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The University of Arizona Health Sciences

Facts and figures for FY 2015

- $126 M in research awards, >950 faculty
- $15 M in corporate research expenditures
- 70 inventions submitted
- 11 new patents issued
- 5 new companies started
- 11 new patents issued

Precision medicine and biomarkers: intersection of the -*omics* ecosystem and healthcare policy

A program powered by:

The University of Arizona Health Sciences

THE UNIVERSITY OF ARIZONA TECH LAUNCH ARIZONA

Ken Ramos, MD, PhD, PharmB
Associate Vice President for Precision Health Sciences
Director, Center for Applied Genetics and Genomic Medicine
Director, MD-PhD Program
Professor of Medicine
Elected Member of the National Academy of Medicine

*A major driver for the shift from volume-based to **value-based healthcare** has been the sobering reality that healthcare, as we know it today, will not be sustainable in the long term without novel approaches that help to:*

- *augment diagnostic accuracy and precision;*
- *deliver targeted therapies that improve efficacy and decrease toxicity;*
- *stratify populations into sub-populations that more closely align with established guidelines.*

PART I
BIOMARKERS, -OMICS, and PRECISION MEDICINE

BIOMARKERS, -OMICS, and PRECISION MEDICINE

National Institutes of Health Biomarkers Definitions Working Group defined a ***biomarker*** as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."

- Metabolite
- DNA
- RNA
- Protein
- Imaging

→

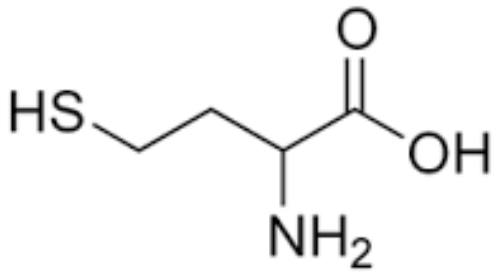
- Presence/absence of disease
- Stage of disease
- Prognosis and risk
- Prediction and/or readout of drug response
- Adverse event

From the Oxford English dictionary, the suffix "-**ome**": in cellular and molecular biology, forming nouns with the sense "all constituents considered collectively". Usually in reference to the interrogation of the metabolome, kinome, proteome, glycome, transcriptome, or genome (as a field of study, as in "**genomics**").

Precision medicine is delivering the right treatment to the right patient at the right time through early diagnosis and individually tailored treatments....

HOMOCYSTEINE AS A BIOMARKER CASE STUDY

- First publication on homocysteine as a biomarker for B-vitamin deficiency (and cardiovascular disease) in 1985
- 1st homocysteine patent filed (US 4,940,658) by R. Allen and Univ CO in 1986
- Metabolite Laboratories formed in partnership with the Univ CO 1988
- First patent on homocysteine as a biomarker issues in 1990
- Metabolite sued Labcorp for infringement of '658 patent in (after initially taking a license and making royalty payments, then stopping) 1999
- United States Court of Appeals Federal Circuit issues a judgment against Labcorp for willful infringement; all other diagnostic labs doing homocysteine assays enter into a license agreement 2004
- SCOTUS agrees to hear the case on appeal, then later dismisses in 2006
- '658 patent expired July 10, 2007

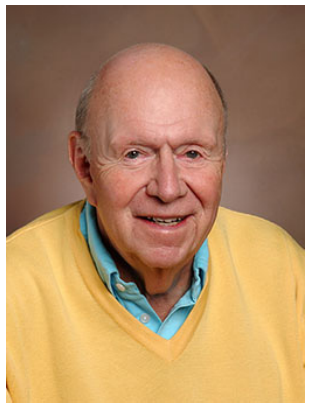


Homocysteine

United States Patent [19]
Allen et al.

[11] **Patent Number: 4,940,658**
[45] **Date of Patent: Jul. 10, 1990**

13. A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
assaying a body fluid for an elevated level of total homocysteine; and
correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.



THE HGP (v 1.0) AS AN OPEN INNOVATION CASE STUDY

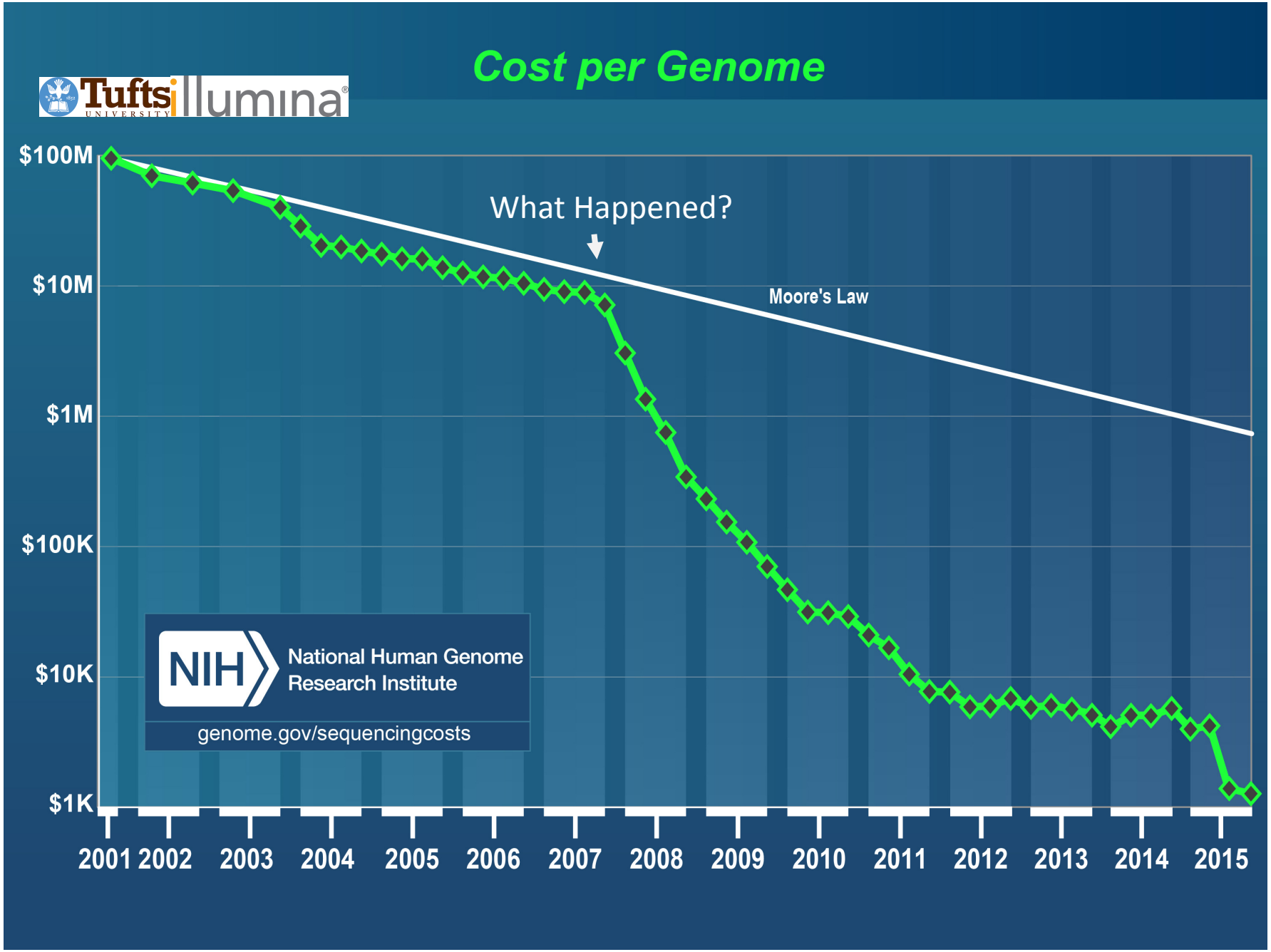
CELERA

- Eugene Meyers pioneered the bioinformatics tools enabling genome alignment (BLAST) and *in silico* genome reassembly
- He left University of Arizona in 1998 to found Celera with Craig Venter
- Open innovation model used- enabled accelerated completion the human genome project
- Was *not* a corporate collaboration with the University of Arizona. (Could it have been?)
- Celera business model was predicated on the annotated genome (we will revisit this later)
  - ❑ Capture?
  - ❑ Own?
  - ❑ Control?

Public project was anonymous individuals from Buffalo NY. Celera project was 3 men, 2 women (including Craig Venter). In a 2001 reference genome sequenced and published representing these individuals. No individual variation or clinical information analyzed- ***$4.8B ($2016) for that first genome.***

Human Genome Map
Science 16 Feb 2001:
Vol. 291, Issue 5507, pp. 1218

…but we knew little about individual differences and similarities in disease populations.
***CLINICAL* ANNOTATION IS CRITICAL TO UNDERSTANDING DISEASE AT THE GENOMIC LEVEL**


Tufts University
illumina
Cost per Genome
$100M
$10M
$1M
$100K
$10K
$1K
What Happened?
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts
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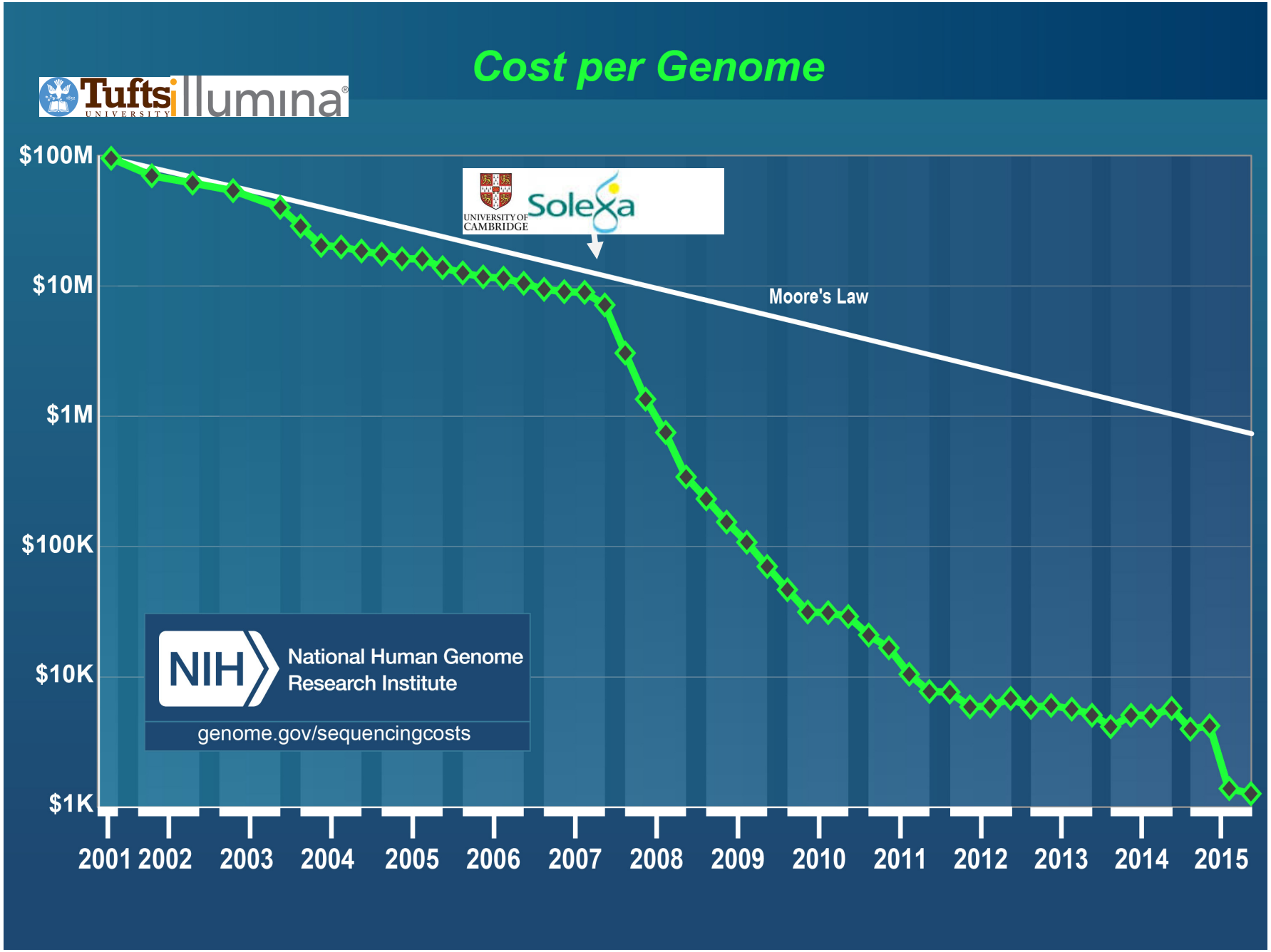

Cost per Genome
Tufts University
illumina
$100M
$10M
$1M
$100K
$10K
$1K
UNIVERSITY OF CAMBRIDGE
Solexa
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015

PART II
-OMICS and PRECISION MEDICINE in HEALTHCARE

THE HUMAN GENOME AND THE REAL WORLD

A full human genome is 3.3 billion base pairs (6.6 B letters in diploid) and now obtainable for a cost bearable by most healthcare payers (but not generally reimbursed yet), and many self-pay and retail patients.

Whole exome sequencing reads all *coding* regions, aka genes- about 21,000 genes (about 5% of the genome or 165 M base pairs). Ignores the increasingly important dark matter of the genome.

23andMe v.4 chip looks for 602k variations - 0.018 % of the genome (targeted genome analysis, not full genome sequencing). You are paying for the report.

FOUNDATIONONE 343 genes commonly mutated in cancers (about 0.00082% of the genome). Targeting sequencing is absolutely practical for known diseases with genetic drivers (cancer).

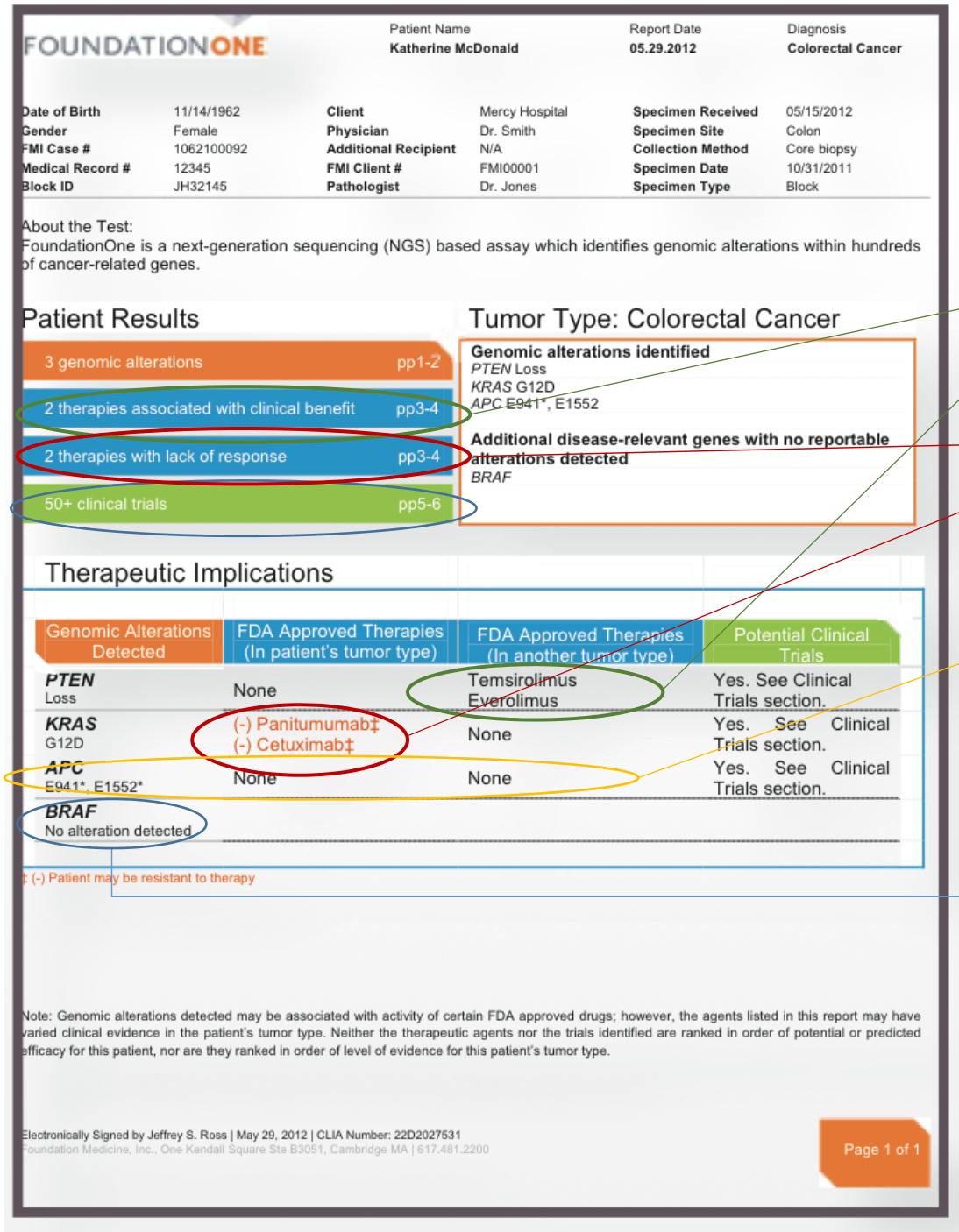
VeritasGenetics **Genome sequence breaks the $1000 threshold.**
https:// www.veritasgenetics.com/documents/VG-launches-999- whole-genome.pdf
"Now that the whole genome is this accessible, it will replace all genetic tests ... because it is all genetic tests, and much, much more," Dr. George Church, March 3rd,2016.

illumina® The TruGenome Undiagnosed Disease Test covers 90% of the germline genome at 30X coverage. Costs $9,500; $17,500 if both parents are included.

Not so fast….

- For statistical reasons, and for some applications, "reads" must cover 7-8 X scans, some up to 100X coverage or 330 billion bases- elimination of errors when the genome is reassembled *in silico*.
- Some cancers have several heterogeneous tumor cell lineages; e.g. multiple genomes in a tumor.
- As we age, our genome is somewhat plastic and evolves in response to toxins and stress, some tissues more than others.

…..so what does it all mean? Interpretation is HIGHLY specialized



FOUNDATIONONE

Patient Name	Report Date	Diagnosis
Katherine McDonald	**05.29.2012**	**Colorectal Cancer**

Date of Birth	11/14/1962	**Client**	Mercy Hospital	**Specimen Received**	05/15/2012
Gender	Female	**Physician**	Dr. Smith	**Specimen Site**	Colon
FMI Case #	1062100092	**Additional Recipient**	N/A	**Collection Method**	Core biopsy
Medical Record #	12345	**FMI Client #**	FMI00001	**Specimen Date**	10/31/2011
Block ID	JH32145	**Pathologist**	Dr. Jones	**Specimen Type**	Block

About the Test:
FoundationOne is a next-generation sequencing (NGS) based assay which identifies genomic alterations within hundreds of cancer-related genes.

Patient Results

- 3 genomic alterations — pp1-2
- 2 therapies associated with clinical benefit — pp3-4
- 2 therapies with lack of response — pp3-4
- 50+ clinical trials — pp5-6

Tumor Type: Colorectal Cancer

Genomic alterations identified
PTEN Loss
KRAS G12D
APC E941*, E1552

Additional disease-relevant genes with no reportable alterations detected
BRAF

Therapeutic Implications

Genomic Alterations Detected	FDA Approved Therapies (In patient's tumor type)	FDA Approved Therapies (In another tumor type)	Potential Clinical Trials
PTEN Loss	None	Temsirolimus Everolimus	Yes. See Clinical Trials section.
KRAS G12D	(-) Panitumumab‡ (-) Cetuximab‡	None	Yes. See Clinical Trials section.
APC E941*, E1552*	None	None	Yes. See Clinical Trials section.
BRAF No alteration detected			

‡ (-) Patient may be resistant to therapy

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type.

Electronically Signed by Jeffrey S. Ross | May 29, 2012 | CLIA Number: 22D2027531
Foundation Medicine, Inc., One Kendall Square Ste B3051, Cambridge MA | 617.481.2200

Page 1 of 1

FOUNDATIONONE

Interpretation: "treat with mTOR inhibitors, but it will be offlabel use if the drug"

Interpretation: DO NOT treat with mabs against EGFr, even though approved for colon cancer

Interpretation: Has two different point mutations. Not an actionable mutation

Interpretation: Among several hundred gene loci sequenced that had no detected (or known) tumor-driving mutations.

PATIENT ENGAGEMENT

illumina®
UNDERSTAND YOUR GENOME®
think BIG

"About 60 people paid $5,000 each to have their genome sequenced. The attendees, a mix of doctors, scientists, genetic counselors, and the curious, gathered for two days of lectures and personal DNA exploration. They got white gift bags that contained an iPad tied with a gold bow, a framed glass slide of their DNA sample, a hard drive holding their entire DNA sequence, and a binder with a clinical report disclosing which markers are tied to which conditions."

Bloomberg Businessweek

January 16, 2014

- Launched in Nov 2013
- Illumina will sequence and individuals genome in a CAP-CLIA sequencing lab
- 18 events held or planned around the world as of Jan 2016
- Allows longitudinal engagement with the participants (vs. a one time snapshot of health and genome)
- Initially, these folks were prominent and expected to be leaders and evangelists for precision medicine
- These participants are uber-research subjects
- *Is this a new model for grateful patient and benefactor engagement as well?*

HGP (v. 2.0) AS A BIG DATA CASE STUDY

In the era of Big Data

HLI HUMAN LONGEVITY, INC.

HEALTH NUCLEUS

- $25,000-50,000 for COMPLETE genome sequence (30X), full body scan, and physician consultation.
- Plan for sequencing 40,000 genomes per year.
- Have a partnership model with AstraZeneca on clinical trials and academic medical centers accessing clinical cases (and clinical annotation), UC San Diego
- Longer term strategy is enabling population health by revealing a trove of genomic determinants of specific ***and actionable*** health and disease outcomes (like every company seeking to collect and analyze mass genomic data).

SEEKING CLINICAL CASES….

Population scale genome sequencing

These Superhumans Are Real and Their DNA Could Be Worth Billions

The Quest for Rare Genes

Bloomberg Businessweek

July 22, 2015

Amgen
The biotech in 2012 got genetic data on 160,000 Icelanders via its **$415 million** buyout of DeCode Genetics

Calico
The Google-backed company, searching for longevity genes, has partnered with Ancestry.com, which has collected millions of public family trees and more than **1 million genetic samples**

Regeneron
Working with Geisinger Health System to sequence genes of **100,000 volunteers**

23andMe
The genetic-testing pioneer has genotyped 1 million customers; it has deals with more than **10 drugmakers**, including Pfizer and Genentech

IBM Watson

GE Healthcare Predix

Artificial intelligence platforms-as-a service (Watson,Predix) will be reliant on "training data" from *in-the-wild* clinical cases, allowing identification of complex patterns of genomic information correlated with clinical patterns. Collaboration models with AMCs will inform those platforms and guide use cases.

Big Science & really, really Big Data

*@ high coverage- 30X

1,000,000 patients
45 M GB = 45 Petabytes = 600years of HD video

200,000 patients
11 M GB = 11 Petabytes = 1.5 centuries of HD video

100,000 patients
4.5 M GB = 4.5 Petabytes = 75 years of HD video

200,000 patients
9 M GB = 9 Petabytes = 12 years of HD video

500,000 patients
23 M GB = 23 Petabytes = 3 centuries of HD video

160,000 patients
6.8 M GB = 6.8 Petabytes = 75 years of HD video

100 Petabytes = 3 centuries of HD video or all the internet traffic in the year 2000

AMGEN

Sequenced 160,00 Icelanders, identified 8000 variants of 1171 genes knocked out in 2600 Icelanders (deCODE Genetics sequenced tens of thousands). Looking to expand to new populations and disease specific cohorts.

Looking for genetic variants with frequencies of >1% in UK populations at 4x coverage.

NIH + White House funded Precision Medicine Initiative to enroll 1 million patients and study clinical parameters with lifestyle, -omic, and health outcome parameters.

Banner Health

ARIZONA

HLI HUMAN LONGEVITY, INC. AstraZeneca

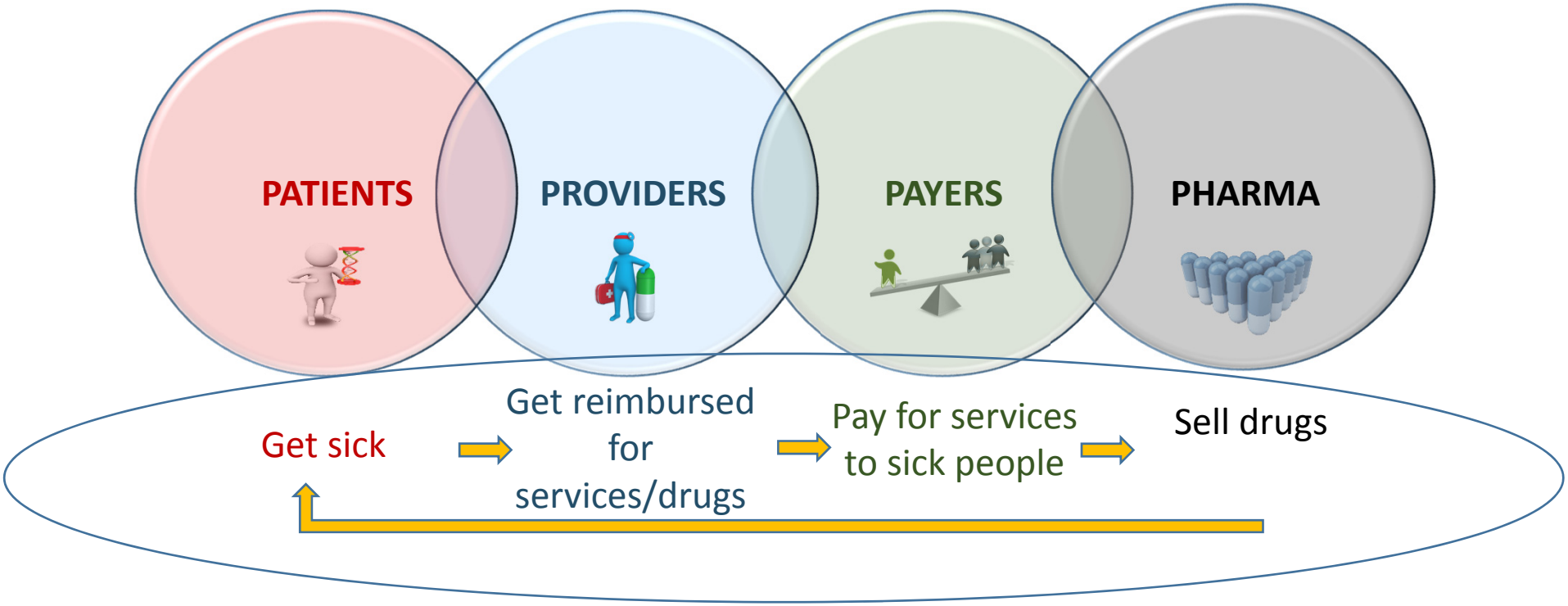
Longevity, Inc. sequencing 200,000 genomes through collaborations over next 5 years and announced a 10 year partnership with AstraZeneca to sequence up to 500,000 DNA samples from AstraZeneca clinical trials. The insights from the collaboration will be added to the HLI Knowledgebase™, building upon what is already the most comprehensive database of its kind.

REGENERON
science to medicine®

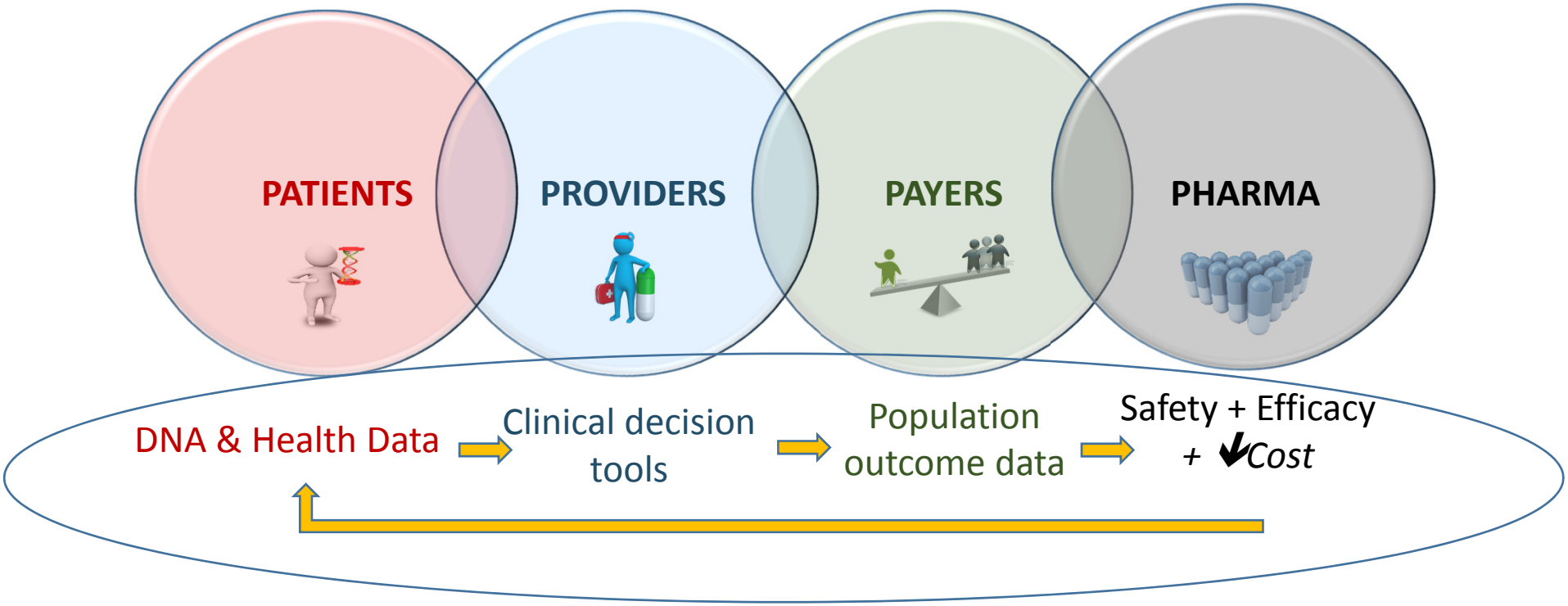
GEISINGER
HEALTH SYSTEM

In 2014 Regeneron enters into an alliance with Geisinger Health System to recruit 250,000 DNA donors to identify genes associated with susceptibility or resilience to disease.

The fading healthcare model

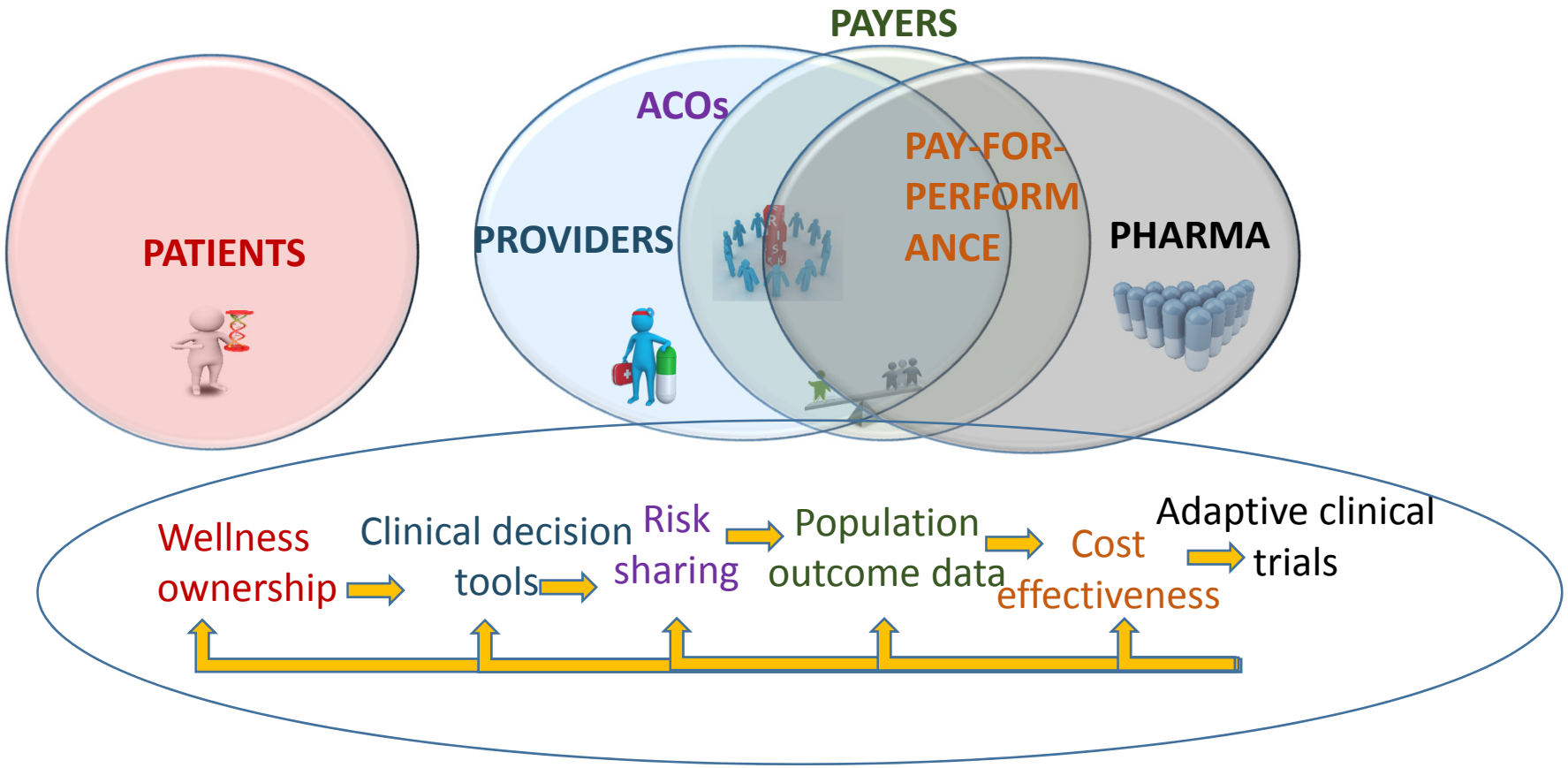


What does the sub-$1000 genome mean for healthcare?



What does the sub-$1000 genome mean for healthcare?

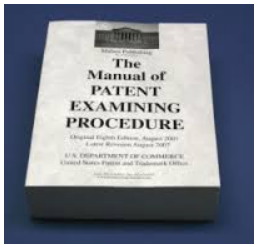
We are in it together



Tools and outcome measures by which to quantify risk, and reward, will alter decision making across the healthcare continuum.

PART III
POLICY and INVESTMENT INCENTIVES in PRECISION MEDICINE

POLICY & POLITICAL HEADWINDS FOR PRECISION MEDICINE



INNOVATION LAW AND POLICY: PRESERVING THE FUTURE OF PERSONALIZED MEDICINE

Rachel Sachs*

This Article proceeds in five Parts. Part I considers the FDA's recent proposal to begin regulating laboratory-developed tests, which would increase the costs of developing diagnostic tests by imposing new regulatory burdens on academic laboratories and diagnostic testing companies who were previously subject only to a much less onerous regulatory system. Part II considers the impact of the Affordable Care Act (ACA) and other recent cuts made to Medicare reimbursement rates for the performance of diagnostic tests, rates that have ripple effects throughout the private insurance market, on the ability of innovators to recoup their investment into a given diagnostic test. Part III will consider recent patent law decisions from the Federal Circuit and Supreme Court that make it more difficult for diagnostic method innovators both to obtain patents and to enforce them. Part III also considers how the ACA and related statutes are restructuring the diagnostics industry in a way that exacerbates these difficulties.

UC Davis Law Review, Vol. 49, June 2016. p. 1881-1940

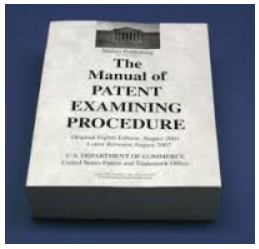
Changes in innovation incentives

- Reduced patent scope and enforceability
- Reduced reimbursement rates
- Increased regulation of LDTs
- ACA Medical Device Tax (suspended through 2017)
- Commoditization of NGS analytics
- Slow adaptation of CPT codes for new technologies
- Higher bar for clinical validation/evidence by payers
- Refined standard clinical decision practices

…in short, reduced incentives to invest in clinical validation at a time when more clinical evidence is required by payers and regulators.

POLICY & POLITICAL HEADWINDS FOR PRECISION MEDICINE

- Labcorp vs Metabolite Labs Inc
- Mayo Collaborative Services vs Prometheus Laboratories Inc
- Association for Molecular Pathology vs Myriad Genetics Inc
- Vanada Pharmaceuticals Inc vs Roxane Labs Inc
- Ameritox LTD vs. MilleniumHealth Inc
- Genetic Veterinary Sciences Inc vs Canine EIC Genetics LLC
- Endo Pharm Inc vs Actavis Inc
- EsoterixGenetic Lab LLC vs. Qiagen LTD
- Cleveland Clinic Foundation vs True Health Diagnostic LLC
- Rutgers vs Qiagen Inc
- IdexxLab Inc v. Charles River Labs Inc
- Oxford Immunotec Ltd. vs Qiagen Inc
- Ariosa Diagnostics Inc vs Sequenom Inc



Patent protecting key elements of a molecular test has become very difficult under US patent law. Recent cases have done little to distinguish and clarify natural law, application of that law, abstract idea, or a universal inventive step that might clarify

See for review: *Diagnostics Need Not Apply. R. Eisenberg. Journal of Science & Technology law, vol. 21.2 Summer 2015*

POLICY & POLITICAL HEADWINDS FOR PRECISION MEDICINE

- Is often the first to reimburse, and is the largest payer (it is really 7 centers and 7 payers) covering 100 million people, so their reimbursement decision are a major driver of medical innovation.

- Oversees CLIA standards; focused on analytic standards, not clinical.

- The clinical evidence standard for 510(k) and LDTs is rising with CMS, so regulatory clearance is really no longer a critical commercialization milestone, *CMS reimbursement is the value driving milestone*.

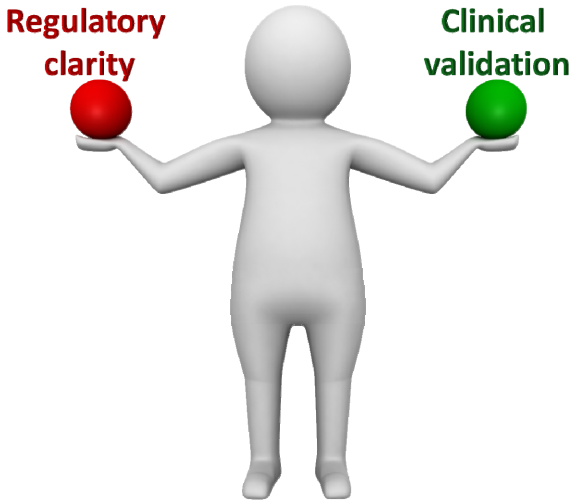
- The Bundled Payments for Care Improvement (BPCI) Initiative was established by the Affordable Care Act and is a move toward value-based payment models to reward outcomes for episodes of care, instead of *ala carte* service.

- Medicare's Date of Service Rule has had the unintended consequence of delaying delivery of test information to clinicians, by many days, if not weeks. This has encumbered utilization molecular diagnostic testing to it's full potential.

POLICY & POLITICAL HEADWINDS FOR PRECISION MEDICINE

- FDA has very recently begun to exercise it's long standing statutory authority to regulate LDTs, in part to establish standards for the use of NGS in *clinical* decision making.
- In fall of 2014 release draft oversight framework for Premarket Approval of High-Risk Laboratory Developed Tests.
- In July 2016 releases draft oversight framework for Next Gen Sequencing in Diagnosing Germline diseases (noncancer).
- Issued guidance for an Expedited Access Program for *De Novo* Medical Devices; parallel CMS and FDA review also possible; predicated on a clinical data development plan.

These frameworks all strive to clarify clinical decision making standards, NGS specific analytic standards (coverage) as well as general analytic standards (accuracy, precision, repeatability, reproducibility, detection limits, analytic specificity).



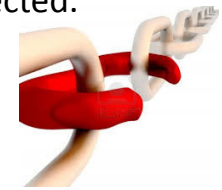
GRAND CHALLENGES IN PRECISION MEDICINE TO BE SOLVED

Clinical workflows and medical training need to adapt to rapidly accelerating changes in medical practice, decision making, and payment models. Teams of specialists will increasingly need to share information and insights across the care continuum.

US patent case law for biomarker technologies has sharply reduced the utility of patents as a tool to promote investment in clinical validation and commercial development of biomarkers.

The use of **biomarkers in clinical decision making**, now requires years and hundreds of clinical cases of validation to drive clinical adoption, regardless of whether IVD, CLIA/LDT, or other and large –omic data sets. **Regulatory and payer requirements** demand more clinical evidence (peer reviewed observation and/or prospective clinical trials) for use (reimbursement) of a test. Clinical actionability has become critically important for commercial investment, and accordingly, reimbursement.

Payer cost management and **quality accountability** will drive increased consumption of diagnostic information, *at least in volume*, perhaps not in dollars. Reimbursement models must evolve to enable the use of valuable new outcome measures, lest their adoption be neglected.



Policy disconnects have diminished investment incentives for diagnostic innovation at a time when clinical validation is increasingly important. Specific policy fixes for diagnostics are a major theme in healthcare innovation policy circles.

The discovery, validation, and clinical deployment of **multianaltye –omics tests** will require a significant step-up in medical specialization. Interpretation of the clinical sequencing assay reports requires expertise that is presently rare among clinicians, and predominantly resides in major academic medical centers. -omic information is increasingly less human readable and it's use highly specialized, and workflows, dashboards, and clinical decision rules must adapt to enable it's use.

PUNCHLINE

- The cost of DNA sequencing has fallen much faster than the rate Moore's Law would indicate.

- High throughput biology, cloud computing, and computational advances are rapidly being commoditized and transforming clinical decision making by delivering individualized molecular information to the point of care at a practical pricepoint.

- As a result, these technologies are finally allowing us to understand molecular basis for difference in disease in individuals by studying these differences in populations.

- Our armamentarium of therapeutics is rapidly accumulating agents designed to address disease at the molecular level, so more biomarkers are actionable than 10 years ago.

- However, rigid clinical workflows, policy constructs, regulatory pathways, reimbursement based on old technologies represent frictions to investment in and adoption of new practices.

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The University of Arizona Health Sciences

Precision medicine and biomarkers: intersection of the -*omics* ecosystem and healthcare policy

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