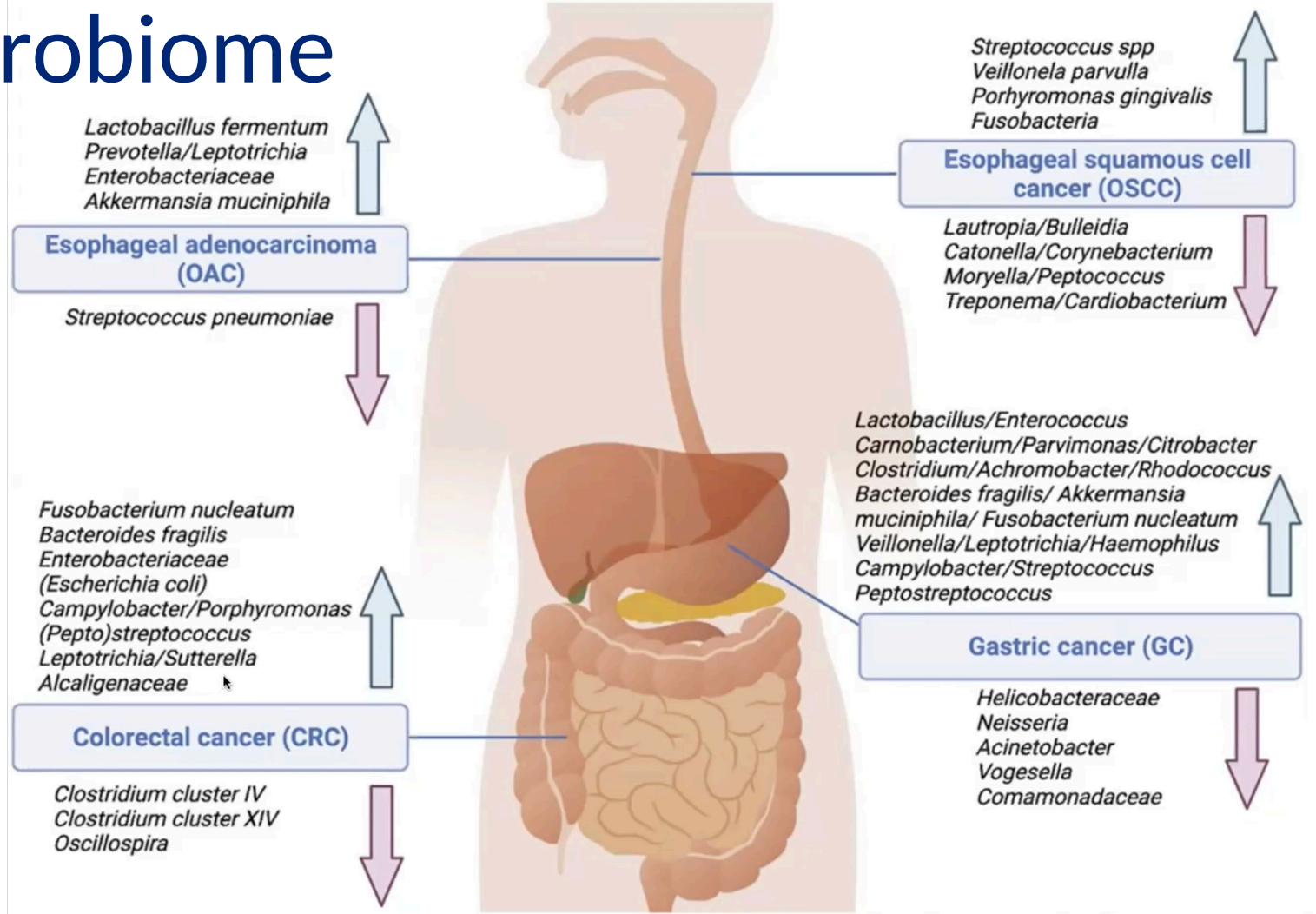
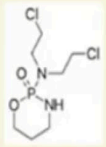
Microbiome


Lactobacillus fermentum
Prevotella/Leptotrichia
Enterobacteriaceae
Akkermansia muciniphila
Esophageal adenocarcinoma (OAC)
Streptococcus pneumoniae
Streptococcus spp
Veillonela parvulla
Porhyromonas gingivalis
Fusobacteria
Esophageal squamous cell cancer (OSCC)
Lautropia/Bulleidia
Catonella/Corynebacterium
Moryella/Peptococcus
Treponema/Cardiobacterium
Fusobacterium nucleatum
Bacteroides fragilis
Enterobacteriaceae
(Escherichia coli)
Campylobacter/Porphyromonas
(Pepto)streptococcus
Leptotrichia/Sutterella
Alcaligenaceae
Colorectal cancer (CRC)
Clostridium cluster IV
Clostridium cluster XIV
Oscillospira
Lactobacillus/Enterococcus
Carnobacterium/Parvimonas/Citrobacter
Clostridium/Achromobacter/Rhodococcus
Bacteroides fragilis/ Akkermansia
muciniphila/ Fusobacterium nucleatum
Veillonella/Leptotrichia/Haemophilus
Campylobacter/Streptococcus
Peptostreptococcus
Gastric cancer (GC)
Helicobacteraceae
Neisseria
Acinetobacter
Vogesella
Comamonadaceae

Promising therapy



Cyclophosphamide

Enterococcus hirae
Lactobacillus johnsonii
Lactobacillus murinus

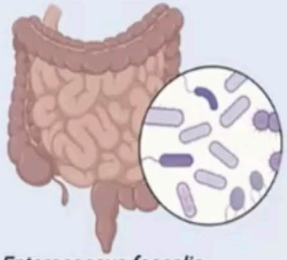
Lactobacillus

Anti-PD-1/PD-L1
Anti-CTLA-4

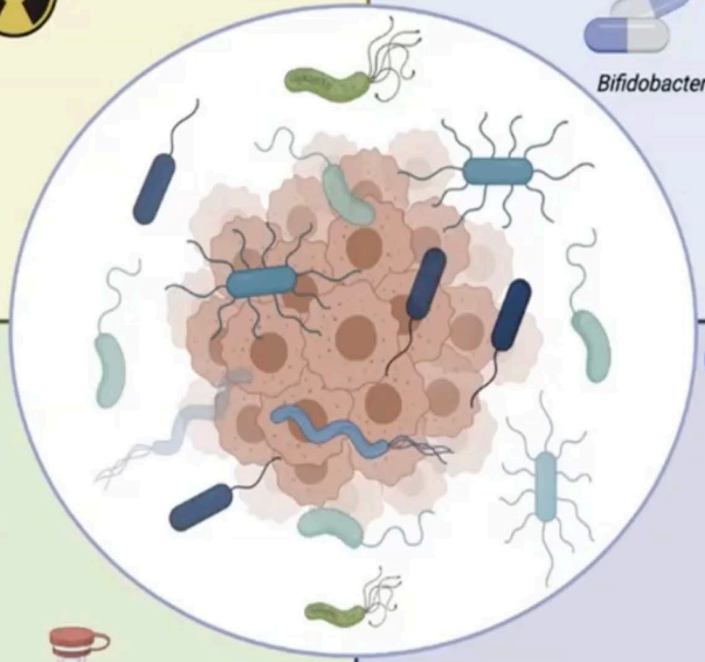
Akkermansia muciniphila
Bifidobacterium longum
Enterococcus hirae
Bacteroides fragilis
Bacteroides thetaiotaomicron
Collinsella aerofaciens
Enterococcus faecium

Potential for prevention

Bifidobacterium



Enterococcus faecalis
Bacillus cereus
Clostridium butyricum
Lactobacillus

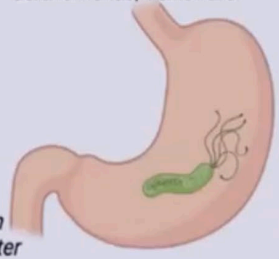


Potential biomarkers

Fusobacterium nucleatum
Enterococcus faecalis
Streptococcus bovis
Streptococcus anginosus
Bacteroides fragilis
Proteobacteria
Porphyromonas
Citrobacter/Slakia

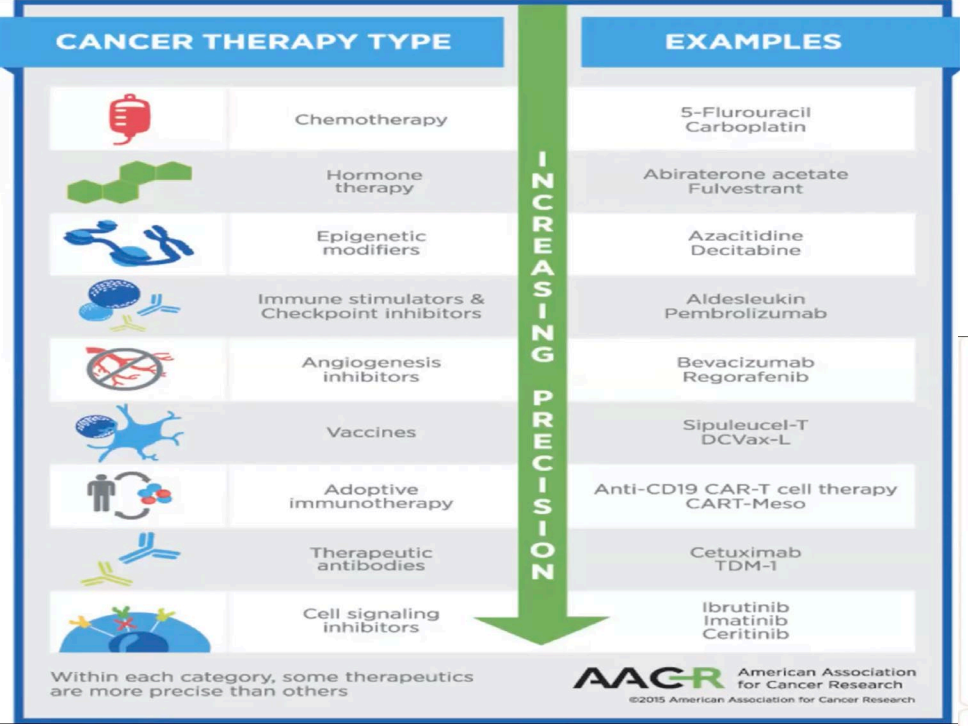
Carcinogenic risk factors

Porphyromonas gingivalis
Streptococcus/Neisseria
Actinomyces/Atopobium
Tanerella forsythia
Selenomonas/Veillonella



Fusobacterium nucleatum
Bacteroides/Campylobacter
Escherichia/Prophyromonas

Precision


CANCER THERAPY TYPE
EXAMPLES
INCREASING PRECISION
Chemotherapy
5-Flurouracil
Carboplatin
Hormone therapy
Abiraterone acetate
Fulvestrant
Epigenetic modifiers
Azacitidine
Decitabine
Immune stimulators & Checkpoint inhibitors
Aldesleukin
Pembrolizumab
Angiogenesis inhibitors
Bevacizumab
Regorafenib
Vaccines
Sipuleucel-T
DCVax-L
Adoptive immunotherapy
Anti-CD19 CAR-T cell therapy
CART-Meso
Therapeutic antibodies
Cetuximab
TDM-1
Cell signaling inhibitors
Ibrutinib
Imatinib
Ceritinib
Within each category, some therapeutics are more precise than others
AACR American Association for Cancer Research
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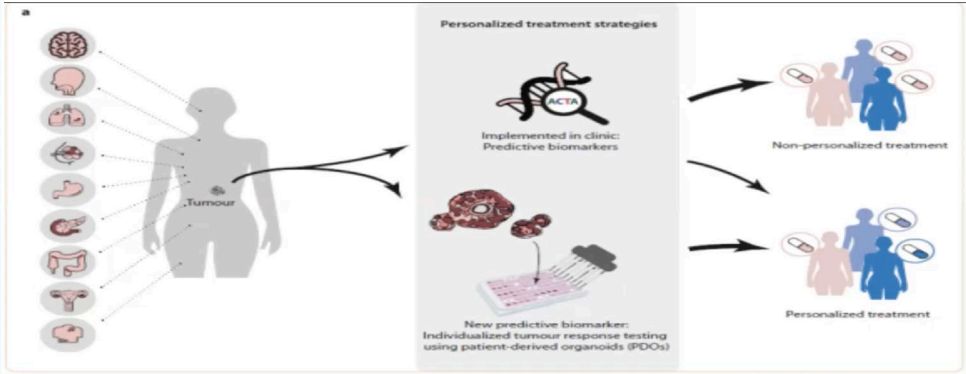
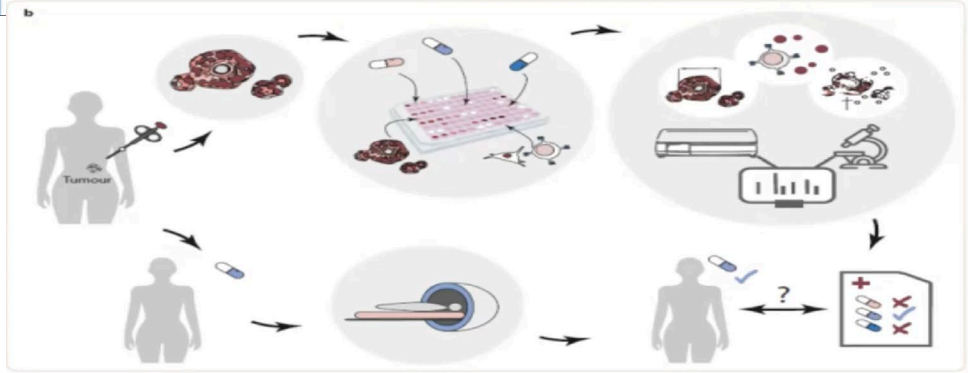
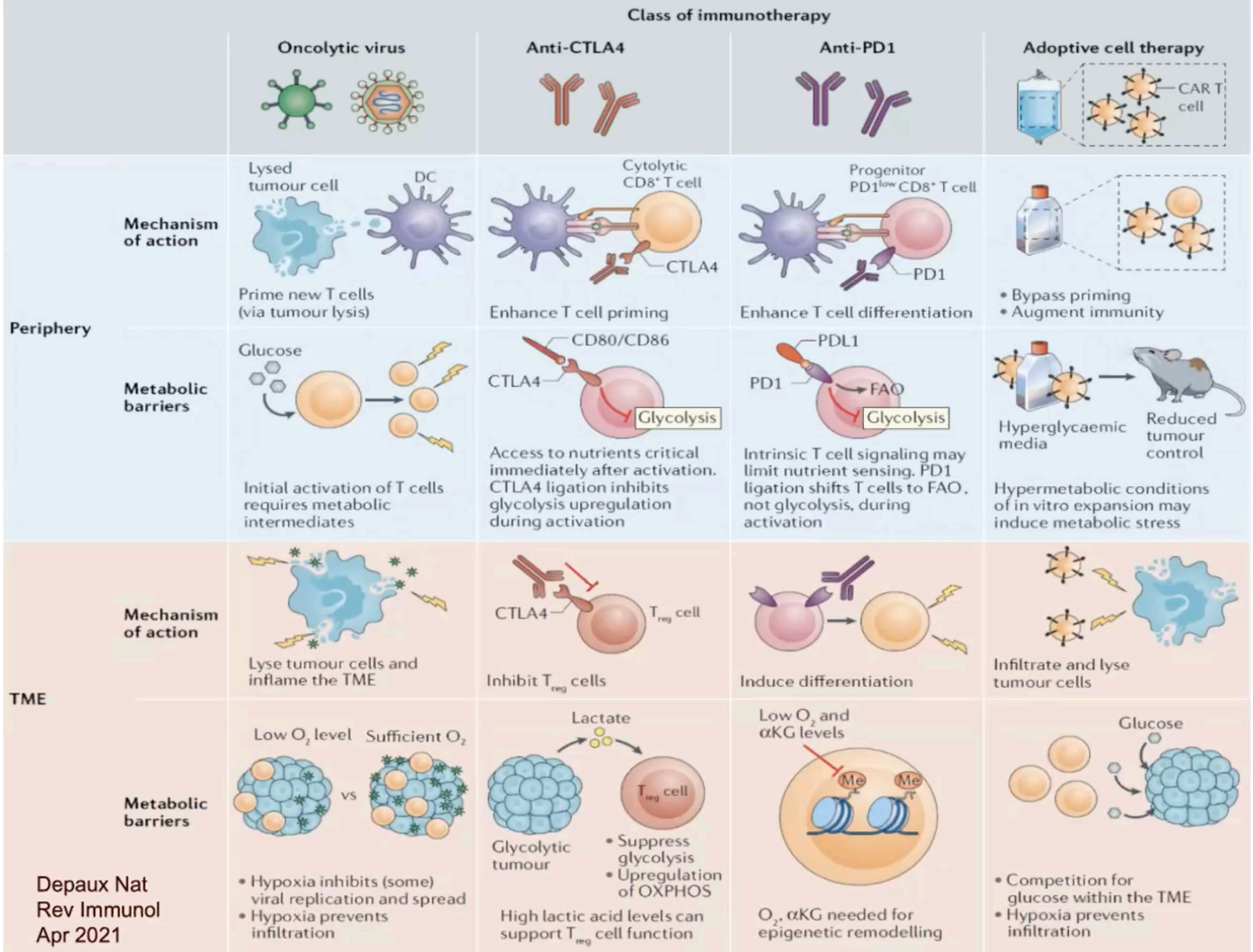
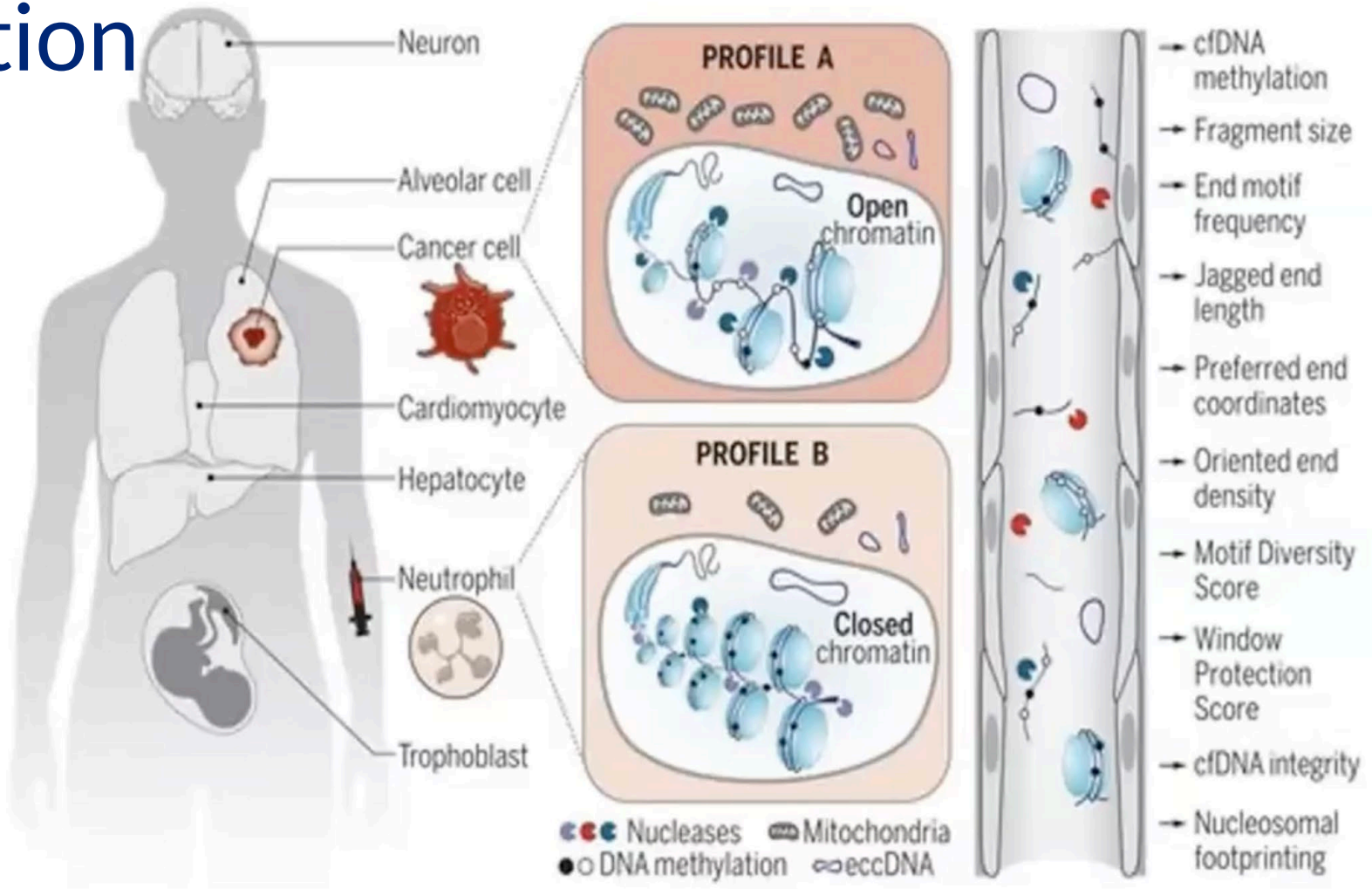

a
Tumour
Personalized treatment strategies
ACTA
Implemented in clinic:
Predictive biomarkers
New predictive biomarker:
Individualized tumour response testing
using patient-derived organoids (PDOs)
Non-personalized treatment
Personalized treatment


b
Tumour
?

Precision


Class of immunotherapy
Oncolytic virus
Anti-CTLA4
Anti-PD1
Adoptive cell therapy
CAR T cell
Periphery
Mechanism of action
Lysed tumour cell
DC
Prime new T cells (via tumour lysis)
Cytolytic CD8+ T cell
CTLA4
Enhance T cell priming
Progenitor PD1low CD8+ T cell
PD1
Enhance T cell differentiation
• Bypass priming
• Augment immunity
Metabolic barriers
Glucose
Initial activation of T cells requires metabolic intermediates
CD80/CD86
CTLA4
Glycolysis
Access to nutrients critical immediately after activation. CTLA4 ligation inhibits glycolysis upregulation during activation
PDL1
PD1
FAO
Glycolysis
Intrinsic T cell signaling may limit nutrient sensing. PD1 ligation shifts T cells to FAO, not glycolysis, during activation
Hyperglycaemic media
Reduced tumour control
Hypermetabolic conditions of in vitro expansion may induce metabolic stress
TME
Mechanism of action
Lyse tumour cells and inflame the TME
CTLA4
Treg cell
Inhibit Treg cells
Induce differentiation
Infiltrate and lyse tumour cells
Metabolic barriers
Low O2 level
Sufficient O2
vs
• Hypoxia inhibits (some) viral replication and spread
• Hypoxia prevents infiltration
Lactate
Treg cell
Glycolytic tumour
• Suppress glycolysis
• Upregulation of OXPHOS
High lactic acid levels can support Treg cell function
Low O2 and αKG levels
Me
Me
O2, αKG needed for epigenetic remodelling
Glucose
• Competition for glucose within the TME
• Hypoxia prevents infiltration
Depaux Nat Rev Immunol Apr 2021

Detection


Neuron
Alveolar cell
Cancer cell
Cardiomyocyte
Hepatocyte
Neutrophil
Trophoblast
PROFILE A
Open chromatin
PROFILE B
Closed chromatin
Nucleases
Mitochondria
DNA methylation
eccDNA
cfDNA methylation
Fragment size
End motif frequency
Jagged end length
Preferred end coordinates
Oriented end density
Motif Diversity Score
Window Protection Score
cfDNA integrity
Nucleosomal footprinting

Active Areas of Research

- Microbiome and diet/metabolomics
- Precision oncology
- Detection and surveillance
- Quality of life
- Surgical clinical trials

Comprehensive PSM Program at OHSU Knight Cancer Institute

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HIPEC Surgery

Dr. Divya Sood is a cancer surgeon and researcher with advanced expertise in HIPEC surgery.

HIPEC surgery is a leading-edge therapy for patients whose cancer has spread inside the abdomen. Key points to know about this therapy:

For patients

Caring for PSM Patients

- Hematologic impacts
- Malnutrition
- Physical deconditioning
- Psychological recovery
- Fertility
- Sexual function
- Bowel/bladder function
- Failure to thrive

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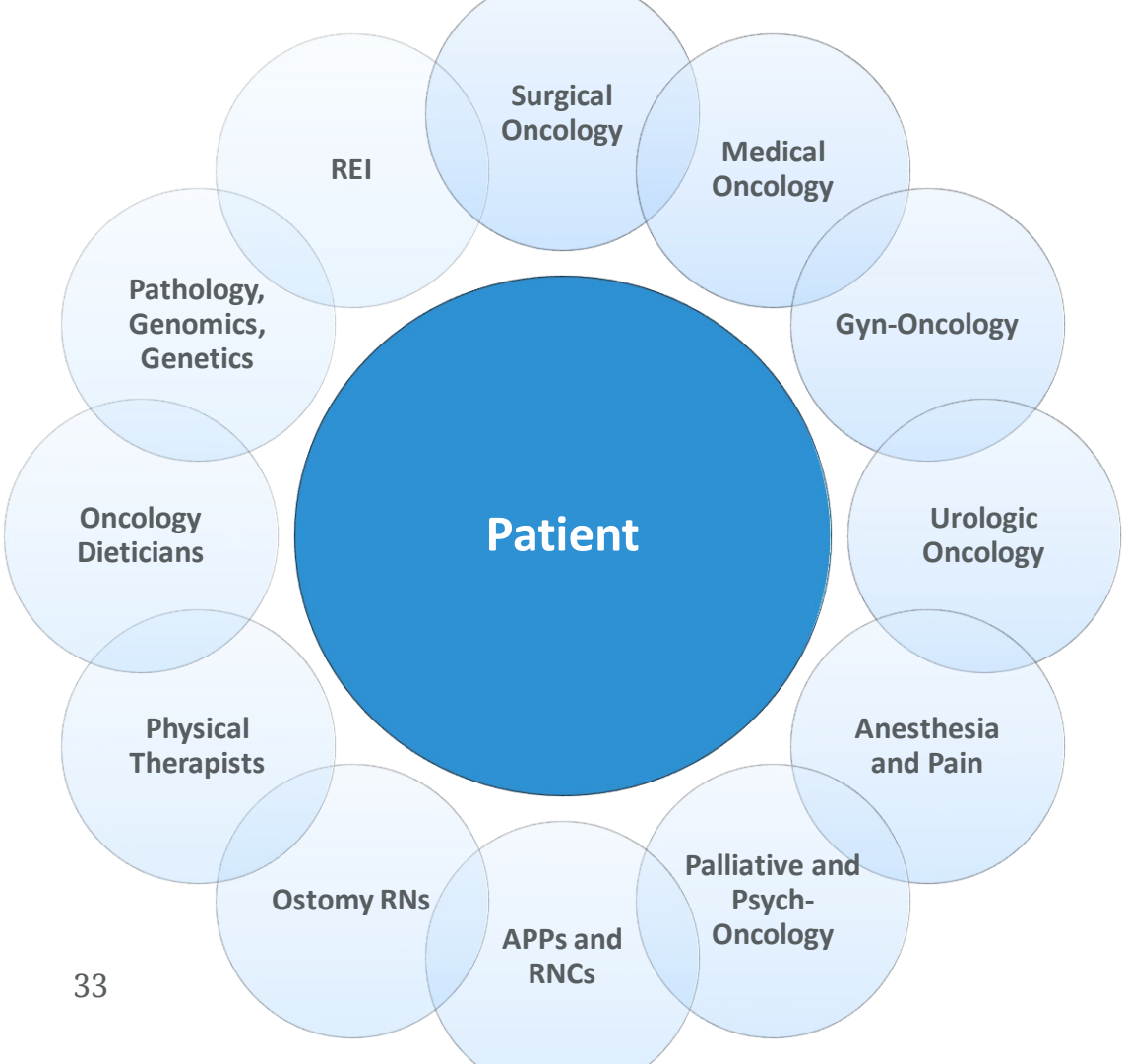
Big Problems :: Big Team



GOALS:

- Improve survival and oncologic outcomes
- Reduce LOS, debility, dependence
- Increase patient satisfaction
- Improve QOL and perioperative outcomes
- Increase clinical trial participation

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Impact of a Comprehensive Program

Metric	OHSU	Benchmark High Volume Programs
Volume	Bases off 2 months - projected to have >40 in first year	100/year (3 surgeons)
Median LOS	5 days	10 days
30-day mortality	0%	4.9%
ICU admission	0%	38%

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Final Thoughts

- PSM is a common but heterogenous group of diseases
- Long-term survival is a realistic goal for this population
- Early referral for consideration of surgery improves outcomes
- Patient selection is key, but still a work in progress
- There are exciting areas of investigation in the pipeline
- A comprehensive multidisciplinary team approach is critical to support PSM patients

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Thank You

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