Cancer Genomics: Revolution in Medical Practice

Jason Park, MD, PhD and Paolo Fortina, MD, PhD

IFCC Cancer Genomics Working Group

IFCC Working Group on Cancer Genomics (WG-CG)

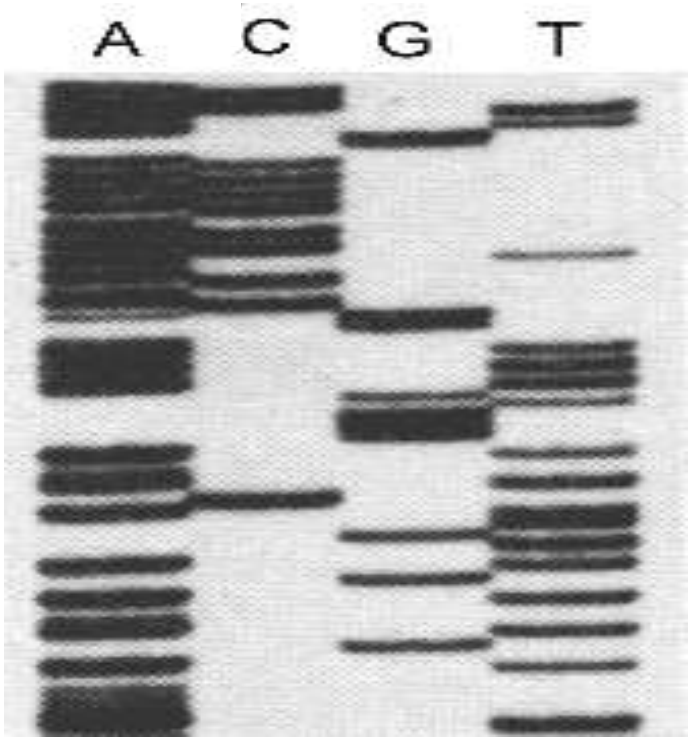
- Established under the Educational Management Division (2015)
- Mission Statement:

  To survey the currently used and emerging technologies in clinical cancer genomics and to establish a framework to guide clinical laboratories

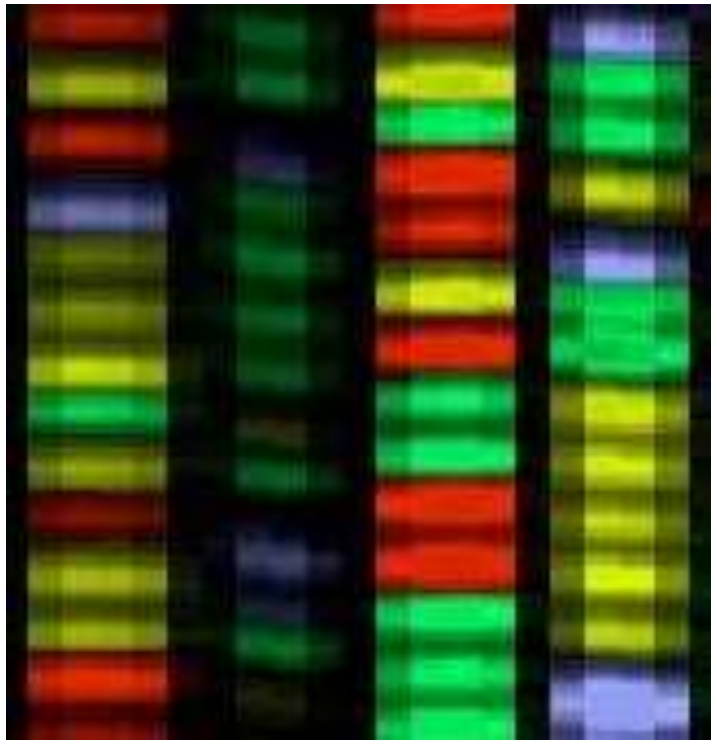
http://www.ifcc.org/ifcc-education-division/working-groups-special-projects/wg-cg/

Genetic Technology: *DNA Sequencing*

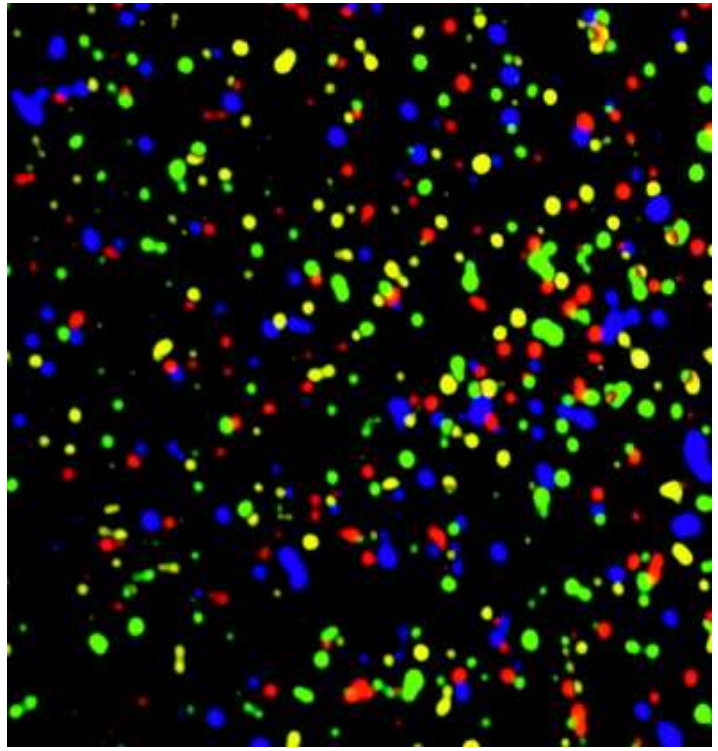
Sanger
Radioactive
100s of bp
1970s



Sanger
Fluorescent
1,000,000 bp
1980-90s



Single Molecule
'Next Gen'
100s Gbp
2000s



3730xl

0.002 Gbp/day

$365,000

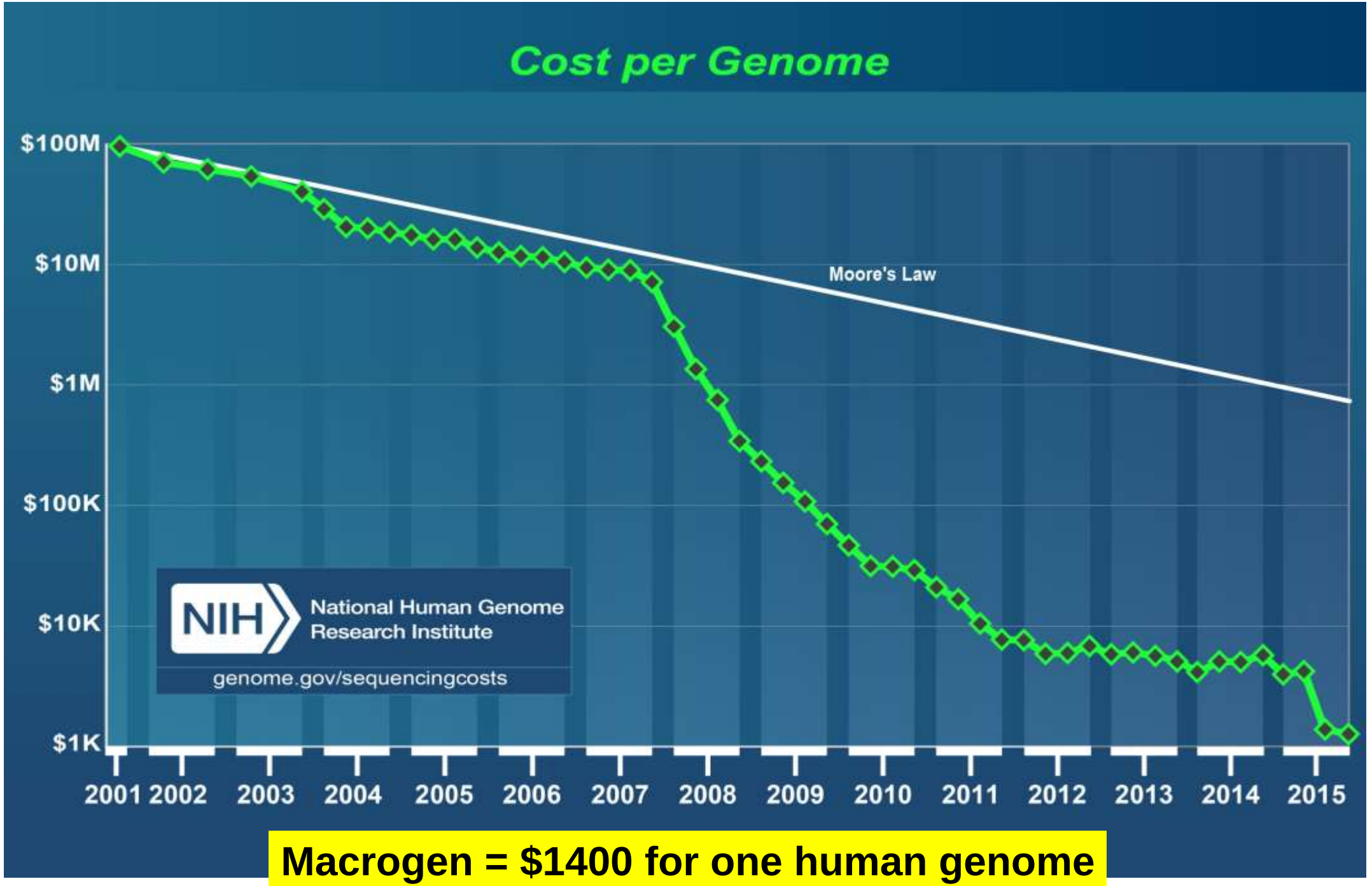
(2006)

NextSeq500

120 Gbp/day

$250,000

(2015)



Macrogen = $1400 for one human genome

Millions of Human Genomes

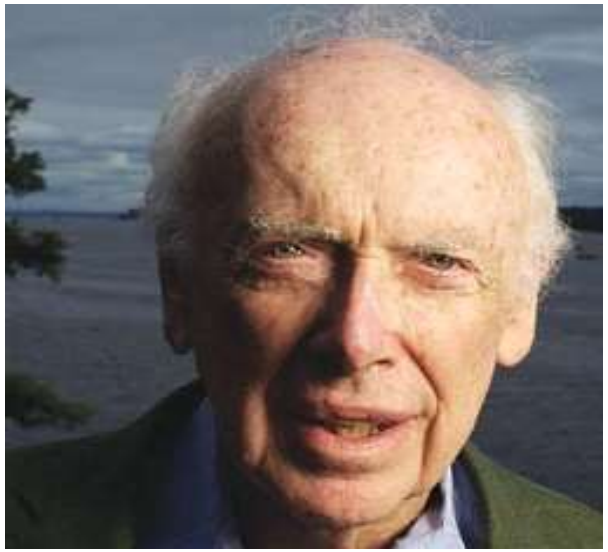
First human genomes

- US HGP – Anonymous donor
- Celera HGP – Craig Venter
- James Watson

Total human genomes sequenced

- 2001 1 (1st draft)
- 2010 3,000
- 2011 30,000
- 2014 228,000
- 2017 1,600,000 (estimated)

Planned: 1 million Genomes, China-BGI



Genomic Reference Material

- Reference materials needed for standardization and quality
- Traditional genetic reference materials are for a single DNA change
- Genome is 3 billion nucleotides
- Exome is >30 million nucleotides
- Need reference materials to assess millions of DNA changes

Genome in a Bottle

US National Institute of Standards and Technology (NIST) initiated a public-private-academic consortium in 2011

- Genome in a Bottle (GIAB)

NIST Reference Material: NA12878

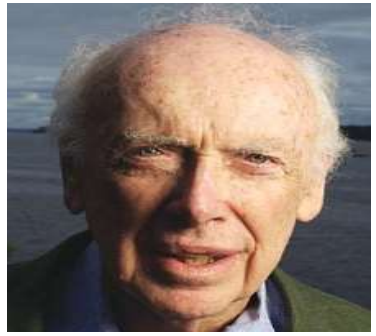
- Genomic DNA from a cell line (GM12878)

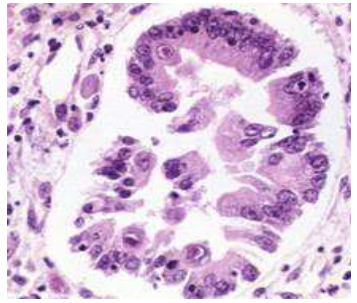
Single reference material with

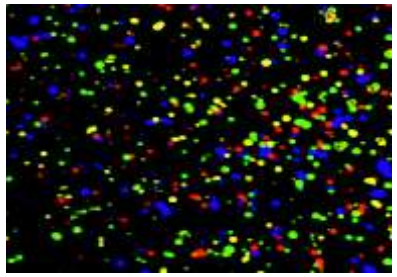
- 2,741,014 single nucleotide polymorphisms (SNPs)
- 174,718 insertions/deletions (indels)

http://www.ncbi.nlm.nih.gov/variation/tools/get-rm/browse/
ftp://ftp-trace.ncbi.nih.gov/giab/ftp/release/NA12878_HG001/

Cancer Genomics







$$m_j = \prod_{z=0,1} \frac{\beta(n_{0zj} + a_{\tau,j},\, n_{1zj} + b_{\tau,j})}{\beta(a_{\tau,j},\, b_{\tau,j})}$$

Patient **Specimen** **Genomic Test** **Informatics** **Diagnosis & Treatment**

Cancer Genomic Testing is Complex

Laboratory issues:

- Technology for sequencing is often incomplete (90-99% of target)
- Formalin-fixed tissue samples have poor quality
- Interpreting clinical significance is difficult

Biology:

- Tumor enrichment – Fraction of tumor in the sample
- Tumor heterogeneity – Within the tumor there are subpopulations

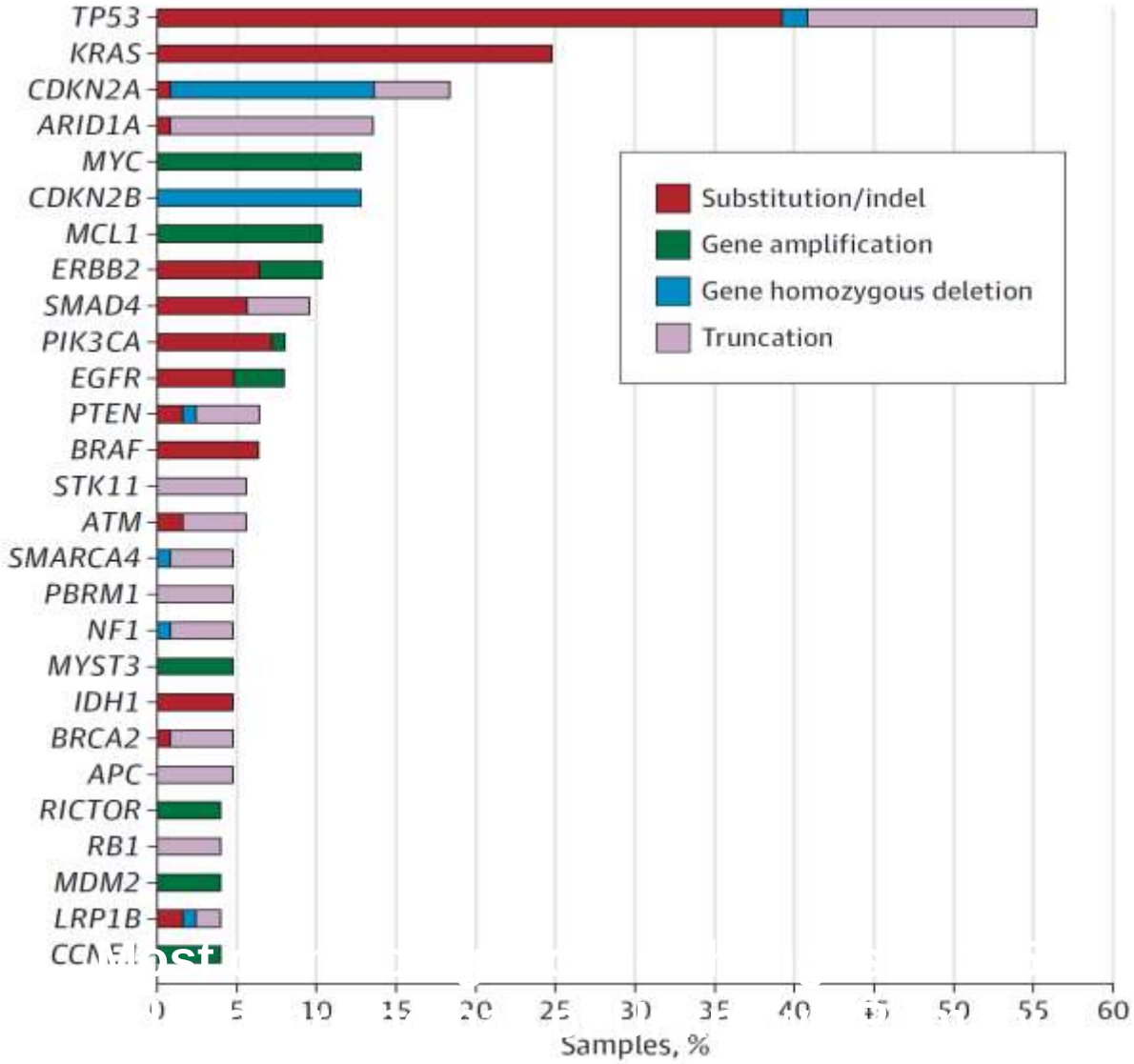
Targeted Oncology Sequencing (Dallas Children's)

- 25 genes hot-spot panel
- Formalin fixed tissue
- >1,000x minimum coverage
- ~14,000x average coverage

AKT1	**ALK**	**APC**	**BRAF**	**CDH1**	**CTNNB1**	**EGFR**	**ERBB2**	**FBXW7**
FGFR2	**FOXL2**	**GNAQ**	**GNAS**	**KIT**	**KRAS**	**MAP2K1**	**MET**	**NRAS**
PDGFRA	**PIK3CA**	**PTEN**	**SMAD4**	**SRC**	**STK11**	**TP53**		

Foundation One (FMI)

- 315 genes - full coding
- 28 introns for fusions or other structural variants
- Formalin-fixed tissue
- 229x average coverage
- Turnaround Time = 2-3 weeks



Ross JS et al 2015 JAMA Oncol 1:40-49

Actionable Variant

- Key to genomic medicine is to find gene variants that can be linked to a therapeutic
- Several dozen drugs are FDA approved as targeted therapeutics
- **Only ~100 Genes linked with therapeutic intervention**
- Additional resources to find clinically available drugs or active drug trials:

  http://www.mycancergenome.org/

  http://www.broadinstitute.org/cancer/cga/target

  https://civic.genome.wustl.edu/#/home

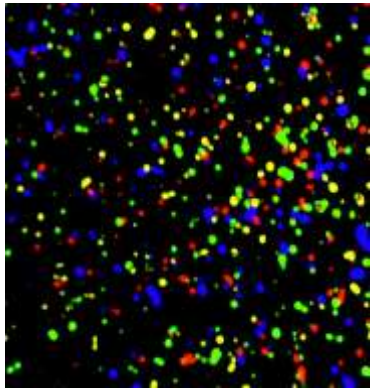
  https://clinicaltrials.gov/

Wang DH and Park JY (in press) Arch Pathol Lab Med

(http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

Cancer Genomics Summary

- Clinical genomic testing is now common in the United States
- Paper genomic standards and reference materials are emerging
- Testing out paces clinical utility
- IFCC WG will provide an international perspective on clinical cancer genomic testing



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