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**
- Fertility preserving
  - Nonsurgical – Chemoprevention
  - Improved surgical procedures
- Survivorship

**Stage I-IV**
- Adherence to Standards
- Effective Chemotherapy
- Biomarkers to guide therapy
- Diverse Workforce

**Advanced/Recurrent**
### Potential Years of Life Lost (PYLL)

Average years of life lost – 20.7 – 23.7 years

#### Top cancers in women in US

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>PYLL per death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bones and joints</td>
<td></td>
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<tr>
<td>Other endocrine including thymus</td>
<td></td>
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<tr>
<td>Cervix uteri</td>
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<tr>
<td>Soft tissue including heart</td>
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<tr>
<td>Hodgkin lymphoma</td>
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<tr>
<td>Brain and other nervous system</td>
<td></td>
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<tr>
<td>Leukemia</td>
<td></td>
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<tr>
<td>Melanoma of the skin</td>
<td></td>
</tr>
<tr>
<td>Nose, nasal cavity, and middle ear</td>
<td></td>
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<tr>
<td>Stomach</td>
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</tr>
</tbody>
</table>

#### Most frequent cancers in Norway

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Ave. YLL per cancer type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer</td>
<td></td>
</tr>
<tr>
<td>CNS tumours</td>
<td></td>
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<tr>
<td>Malignant melanoma</td>
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<tr>
<td>Ovarian cancer</td>
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<tr>
<td>Breast cancer</td>
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<tr>
<td>Oesophageal cancer</td>
<td></td>
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<tr>
<td>Head and neck cancer</td>
<td></td>
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<tr>
<td>Lung cancer</td>
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<tr>
<td>Pancreatic cancer</td>
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<tr>
<td>Kidney cancer</td>
<td></td>
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<tr>
<td>Leukaemia</td>
<td></td>
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<tr>
<td>Anorectal cancer</td>
<td></td>
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<tr>
<td>Gastric cancer</td>
<td></td>
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<tr>
<td>Uterine cancer</td>
<td></td>
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<tr>
<td>Colon cancer</td>
<td></td>
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<tr>
<td>Lymphoma</td>
<td></td>
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<tr>
<td>Bladder(urinary tract) cancer</td>
<td></td>
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<tr>
<td>Prostate cancer</td>
<td></td>
</tr>
</tbody>
</table>

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*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

- Misalignment of $ to quality treatment
- Lack of Skilled Workforce
  Poor training in brachytherapy
- Fragmented Care
  Poor patient resources; low volume hospitals
- Stagnant Survival Rates
  Inadequate treatment

< 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
Pfaendler et al. Obstet & Gynecol 2018
Robin et al. Gynecol Oncol 2016
Expand the Science

Advanced-Recurrent Cervical cancer
median age women - 50 years

GOG 240 - NCT00803062
Chemotherapy +/- Bevacizumab

KEYNOTE-826 - NCT03635567
Platinum-based chemotherapy with or without bevacizumab +/- pembrolizumab

Tewari et al. NEJM 2014 & Lancet 2017

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

<table>
<thead>
<tr>
<th>Normal</th>
<th>VCE</th>
<th>CIN I</th>
<th>CIN II</th>
<th>CIN III</th>
<th>Cancer</th>
</tr>
</thead>
</table>

Drivers 1
- TP53
- RB 96%

Drivers 2
- PIK3CA - 40% / APOBEC
- 3q amp (TP63) - 66%

Drivers 3
- EP300
- FBXW7
- PTEN
- HLA-A
- ARID1A
- NFE2L2
- HLA-B
- ERRB3
- KRAS
- MAPK1
- 
- ?
- ≤ 11%

Viral Integration

HPV Oncoproteins
- E6, E7
Focus on the Cancer Gaps at Cancer Funding

Drivers 1
- TP53
- RB

Viral Integration
- HPV Oncoproteins E6, E7

Drivers 2
- PIK3CA - 40%
- APOBEC
- 3q amp (TP63) - 66%

Drivers 3
- EP300
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- HLA-A
- ARID1A
- NF2E2L2
- HLA-B
- ERRB3
- KRAS
- MAPK1

NIH Cervical 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

Gagliardi et al. Nature Genetics 2020
TCGA et al. Nature 2017

Tools - MSK cBioPortal; UCSC Xena; Broad IGV, Firehose........
Pancancer survival analysis of cancer hallmark genes

Nam-Phuong D. Nguyen1, Viraj Deshpande1, Jens Luebeck2, Paul S. Mischel3,4,5,6,7 and Vinita Bhatia1

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

Linyang Yang1,2,3,4, Yang Yang1,2,3,4, Mingyao Meng1,2,3,4, Wenjie Wang1,3,4, Shan He1,3,4, Yiyi Zhao1,2,5, Hui Gao1,2,5, Weiwei Tang1,2, Shijie Liu1,3,4, Zhiqun Lin1,3,4, Lin Li1,3,4,8, Zongli Han1,3,4,5,6,7,8

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

Yumei Gu1,2,3,4, Jian-Liang Li1,2,3,4,5, Quan Shi1,2,3,4,5, Jun-Li Guan1,2,3,4,5, Li He1,2,3,4,5,6, Heng-Hong Wu1,2,3,4,5,6,7, Xin-Ping Peng1,2,3,4,5,6,7,8, Wei-Cheng Cheng1,2,3,4,5,6,7,8

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

Aashin C. Barger1, Anil Korukut1,2, Rupas K. Kancherla1, Saurabh M. Hegde1, Walter Lenoir1, Wenbin Liu1, Yuanxin Liu1, Huihui Fan1, Hui Shen1, Vinodwararao Ravukorma1, Anirudha Roy1, Andre Schultz1, Xiaolin Li1, Pavel Sumazin1, Cecilia Williams1, Peter Mestdagt1, Preethi H. Gunaratne2, Christina Yau1, Reanne Bowley1, Gordon Robertson1, Daniel G. Tietz1, Chen Wang1, Andrew D. Chernyshev1, Andrew K. Gowda1, Nicole M. Kuteiner1, Janet S. Rader1, Rosamary E. Zuna1, Amir K. Sood1, Alexander J. Lazzaro1, Alinyemi I. Osinubi1, Clement Adelabum1, Yalena S. Adelabum1, Keith A. Baggerly1, Ting-Wen Chen1, Hu-Sheng Chiu1, Steve Lofeiever1, Lungan Liu1, Karen MacKenzie1, Sandra Grigoleit1, Jason Rousk1, Carl Simonshaw1, Qiangwen Song1, Christopher P. Vellano1, Nicolas Wenzel1,2, The Cancer Genome Atlas Research Network, John N. Weinstein1,2,3,4,5,6,7,8,9, Gordon B. Mills1,2,3,4,5,6,7,8,9, Douglas A. Levine1,2,3,4,5,6,7,8,9,10, and Reiham Alkhali1,2,3,4,5,6,7,8,9,10

Identification and validation of a prognostic proteomic signature for cervical cancer

Janet S. Rader1,2,3, Amy Pan4,5, Bradley Corbin6, Marissa Iden7, Yiling Lu7, Christopher P. Vellano2,3,4,5,6, Rehan Akbari7, Gordon B. Mills7,8,9, Pippa Simpson7,8,9

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

Eun Jung Kwon1, Mihyung Ha1, Jeon Yoo-Hang1,2 and Yun Hak Kim3,4

Prediction of DNA methylation from genetic data lacking racial diversity using shared classifier random effects

J. Sunil Rau1,2,3,4, Hong Zhang1,2,3,4, Erin Kobetz3,4, Melissa C. Aldrich3,4, Douglas Conway3,4

Cellular Response to Infection

Volume: 95, Issue: 6, 26 February 2021
https://doi.org/10.1128/PM.02384-20

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

Xiaofang Lan1, Yun Tian1, Haitao He1, Longhao Wang1, Zhiyuan Li1, Xueying Wang1, Zhenhui Wang1, Xuefeng Wang1 and Vinita Bhatia1
Follow the Science - HPV integration impacts human genome

- Extrachromosomal DNA - oncogene amplification
- Regional amplification
- Regional sites of epigenetic changes
- Enhancer - activation or acquired
- eRNA - regulate target gene
- Alter transcription of oncogenes or tumor suppressor genes

- Disruption of TF binding sites
- Extrachromosomal DNA - oncogene amplification
- 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

EcDNA

Allele specific expression

In-vitro & in-vivo tests of new targets

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

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.
Daniela Gerhard, PhD
Director of NCI’s Office of Cancer Genomics

1953 - 2021

TCGA and HTMCP projects

NCI’s Gerhard Remembered
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