# Translating Science into Improved Patient Care

Advancing NIH Research on the Health of Women: A 2021 Conference


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# Opportunities - Cervical cancer

Stage 0-I

Stage I-IV

Advanced/ Recurrent

Fertility preserving

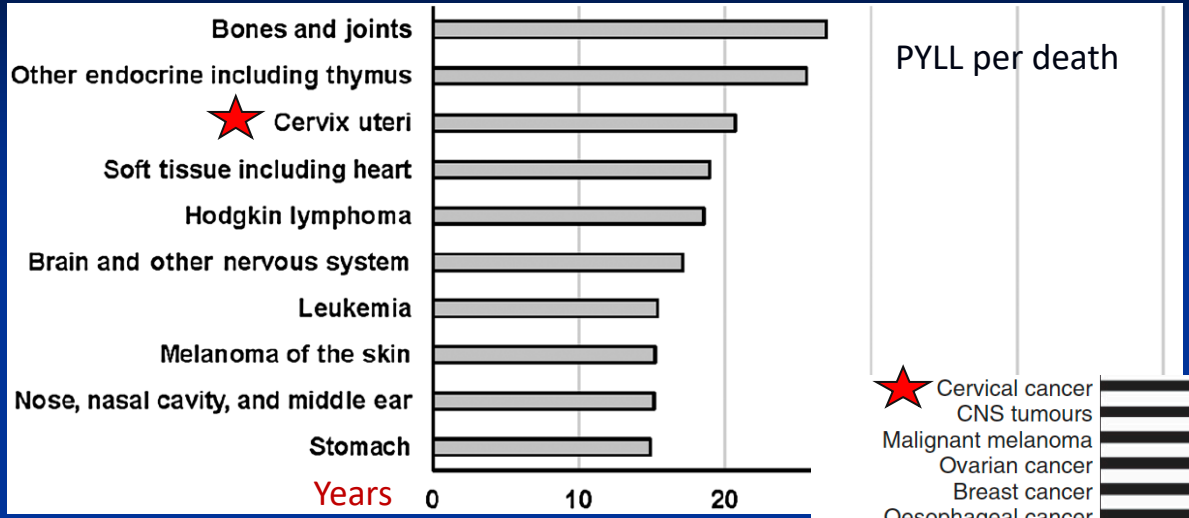
- Nonsurgical – Chemoprevention
- Improved surgical procedures

- Adherence to Standards
- Effective Chemotherapy
- Biomarkers to guide therapy
- Diverse Workforce

- Survivorship

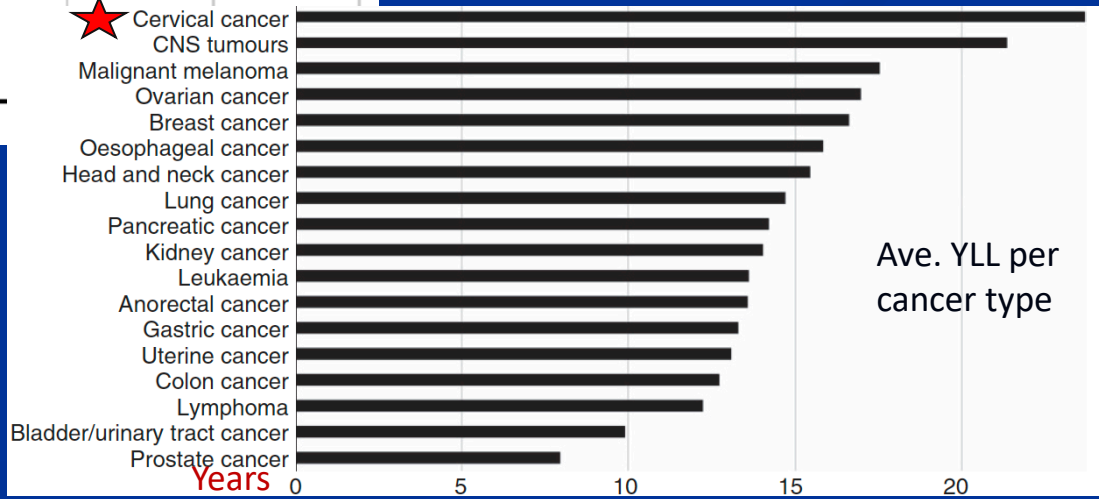
# Potential Years of Life Lost (PYLL)

Average years of life lost – 20.7 – 23.7 years




PYLL per death

Top cancers in women in US




Ave. YLL per cancer type

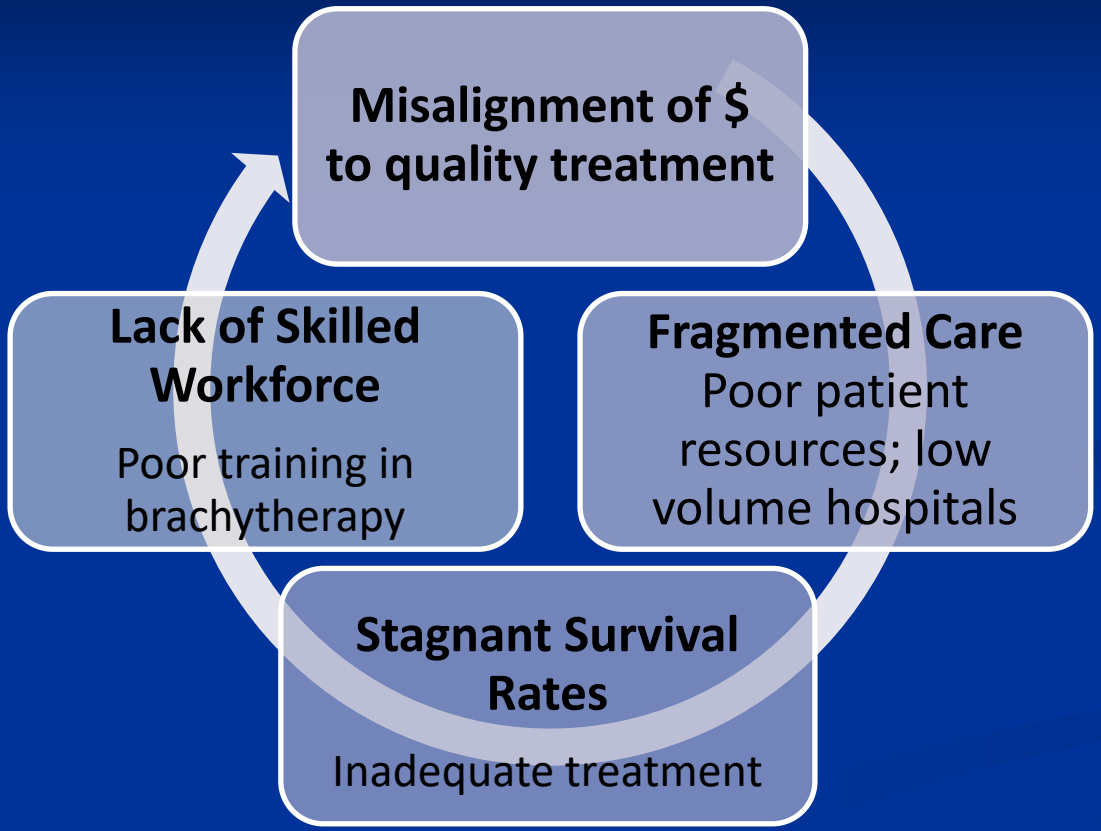
Most frequent cancers in Norway

Song *et al*. Cancer Epidemiol Biomarkers Prev 2020

Brustugun *et al*. B J Cancer 2014

# Adhere to the Science

## External Beam Radiation • Brachytherapy • Chemo • Time




< 50% women receive National Comprehensive Cancer Network (NCCN) guideline treatment


Gaffney *et al*. Gynecol Oncol 2018
Han *et al*. Int J Radiat Oncol Biol Phys 2013
Gill *et al*. Int J Radiat Oncol Biol Phys 2014
Pfaendler *et a*l. Obstet & Gynecol 2018
Robin *et a*l. Gynecol Oncol 2016

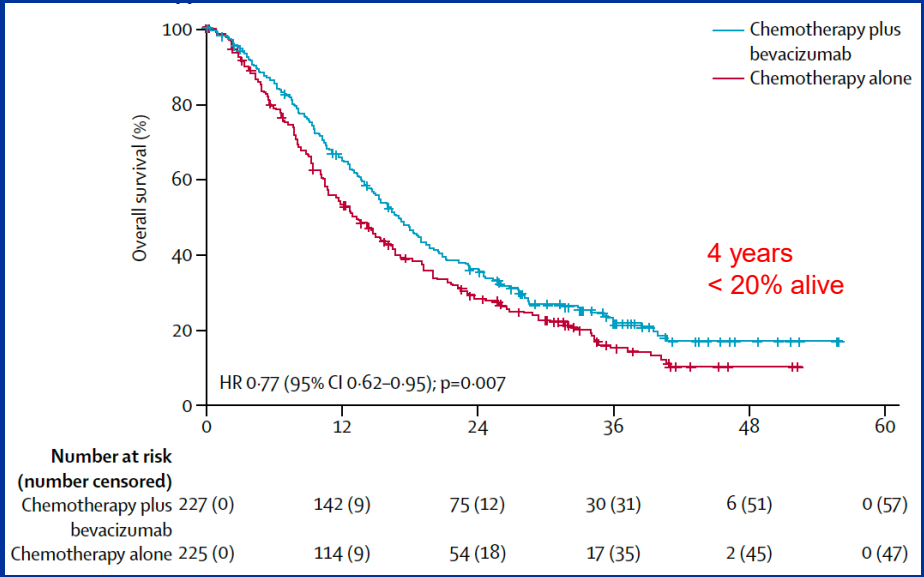
# Expand the Science

# Advanced-Recurrent Cervical cancer

median age women - 50 years

## GOG 240 - NCT00803062

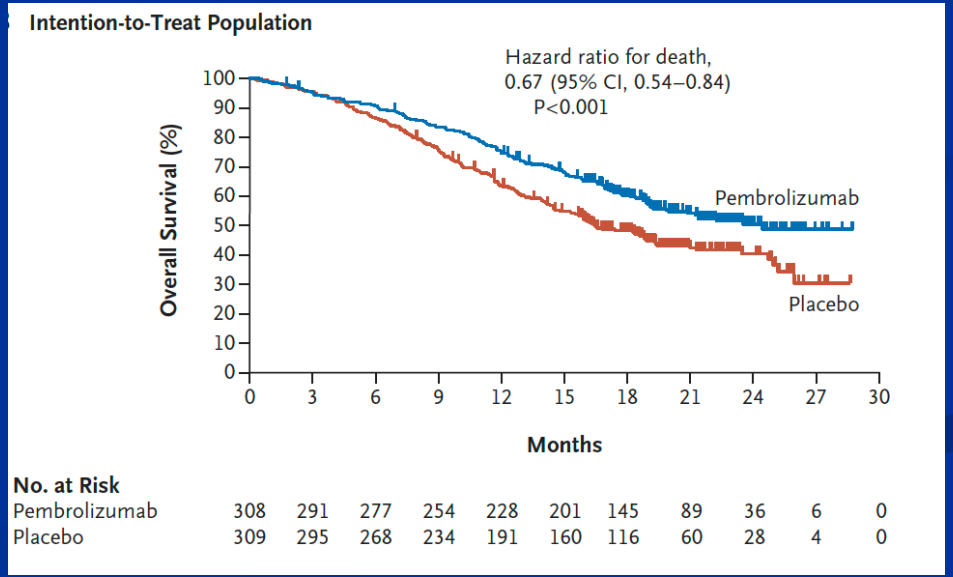
Chemotherapy +/- Bevacizumab




Tewari *et al*. NEJM 2014 & Lancet 2017

## KEYNOTE-826 - NCT03635567

Platinum-based chemotherapy with or without bevacizumab +/- pembrolizumab




Colombo *et al*. NEJM 2021

# Expand the Science
# Advanced-Recurrent Cervical cancer

Chemotherapy landscape

Cisplatin/Carboplatin >30-40% response without previous chemo and < 20% with previous chemo
Paclitaxel/Docetaxel
Topotecan
Ifosfamide

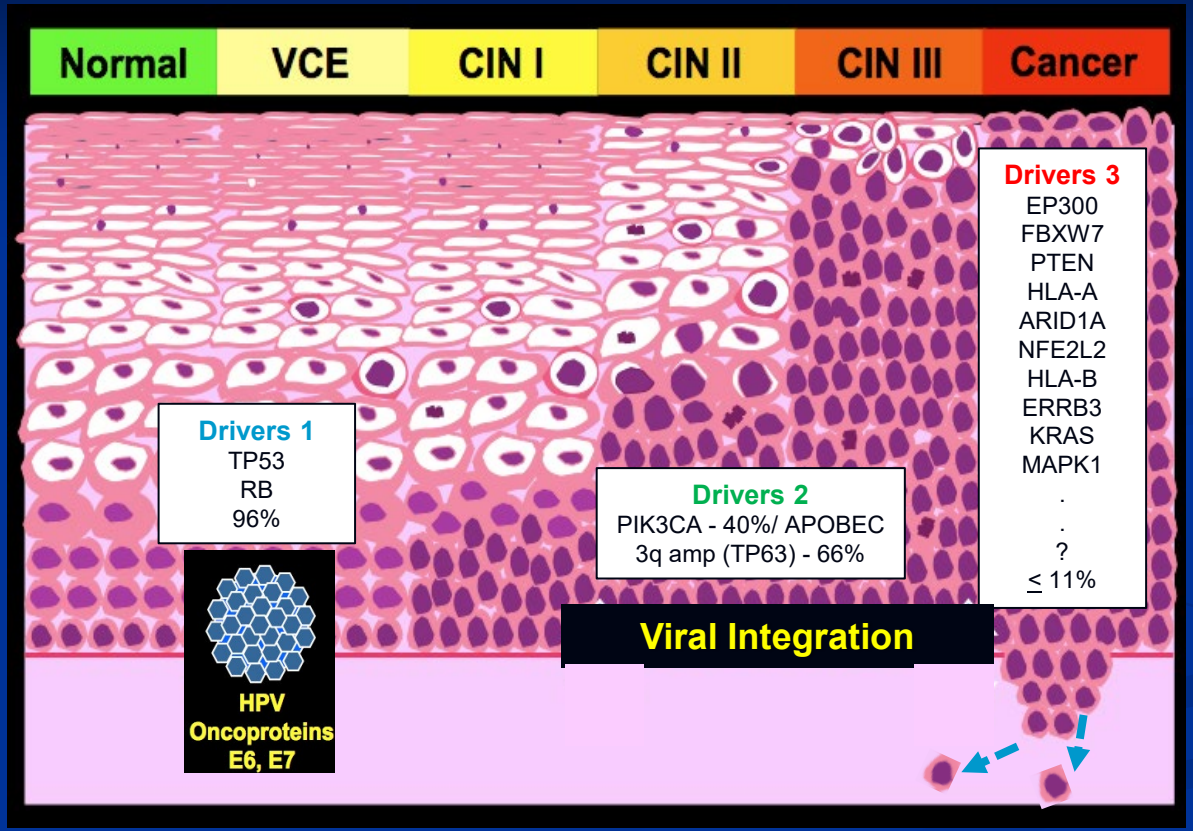
Bevacizumab. anti-VEGF – 10.9% response (with cisplatin and paclitaxel – 50% response)
Pebrolizumab, anti-PD-1 – 12.2% response in phase II (with platinum-based treatment – 65.9%)
Tisotumab, antibody drug conjugate directed to Tissue factor-MMAE – 24% response in phase II

Underdevelopment

Anti-CTLA-4
DNA vaccines
Cell-based therapies
PARPs, fusion proteins

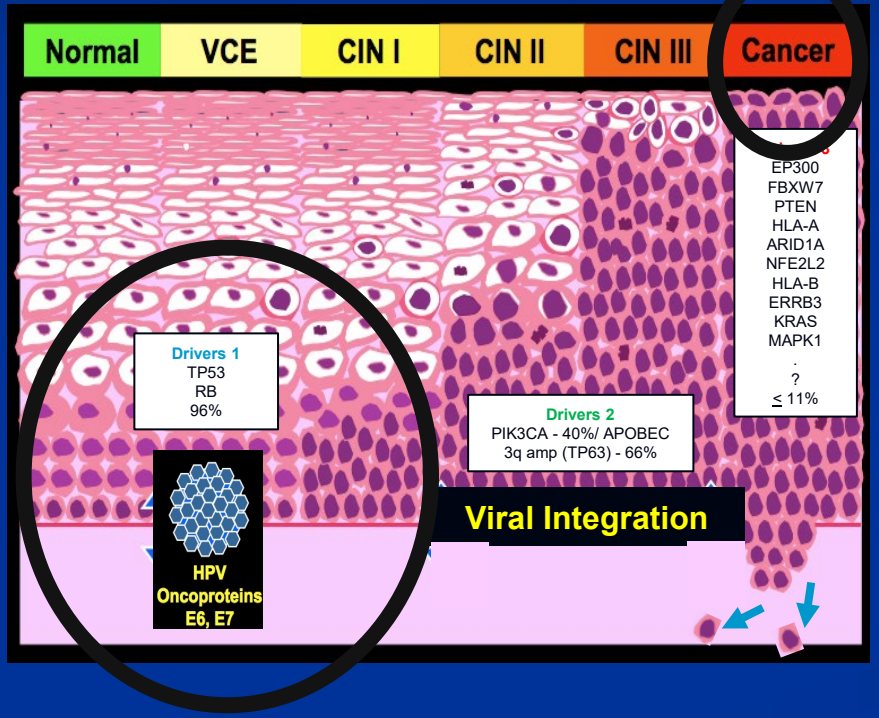
# Focus on the Cancer - Tissue Specificity

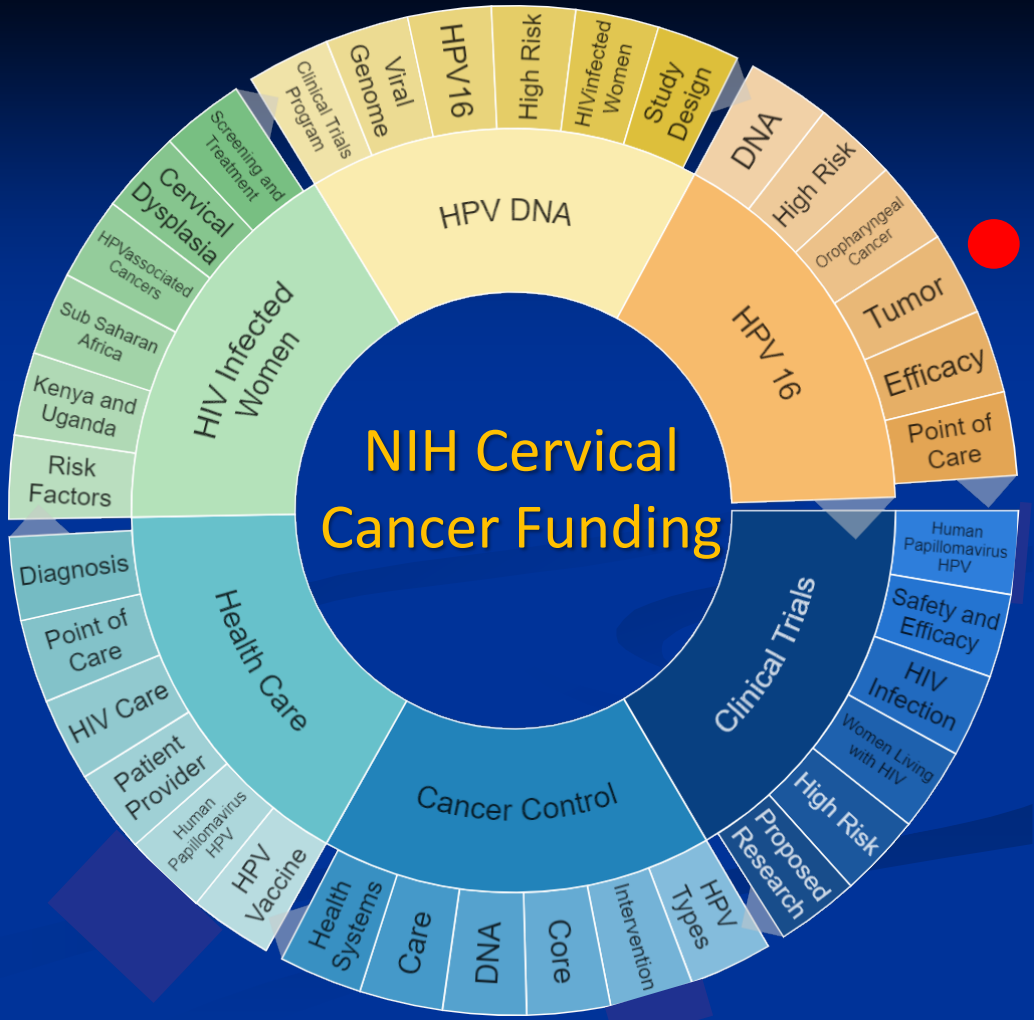
Not all cancers are the same and not all cervical tumors are the same



# Focus on the Cancer

## Gaps at Cancer Funding

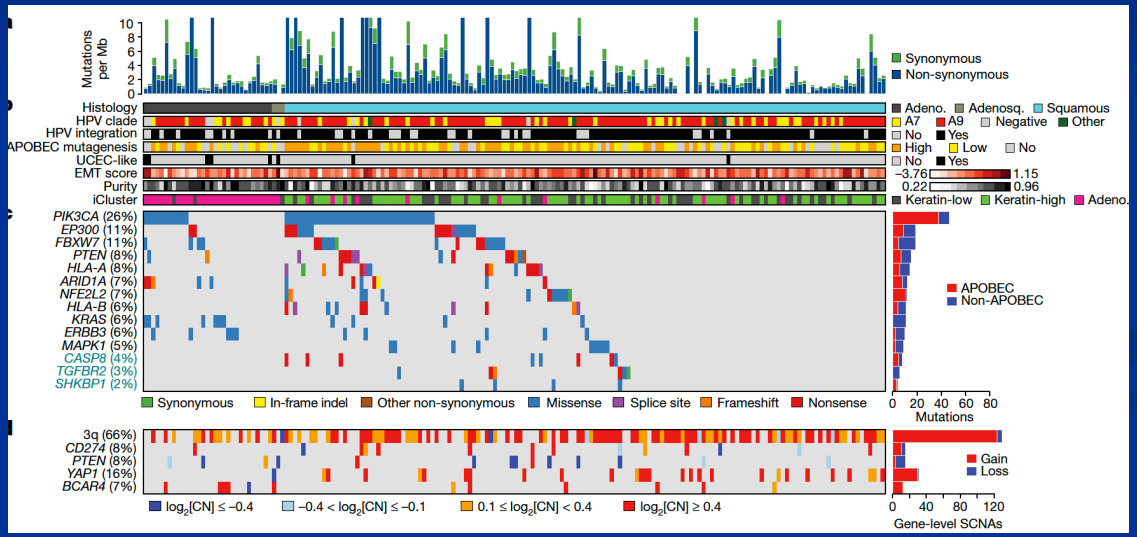


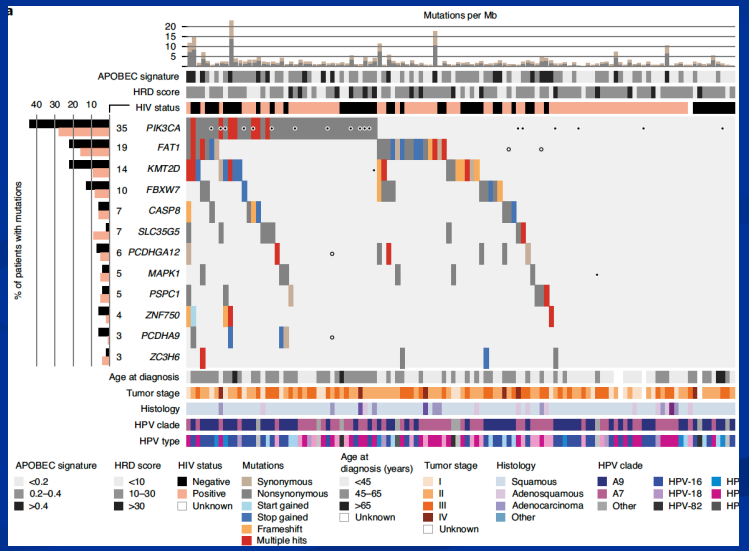
# Expand the Data and Sharing – NIH big science collaborations

Window into 422 invasive cervical cancers

## The Cancer Genome Atlas (TCGA) NCI - NHGRI




## HIV+ Tumor Molecular Characterization Project (HTMCP) NCI - OGC & OHAM




NIH NATIONAL CANCER INSTITUTE GDC Data Portal

Tools - MSK cBioPortal; UCSC Xena; Broad IGV, Firehose……

Gagliardi *et al*. Nature Genetics 2020

TCGA *et al*. Nature 2017

scientific reports

OPEN

# Pancancer survival analysis of cancer hallmark genes

Ádám Nagy[1,2], Gyöngyi Munkácsy[1] & Balázs Győrffy[1,2]✉

*Nucleic Acids Research, 2018* 1
doi: 10.1093/nar/gky180

# ViFi: accurate detection of viral integration and mRNA fusion reveals indiscriminate and unregulated transcription in proximal genomic regions in cervical cancer

Nam-phuong D. Nguyen[1], Viraj Deshpande[1], Jens Luebeck[2], Paul S. Mischel[3,4,5,*] and Vineet Bafna[1,*]

[1]ence and Engineering, University of California San Diego, 9500 Gilman Dr, La Jolla, CA 92093, USA, [2]s and Systems Biology Program, University of California San Diego, 9500 Gilman Dr, La Jolla, CA [3]Ludwig Institute for Cancer Research, University of California, San Diego, 9500 Gilman Dr, La Jolla, A, [4]Department of Pathology, University of California, San Diego, 9500 Gilman Dr, La Jolla, CA 92093 [5]res Cancer Center, University of California San Diego, 9500 Gilman Dr, La Jolla, CA 92093, USA

Oncogene (2021) 40:2112–2129
https://doi.org/10.1038/s41388-021-01679-8

ARTICLE

# The deubiquitinase (DUB) USP13 promotes Mcl-1 stabilisation in cervical cancer

Ethan L. Morgan[1,2,3] · Molly R. Patterson[1,2] · Diego Barba-Moreno[1,2] · James A. Scarth[1,2] · Adam Wilson[1,2] · Andrew Macdonald[1,2]

Gene
Volume 766, 15 January 2021, 145119

Contents lists available at ScienceDirect
Gynecologic Oncology
journal homepage: www.elsevier.com/locate/ygyno

Research paper

# Identification of prognosis-related genes in the cervical cancer immune microenvironment

Lirong Yang [a, b, d], Yang Yang [a, b, d], Mingyao Meng [a, b, c], Wenju Wang [a, b, c], Shan He [a, b, c], Yiyi Zhao [a, b], Hui Gao [a, b], Weiwei Tang [a, b], Shijie Liu [a, b, d], Zhuying Lin [a, b, d], Lin Li [a, b, c] ✉, Zongliu Hou [a, b, c, *]

100's publications

Cancer Cell
Article

# Identification and validation of a prognostic proteomic signature for cervical cancer

Janet S. Rader [a, *], Amy Pan [b], Bradley Corbin [a], Marissa Iden [a], Yiling Lu [c], Christopher P. Vellano [d], Rehan Akbani [e], Gordon B. Mills [f], Pippa Simpson [b]

[a] Department of Obstetrics and Gynecology, Medical College of Wisconsin, United States of America
[b] Department of Pediatrics, Medical College of Wisconsin, United States of America
[c] Department of Systems Biology, The University of Texas MD Anderson Cancer Center, United States of America
[d] Translational Research to Advance Therapeutics and Innovation in Oncology Platform, The University of Texas MD Anderson Cancer Center, United States of America
[e] Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, United States of America
[f] Cell, Development and Cancer Biology, Knight Cancer Institute, Oregon Health & Science University, United States of America

scientific reports

OPEN

# Identification and validation of a miRNA-based prognostic signature for cervical cancer through an integrated bioinformatics approach

Yumei Qi[1,12], Yo-Liang Lai[2,3,12], Pei-Chun Shen[4], Fang-Hsin Chen[5,6,7], Li-Jie Lin[8], Heng-Hsiung Wu[8,2,4,9], Pei-Hua Peng[10], Kai-Wen Hsu[4,9,11]✉ & Wei-Chung Cheng[2,4,8]✉

# A Comprehensive Pan-Cancer Molecular Study of Gynecologic and Breast Cancers

Ashton C. Berger,[1,36] Anil Korkut,[2,36] Rupa S. Kanchi,[2,36] Apurva M. Hegde,[2] Walter Lenoir,[2] Wenbin Liu,[2] Yuexin Liu,[2] Huihui Fan,[3] Hui Shen,[3] Visweswaran Ravikumar,[2] Arvind Rao,[2] Andre Schultz,[2] Xubin Li,[2] Pavel Sumazin,[4] Cecilia Williams,[5] Pieter Mestdagh,[6] Preethi H. Gunaratne,[7,8] Christina Yau,[9,10] Reanne Bowlby,[11] A. Gordon Robertson,[11] Daniel G. Tiezzi,[12] Chen Wang,[13,14] Andrew D. Cherniack,[1,15] Andrew K. Godwin,[16] Nicole M. Kuderer,[17] Janet S. Rader,[18] Rosemary E. Zuna,[19] Anil K. Sood,[20] Alexander J. Lazar,[21,22,23] Akinyemi I. Ojesina,[24] Clement Adebamowo,[25,26] Sally N. Adebamowo,[25] Keith A. Baggerly,[2] Ting-Wen Chen,[4,27] Hua-Sheng Chiu,[4] Steve Lefever,[6] Liang Liu,[28] Karen MacKenzie,[29] Sandra Orsulic,[30] Jason Roszik,[22,31] Carl Simon Shelley,[32] Qianqian Song,[28] Christopher P. Vellano,[33] Nicolas Wentzensen,[34] The Cancer Genome Atlas Research Network, John N. Weinstein,[2,33,*] Gordon B. Mills,[33,*] Douglas A. Levine,[35,*] and Rehan Akbani[2,37,*]

doi: 10.3389/fgene.2020.616998

# Application of an Autophagy-Related Gene Prognostic Risk Model Based on TCGA Database in Cervical Cancer

*Huadi Shi, Fulan Zhong, Xiaoqiong Yi, Zhenyi Shi, Feiyan Ou, Zumin Xu* and Yufang Zuo**

Volume 95, Issue 6, 24 February 2021
https://doi.org/10.1128/JVI.02354-20

Cellular Response to Infection

# Identification and Complete Validation of Prognostic Gene Signatures for Human Papillomavirus-Associated Cancers: Integrated Approach Covering Different Anatomical Locations

Eun Jung Kwon[a], Mihyang Ha[a], Jeon Yeob Jang[b,c], and Yun Hak Kim[d,e]

SCIENTIFIC REPORTS

OPEN

# Identification of a histone family gene signature for predicting the prognosis of cervical cancer patients

Received: 21 August 2017
Accepted: 13 November 2017
Published online: 28 November 2017

Xiaofang Li[1], Run Tian[2], Hugh Gao[3,4], Yongkang Yang[1], Bryan R. G. Williams[3,4], Michael P. Gantier[3,4], Nigel A. J. McMillan[5], Dakang Xu[3,4,6], Yiqun Hu[6] & Yan'e Gao[1]

Contents lists available at ScienceDirect
Genomics
journal homepage: www.elsevier.com/locate/ygeno

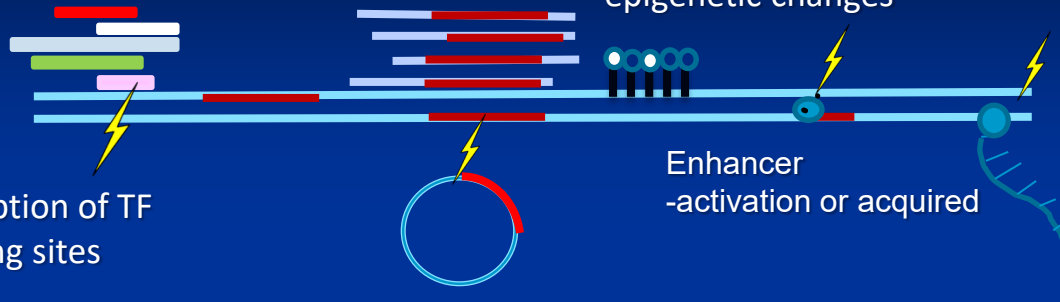
Original Article

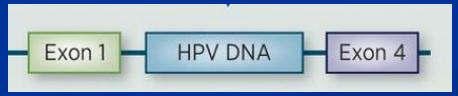
# Predicting DNA methylation from genetic data lacking racial diversity using shared classified random effects

J. Sunil Rao [a, *, 1], Hang Zhang [a, 1], Erin Kobetz [a], Melinda C. Aldrich [b], Douglas Conway [b]

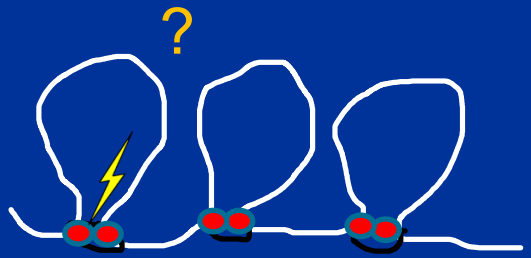
[a] University of Miami, FL, United States of America
[b] Vanderbilt University Medical Center, Nashville, TN, United States of America

# Follow the Science - HPV integration impacts human genome

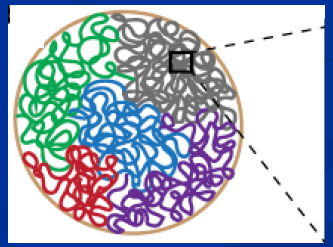



Alter transcription of oncogenes or tumor suppressor genes



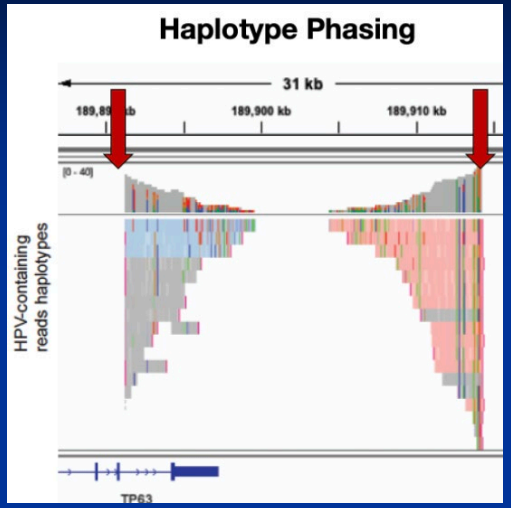

Loss of TAD organization
- Facilitate enhancer-promoter communication
- Impairment of loop extrusion



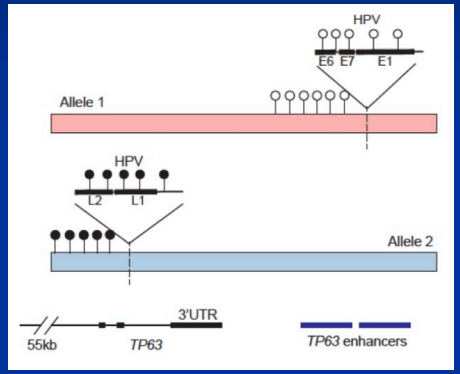

Chromatin interactions (spatial organization of the genome)

# Using integration sites to illuminate novel cervical cancer target genes

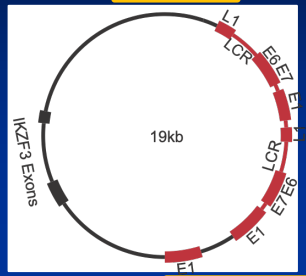
## Long-read DNA & cDNA sequencing technology



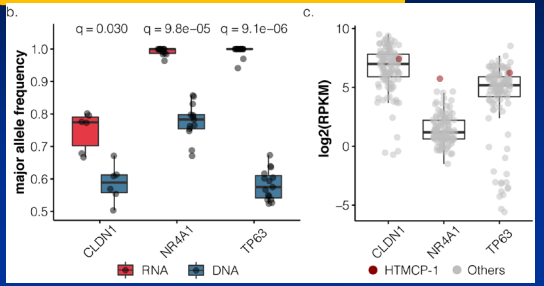

Allele specific methylation



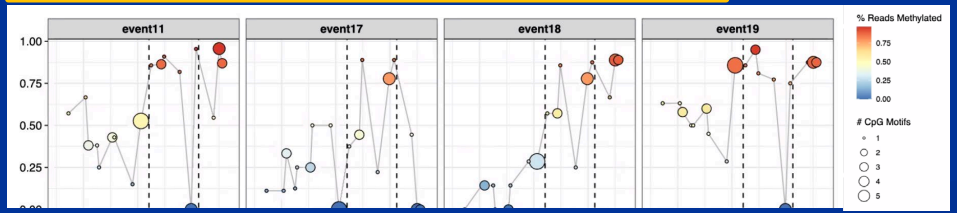

ecDNA



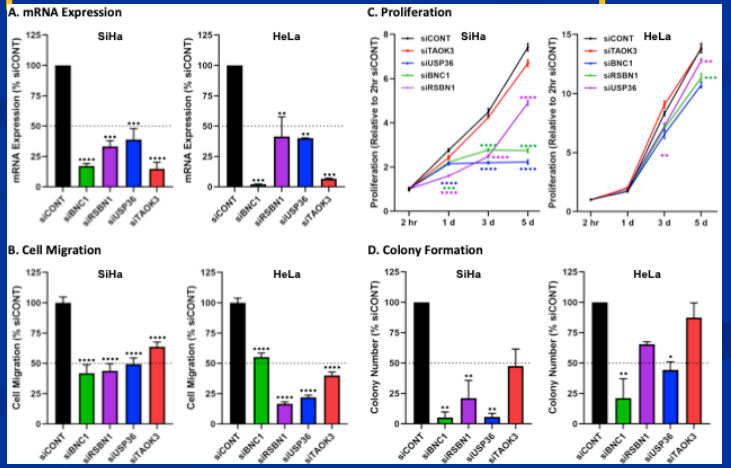

Allele specific expression




Methylation at HPV integration events – HPV genes and nearby human genome




*In-vitro* & *in-vivo* tests of new targets





MCW – Marissa Iden, Sharon Tsaih, Rachel Mutchler
BCGSC – Marco Marra Vanessa Porter, Kieran O'Neill



Iden *et al*. Br J Cancer 2021
R21 CA241013

# Translating Science through Diverse Workforce

Recruit and train ethnically, racially, and linguistically diverse individuals to be clinical research professionals

SPARCC

Student Centered Pipeline to Advance Research in Cancer Careers

R25CA221715

# Daniela Gerhard, PhD

Director of NCI's Office of Cancer Genomics


1953 - 2021

[NCI's Gerhard Remembered]

TCGA and HTMCP projects

# Translating Science to improve Stagnant Cervical Cancer Survival Rates

- **Expand the Science** - Until primary and secondary preventive measures have eliminated cervical cancer - - increase basic and translational cancer research, clinical trials, *in-vivo* models, biobanking and data sharing for stage 0-IV cervical cancer
- **Encourage Adherence** - Align cancer care payments to high-quality, evidence-based care models
- **Mobilize Resources** - Improve access to high quality care for all patients – through funding for travel, housing, and provide infrastructure for collaboration with regional hospitals
- **Expand Trial Access** - Step up clinical trial enrollment for novel agents through funding and international collaborations
- **Develop the Workforce** - Increase diversity and investment in work force training to deliver complex multi-disciplinary care and increase clinical trial participation


Questions