Cancer Genomics: Revolution in Medical Practice

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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 (1\textsuperscript{st} 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)

Cancer Genomics

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

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
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
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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