Improving Treatment for Cervical Cancer: What Can Tumor Biology Tell Us?

Julie K. Schwarz MD, PhD

Vice Chair for Research and Cancer Biology Division Director, Department of Radiation Oncology

Washington University School of Medicine (St. Louis, MO USA)

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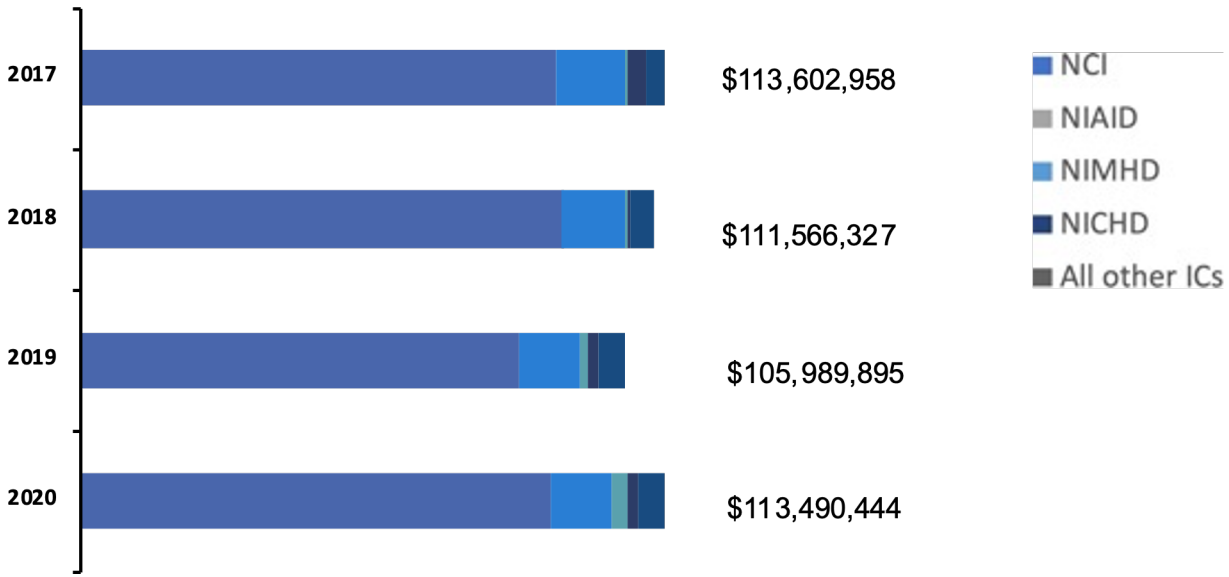
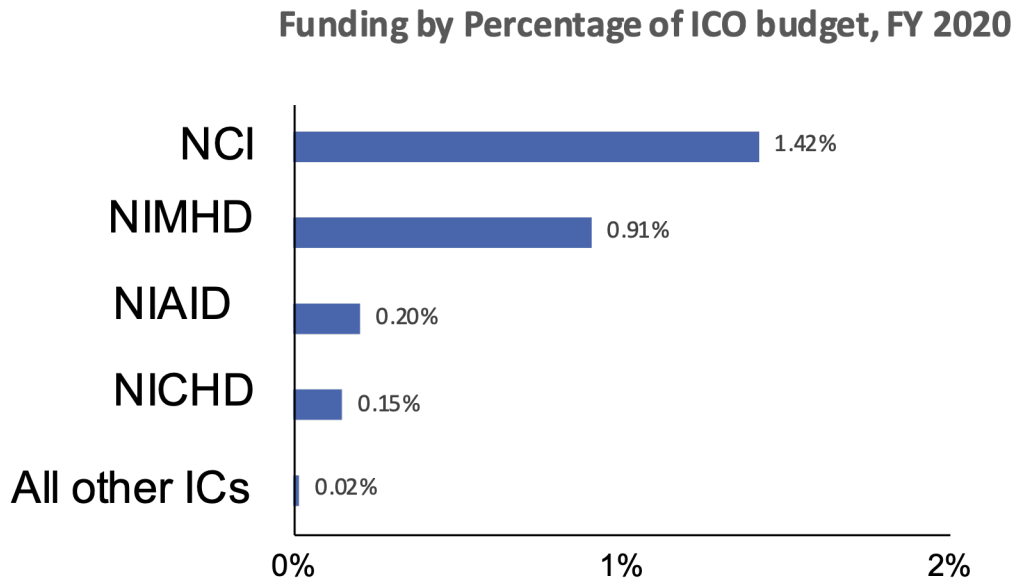
NIH Cervical Cancer Funding





Cervical Cancer – RCDC Official Public Category

Basic Research - Translational Research - Clinical Research

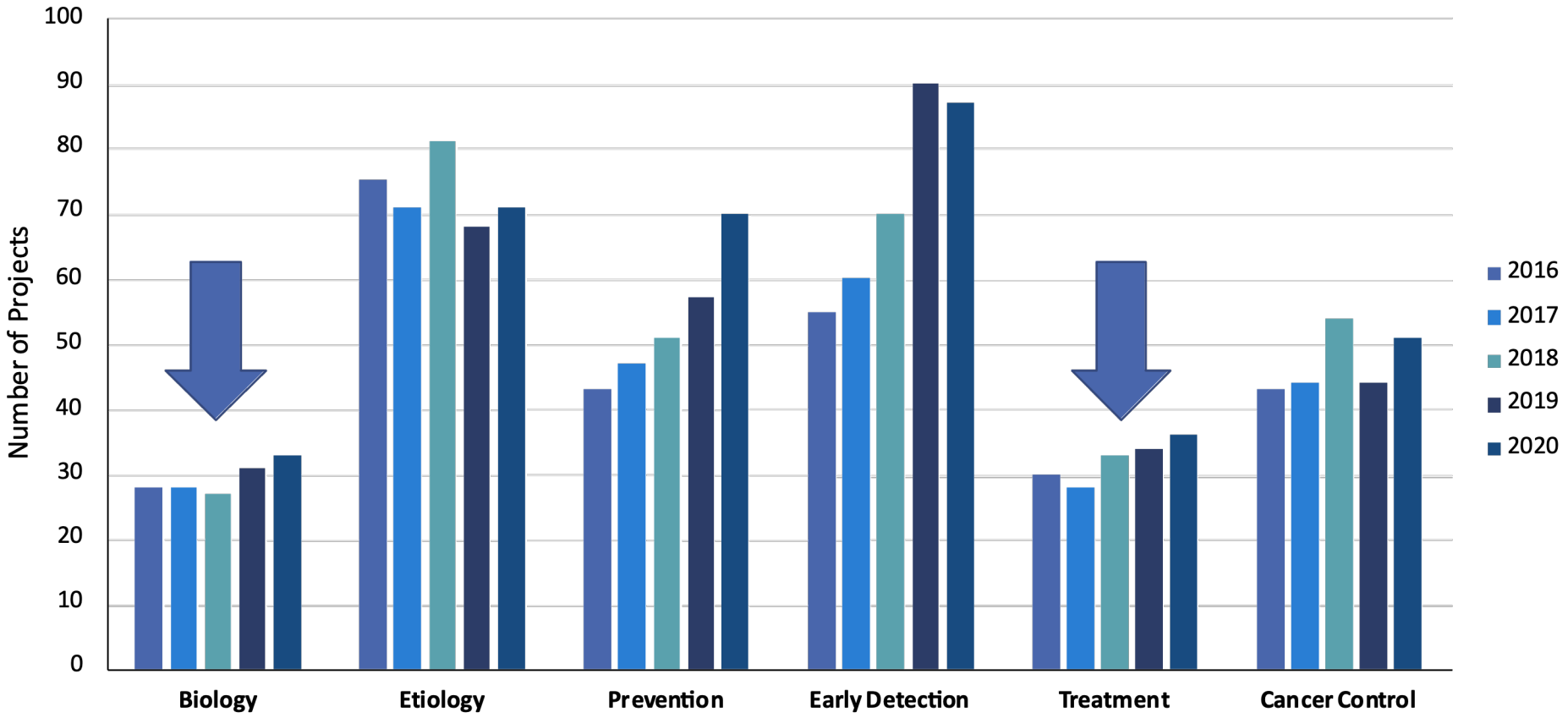
Pre-Malignant - Malignant - Invasive

Prevention - Screening - Detection - Diagnosis - Treatment

HPV - Vaccines - Vaccination

Data from RCDC Categorical Spending Reporting
https://report.nih.gov/funding/categorical-spending#/

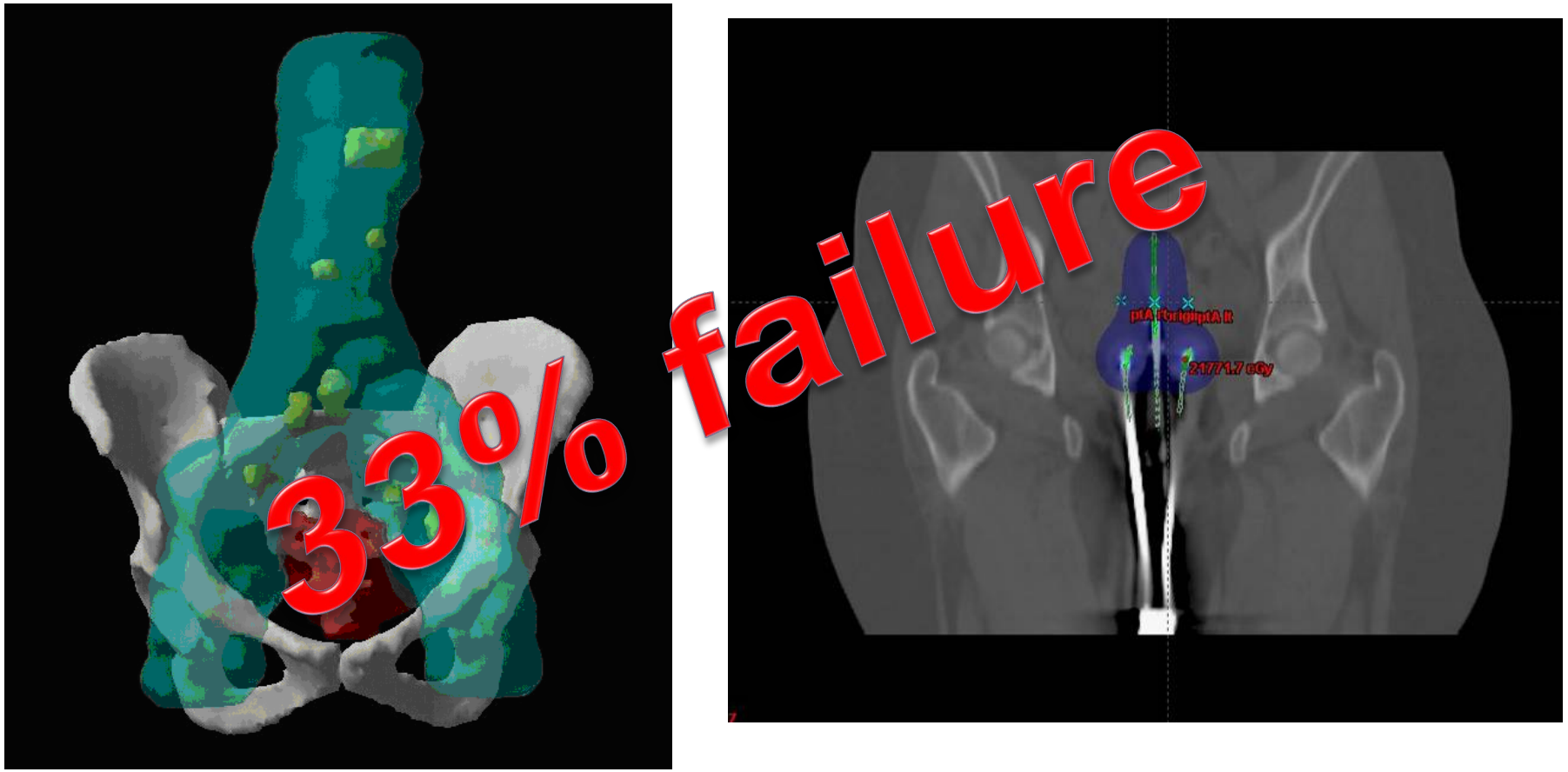
NIH- Funds Cervical Cancer Research



- Projects were assigned to ICRP Common Scientific Outline (CSO) classifications using a Dimensions Machine Learning process
- Individual projects can be assigned to multiple categories
- Not all projects are classified and those have been excluded from the data shown

Cervical Cancer Treatment

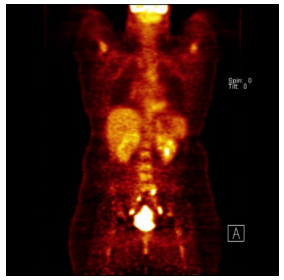
- **Pelvic irradiation and concurrently administered cisplatin chemotherapy**



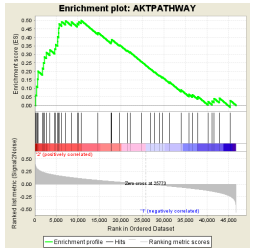
Our approach

Patient data

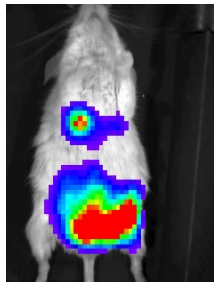
Functional imaging



Tumor biology

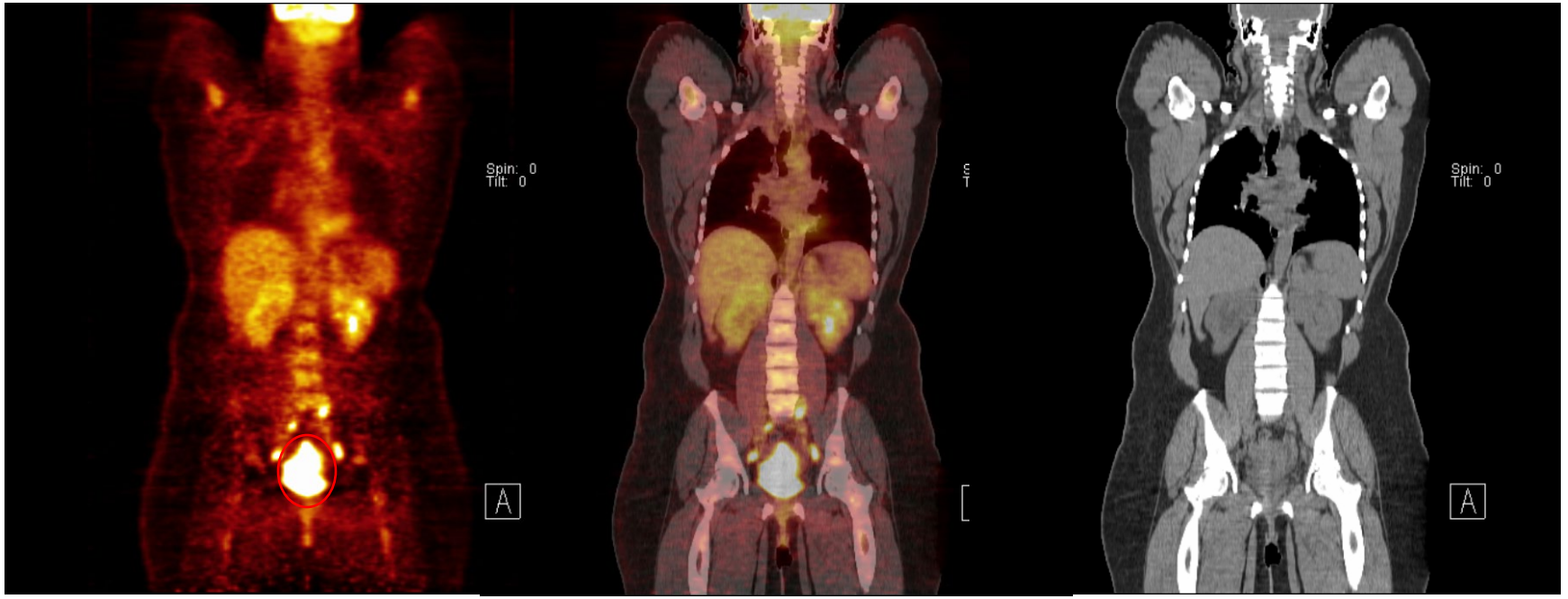


Model systems



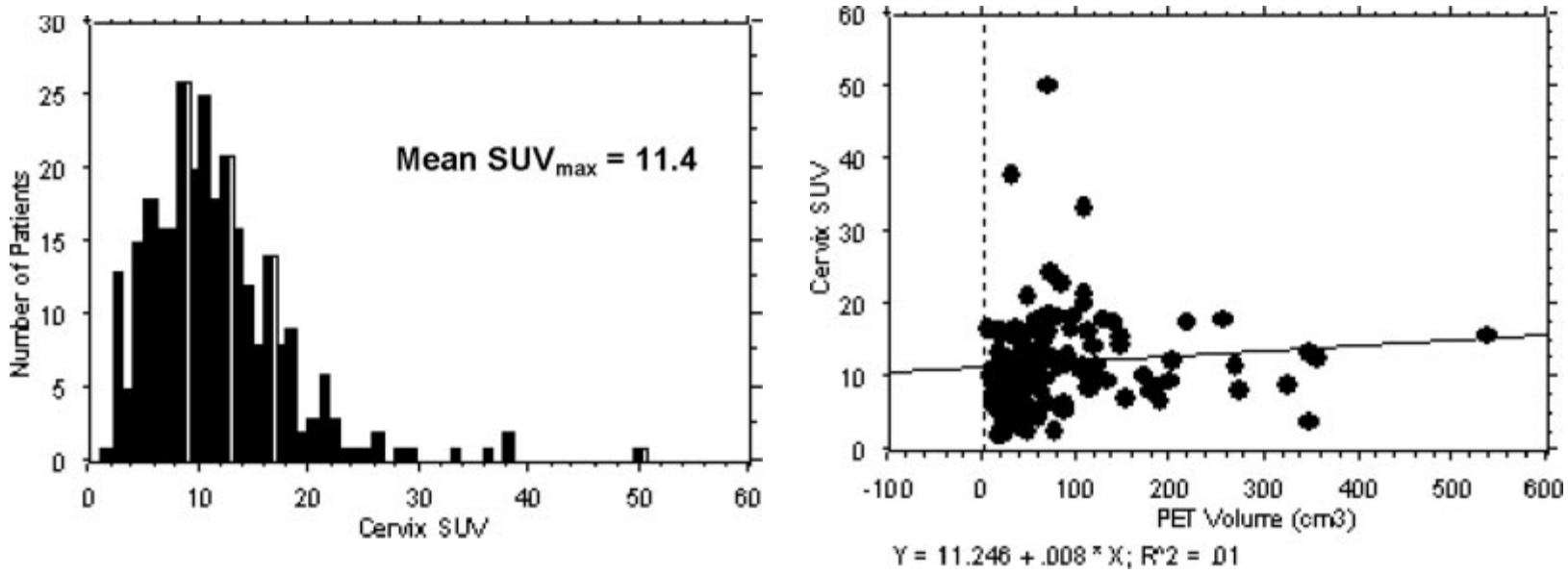
New therapies

FDG-PET/CT



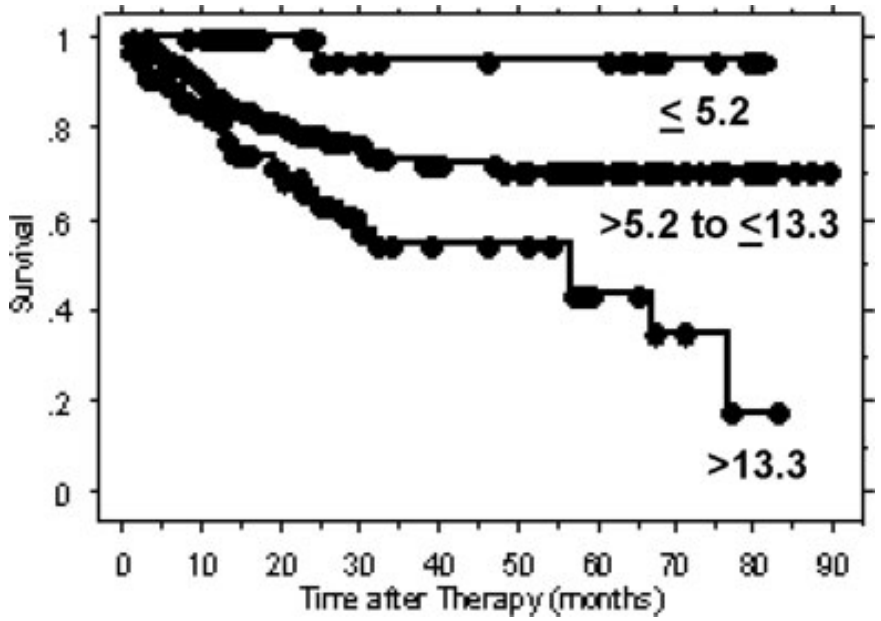
SUV = tissue radioactivity concentration (nCi/mL) / injected dose(mCi)/patient weight (g)

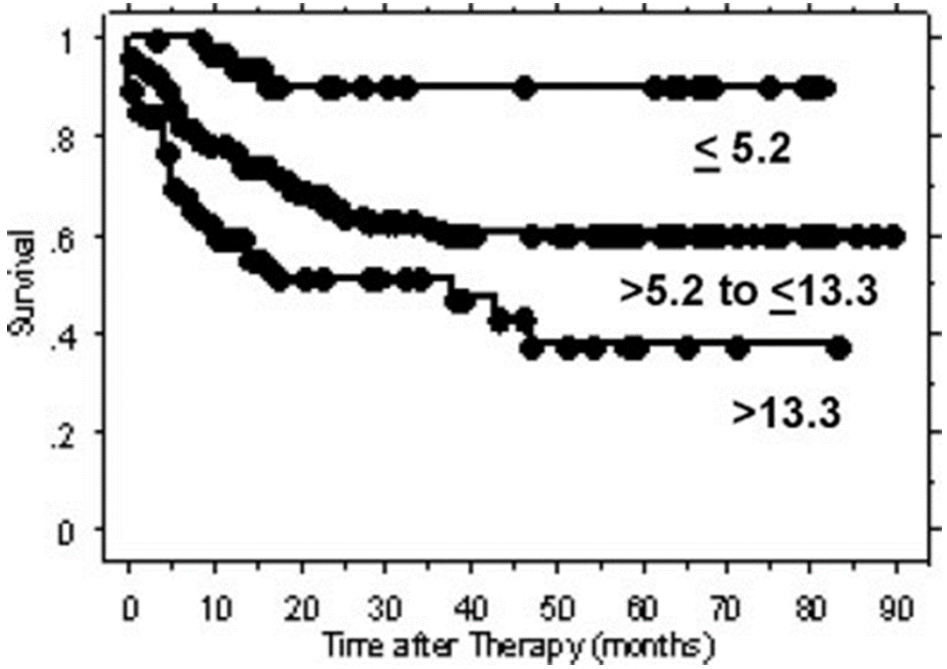
SUV_{max} and cervical tumors



Kidd EA et al, *Cancer* 2007

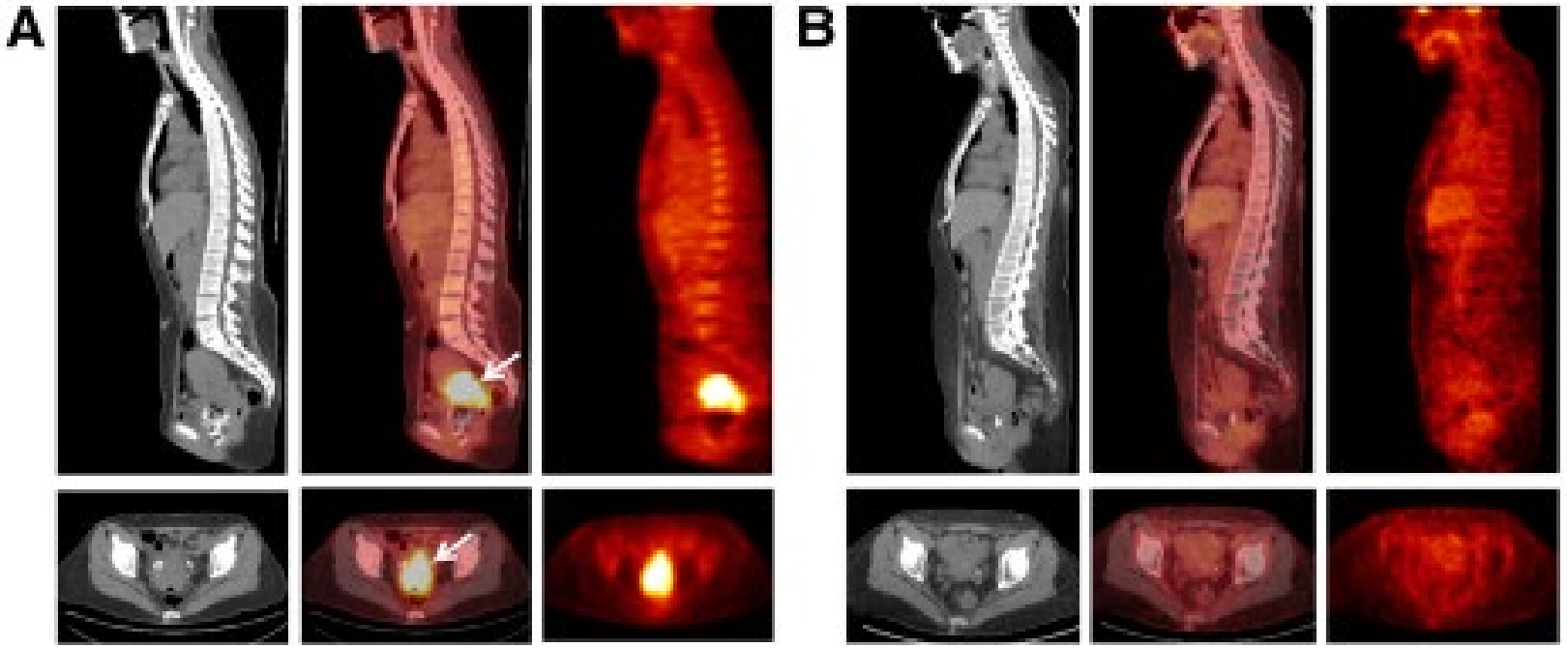
Survival outcomes **and SUV_{max}**





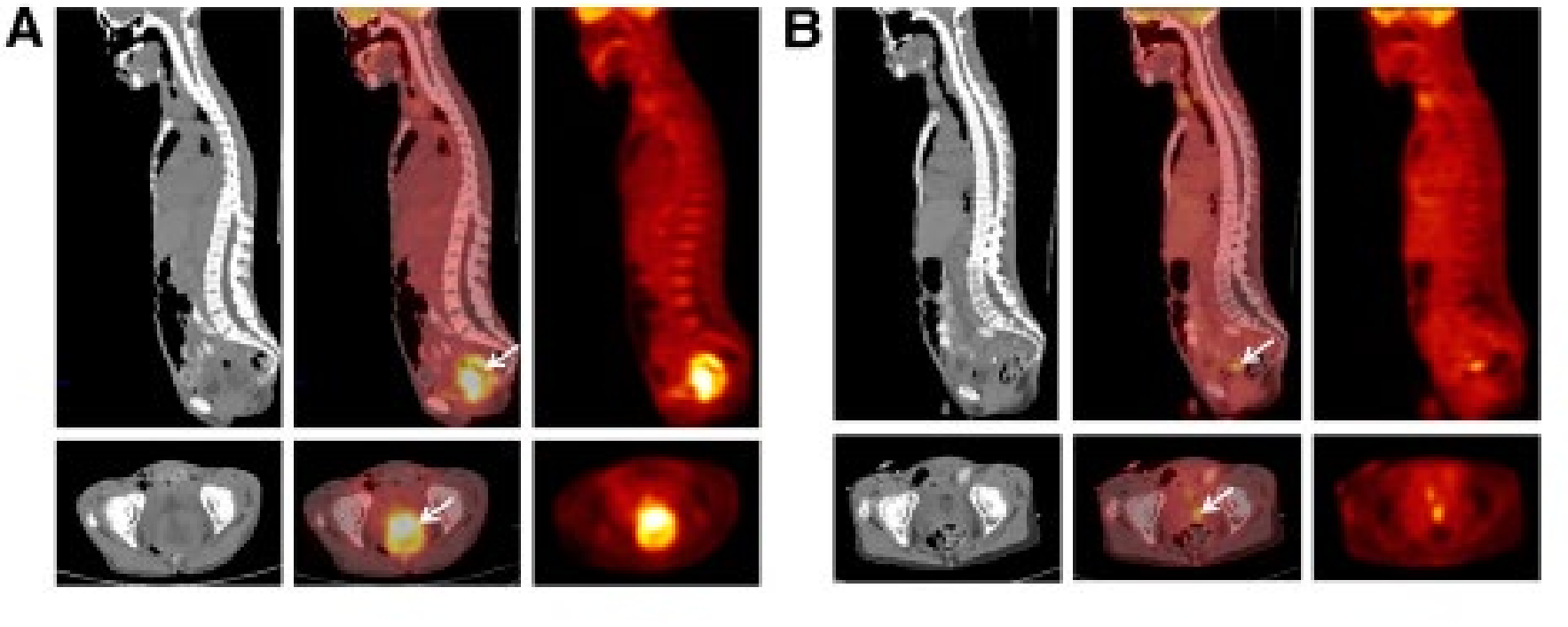
Kidd EA et al, *Cancer* 2007

Complete Metabolic Response



Schwarz JK et al, JNM 2009

Partial Metabolic Response



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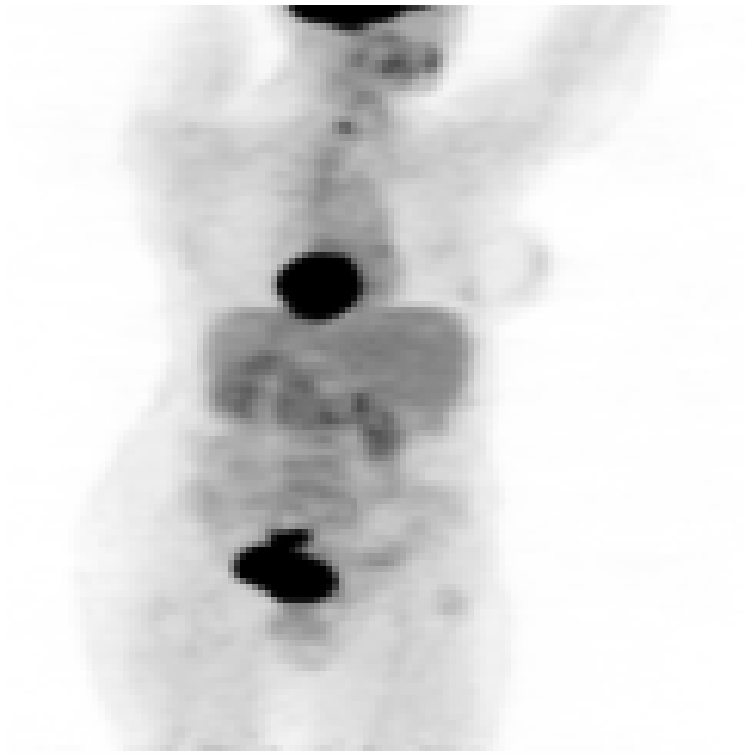
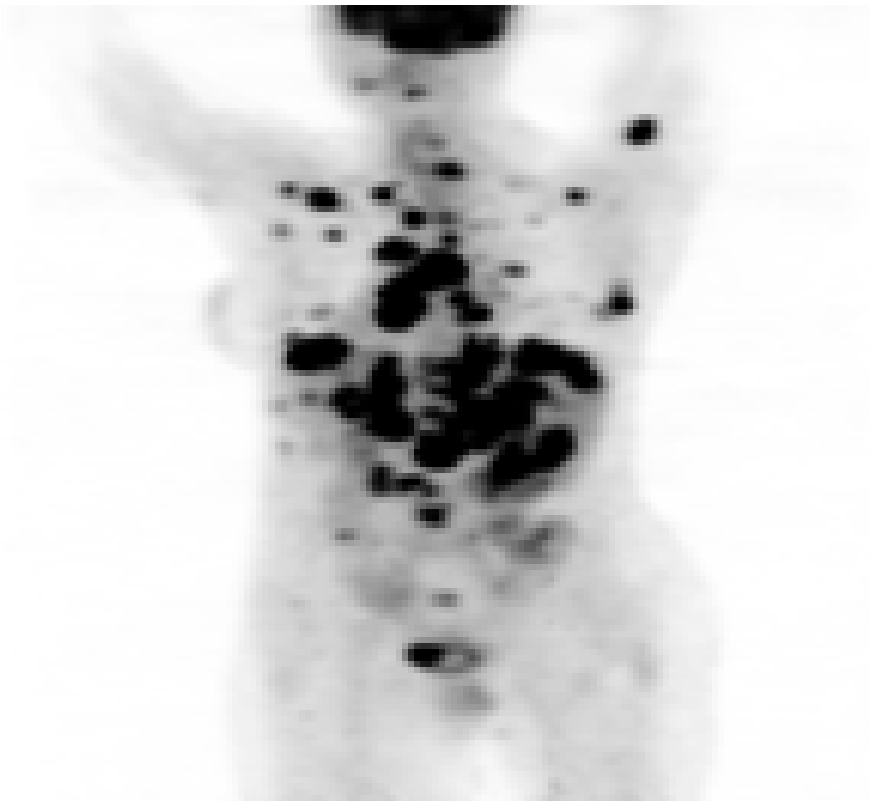
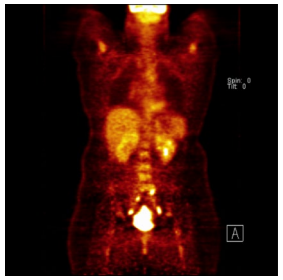




Our approach

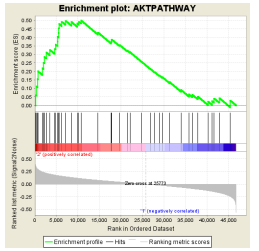
Patient data

Functional imaging



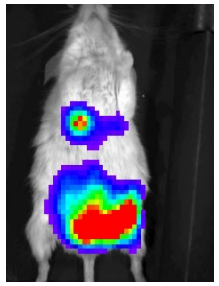
2007

Tumor biology



2012

Model systems

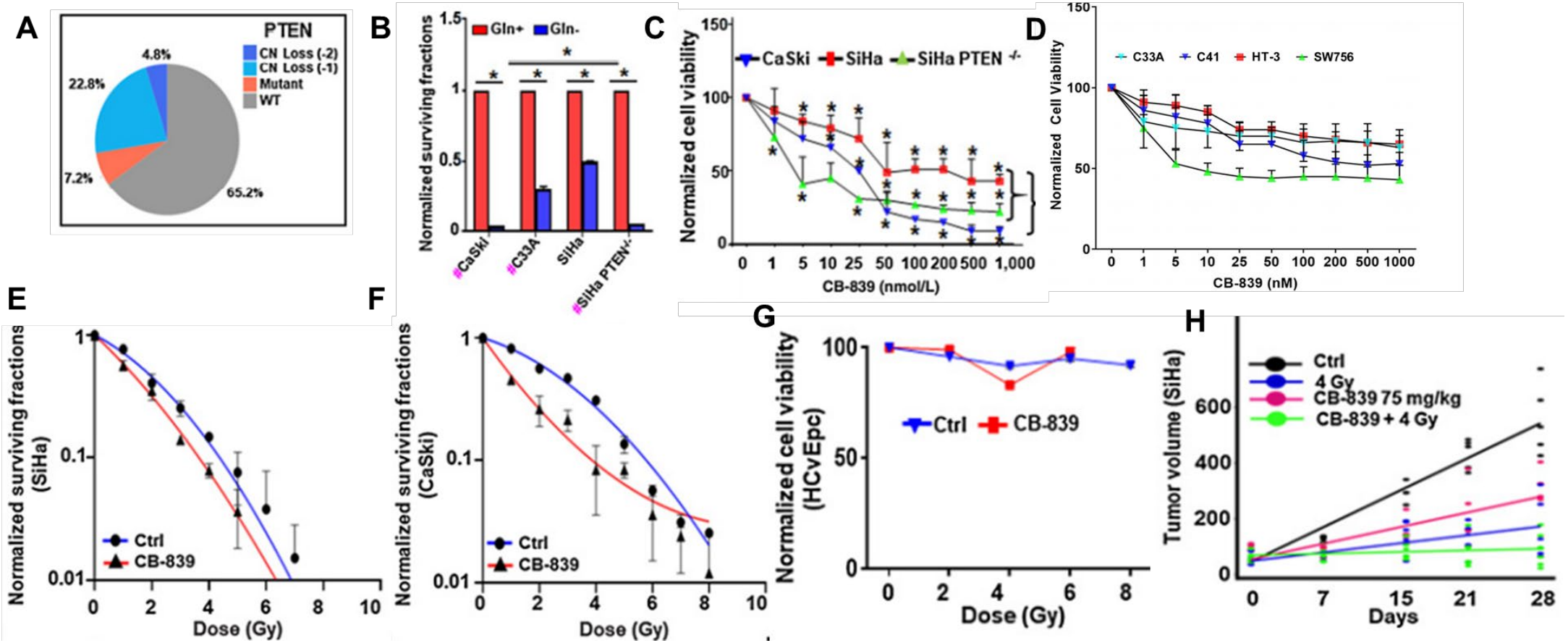


2012-2017

New therapies

2017-2020

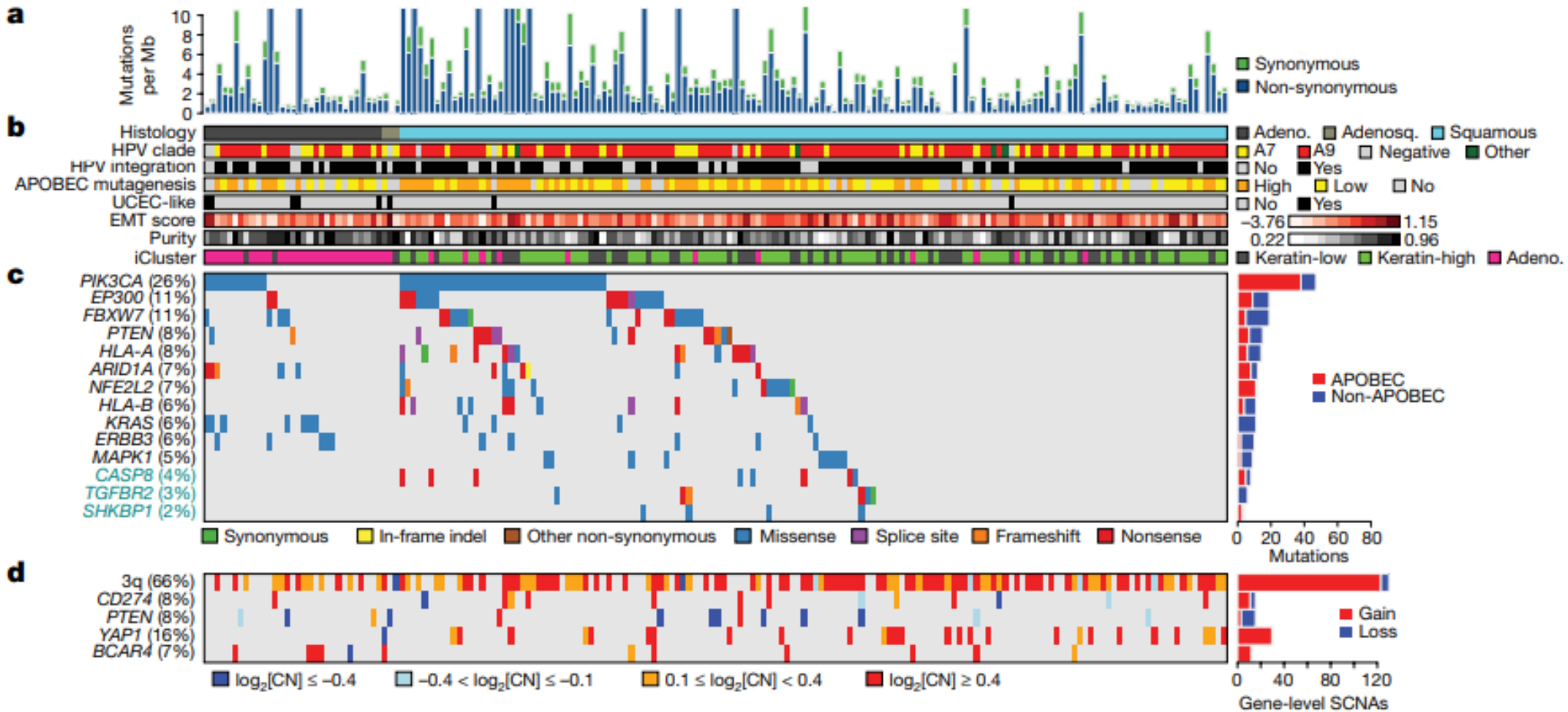
Radio-resistant cervical cancers respond to metabolic drugs



Rashmi R et al *Mol Cancer Ther* 2020

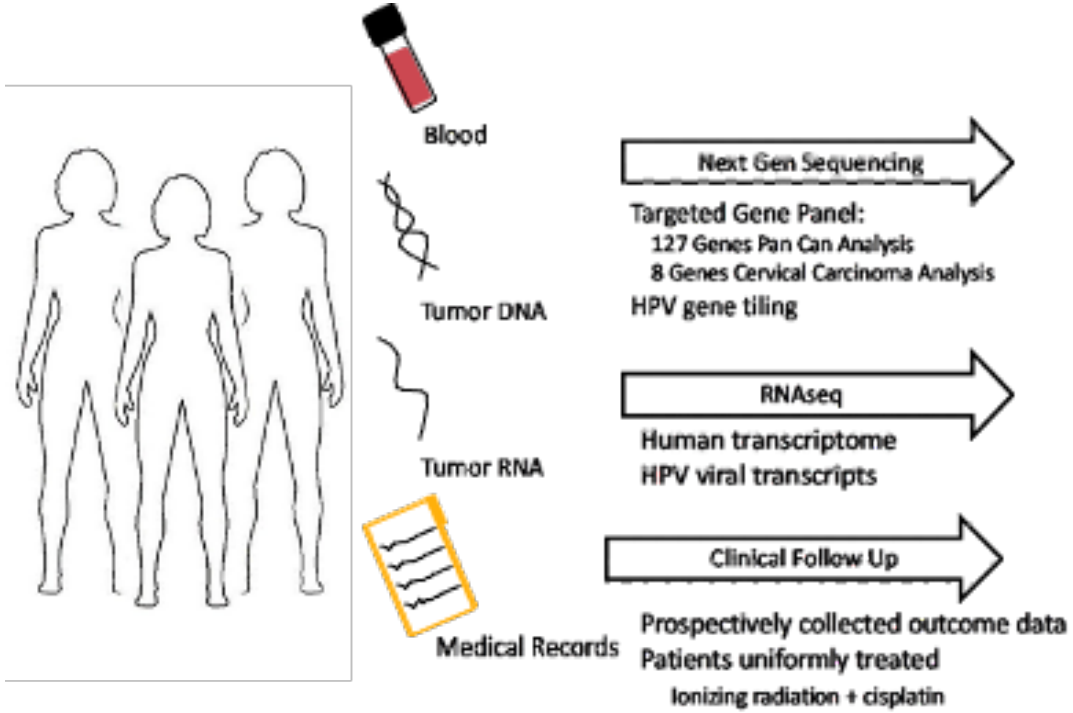
Can genomic biomarkers be used to personalize treatment?

- Cervical Cancer TCGA
- HPV genotype and HPV gene expression
  - Not all HPVs are created equal!
- mRNAs, miRNAs, lncRNA
  - GARD – gene expression derived from cancer cell lines + linear quadratic modeling
    - Scott, JG et al *Lancet* 2017
- Proteomics
  - Rader, JS et al Gyn Onc 2019



TCGA Network, *Nature* 2017

Prospective evaluation of host and viral biomarkers in cervical cancer



Tumor Profiling

- Mutational landscape
- Transcriptome - Viral and host
- HPV genotype

Clinical parameters of interest

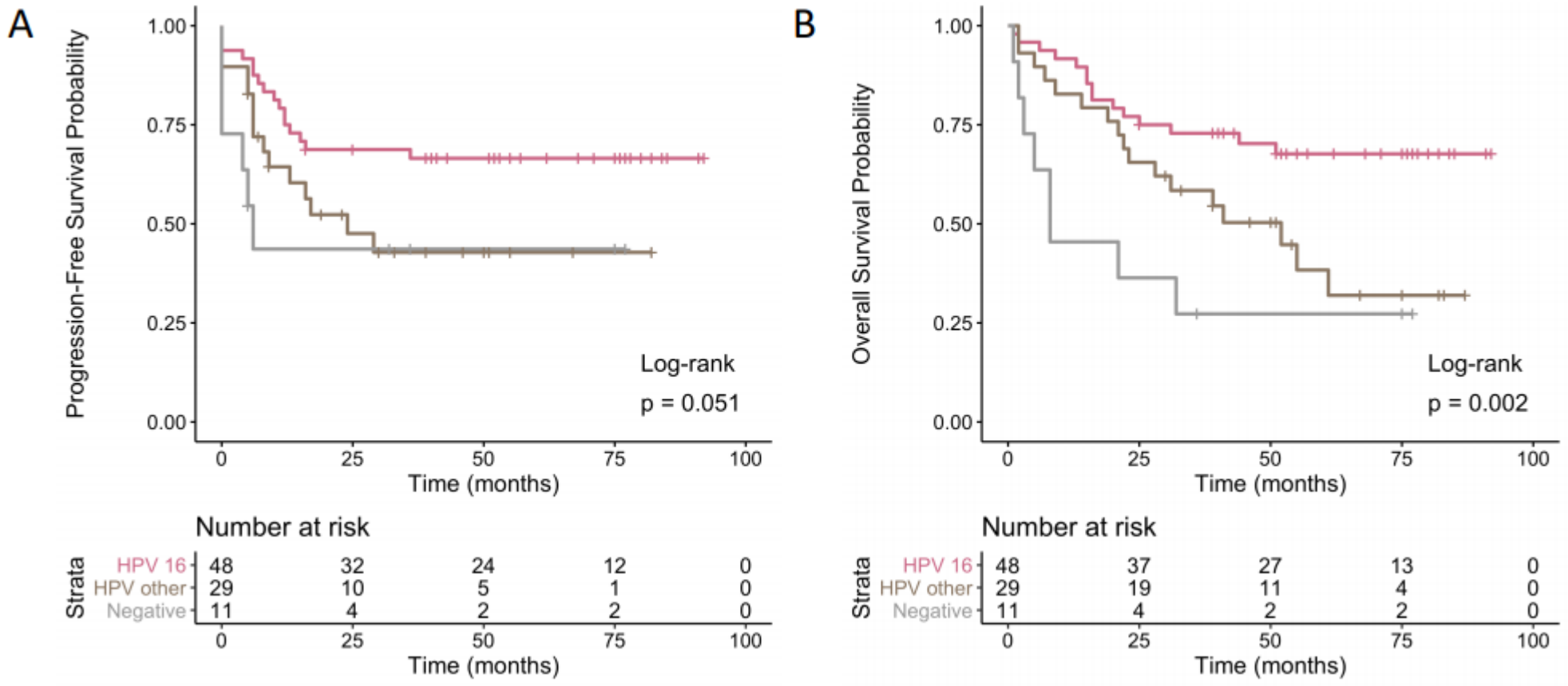
- Recurrence status
- Overall survival outcome

Analysis

- Univariate Cox regression for features correlated with survival outcomes
- Kaplain-Meier survival curves
- Differential expression of viral and host transcripts

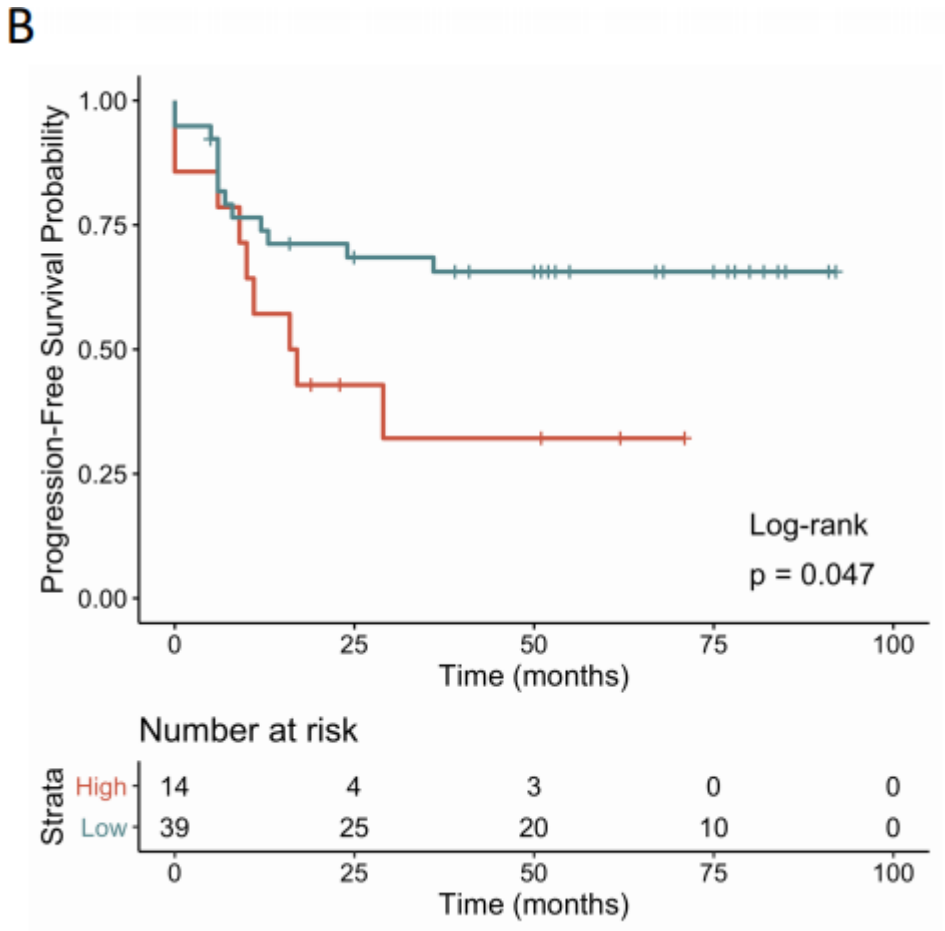
Ruiz and Schwarz, *In preparation*

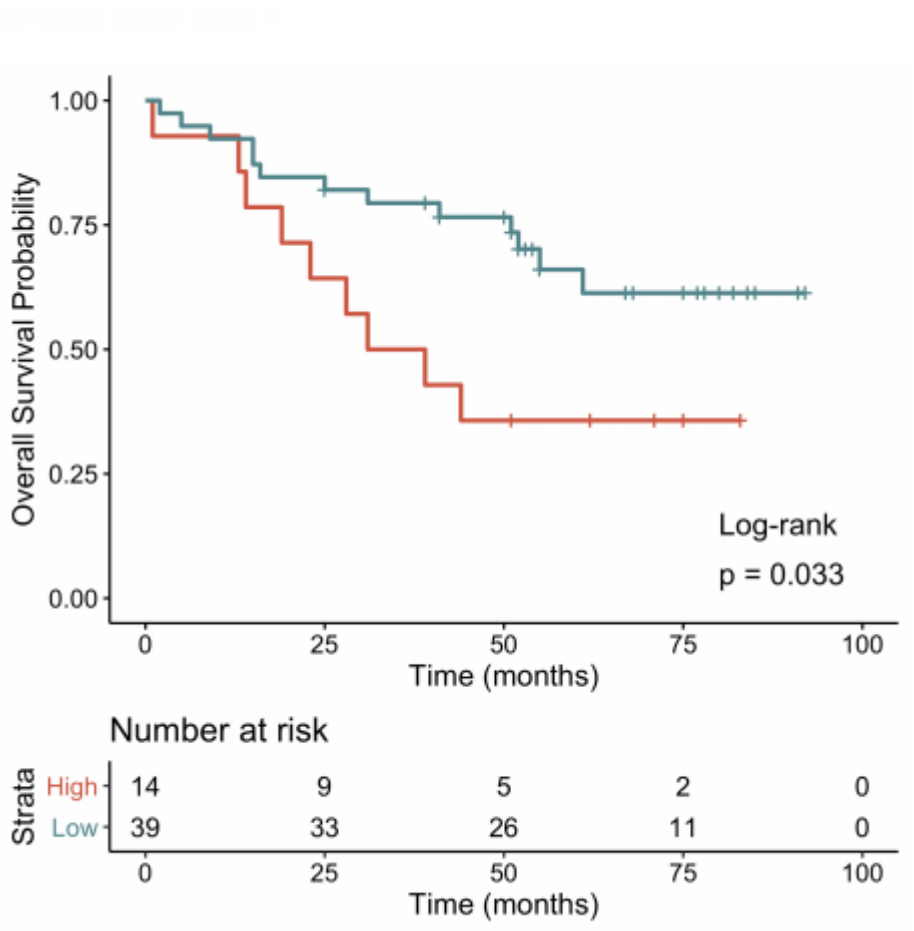
HPV genotype and outcome after chemoradiation in cervical cancer



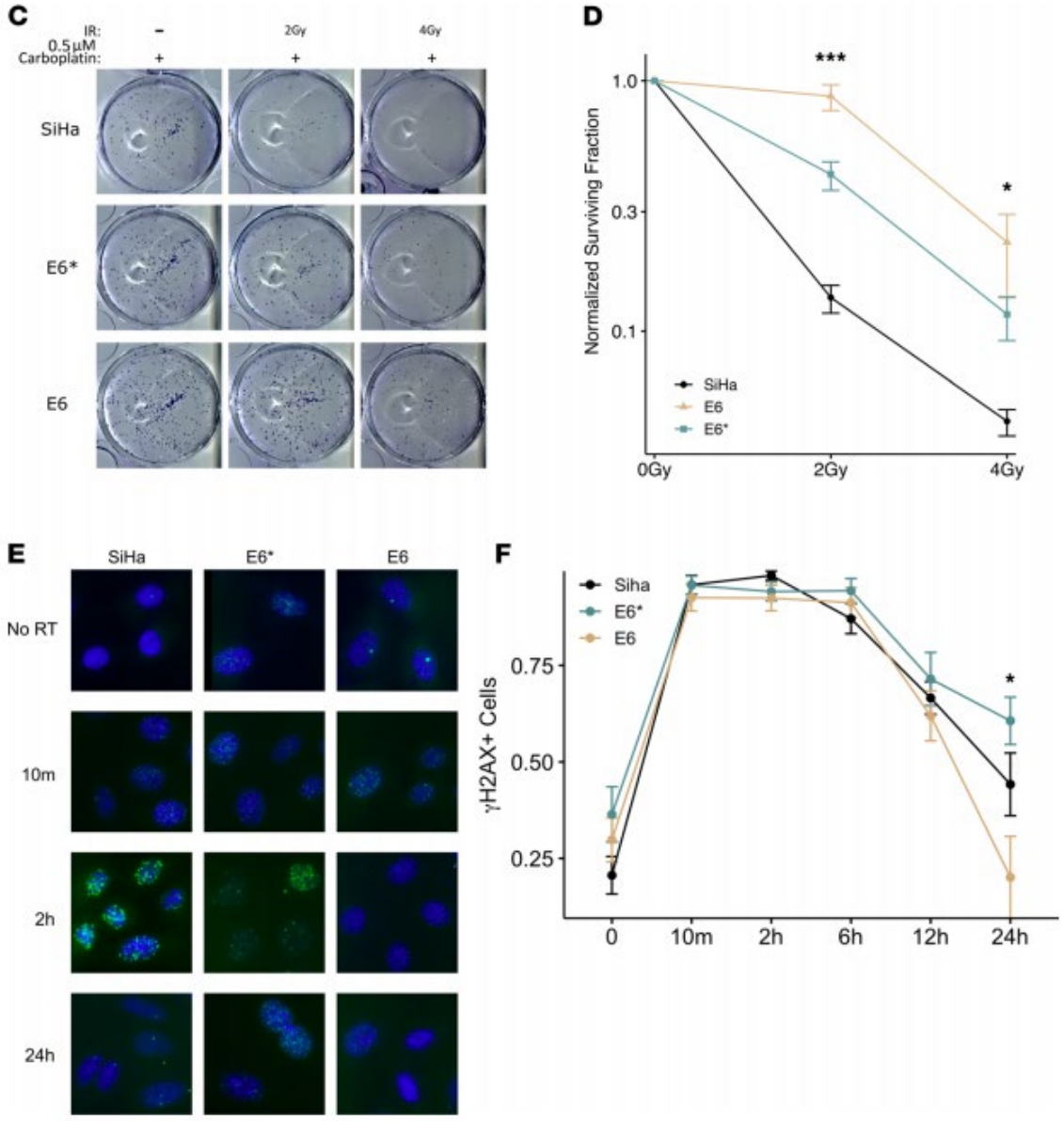
Ruiz, F et al *JCI Insight* 2021

Relative expression of HPV E6*I and outcome after chemoradiation





Ruiz, F et al *JCI Insight* 2021

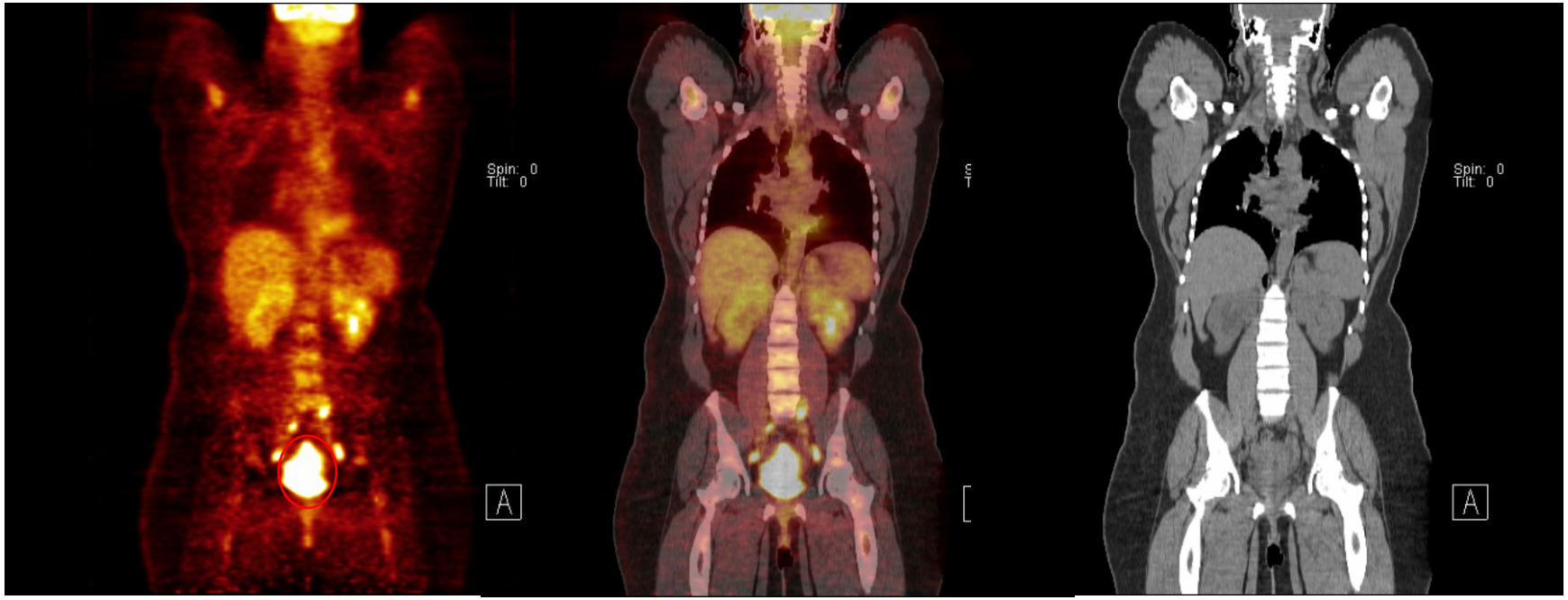


<u>HPV E6* overexpressing cancers</u>
are resistant to chemoRT
-senescence
-role for senolytics?

<u>HPV E6 overexpressing cancers</u>
are also resistant to chemoRT
-DNA repair
-role for DDRi?

Ruiz, F et al *JCI Insight* 2021

Imaging biomarkers



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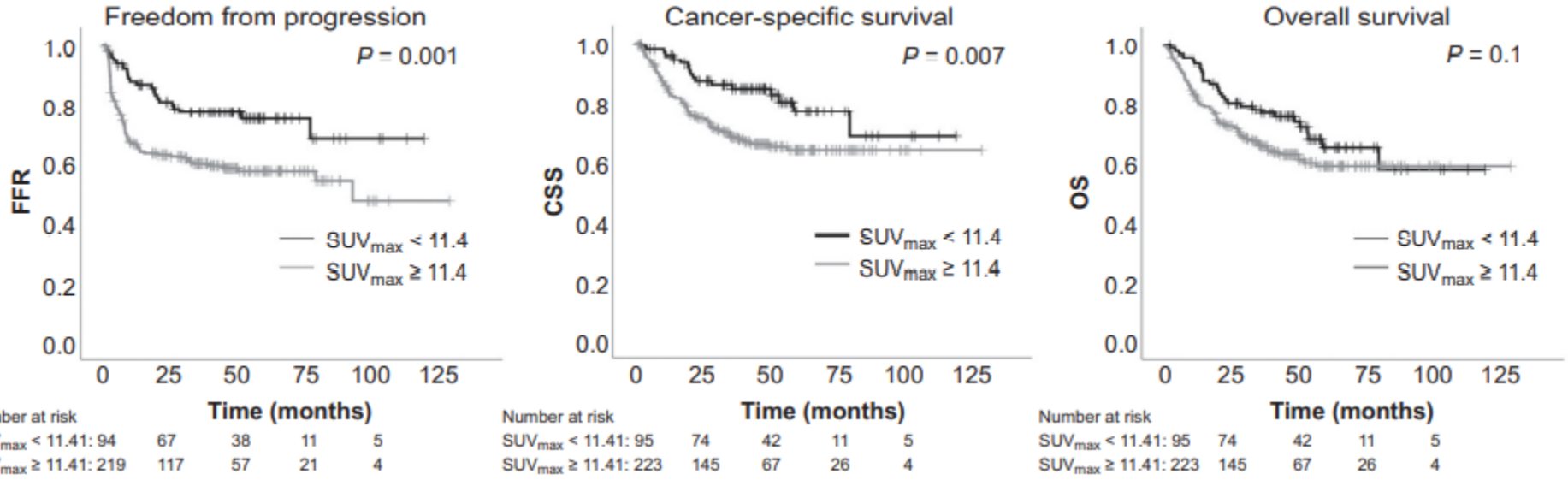

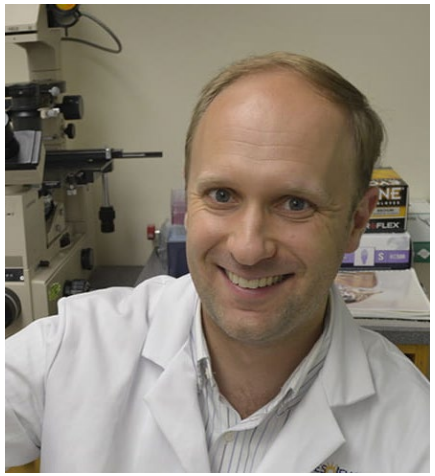

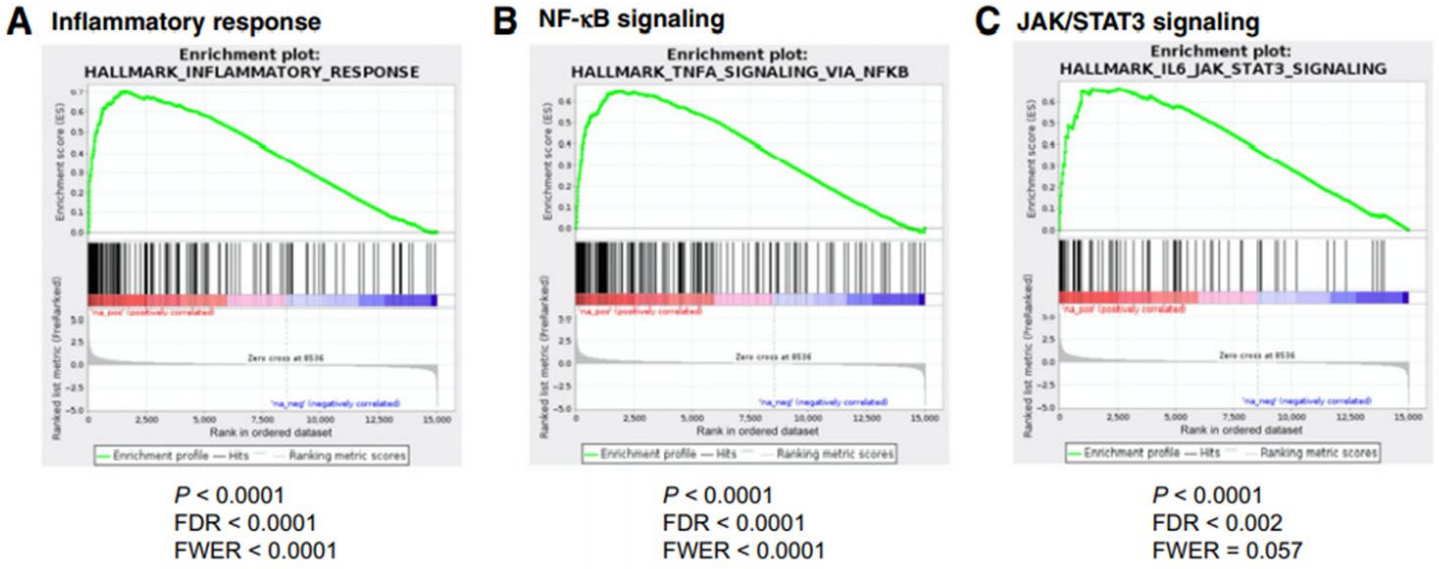

$P < 0.0001$
FDR < 0.0001
FWER < 0.0001

$P < 0.0001$
FDR < 0.0001
FWER < 0.0001

$P < 0.0001$
FDR < 0.002
FWER = 0.057

Floberg, JM et al *Clinical Cancer Research* 2021

Future Directions

- **New Targets:**
  - **DNA Damage Response Inhibitors**
  - **Metabolism/ROS**
  - **Inflammatory pathways**

- **Better Model Systems**
  - **2D Co-Culture**
  - **3D culture**
  - **PDX**
  - **GEMMs**

- **Personalized medicine approaches to better suit our patients**
  - **Genomics**
  - **Imaging**

What can we do to shorten the timeline to get new approaches to our patients?

- **Funding, funding, funding!**
  - **Especially as it pertains to local control for solid tumors**
    - **Gynecologic oncology**
    - **Radiation oncology**

- **Faster path to establish safety for lead drug + RT combinations (Phase I)**
  - **Support for generation of key preclinical data**
    - **Monotherapy + drug combinations**
    - **RT alone**
    - **SOC CRT – needs to reflect current paradigms**
      - **Clinically relevant drug concentrations**
      - **RT dose, fractionation and image guidance**
  - **Better model systems (in vitro and in vivo)**

- **Collaboration across centers within the US and globally**
  - **Team Science and resource sharing rather than competition**

Opportunities

- Training grants to support research workforce development in Gyn Onc/Rad Onc
  - NIH K12 BIRCWH
- Group Grants to improve innovation in treatment approaches for cervical cancer
  - SPORE, P, U level grants
- Increase R01 level funding for investigators working on tumor biology and treatment
  - Gyn Onc specific study section that prioritizes needs
    - cervical cancer treatment innovation
  - Sample RFAs
    1. Improving Preclinical Models for Treatment Assessment in HPV Associated Cancers
    2. Novel Imaging and Genomic biomarkers for Outcome Prediction in Cervical Cancer
    3. Optimizing technology to improve outcomes in resource poor settings
    4. Novel targeted therapy approaches +/- RT in cervical cancer
       - DNA Damage Response Inhbitors (DDRis)
       - Metabolic therapy (drugs and diet)
       - Immunotherapy
    5. Personalized treatment to improve outcomes in cervical cancer

Acknowledgements

OUR PATIENTS!!!!!!

NIH K12 ORWH BIRCWH (Wash U)
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Muhammad – CBD seed grant
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My Lab:

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Fiona Ruiz (PhD student)
John Floberg (Holman Pathway Resident)
Isabelle Eng (undergraduate student)
Mike Zahner (research technician)
Xiaojing Huang (MSTP student)

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David Denardo
Brian Edelson

Redox and the radiation response

Doug Spitz (Iowa)
Mike McCormick

Mass Spectroscopy

Gary Patti

Cervical Cancer Genomics

Cervix Cancer TCGA project
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Li Ding

Bioinformatics

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Jin Zhang