

Personalized Genomic Medicine

A Pathologist's Perspective

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July 19, 2011



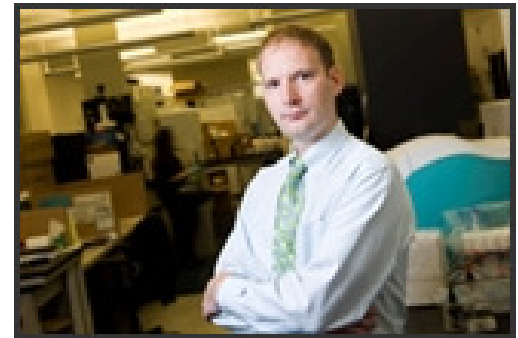
Beth Israel Deaconess
Medical Center



A teaching hospital of
Harvard Medical School

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

-- D.P. Dimmock
ACMG, Vancouver
18 March 2011

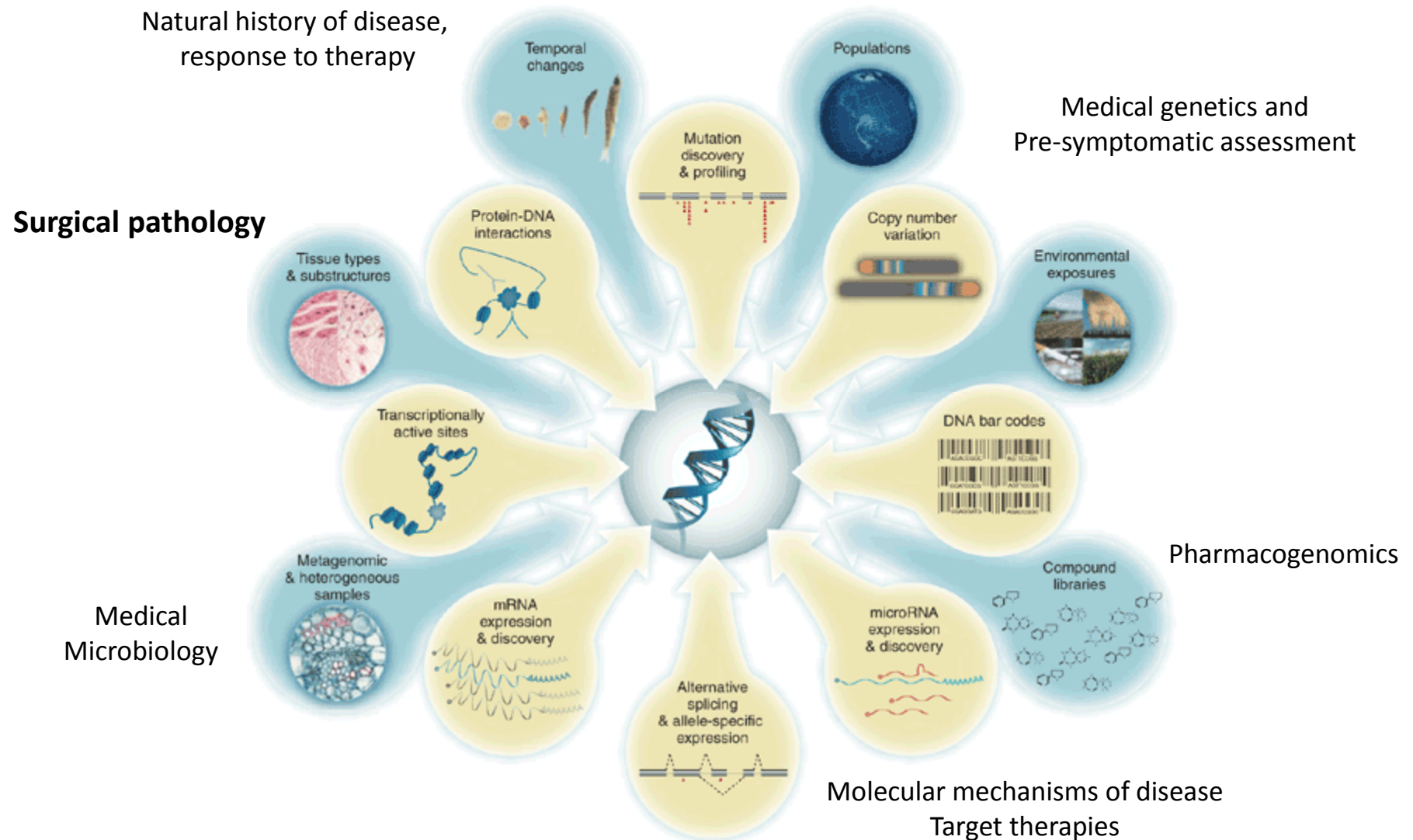


Genetics in Medicine 2011; 13(3):255-262

Medical Genomics: Drivers and Potential for Disruptive Change

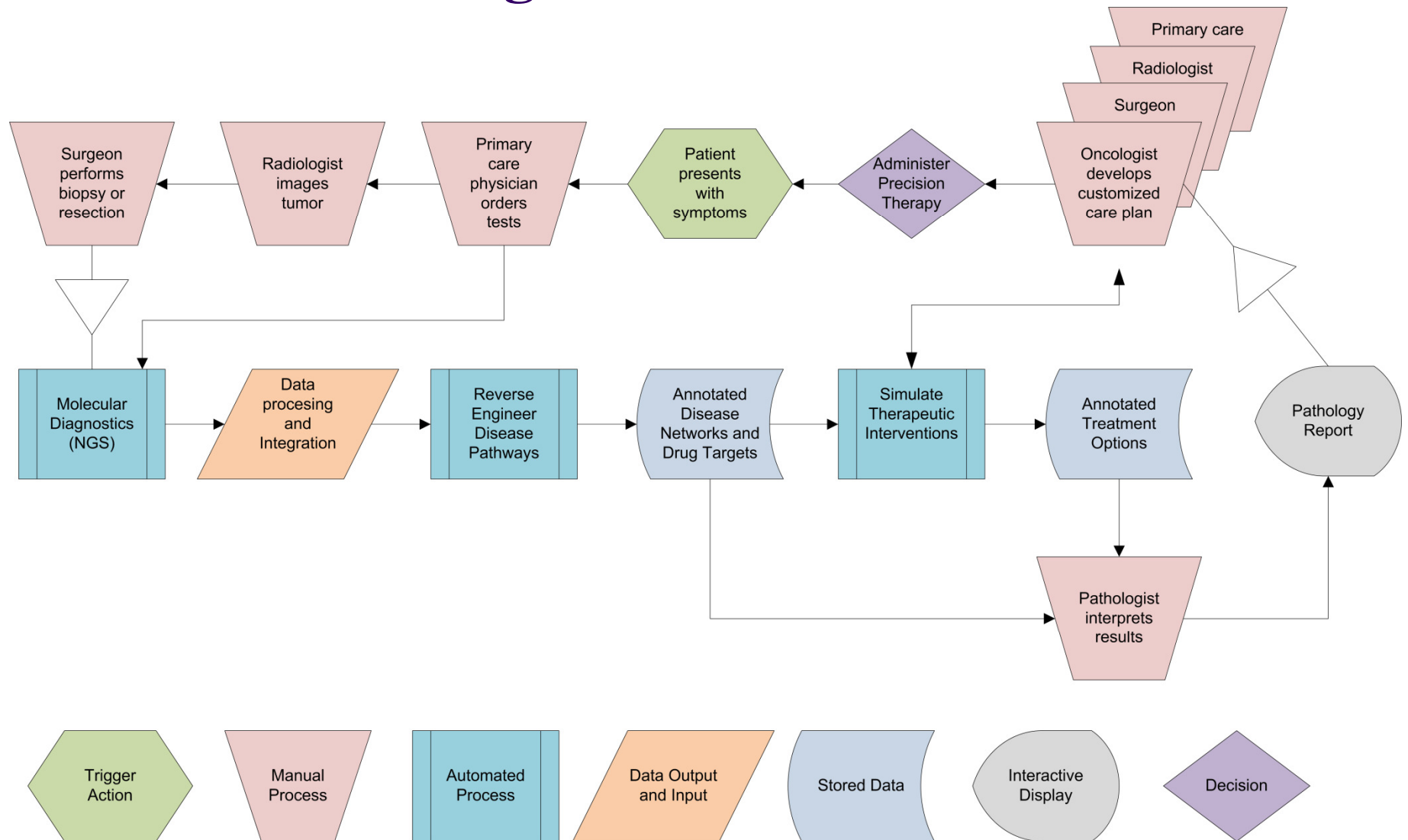
Time Period	Genomes	Turn-around time	FTEs	Cost per genome
1998-2003	1. NIH reference 2. Celera reference	~5 years	~2,000	~\$2-3 billion
2003-2009	~10 additional	~6 months	Dozens	\$300,000→38,000
2010-2011	10^3 - 10^4	4-6 weeks	3-4	\$ 6,000 exome \$ 9,500 genome
2012-2014	10^5	2 weeks	2	\$5,000→\$1,000
2015-2020	Millions	Hours?	<1	<\$1,000

Whole Genome Analysis as a Universal Diagnostic



Kahvejian A., Quackenbush J., Thompson J.F. What would you do if you could sequence everything?
Nat Biotechnol. 26(10):1125-33, 2008

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

The Future is Now!

Jones et al. *Genome Biology* 2010, **11**:R82
<http://genomebiology.com/2010/11/8/R82>



RESEARCH

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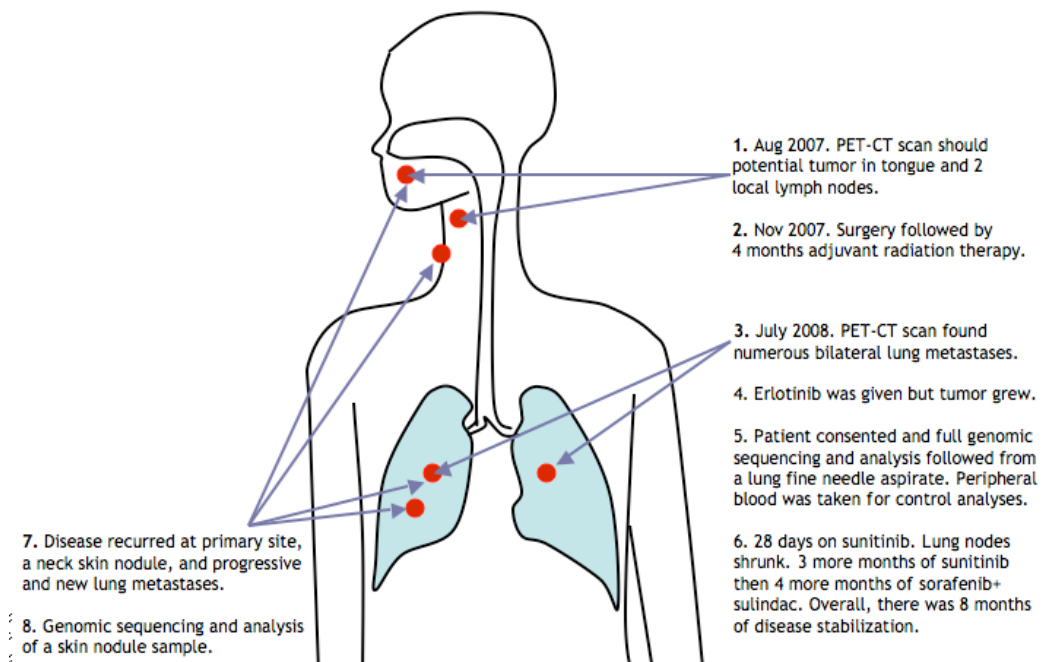
Evolution of an adenocarcinoma in response to selection by targeted kinase inhibitors

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 (Tarceva®) started
 - Lack of response and tumor progression
- Diagnostic Whole Genome and Transcriptome Analyses

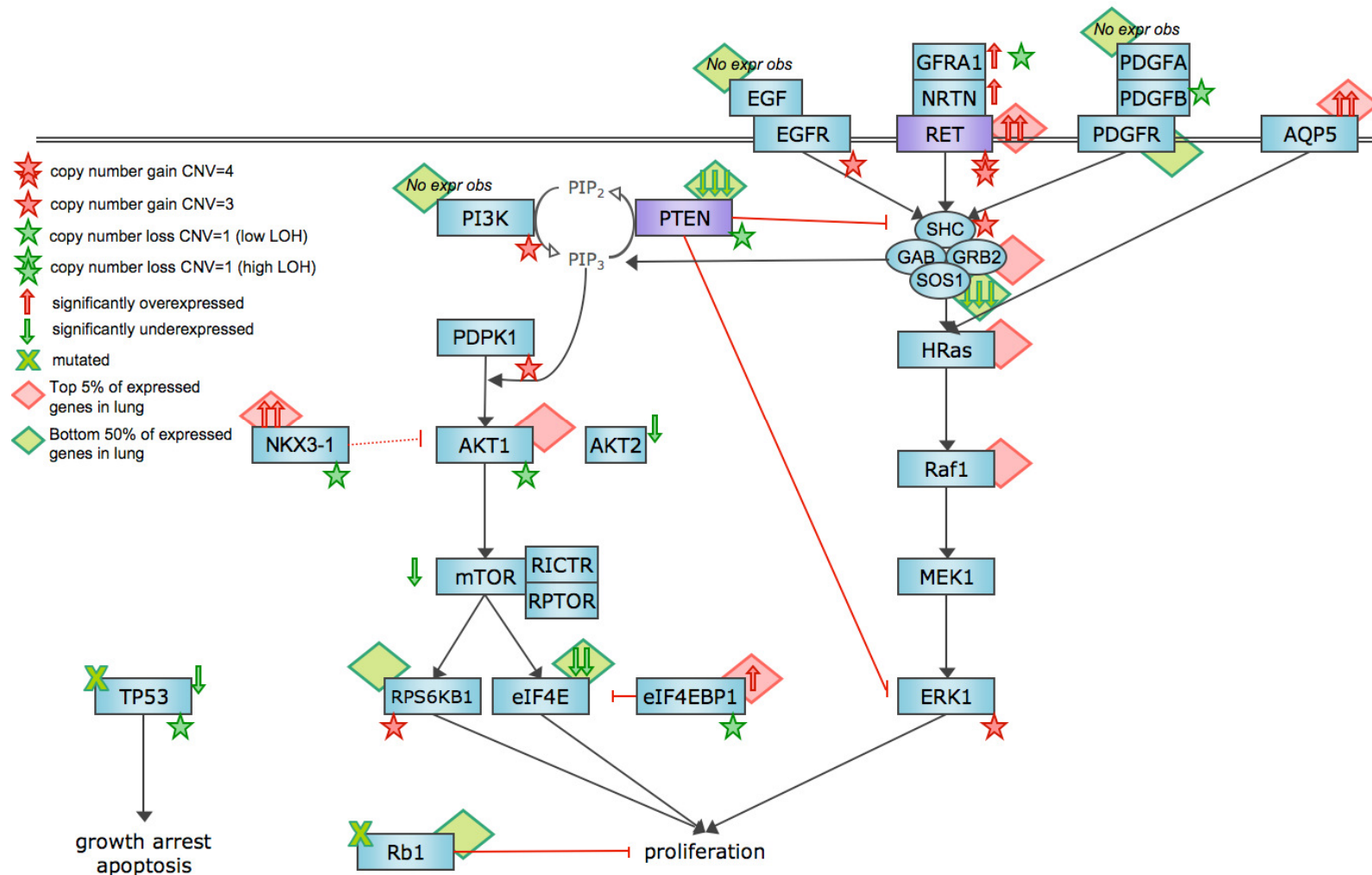


Sequence Analyses of Tumor to Guide Therapy

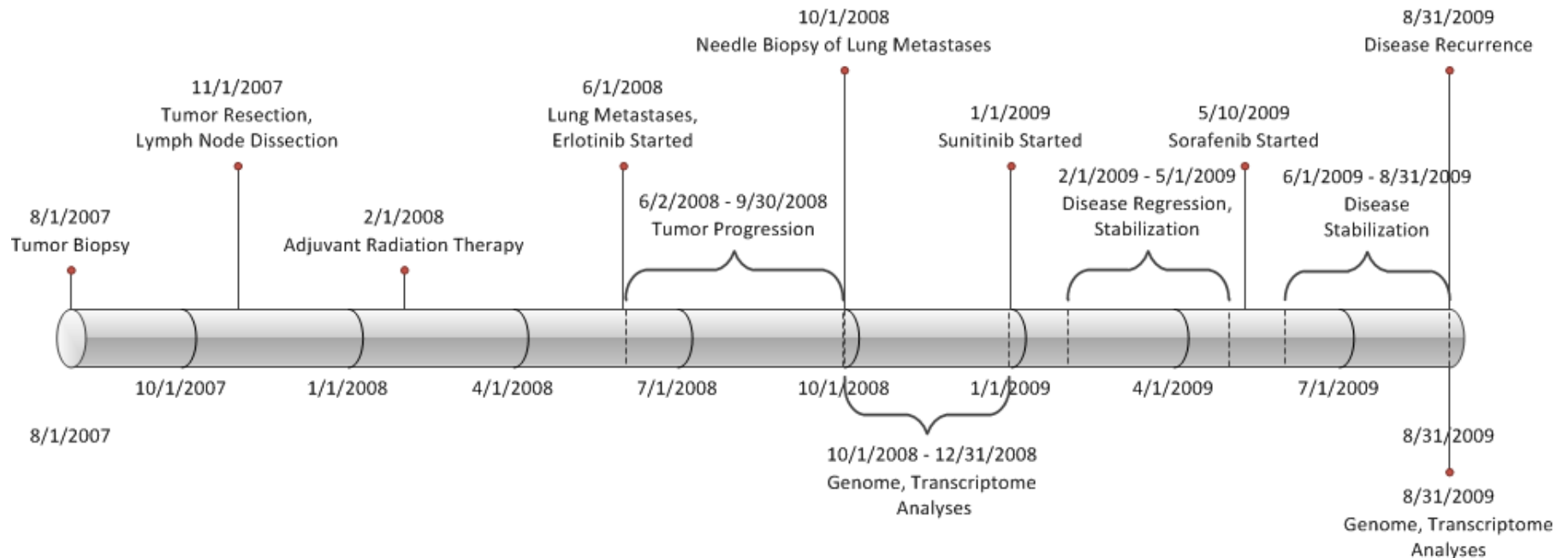
- Genome sequencing and analysis:
 - Comparing tumor genome sequence to peripheral blood lymphocyte (normal, somatic) genome
 - Mutation detection
- Transcriptome analysis:
 - Digital gene expression profiling of tumor
- Search of DrugBank.ca
 - Relate mutations and gene expression data to drugs with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

“Whole Genome Analysis” requires a variable **data package** of 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

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

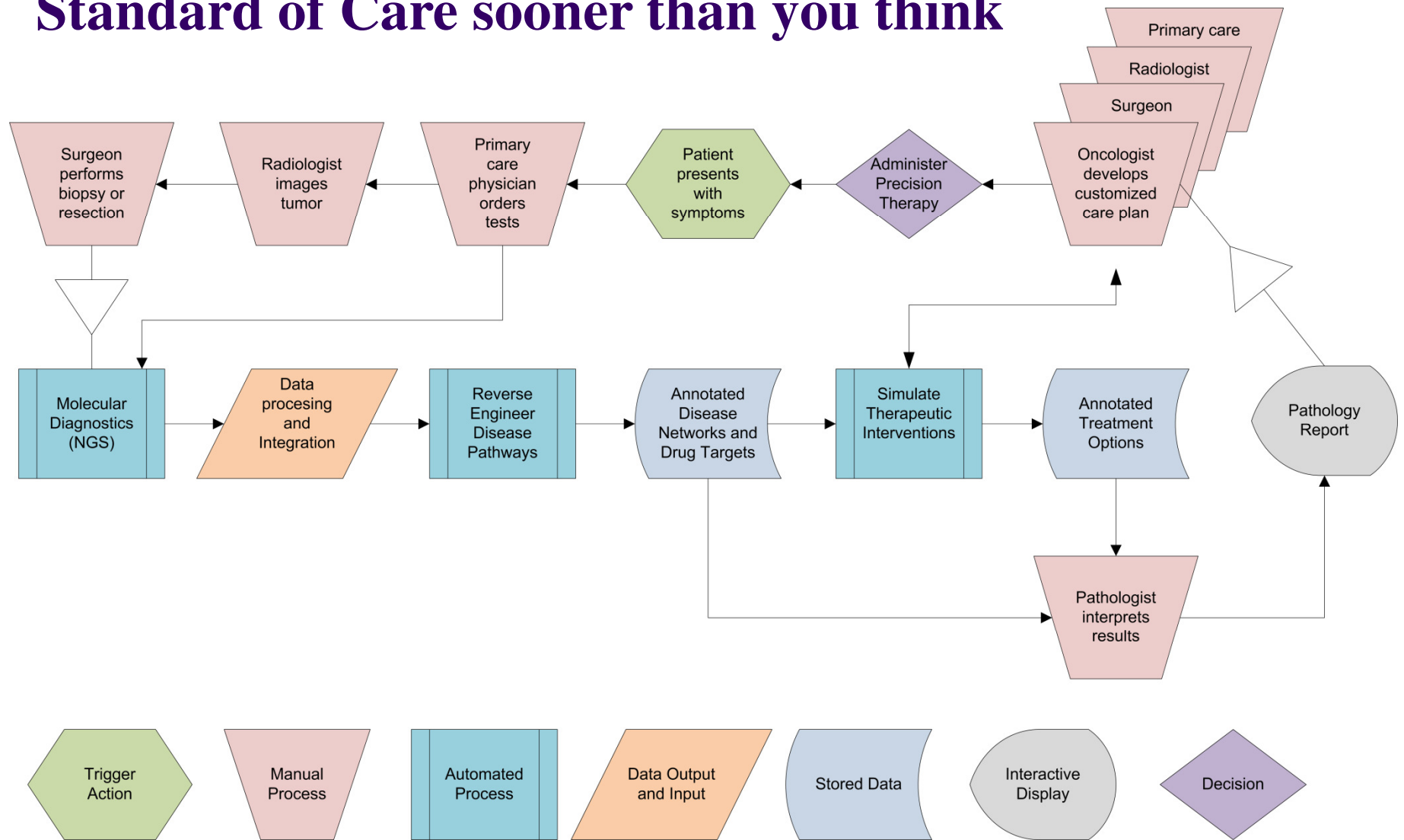
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Conclusion:

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

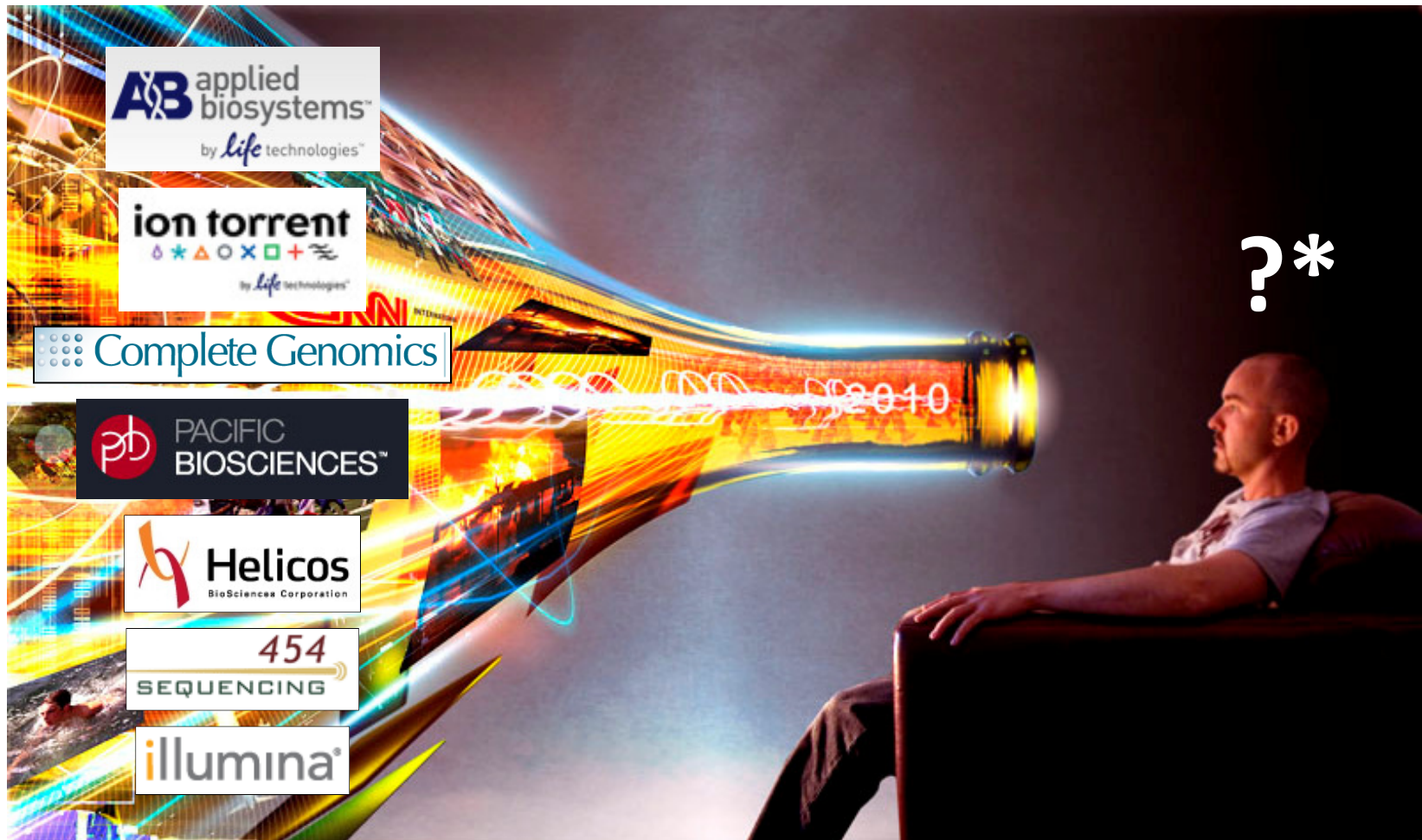
~~Futuristic Paradigm for Cancer Care?~~

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”

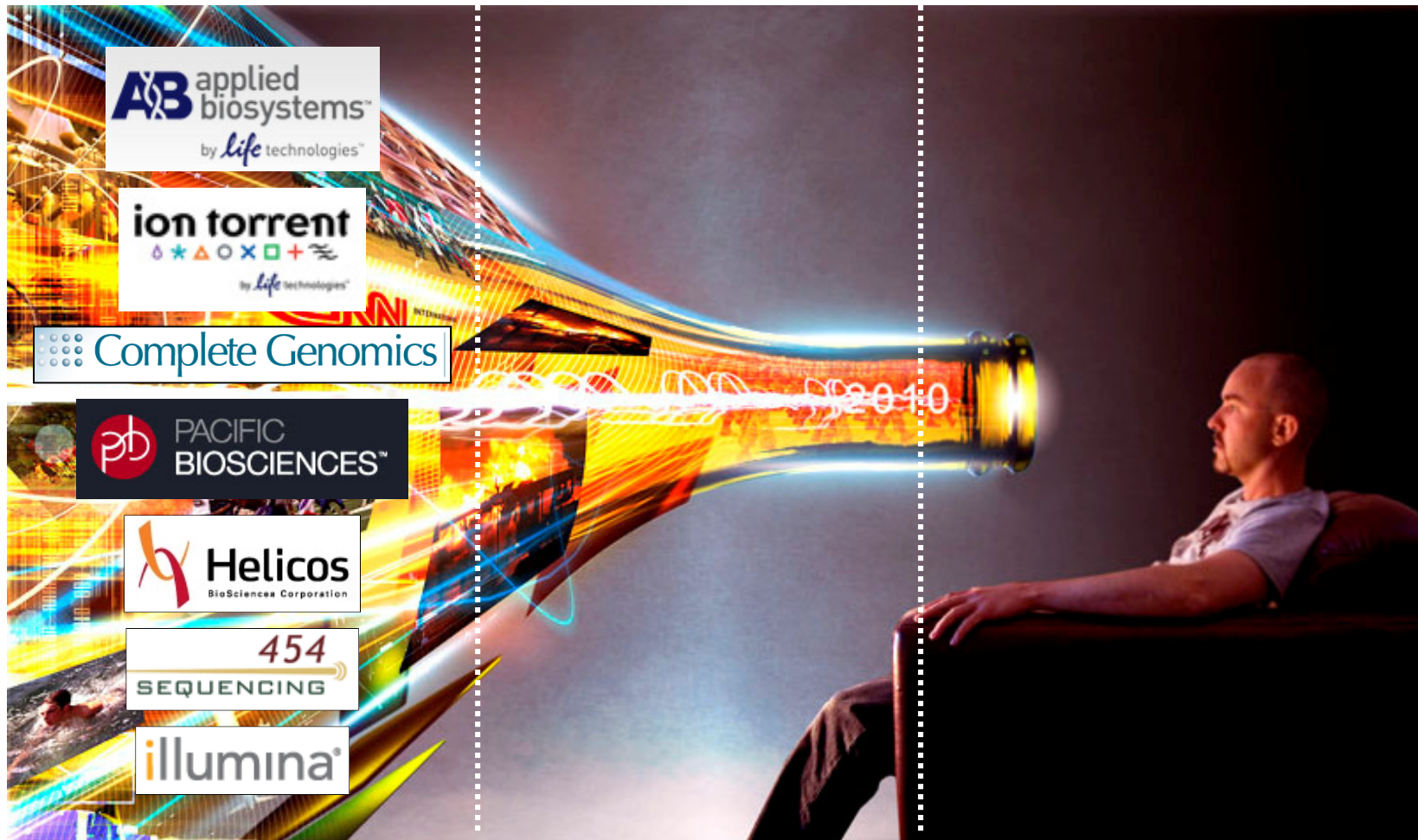


*3-4 bioinformaticians x ~4 weeks per genome to medically annotate the data

Data Production

Data Annotation

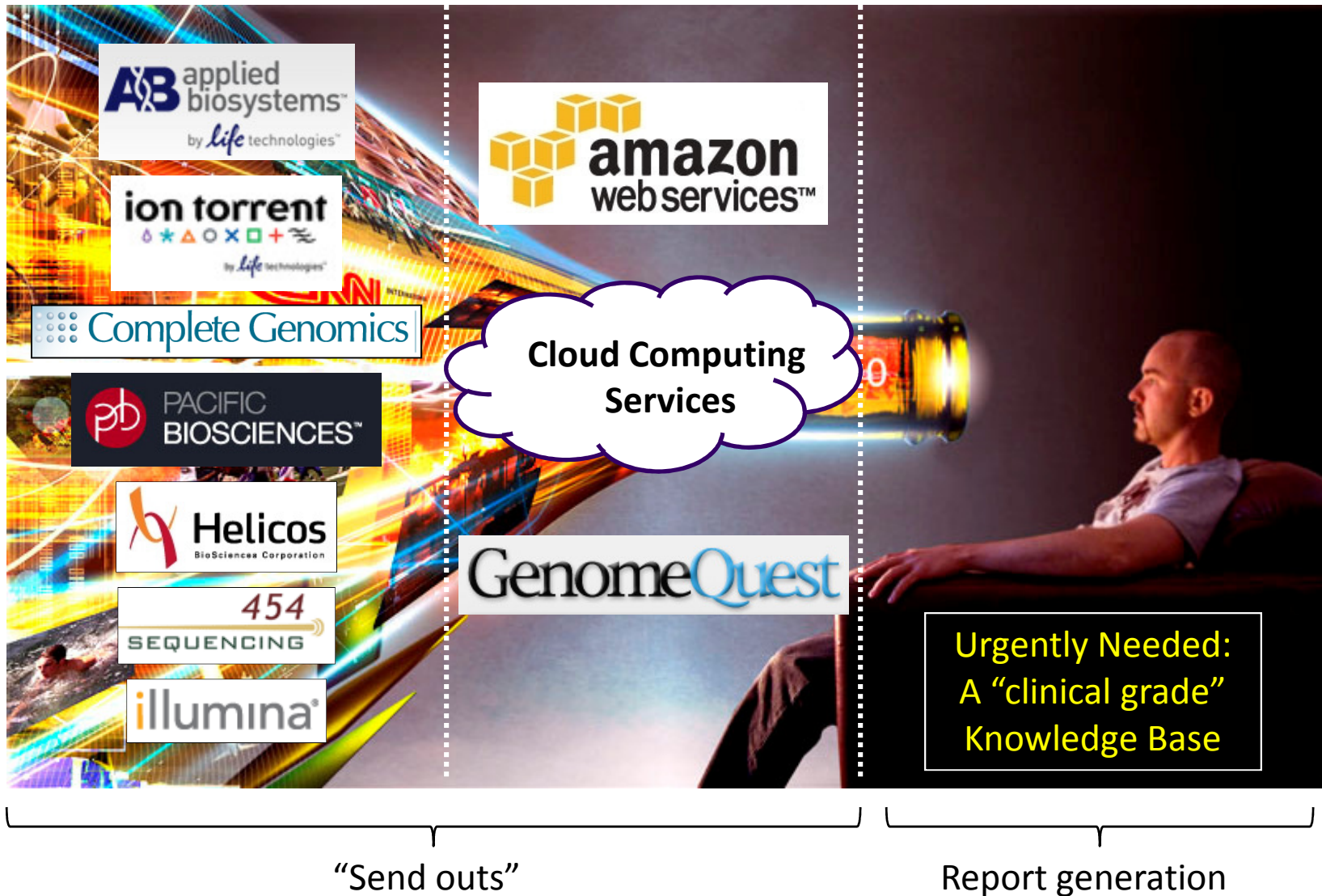
Data Interpretation



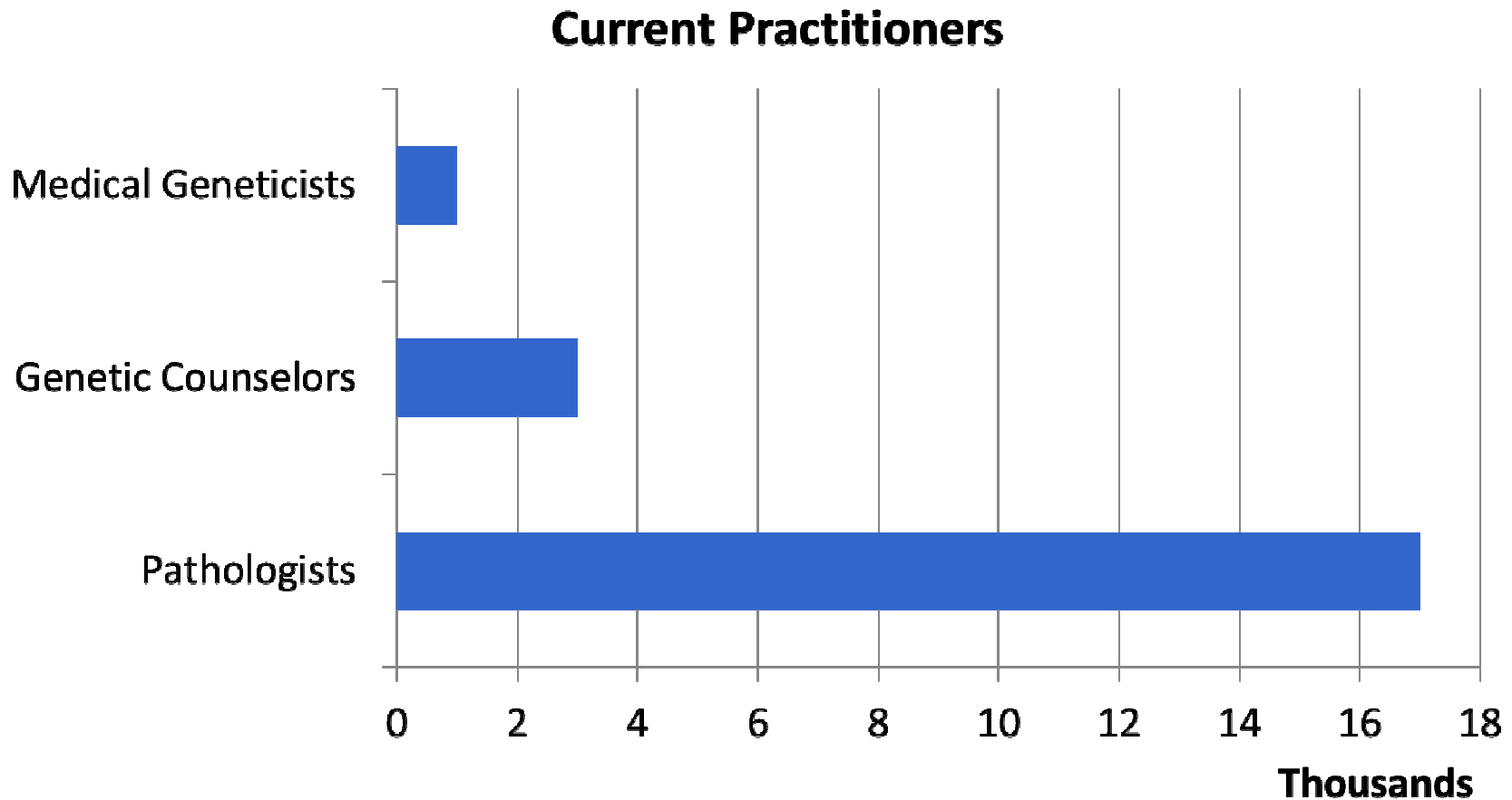
Data Production

Data Annotation

Data Interpretation



Potential Workforces for Personalized Genomic Medicine



GENOMIC MEDICINE INITIATIVE

Department of Pathology



Beth Israel Deaconess
Medical Center

A TEACHING HOSPITAL OF HARVARD MEDICAL SCHOOL



National Agenda

[The Call to Action](#) June 2010

[Banbury Summit on Genome-Era Pathology](#) October 13-15, 2010

[The Future of Pathology in Personalized Medicine](#) Boston, May 23-24, 2011

Location.....Harvard Medical School, Countway Library of Medicine, 10 Shattuck
St., Boston, MA 02115 [Directions & Maps](#)

Participants... [Summit Participants](#)



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GenomicMedicineInitiative.org

Banbury Summit on Genome-Era Pathology



October 13-15, 2010

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

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

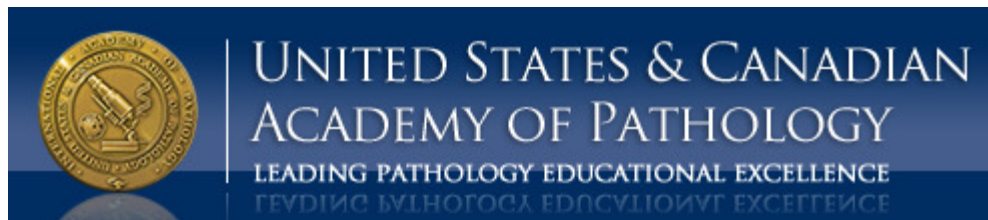
1. Establish nationwide program for residency training by July 2012
2. Compile and analyze current genetic, newborn and molecular pathology tests and create a WGA “replacement map”
3. Establish a prototype “clinical grade” disease variant database for one disease area by December 2011
4. Identify and 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)

BLUE DOT PROJECT #1

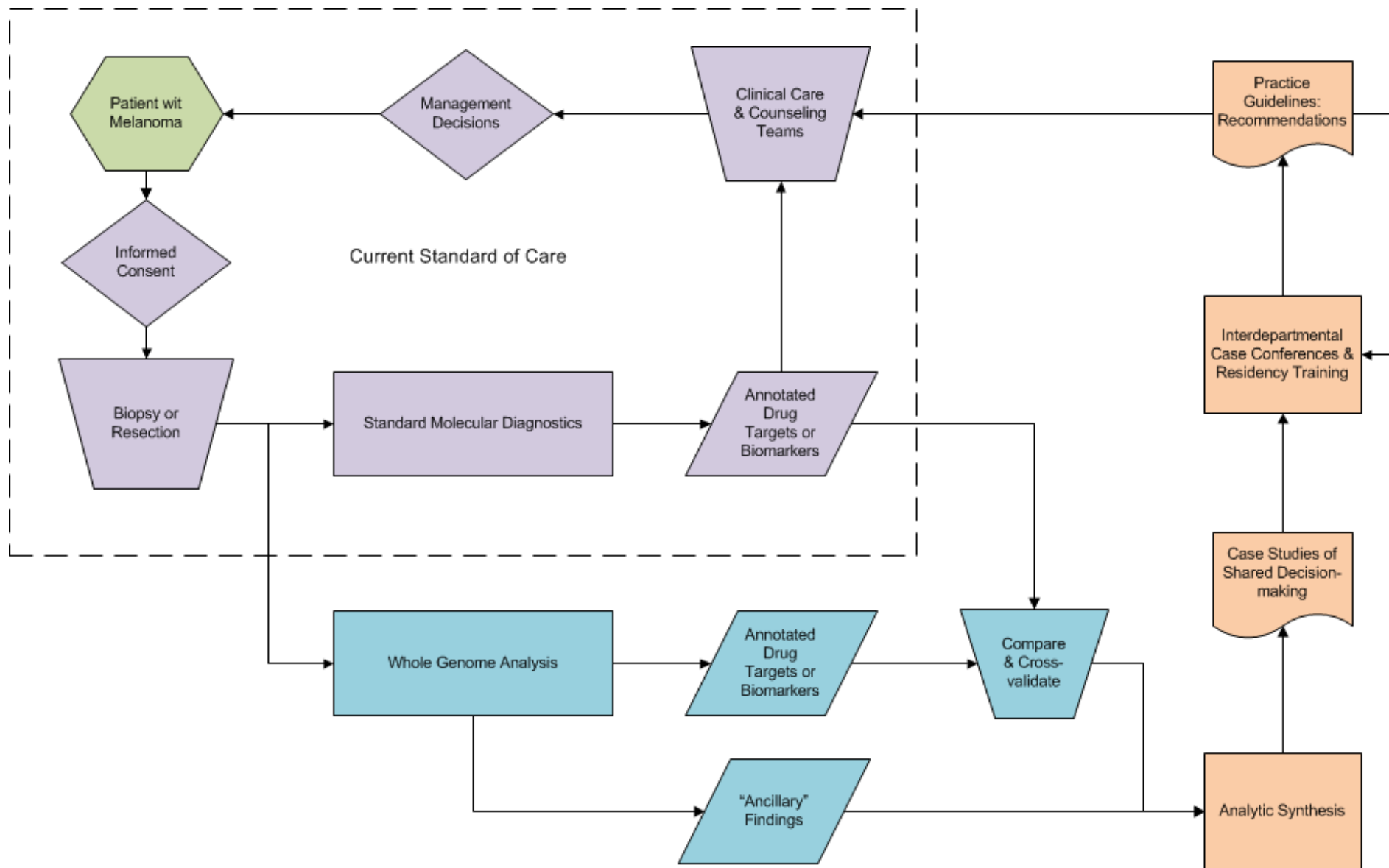
Training Residents in Genomics (T.R.I.G)

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



Association of Pathology Chairs

BLUE DOT PROJECT #4 WGA Validation



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., Ph.D.



www.medpagetoday.com/Blogs/25732

CME Quiz

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?
 - A. About the same amount as a routine staging MRI or CT scan
 - B. About the same amount as FDA-recommended pharmacogenetic testing for Coumadin or Plavix dosing
 - C. About \$10,000

Implications for future practice and business models

- ✓ The “disruptive” emergence of *precision diagnostics* will shift the emphasis from evidence-based medicine to “precision medicine”
- ✓ Precision diagnostics will lead to “money back” guarantees on the efficacy of certain therapeutics

