Are We Ready for the $1000 Genome?

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Disclosures

Only academic self-interest
Unfortunately
Are We Ready for the $1000 Genome and Its Ethical Implications?

• Evolution of genomic and genetic technologies
• Current applications
• Some Ethical, Legal, Social & Economic (ELSI) considerations

Cytogenetics: The FIRST whole genome technology

• When I was born, I had 48 chromosomes
• In 1956, Tijo and Levan correctly deduced that I had only 46
Cytogenetics:
The FIRST whole genome technology

- In 1959, Lejune associated an extra G-group chromosome with “mongolism”, now called Down syndrome

Cytogenetics:
The FIRST whole genome technology!

- In 1968, Caspersson and colleagues introduced banding of chromosomes
- Permitted definitive assignment of chromosomes
Key Features of G-banded Karyotype

• First whole-genome technology to detect clinically significant copy number imbalances (deletions, duplications)
• Benign polymorphisms (copy number variants -- CNVs) identified by empiric experience over a number of years

Clinical significance of imbalance in proband sometimes requires parental studies to determine if pathogenic or benign (de novo taken as evidence likely pathogenic)

• But, limited resolution (5-10 Mb), variable quality and subjective interpretation

The “Gold Standard” karyotype became tarnished
“During these 22 months the number of observations obtained in many laboratories is so vast that at least 23 different aberrations have been collected. At the present rate of about a syndrome a month, the task of a reviewer becomes exceedingly difficult.”

Stated 22 months after the discovery of the first human chromosome abnormality, trisomy 21.

40 Years Later: Cytogenetics ➔ Cytogenomics


Consensus Statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies

Where We Were in 1990

Where We Have Come

December 1998
- 10,000 phenotypes identified
August 2010
- >20,000 loci identified
The Human Genome Project

• Begun in 1990, $3 billion over 15 years
• First draft in 2000
• A government project under budget and ahead of schedule
Venter-led Sequencing: 1995

- *H. influenzae*
- First complete sequence of a free-living organism by The Institute for Genomic Research
- 1,830,140 base pairs
- Cost $900,000—$1.5 million inflation-adjusted
- Consumed a year

Venter-led Sequencing: 1995

- *H. influenzae*
- Today can be sequenced in 24 hours for $150, a thousand-fold decrease
Venter-led Human Genome Project

- The private approach: shotgun sequencing by Celera Genomics
- Cost ~ $100 million

Sequencing a Genome in 2005 Required a ‘Farm’ of Sequencers
Celera’s Human Genome Project = Craig Venter’s Personal Genome

- Some of the sequences in Venter's genome are associated with wet earwax, increased risk of antisocial behavior, Alzheimer disease and cardiovascular diseases


Your Personal Genome
James D. Watson

- 7.4x redundancy in 2 months
- **Cost ~ $1 million**
Your Personal Genome
James D. Watson

• Watson permitted his entire genome sequence to be published...
• ...except for apoE, which specifies the risk of Alzheimer disease

Personalized Genomics—to the Extreme

Wall Street Journal
1 Oct 2010

Anne West, 17 y/o, is analyzing all 3.2 billion basepairs of her genome
The sequence was a gift from her father and cost $40,000
She entered the data in Excel and started looking
“I’m finding it a bit of a slog.”
Personalized Genomics—to the Extreme

The family became interested in genetics after several members developed blood clots in their legs. They could have saved a lot of time and money by focusing on the several genes known to predispose to clotting disorders. Indeed, there is a mutation in Factor V.

The family history remains the cheapest genetic test today!

2010: The Costs of Sequencing Have Plummeted

Baseline information: Cost of genome sequencing compared with Moore's law for computers.
Where We Have Come

The Cause of Many “Simple” Mendelian Disorders Still Has Not Been Discovered: Charcot-Marie Tooth Disease

Richard Gibbs & James Lupski
Baylor Genome Center
Many different genes can cause CMT, but none found in Lupski
Charcot-Marie Tooth Disease: Solved by Whole Genome Sequencing


Whole Genome Sequencing: A Lot of Data!

One zettabyte (ZB) =
1,000,000,000,000,000,000,000 bytes (10²¹ bytes)

From 11,000 BCE→2003, we produced 0.001 ZB
2009 the World Wide Web = 0.5 ZB
2012 = 2.7 ZB
2020 we will produce 35 ZB/year
Whole Genome Sequencing: A Lot of Data!

Stars in the Milky Way = $2 \times 10^{11}$

One whole genome sequence (WGS) = $6.4 \times 10^9$ bytes

The Milky Way = 31 genomes

Whole Genome Sequencing: A Lot of Data!
Saved Not on a CD, ? a PC, or ? the cloud
Whole Genome Sequencing: A Lot of Data! Or Never Saved at All

- When sequencing is cheap enough (? $100), the data never have to be saved at all.
- Simply re-sequence whenever a clinical issue arises.
- A way to protect confidentiality.
- But counter to the notion of using the electronic health record to save data and re-interpret.

Speaking of Costs
Major Disappointment with Applying the Results of the Human Genome Project

“A Decade Later, Genetic Map Yields Few New Cures”
Nicholas Wade
New York Times, June 12, 2010

“The Failed Promise of Genomics”
Matt Ridley
Wall Street Journal, October 9-10, 2010

“Expectations Exceed Understanding in Unraveling the Genome”
W. Gregory Feero, MD, PhD
ACP Internist, September, 2010

Genetic Testing
A Major Paradox

Most health care professionals and virtually all consumers view ‘genetic testing’ as the most sensitive and specific type of testing possible
– Looking at as little as one nucleotide out of 6.4 billion
Genetic Testing
A Major Paradox

We have been brainwashed into believing that (epigenetics aside) genes determine our fate. Afterall...

Yet many genetic test results, even from the most reputable academic and commercial labs result in considerable uncertainty.
Genetic Testing
Uncertainty

• The result has not been seen before, so no genotype-phenotype correlation exists
• The ‘mutation’ may not alter the gene product in an important way, or in any way
• Even ‘mutations’ that do not alter the protein can be harmful
• DNA changes of unclear importance need to be explored in relatives

Current Costs of Genetic Testing

Hypertrophic cardiomyopathy panel = $3,200
Dilated cardiomyopathy panel = $3,850
either takes 8-12 weeks

Whole exome sequencing = $7,000
takes 15 weeks
Individual Data

The whole genome sequence of every person will reveal:
• 60-100 changes predicted to be loss of function mutations
• 500-800 missense mutations
• False positives
• False negatives
• Uninterruptable results

Individual Data

...and the interpretation of the data will change over time.
The End Game...Maybe

Where We Were Four Years Ago

• Stephen Quake, DPhil
• Co-chair, Department of Bioengineering, Stanford
• Co-developed a means of whole genome sequencing for $50K
Where We Were Four Years Ago

The rest of the story...
It took 30 colleagues a month of full-time work to analyze the sequence.
The cost...many-fold greater than $50,000.
"You have to have a strong stomach when you look at your own genome" Quake concluded.
Where We Are Today

The rest of the story...Quake has

• Increased risk for myocardial infarction, type 2 diabetes, and some cancers
• Resistance to a common anti-platelet drug
• Enhanced responsiveness to statins
• Many variants of unknown significance
Advice to Quake

Because of the family history of sudden cardiac death and responsiveness to lipid-lowering drugs, he was advised to begin taking a statin

Quake’s Response

He is still thinking about it
What Does the Future Hold?

The simple availability of technology does not insure it will be used appropriately

Clinical Sequencing Exploratory Research

- 5 UO1’s from NHGRI
- CHOP + Penn (Krantz & Spinner, PIs) studying use of WES for 4 pediatric disorders
- Current methods for assessing the importance of a given variant requires 1-2 hrs
  - Filtering of the data is crucial
- Bernhardt & Pyeritz leading the ELSI core
  - Studying how consent is obtained, what is retained over time, how parents (and patients) respond to results (both for the primary diagnosis and incidental findings)
The Burden of Uncertainty Will Be Greater with Whole Exome or Genome Sequencing

• Many alterations that have no direct relevance for the clinical indication that led to the test, but of likely or potential relevance to the patient, will be found—the dreaded ‘incidentalome’.

Kohane et al. JAMA 2006;296:2122-5.

Incidental (Secondary) Findings

Am College of Medical Genetics recommended that pathogenic results of 56 genes be reported even if the physician and the patient did not request them.

Do People Want Access to Their Genotypes & Genomes and Why?

Invention of the Year

*Time*, 2008

The Retail DNA Test
Direct-to-Consumer Genotyping

Navigenics
Coriell Personalized Medicine Collaborative
23andMe

Co-founded by Linda Avey and Anne Wojcicki (then-wife of Sergey Brin)
“Knowledge is Power—Take Hold”

Not clear if or how the direct-to-consumer business model will survive.

Do People Want Access to Their Genotypes & Genomes and Why?

We surveyed 369 participants in the Coriell Personalized Medicine Collaborative
They were motivated by
curiosity
disease risk
improve their own health
92% intended to share results with their PCPs

Do PCPs Want Access to Patient Genotypes?

We surveyed 502 PCPs
50% order a ‘genetic test’ once a month
16% order once a week or more
165/361 order BRCA mutation analysis
Next most frequent are hemochromatosis and carrier screening


Do PCPs Want Access to Patient Genotypes & Genomes?

7% of PCPs had ever seen a DTC report
<50% feel prepared to incorporate genotypic information into health care
Most do not think DTC information would be useful (except pharmacogenetic profiles)
But most would include DTC genetic information in the health record if asked

Consumer Empowerment

• Eighth, all of these concerns are magnified by direct-to-consumer (DTC) genetic testing.
  – Consumers are likely to bring their results to their primary healthcare provider.
  – If the results are inserted in the medical record, does that incur a responsibility to recontact?

Whole Genome/Exome Sequencing
Practical Issues

WES of 250 patients with undiagnosed conditions likely to be primarily genetic discovered the specific cause in 62—a yield of ~25%.

All the patients had undergone extensive (and expensive) testing before WES.

126/129 claims for reimbursement of WES were paid.

Whole Genome/Exome Sequencing
Ethical Issues

Individuals’ privacy values should be respected
Concern for those who cannot represent themselves
Informed consent
Burdens should not fall on any one group; benefits should be broadly shared
Is there a duty to recontact?

Whole Genome/Exome Sequencing
Current Protections

No comprehensive law protects genetic privacy
• GINA protects against discrimination in certain circumstances
• HIPAA protects against disclosure of ‘protected health information’ sometimes
• The Common Rule provides research protections only if data are readily identifiable
• No overarching federal or industry privacy guidelines of commercial genetic testing
Presidential Commission for the Study of Bioethical Issues

*What about Privacy and Progress in Whole Genome Sequencing?* 2012
Chair: Amy Gutmann, PhD

[bioethics.gov/cms/sites/default/files/PrivacyProgress508_1.pdf](http://bioethics.gov/cms/sites/default/files/PrivacyProgress508_1.pdf)

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**Take-home Lessons**

We can obtain more information than we know what to do with through genomic analysis

The family history remains a very powerful—and inexpensive—predictor of risk

But does the family history make a difference in outcomes?

People are interested in their genetic risks, and want the data in their health records
Take-home Lessons

Despite obvious genetic risks, people may choose to ignore them.
For now, place the burden of updating patient risks on the patient.
Numerous logistic, ethical, legal & social issues need to be understood before the $1000 genome will be useful in most situations.
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