Clinical Issues with the Return of Next-Generation Sequencing Results

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UTAH FOUNDATION FOR BIOMEDICAL RESEARCH

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Conflicts of Interest

- I do not receive salary compensation from any for-profit companies.
- I do some consulting work for free, i.e. I do not accept $$$ as salary from anyone other than my current employer, CSHL.
- I am involved in the nonprofit Utah Foundation for Biomedical Research, along with working as an academic researcher at Cold Spring Harbor Laboratory.
- I see many people in my clinic, so I tend to be most influenced by wanting to help them. Any revenue that I earn from providing consultation to consumers is donated to UFBR for the genetics research.

The Emperor has NO Clothes!

Beware the creeping cracks of bias

Evidence is mounting that research is riddled with systematic errors. Left unchecked, this could erode public trust, warns **Daniel Sarewitz**.

Strengthen and stabilize the FDA

The US Food and Drug Administration needs to be more independent, says **Daniel Carpenter**.

A recipe for disaster

Manufacturers of commercial reagents should follow scientific norms and be open about the ingredients of their products, says **Anna Git**.

Buyer beware

An investigation by Nature *shows the scale of the market for unapproved stem-cell therapies in China. Hype and unrealistic hope must not be allowed to undermine genuine promise.*

Must try harder

Too many sloppy mistakes are creeping into scientific papers. Lab heads must look more rigorously at the data — and at themselves.

Perverse incentives

Counterproductive financial incentives divert time and resources from the scientific enterprise. We should spend the money more wisely, says **Paula Stephan**.

The darker side of stem cells

An investigation by Nature *has found that patients in Texas are receiving unproven stem-cell treatments. The state and the company involved need to ensure that they follow FDA guidelines.*

Gold in the text?

Publishers and scientists should do more to foster the mining of research literature by computer.

IN THE WAKE OF HIGH-PROFILE CONTROVERSIES, PSYCHOLOGISTS ARE FACING UP TO PROBLEMS WITH REPLICATION.

BY ED YONG

FIRST, DO HARM

In the 1940s, US doctors deliberately infected thousands of Guatemalans with venereal diseases. The wound is still raw.

BY MATTHEW WALTER

The paper is not sacred

Peer review continues long after a paper is published, and that analysis should become part of the scientific record, say **Adam Marcus** and **Ivan Oransky**.

Hypocritical oaths

History judges some research as unethical, despite approval at the time.

Raise standards for preclinical cancer research

C. Glenn Begley and **Lee M. Ellis** propose how methods, publications and incentives must change if patients are to benefit.

Incidental benefits

Scientists who screen the genes of volunteers for research should tell participants if they find information relevant to their health.

Bring clinical standards to human-genetics research

Study protocols need to be rigorous, because more than science is at stake. Sometimes participants' lives depend on the results, writes **Gholson J. Lyon**.

genomes unzipped
public personal genomics

Guest post: Time to bring human genome sequencing into the clinic
02/16/2012

Need Minimal Regulatory Standards!

In Choosing a Sperm Donor, a Roll of the Genetic Dice
Sarah Phipps for The New York Times

Jaxon Kretchmar, 2, who was conceived with donated sperm, has cystic fibrosis.

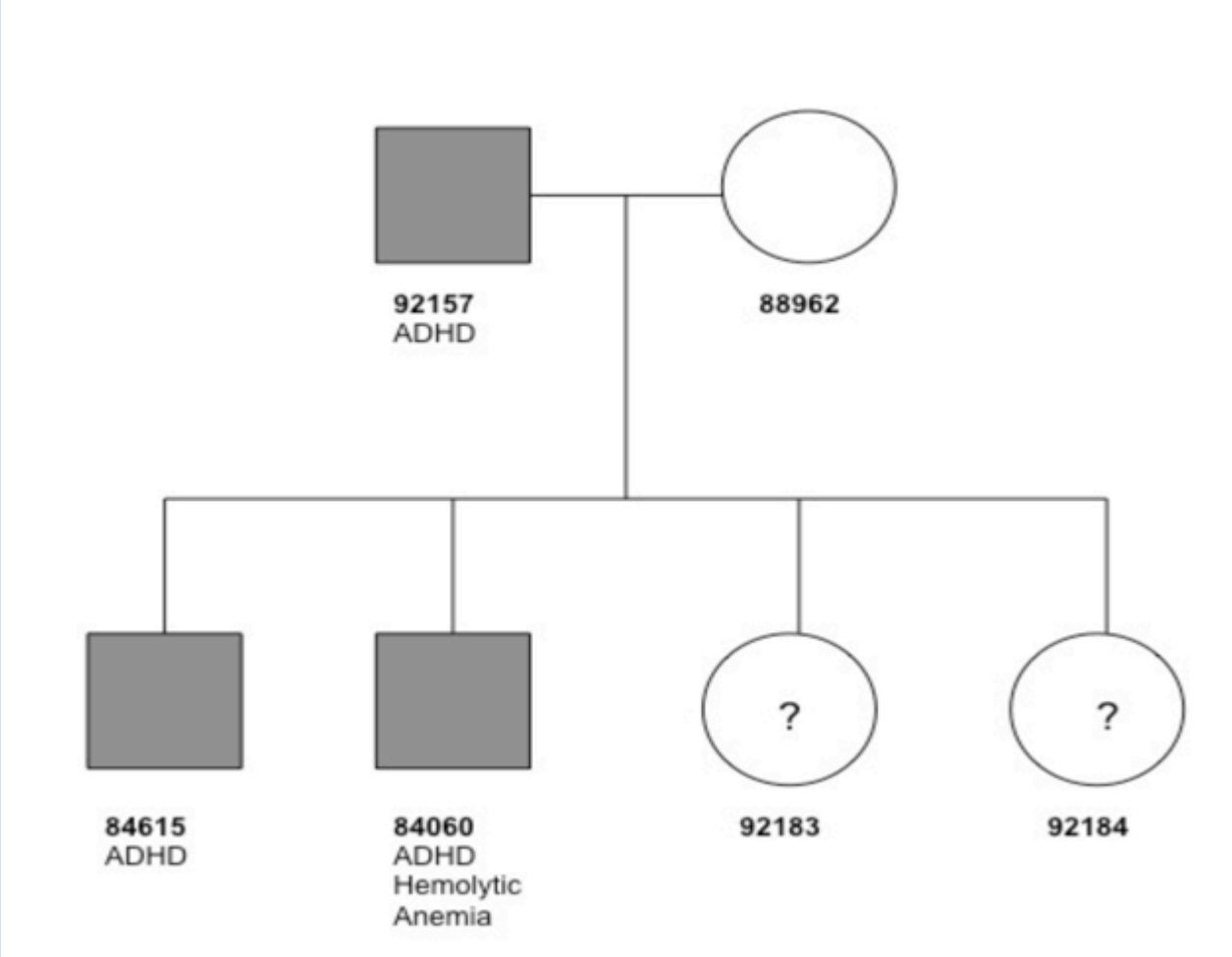
Exome Sequencing and Unrelated Findings in the Context of Complex Disease Research: Ethical and Clinical Implications

Gholson J. Lyon, Tao Jiang, Richard Van Wijk, Wei Wang, Paul Mark Bodily, Jinchuan Xing, Lifeng Tian, Reid J. Robison, Mark Clement, Lin Yang, Peng Zhang, Ying Liu, Barry Moore, Joseph T. Glessner, Josephine Elia, Fred Reimherr, Wouter W. van Solinge, Mark Yandell, Hakon Hakonarson, Jun Wang, William Evan Johnson, Zhi Wei, and Kai Wang

Discov Med. 2011 Jul;12(62):41-55.

- **There is NOTHING "Incidental" about Unrelated Findings.**
- Sequencing a bunch of exomes and finding random rare variants MIGHT be "incidental", but actually proving that these variants CAUSE the disease is NOT simple or "incidental" or "accidental" or "coincidental".
- I would suggest calling these "unrelated or secondary findings", rather than "incidental**".**
- Continuing to call these "incidental findings" trivializes the amount of work that ought to go into proving causality. Lyon, *Personalized Medicine*, 2012.

Exome sequencing of one pedigree in a research setting.



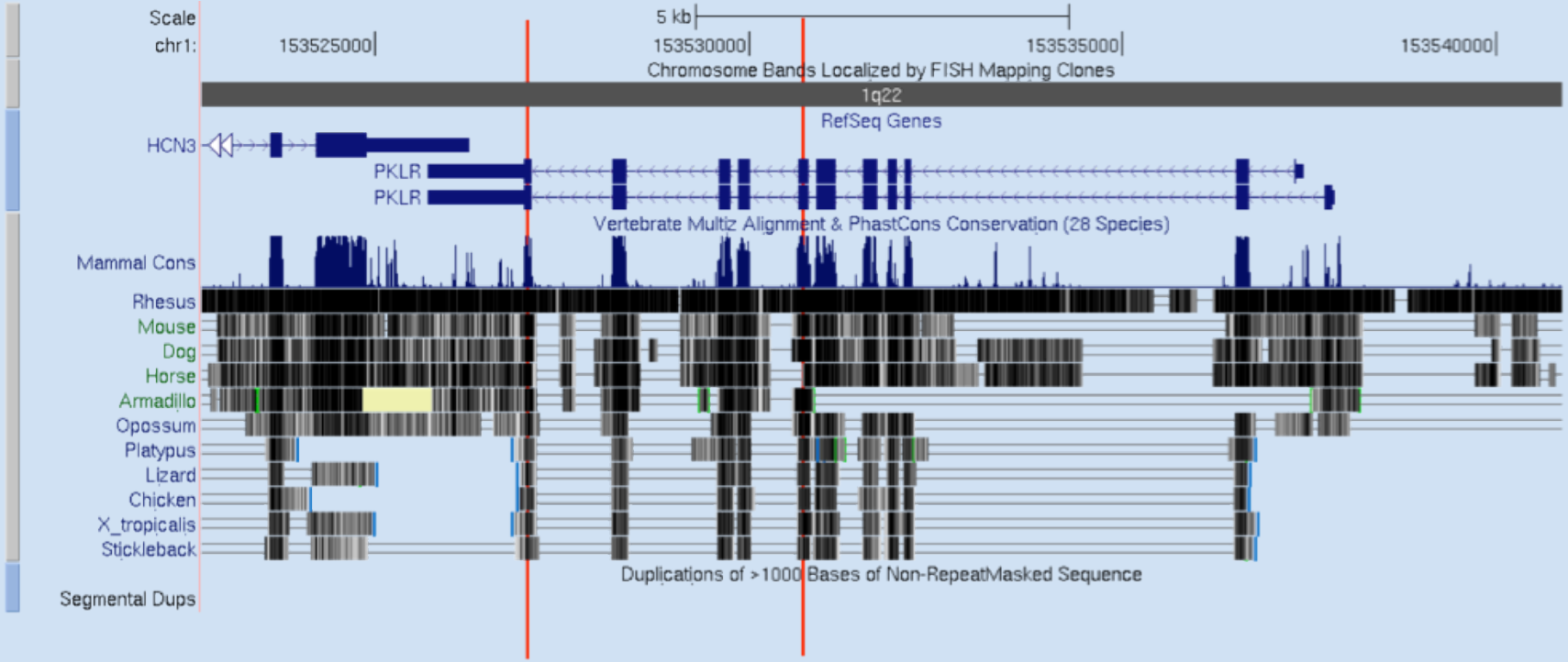
Exome Sequencing performed early 2010

While analyzing the exome data, research participant (age ~24) informs me that he recently had his spleen removed!

He has idiopathic hemolytic anemia, since childhood.

Although I am not his physician, I still feel an ethical and moral obligation to try to figure out what is going on.

Compound Heterozygote in *PKLR*, with each mutation inherited from one parent.



Some Additional Data to support the causation of these variants for idiopathic hemolytic anemia.

Table 2: Biochemical assays of enzyme activities in the patient affected with idiopathic hemolytic anemia confirmed *PKLR* deficiency. PK, pyruvate kinase; HK, hexokinase; G6PD, glucose-6-phosphate dehydrogenase.

	Patient 84060	Control	Reference values
PK (U/gHb)	3.3 L	8.6	6.1 – 12.3
HK (U/gHb)	3.2 H	1.1	0.8 – 1.5
G6PD (U/gHb)	15.8 H	9.2	6.4 – 10.5

Table 3: Bioinformatics prediction on the functional impact of two PKLR mutations. A mutation is regarded as deleterious if the SIFT<0.05, or PolyPhen>0.85, or PhyloP>0.95, or MutationTaster/LRT prediction as "D" (deleterious).

Mutation	SIFT	PolyPhen 2	PhyloP	LRT	MutationTaster
R569Q	0.03	0.84	0.97	D	D
G341A	0	0.889	1	D	D

Structural Modeling is also consistent with deleterious effects of these mutations.

Yet, it is June 2012 and this research participant still has not come back to give blood for CLIA-certified results. Why?

Major Barriers to the implementation of Genomic Medicine in the clinic:

1) Lack of public education – consumer not sure it matters.
2) Lack of physician knowledge about genetics.
3) Apathy on the part of populace, as they have "learned" to be apathetic and to not be empowered about their own health.
4) Refusal of insurance companies to pay for "not useful" genetic testing.
5) Focus in our society on Treatment, NOT on early diagnosis and prevention.
6) Societal marginalization of 99% who are not the wealthy elite.

Emphasis Should be on Diagnosis and Prevention, NOT just on Treatment

- 15 year old girl with Type I diabetes, hospitalized dozens of times with diabetic ketoacidosis. Millions spent to save life repeatedly, but very little on therapy or education – WHY?
- 14 year old boy hospitalized >10 times with pancreatitis over > ten years. Finally, someone gets genetics consult. Patient has cystic fibrosis, undiagnosed till then. Benefits from pancreatic enzyme supplementation, plus therapy and education. WHY so LONG to diagnose?

I would suggest that researchers working on DNA samples from living humans perform CLIA-certified sequencing UP FRONT, either with exomes or whole genomes, so that we can return results to consumers, research participants and families.

Secrets of the human genome disclosed

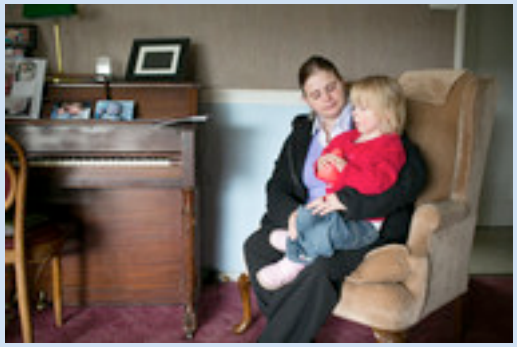
Meeting debates ethics of revealing genetic findings.

Erika Check Hayden

Published online 4 October 2011 | Nature 478, 17 (2011) | doi:10.1038/478017a

Returning Results and Sharing Data

College or Funeral Is Mother's Wish Denied on DNA Results
By John Lauerman - May 14, 2012 12:01 AM ET
Bloomberg News



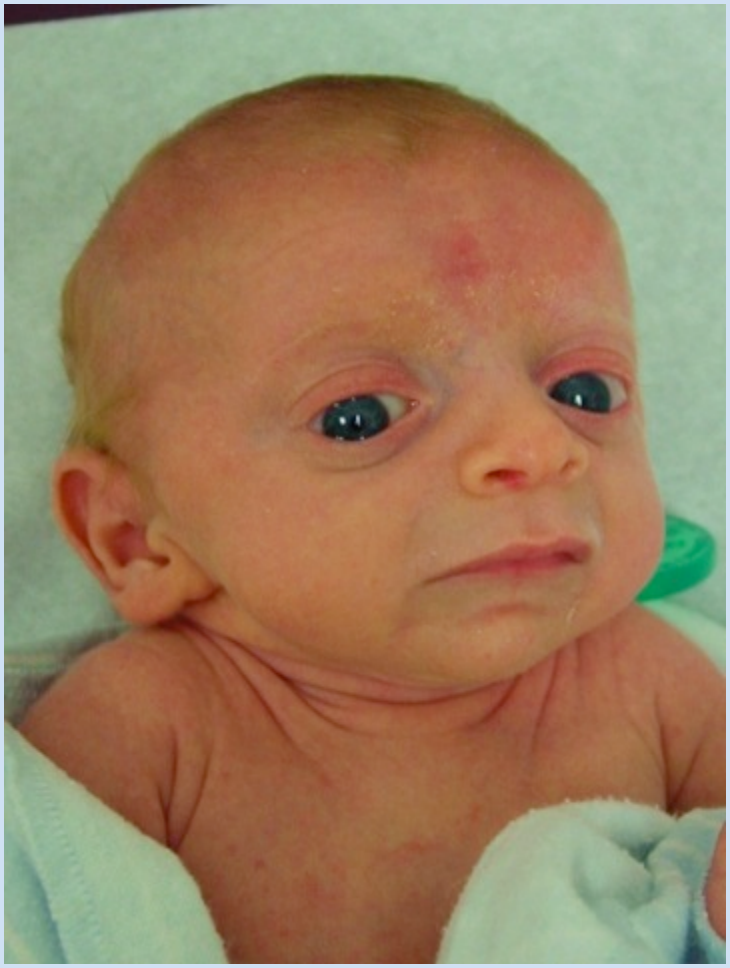
ARTICLE

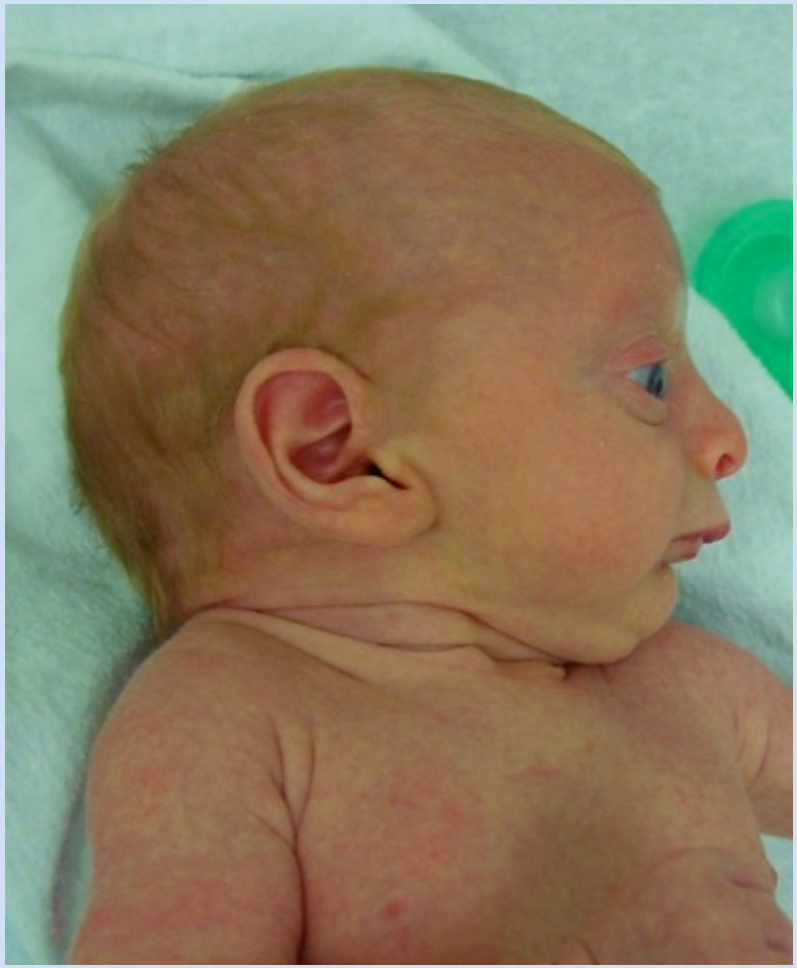
Using VAAST to Identify an X-Linked Disorder Resulting in Lethality in Male Infants Due to N-Terminal Acetyltransferase Deficiency

Alan F. Rope,[1] Kai Wang,[2,19] Rune Evjenth,[3] Jinchuan Xing,[4] Jennifer J. Johnston,[5] Jeffrey J. Swensen,[6,7] W. Evan Johnson,[8] Barry Moore,[4] Chad D. Huff,[4] Lynne M. Bird,[9] John C. Carey,[1] John M. Opitz,[1,4,6,10,11] Cathy A. Stevens,[12] Tao Jiang,[13,14] Christa Schank,[8] Heidi Deborah Fain,[15] Reid Robison,[15] Brian Dalley,[16] Steven Chin,[6] Sarah T. South,[1,7] Theodore J. Pysher,[6] Lynn B. Jorde,[4] Hakon Hakonarson,[2] Johan R. Lillehaug,[3] Leslie G. Biesecker,[5] Mark Yandell,[4] Thomas Arnesen,[3,17] and Gholson J. Lyon[15,18,20,*]

The American Journal of Human Genetics *89*, 1–16, July 15, 2011

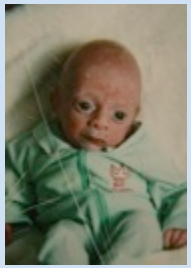
Using Next Gen Seq to figure out genetic basis of a New Disease

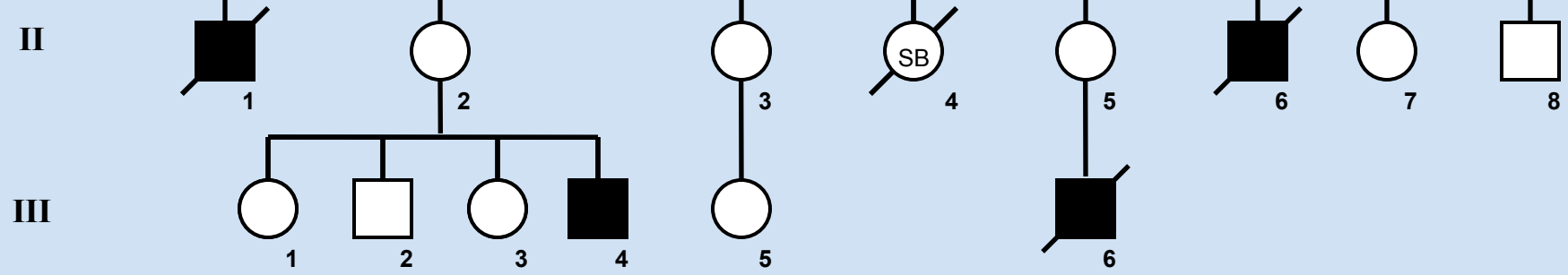


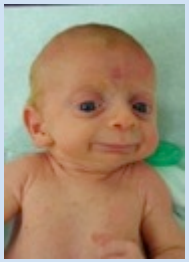


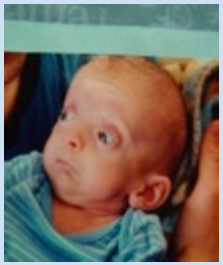
prominence of eyes, down-sloping palpebral fissures, thickened eyelids, large ears, beaking of nose, flared nares, hypoplastic nasal alae, short columella, protruding upper lip, micro-retrognathia

Family Pedigree





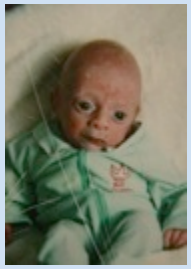


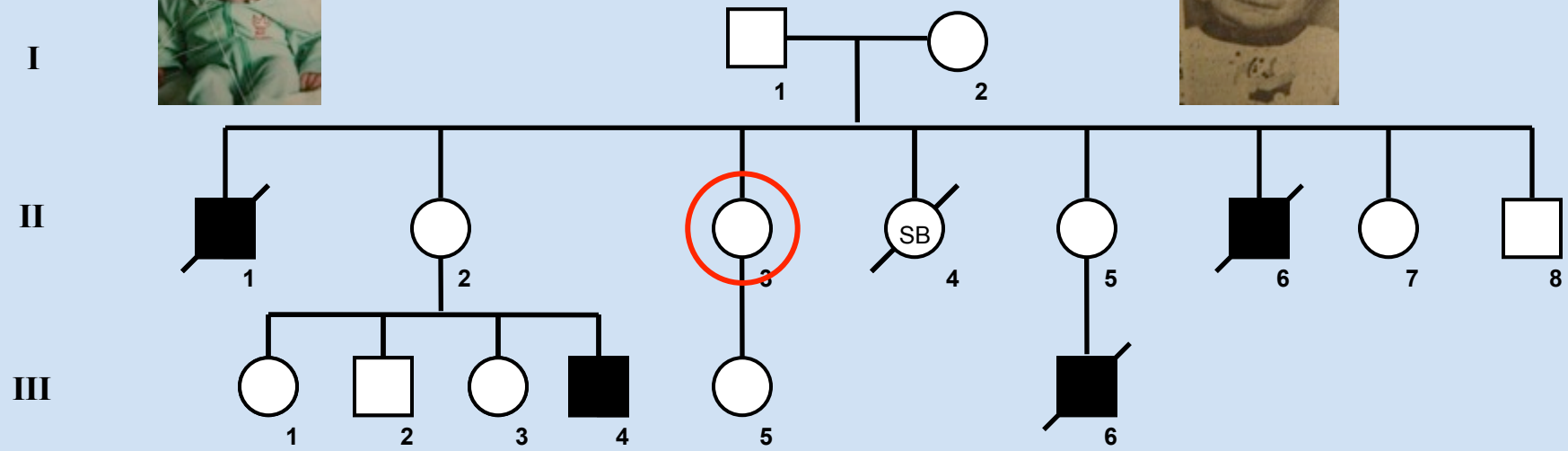


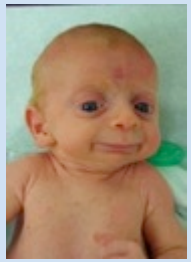
By November 2010, we had good functional data *in vitro* (bacterially expressed proteins) and *in vivo* (yeast, unpublished), leading me to believe we had identified the causative mutation.

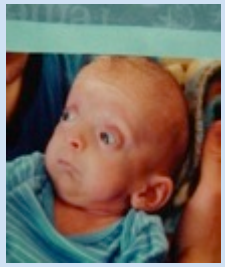
A new mother in the family informs me she is 4 months pregnant, with a boy!

The now pregnant mother-to-be is circled in red. Our Sanger Sequencing had shown her to be a carrier of the mutation.









BUT, as a researcher, I was naive and ignorant concerning the following question:

How do we give such research results back to research participants?

MAJOR ISSUES that I learned about

- I am a physician but not HER physician, therefore I had NOT entered into a “physician-patient contract” with her.

- This was not a “diagnostic test”. This was research, and not “CLIA-certified”. All Clinical Diagnostic Tests are regulated in America with the Clinical Laboratory Improvement Amendments act.

- How does one return research results to participants without breaking the law or doing something that might inadvertently harm the person?

- Please remember that CLIA was implemented to prevent people from being given wrong test results (due to poor quality).

Societal Issues

- Test tube babies are a success because the first baby born, Louise Brown, was fine and free of genetic defects.
- Gene Therapy was set back by >10 years due to the death of Jesse Geisinger and a disregard of rules and regulation by certain researchers.
- We have Nicholas Volcker as a shining example of success with WGS.
- But, we don't want to screw this up with some research lab giving back **incorrect** results to someone, leading to some calamitous outcome, such as someone thinking they have Huntington's mutation when they don't, and committing suicide.

Technically, clinical grade DNA testing currently means the following:

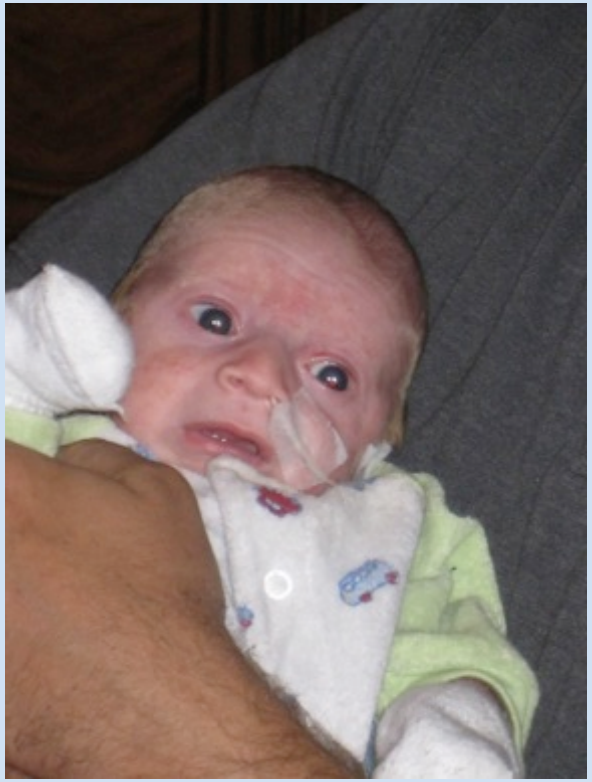
1) Blood or saliva collected with rigorous, automated sample tracking.

2) DNA isolated in a CLIA-certified facility.

3) Sequencing performed in a CLIA-certified facility.

4) Analysis performed with a CLIA-certified bioinformatics pipeline.

This is what should happen with any sample with possible return of results!!!



Many barriers in the way of developing a test at ARUP (genetic laboratory I was using in Utah) – in retrospect, should have tried GeneDx.

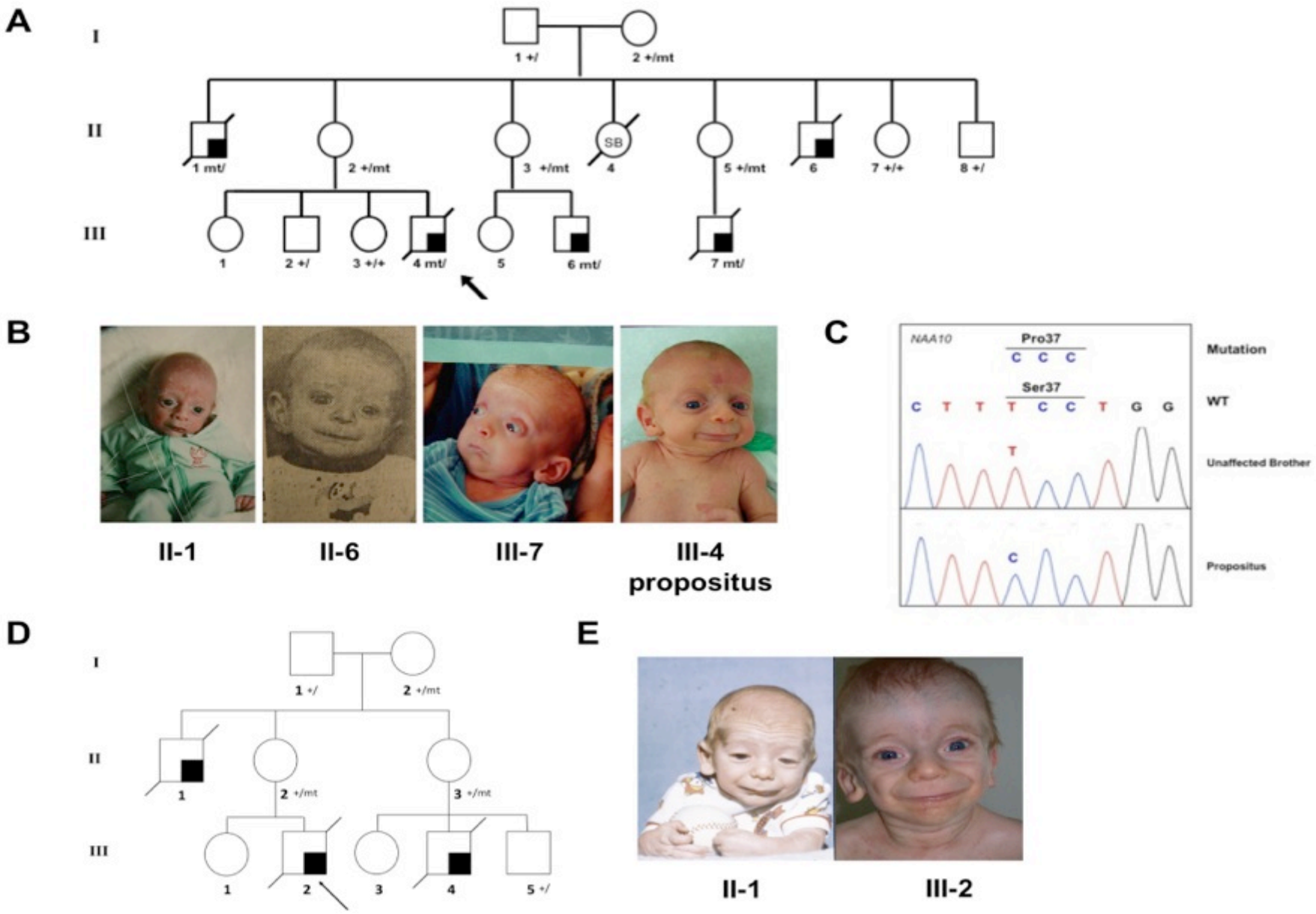
Mother four months pregnant Nov 2010

Baby born March 2011.

Affected with Disease.

He died June 2011, same week as publication of our paper in AJHG.

For several reasons, it is not clear anything would have changed even if she had received the result during pregnancy.


A
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Ser37
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Unaffected Brother
Propositus
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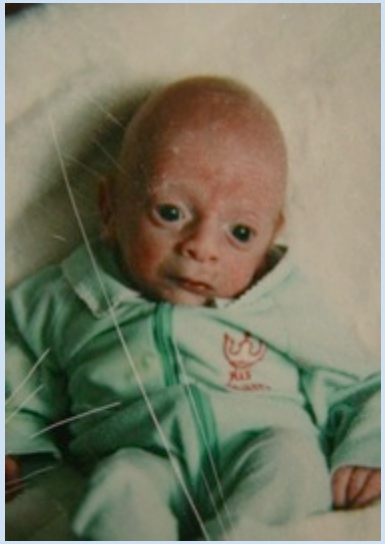
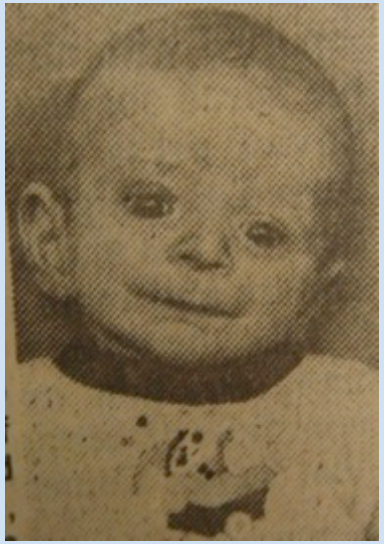
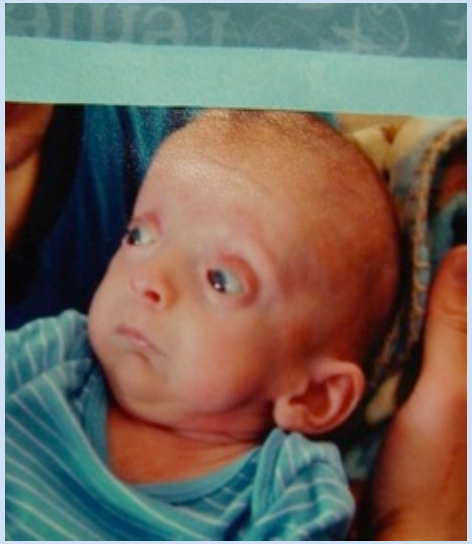
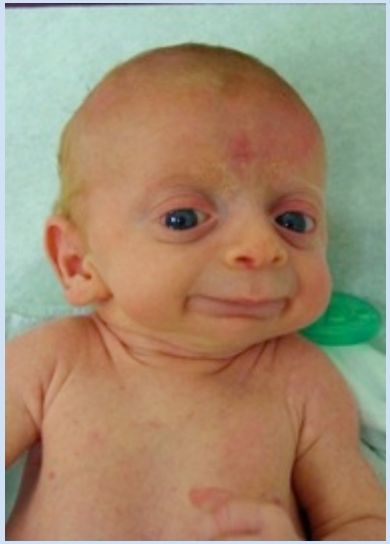
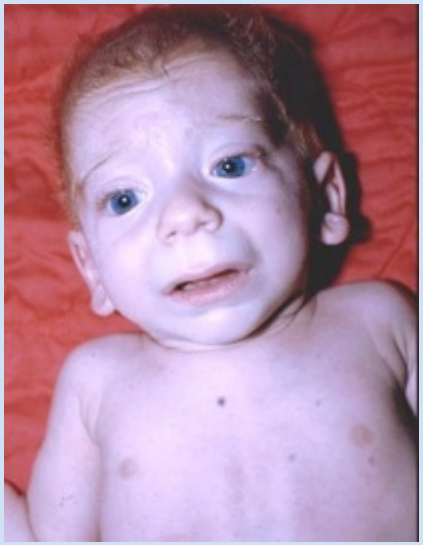
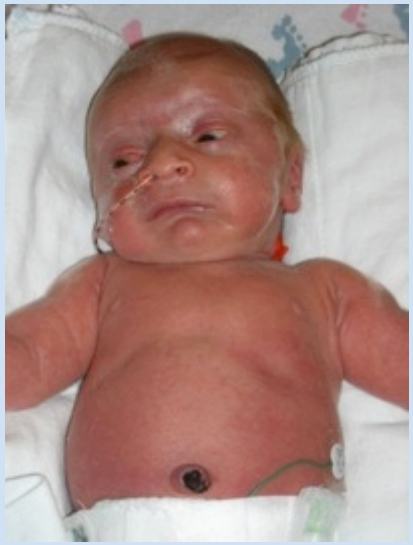
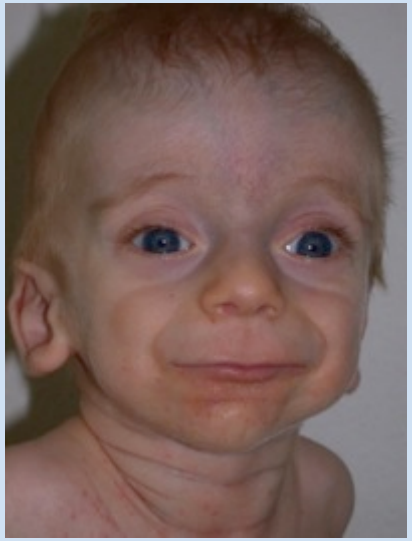
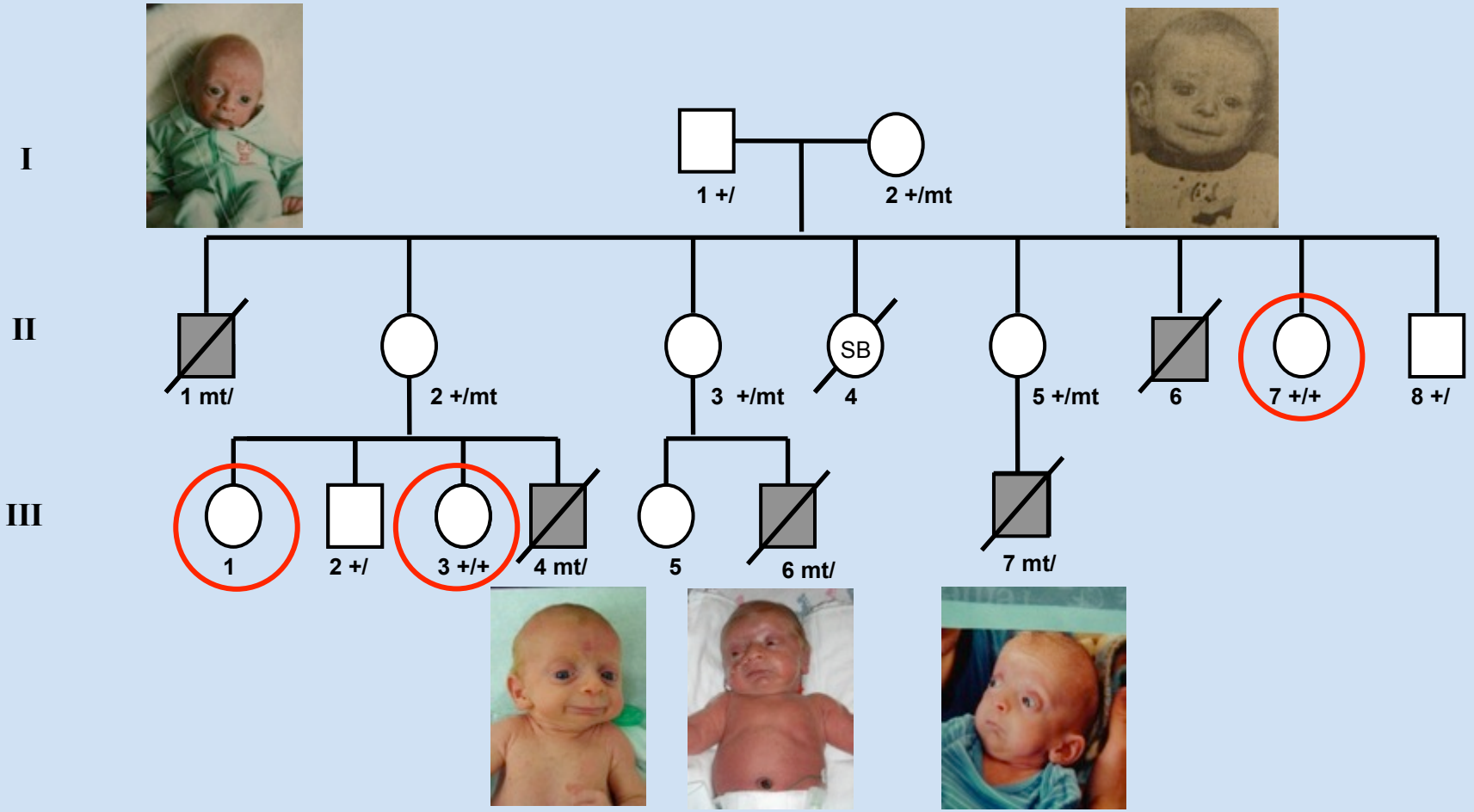
Ogden Syndrome, in honor of where the first family lives, in Ogden, Utah

What about the other women in the family? Are they carriers? Once again, this was “research”.



Results from Next Gen Seq requires both Analytic and Clinical Validity

- Analytical Validity: the test is accurate with high sensitivity and specificity.

- Clinical Validity: Given an accurate test result, what impact and/or outcome does this have on the person?

Analytical Validity of Exome and WGS?

Minimal Standard: exomes and genomes ought to be performed in a CLIA-certified environment for germline genomic DNA from live humans .

Easier said than done in academia, but some companies offer this now: Illumina, 23andMe, Ambry Genetics, and some academic places do offer this now: Baylor and WashU for exomes.

I do NOT think the FDA should get involved to regulate this, nor do the results have to go through a physician, i.e. DTC is fine as long as CLIA-certified.

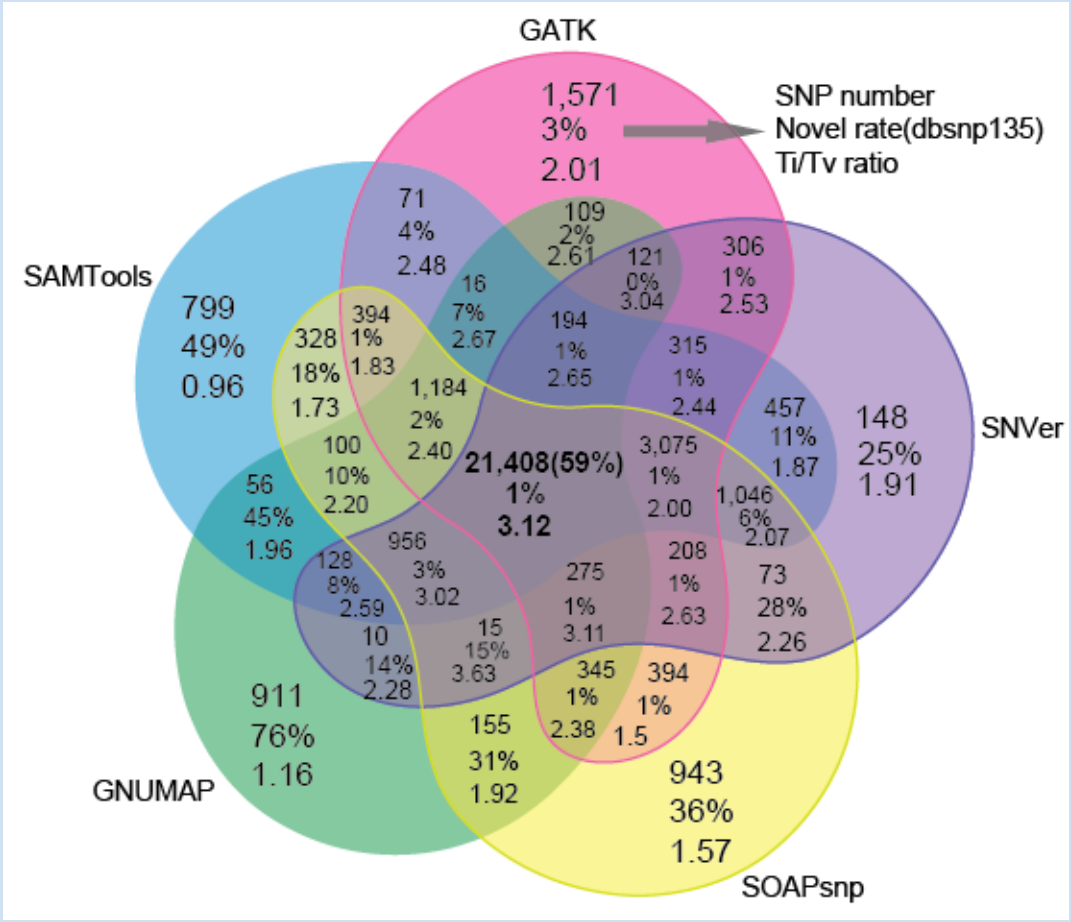
CLIA-certified exomes and WGS

- The CLIA-certified pipelines attempt to minimize false positives with increased stringency, but this results in many no-calls and other areas of uncertainty, which should be reported as No-Call Regions.
- BUT, this is ok, as minimizing false positives is very important in clinical medicine.

Optimizing Variant Calling in Exomes

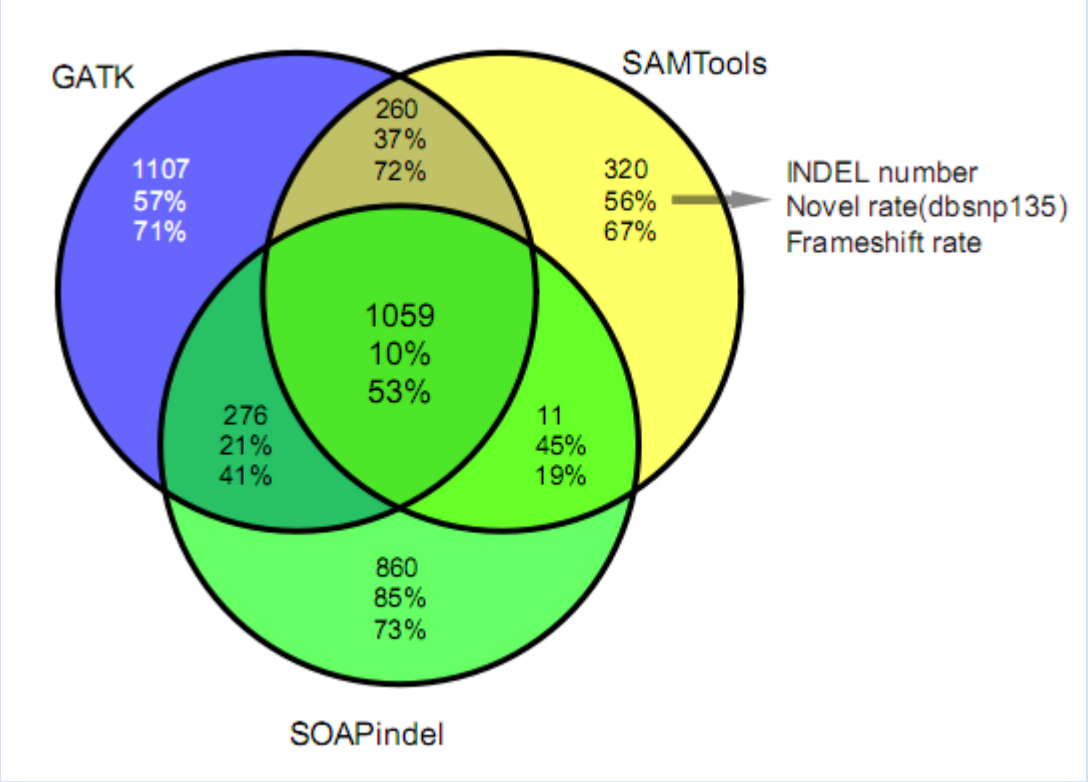
- Agilent v2 44 MB exome kit
- Illumina Hi-Seq for sequencing.
- Average coverage ~100-150x.
- Depth of sequencing of >80% of the target region with >20 reads or more per base pair.
- Comparing various pipelines for alignment and variant-calling.

SNV venn plot



Total SNP

INDEL venn plot



Total INDEL

Genomic Dark Matter: The reliability of short read mapping illustrated by the Genome Mappability Score

Hayan Lee[1,2*] and Michael C. Schatz [1,2]

[1]Department of Computer Science, Stony Brook University, Stony Brook, NY
[2]Simons Center for Quantitive Biology, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY

Bioinformatics Advance Access published June 4, 2012

- Genome Mappability Score (GMS) -- measure of the complexity of resequencing a genome = a weighted probability that any read could be unambiguously mapped to a given position, and thus measures the overall composition of the genome itself.
- Genome Mappability Analyzer (GMA) -- to compute the GMS of every position in a genome. Helps identify the 5-14% of the human, mouse, fly, and yeast genomes that are difficult to analyze with short reads.
- With BWA/SAMtools polymorphism discovery pipeline, discovery errors are dominated by false negatives, especially in regions with poor GMS. These errors are fundamental to the mapping process and cannot be overcome by increasing coverage.
- The GMS should be considered in every resequencing project to pinpoint the dark matter of the genome, including of known clinically relevant variations in these regions.

Hype and Genetic Determinism

GENOMICS

Noninvasive Whole-Genome Sequencing of a Human Fetus

Jacob O. Kitzman,[1]* Matthew W. Snyder,[1] Mario Ventura,[1,2] Alexandra P. Lewis,[1] Ruolan Qiu,[1] LaVone E. Simmons,[3] Hilary S. Gammill,[3,4] Craig E. Rubens,[5,6] Donna A. Santillan,[7] Jeffrey C. Murray,[8] Holly K. Tabor,[5,9] Michael J. Bamshad,[1,5] Evan E. Eichler,[1,10] Jay Shendure[1]*

- "The ability to noninvasively sequence a fetal genome to high accuracy and completeness will undoubtedly have profound implications for the future of prenatal genetic diagnostics."

- Yes, but this is NOT that study!

Actual Data

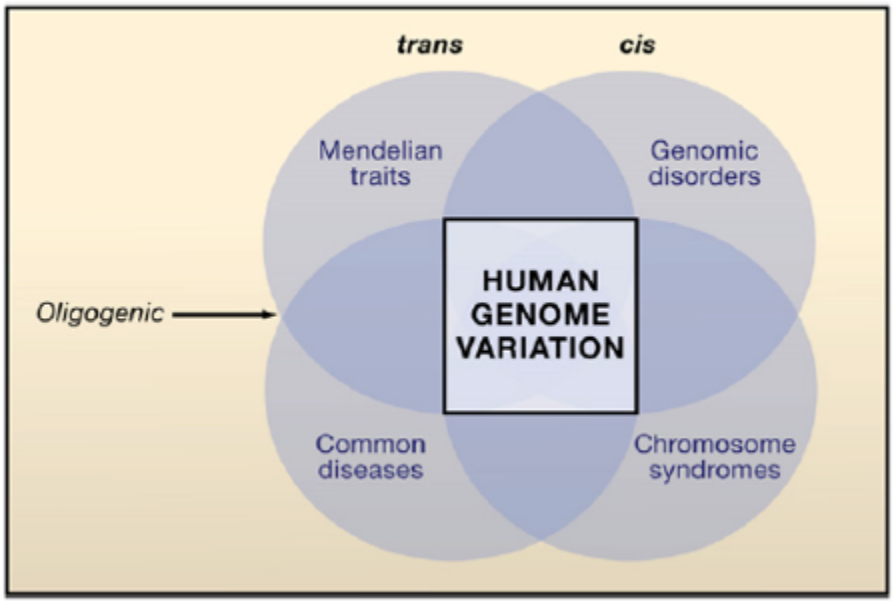
- "we found 2.5×10^7 candidate de novo sites, including 39 of the 44 true de novo sites. At baseline, this corresponds to sensitivity of 88.6% with a signal- to-noise ratio of 1-to-640,000"
- With other filters, they reduce number of "total positives" to 3884, of which 17 are true positives, from total known true positives of 44), so sensitivity= 38.6%.
- This is nowhere near accurate, or anything remotely close to a clinical grade test!

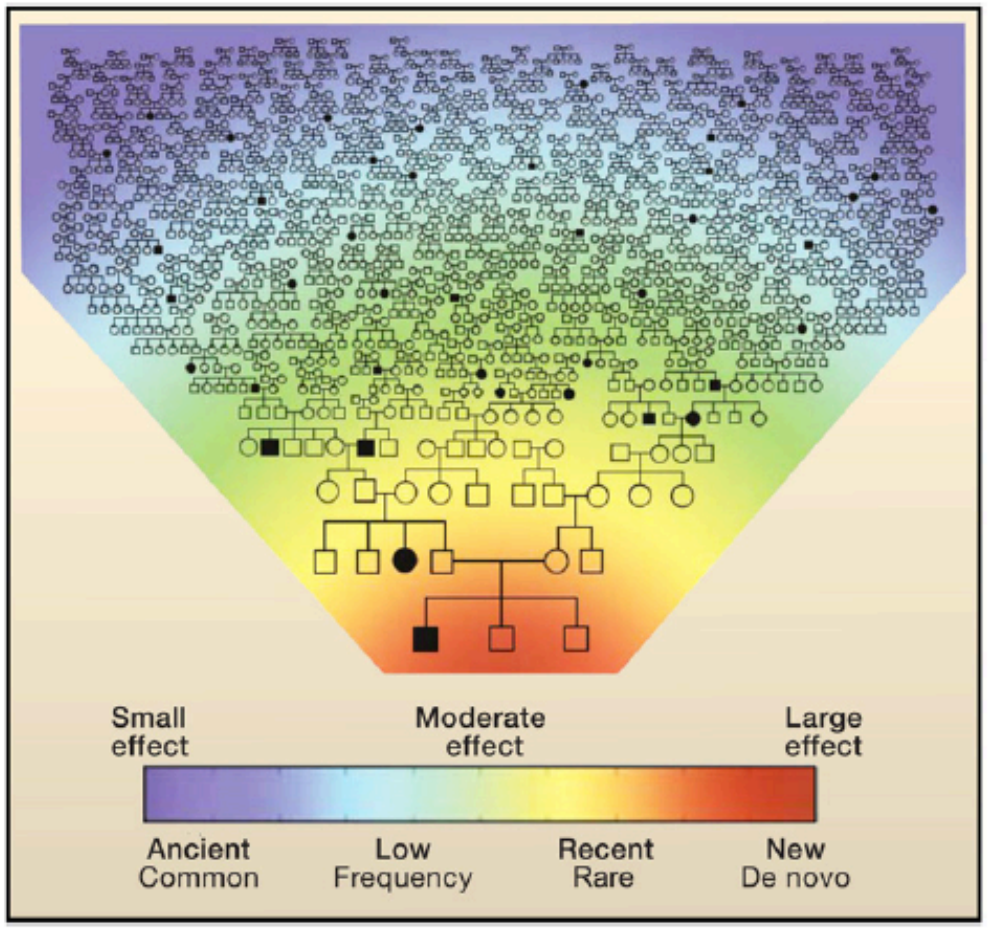
Clinical Validity?

This is SO complex that the only way forward is with a “networking of science” model.

Clan Genomics and the Complex Architecture of Human Disease

James R. Lupski,[1,2,3,*] John W. Belmont,[1,2] Eric Boerwinkle,[4,5] and Richard A. Gibbs[1,5,*]





Rare Variants – CNVs, SNVs, indels, etc… in Rare AND Common diseases

High Frequencies of De Novo CNVs in Bipolar Disorder and Schizophrenia

Dheeraj Malhotra,[1,2,22] Shane McCarthy,[22] Jacob J. Michaelson,[1,2] Vladimir Vacic,[15,22] Katherine E. Burdick,[23] Seungtai Yoon,[5,22] Sven Cichon,[10,11,12] Aiden Corvin,[17] Sydney Gary,[22] Elliot S. Gershon,[21] Michael Gill,[17] Maria Karayiorgou,[18] John R. Kelsoe,[2,4,20] Olga Krastoshevsky,[19] Verena Krause,[19] Ellen Leibenluft,[7] Deborah L. Levy,[19] Vladimir Makarov,[5,22] Abhishek Bhandari,[1,2,22] Anil K. Malhotra,[6] Francis J. McMahon,[14] Markus M. Nöthen,[10,11,16] James B. Potash,[8] Marcella Rietschel,[13] Thomas G. Schulze,[9] and Jonathan Sebat[1,2,3,4,22,*]

Deep resequencing of GWAS loci identifies independent rare variants associated with inflammatory bowel disease

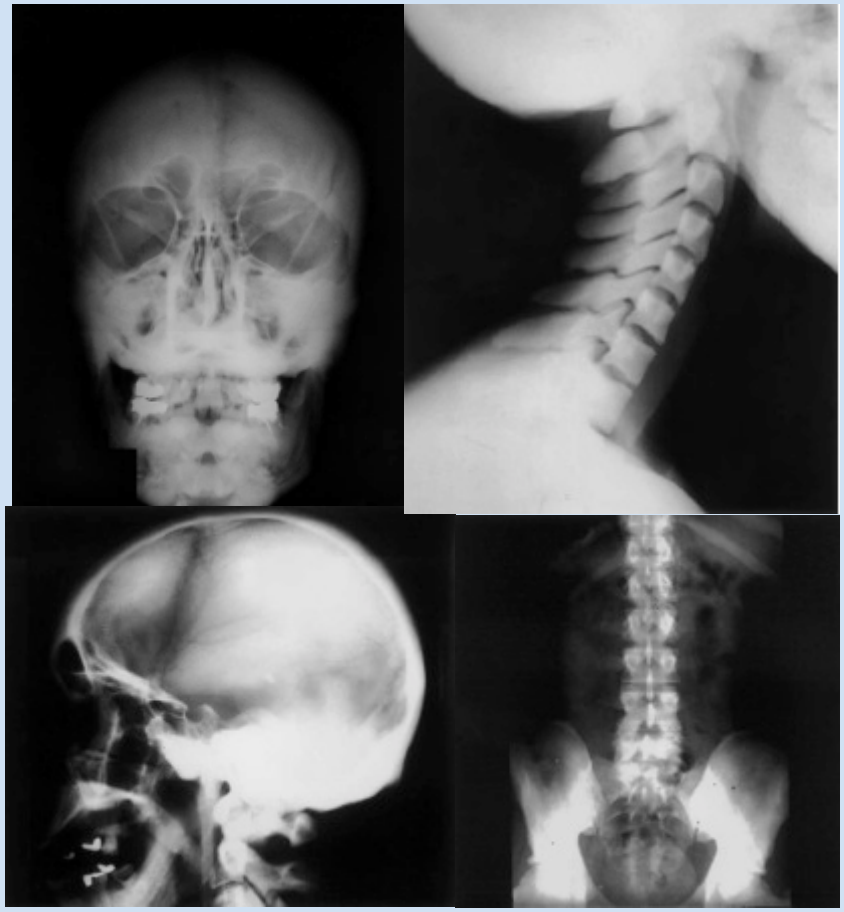
Manuel A Rivas[1–3], Mélissa Beaudoin[4,23], Agnes Gardet[5,23], Christine Stevens[2,23], Yashoda Sharma[6], Clarence K Zhang[6], Gabrielle Boucher[4], Stephan Ripke[1,2], David Ellinghaus[7], Noel Burtt[2], Tim Fennell[2], Andrew Kirby[1,2], Anna Latiano[8], Philippe Goyette[4], Todd Green[2], Jonas Halfvarson[9], Talin Haritunians[10], Joshua M Korn[2], Finny Kuruvilla[2,11], Caroline Lagacé[4], Benjamin Neale[1,2], Ken Sin Lo[4], Phil Schumm[12], Leif Törkvist[13], National Institute of Diabetes and Digestive Kidney Diseases Inflammatory Bowel Disease Genetics Consortium (NIDDK IBDGC)[14], United Kingdom Inflammatory Bowel Disease Genetics Consortium[14], International Inflammatory Bowel Disease Genetics Consortium[14], Marla C Dubinsky[15], Steven R Brant[16,17], Mark S Silverberg[18], Richard H Duerr[19,20], David Altshuler[1,2], Stacey Gabriel[2], Guillaume Lettre[4], Andre Franke[7], Mauro D'Amato[21], Dermot P B McGovern[10,22], Judy H Cho[6], John D Rioux[4], Ramnik J Xavier[1,2,5] & Mark J Daly[1,2]

Evolution and Functional Impact of Rare Coding Variation from Deep Sequencing of Human Exomes

Jacob A. Tennessen,[1*] Abigail W. Bigham,[2*†] Timothy D. O'Connor,[1*] Wenqing Fu,[1] Eimear E. Kenny,[3] Simon Gravel,[3] Sean McGee,[1] Ron Do,[4,5] Xiaoming Liu,[6] Goo Jun,[7] Hyun Min Kang,[7] Daniel Jordan,[8] Suzanne M. Leal,[9] Stacey Gabriel,[4] Mark J. Rieder,[1] Goncalo Abecasis,[7] David Altshuler,[4] Deborah A. Nickerson,[1] Eric Boerwinkle,[6,10] Shamil Sunyaev,[4,8] Carlos D. Bustamante,[3] Michael J. Bamshad,[1,2‡] Joshua M. Akey,[1‡] Broad GO, Seattle GO, on behalf of the NHLBI Exome Sequencing Project

“Superpower” mutations???

Myostatin mutation
Exon 2 allele P198A



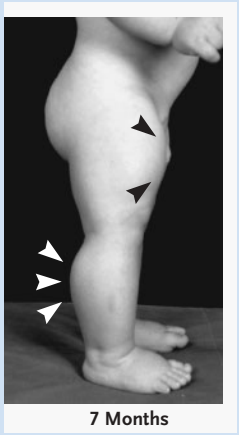
LRP5 mutation
D111Y, G171R, A214T, A214V, A242T, and T253I

**Thanks to George Church for discussions on this.

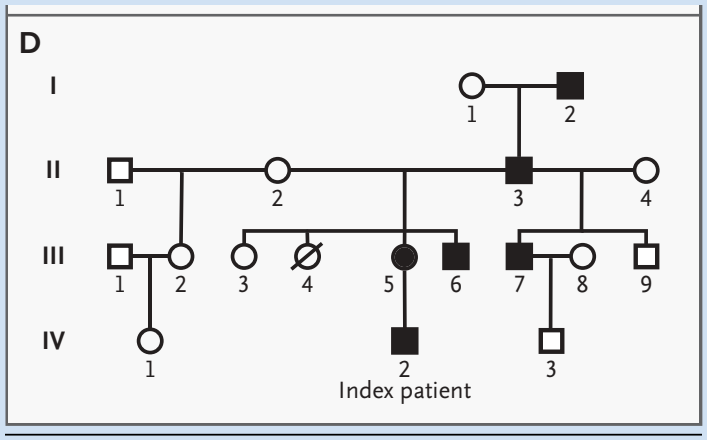
Myostatin Mutation Associated with Gross Muscle Hypertrophy in a Child

Markus Schuelke, M.D., Kathryn R. Wagner, M.D., Ph.D., Leslie E. Stolz, Ph.D., Christoph Hübner, M.D., Thomas Riebel, M.D., Wolfgang Kömen, M.D., Thomas Braun, M.D., Ph.D., James F. Tobin, Ph.D., and Se-Jin Lee, M.D., Ph.D.

N ENGL J MED 350;26 WWW.NEJM.ORG JUNE 24, 2004



7 Months



Liam is homozygous for the mutation.

Another example: Liam Hoekstra, known as the world's strongest toddler at age 3, has a condition called myostatin-related muscle hypertrophy which results in increased muscle mass and reduced body fat. Myostatin-related muscle hypertrophy, or muscle enlargement, is an extremely rare genetic condition. – How rare???

http://videos.disabled-world.com/video/159/liam-hoekstra-strongest-boy-in

Belgian Blue is a breed of beef cattle from Belgium. The Belgian Blue has a natural mutation in the myostatin gene which codes for the protein, myostatin.

http://en.wikipedia.org/wiki/Belgian_Blue

A Mutation in the Myostatin Gene Increases Muscle Mass and Enhances Racing Performance in Heterozygote Dogs

Dana S. Mosher[1], Pascale Quignon[1], Carlos D. Bustamante[2], Nathan B. Sutter[1], Cathryn S. Mellersh[3], Heidi G. Parker[1], Elaine A. Ostrander[1*]

1 National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, United States of America, **2** Department of Biological Statistics and Computational Biology, Cornell University, Ithaca, New York, United States of America, **3** Animal Health Trust, Center for Preventive Medicine, Newmarket, United Kingdom

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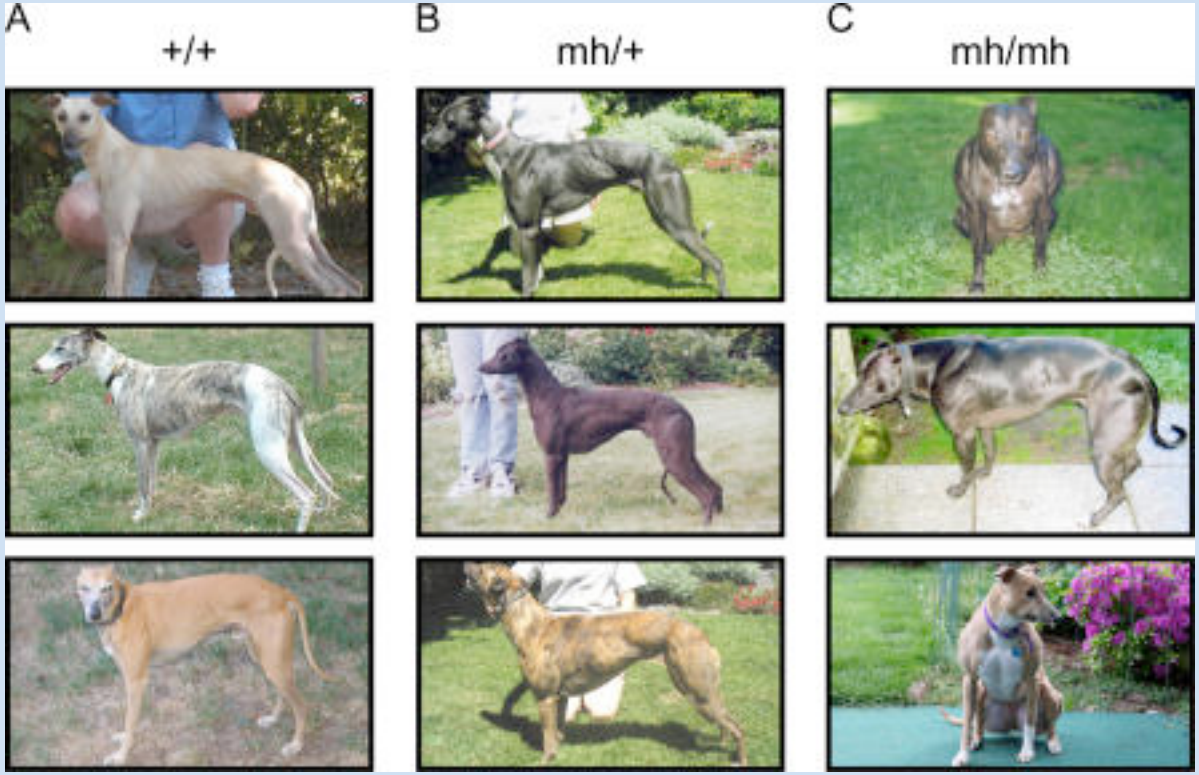


Penetrance and Expressivity

- We do not really know the penetrance or expressivity of ANY mutations in **humans**, as we have not systematically sequenced or karyotyped any genetic alteration in **MILLIONS** of people, nor categorized into ethnic classes, i.e. clans.

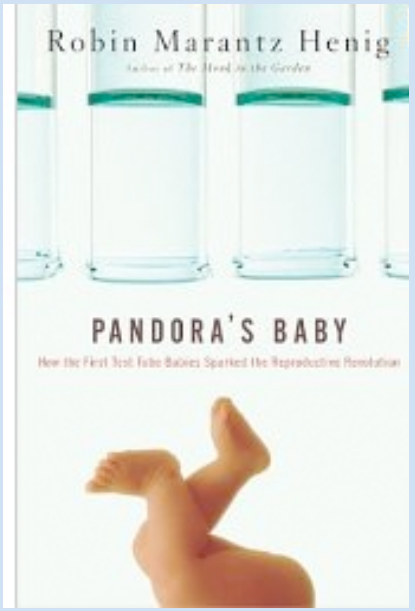
- There is a **MAJOR** clash of world-views, i.e. does genetics drive outcome predominately, or are the results modified substantially by environment? i.e. is there really such a thing as genetic determinism for **MANY** mutations?

For now, more effort should be placed on the following:

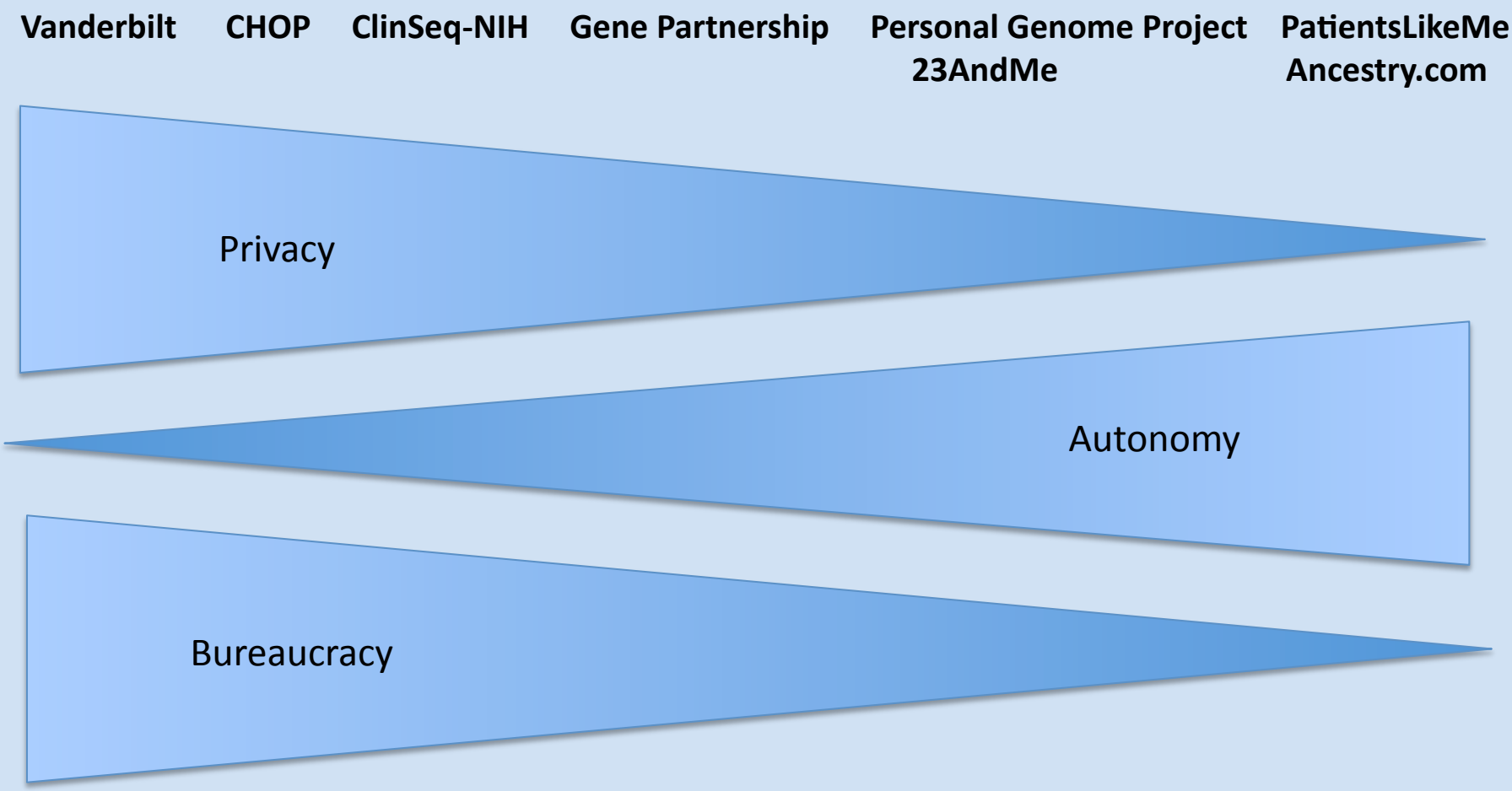
- Rare, highly penetrant mutations running in families, with cascade carrier testing.
- The genomic background is much more constant in families.
- The environmental background is sometimes more constant in families.
- This allows one to know much more about issues with penetrance of rare variants in these families.

Pandora's Baby

- "It seemed to boil down to a struggle between two competing impulses: the creative drive to understand nature versus the conservative drive to impose limits and maintain the status quo."



Autonomy vs. Privacy vs. Bureaucracy



Killing Innovation with Bureaucracy

- These are NOT evil people, but rather very cautious people.
- Endless meetings at FDA and CMS, which takes substantial time.
- People become used to the system within which they function, making it very difficult for them to envision changing the status quo.

An alternate universe

- Genomes sequenced by companies and academics with the minimal standards in place (i.e. CLIA in America).
- All data, including variant lists, added to "the cloud" that consumers can access.
- Consumers can go back and repeatedly look at their own genome.
- Consumers own and manage these data, and they can pay anyone they like to help them interpret the data for them.
- These are CONSUMERS, not patients, and we need to **move away from paternalistic medicine**.
- I am concerned that regulation requiring delivery of genetic data by "physicians" will choke off and kill the genomic revolution and individualized medicine.

One Solution

- Require that all **initial** germline exome and whole genome sequencing in live humans be performed in a CLIA-certified or other clinical-grade manner.
- I pray and hope that industry will collate and distribute mutations in an international human variation database, allowing for calculation of penetrance and extensive burden testing.
- CLIA-certified (clinical grade) sequencing up front allows return of all data, including rare, highly penetrant mutations, to families, facilitating carrier screening and counseling.
- Require return of genomic data to participants, allowing the participants to distribute and "crowd-source" their own data.
- Government should divert funds toward a 10 to 100 fold increase for genetic counselors, so that we can have compassionate engagement with families.

Ancestry.com *meets* 23andMe *meets* PatientsLikeMe *meets* Illumina?

Clinical Validity with Worldwide Human Genetic Variation "database"?

PatientsLikeMe

Need to change the Tenor of the debate

- Evolving ethics.
- Sequencing live humans without method in place to return results, perhaps no longer acceptable?
- These are human beings, not “patients”. PLEASE get rid of this paternalism!!! And get rid of this term “patient”!
- “What kind of work deemed as accepted today will be denounced by future generations? The question is one that all researchers should bear in mind, because history may judge them more harshly than their peers do.”
  -Nature editorial, February 9, 2012

Acknowledgments

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Reid Robison
Edwin Nyambi
Matt Adams
Edwin Nyambi

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Rune Evjenth
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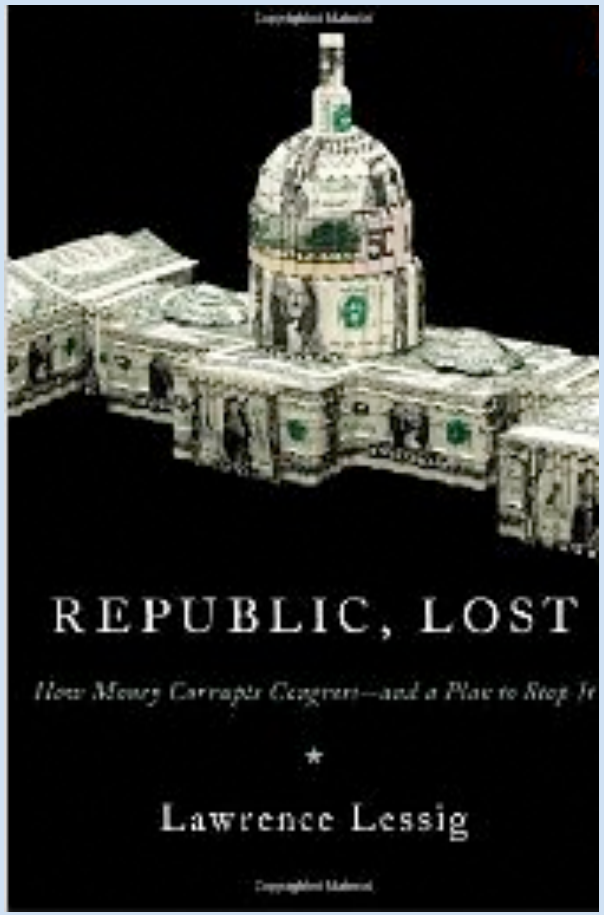
Kai Wang
Zhi Wei
Lifeng Tian
Hakon Hakonarson

Michael Schatz
Giuseppe Narzisi

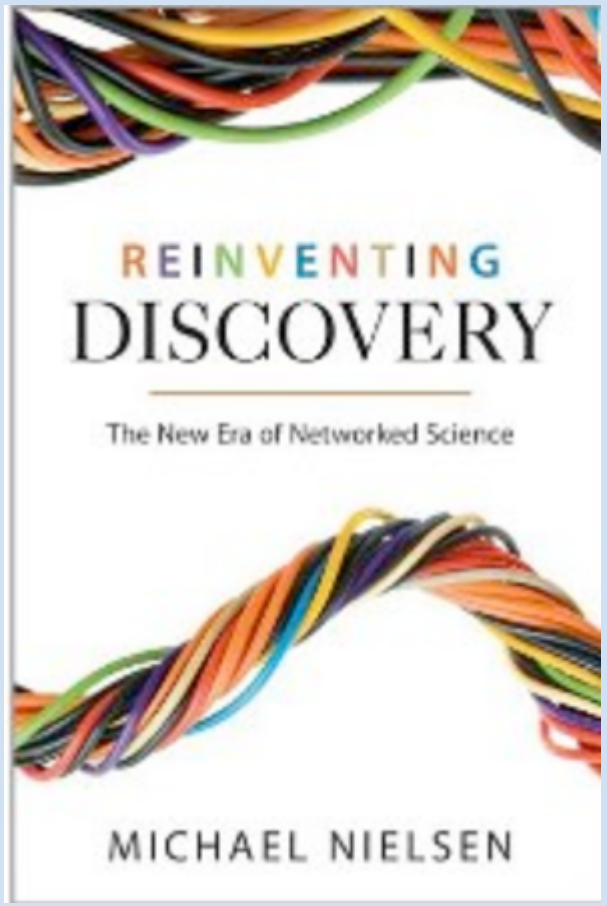
Tao Jiang
Jun Wang

our study families

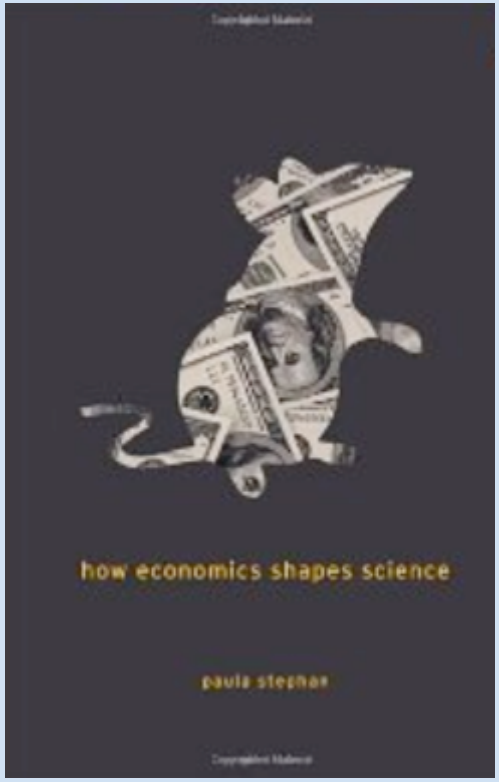
References

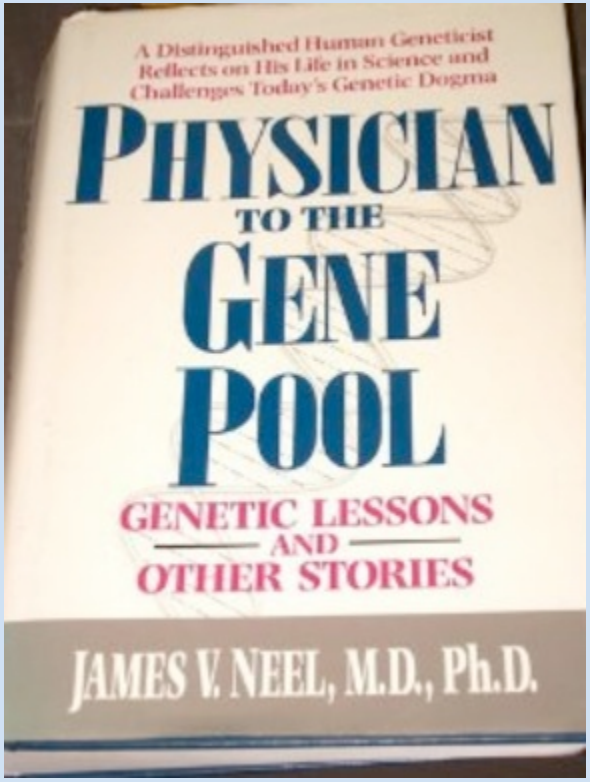

REPUBLIC, LOST
Lawrence Lessig

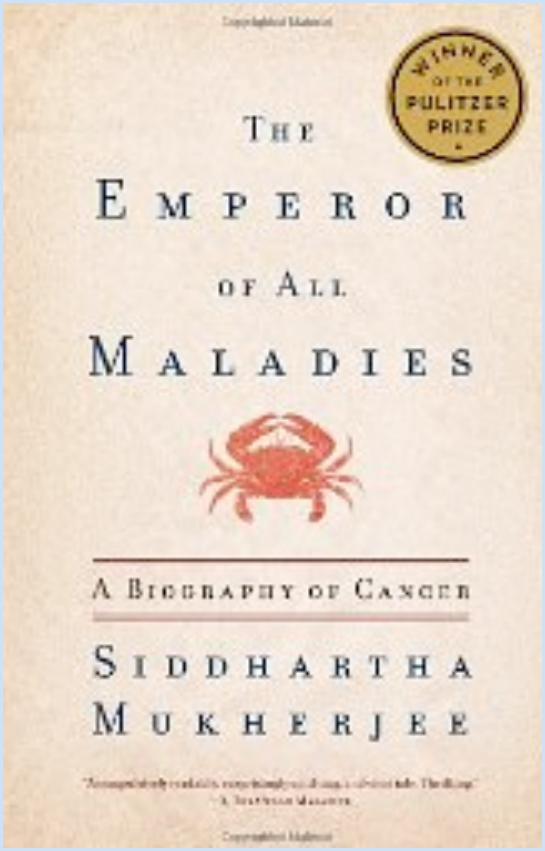

The Creative Destruction of
MEDICINE
HOW THE DIGITAL REVOLUTION WILL CREATE BETTER HEALTH CARE
ERIC TOPOL, M.D.


REINVENTING
DISCOVERY
The New Era of Networked Science
MICHAEL NIELSEN

References cont…







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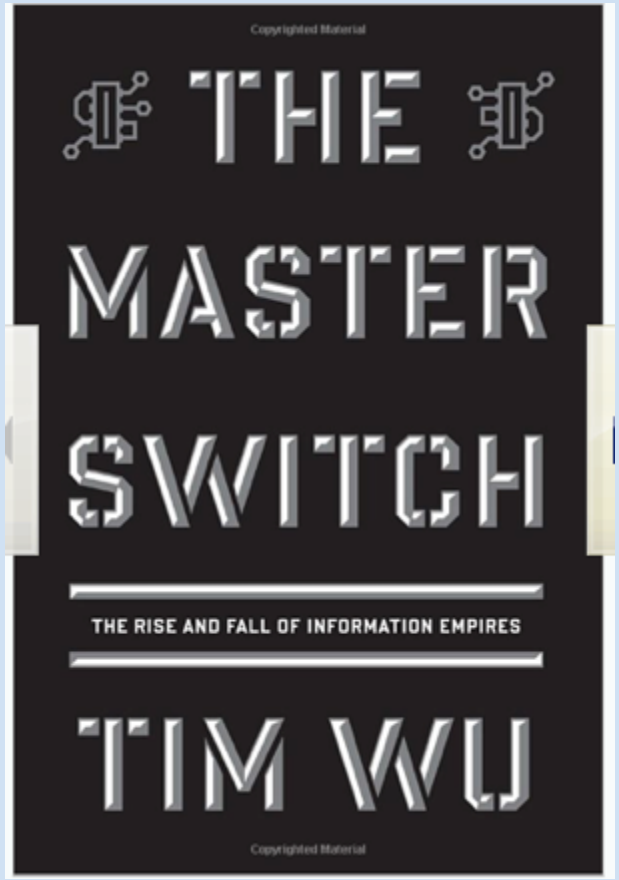

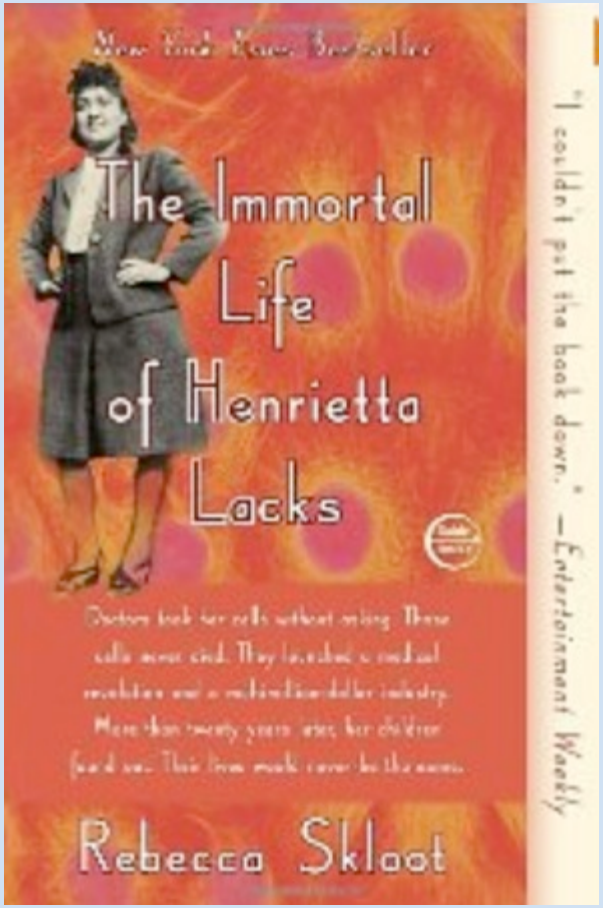

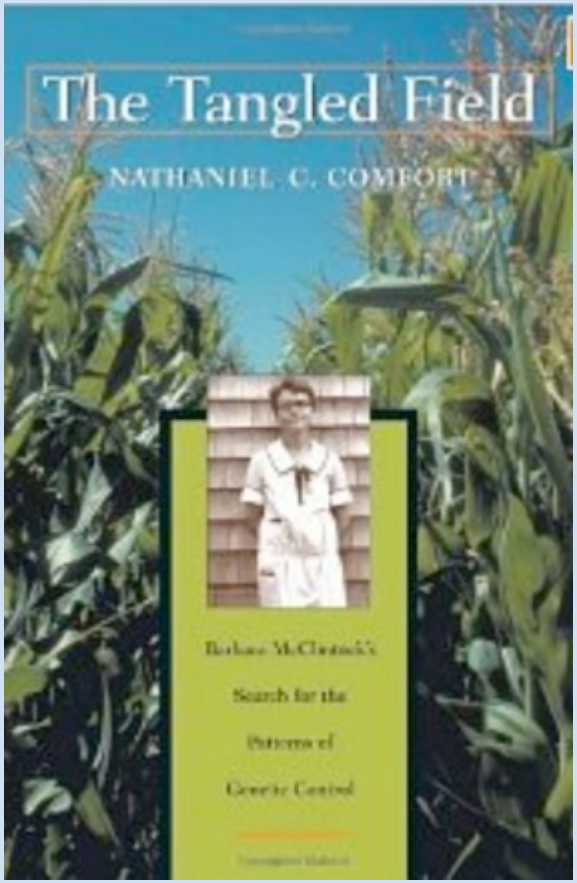

References

- **@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.