Clinical Next Generation Sequencing-Value to Drug Developers

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Cancer Diagnostic Market is Rapidly Evolving

Molecular profiling is driving many new targeted cancer therapies, biomarkers and diagnostics tests

~15 approved drugs hitting ~15 targets

Today

~500 compounds hitting ~140 targets in development

Subset of analyzed targets listed; data from BioCentury Online Intelligence Database
Current Model of Drug Development not Sustainable

- Limited tissue biopsies to search for markers
- Turn-around-time (TAT) issues for prospective studies
- Need to work in FFPE for retrospective studies
- Inefficiency of patient screening for rarer markers
- Relatively short duration of responses for some targeted drugs
- Complex biology requiring increased knowledge of pathways
- Complex biology requiring interpretation, not just raw data
- Clinical Next Generation Sequencing can address these issues
Challenges Of Sequencing Clinical Cancer Samples

- Low purity – cancerous cells may only be a minor fraction of total sample
- Heterogeneity – multiple sub-clones of cancer may be present in one tumor sample
  - Mutation of interest (e.g., a resistance mutation) may be present in a low abundance sub-clone
- Aneuploidy – chromosomal gains and losses may modify mutation abundance

Relevant mutations may be rare in the pool of sequenced DNA
Founders of Foundation Medicine

Eric Lander, PhD
- Recognized driving force in genomics
- Founding Director of the Broad Institute
- MIT, Harvard Medical School
- Founder Millennium Pharmaceuticals

Levi Garraway, MD, PhD
- Cancer genomics innovator and creator of OncoMap project
- Medical Oncology, Dana Farber Cancer Institute, Broad Institute
- NIH “New Innovator”

Todd Golub, MD
- Recognized leader in cancer genomics, targeted therapeutics
- Founding director of Broad Institute Cancer Program
- Dana Farber, HHMI, NCI advisor

Matthew Meyerson, MD, PhD
- Principal Investigator of The Cancer Genome Atlas program
- Clinical Pathology, Dana Farber Cancer Institute, Broad Institute
- Co-discoverer of EGFR mutations in lung cancer

Alexis Borisy
- Successful biotechnology entrepreneur
- Founder, CEO of CombinatoRx, $750M, public listing
- TR Innovator of the Year
- Boards of BIO, Forma Therapeutics, Science Museum
Senior Management Team

**Michael Pellini, MD**  
President & Chief Executive Officer  
- Breadth of experience in life sciences clinical diagnostics and lab industries  
- GE Healthcare/Clarinet, Safeguard, Genomics Collaborative

**Ronald Collette**  
Chief Information Officer  
- 25 years in management of information technologies and security; highly regarded author and speaker  
- Clarient, Traxx Consulting (Irvine Company, Pacific Life), Fluor Corporation

**Vincent Miller, MD**  
SVP, Clinical Development  
- 20 years at Memorial Sloan-Kettering Cancer Center (Attending Physician)  
- Pioneer in EGFR mutation; clinical application  
- Expert in lung cancer & clinical trial design

**Phil Stephens, PhD**  
Vice President, Cancer Genomics & Director, R&D  
- World renowned expert in cancer genomics, formerly of the Wellcome Trust Sanger Institute  
- Lead author in the discovery of BRAF in melanoma and ERBB2 in lung cancer  
- Author of dozens of high-profile publications in *Nature, Nature Genetics, Cell*

**Kevin Krenitsky, MD**  
Chief Operating Officer  
- 15 years of experience in global diagnostic and biotechnology operations  
- Enzo Clinical Labs, BioServe Biotechnologies, Genomics Collaborative

**Maureen Cronin, PhD**  
SVP, Research & Product Development  
- More than 20 years experience leading R&D of diagnostic tests based on genomic biomarkers  
- Genomic Health, ACLARA Biosciences, Affymetrix

**Gary Palmer, MD, JD, MBA, MPH**  
SVP, Medical Affairs & Commercial Development  
- Three decades in oncology, as a clinician in academic and community settings and executive in the biotech and diagnostic industries  
- Genomic Health, Kosan Biosciences, Amgen

**Jason Ryan, CPA, MBA**  
Vice President, Finance  
- Broad financial and operational experience in high growth life science companies  
- Taligen Therapeutics, Codon Devices, Genomics Collaborative, Deloitte
NGS-Based Genomic Profiling Test

Fixed sample slides

Sequencing (Illumina HiSeq™ 2000)

DNA extraction, Library construction, Hybrid capture (Agilent SureSelect™)

189 cancer genes 500x-1000x unique coverage

Optimized for accuracy 14-21 days

ANALYSIS PIPELINE

Point Mutations
Bayesian algorithm

Short Insertions/deletions
Local assembly

Copy Number Alterations
Comparison with process-matched normal control

Rearrangements
Analysis of chimeric pairs

Annotation & Interpretation
- dbSNP
- COSMIC
- Med. Literature

Clinical Report
Current Model Misses Therapeutic Options

Non small cell lung cancer example

- Genes with Actionable Mutations
- Genes with Mutations, Actionability Unknown
Pharma Partners

- Only end to end solution
- Early and consistent revenue
- Dx rights/commercial positioning
- Biomarker ID, development drives discovery
- Multiple trial scenarios

Multiple and significant pharmaceutical company collaborations underway:
Varieties of Pharma Interactions

- Single agent clinical trials
- Longitudinal studies
- Multiple Phase I trials
- Studies not meeting primary endpoints
Example 1: Single Agent Trial

- Single agent clinical trial
- Foundation Medicine’s core test provides:
  - Identifies all relevant genomic aberrations
  - Stratifies/accrues patients in multi-arm trial
  - Data to identify genomic biomarkers for response and/or primary resistance
- Pharma/Biotech Requirements:
  - Clinical grade reliability, sensitivity, specificity
  - Clinically relevant turn-around time
  - Extensive number of genes analyzed to develop biomarker(s)
  - Excellent performance with minimum DNA
Example 2: Longitudinal Disease/Targeted Therapy Study

• Longitudinal study (at relapse, patient is re-biopsied)
• Foundation Medicine’s core test provides:
  – Biomarkers of rational drug combinations
  – Identification of biomarkers for response
  – Identification of biomarkers of primary and acquired resistance
• Pharma/Biotech Requirements:
  – Clinical grade reliability, sensitivity, specificity
  – Clinically relevant turn-around time
  – Extensive number of genes analyzed to develop biomarker(s)
  – Excellent performance with minimum DNA
Example 3: Multiple Simultaneous Clinical Studies

• Foundation Medicine’s core test provides:
  – High likelihood of identifying eligible patients since all key genomic aberrations are tested upfront
  – PI’s having all of relevant information about clinical trial participants enabling improved research opportunities
  – Pharma/Biotech experiences better accrual, appropriate selection of patients for trials and improved PI recruitment

• Pharma/Biotech Requirements:
  – Clinical grade reliability, sensitivity, specificity
  – Clinically relevant turn-around time
  – Extensive number of genes analyzed to develop biomarker(s)
  – Excellent performance with minimum DNA
Example 4: Clinical Trial That Did Not Meet Primary Endpoint

• Opportunity to explore data from unsuccessful clinical trial for mechanism of drug effect and markers for response/resistance
• Foundation Medicine’s core test provides:
  – Data to suggest alternative hypotheses to explain unexpected clinical trial outcomes
  – Explanation for lack of statistically significant differences in response rates between groups
  – Identification of relevant biomarker/signature of response and/or resistance
• Pharma/Biotech Requirements:
  – Clinical grade reliability, sensitivity, specificity
  – Clinically relevant turn-around time
  – Extensive number of genes analyzed to develop biomarker(s)
  – Excellent performance with minimum DNA
What Does Pharma Want?

• Ability to work with FFPE samples
• For prospective work, clinically relevant turn-around time
• Deep coverage (so relevant alterations won’t be missed)
• Genomic “insight”—what does this mean biologically?
• Computational biology assistance
What Can NGS Do for Pharma?

• Aid in biomarker identification
  – Need “broad” but “deep” coverage so don’t miss any
• Help stratify patients for clinical trials
  – Increase “hit rate”
  – Needs to be “cost effective”—NGS can be
• Help to determine resistance markers
  – NGS on re-biopsies compared to original biopsies
• Enable combination therapy
• Assist in resurrecting “failed trials”
  – Much interest here
  – Many $$ spent on these “failed” assets
What Can’t NGS Do for pharma?

• Can’t overcome problem of very rare but actionable alterations that will require many patients be screened
• Can’t overcome problems with statistical power
What Policy Issues (FDA, etc.) Are Top of Mind?

- Critical that policy makers understand the stakes
- All of the “logistical” issues mentioned already
  - Decreasing biopsy sizes, increasing number of markers
- But oncologists can’t keep up with knowledge
  - Patients are NOT getting proper testing
  - Therefore they are NOT getting proper therapy
  - Situation will get more grave over time
- So educational forums to educate FDA and stakeholders are critical
What Policy Issues (FDA, etc.) Are Top of mind?

- We need a pathway for approval that is manageable
  - Separate validation for each “marker” is unworkable
  - NGS does not test for a specific marker
    - Literally thousands or possible results
- We need a clear path for pharma regarding
  - Companion diagnostics
The Future for NGS in Drug Development

• All clinical trials may have NGS run in Phase 1
  – This will move some trials back to pre-clinical stage

• Clinical trial paradigm will change
  – Potential patients placed on appropriate trial through NGS screening
  – Combination therapy trial
  – “Case Report” trial
    • Impossible to recruit enough patients for rare alterations
    • Label extension based on multiple N=1 case reports?
THANK YOU