CAN TOOLS FOR PERSONALIZED MEDICINE MEET THE PROMISE? HOW SOON?

Timothy Triche, MD, PhD, Director
Center for Personalized Medicine
Children's Hospital Los Angeles
USC KSOM

Promising Applications of Personalized Medicine

Drug Discovery	Clinical Development	Patient Treatment Innovations	Healthcare Providers	Healthcare Payers
▪ Pharmaco-genomics ▪ Molecular Profiling ▪ Knowledge-based drug development ▪ Systems biology ▪ SNP's ▪ Translational medicine ▪ Allelic variability	▪ Clinical trial stratification ▪ Retrospective biomarker analysis ▪ Molecular imaging ▪ Population genetics	▪ Personalized diagnostics ▪ Companion diagnostics ▪ Targeted therapeutics ▪ Circulating tumor cells (CTCs) ▪ Personalized efficacy/dosing	▪ Objective diagnostics ▪ Evidence-based medicine ▪ Clinical trial resource ▪ Wellness programs ▪ Telemedicine	▪ Outcomes-based medicine ▪ Efficiency improvement ▪ Reduced costs ▪ Disease management

Source: IDC Health Industry Insights

Realizing Personalized Medicine

- Human Genome Research:
  - **Launched fundamental discovery and development that led to medical application**
- Healthcare Transformation:
  - **New technology is only enabled when integrated with the clinical setting**
- Time Line:
  - **Integrated efforts all launched in last 6 years**
- Initial funding:
  - **between $100M -$200M**
- Impact:
  - **Already leading to transformation of clinical care, self supporting research, innovative biotechnology spin-offs, and job and program growth.**

Dedicated Facilities for Personalized Medicine are Rapidly Expanding

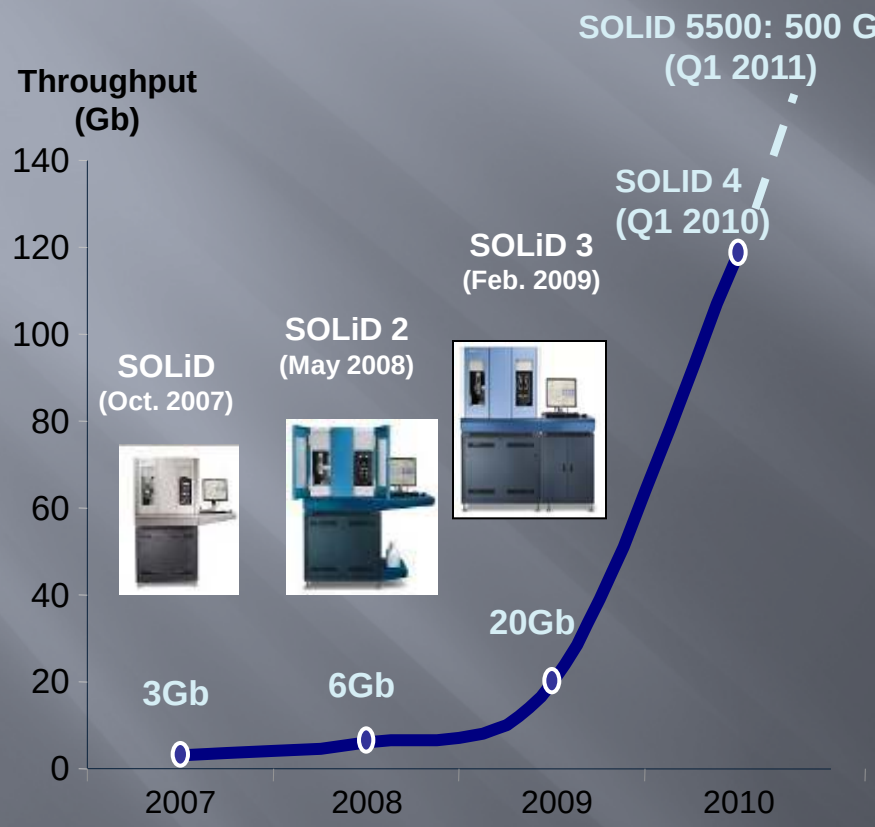
Centers for Personalized Medicine

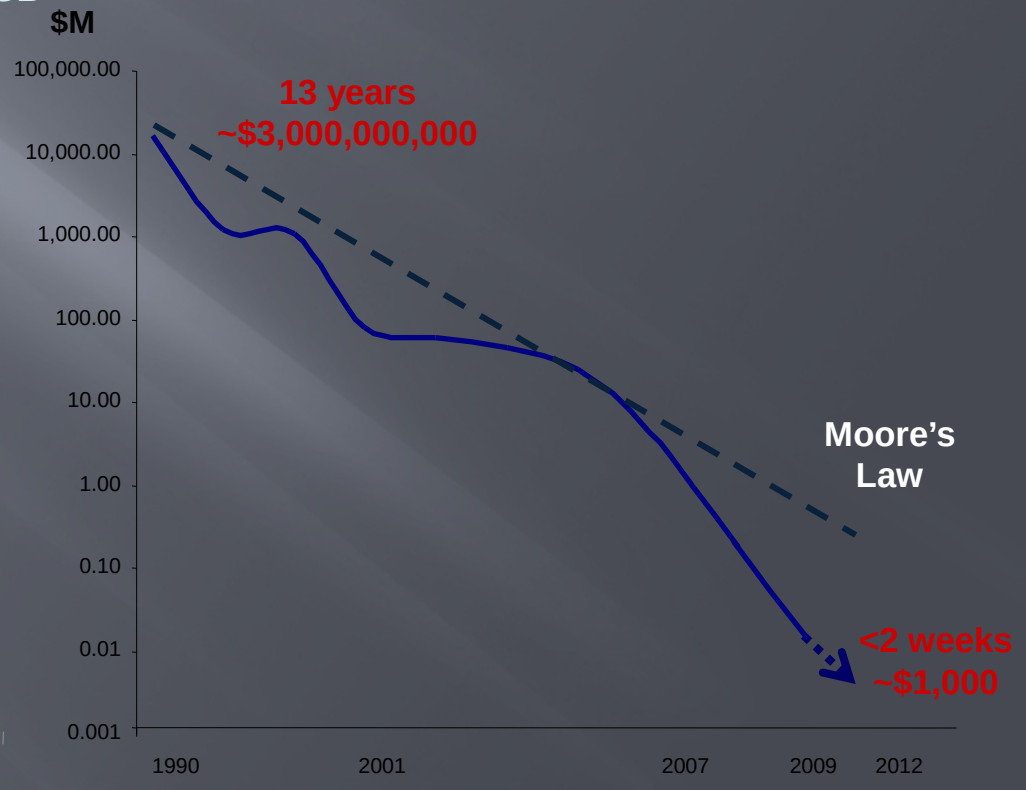
- Arizona: Translational Genomics Research Institute (TGen)
- Seattle: Institute for Systems Biology (ISB)
- Fox Chase Cancer Center: (new)
- Mayo Clinic: Center for Translational Science Activities
- Harvard/MIT: Broad Institute/ Foundation Medicine
- Cleveland Clinic: Genomic Medicine Institute (GMI)
- Ohio State University: Center for Personalized Healthcare
- Duke University: Institute for Genome and Science Policy
- El Camino Hospital: Genomic Medicine Institute
- The Scripps Research Institute (TSRI)
- Vancouver, Canada: PROOF

Examples of 'Personalized Medicine' in Cancer

- Breast cancer:
  - Oncotype Dx detects 21 gene profile to guide chemotherapy strategies in individuals with low, intermediate and high risk of recurrence
  - BRCA1/2 test identifies ~1/500 women with mutation associated with high risk of breast cancer, triggering frequent surveillance or preventive treatments
  - HercepTest detects HER2 to identify 20-30% responders to Herceptin
- Colorectal cancer:
  - UGT1A test guides dosage adjustment for 10% of individuals likely to experience toxicity from Camptostar (Irinotecan)
  - KRAS mutation testing dictates use of Cetuximab
- Acute lymphoblastic leukemia:
  - TPMT test guides dosage adjustment for 1/300 individuals likely to experience toxicity from Purinethol (mercaptopurine)
- Melanoma:
  - BRAF mutation test identified patients who will likely respond to PLX2032

The Cost of Whole Genome Sequencing is Plummeting





But the true cost, when data storage and analysis are included, is increasing:
'the $1,000 genome that only costs $1,000,000 to analyze'

Currently Available DNA Sequencing Technologies

Company	Method	Thru-put	Device Cost	Error Rate	Read Length	TAT
Roche 454	Amp beads	Whole genome	$500,000, $100,000	good	500 (mode)	2 days
Illumina	Amp beads	Whole genome	$600,000	fair	75	11 days
SOLiD	Amp emulsion	Whole genome	<$500,000	better	75	8 days
Helicos	SMS	Whole genome	service	high	35	8 days
Pacific Biosciences	SMS	Targeted	$750,000	Very high	>1,000	1 hour
Starlight	SMS	Targeted	$750,000	Very high	>2,000	?
Complete Genomics	Amp rolling O	Whole genome	service	high	?	1 week
Ion Torrent	**Amp**	**Targeted**	**$50,000**	**fair**	**100-500**	**2 hours**

A Promising Start for Medically Relevant Whole Genome Sequencing

But so far limited to inherited monogenic disorders in children

Sequencing A Child's DNA — And Convincing An Insurance Company To Pay

Mar. 2 2011 - 10:19 am | *2,838 views* | *0 recommendations* | *3 comments*

66 Share

98 Tweet

1

1 Digg

Share

Geneticist Elizabeth Worthey worked on the first-ever treatment of a patient based on DNA sequencing, helping doctors decide to give a bone marrow transplant to a 6-year-old boy who had suffered through more than a hundred operations. Now Worthey, an assistant professor at the Medical College of Wisconsin, is part of a team working to comb through the sequences of five more children.

Elizabeth Worthey, geneticist

Worthey is hoping that eventually the hospital will be able to do sequencing in house. She also hopes that newer technologies, such as Pacific Biosciences machine, might allow geneticists to look at longer stretches of DNA; MCW is getting a PacBio machine. Many researchers worry however, that this device has a high error rate, which might limit its usefulness. Illumina rival Life Technologies is betting heavily on a smaller, less expensive to buy machine that might be good for smaller projects.

The questions – how to regulate this new technology, how insurers will pay for it, and exactly what it can really do – are still huge, but so is the potential. "It's really starting to be adopted," Worthey says, "at least in children."

Does Next-Gen Sequencing Technology Enable Personalized Medicine?

Whole Genome Sequencing Facts:

- **Turn around time:**
  - Machine time: > 8 days
  - Data alignment: days
  - Data interpretation: weeks
- **Cost:**
  - $10,000 for reagents
  - Data analysis: ? (much more)
- **Complexity:**
  - The normal human genome is riddled with anomalies that must be distinguished from disease associated abnormalities

Genomic Structural Variants:
Vastly greater than previously known

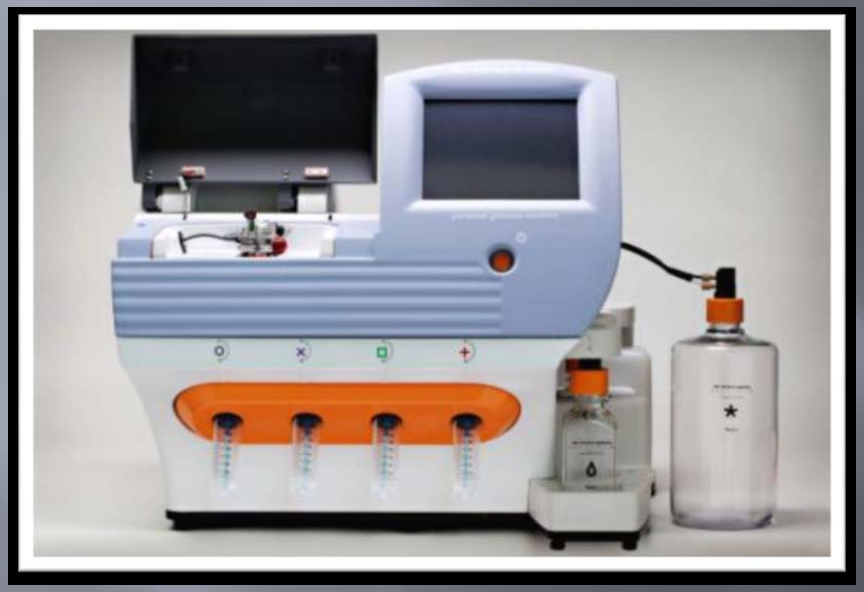
- >3 million germline SVs (~0.1% of genome)
- ~ 600 thousand per tumor
- ~ 30 thousand regions of LOH
- Similar number of regions of CNV

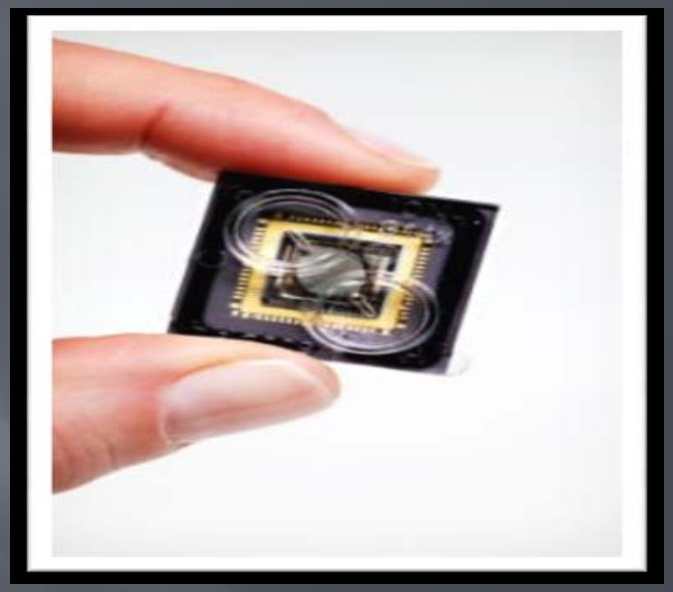
Tumor	LOH	Somatic	Unknown*	Germline
1	20,700	10,648	650,045	3,112,663
2	32,622	10,257	533,029	3,104,337
3	42,250	7594	605,505	3,326,664

If not WGS, then what?

- Whole exome sequencing is currently popular (low hanging fruit)
- Medical use will likely require targeted sequencing of DNA, RNA (as cDNA), and epigenomic features (methylated CpGs)
- Emphasis will be on sample prep, turn around time, data quality, and cost, not platform throughput

Ion Torrent Personal Genome Machine:
Targeted Sequencing for Patient Testing



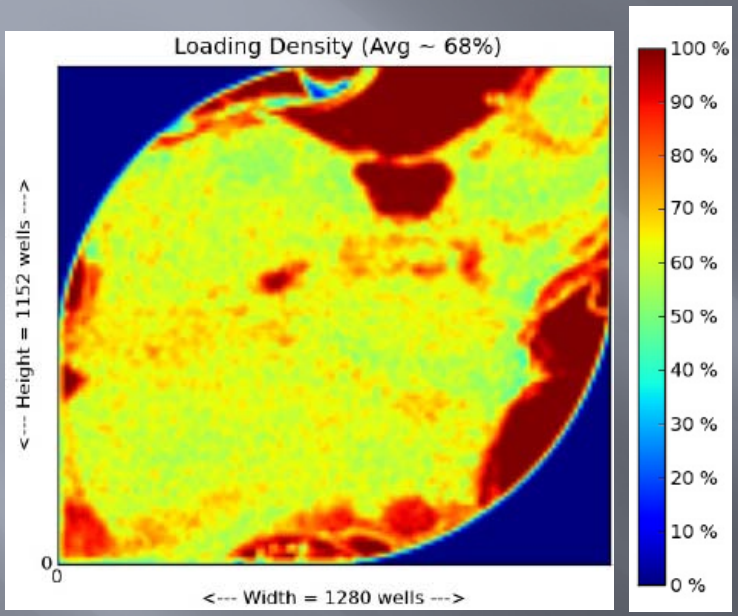


Affordable device, easy set up, rapid TAT (2 hours on machine, <2 days total)

Low cost, convenient, single use chip

- 1/11 → **314: > 10 mbs**
- 5/11 → **316: > 100 mbs**
- 9/11 → **318: > 1,000 mbs**

Typical Ion Torrent Data
(Produced and analyzed in 1 day)



Wells with Ion Sphere Particles	880,806
Live Ion Sphere Particles	545,991
Test Fragment Ion Sphere Particles	99,762
Library Ion Sphere Particles	446,229
Template-Positive Ion Sphere Particles	57%
Library key	TCAG
Verified Library Ion Sphere Particles	276,087

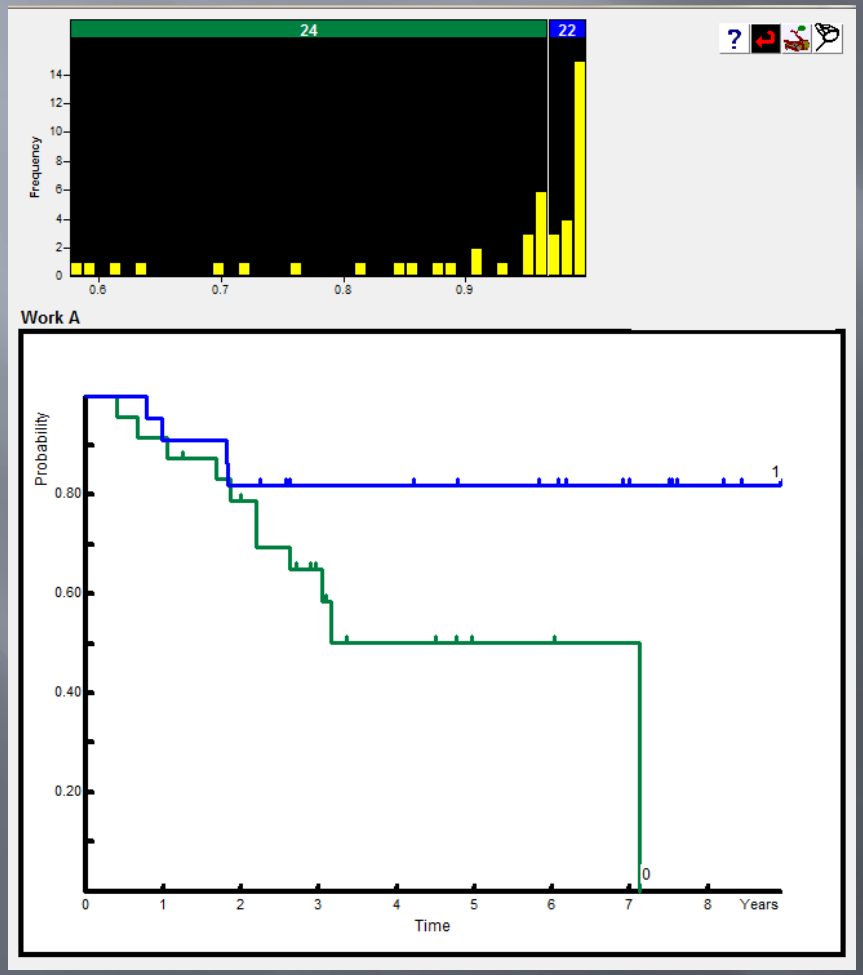
Based on Full Library Alignment to Provided Reference

	AQ17	AQ20
Total Number of Bases [Mbp]	15.39	12.49
Total Number of Reads	210,470	198,062
▸ At Least 50 bp Long	178,226	133,756
▸ At Least 100 bp Long	34,107	22,386
Mean Length [bp]	73	63
Longest Alignment [bp]	116	116
Mean Coverage Depth	3.3×	2.7×
Percentage of Library Covered	94%	90%

Typical Potential Applications

- NGS-based diagnostic testing (mutations, CNV, LOH, InDels, translocations)
- Total RNA expression profiling (expressed mutations, splice variants, allele specific expression) for prognosis & stratified Rx
- Targeted sequencing (exome or user selected)
- Mitochondrial genome sequencing (with multiplexing)
- Prokaryote sequencing
- Metagenomics

Multi-Analyte Prognostic Predictor:
RNA Expression, CNV, LOH, Genotype (Cross-validated)



Most frequently selected features:

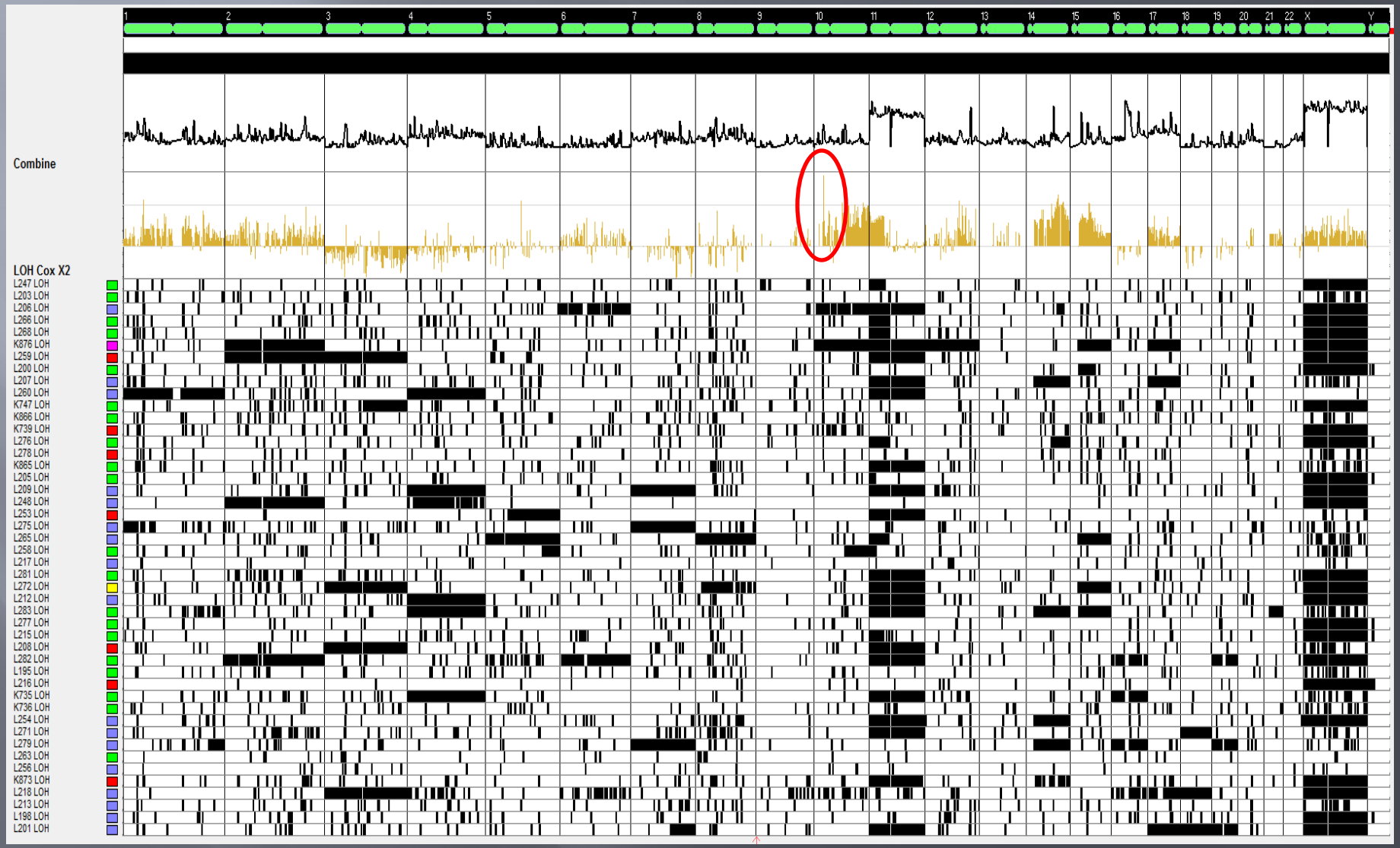
- ✓ 6 ncRNAs
- ✓ 1 LOH
- ✓ 2 coding RNAs

Rank Order:

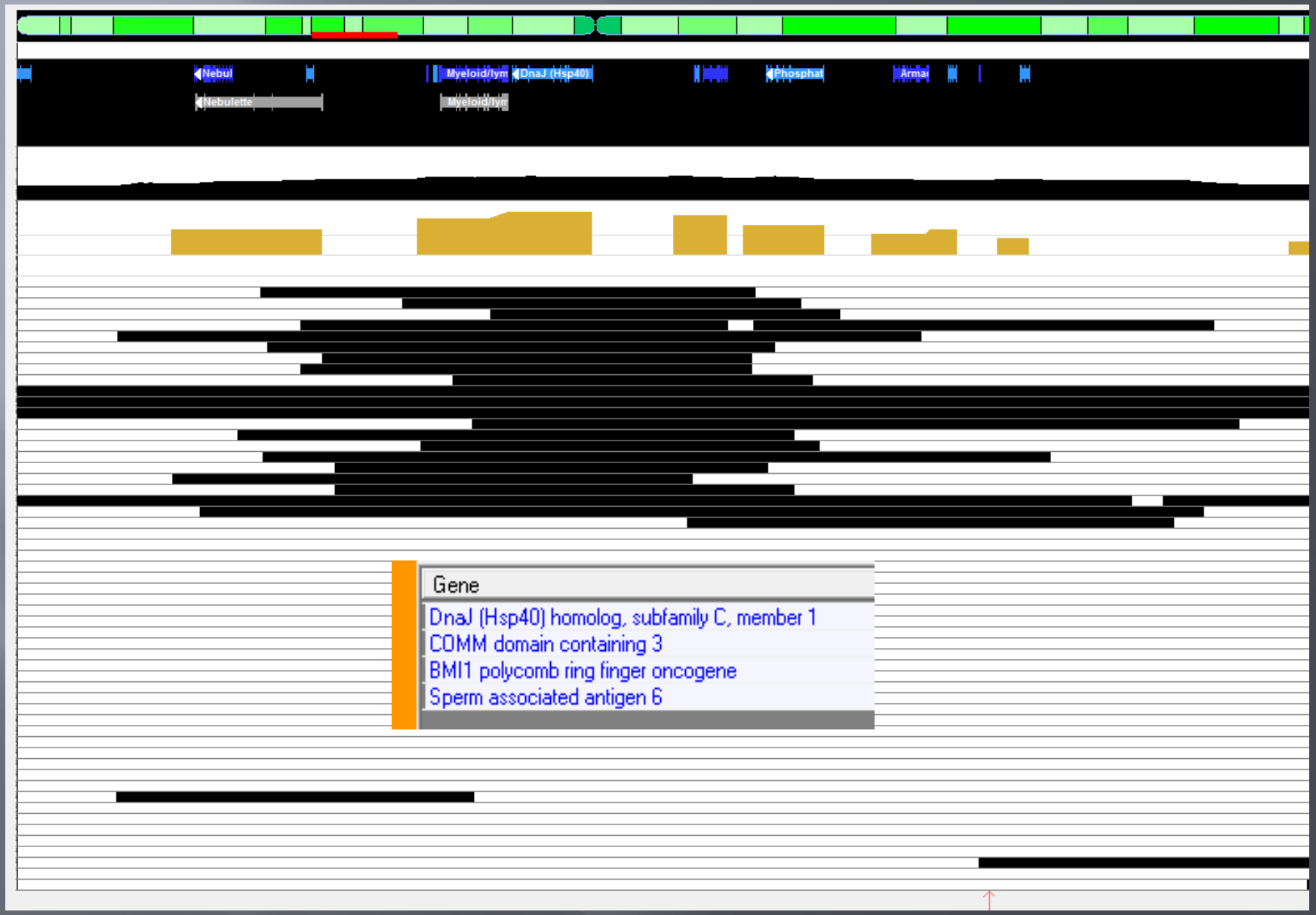
3384809
10:22085484-22332656-
3384815
3384739
3384700
3384927
Oxoeicosanoid (OXE) receptor 1
3936632
Alpha-kinase 2

Multianalyte Genomic Prognostics:

LOH/CNV/mRNA/ncRNA/5Me

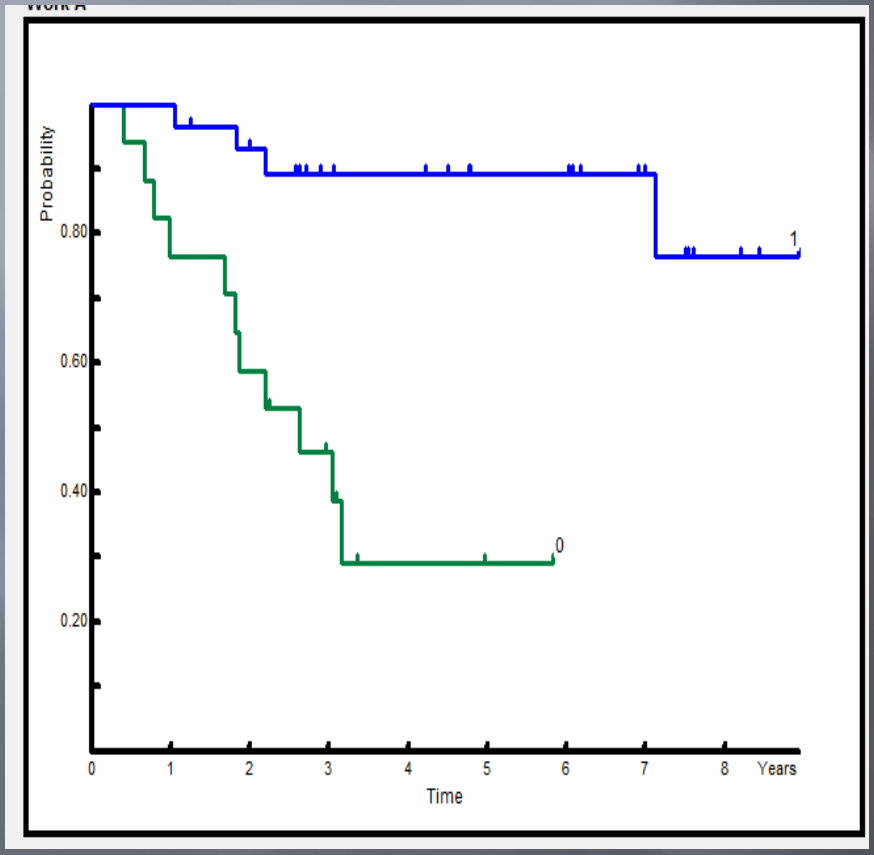


A Single700 kb LOH ROI

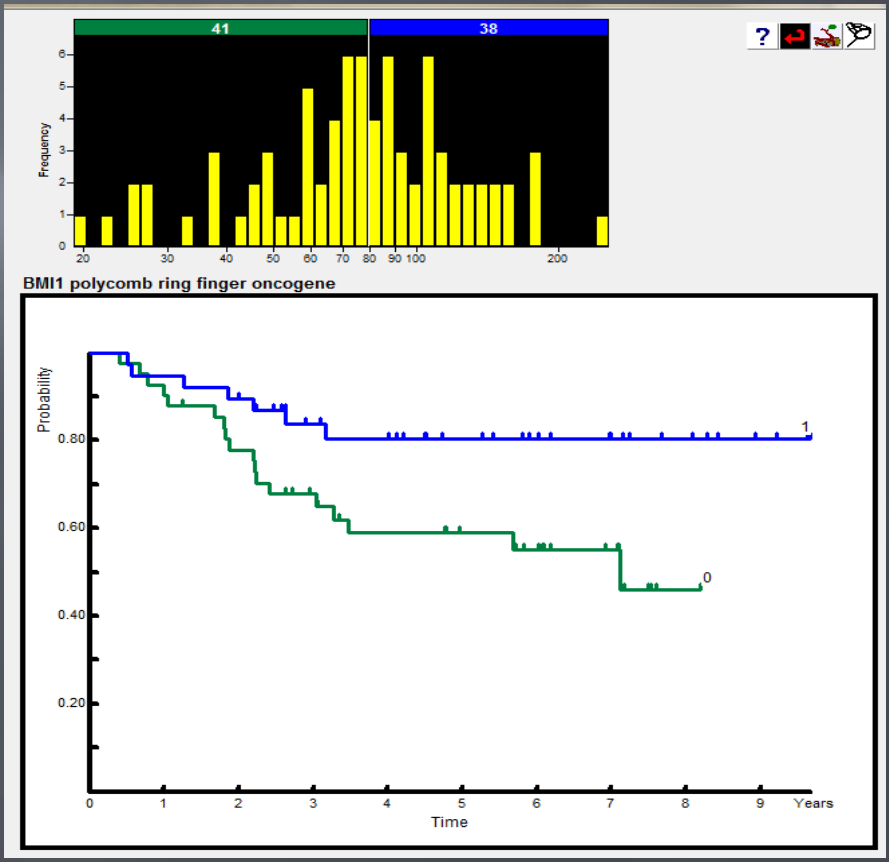


Prognosis: LOH vs. RNA Expression

LOH



Expression



Summary

- Most current medical applications are based on qPCR, Sanger sequencing, and microarry data
- 'Next Gen Sequencing' (NGS) Technology will contribute to true 'personalized medicine', but not in its current form
- Whole genome data is unlikely to be useful for most medical use until these challenges are met
- Promising platforms like the Ion Torrent Personal Genome Machine have already appeared, with more to follow (MiSeq, 454 Jr., etc)
- Targeted sequencing based on current discovery work is most likely to facilitate true 'personalized medicine'
- Broad use of NGS will require better data, better knowledge, and reduced turn around time at reduced cost


QUESTIONS?