

Viral Metagenomics in Epidemiology:

~~A computational recycling program~~

A critical technology for understand viruses

Stephen S. Francis MS PhD

Neuro and Molecular Epidemiology Laboratory

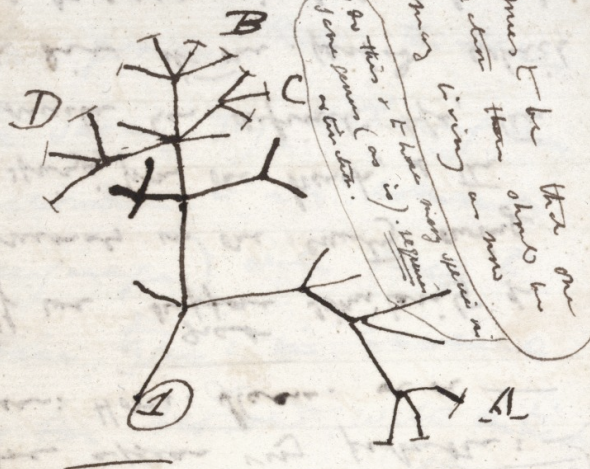
Department of Neurological Surgery, UCSF



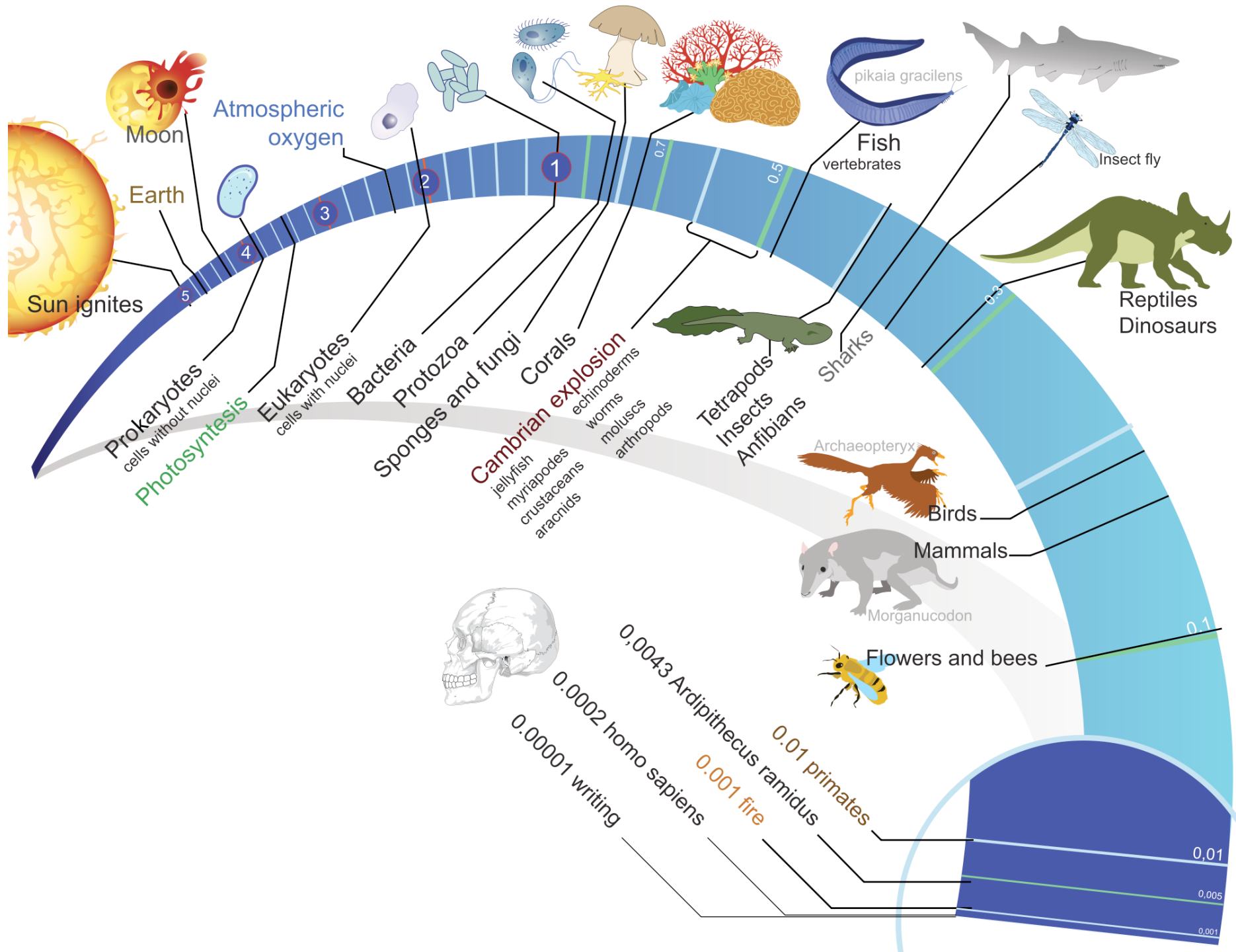
Outline

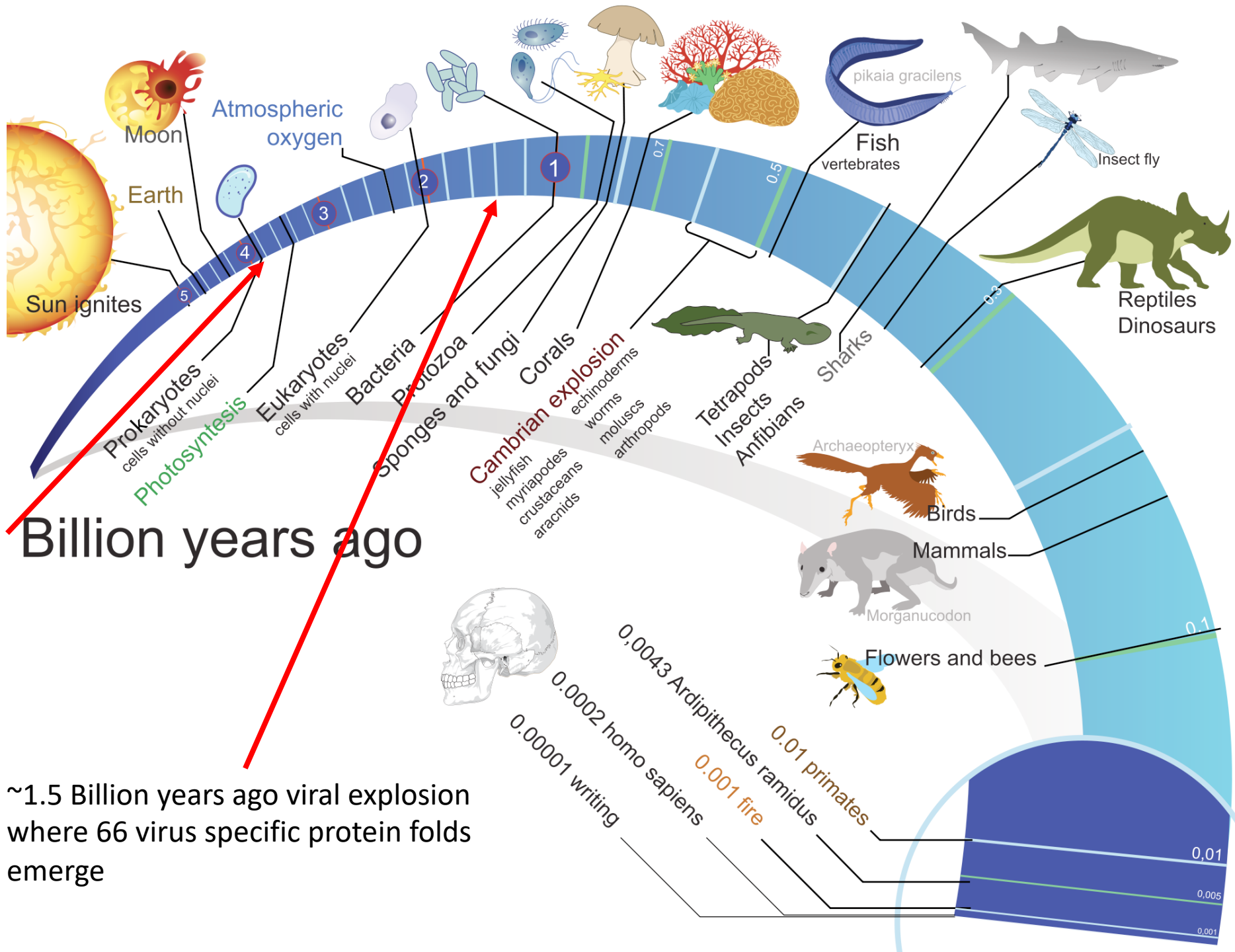
- A (very) brief background of viruses
- General metagenomic approaches
- NIPT China study
- UAE SARS

I think



Then between A & B. various
 sort of relation. C & B. The
 finest gradation, B & D
 rather greater distinction
 Then genera would be
 formed. - bearing relation





~3.5-4 Billion
years ago
viruses arrived

~1.5 Billion years ago viral explosion
where 66 virus specific protein folds
emerge

A phylogenomic data-driven exploration of viral origins and evolution

Arshan Nasir* and Gustavo Caetano-Anollés†

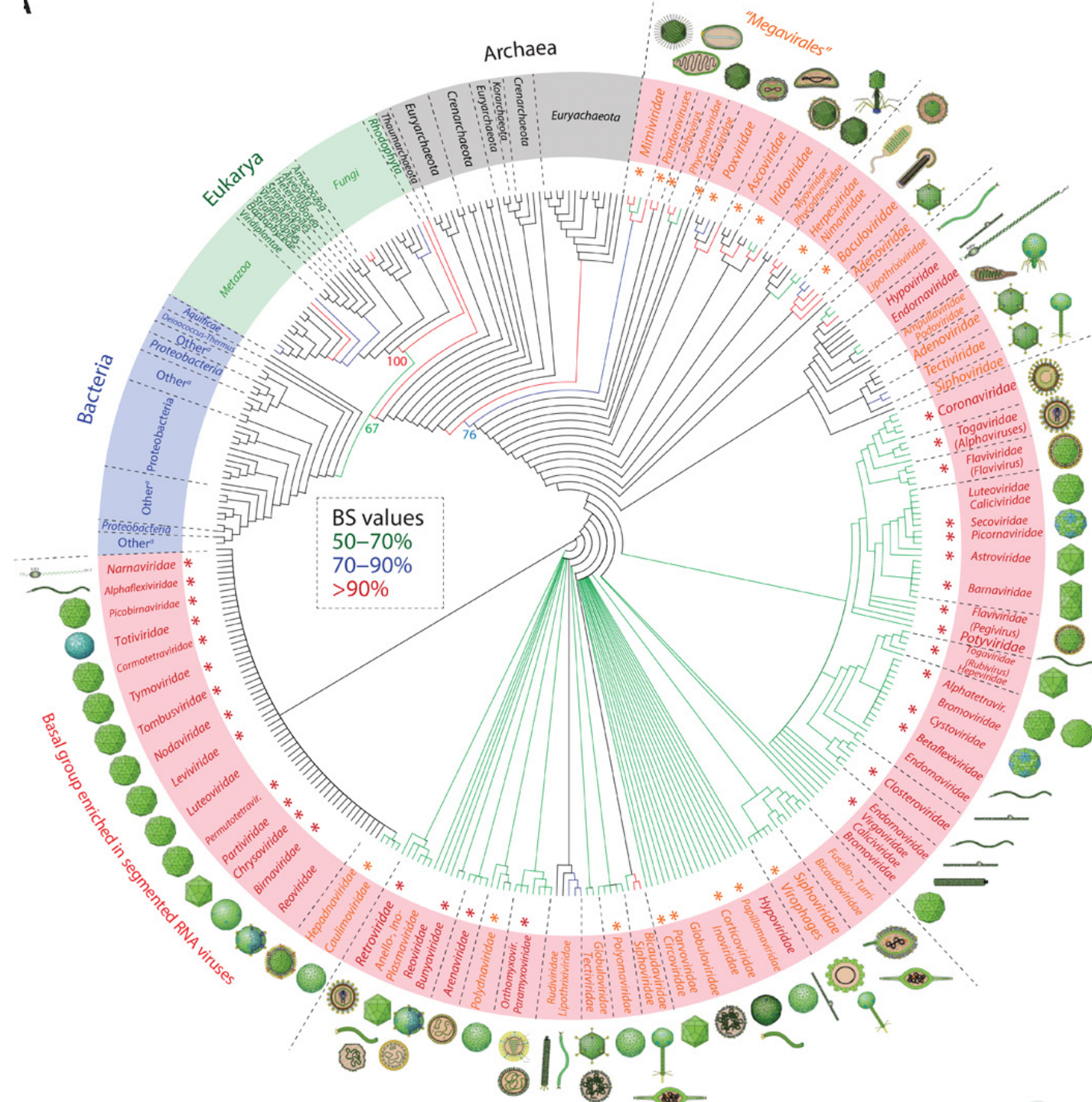
† See all authors and affiliations

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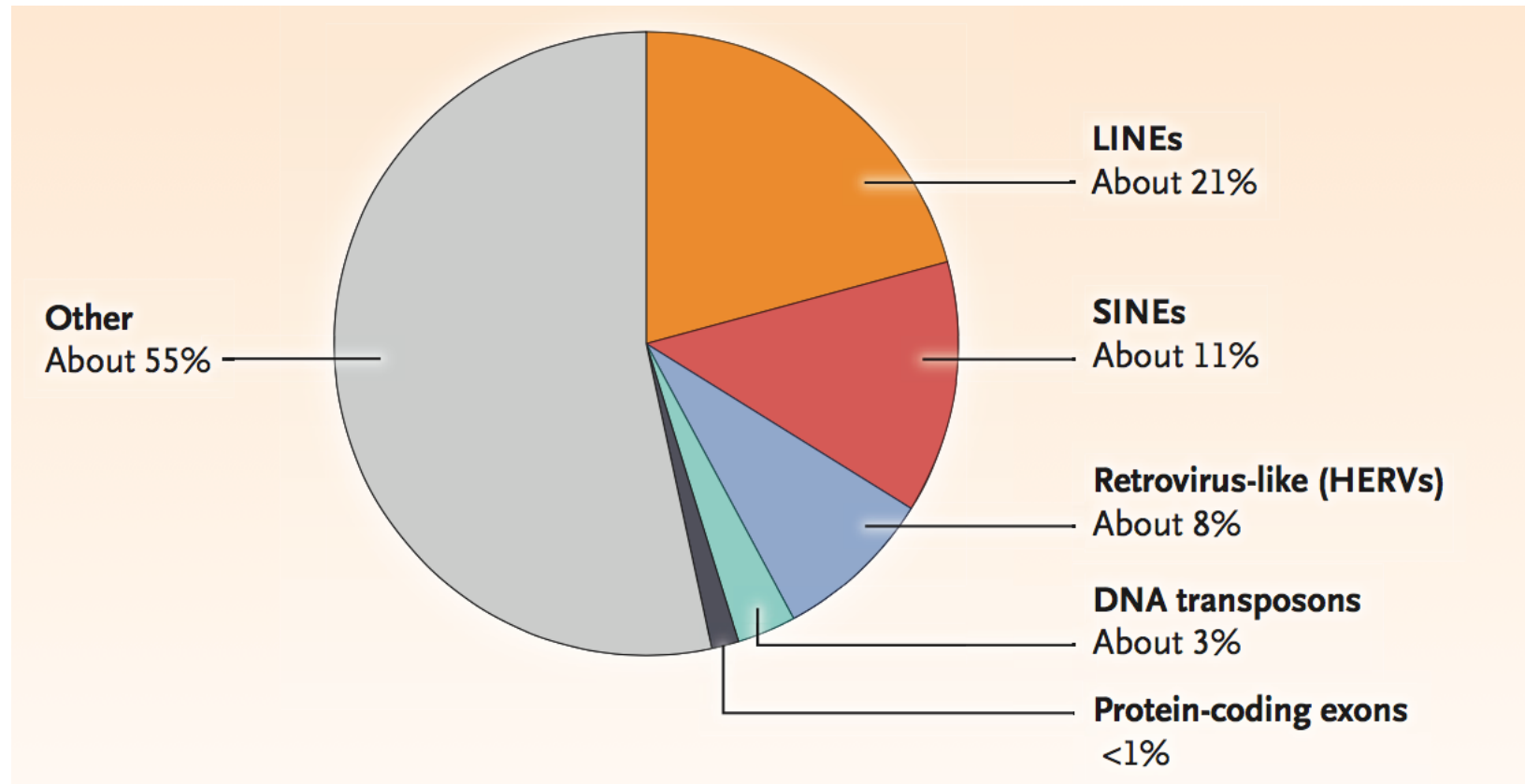
-Viruses are incredibly diverse and have existed since cellular organisms evolved.

-Many viruses have independent lineages

-They, we, have all evolved together.



Your Genome



Origins of Human Infectious Diseases

Hunter Gatherer



Babylon

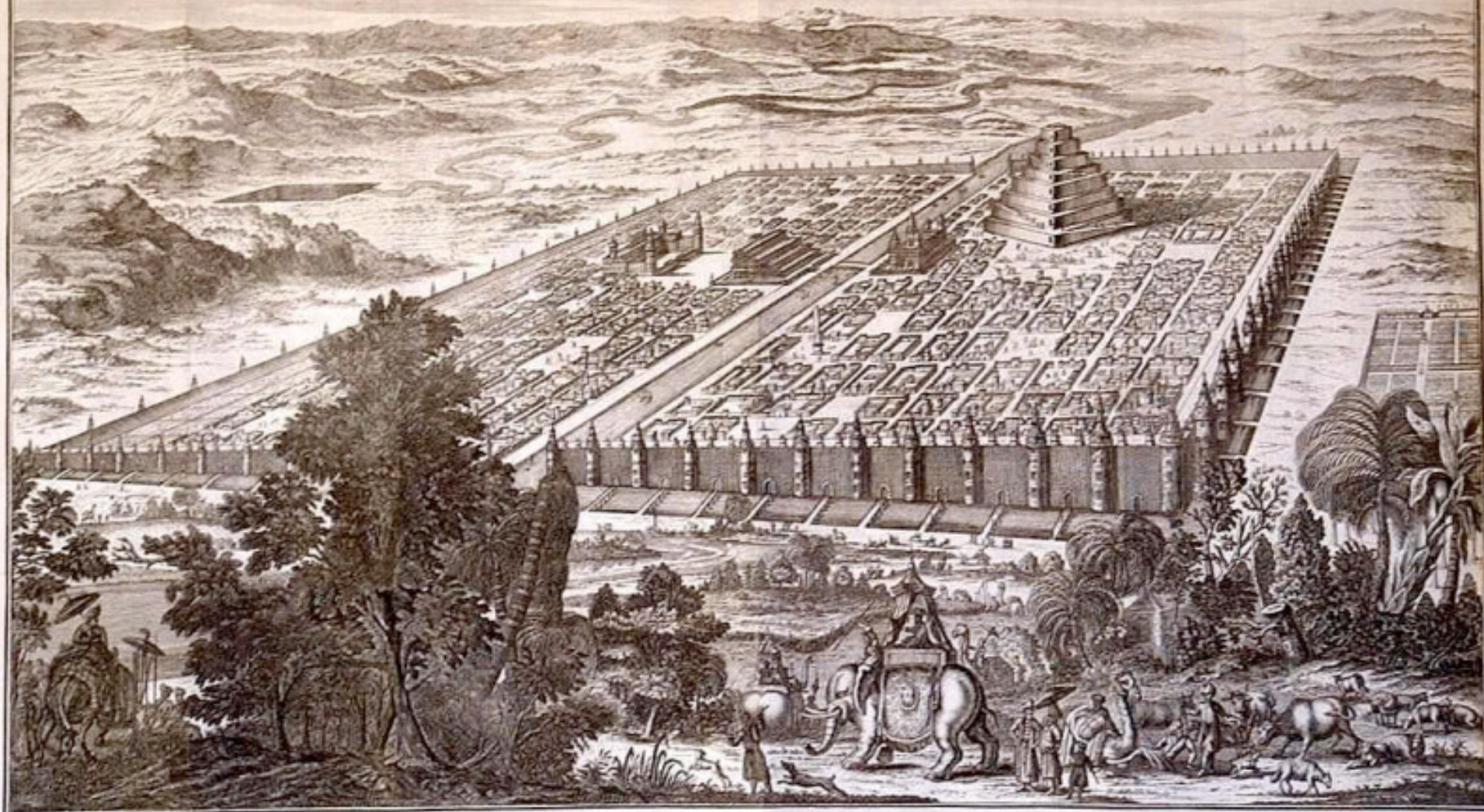


Agriculture + Domestication



Read:
Guns, Germs, and Steel

DE STAD BABILON.



The Code of Hammurabi

~1700 BC



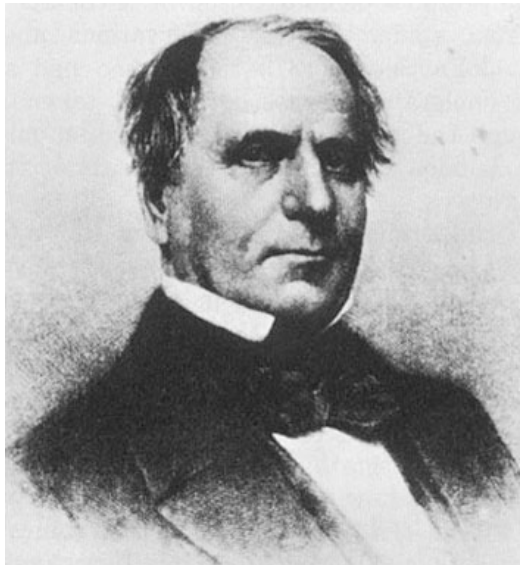
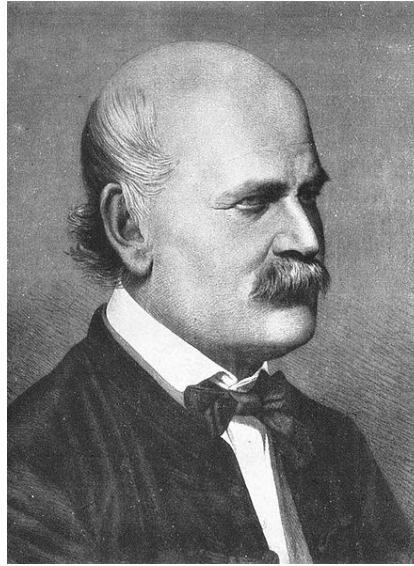
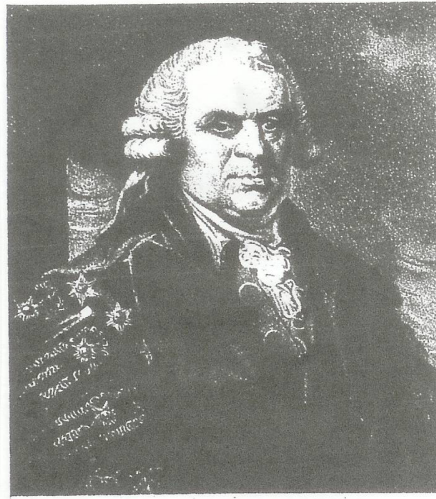


“History is more than just a record of the accomplishments of a field in the past and development of its theory, principals, methods and achievements. History provides the context in which the continuing paradigm changes of the field occur.”

-Dr Warren Winkelstein Jr.



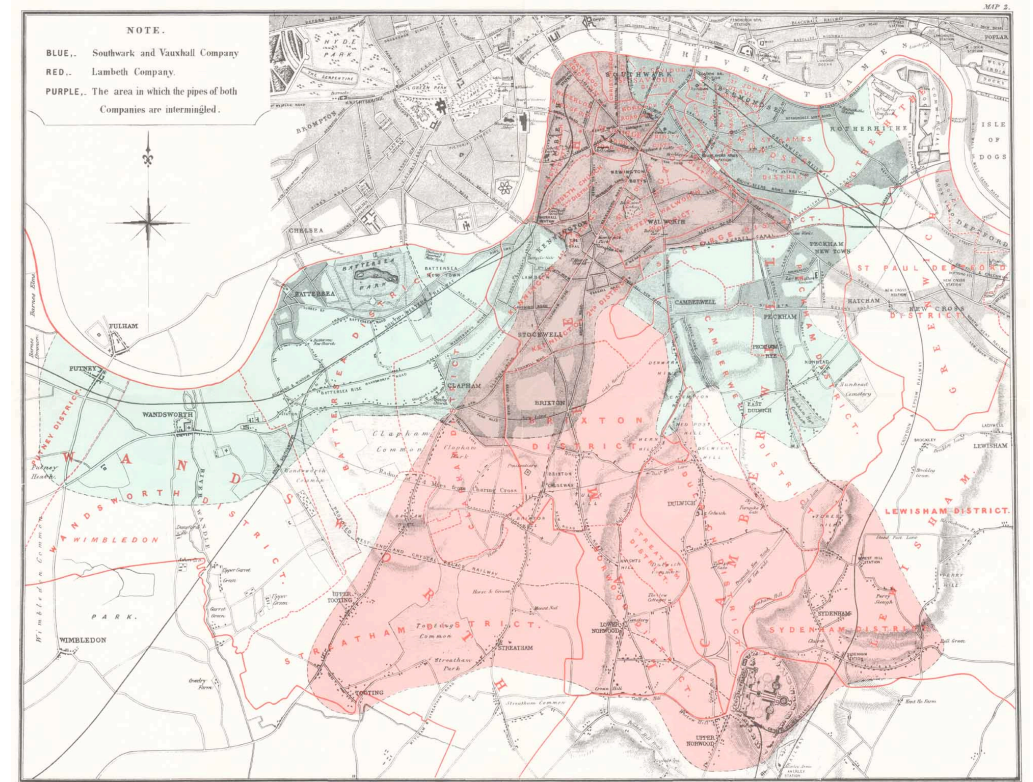
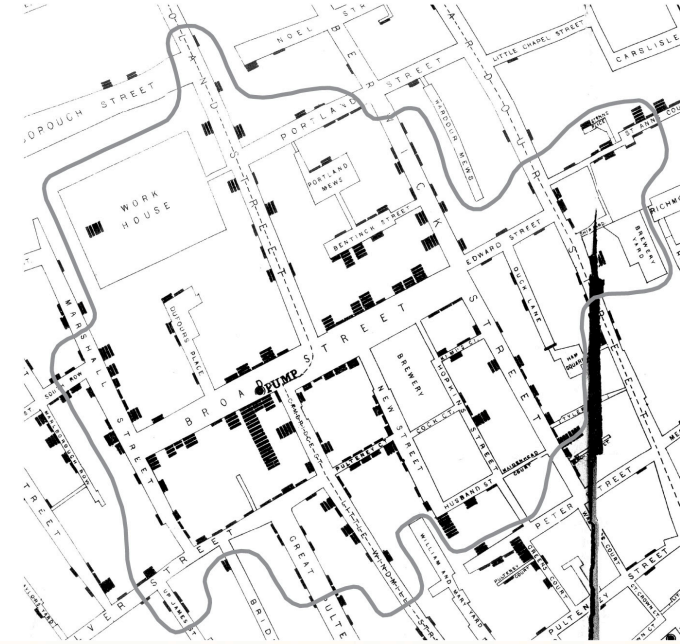
CAPTAIN JOHN GRAUNT



Janet Elizabeth Lane-Claypon

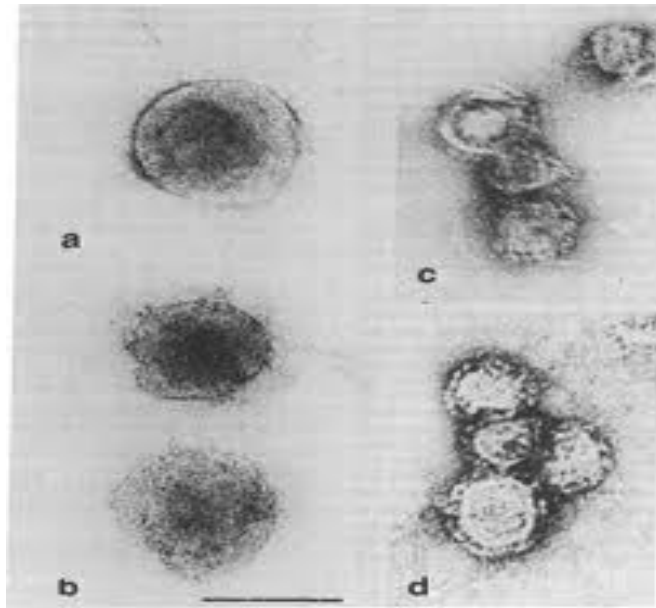
The Broad Street Pump & The “Grand experiment”

- Miasmatic theory dominated medicine
- Under that paradigm contaminated water with a microscopic pathogen was impossible
- Detailed measurement and comparison
- Later proven by Koch and others the Infectious Disease Paradigm took hold



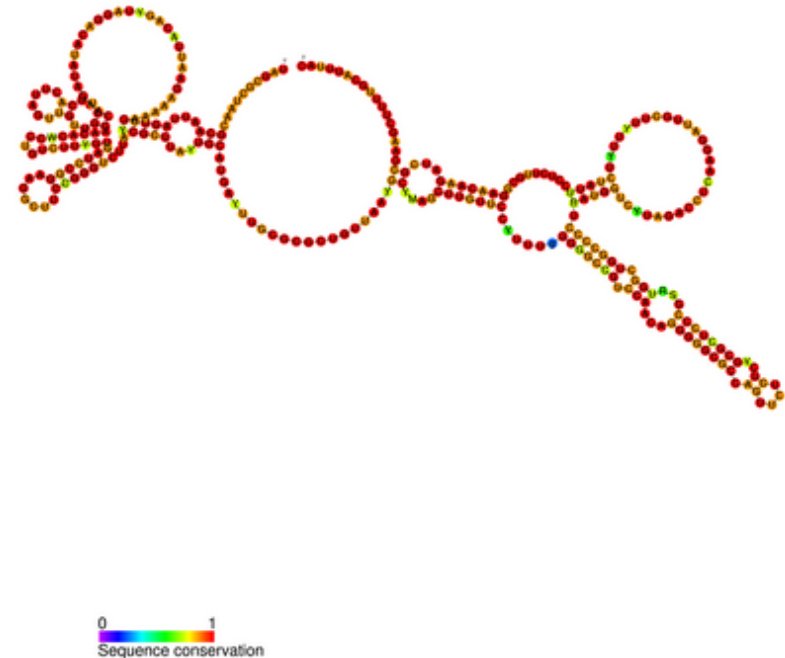
Paradigm Shift in Cancer: Oncogenic Viruses

- In 1911 Peyton Rous showed that spontaneous spindle cell sarcoma derived from a Plymouth Rock chicken could be transmitted to healthy chickens using filtered cell-free tumor extracts
- Rous Sarcoma Virus (RSV) is the 'first' oncogenic virus described
- Noble Prize awarded to Rous



Lead to the discovery of the Oncogene

- *SRC*- Proto-oncogene tyrosine-protein kinase src
- c-Src ="cellular Src kinase"
- v-Src ="viral Src kinase"
- G. Steve Martin (at Berkeley) demonstrated that v-src was oncogene, the causative RSV oncogene
- in 1976 J. Michael Bishop and Harold E. Varmus (at UCSF) showed that oncogenes (v-src) were activated proto-oncogenes (c-src).
- **This was a paradigm shift – dysregulated normal genes can cause cancer**



Human Papilloma Virus (HPV)

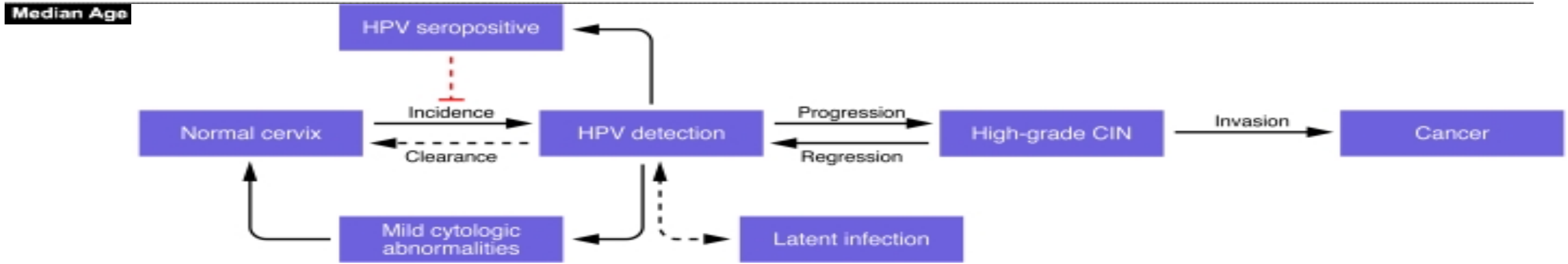
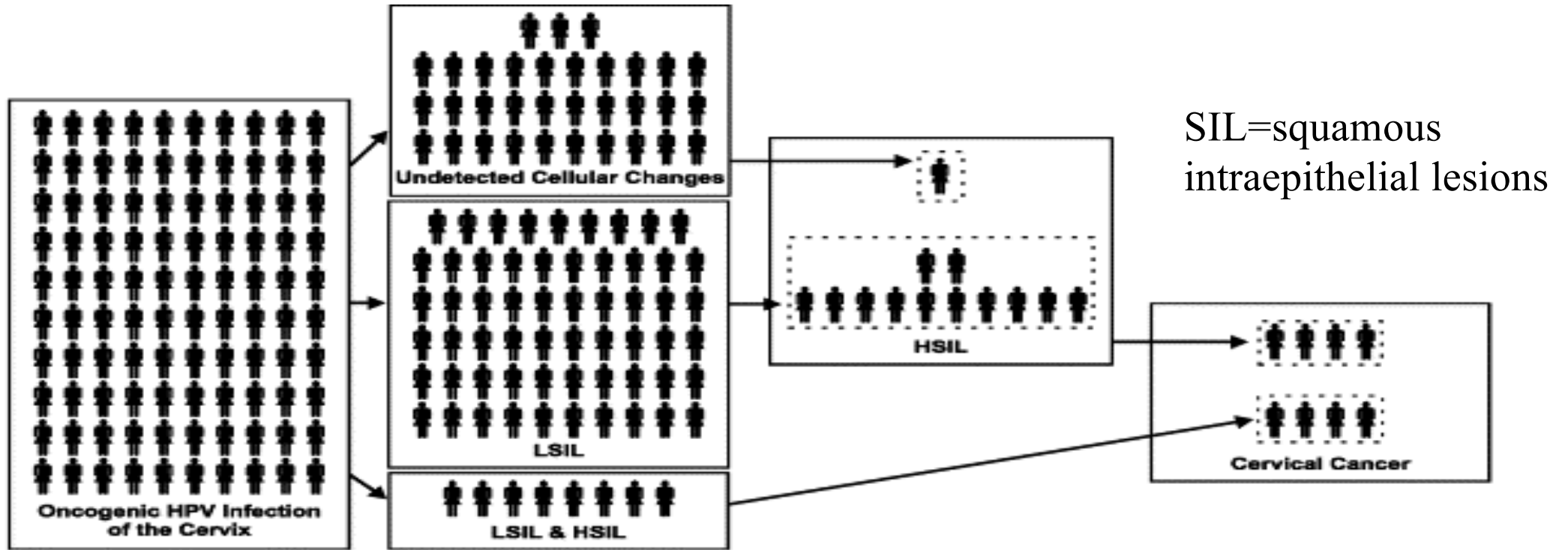
- In 1842 Italian investigators observed little cervical cancer in nuns compared to other Italian women
- 1970 Harald zur Hausen found HPV DNA in cervical cancers
- Robust epidemiologic studies noted increased risk based on marital status, age at first intercourse, number of sexual partners and commercial sex workers
- HPV is found in 90-95% of cervical cancers

Harold zur Hausen received 2008 Nobel Prize for his work on HPV



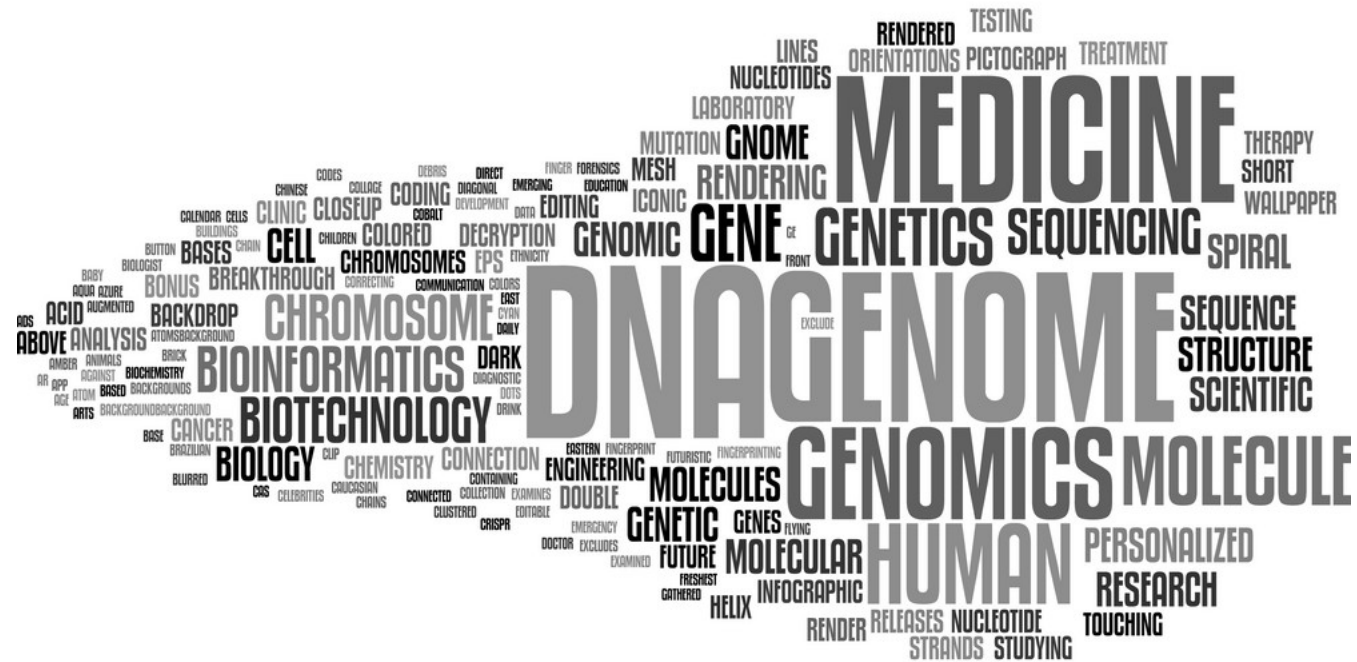
Natural history of cervical cancer associated with HPV

(from Baseman & Koutsky, J Clin Virol, 2005; Gravitt, JCI, 2011)



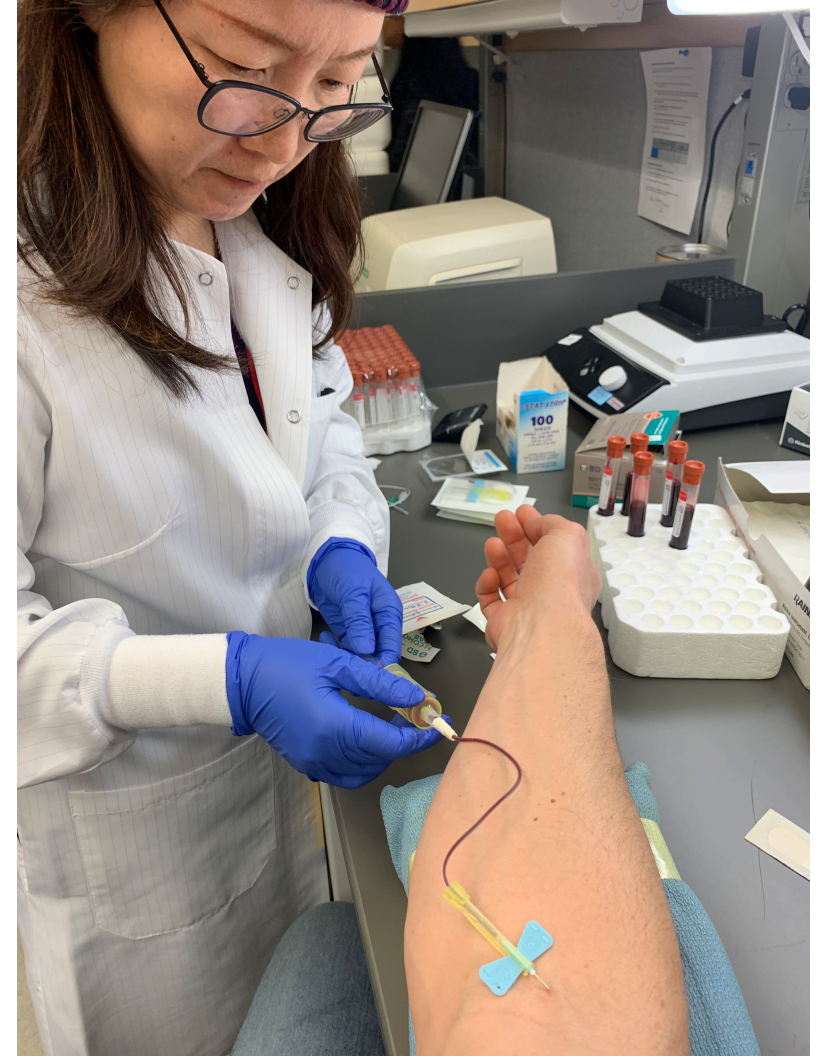
Technologies can drive paradigm shifts

- The ability to decode the genetics of organisms has exponentially increased our understanding of biology and disease
- GWAS, WGS, RNAseq, CHIP-seq, methy-seq, proteomics, metabolomics, metagenomics... CRISPR
- But these technologies come with caveats...



Wet Lab is Important!

- For GenEpi the lab is our questionnaire
- Understanding exactly what is happening from sample collection, to processing, to data generation is critical in epidemiologic studies
- Understanding the molecular mechanisms of how data is generated will open new research directions
- You are allowed to use your self as a Guinea pig



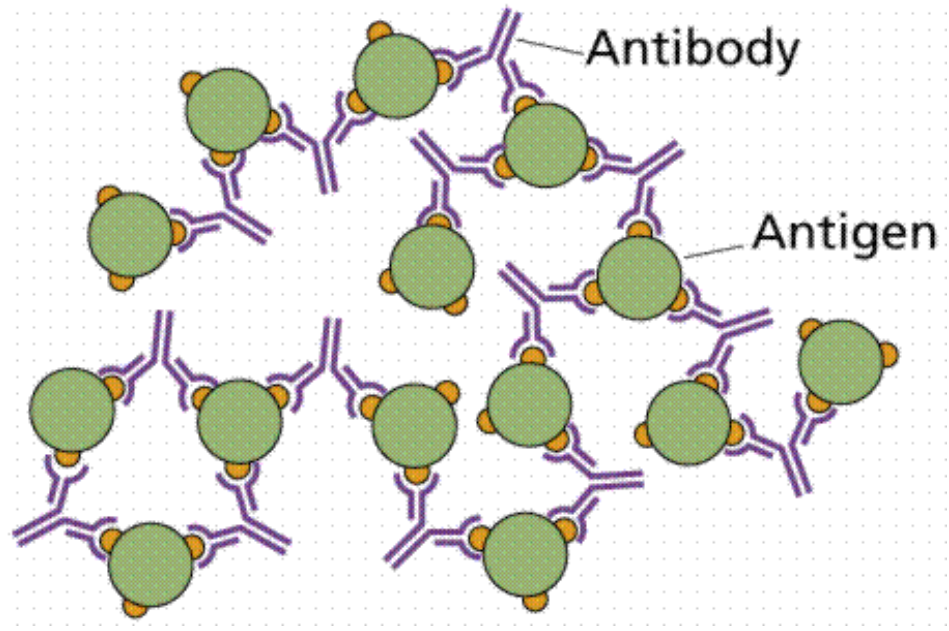
Understand your Pipelines!

- We have become too comfortable with the 'Black Box' in bioinformatic analyses
- Test your tools- Run simulations with known answers
- Understand the strengths and limitations
- Test and validation datasets are critical
- Check and recheck, then check again using a different tool

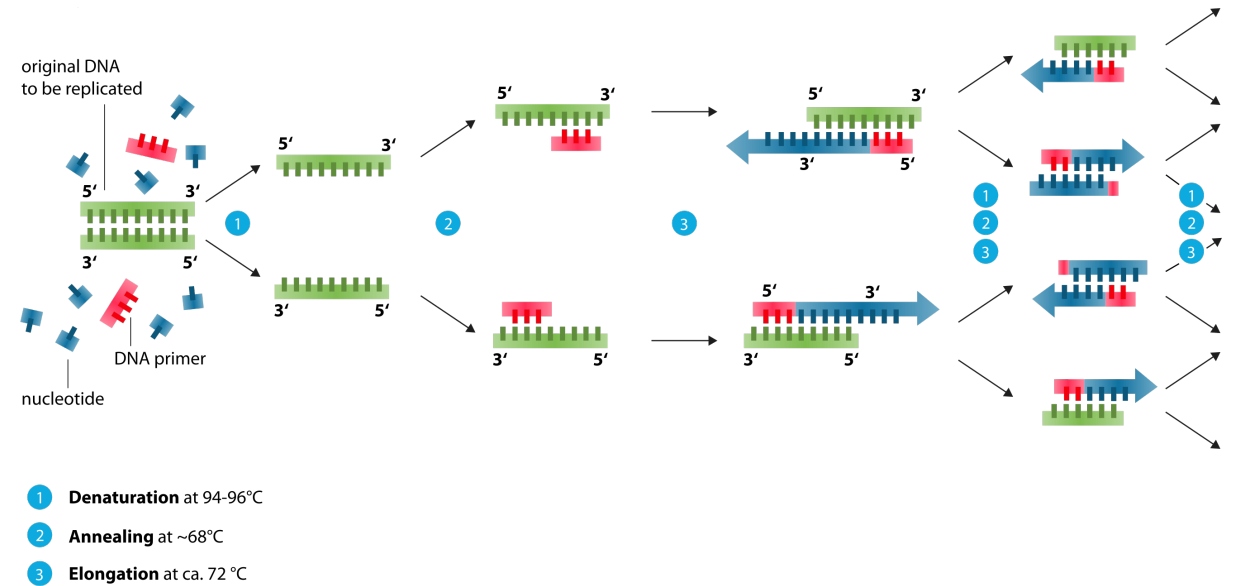


How do you look for viruses in a sample?

Antibody & Antigen



Polymerase Chain Reaction (PCR)



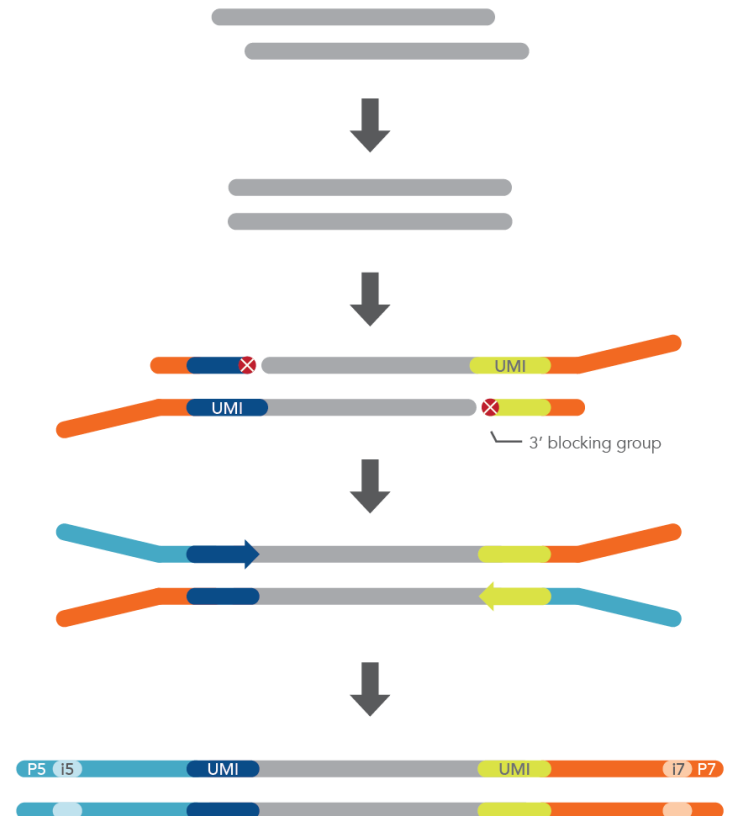
Illumina Next Generation Sequencing

It sequences whatever you put in it!
(Watch below for additional info)

<https://youtu.be/fCd6B5HRaZ8>

The Devil is in the details

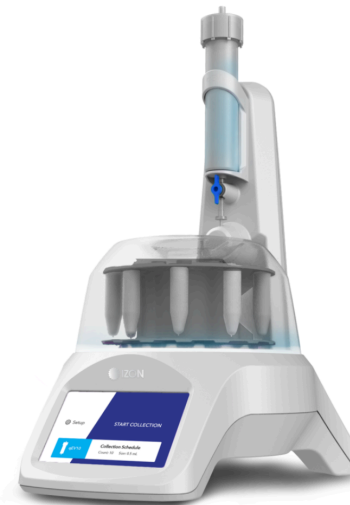
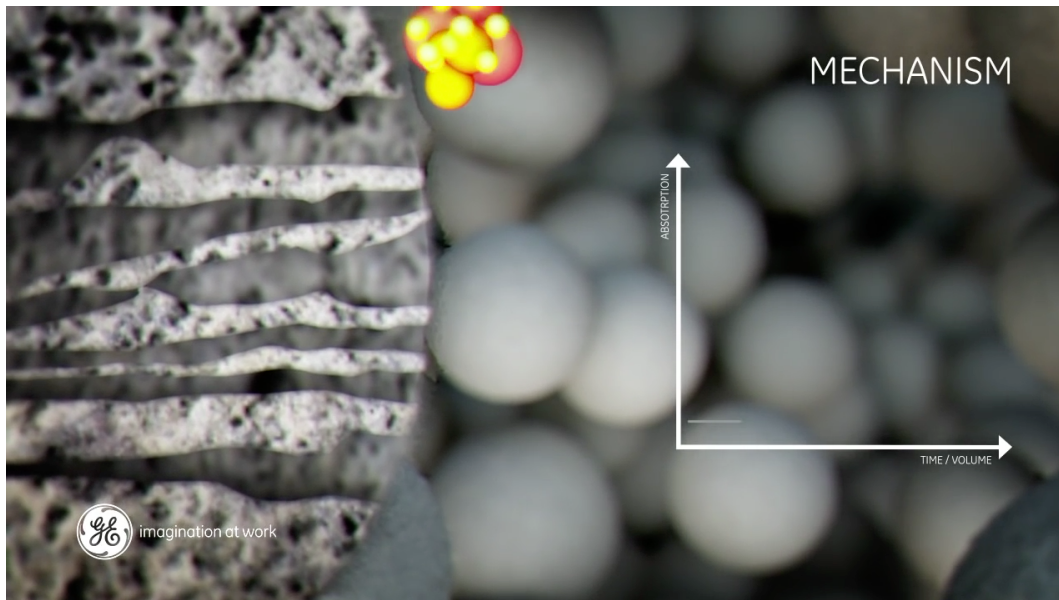
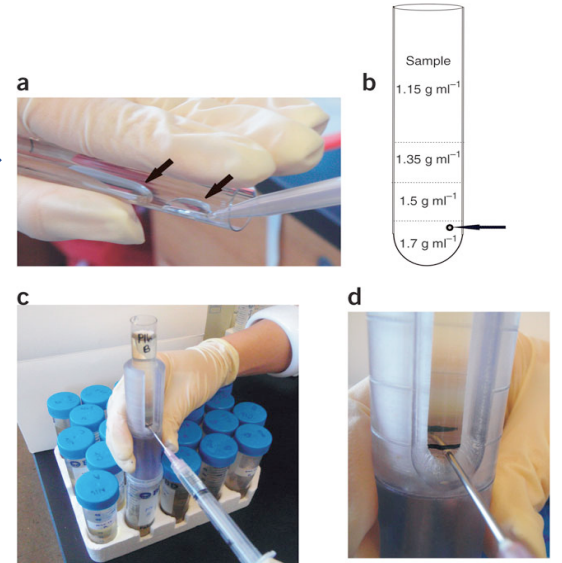
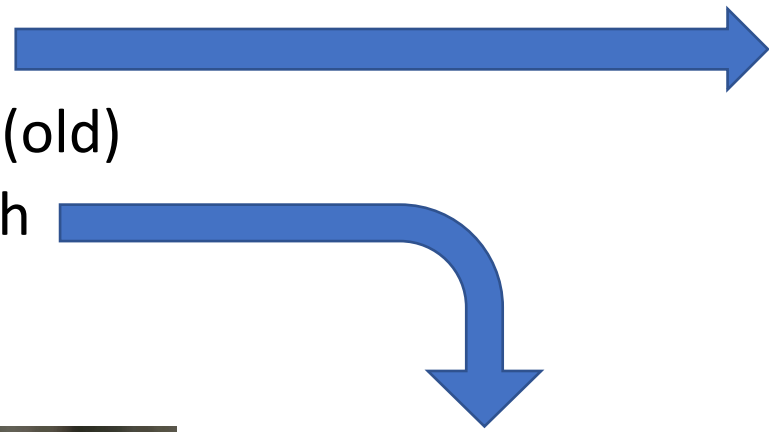
- Sample quality
- RNA or DNA?
- Isolation technique
- Library preparation
- It all matters



How do you look for viruses in a sample?

- Next Generation Methods:

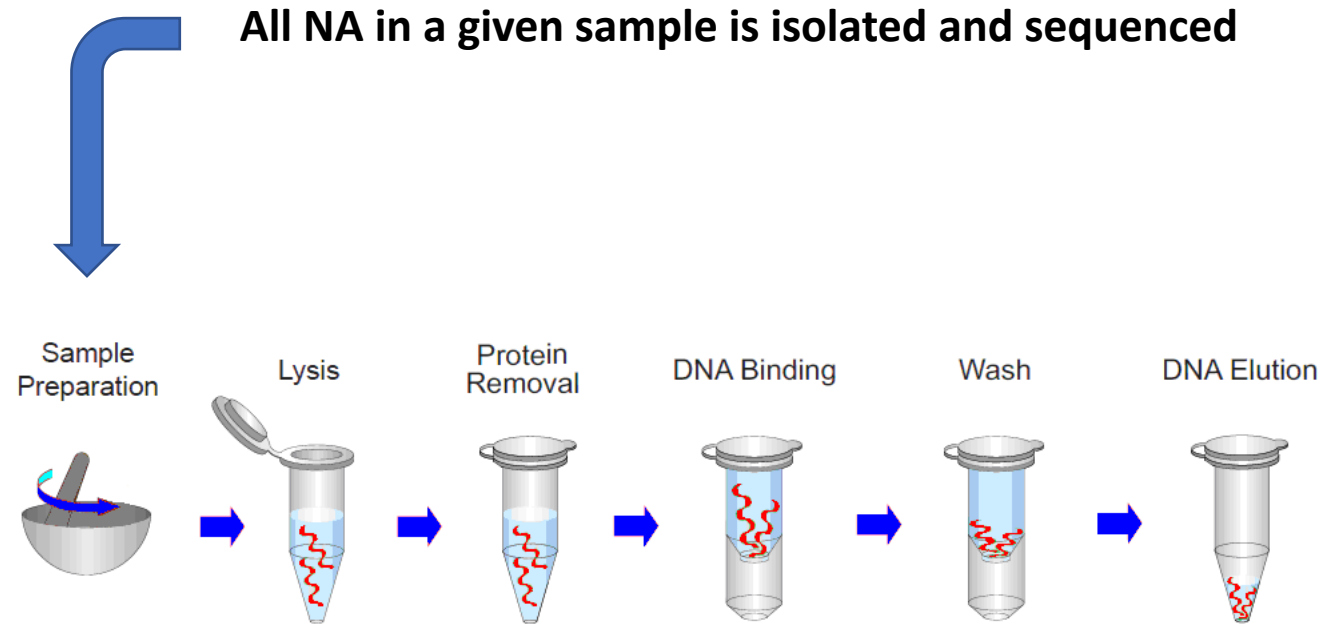
- Virus Isolation through ultra-centrifuge and 454 sequencing (old)
- Virus Isolation through SEC with illumina sequencing



**Physical enrichment
of viral sequences**

How do you look for viruses in a sample?

- Next Generation Methods:
- Bulk DNA and RNA sequencing
 - Total RNA or DNA is extracted
 - Library is prepared and indexed
 - Bulk sequencing of all NA in sample



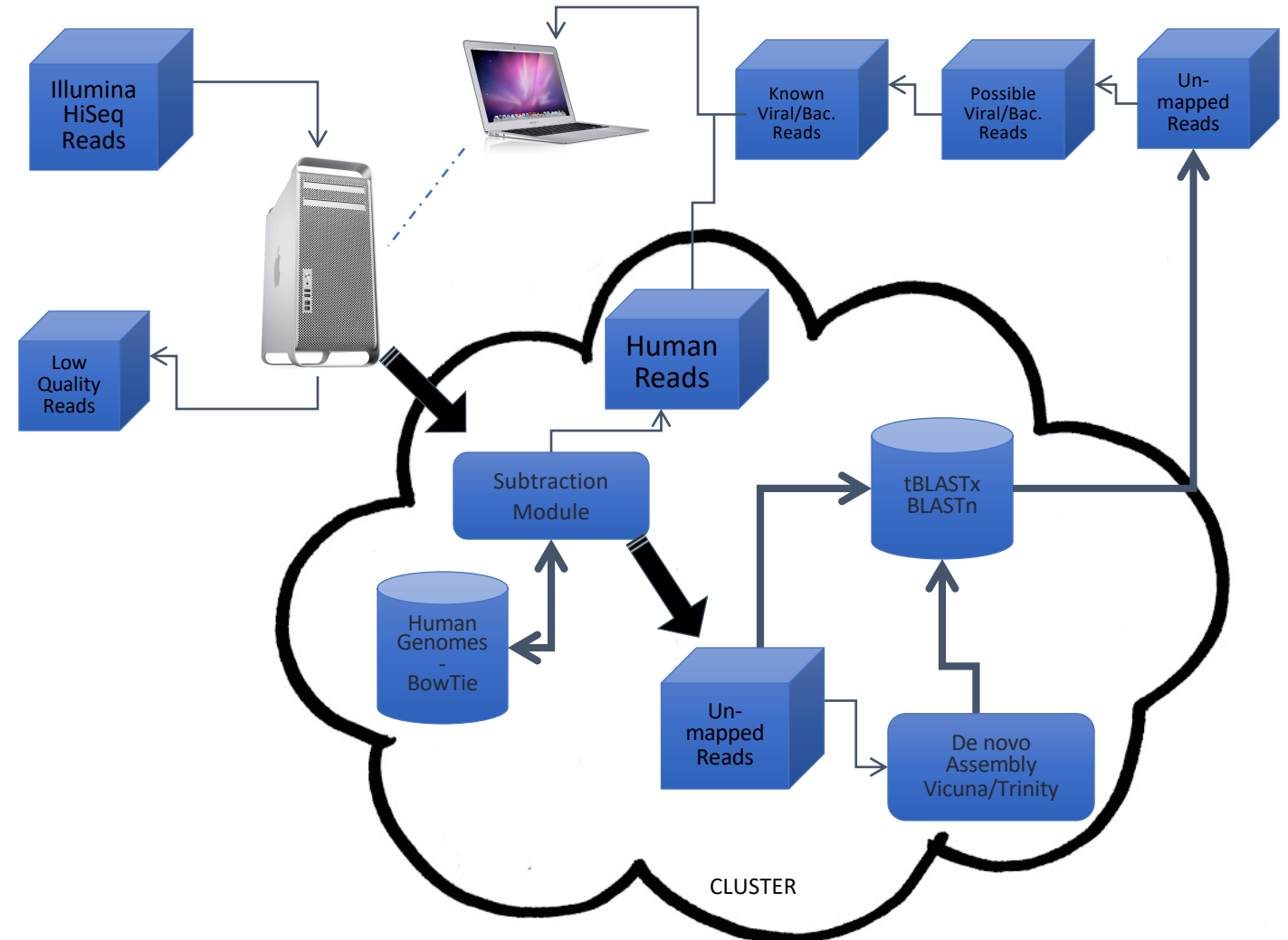
No Physical Enrichment of Viral Sequences

Hundreds of millions of reads per subject... now what?

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C T C A A T T C A T G T A G A C T G T G T T C G T G G A C A T C T C C G G G T C A T T A T A G A C T C T G C C T G A T A T C T T G T G T G T A C T T T G A C T C C C A C T A C T G G G T T T G A T

How do you look for viruses in a sample?

- Bioinformatic analyses:
 - Remove human sequences through alignment (Bowtie, TopHat etc)
 - Non-human sequences are queried:
 - 1- BLAST (x or n) to complete nt database or Ref Seq Viral (SLOW)
 - Newer 'BLAST'-like aligners like DIAMOND are faster
 - 2- Align to curated viral database (FAST)



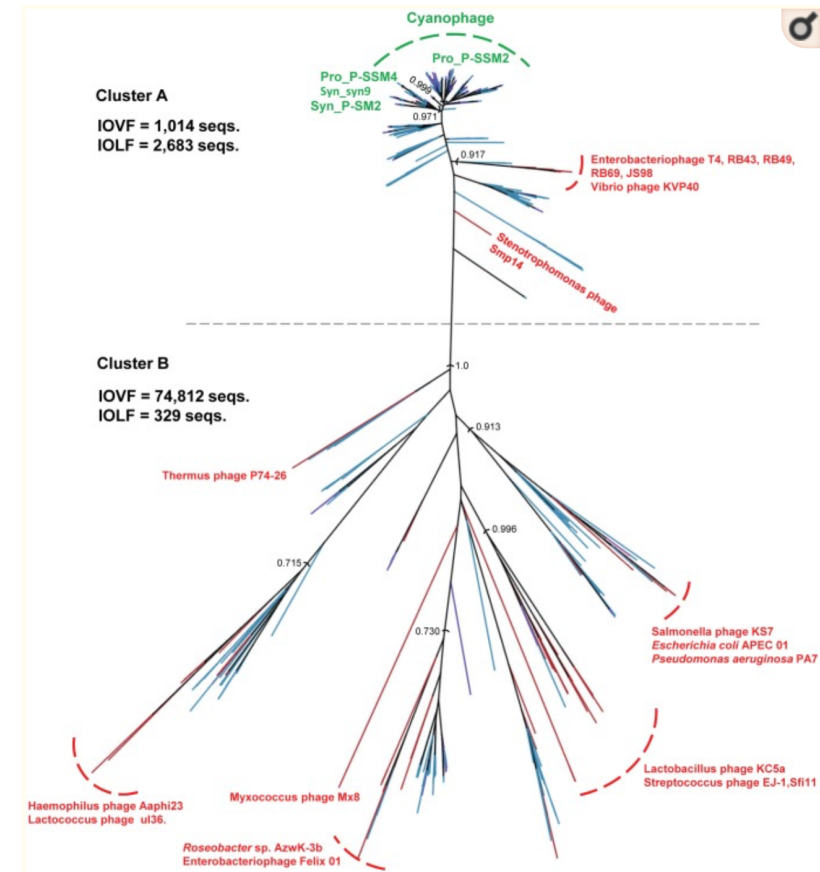
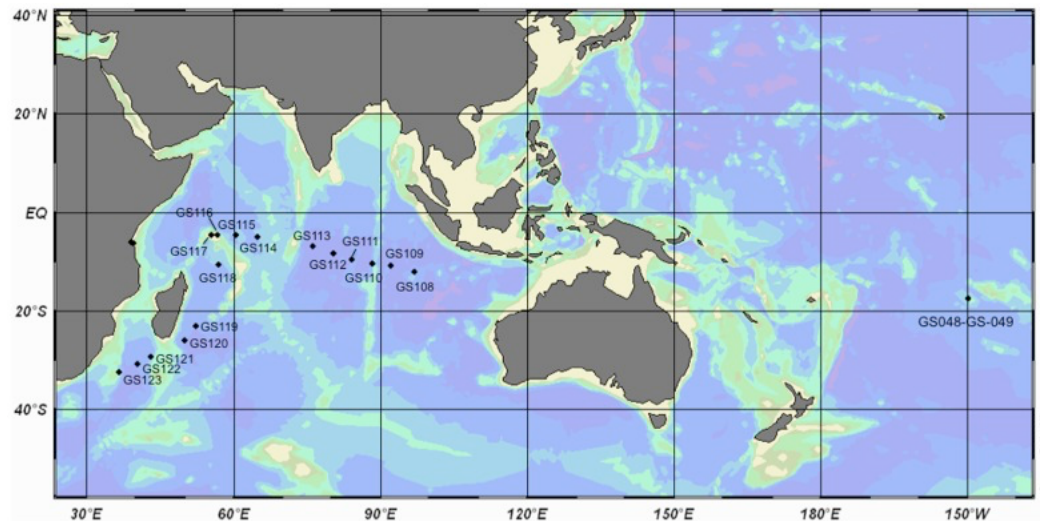
The Baltic Sea Virome: Diversity and Transcriptional Activity of DNA and RNA Viruses

Lisa Zeigler Allen, John P. McCrow, Karolina Ininbergs, Christopher L. Dupont, Jonathan H. Badger, Jeffery M. Hoffman, Martin Ekman, Andrew E. Allen, Birgitta Bergman, J. Craig Venter

Joshua Weitz, Editor

Metagenomic Exploration of Viruses throughout the Indian Ocean

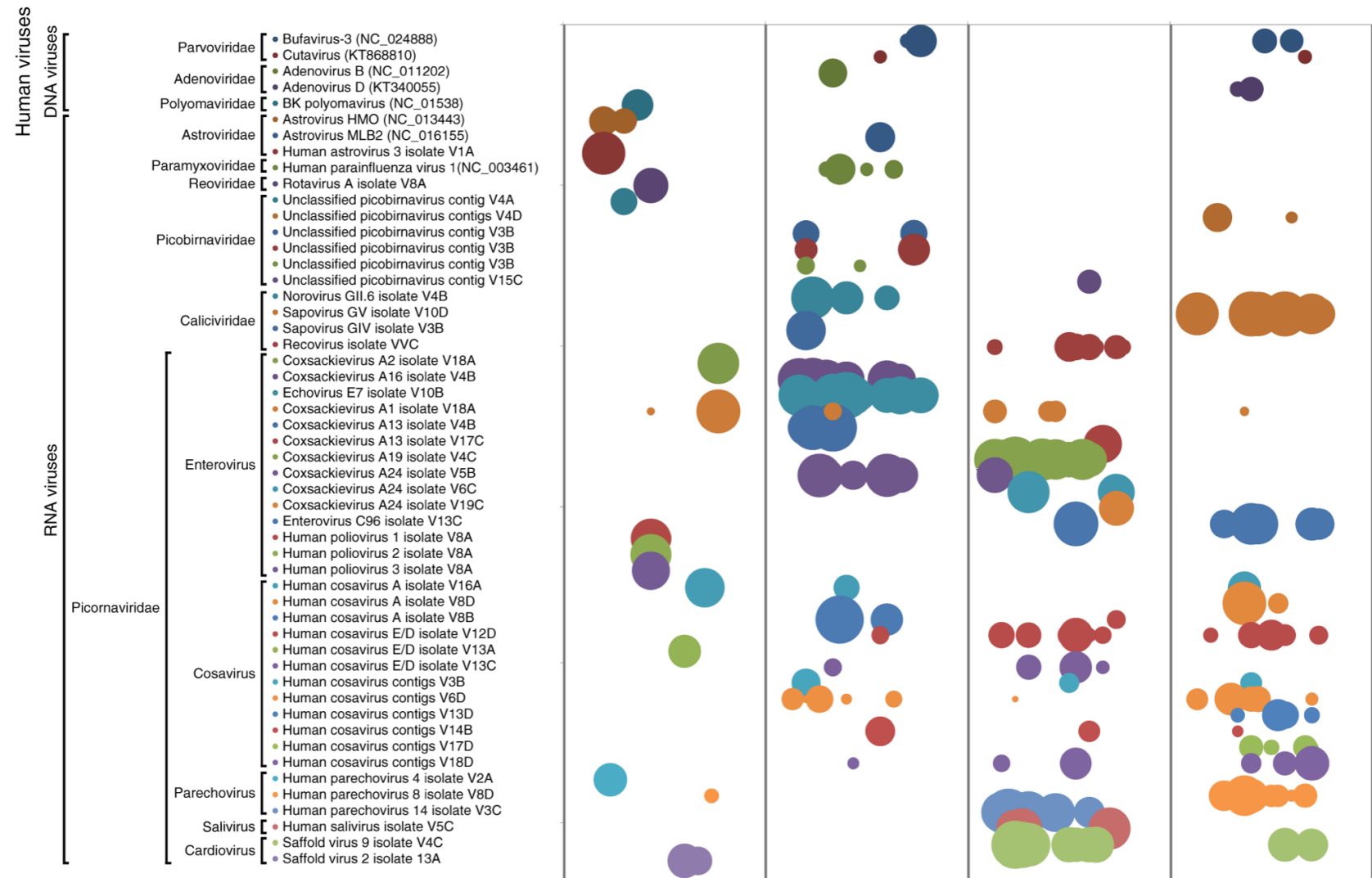
[Shannon J. Williamson](#),^{# 1, *} [Lisa Zeigler Allen](#),^{# 1, 4} [Hernan A. Lorenzi](#),² [Douglas W. Fadrosh](#),¹ [Daniel Bami](#),³ [Mathangi Thiagarajan](#),² [John P. McCrow](#),¹ [Andrey Tovchigrechko](#),² [Shibu Yooseph](#),³ and [J. Craig Venter](#)¹



Complex virome in feces from Amerindian children in isolated Amazonian villages

Juliana D. Siqueira, Maria Gloria Dominguez-Bello, Monica Contreras, Orlana Lander, Hortensia Caballero-Arias, Deng Xutao, Oscar Noya-Alarcon & Eric Delwart

✉



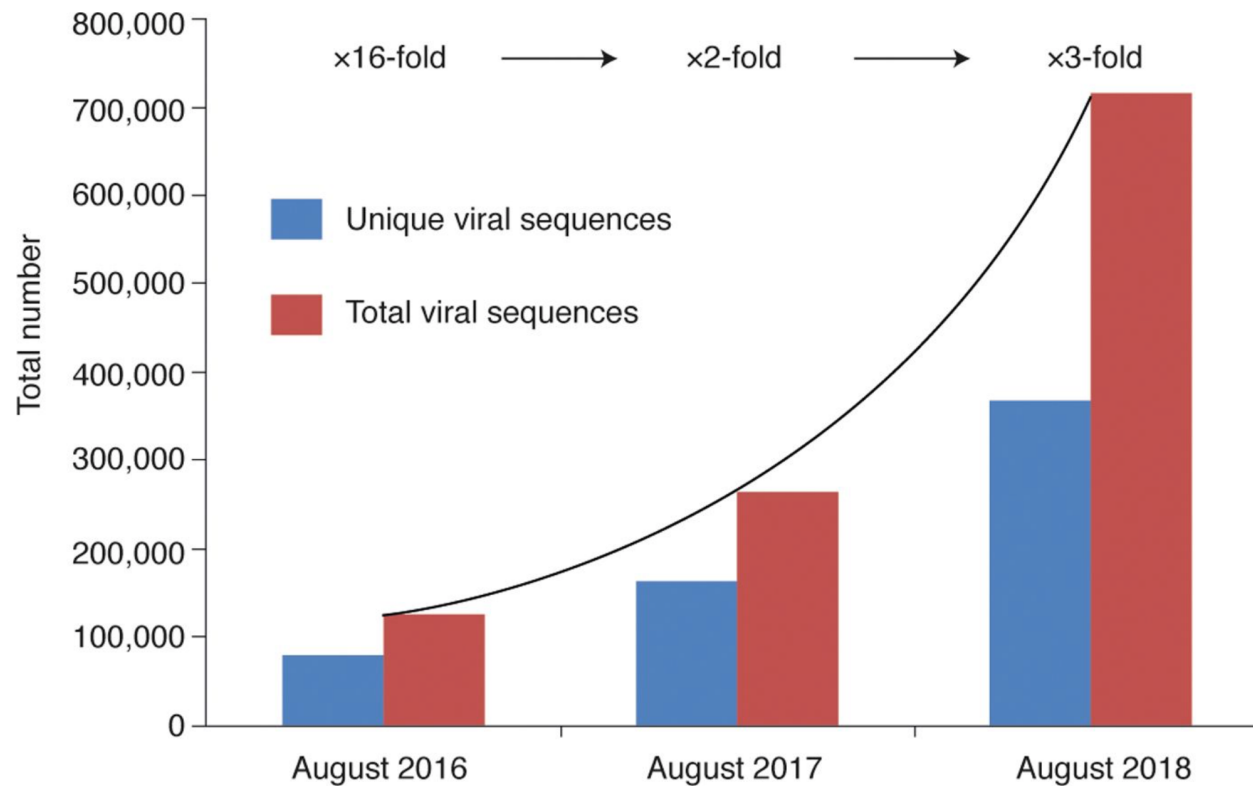
The virome hunters

Charles Schmidt

Nature Biotechnology **36**, 916–919(2018) | [Cite this article](#)

Figure 1: Growth rate of virus identification and microbial host prediction.

From: [The virome hunters](#)



Growth over time in the total and unique number of viral sequences in the January 2018 release of the IMG database. The first data point represents a 16-fold increase in the number of species in comparison to the number of previously identified viruses. Subsequent points are twofold and threefold higher, respectively (image by David Paez Espino, JGI).

Genomic Analyses from Non-invasive Prenatal Testing Reveal Genetic Associations, Patterns of Viral Infections, and Chinese Population History

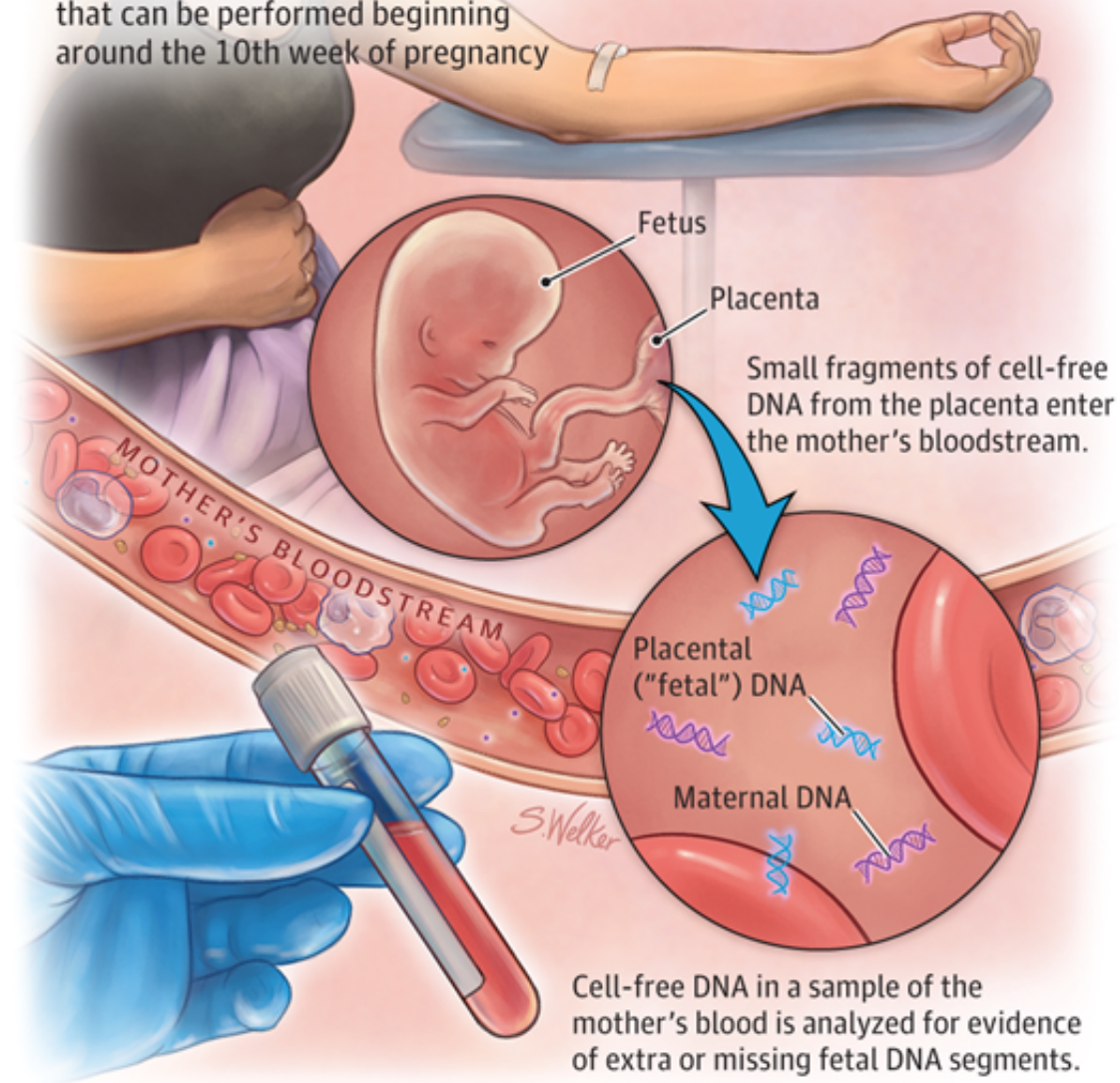
Siyang Liu,^{1,2,25} Shujia Huang,^{1,3,25} Fang Chen,^{1,23,24,25} Lijian Zhao,^{1,25} Yuying Yuan,^{1,25} Stephen Starko Francis,^{4,5} Lin Fang,¹ Zilong Li,⁶ Long Lin,⁶ Rong Liu,¹ Yong Zhang,¹ Huixin Xu,¹ Shengkang Li,¹ Yuwen Zhou,^{1,6} Robert W. Davies,⁷ Qiang Liu,¹ Robin G. Walters,⁸ Kuang Lin,⁸ Jia Ju,¹ Thorfinn Korneliussen,⁹ Melinda A. Yang,¹⁰ Qiaomei Fu,^{10,11,12} Jun Wang,¹ Lijun Zhou,¹ Anders Krogh,² Hongyun Zhang,¹ Wei Wang,¹ Zhengming Chen,⁸ Zhiming Cai,^{13,14,15} Ye Yin,¹ Huanming Yang,^{1,16} Mao Mao,¹ Jay Shendure,^{17,18,19} Jian Wang,^{1,16,*} Anders Albrechtsen,^{2,*} Xin Jin,^{1,3,*} Rasmus Nielsen,^{20,21,22,*} and Xun Xu^{1,26,*}



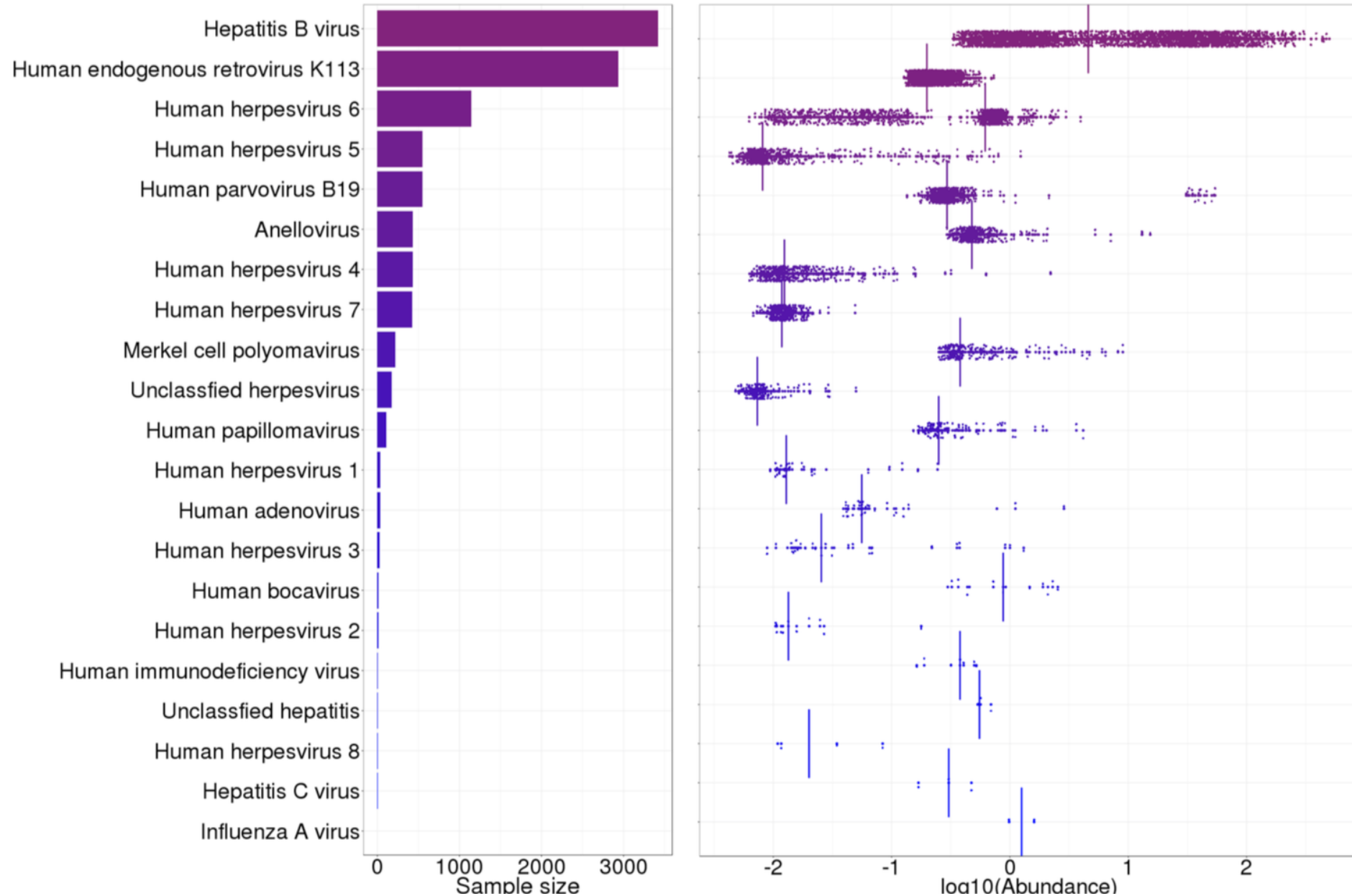
华大基因
BGI

Noninvasive Prenatal Testing (NIPT)

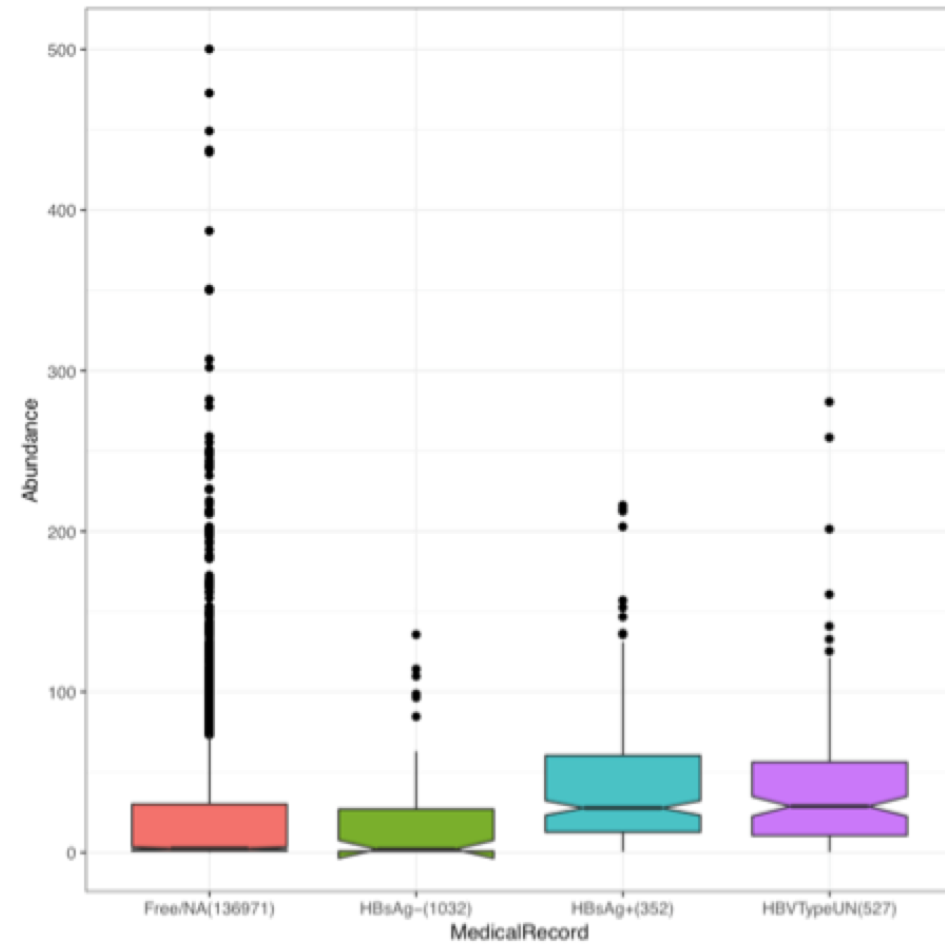
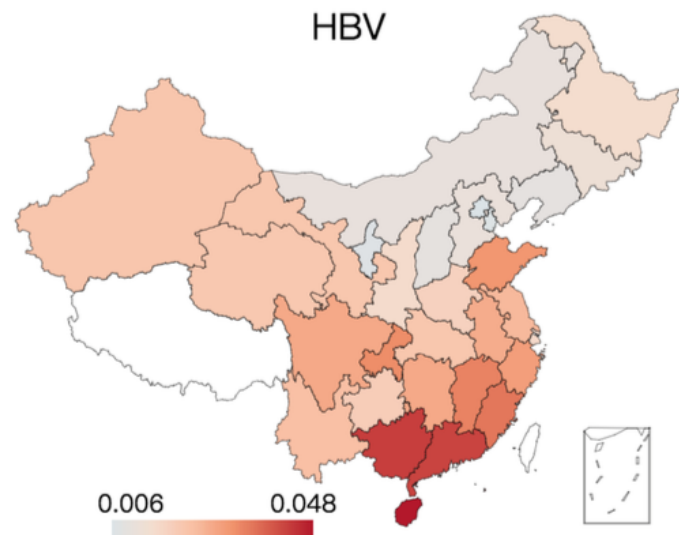
NIPT is a prenatal screening test that can be performed beginning around the 10th week of pregnancy



Largest agnostic viral screen in human to date

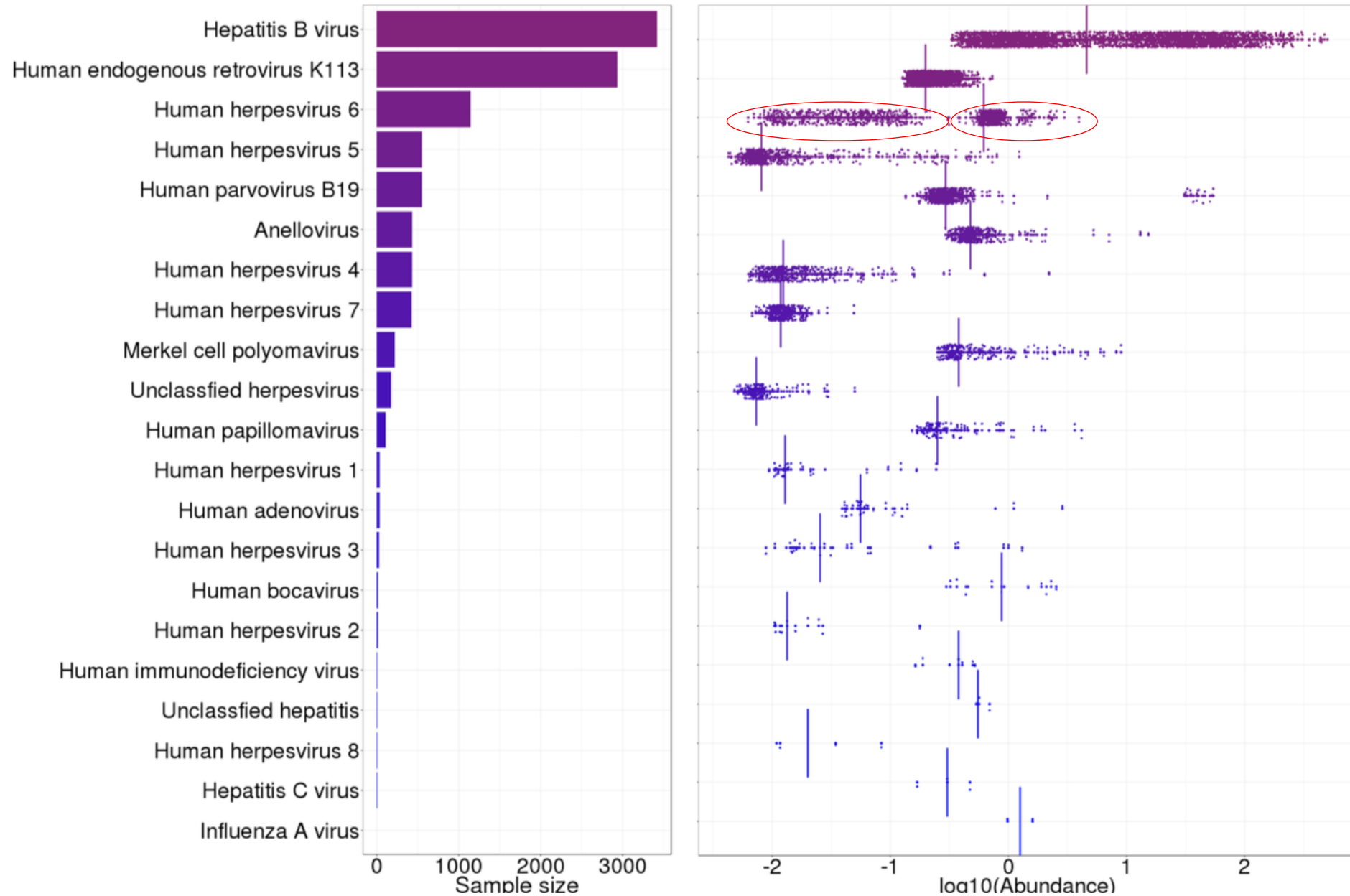


Hepatitis B Virus



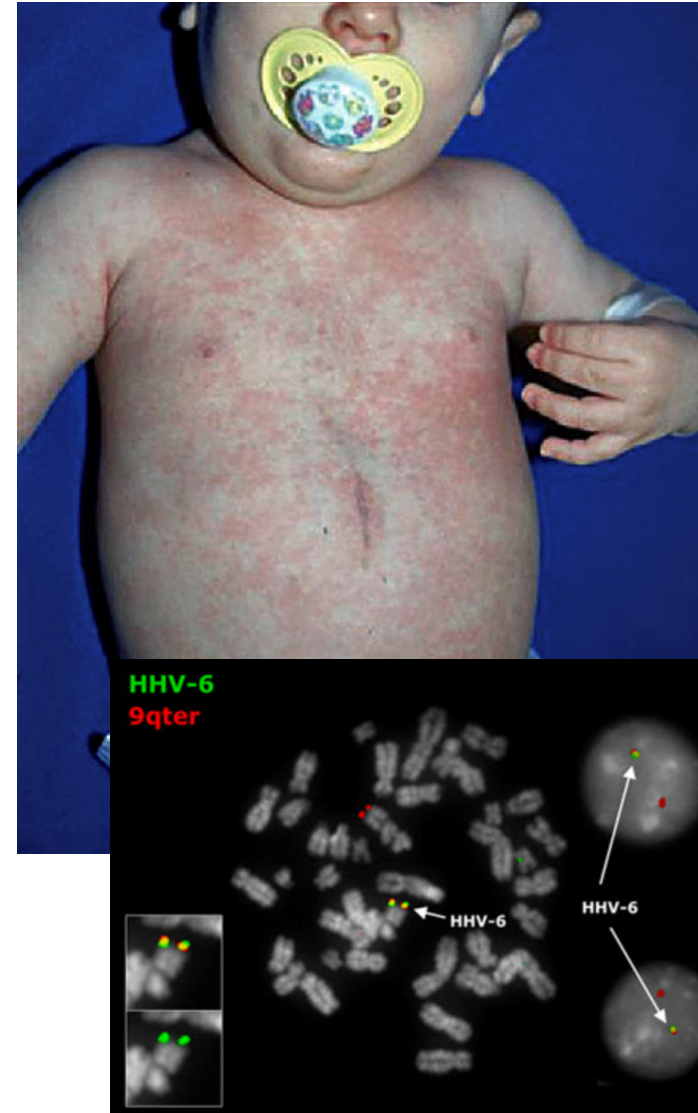
	Free/NA	HBsAg-	HBsAg+	HBVTypeUN
HBV DNA+	2959	53	277	139
HBV DNA-	134012	979	75	388
Sensitivity (%)	2.16	5.14	78.69	26.38

Bimodal distribution of HHV-6A/B abundance



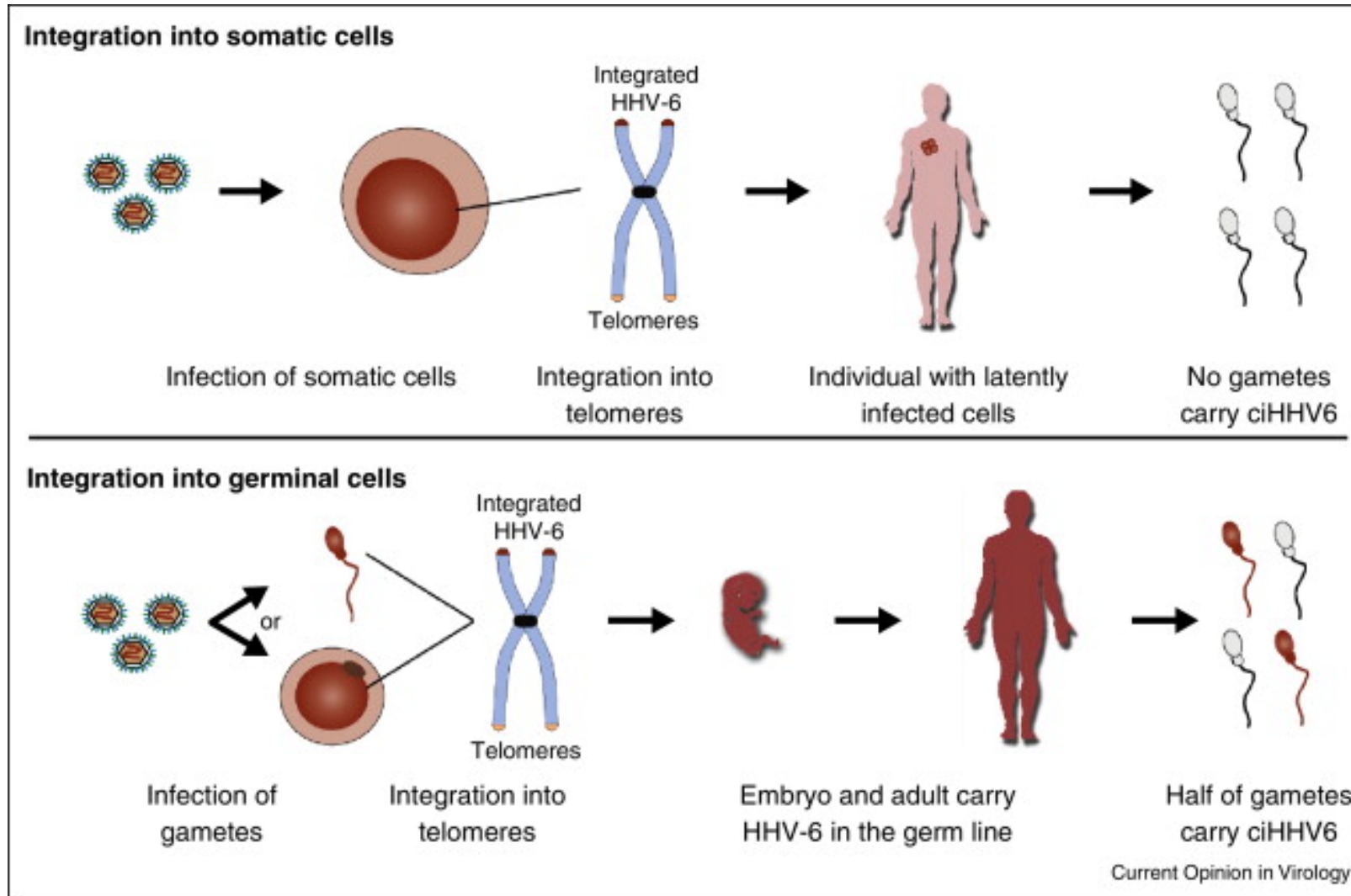
Human Herpes Virus 6A/B

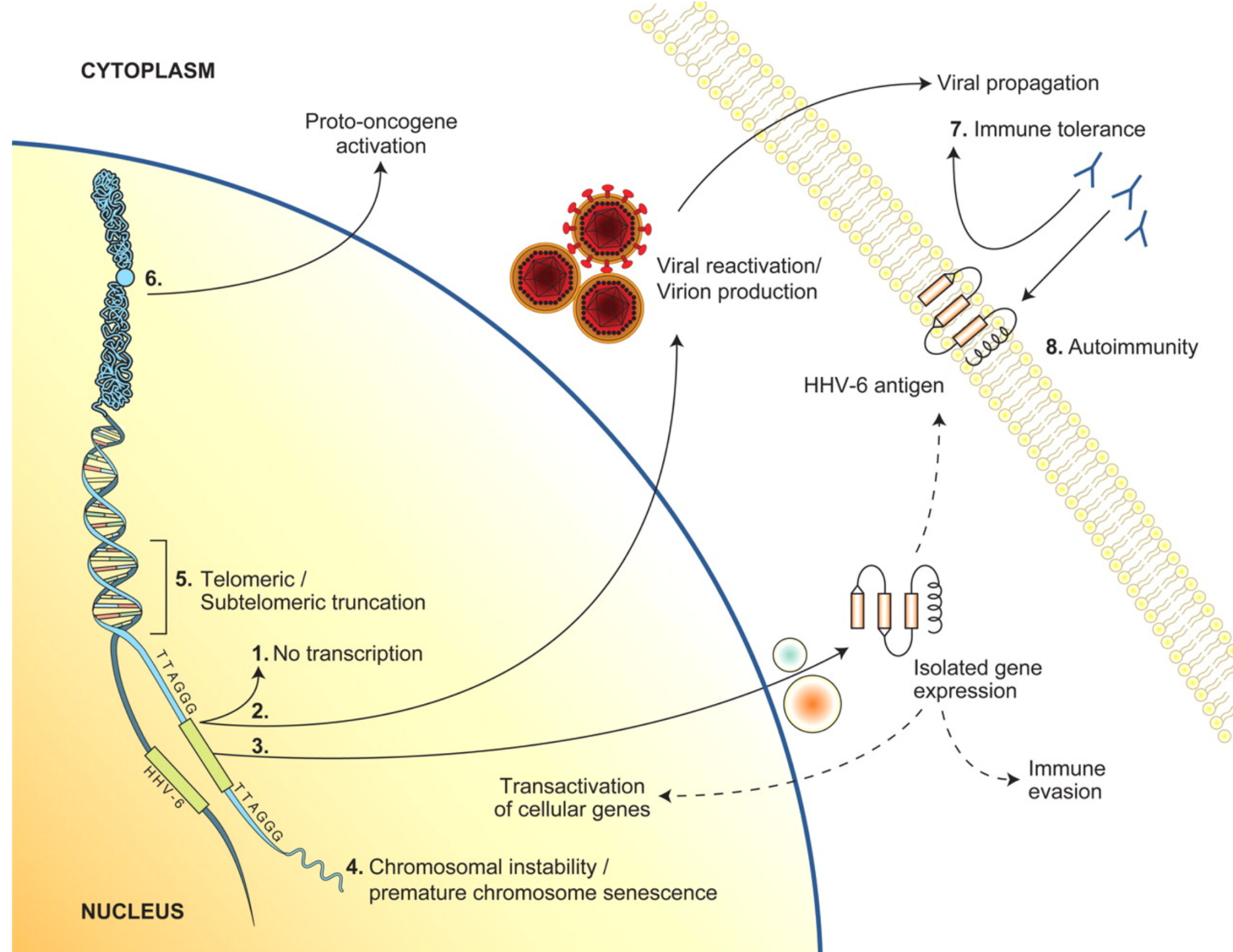
- HHV's are highly evolved human viruses
- Interact: HHV-6 <-> CMV
- HHV-6 ~99% seroprevalence in humans
- 2 variants: A/B with ~90% homology
- Infects CNS
 - 30-75% prevalence in healthy brain (Chan et al. Virology)
 - Tropism for glial cells
 - Route of entry likely through olfactory system (Halberts et al PNAS 2011)
- Recent evidence associated HHV-6 to many complex diseases
- **1-2% of population retains integrated HHV-6A/B in telomeres (ciHHV-6)**
 - Population surveys of ciHHV-6A/B suggest:
 - ~26% HHV6-A ~76%HHV-6B



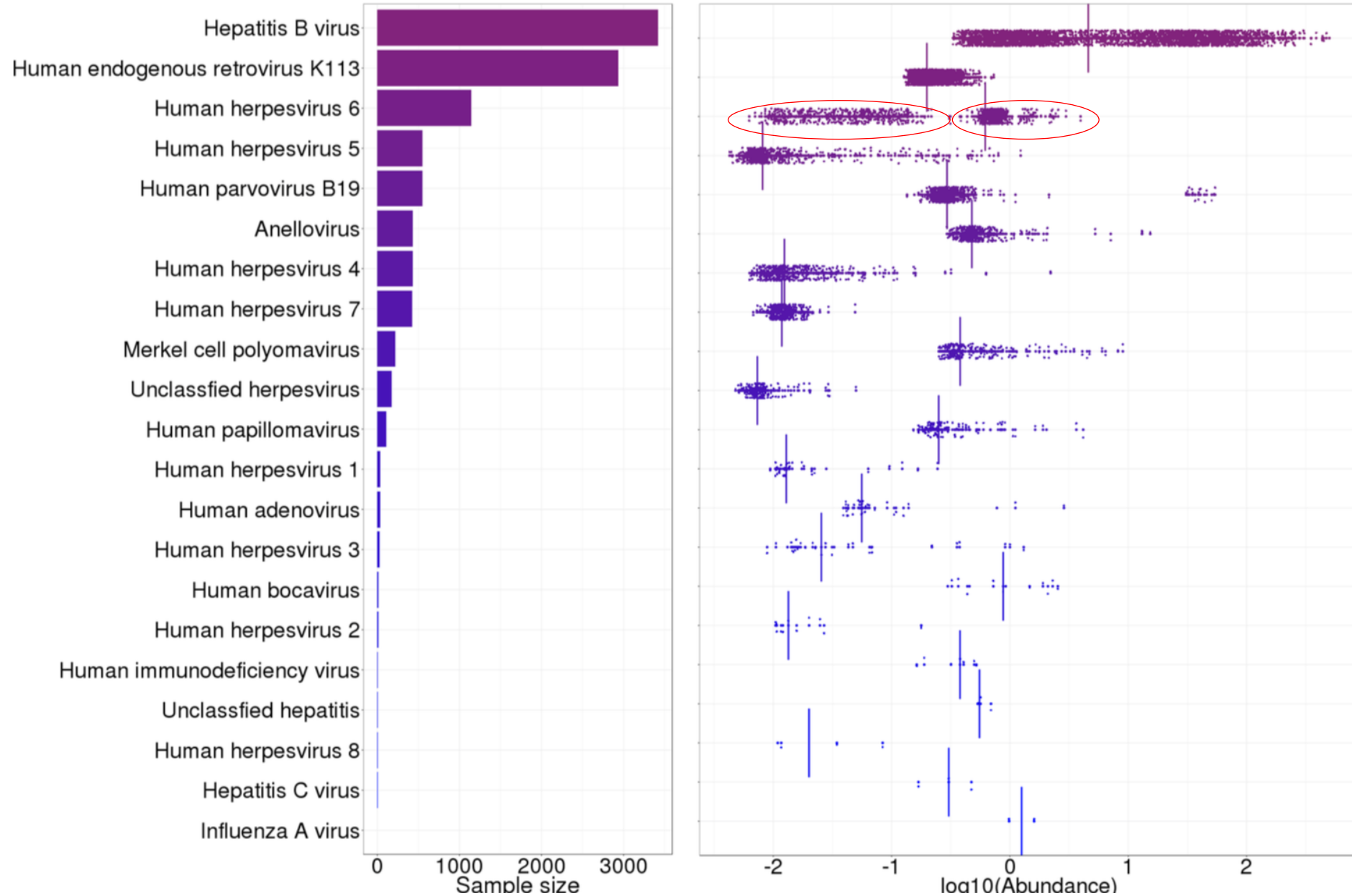
Arbuckle et al PNAS

INSERT ciHHV6 Background



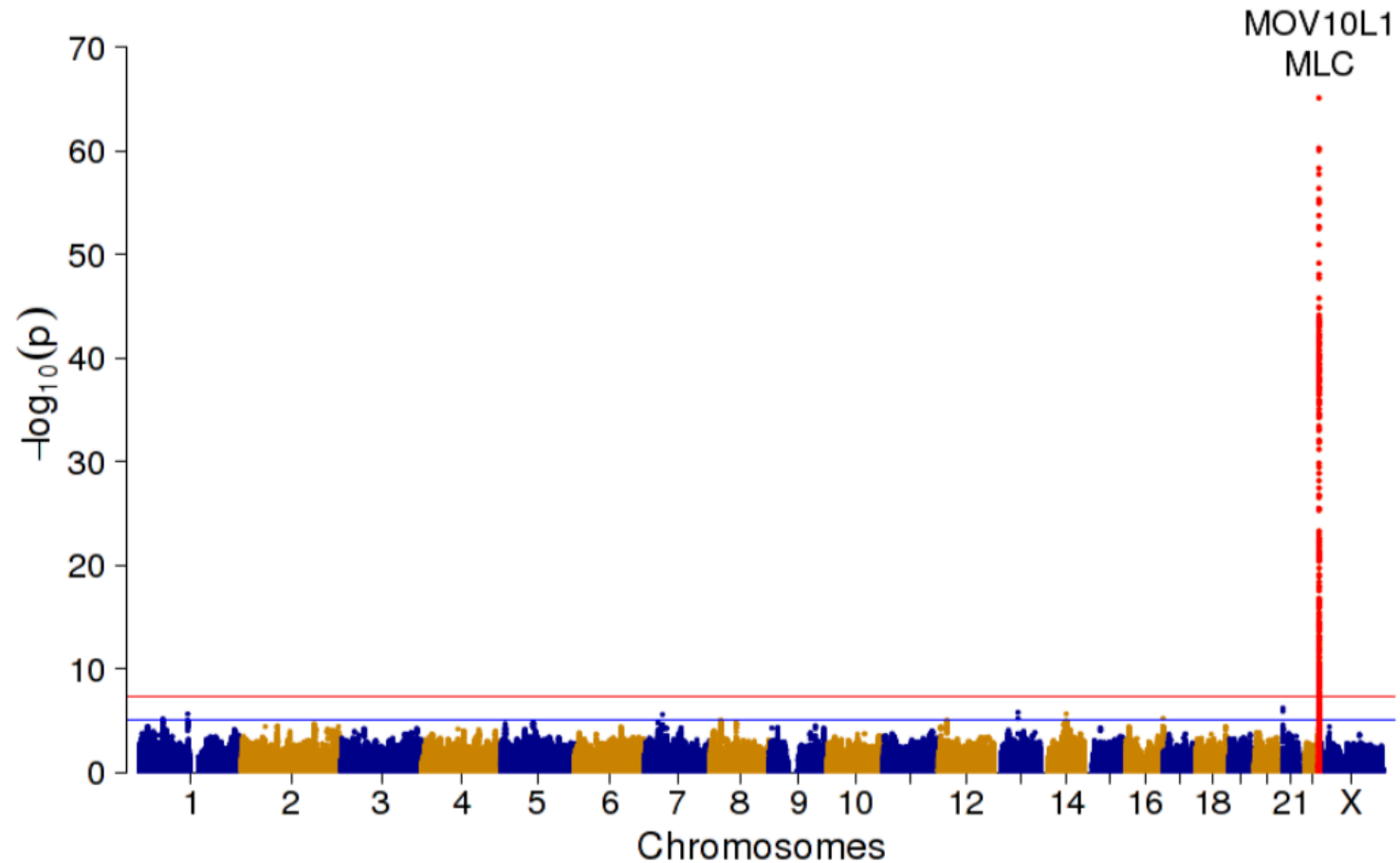


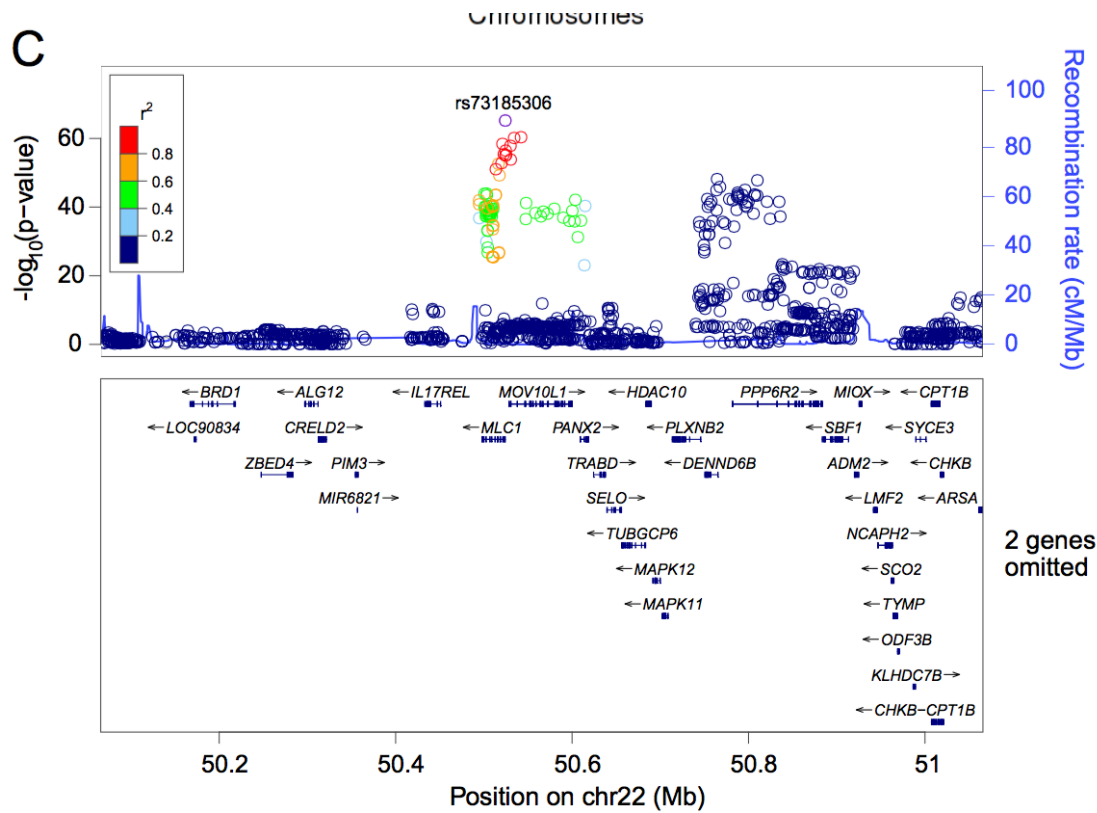
Gene x Virus Association Study



Only associated with integrated HHV-6A/B

B





- **MLC1**- Unknown function, membrane transporter
- Associated with subcortical cysts
- Expressed mostly in brain tissues

- **MOV10L**-ATP-dependent RNA helicase required during spermatogenesis to repress transposable elements- Forms complexes of piRNAs and Piwi proteins and governs the methylation and subsequent repression of transposons.
- Further functional validation is required.

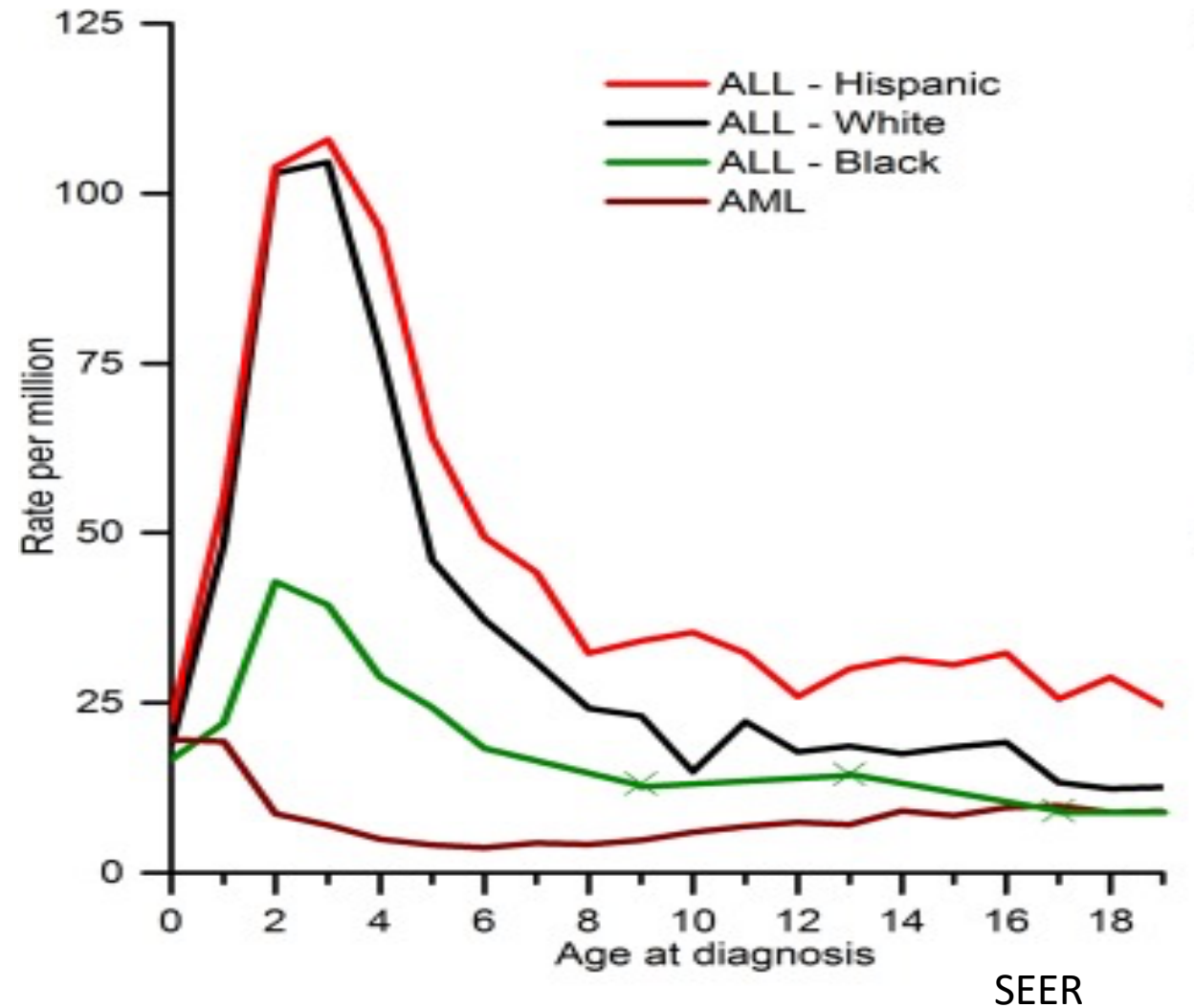
Millinome

Analysis of the 1 million woman cohort

Case Study:

Childhood Acute Lymphoblastic Leukemia (ALL)

- ~70% of all childhood leukemia's- Most common Childhood Cancer
- Peak incidence from 2-6 years of age
- ALL survival is high... ~80%
 - 2.8 fold greater risk of a life threatening chronic illness
 - 50% increase in infertility
 - 4.7 fold risk of a functional impairment

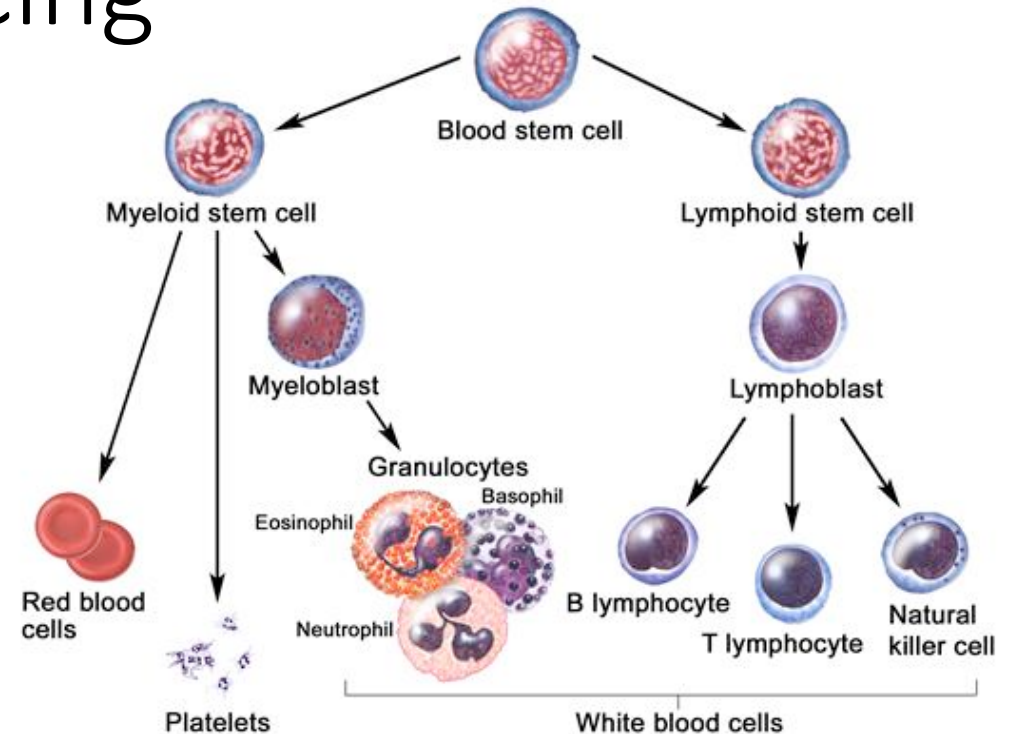


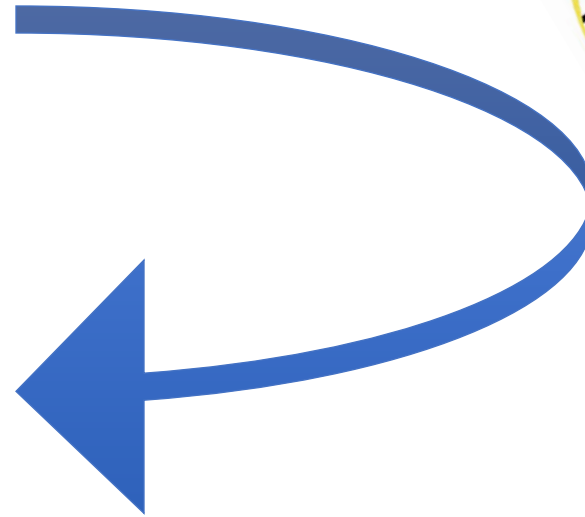
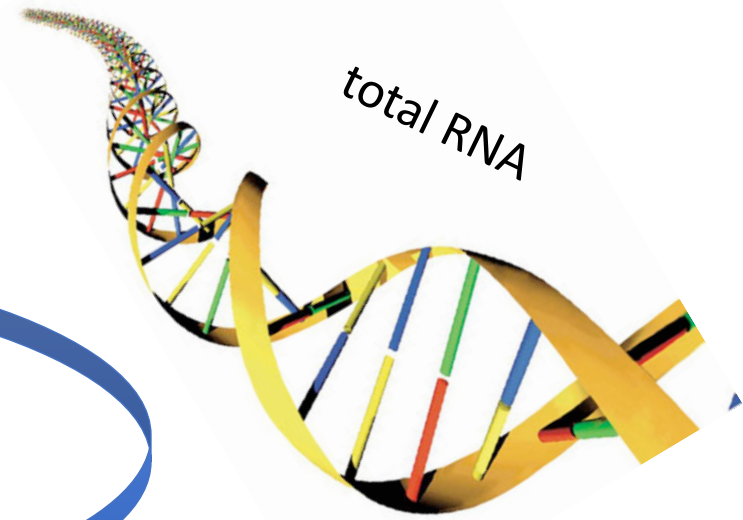
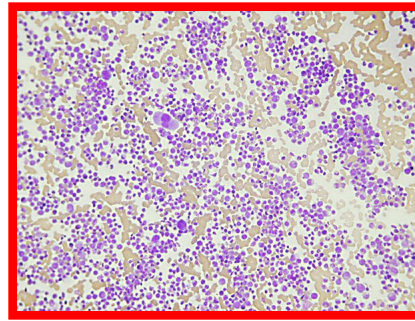
What infections are present in ALL at diagnosis?

In Bone Marrow:

- 1- RNAseq based viral discovery
- 2- Virus isolation and sequencing

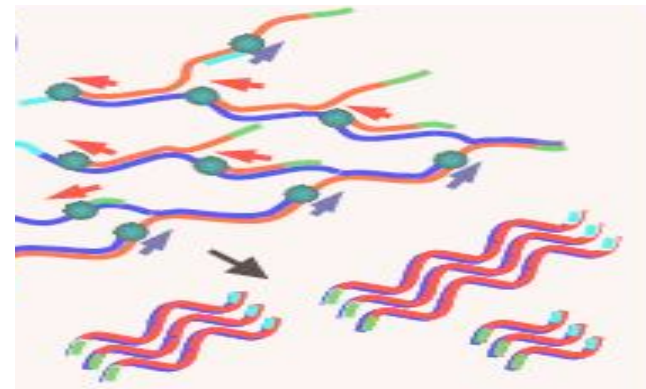
- **AML's used as controls** to estimate the infection exposure history of an immune suppressed child

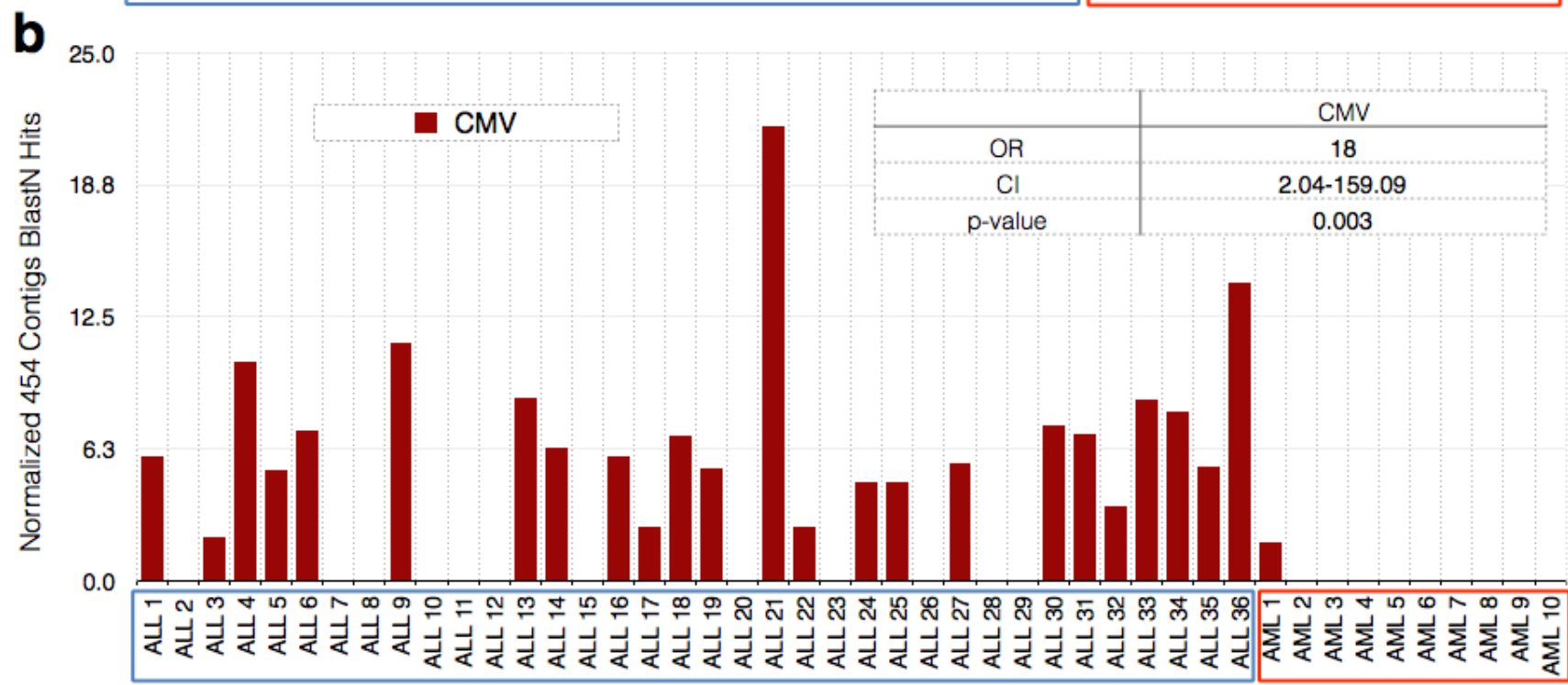
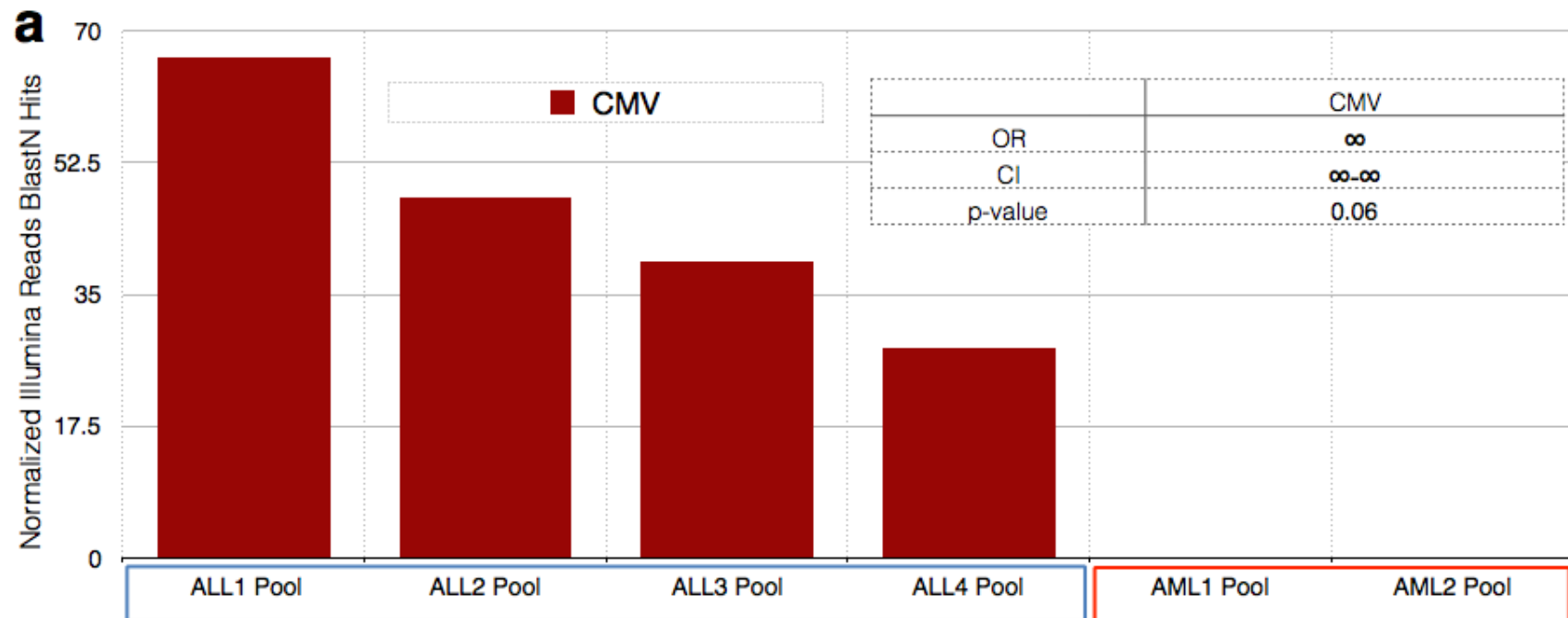




rRNA reduction + RNA-seq prep

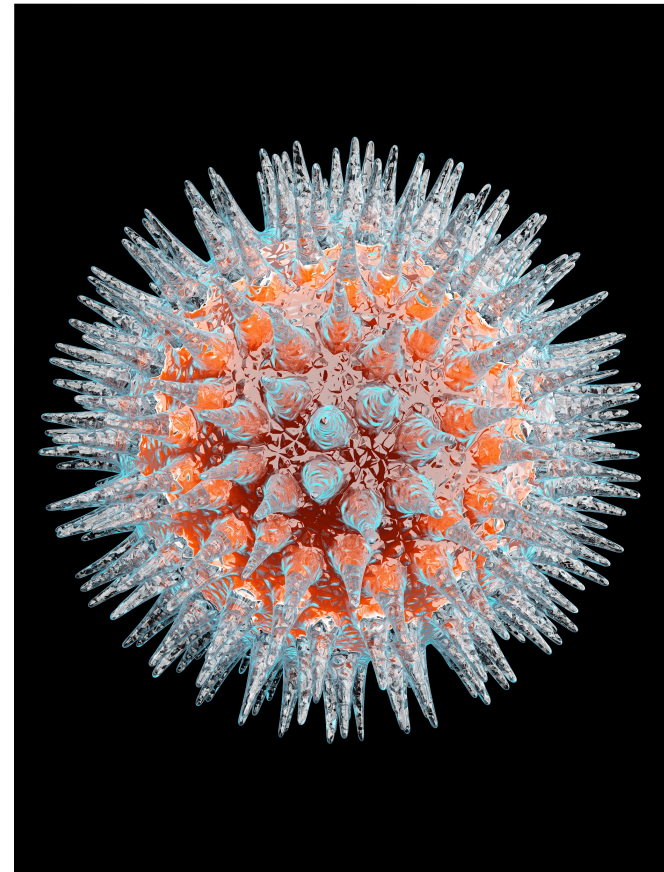
```
@SRRO06511.105 8_1_663_27 length=36
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+
IIII7II-9/0 ;+8I<03. +%- ,&"+' ($,#"' '&"
@SRRO06511.112 8_1_829_108 length=36
AGAATTTTATGTATCTGGATGCAATAAAAAATGATG
+
II@III
@SRROC
AGCACC
+
IO>OA,
@SRROC
ATGCCG
+
IIIIII
@SRROC
ACCACG
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I1B> :I
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High Prevalence in ALL- What is CMV?

- 60-90% worldwide prevalence
- Mean age of infection in US = 28.5
 - 17.5 years old in Hispanics
- Co-evolved with humans
- CMV = largest genome of any human virus
- Extremely complex immune evasion capabilities
- Prefer to lie dormant- latent -> 'stealth virus'
- Can be reactivated during times of stress/immune suppression
- Congenital infection causes birth defects
 - Highest risk in Hispanics



CMV Is a Greater Threat to Infants Than Zika, but Far Less Often Discussed

By CATHERINE SAINT LOUIS OCT. 24, 2016



Is CMV transmitted during pregnancy in children that develop ALL?



California Neonatal Blood spots

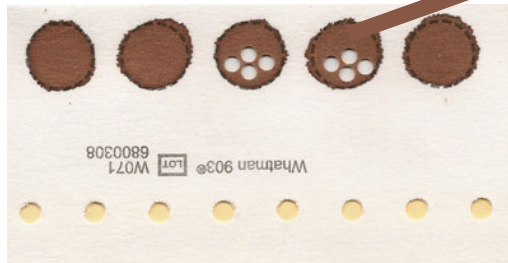


In utero cytomegalovirus infection and development of childhood acute lymphoblastic leukemia

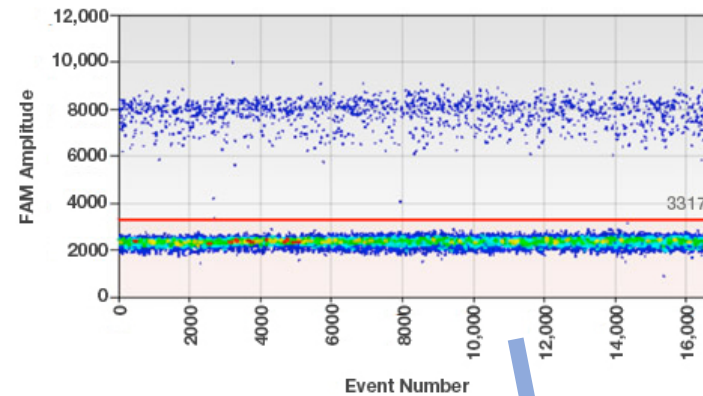
Stephen Starko Francis, Amelia D. Wallace, George A. Wendt, Linlin Li, Fenyong Liu, Lee W. Riley, Scott Kogan, Kyle M. Walsh, Adam J. de Smith, Gary V. Dahl, Xiaomei Ma, Eric Delwart, Catherine Metayer and Joseph L. Wiemels

242
Controls

262
Cases



ddPCR

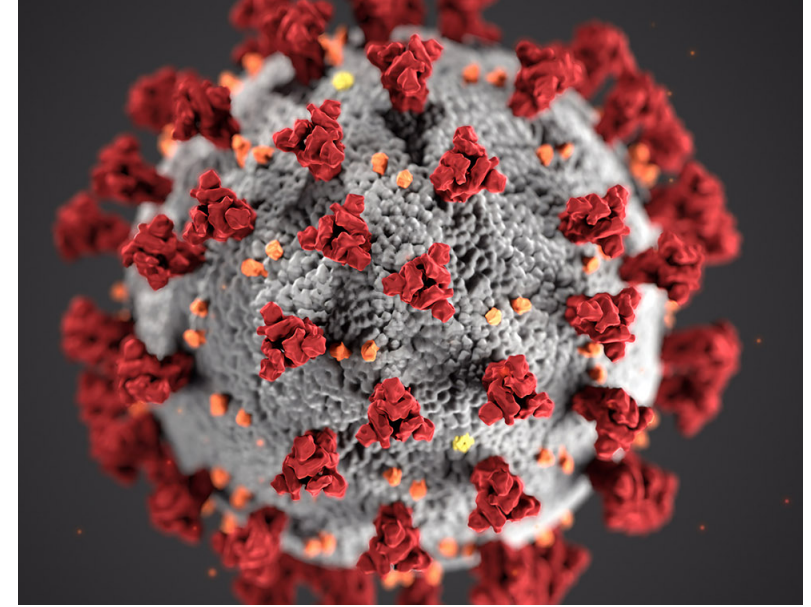


Overall: OR= 3.71 (p=0.0016)

Hispanics= OR=5.90 (p=0.006)

SARS-CoV-2

- Changed everything (maybe)
- Product of animal->human zoonosis
- Advances in technology make studying the distributiona of genetic variants possible
- Most are targeted SARS-CoV-2 sequencing
- Relatively few true metagenomic studies



<https://www.gisaid.org>



Login



About us

Database Features

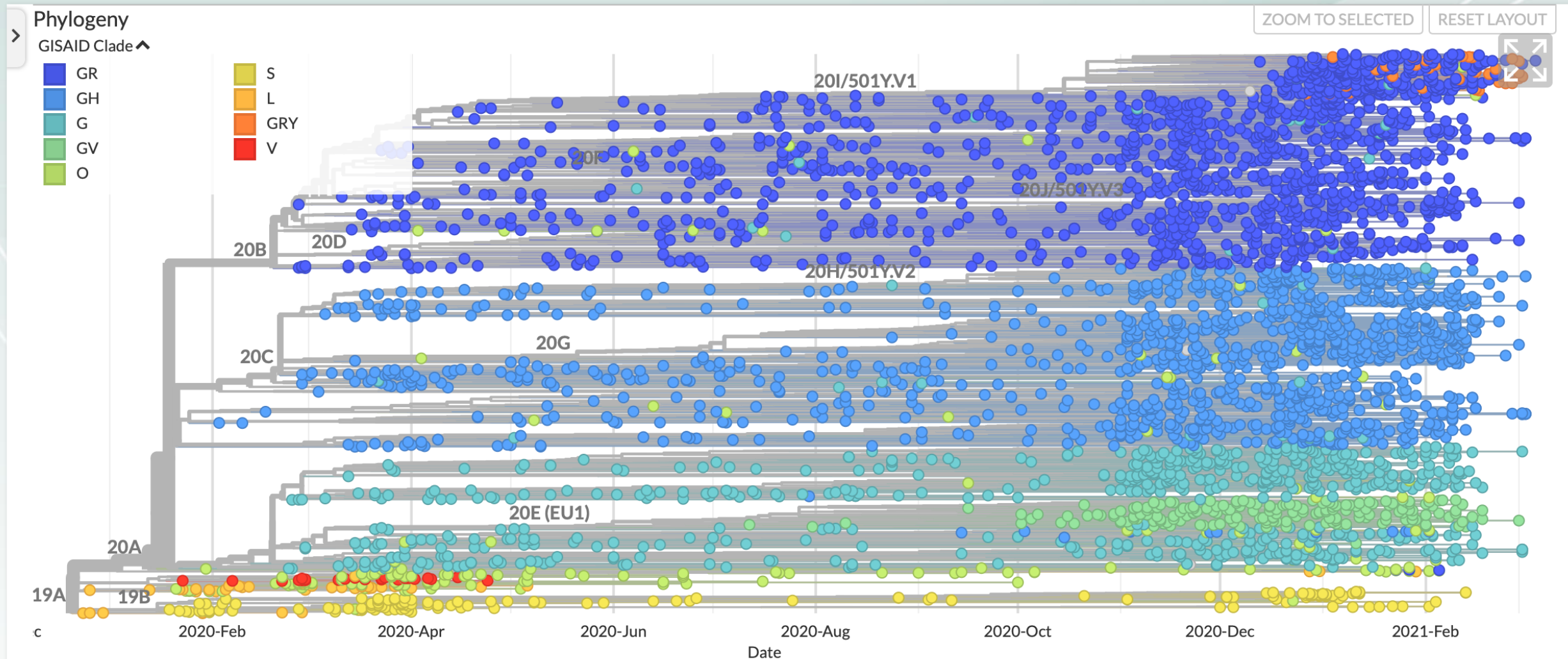
Events

Collaborations

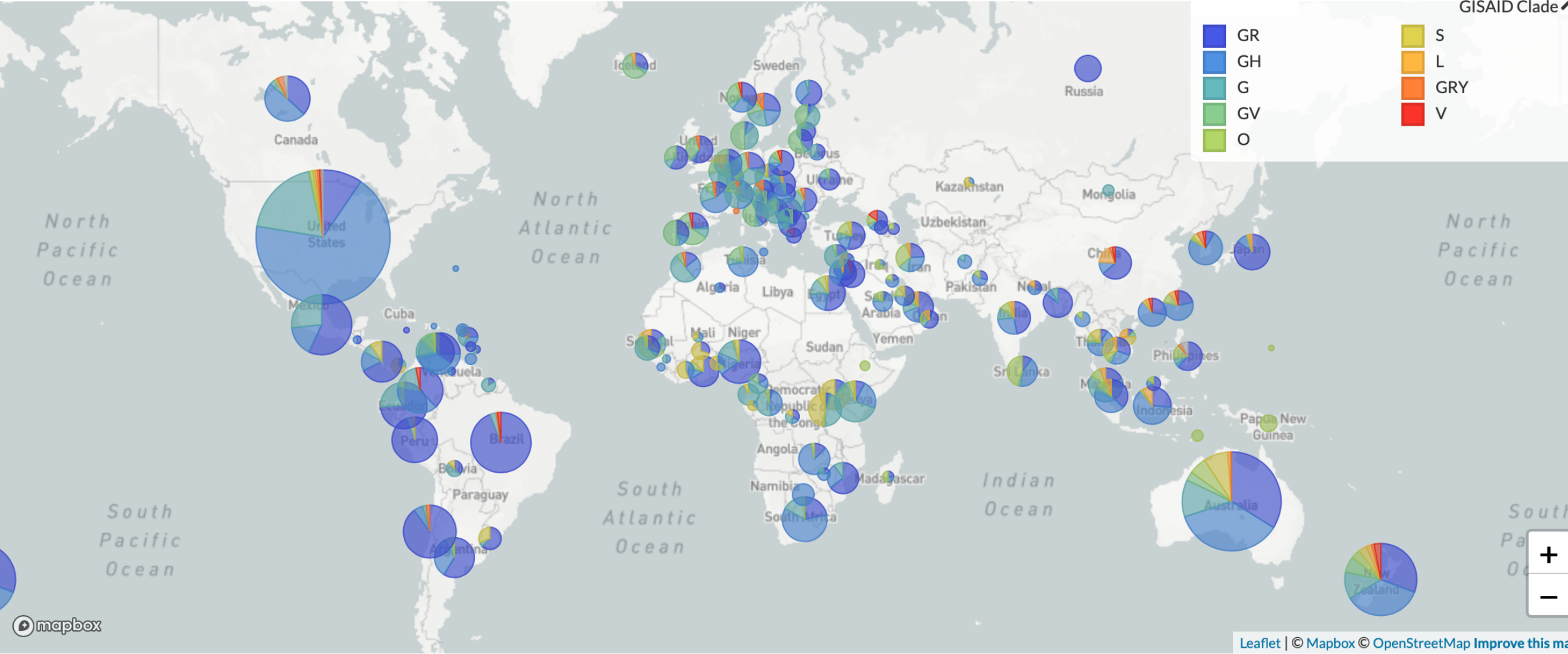
References

Registration

Help



Geography

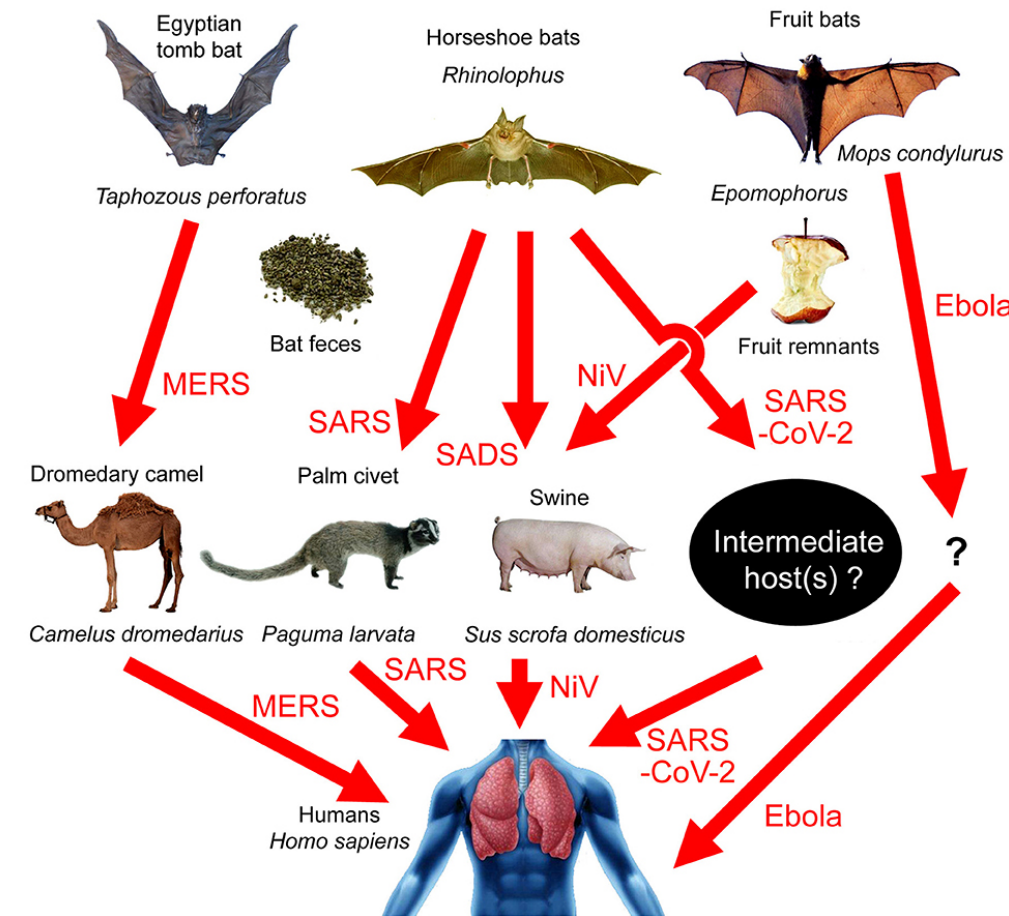


Track variants

- <https://www.gisaid.org/hcov19-variants/>

Parting thoughts

- The co-evolution of viruses and humans has a deep evolutionary history dating back to the first cell
- Alterations in our behavior have altered that relationship
 - This is how epidemics happen and will continue to happen
- SARS-CoV-2 will increase awareness and hopefully funding for metagenomic surveillance
- An unanswered (and difficult) question is how common viruses interact with our genome to potentially cause disease
- Metagenomics allows us to examine novel aspects of co-infection, host interaction and virus dynamics.
- Epidemiology is the key to drawing inference from applications of Next-Gen technologies



Thank You

Francis Lab:

Geno Guerra

Jake Wendt

Shahil Pema

Helen Hansen

Mi Zhou

Collaborators:

Rasmus Neilson

Eric Delwart

Siyang Liu

Joseph Wiemels

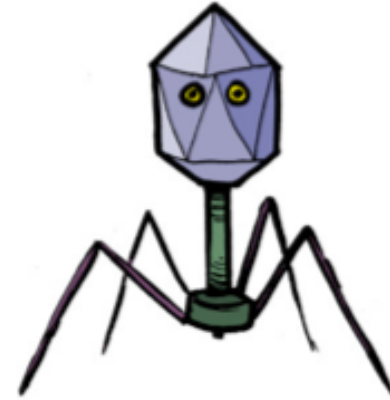
Catherine Metayer

Margaret Wensch

John Wienke

Lee Riley

stephen.francis@ucsf.edu



Virus



Retrovirus