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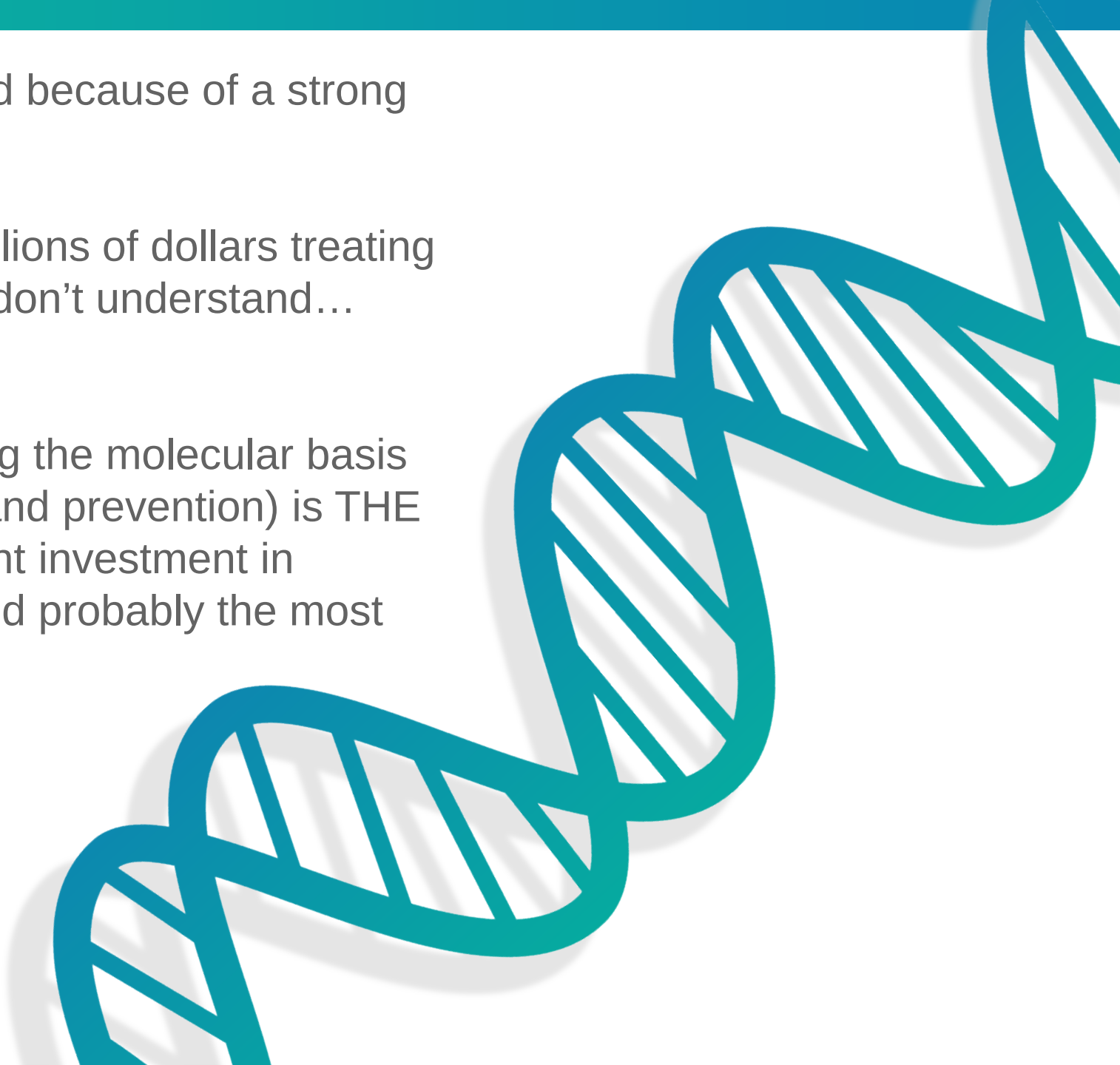
State of the (Genetic) Diagnostics Industry

… A “BIASED” PERSPECTIVE FROM 27 YEARS AT THE INTERSECTION OF GENOMIC SCIENCE, ECONOMICS, AND MEDICINE

I’m in this field because of a strong bias:

We spend billions of dollars treating diseases we don’t understand…
…poorly!

Understanding the molecular basis for disease (and prevention) is THE most important investment in healthcare and probably the most undervalued



The genetic diagnostic industry has the opportunity to affect billions of people around the globe

Big Trends in Genetic Diagnostics

Major technology trends: exponentially accelerating technology

- Disruptive technology is rapidly driving down costs and increasing data
- Moore's law and Metcalfe's law applied across a finite human disease problem
- More and more genetic content at lower and lower prices every year

Major medical trends: Genetics "disorders" are vastly more common than thought

- Genetic information is re-defining disease at the molecular level
- Genetic disorders are not rare (and common disease is an oxymoron)
- High resolution genetic testing is becoming increasingly accessible across all diseases

Major economic trends: Moving from scarcity to abundance

- Decreasing costs will make genetic testing affordable and accessible for all
- Test aggregation, Economy of scale, Volume-price relationship, (see Amazon)
- New payers are emerging to bypass health insurance

Policy implications: How do we embrace technology and encourage innovation while protecting patients?

- Reimbursement, regulation, privacy,

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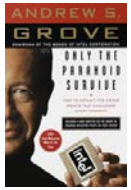
Disclaimer: conflict disclosure from three decades of building genetics companies



Incyte

Race to sequence all the genes in the human genome

1991

Genomic Health™

One of the first personalized medicine companies

2000

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Aggregating all the world's genetic tests into a single low-cost platform

2010

genome MEDICAL

Solving the "last mile" problem – delivery to patients

2016

TALIS

Infectious disease point of care

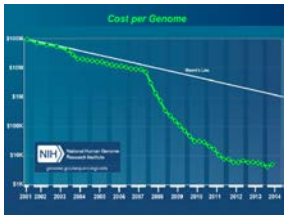
freenome

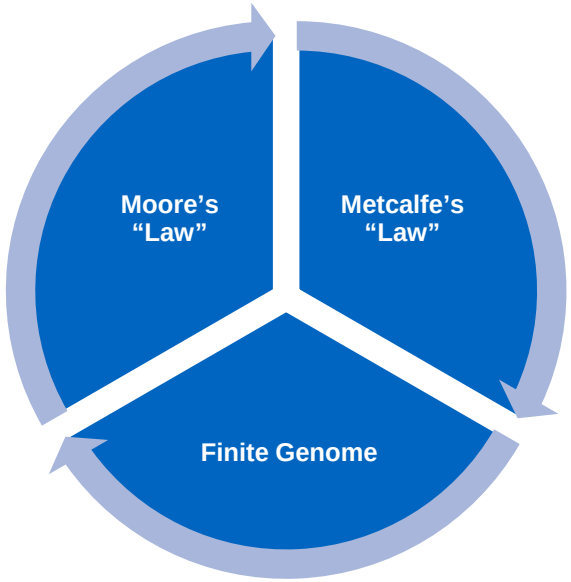
AI applied to next gen cancer screening

Technology Trends

Accelerating technologies are driving the future of medicine

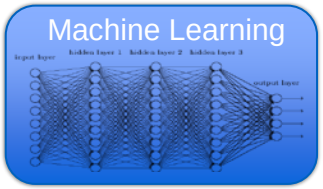
The cost of DNA sequencing is decreasing rapidly





The "internet of genetics" is emerging

Understanding the genetic basis of disease is like a finite puzzle… it's a reverse engineering problem!



Medicine is entering a technology wave of exponential growth in information

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As an industry we are now tasked with turning that technology into massively scaleable infrastructure for genetic analysis… and its working

Industrial scale automation and massively parallel processing allows us to analyze thousands of genes across thousands of patients per day

Sample processing gets more economical at scale

Illumina's new Novaseq platform reduced our sequencing costs by 80%

Software, bioinformatics, and artificial intelligence are revolutionizing data analysis

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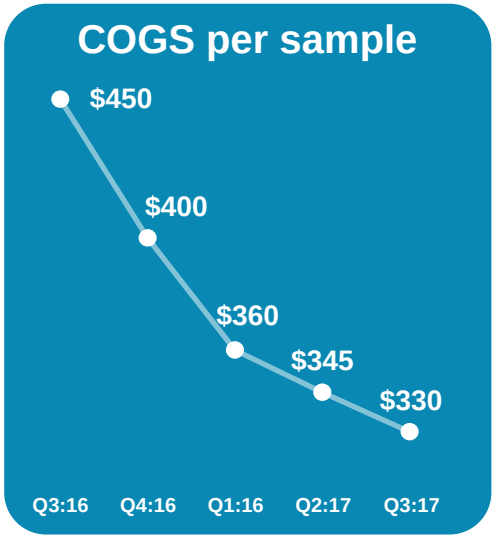
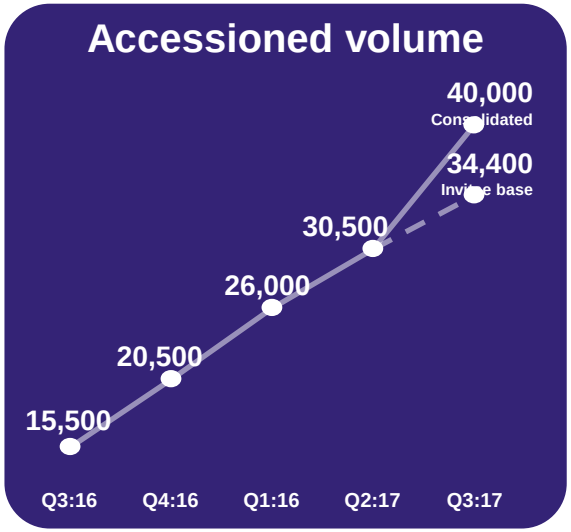
Invitae is an example of technology driving economy of scale

Aggregating thousands of genetic tests into a single platform:

- Technology is rapidly driving down the cost of genetic testing
- Economy of scale allows aggregation of large numbers of tests into a single production line
- Volume is growing rapidly as prices decrease, content increases and genetics becomes more affordable and accessible to customers





Super panels of hundreds of genes (all cancer, all cardio etc. on a single panel) all at prices dropping into the hundreds of dollars

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Medical Trends

Why is it we can put a man on the moon and can't cure the common cold?

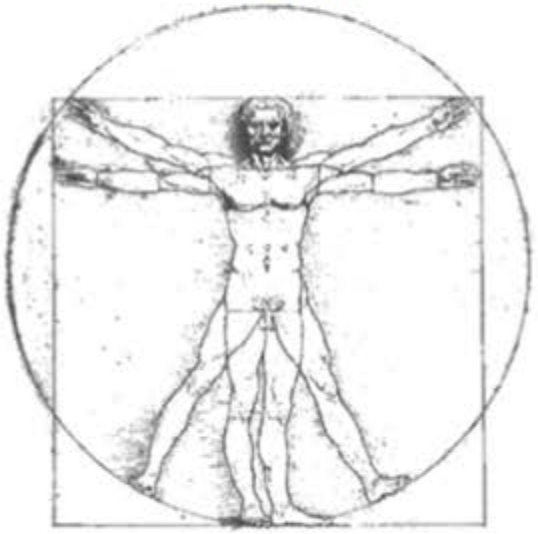
BECAUSE BIOLOGY IS MILLIONS OF TIMES MORE COMPLEX!

The Human Genome Project

Technology is now moving fast enough to uncover the complexity of human genetic variation

1-2 x 10^{-8} error rate in DNA replication results in 30-60 variants per generation -- creating significant variation in the human population over time

~34 trillion cells in the human body creates somatic variation as well (cancer)



Many healthcare companies, even in the genomics industry, are naïve about the complexity of genetics

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Everywhere we look… the prevalence of genetic conditions is increasing

- Whole genome studies by academic groups suggest that as much as 20% of the population has a pathogenic mutation in one or more Mendelian inherited conditions
- Geisinger whole exome studies suggest the pathogenicity rate is much higher than previously thought across all areas of disease
- Multiple studies have demonstrated that even low risk cancer patients have a relatively high rate of positive mutations
- Invitae has further demonstrated that the general population has about a 15% chance of a pathogenic mutation in one of just 139 genes in our proactive health panel – with the largest area being cancer findings

Perhaps most strikingly, MyCode results are demonstrating a prevalence of *BRCA* mutations in the population, double the results found in published literature. Most risks were previously unknown to patients.

"We are years ahead of any other health care system in implementing genomic screening and we are already establishing some clinical utility," Dr. Ledbetter said. "Population screening programs, such as MyCode, are identifying a much greater prevalence of almost any Mendelian (inherited) disease than was thought before."

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Historically we only looked for our dime under the lamp post

We only looked at the few number of genes we could see…

i.e. BRCA for breast cancer

BRCA ½ only account for about a third of hereditary breast and ovarian cancer…

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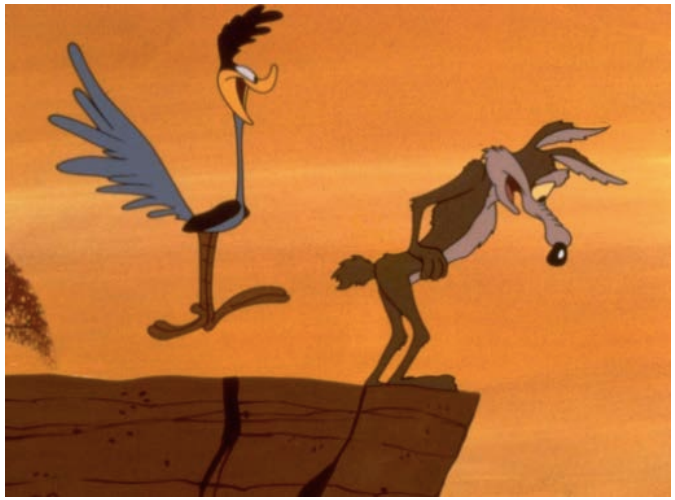
Historically we only diagnosed genetic conditions when people “fell off a cliff” clinically

Genetic testing is limited to dramatic early onset of disease or extreme conditions

… when in effect…

Many more people are sitting at the edge of a medical cliff with symptoms that only show up in later stages of life or are mild in nature



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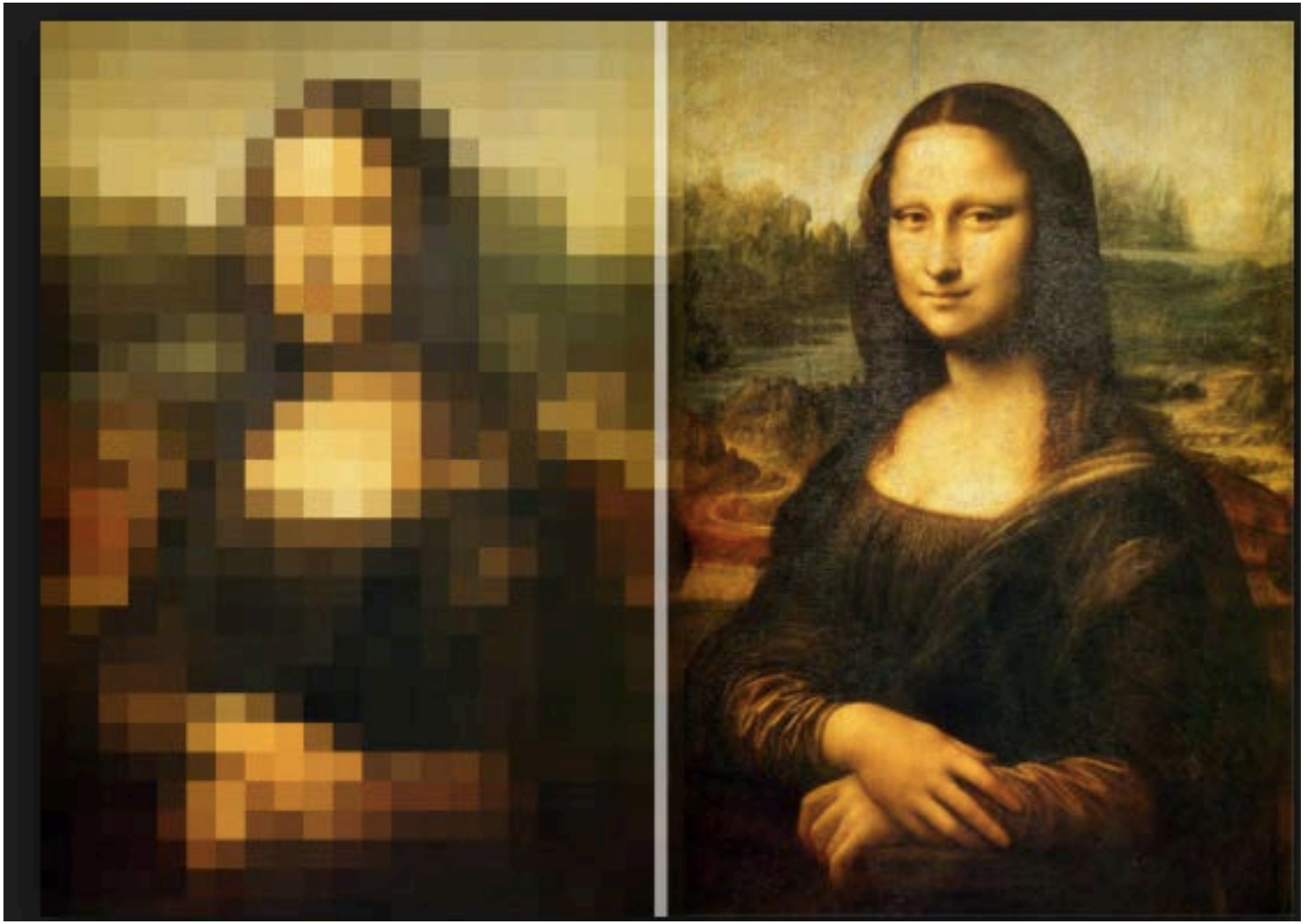
All this technology now gives us a much higher resolution picture of disease



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As costs decrease we believe the medical world is going to demand the highest resolution genetic testing

… HIGH RESOLUTION TESTING IS THE FUTURE…

Low-resolution genetic screens only cover a portion of the potential genetic risk

- Limited gene coverage
  - (i.e., *BRCA1* and *BRCA2* only account for 30-40% of breast cancer risk)
- Limited sequence coverage
  - Many assays, including "whole" genome and exome analysis, contain gaps that miss important variants
- Limited or no coverage of complex variant types
  - **"DARK MATTER*"**: Large deletions/duplications, inversions, pseudo genes, splice sites, trinucleotide repeats
- Limited quality of variant interpretation
  - Analysis that doesn't meet the American College of Medical Genetics (ACMG) standards or limits VUS interpretation

High-resolution genetic tests are designed to cover all known genes and mutations

- Coverage of all medically relevant genes
  - Hereditary gene panels
- Deep sequence coverage across all known pathogenic regions for the disease of interest
  - Minimum coverage across all difficult sequencing regions (targeted panels and "boosted" exomes or genomes)
- Complete analysis of complex variant types
  - Special workflows for complex variants expose the **"DARK MATTER*"** or hard-to-do regions of the genome
- High-quality interpretation of variants of uncertain significance
  - Comprehensive review of all variants by ACMG standards, including VUS interpretation

*Complex variant types are often the same as the regions that are hard to sequence!

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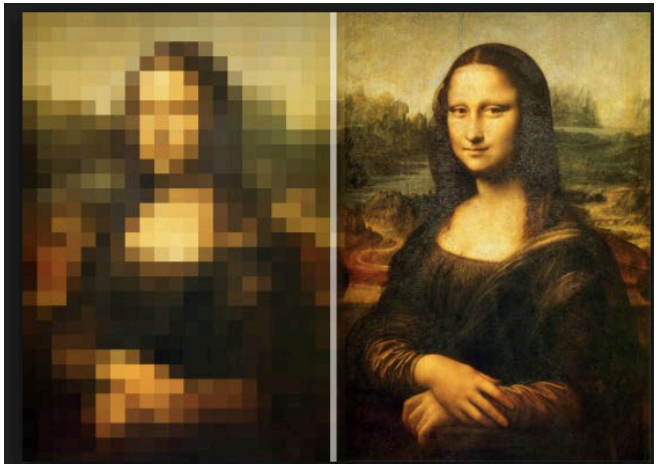
High resolution at low cost is the future

Hereditary Breast and Ovarian Cancer Testing

Low Resolution

3 SNP Ashkenazi screen



High Resolution

>10,000 genetic variants across BRCA 1&2

+

10s of thousands of variants across all known hereditary cancer genes

~$99 patient pay

$250 patient pay

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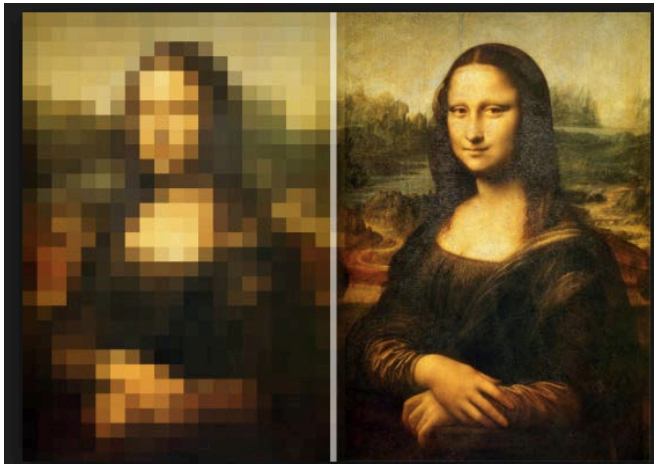
High resolution at low cost is the future

Hereditary Breast and Ovarian Cancer Testing

Low Resolution

Whole Genome Sequence



High Resolution

10,000 genetic variants across BRCA 1&2

+

10s of thousands of variants across all known hereditary cancer genes

$2,000 -$5,000 patient pay

$250 patient pay

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Medical trends in genetics

- Genetic conditions are far more prevalent than previously thought
- Family history is a very crude tool that often misses a significant portion of genetic risk
- High resolution testing across large gene panels is revealing that we can't predict in advance what gene will correlate with which specific disease
- The cost are now bringing us closer to a tipping point… when we can just test all individuals in a modern health care system for all known genetic conditions…
- The complexity of biology and disease is ultimately not a consumer game... We will only be successful if the medical community is engaged and data is used to improve diagnosis, prevention and treatment
- PREDICTION: In 20 years we will rarely run a genetic diagnostic test because everyone will be sequenced early in life at very low cost and the information managed by their medical provider over the course of their life and paid for by their health system

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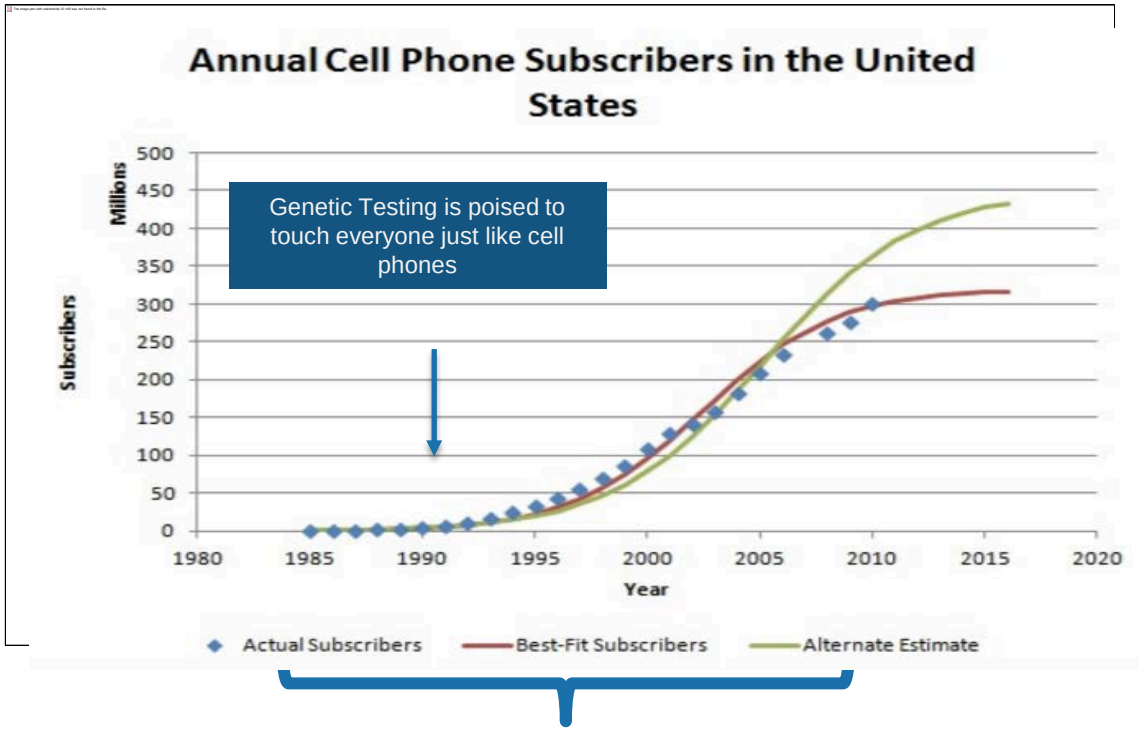
Theoretical market for genetics is everyone on the planet!



25 years from commercialization to “saturation”

Economic Trends

Two giant leaps in the genetic testing industry have forever changed the cost structure in recent years

- The 2013 supreme court decision to eliminate patents on naturally-occurring DNA rendered the field generic and opened up free market competition

- A dramatic reduction in the cost of genetic analysis led by massively parallel DNA sequencing and bioinformatics changed the economies of scale

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Economic Trends

- Technology and competition will drive down prices for many years to come but the decrease in margins will be offset by growing volumes and free cash flow as millions of individuals access genetic information
- Our outdated payer system based on old CPT codes is increasingly overwhelmed by new technology and often obscures “obscene” pricing games by labs stacking codes in hopes of a big pay out… as well as protecting out of date payer policies
- Nonetheless, third party health insurers will play a critical role in the future of genetics… they are a customer and we as an industry need to help serve their needs
- Industry-wide aggregation of molecular tests will create shift from thousands of small independent labs and tests to a smaller number of labs with massive scale (think Walmart and Amazon) and very low prices
- The value of networks of genetic information will eventually exceed the value of the genetic tests themselves (think Google and Facebook only with patient privacy and control)

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Key economic principles we can learn from Amazon

1) We're not out to optimize percentage margins (earnings per share). We're out to maximize the absolute dollar free cash flow.

2) Our competitor's high margins are our opportunity to take away their market share.

3) Market leadership can translate directly to higher volume, higher revenue, greater cash flow, greater capital velocity, and correspondingly stronger returns on invested capital."

4) "On the Internet, companies are scale businesses, characterized by high fixed costs and relatively low variable costs. You can be two sizes: You can be big, or you can be small. It's very hard to be medium."

5) "If everything you do needs to work on a three-year time horizon, then you're competing against a lot of people. But if you're willing to invest on a seven-year time horizon, you're now competing against a fraction of those people, because very few companies are willing to do that. Just by lengthening the time horizon, you can engage in endeavors that you could never otherwise pursue. At Amazon we like things to work in five to seven years. We're willing to plant seeds, let them grow—and we're very stubborn." "We've had three big ideas at Amazon that we've stuck with for 18 years, and they're the reason we're successful: Put the customer first. Invent. And be patient."

Policy Trends

In a nascent industry regulation needs to evolve like biology

- In the early stage of disruptive innovation low levels of regulation allow the first survivors (companies and investors) to reproduce and begin to thrive
- In the middle stages of evolution the industry and regulators need to work together to better define the quality infrastructure and industry will compete based on quality
- In the latter stages of evolution as technology stabilizes and scales the industry and investors will welcome smart regulation as an ongoing part of business
- It “feels” like we’re doing this right… smart folks in the FDA and in industry working more closely together all the time

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Reimbursement, on the other hand is a mess… and susceptible to disruption

- Payers are financial institutions NOT healthcare companies and don't have the resources to evaluate technology, quality or outcomes
  - The best response to lack of information/knowledge is to delay making a decision
  - During exponential technology curves… that will result in bad decisions and extreme disruption as employers and patients increasingly demand access to genetic information
- Labs have conducted extreme billing practices for years that have lost the trust of payers by stacking CPT codes and overcharging millions of dollars… WE MUST HAVE TRANSPARENCY IN PRICING!
- The CPT coding system is outdated and will not keep up with the disruptive economic forces that are coming, in the end we will only need one CPT code for all hereditary genetics…
- Business models are figuring out how to bypass the payers and go direct to patients, pharmas, employers or other sources of revenue to pay for tests

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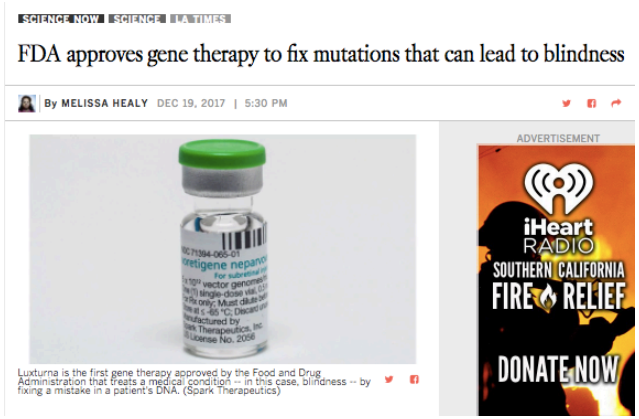
There is something fundamental about the code of life (DNA) that demands a priori knowledge in order to fully understand biology and disease.

Without it, we are practicing medicine in an incomplete way.

With advances in CRISPR technology and genetic therapy all genetic diseases now have reason for hope!



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