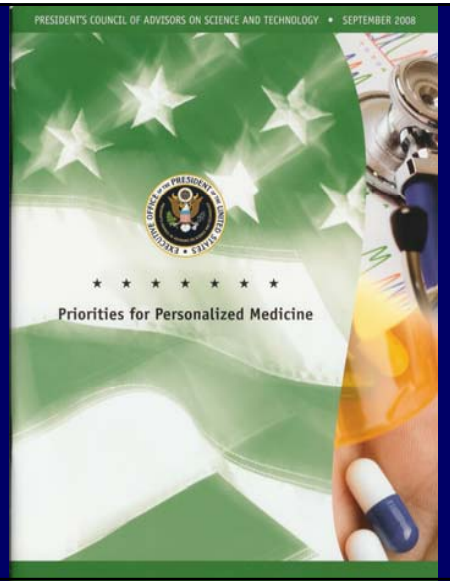
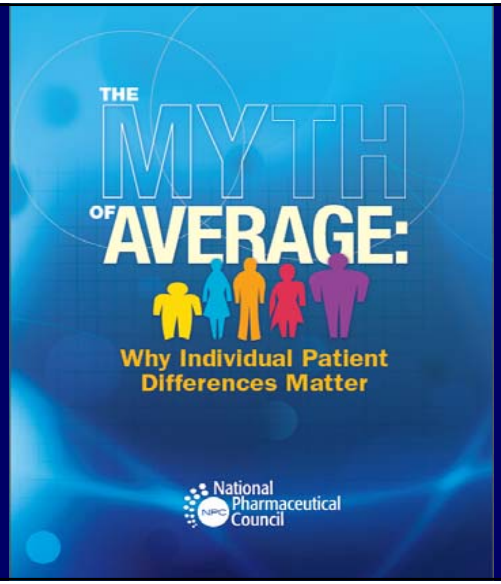
Think Tank Meeting
November 4, 2014

Issues in Molecular Diagnostics

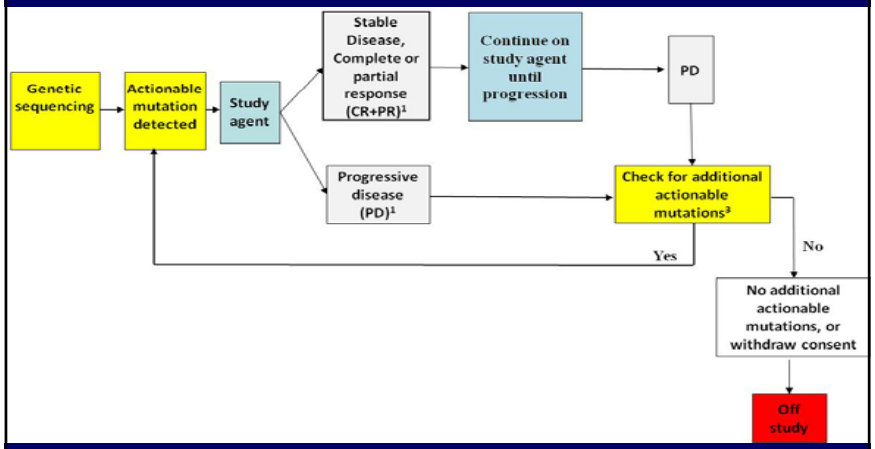
Stan Hamilton, MD
Head, Pathology and Laboratory Medicine
ECOG-ACRIN Deputy Chair for Laboratory Science

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®





Schema for NCI MATCH EAY131 Trial



Organizations advocating for molecular data use

- **Patient advocates**
  - Friends of Cancer Research
  - Green Park Consortium
- **Professional societies**
  - American Society of Clinical Oncology (ASCO)*
  - National Comprehensive Cancer Network (NCCN)
  - College of American Pathologists (CAP)*
  - Association for Molecular Pathology (AMP)*
  - American Society of Clinical Pathologists (ASCP)*
  - American College of Medical Genetics and Genomics
- **Others**
  - Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP WG)
  - Technology Evaluation Center
  - Actionable Genome Consortium

A major problem

Medical Officer of a major health care system, September, 2014:

"I don't see why I should pay for this stuff."

Molecular Diagnostics Lab

Faculty

- Raja Luthra, PhD
- Rajesh Singh, PhD
- Keyur Patel, MD, PhD
- Russell Broaddus, MD, PhD
- Alex Lazar, MD, PhD
- Sinchita Roy-Chowdhuri, MD, PhD
- Zhuang (John) Zuo, MD, PhD
- Asif Rashid, MD, PhD
- C. Cameron Yin, MD, PhD
- Hui Chen, MD, PhD

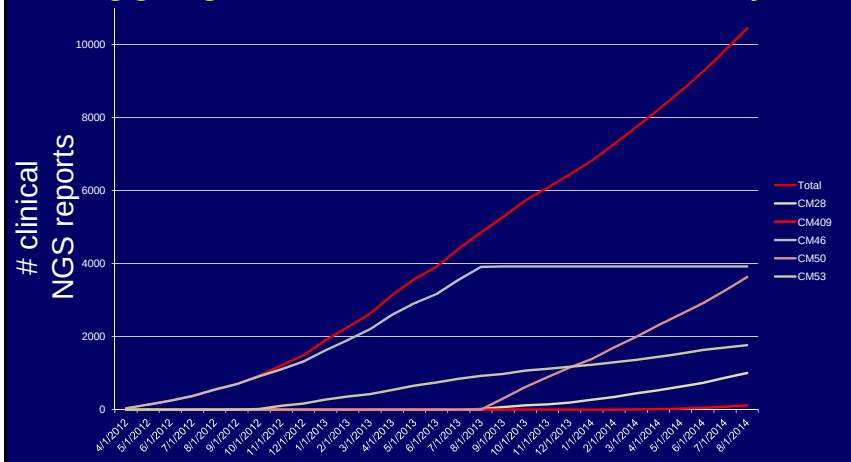
MGP fellows

- Bryce Portier, MD, PhD
- Rashmi Kanagal-Shammana, MD
- Rashmi Goswami, MD, PhD
- Kausar Jabbar, MD

NGS cancer panels at MD Anderson

- **CM46**
  - Original hotspot solid tumor panel, live March 2012
  - Best known solid-organ high-frequency oncogenes and some tumor suppressor genes
- **CM50**
  - Minor upgrade from CM46, live September 2013
  - Adds GNAQ; GNA11; IDH2; EZH2
- **CM409**
  - 409 genes, close to full-exon coverage
  - Includes germline subtraction
  - Available as part of an institutional trial, live May 2014
- **CM53**
  - Original hotspot-based hematologic malignancy panel
  - Coverage of genes/hotspots relevant in AML, MDS, MPN
- **CM28**
  - Refined hematologic malignancy panel
  - Fewer genes, but greater relevance, and close to full-exon coverage

Aggregate volumes of NGS assays



Drivers of clinical assay development

- **Patient needs**
  - Standard-of-care management decisions
  - Integral-marker clinical trials
- **Clinical faculty members' requests for services**
- **Regulatory requirements**
  - Clinical Laboratory Improvement Amendments (CLIA)
  - United States Food and Drug Administration (FDA)
- **Third-party payers**
  - Center for Medicare and Medicaid Services (CMS)
  - Medical insurers

Interpretation of molecular data:
Genomic literacy

Paper tower of babble?
Encyclopedia Genomica, University of Leicester

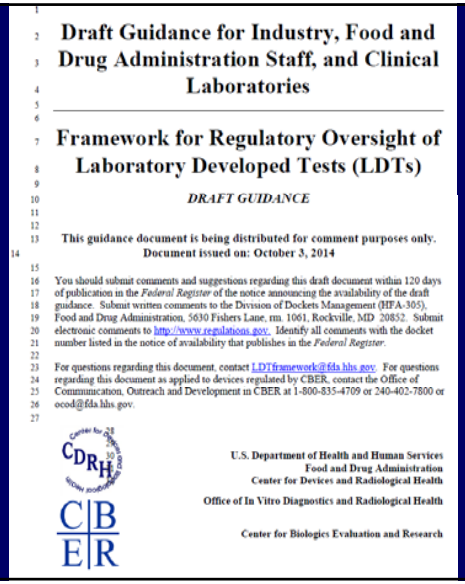
Scope of genomic data

- **Haploid genome ~3 billion base pairs**
- **~20,000 genes**
  - **About 45 million base pairs (coding)**
- **What should we assay?**
  - **Individually actionable single mutations**
  - **Targeted amplicons: Selected small stretches of cancer genes with coverage of known "hotspots"**
  - **Whole exome or selected full exomes**
  - **Whole genome**
  - **Pathways**
  - **Reimbursement (myth of the $1,000 genome)**

Issues for interpretation of molecular data

- **Biological complexity**
- **Rapidly expanding information**
- **Methodological differences**
- **Fit-for-purpose assays**
- **Regulatory environment**
- **Criteria for clinical utility**
- **Heterogeneous reimbursement**

Regulatory environment



Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories

Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: October 3, 2014

You should submit comments and suggestions regarding this draft document within 120 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact LDTframework@fda.hhs.gov. For questions regarding this document as applied to devices regulated by CBER, contact the Office of Communication, Outreach and Development in CBER at 1-800-835-4709 or 240-402-7800 or ocod@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostics and Radiological Health

Center for Biologics Evaluation and Research

Regulatory environment

- **CAP: Clinical Laboratory Improvement Amendments (CLIA)**
- **FDA: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs), issued October 3, 2014**
- **FDA: Regulatory-grade databases, pending**

Delivering information, not data

Vocabulary discordance

- **"Actionable"**
  - **Therapeutic target**
    - **Activating mutations**
    - **Amplifications**
    - **Re-arrangements**
  - **Therapeutic effect**
  - **Clinically pertinent (prognostic)**
  - **Biologically relevant**
  - **Levels of evidence needed for clinical use and reimbursement**

Molecular Testing Evaluation Committee (MTEC)

Charge to the MTEC (8/27/10)

- Define criteria and establish processes for determining that a CLIA-compliant molecular diagnostics test is considered "standard of care" in a specific clinical setting at MDACC.
- Determine if a specific-proposed CLIA-compliant molecular diagnostics test has satisfied the institutionally defined criteria to be added to the P&LM roster of services for routine clinical ordering on the CSR/eCSR.

Charge to the MTEC (con't)

- Vet organ-site specific electronic order entry sets of molecular diagnostics tests for ClinicStation.
- Determine if a proposed investigational molecular diagnostic test is of sufficient scientific and clinical interest to merit investment of institutional funds to develop clinical data to achieve standard-of-care status.

Charge to the MTEC (con't)

- Develop documentation for use by Patient Billing Services and the Managed Care Contract Office in negotiations with third-party and second-party payers.
- Support development of an Advance Beneficiary Notification (ABN) system for molecular diagnostics tests. (Not done)

Charge to the MTEC (con't)

- Monitor reports on documentation of medical necessity for, billing compliance for, and utilization of molecular diagnostics tests by MDACC physicians.
- Review reports of outcomes/clinical effectiveness studies of molecular diagnostics tests to provide input on the P&LM roster of services.

MTEC roster and governance

- Multidisciplinary clinical Division Heads, Department Chairs, and faculty
- Administrative personnel: Clinical activities, patient services, compliance, billing, and clinical research
- Patient data acquisition and analysis
- Subcommittee of the Executive Committee of the Medical Staff and reports to the Medical Practice Committee

MTEC responsibilities

- Hearing presentations of requests and voting for or against additions to electronic order sets
- Reviewing documentation prepared for Patient Billing Services appeals to Medical Directors of insurers
- Serving as model for Medicare intermediary processes and procedures

What now?

What now?

- Continue to accumulate high-quality evidence for clinical utility (e.g. NCI MATCH EAY131)
- Clarify Variants of Unknown Functional Significance
  - Tumor
  - Germline
- Partner with regulatory agencies
- Address costs and charges: Value and reimbursement
- Deeper characterization of pathways

Thanks for your attention.