‘Clinical Grade’ Biomarkers in the Genomic Era—Observations & Challenges

IOM Committee on Policy Issues in the Clinical Development & Use of Biomarkers for Molecularly Targeted Therapies

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Disclosures

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- **Financial:** None

- **Consultant:** PierianDx

- **Genome:** Red-Green Colorblind (among other things)
WUSM efforts in cancer genomics—From cancer biology to clinical applications

Institutional Highlights

• **Acute Myelogenous Leukemia** (JM Klco, MJ Walter, TJ Ley, et al.)
• **Breast cancer** (MJ Ellis, ER Mardis, et al.)
• **Lung cancer** (D Morgensztern, R Govindan, et al.)
• **Cancer immunotherapy** (M Gubin, WE Gillanders, RD Schreiber, et al.)

Large Collaborative Group Highlights

• St-Jude Children’s Research Hospital-Washington University: *Pediatric Cancer Genome Project* ([http://www.stjude.org/pcgp](http://www.stjude.org/pcgp))

• **NCI/The Cancer Genome Atlas**: Acute Myelogenous Leukemia, Breast Cancer, Lung Cancer
Clinical NGS testing

- **Clinical NGS for cancer—2011**, 1st clinical NGS test & Constitutional diseases —exome-based panels (cardiovascular, renal)

- Comprehensive hybrid capture-based assays (Illumina platform)

- Custom-built data analysis and test management application:
  - NGS data analysis pipeline for variant calling, annotation & classification
  - Facilitates variant interpretation (weblinks to various ‘clinical grade’ resources)
  - Customized report generation and linkage to LIS/HIS
  - Clinical Grade variant database
  - User networking → Sharing
GPS comprehensive cancer gene set—Divining ‘actionable’ genes

>2000 cases

**Hematologic Malignancies**
- ABL1
- ASXL1
- CEBPA
- DNMT3A
- FLT3
- JAK2
- KTM2A
- MPL
- MYC
- MYD88
- NOTCH1
- NPM1
- PTPN11
- RUNX1
- TET2

**Solid Tumors**
- BRAF
- IDH1
- IDH2
- KIT
- TP53
- PDGFRα
- AKT1
- ALK
- APC
- ATM
- BRCA1
- BRCA2
- CDKN2A
- CTNNB1
- EGFR
- FGFR2
- ERBB2
- ESR1
- HRAS
- KRAS
- MAP2K2
- MET
- MTOR
- NF1
- NRAS
- PIK3CA
- PTCH1
- PTEN
- RB1
- RET
- SMO
- STK11
- VHL
- WT1

**Genes**
- BRAF
- IDH1
- IDH2
- KIT
- TP53
- PDGFRα
- AKT1
- ALK
- APC
- ATM
- BRCA1
- BRCA2
- CDKN2A
- CTNNB1
- EGFR
- FGFR2
- ERBB2
- ESR1
- HRAS
- KRAS
- MAP2K2
- MET
- MTOR
- NF1
- NRAS
- PIK3CA
- PTCH1
- PTEN
- RB1
- RET
- SMO
- STK11
- VHL
- WT1

**VUS, SNPs**
- 47%
  - (variable clinical evidence)

**Level 1**
- 16%
  - Actionable in patient’s tumor type

**Level 2**
- 14%
  - Actionable in a different tumor type

**Level 3**
- 23%
  - Reported in cancer or other disease

**Cancers**
- Lung 35%
- Breast 2%
- Brain 4%
- Colorectal 14%
- Head & Neck 11%
- GI 8%
- Hematologic 5%
- Gynecologic 5%
- Pancreas 6%
- Sarcoma 7%
Clinical NGS and biomarkers—Cautionary considerations

Your specimens are contaminated

- Tumor ‘contamination’ in normal/healthy specimens—for AML at presentation, up to 15%
- FFPE specimens are contaminated with tissue from distinct human and non-human material

What is the real error rate of that ‘high-fidelity’ DNA polymerase? Ultra-high sensitivity assays (e.g., circulating cfDNA for minimal residual disease) are confounded by lot-to-lot variability in polymerase performance...QC considerations
Clinical NGS and biomarkers—Cautionary considerations

Clinical NGS: not ‘what can we find?’, but rather, ‘where are we blind?’

DNA testing alone is not sufficient—integrated/combination assays will be required for truly comprehensive analysis

Whole genome (best for CNVs) combined with transcriptome, methylome...what coverage/depth is needed?

Clinical NGS and biomarkers—Cautionary considerations

Clinical NGS—Intended Use matters

• Looming FDA oversight of LDTs and ALDTs

• Diagnostic? Minimal Residual Disease? –the intended use dictates the relative emphasis placed on assay performance parameters

• Amplicon- vs hybrid capture-based NGS assays have important differences in performance and sources of error

• Consider intended use of NGS-based cancer panels for

  • Early-stage/diagnosis: narrowly defined, small number of genes (e.g., recent Palmetto LCD for NSCLC)

  • Refractory/recurrent disease: actionability more broadly defined, large gene panel to maximize detection of predictive targets or possibly (emerging) immunotherapies

  • Enrollment into ‘Umbrella’ and ‘Basket’ type clinical trials
Dynamic evolution of actionable targets—Lung adenocarcinoma

2012:
Activating mutations in \textit{EGFR} & \textit{KRAS}, and \textit{EML4-ALK} translocations

2014:

\begin{itemize}
  \item \textit{MET} amp (2.2%)
  \item \textit{ERBB2} amp (0.9%)
  \item \textit{RIT1} (2.2%)
  \item HRAS (0.4%)
  \item NRAS (0.4%)
  \item RET fusion (0.9%)
  \item MAP2K1 (0.9%)
  \item ALK fusion (1.3%)
  \item ROS1 fusion (1.7%)
  \item \textit{ERBB2} (1.7%)
  \item MET ex14 (4.3%)
  \item BRAF (7.0%)
  \item EGFR (11.3%)
  \item KRAS (32.2%)
  \item None (24.4%)
\end{itemize}

\textit{TCGA adenocarcinoma, Nature (online July 9 2014)}
NGS-based assessment & disease heterogeneity—Synchronous tumors

**Tumor 1**
- MSI-High (5/5)
- *MLH1*-methylated
- *BRAF* c.1799T>A, p.V600E
- *KRAS*wt, *EGFR*wt

**Tumor 2**
- MSS (0/5)
- *MLH1*-unmethylated
- *BRAF* c.1803A>C, p.K601N
- *KRAS*wt, *EGFR*wt

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**Microsatellite Instability by CE**

J Savage, et al., 2012; AMP Abst ST45

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100 cm apart, distal colon
Challenges—How to find & exploit therapeutic synthetic lethality opportunities

- Exciting possibilities beyond DNA homologous repair lesions (e.g., BRCA1/2) and PARPi
- Not all patients will respond—learning from both extreme responders and non-responders advances the knowledgebase


Challenges—How do we generate the clinical utility data?

Finding a majority of the clinically relevant mutations for many tumor types will require very large numbers of specimens.

Tumor Portal Website: http://www.tumorportal.org/ MS Lawrence et al., 2014; Nature 505, 495–501. doi:10.1038/nature12912
Challenges—Clinical NGS testing in cancer and beyond

• Cancer oligoclonality, clonal evolution and the need to move past single-point NGS testing
  • Serial testing for disease
  • progression, recurrence & metastases
• Minimal residual disease monitoring
  • Warm autopsy programs for comprehensive analysis

• How do we define the relevant biomarkers?
  • Will likely be different for each disease
  • Implications for synthetic lethality therapies
• How do improve and maintain quality of ‘clinical grade’ variant databases and knowledgebases?

*Nature 481, 506–510 (26 January 2012)*
Clinical genomics education at WUSM

- **Open-Access & Community**
  - Intramural—“Genomics in the Era of Personalized Medicine” seminar series covering technical, bioinformatical, and clinical aspects
  - Regional—disease-specific public presentations in partnership with Siteman Cancer Center outreach events
  - R25 award to develop web-based Cancer Genomics materials

- **Graduate-level—“Genetics and Genomics of Disease”**
  - Human genetics, statistical genetics, bioinformatics and computational biology students learn about clinical genomics, including ‘hands-on’ case analysis

- **Medical Education**
  - Revised Medical Genetics course including clinical genetics and cytogenetics, cancer genetics & genomics, pharmacogenomics, exomes, genetic counseling and ethics of genetics modules
  - Enhanced Statistics (GWAS) and Computational Biology components

- **Post-graduate**
  - Accredited fellowships in medical genetics, clinical cytogenetics, molecular-genetic pathology
  - K12 program for Cancer Genomics (for both MDs and PhDs)—since 2013; 8 Paul Calabresi Scholars; 24 publications; R01 (1) and K07 (1) awards
Summary and final points

• NGS-based methods are expanding our understanding of the biology of cancer and other diseases
  • Disease stratification and clonal architecture
  • Discovery of new actionable targets

• Rapid advancement of NGS and related genomic technologies has a risk for incomplete understanding of sources for errors

• NGS-based and other testing involving large data sets performed in clinical labs must develop appropriate standards and quality controls for both technical and data analysis components—organizations such as CAP, ACMG, and AMP are collaborating to develop these materials

• Regulatory oversight (FDA) and reporting (PAMA) threaten to widen the gap between research and clinical genomics
  • Increased burden → reduction of CLIA labs → reduce access & innovation
Summary and Final Points

**Given that:** The expected harvest of biomarkers that can guide molecularly targeted therapies MUST involve testing performed in clinical laboratories if these therapies are to be generally applied as healthcare solutions...

**Then:** The most important issue at present is to ensure adequate support for the development and validation of these complex tests as well as fair and stable reimbursement.