NIH Update

Kathy Hudson, PhD
Deputy Director for Science, Outreach, and Policy

December 15, 2014

FY15 Omnibus Appropriations

- Congress passed the FY15 Omnibus this weekend
- Includes $30.3 billion for NIH, a $150 million increase over 2014
- NIH total still below 2012 pre-sequestration budget
- Bill provides $238 million to NIAID in emergency funding to address Ebola crisis

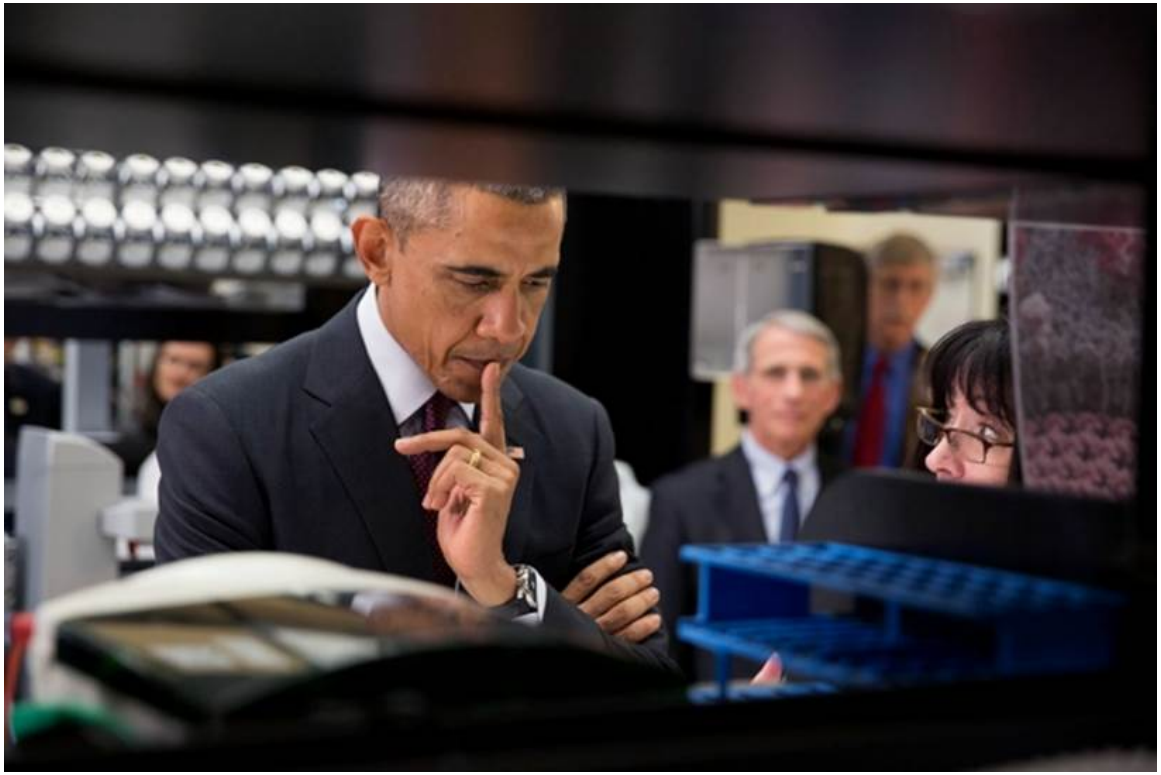
FY15 Omnibus Appropriations *(cont.)*

- New name for NCCAM: National Center for Complementary and Integrative Health (NCCIH)
- Requirement to develop 5-year NIH-wide strategic plan
- Requirement to support a National Academy of Sciences study to develop recommendations to improve scientific literacy, education, and enhance scientific regard amongst the American public

FY15 Omnibus Appropriations *(cont.)*

- Bill and Report Language concerning the National Children's Study, to maintain the mission and goals of the National Children's Study, with flexibility on how to carry this out.
- Expressed Congressional interest in issues also of concern to NIH:
  - Clinical trials
  - Data sharing
  - Reproducibility of research results
  - Inclusion of women in clinical research
  - Sex as a biological variable in research
  - Health disparities

President Obama's Visit to NIH Dec. 2



President Obama listening to Dr. Nancy Sullivan

- Toured Vaccine Research Center
- Met with Ebola researchers
- Spoke to NIH staff

New NIH Policies: *Clinical Trial Data Sharing*

- Researchers have ethical obligation to share clinical trial results swiftly and transparently
- Prompt dissemination of results is essential for guiding future research
- 11-19 HHS draft regulation to require registration and results reporting for trials covered by FDAAA
- NIH released draft policy to apply data reporting requirements to all NIH-funded clinical trials
  - Comments due February 19, 2015

New NIH Policies: *Single Institutional Review Board*

- Obtaining approval from multiple IRBs
  - Takes time, money, and lots of patience
  - Does not increase protections for participants
- 12-2 NIH draft policy to require single IRBs in multi-site clinical research studies
  - Exceptions allowed if local IRB review is needed for special populations or required by state, local, or tribal laws
  - Comments due January 29, 2015

Advisory Committee to the Director (ACD)

- Met December 11-12
- Presentations on Ebola, Peer Review, Reproducibility, NIGMS research, others
- Reports from working groups
  - Physician Scientist Working Group
  - Intramural Research Program Working Group
  - National Children's Study Working Group
  - HeLa Working Group
- Created new Future of NLM Working Group

- **Huda Akil, Ph.D.***
  University of Michigan
- **Russ B. Altman, M.D., Ph.D.**
  Stanford University
- **Cori Bargmann, Ph.D.**
  The Rockefeller University
- **Mary Sue Coleman , Ph.D.**
  Past President University of Michigan
- **Lisa A. Cooper, M.D., M.P.H.***
  Johns Hopkins
- **David Ginsburg, M.D.**
  University of Michigan
- **Eric P. Goosby, M.D.***
  University of California at San Francisco
- **Helen Haskell Hobbs, M.D.**
  University of Texas Southwestern Medical Center
- **H. Robert Horvitz, Ph.D.**
  Massachusetts Institute of Technology
- **Renee R. Jenkins, M.D.**
  Howard University
- **Harlan M. Krumholz, M.D.***
  Yale School of Medicine
- **Cato T. Laurencin, M.D., Ph.D.**
  The University of Connecticut
- **Richard P. Lifton, M.D., Ph.D.***
  Yale
- **W. Ian Lipkin, M.D.**
  Columbia University
- **Peter R. MacLeish, Ph.D.**
  Morehouse School of Medicine
- **Elba E. Serrano, Ph.D.***
  New Mexico State University
- **Moncef M. Slaoui, Ph.D.**
  GlaxoSmithKline
- **Reed Tuckson, M.D.**
  Tuckson Health Connections, LLC
- **Michael J. Welsh, M.D.**
  University of Iowa
- **Christopher B. Wilson, M.D.**
  Bill & Melinda Gates Foundation

National Children's Study (NCS)

- Long and tumultuous evolution
- Planned to be launched in two phases:
  - The **Vanguard Study** *(pilot study to evaluate the feasibility, acceptability, and cost of different recruitment strategies, study procedures, and outcome assessments for use in the Main Study)*
  - The **Main Study** *(l*ongitudinal, observational cohort study to examine a broad range of environmental and biological factors on children's health, growth, and development
  - *100,000 children from womb to age 21 (not yet initiated)*
- Up to $1.3 billion dollars have been appropriated for NCS

NCS: *Impetus for ACD Working Group*

- Persistent concerns - echoed in a 2014 NAS report - about
  - Study design
  - Management and oversight structures
  - Escalating costs of the NCS
  - Need to consider evolving scientific and technological landscape
  - Newer models for conducting robust and cost-effective research
- NCS put on hold on June 16, 2014
- ACD Working Group established

NCS: *Roster for ACD Working Group*

Russ Altman* ***(co-chair)*** – Stanford *(*computational sciences)

Philip Pizzo (co-chair) – Stanford (pediatrics)

Robert Gibbons – U Chicago (biostatistics)

Kathy Hudson – NIH (policy/genetics)

Renee Jenkins* – Howard U (pediatrics)

Brendan Lee – Baylor College of Medicine (pediatrics)

Maureen Lichtveld – Tulane U (environmental health policy)

Marie Lynn Miranda – U Michigan (pediatric environmental health)

Cheryl Perry – U of Texas Health Sciences Center (behavior and prevention)

Huda Zoghbi – Baylor College of Medicine (developmental genetics)

Lyric Jorgenson ***(exec. sec.)*** – NIH (policy, developmental neuroscience)

**indicates ACD member*

NCS: *Charge to ACD Working Group*

- The NCS Working Group of the ACD is ***charged with evaluating whether the NCS is feasible***, as currently outlined, especially in light of increasing and significant budget constraints.
  - ***If "yes",*** assessing how NIH can move forward to implement necessary changes, including some of those outlined in the NAS report.
  - ***If "no",*** identifying whether there are new methods to answer key research questions that are most important to pediatric health today that capitalize on research and technology advances developed in the intervening years since the inception of the study.
- The NCS Working Group of the ACD presented a final report for consideration by the ACD at its December 11-12, 2014 meeting.

NCS: *Findings of ACD Working Group*

Working Group reached unanimity in its core finding

While the overall goals of examining how environmental factors – defined broadly – influence health and development are meritorious and should be a priority for future scientific support, **the NCS, as currently outlined, is not feasible.**

NCS: *Recommendations of ACD WG*

- The NICHD NCS Program Office should be dissolved
- Given the breadth and depth of the topics that reside around the NCS, a trans-NIH approach should be pursued, ideally convened and supported by the Office of the Director
- Vanguard Study data should be archived and available for request by investigators for secondary analyses
- The Vanguard Study should not collect any further data

NCS: *Recommendations of ACD WG (cont.)*

- Time did not allow full consideration of the wide range of options regarding optimal study designs
- The following approaches offered for consideration:
  - **A series of smaller focused studies** designed as tailored explorations
  - **A multi-center collaborative network of scientific teams**, who compete on responses to a well-considered funding announcement
  - **A focused cohort design to facilitate longitudinal biospecimen collection and banking**
  - **Probability sampling should be an integral feature** of the methodological approach

NCS: *Recommendations of ACD WG (cont.)*

With the conclusion that the NCS is not feasible as currently outlined:

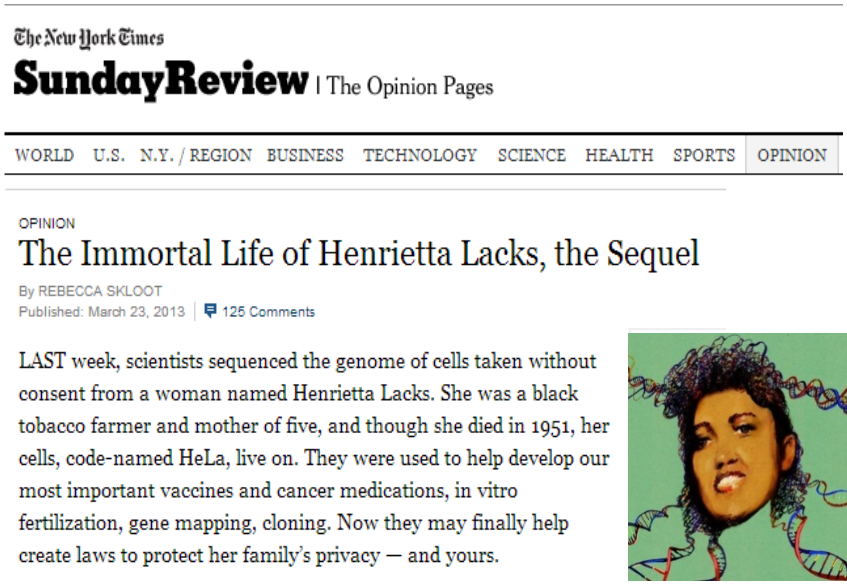
The Working Group recommends that **NIH champion and support new study designs, informed by advances in technology and basic and applied research**, that could make the original goals of the NCS more achievable, feasible and affordable.

NIH Reaction to NCS Working Group Report

- NIH Director accepted ACD findings and recommendations
- Oversight of NCS office turned over to Dr. David Murray, NIH Associate Director for Prevention
  - Close out current contracts
  - Establish plan for data and specimens that have been collected
- NIH will move quickly to devise an alternative approach to achieve goals of NCS

HeLa Working Group: Genesis

- March 2013 – researchers in Germany posted the first HeLa whole genome sequence
- Lacks family asked that the sequence be removed
- A 2nd publication pending with Nature
- Growing public and media attention
- NIH reached out to the family



The New York Times
SundayReview | The Opinion Pages

WORLD U.S. N.Y. / REGION BUSINESS TECHNOLOGY SCIENCE HEALTH SPORTS OPINION

OPINION

The Immortal Life of Henrietta Lacks, the Sequel

By REBECCA SKLOOT
Published: March 23, 2013 | 126 Comments

LAST week, scientists sequenced the genome of cells taken without consent from a woman named Henrietta Lacks. She was a black tobacco farmer and mother of five, and though she died in 1951, her cells, code-named HeLa, live on. They were used to help develop our most important vaccines and cancer medications, in vitro fertilization, gene mapping, cloning. Now they may finally help create laws to protect her family's privacy — and yours.

"I look at it as though these are my grandmother's medical records that are just out there for the world to see." **- Jeri Lacks-Whye, granddaughter**

NIH & the Lacks Family: Working Together

- HeLa cells and data are ubiquitous
- Approximately 1,700 gigabases of HeLa genomic data is available in public databases
- HeLa cells can be sequenced and the genomic data can be analyzed at any time
- The family has been through decades of unwanted intrusions and surprises
- No one had broken any laws
- Solution needed to advance science, respect family, and catalyze policy advances.

August 7, 2013: An Historic Agreement

LETTER

doi:10.1038/natu

The haplotype-resolved genome and epigenome
the aneuploid HeLa cancer cell line

Andrew Adey[1]*, Joshua N. Burton[1]*, Jacob O. Kitzman[1]*, Joseph B. Hiatt[1], Alexandra P. Lewis[1], Beth K. Martin[1], Ruolan
Choli Lee[1] & Jay Shendure[1]

The HeLa cell line was established in 1951 from cervical cancer cells taken from a patient, Henrietta Lacks. This was the first successful attempt to immortalize human-derived cells *in vitro*[1]. The robust growth and unrestricted distribution of HeLa cells resulted in its broad adoption—both intentionally and through widespread cross-contamination[2]—and for the past 60 years it has served a role analogous to that of a model organism[3]. The cumulative impact of the HeLa cell line on research is demonstrated by its occurrence in more than 74,000 PubMed abstracts (approximately 0.3%). The genomic architecture of HeLa remains largely unexplored beyond its karyotype[4], partly because like many cancers, its extensive aneuploidy renders such analyses challenging. We carried out haplotype-resolved whole-genome sequencing[5] of the HeLa CCL-2 strain, examined point- and indel-mutation variations, mapped copy-number variations and loss of heterozygosity regions, and phased variants across full chromosome arms. We also investigated variation and copy-number profiles for HeLa S3 and eight additional strains. We find that HeLa is relatively stable in terms of point variation, with few new mutations accumulating after early passaging. Haplotype resolution facilitated reconstruction of an amplified, highly rearranged region of chromosome 8q24.21 at which integration of the human papilloma virus type 18 (HPV-18) genome occurred and that is likely to be the event that initiated tumorigenesis. We combined these maps with RNA-seq[6] and ENCODE Project[7] data sets to phase the HeLa epigenome. This revealed strong, haplotype-specific activation of the proto-oncogene *MYC* by the integrated HPV-18 genome approximately 500 kilobases upstream, and enabled global analyses of the relationship between gene dosage and expression. These data provide an extensively phased, high-quality reference genome for past and future experiments relying on HeLa, and demonstrate the value of haplotype resolution for characterizing cancer genomes and epigenomes.

We generated a haplotype-resolved genome sequence of HeLa CCL-2 using a multifaceted approach that included shotgun, mate-pair and long-read sequencing, as well as sequencing of pools of fosmid clones[5] (Supplementary Table 1). To catalogue variants, we carried out conventional shotgun sequencing to 88× non-duplicate coverage and reanalysed 11 control germline genomes in parallel[8] (Supplementary Tables 2 and 3). Although normal tissue corresponding to HeLa is unavailable, the total number of single-nucleotide variants (SNVs) identified in HeLa CCL-2 ($n = 4.1 \times 10^6$) and the proportion overlapping with the 1000 Genomes Project[9] (90.2%) were similar to controls (mean $n = 4.2 \times 10^6$ and 87.7%, respectively), suggesting that HeLa has not accumulated appreciably large numbers of somatic SNVs relative to inherited variants. Indel variation was unremarkable after accounting for differences in coverage (Supplementary Fig. 1). Short tandem repeat profiles of HeLa also resembled controls, consistent with mismatch repair proficiency (Supplementary Fig. 2).

After removing protein-altering variants that overlapped with the 1000 Genomes Project or the Exome Sequencing Project[10], similar numbers of private protein-altering (PPA) SNVs were found in HeLa ($n = 269$) and controls (mean $n = 391$). Gene ontology found that all terms enriched for PPA variants in HeLa ($P \leq 0.$ also enriched in at least one control (except for 'startle resp HeLa), suggesting that known cancer-related pathways are turbed extensively by point or indel mutations (Supplementary Although a previous study of the HeLa transcriptome[11] repo enrichment of putative mutations in cell-cycle- and E2F-relate subsequently generated population-scale data sets contain all that we observed in these genes, suggesting that they are inher benign rather than somatic and pathogenic.

The overlap between PPA variants and the Catalogue of Mutations in Cancer (COSMIC)[12] was similar for HeLa ($n =$ control genomes (mean $n = 2.6$). The gene-level overlap Sanger Cancer Gene Census (SCGC)[12] was also similar fo ($n = 4$) and control genomes (mean $n = 8.7$). Canonical tumo pressors and oncogenes were notably absent among the fiv genes with PPA variants in HeLa (*BCL11B* (B-cell CLL/lympho (zinc finger protein)), *EP300* (E1A binding protein p300), (fibroblast growth factor receptor 3), *NOTCH1* and *PRDM* domain containing 16), Supplementary Tables 3–6). Howeve are associated with HPV-mediated oncogenesis (*FGFR3*, *NOTCH1*) and may be ancillary to the dominant role of HP proteins in HeLa and other HPV$^+$ cervical carcinomas[13]. Muta *FGFR3* have been noted previously in cervical carcinomas, a infrequently and at different residues than observed here *EP300* and *NOTCH1* are recurrently mutated in diverse canc are involved in Notch signalling, a pathway that is dysregu HeLa[14]. *EP300*, which encodes the transcriptional co-activat interacts directly with viral oncoproteins such as HPV-16 HPV-16 E7 (ref. 16). Although the in-frame deletion of a hig served amino acid in *EP300* seems to be somatic (heterozygous loss-of-heterozygosity (LOH) region), it is still possible that th are rare, inherited variants or passenger mutations. Further stu required to resolve their functional relevance and to assess these genes are recurrently altered in HPV$^+$ cervical carcinon

Aneuploidy and LOH, which are hallmarks of cancer g were mapped in HeLa by constructing a digital copy-number p kilobase resolution (Fig. 1, Supplementary Fig. 4 and Supple Table 7). Read coverage profiles were segmented by a Hidden Model (HMM) and recalibrated to account for widespread an (Supplementary Figs 5 and 6). Sixty-one per cent of the genon baseline copy number of three, and only a small minority (3%) ha number of greater than four or less than two (Supplementary T LOH encompassed 15.7% of the genome, including several enti mosome arms (5p, 6q, Xp, Xq) or large distal portions (2q, 3q, 13q, 19p, 22q) (Supplementary Fig. 7 and Supplementary Table sistent with previous descriptions of LOH in cervical carcinom overall profile is consistent with published karyotypes of vario strains[4], suggesting that the hypertriploid state arose either durin rigenesis or early in the establishment of the HeLa cell line.

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*These authors contributed equally to this work.

COMMENT

COURTESY OF LACKS FAMILY

Henrietta Lacks' family gather around a historical marker dedicated to her in Virginia in 2011.

Family matters

Kathy L. Hudson and **Francis S. Collins** discuss how and why the US National Institutes of Health worked with the family of Henrietta Lacks, the unwitting source of the HeLa cell line, to craft an agreement for access to HeLa genome data.

In March, two of the most deeply held values in the medical-research community — public data-sharing and respect for research participants — collided when the genome of the ubiquitous cell line HeLa was published[1] and posted in a public database. Controversy ensued. The full sequence data could potentially uncover unwanted information about people whose identity is widely known: the family of the woman from whom this immortal line was derived 62 years ago, Henrietta Lacks.

So, since March, the US National Institutes of Health (NIH) in Bethesda, Maryland, has worked closely with Lacks' family. Together, we have crafted a path that addresses the family's concerns, including consent and privacy, while making the HeLa genomic sequence data available to scientists to further the family's commitment to biomedical research.

The agreement that we reached goes into effect this week. We hope that it, and its genesis, will spur broader discussions regarding consent for future use of biospecimens, with a goal of fostering true partnerships between researchers and research participants.

MEDICAL HISTORY

In 1951, physicians at Johns Hopkins Hospital in Baltimore, Maryland, took a biopsy from Henrietta Lacks, a 31-year-old African American woman who had an aggressive form of cervical cancer. This biospecimen was taken without her permission or knowledge; US regulations requiring consent ▸

The Agreement

A**ll researchers must**:

- Apply for access to HeLa whole genome sequence
- Abide by terms defined by the Lacks family
  - Biomedical research only
  - No contact with family
  - Disclosure of commercial plans
  - Include acknowledgment in publications and presentations
- Deposit future whole genome sequence data into dbGaP
- The HeLa Genome Data Access Working Group evaluates requests

May 2014: Workshop

Should the HeLa controlled-access policy be expanded beyond the full genome sequence?

Family Preferences:

- Scientists should have efficient access to HeLa genomic data
- Don’t want to delay science
- Want to be informed about advances from HeLa cells in research

ACD Recommendation to NIH Director:

- No change to the NIH HeLa genome data policy
- Special session at a national scientific meeting to focus on advances from research utilizing HeLa cells

December 2014: Consulting the Family

- In-person meeting with members of the Lacks family
- Consulted on the outcomes of the workshop:
  - keep the policy limited to WGS. They don't want to delay science; want to be sure others benefit
  - Liked the idea of a symposium on scientific advances from HeLa; one for science crowd, one for lay crowd
- This family is proud of what has been learned from HeLa
- Want to be part of the discussion

Moving Forward: An Entire Community

- There are now 4 HeLa sequences in dbGaP
- 30 Data Access Requests evaluated by the Working Group
- Newest paper in Cell last Thursday, included acknowledgment to Henrietta Lacks & family
- Unique moment in the history of science:
  - A reminder to all researchers – there are individuals behind the samples and data
  - Catalyst for national policies on consent

Lacks Family Members & the HeLa Working Group