
Cancer Metabolism:
From molecules to medicine
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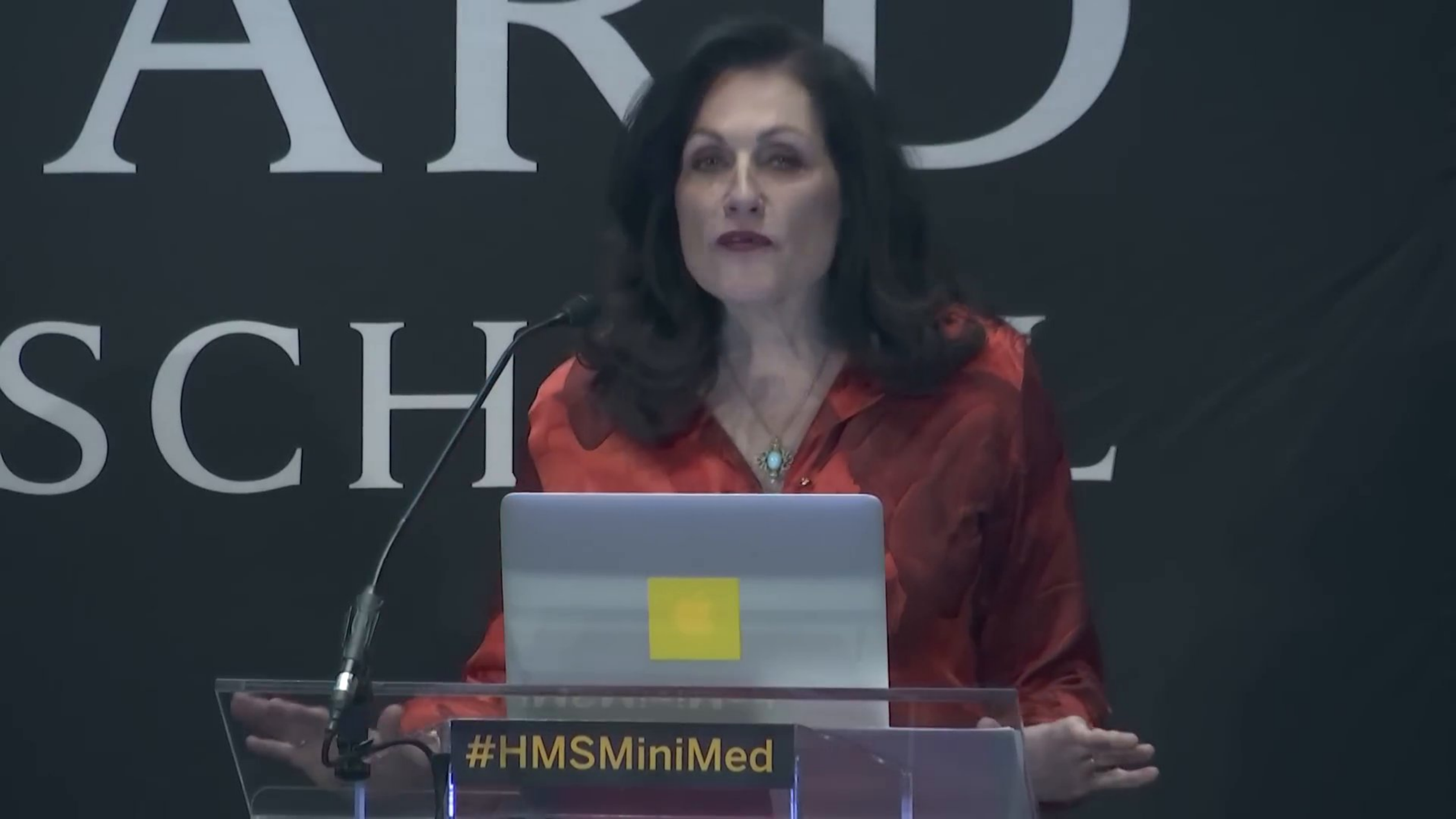
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April 10, 6:00–7:30 pm

Decoding Depression

April 17, 6:00–7:30 pm

MD vs Machine:
Artifical Intelligence in health care

April 30, 6:00–7:30 pm

Why Sleep Matters

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SEMINARS


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Please note:

- Certificate of completion for attending at least 3 seminars
- PDPs for teachers who attend all 4 sessions and complete an evaluation form
- Q+A: write questions on cards distributed and collected by staff

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Longwood SEMINARS


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Medicine
Marcia Haigis
Department of Cell Biology
Harvard Medical School
2019
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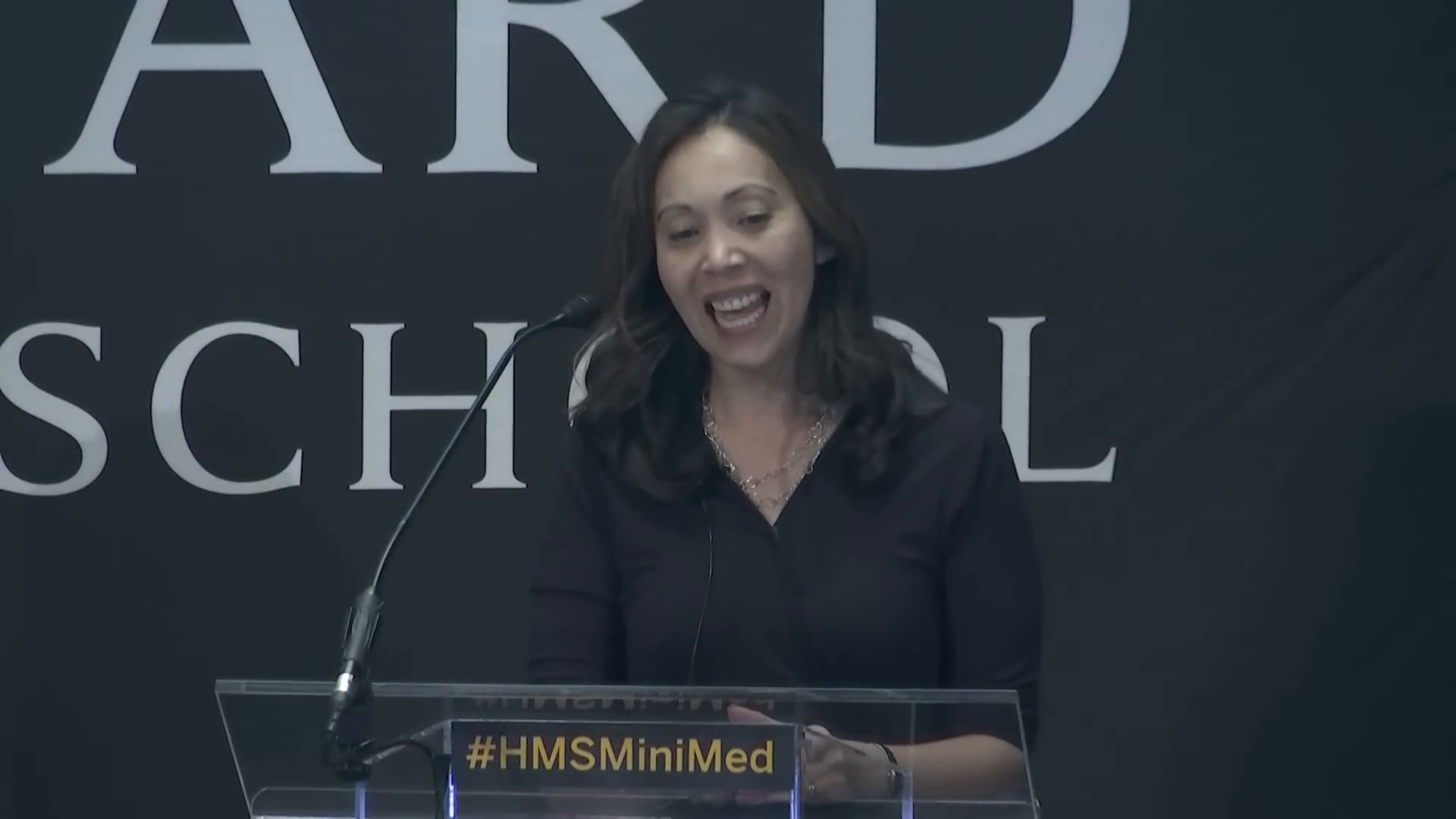
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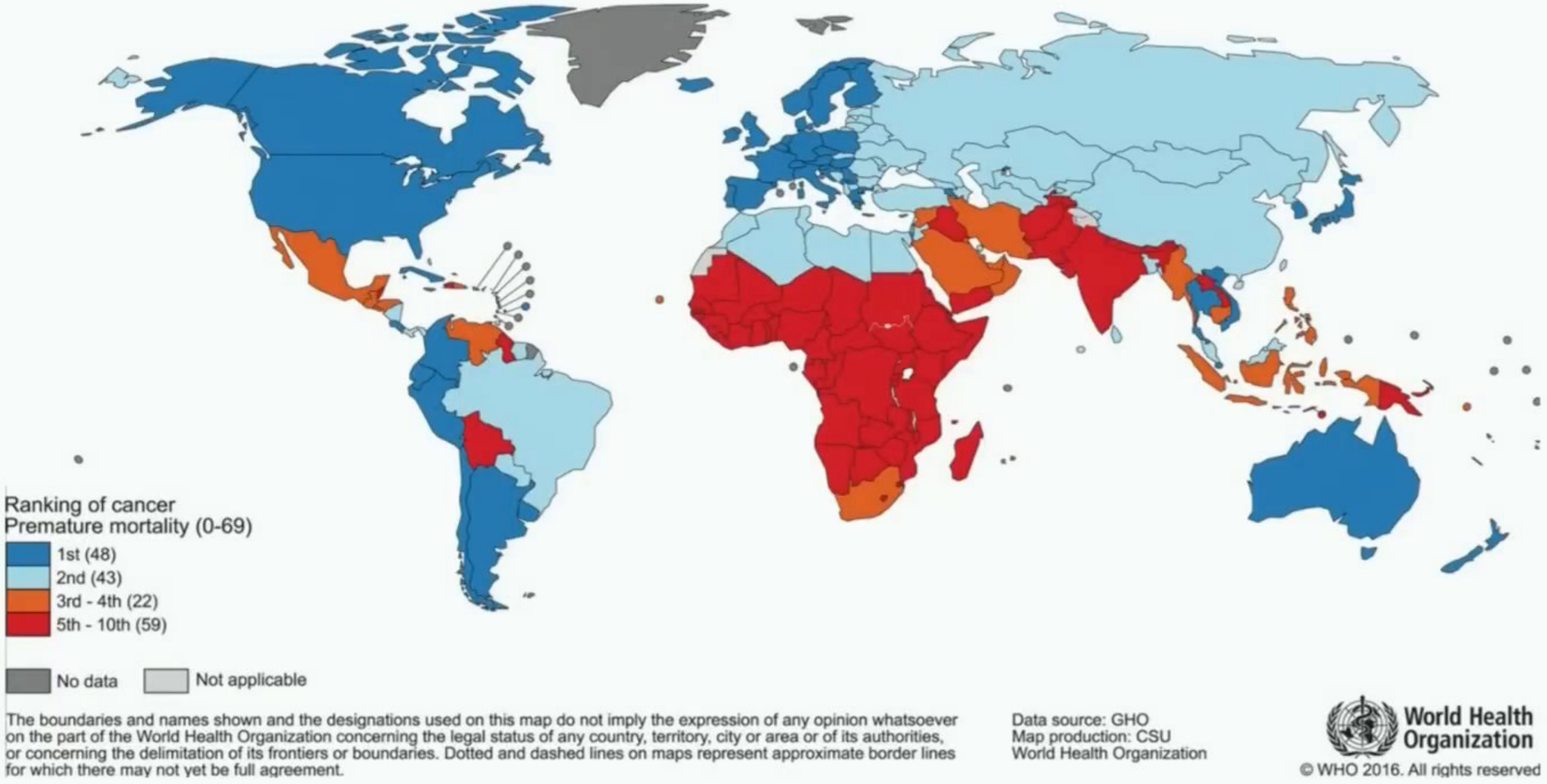
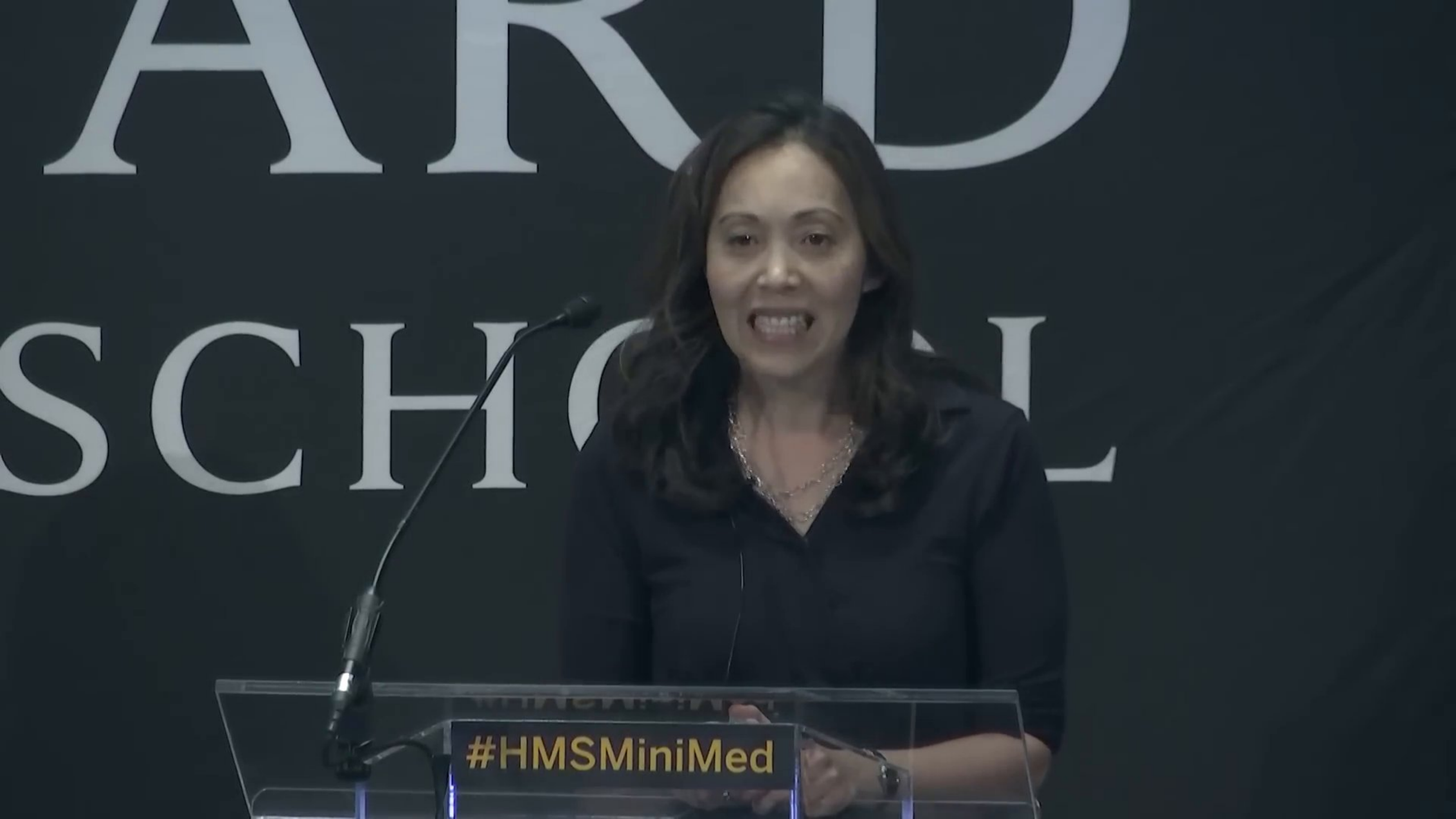
The Problem: Cancer remains a leading cause of death globally



CA: A Cancer Journal for Clinicians, Volume: 68, Issue: 6, Pages: 394-424, First published: 12 September 2018, DOI: (10.3322/caac.21492)

Fuels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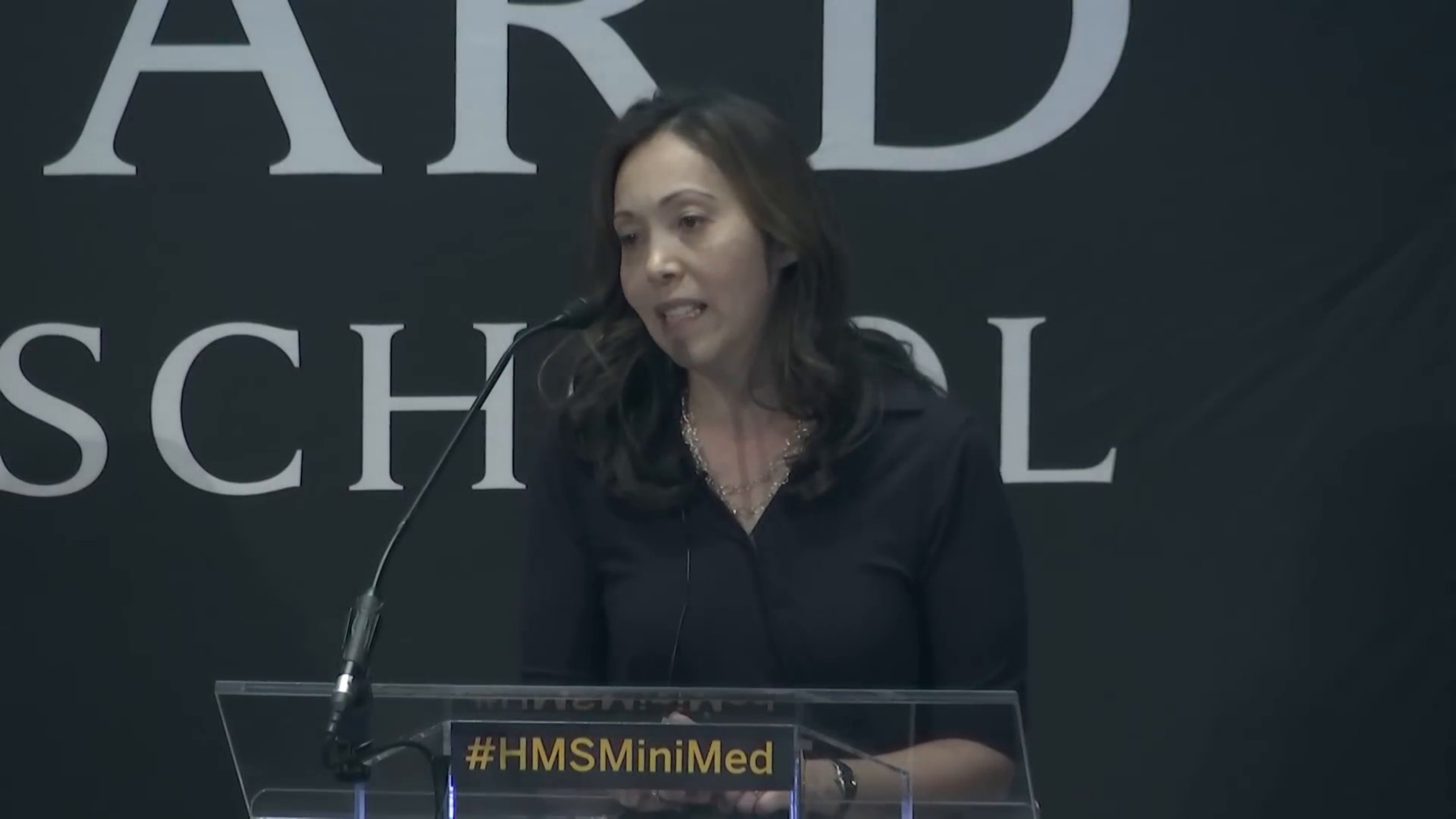
Burning fuels generate byproducts

What does this have to do with Cancer?

What does this have to do with Cancer?

Fuels our bodies use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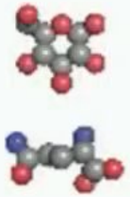
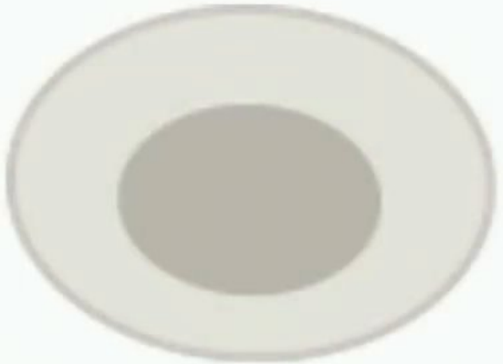
Cancer Metabolism

Fuels





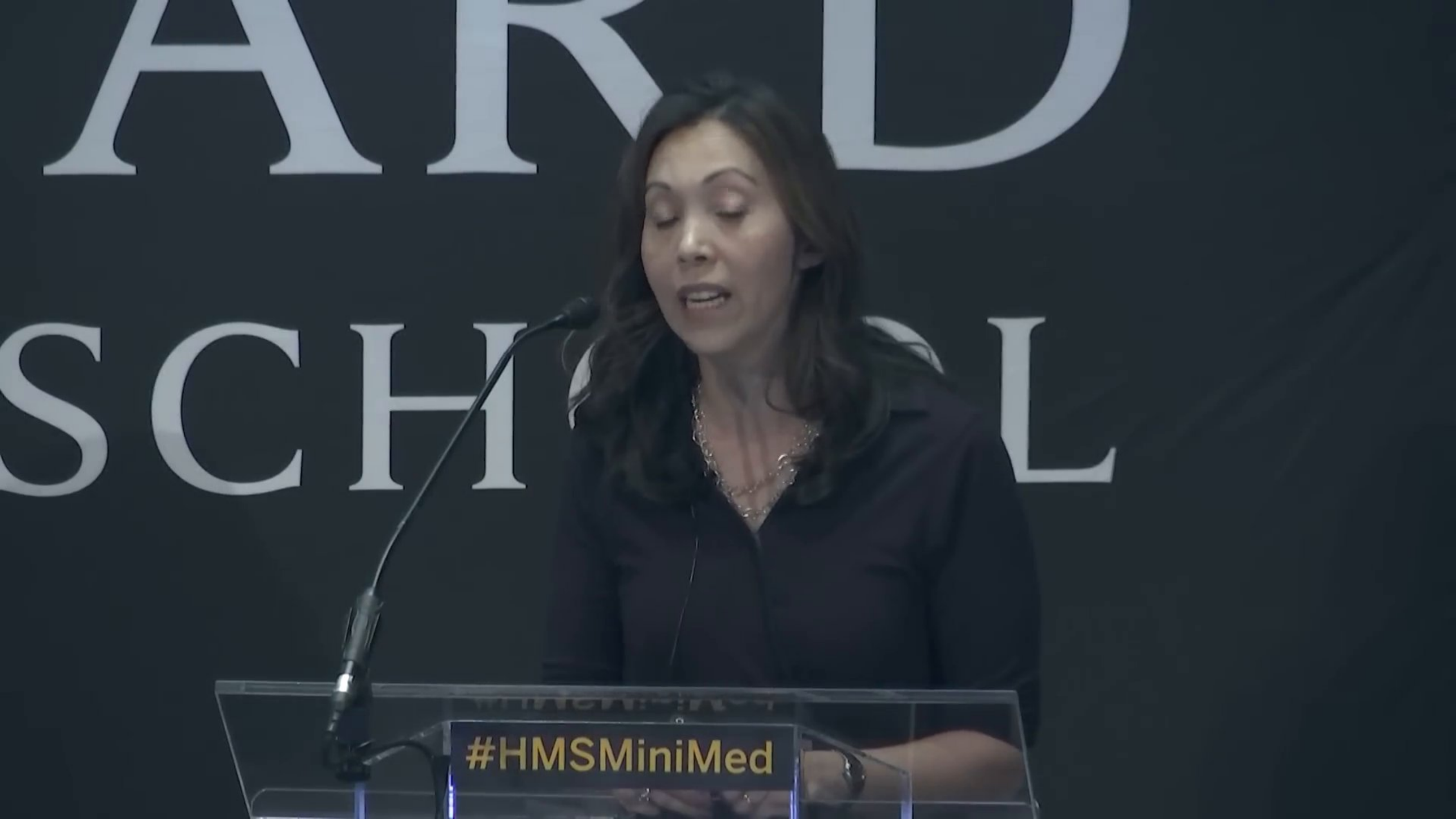
Cancer Metabolism: An Achilles Heel?

Illustration by Holly Adams Hebert

Driving questions

- How do tumor cells differ from normal cells in their metabolism of fuels?
- How do tumor cells integrate growth signals and nutrients to proliferate?
- What is the metabolic communication between tumor cells and their surrounding environment?

Can we exploit the unique metabolic vulnerabilities of cancers to improve patient care and therapy?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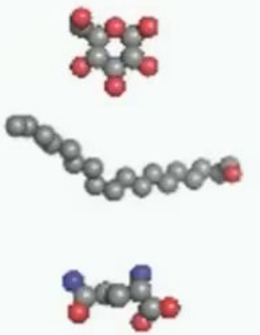
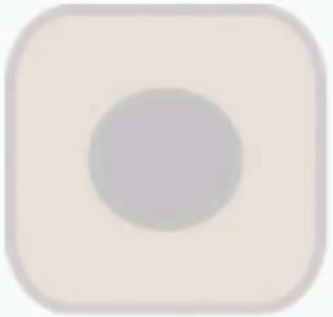
Cells use fuels to generate energy and macromolecules

fuels

(sugars, fats
amino acids)





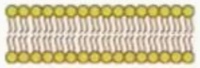
Energy and macromolecules

ATP - energy

DNA

RNA

Proteins



Membranes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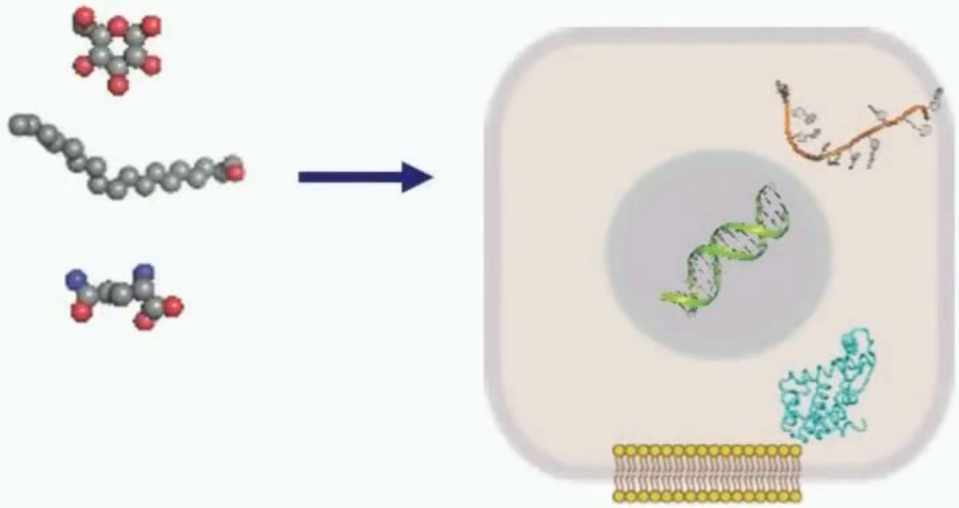
Macromolecules are the building blocks of a cell

fuels

(sugars, fats
amino acids)



Energy and building blocks

ATP - energy

DNA

RNA

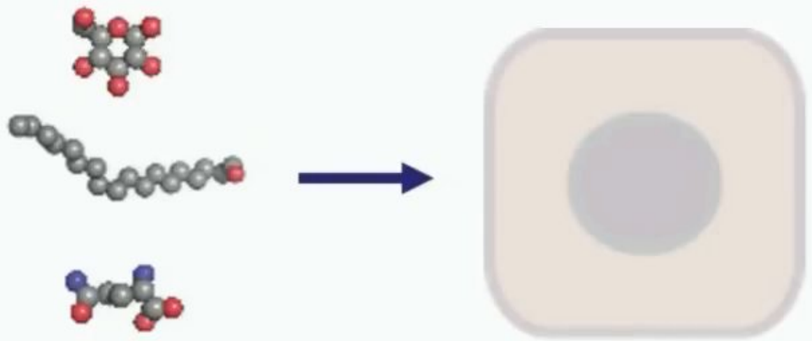
Proteins

Membranes

Normal cells use fuels to generate energy and maintain homeostasis

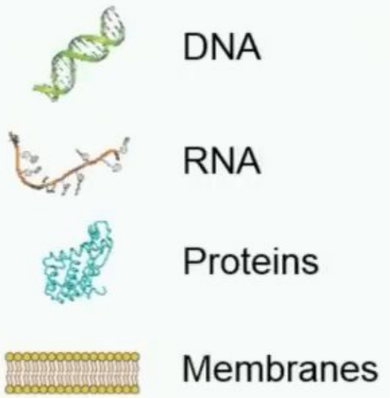
fuels

(sugars, fats
amino acids)



Energy and building blocks

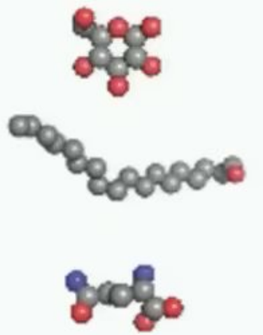
ATP - energy



Cancer cells require more fuels to generate extra building blocks

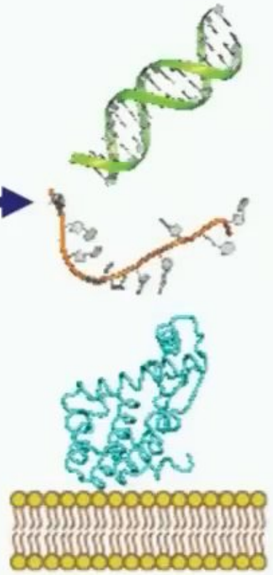
fuels

(sugars, fats
amino acids)



Energy and macromolecules

ATP - energy



DNA

RNA

Proteins

Membranes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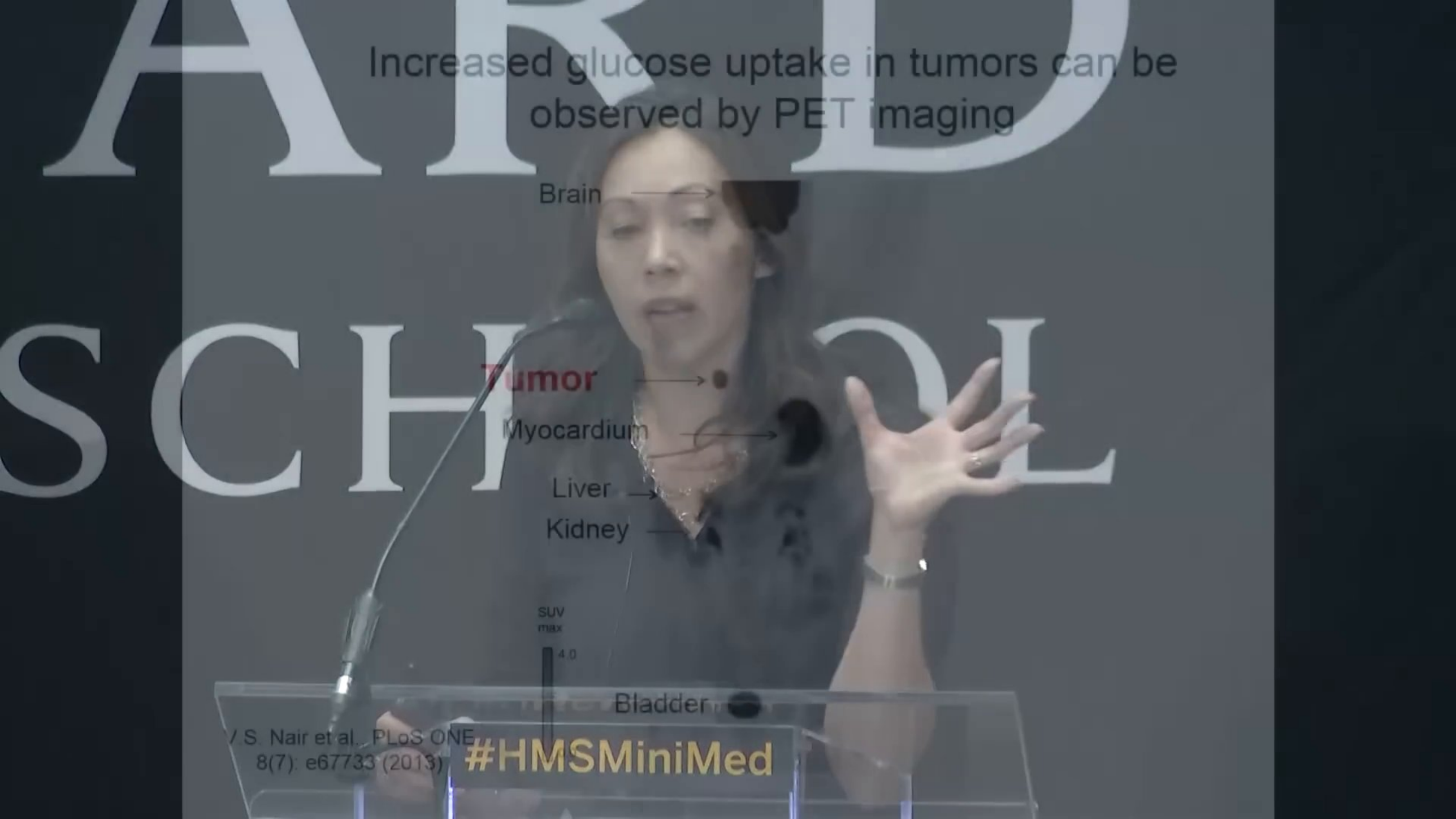
Increased glucose uptake in tumors can be observed by PET imaging
Brain
Tumor
Myocardium
Liver
Kidney
SUV max
4.0
Bladder
/ S. Nair et al., PLoS ONE 8(7): e67733 (2013)
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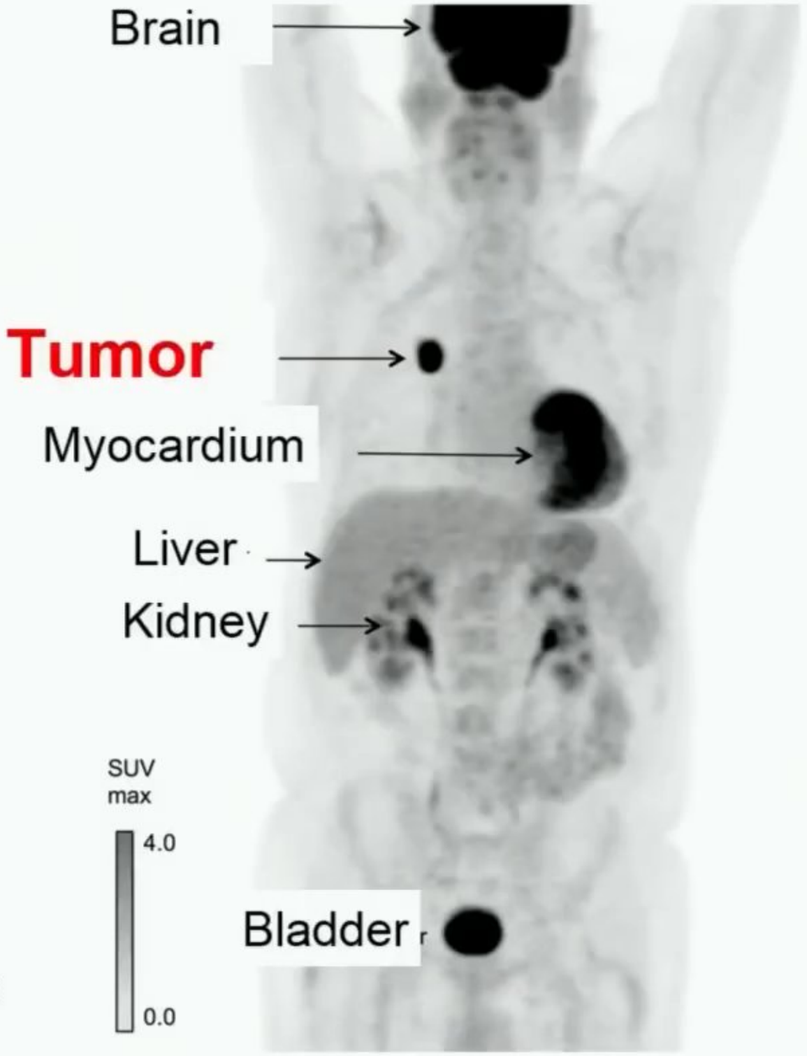
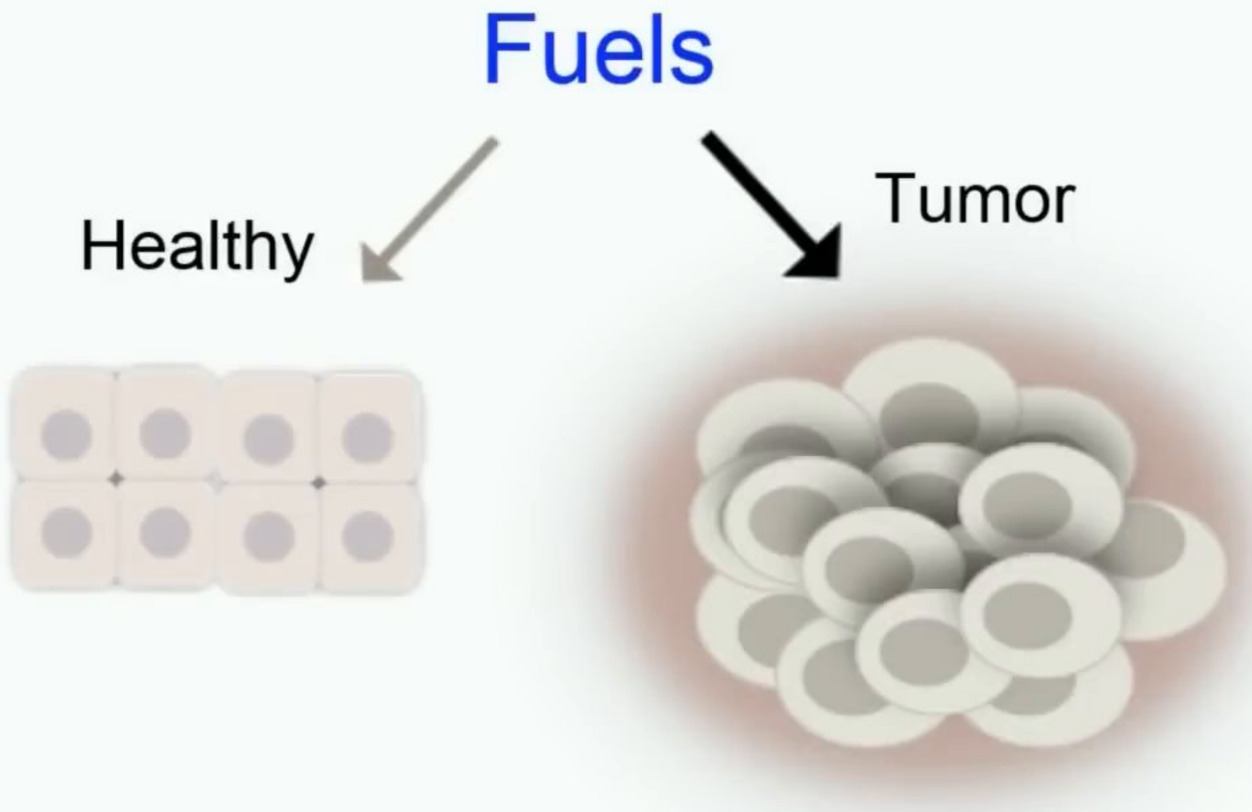
Increased glucose uptake in tumors can be observed by PET imaging



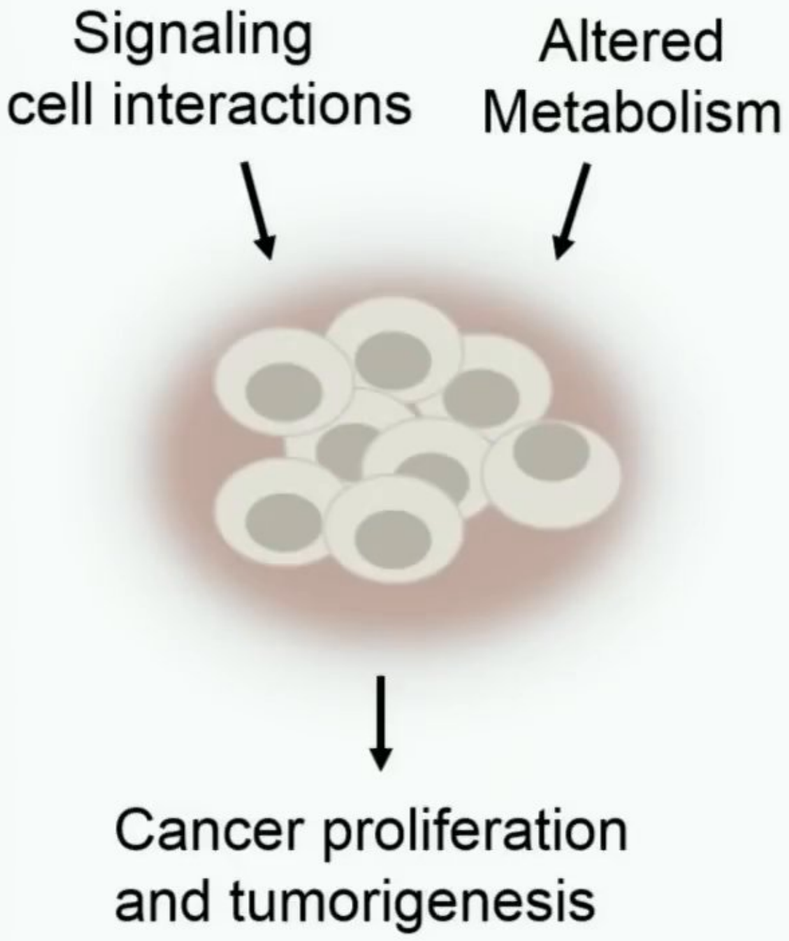
V.S. Nair et al., PLoS ONE 8(7): e67733 (2013)

A Metabolic Competition



Can we identify the precise pathways that tumors use in order to exploit metabolic fuel preference for new therapeutic targets?

Targeting Cancer Metabolism

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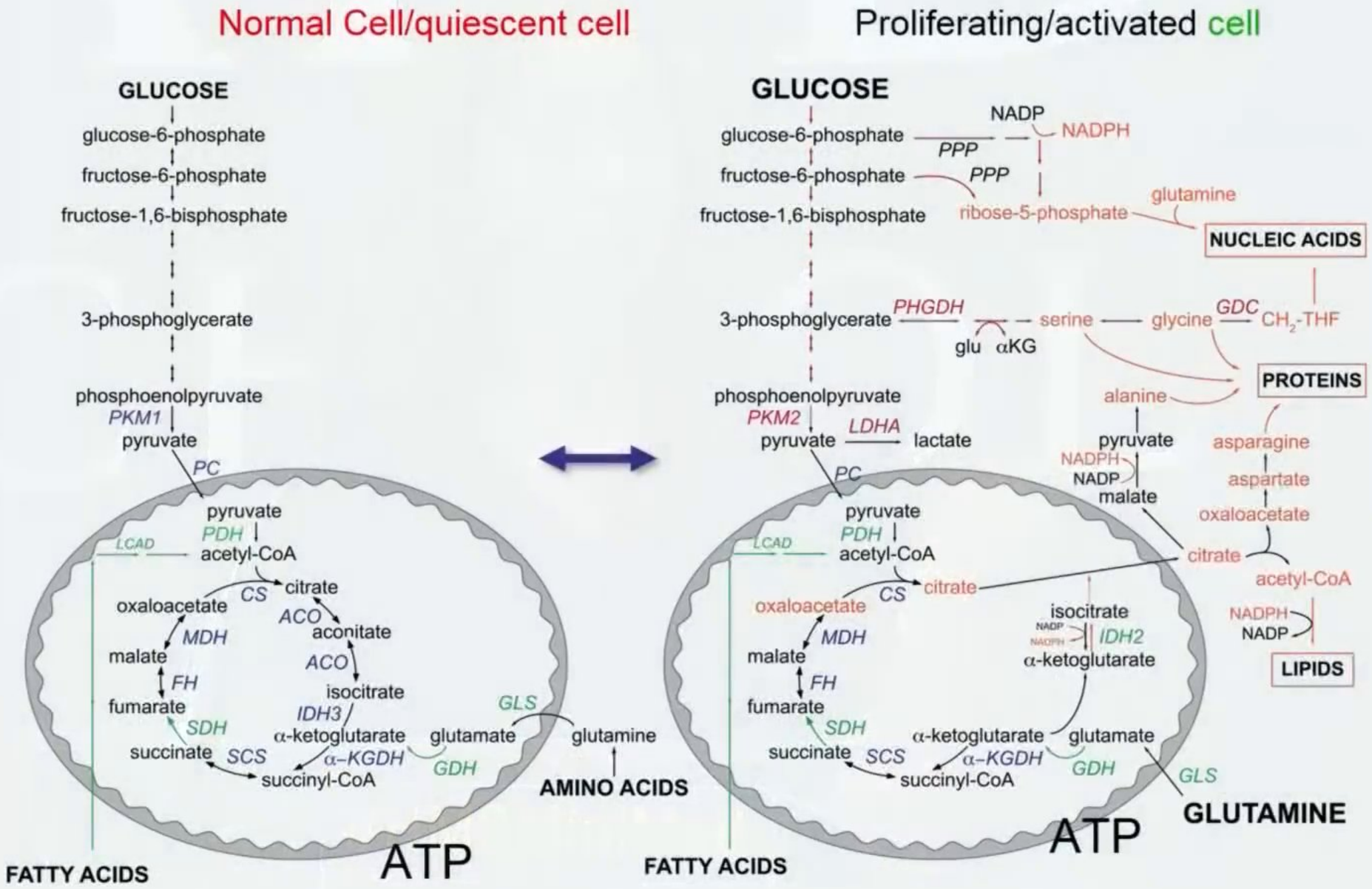
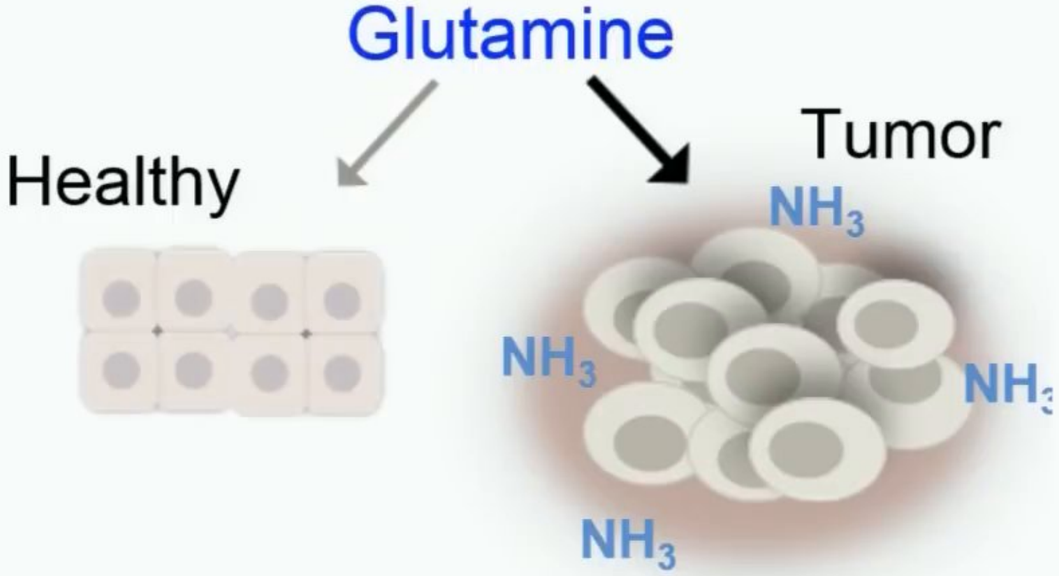
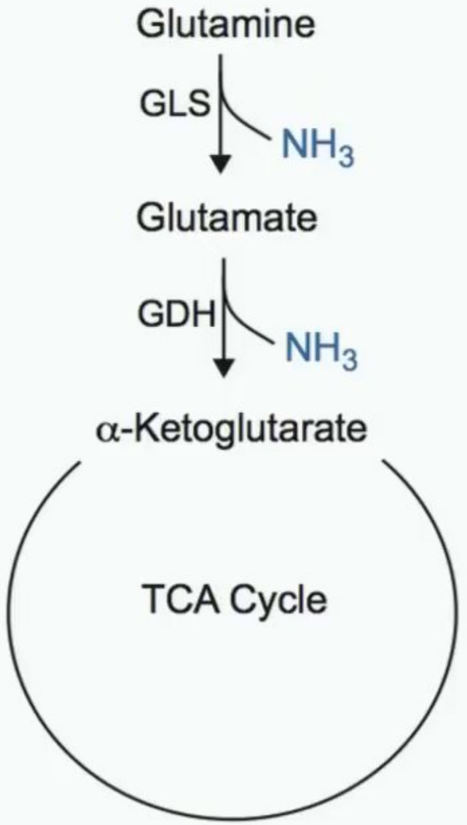
Proliferating tumor cells rewire metabolism



Tumors produce metabolic byproducts from amino acids



Glutamine breakdown generates ammonia



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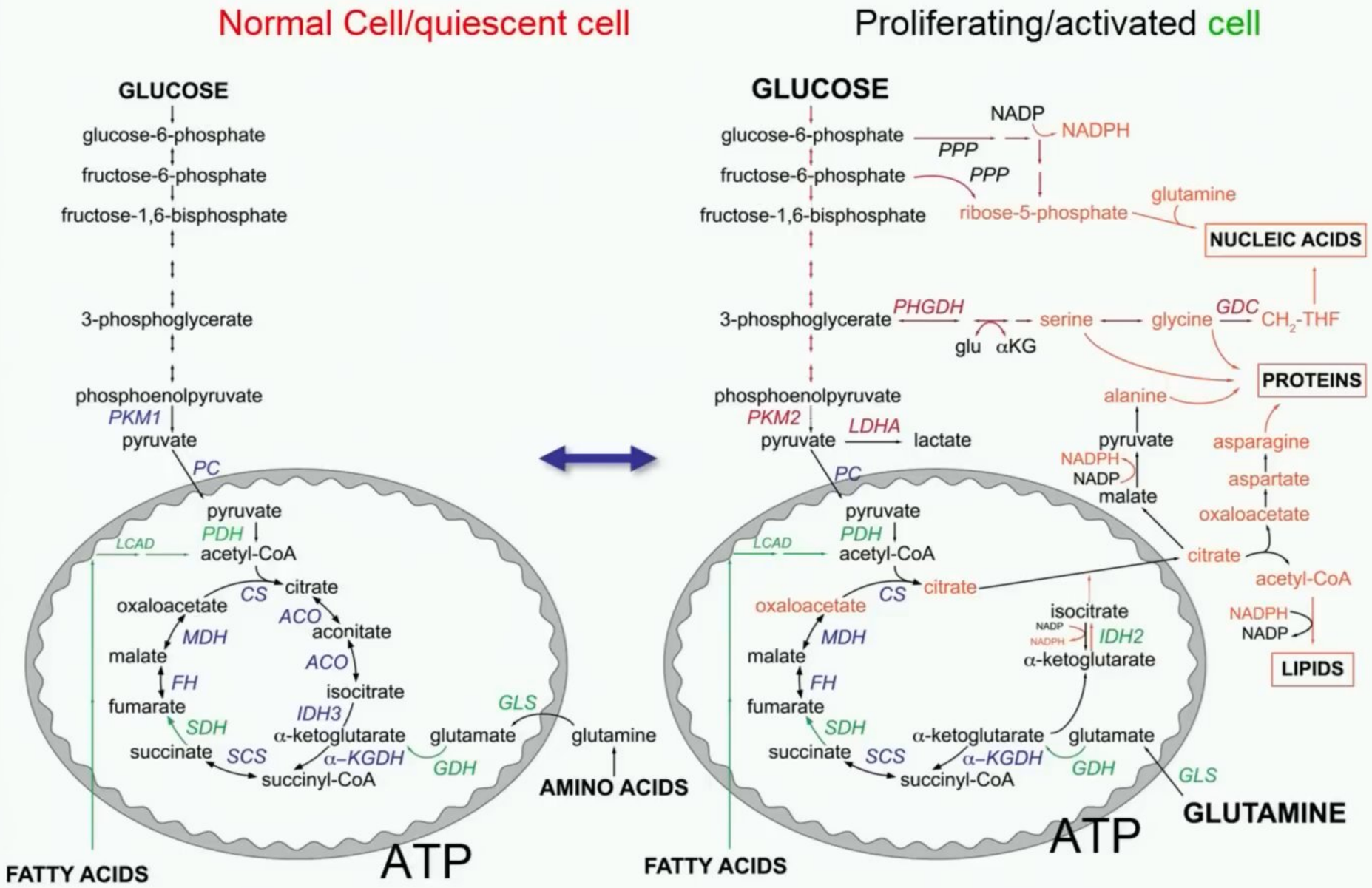

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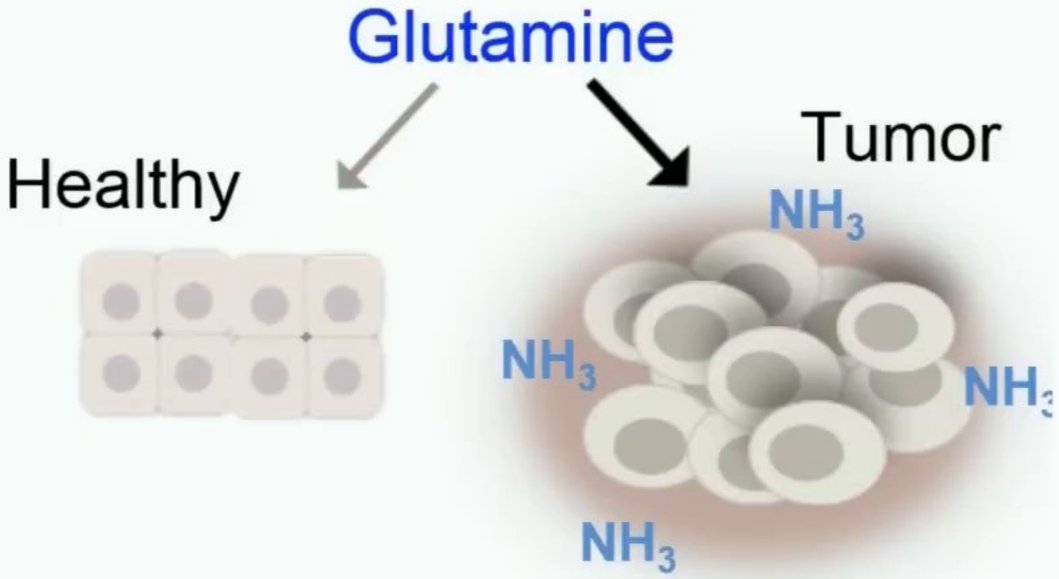

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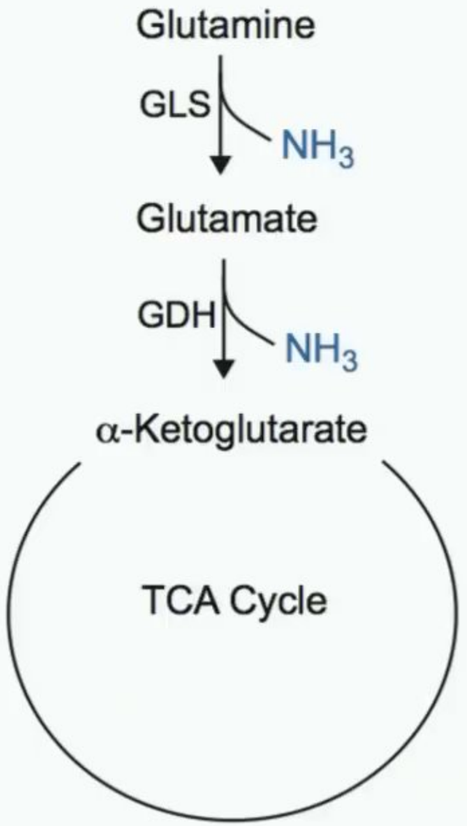
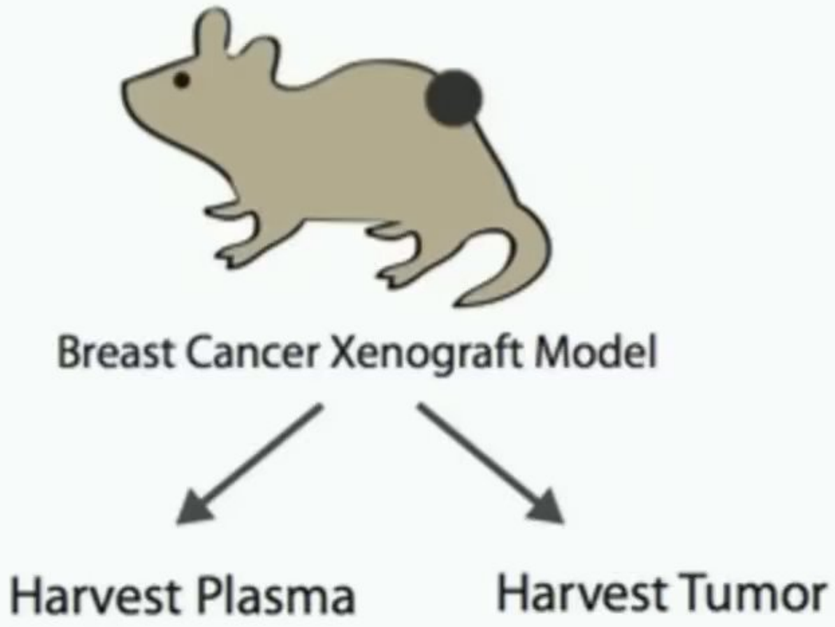
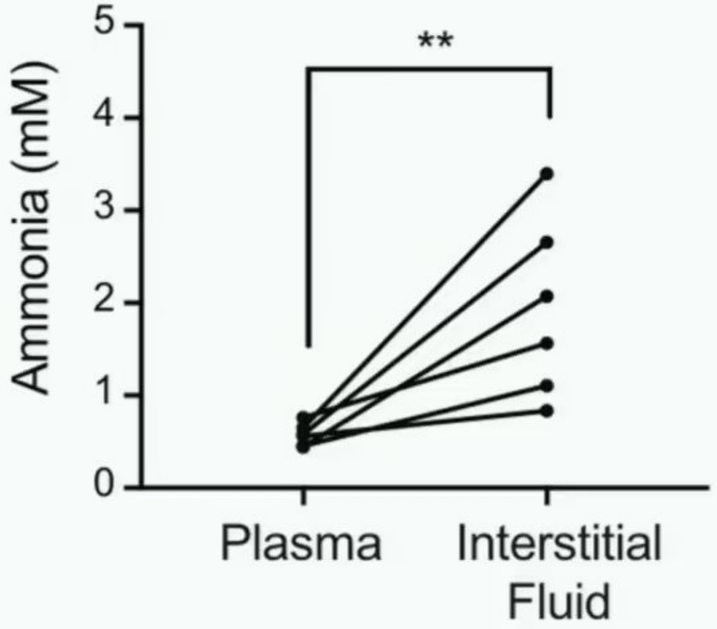
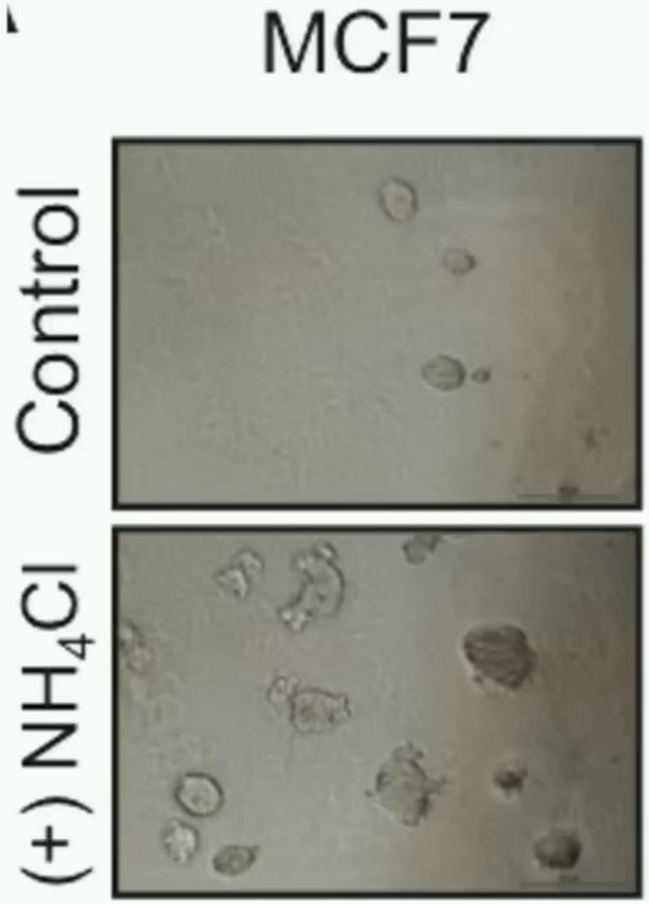


Ammonia Accumulates in the Tumor Microenvironment

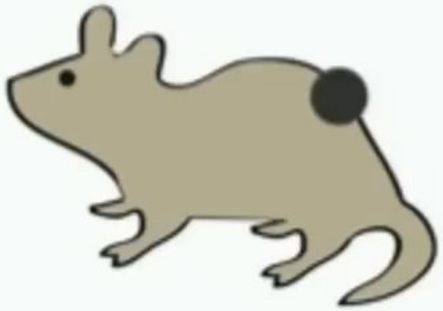




Ammonia accelerates proliferation of Estrogen Receptor positive (ER+) breast cancers



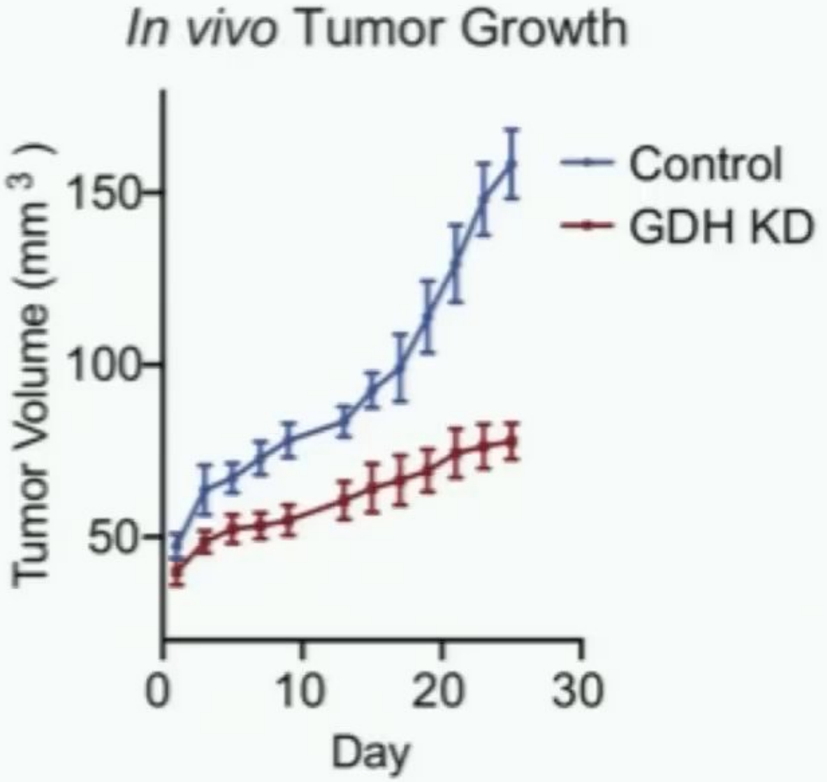
Reducing levels of Glutamate Dehydrogenase inhibits tumors in vivo



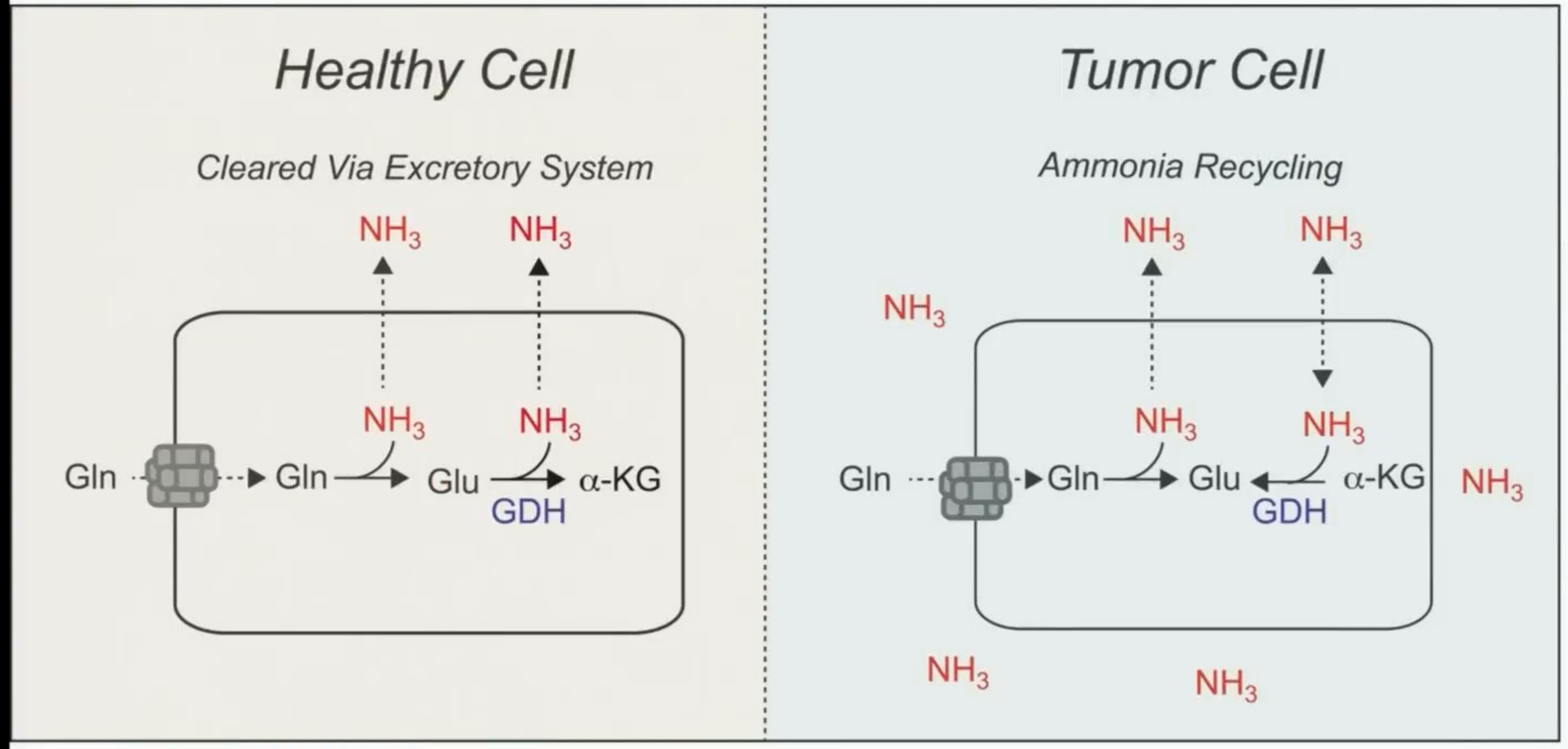
Breast Cancer Xenograft Model

ER+ Tumors

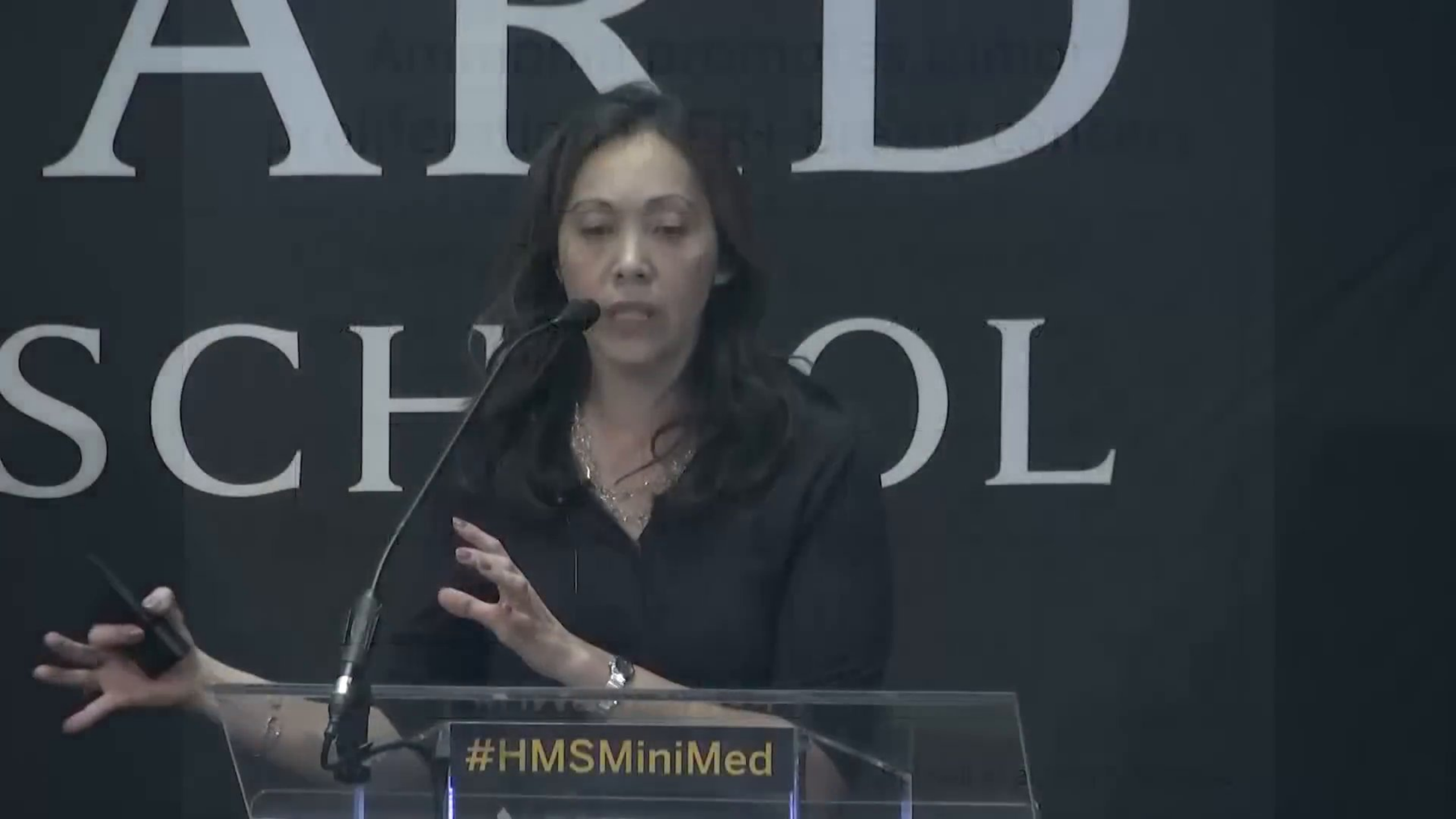
ER+ Tumors lacking glutamate dehydrogenase



Ammonia promotes tumor proliferation in ER+ breast cancers



Spinelli et al, 2017, Science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Cancer Metabolism: An Achilles Heel?

- What are the metabolic signatures of specific tumor types?
- Can metabolic inhibitors combine with approved drugs?

- How does tumor metabolism differ with tumor genotype and signaling? Important to understand which genotypes may be vulnerable to the inhibition of specific metabolic enzymes.
- What are the biomarkers that will predict patient response to therapy?


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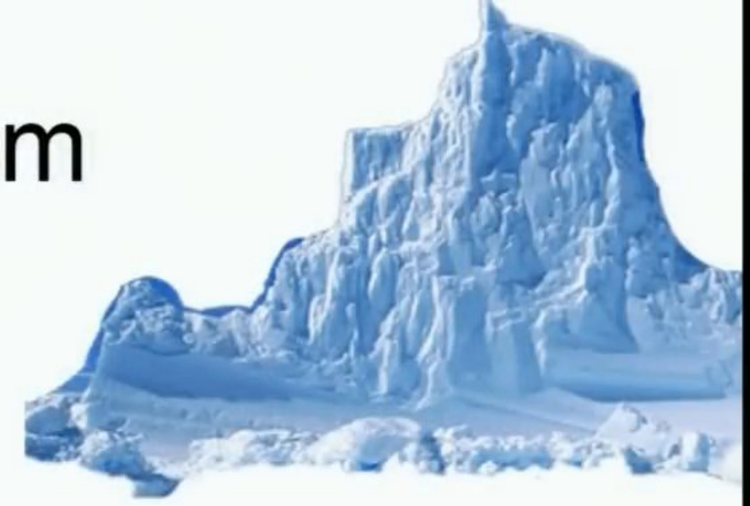
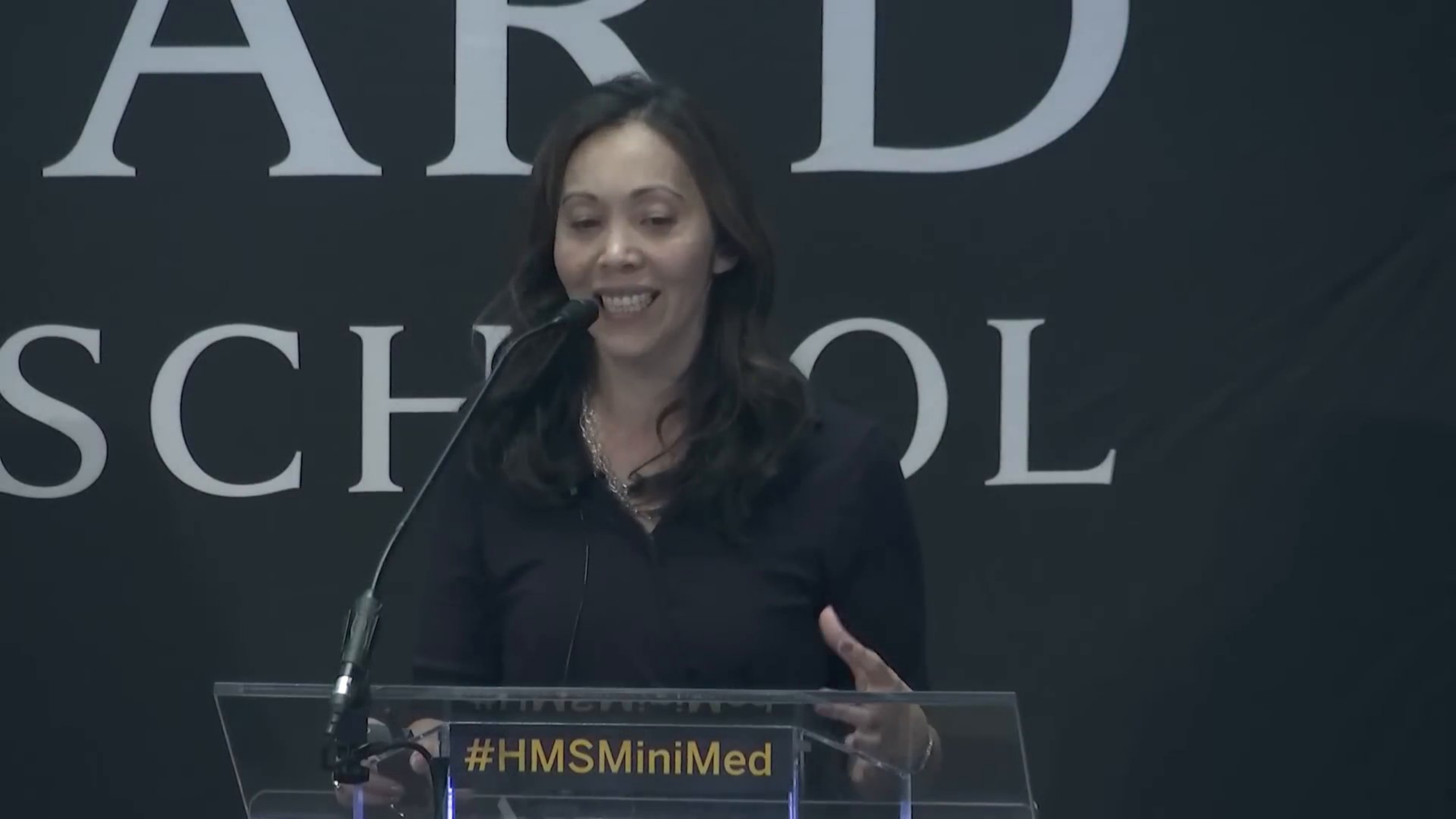
Cancer Metabolism



- New lessons about how metabolism supports tumor cell survival, proliferation and progression.
- Opened new fields of metabolism in other biological systems, ranging from immunology to stem cell biology.
- Discoveries of fundamental principles about normal cell biology.
- Pushed technology development.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Acknowledgements

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Yoshi Tsubosaga
Sarah Tucker
Robert Van de Ven
Jiska van der Reest
Samantha Wong
Haejin Yoon
Elma Zaganjor

Collaborators
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Clary Clish (Broad Institute)
Steve Gygi (HMS)
Leif Ellisen (MGH)
Nathalie Agar (BWH)

Former Lab members
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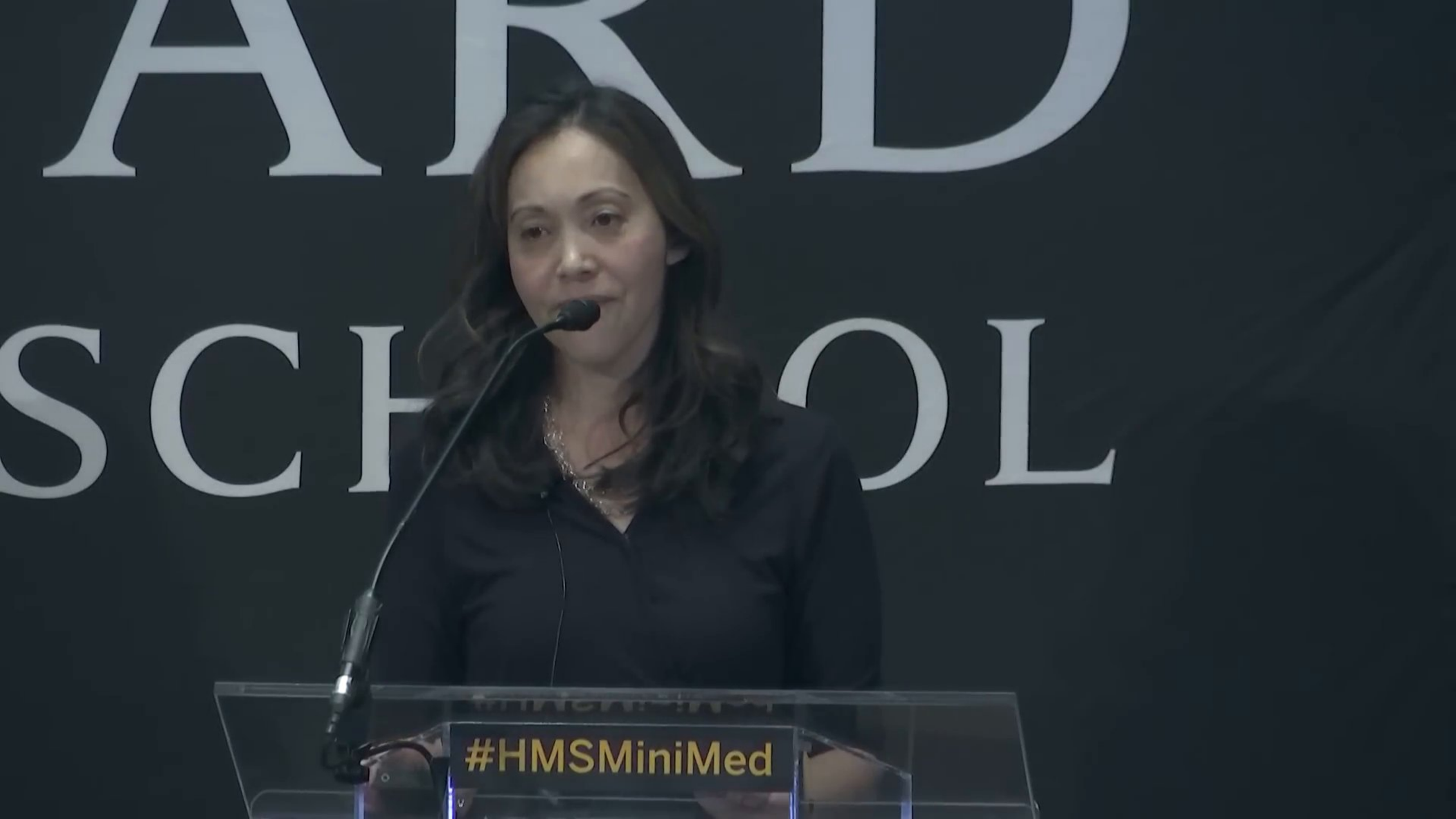
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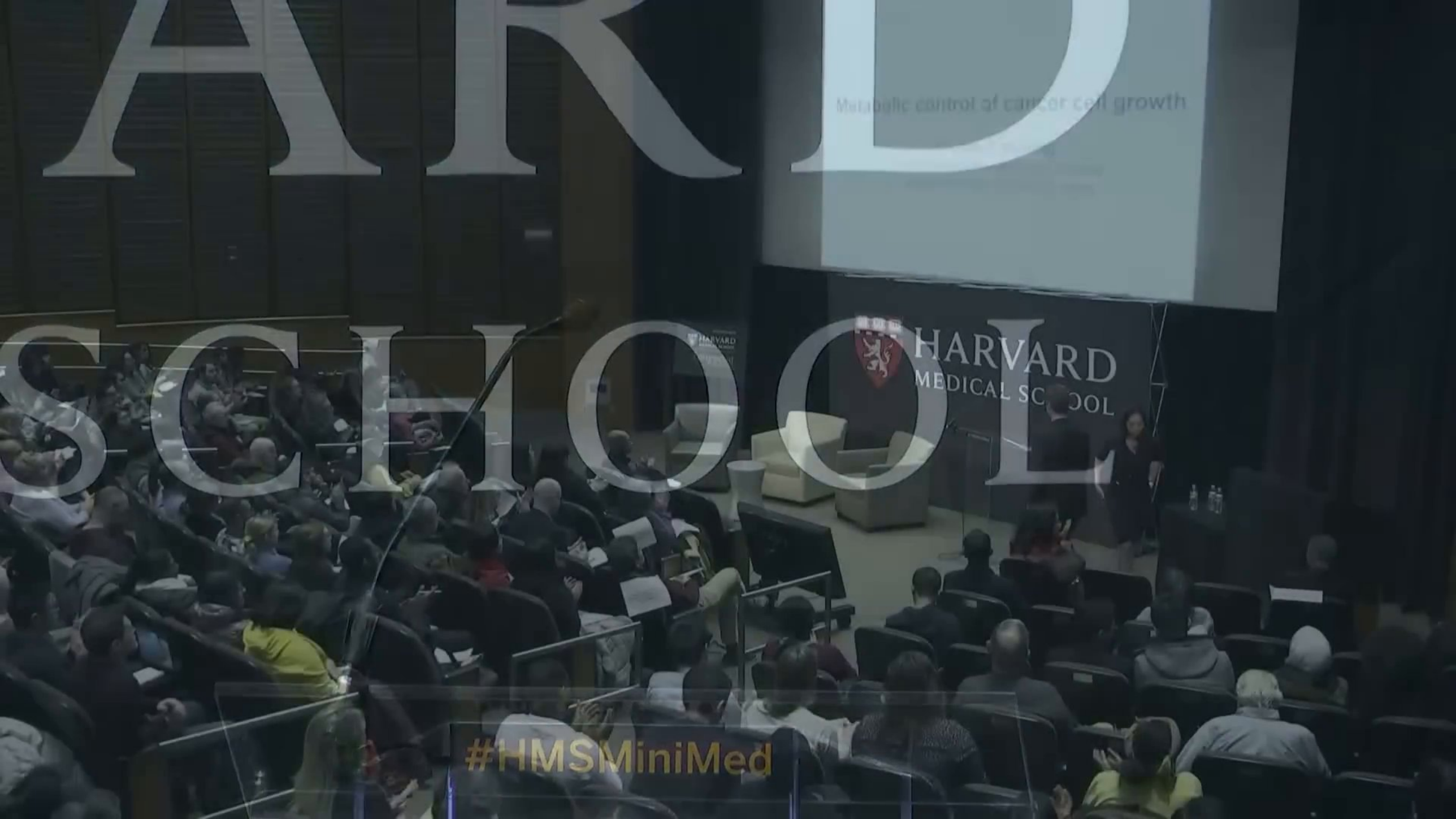
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Metabolic control of cancer cell growth
Brendan D. Manning
Department of Genetics & Complex Diseases
Harvard T.H. Chan School of Public Health
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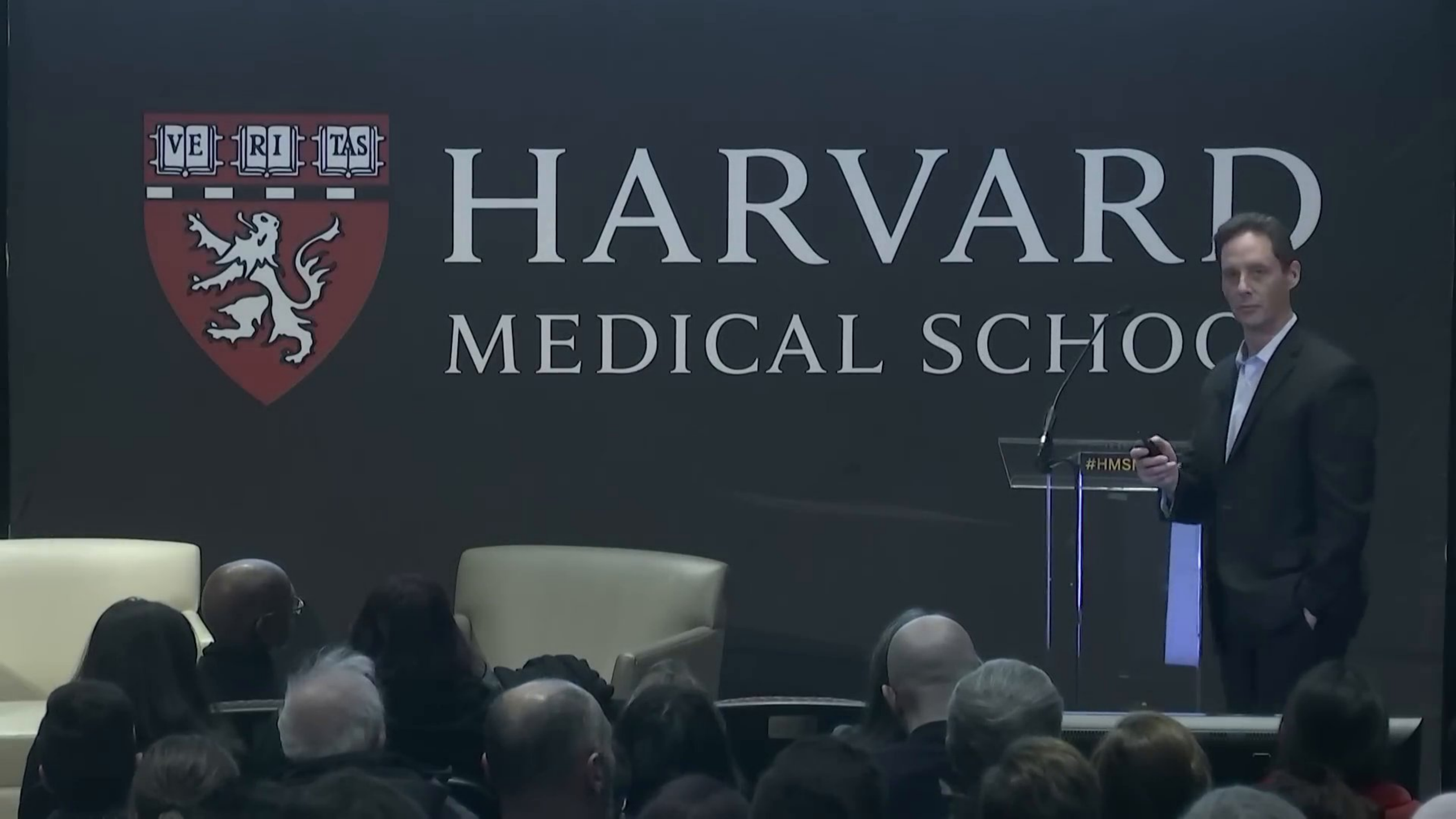
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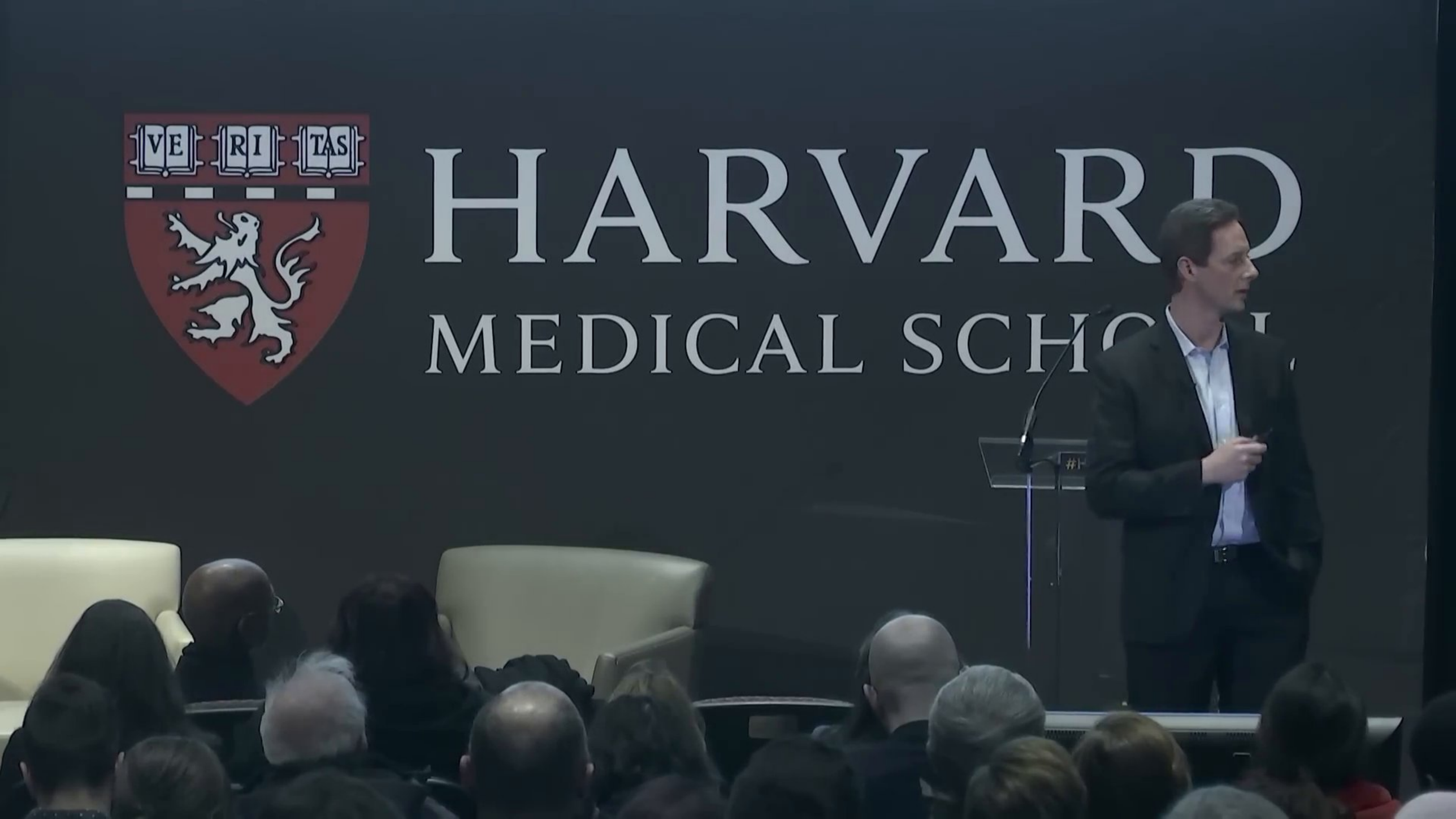
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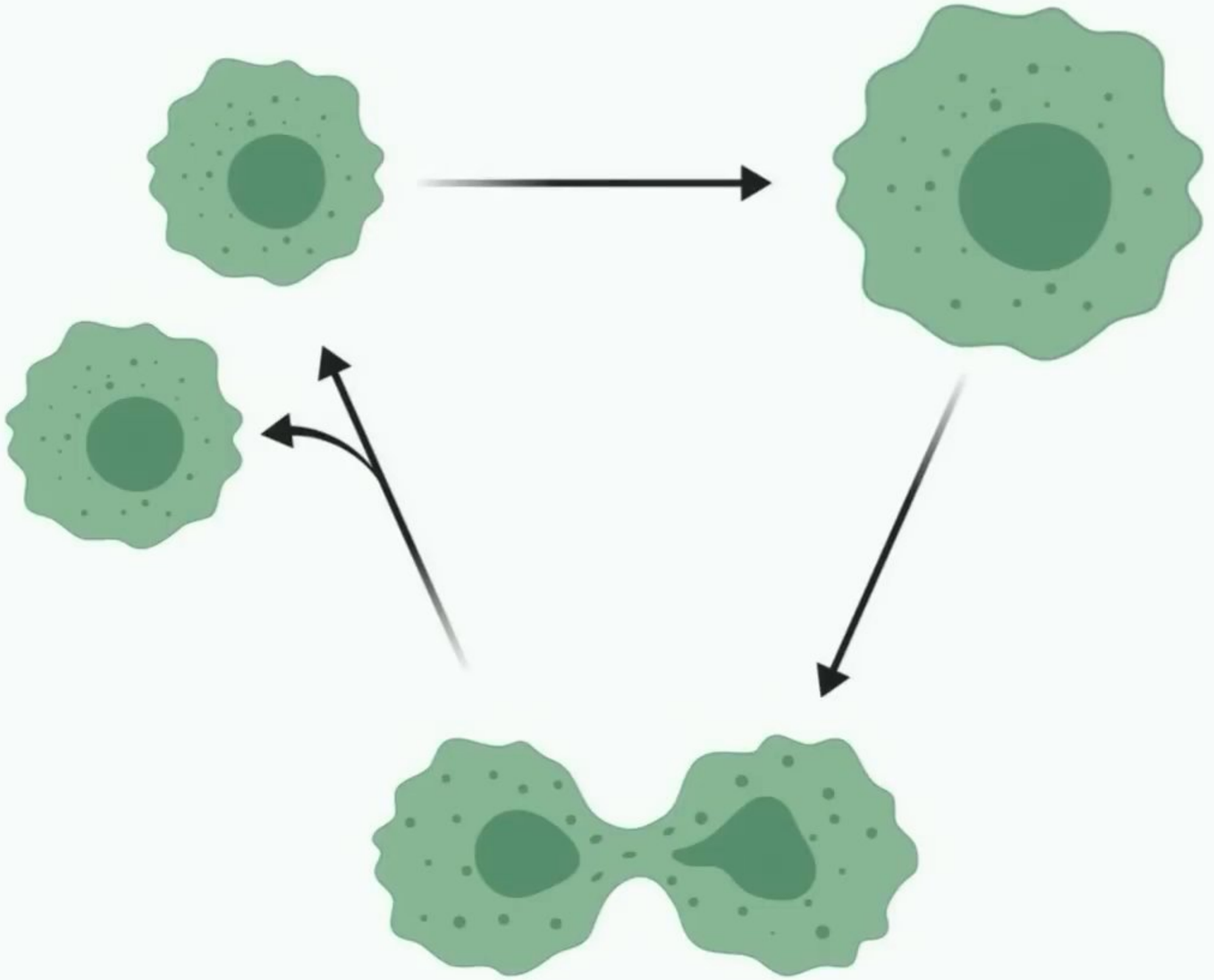
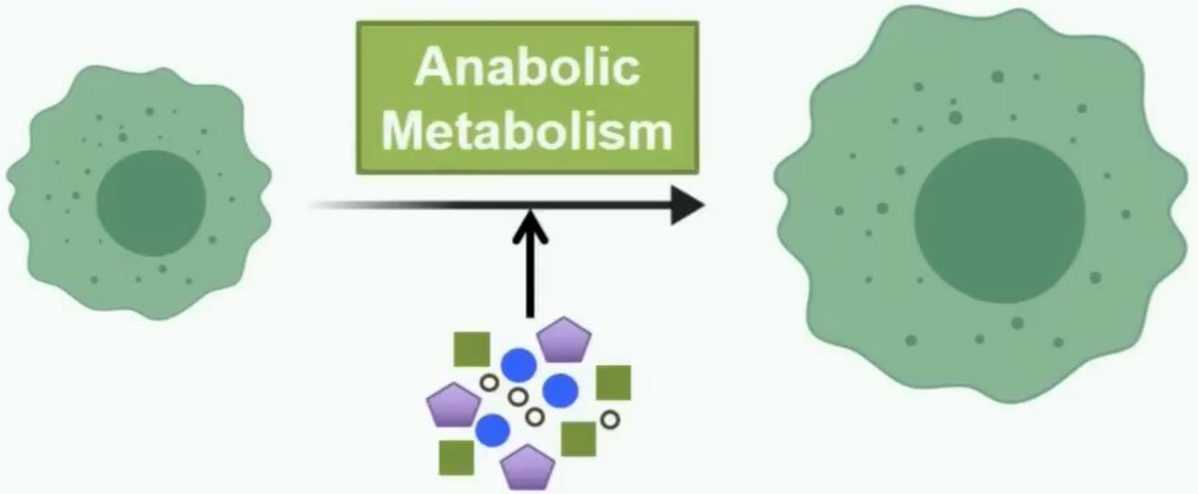
Cell Growth



Cell Growth



Nutrients & Energy

Cell Biomass:
(dry weight)

55% Protein

25% Nucleic Acid

15% Lipid

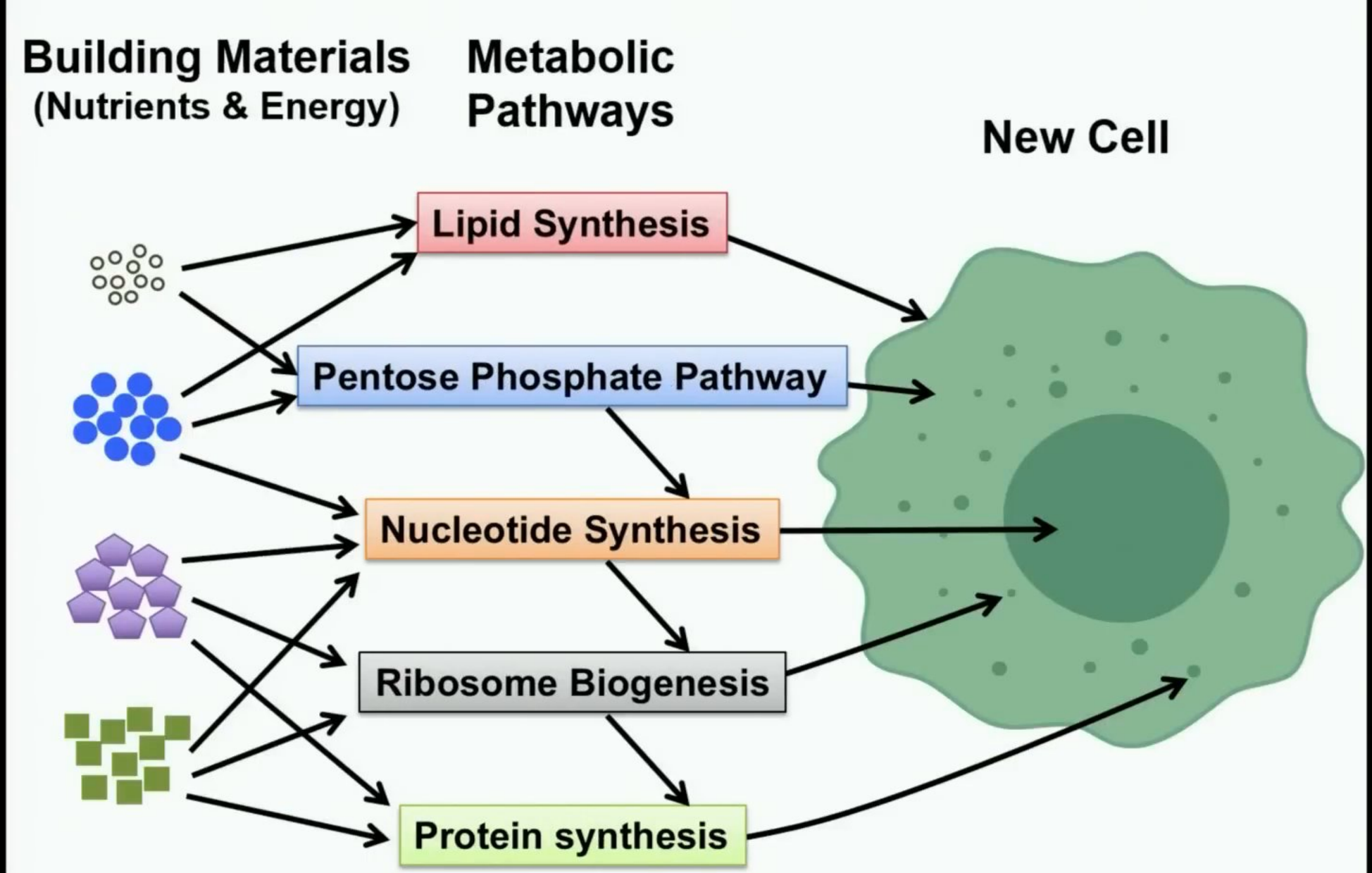
5% Carbohydrate

Building Materials

Contractors

- Roofer
- Carpenter
- Electrician
- Mason
- Landscaper

New House


Building Materials
(Nutrients & Energy)
Metabolic
Pathways
New Cell
Lipid Synthesis
Pentose Phosphate Pathway
Nucleotide Synthesis
Ribosome Biogenesis
Protein synthesis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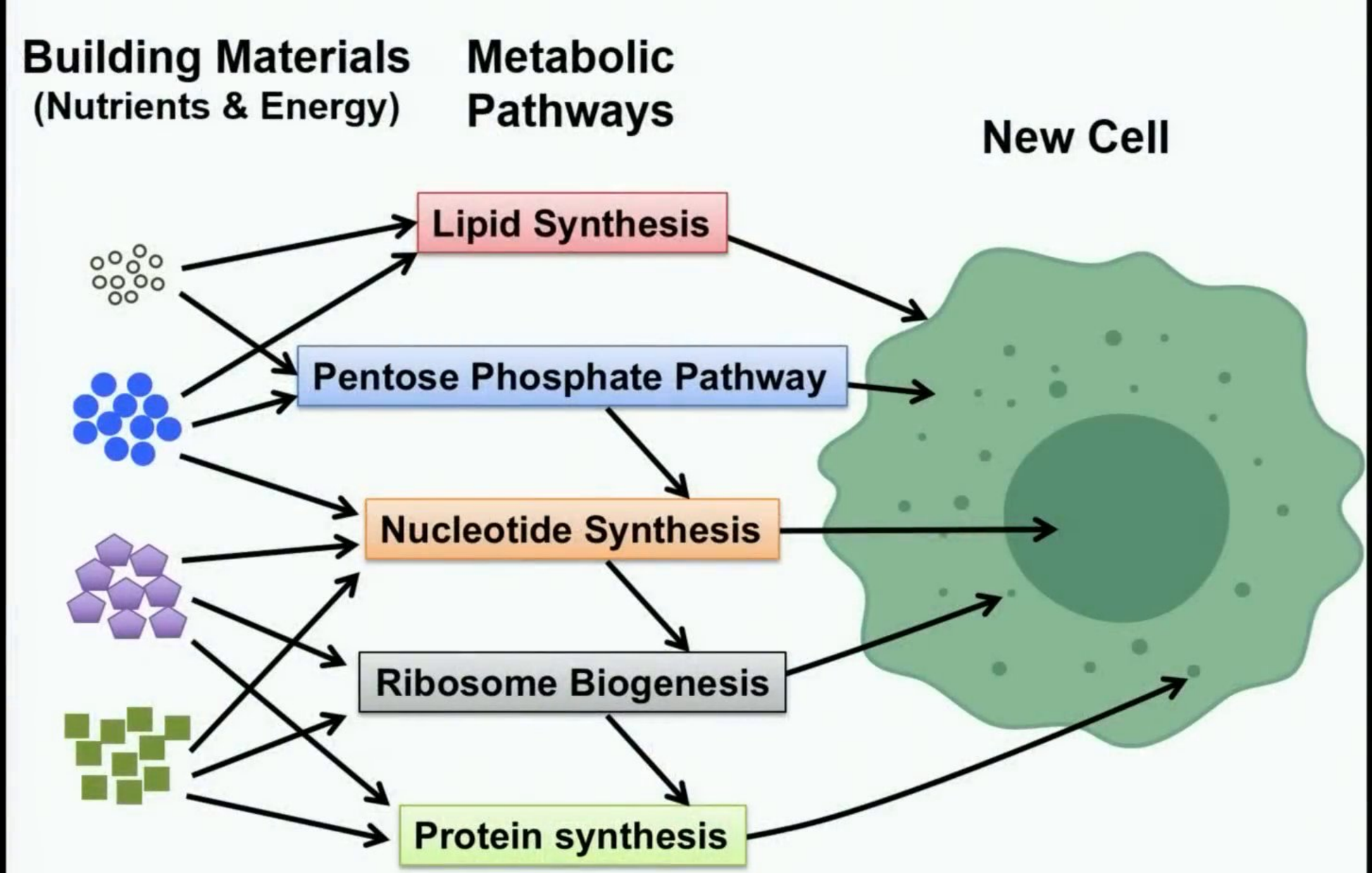
Building Materials
(Nutrients & Energy)
Metabolic Pathways
New Cell
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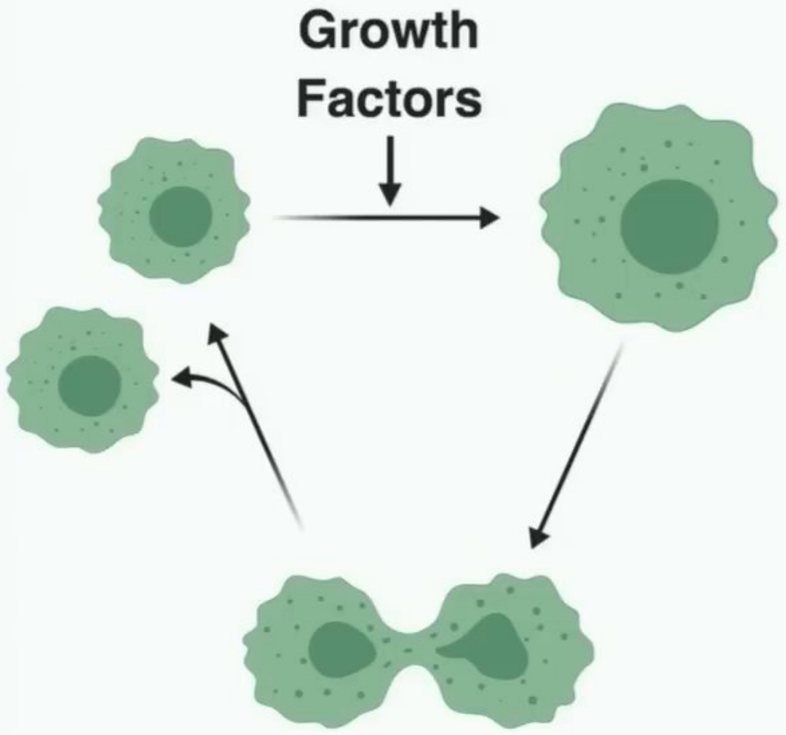
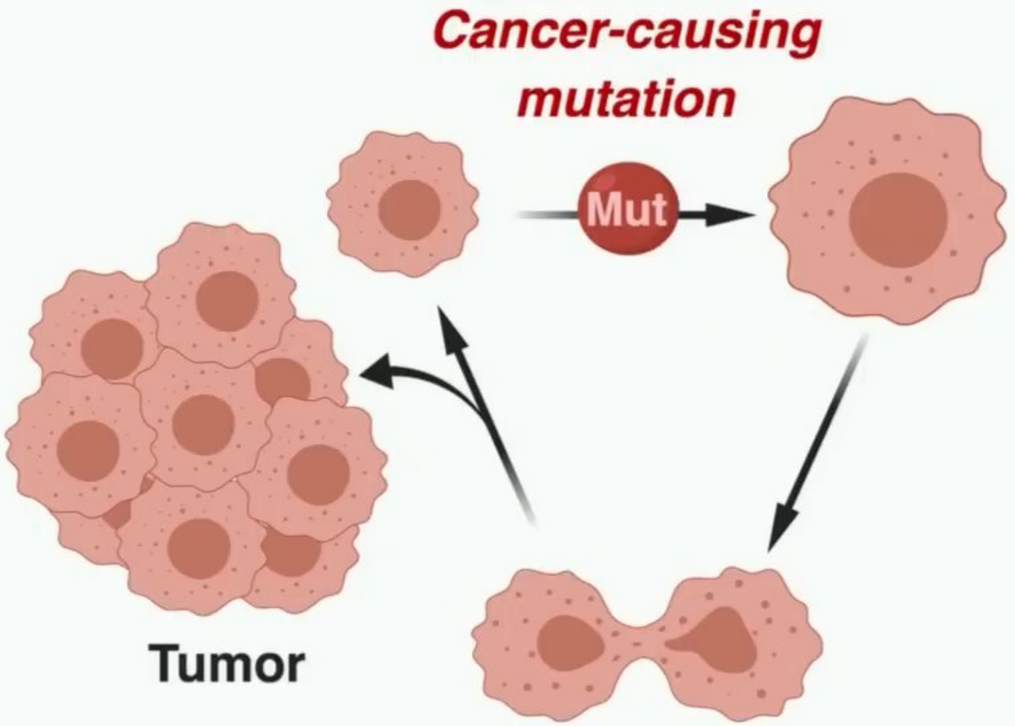
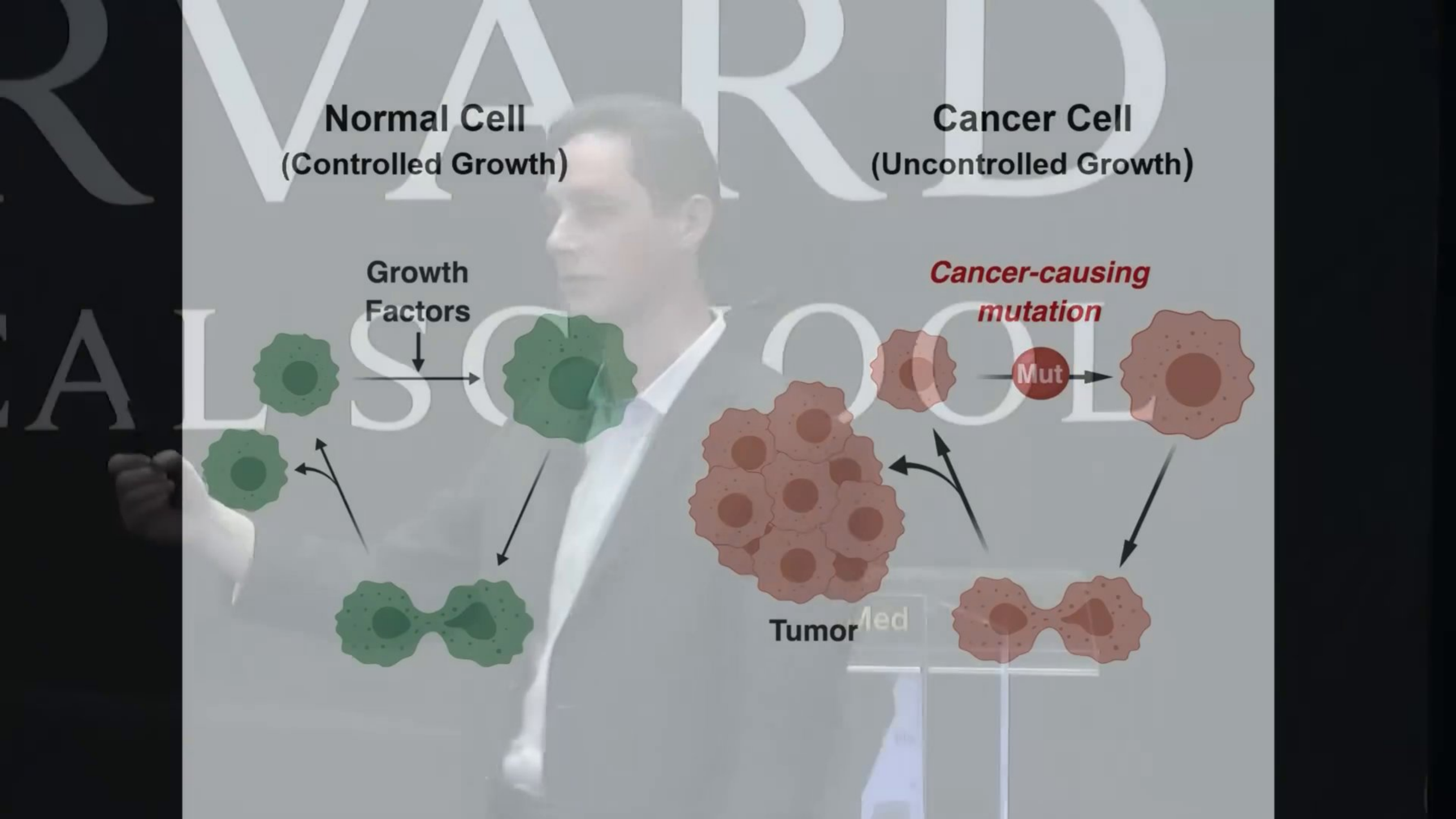
Ribosome Biogenesis
Protein synthesis

Normal Cell
(Controlled Growth)



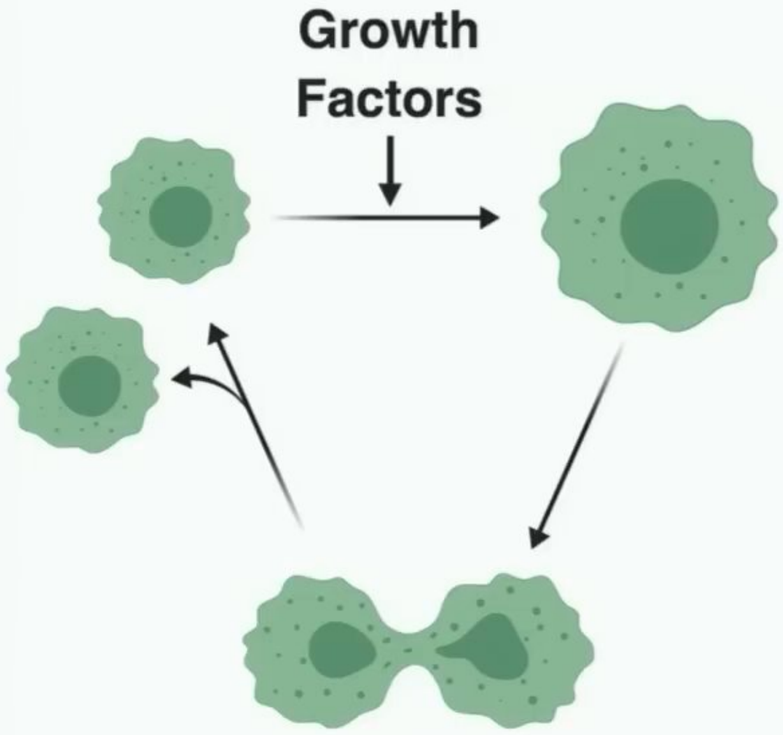
Cancer Cell
(Uncontrolled Growth)



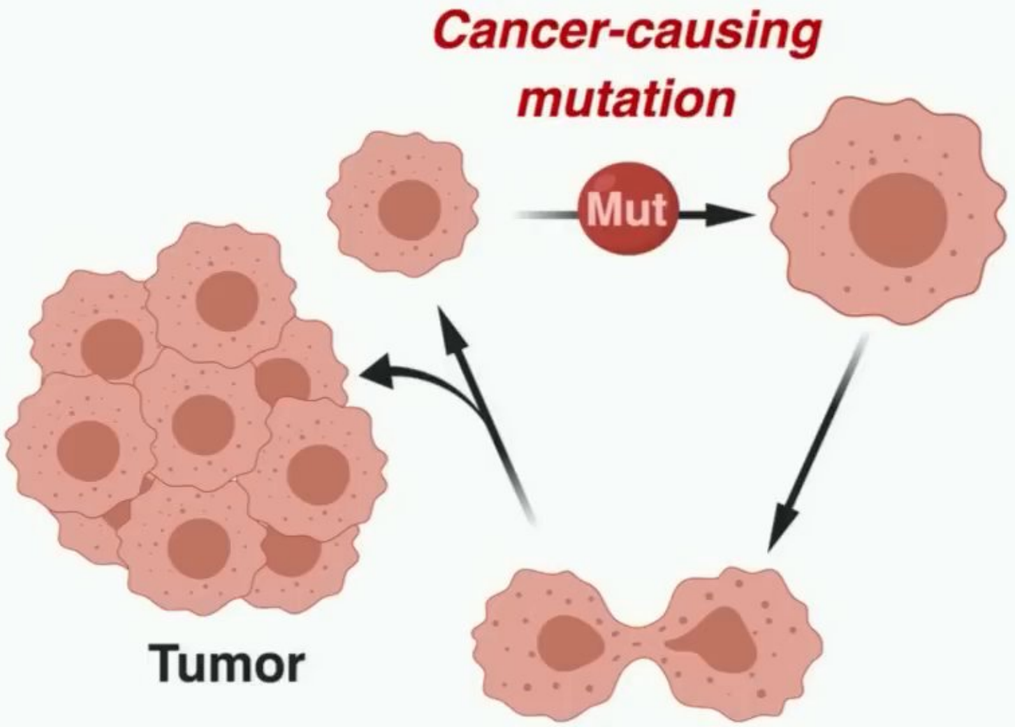

Normal Cell
(Controlled Growth)
Cancer Cell
(Uncontrolled Growth)
Growth
Factors
Cancer-causing
mutation
Mut
Tumor


RVARD
AL SCH OL

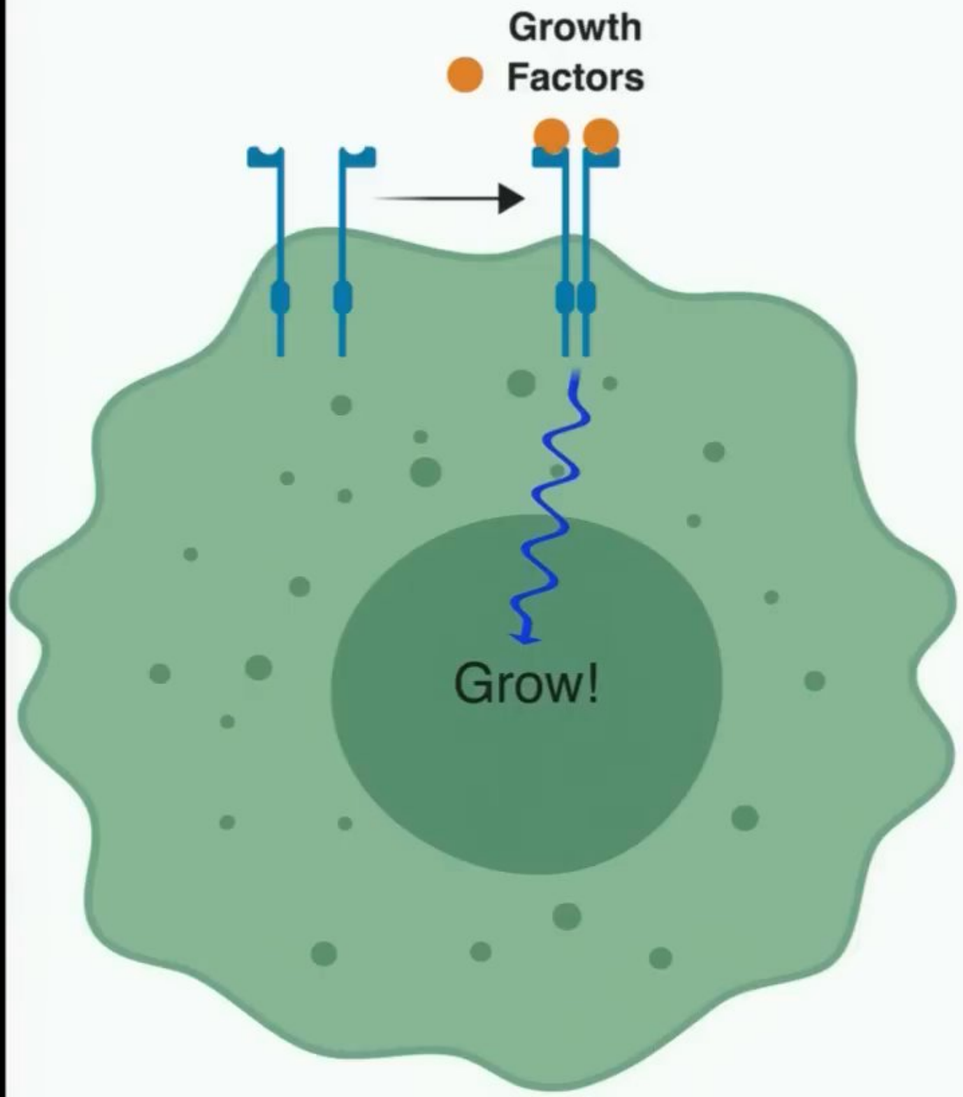
Normal Cell
(Controlled Growth)



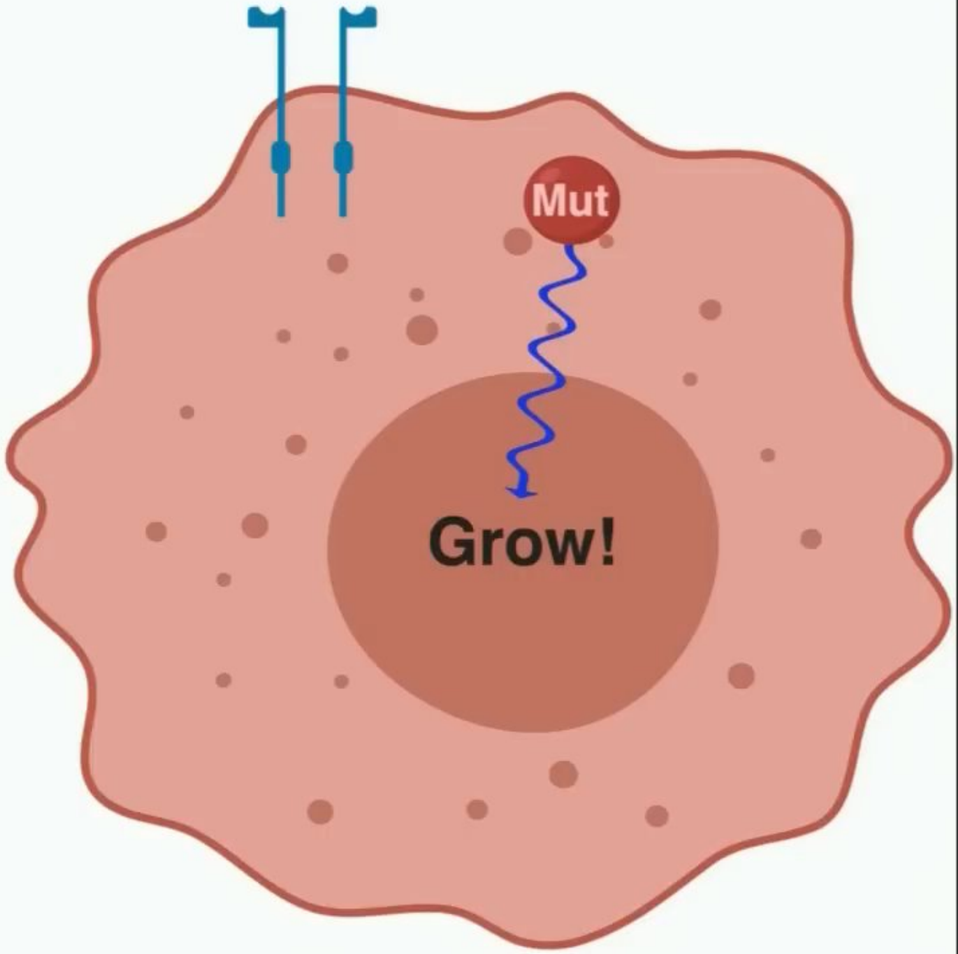
Cancer Cell
(Uncontrolled Growth)



Normal Cell
(Controlled Growth)



Cancer Cell
(Uncontrolled Growth)



Normal Cell
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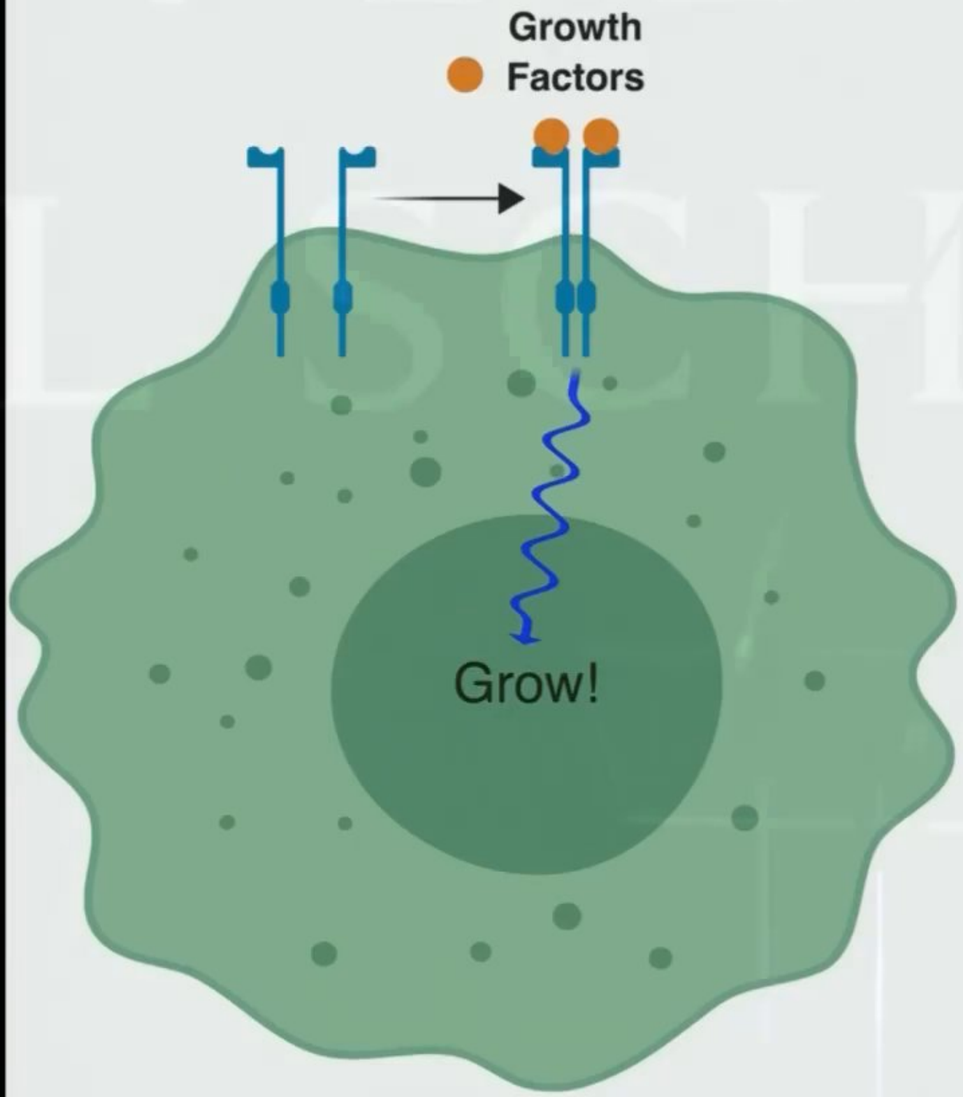
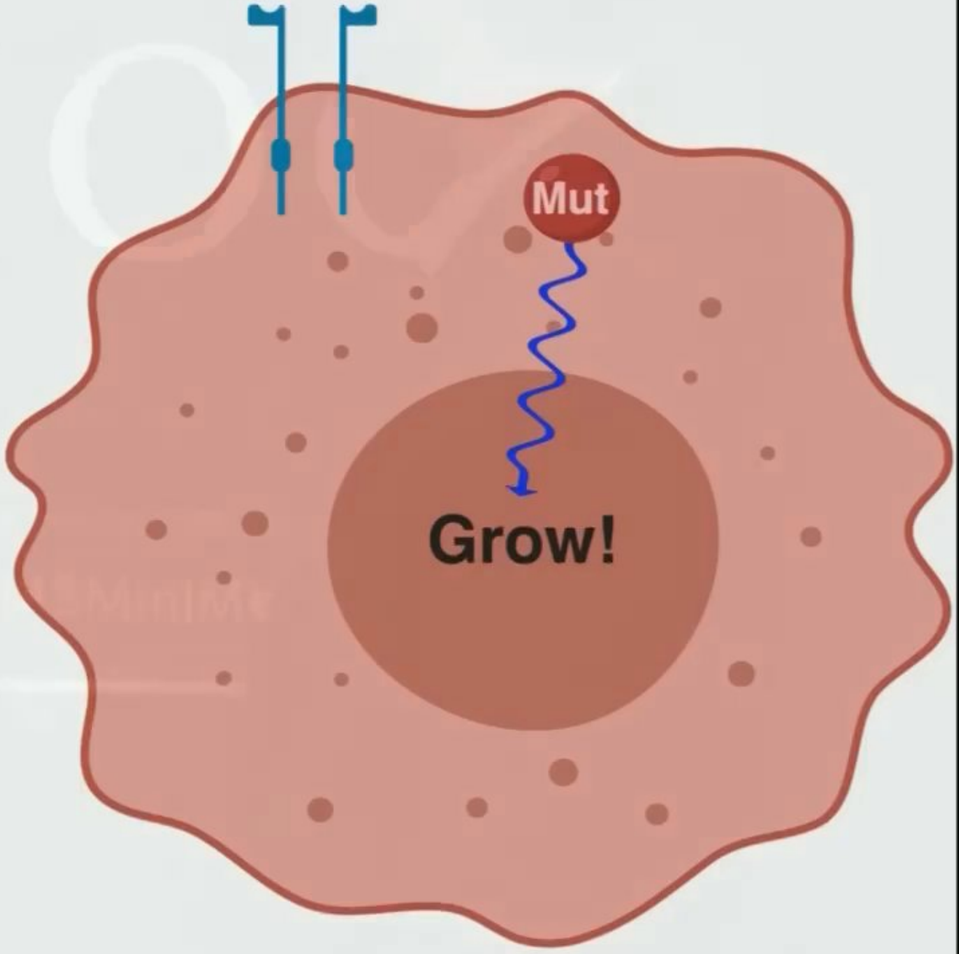


Cancer Cell
(Uncontrolled Growth)




RVARD
AL SCHOO
#HMSMiniMed

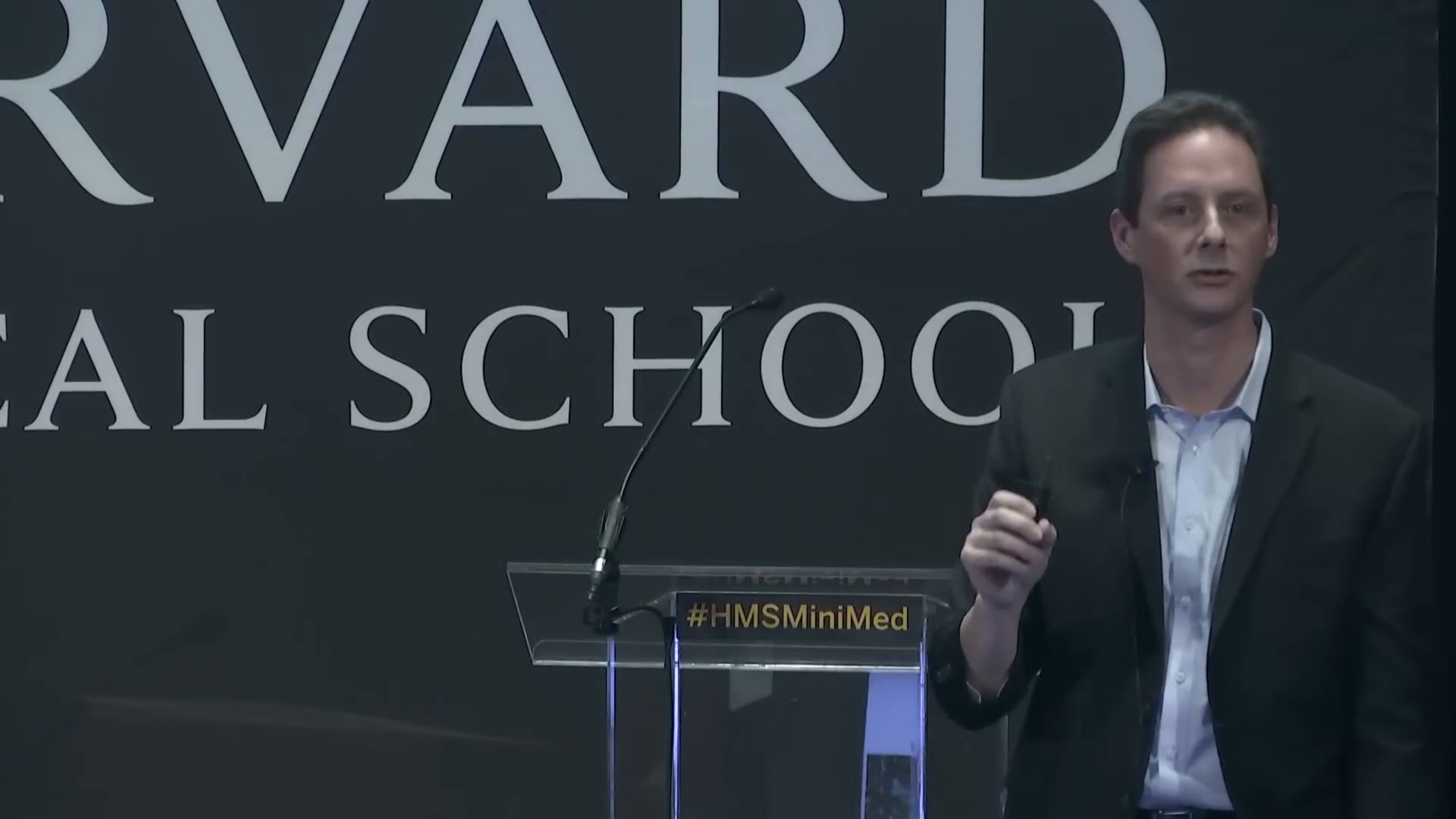
General Contractor

- Roofer
- Carpenter
- Electrician
- Mason
- Landscaper

New House


RVARD
AL SCHOO
#HMSMiniM


RVARD
CAL SCHOOL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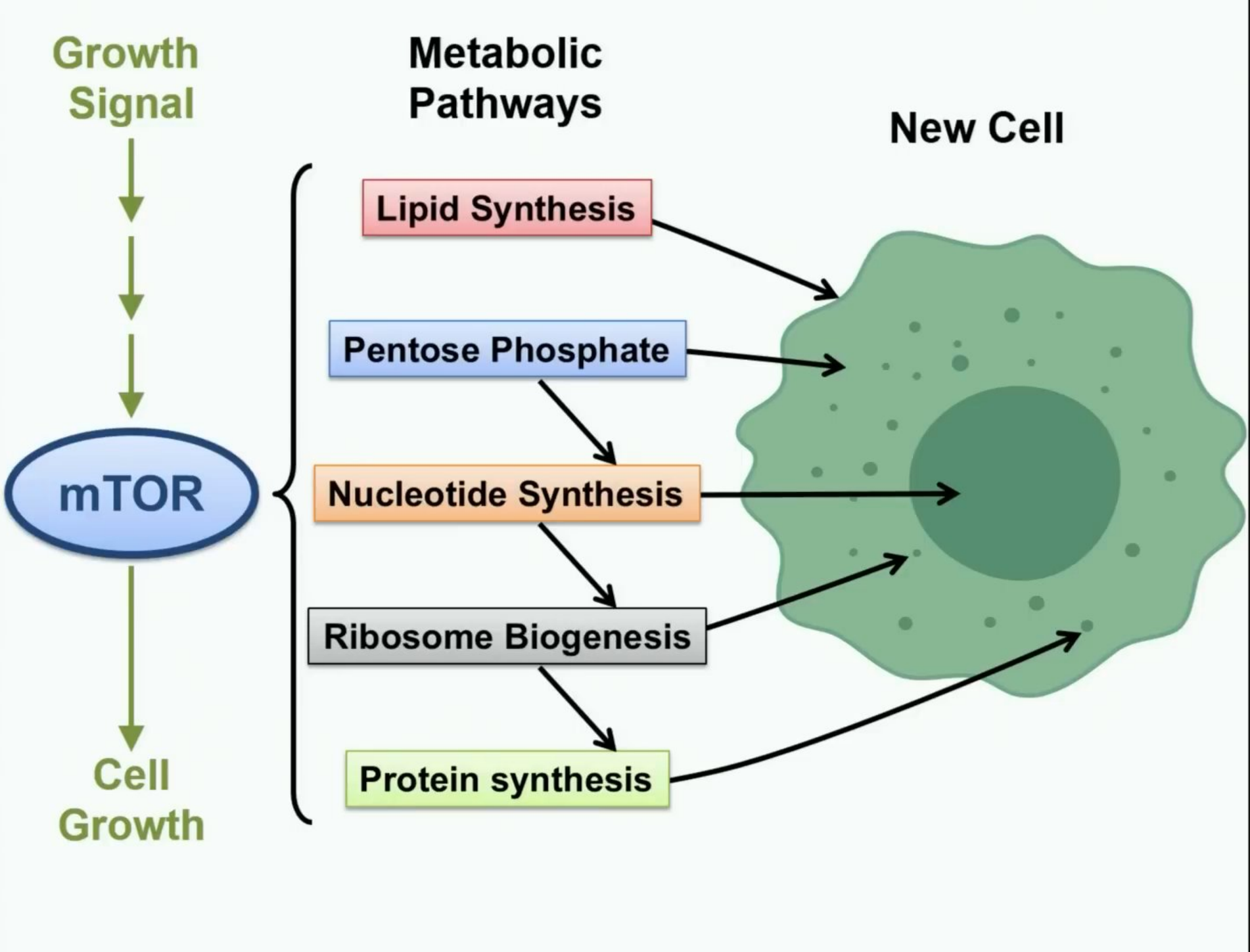
AL SCHOOL
#HMSMiniMed


RVARD
AL SCHOOL
#HMSM


Growth Signal
Metabolic Pathways
New Cell
mTOR
Lipid Synthesis
Pentose Phosphate
Nucleotide Synthesis
Ribosome Biogenesis
Protein synthesis
Cell Growth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AL SCHOOL


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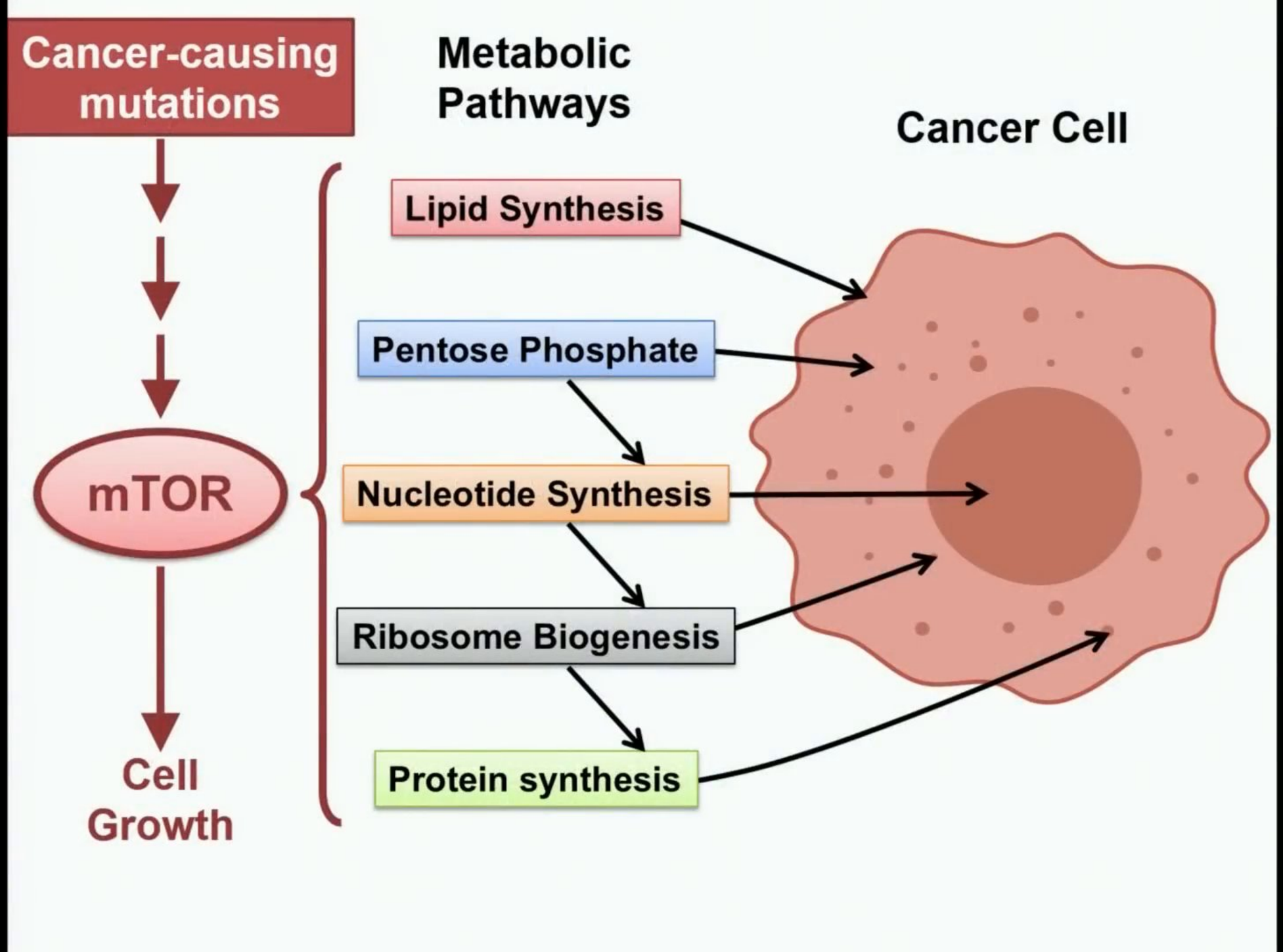
AL SCHO
#HMSMini


Cancer-causing mutations
Metabolic Pathways
Cancer Cell
mTOR
Cell Growth
Lipid Synthesis
Pentose Phosphate
Nucleotide Synthesis
Ribosome Biogenesis
Protein synthesis

General Contractor

Roofer

Carpenter

Electrician

Mason

Landscaper

New House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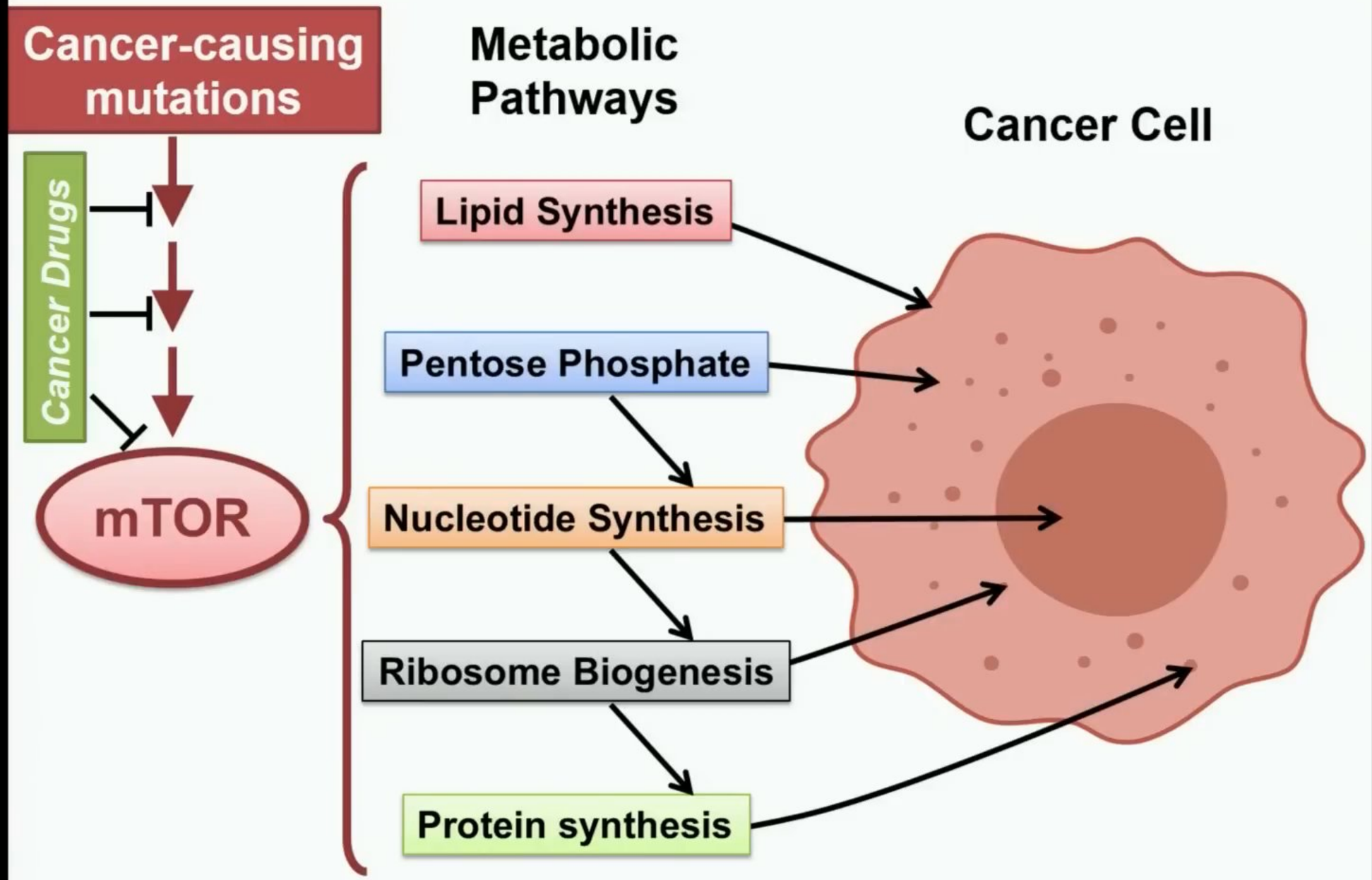
AL SCHO
#HMSM


RVARD
AL SCHOOL

General Contractor

- Roofer
- ~~Carpenter~~
- Electrician
- Mason
- Landscaper

Structural Imbalance


Cancer-causing mutations
Cancer Drugs
mTOR
Metabolic Pathways
Lipid Synthesis
Pentose Phosphate
Nucleotide Synthesis
Ribosome Biogenesis
Protein synthesis
Cancer Cell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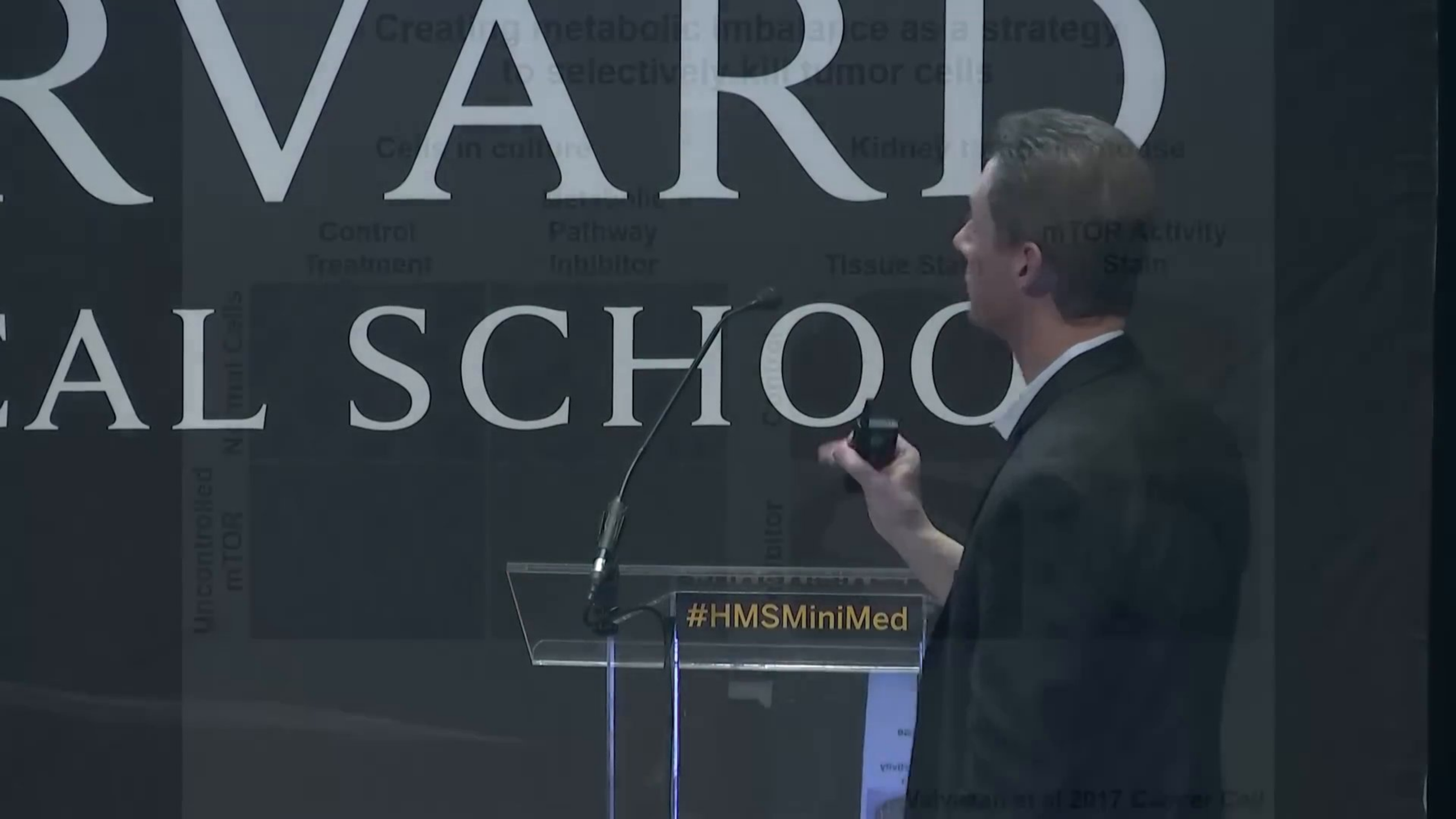
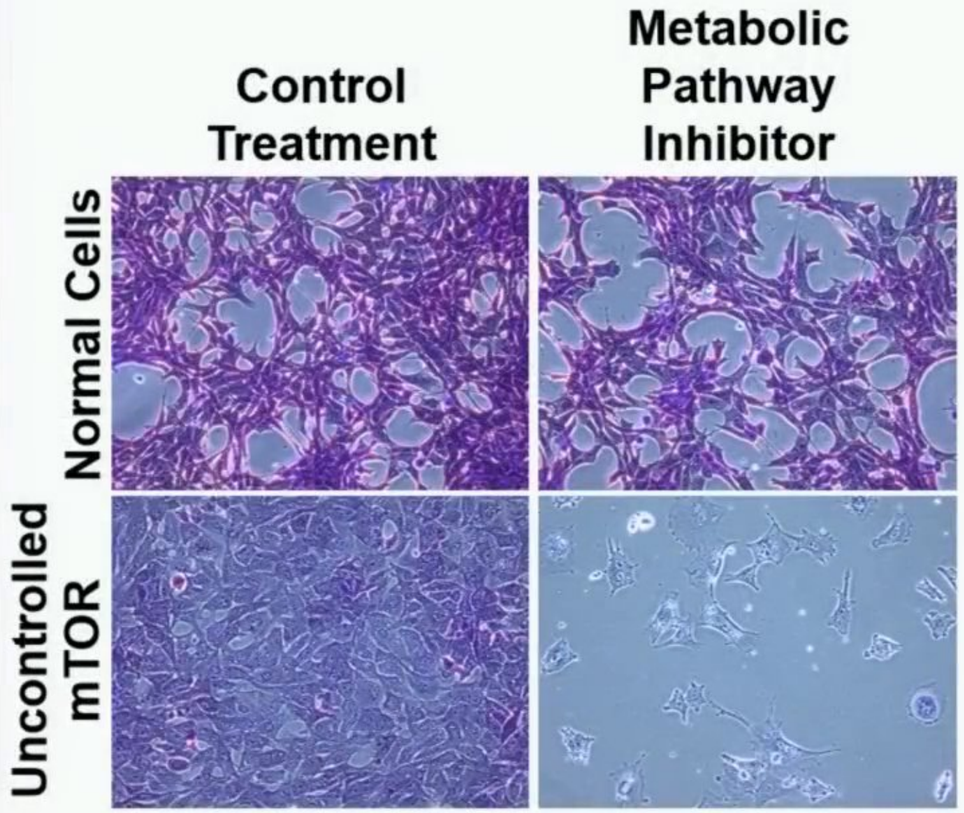
RVARD
AL SCHOOL

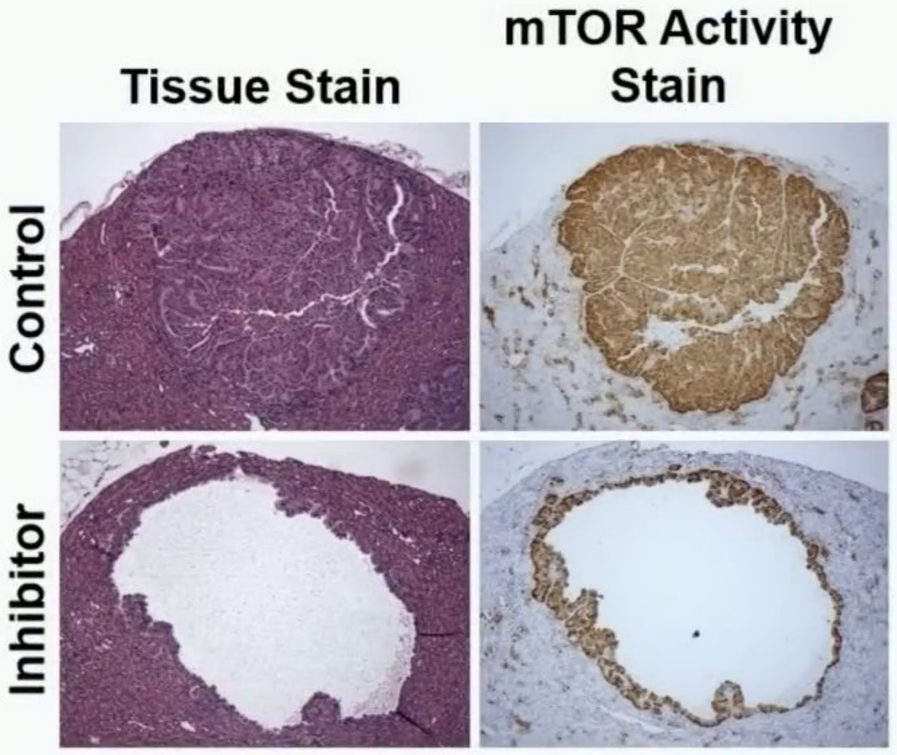

#HMSMiniMed

Creating metabolic imbalance as a strategy to selectively kill tumor cells

Cells in culture

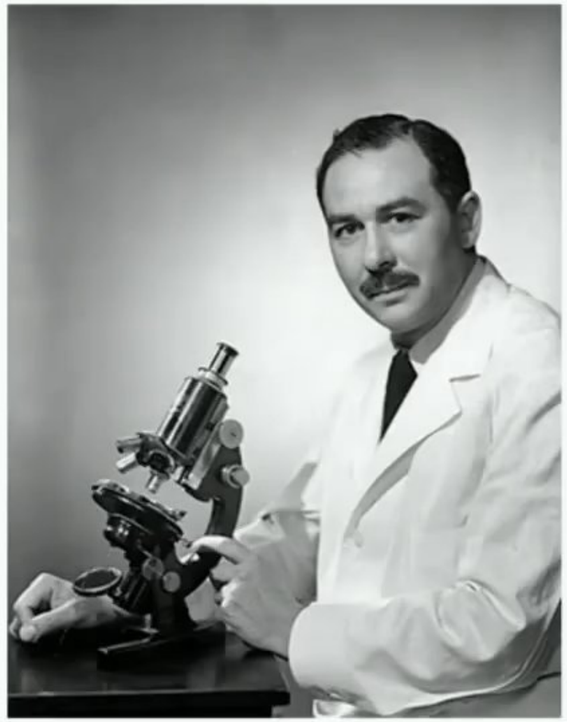


Kidney tumor in mouse



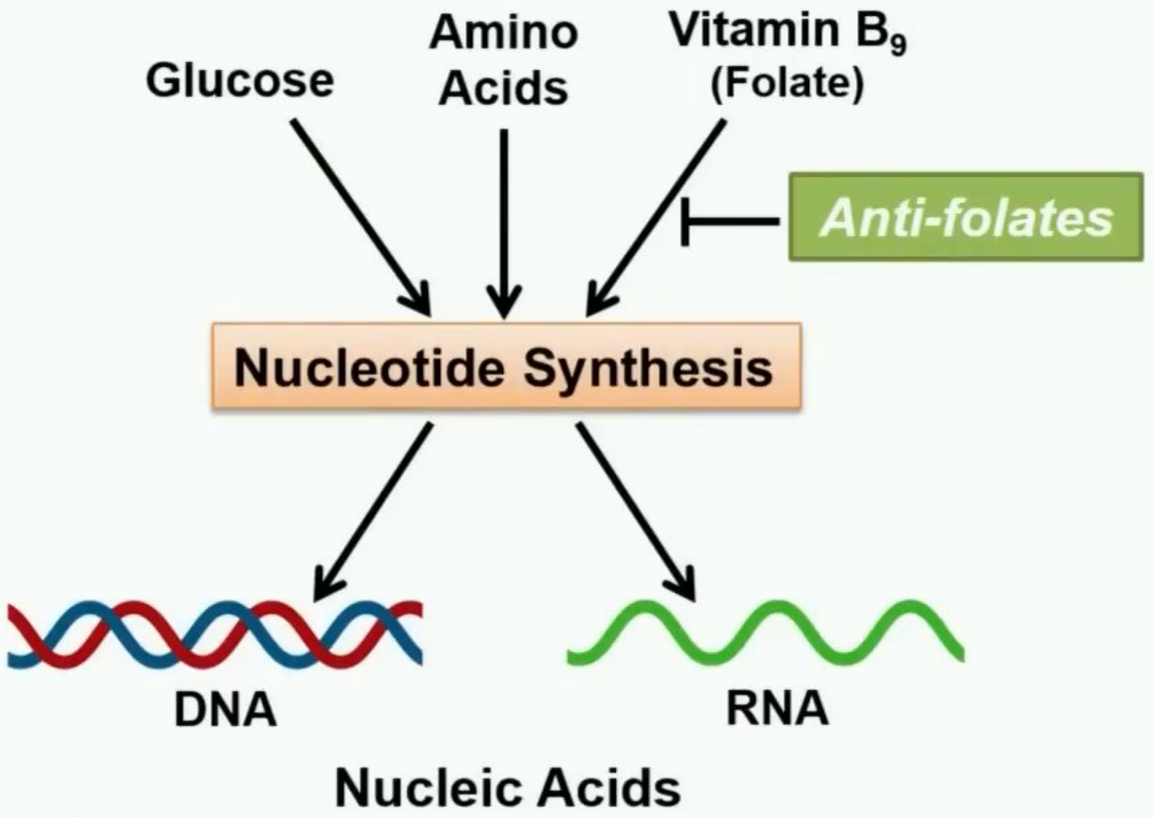
Valvezan et al 2017 *Cancer Cell*

Targeting the metabolic pathways essential for cancer cell growth is not a new idea



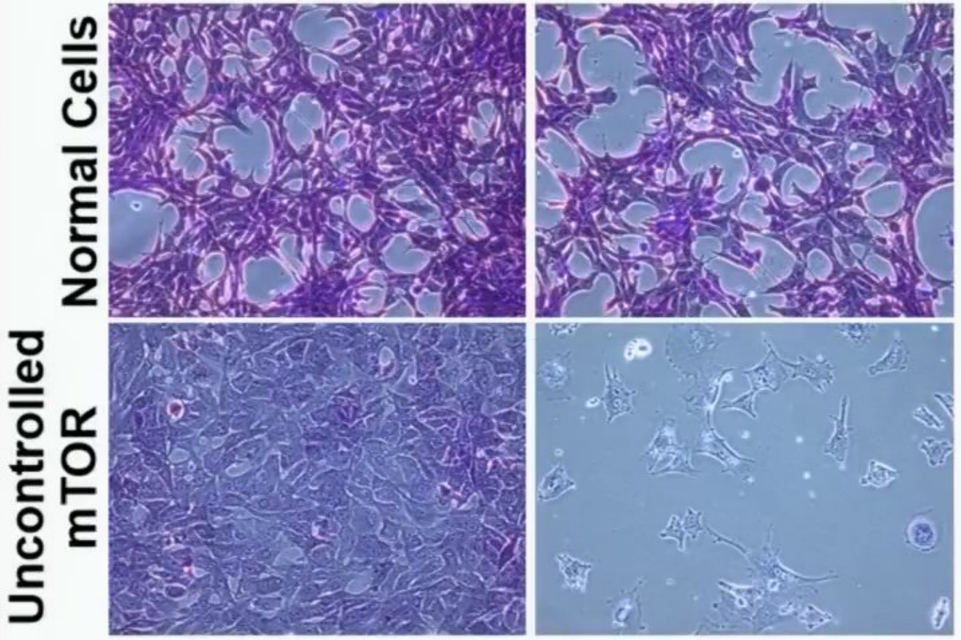
Dr. Sidney Farber (1947)

M.D. 1927 Harvard Medical School
Pathologist, Children's Hospital, Boston
Professor of Pathology, HMS

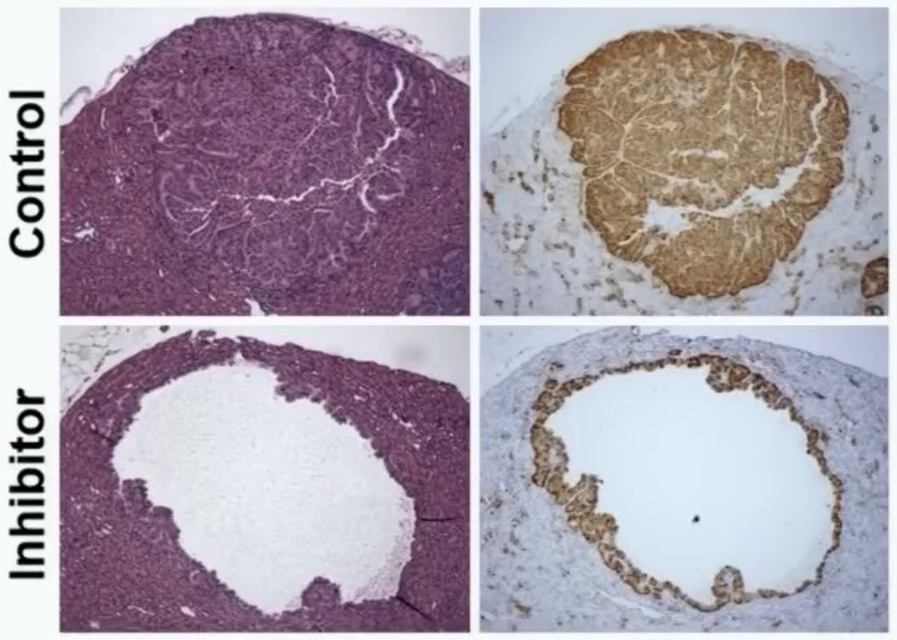


Creating metabolic imbalance as a strategy to selectively kill tumor cells

Cells in culture



Kidney tumor in mouse



Valvezan et al 2017 *Cancer Cell*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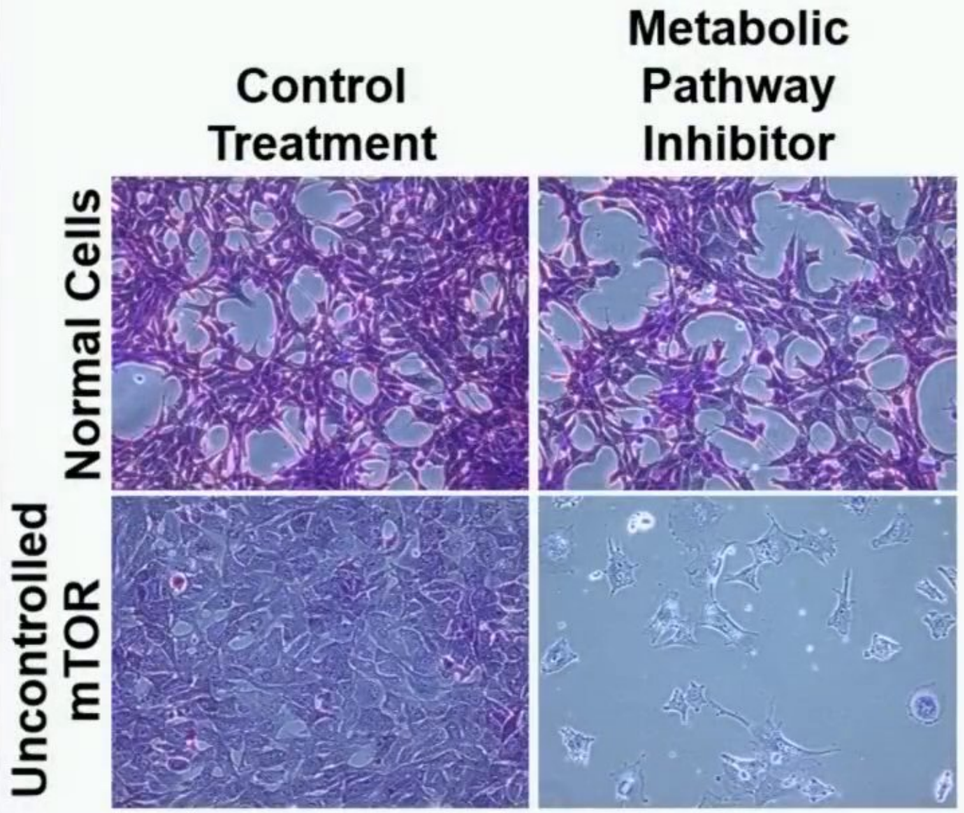
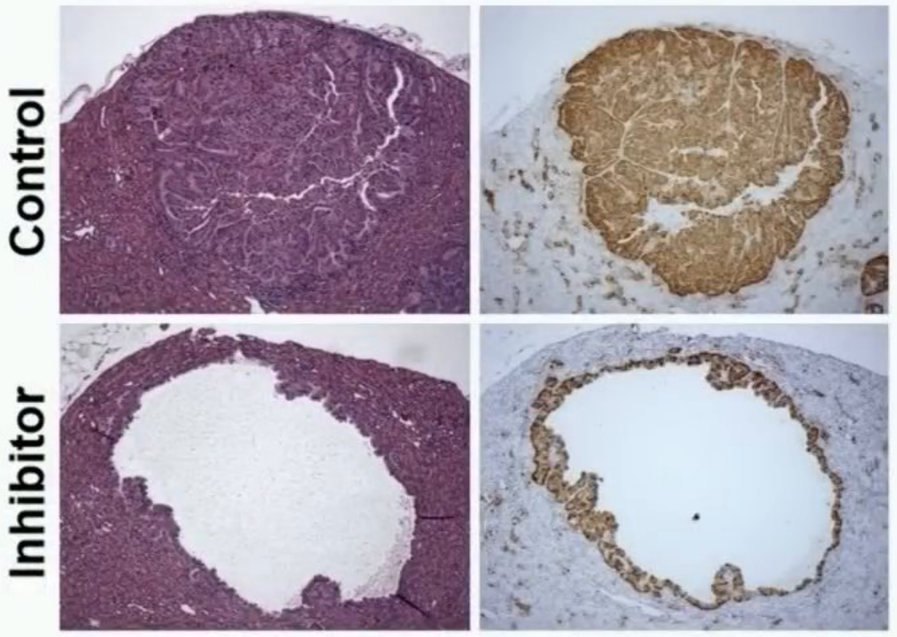
Creating metabolic imbalance as a strategy to selectively kill tumor cells

Cells in culture

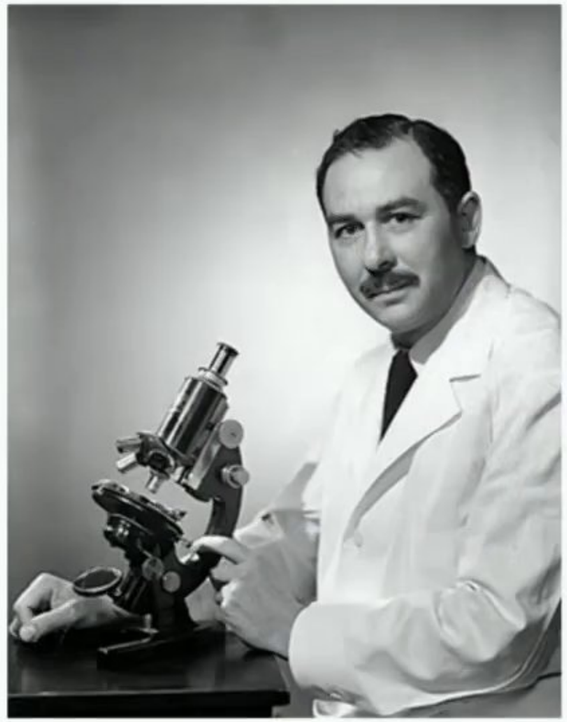


Kidney tumor in mouse



Valvezan et al 2017 *Cancer Cell*

Targeting the metabolic pathways essential for cancer cell growth is not a new idea



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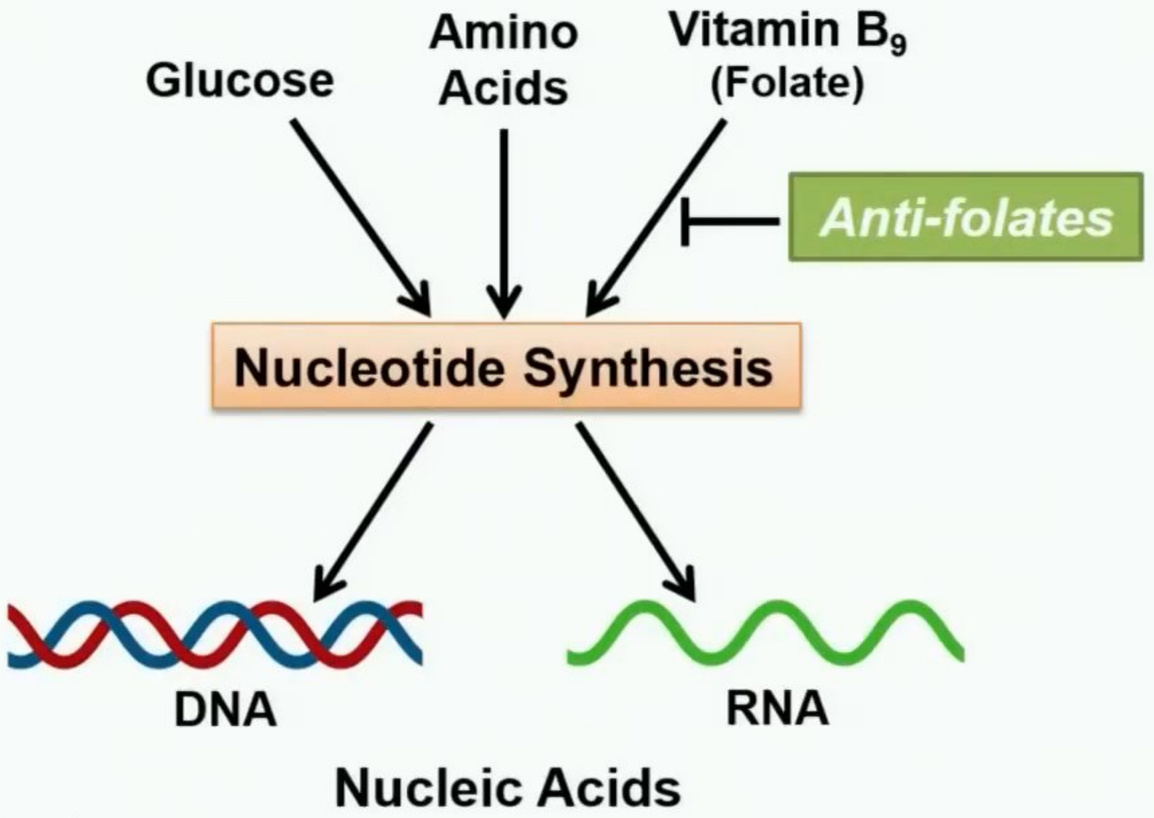
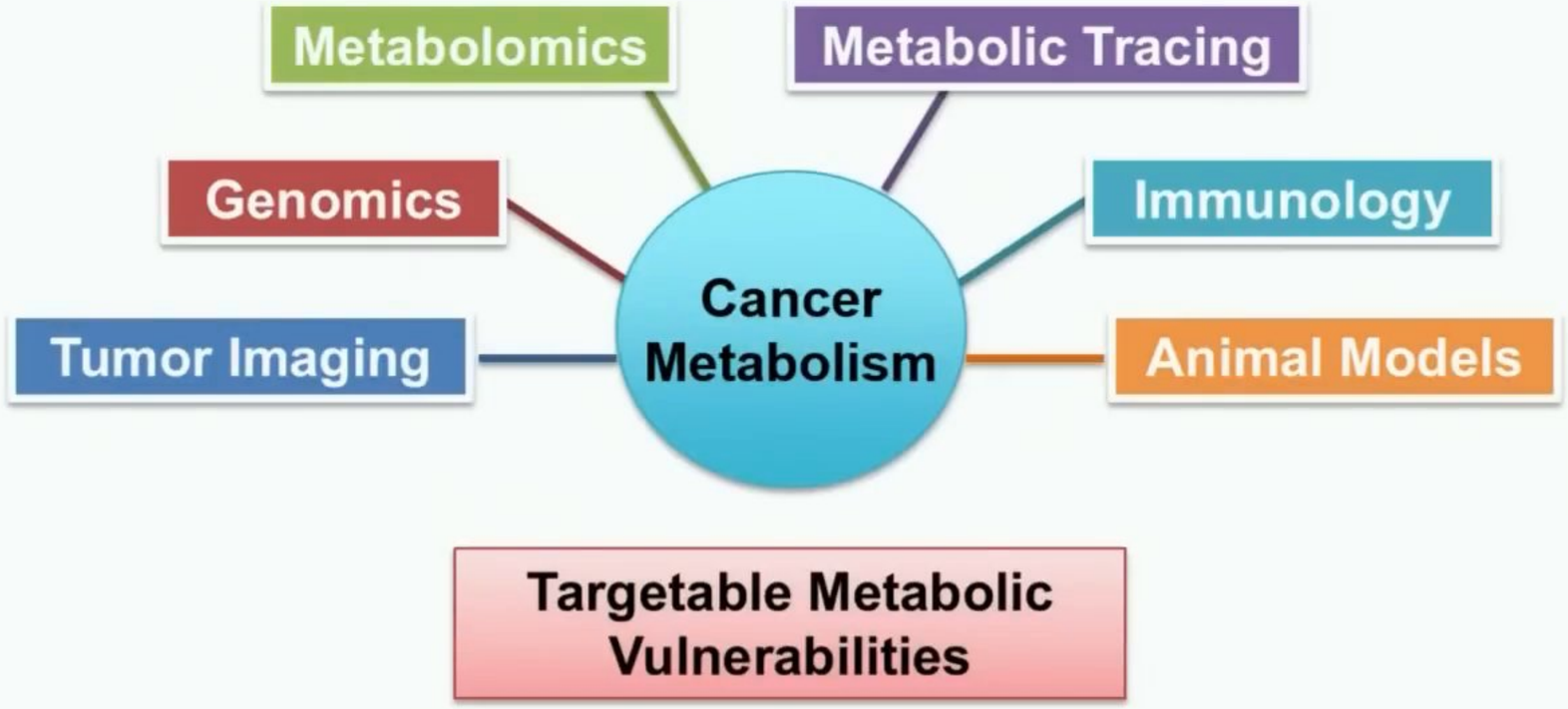


Nucleic Acids

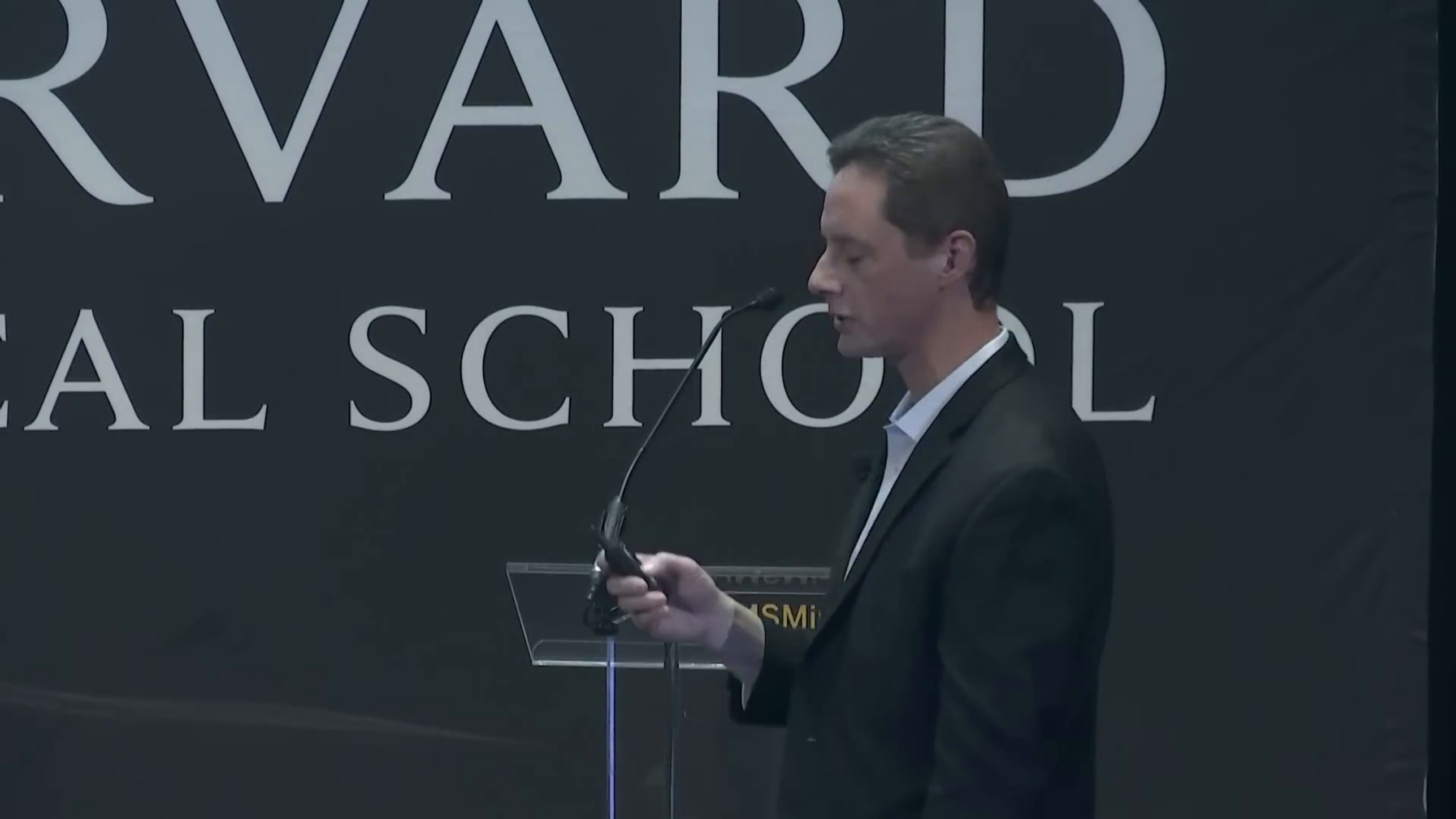
Targeting the metabolic pathways essential for cancer cell growth is not a new idea

BUT, the study of cancer metabolism has been re-energized by modern technology and knowledge of cancer biology

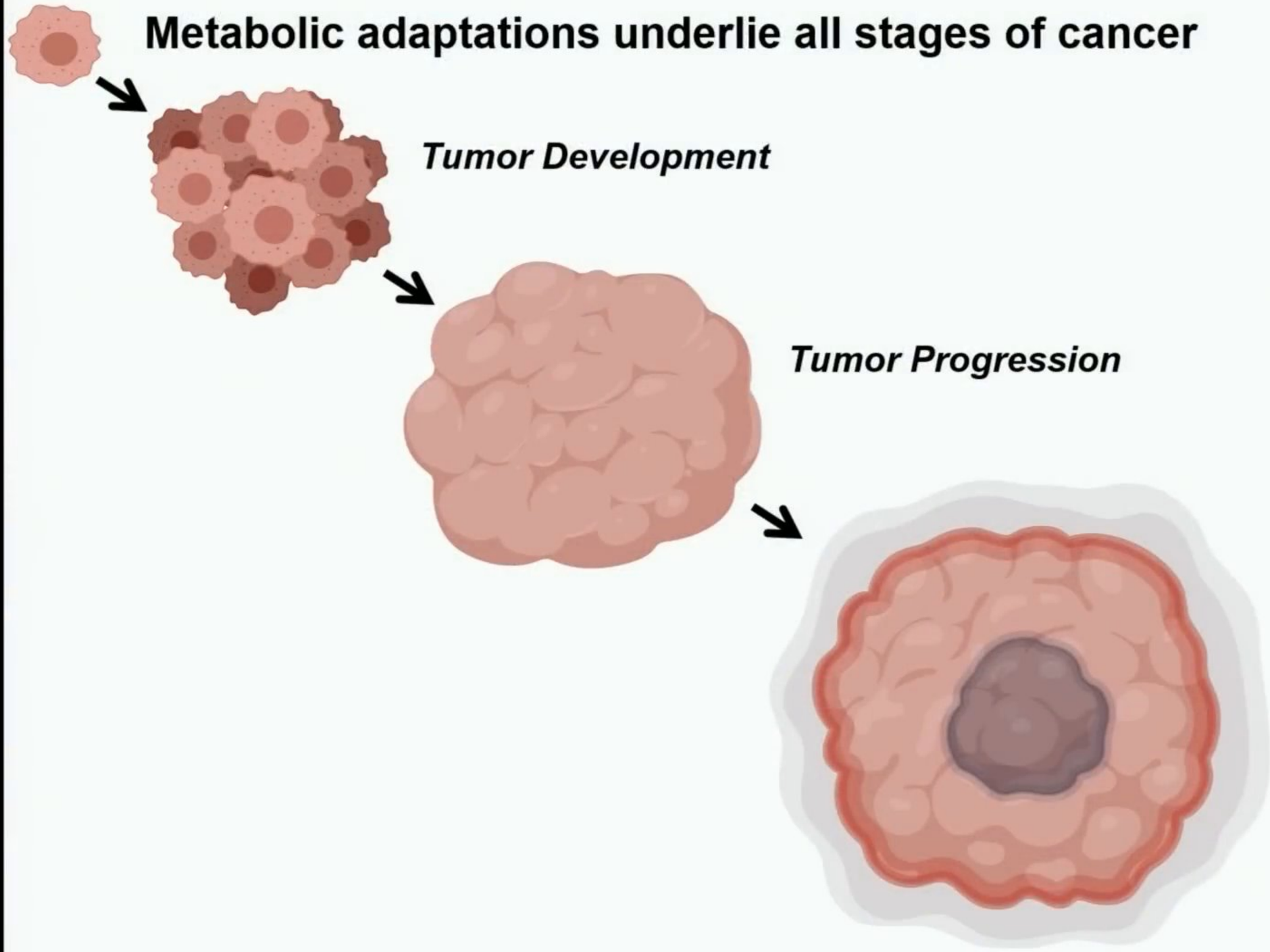



RVARD
AL SCHOOL


RVARD
AL SCHOO
#HMSMiniMe


RVARD
AL SCHO L

Metabolic adaptations underlie all stages of cancer

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AL SCHOOL
#HMSMiniMed


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CAL SCHOOL


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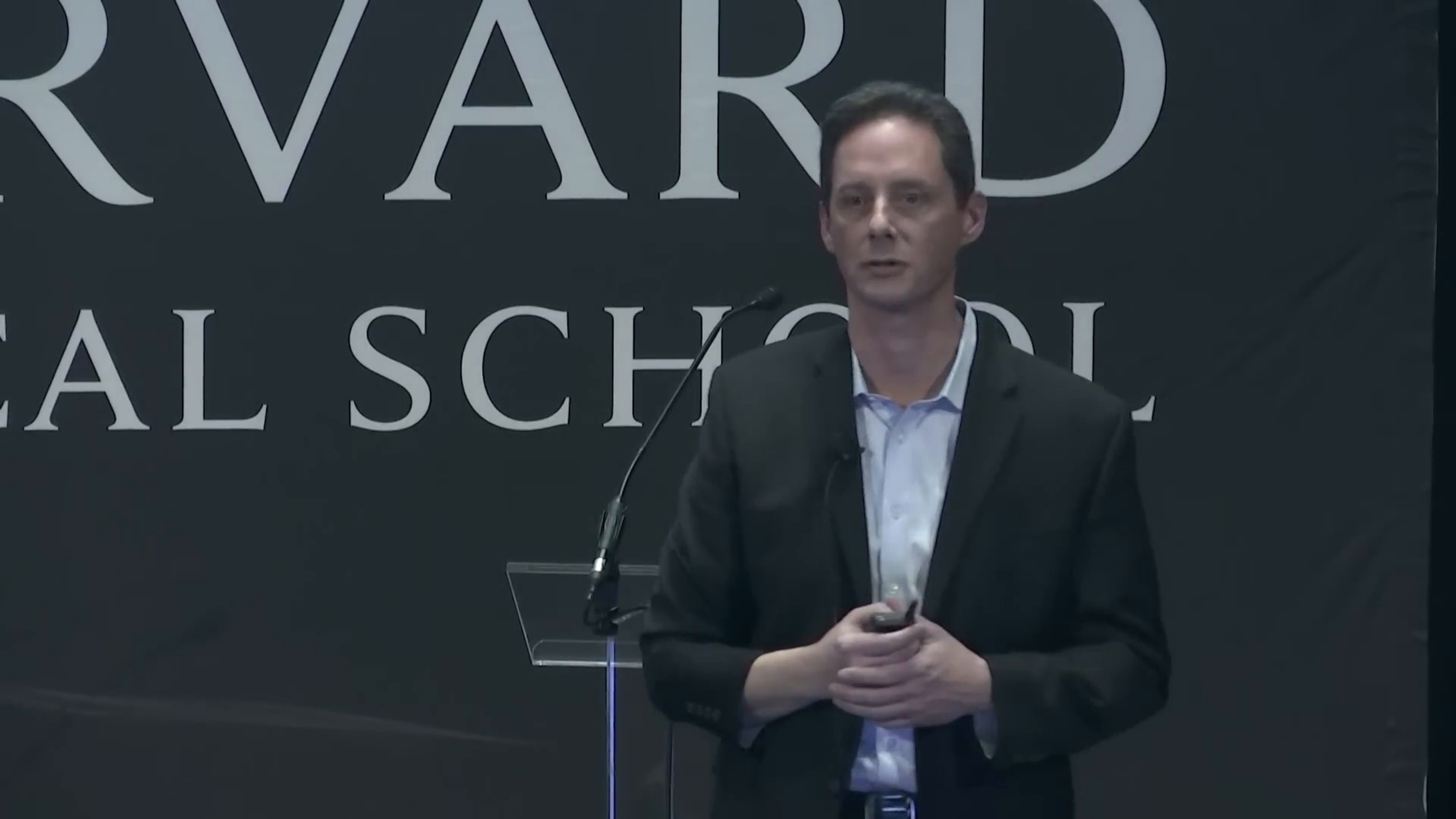
#HMSMi

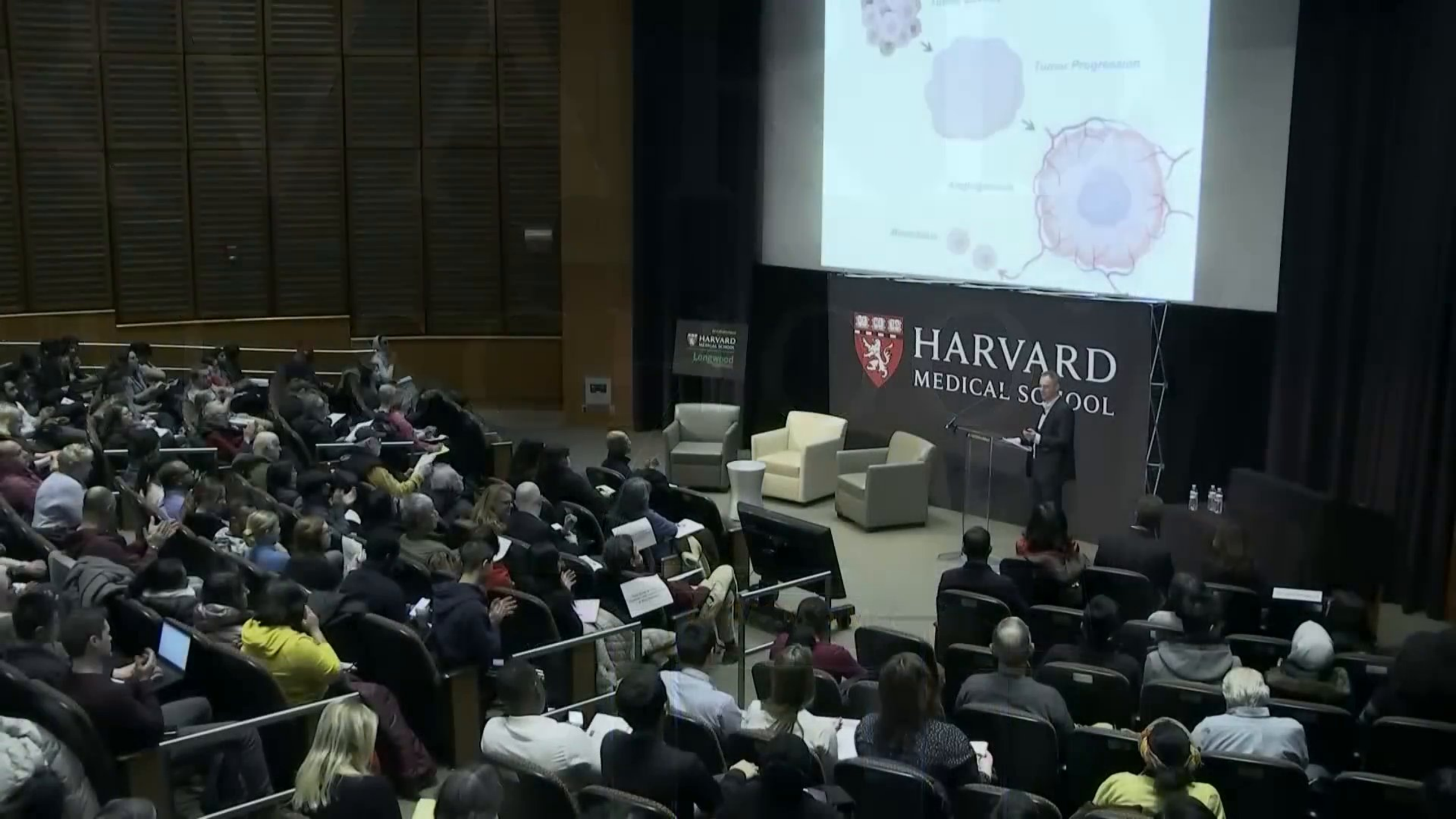

RVARD
CAL SCHOOL
MiniMed

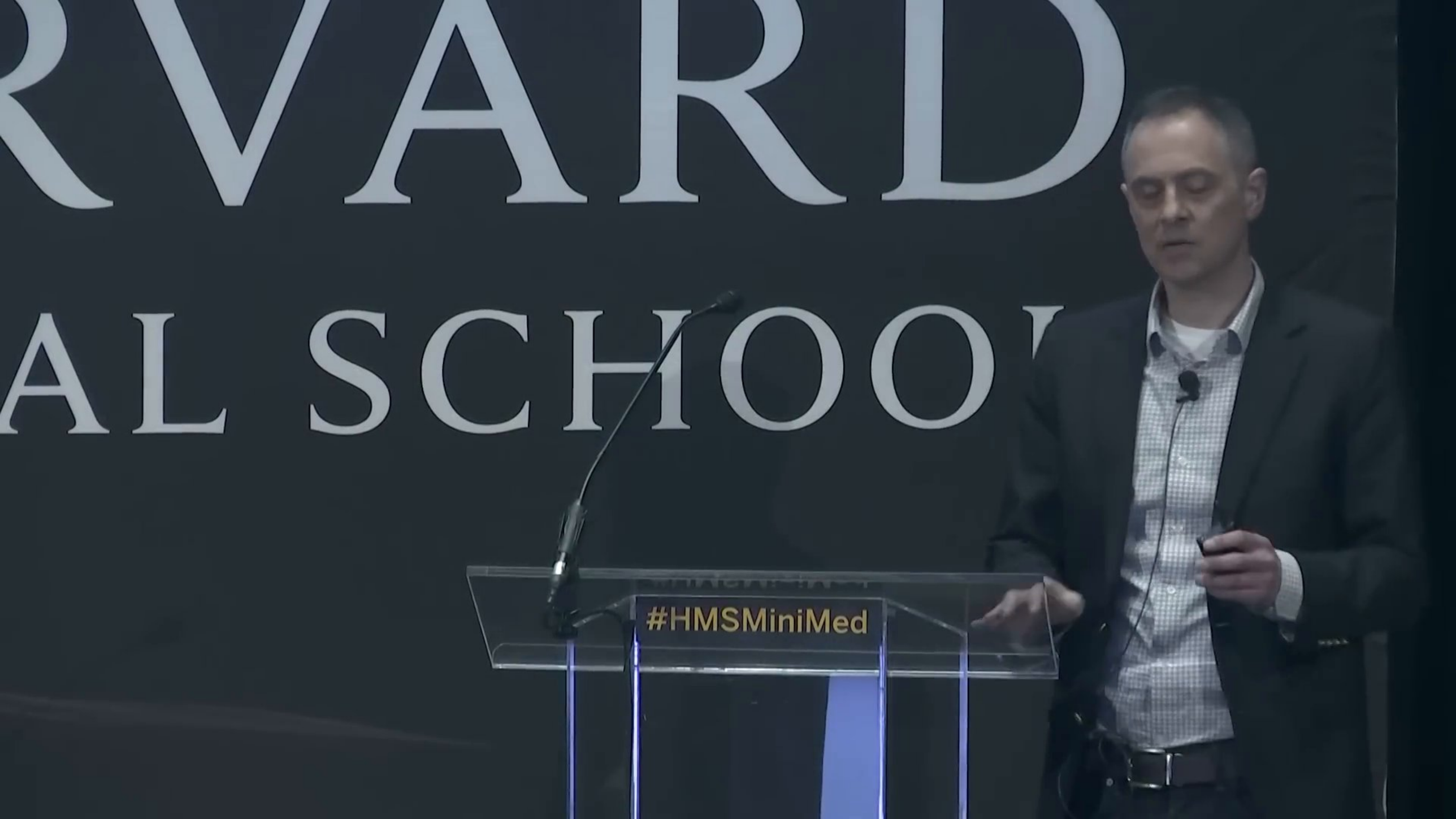

RVARD
AL SCHOOL


RVARD
CAL SCHOOL


RVARD
AL SCH OL


RVARD
AL SCHOO
#HMSMiniMed


Tumor Progression
HARVARD
MEDICAL SCHOOL
Longwood


RVARD
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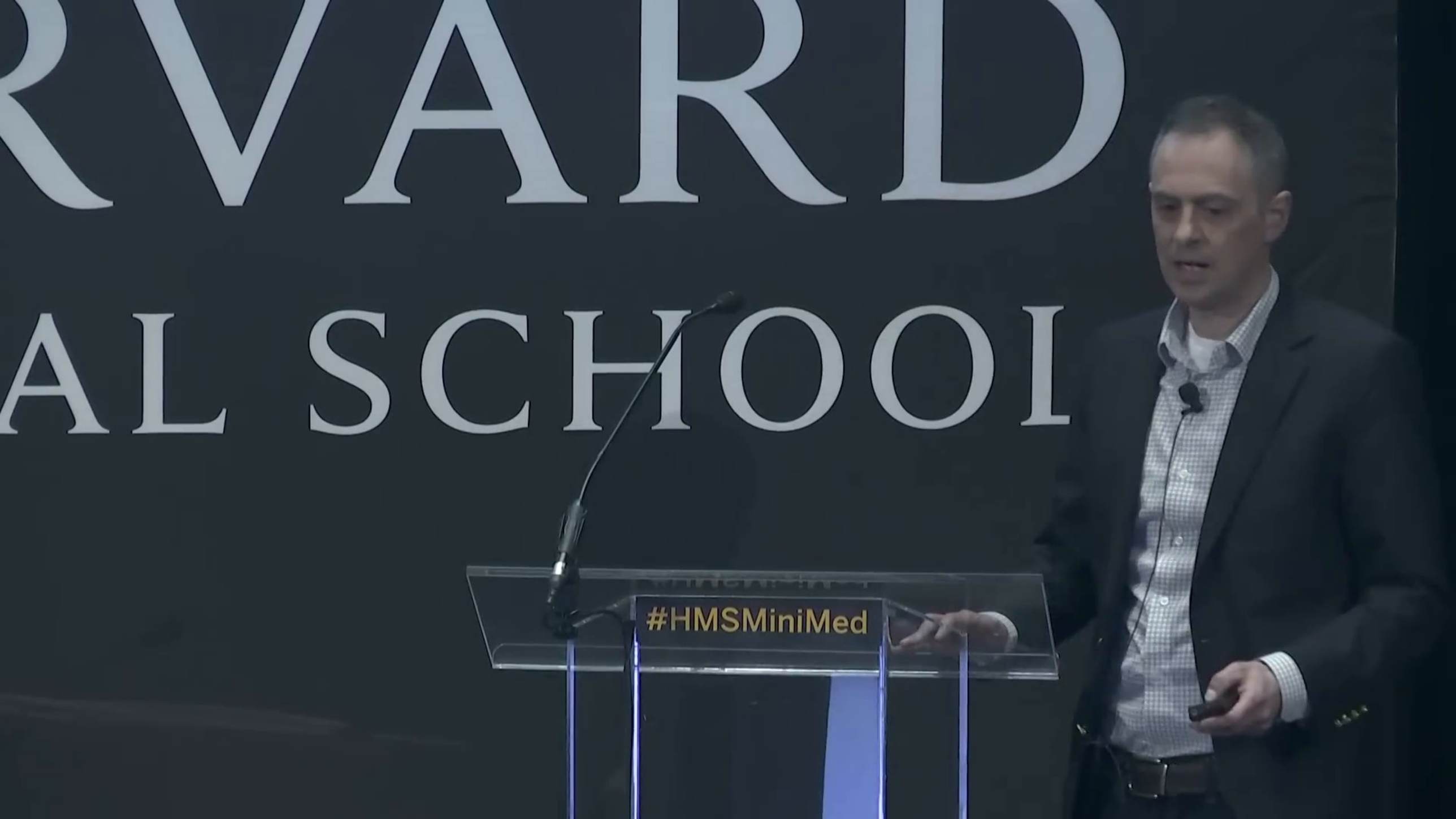
#HMSMiniMed


#HMSMiniMed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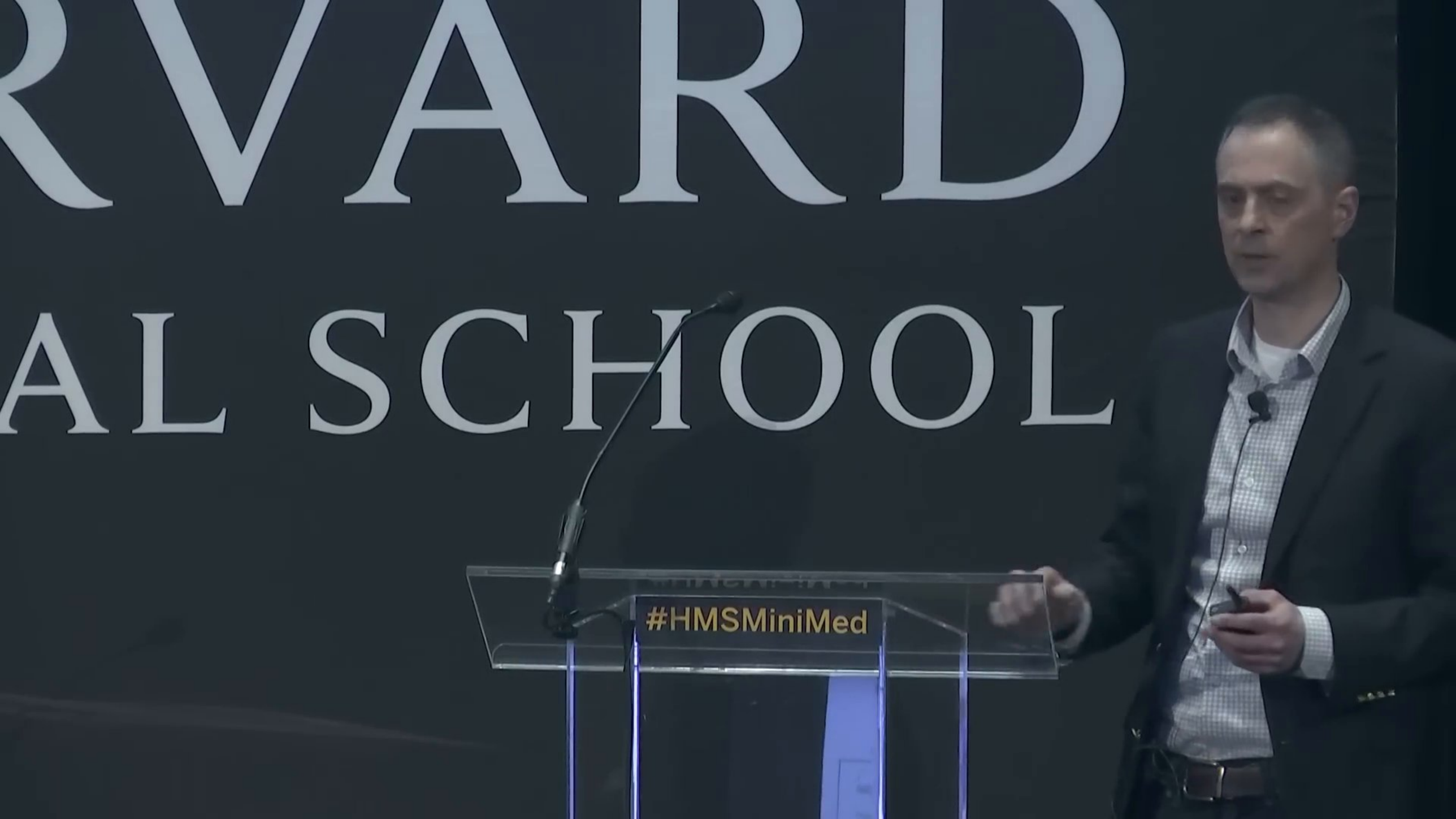
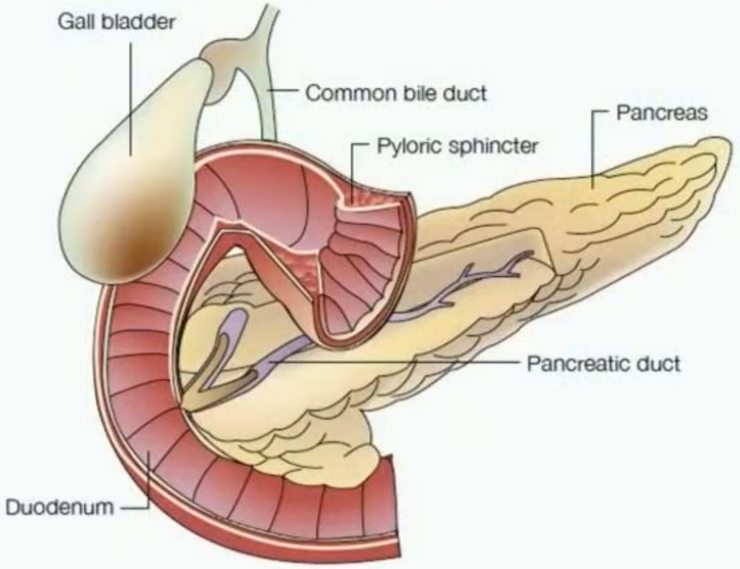
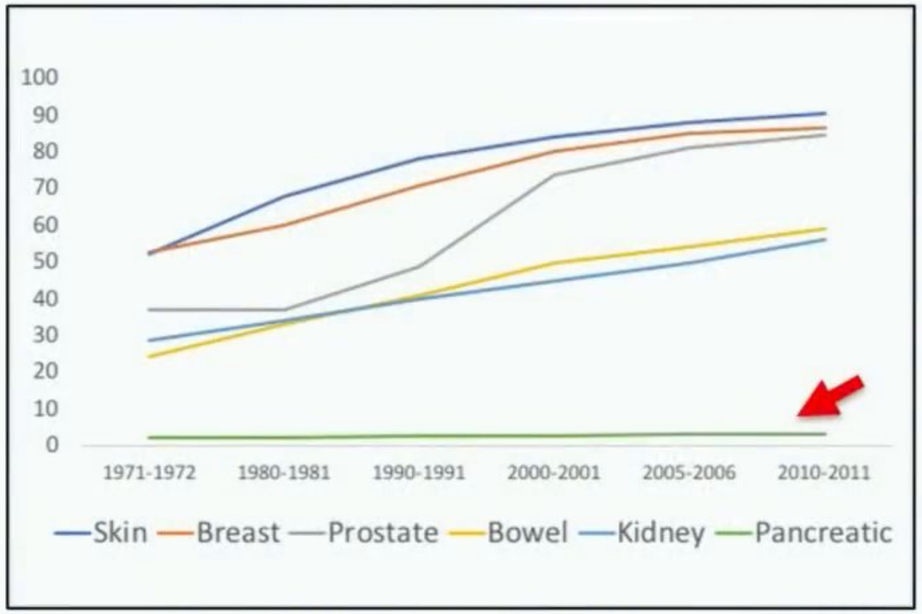
#HMSMiniMed


RVARD
AL SCHOOL
#HMSMiniMed

Pancreatic Cancer



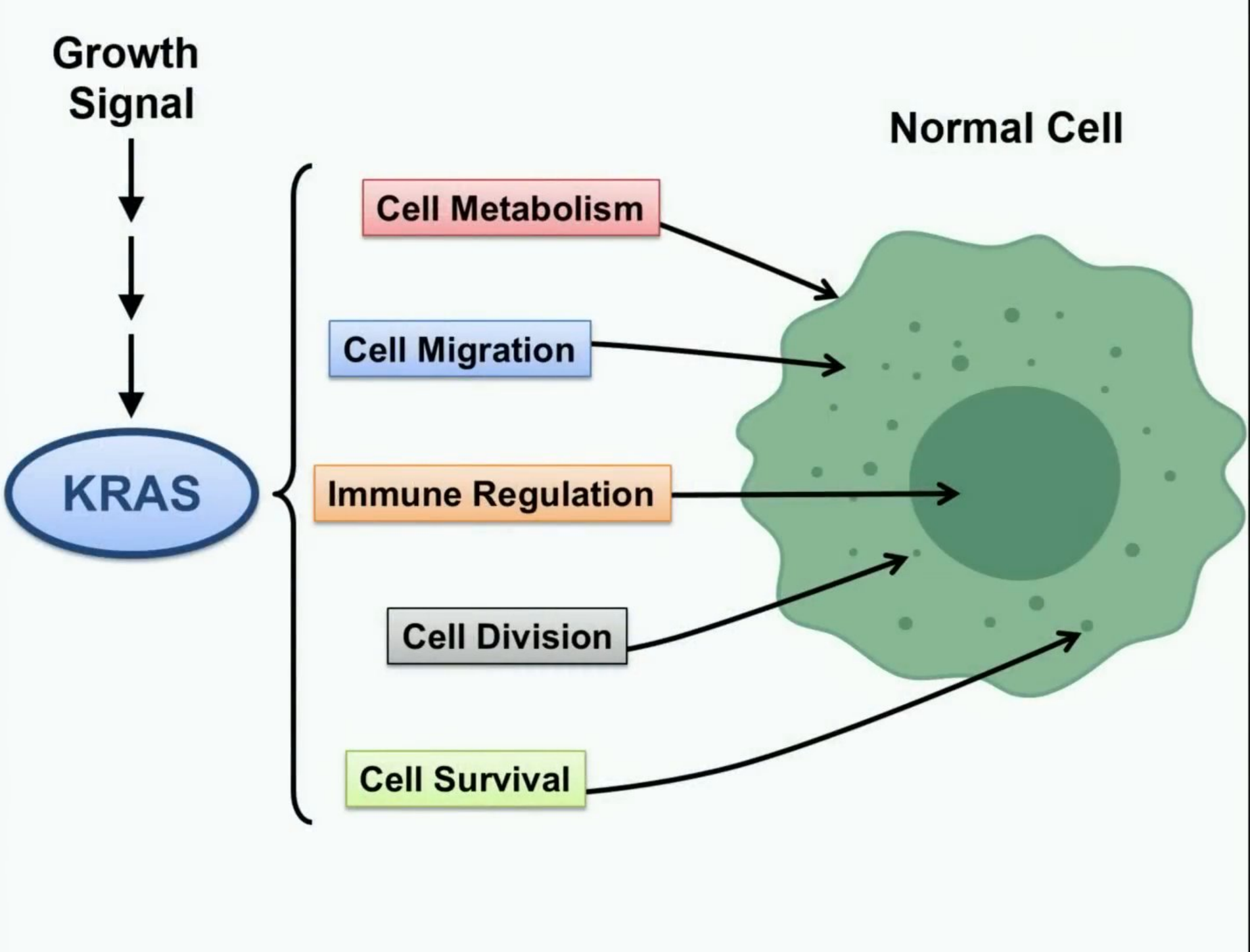



#HMSMiniMed

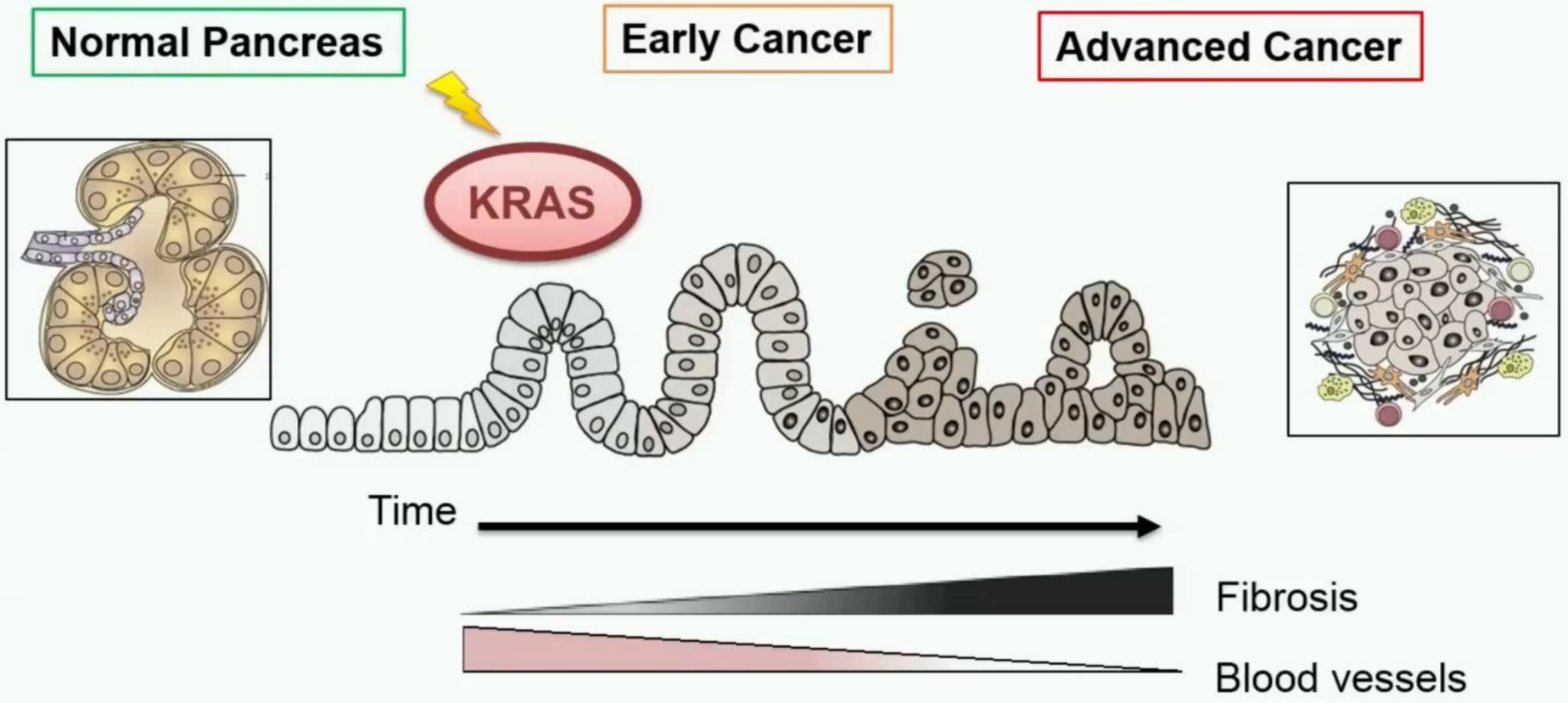

#HMSMiniMed

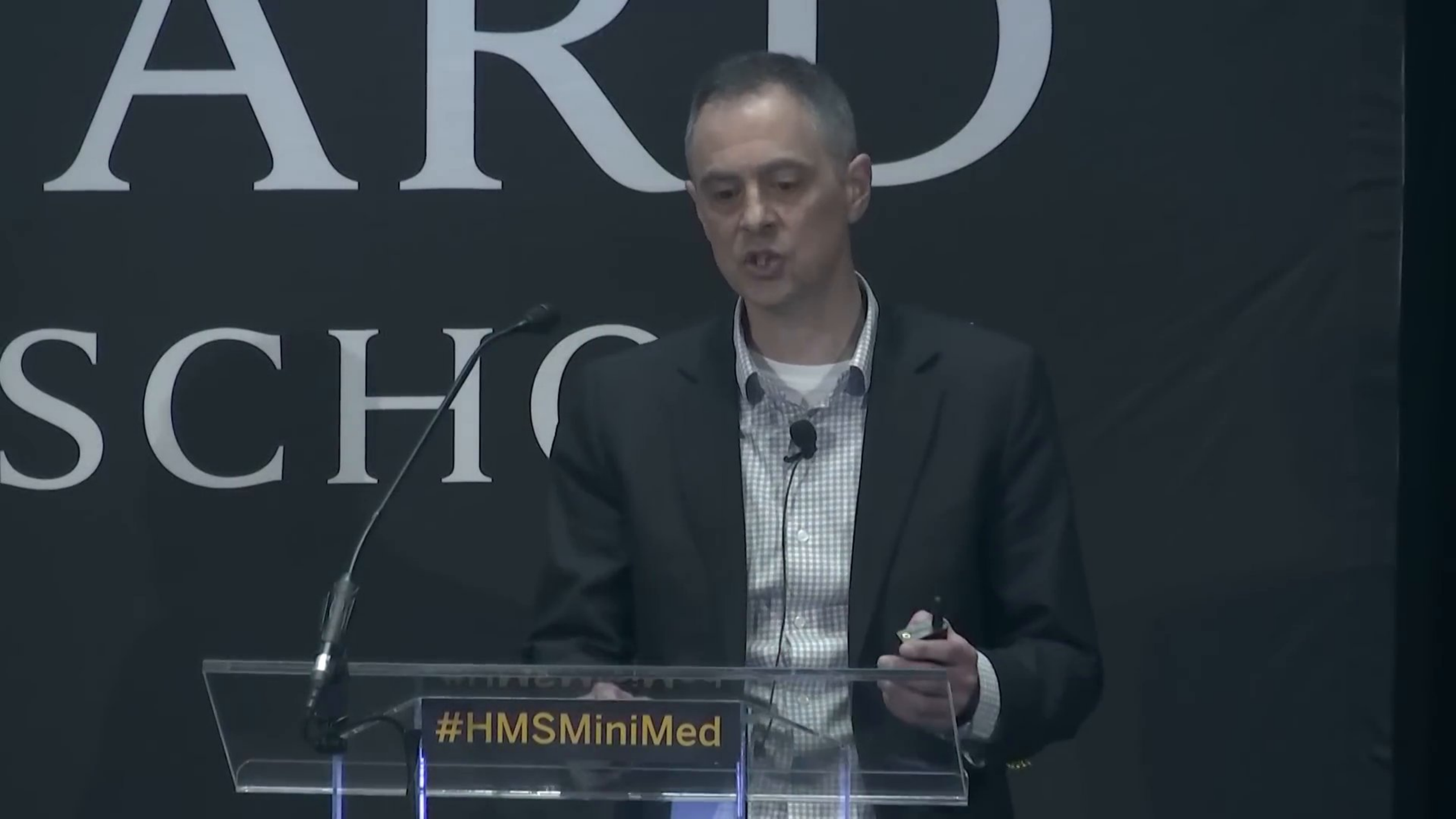

#HMSMiniMed

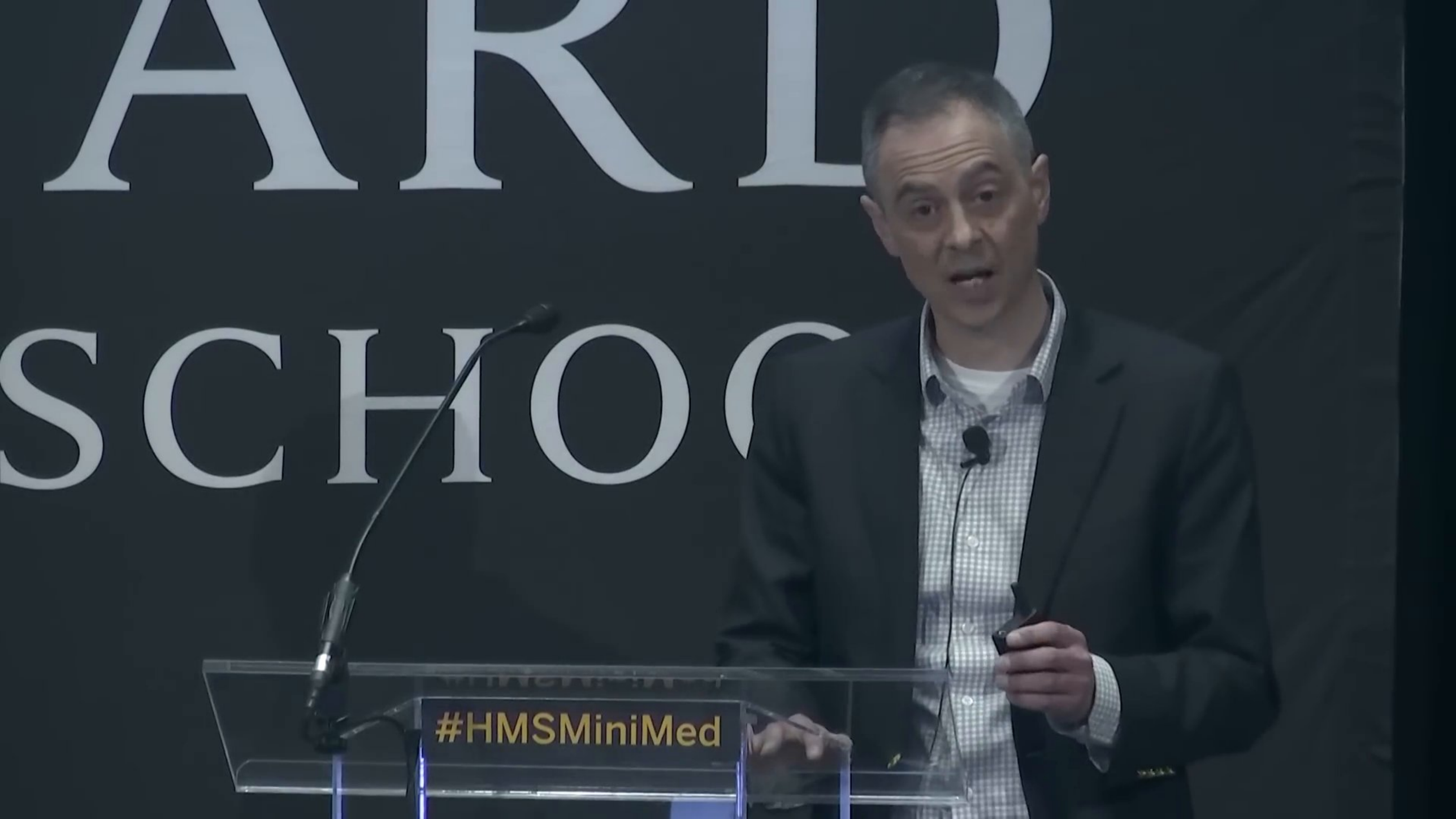

#HMSMiniMed


Growth Signal
KRAS
Normal Cell
Cell Metabolism
Cell Migration
Immune Regulation
Cell Division
Cell Survival

The Evolution of Pancreatic Cancer




#HMSMiniMed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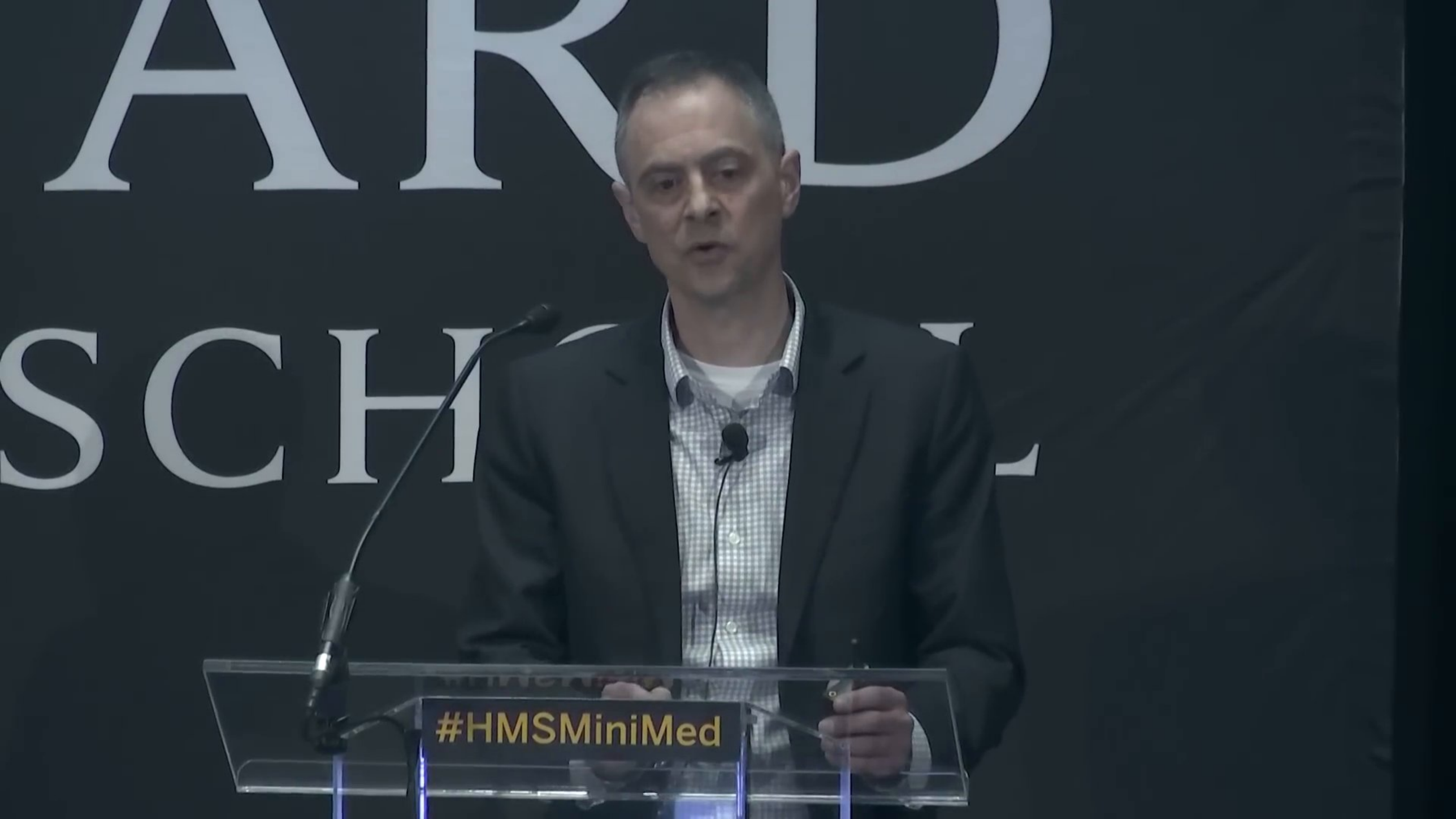
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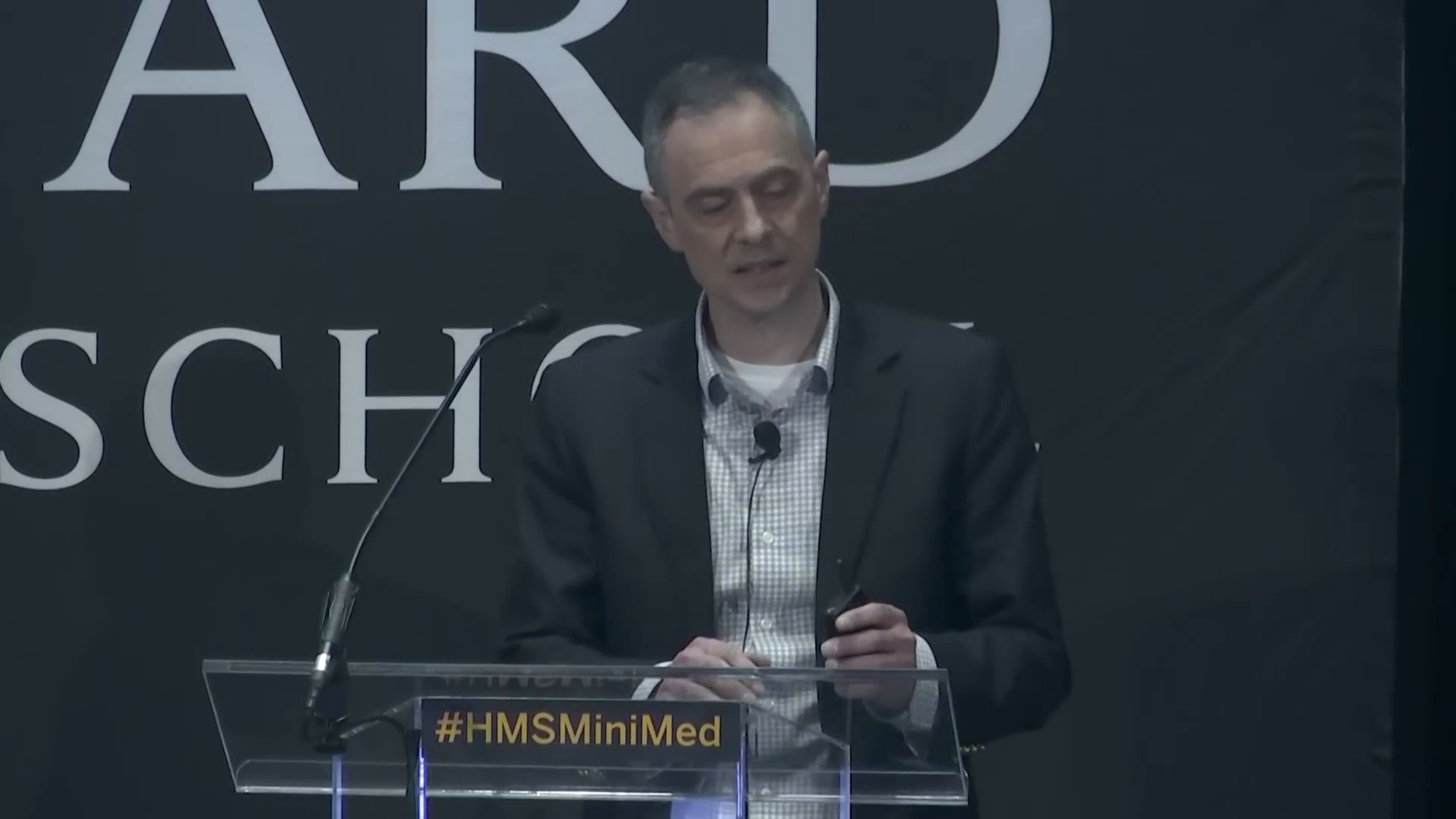
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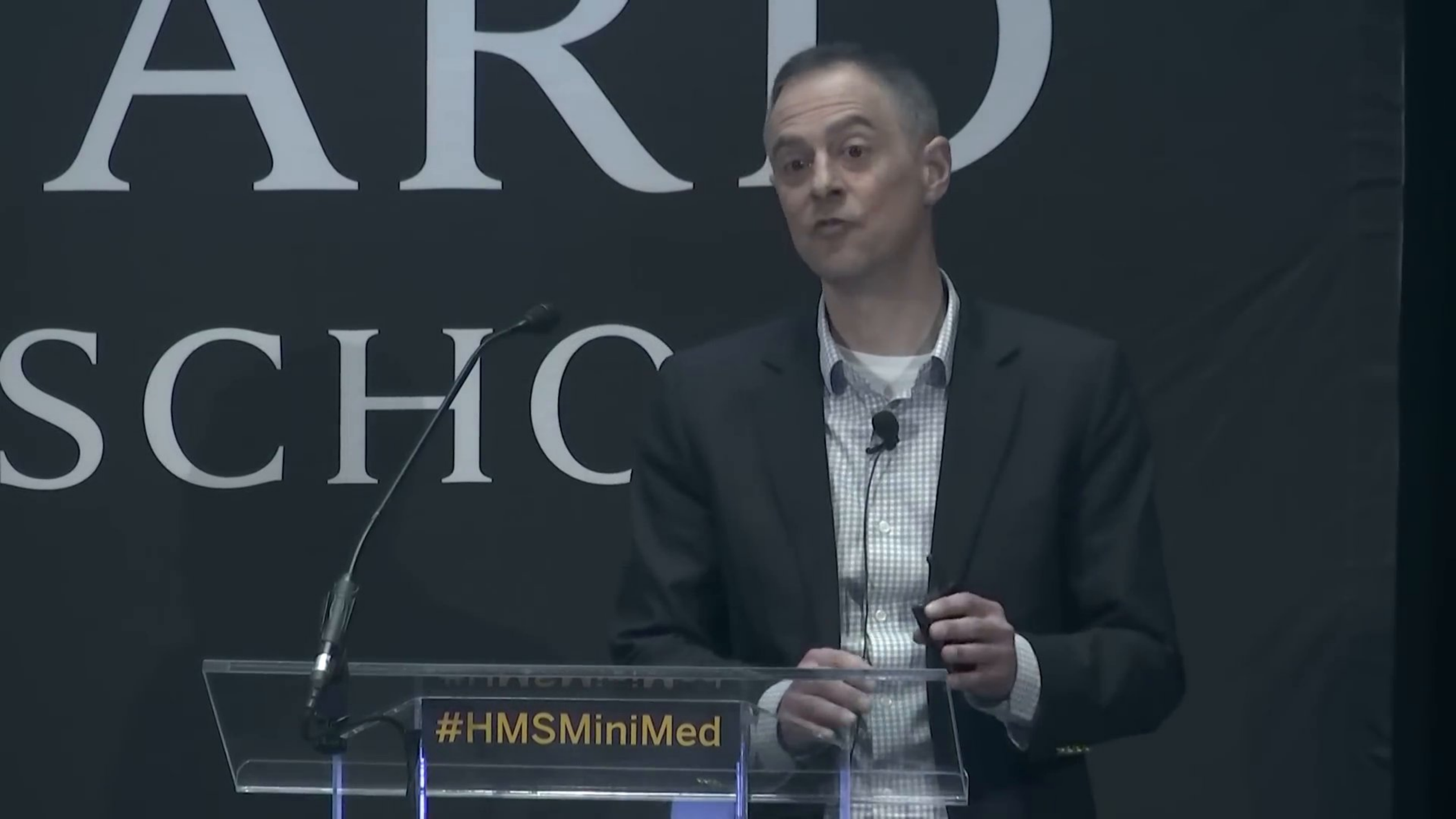
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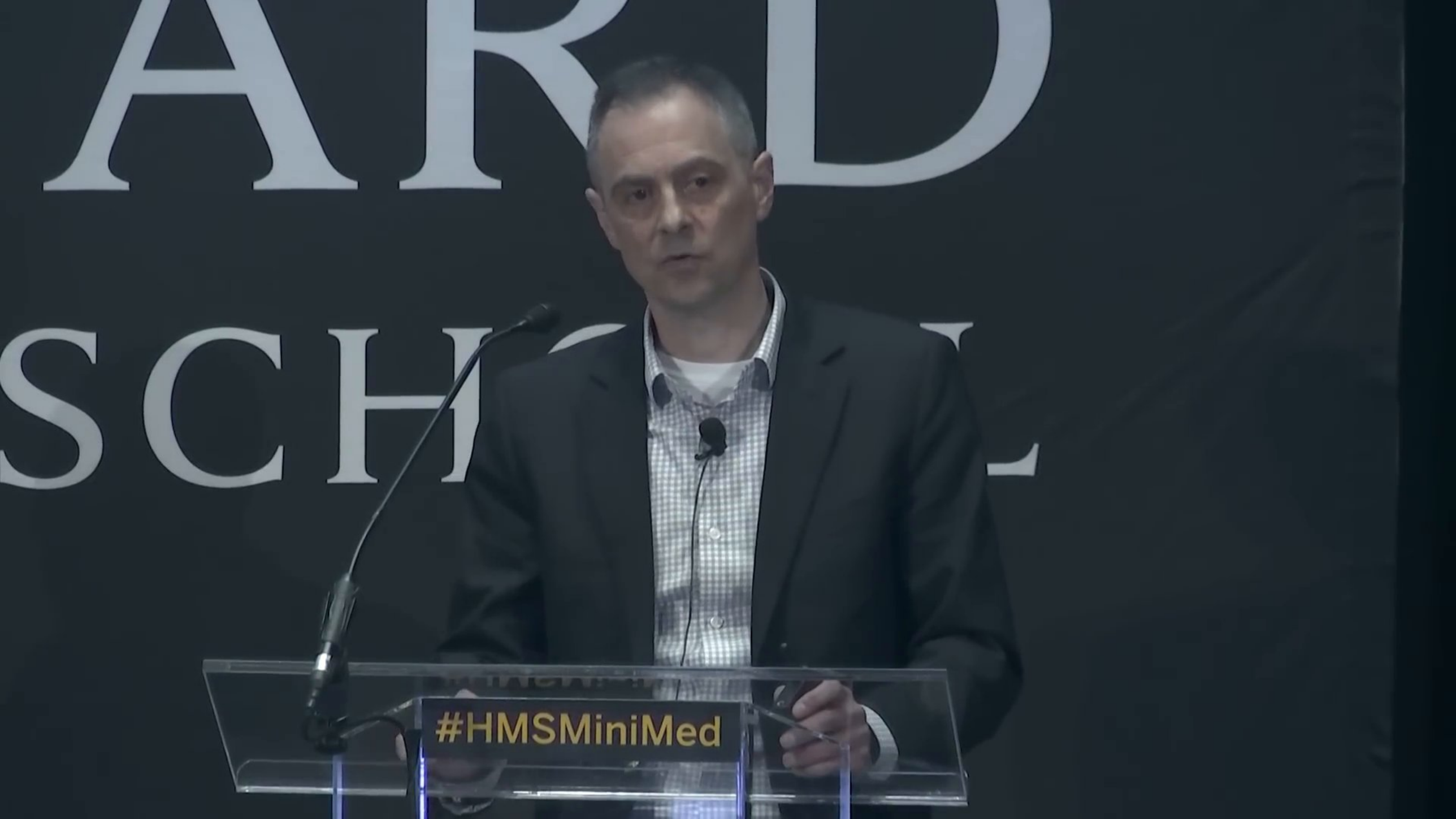
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Pancreatic cancer grow in a nutrient-poor environment

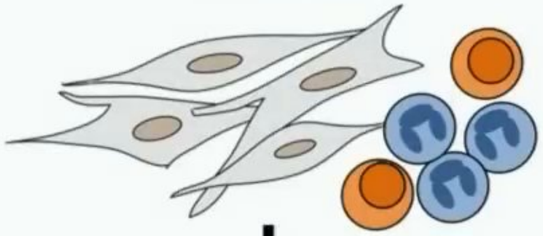
Dense network of connective tissue

COMPRESSION OF BLOOD VESSELS

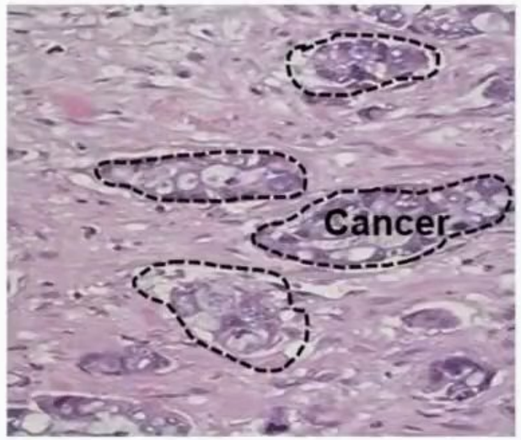
Low blood vessel number

LOW OXYGEN
LOW NUTRIENTS

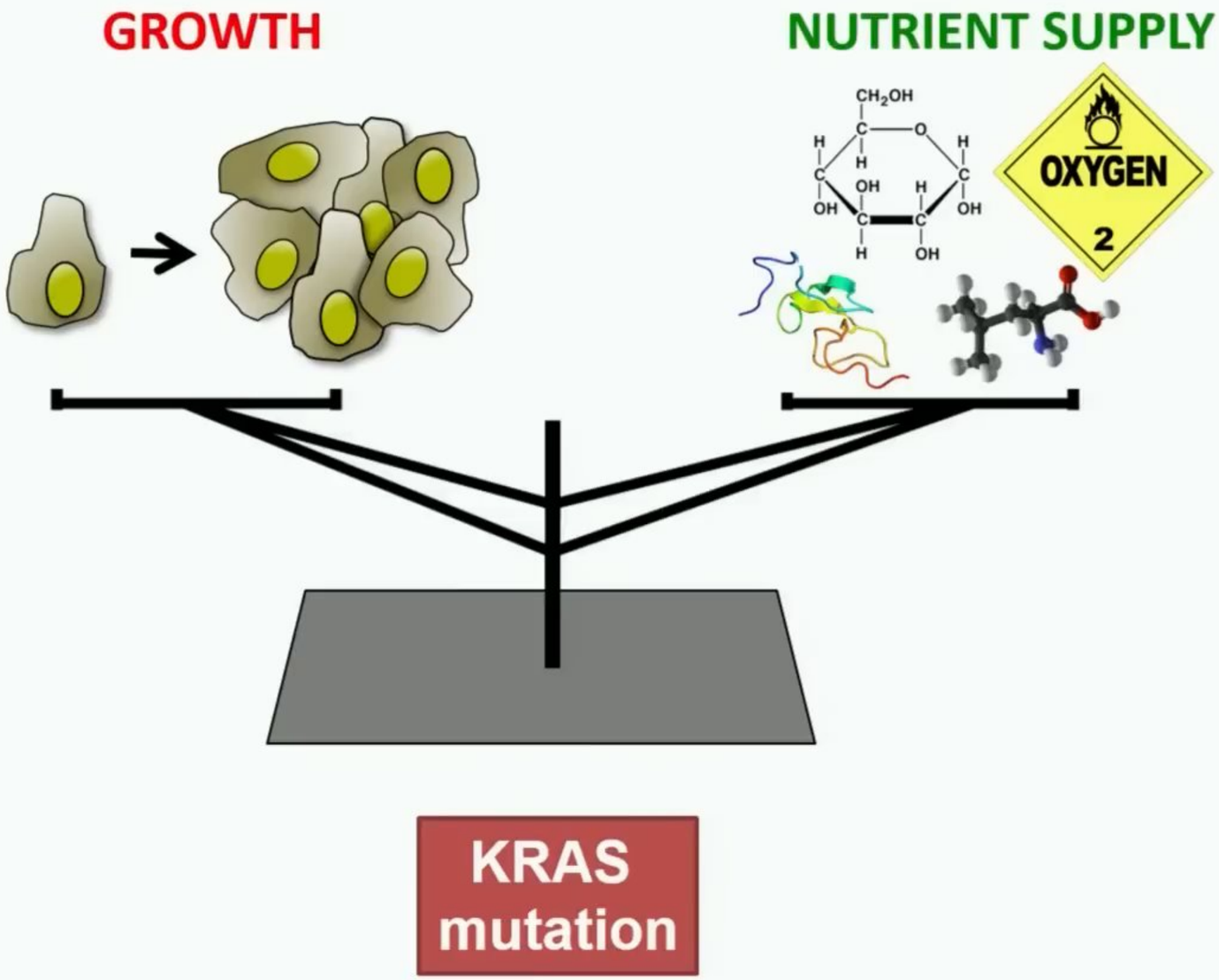
Immune & connective tissue cells



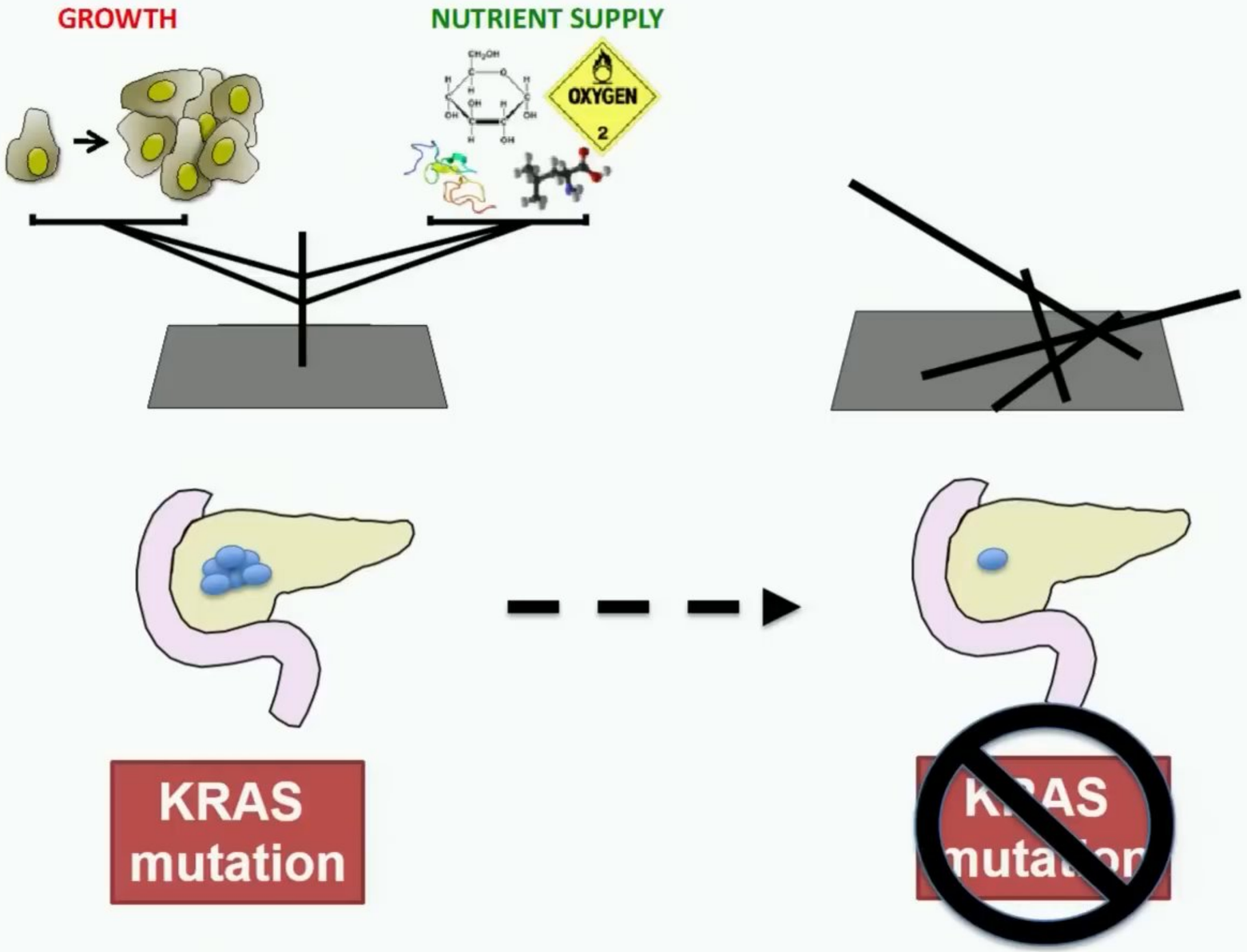
COMPETITION FOR NUTRIENTS



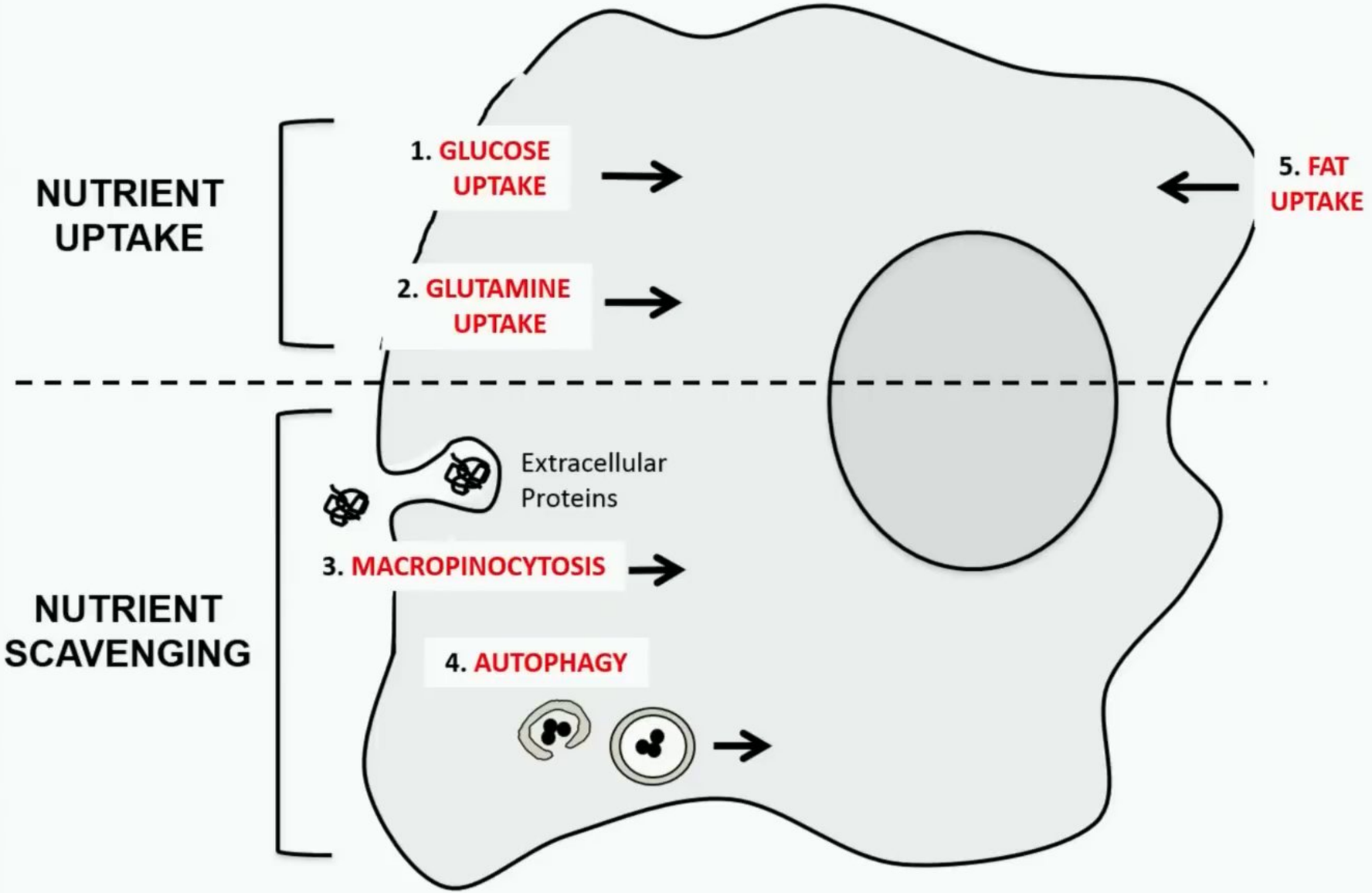
A balancing act in cancer growth



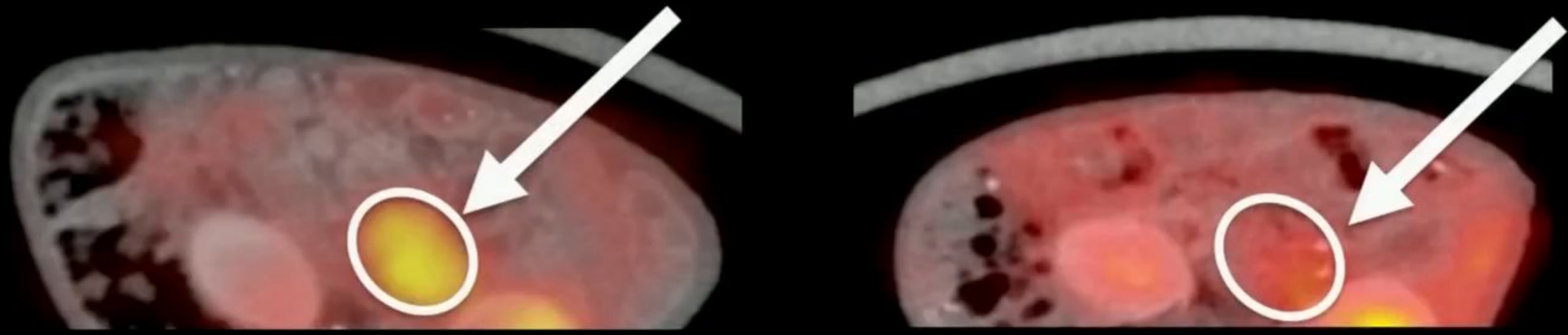
A balancing act in cancer growth



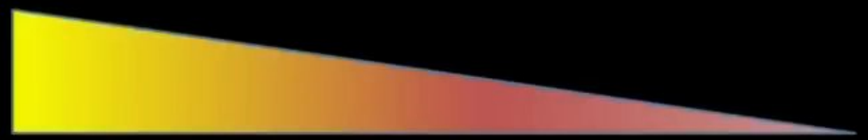
Metabolic reprogramming in pancreatic cancers



Many cancer genes increase glucose uptake

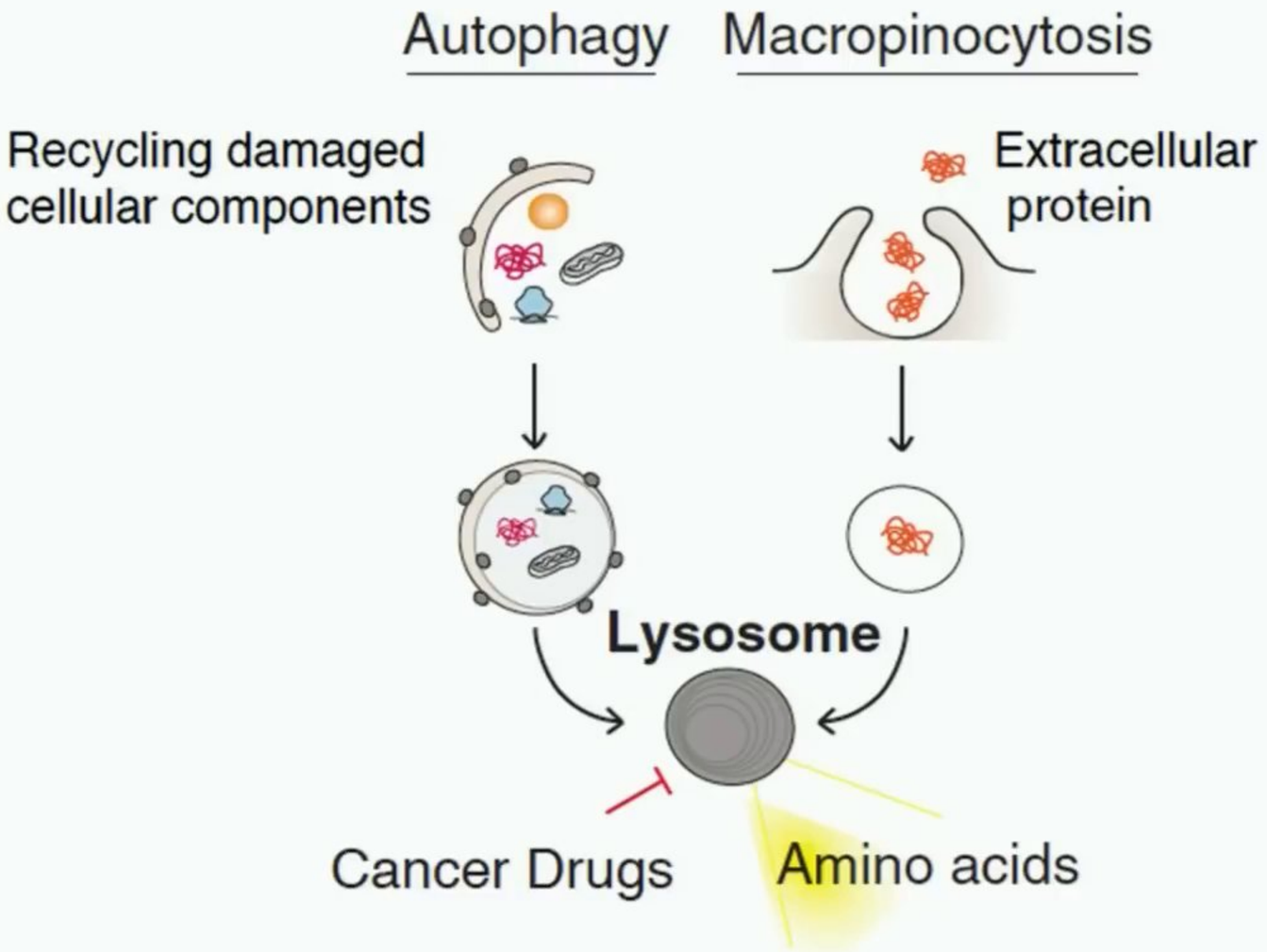


KRAS mutation



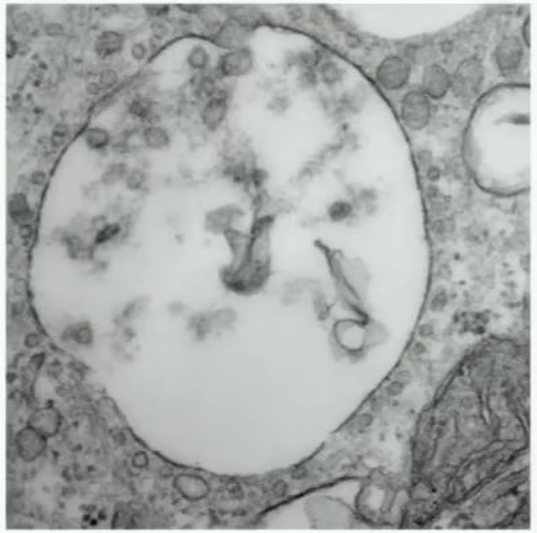
Glucose Level

Pancreatic cancers are specialized nutrient scavengers

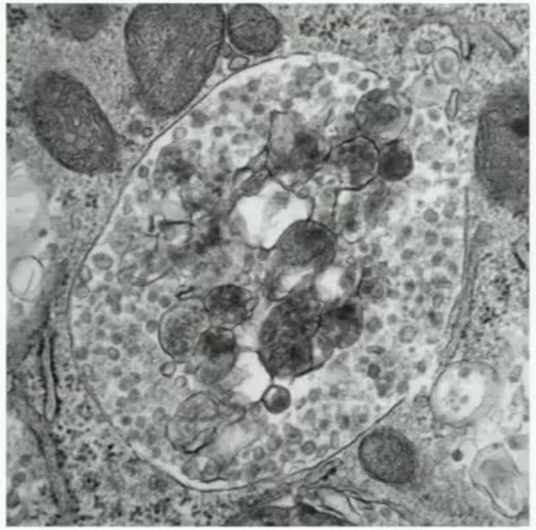


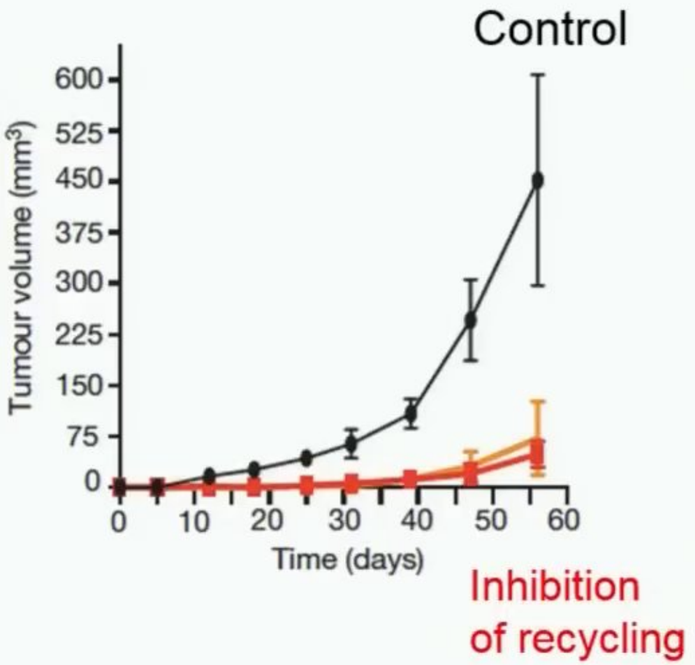
Inhibiting nutrient scavenging slows tumor growth

Control treatment



Inhibition of recycling





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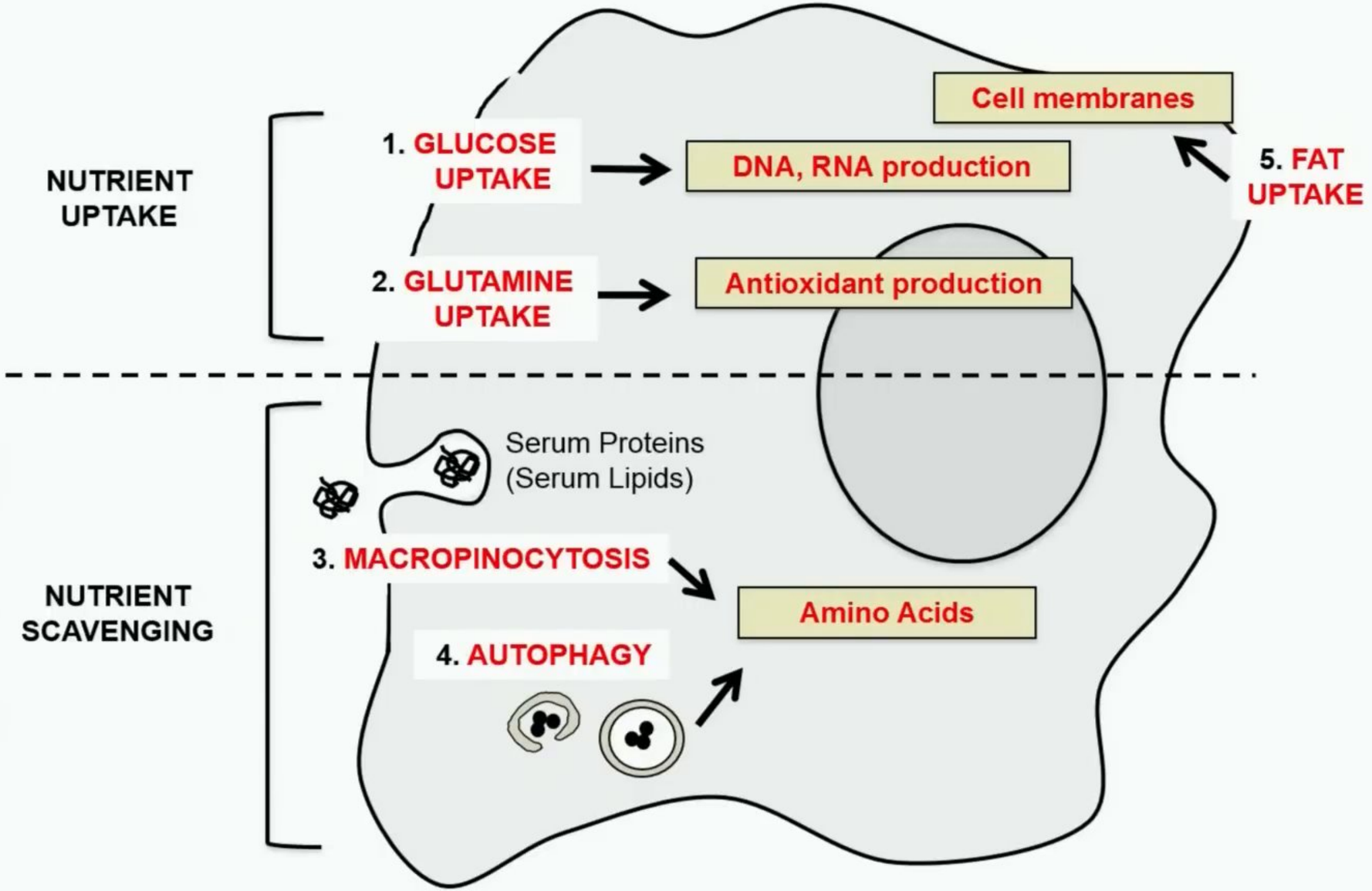
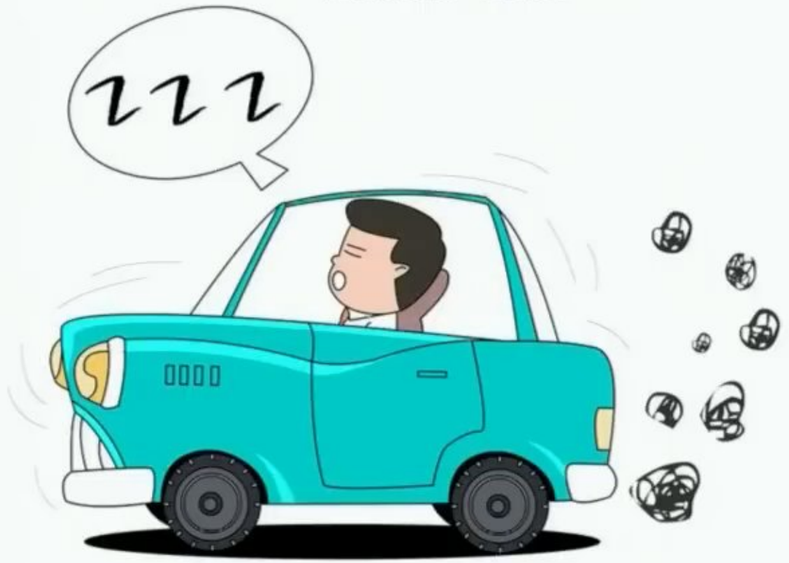


Cancers need to cope with additional stresses

Nutrients

Normal Cells

Cancer Cells



Toxic waste products and Reactive Oxygen Species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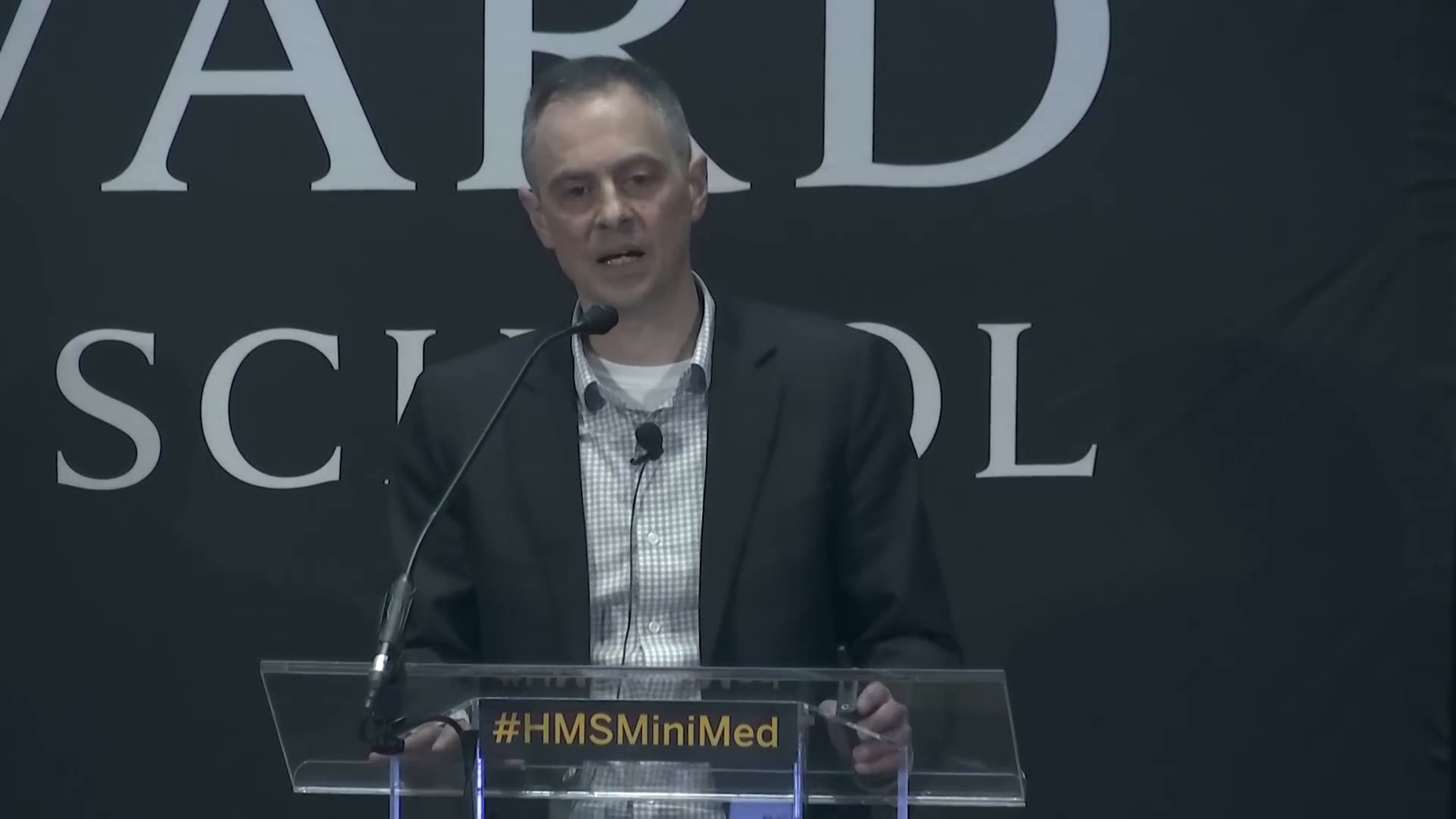
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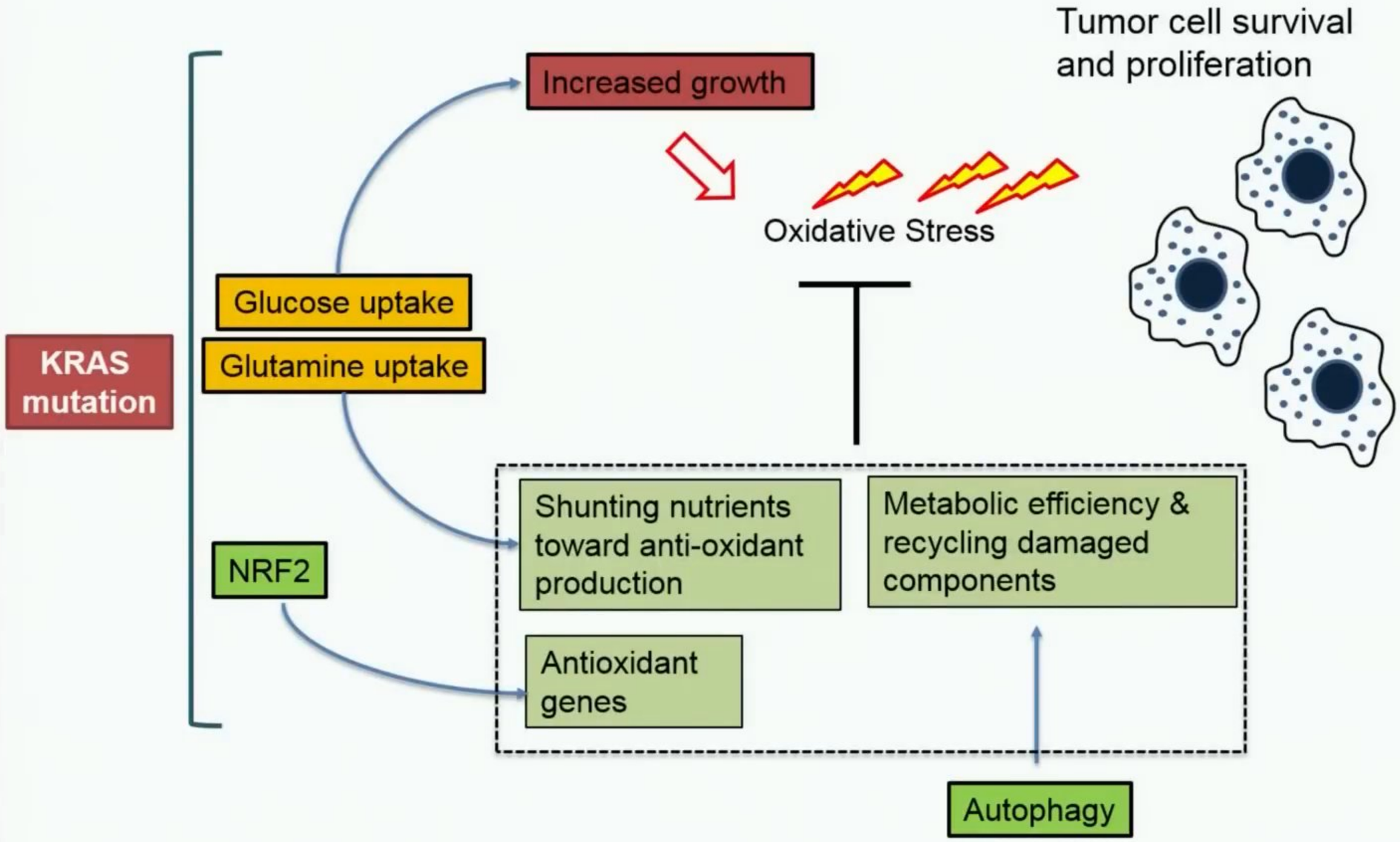
KRAS coordinates both growth and protection



Exploiting metabolic reprogramming for pancreatic cancer detection and treatment: Challenges and opportunities

- Metabolic changes for early diagnosis
- Immunometabolism: potential impact of cancer treatments on immune cells
- Effect of diet and whole-body metabolism on tumor growth and response to therapy
- Cross-talk between cancer cells and other cell types within the tumor
- Metabolic plasticity as a challenge for therapy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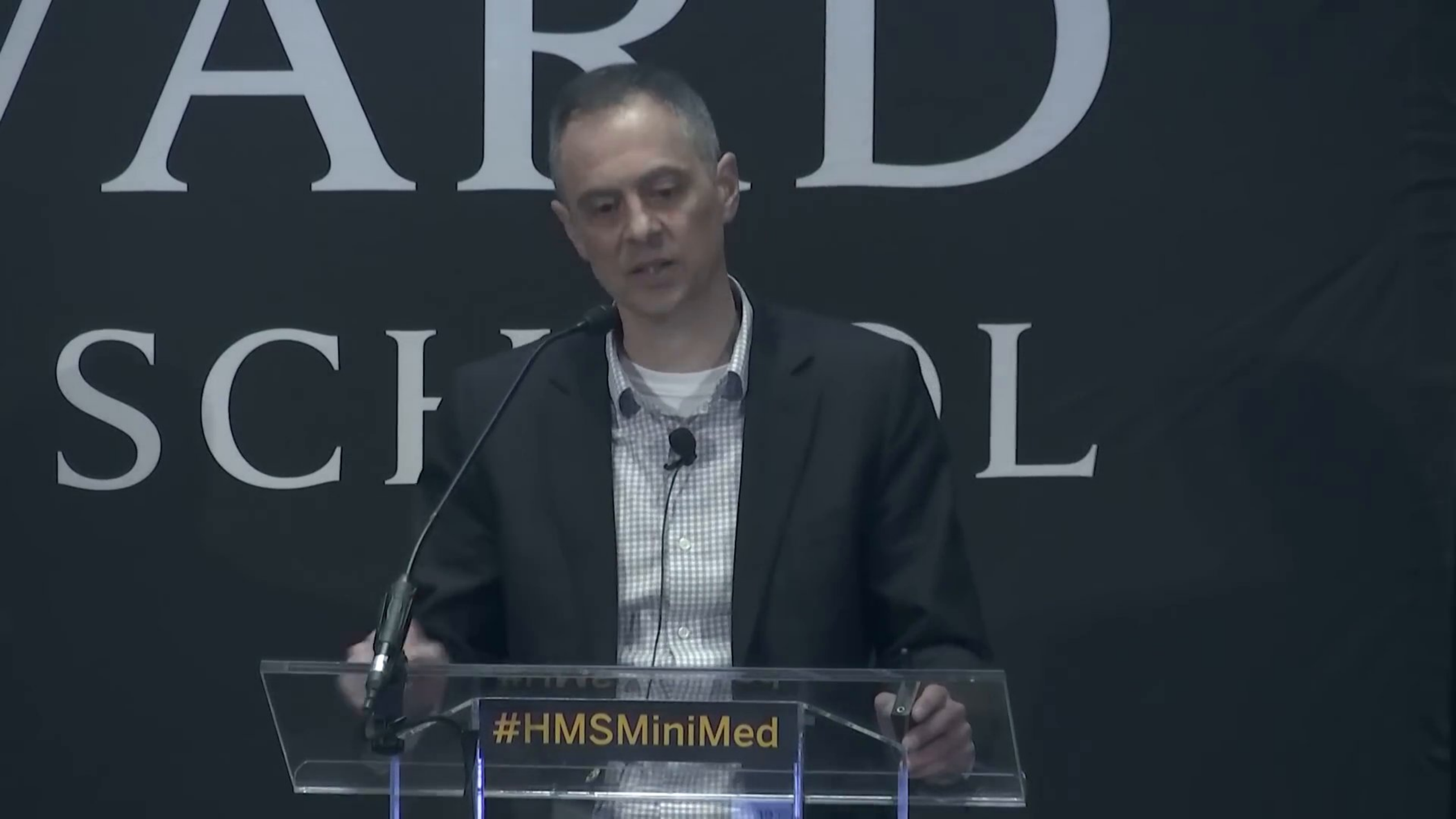
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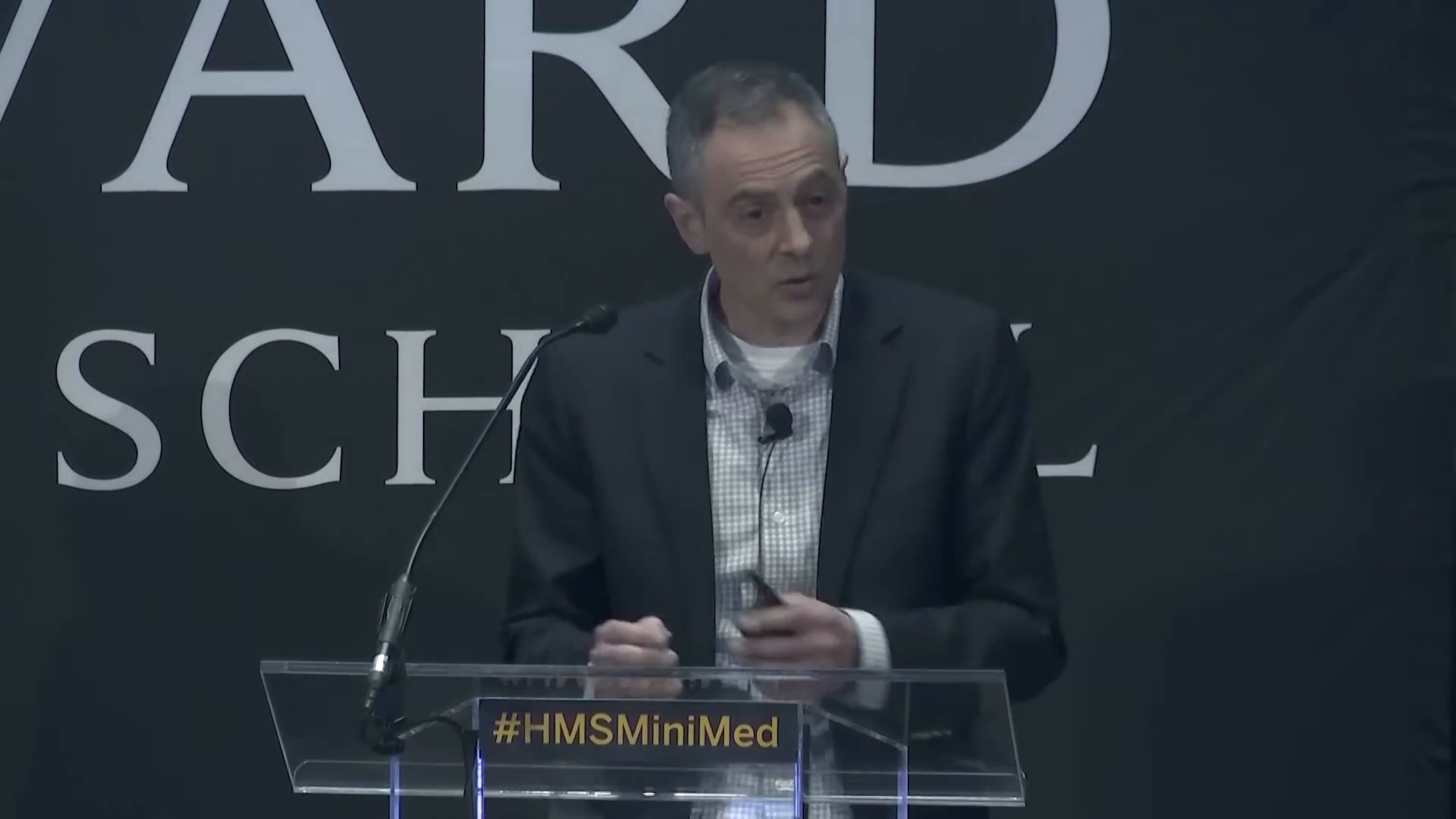
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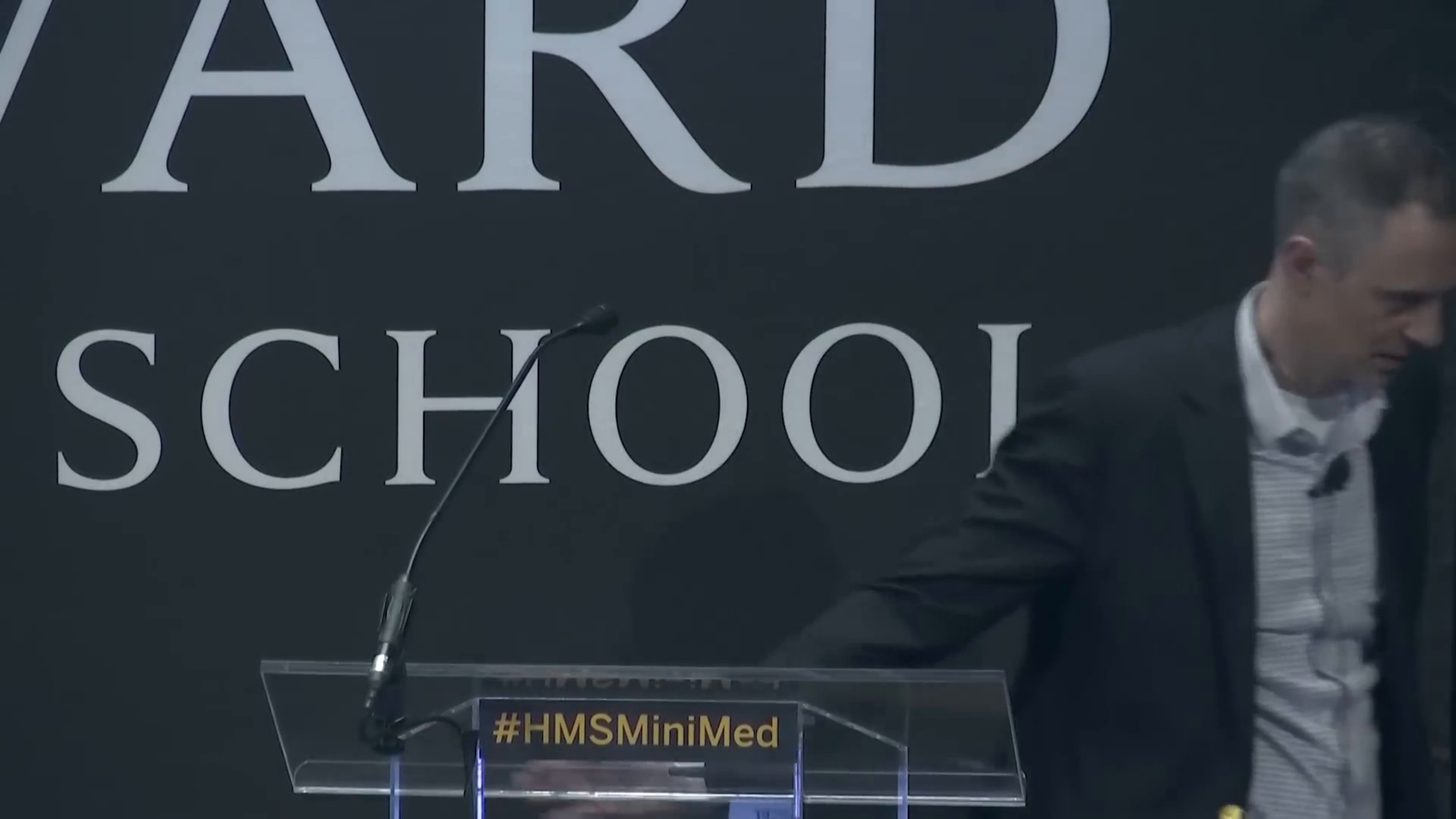
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Cancer Metabolism:
From molecules to medicine
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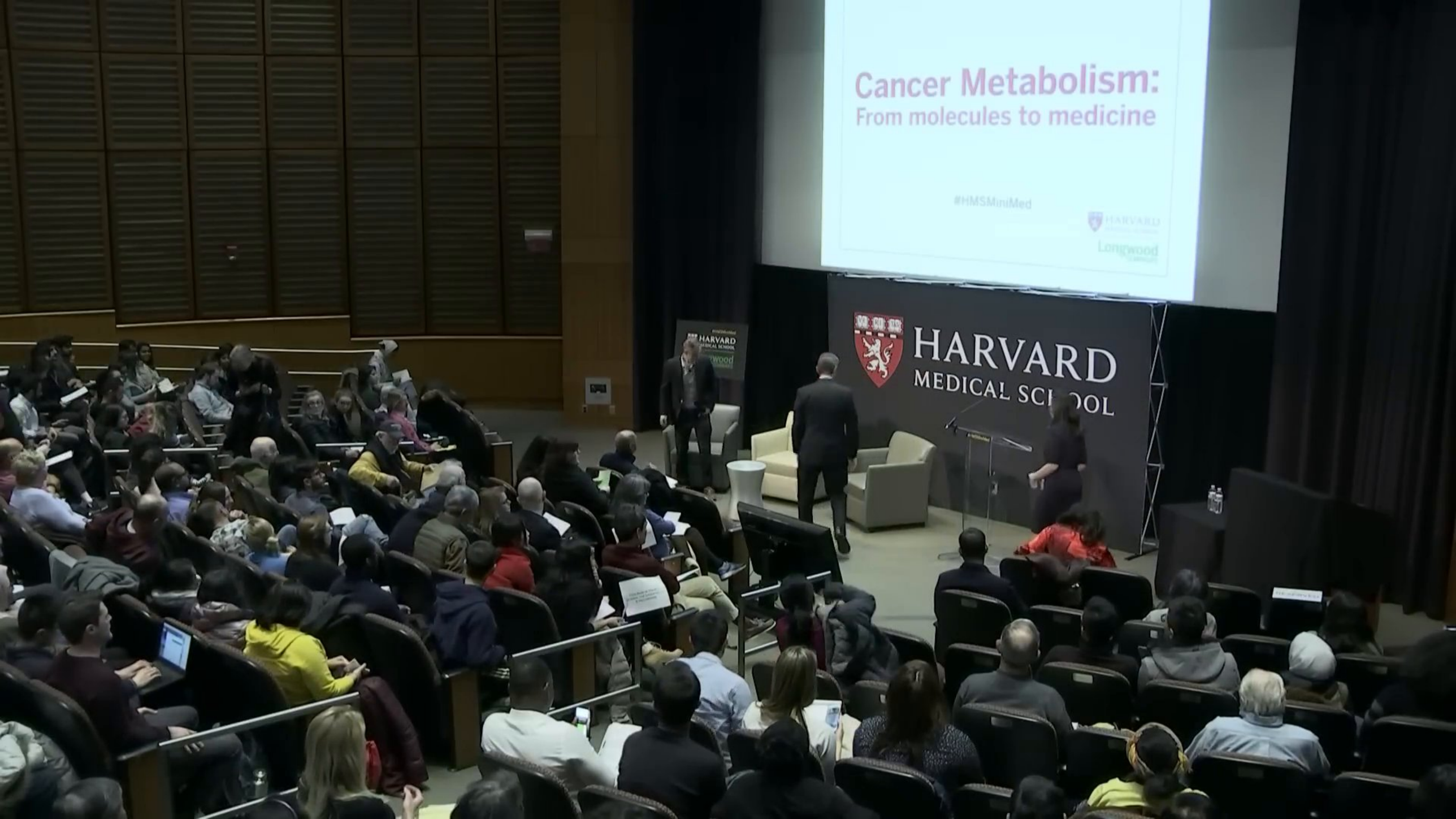
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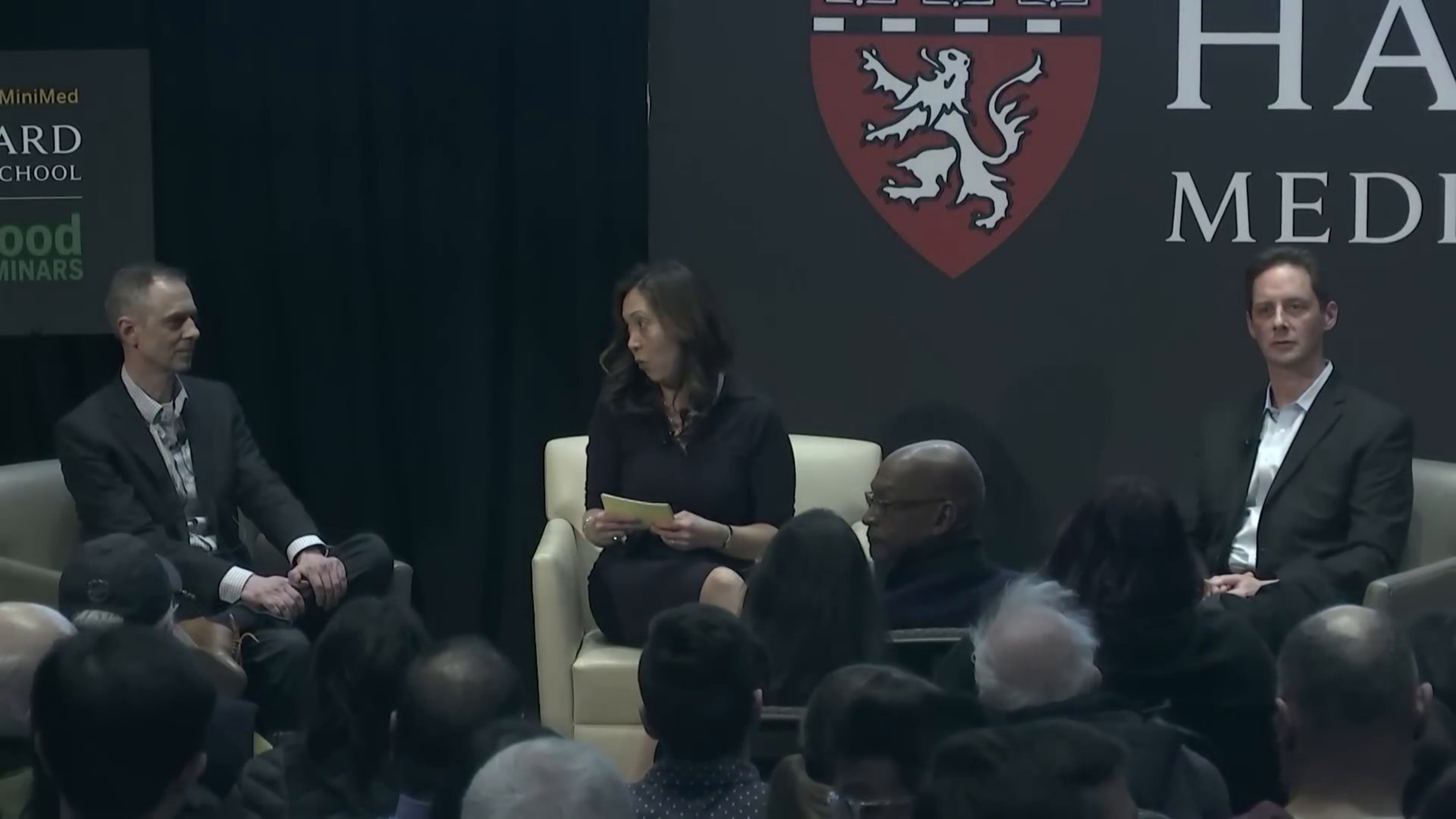
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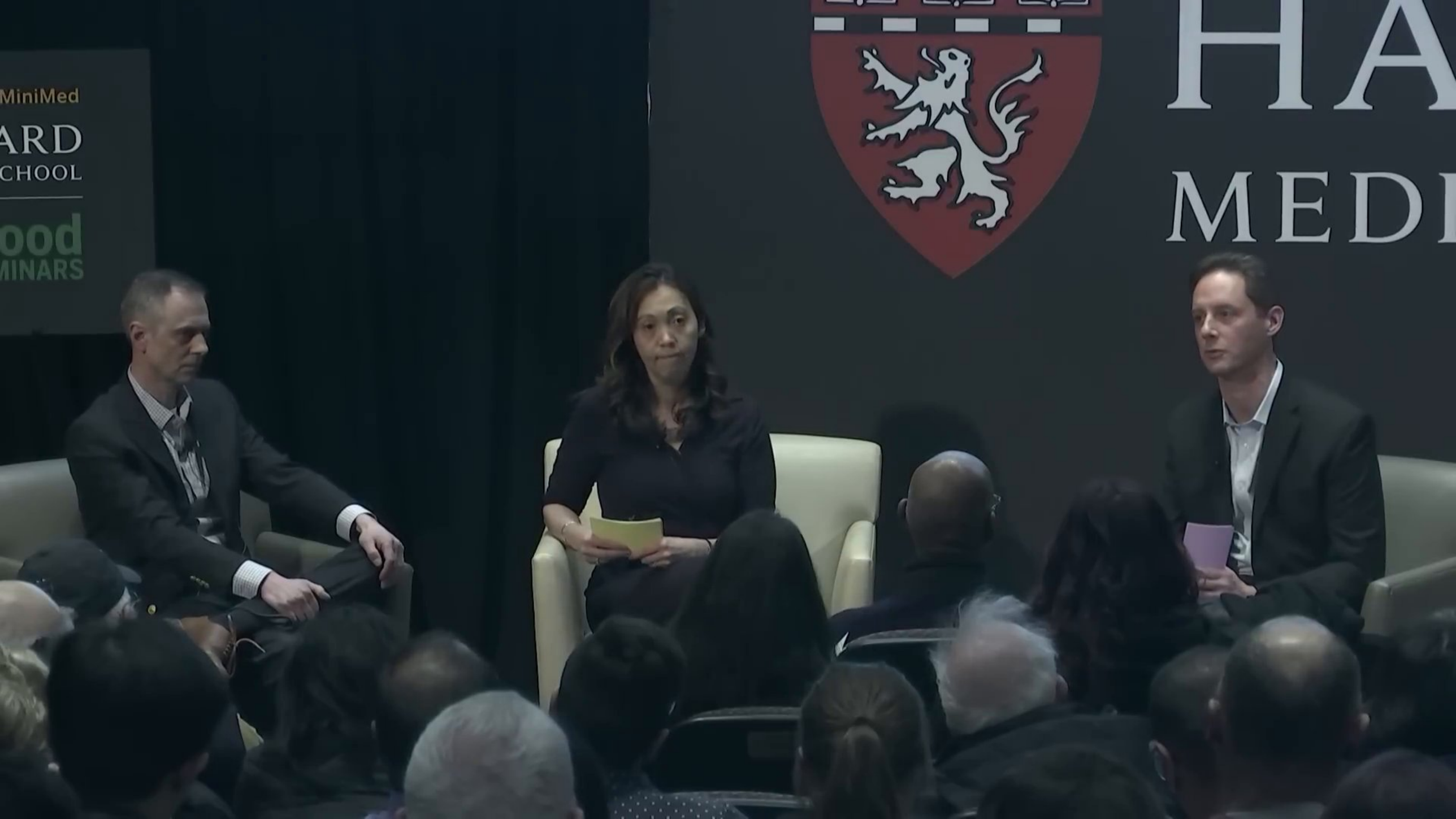
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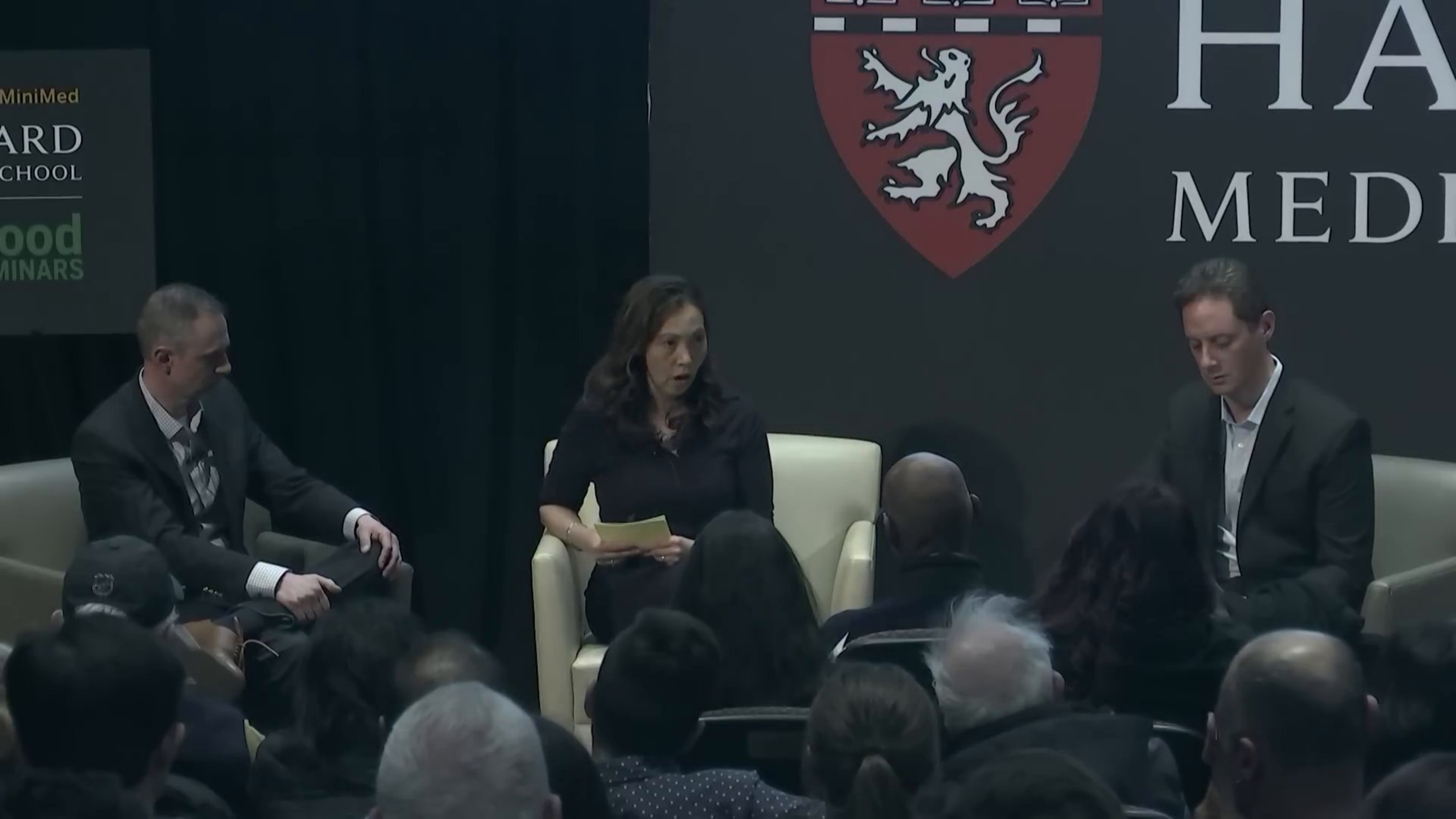
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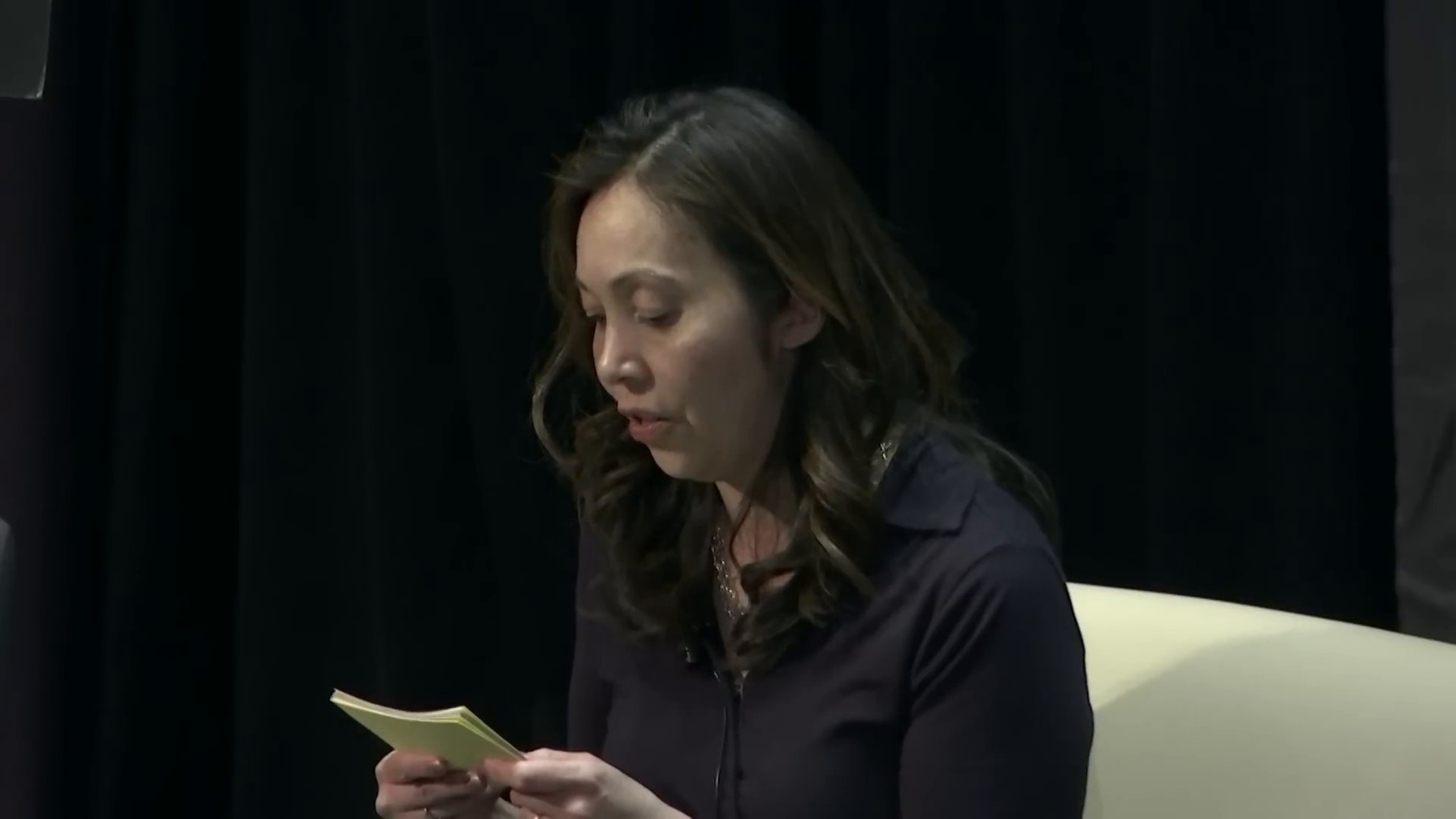

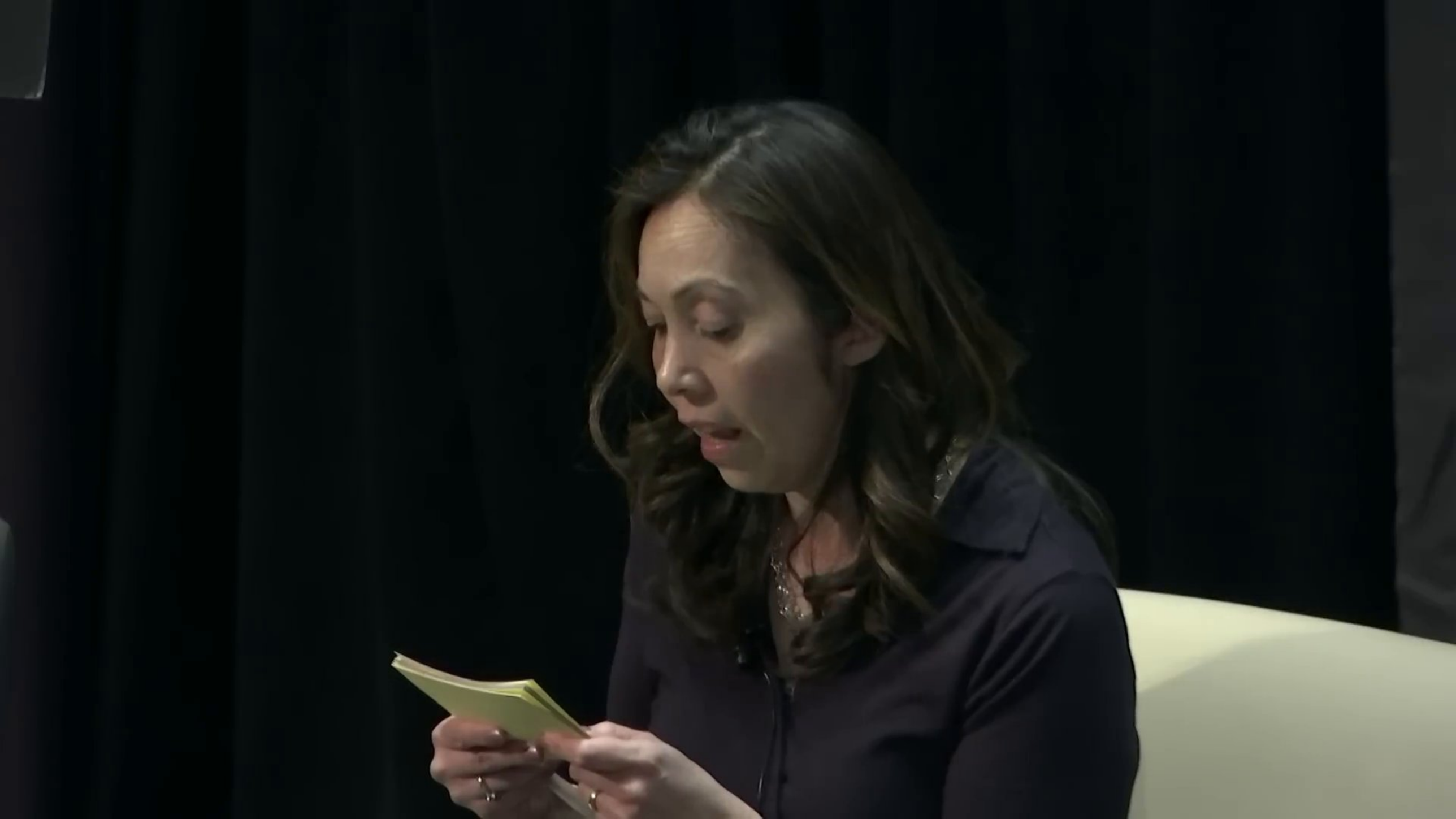


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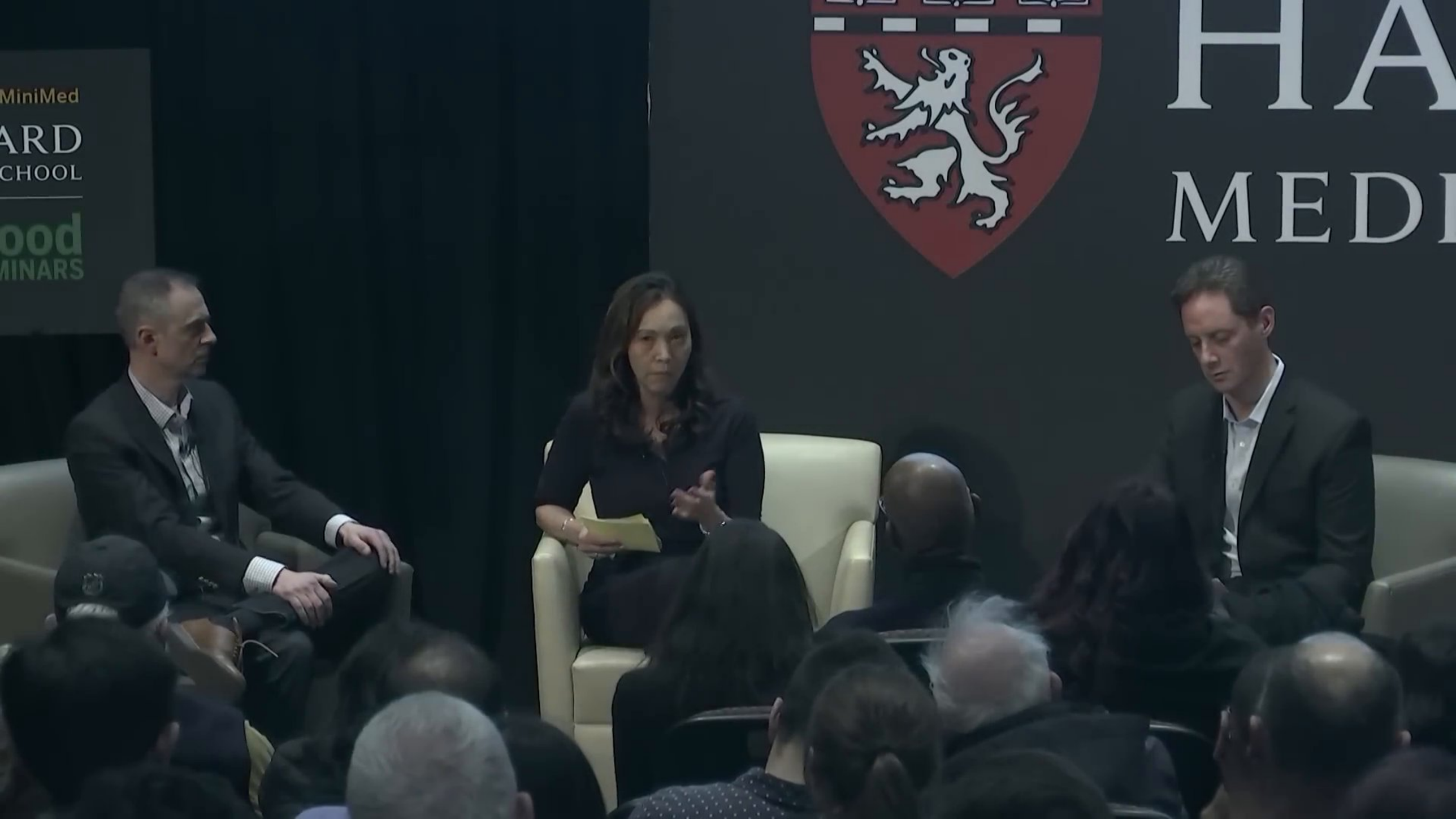
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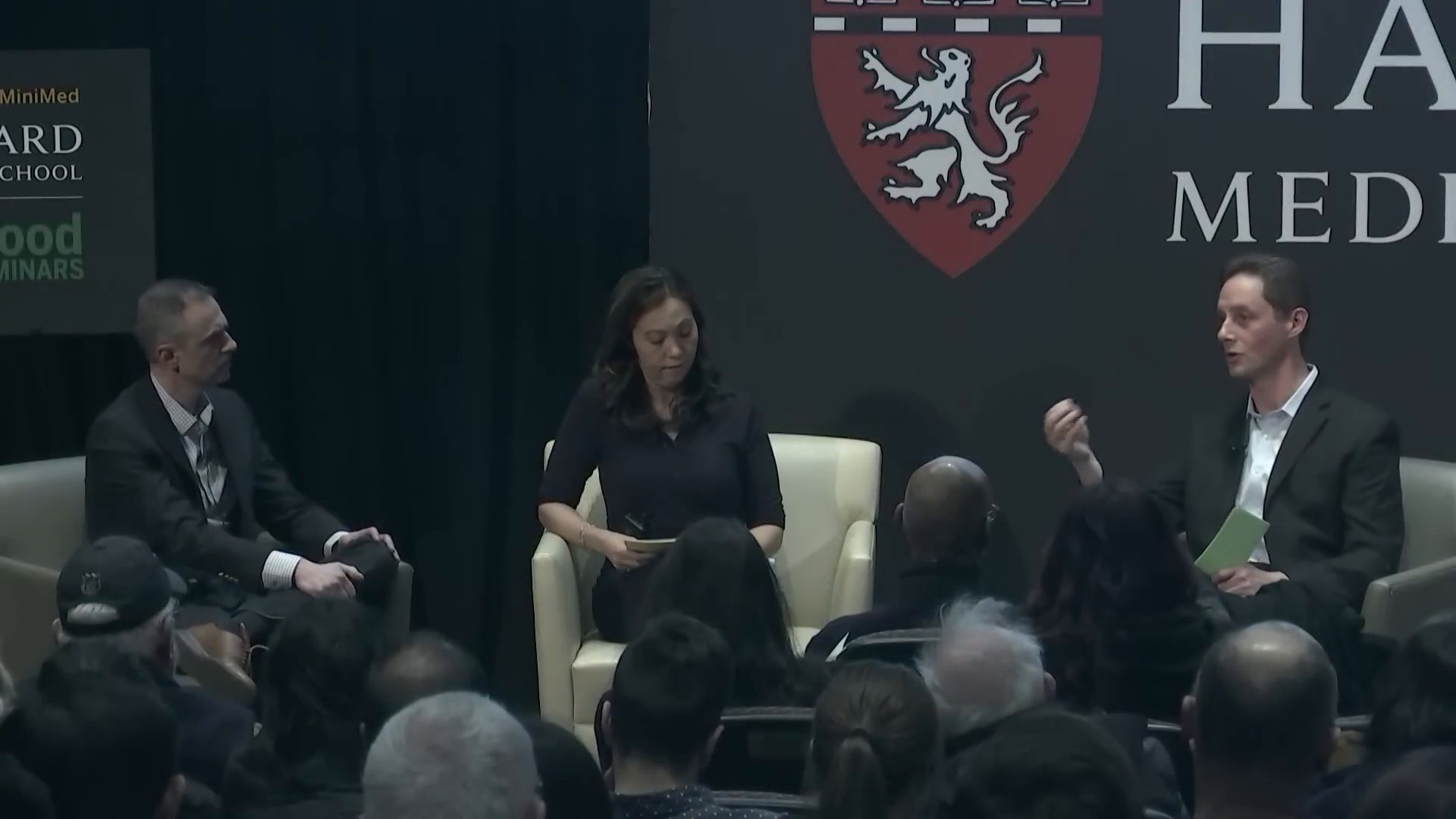
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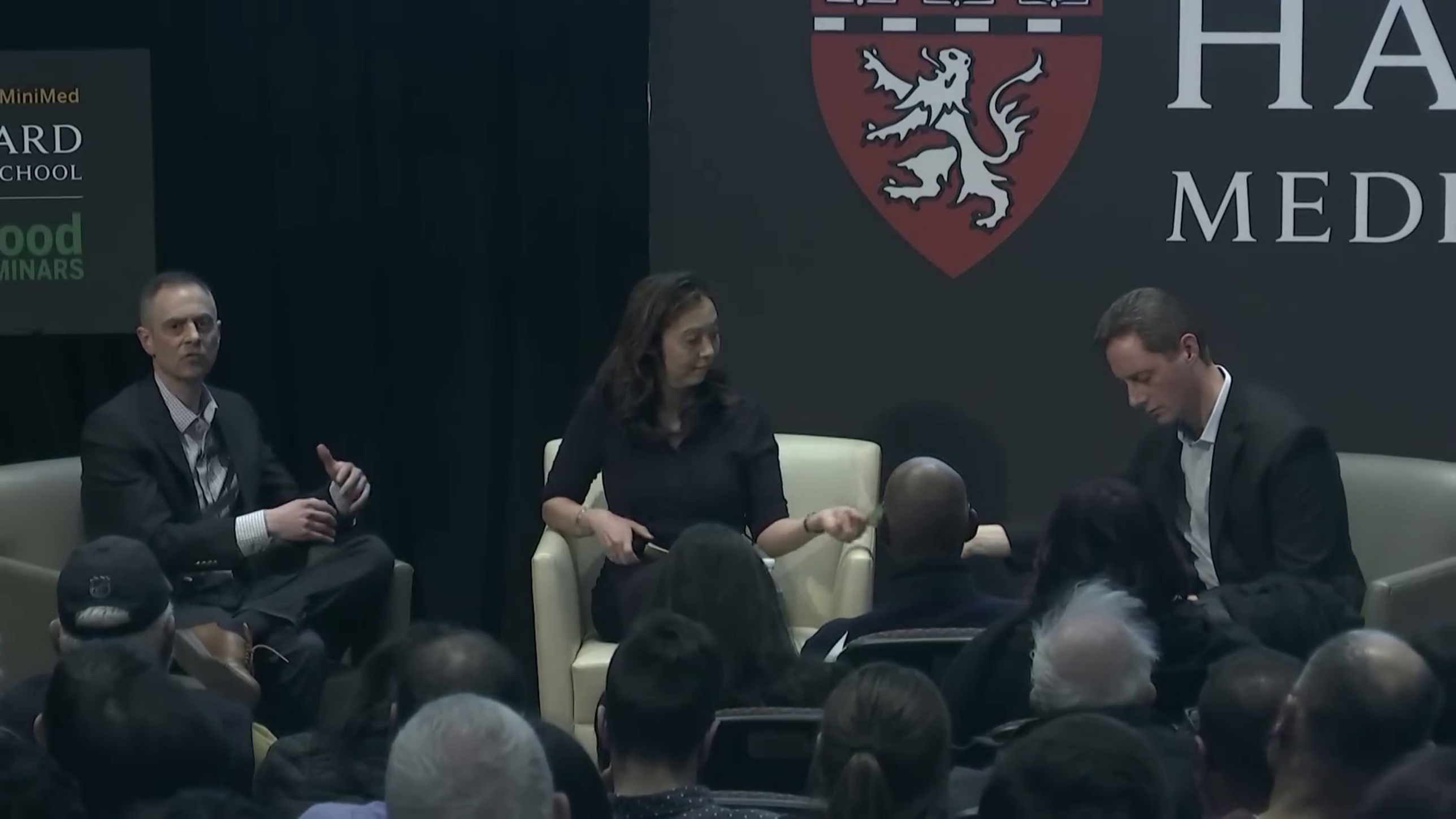
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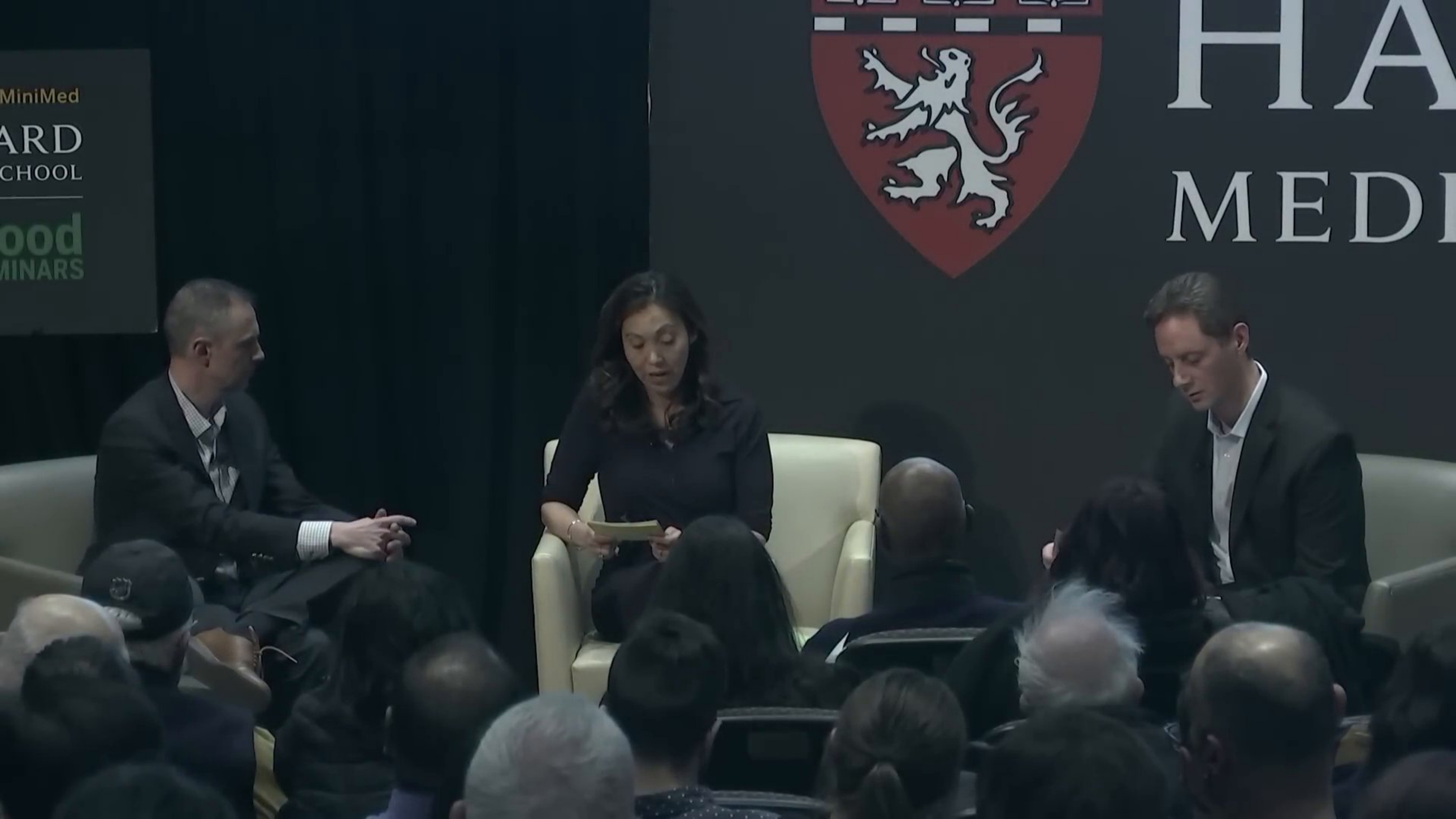
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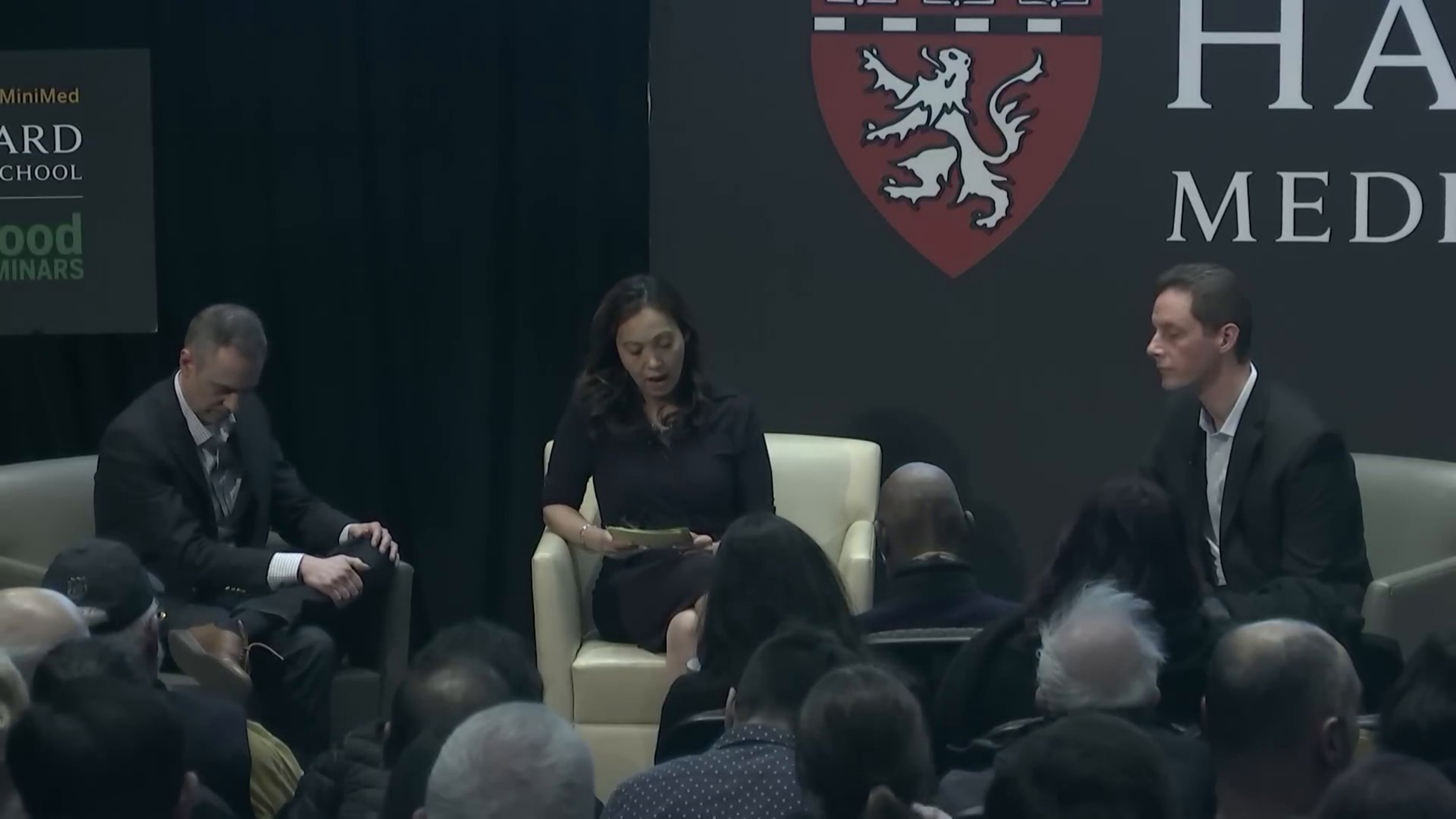
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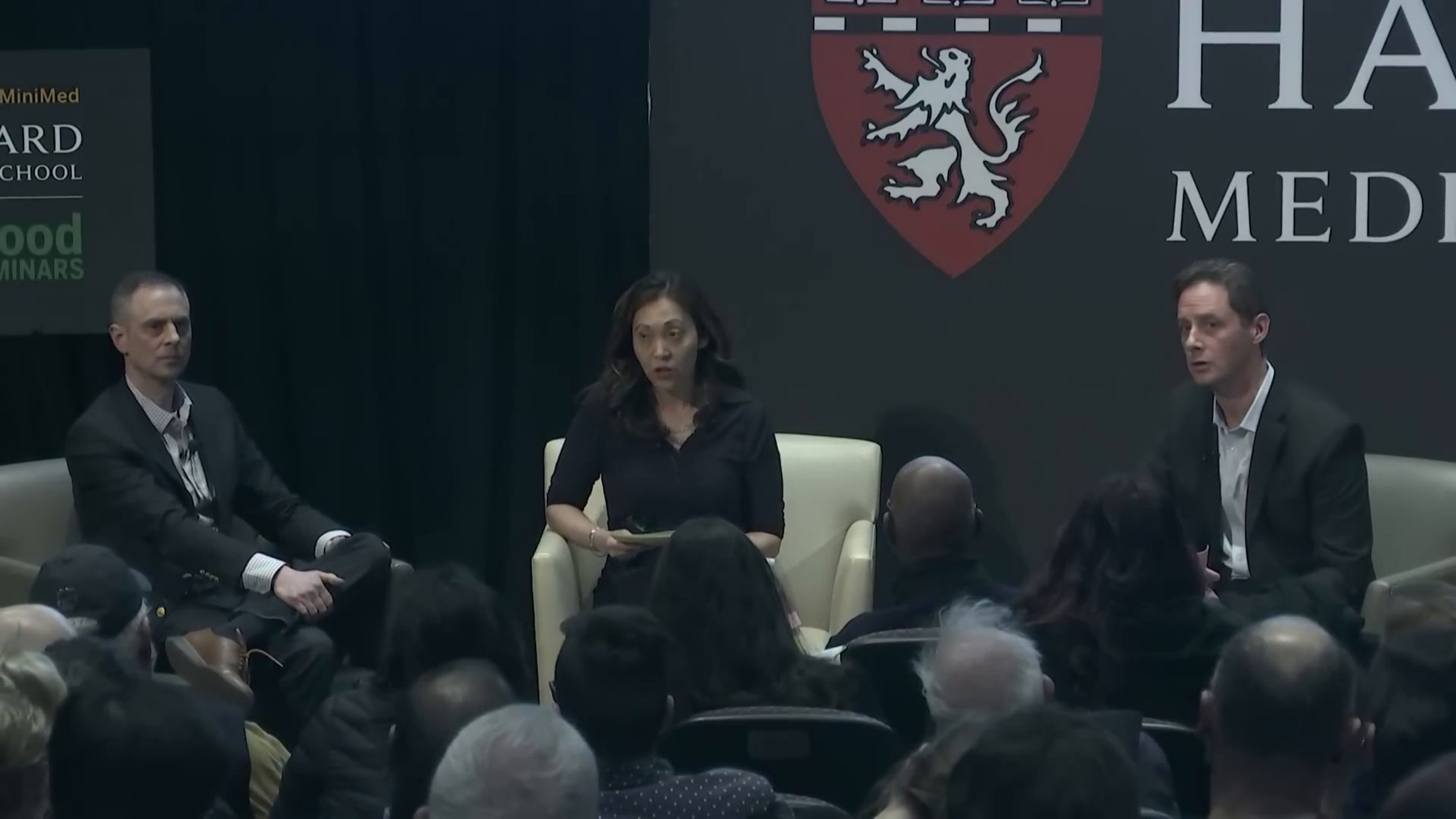
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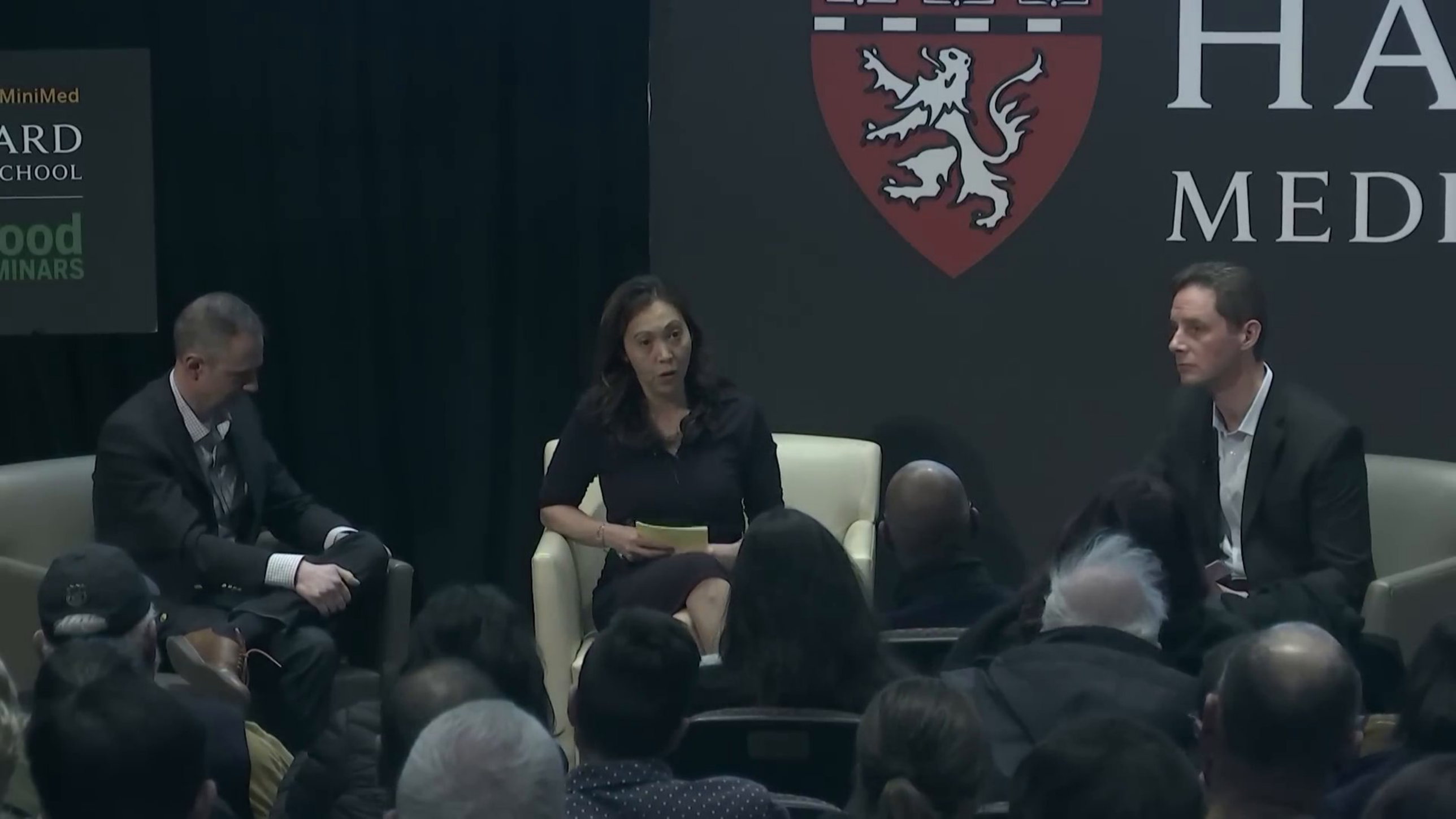
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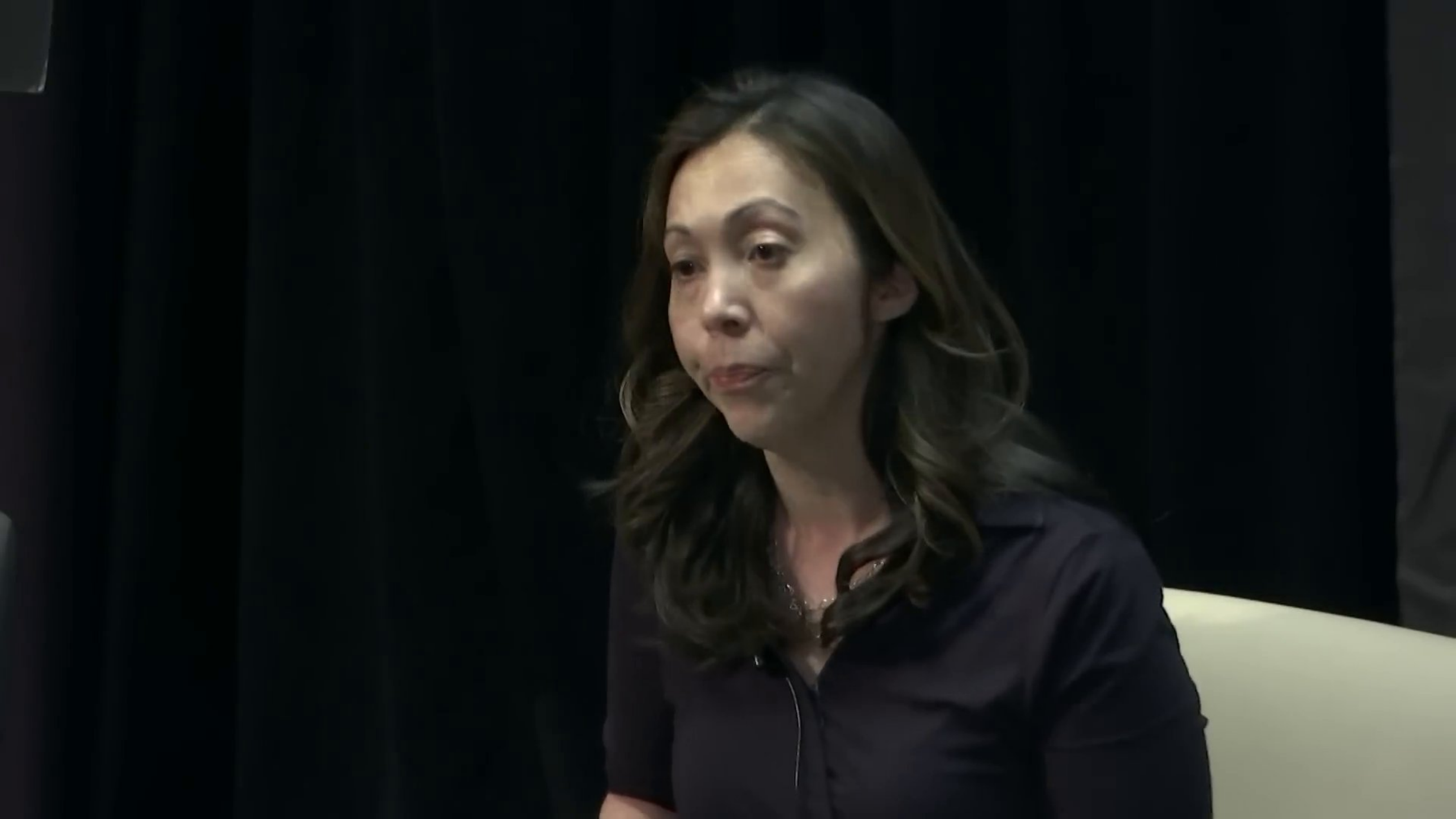

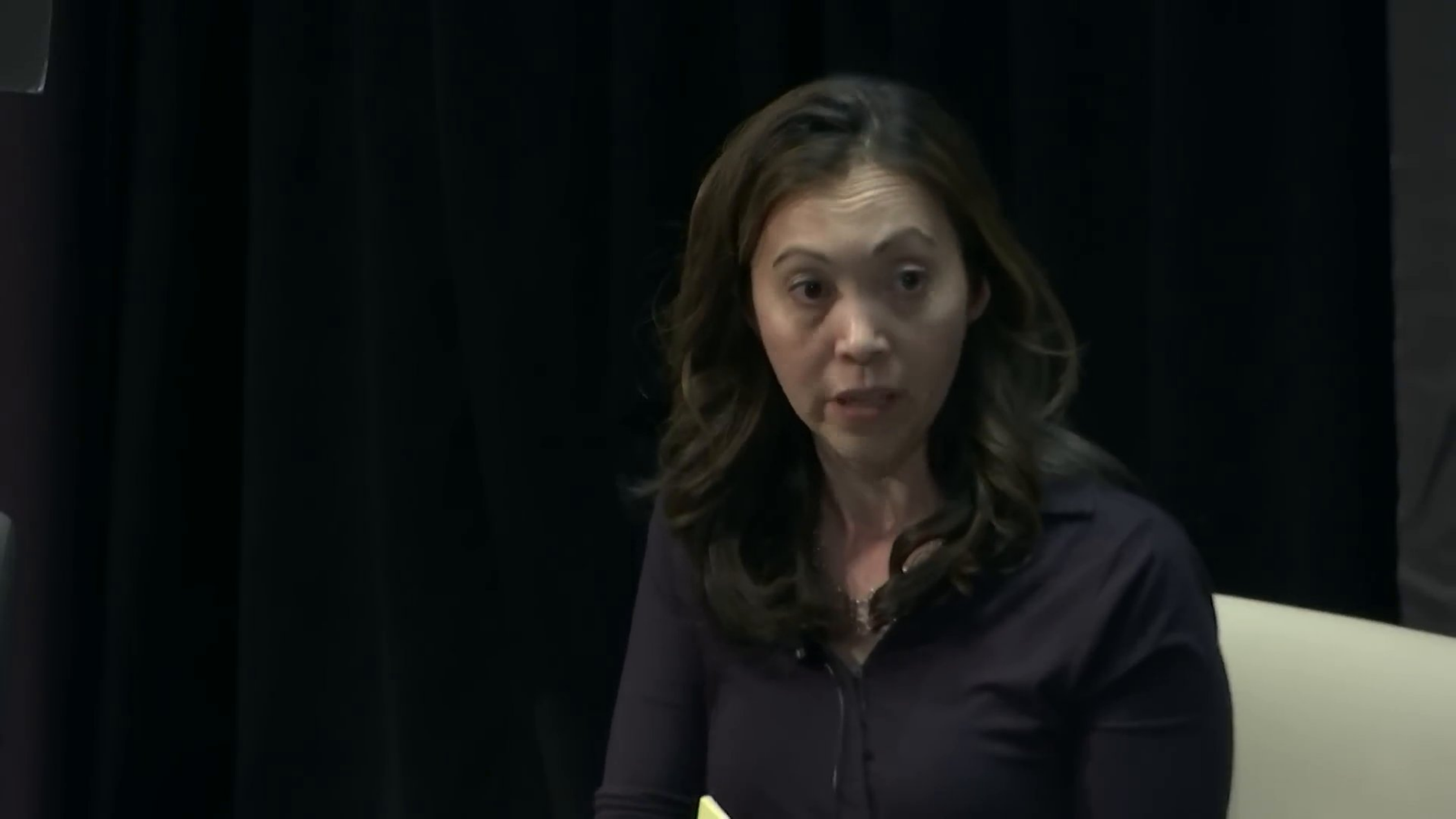

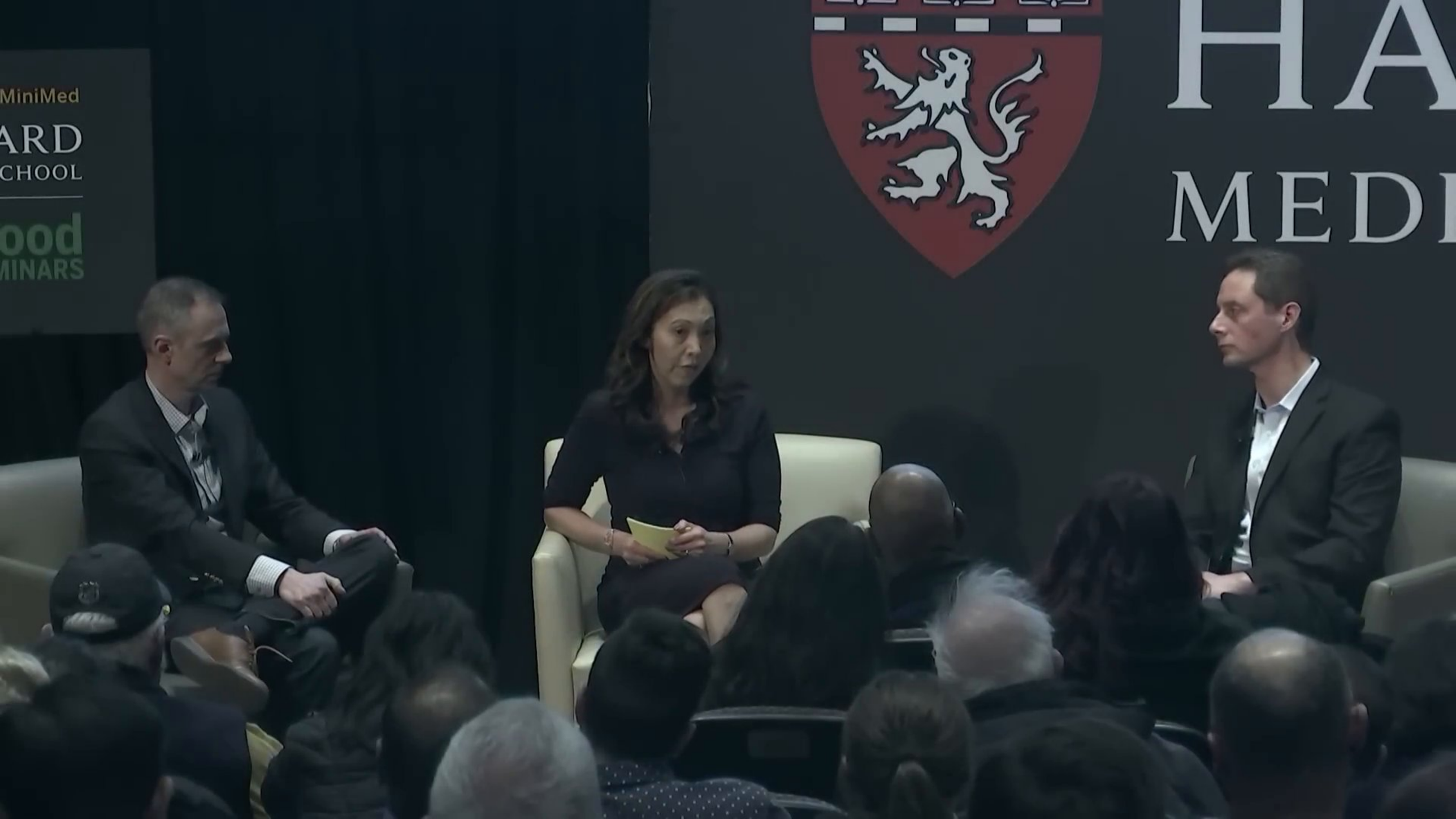
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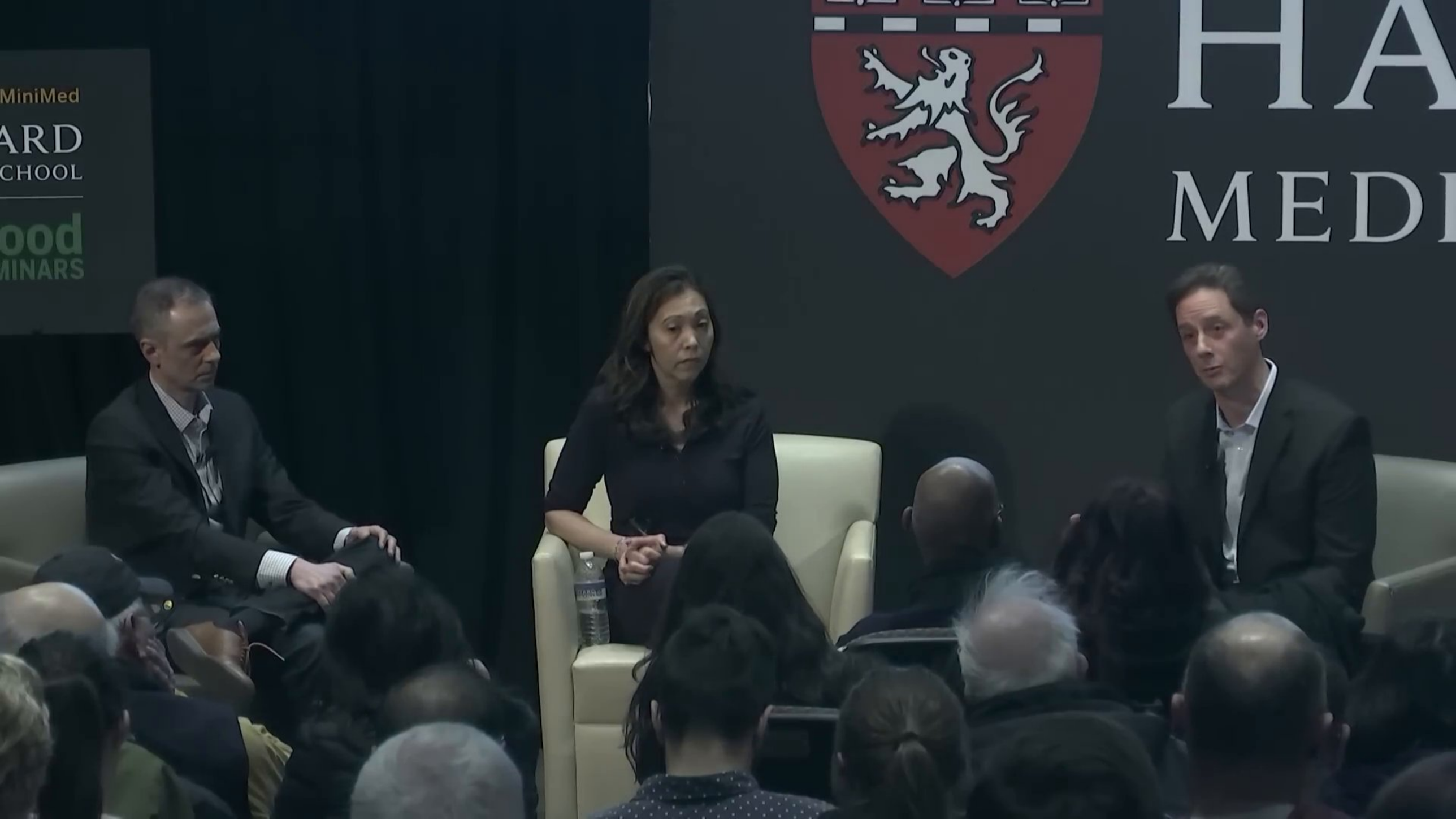
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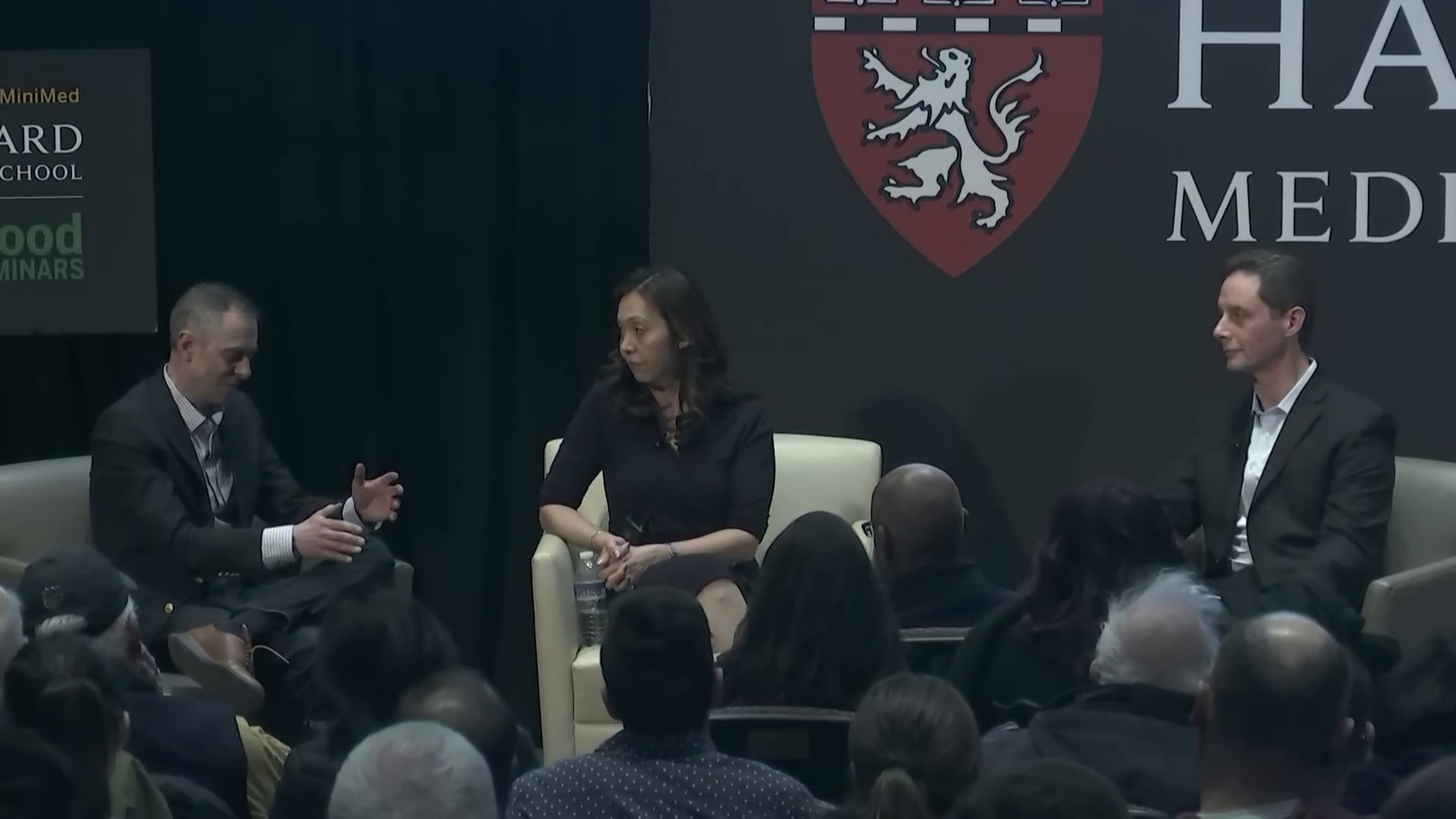
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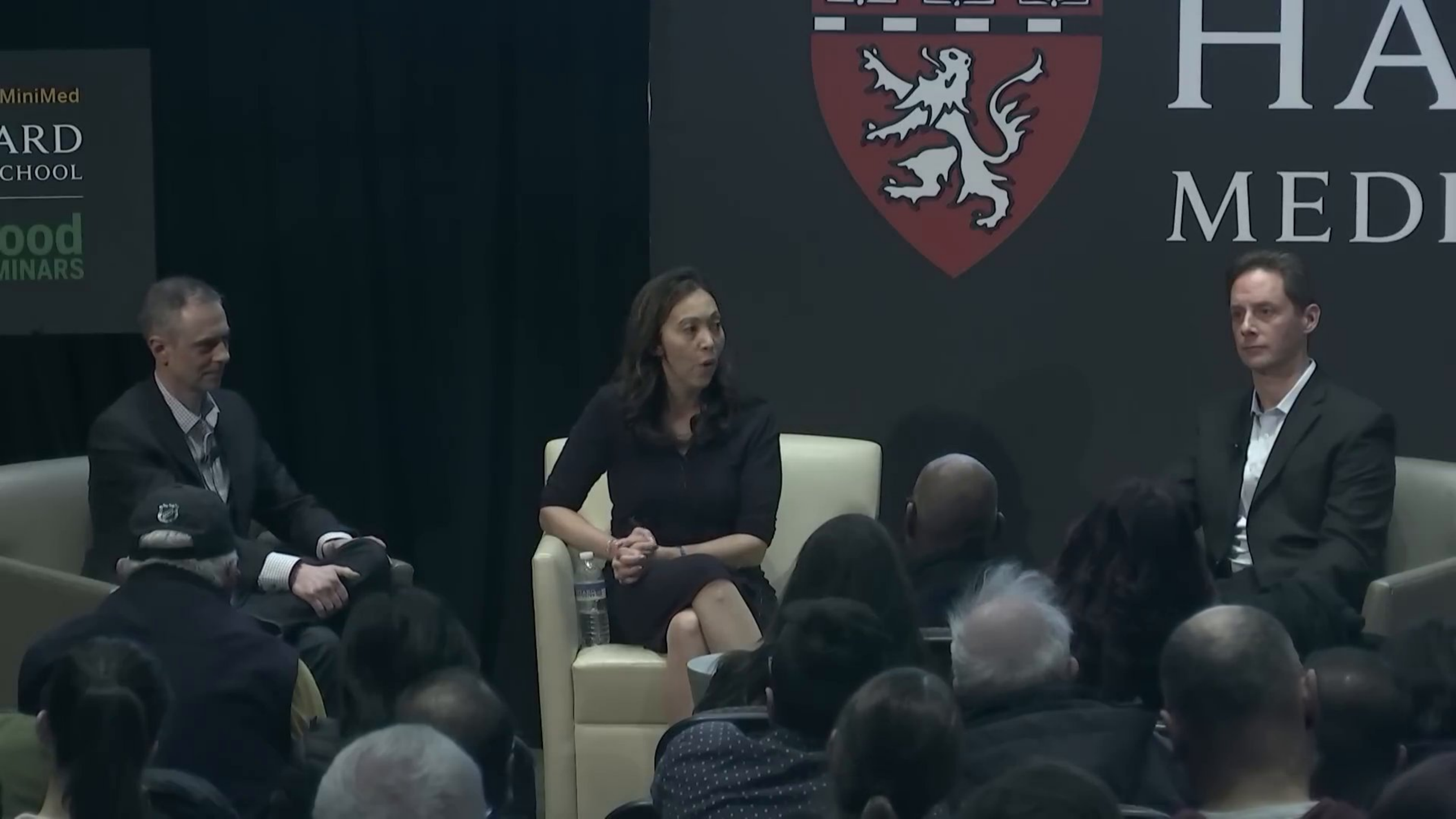
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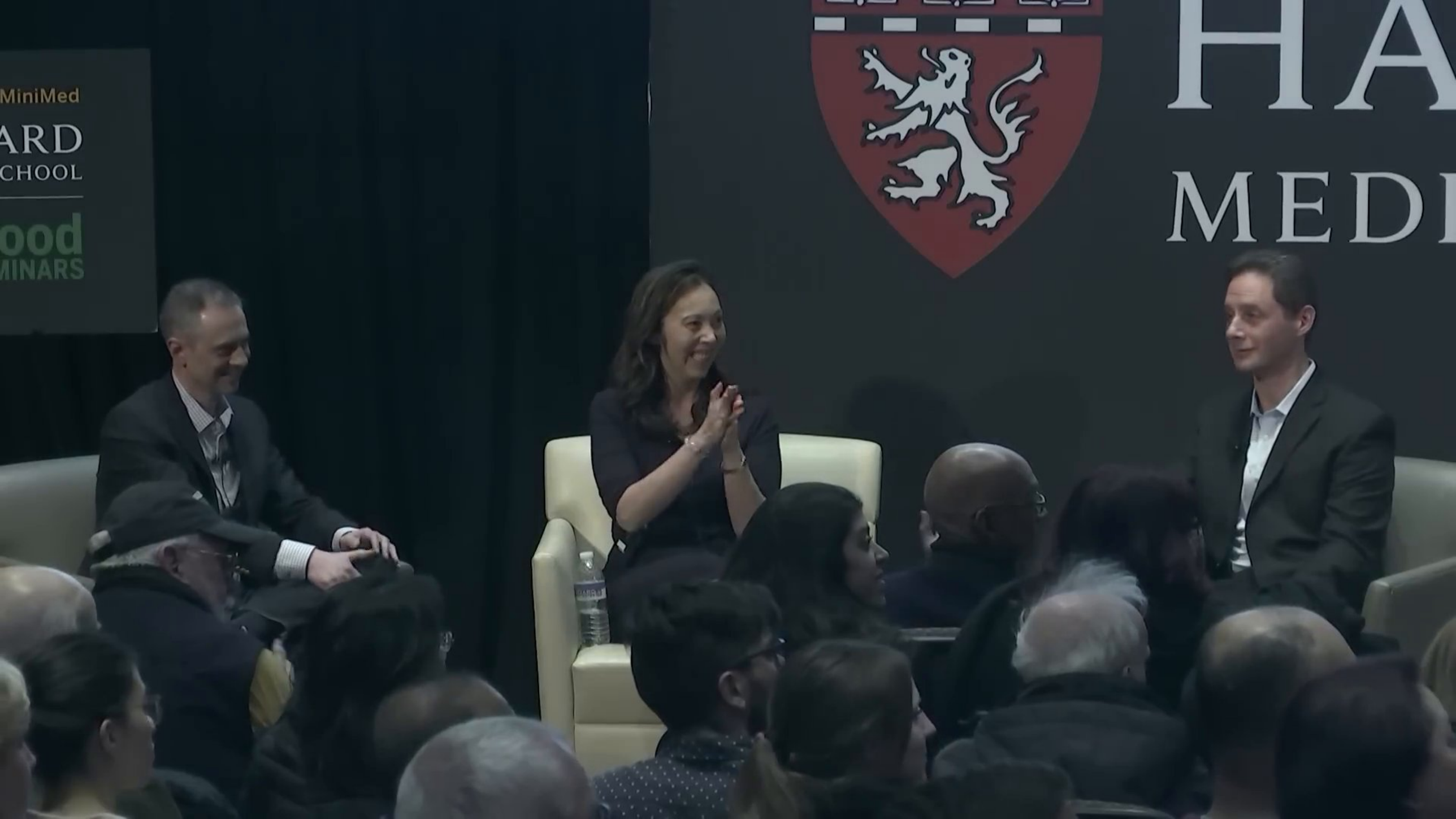
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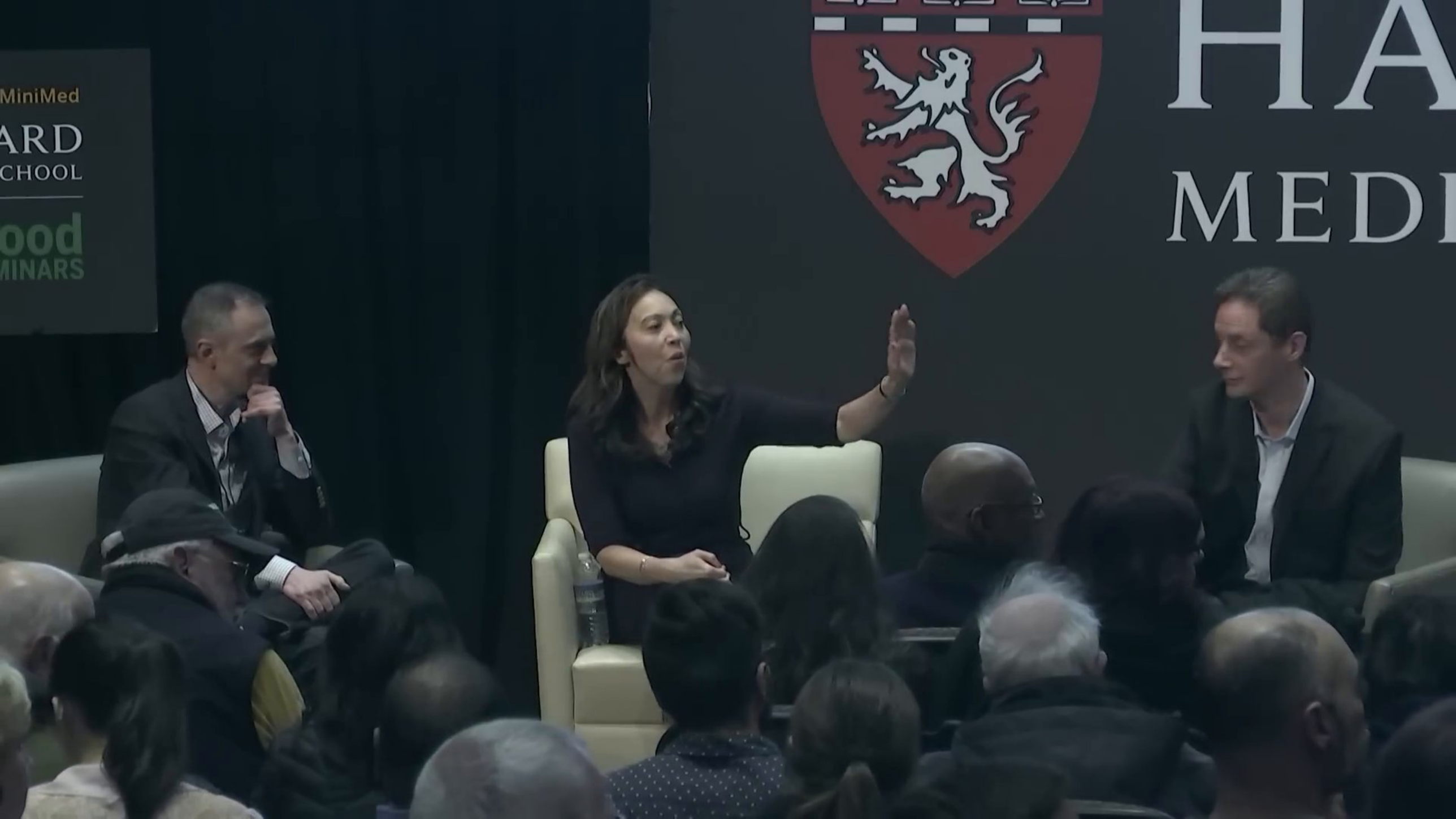
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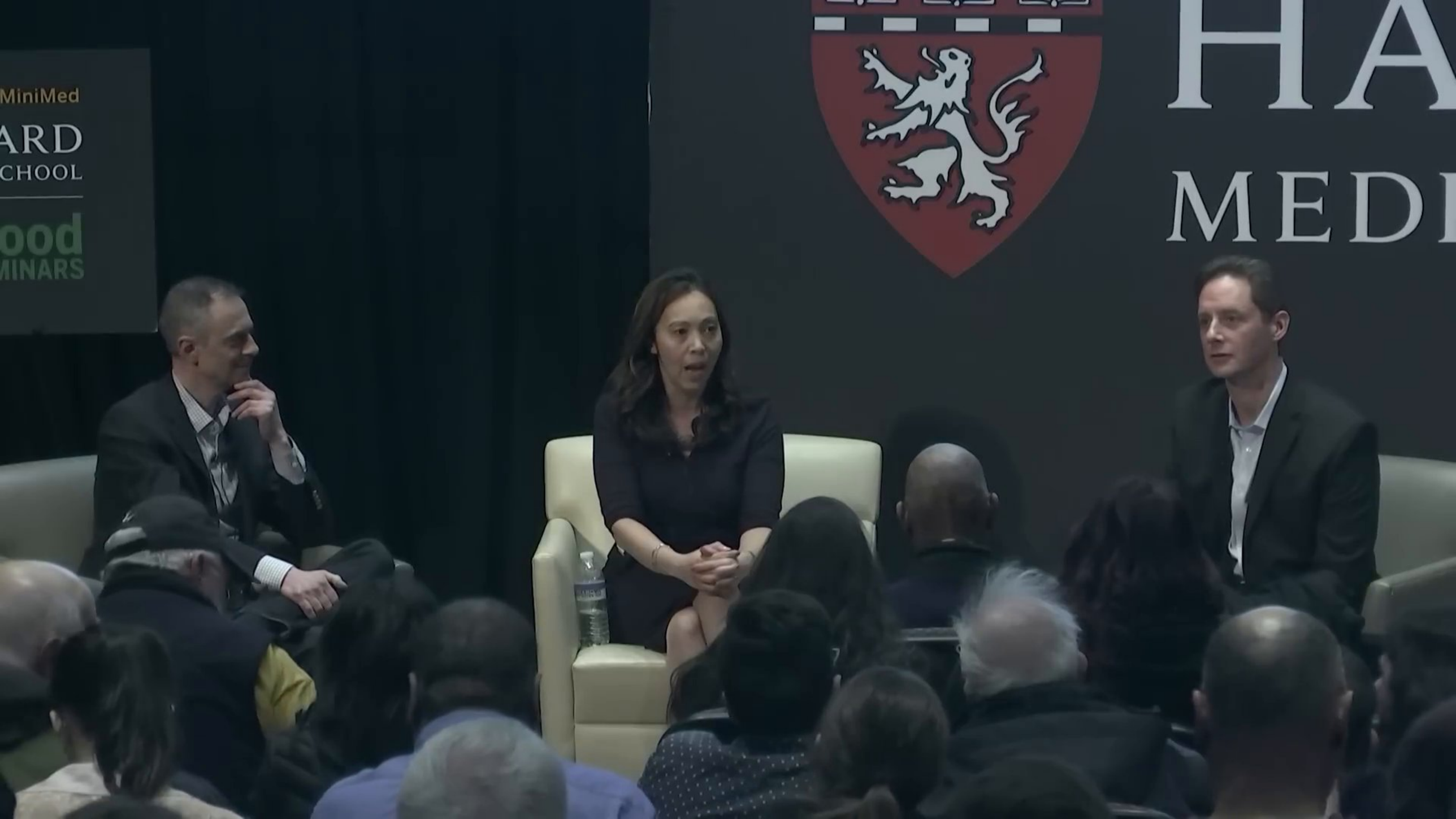
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