

Epigenomes, DNA Modifications, and Single-Molecule genome sequencing



@mason_lab

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Fellow of the Information Society Project, Yale Law School

April 16th, 2024

Precision Medicine



Weill Cornell Medicine

Englander Institute
for Precision Medicine

About

Patients

Clinicians

News

Resources

Education

Contact

A large graphic on the left side of the page features silhouettes of diverse individuals in shades of blue and purple. Overlaid on this is text for "The Precision Medicine Initiative" and a magnifying glass resting on a stack of papers.

The Precision
THE PRECISION ME Medicine Initiative

● ● ● ●

A grid of four images representing different aspects of precision medicine:

- Patients:** A smiling patient interacting with a healthcare professional.
- Clinicians:** A close-up of a gloved hand holding a test tube, with a DNA sequencing gel image in the background.
- Publications:** A stack of papers and a magnifying glass.
- All Of Us Program:** Silhouettes of diverse individuals.

to Predictive Medicine



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Home > News > WorldQuant Initiative for Quantitative Prediction Established at Weill Cornell Medicine

WorldQuant Initiative for Quantitative Prediction Established at Weill Cornell Medicine

Initiative Combines State-of-the-Art Molecular Profiling Technologies with Advanced Financial Algorithms and Computational Methods to Enhance Precision Medicine

APRIL 28, 2017



From left: Igor Tulchinsky, Dr. Christopher Mason and Dr. Olivier Elemento.

[Back to News](#)



Weill Cornell Medicine

Office of External Affairs

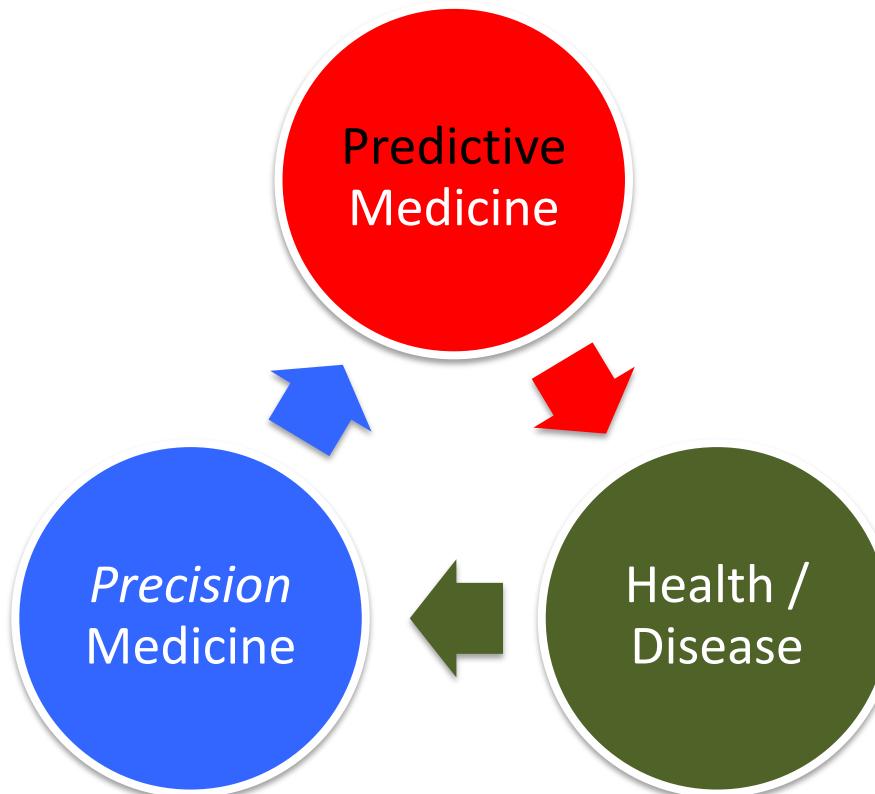
1300 York Ave.

Box 314

New York, NY 10065

Phone: (646) 962-9564

The model





Home » Research & Training » All of Us Research Program

ALL OF USSM RESEARCH PROGRAM

All of Us Research Program

October 12, 2016

[Scale and Scope](#)

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PMI Cohort Program announces new name: the All of Us Research Program

The Precision Medicine Initiative® (PMI) Cohort Program will now be called the *All of Us* Research Program and will be the largest health and medical research program on precision medicine. A set of core values is guiding its development and implementation:

- Participation is open to all.
- Participants reflect the rich diversity of the U.S.
- Participants are partners.



1 million U.S. Veterans WGS and epigenomes

 U.S. Department of Veterans Affairs

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Cooperative Studies Program (CSP)
Health Disparities & Minority Health
Million Veteran Program (MVP)

Million Veteran Program (MVP)

MVP is a national, **voluntary** research program funded entirely by the Department of Veterans Affairs Office of Research & Development. The goal of MVP is to partner with Veterans receiving their care in the VA Healthcare System to study how genes affect health. To do this, MVP will build one of the world's largest medical databases by safely collecting blood samples and health information from one million Veteran volunteers. Data collected from MVP will be stored anonymously for research on diseases like diabetes and cancer, and military-related illnesses, such as post-traumatic stress disorder. [Learn more](#).

Frequently Asked Questions

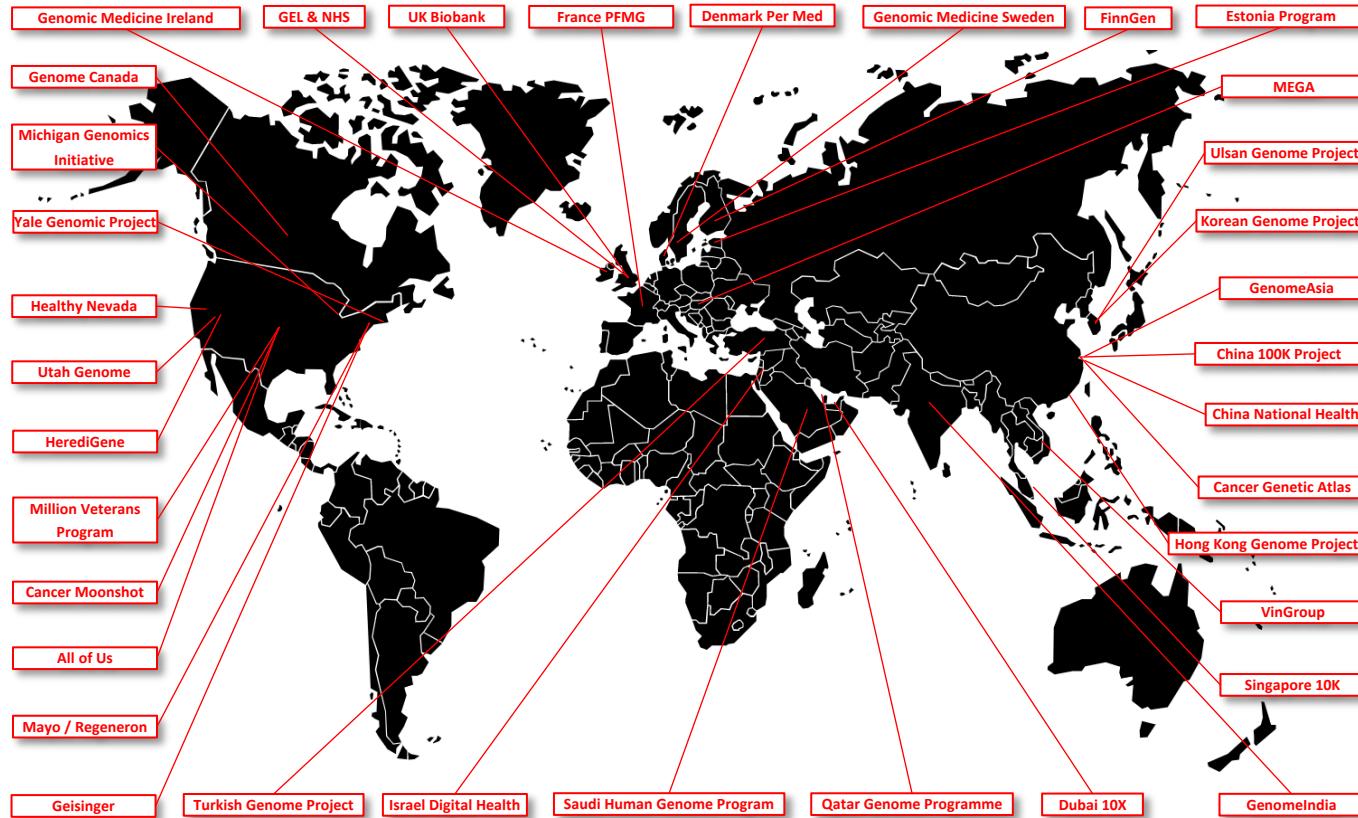
- [How do I participate?](#)
- [Do I need to schedule an appointment to participate?](#)

Text size: [+/-](#)

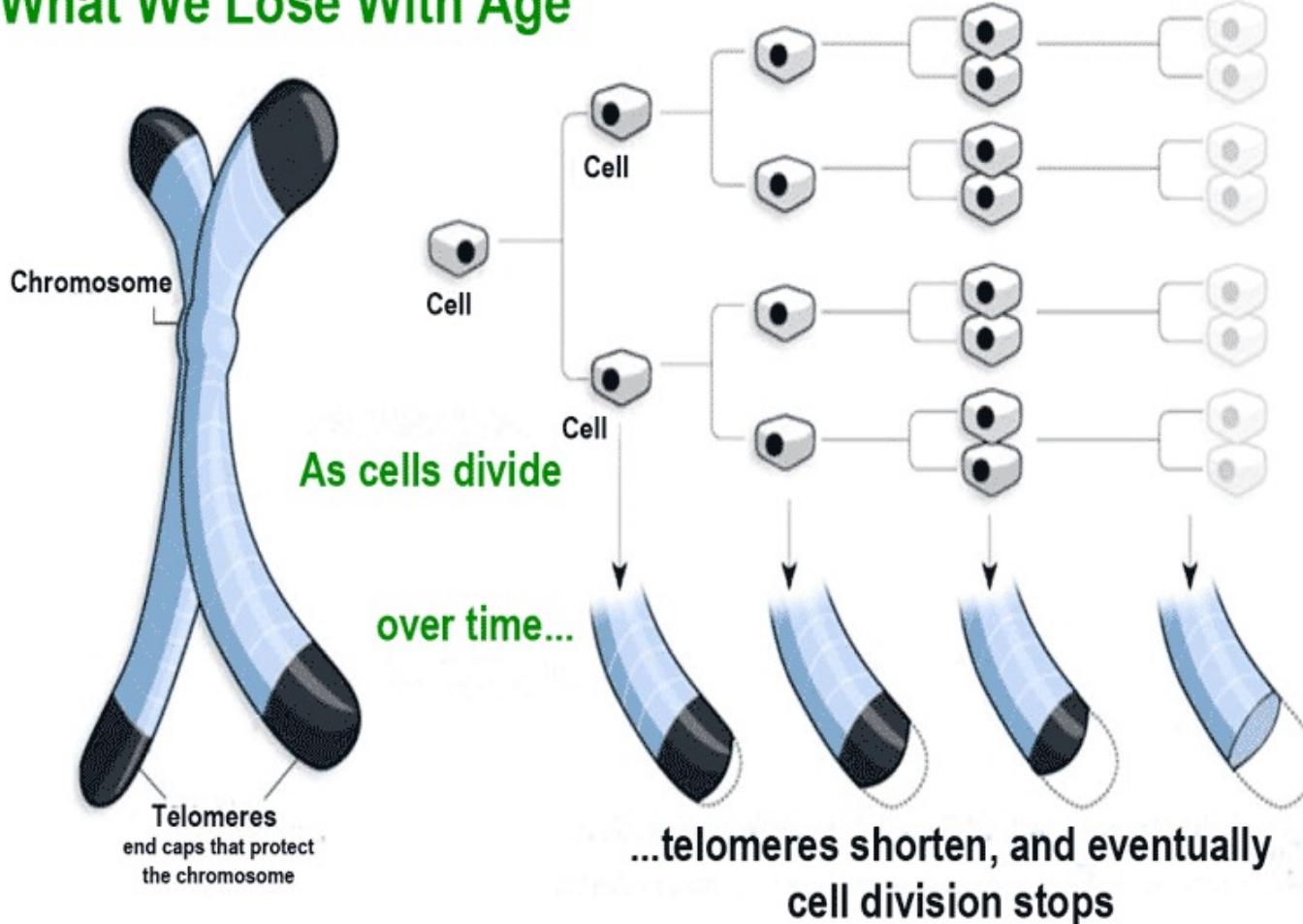
CONTACT MVP
Contact the MVP Information Center toll-free at:
866-441-6075

INFORMED CONSENT

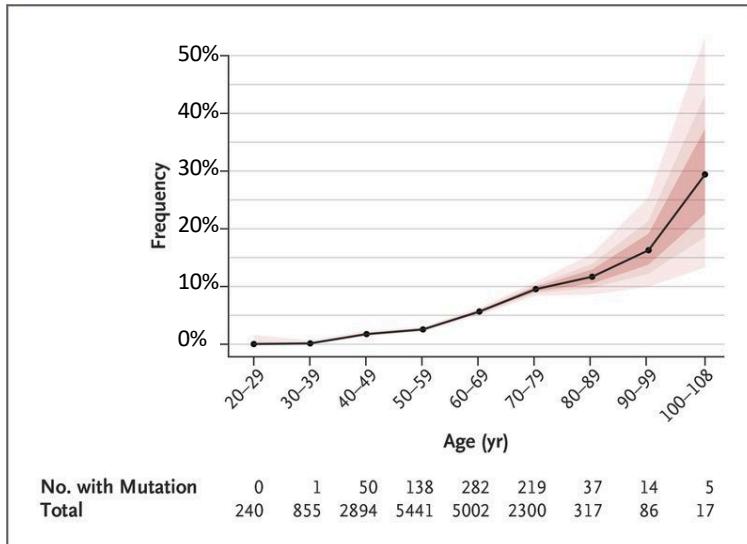

POPULATION-SCALE NGS 2024 IS GLOBAL



What We Lose With Age



What we gain with age: Clonal Hematopoiesis of Indeterminate Potential (CHIP)

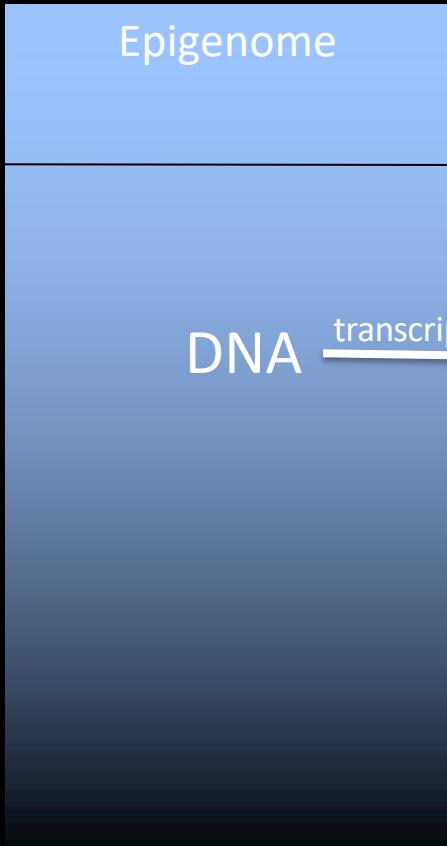


Article | Published: 09 July 2018

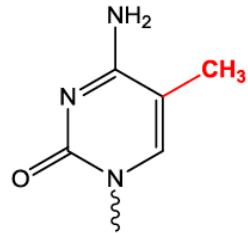
Somatic mutations precede acute myeloid leukemia years before diagnosis

Pinkal Desai , Nuria Mencia-Trinchant, Oleksandr Savenkov, Michael S. Simon, Gloria Cheang, Sangmin Lee, Michael Samuel, Ellen K. Ritchie, Monica L. Guzman, Karla V. Ballman, Gail J. Roboz & Duane C. Hassane

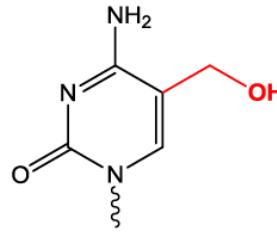
Nature Medicine **24**, 1015–1023 (2018) | Download Citation



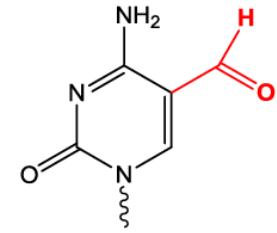
The four-base genome (black) and epigenome marks (red)



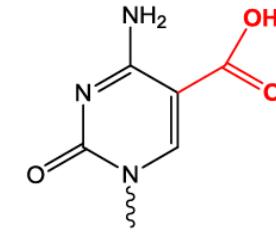
5-mC



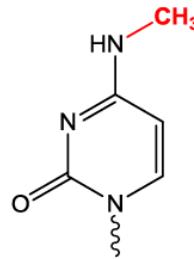
5-hmC



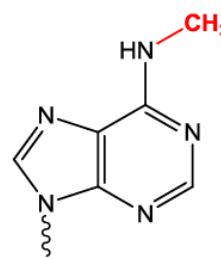
5-fC



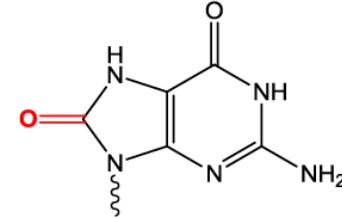
5-caC



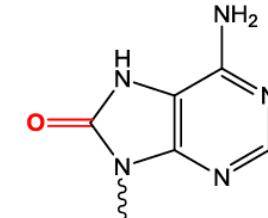
4-mC



6-mA

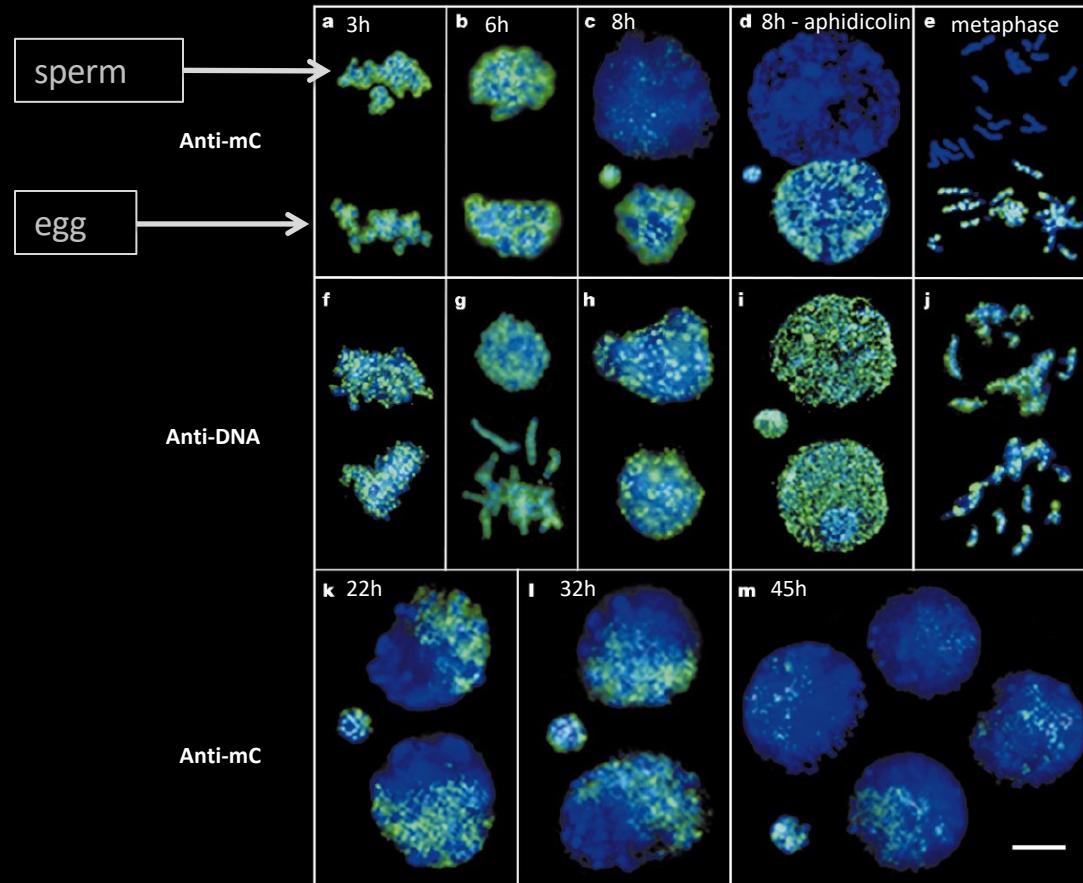


8-oxoG

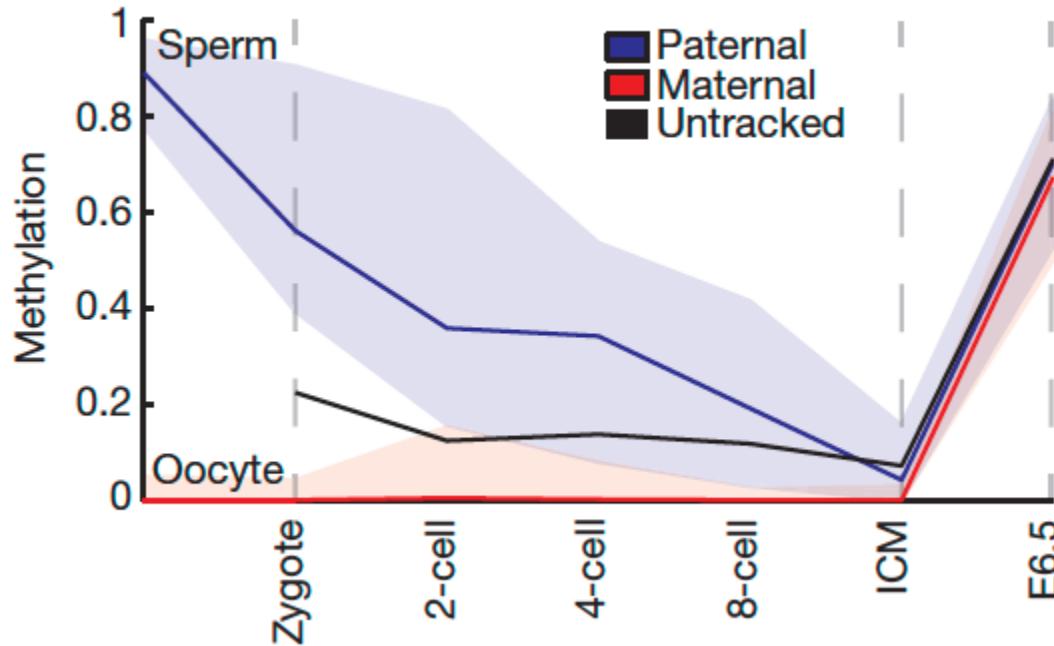


8-oxoA

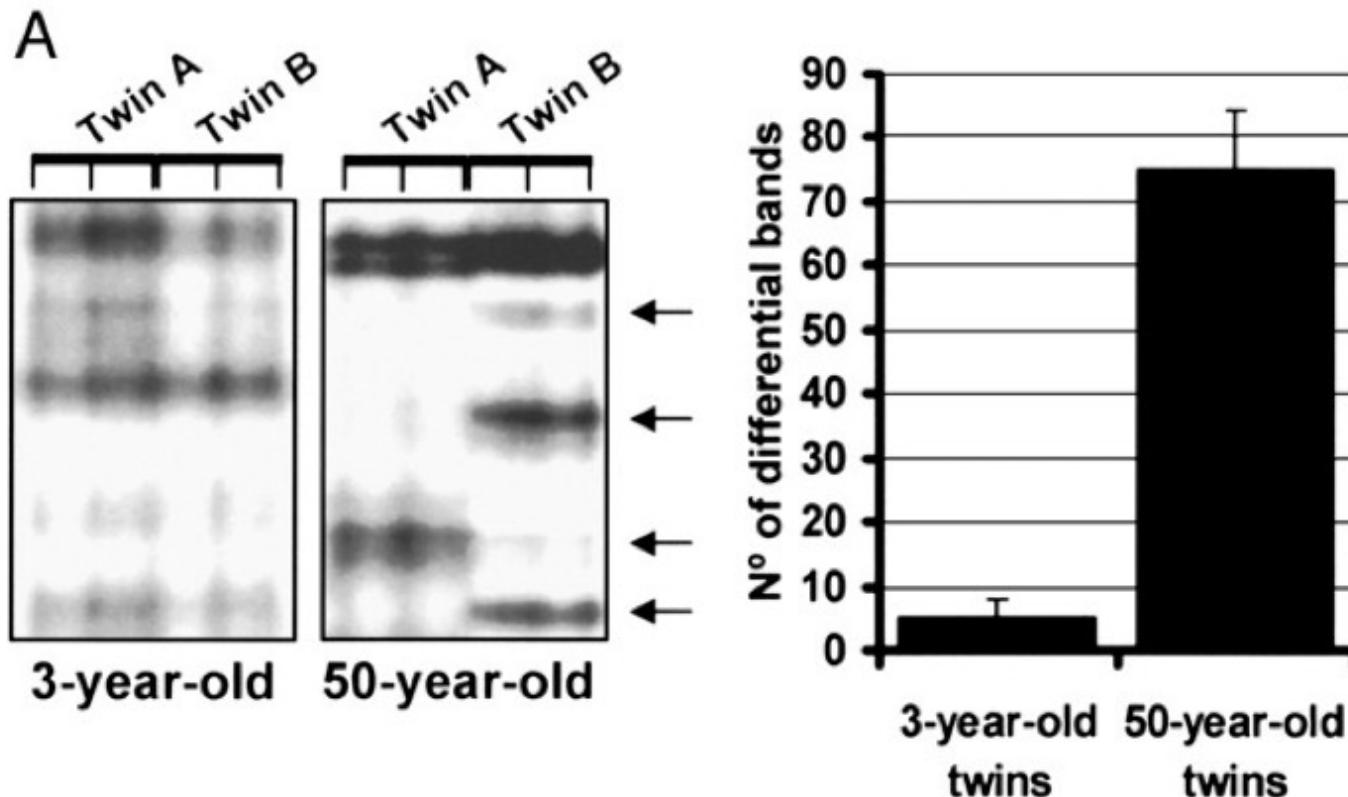
mC is important on day one



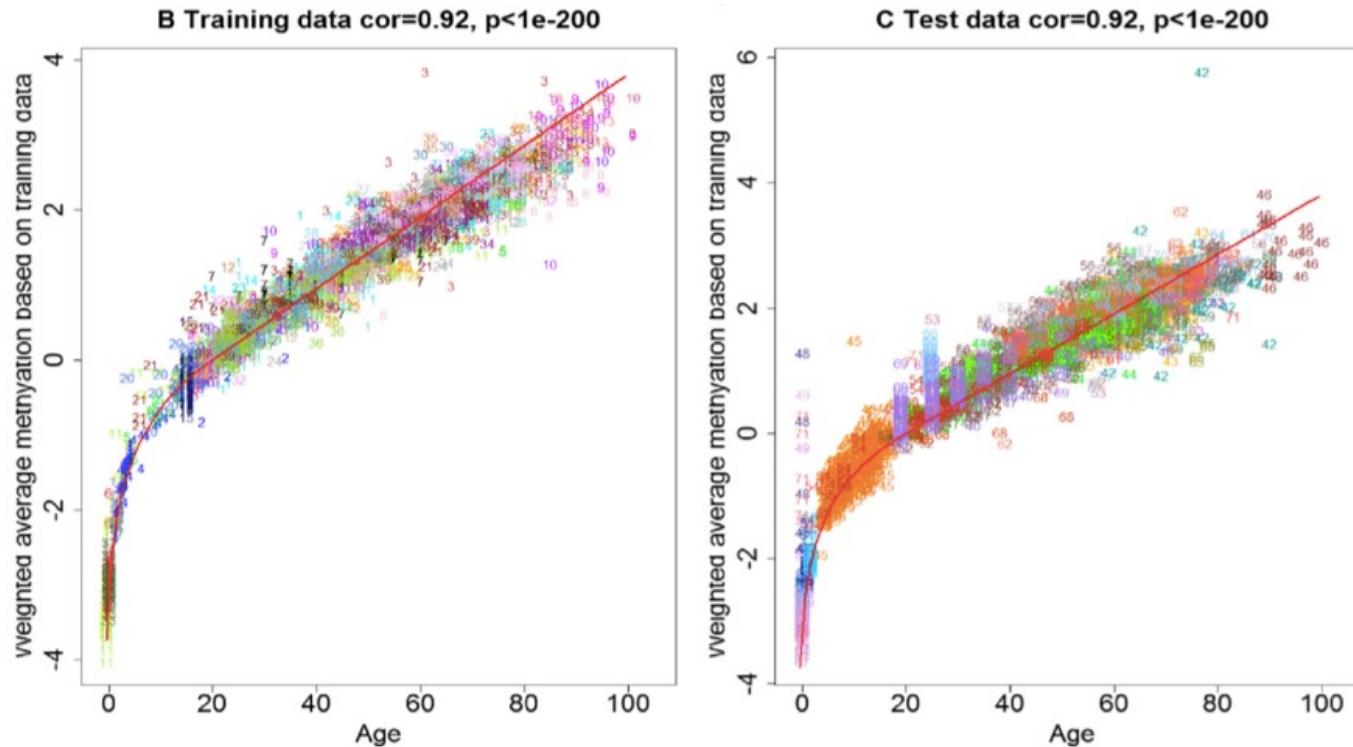
Methylation is critical for specification of embryonic cells after the inner cell mass



Epigenetic Drift in Twins (5mC)

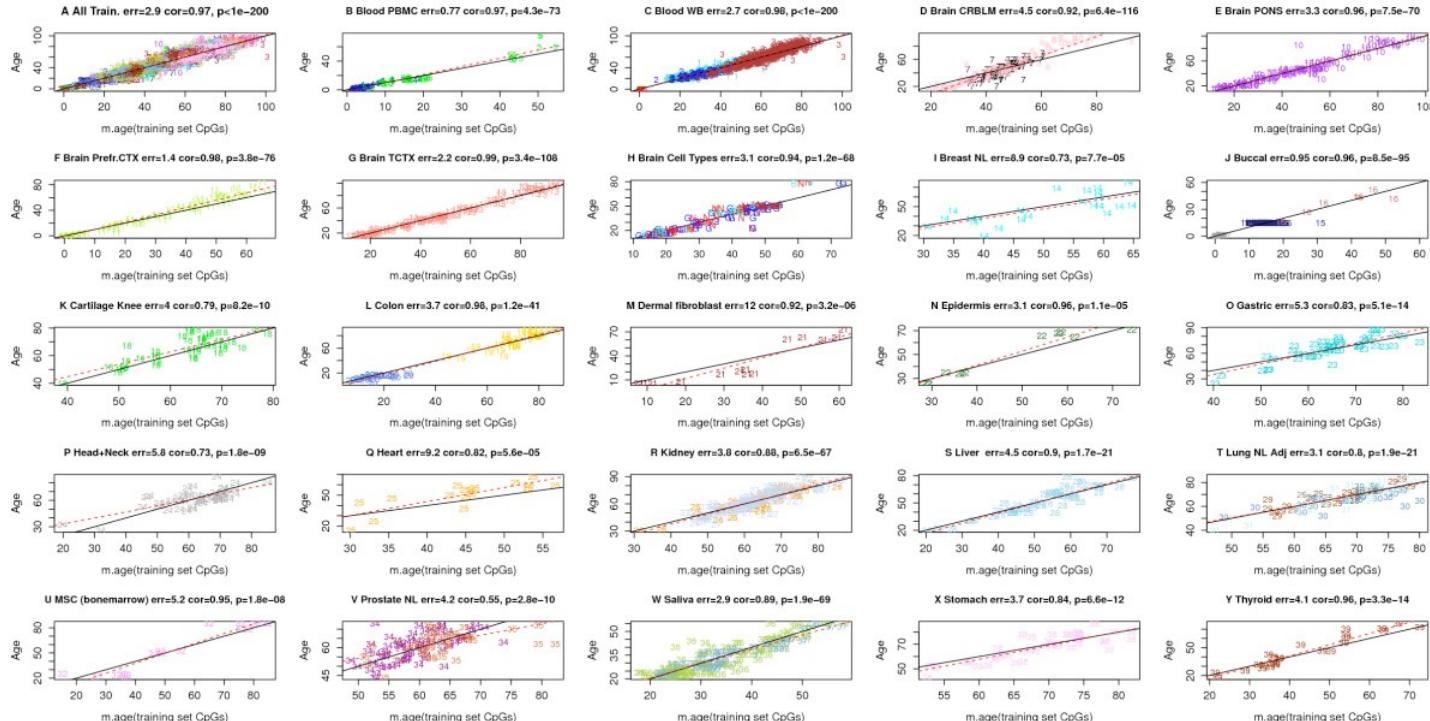


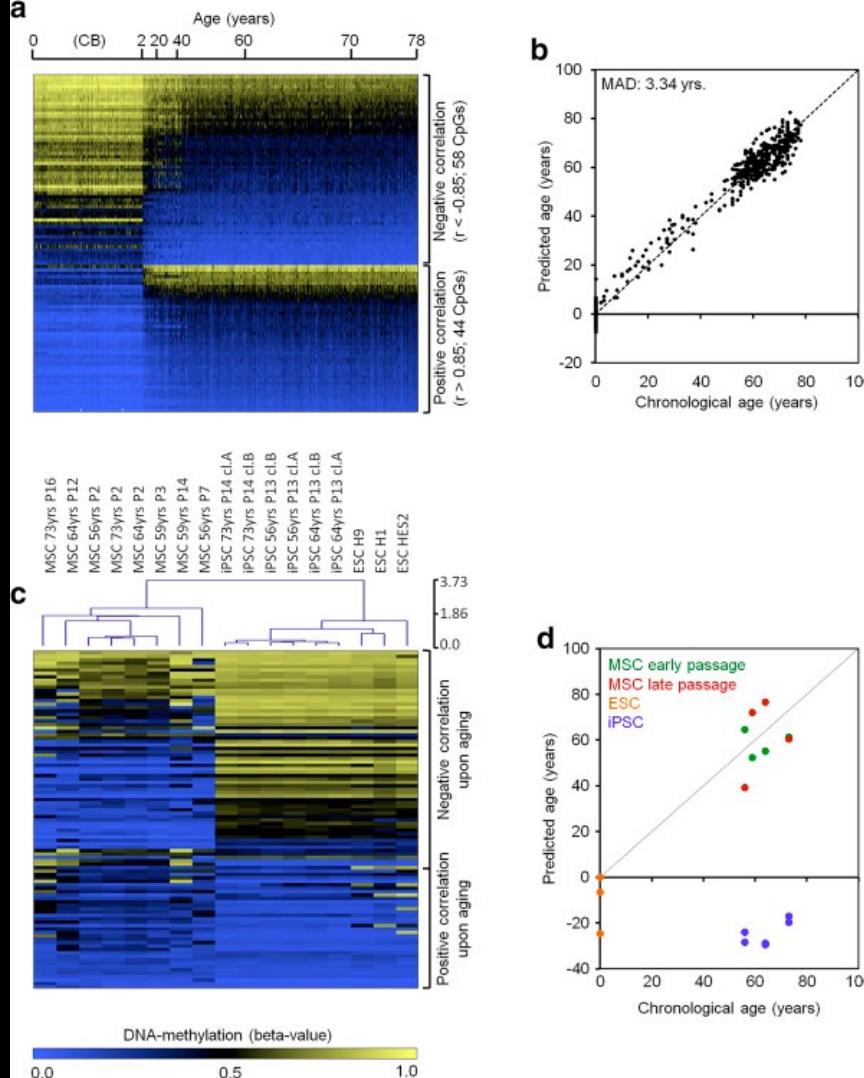
DNA Methylation can predict your age



Horvath S. "DNA methylation age of human tissues and cell types." *Genome Biology*. 2013;14(10):R115.

“Epigenetic age” increases in all tissues as time passes





Epigenetic marks
(DNA methylation)
can reveal
your age.

Weidner CI *et al.*,
“Aging of blood can be tracked by
DNA methylation changes at just
three CpG sites.”
Genome Biology 2014
Feb 3;15(2):R24.

Epigenetic age

WIRED

BACKCHANNEL BUSINESS CULTURE GEAR IDEAS SCIENCE SECURITY

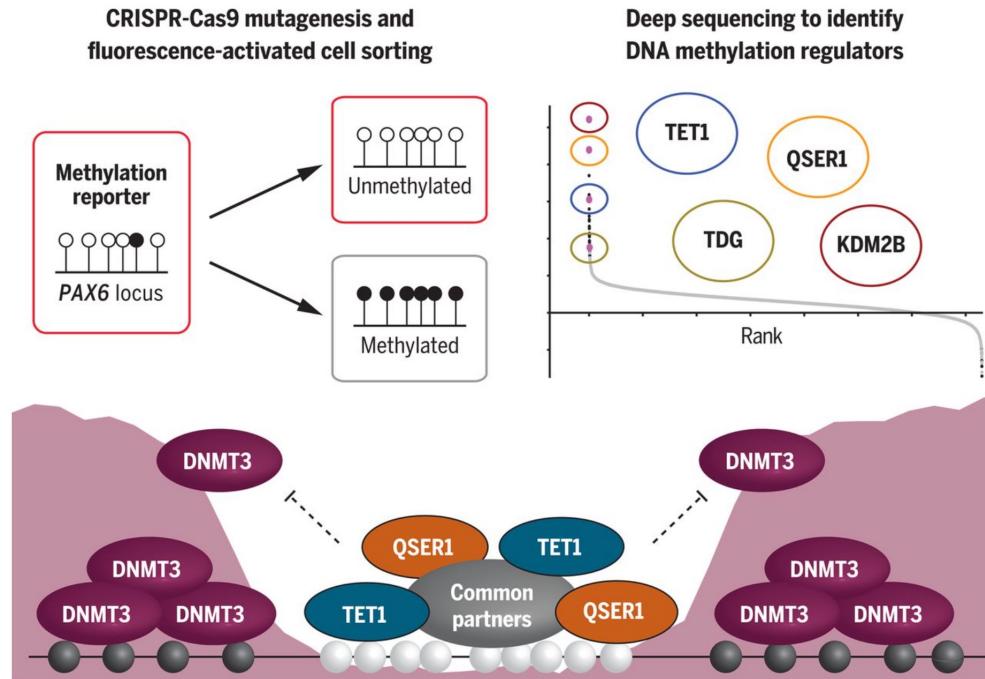
How Old Are You, Really? New Tests Want to Tell You

About a dozen such consumer tests are now on the market, but the science of reading DNA for insights about longevity is still young.



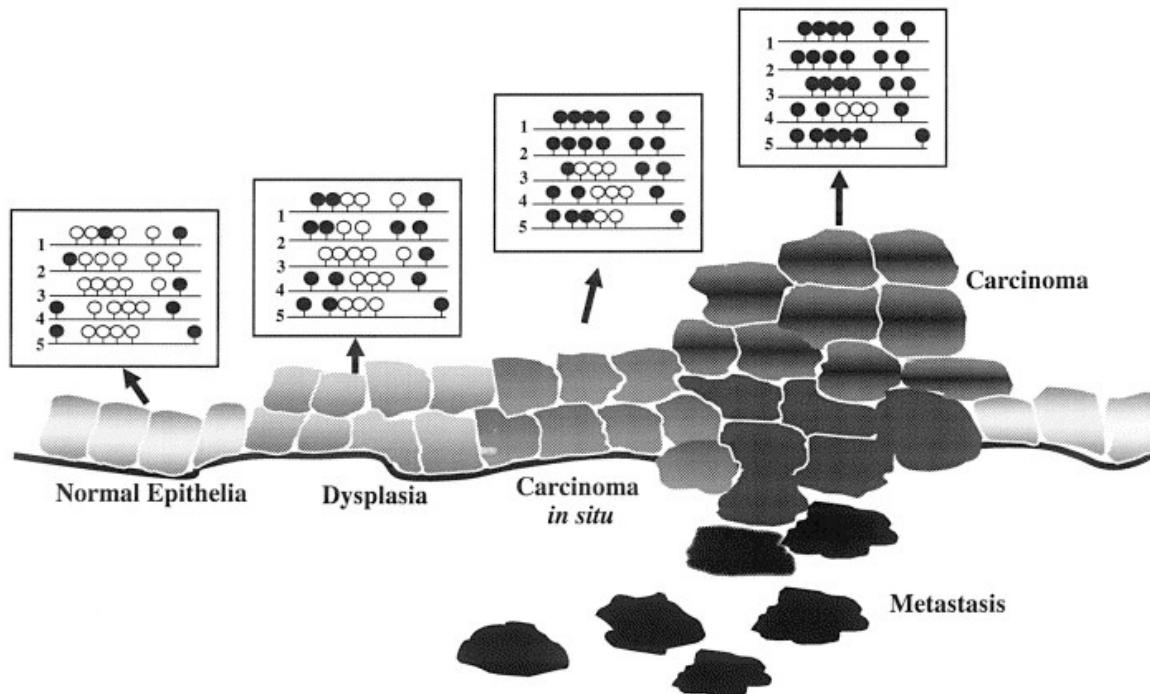
<https://www.wired.com/story/how-old-are-you-really-new-tests-want-to-tell-you/>

We are still finding new tools in the molecular toolbox



In disease

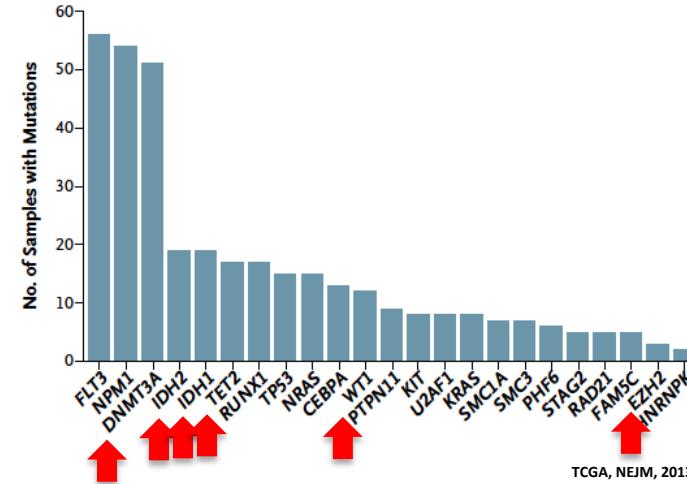
Methylation changes are also a hallmark of cancer



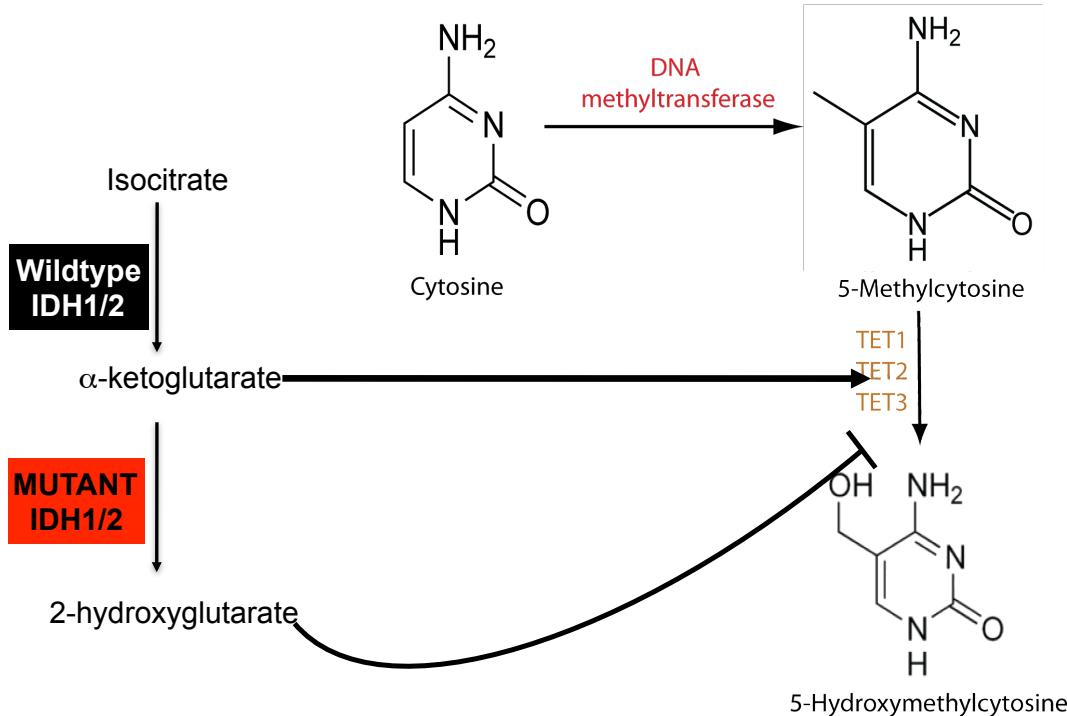
Recurrent somatic mutations in AML are epigenetic modifiers



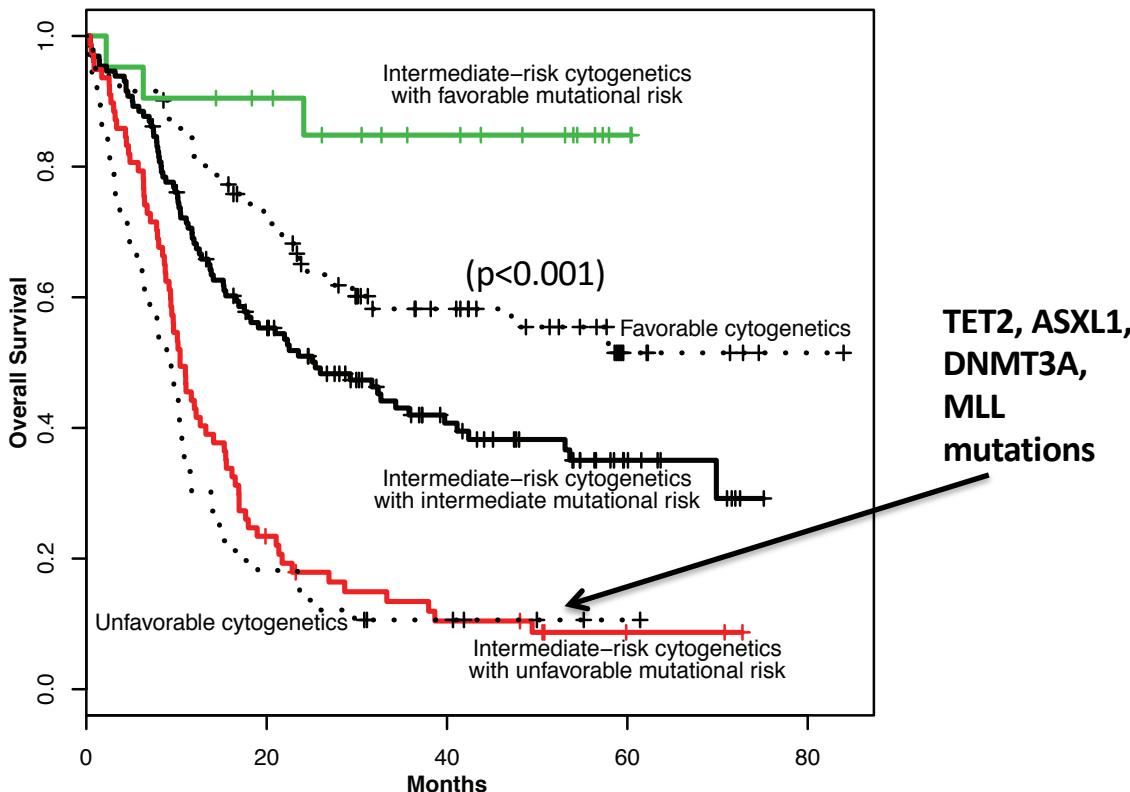
200 patients



Mutations in *IDH1/2* and *TET2* lead to impaired DNA Hydroxymethylation and Increased DNA Methylation



Adverse Outcome in AML Patients With Mutations in Specific Epigenetic Modifiers





Top

Abstract

Rationale

Flexible data...

Whole methylo...

Differential ...

Annotating di...

Analyzing 5-h...

Customizing a...

This article is part of a [special issue on epigenomics](#).**Software****Highly accessed****Open Access****methylKit: a comprehensive R package for the analysis of genome-wide DNA methylation profiles**

Altuna Akalin^{1,2*}, Matthias Kormaksson³, Sheng Li^{1,2}, Francine E Garrett-Bakelman⁴, Maria E Figueroa⁵, Ari Melnick^{4,6} and Christopher E Mason^{1,2*}

* Corresponding authors: Altuna Akalin ala2027@med.cornell.edu -

Christopher E Mason chm2042@med.cornell.edu

▼ Author Affiliations

Proceedings**Open Access****An optimized algorithm for detecting and annotating regional differential methylation**

Sheng Li^{1,2}, Francine E Garrett-Bakelman³, Altuna Akalin^{1,2}, Paul Zumbo^{1,2}, Ross Levine⁴, Bik L To⁵, Ian D Lewis⁵, Anna L Brown⁶, Richard J D'Andrea^{6,7}, Ari Melnick^{3,8} and Christopher E Mason^{1,2*}

Viewing options**Abstract****Full text**

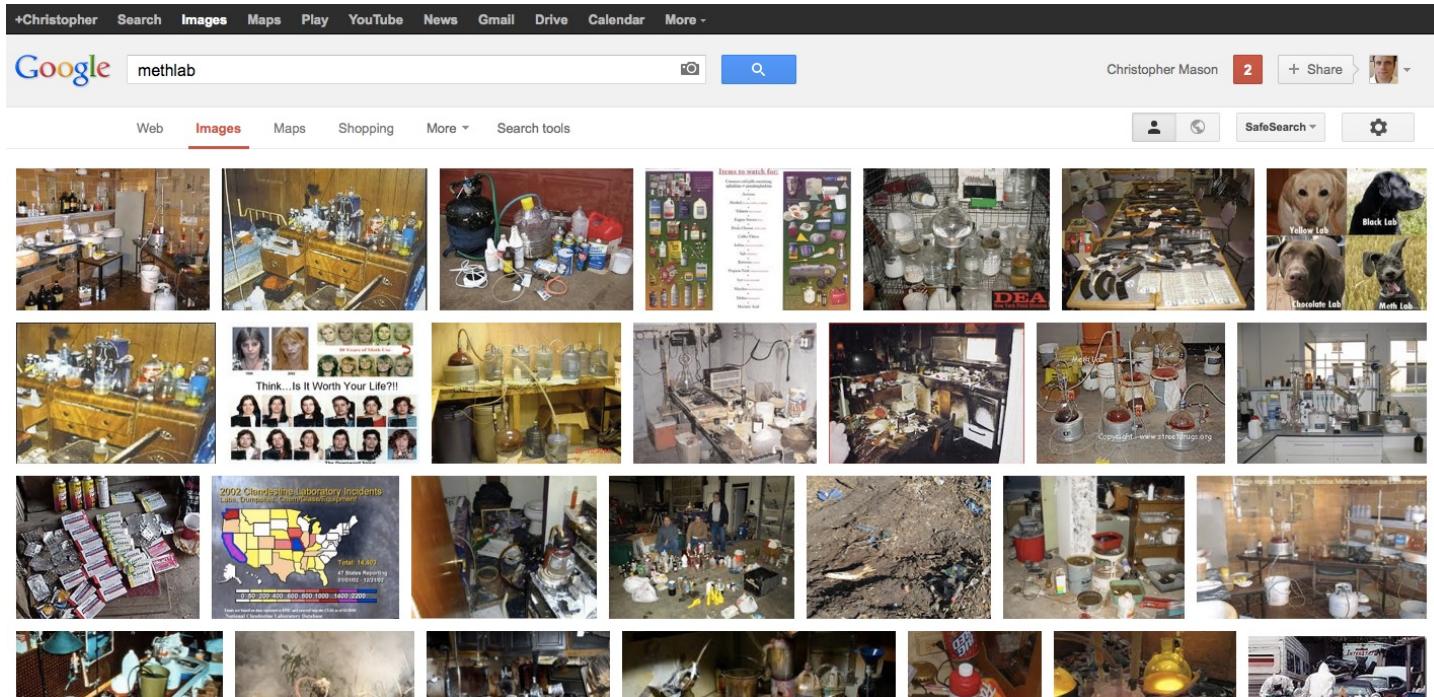
PDF (1.1MB)

ePUB (167KB)

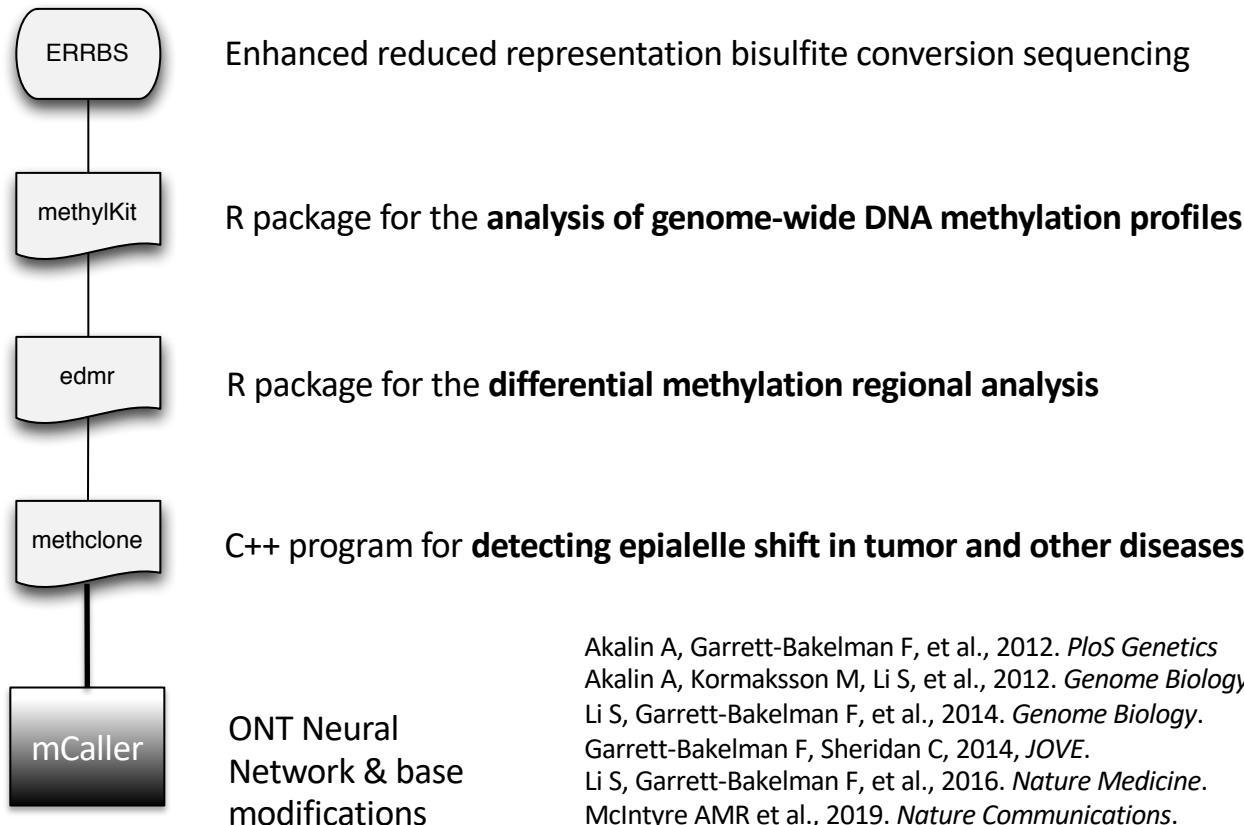
Additional files

“MethLab”

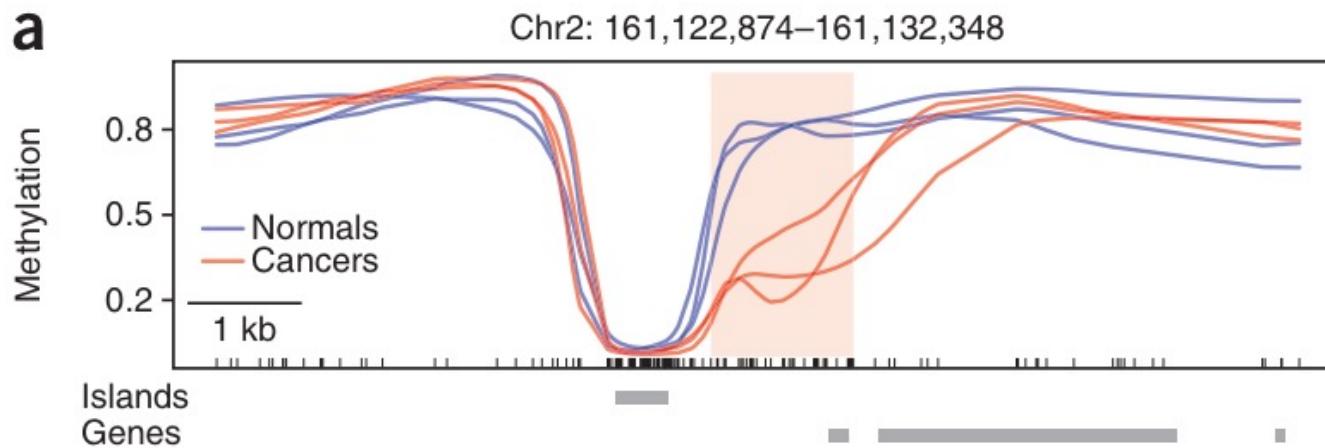
Google Image Search



EpiSuite: Epigenetics sequencing and analysis suite



Methylation can shift in cancers



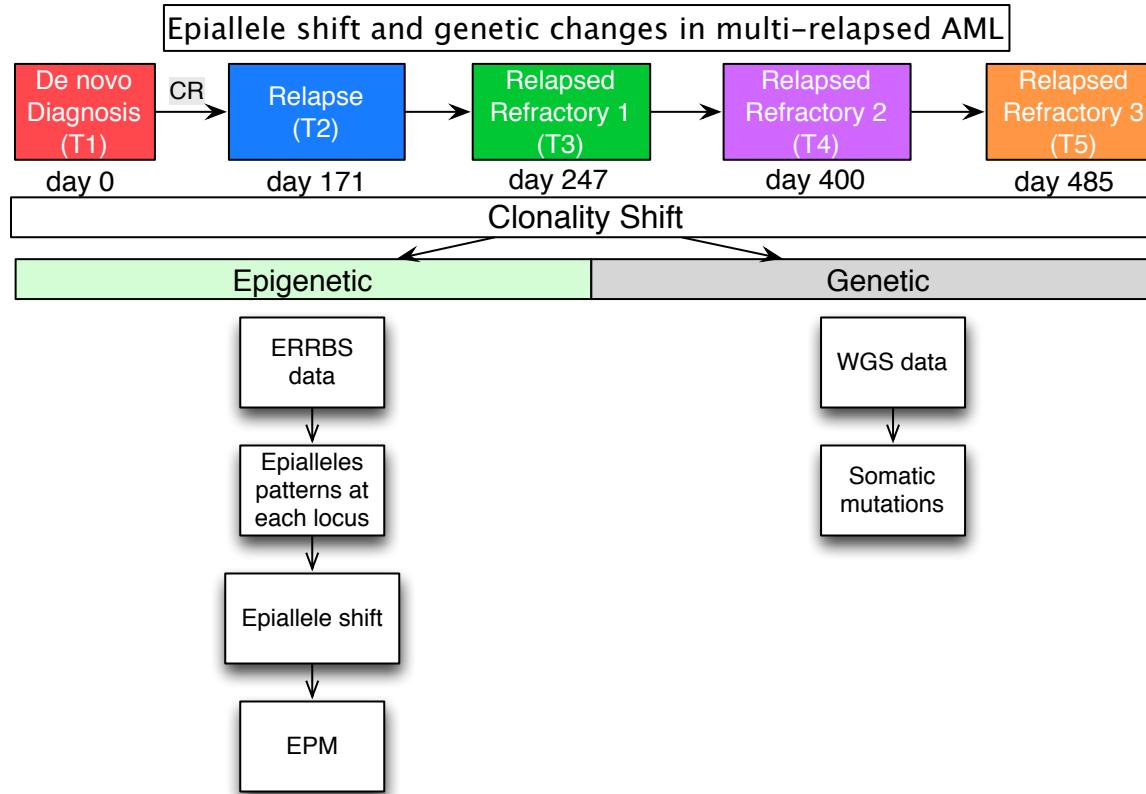
Nat Genet. 2011 Jun 26;43(8):768-75.

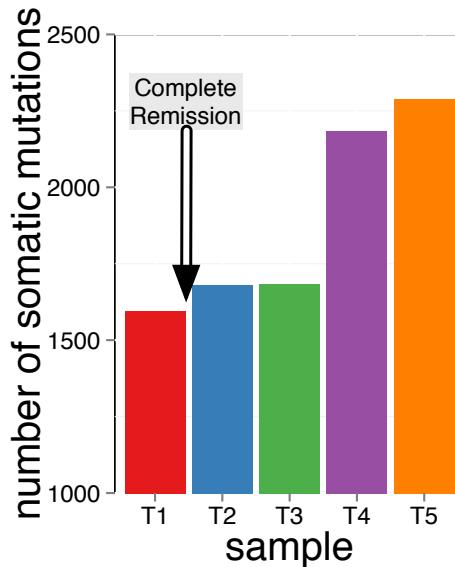
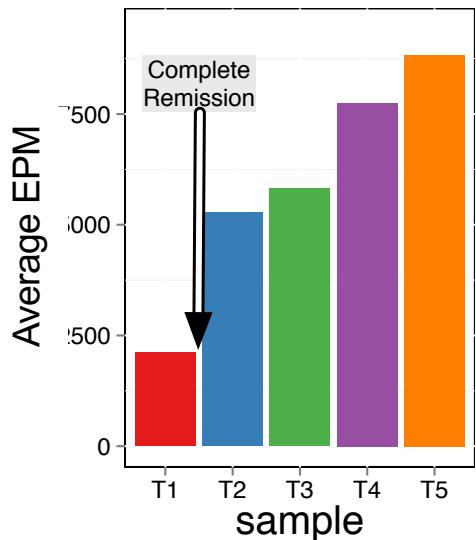
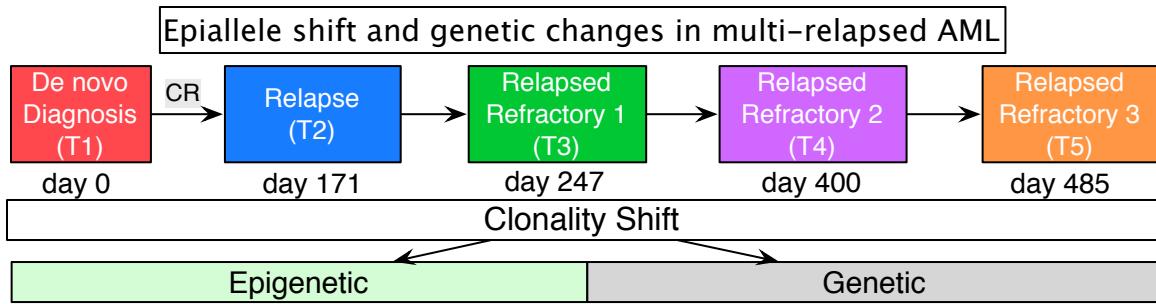
Longitudinal
changes

Chernobyl, 1986

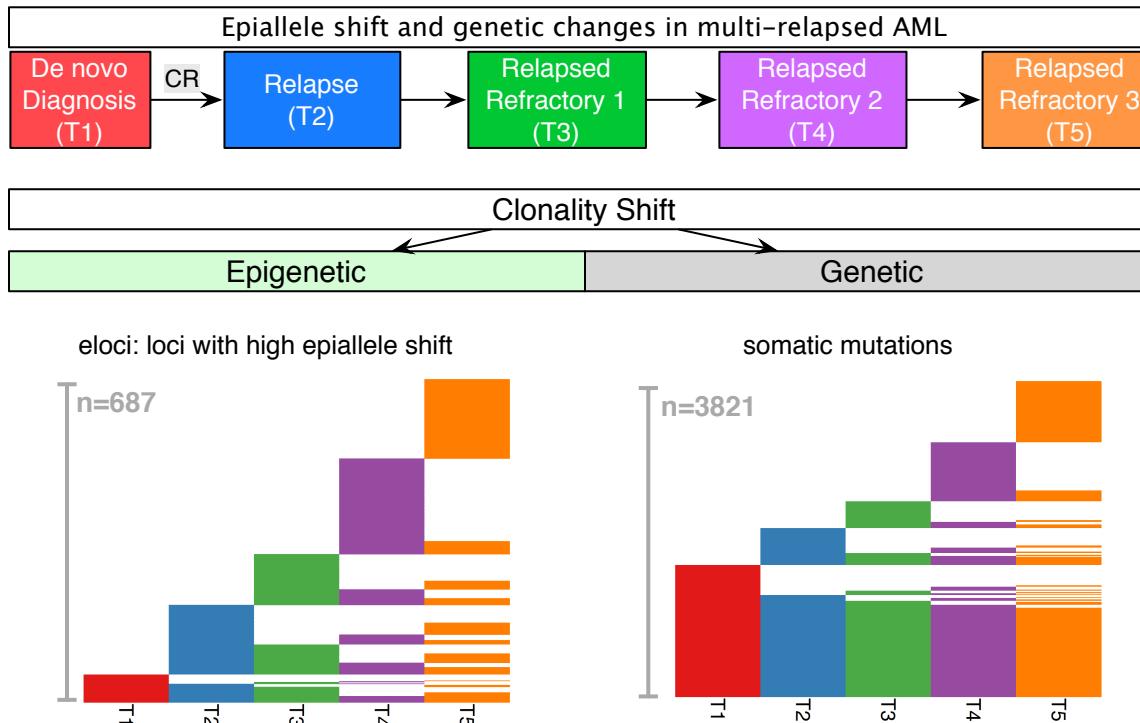


Chernobyl man

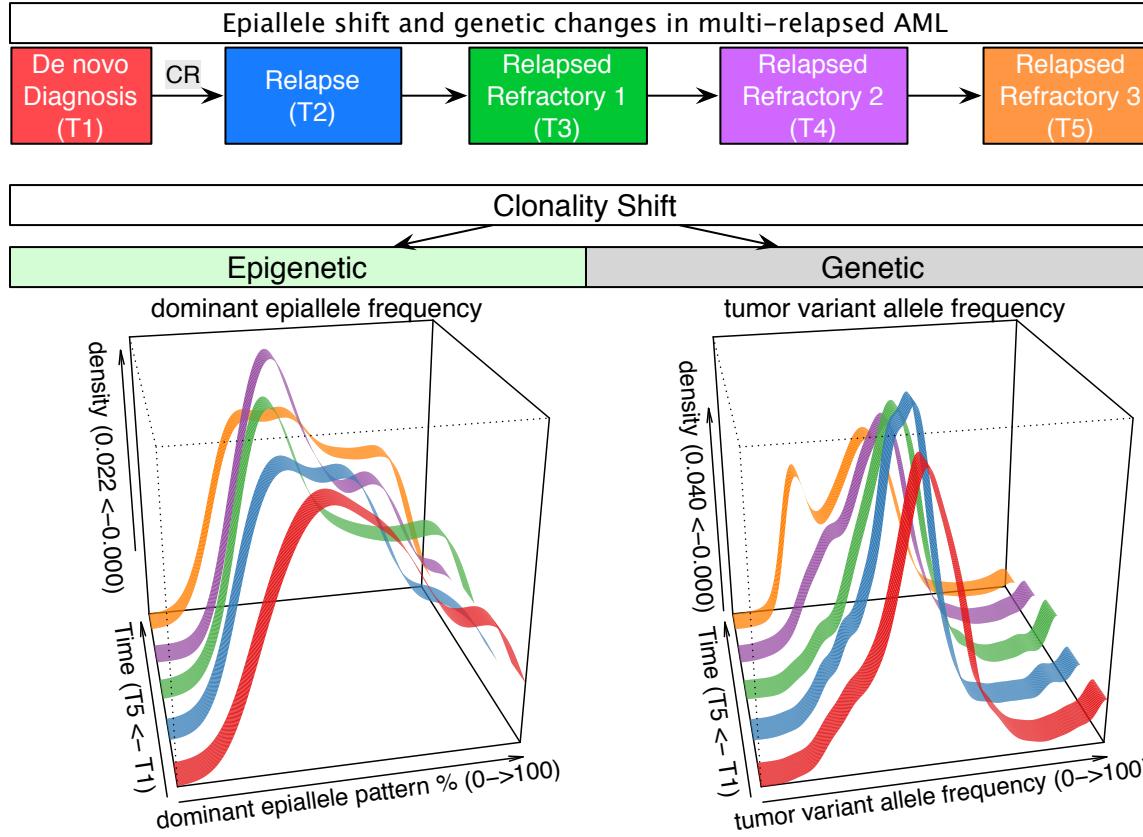




The eloci/mutations shared among time points were different

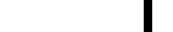


Low EAF (epigenetic evolution) is antecedent to low VAF (genetic evolution)



From a single read...

16 Possible Patterns for Epiallele of 4 CpGs

4	3	2	1	0
	       	       	       	

Number on the top of each column stands for the number of methylated CpG site(s).

Each circle stands for a CpG site.

Open circle strands for a unmethylated CpG site.

Fill circle strands for a methylated CpG site.

Entropy measurement

- Entropy is an expression of the disorder, or randomness of a system.
- Boltzmann's entropy formula (1875):

$$S = k_B \ln W$$

W is the number of microstates corresponding to a given macrostate, and can be counted using the

formula for permutations: $W = N! / \prod_i N_i!$

- Previously being applied to amino acid sequence classification as combinatorial entropy.

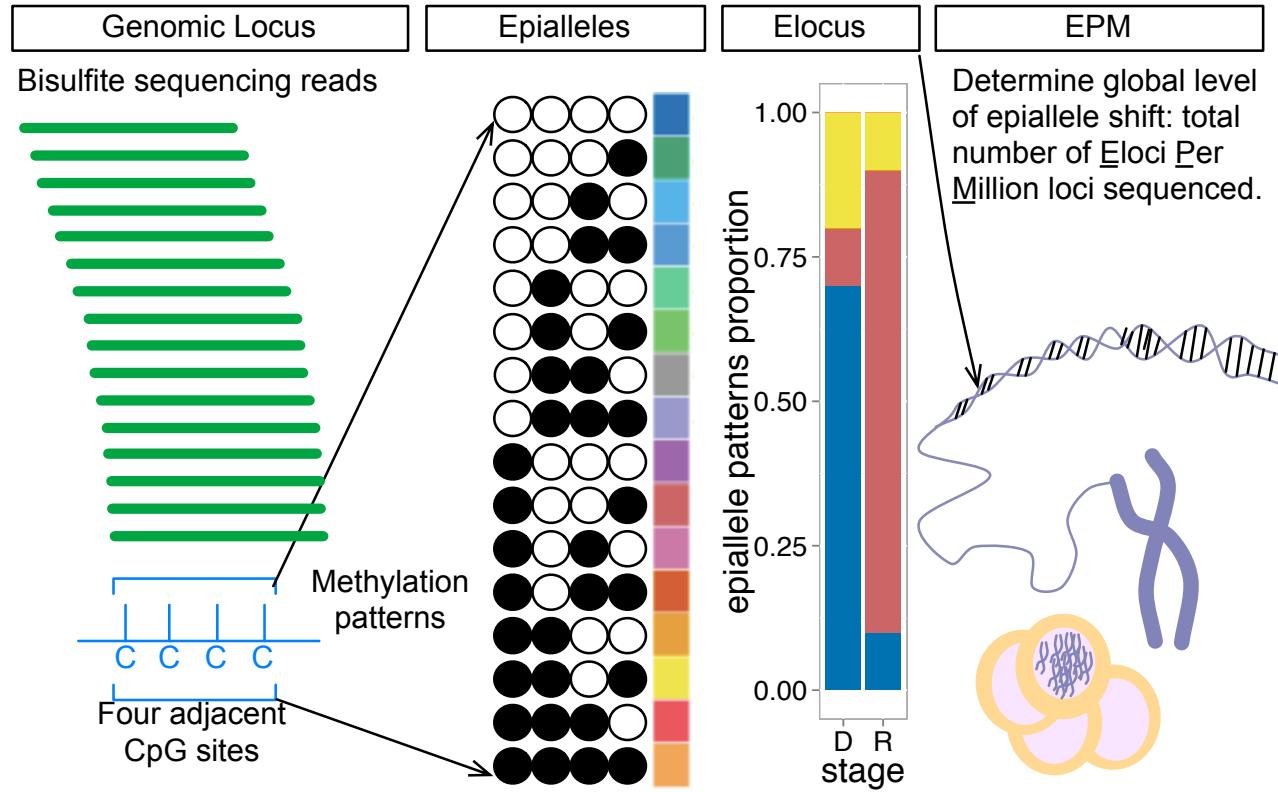


mutationassessor.org

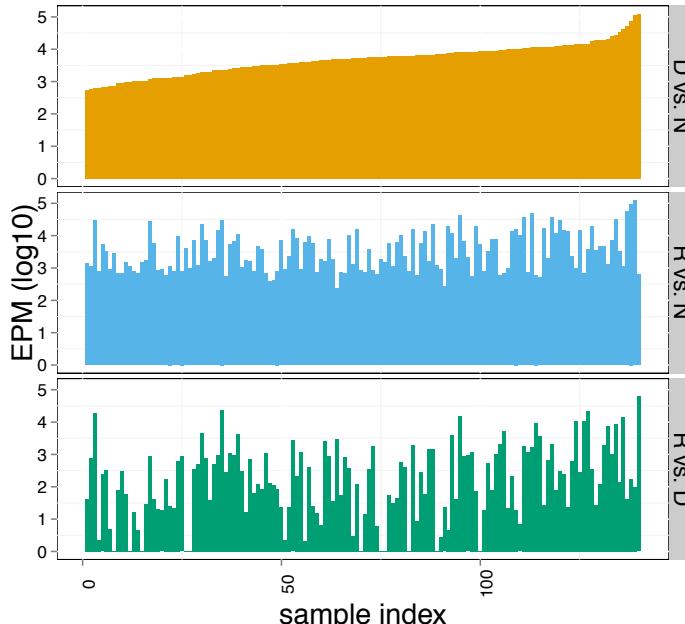
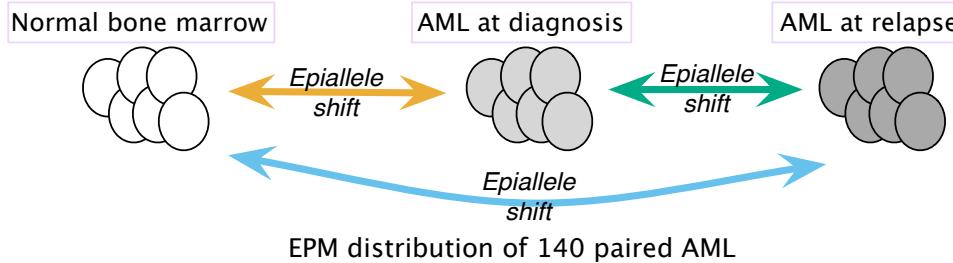
functional impact of protein mutations
release 2

Perrot, Pierre. 1998. A to Z of Thermodynamics.
Reva B, Antipin Y, Sander C. 2007. Genome Biology
Reva B, Antipin Y, Sander C. 2011. Nucleic Acids Research

Epiallele dynamics calculation

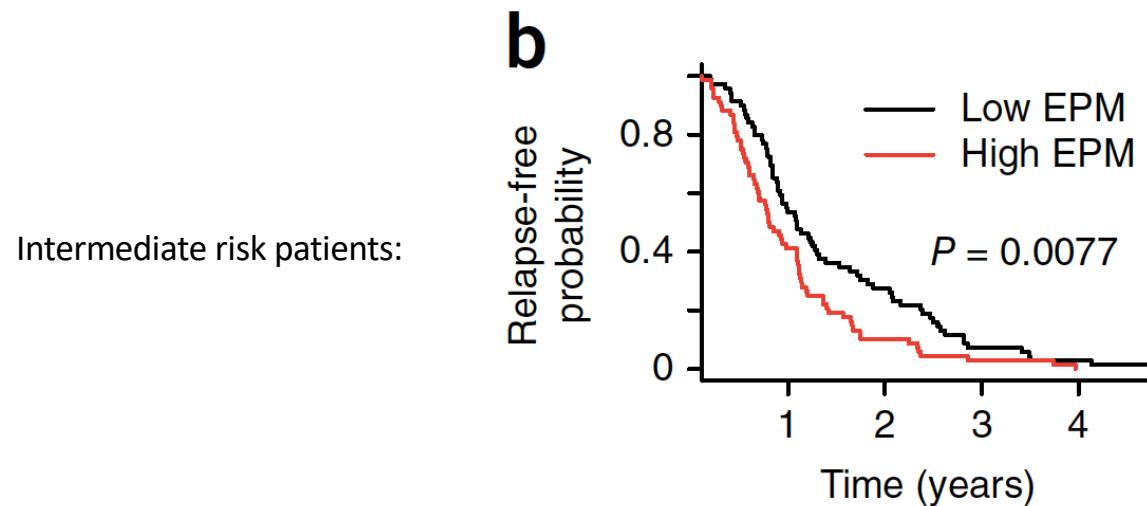
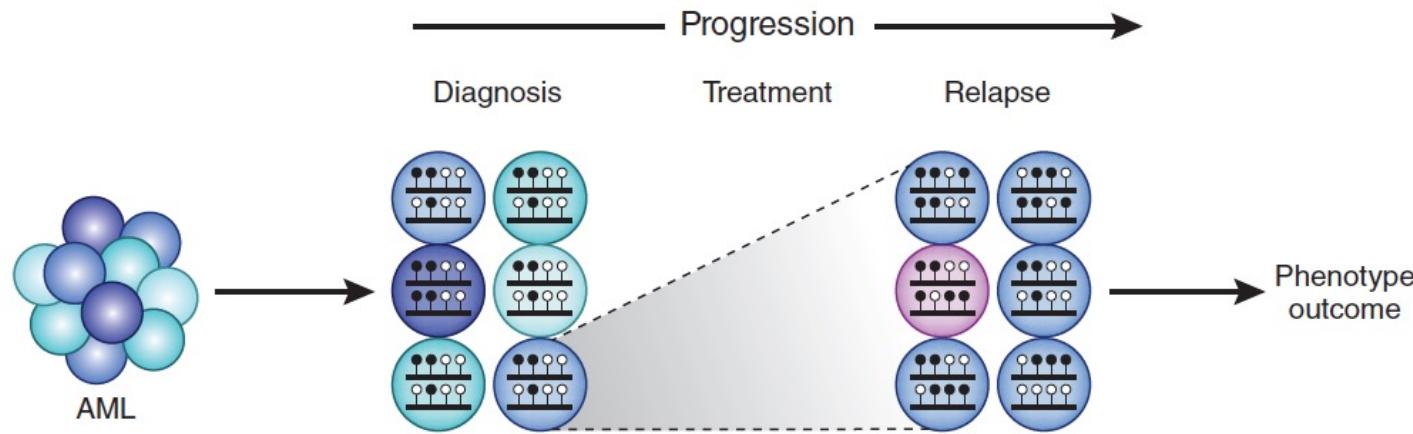


EPM: total number of Eloci Per Million loci sequenced



■ diagnosis vs. NBM ■ relapse vs. NBM ■ relapse vs. diagnosis





Li S, et al., "Dynamic Evolution of Clonal Epialleles Revealed by Methclone." *Genome Biology*, 2014.

Li S, Garrett-Bakelman F, et al., *Distinct Evolution and dynamics of epigenetic and genetic heterogeneity in AML*. *Nature Medicine*, 2016.

Distinct evolution and dynamics of epigenetic and genetic heterogeneity in acute myeloid leukemia

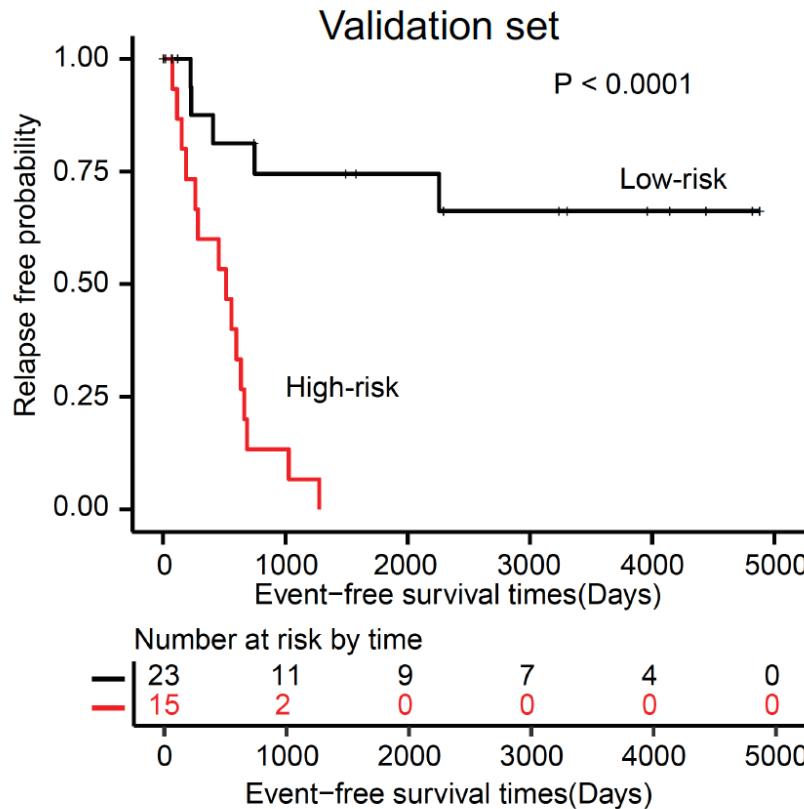
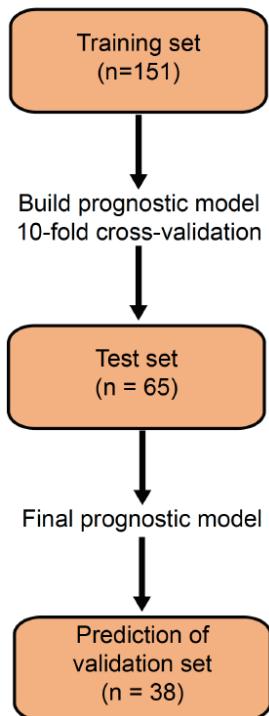
Sheng Li^{1,18,19}, Francine E Garrett-Bakelman^{2,19}, Stephen S Chung³, Mathijs A Sanders⁴, Todd Hricik³, Franck Rapaport³, Jay Patel³, Richard Dillon⁵, Priyanka Vijay⁶, Anna L Brown^{7–9}, Alexander E Perl¹⁰, Joy Cannon¹⁰, Lars Bullinger¹¹, Selina Luger¹⁰, Michael Becker¹², Ian D Lewis^{7,9,13}, Luen Bik To^{9,13}, Ruud Delwel⁴, Bob Löwenberg⁴, Hartmut Döhner¹¹, Konstanze Döhner¹¹, Monica L Guzman², Duane C Hassane², Gail J Roboz², David Grimwade⁵, Peter J M Valk⁴, Richard J D'Andrea^{7–9}, Martin Carroll¹⁰, Christopher Y Park^{14,15}, Donna Neuberg¹⁶, Ross Levine³, Ari M Melnick² & Christopher E Mason^{1,17}

**EPIGENETICS**

Separate paths for epigenomes
and genomes in cancer evolution?

NATURE REVIEWS | GENETICS

An epiallele prognostic classifier predicts clinical outcome in AML



cfDNA methylation also holds signatures of disease



Annals of Oncology

Volume 32, Issue 9, September 2021, Pages 1167-

1177



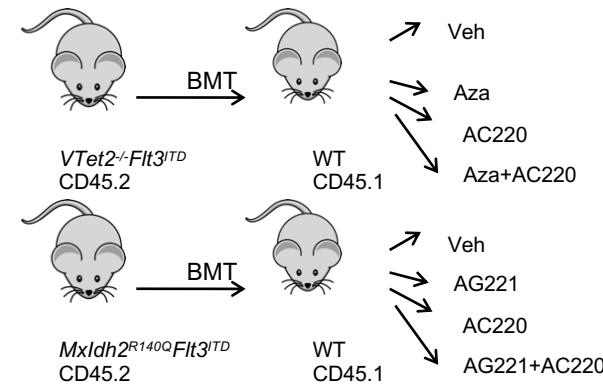
Original Article

Clinical validation of a
targeted methylation-based
multi-cancer early detection
test using an independent
validation set

Can we target
them better?

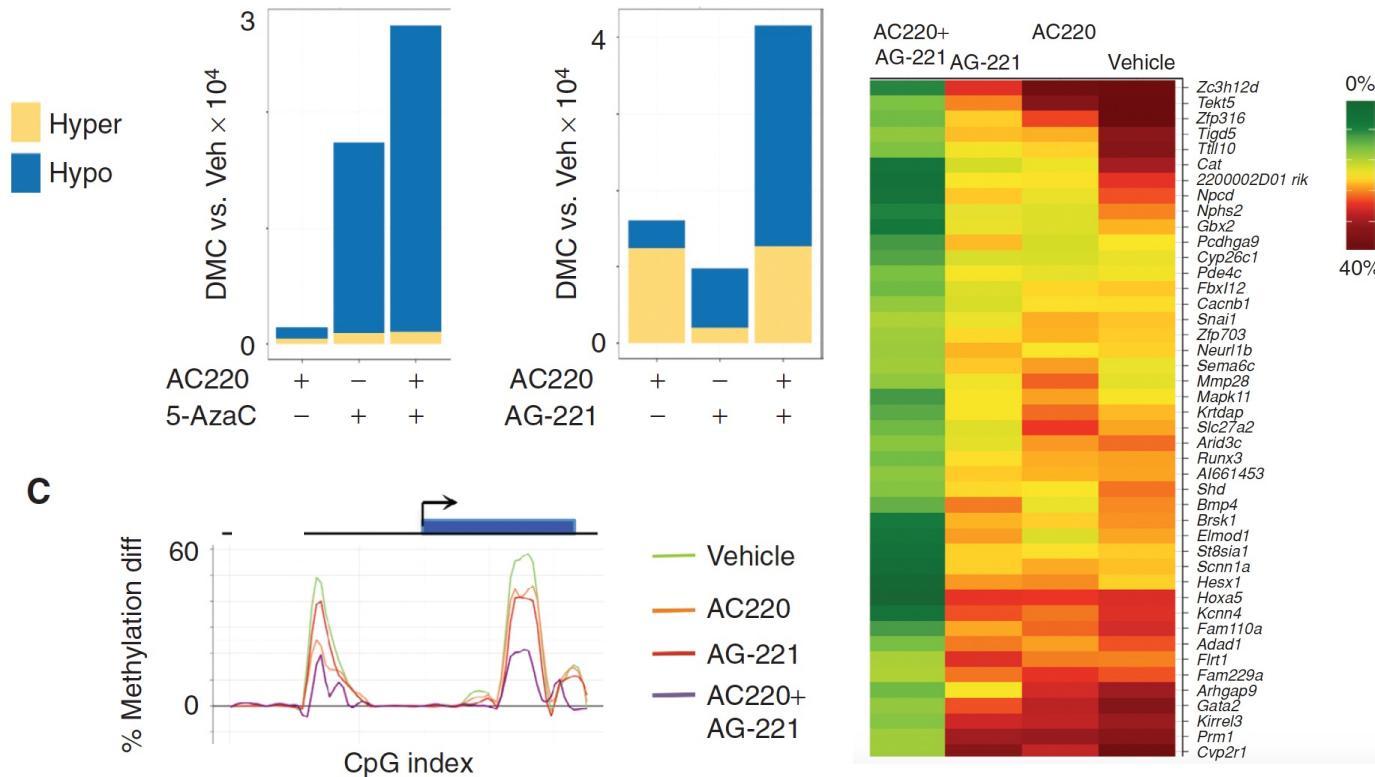
Combination Therapy

- Two models
 - TET2+FLT3
 - IDH2+FLT3
- Drugs
 - AC220 – FLT3 inhibitor (Ambit)
 - AG221 – IDH inhibitor (Agios)
 - AzaC – hypomethylating agent



- TET2+FLT3 → Treat with AC220, AzaC or both
- IDH2+FLT3 → Treat with AC220, AG221 or both

Reversal of hypomethylation improved with combination therapy

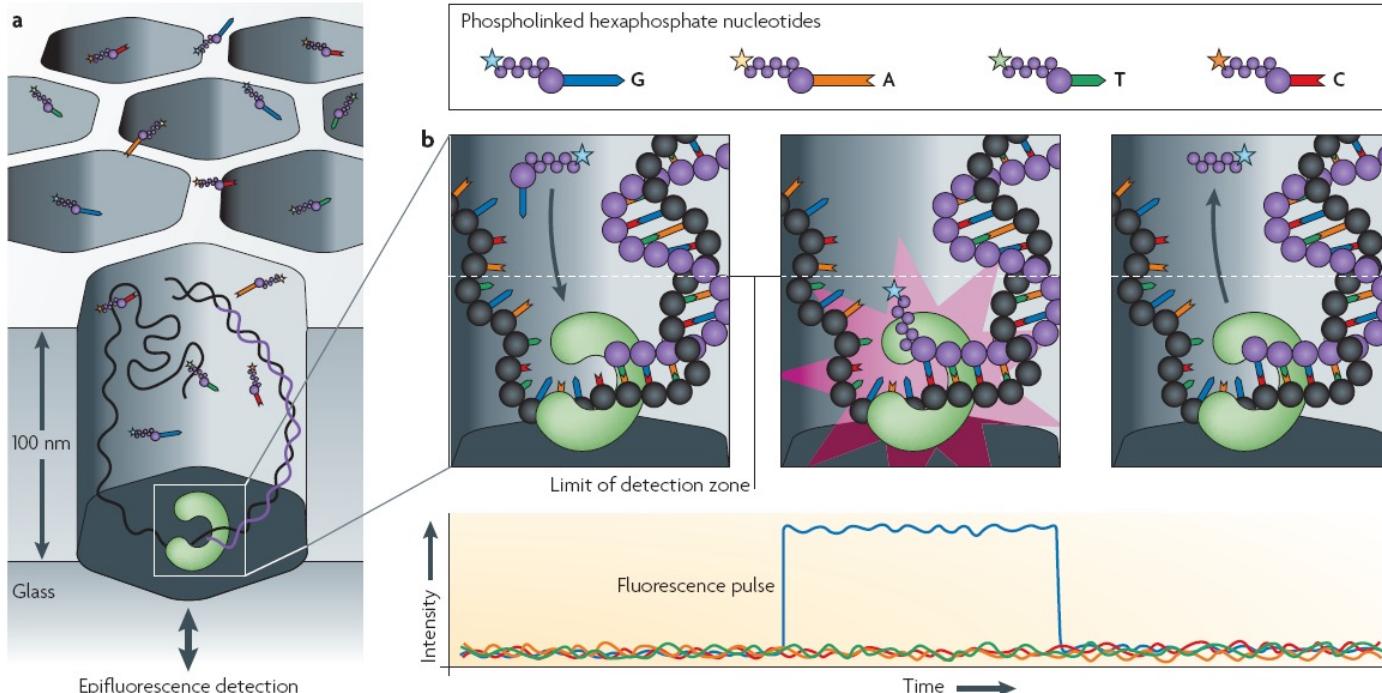


Can we detect
them better?

Pacific Biosciences

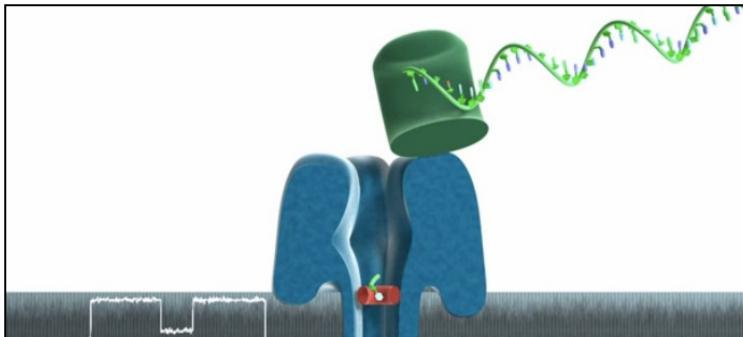
Single Molecule Real-Time (SMRT) Sequencing

Pacific Biosciences — Real-time sequencing

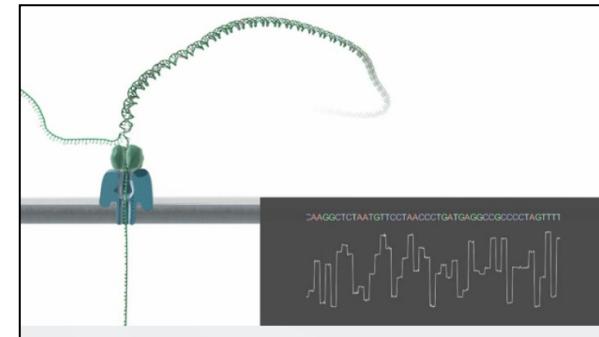


<https://www.pacb.com/videos/video-overview-of-smrt-technology/>

Metzker, 2010



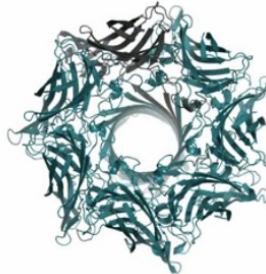
Exonuclease-Seq



Strand-Seq



MinION



PromethION



New Methods
need
Standards

To know what's real, we will need standards



Genome in a Bottle
Consortium

<http://genomeinabottle.org>

SEQC2!



On Earth
and in Space

Are you lonely?

Tired of working on your own?

Do you hate making decisions?

HOLD A MEETING!

You can –

- See people
- Show charts
- Feel important
- Point with a stick
- Eat donuts
- Impress your colleagues

All on company time!



MEETINGS

THE PRACTICAL ALTERNATIVE TO WORK

Products to ensure meetings are not just loneliness' avoidance:

National Institute of Standards and Technology (NIST), SEQC
Genome in a Bottle Consortium (GIAB)

- *Genome in a Bottle Consortium* is developing standards to address:
 - well-characterized human genomes as *Reference Materials* (RMs)
 - tools and methods to use these RMs
 - Work with GA4GH
- Testing protocols and methods as part of the ABRF-NGS Phase II Project and the FDA's Sequencing Quality Control Consortium (SEQC)



Genome in a Bottle
Consortium

<http://genomeinabottle.org>

SEQC2!

History

In 2014, the FDA and the ABRF-NGS groups completed three large-scale studies on RNA-seq (Sequencing Quality Control, or SEQC), which compared all major platforms for NGS and RNA-seq, including Illumina, Proton, PGM, 454, and Pacbio:

<http://www.nature.com/nbt/journal/v32/n9/full/nbt.2972.html>,
<http://www.nature.com/nbt/journal/v32/n9/full/nbt.3000.html>,
<http://www.nature.com/nbt/journal/v32/n9/full/nbt.2957.html>.

Then came the **FDA SEQC2** and ABRF-NGS Phase 2 Study and EpiQC Study....



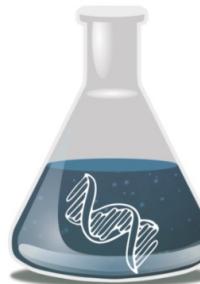


SEXYBACK

JUSTIN TIMBERLAKE

GENOME IN A BOTTLE

Our mission is to provide the authoritative characterization of human genomes.



OVERVIEW

WORKSHOPS

NEWS

RESOURCES

GOOGLE GROUP

ANALYSIS TEAM

Reference Materials and Data

The Genome in a Bottle Consortium has selected several genomes to produce and characterize as reference materials. The National Institute of Standards and Technology (NIST) is developing NIST Reference Materials from these genomes, which are DNA extracted from a large homogenized growth of B lymphoblastoid cell lines from the Coriell Institute for Medical Research.

Note that there may be small differences between the NIST DNA and the Coriell DNA since they come from different growths of cells, though we do not expect these differences to be large for most applications.

The NIST Reference Materials available and planned are listed below, along with links to their data.

A description of data generated by GIAB for all the genomes below is published [here](#), and characterization of small variants is published [here](#). Ongoing work to characterize more difficult variants and regions is announced in the [GIAB Analysis Team google group](#).



genome-in-a-bottle

A public-private-academic consortium hosted by NIST to develop reference materials and standards for clinical sequencing

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giab_publications

This repository contains a list of publications pertinent to the Genome in a Bottle project

3 issues 6 stars 0 forks 0 updated on Nov 5, 2020

genome-stratifications

Stratification BED files from the Global Alliance for Genomics and Health (GA4GH) Benchmarking Team and the Genome in a Bottle Consortium. These files can be used as standard resource of BED files for use with GA4GH benchmarking tools such as hap.py to stratify true positive, false positive, and false negative variant calls based on genomic cont...

1 Jupyter Notebook 0 issues 13 stars 0 forks 0 updated on Jul 20, 2020

giab_data_indexes

This repository contains data indexes from NIST's Genome in a Bottle project.

1 Roff 44 issues 122 stars 2 forks 0 updated on Apr 20, 2020

Top languages

Jupyter Notebook Roff

People

This organization has no public members. You must be a member to see who's a part of this organization.

<https://github.com/genome-in-a-bottle>

Table 2 Genome in a Bottle Consortium Genomes.

From: Extensive sequencing of seven human genomes to characterize benchmark reference materials

Genome	Coriell cell line ID	NIST ID	NIST RM #	NCBI BioSample	PGP ID
CEPH Mother/Daughter	GM12878	HG001	RM8398	SAMN03492678	Not PGP
AJ Son	GM24385	HG002	RM8391* (son)/RM8392* (trio)	SAMN03283347	huAA53E0
AJ Father	GM24149	HG003	RM8392* (trio)	SAMN03283345	hu6E4515
AJ Mother	GM24143	HG004	RM8392* (trio)	SAMN03283346	hu8E87A9
Chinese Son	GM24631	HG005	RM8393*	SAMN03283350	hu91BD69
Chinese Father	GM24694	N/A [†]	N/A [†]	SAMN03283348	huCA017E
Chinese Mother	GM24695	N/A [†]	N/A [†]	SAMN03283349	hu38168C

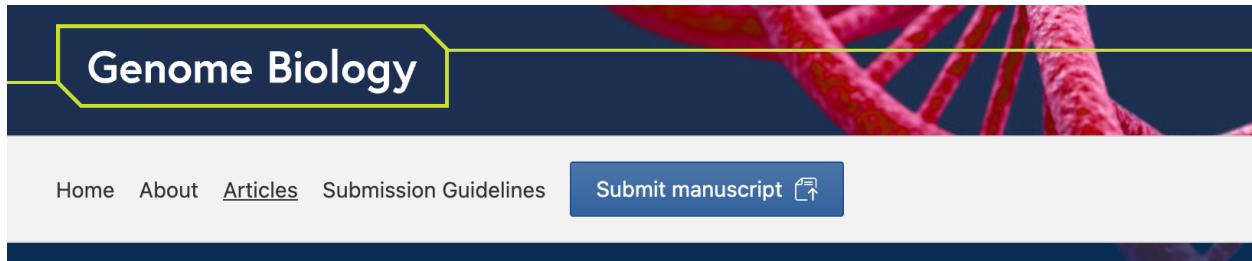
Identifiers associated with genomes currently being characterized by GIAB. The NCBI BioProject for GIAB is PRJNA200694.

* Not currently available. Planned release as NIST RMs in mid-2016.

† NIST Reference Materials are not planned for the Chinese parents, but cells and DNA are available from Coriell.

Zook, J., Catoe, D., McDaniel, J. *et al.* Extensive sequencing of seven human genomes to characterize benchmark reference materials. *Sci Data* **3**, 160025 (2016). <https://doi.org/10.1038/sdata.2016.25>

EpiQC



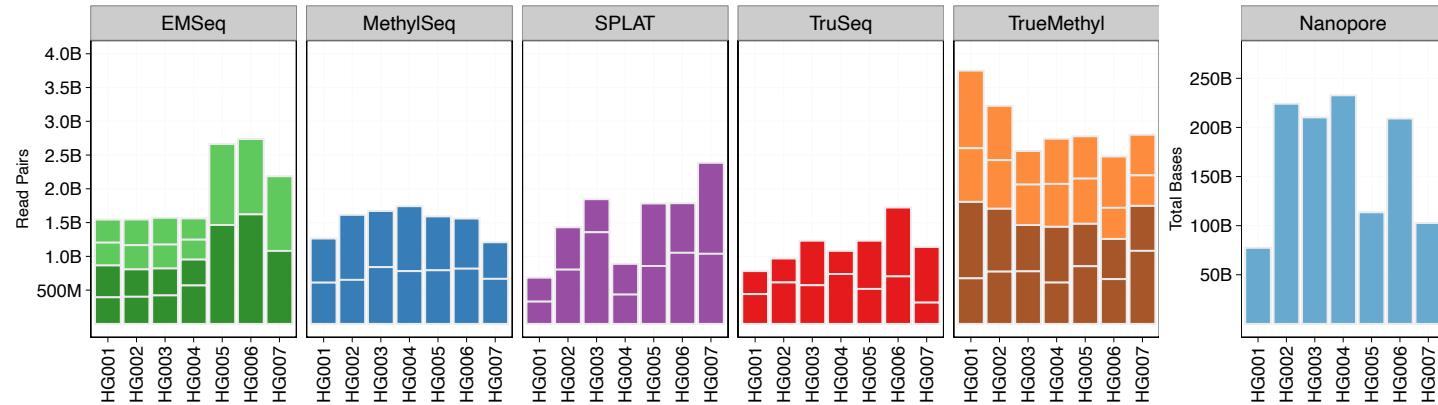
Research | [Open access](#) | Published: 06 December 2021

The SEQC2 epigenomics quality control (EpiQC) study

[Jonathan Foox](#), [Jessica Nordlund](#), [Claudia Lalancette](#), [Ting Gong](#), [Michelle Lacey](#), [Samantha Lent](#),
[Bradley W. Langhorst](#), [V. K. Chaithanya Ponnaluri](#), [Louise Williams](#), [Karthik Ramaswamy Padmanabhan](#),
[Raymond Cavalcante](#), [Anders Lundmark](#), [Daniel Butler](#), [Christopher Mozsary](#), [Justin Gurvitch](#), [John M. Greally](#), [Masako Suzuki](#), [Mark Menor](#), [Masaki Nasu](#), [Alicia Alonso](#), [Caroline Sheridan](#), [Andreas Scherer](#),
[Stephen Bruinsma](#), [Gosia Golda](#), ... [Christopher E. Mason](#) + Show authors

[Genome Biology](#) 22, Article number: 332 (2021) | [Cite this article](#)

Genome	Coriell ID	NIST ID	NCBI BioSample	Whole Genome												Targeted	
				EM-Seq						MethylSeq	PromethION	SPLAT	TrueMethyl				
				100ng		50ng		10ng					Bisulfite	Oxidative	TruSeq		
				Lab 1	Lab 2	Lab 1	Lab 2	Lab 1	Lab 2	Lab 1	Lab 1	Lab 1	Lab 1	Lab 1	Lab 1		
CEPH Mother/Daughter	GM12878	HG001	SAMN03492678	340 337	468 392					652 609	7.8 (4085) 5.1 (6117) 2.5 (5583)	353 329	1093 395	514 508	338 437	267 326	
AJ Son	GM24385	HG002	SAMN03283347	379 357	403 399					960 650	13.3 (3867) 4.5 (7346) 1.6 (5126) 1.4 (5064)	625 801	901 504	508 447	351 609	239 335	
AJ Father	GM24149	HG003	SAMN03283345	77 354	397 419					829 838	17.5 (3533) 4.8 (3760) 1.1 (5162) 1.4 (5231)	484 1353	664 367	272 344	654 568	288 337	
AJ Mother	GM24143	HG004	SAMN03283346	313 294	381 173					959 779	17.4 (3492) 6.0 (4315) 1.1 (5821) 1.5 (5590)	453 433	802 321	519 345	340 733	235 339	
Chinese Son	GM24631	HG005	SAMN03283350	89	451	430	497	313	244	796 791	2.5 (2984) 7.0 (5087) 13.8 (5073)	922 855	605 447	360 450	709 514	243 321	
Chinese Father	GM24694	HG006	SAMN03283348	359	451	344	422	412	186	741 815	2.0 (3987) 1.4 (5197) 1.0 (5505)	733 1050	573 631	730 220	1012 698	247 265	
Chinese Mother	GM24695	HG007	SAMN03283349	352	466	365	480	387	176	714 665	4.5 (4907) 16.1 (5022)	1343 1035	638 1015	575 199	993 312	234 243	



5mC Detection — Bisulfite conversion

GCAACG"mC"GAACT"mC"GCAAGCG

Base conversion

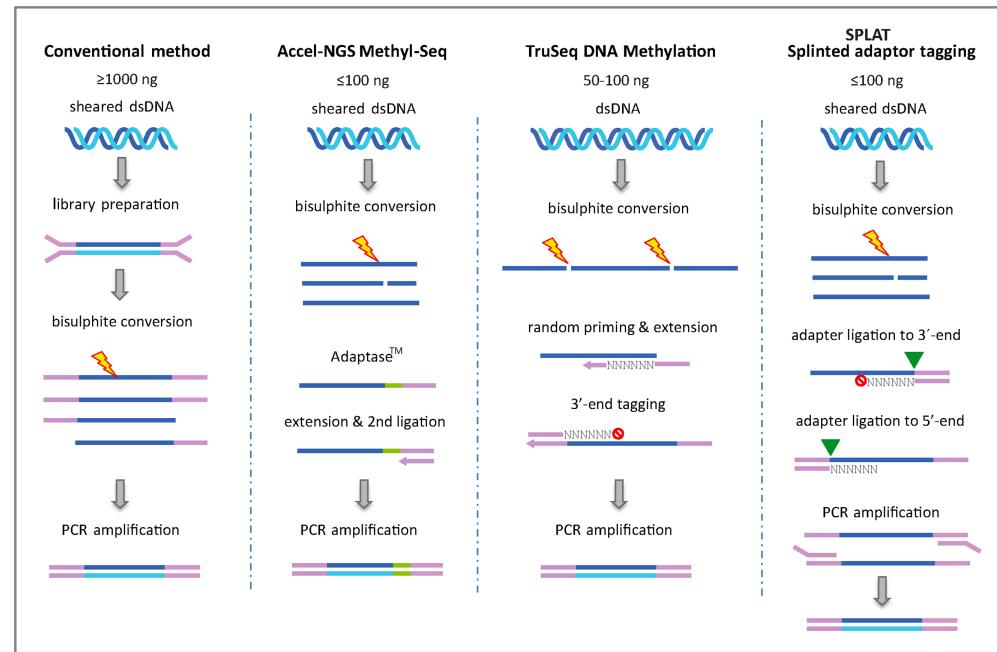


GUAAUG"mC"GAAUT"mC"GUAGUG

PCR



GTAATG"C"GAATT"C"GTAAGTG

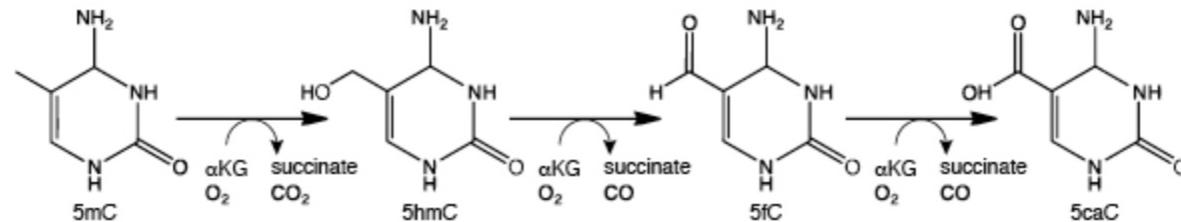


Amanda Raine, Erika Manlig, Per Wahlberg, Ann-Christine Syvänen, Jessica Nordlund,
SPlianted Ligation Adapter Tagging (SPLAT), a novel library preparation method for whole
genome bisulfite sequencing, *Nucleic Acids Research*, Volume 45, Issue 6, 7 April 2017,
Page e36, <https://doi.org/10.1093/nar/gkw1110>

Enzymatic Methyl-seq – A New Approach

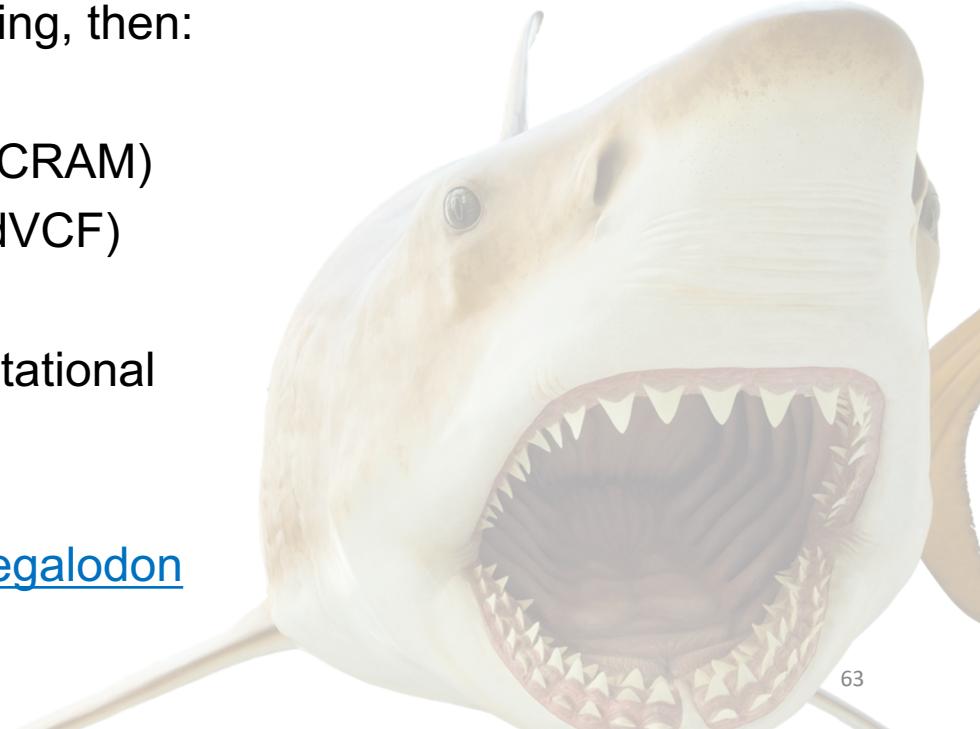
The enzymatic methyl-seq workflow developed at NEB provides a much-needed alternative to bisulfite sequencing. This method relies on the ability of APOBEC to deaminate cytosines to uracils. Unfortunately, APOBEC also deaminates 5mC and 5hmC, making it impossible to differentiate between cytosine and its modified forms (7,8). In order to detect 5mC and 5hmC, this method also utilizes TET2 and an Oxidation Enhancer, which enzymatically modifies 5mC and 5hmC to forms that are not substrates for APOBEC. The TET2 enzyme converts 5mC to 5caC (Figure 2) and the Oxidation Enhancer converts 5hmC to 5ghmC (9,10,11). Ultimately, cytosines are sequenced as thymines and 5mC and 5hmC are sequenced as cytosines, thereby protecting the integrity of the original 5mC and 5hmC sequence information.

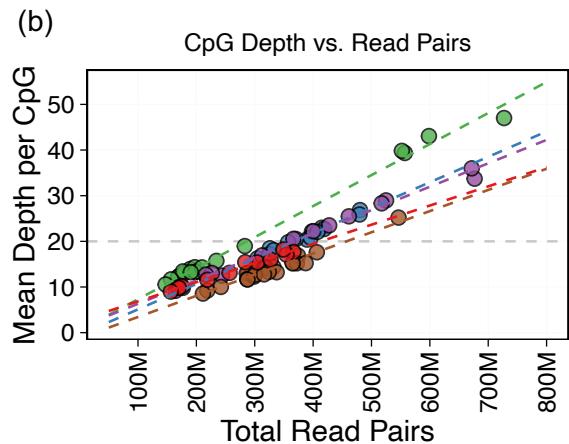
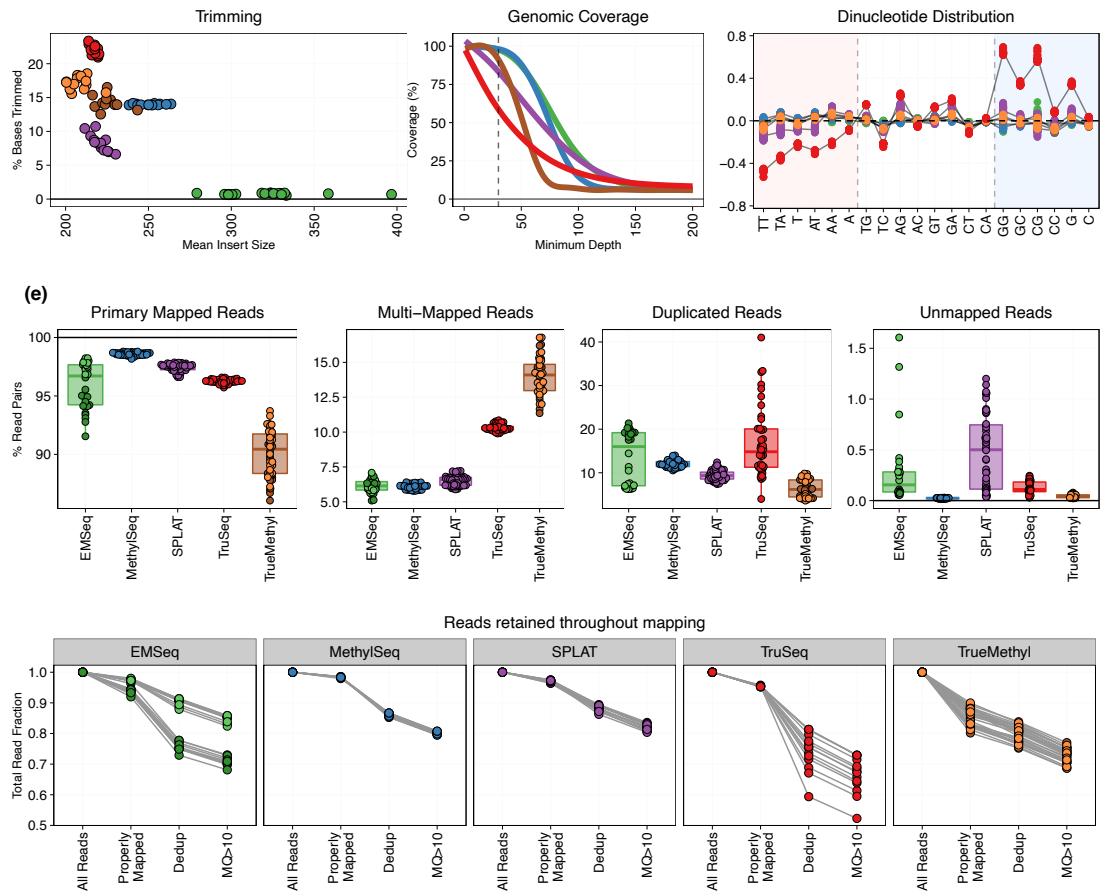
FIGURE 2: Enzymatic modification of cytosine



Megalodon (v2.2)

- Built on guppy (min. version 4.0.15)
- Guppy under the hood for base calling, then:
 - base calls (FASTA/Q)
 - reference mapping (SAM/BAM/CRAM)
 - base mod calls (bedMethyl/modVCF)
- Highest accuracy, optimized computational performance
- <https://github.com/nanoporetech/megalodon>

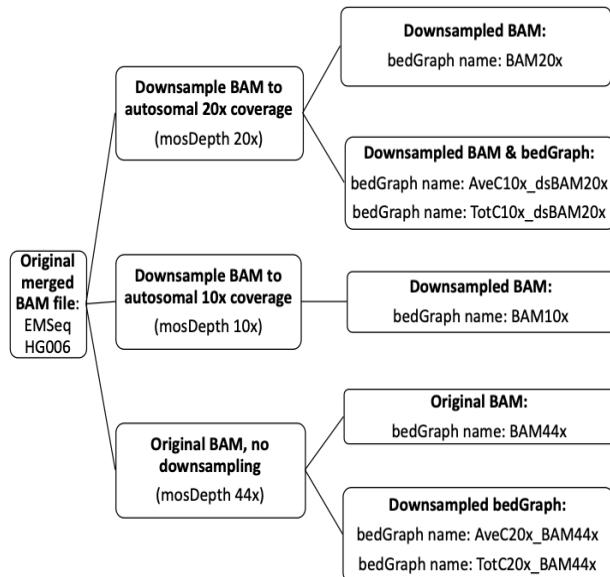




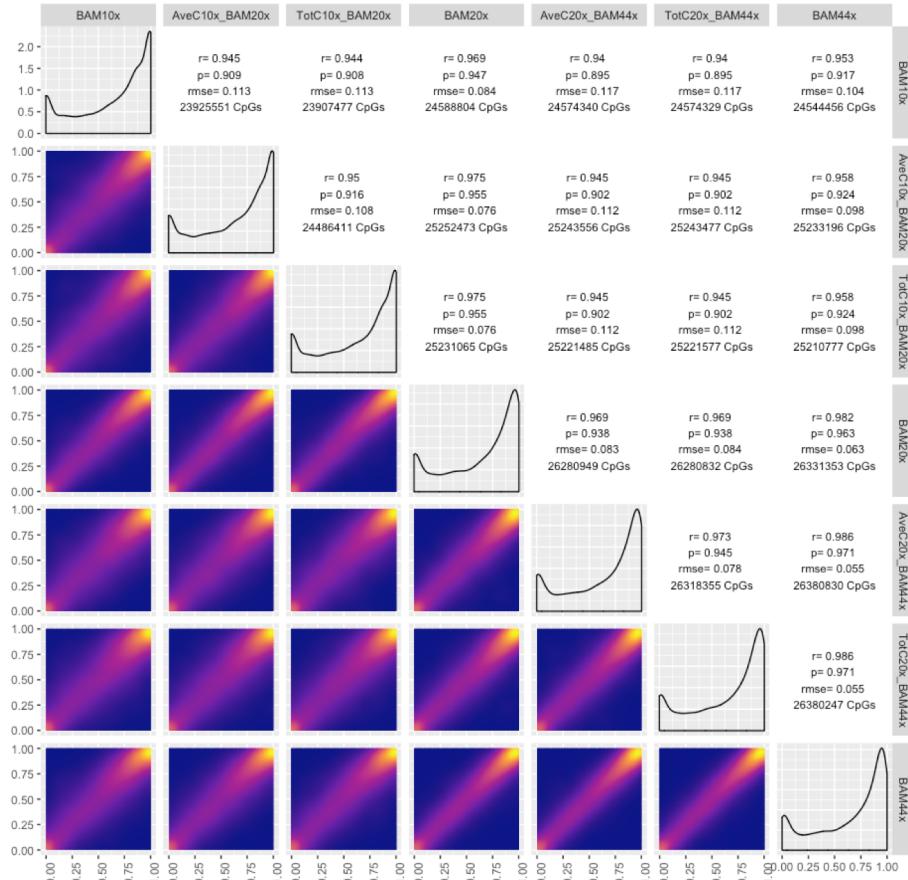
	EMSeq Lab 1	EMSeq Lab 2	Methyl Seq	SPLAT	True Methyl	TruSeq
Insert Size (bp)	299	327	250	221	217	215
Mapping Rate (%)	97	93	98	97	86	95
Duplicate Rate (%)	9	25	12	8	6	21
Dinucleotide Bias Score	3	1	4	10	2	27
Useable Bases (%)	90	77	74	81	69	60
Reads to reach 20x CpG coverage (M)	275	303	366	369	461	692
% CpGs ≥ 1 x coverage	100	100	100	100	100	100
% CpGs > 10 x coverage	94	92	91	89	94	74

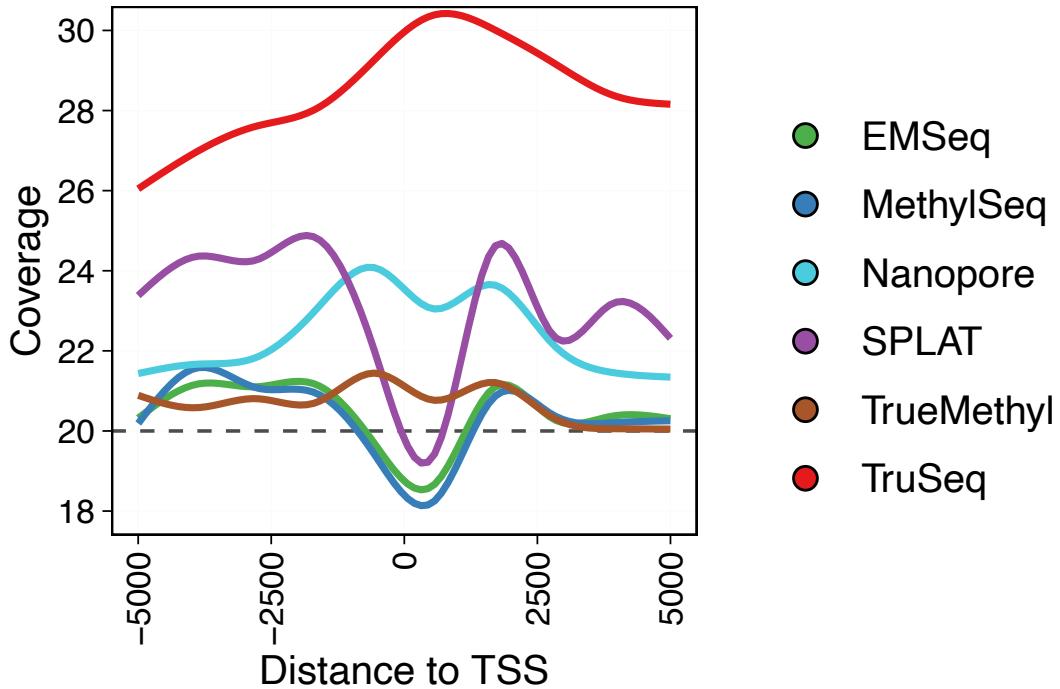
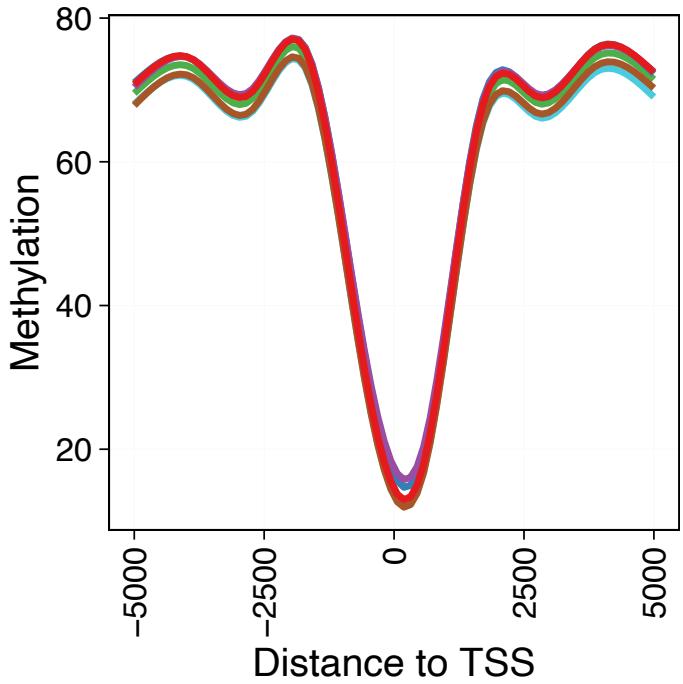
Downsampling at BAM and BED are comparable

a)



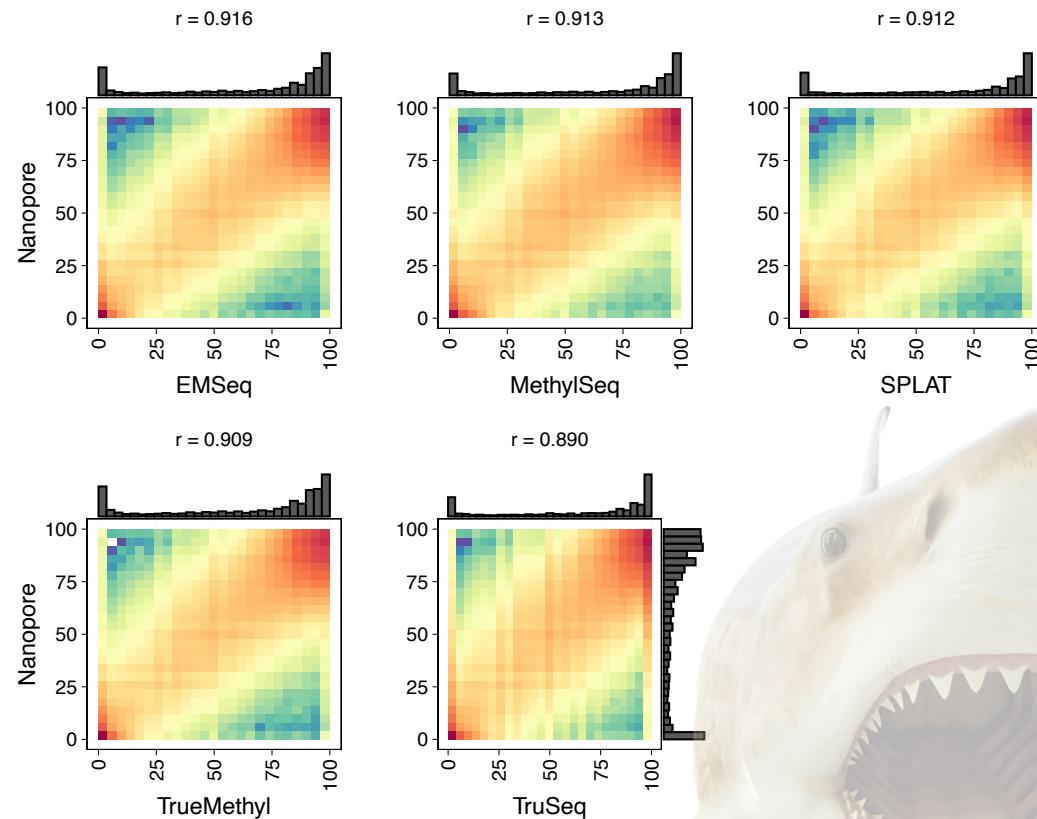
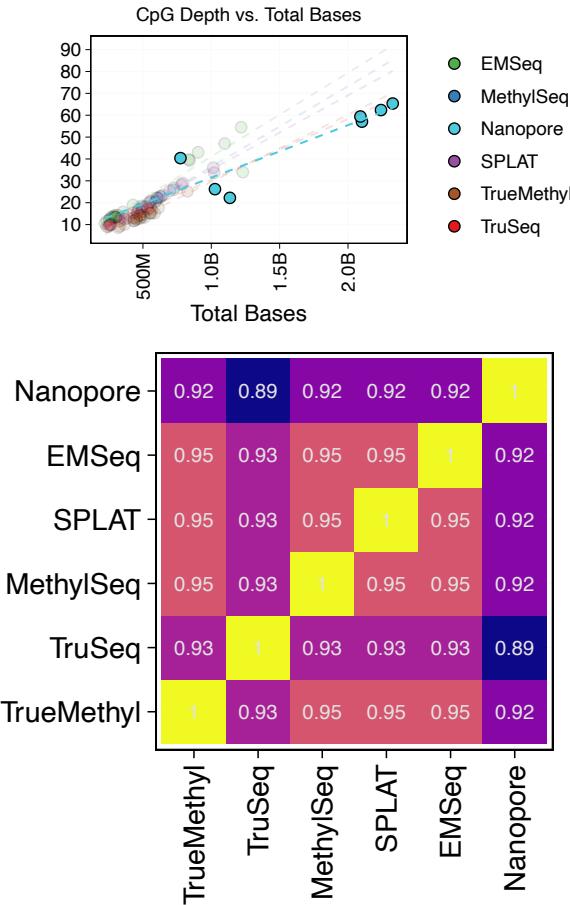
c)



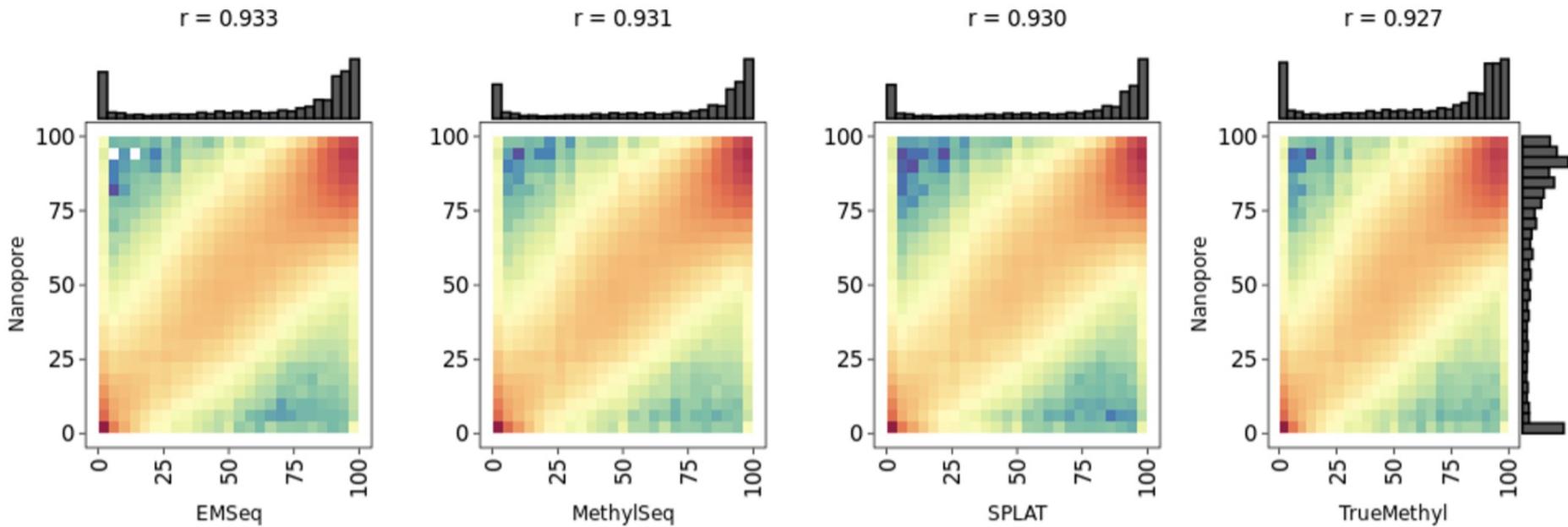


- EMSeq
- MethylSeq
- Nanopore
- SPLAT
- TrueMethyl
- TruSeq

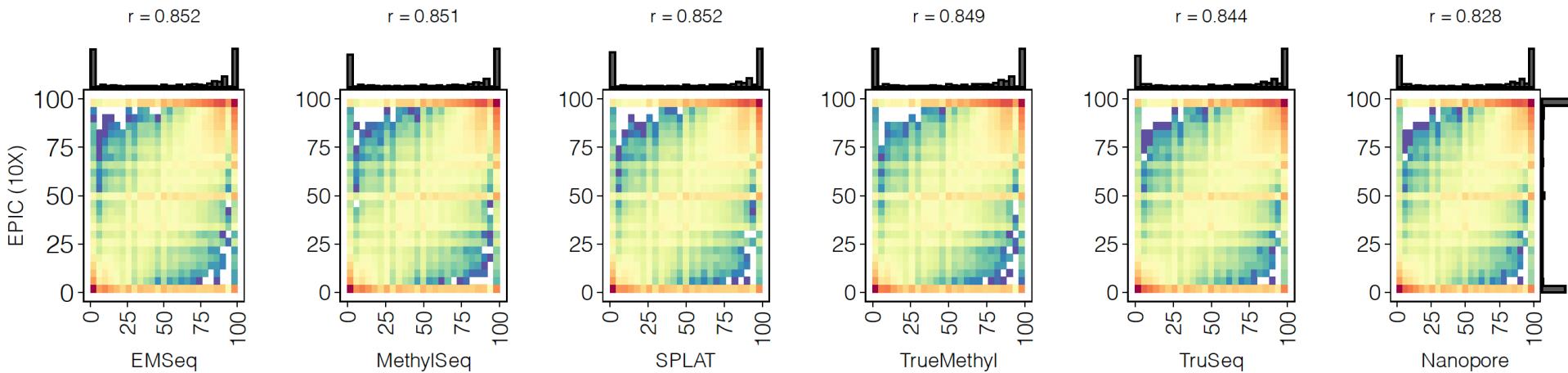
Nanopore 5mC calls stacking up against WGBS



At 20x

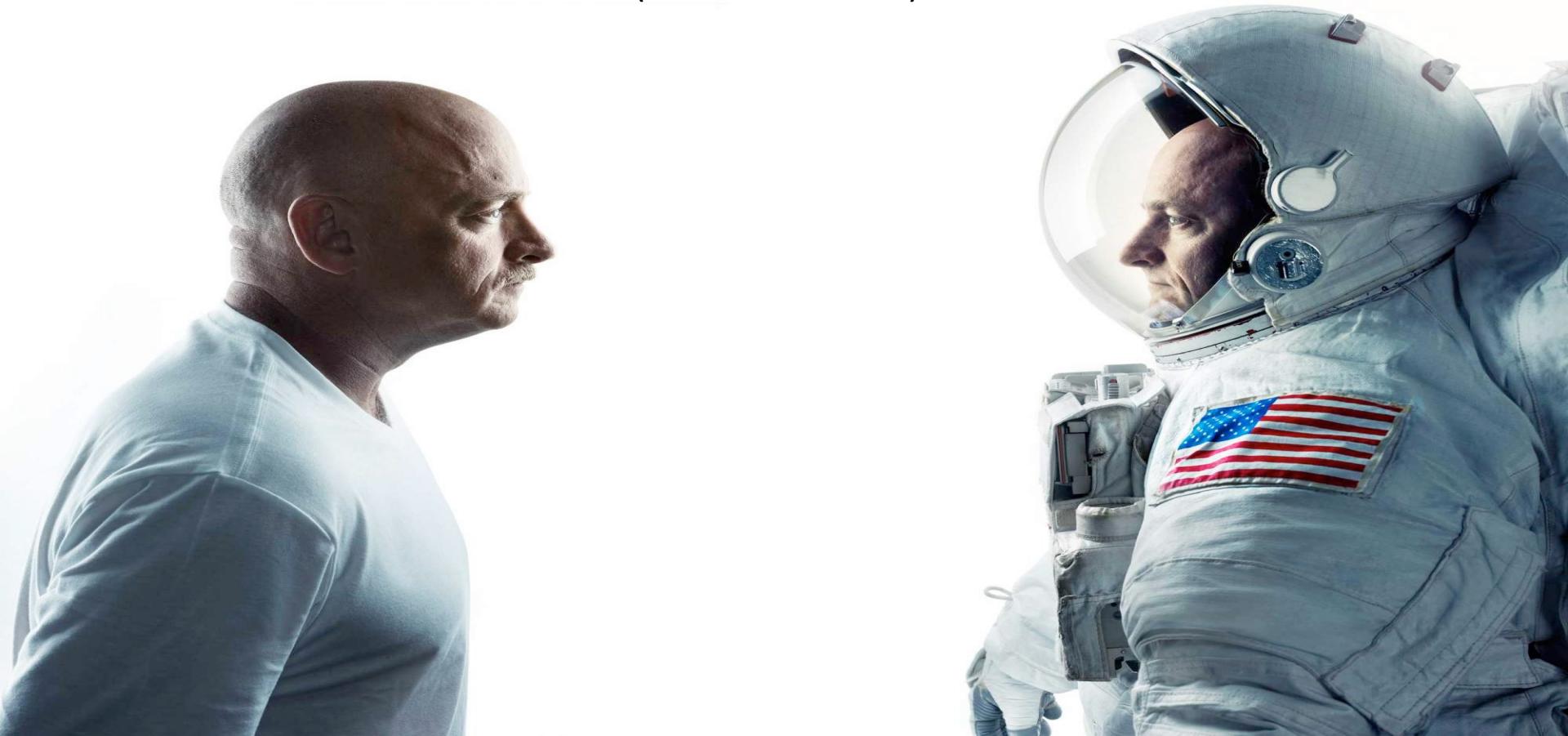


Or even 10x

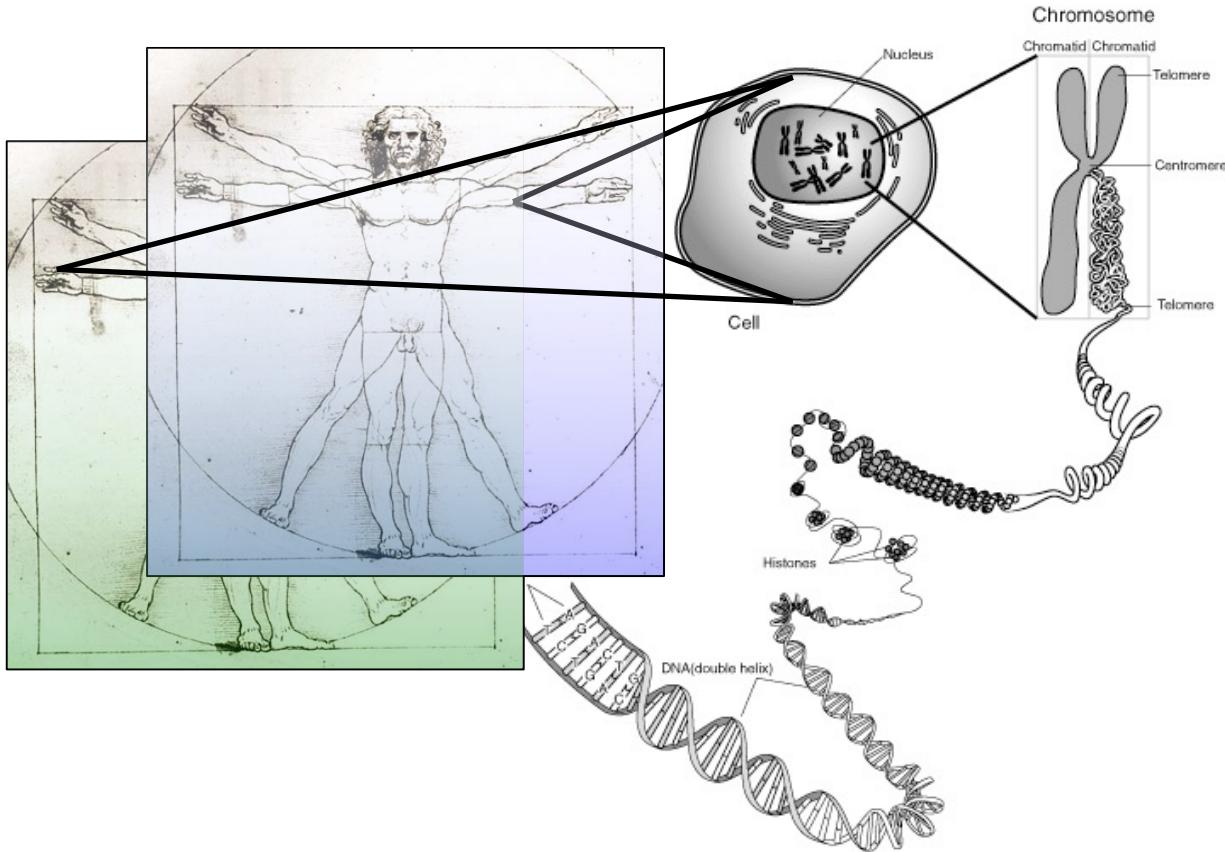


What about in
Space?

Integrative medicine with twin astronauts (and one Senator)









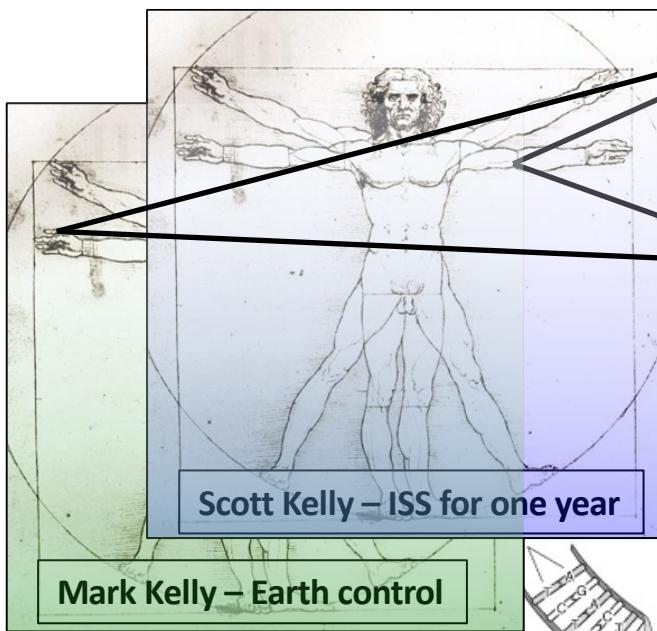
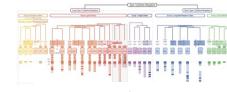
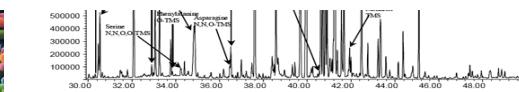
Vasculature



Cognition

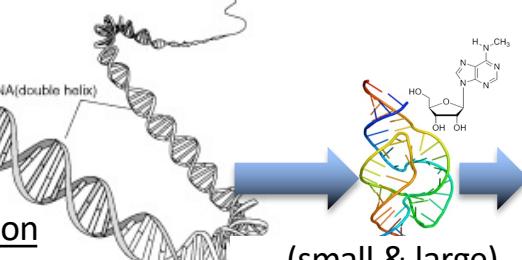
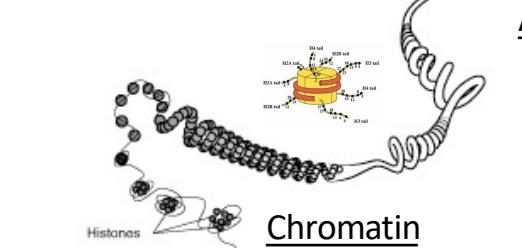
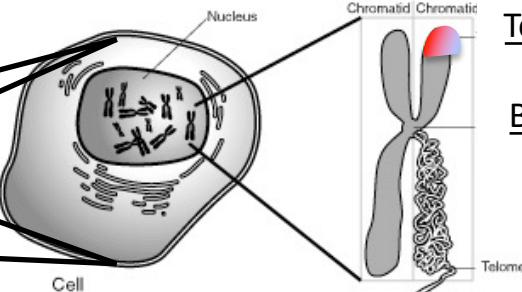


Microbiome



Targeted and Global Metabolomics

Chromosome



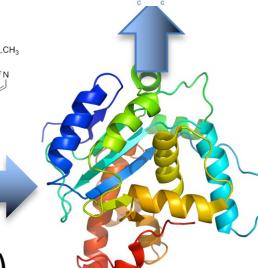
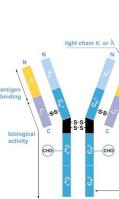
(small & large)
RNA expression
& RNA Methylation

Telomere Length

B-cells / T-cells



Antibody Titers

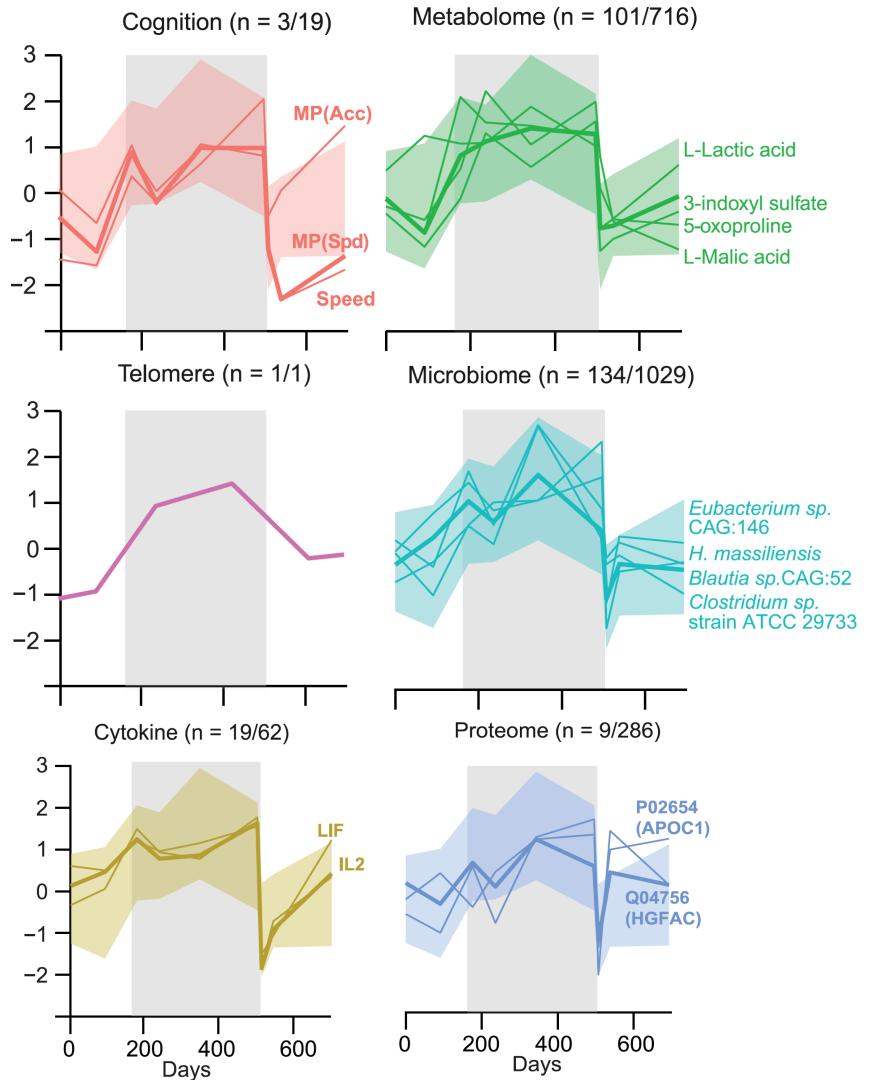


Multi-omics
analysis of human
spaceflight

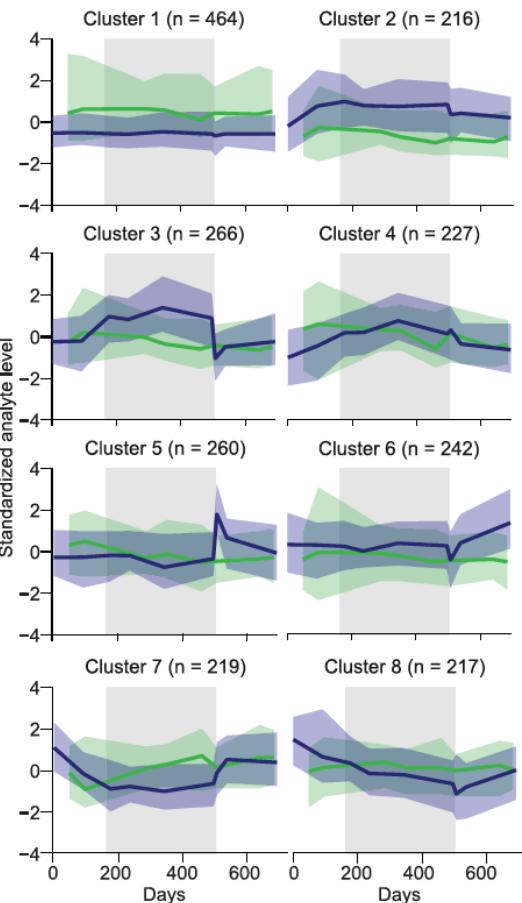


Analyte Type

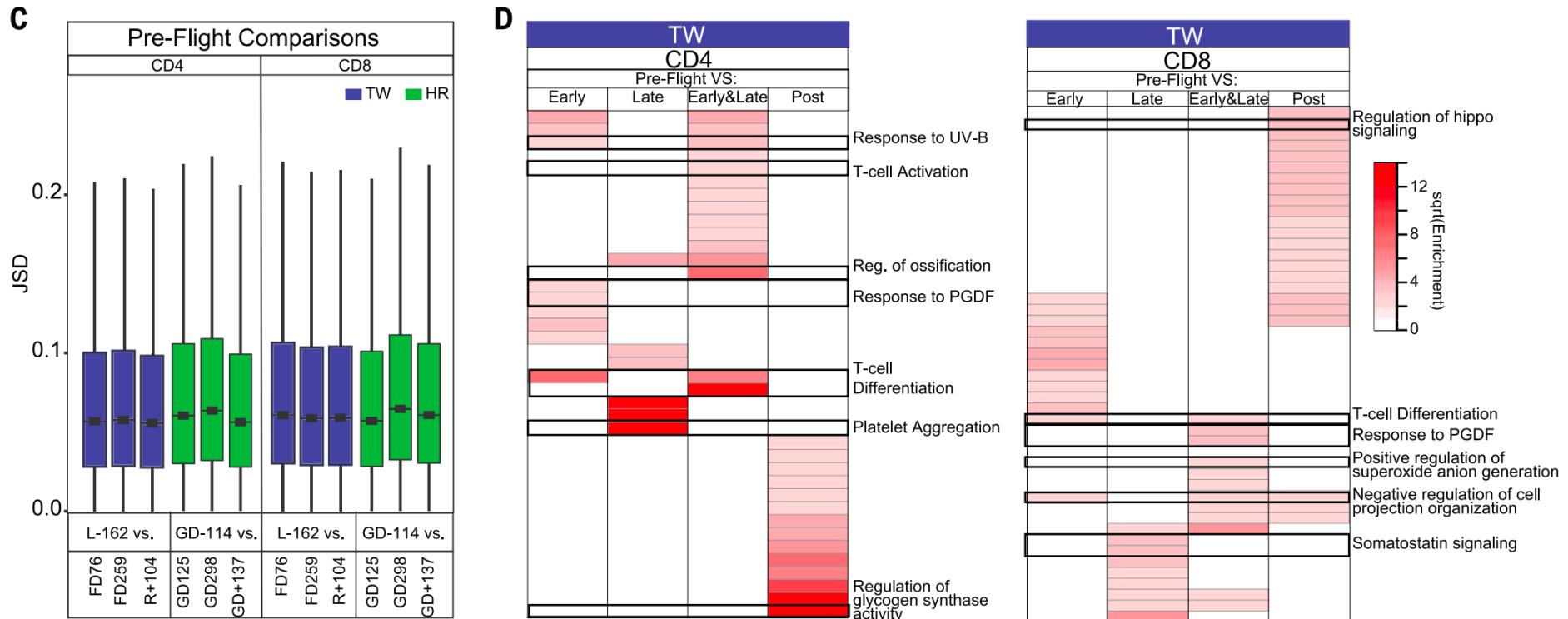
- Cognition
- Cytokine
- Metabolite
- Microbiome
- Proteome
- Telomere



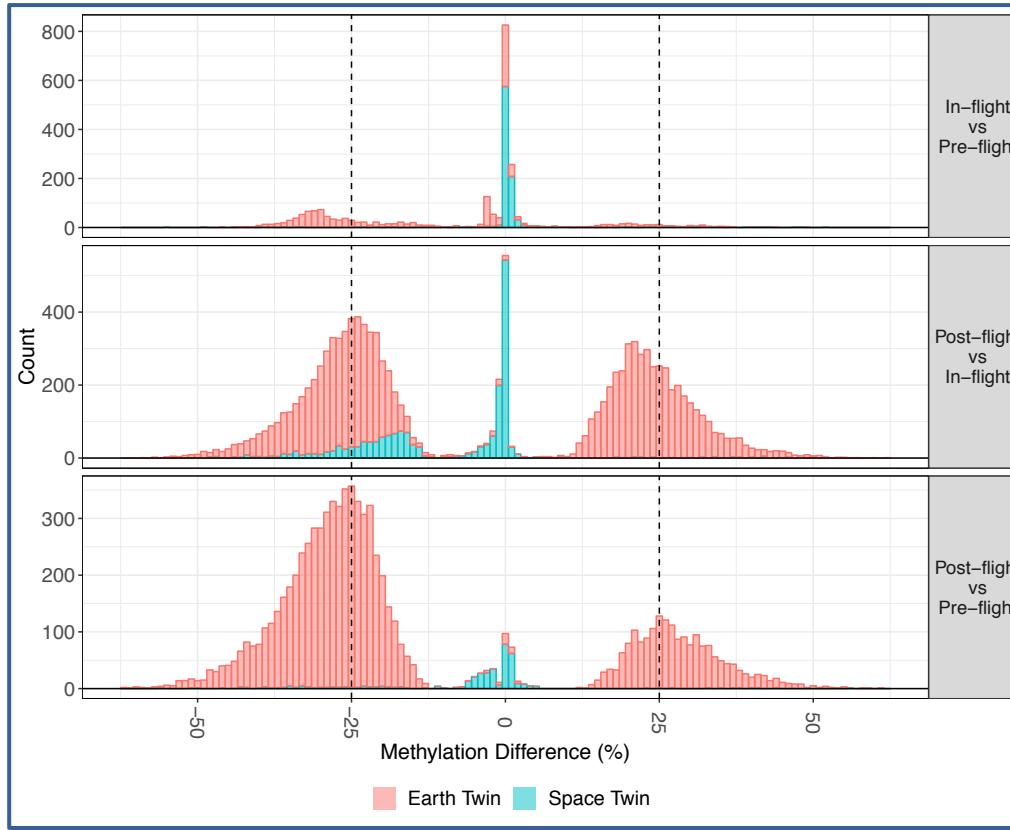
Subject: HR TW



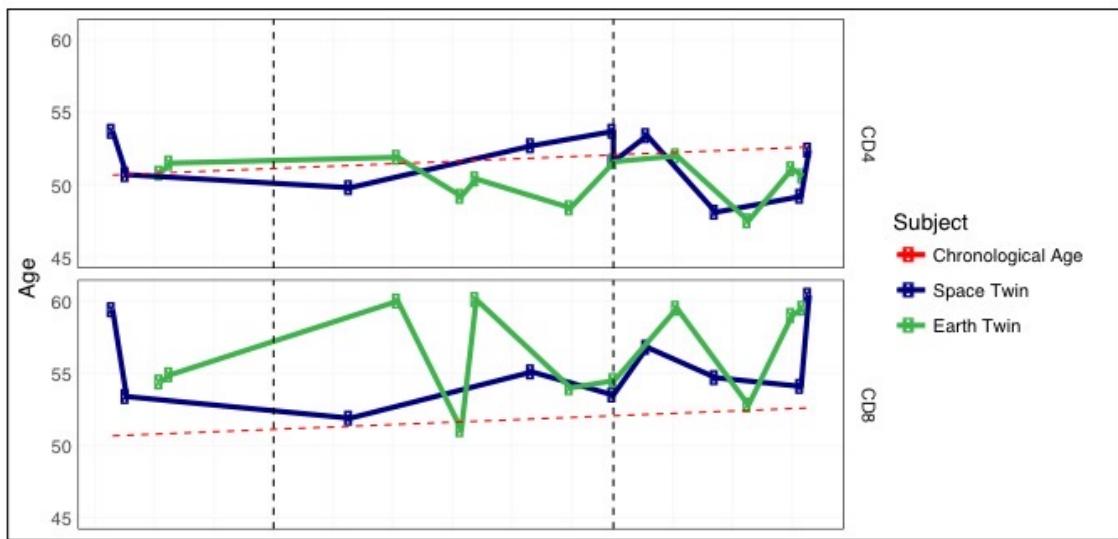
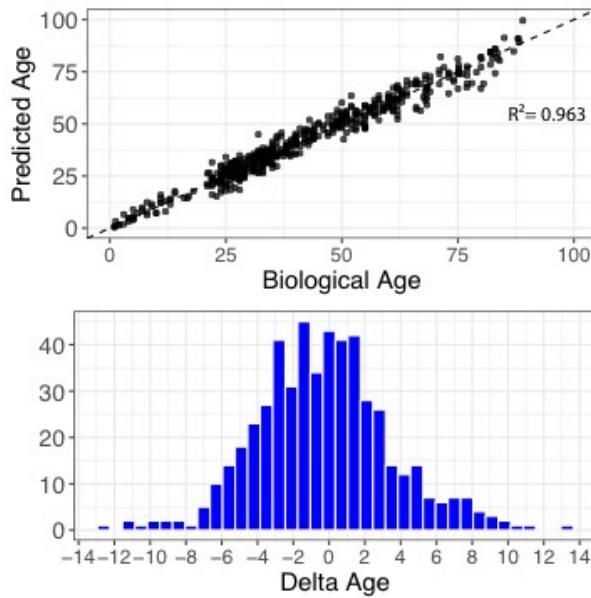
Significant shifts in the epigenome



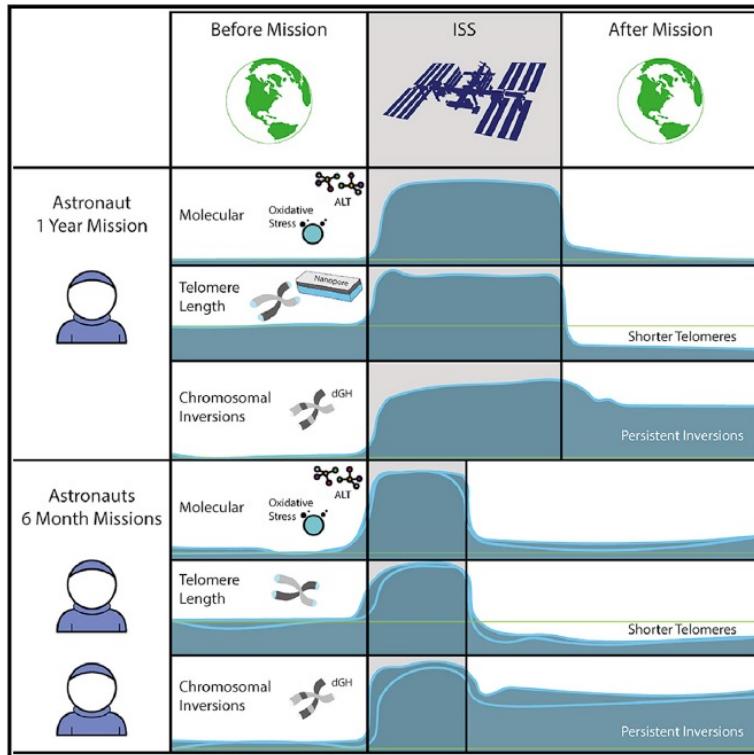
Dynamic on earth; stable in space



Age mostly stable



Telomere elongation validated in two other astronauts



SHARE



817



28



Matt Moniz (right) ascends the world's sixth-tallest peak, Mount Cho Oyu, during a 2014 climb. WILLIE BENEGAS

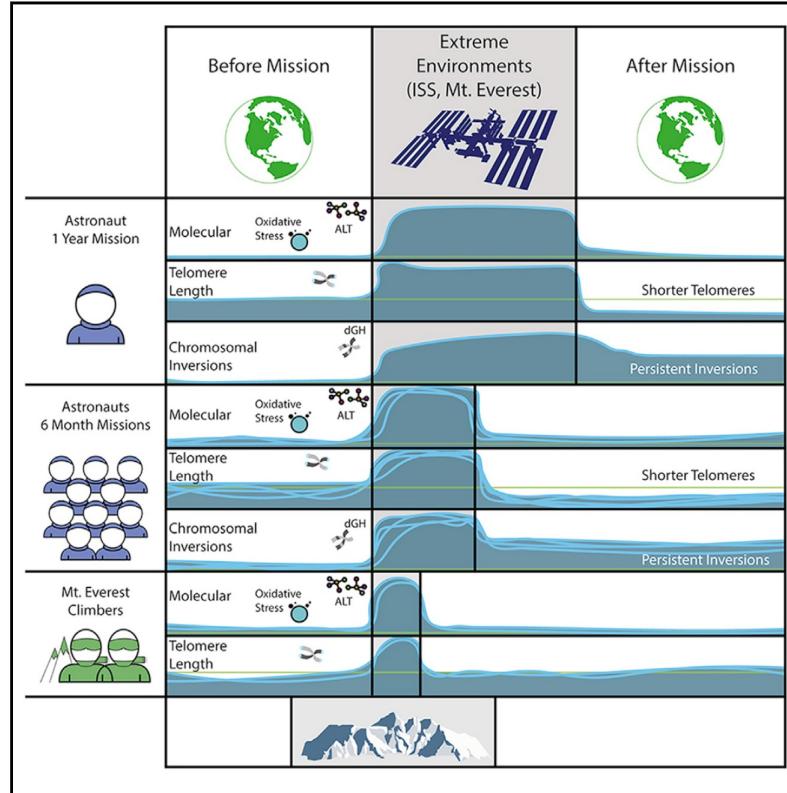
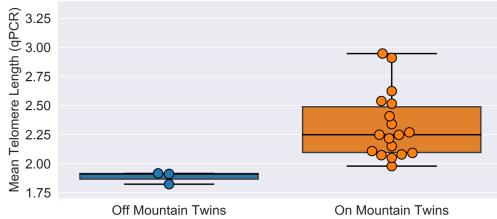
Two mountaineers are trying to recreate NASA's twin study—on Mount Everest

By Vedrana Simicevic | May. 4, 2018 , 12:15 PM

NASA's widely publicized twin study—which compared astronaut Scott Kelly's bodily functions to

<http://www.sciencemag.org/news/2018/05/two-mountaineers-are-trying-recreate-nasa-s-twin-study-mount-everest>

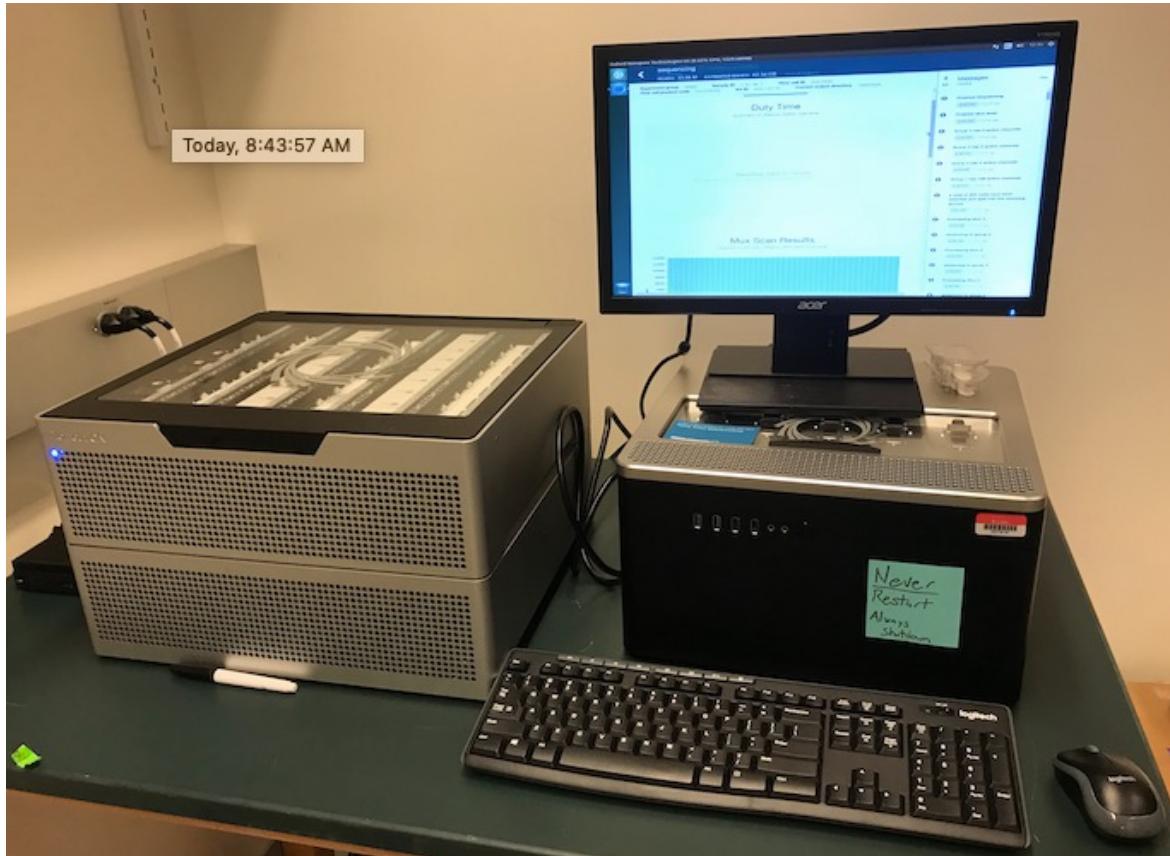
Then 11 other astronauts & on Mt. Everest



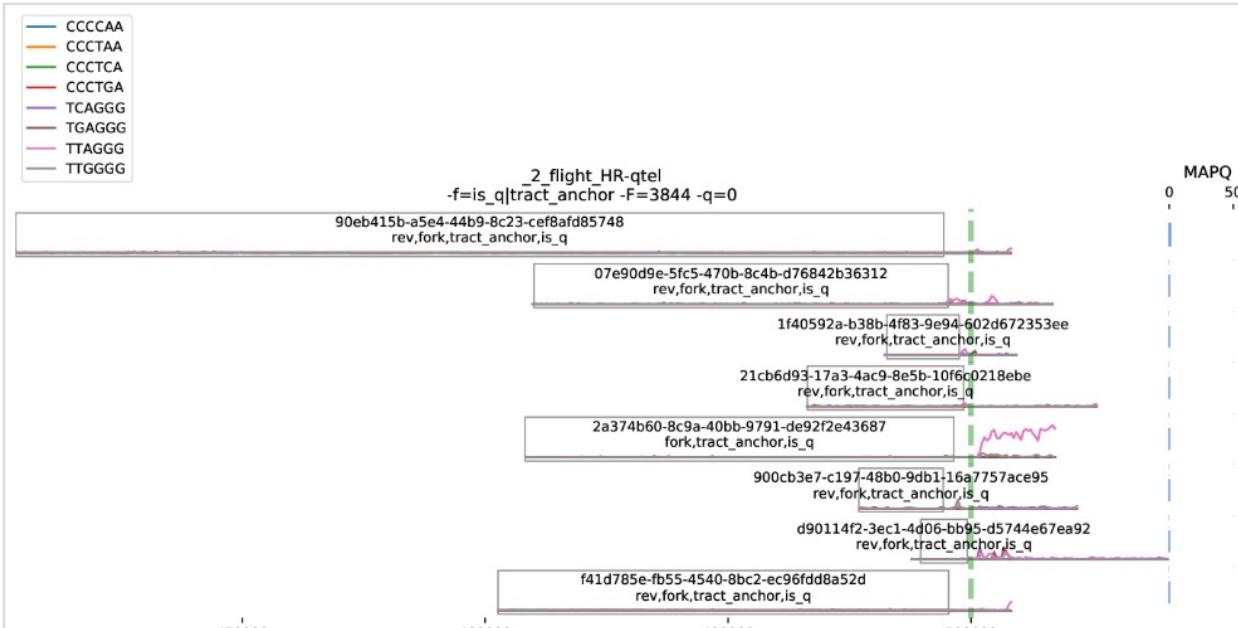
Luxton et al., *Cell Reports*, 2020

[https://www.cell.com/cell-reports/fulltext/S2211-1247\(20\)31446-7](https://www.cell.com/cell-reports/fulltext/S2211-1247(20)31446-7)

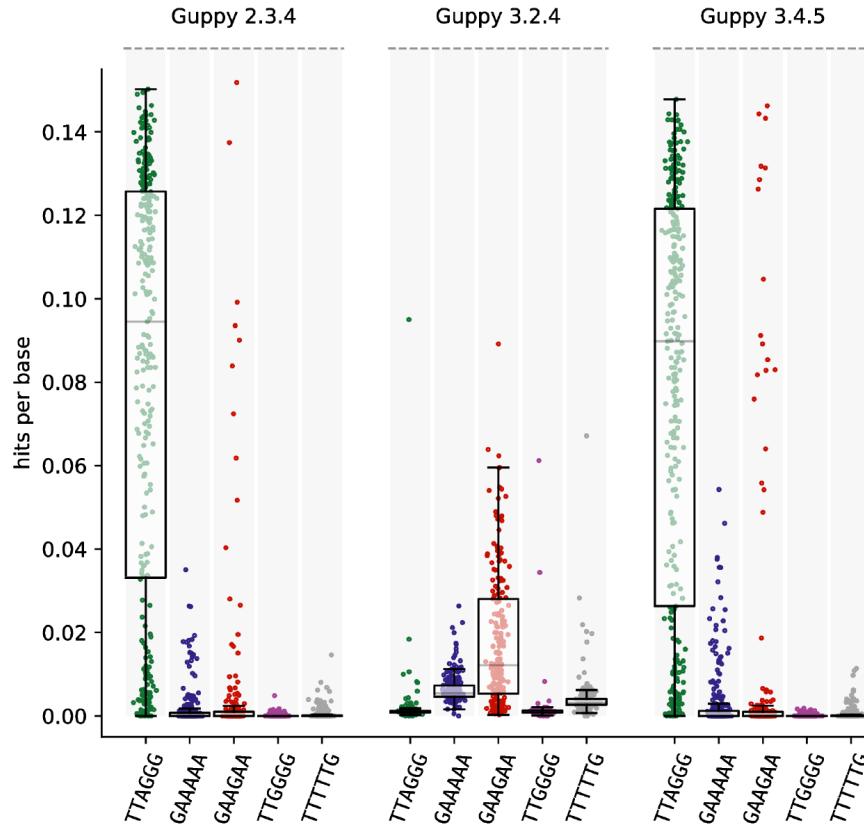
Break out the long reads! ONT PromethION



Mapping is a challenge (Minimap2) – TTAGGG not always clear



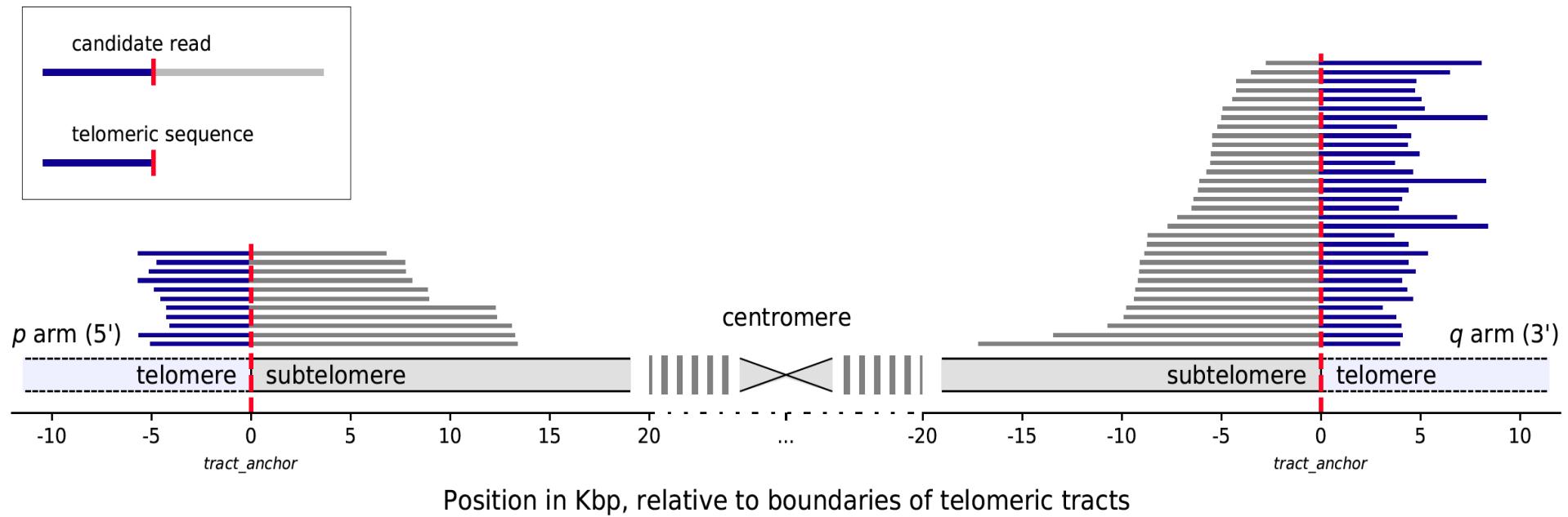
The base caller determined the motif



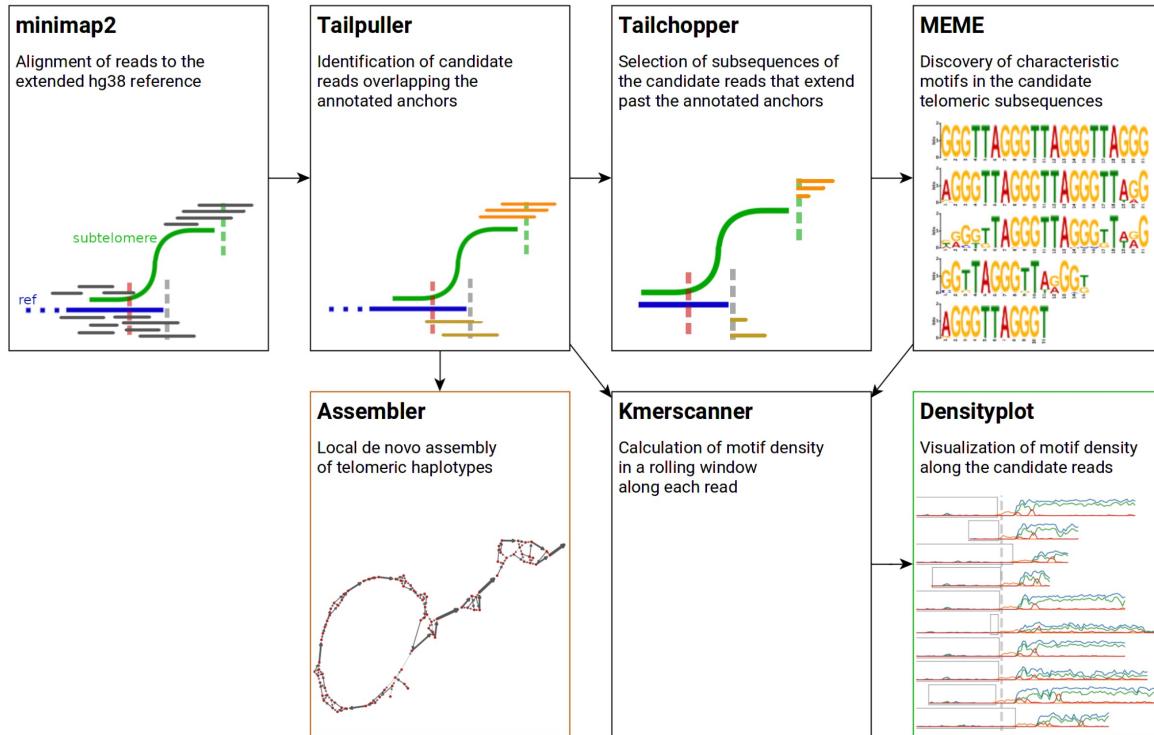
These aren't the telomeres you're looking for



Line up the reads



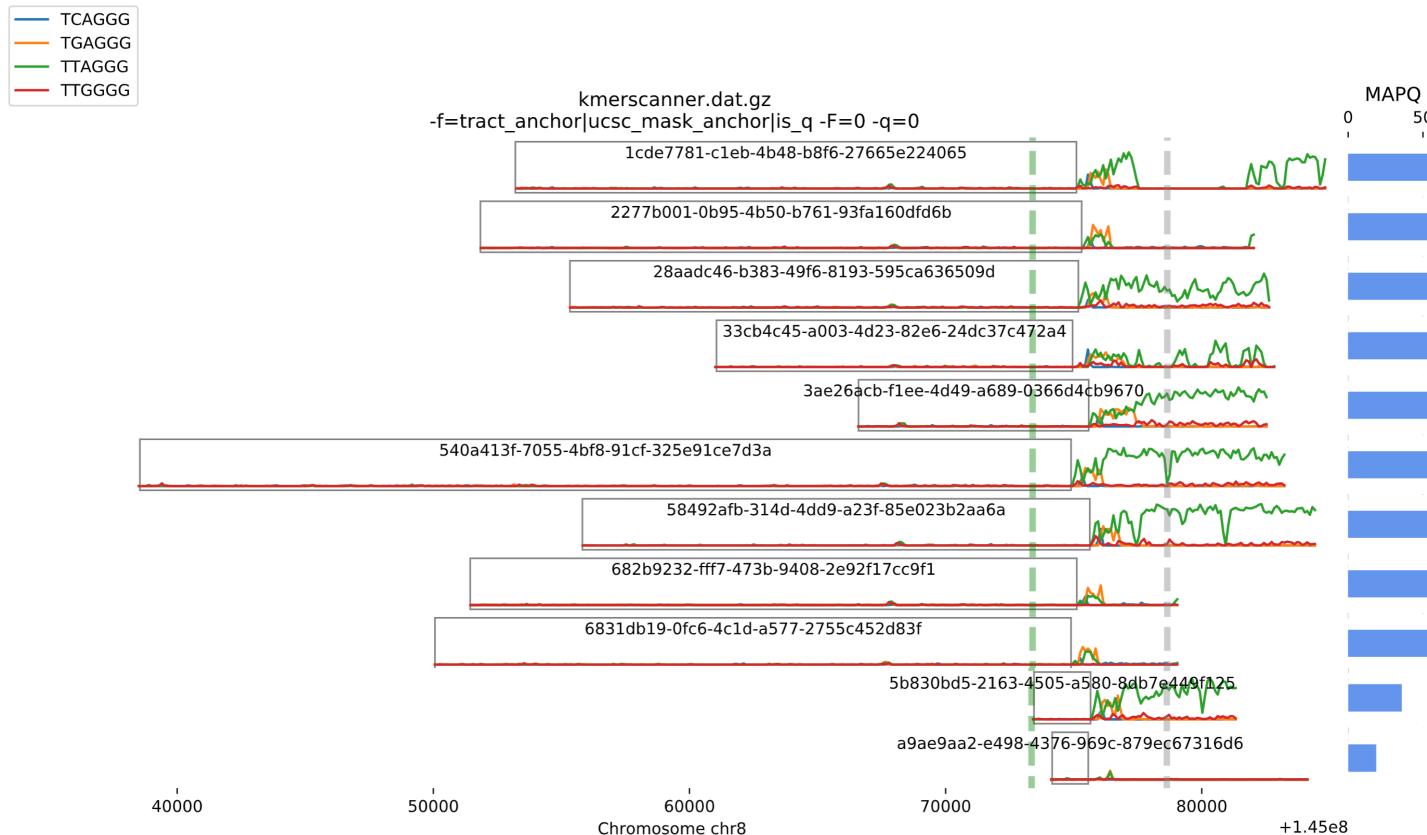
Looking for the Edge Cases (EdgeCase)



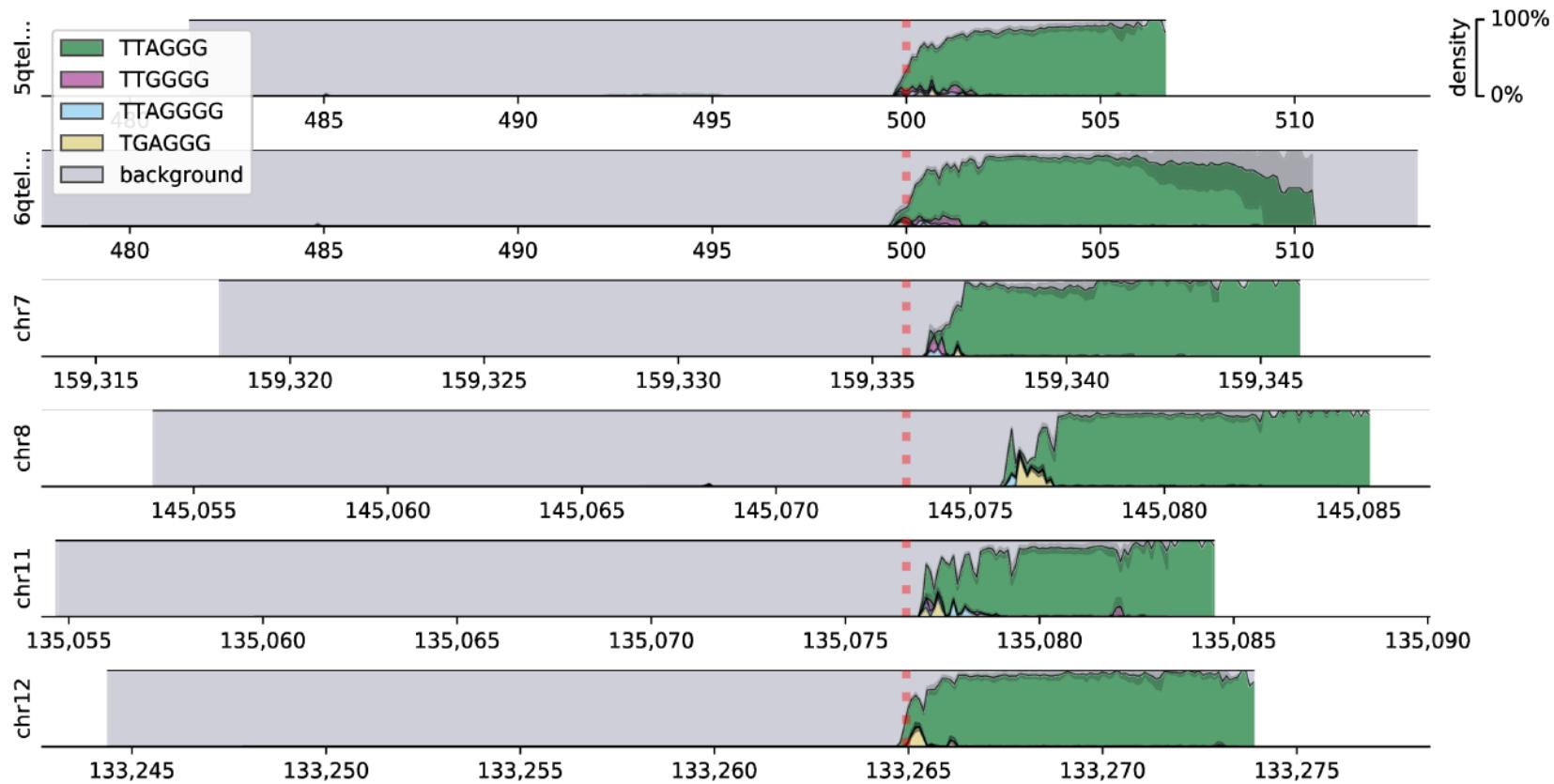
<https://github.com/LankyCyril/edgecase>

Kirill Grigorev, Jon Foox, Daniela Bezdan

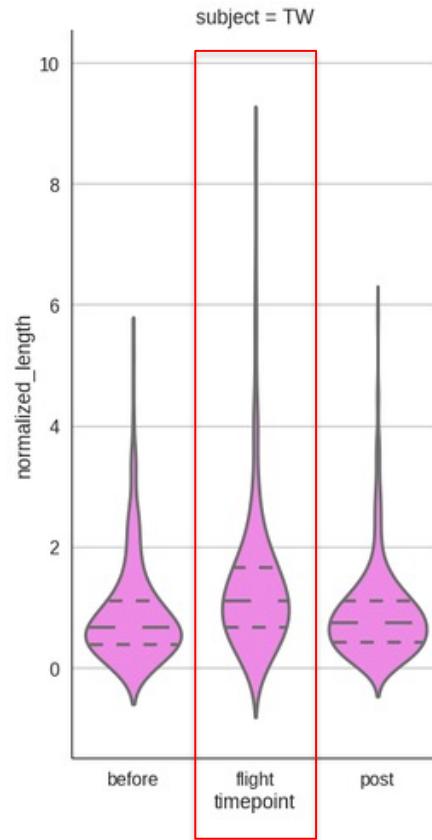
Now we can see it: nanopore data



And PacBio HiFi reads



Indeed the telomeres are longer



Telomere still have many stories to tell...



ISSN: 1088-9051

CSH PRESS GENOME RESEARCH

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Haplotype diversity and sequence heterogeneity of human telomeres

Kirill Grigorev^{1,2,10}, Jonathan Fook^{1,2,3,10}, Daniela Bezdan^{1,2,3,4,5}, Daniel Butler¹,
Jared J. Luxton^{6,7}, Jake Reed¹, Miles J. McKenna^{6,7}, Lynn Taylor⁶,
Kerry A. George⁸, Cem Meydan^{1,2,3}, Susan M. Bailey^{6,7} and
Christopher E. Mason^{1,2,3,9}

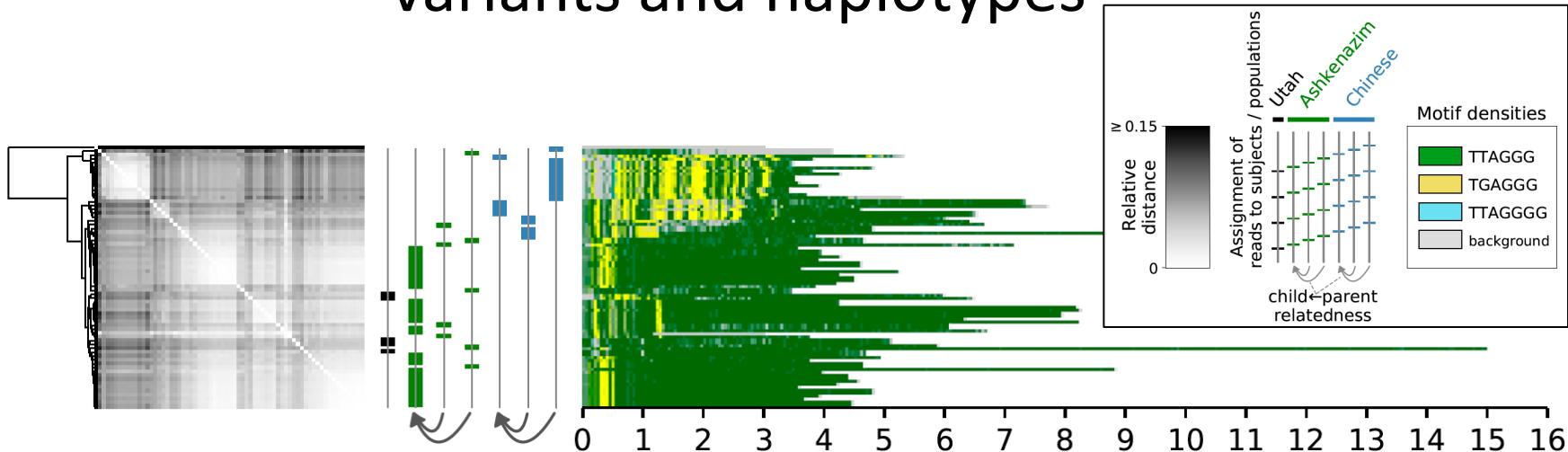
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This Article
Published in Advance June 23, 2021, doi:
10.1101/gr.274639.120
Genome Res. 2021; 31: 1269-1279
© 2021 Grigorev et al.; Published

<https://genome.cshlp.org/content/31/7/1269>

Population-specific, non-canonical variants and haplotypes

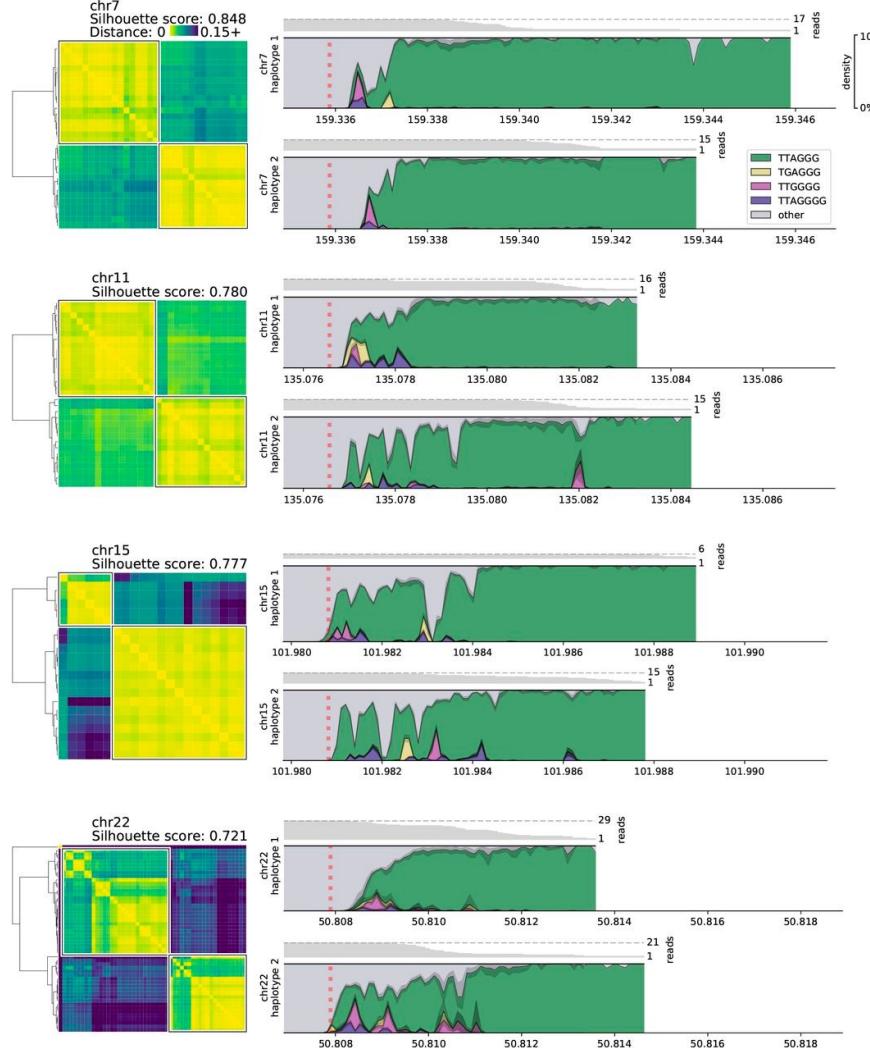
12q (chr12)



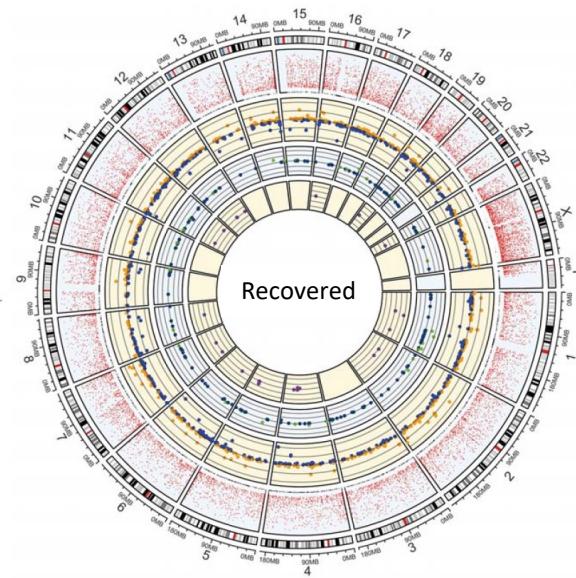
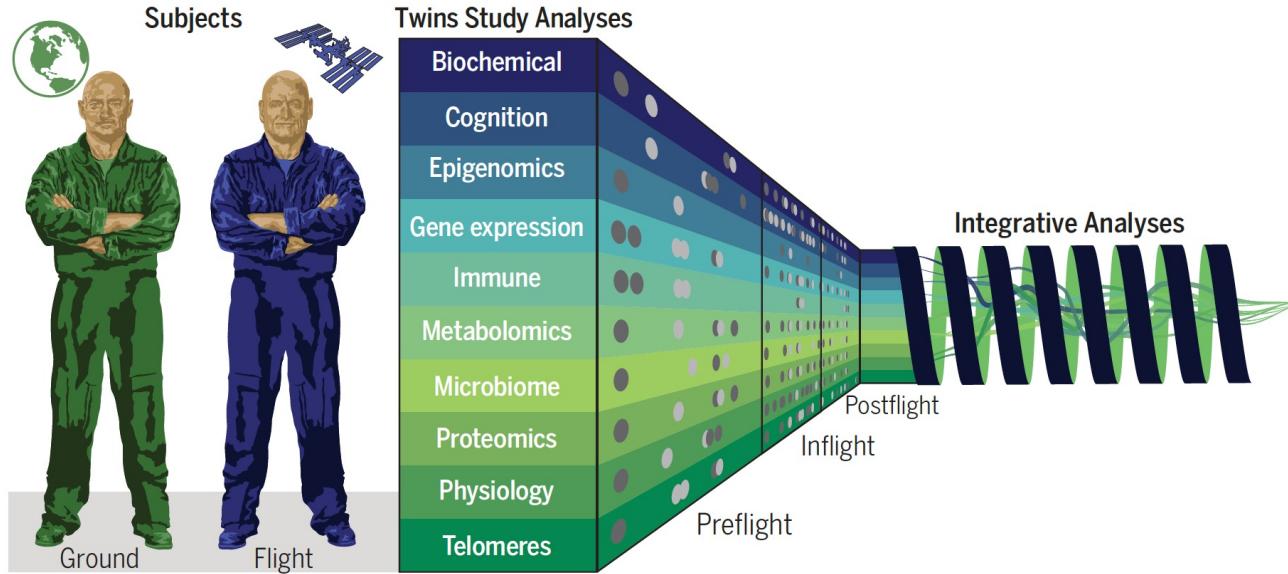
Pulling out more: Haplotypes to diplotypes

Levenshtein distances

$$\text{lev}_{a,b}(i,j) = \begin{cases} \max(i,j) \\ \min \begin{cases} \text{lev}_{a,b}(i-1,j) + 1 \\ \text{lev}_{a,b}(i,j-1) + 1 \\ \text{lev}_{a,b}(i-1,j-1) + 1_{(a_i \neq b_j)} \end{cases} \end{cases}$$

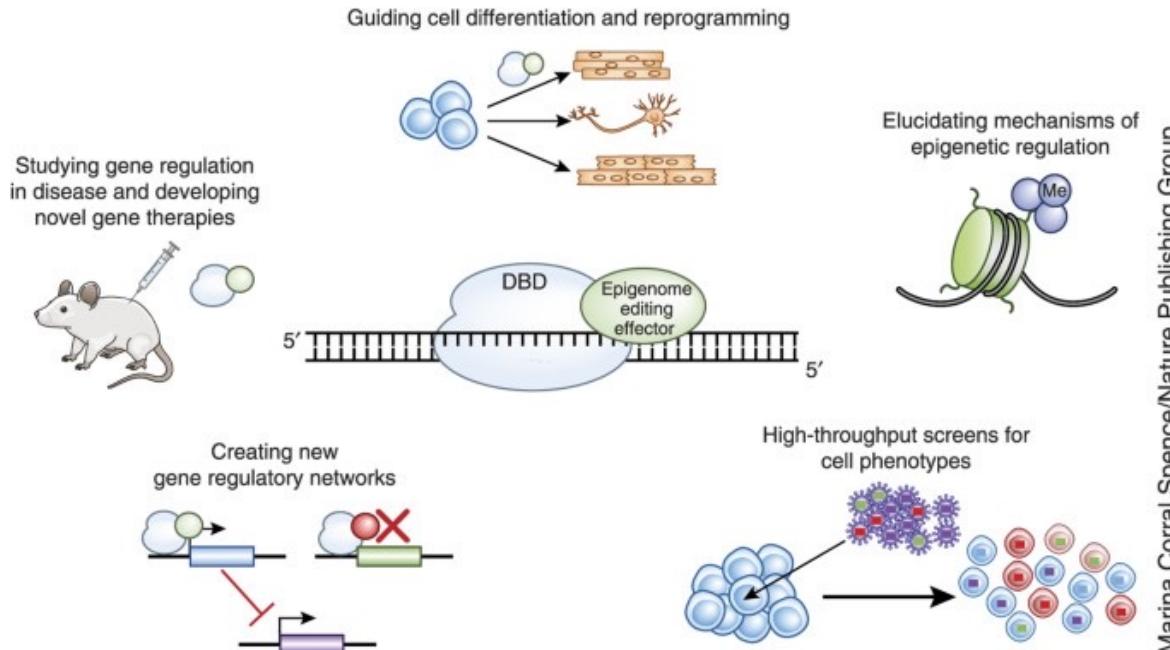


Overall good news

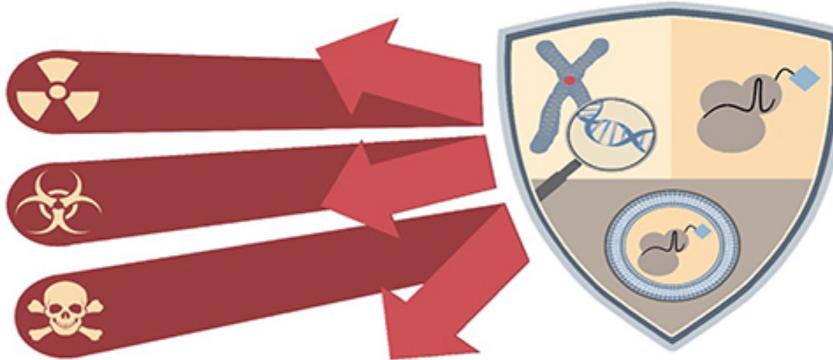


Can we just
tweak the
epigenome?

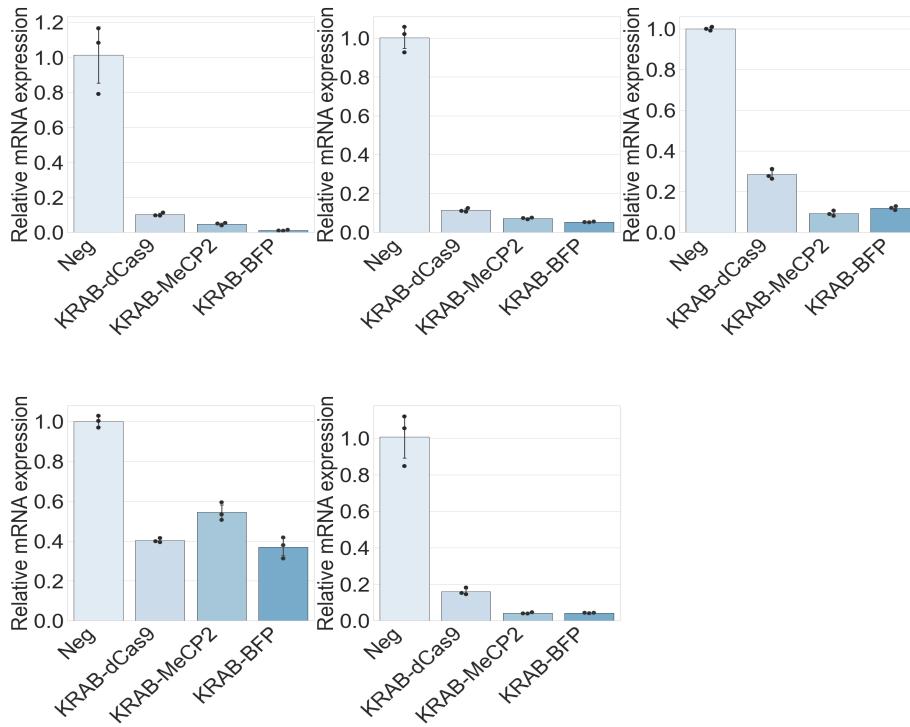
Tools to modify the epigenome (e.g. Cas9-TET1)



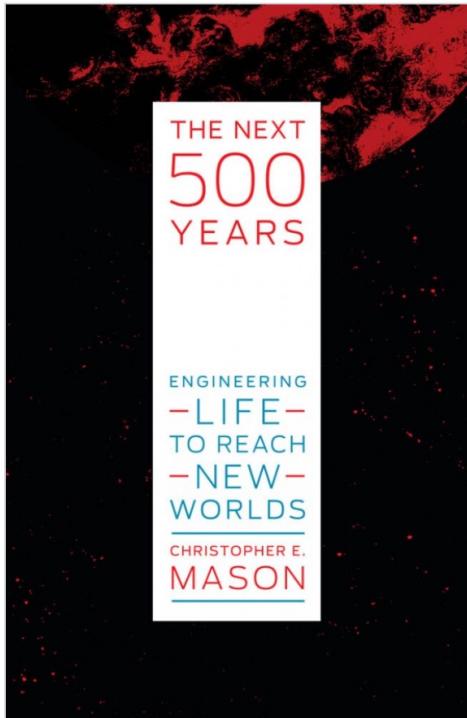
PREemptive Expression of Protective Alleles and Response Elements (PREPARE)



Now deploying CRISPRi with dCas9-KRAB and MeCP2/BFP constructs for radiation-responsive genes



Other places to use it (shameless plug)



The Next 500 Years

Engineering Life to Reach New Worlds

By Christopher E. Mason

An argument that we have a moral duty to explore other planets and solar systems – because human life on Earth has an expiration date.

<https://mitpress.mit.edu/books/next-500-years>



These People are Awesome





Thanks to Support & Funding from:



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GATES *foundation*



THE
VALLEE
FOUNDATION

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Deep Gratitude to Many People:

Mason Lab

Evan Afshin
Chandrima Bhattacharya

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Kirill Grigorev

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