Clinical Next Generation Sequencing- Value to Drug Developers

Gary Palmer, MD, JD, MBA, MPH
Senior VP, Medical Affairs
Foundation Medicine
Cambridge, MA

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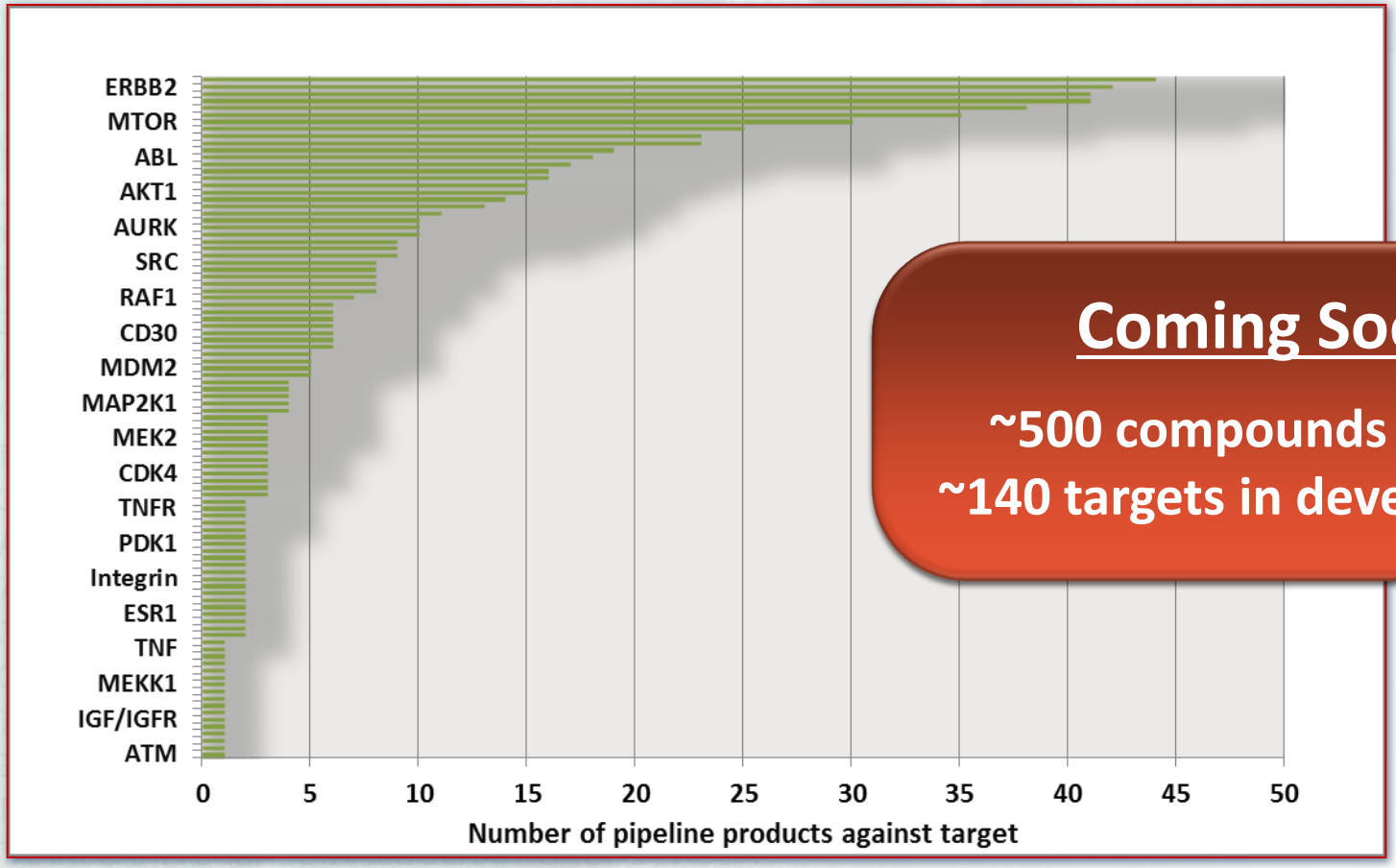
Cancer Diagnostic Market is Rapidly Evolving

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



Coming Soon

~500 compounds hitting
~140 targets in development

Subset of analyzed targets listed; data from BioCentury Online Intelligence Database

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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

Todd Golub, MD

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

Levi Garraway, MD, PhD

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

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/Clarient, 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

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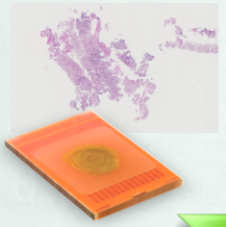
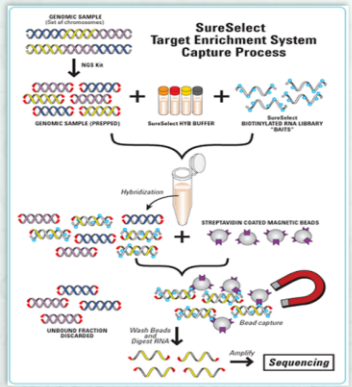
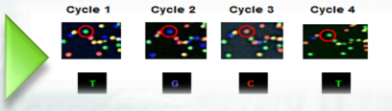
NGS-Based Genomic Profiling Test



Fixed sample slides



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



Sequencing
(Illumina
HiSeq™ 2000)

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

189
cancer genes

500x-1000x
unique coverage

Optimized for
accuracy

14-21
days

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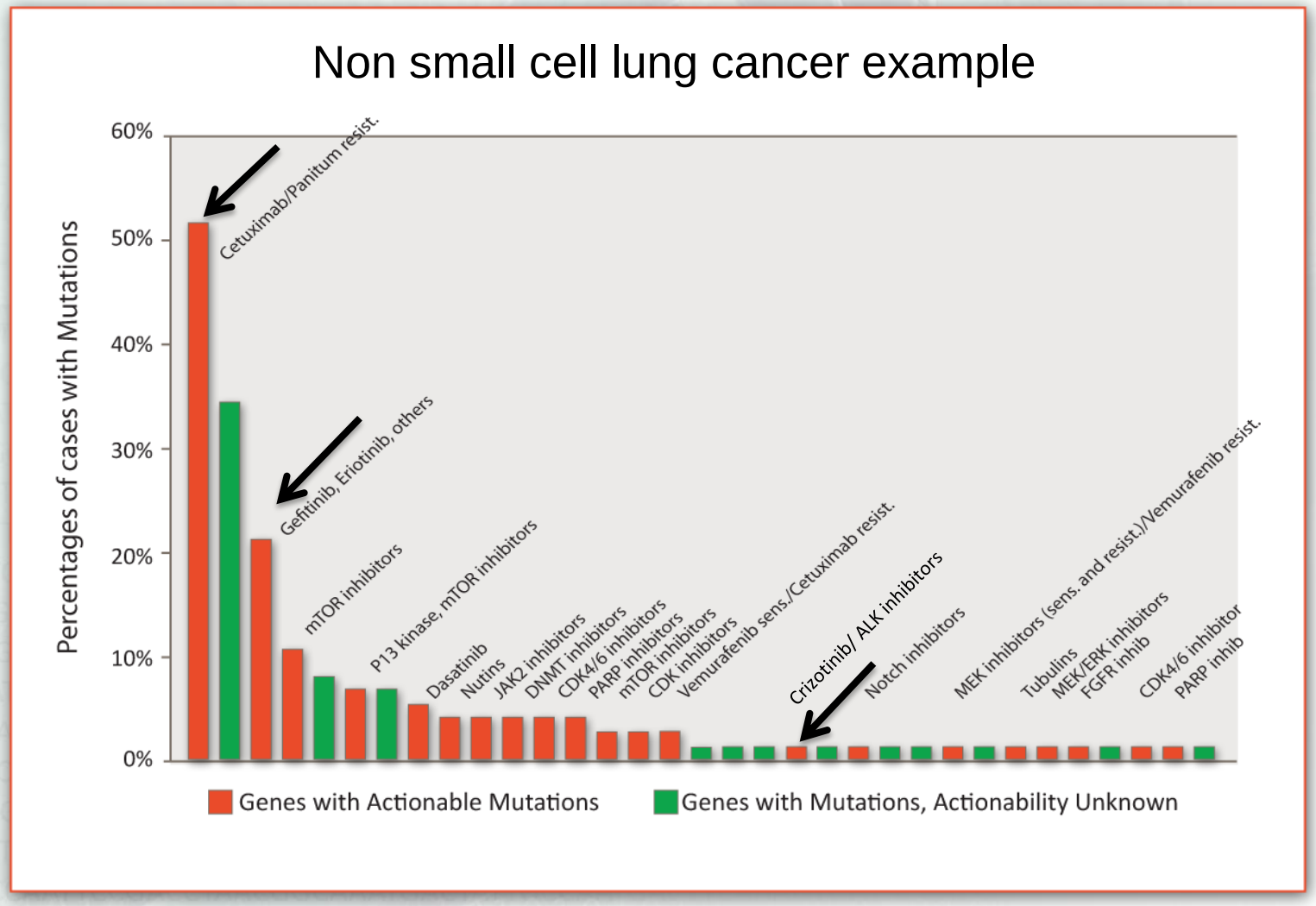
Current Model Misses Therapeutic Options



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:

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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

Sample Report Used in Clinical Trials

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Sample Report – Research Use Only

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Partner/Study Information

FMI Partner	Collaborator
Partner Study #	C-123
FMI Study #	FMI-001

Sample Information

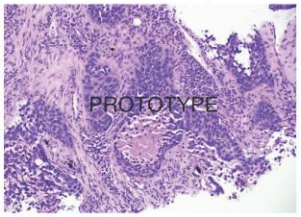
Partner Sample ID	C-456	FMI Sample ID	FMI-003
Date Collected	Date Received	Date Reported	
02/25/2011	03/01/2011	03/15/2011	

Specimen Description (to be provided by FMI partner)

Tumor Type	Lung	Normal Sample Provided	Blood
Specimen Site	Lung	Gender	Male
Collection Method	Surgical Resection	Pathology Diagnosis	NSCLC, Stage IV

FMI Pathology & Process Report

Image of material used to acquire DNA



Pathology Review

Initial tumor nuclei content (est. %)	10%
Tumor nuclei content after enrichment (est. %)	30%

Additional comments
(none)

Processing Results

Quantity of DNA Extracted	0.8 µg
Sample Pass/Fail QC	Pass
Failure Reason	n/a

FMI Sequence Report

Non-Synonymous Point Mutations/Indels

Known Somatic Mutations	BRAF_c.1397G>C_p.G466A(12%) KRAS_c.34G>T_p.G12C(11%)
Likely Somatic Mutations	TP53_c.499C>T_p.Q167*(15%)
Variants of Unknown Significance	FLT1:c.2178_2180del3:nonframeshift(10%)

Structural Variants (exploratory)

Amplifications	MDM2 (3.3x)
Deletions	TP53 (0.6x)
Rearrangements	None Detected

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Glossary for the FMI Process and Sequence Report

Pathology & Process Report

Initial tumor nuclei content (est. %)	An image-based, expert estimate of the % tumor of total nuclei present in the sample before enrichment
Tumor nuclei content after enrichment (est. %)	An image-based, expert estimate of the % tumor of total nuclei present in the sample after enrichment, if enrichment is performed
Sample Pass/Fail QC	An indication whether the sample passed or failed the overall FMI process. Possible values: Pass/Fail/Provisional. Provisional status indicates that the sample did not meet strict Pass criteria, but allowed for some sequence information to be acquired and is being reported on a provisional basis

Sequence Report

Status of Genes of Interest

If the overall mutation status for a particular gene (or genes) is of primary interest, the mutation status for the gene is indicated in this section. Possible values are Mutated, No Variant Detected, or Indeterminate:

Mutated	A known or likely somatic non-synonymous point mutation/indel (defined below) or large structural variant (copy number alteration or translocation) was observed in the gene of interest
No Variant Detected	No non-synonymous point mutations/indels or structural variants were observed in the gene of interest
Indeterminate	A non-synonymous point mutation or indel of unknown significance (defined below) was observed in the gene of interest

Non-Synonymous Point Mutations/Indels

In the absence of an individual-matched normal control, a definitive determination of somatic status for all variants observed in the sample cannot be made in general. After removal of known germ-line variation using dbSNP, remaining variants are therefore interpreted in light of cancer databases and literature to arrive at an assessment of somatic status.

Known somatic mutations	Non-synonymous variants observed in the sample that are highly likely to be somatic mutations. These include confirmed somatic mutations listed in (an FMI-curated version of) the COSMIC database and variants in known mutations hotspots
Likely somatic mutations	Non-synonymous variants observed in the sample that are likely to be somatic mutations. These include novel variants that result in the truncation of known tumor suppressor genes
Variants of unknown significance	Non-synonymous variants observed in the sample where somatic status cannot be determined. These include all variants that cannot be assigned as either known or likely somatic mutations or known germ-line variation. This group may include both novel somatic mutations and rarer germ-line variation

Structural Variants

Structural variation (re-arrangement/translocation and copy number alteration) information is provided in three components:

Amplifications	Genes where all or a subset of exons are observed present in the sample at greater than normal levels. The factor of copy number elevation (e.g., 3.0x) relative to a process-matched normal-DNA control is provided
Deletions	Genes where all or a subset of exons are observed present in the sample at lower than normal levels. The factor of copy number reduction (e.g., 0.5x) relative to a process-matched normal-DNA control is provided
Rearrangements	Genes for which a genomic re-arrangement (e.g., a fusion gene) event was observed. A description of the re-arrangement event is provided

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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

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