Controversies in Giving Data Back

Gholson J. Lyon, M.D. Ph.D.

STANLEY INSTITUTE FOR COGNITIVE GENOMICS
COLD SPRING HARBOR LABORATORY

UFBR
UTAH FOUNDATION FOR BIOMEDICAL RESEARCH

INSTITUTE FOR GENOMIC MEDICINE
Your genome, your medicine.

@GholsonLyon

Conflicts of Interest

- I do not accept $$$ as salary from anyone other than my current employer, CSHL.

- I also work with the **nonprofit** Utah Foundation for Biomedical Research (UFBR) and the Institute for Genomic Medicine (IGM).

- Any revenue that I earn from providing medical consultation to people is donated to UFBR and IGM for the genetics research.

“Prevention” has been and will continue to be the best way to improve health.

Better sanitation = reduce infectious disease

Iodine supplementation = eliminate cretinism

Folate during pregnancy = reduce neural tube defects

PAP smears = detect pre-cancerous lesions

Reduce cigarette smoking = decrease cancer

From Base Pair to Body Plan:
Celebrating 60 years of DNA

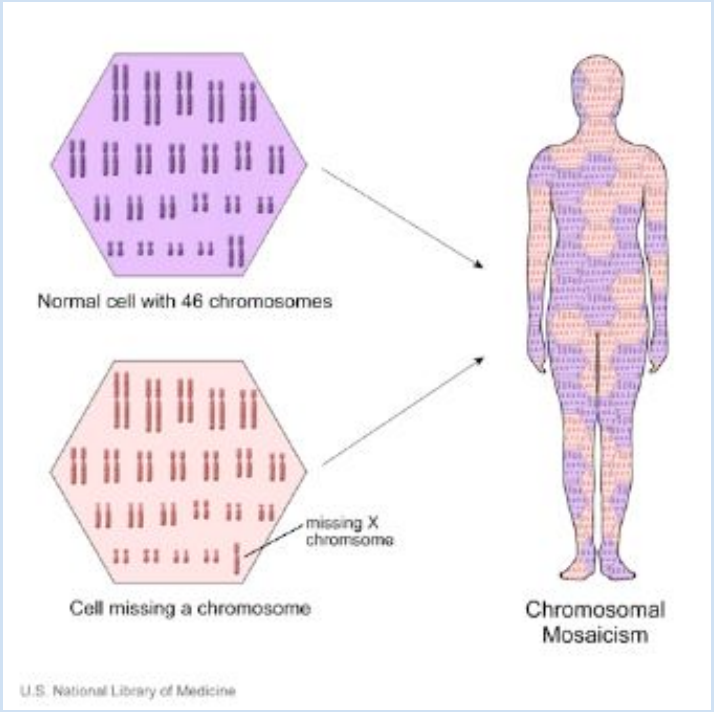
Organizers:
Alex Gann, Cold Spring Harbor Laboratory
Robert Martienssen, Cold Spring Harbor Laboratory/HHMI

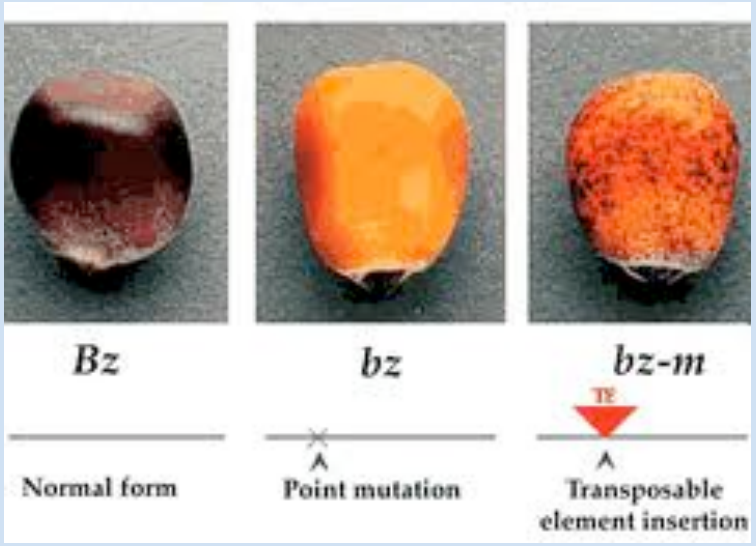
"We don't have to look for a model organism anymore, because we *are* the model organisms."

– Sydney Brenner, Nobel Laureate, quote in 2008

Complexity

- There are ~25-100 TRILLION cells in each human body, with ~6 billion nucleotides per cell.
- There is extensive modification of DNA, RNA and proteins both spatially and temporally.
- There are higher level mechanisms of somatic mosaicism, heterosis, and likely ancestral inheritance.





Source: http://www.thenakedscientists.com/HTML/features/article/jamilcolumn1.htm/

OPEN ACCESS Freely available online

PLoS one

Circular RNAs Are the Predominant Transcript Isoform from Hundreds of Human Genes in Diverse Cell Types

Julia Salzman[1☯], Charles Gawad[1,3☯], Peter Lincoln Wang[1], Norman Lacayo[3], Patrick O. Brown[1,2*]

1 Department of Biochemistry, Stanford University School of Medicine, Stanford, California, United States of America, **2** Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, California, United States of America, **3** Department of Pediatric Hematology/Oncology, Stanford University School of Medicine, Stanford, California, United States of America

Abstract

Most human pre-mRNAs are spliced into linear molecules that retain the exon order defined by the genomic sequence. By deep sequencing of RNA from a variety of normal and malignant human cells, we found RNA transcripts from many human genes in which the exons were arranged in a non-canonical order. Statistical estimates and biochemical assays provided strong evidence that a substantial fraction of the spliced transcripts from hundreds of genes are circular RNAs. Our results suggest that a non-canonical mode of RNA splicing, resulting in a circular RNA isoform, is a general feature of the gene expression program in human cells.

Citation: Salzman J, Gawad C, Wang PL, Lacayo N, Brown PO (2012) Circular RNAs Are the Predominant Transcript Isoform from Hundreds of Human Genes in Diverse Cell Types. PLoS ONE 7(2): e30733. doi:10.1371/journal.pone.0030733

Editor: Thomas Preiss, The John Curtin School of Medical Research, Australia

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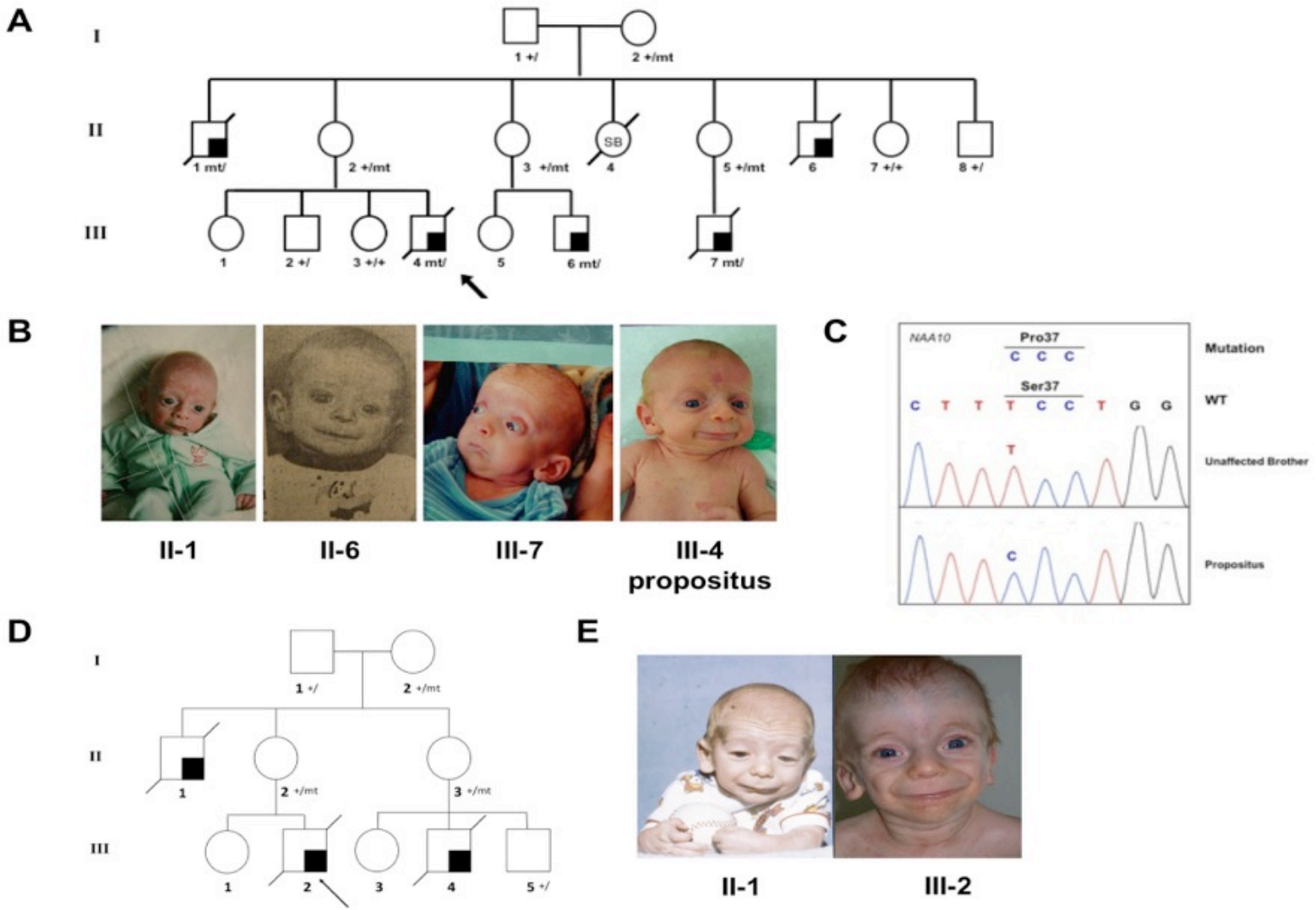
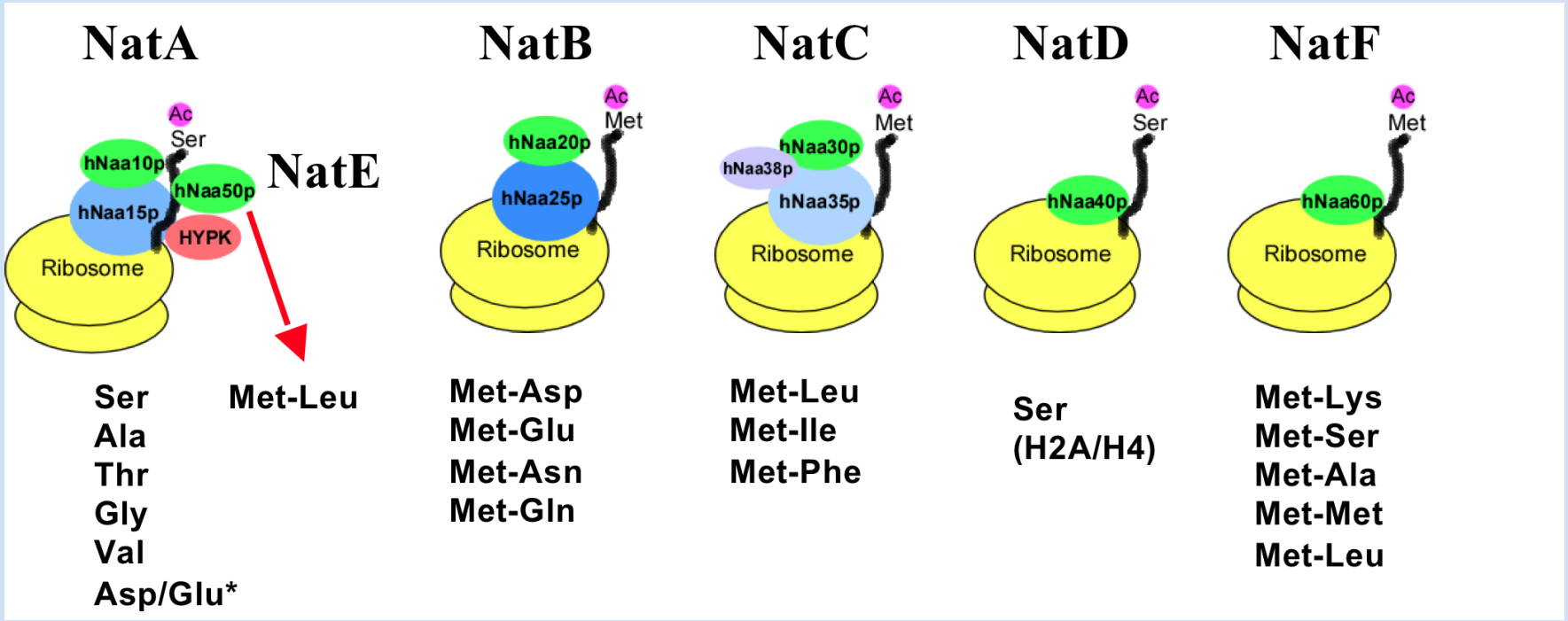
Ogden Syndrome – in 2011



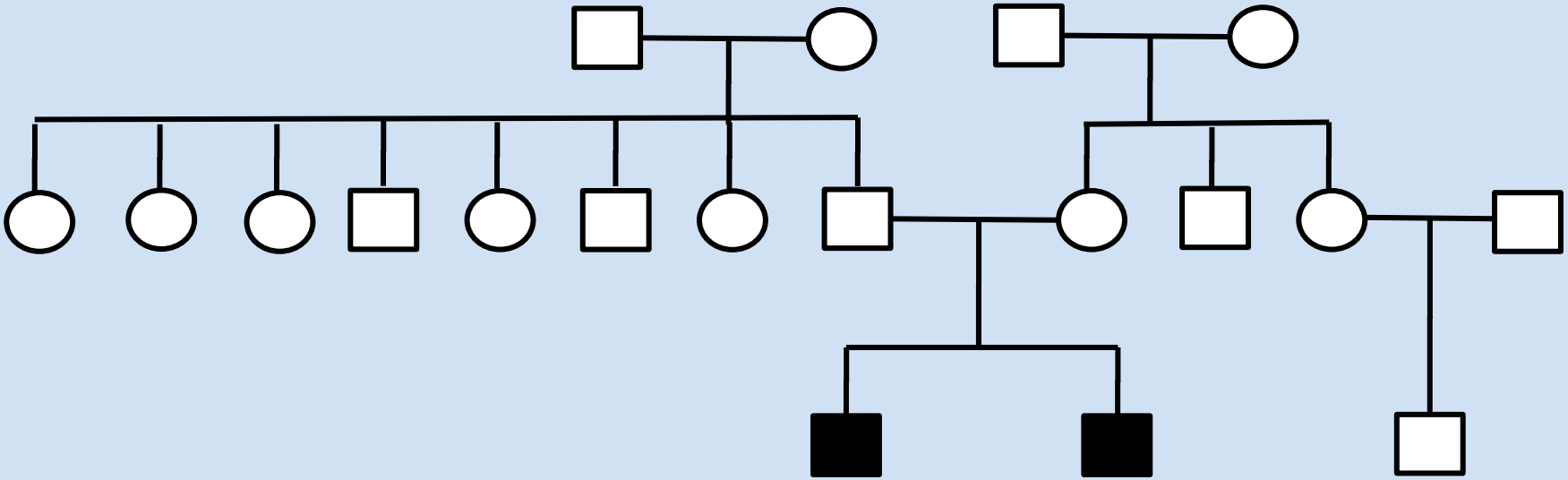
We found the SAME mutation in two unrelated families, with a very similar phenotype in both families, helping prove that this genotype contributes to the phenotype observed.

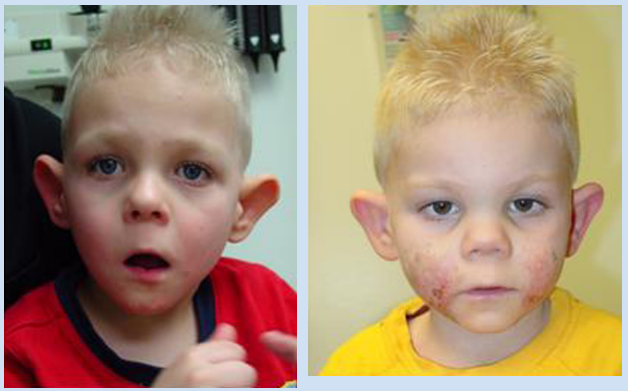
The mutation disrupts the N-terminal acetylation machinery (NatA) in human cells.



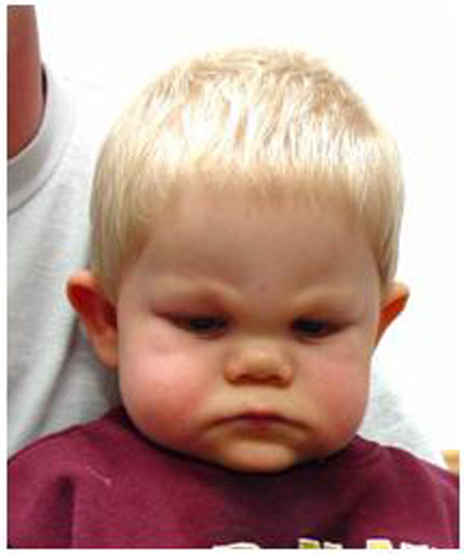
Slide courtesy of Thomas Arnesen

New Syndrome with Dysmorphology, Mental Retardation, “Autism”, “ADHD”

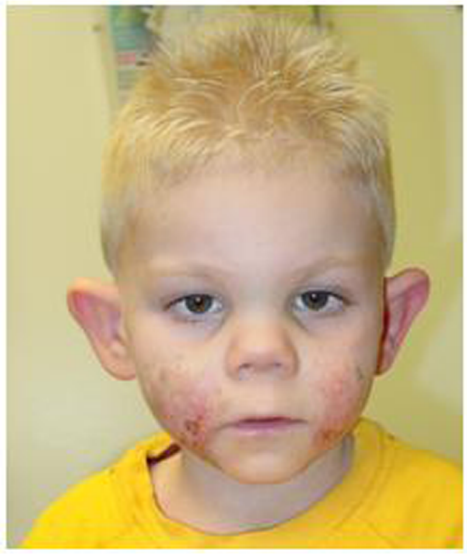




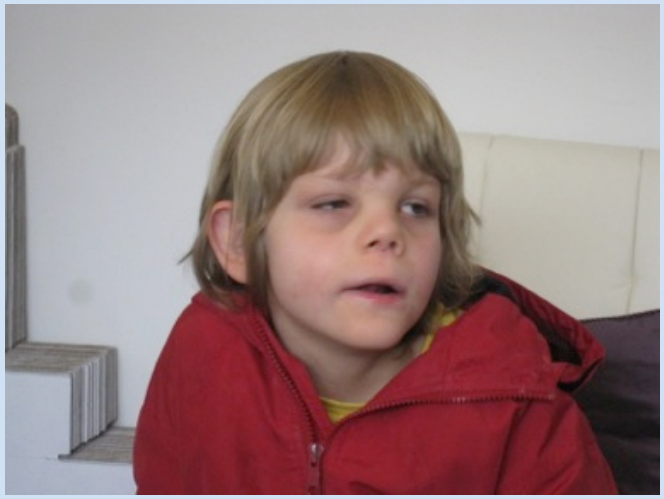
Could be X-linked, Autosomal Recessive, multi-allelic or polygenic threshold effect?



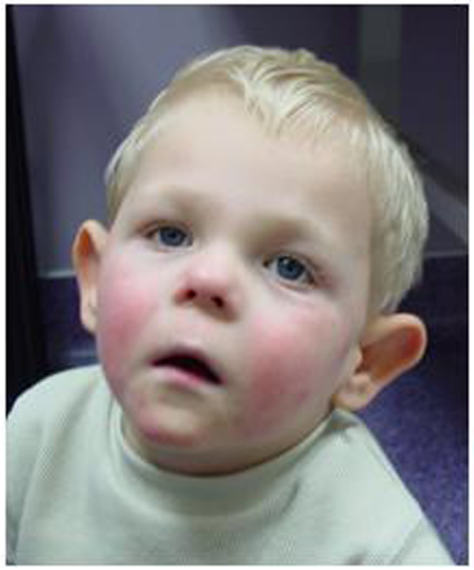
1.5 years old



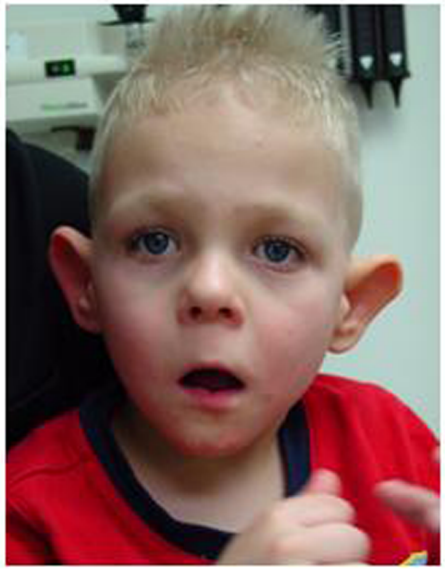
3.5 years old



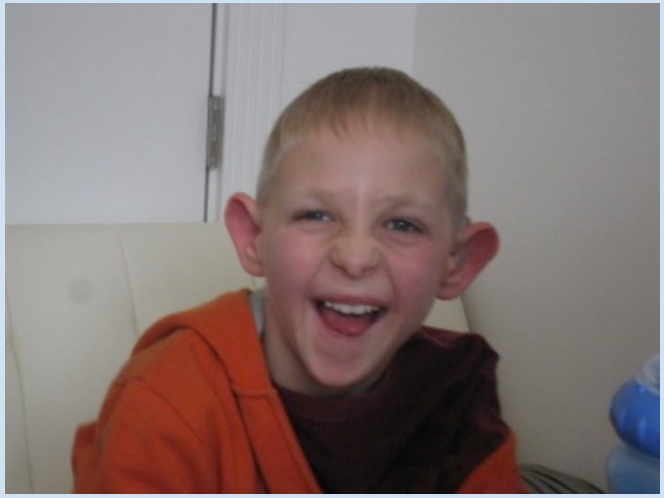
7 years old



3 years old



5 years old



9 years old

Workup Ongoing for past 10 years

- Numerous genetic tests negative, including negative for Fragile X and many candidate genes.
- No obvious pathogenic CNVs – several microarrays without any definitive result.
- Sequenced whole genomes of Mother, Father and Two Boys, using Complete Genomics, version 2.0 CG pipeline.
- But VERY difficult to prove in this instance that any mutation (or mutations) are definitely contributing to the illness.

Worldwide Database?

- We need at least ONE Million humans with detailed phenotype, genomic, and other data followed longitudinally, and all available for analysis to anyone online.

- A “Medical Donor Information Network”, in the words of Maynard Olson.

But how do ever achieve this?

Lyon and Wang *Genome Medicine* 2012, **4**:58
http://genomemedicine.com/content/4/7/58

REVIEW

Identifying disease mutations in genomic medicine settings: current challenges and how to accelerate progress

Gholson J Lyon*[1,2] and Kai Wang*[2,3]

Clinical Validity with Worldwide Human Genetic Variation "database"?

ancestry.com

PatientsLikeMe

Google

23andMe

Million Veteran Program:
A Partnership with Veterans

100,000 British Genomes

Lyon and Wang *Genome Medicine* 2012, 4:58
http://genomemedicine.com/content/4/7/58

REVIEW

Identifying disease mutations in genomic medicine settings: current challenges and how to accelerate progress

Gholson J Lyon*[1,2] and Kai Wang*[2,3]

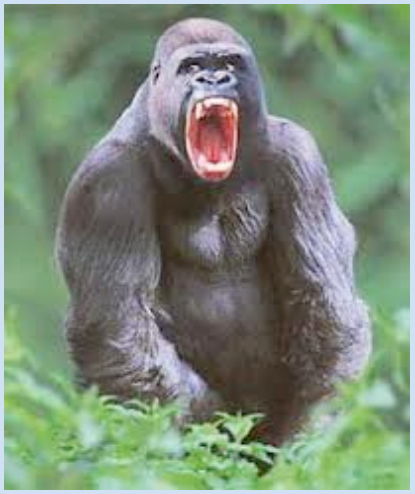
Networking of Science Model

http://lyonlab.cshl.edu/publications.html

The dreaded “Reviewer #3”

The dreaded “Reviewer #3”

- “The authors should stop and take a breath. Topol’s book (The Creative Destruction of Medicine) is a popularization of the “flying cars” variety.”



Scenic drive: In this undated photo, Dr. Paul Moller stands with two prototypes of his SkyCar and his company's flying saucer, the Neuera, which he helped develop and himself piloted in the 1970s
http://www.dailymail.co.uk/news/article-2268402/Flying-car-developer-says-hes-80-million-closer-making-sci-fi-dream-reality.html#ixzz2Ld7gJqiT

It takes a LONG time and Persistence to introduce new technologies and change the Status Quo

MRI ~1977

First Human Image July 3, 1977, showing heart, lungs, vertebra, musculature.

Figure 9.3 Raymond Damadian, Lawrence Minkoff, and Michael Goldsmith (left to right) and the completed *Indomitable*, presented as the world's first MR scanner. [RD]

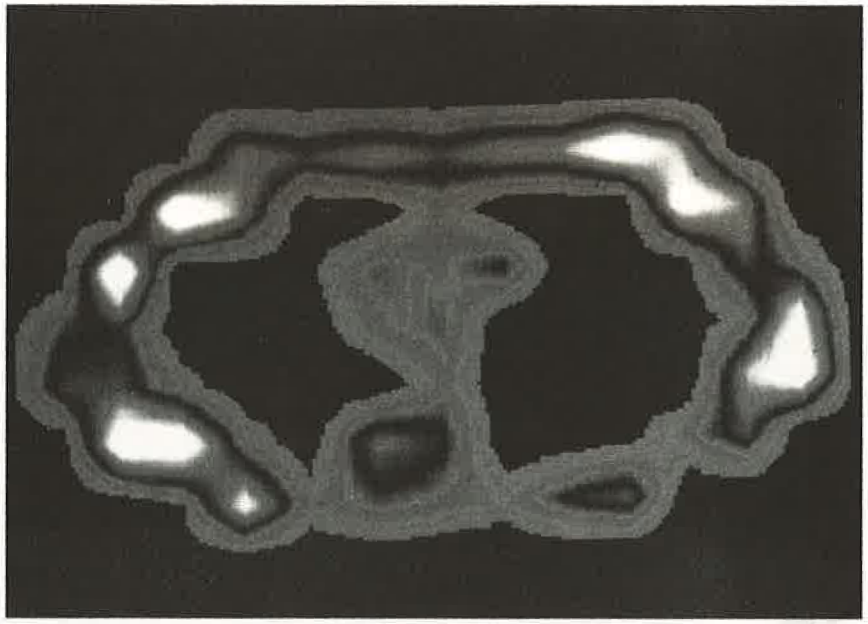
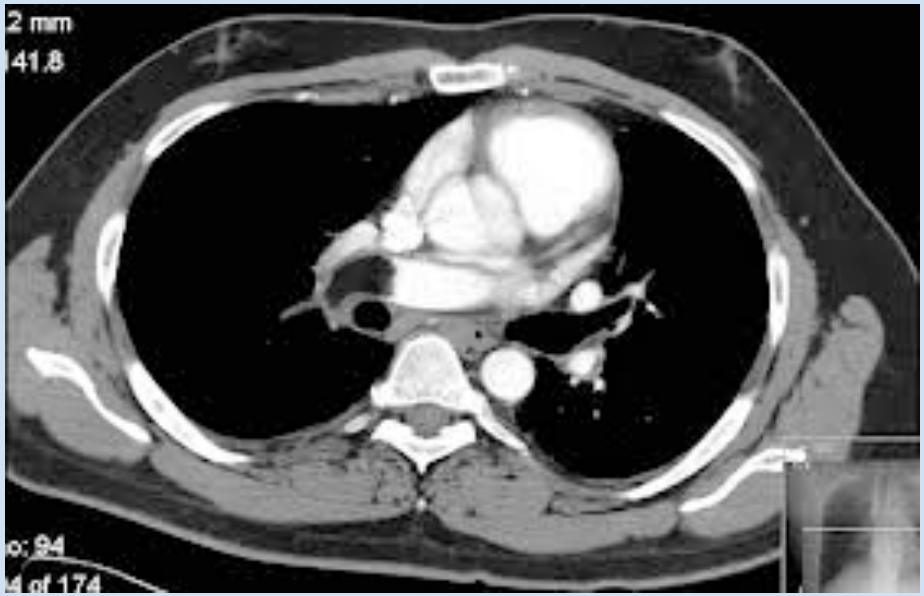
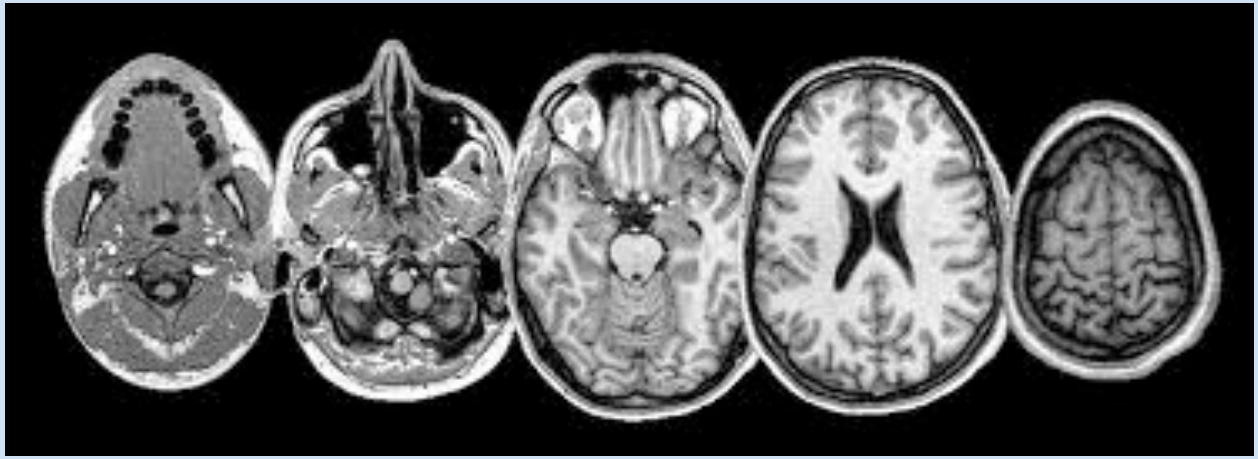


Figure 9.6 First MRI seen of a live human body, further computer-enhanced. Cross-section of Lawrence Minkoff's chest. Top of the image is anterior boundary of the chest wall. Left area is left side of chest. The heart is the principal structure in the middle and the lungs (black cavities) are on either side. More posteriorly on the left, the circular structure corresponds to the descending aorta. In the body wall, the sternum is seen anteriorly and proceeding around the ellipse alteration of light, and dark areas correspond to the intercostal muscles with rib. [RD]

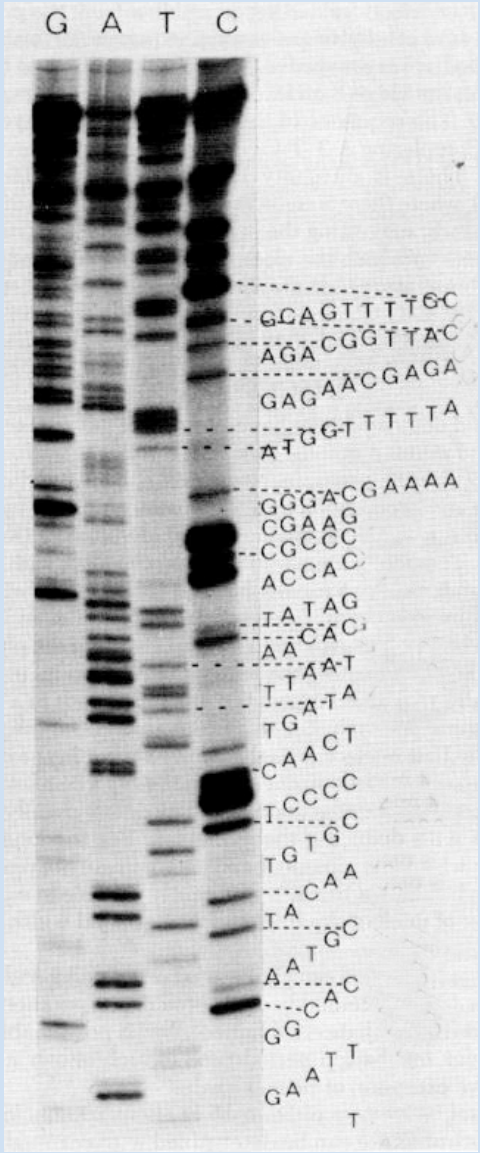
From Prize Fight: The Race and Rivalry to be First in Science, by Morton Meyers, M.D., 2012

Present Day 2013, ~35 years later



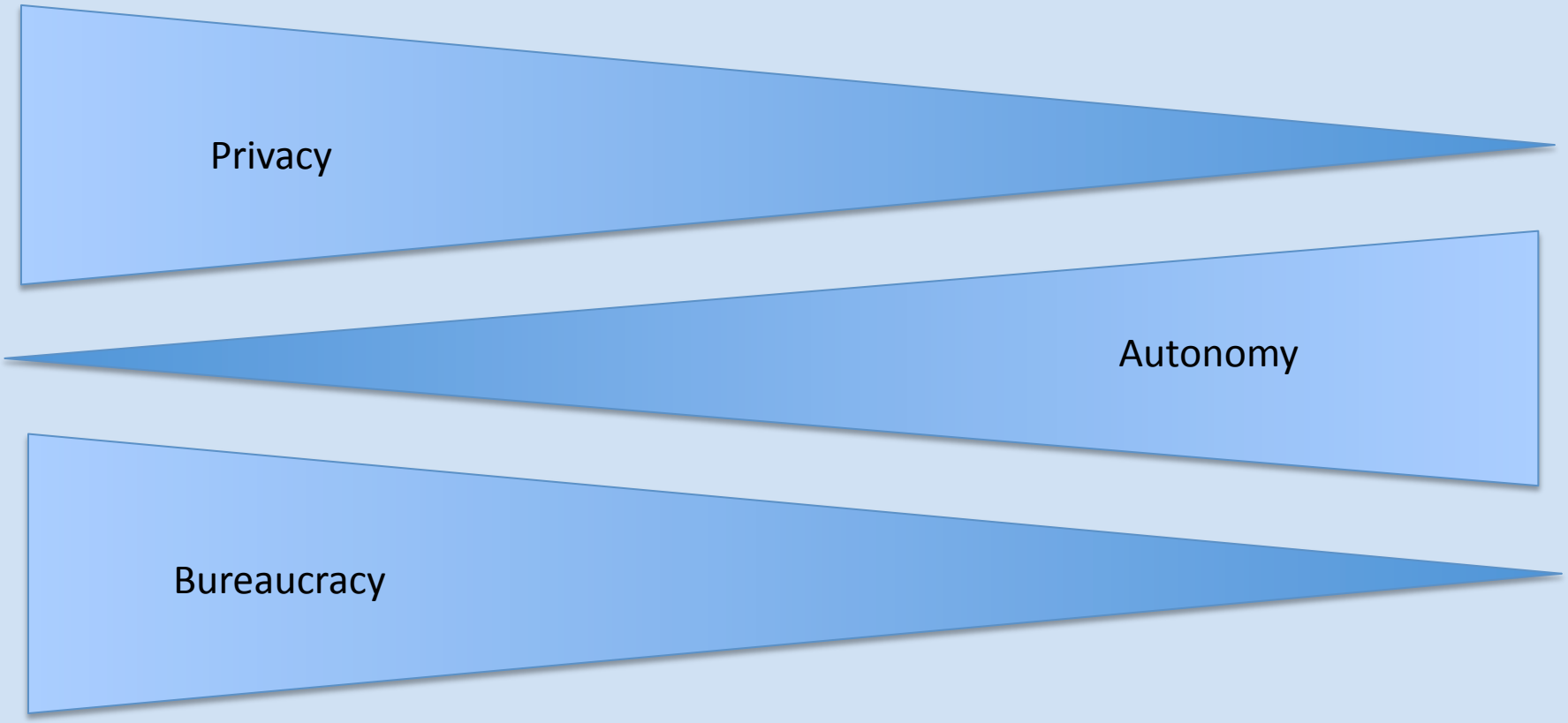


Industrialization of Sequencing



to

Autonomy vs. Privacy vs. Bureaucracy

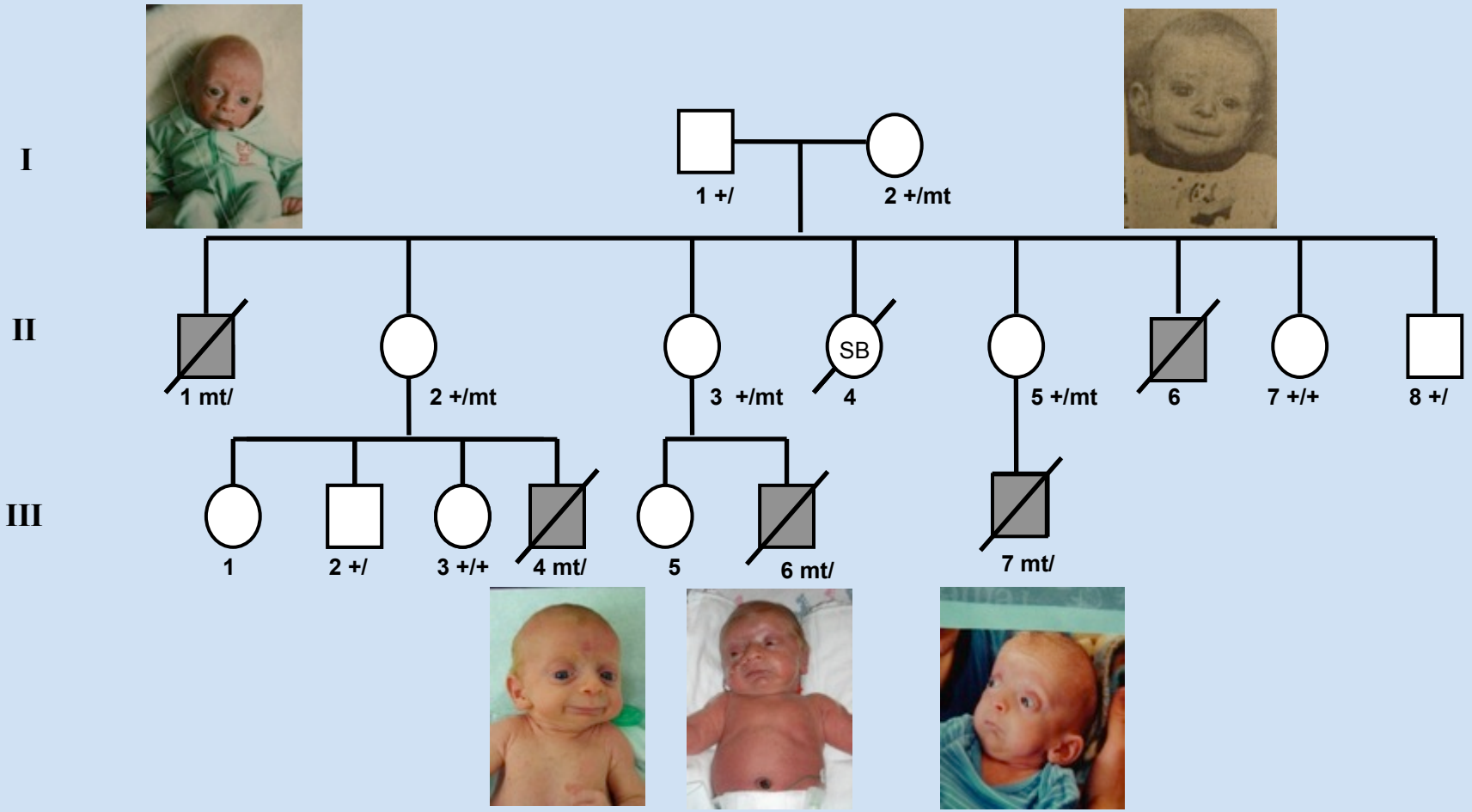


PRIVACY and PROGRESS in Whole Genome Sequencing

Presidential Commission
for the Study of Bioethical Issues

October 2012

Family in Utah - Ogden Syndrome.



Policy and Governance

"If you sequence people's exomes you're going to find stuff," said Gholson Lyon, a physician and researcher previously at the University of Utah, now at Cold Spring Harbor Laboratory.

As part of his research, Dr. Lyon worked with a family in Ogden, Utah. Over two generations, four boys had died from an unknown disease with a distinct combination of symptoms—an aged appearance, facial abnormalities, and developmental delay. Dr. Lyon sought to identify the genetic cause of this disease, and collected blood samples from 12 family members who had signed consent forms. The family members understood these forms to mean that they would have access to their results.

Dr. Lyon has become an outspoken advocate for conducting whole genome sequencing in laboratories that satisfy the federal standards so that researchers can return results to participants, if appropriate. Dr. Lyon wants clear guidance for laboratories conducting genetic research and clear language in consent forms that clarifies the results that participants should expect to have returned from the researchers.

Recommendation 4.1

Funders of whole genome sequencing research, relevant clinical entities, and the commercial sector should facilitate explicit exchange of information between genomic researchers and clinicians, while maintaining robust data protection safeguards, so that whole genome sequence and health data can be shared to advance genomic medicine.

Performing all whole genome sequencing in CLIA-approved laboratories would remove one of the barriers to data sharing. It would help ensure that whole genome sequencing generates high-quality data that clinicians and researchers can use to draw clinically relevant conclusions. It would also ensure that individuals who obtain their whole genome sequence data could share them more confidently in patient-driven research initiatives, producing more meaningful data. That said, current sequencing technologies and those in development are diverse and evolving, and standardization is a substantial challenge. Ongoing efforts, such as those by the Standardization of Clinical Testing working group are critical to achieving standards for ensuring the reliability of whole genome sequencing results, and facilitating the exchange and use of these data.[216]

Applied & Translational Genomics

Practical, ethical and regulatory considerations for the evolving medical and research genomics landscape.

Gholson J. Lyon[1,2*] and Jeremy P. Segal[3*]

1) Stanley Institute for Cognitive Genomics, Cold Spring Harbor Laboratory, NY; 2) Utah Foundation for Biomedical Research, Salt Lake City, UT; 3) New York Genome Center, New York City, NY.

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Jeremy P. Segal, M.D. Ph.D.
Email: jpsegal@nygenome.org

CLIA and Genetics

Table 1. Processes involved in a CLIA-certified genetic test.
Preanalytic System:
1) test request and specimen collection criteria
2) specimen submission, handling and referral procedures
3) preanalytic systems assessment
Analytic System:
1) a detailed step-by-step procedure manual
2) test systems, equipment, instruments, reagents, materials and supplies
3) establishment and verification of performance specifications
4) maintenance and function checks
5) calibration and calibration verification procedures
6) control procedures, test records, and corrective actions
7) analytic systems assessment
Post-Analytic System:
1) test report, including (among other things): a) interpretation b) reference ranges and normal values
2) Post-analytic systems assessment

I have ordered and obtained whole genome sequencing from the CLIA-certified WGS lab at Illumina. It ALREADY exists.

Will results from my blood tests be forwarded to me?

It will not be possible to give participants results of the blood tests. Due to regulations under the Clinical Laboratory Improvement Amendments (CLIA), we are legally unable to return research results to participants. Results from the blood tests will **not** be placed in participants' electronic health record. Participants should discuss any health concerns with their doctor or other health care provider, who can arrange any necessary and appropriate tests.

http://www.research.va.gov/mvp/veterans.cfm
accessed March 6, 2013

"A **partnership** is an arrangement where parties agree to cooperate to advance their mutual interests."- *Wikipedia*

PeerJ

Dealing with the unexpected: consumer responses to direct-access *BRCA* mutation testing

Uta Francke[1,2], Cheri Dijamco[1], Amy K. Kiefer[1], Nicholas Eriksson[1], Bianca Moiseff[1], Joyce Y. Tung[1], and Joanna L. Mountain[1]

[1] 23andMe, Inc., Mountain View, CA, USA
[2] Department of Genetics, Stanford University School of Medicine, Stanford, CA, USA

204 *BRCA1* (185delAG or 5382insC) or *BRCA2* 6174delT mutation carriers (130 males and 74 females) in the 23andMe database of 114,627 customers who were at least 18 years of age and had consented to participate in research.

Clinical Validity with "Worldwide Human Genetic Variation Database" and/or "Medical Donor Information Network"?

ancestry.com

PatientsLikeMe

Google

23andMe

Million Veteran Program:
A Partnership with Veterans

100,000 British Genomes

UFBR
UTAH FOUNDATION FOR BIOMEDICAL RESEARCH

INSTITUTE FOR GENOMIC MEDICINE

Your genome, your medicine.

Our Mission

- Implement an infrastructure for clinical genomic sequencing and interpretation.
- Build public trust in genomic medicine.
- Urge insurance companies to reimburse genome sequencing in clinical settings.

http://www.utahresearch.org/

http://www.gmedicine.org

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Christa Schank
Sarah T. South
Jeffrey J Swensen
Jinchuan Xing
Mark Yandell

Reid Robison
Clark Johnson
Diane Gardner

Kai Wang

Zhi Wei
Lifeng Tian
Hakon Hakonarson

Thomas Arnesen
Rune Evjenth
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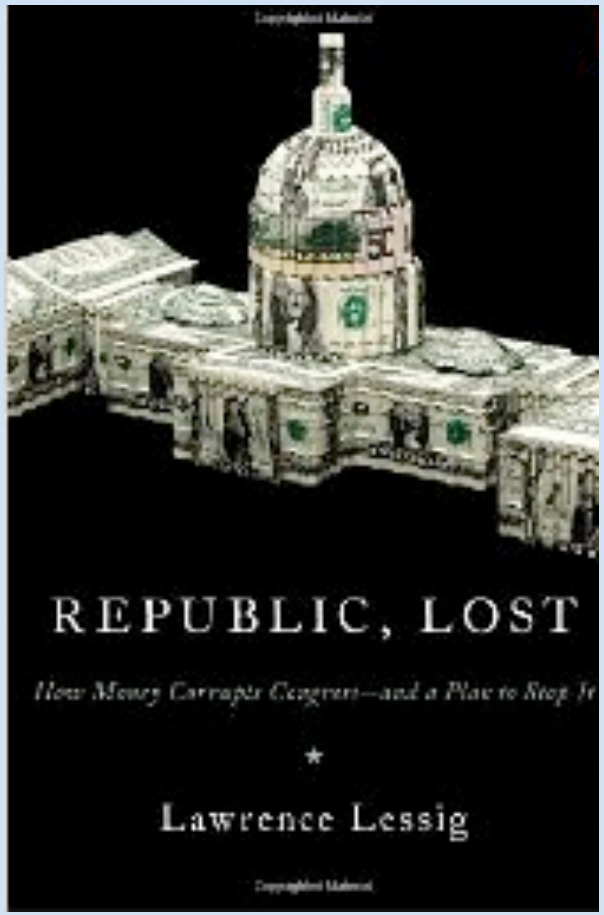
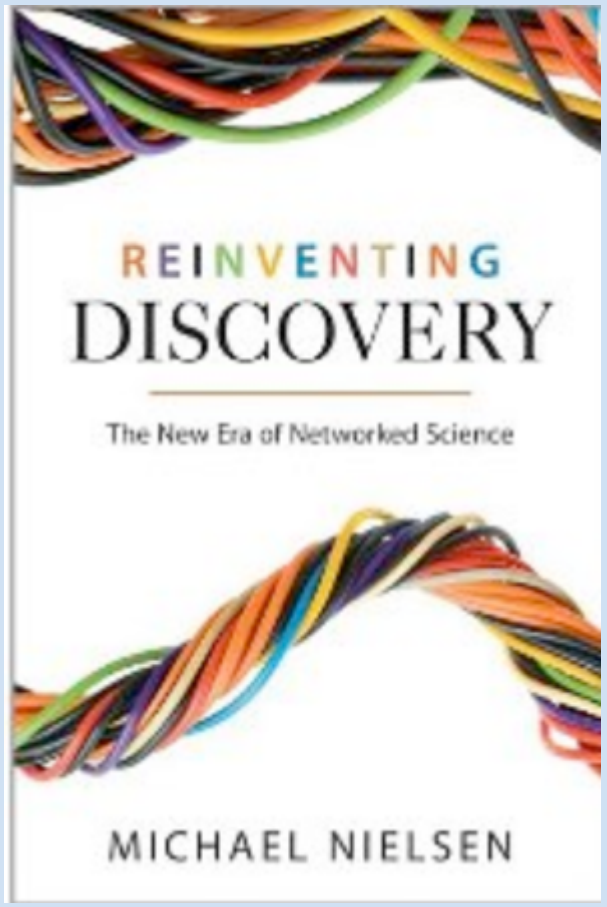
Yiyang Wu
Max Doerfel
Michael Schatz
Giuseppe Narzisi

Tao Jiang
Jun Wang

our study families

Further Acknowledgements





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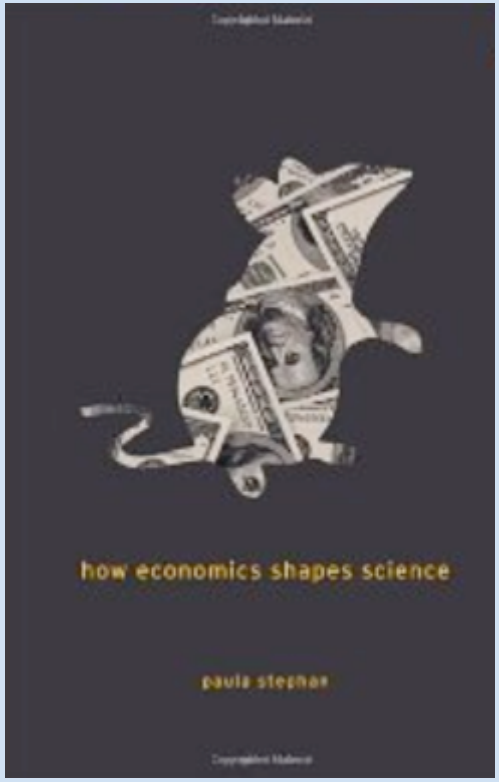

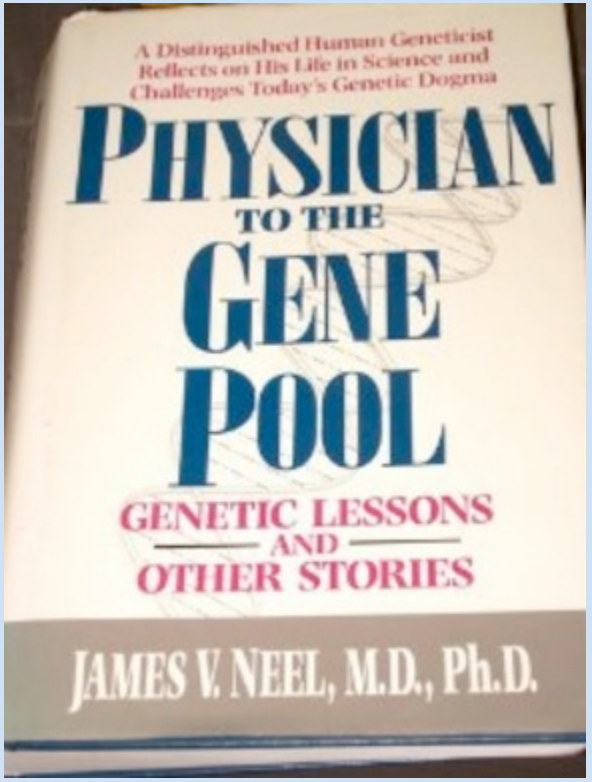

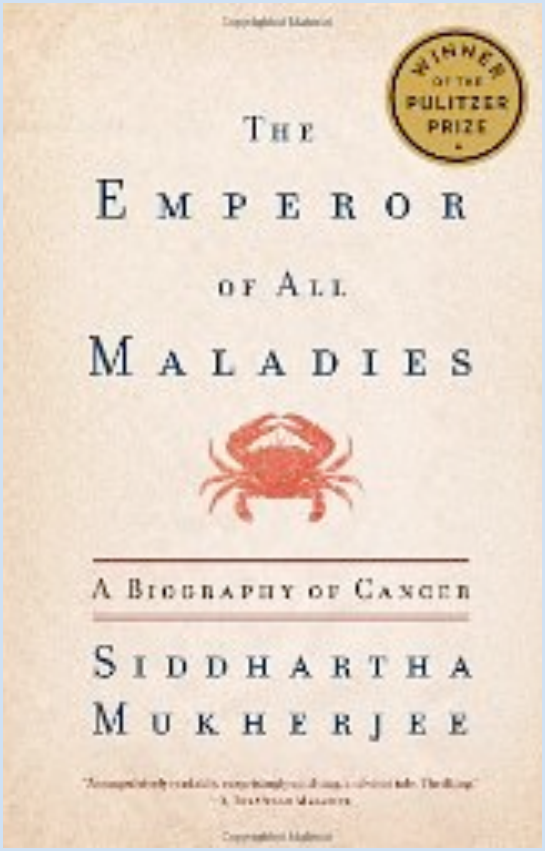

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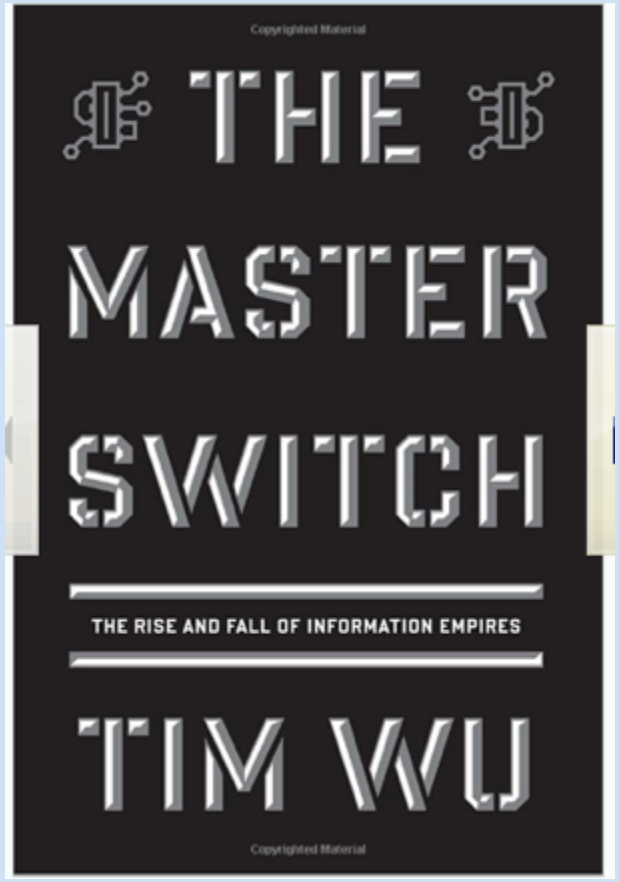

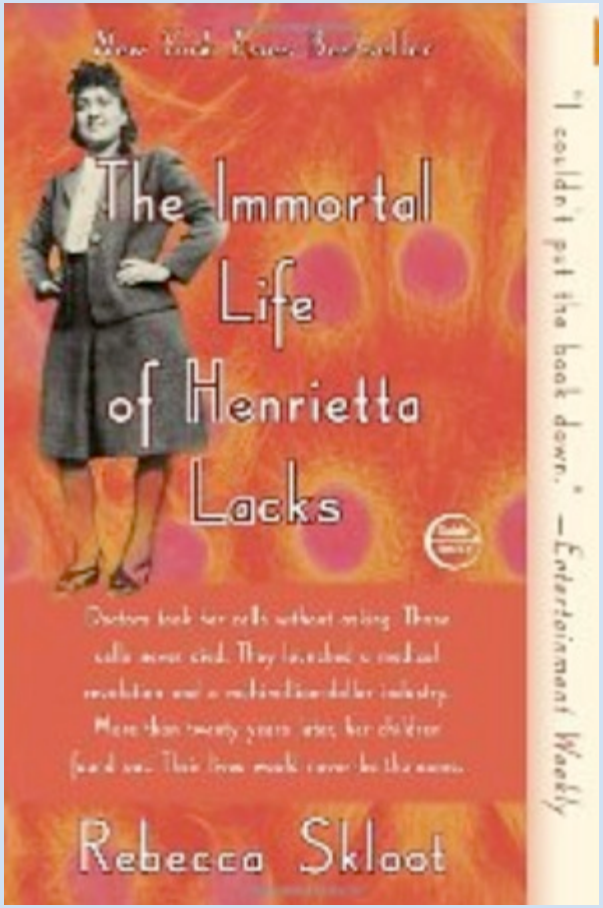

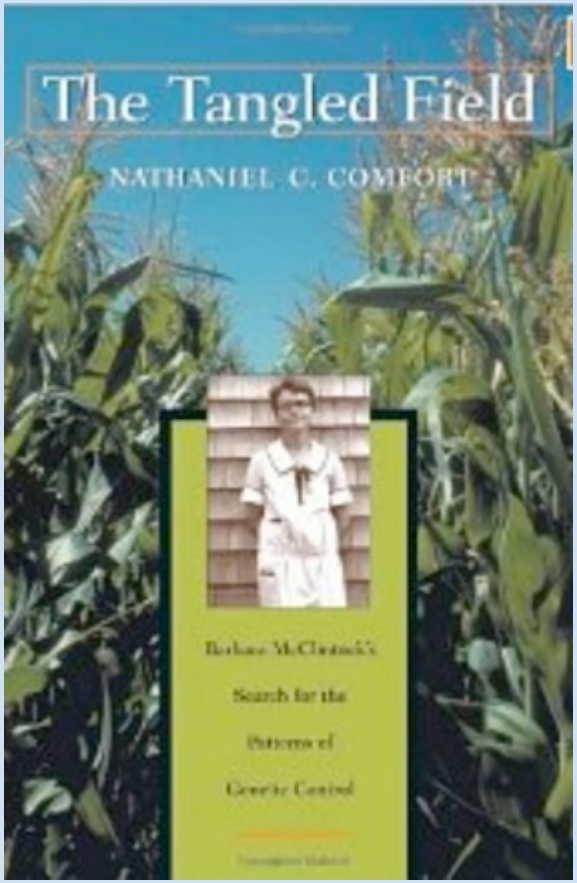

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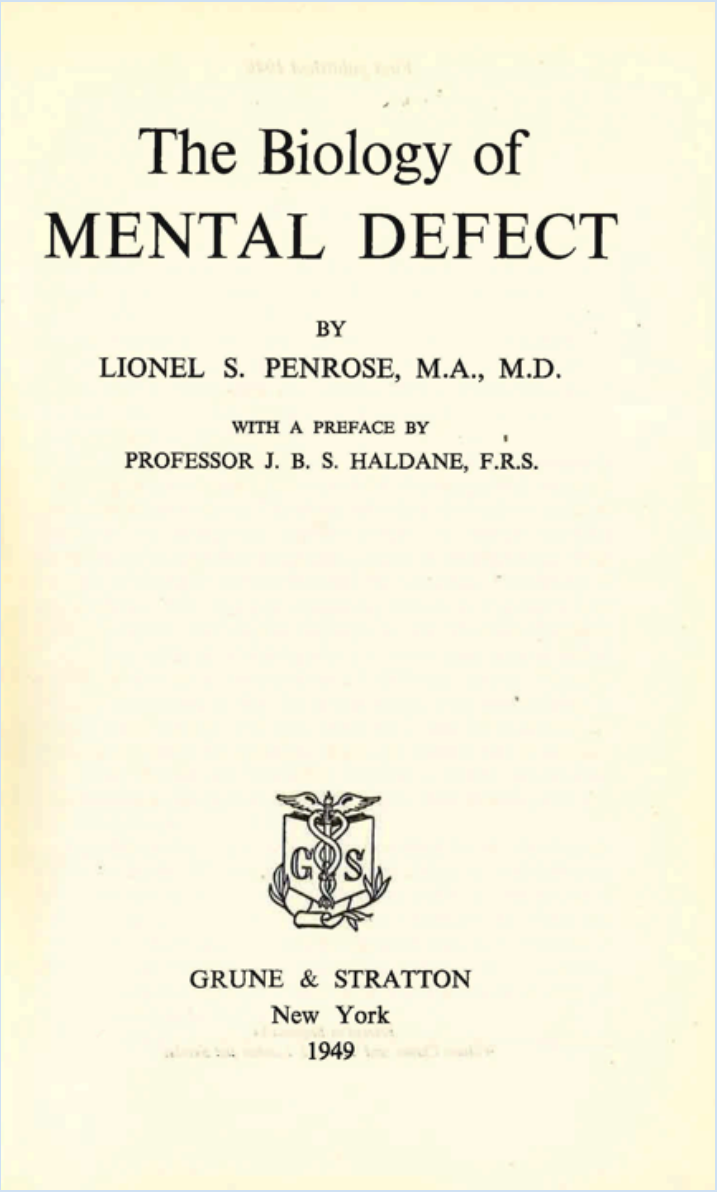
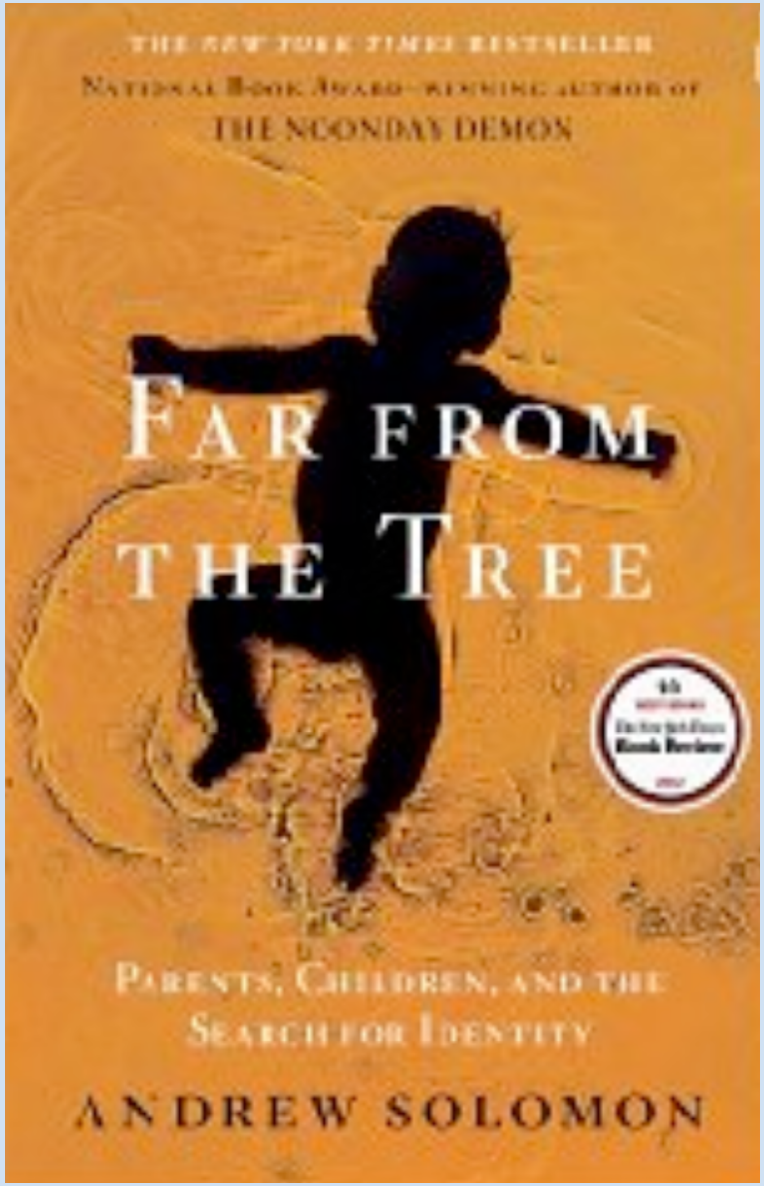


The Biology of
MENTAL DEFECT

BY
LIONEL S. PENROSE, M.A., M.D.

WITH A PREFACE BY
PROFESSOR J. B. S. HALDANE, F.R.S.

GRUNE & STRATTON
New York
1949



Further Acknowledgements

- **@Katy_Read**: Like many writers, I have rituals. Before writing, I pour some coffee, open the window by my desk, and attempt to read the entire internet.