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This lecture on **“Whole Genome Analysis as a Universal Diagnostic: A Pathologist’s Perspective”** is given by Mark Boguski MD, PhD, FCAP

Your host is Jill Kaufman, PhD.
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THE WEBINAR WILL BEGIN MOMENTARILY. ENJOY!

Mark Boguski, MD, PhD, FCAP

- Faculty of Harvard Medical School at the Center for Biomedical Informatics and the Department of Pathology at Beth Israel Deaconess Medical Center in Boston
- He was honored as a Visionary and Influencer by the Personalized Medicine Coalition and a Pioneer of Proteomics by the U.S. National Cancer Institute in 2006
- He was elected to the Institute of Medicine of the U.S. National Academy of Sciences and the American College of Medical Informatics in 2001





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Whole Genome Analysis as a Universal Diagnostic

A Pathologist's Perspective

Mark S. Boguski, M.D., Ph.D., F.C.A.P.

Center for Biomedical Informatics, Harvard Medical School

Department of Pathology, BIDMC

April 26, 2011

www.cap.org

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PRESENTER DISCLOSURE INFORMATION

Mark Boguski

The following relationships exist related to this presentation:

Scientific Advisory Board, consulting fees, modest level of relationship



Co-founder, ownership, minority partner in LLC



**“[a patient’s genome] is
just another lab value.”**

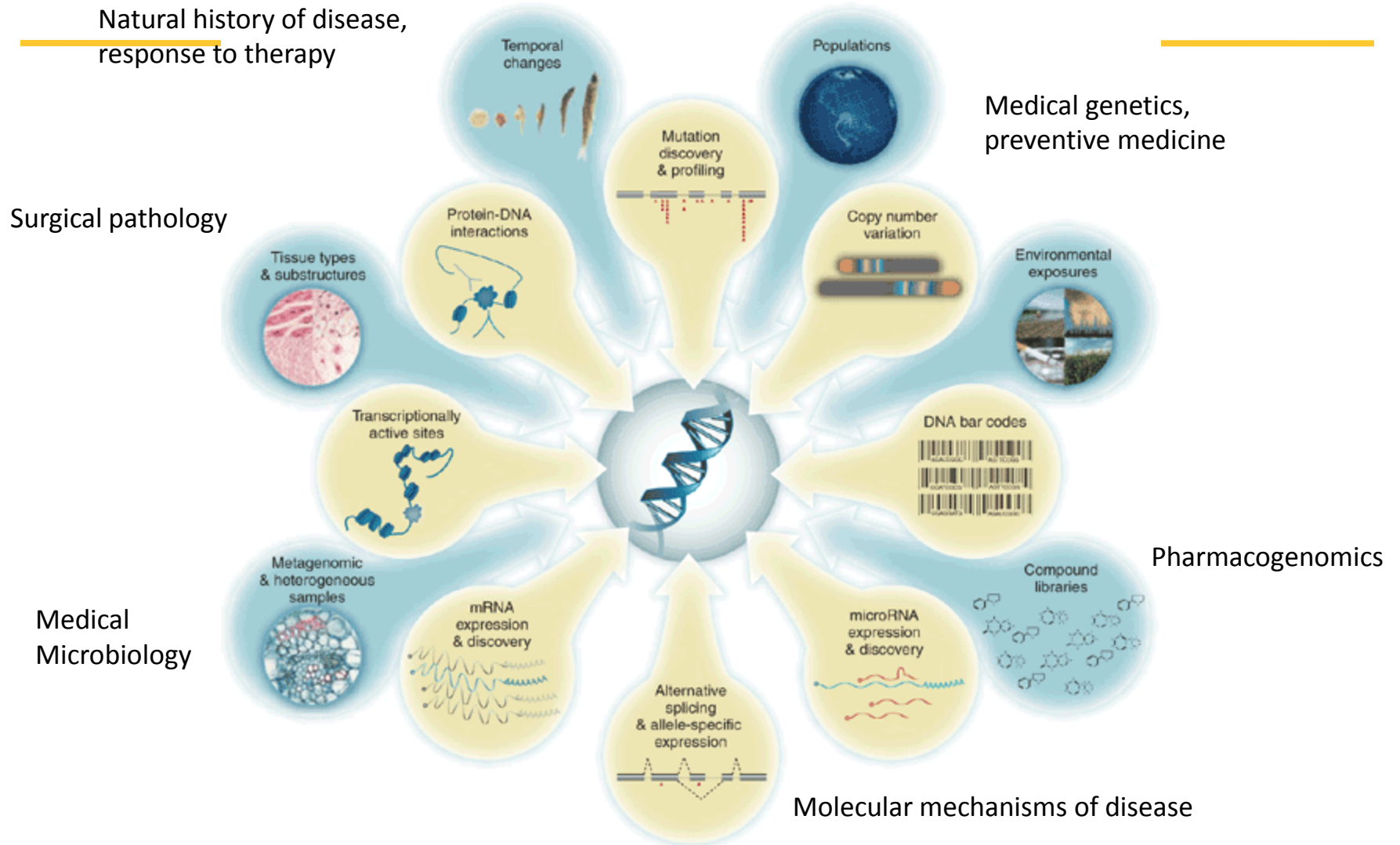
-- D. Dimmock
ACMG, Vancouver
18 March 2011



Medical Genomics: Drivers and Potential for Disruptive Change

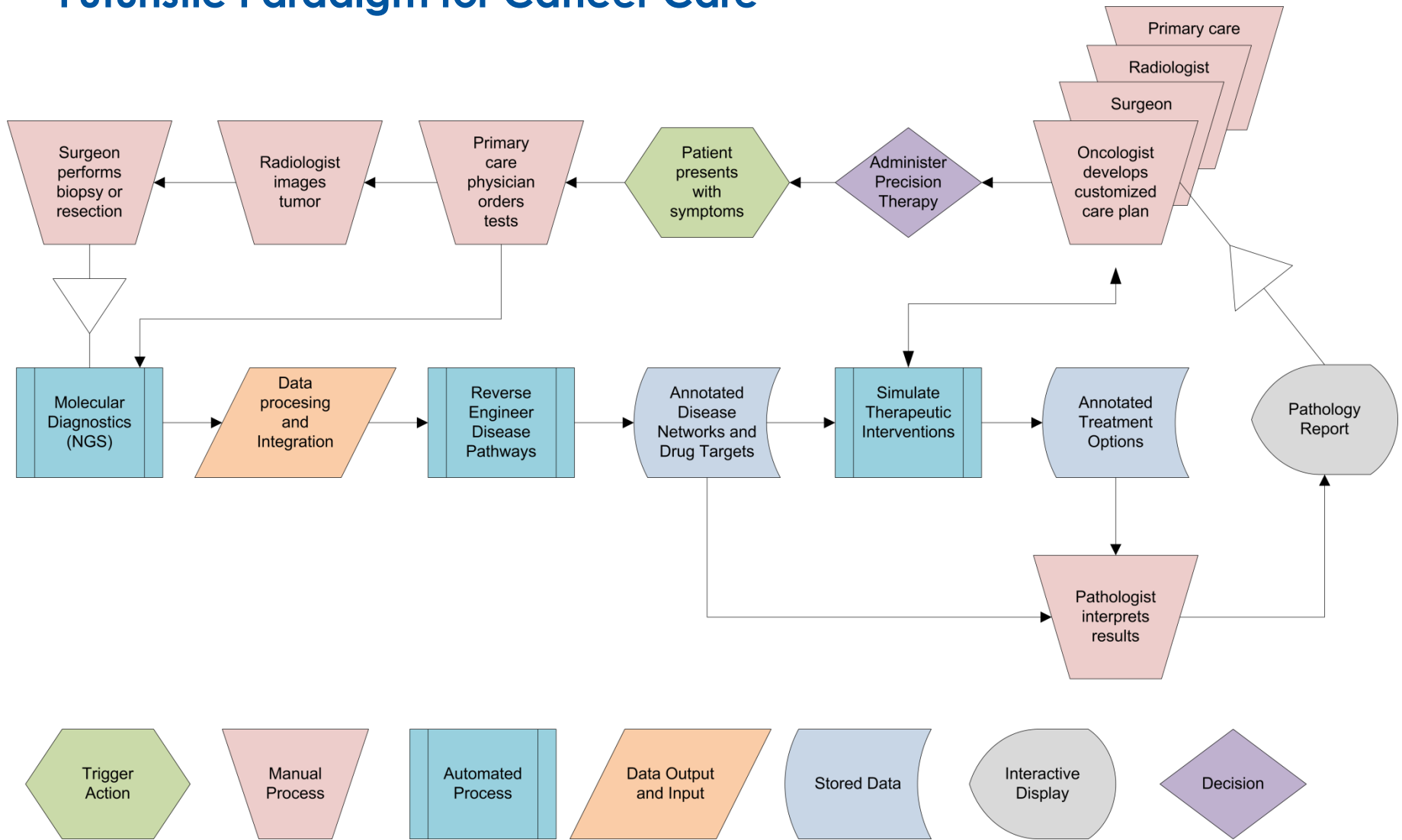
Time Period	Genomes	Turn-around time	FTEs	Cost per genome
1990-2003	1. NIH reference 2. Celera reference	~5 years	~2,000	~\$2-3 billion
2003-2009	~10 additional	~6 months	Dozens	\$300,000→38,000
2010-2014	10 ³ -10 ⁵	4-6 weeks	3-4	\$ 6,000 exome \$ 9,500 genome
2015-2020	Millions	15 minutes	<<1	\$100-250

Whole Genome Analysis as a Universal Diagnostic



Kahvejian A., Quackenbush J., Thompson J.F. What would you do if you could sequence everything?

Futuristic Paradigm for Cancer Care



Boguski MS, Arnaout R, Hill C. Customized care 2020: how medical sequencing and network biology will enable personalized medicine. *F1000 Biol Rep.* 1:7 doi:10.3410/B1-73, 2009

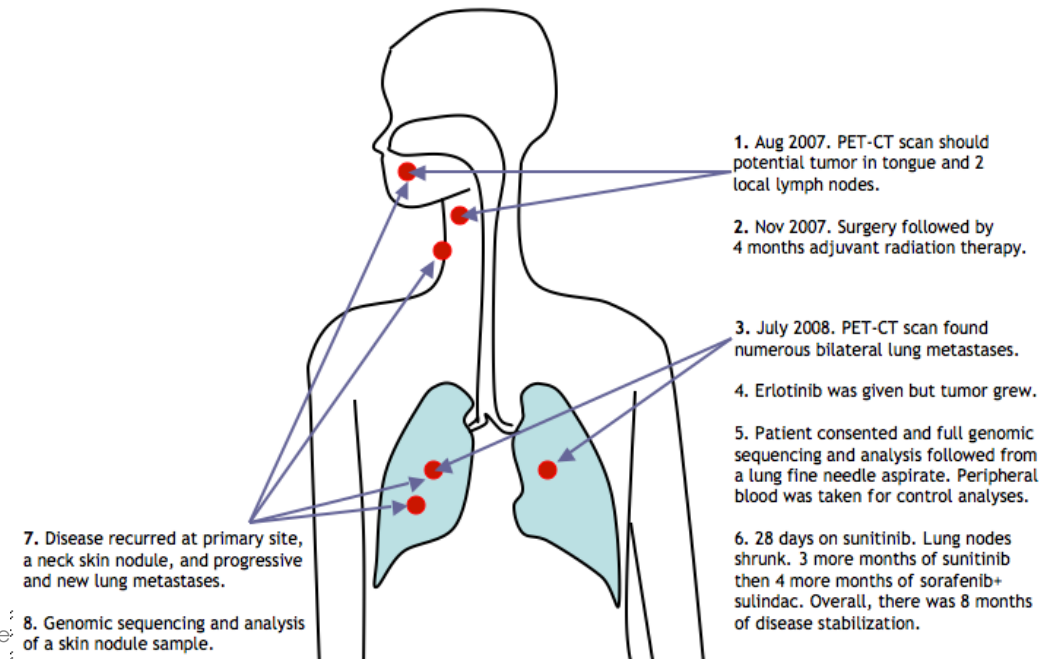
Evolution of an adenocarcinoma in response to selection by targeted kinase inhibitors

Steven JM Jones^{1*}, Janessa Laskin², Yvonne Y Li¹, Obi L Griffith¹, Jianghong An¹, Mikhail Bilenky¹, Yaron S Butterfield¹, Timothee Cezard¹, Eric Chuah¹, Richard Corbett¹, Anthony P Fejes¹, Malachi Griffith¹, John Yee³, Montgomery Martin², Michael Mayo¹, Nataliya Melnyk⁴, Ryan D Morin¹, Trevor J Pugh¹, Tesa Severson¹, Sohrab P Shah^{4,5}, Margaret Sutcliffe², Angela Tam¹, Jefferson Terry⁴, Nina Thiessen¹, Thomas Thomson², Richard Varhol¹, Thomas Zeng¹, Yongjun Zhao¹, Richard A Moore¹, David G Huntsman³, Inanc Birol¹, Martin Hirst¹, Robert A Holt¹, Marco A Marra¹

- 1 Genome Sciences Centre, British Columbia Cancer Agency, 570 West 7th Avenue, Vancouver, BC, V5Z 4S6, Canada
- 2 British Columbia Cancer Agency, 600 West 10th Avenue, Vancouver, BC, V5Z 4E6, Canada
- 3 Vancouver General Hospital, West 12th Avenue, Vancouver, BC, V5Z 1M9, Canada
- 4 Centre for Translational and Applied Genomics of British Columbia Cancer Agency and the Provincial Health Services Authority Laboratories, 600 West 10th Avenue, Vancouver, V5Z 4E6, BC, Canada
- 5 Molecular Oncology, BC Cancer Research Centre, 601 West 10th Avenue, Vancouver, BC, V5Z 1L3, Canada

Case History No. 1

- 78 y/o male, no prior H/O Ca, presented with throat discomfort
 - Biopsy revealed papillary adenocarcinoma
- Laser resection and lymph node dissection, 3/21 nodes positive
 - 60 Gy adjuvant radiation therapy administered
- 4 months later, PET-CT revealed numerous small bilateral pulmonary mets
 - No standard chemo (rare tumor); pathology review indicated 2+ EGFR
- Erlotinib started
 - Lack of response and tumor progression
- Diagnostic Whole Genome and Transcriptome Analyses

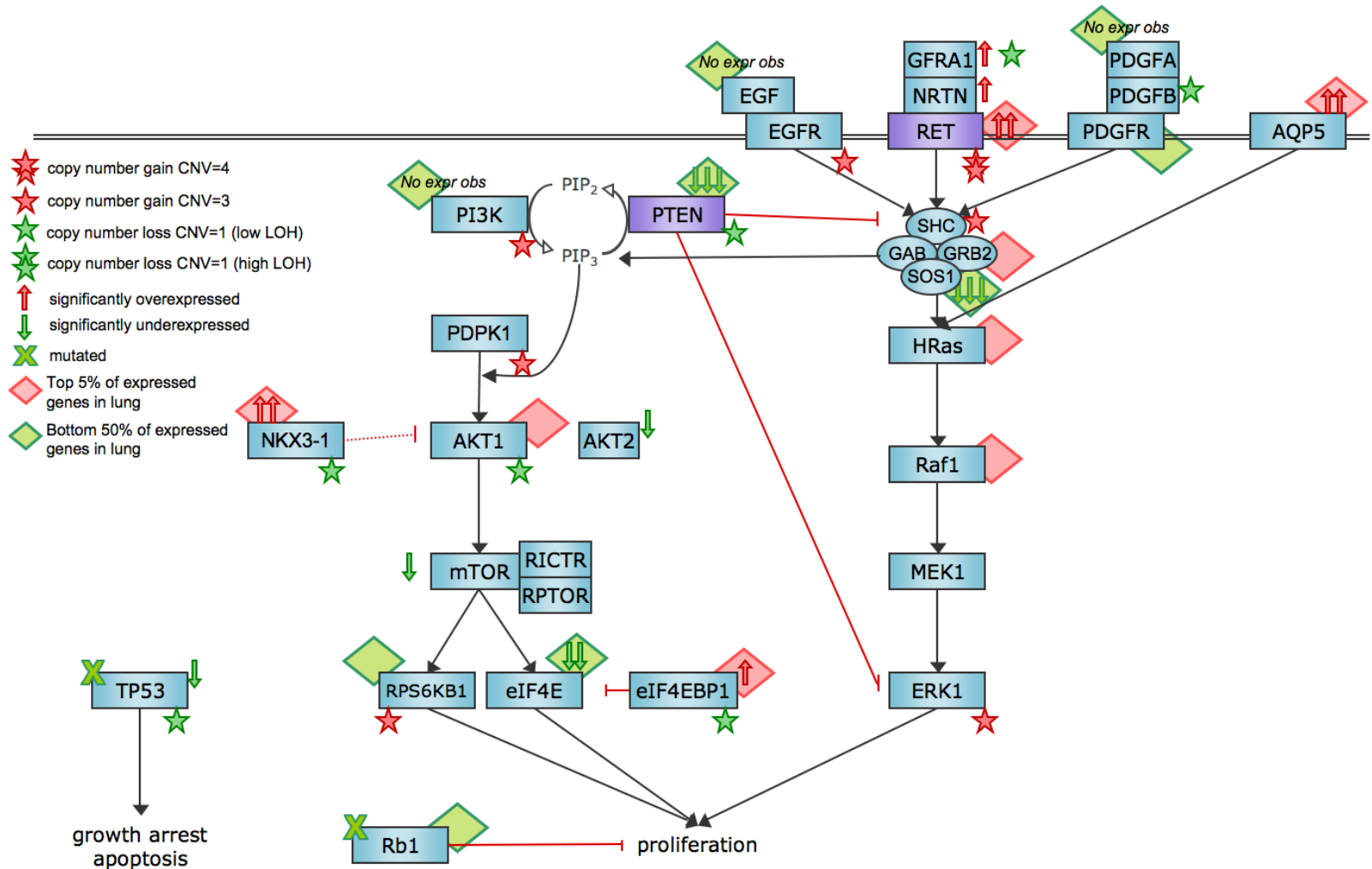


Sequence Analyses of Tumor to Guide Therapy

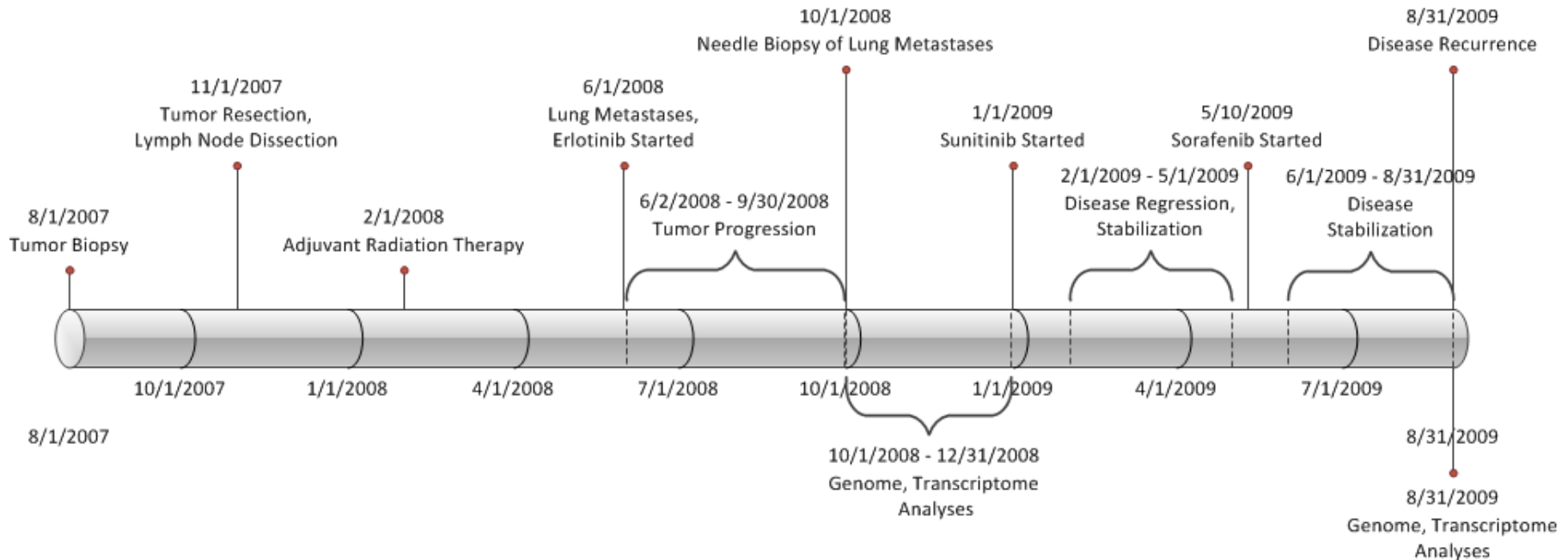
- Genome sequencing and analysis:
 - Comparing tumor genome sequence to peripheral blood lymphocyte (normal, somatic) genome
 - Mutation detection
- Transcriptome analysis:
 - Digital gene expression profiling of tumor
- Search of pharmacopeia
 - Relate mutations and gene expression data to drugs with known therapeutic targets and mechanisms of action

“Whole Genome Analysis” may encompass genome or exome +/- transcriptome depending upon clinical indication and diagnostic goals

Pathology Report



Clinical Course



In cancer, **whole genome analysis** will be done **not once, but multiple times** during the course of the disease for tumor subtyping, monitoring response to therapy and diagnosing the reasons for recurrences or therapeutic failures.

RESEARCH

Open Access

Evolution of an adenocarcinoma in response to selection by targeted kinase inhibitors

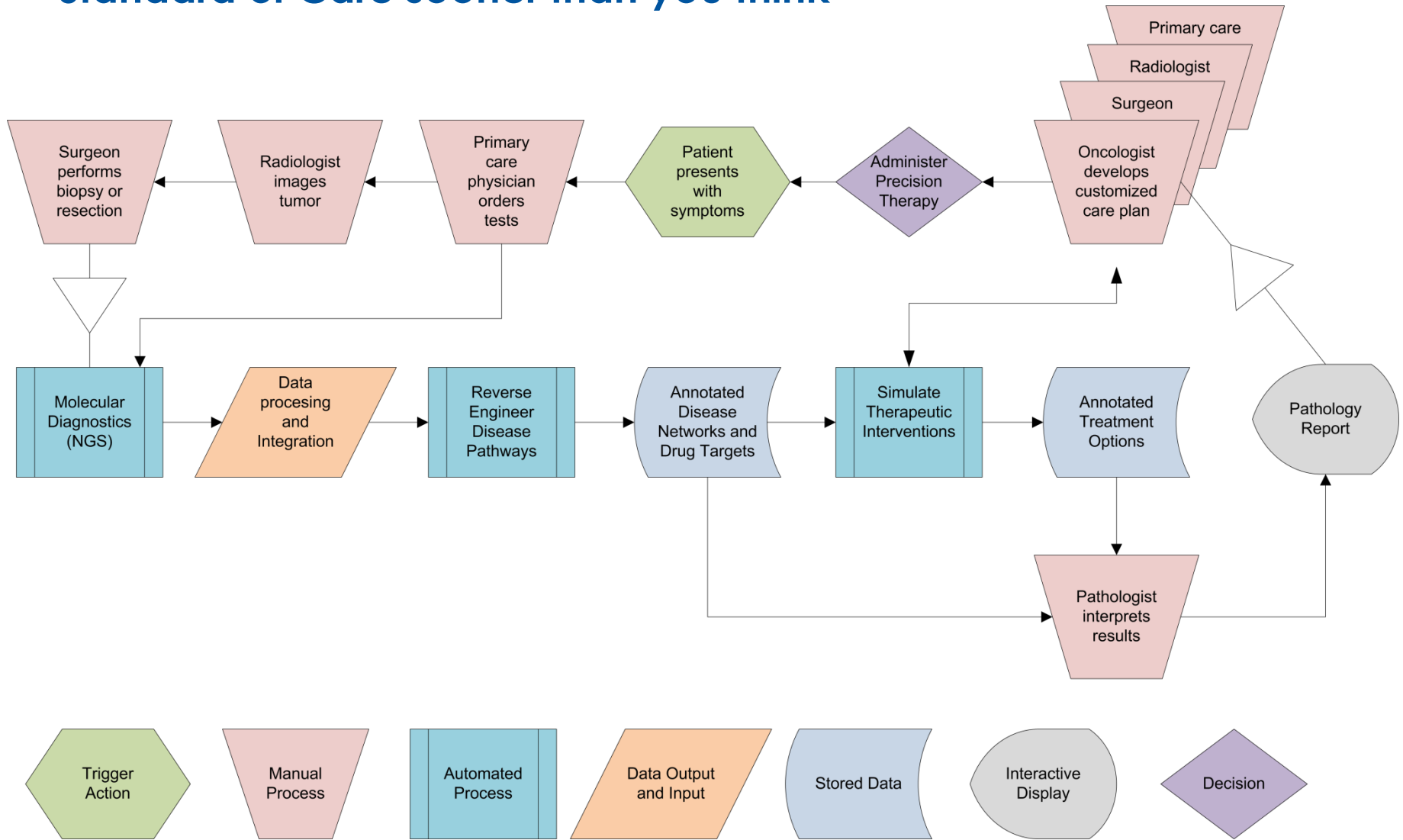
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Conclusion:

“...whole genome characterization will become a routine part of cancer pathology.”

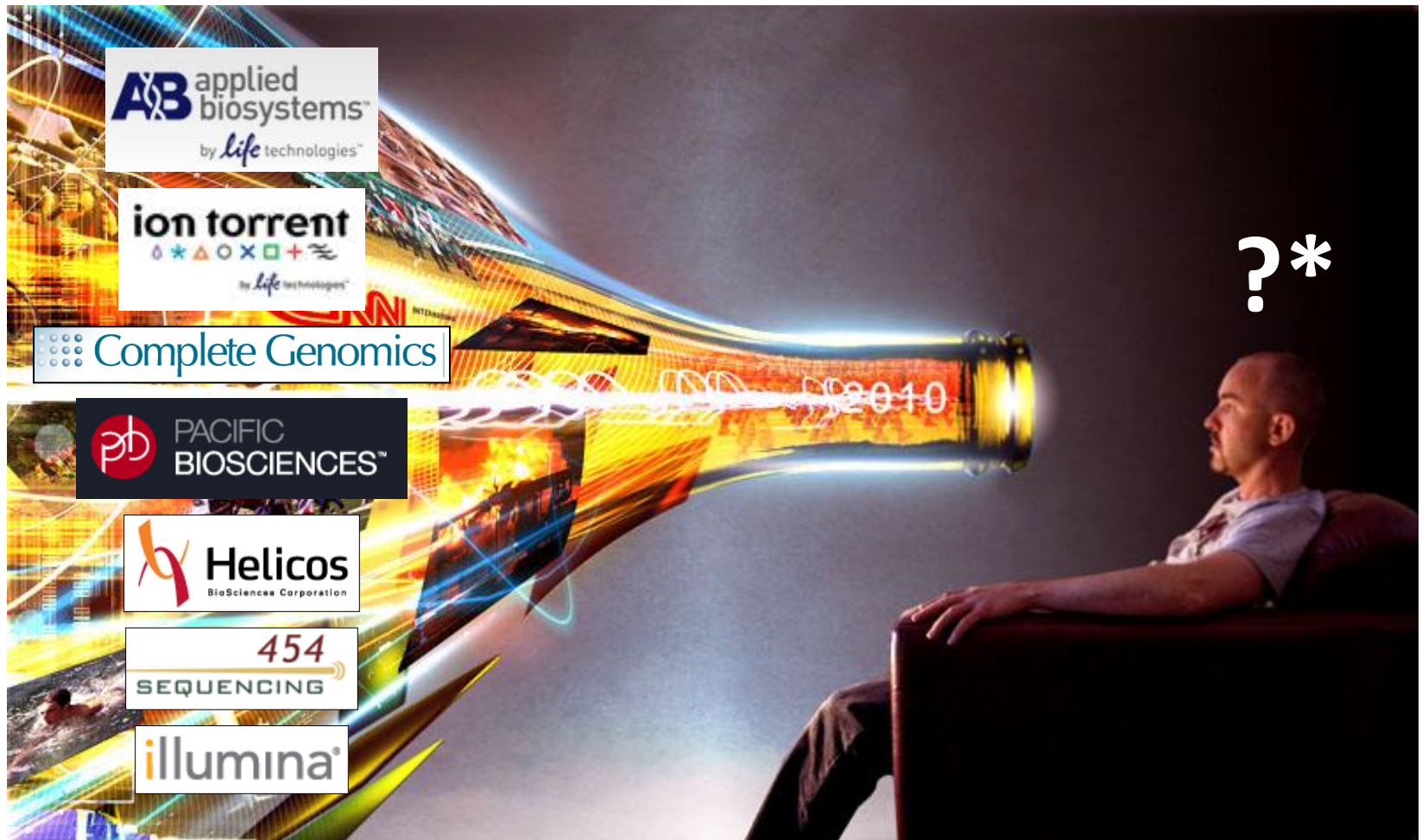
Futuristic Paradigm for Cancer Care?

Standard of Care sooner than you think



Boguski MS, Arnaout R, Hill C. Customized care 2020: how medical sequencing and network biology will enable personalized medicine. *F1000 Biol Rep.* 1:7 doi:10.3410/B1-73, 2009

Pathologist's New "Microscope"

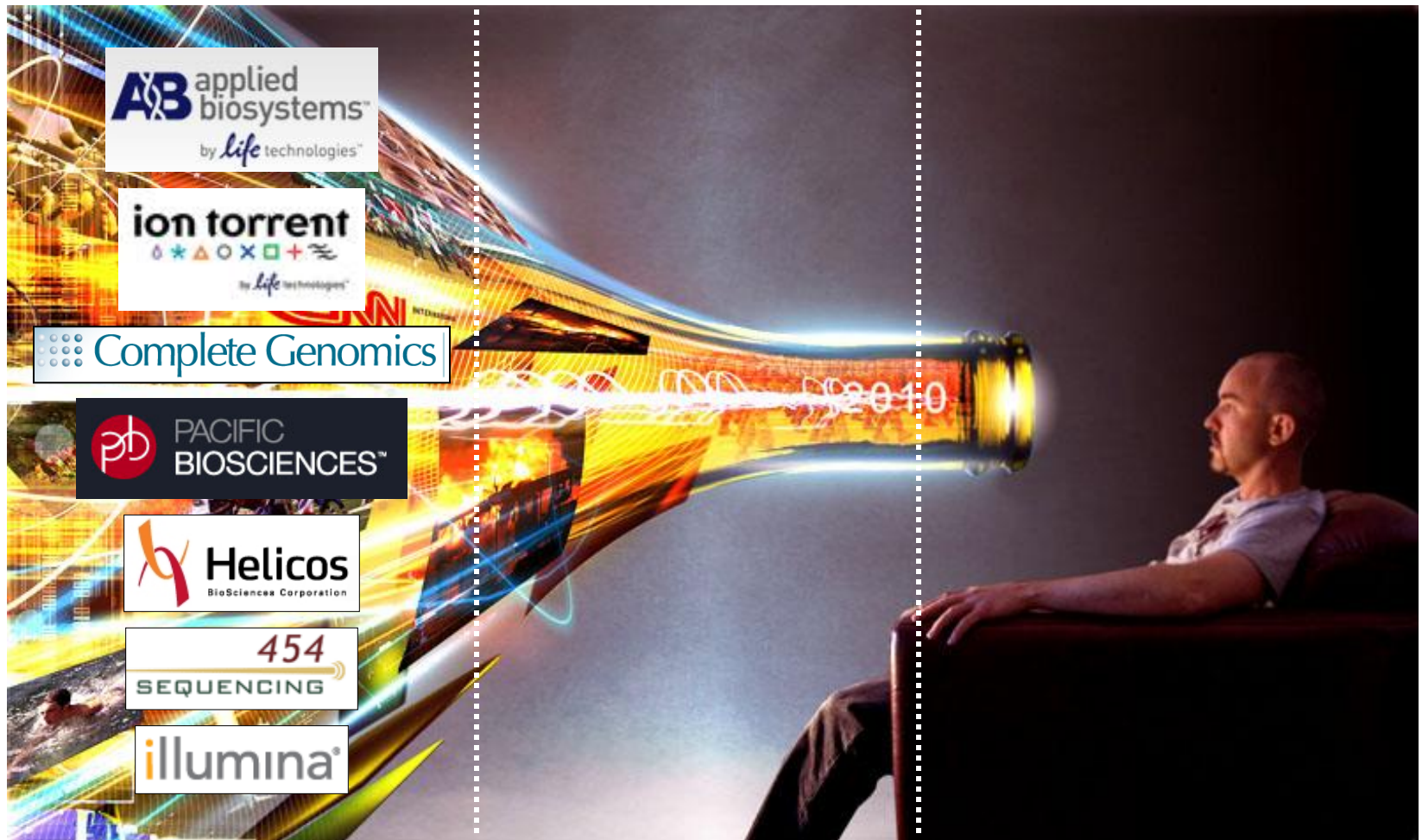


*3-4 bioinformaticians x ~4 weeks per genome to medically annotate the data

Data Production

Data Annotation

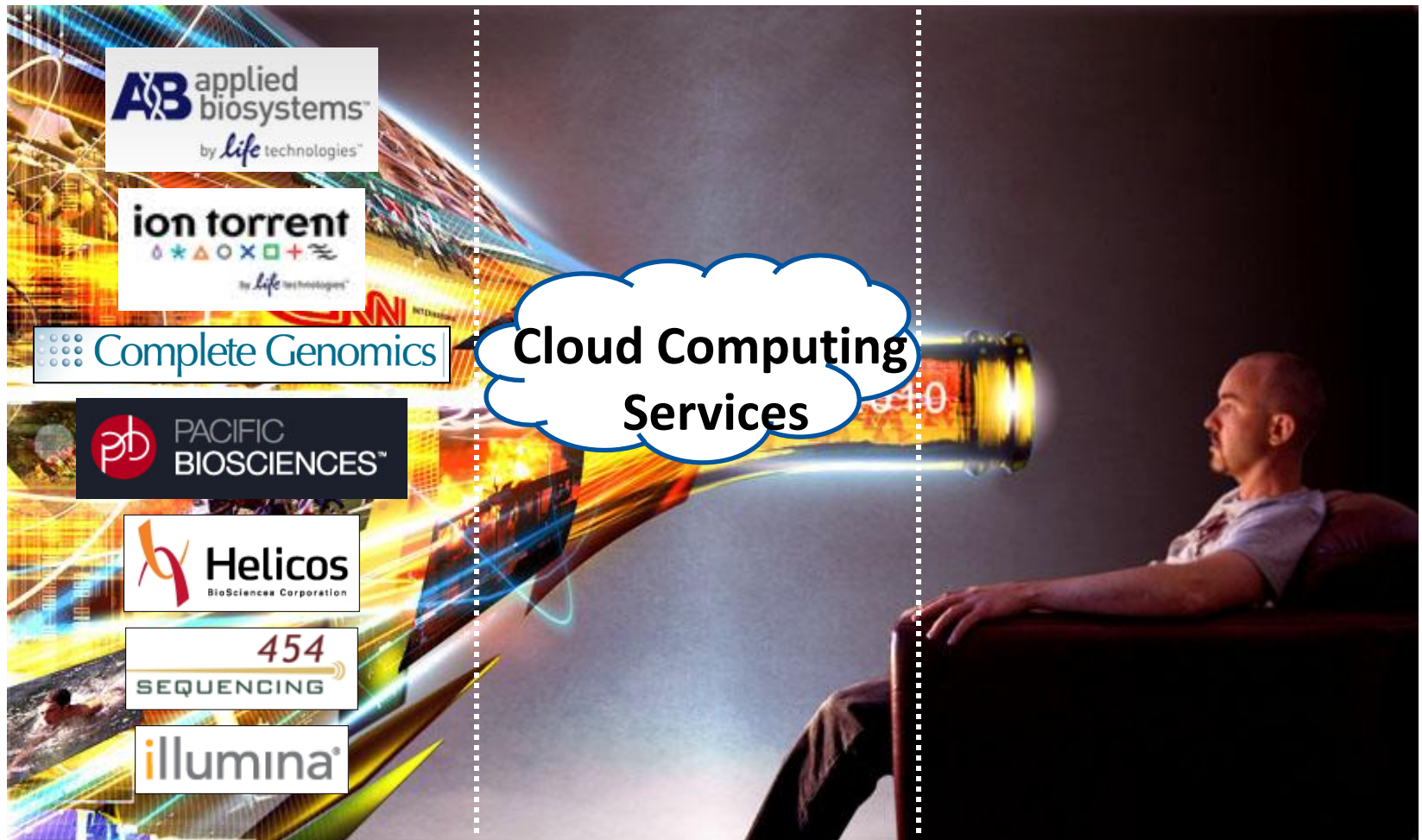
Data Interpretation



Data Production

Data Annotation

Data Interpretation



“Send outs”

Report generation

Data Production

Data Annotation

Data Interpretation



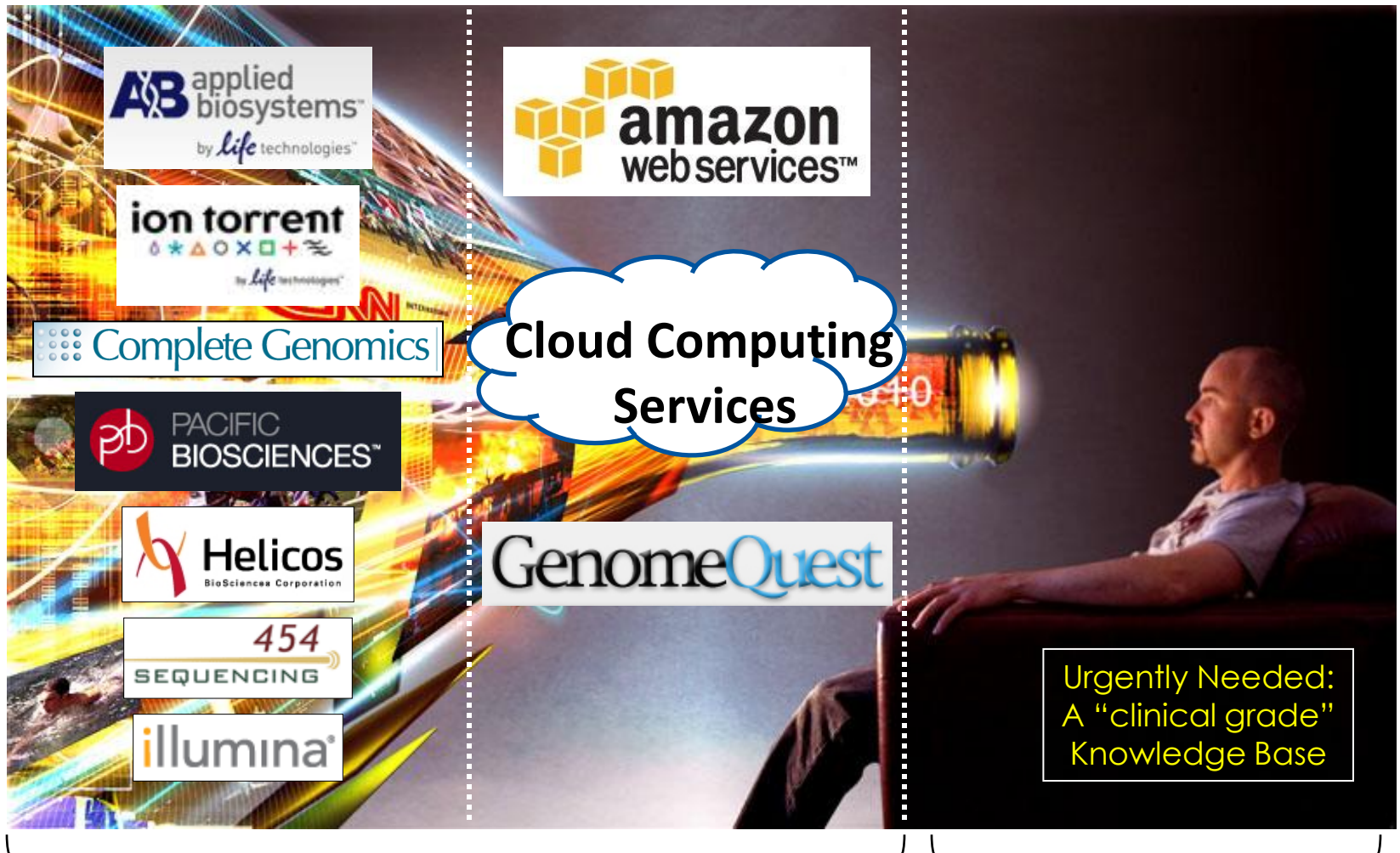
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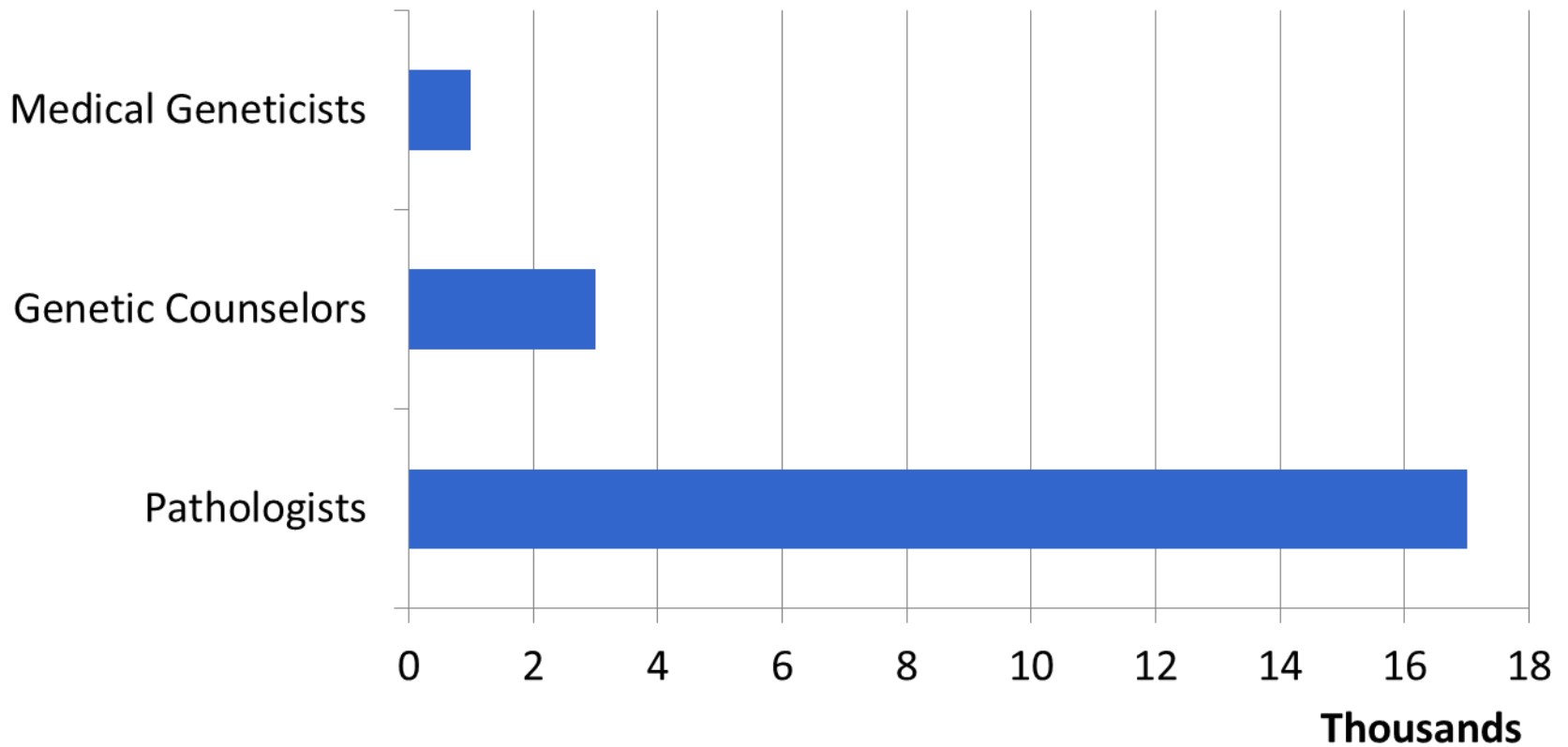


“Send outs”

Report generation

Potential Workforces for Personalized Genomic Medicine

Current Practitioners



GENOMIC MEDICINE INITIATIVE

Department of Pathology



Beth Israel Deaconess
Medical Center

A TEACHING HOSPITAL OF HARVARD MEDICAL SCHOOL



Home

Personalized medicine refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not. –**President's Council of Advisors on Science and Technology (PCAST)**

September 2008 quoted in [The Case for Personalized Medicine](#)

Medical Sequencing and the Enablement of Personalized Healthcare – [Faculty of 1000 Report September 2009](#)

A Call to Action

[American Journal of Clinical Pathology June 2010](#)

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www.GenomicMedicineInitiative.org

Banbury Center Meeting on Genome-Era Pathology

Oct 13-15, 2010: 27 stakeholders from gov't, academe, ...

- Industry (PMC, Aetna, Medco, et al.) and
- Pathology professional organizations (CAP, AMP, ASCP, USCAP)

Action Plan: Seven “Blue Dot”* pilot projects with 2-20 month timelines

1. Establish nationwide program for residency training by July 2012
2. Compile and analyze current genetic, newborn and molecular pathology tests and create a WGA “replacement map”
3. Establish a prototype “clinical grade” disease variant database for one disease area by December 2011
4. Identify and validate operational models for WGA
5. Formulate the regulatory guidelines to conduct WGA test accreditation
6. Define the concept of the “primary care pathologist” in genome-era medicine
7. Address reimbursement issues

*E D. Green *et al.* Charting a course for genomic medicine from base pairs to bedside. *Nature* **470**, 204-213 (2011)

A National Agenda for the Future of Pathology in Personalized Medicine

Report of the Proceedings of a Meeting at the Banbury Conference Center on Genome-Era Pathology, Precision Diagnostics, and Preemptive Care: A Stakeholder Summit

Peter J. Tonellato, PhD,^{1,2} James M. Crawford, MD, PhD,³ Mark S. Boguski, MD, PhD,^{1,2} and Jeffrey E. Saffitz, MD, PhD¹

Key Words: Next-generation sequencing; Whole genome analysis; Personalized medicine; Pathology

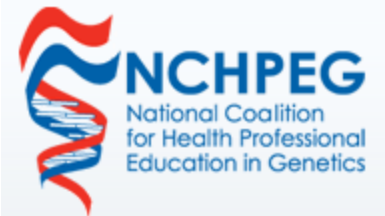
DOI: 10.1309/AJCP9GDNLWB4GACI

Am J Clin Pathol 2011; 135:668-672

BLUE DOT PROJECT #1

Training Residents in Genomics (T.R.I.G)

Co-chairs: R. Haspel (BIDMC) and Debra Leonard (Weill Cornell)



Case History No. 2

- 60 year-old man with a long history of alcohol and tobacco abuse presents with difficulty breathing and heart palpitations
- Physical examination revealed palpable right supraclavicular lymph nodes; a biopsy revealed metastatic squamous cell carcinoma originating in the esophagus
- Standard cytotoxic chemotherapy was initiated
- The tumor genome was sequenced along with the genome of the patient's peripheral blood lymphocytes
- Following analysis of the data, cytotoxic chemotherapy was discontinued and the patient was started on Imatinib (and prayer)

Evangelical Christian uses “The Language of God” to Diagnose and Treat Atheist's Cancer

Christopher Hitchens



Francis Collins, M.D.



www.medpagetoday.com/Blogs/25732

Do you know?

1. For which cancer(s) is Imatininb/Gleevec an approved treatment?
2. Which of Mr. Hitchens' 22,000 genes suggested that his tumor might respond to this drug?
3. Are there any CLIA-certified, CAP-accredited laboratories for human genome sequencing?
4. Is there a CPT code for Whole Genome Analysis as diagnostic procedure?
5. The first human genome cost \$2.6 billion to sequence and analyze. What is the current cost of a genome sequence?
 1. About the same amount as a routine staging MRI or CT scan
 2. About the same amount as FDA-recommended pharmacogenetic testing for Coumadin or Plavix dosing
 3. About \$10,000

Challenges and Opportunities

- Education & Training
 - Residents
 - Current practitioners (CME)
 - Medical students
- Technology Access
 - In-house vs. “send outs”
- Support practice infrastructure
 - “Clinical grade” annotation database
- Interface with other specialties
 - Medical geneticists & Genetic counselors
 - Why Pathologists?
- Regulatory regimes
 - FDA
 - CMS (CLIA)
- Reimbursement
 - CMS & Private
 - Out of pocket?

Acknowledgements

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Stuart Schnitt • Peter Tonellato • Dennis Wall

www.GenomicMedicineInitiative.org



Beth Israel Deaconess
Medical Center



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 - Molecular Diagnosis for Lung Cancer
 - Molecular Diagnosis for Colorectal Cancer
 - Endoscopic Microscopy: Bridging the Radiology/Pathology Divide
 - Considerations in Setting up a Biorepository
 - Personalized Pathology: PHC in the General Pathology Practice
 - Introduction to the Medical Home