Rodger C. Haggitt Memorial Lecture

# The NCI-MATCH Initiative and the Roles of the GI Pathologist in Oncologic Management

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MD Anderson Cancer Center
Making Cancer History®

# Relevant disclosures

**ECOG-ACRIN Laboratory Lead and Pathology Co-chair, NCI-MATCH (EAY121)**
**MEDCAC and CLDT Advisory Committee, CMS**
**Halio DX, Scientific Advisory Board**
**Intervention Insights, Advisory Board**
**MolDX, Palmetto**
**Ludwig Boltzmann Institute for Applied Diagnostics, Consultant**
**Thermo Fisher Scientific, Speaker**

# Outline

- Precision medicine
- The NCI-MATCH initiative
- The pathologist's roles in oncologic management
  - Molecular pathology: Pre-analytics, analytics and post-analytics
- Summary

# Precision medicine

- Personalized/individualized
- Rational
- Molecular target-focused
- Biomarker-directed
- Improved outcomes for patients
  - More efficacious
  - Fewer adverse events
  - Lower cost
- High visibility and priority

**A bad predictive marker for a drug is as bad as a bad drug.**

**Dan Hayes, MD**

# NCI-Molecular Analysis for Therapy Choice (NCI-MATCH EAY131)

## A phase II precision medicine cancer trial

Co-developed by the ECOG-ACRIN Cancer Research Group and the National Cancer Institute

ECOG-ACRIN cancer research group | NIH NATIONAL CANCER INSTITUTE

DRAFT Version Date: 03/11/2016

# NCI-MATCH Hypotheses

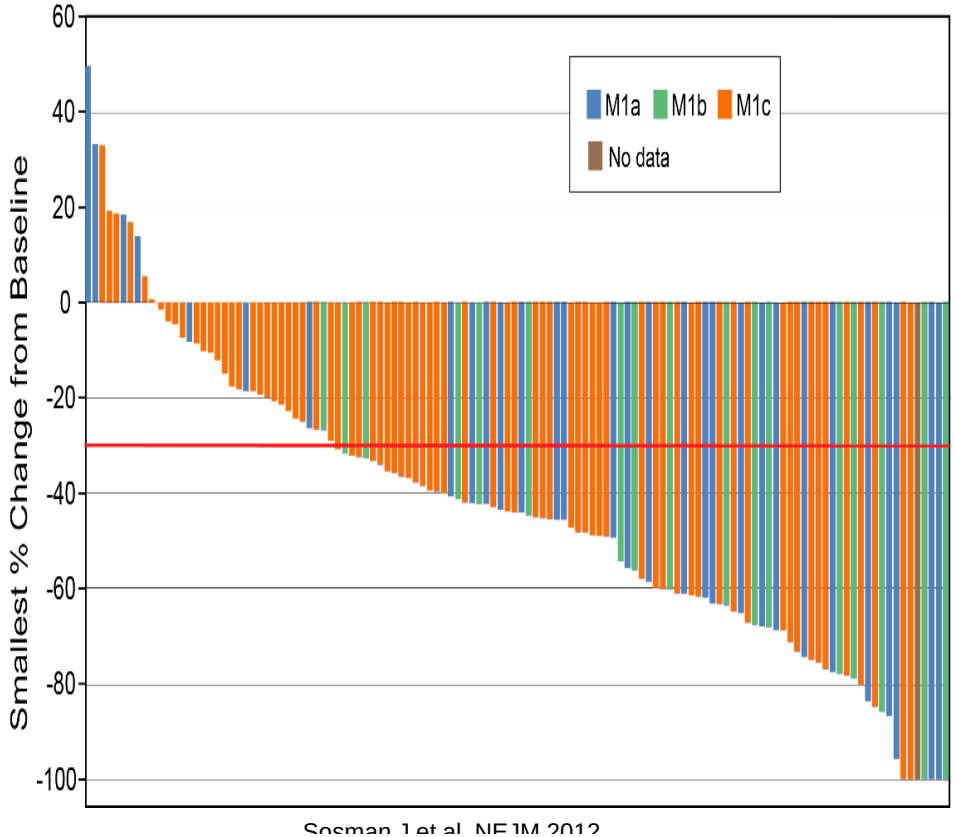
**Primary:**

**Tumors that share common somatic genetic alterations in oncogenes will be variably responsive to therapies targeting the oncogenic pathway based on lineage specific factors.**

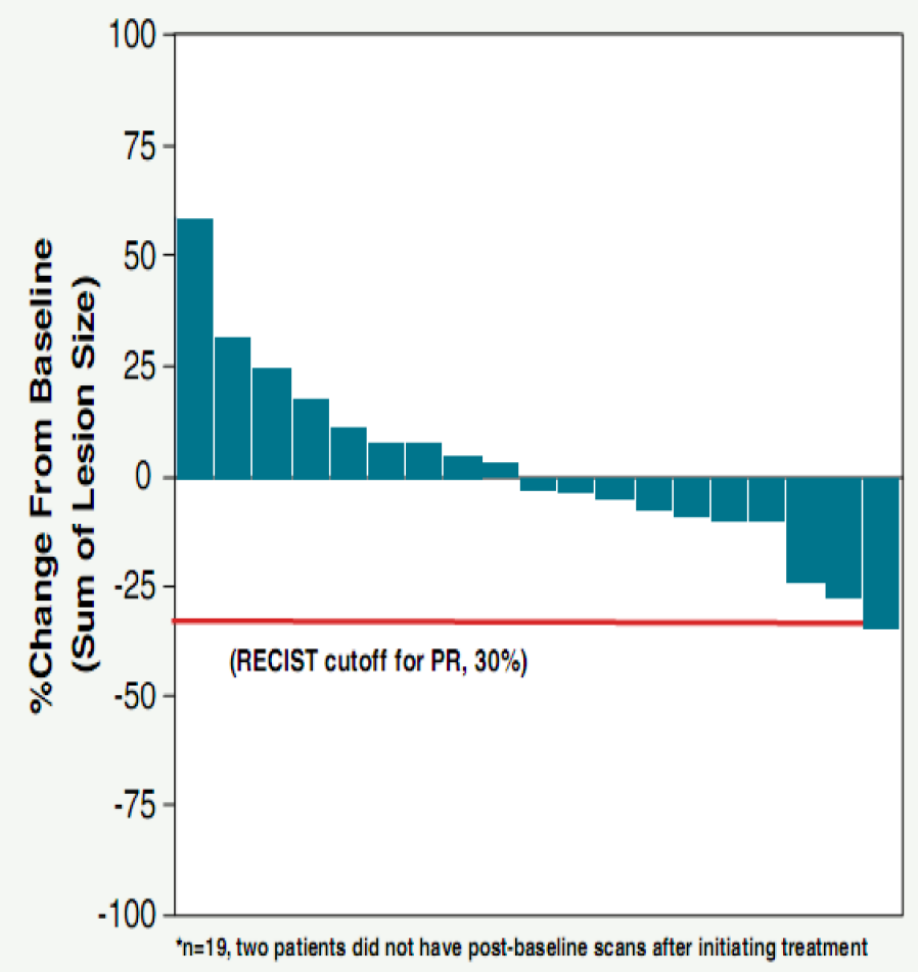
**Secondary:**

**Concomitant somatic genetic alterations will predict responsiveness or resistance.**

# BRAF inhibitor therapy markedly more effective for BRAF V600E-mutated melanoma compared to colon cancer

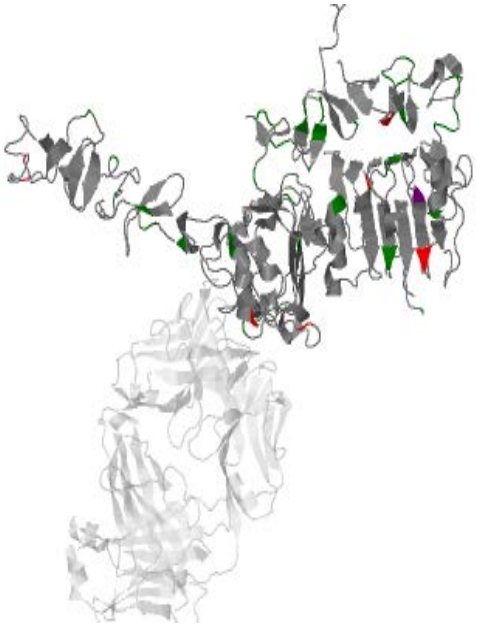


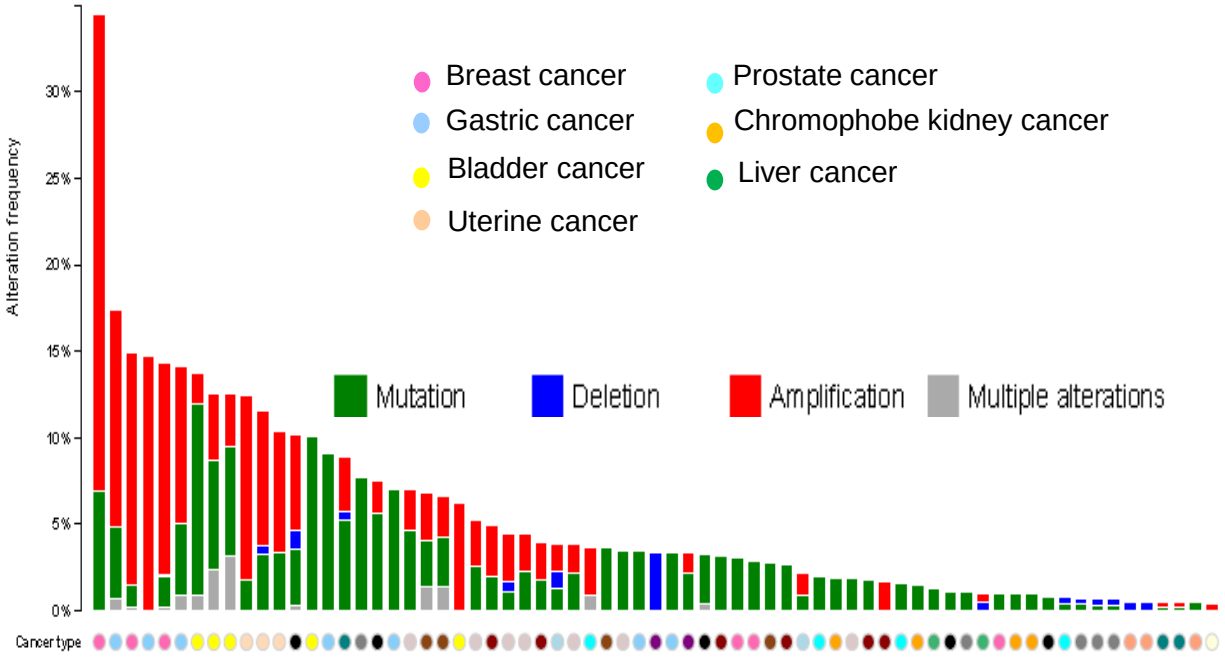

Sosman J et al. NEJM 2012

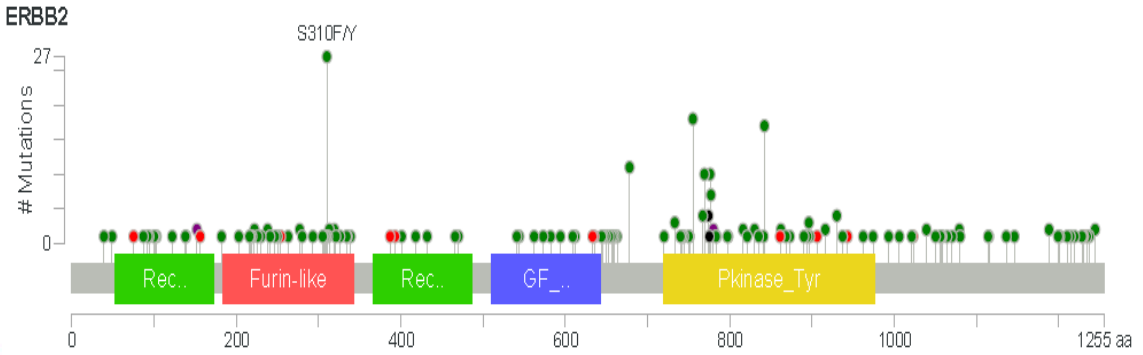



Kopetz, ASCO 2010

# Decoding the cancer genome: ERBB2 (HER2)



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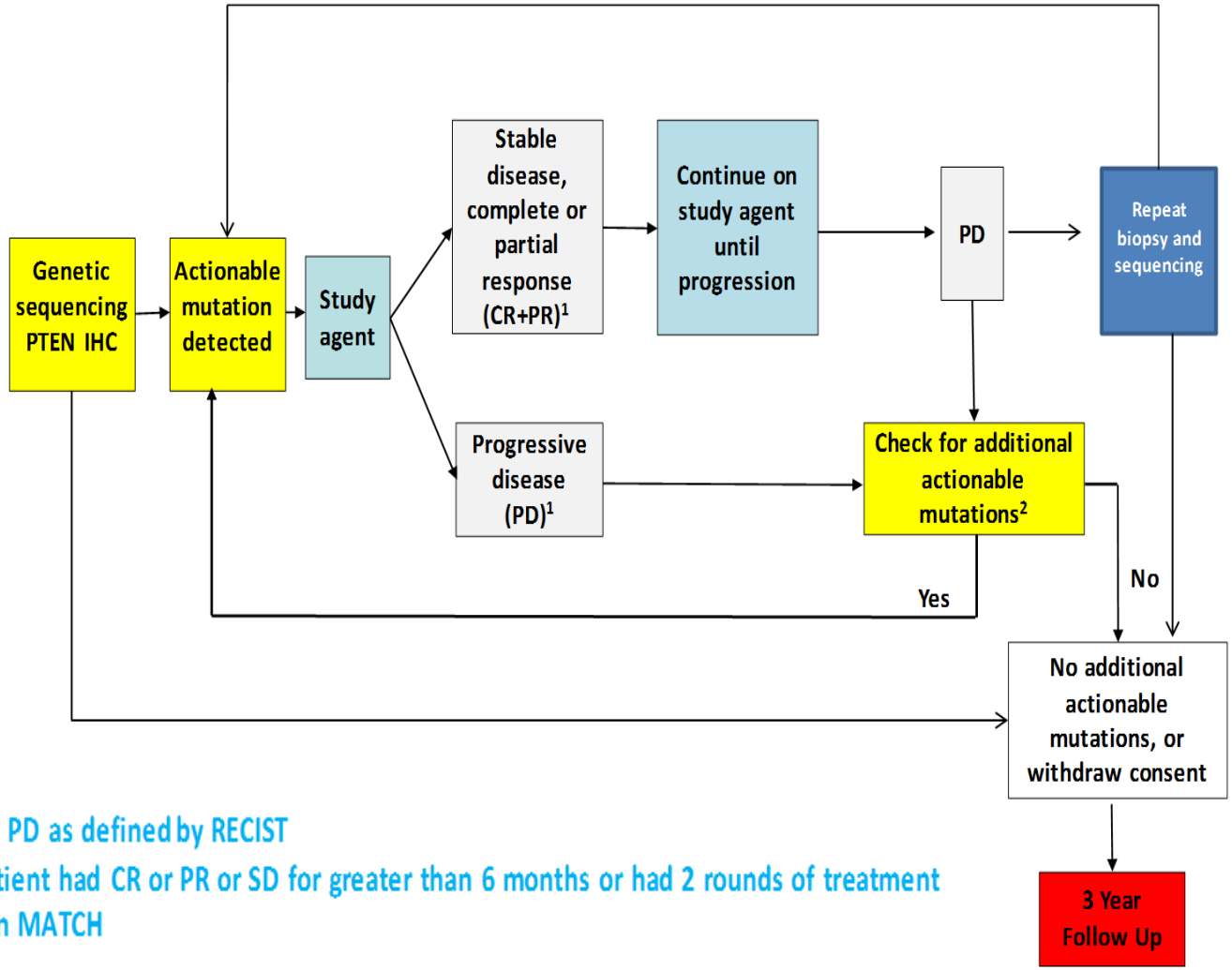
# NCI-MATCH Objective

**To understand the relative efficacy of the same therapy applied to oncogene-defined subsets across different tumor histologies, we propose to initiate a broad-based genomic prescreening study to assign patients whose tumors harbor specific molecular abnormalities to relevant targeted treatments, regardless of tumor histology type.**

# NCI-MATCH Schema




[1]CR, PR, SD, and PD as defined by RECIST

[2]Rebiopsy; if patient had CR or PR or SD for greater than 6 months or had 2 rounds of treatment after a biopsy on MATCH

# NCI-MATCH Design Features

- Test many patients to find widely distributed genetic alterations
- Biopsy needed at time of study entry (cost covered by NCI)
- Response rate (tumor regression) will be primary efficacy measure.
- Highly collabortive clinical trial
  - Across initial 22-24 arms, PIs drawn from:
    - 37% ECOG-ACRIN, 30% Alliance, 16% SWOG, 16% NRG
  - 150+ NCI and NCTN members of 10 subcommittees
  - Advocates involved in trial design and help oversee conduct

# Tumor Biopsy in NCI-MATCH

- Upon entry to initial screening (Step 0), a biopsy (4 cores) in formalin, shipped to MDACC for processing to FFPE blocks
- H&E sections examined by pathologist for tumor type, tumor content, % necrosis, and inflammation, and scanned into high-resolution image database
- Block selected, slides cut for IHC and nucleic acid extraction; RNA and DNA extracted from the same tissue section(s)
- Planned research assays:
  - If sufficient DNA available, whole-exome sequencing performed for research
  - RNA will be used for research-grade gene expression profiling by either whole-transcriptome or miRNA microarray analysis.
- Repeat biopsy and sequencing on progression

# Mutation Frequency in TCGA

| Gene | Bladder | Breast | Cervix | Colo-rectal | GBM | Glioma | Head and Neck | Lung (Adeno) | Lung (Squam) | Melanoma | Ovarian | Pancreas | Prostate | Stomach | Thyroid | Uterine |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AKT | 0 | 2.4 | 0 | 0.9 | 0.4 | 0 | 0.7 | 0.9 | 0.6 | 1.4 | 0 | 3.5 | 0.4 | 1.4 | 0.7 | 1.6 |
| BRAF | 0.8 | 0.6 | 2.6 | 9.9 | 2.1 | 1 | 1.4 | 9.6 | 4.5 | 50.2 | 0.6 | 1.8 | 2.4 | 4.1 | 61.3 | 2.8 |
| EGFR | 1.5 | 0.8 | 2.6 | 4.5 | 26.1 | 5.9 | 4.7 | 14.3 | 3.9 | 6.5 | 2.2 | 1.8 | 1.2 | 5 | 0 | 3.2 |
| FGFR1 | 3.1 | 0.3 | 0 | 1.3 | 1.1 | 0 | 0.4 | 1.3 | 1.7 | 3.6 | 0 | 0 | 0 | 4.5 | 0 | 3.2 |
| FGFR2 | 2.3 | 1.1 | 0 | 1.3 | 1.1 | 0.3 | 0.7 | 3.1 | 3.9 | 9.3 | 0 | 1.8 | 1.2 | 3.6 | 0.2 | 12.5 |
| FGFR3 | 14.6 | 0.4 | 0 | 0.9 | 1.1 | 0 | 2.2 | 0.9 | 2.3 | 2.9 | 0.3 | 1.8 | 0.4 | 1.4 | 0 | 2 |
| HRAS | 4.6 | 0.2 | 0 | 0 | 0 | 0 | 3.9 | 0.4 | 2.8 | 1.1 | 0 | 1.8 | 0.8 | 0 | 3.5 | 0.4 |
| IDH1 | 3.6 | 0.4 | 0 | 1.3 | 4.9 | 76.1 | 0.7 | 1.3 | 1.1 | 5.7 | 0 | 1.8 | 1.6 | 0.5 | 0 | 1.6 |
| IDH2 | 0 | 0 | 0 | 3.1 | 0 | 4.2 | 0 | 0.9 | 0.6 | 0.4 | 0 | 1.8 | 0 | 0.5 | 0 | 1.6 |
| KIT | 2.3 | 1 | 0 | 2.7 | 1.1 | 0.7 | 1.3 | 2.2 | 3.9 | 3.9 | 2.2 | 1.8 | 0 | 4.1 | 0 | 6.9 |
| KRAS | 0 | 0.8 | 2.6 | 43 | 1.1 | 0.3 | 0.4 | 32.6 | 1.1 | 1.4 | 0.6 | 57.9 | 0 | 11.4 | 1 | 21.4 |
| NF1 | 9.2 | 2.8 | 7.7 | 3.6 | 14.3 | 6.6 | 2.9 | 11.8 | 11.9 | 13.3 | 4.4 | 1.8 | 0.4 | 5.9 | 0.5 | 8.1 |
| NF2 | 3.6 | 0.4 | 5.1 | 1.3 | 0 | 0.3 | 1.4 | 0.9 | 1.1 | 1.1 | 0.3 | 1.8 | 0.8 | 1.4 | 0.2 | 2.4 |
| NRAS | 0 | 3.6 | 0 | 9 | 1.1 | 0.3 | 0.4 | 1.7 | 0.6 | 30.8 | 0.6 | 0 | 0 | 0.9 | 8.5 | 3.6 |
| PIK3CA | 20 | 35.1 | 23.1 | 20.1 | 10.6 | 0 | 20.9 | 6.5 | 15.7 | 3.6 | 0.6 | 1.8 | 3.2 | 21.8 | 0.5 | 53.2 |
| PIK3R1 | 3.6 | 2.6 | 2.6 | 4 | 11.3 | 4.5 | 2 | 1.3 | 1.1 | 0.7 | 0.3 | 1.8 | 0.8 | 3.6 | 0.2 | 33.1 |
| PTCH | 7.1 | 1.2 | 2.6 | 4 | 1.1 | 0.3 | 3.6 | 4.8 | 2.8 | 2.5 | 1.9 | 1.8 | 0.8 | 5 | 0.5 | 7.7 |
| PTEN | 3.1 | 3.6 | 7.7 | 3.6 | 31.9 | 4.5 | 2 | 3.1 | 7.9 | 8.2 | 0.6 | 1.8 | 5.2 | 6.4 | 0.5 | 64.9 |
| SMO | 3.6 | 0.5 | 0 | 0.4 | 0.4 | 0 | 0.3 | 2.6 | 0.6 | 3.6 | 0 | 3.5 | 0 | 4.1 | 0 | 2 |
| TSC1 | 10.7 | 0.6 | 2.6 | 2.2 | 1.1 | 0.3 | 0.7 | 2.6 | 3.4 | 3.2 | 0.9 | 1.8 | 0 | 1.4 | 0 | 4 |
| TSC2 | 2.3 | 0.6 | 2.6 | 0.9 | 2.2 | 0.7 | 1.1 | 2.2 | 3.4 | 3.9 | 0.6 | 2 | 0.8 | 3.2 | 0 | 4.8 |

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# Amplification Frequency in TCGA

| Gene | Bladder | Breast | Cervix | Colo-rectal | GBM | Glioma | Head and Neck | Lung (Adeno) | Lung (Squam) | Melanoma | Ovarian | pancreas | Prostate | Stomach | Thyroid | Uterine |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HER2 | 6.3 | 12.9 | 2.3 | 3.1 | | | 2.6 | 2.6 | 2.2 | 0.6 | 2.6 | | | 13 | 0.6 | 5.5 |
| FGFR1 | 9.4 | 12 | 1.2 | 3.6 | | 0.4 | 8.5 | 3.5 | 16.9 | 0.3 | 3.5 | 4 | 2 | 1 | | 2.5 |
| FGFR2 | 0.5 | 1.8 | | 0.3 | 0.6 | | 0.7 | 0.9 | | | 3.5 | | | 5.1 | | |
| FGFR3 | 5.5 | 0.5 | | 0.4 | 1.8 | 0.8 | 0.7 | 1.3 | 0.6 | 1.5 | 7.9 | 2 | 0.8 | 0.7 | 0.2 | 2.2 |
| MET | 0.5 | 0.8 | 1.8 | 0.4 | 8.9 | 0.8 | 0.7 | 3.5 | 1.1 | 3.9 | 6.3 | | 1.2 | 4.1 | | 0.3 |
| PIK3CA | 5.5 | 4.9 | 19.3 | | 2.9 | 1.1 | 21.1 | 2.2 | 38.2 | | 28.8 | 4 | 2.8 | 5.5 | | 14.3 |

# Oncomine$^{R}$ Comprehensive Assay Gene List

**Hotspot genes, n=73**

| | | |
|---|---|---|
| ABL1 | GNA11 | MYD88 |
| AKT1 | GNAQ | NFE2L2 |
| ALK | GNAS | NPM1 |
| AR | HNF1A | NRAS |
| ARAF | HRAS | PAX5 |
| BRAF | IDH1 | PDGFRA |
| BTK | IDH2 | PIK3CA |
| CBL | IFITM1 | PPP2R1A |
| CDK4 | IFITM3 | PTPN11 |
| CHEK2 | JAK1 | RAC1 |
| CSF1R | JAK2 | RAF1 |
| CTNNB1 | JAK3 | RET |
| DDR2 | KDR | RHEB |
| DNMT3A | KIT | RHOA |
| EGFR | KNSTRN | SF3B1 |
| ERBB2 | KRAS | SMO |
| ERBB3 | MAGOH | SPOP |
| ERBB4 | MAP2K1 | SRC |
| ESR1 | MAP2K2 | STAT3 |
| EZH2 | MAPK1 | U2AF1 |
| FGFR1 | MAX | XPO1 |
| FGFR2 | MED12 | |
| FGFR3 | MET | |
| FLT3 | MLH1 | |
| FOXL2 | MPL | |
| GATA2 | MTOR | |

**Full-gene coverage, n=26**

APC
ATM
BAP1
BRCA1
BRCA2
CDH1
CDKN2A
FBXW7
GATA3
MSH2
NF1
NF2
NOTCH1
PIK3R1
PTCH1
PTEN
RB1
SMAD4
SMARCB1
STK11
TET2
TP53
TSC1
TSC2
VHL
WT1

**Copy Number Variants, n=49**

| | |
|---|---|
| ACVRL1 | IGF1R |
| AKT1 | IL6 |
| APEX1 | KIT |
| AR | KRAS |
| ATP11B | MCL1 |
| BCL2L1 | MDM2 |
| BCL9 | MDM4 |
| BIRC2 | MET |
| BIRC3 | MYC |
| CCND1 | MYCL |
| CCNE1 | MYCN |
| CD274 | MYO18A |
| CD44 | NKX2-1 |
| CDK4 | NKX2-8 |
| CDK6 | PDCD1LG |
| CSNK2A1 | 2 |
| DCUN1D1 | PDGFRA |
| EGFR | PIK3CA |
| ERBB2 | PNP |
| FGFR1 | PPARG |
| FGFR2 | RPS6KB1 |
| FGFR3 | SOX2 |
| FGFR4 | TERT |
| FLT3 | TIAF1 |
| GAS6 | ZNF217 |

**Fusion drivers, n=22**

ALK
RET
ROS1
NTRK1
NTRK3
FGFR1
FGFR2
FGFR3
BRAF
RAF1
ERG
ETV1
ETV4
ETV5
ABL1
AKT3
AXL
EGFR
ERBB2
PDGFRA
PPARG

- **143 unique genes**
- **2530 amplicons in DNA panel**
- **207 amplicons in RNA panel**

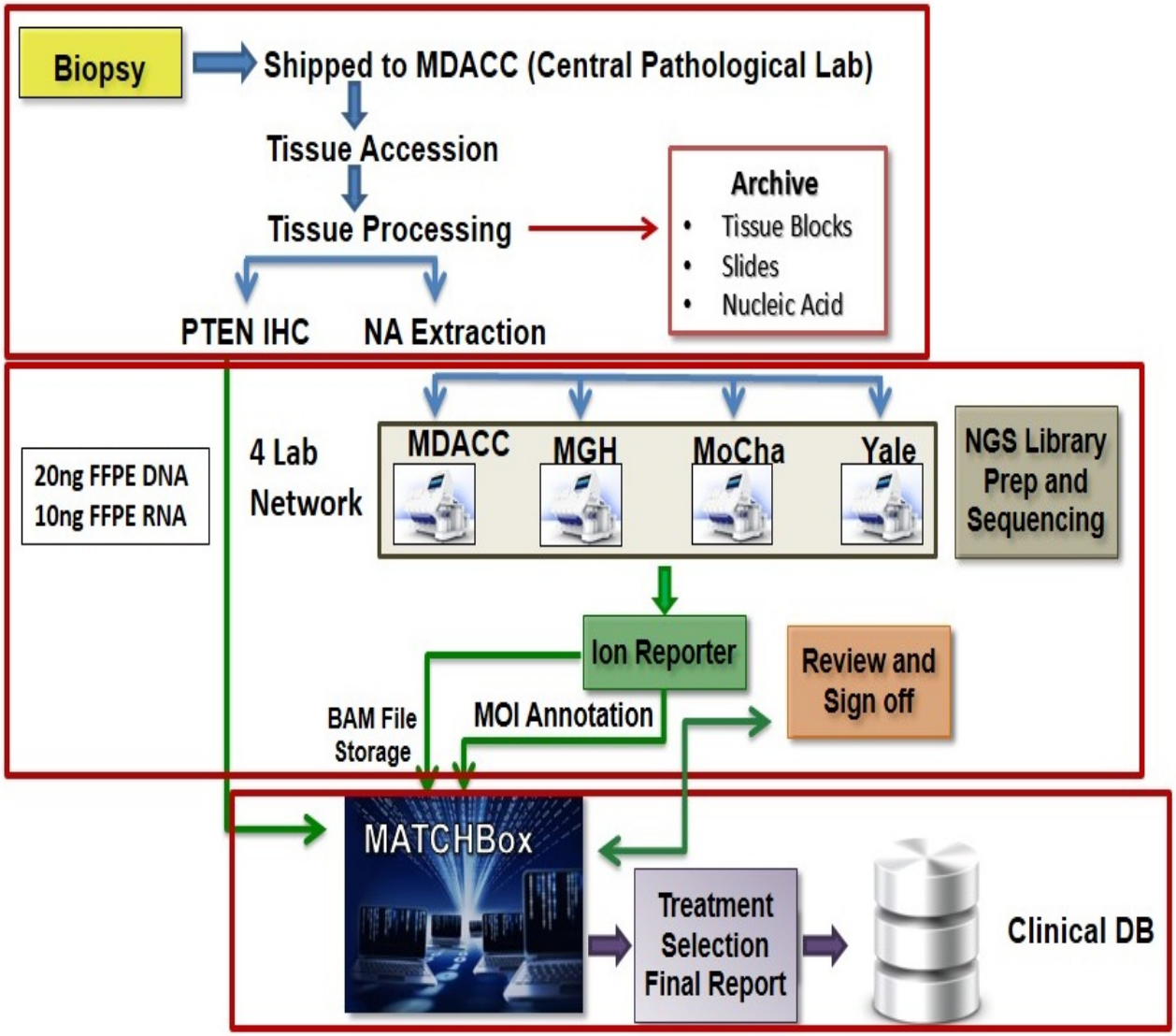
# Reporting and Actionable Mutations by NCI-MATCH Assay

- **Total genes: 143**
- **Mutations of interest (MOI) reported by assay:**
  - 4066 pre-defined hotspot
    - 3259 SNVs
    - 114 Small indels
    - 435 Large indels (gap >=4bp)
    - 75 CNVs
    - 183 Gene fusions
  - Deleterious mutations in 26 tumor suppressor gene
  - EGFR exon 19 inframe deletions and insertions
  - ERBB2 exon 20 inframe insertions
  - KIT exons 9 and 11 inframe deletions/ insertions
- **Actionable MOI (aMOI) =** Subset of MOIs with level of evidence

# Genetic Platform and Laboratory Network in NCI-MATCH

- Ion Personal Genome Machine® (PGM™) System and Ion Torrent™ Server
- Ion Ampliseq™ custom DNA panel
  - 143 genes
  - SNV, indel, CNV, targeted translocations
- Selected IHC (PTEN; MLH1, MSH2; Rb)
- Network of four CLIA-approved molecular diagnostics laboratories provides capacity
  - NCI Molecular Characterization Laboratory (Dr. Mickey Williams)
  - Plus competitively chosen lab sites: MD Anderson (Dr. Stan Hamilton), Massachusetts General (Dr. John Iafrate), Yale (Dr. Jeffrey Sklar)
- Validation within and across all four labs: same SOPs

# NCI-MATCH Assay Workflow



# NCI-MATCH Eligibility Defined Molecularly

- Initial tumor biopsy to identify mutations/amplifications/ translocations
- Patients can be screened with local NGS but results must be confirmed on NCI-MATCH assay
- Patient assignment to relevant agent(s)/subprotocol
- Perform repeat tumor biopsy and sequencing at progression to illuminate resistance mechanisms
  - Submit de-identified samples to central labs
  - Conduct whole-exome, mRNA sequencing (research purposes)

# NCI-MATCH Eligibility

- **Patients with a solid tumor or lymphoma whose disease has progressed following at least one line of standard systemic therapy – or with a tumor that does not have standard therapy**
  - **Exclude histologies that had been approved by the FDA or had shown lack of efficacy with an agent**
- **Tumor accessible to biopsy and patient willing to undergo biopsy**
- **Adults ≥ 18 year of age**
- **ECOG performance status ≤ 1**

# NCI-MATCH Patient Population Considerations

- Target: at least 25% of total enrollment to be patients who have “rare” tumors
- “Common” cancers defined as:
  - Breast
  - Non-small cell lung
  - Colorectal
  - Prostate

# Statistical Considerations for Each Molecularly-Defined Arm

- Primary endpoint: Overall Response Rate (ORR) 5% vs 25%
- Secondary endpoints:
  - Progression Free Survival (PFS) 6 months 15% (median PFS 2.2 m) vs 35% (median PFS 4 m)
  - Time to progression (TTP)
  - Toxicity
  - Biomarker
- One-stage design:
  - 35 evaluable patients per arm

# NCI-MATCH Treatment Arms: n=24, expected in Late May 2016

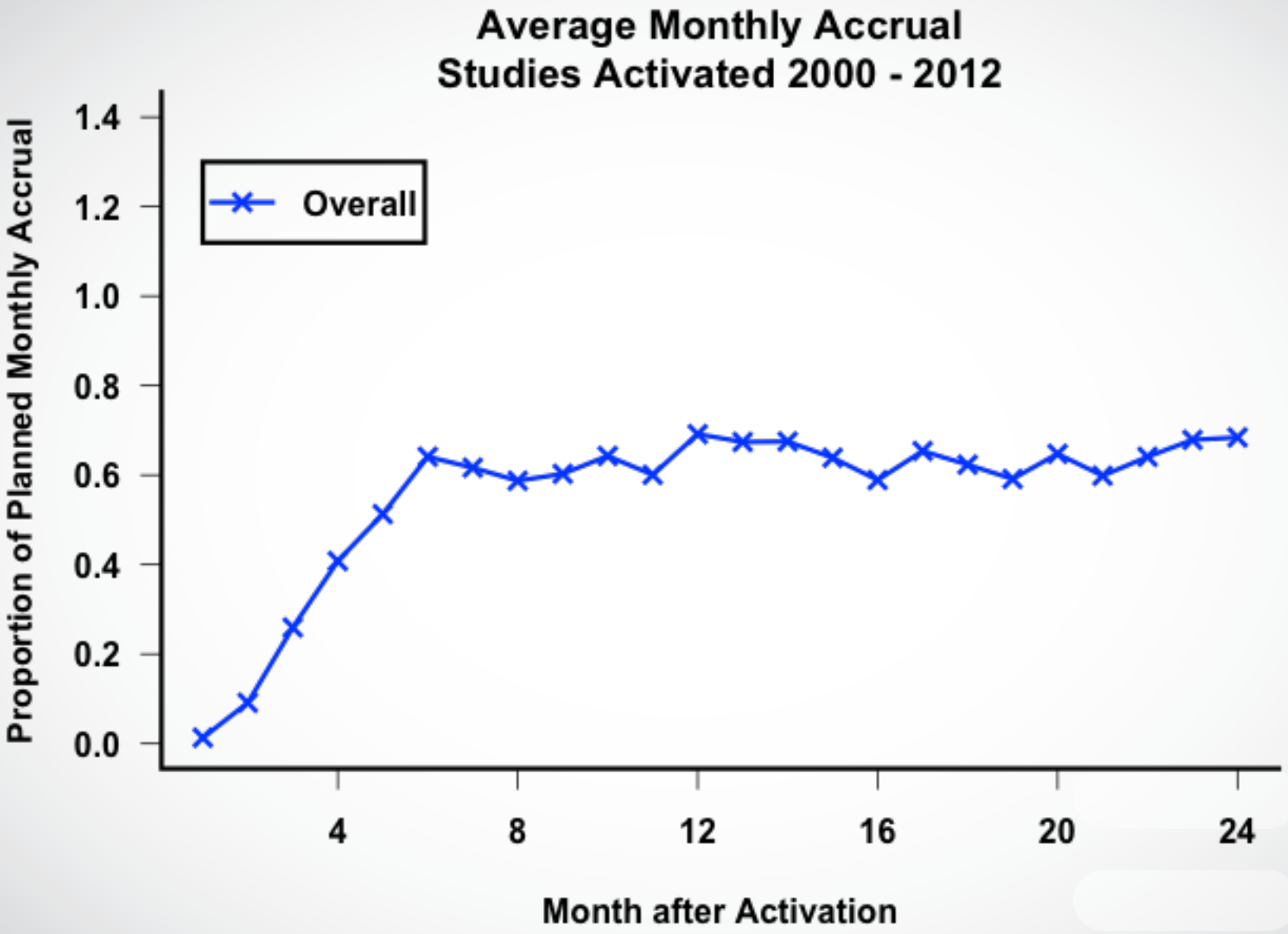
| Arm/ Target | Drus(s) | Est Prevalence % |
|---|---|---|
| A EGFR | Afatinib | 1-4 |
| B HER2 mut | Afatinib | 2-5 |
| C1 MET amp | * | 4 |
| C2 MET ex 14 skip | * | 4 |
| E EGFR | AZD9291 | 7-7 |
| F ALK | Crizotinib | <2 |
| G ROS1 | Crizotinib | <2 |
| H BRAF V600 | Dabrafenib + trametinib | 7 |
| I PIK3CA | Taselisib | 17-18 |
| N PTEN mut | GSK2636771 | 11 |
| P PTEN loss | GSK2636771 | 11 |
| Q HER 2 amp | Adotrastuzumab | 5 |
| R BRAF nonV600 | Trametinib | 2.8 |
| S1 NF1 | Trametinib | 7-7 |

| Arm/ Target | Drug(s) | Est Prevalence % |
|---|---|---|
| S2 GNAQ/GNA11 | Trametinib | 2/1.6 |
| T SMO/PTCH1 | Vismodegib | <2 |
| U NF2 | Defactinib | 2 |
| V cKIT | Sunitinib | 2 |
| W FGFR1/2/3 | * | 5 |
| X DDR2 | Dasatinib | 2 |
| Y AKT1 | * | 1-10 |
| Z1A NRAS | * | 1-5 |
| Z1B CCND1, 2, 3 | * | 4 |
| Z1D dMMR | * | 2 |

*To be announced upon final approval

# NCI-MATCH Pause on New Accrual for Interim Analysis

- **Protocol design has built-in review after 500 patients enrolled for screening.**
- **Pause on *new* patient accrual went into effect 11/04/15 to complete scientific analysis of initial patient cases.**
- **During the pause, changes are being made to accommodate higher enrollment rate:**
  - **Adding subprotocols**
  - **Expanding laboratory capacity**
  - **Upgrading sequencing technology**
  - **Addressing specimen quality**
  - **Establishing guidelines for patient selection**
- **Accrual will resume in late May 2016 upon completion of all of these activities.**
- **Meanwhile, no change for patients on a treatment arm**



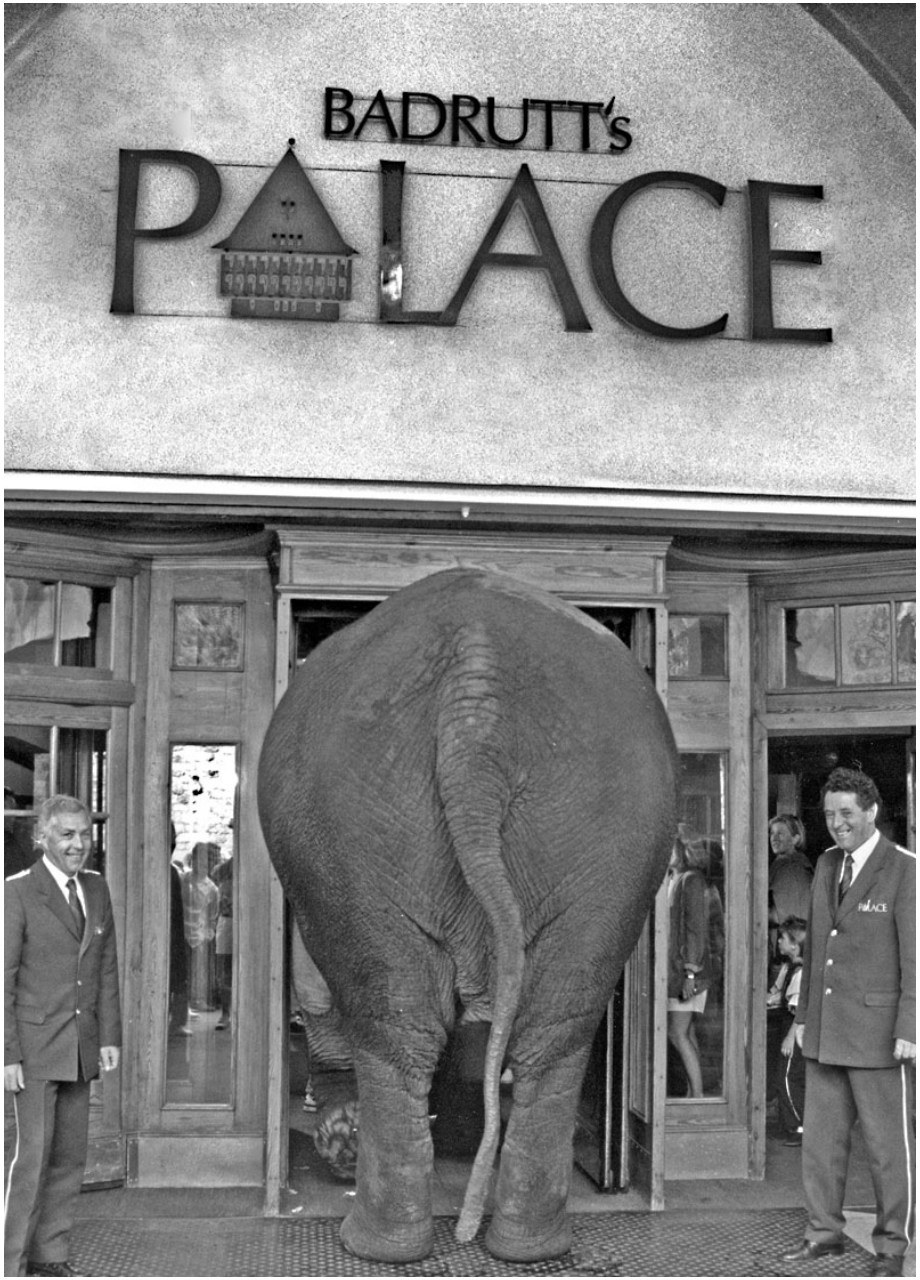



Slide courtesy of Robert Gray, PhD

# NCI-MATCH Accrual Metrics

- **Patient enrollment surpassed expectations with 795 enrolled in first 3 months**

| Activated 08/12/15; paused 11/11/15: 92 days | |
|---|---|
| Patient cases registered for screening | 795 |
| Cases with specimens submitted | 739 |
| Cases labs able to analyze successfully | 645 (87%) |
| Cases with mutation matching 1 of the 10 available treatment arms | 56 (9%) |
| Patients matching specific eligibility criteria for, and assigned to, a treatment arm | 33 (5%) |
| Patients who entered 7 of 10 open treatment arms | 16 |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PALACE

# Team Approach to NCI-MATCH

- NCI-MATCH Steering Committee
  - Agent & Gene Selection Committee
    - Vetting of actionable genetic alterations and robust agents
  - Informatics Committee
  - Imaging Committee (radiology)
  - Specimen/Assay Committee
    - Developed and validated next-generation sequencing platform
    - Additional IHC or other assays developed at CLIA-accredited ECOG-ACRIN Central Biorepository and Pathology Facility at MDACC

# NCI-MATCH Steering Committee

- **Clinical Study Chairs**: Drs. Alice Chen, Keith Flaherty, Peter O'Dwyer
- **Scientific Chairs**: Drs. Barbara Conley, Stan Hamilton, Mickey Williams, Carlos Arteaga
- **Statistical Chairs**: Drs. Robert Gray, Shuli Li, Lisa McShane, Larry Rubenstein
- **Safety Chairs**: Drs. Edith Mitchell, James Zwiebel
- **Informatics Chairs**: Warren Kibbe, Jose Galvez, Rick Magnan, Mark Routbort

# NCI-MATCH Summary

- NCI-MATCH is a signal-finding trial.
- Largest, most rigorous precision medicine cancer trial in history
- Conducted by ECOG-ACRIN, but has PIs on subprotocols from across the NCTN
- Target selection based on levels of evidence
- Coordinated sample collection and centralized pre-analytics
- Validated, standardized gene sequencing through MATCHbox
- Using NCI-MATCH to inform other trials (pMATCH)

# Resources for NCI-MATCH

- Main Webpages: cancer.gov/nci-match
  ecog-acrin.org/nci-match-eay131
- Protocol Documents: ctsu.org (password required)
- Spanish: cancer.gov/espanol/nci-match
- Email Inquiries: match@jimmy.harvard.edu
- Patient Brochure: EA website (above)
- Site Process Brochure: EA website (above)
- NCI's Cancer Information Service: 1-800-4-CANCER and cancer.gov/contact

*This slide presentation is updated regularly. For the latest version, visit ecog-acrin.org.*

# The roles of the pathologist in oncologic management

# Molecular Pathology Assay Issues

- **Discordant results in same tumor: Intra-tumoral heterogeneity (biology), methodologies**
- **Discordant sequencing results with same starting material: Methodologies, informatics of alignment and variants**
- **Post-analytic decision support: Databases for actionability, algorithms**
- **Level of risk for patients**

# Parties Interested in Assay Issues

- **Clinical laboratorians**
- **Clinicians**
- **Patients**
- **Regulatory agencies**
- **Professional organizations**
- **Payers**
- **Others**

# Examples of Interested Parties

- **For regulations with enforcement powers:**

***Regulatory agencies*:**

- **FDA**
- **Center for Medicare and Medicaid Services (CMS) for federal Clinical Laboratory Improvement Amendments (CLIA)**
- **College of American Pathologists (CAP) for CLIA**
- **New York State Board of Health**

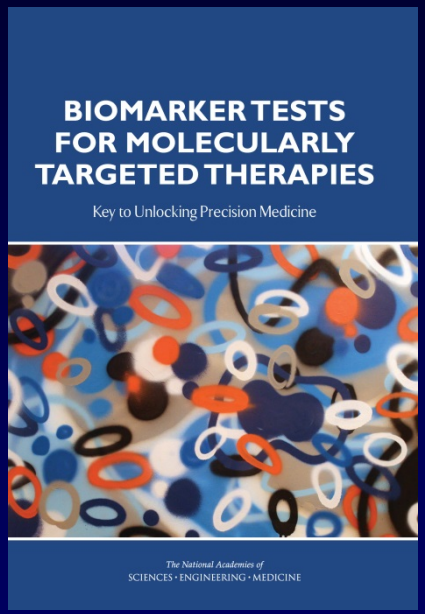
# Examples of Interested Parties

- **For guidelines with recommendations (format of Institute of Medicine of the National Academy of Sciences of the USA):**

***Professional organizations*:**

- **The Institute of Medicine (IOM) itself**
- **College of American Pathologists (CAP)**
- **American College of Medical Genetics and Genomics (ACMG)**
- **American Society of Clinical Oncologists (ASCO)**

# Biomarker Tests for Molecularly Targeted Therapies: Key to Unlocking Precision Medicine




**Suggested citation:** National Academies of Sciences, Engineering, and Medicine. 2016. *Biomarker tests for molecularly targeted therapies: Key to unlocking precision medicine.* Washington, DC: The National Academies Press.

The National Academies of
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# Examples of Interested Parties

***Professional organizations (continued):***

- **Association of Molecular Pathologists (AMP)**
- **Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (EWG) of Center for Disease Control and Prevention's Office of Public Health Genomics**
- **Et cetera**

# Examples of Interested Parties

***Professional organizations (continued):***

- **Partnerships:**
  - **CAP, IASLC, AMP for lung cancer biomarker guidelines**
  - **CAP, ASCO, AMP, American Society of Clinical Pathologists/ASCP for colorectal cancer biomarkers**
  - **ASCO, CAP for HER2 in breast cancer**

# Examples of Interested Parties

- ***Payers with power of the purse:***
- **Blue Cross/Blue Shield Association Center for Clinical Effectiveness (formerly Technology Evaluation Center)**
- **Palmetto Molecular Diagnostics Services (MolDX) Program**
- ***Patient advocates:*** **The Green Park Collaborative**
- ***Vendors:*** **Actionable Genome Consortium (Illumina), Developers' Network (Thermo Fisher Scientific)**

# Examples of Interested Parties

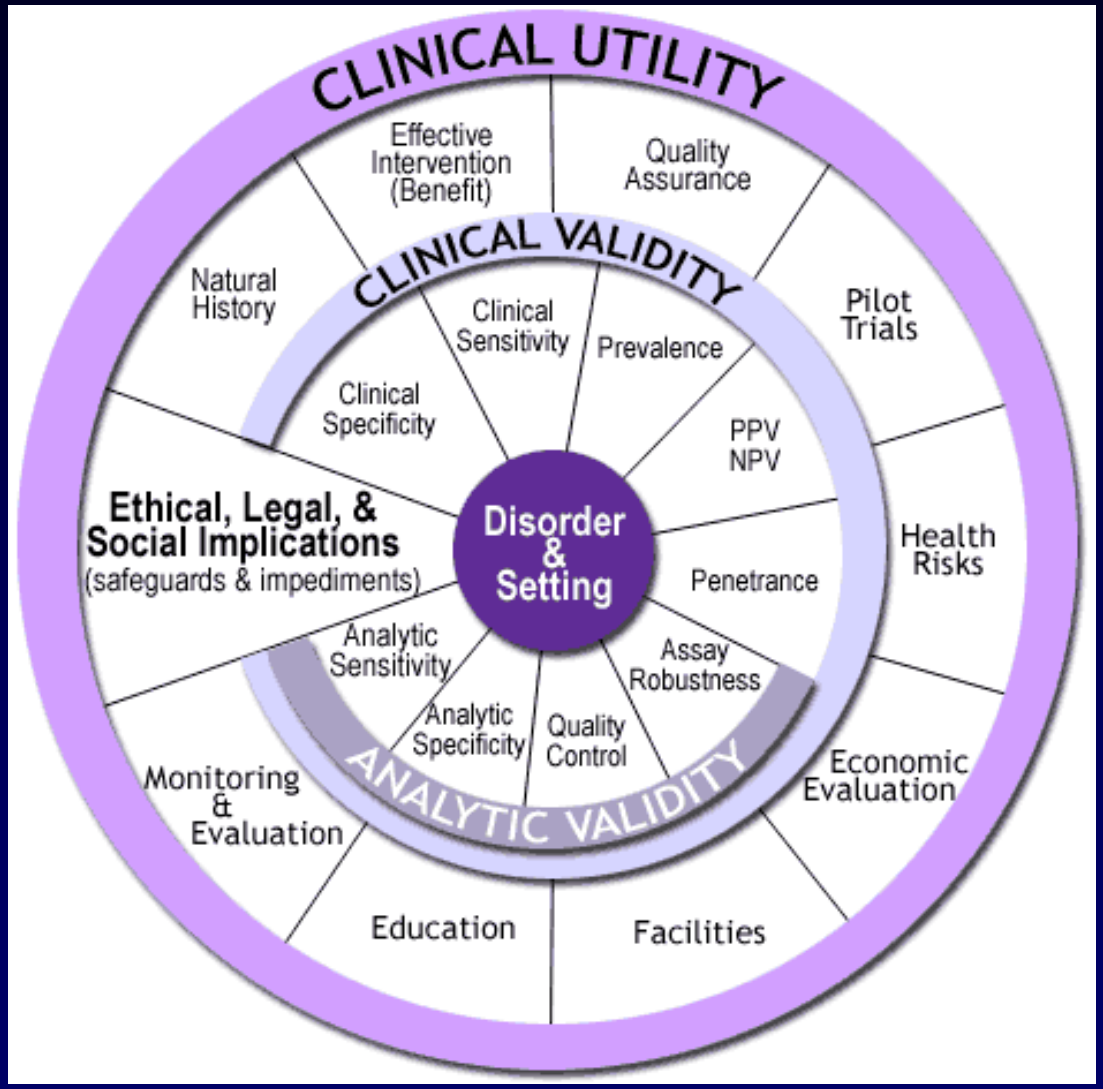
- ***Others:***

- **Medical Evidence Development Consortium (MED-C) with academic institutions, payers, commercial laboratories, vendors, medical data analysis companies, etc.)**
- **National Institute of Standards and Technology (NIST) Genome in a Bottle Consortium with academic institution**
- **National Comprehensive Cancer Network (NCCN)**

# Molecular Pathology Assay Issues

- **Criteria for evaluating assays (Centers for Disease Control and Prevention's Office of Public Health Genomics):**
  - **Analytic validity: Lab parameters**
  - **Clinical validity: Health condition**
  - **Clinical utility: Patient management**
  - **Ethical, legal, and social implications (ELSI)**

# ACCE Model Process for Evaluating Genetic Tests



# The who, what, when, where, why, how, and how much

- **Components and transitions of integral biomarkers**
  - **Basic and translational science**
  - **Clinical studies**
  - **Clinical trials***
  - **Standard-of-care***

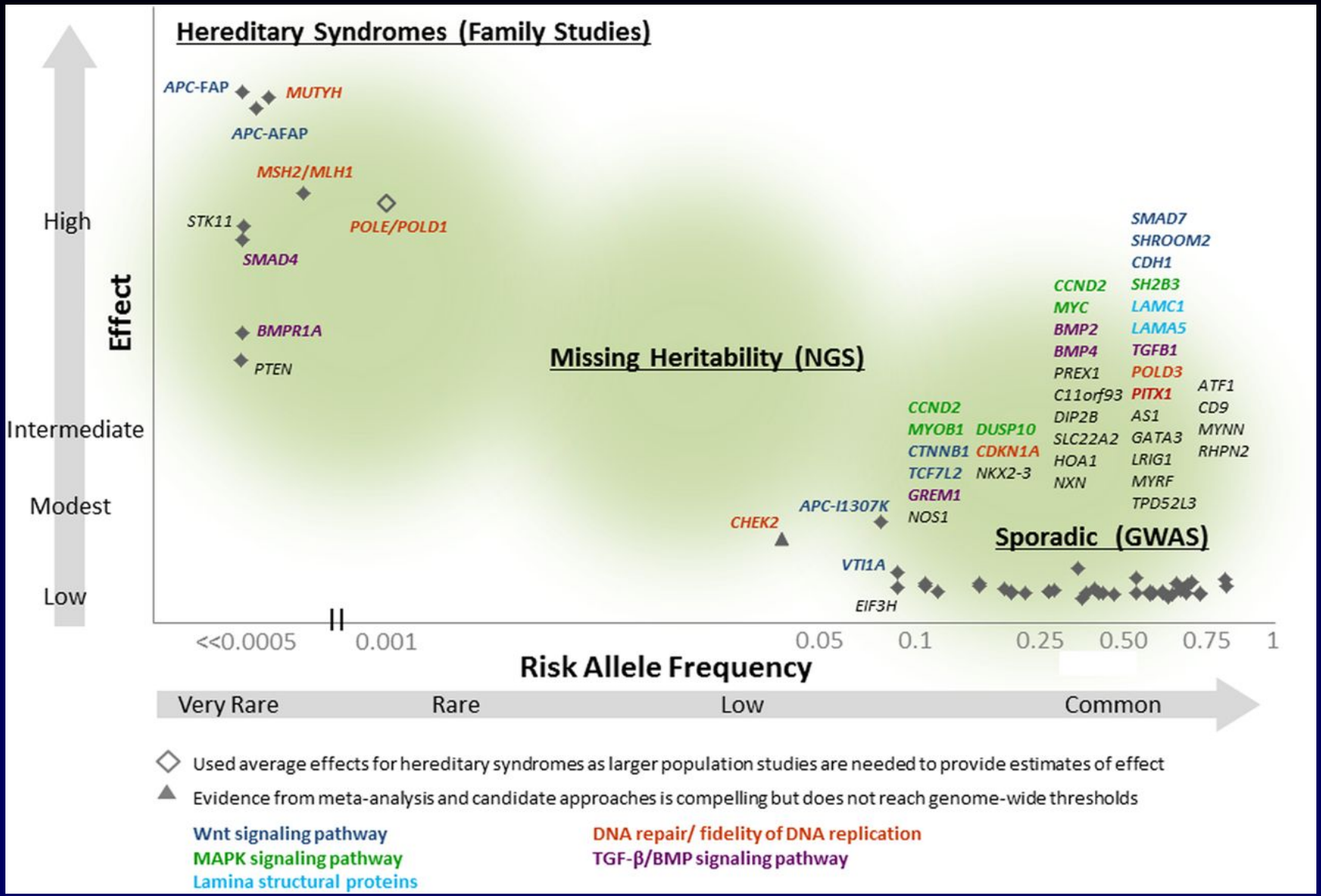
  ***Regulatory-compliant laboratories:**

  **Clinical Laboratory Improvement Amendments (CMS)**

  **US Food and Drug Administration**
  - **Analytical and clinical validation**

# Pre-analytic issues for integral biomarkers

- **Fit-for-purpose, clinical question(s) to be answered:**
  - **Risk analysis**
  - **Screening**
  - **Surveillance**
  - **Diagnosis**
  - **Classification**
  - **Prognosis**
  - **Prediction**
  - **Monitoring**




Ulrike Peters et al. Gut 2015;64:1623-1636

# Pre-analytic issues for integral biomarkers

- **Most common use: Patients with advanced disease**
  - **Neoplastic progression**
  - **Selective effects of therapy**
  - **Tumor microenvironment**
- **Recommendation: Proximate tumor that threatens the patient**
- **Small formalin-fixed paraffin-embedded specimens**

# Molecular Pathology Assay Issues

- **Pre-analytics: Caveats**
  - **Relatively little attention so far**
  - **Quality of labile analytes: mRNAs, proteins**
  - **Effects vary with needed sensitivity**
    - **Mutations**
    - **Copy number variations (ratios)**
    - **Re-arrangements (RNA-based)**

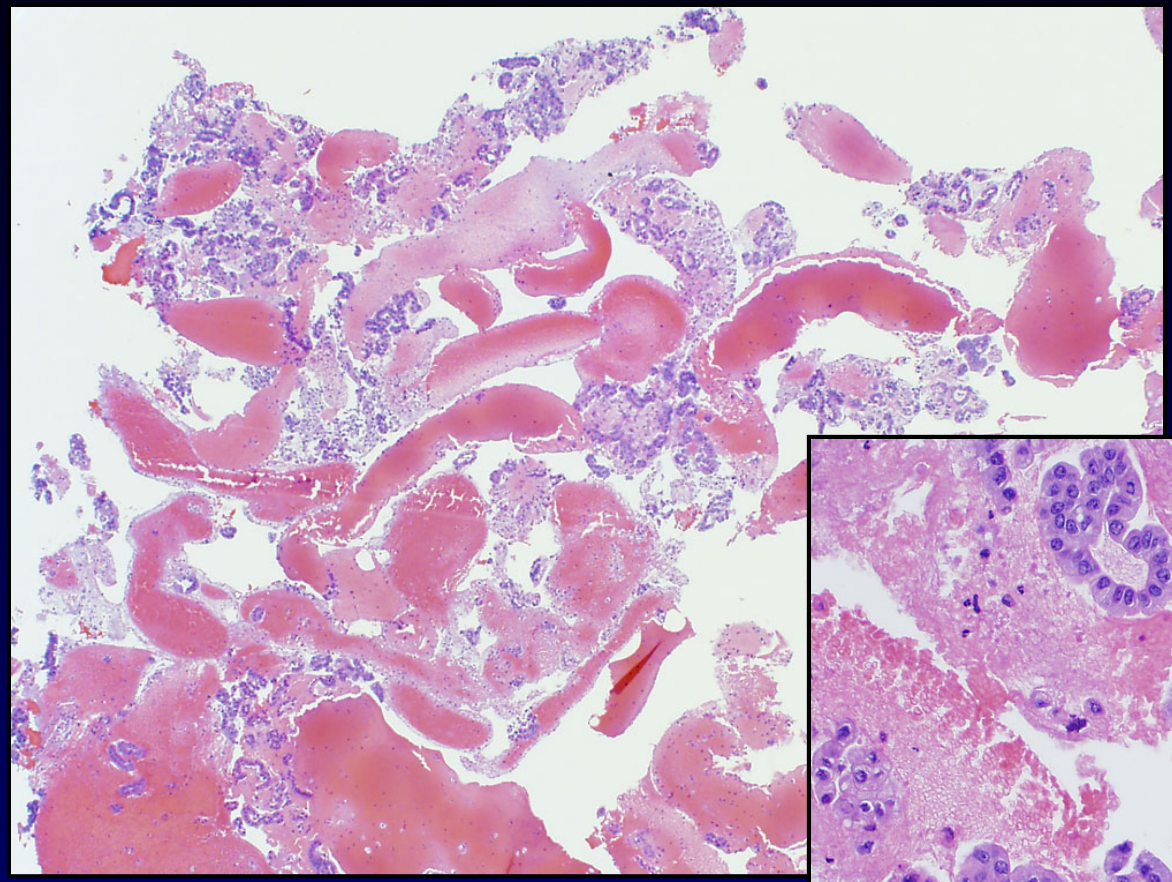
# Specimen types

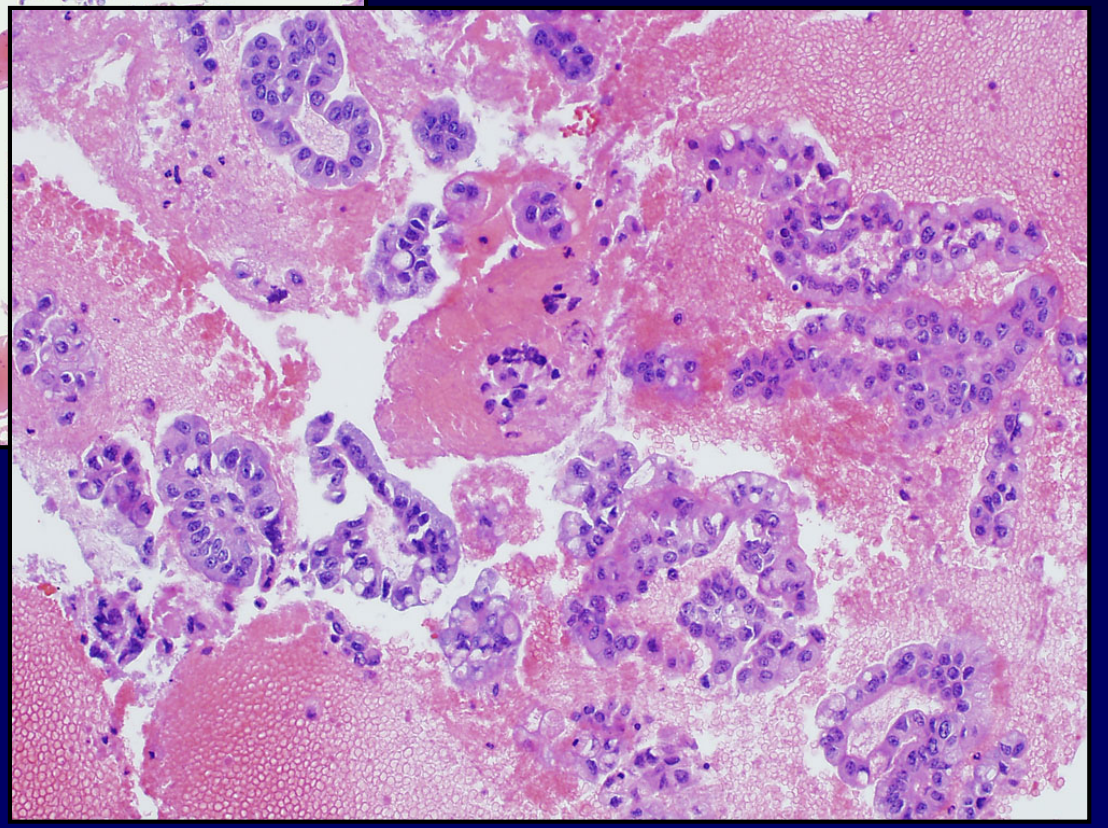
# Fine Needle Aspiration and Core Needle Biopsy Specimens

FNA smear

FNA cell block

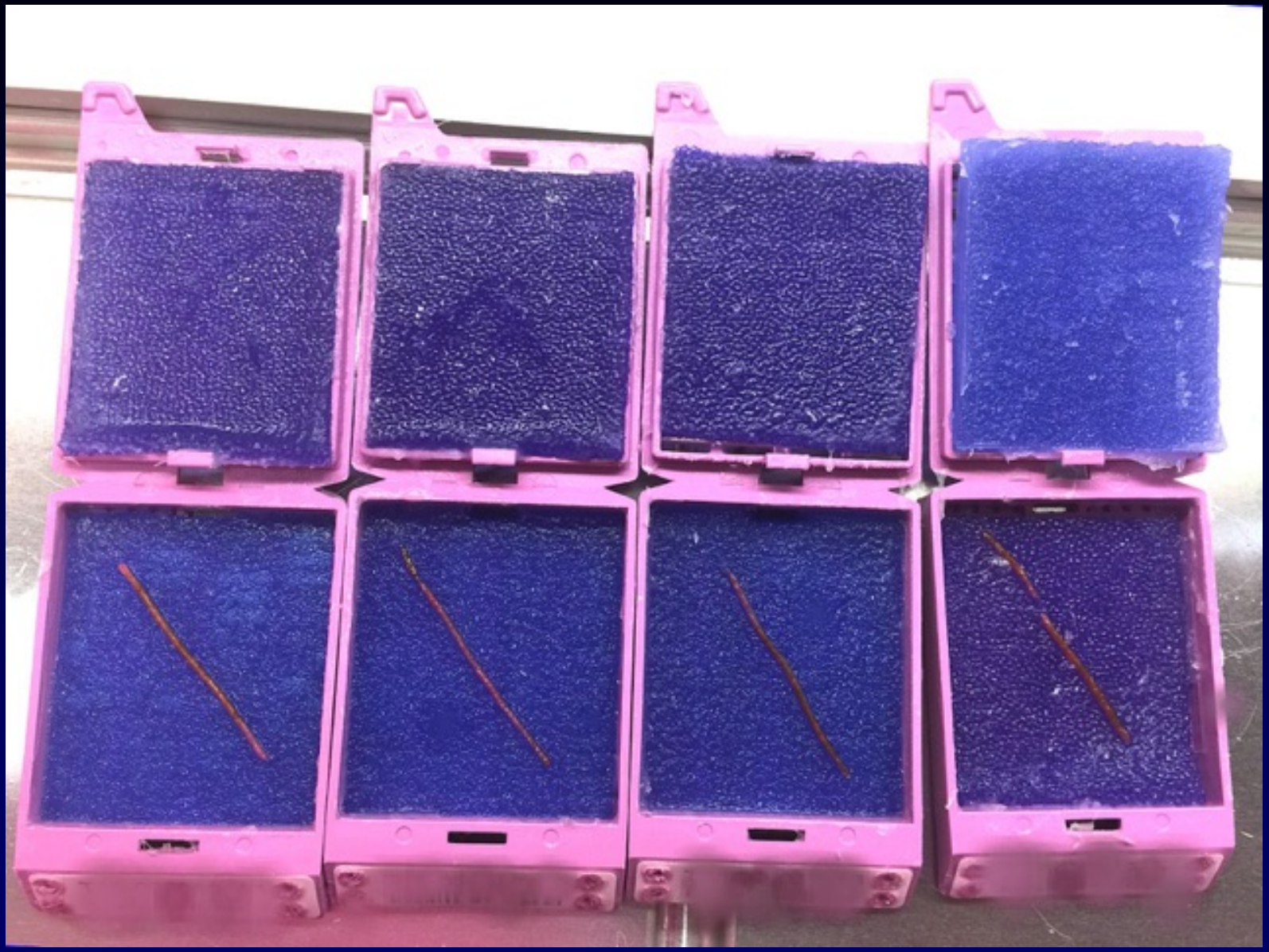
Core Biopsy

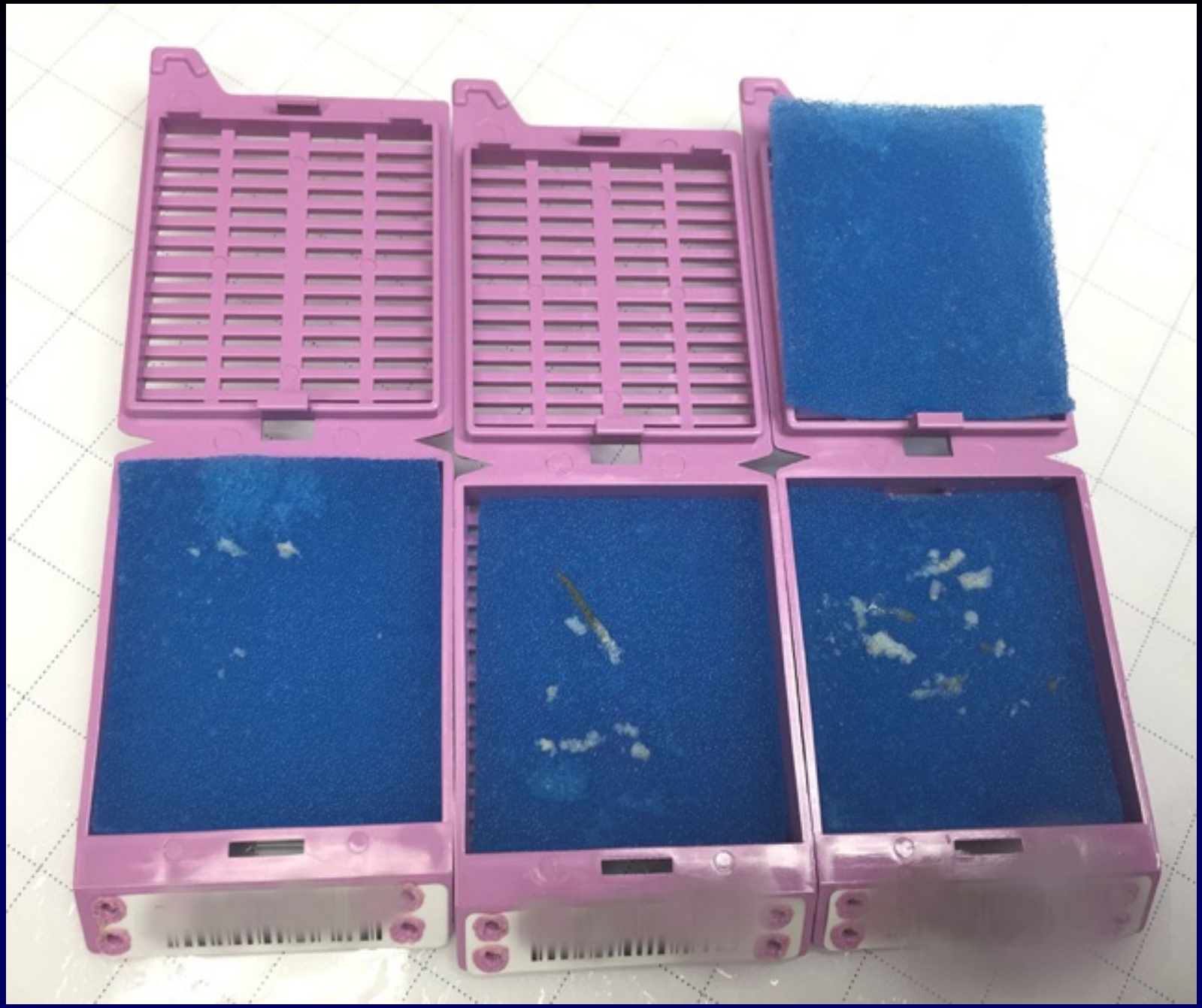


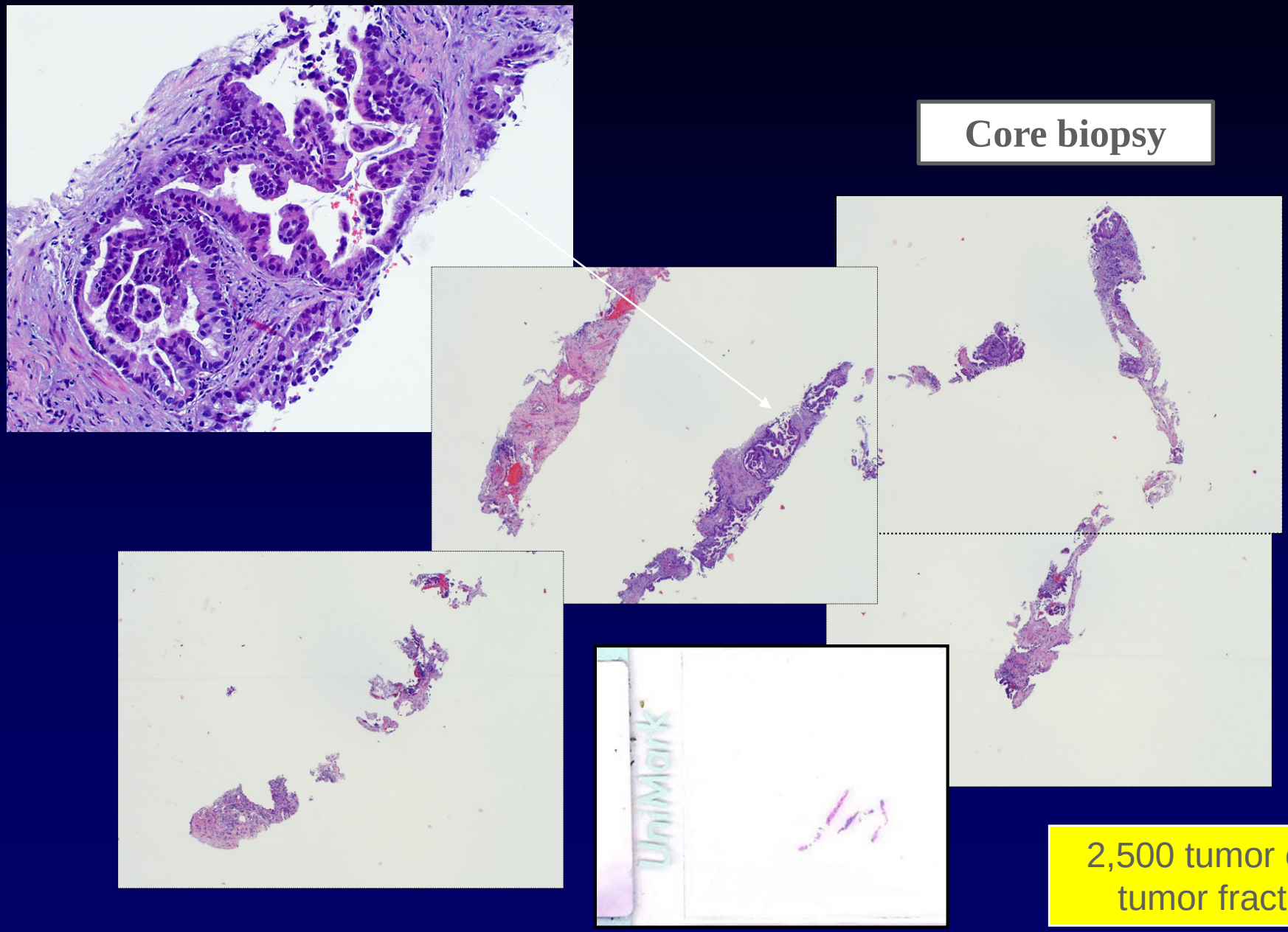


FNA cell block

**You can’t always get what you want…**






Core biopsy
2,500 tumor cells,
tumor fraction

# Molecular Pathology Assay Issues

- **Pre-analytics: "Liquid biopsies"**
  - **Phlebotomy or body fluid instead of tumor tissue acquistion**
  - **Analytes**
    - **Circulating tumor cells**
    - **Cell-free DNA (cfDNA) and microRNAs**
    - **Exosomes**
    - **Vesicles**
  - **Theoretical advantage of addressing heterogeneity**
  - **At least 27 companies**

# Molecular Pathology Assay Issues

- **Analytics:**
  - **Focus area for most of the interested parties**
  - **Methodologies have different advantages and disadvantages:**
    - **Content actionability**
    - **Number of genes covered**
    - **Formalin-fixed, paraffin-embedded tissue: Quality of analytes**
    - **Quantity of analytes (FNA, liquid biopsy)**
    - **Turnaround time (batch size)**

# Molecular Pathology Assay Issues

- **Analytics:**
  - **Single genes and alterations or panels**
  - **Definition of actionable: “Able to be done or acted upon; having practical value”.**
  - **Standards, quality control materials, and proficiency testing**
  - **Assays beyond nucleic acid sequencing: Transcriptomics, proteomics**
  - **Reimbursement issues**

# Clinical NGS requirements

- Stable multiplex assay for expanding actionability
- Extensive data from small specimens: FNAs
- Formalin-fixed paraffin-embedded tissue
- Declining costs, fast turnaround, robustness
- Value relative to costs of targeted agents
- Sensitivity to subclones with resistance
- Biology of cancers: Clinical-molecular annotation
- Data for broad research use by faculty
- Demand from patients and referring physicians
- Competitiveness: For patients, pharma partners

We need to change from
"companion diagnostics"
(CoDx; a test for use of a specific drug)

to

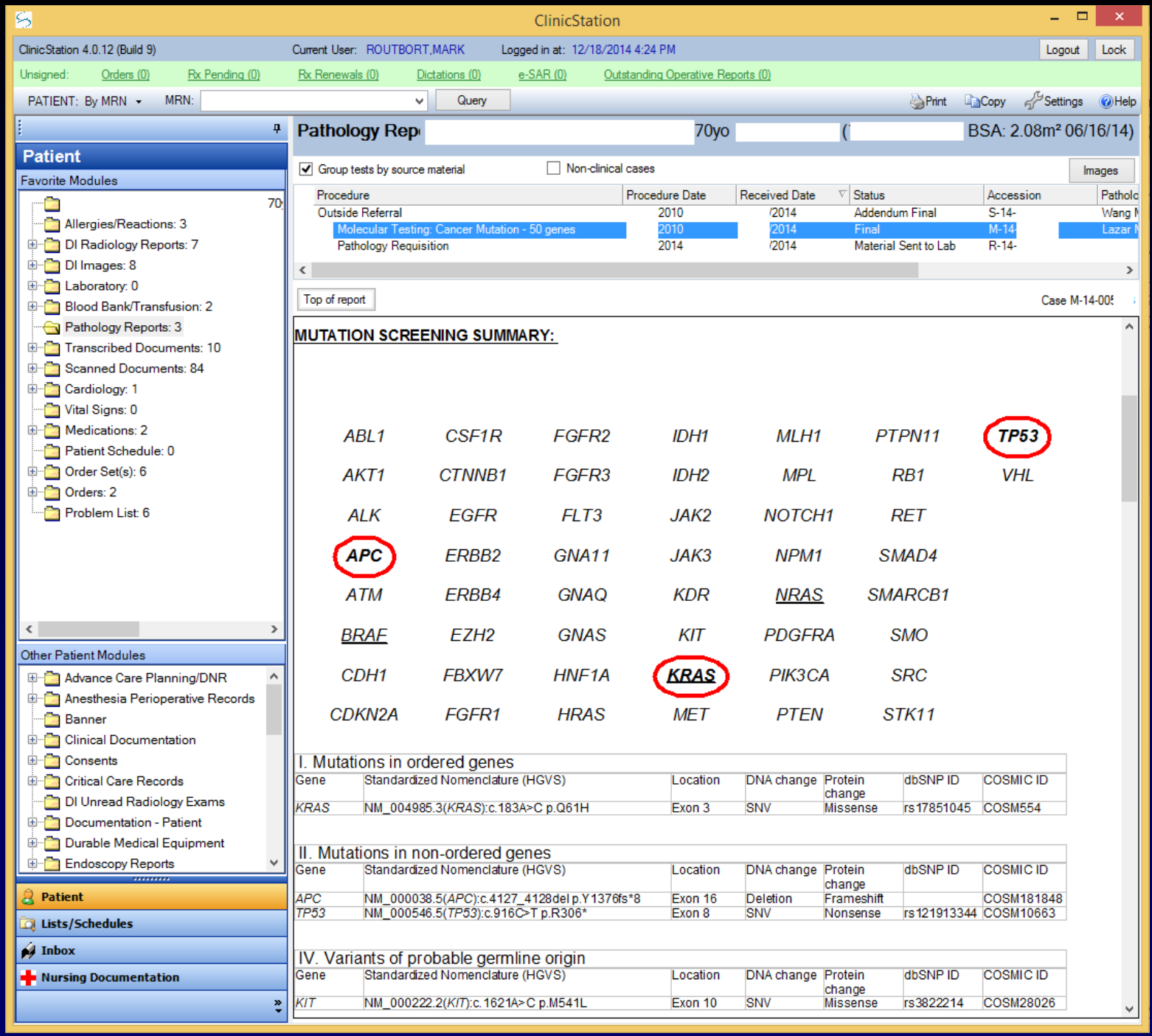
"companion therapeutics"
(CoRx; a panel of tests for drug selection from the formulary).

# “Smart” biomarker panels

- **Fit-for-purpose system**
- **Semi-universal, not organ system-based**
- **Multimodality assays**
  - **NGS**
  - **FISH**
  - **Gene expression**
  - **IHC with image analysis**
  - **Flow cytometry**

# Molecular Pathology Assay Issues

- **Post-analytics:**
  - **Variants of unknown significance**
  - **Germline findings**
  - **Co-alterations and pathway analyses**
  - **Alignment and variant-calling software**
  - **Report understandability by physicians and by patients (required by CLIA)**
  - **FDA Regulatory-grade Database initiative:**
    - **Curation of actionability, treatment, trials**


ClinicStation
ClinicStation 4.0.12 (Build 9)
Current User: ROUTBORT,MARK
Logged in at: 12/18/2014 4:24 PM
Logout
Lock
Unsigned:
Orders (0)
Rx Pending (0)
Rx Renewals (0)
Dictations (0)
e-SAR (0)
Outstanding Operative Reports (0)
PATIENT: By MRN
MRN:
Query
Print
Copy
Settings
Help
Patient
Favorite Modules
Allergies/Reactions: 3
DI Radiology Reports: 7
DI Images: 8
Laboratory: 0
Blood Bank/Transfusion: 2
Pathology Reports: 3
Transcribed Documents: 10
Scanned Documents: 84
Cardiology: 1
Vital Signs: 0
Medications: 2
Patient Schedule: 0
Order Set(s): 6
Orders: 2
Problem List: 6
Other Patient Modules
Advance Care Planning/DNR
Anesthesia Perioperative Records
Banner
Clinical Documentation
Consents
Critical Care Records
DI Unread Radiology Exams
Documentation - Patient
Durable Medical Equipment
Endoscopy Reports
Patient
Lists/Schedules
Inbox
Nursing Documentation
Pathology Rep
70yo
BSA: 2.08m² 06/16/14)
Group tests by source material
Non-clinical cases
Images
Procedure
Procedure Date
Received Date
Status
Accession
Outside Referral
2010
Addendum Final
S-14-
Molecular Testing: Cancer Mutation - 50 genes
2010
Final
M-14
Pathology Requisition
2014
Material Sent to Lab
R-14-
Top of report
Case M-14-00
MUTATION SCREENING SUMMARY:
ABL1 CSF1R FGFR2 IDH1 MLH1 PTPN11 TP53
AKT1 CTNNB1 FGFR3 IDH2 MPL RB1 VHL
ALK EGFR FLT3 JAK2 NOTCH1 RET
APC ERBB2 GNA11 JAK3 NPM1 SMAD4
ATM ERBB4 GNAQ KDR NRAS SMARCB1
BRAF EZH2 GNAS KIT PDGFRA SMO
CDH1 FBXW7 HNF1A KRAS PIK3CA SRC
CDKN2A FGFR1 HRAS MET PTEN STK11
I. Mutations in ordered genes
Gene | Standardized Nomenclature (HGVS) | Location | DNA change | Protein change | dbSNP ID | COSMIC ID
KRAS | NM_004985.3(KRAS):c.183A>C p.Q61H | Exon 3 | SNV | Missense | rs17851045 | COSM554
II. Mutations in non-ordered genes
Gene | Standardized Nomenclature (HGVS) | Location | DNA change | Protein change | dbSNP ID | COSMIC ID
APC | NM_000038.5(APC):c.4127_4128del p.Y1376fs*8 | Exon 16 | Deletion | Frameshift | | COSM181848
TP53 | NM_000546.5(TP53):c.916C>T p.R306* | Exon 8 | SNV | Nonsense | rs121913344 | COSM10663
IV. Variants of probable germline origin
Gene | Standardized Nomenclature (HGVS) | Location | DNA change | Protein change | dbSNP ID | COSMIC ID
KIT | NM_000222.2(KIT):c.1621A>C p.M541L | Exon 10 | SNV | Missense | rs3822214 | COSM28026

# Future directions

- **The end of the beginning**
- **Heterogeneity: Inter-tumoral, intra-tumoral, progression, primaries/mets**
- **Co-alterations**
- **Drivers and passengers**
- **Signaling in pathways**
- **Therapy-induced changes**
- **Immunotherapy**
- **Circulating nucleic acids**

# Future directions

- **Patient fitness**
- **Clinical utility of “liquid biopsies”**
- **Versioning of assays for additional therapeutic targets**
  - **Standard-of-care**
  - **Clinical studies**
  - **Integral-marker clinical trials**
- **Co-mutations and pathways**
- **Effector-based biomarkers**

# Summary

- **Numerous organizations are addressing improvements in the quality of molecular testing: No shortage of efforts, but parallelism and lack of coordination.**

- **Those organizations with regulatory enforcement authority (CMS, FDA) and payers have the most impact on the use of molecular testing for patient care and clinical trials.**

*For the Purpose of Notification to Congress Only*

# Anticipated Details of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories

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# Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

**This document provides the anticipated details of the *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)* that FDA intends to issue in 60 days, and is being provided to Congress pursuant to section 1143 of the Food and Drug Administration Safety and Innovation Act of 2012**


**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**

# Summary

- **Methodologies are evolving rapidly, making certification efforts rapidly obsolete.**

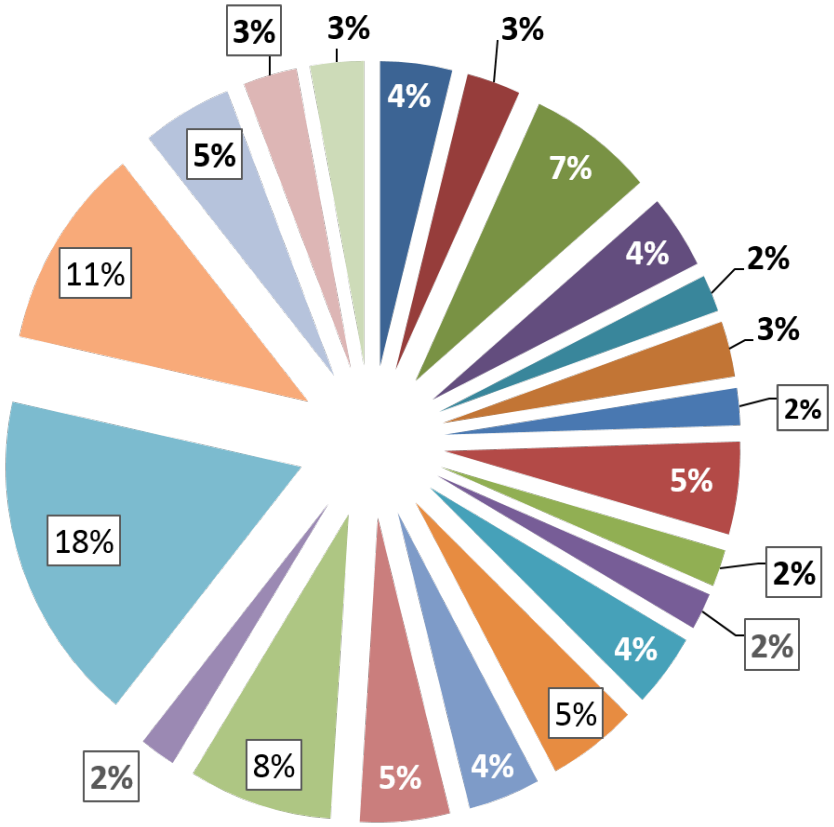
- **Communication among clinicians and molecular diagnostics labs is essential to meeting the needs for high-quality patient care and clinical research.**

# Summary

- **Clinical trials provide the highest levels of evidence for efficacy of agents, but other acceptable processes are needed.**

- **The low frequency of actionable targets in the face of numerous alterations in tumors and the emergence of resistance demand continued development of novel agents and combinations.**

# Alterations in NCI MATCH and estimated prevalence

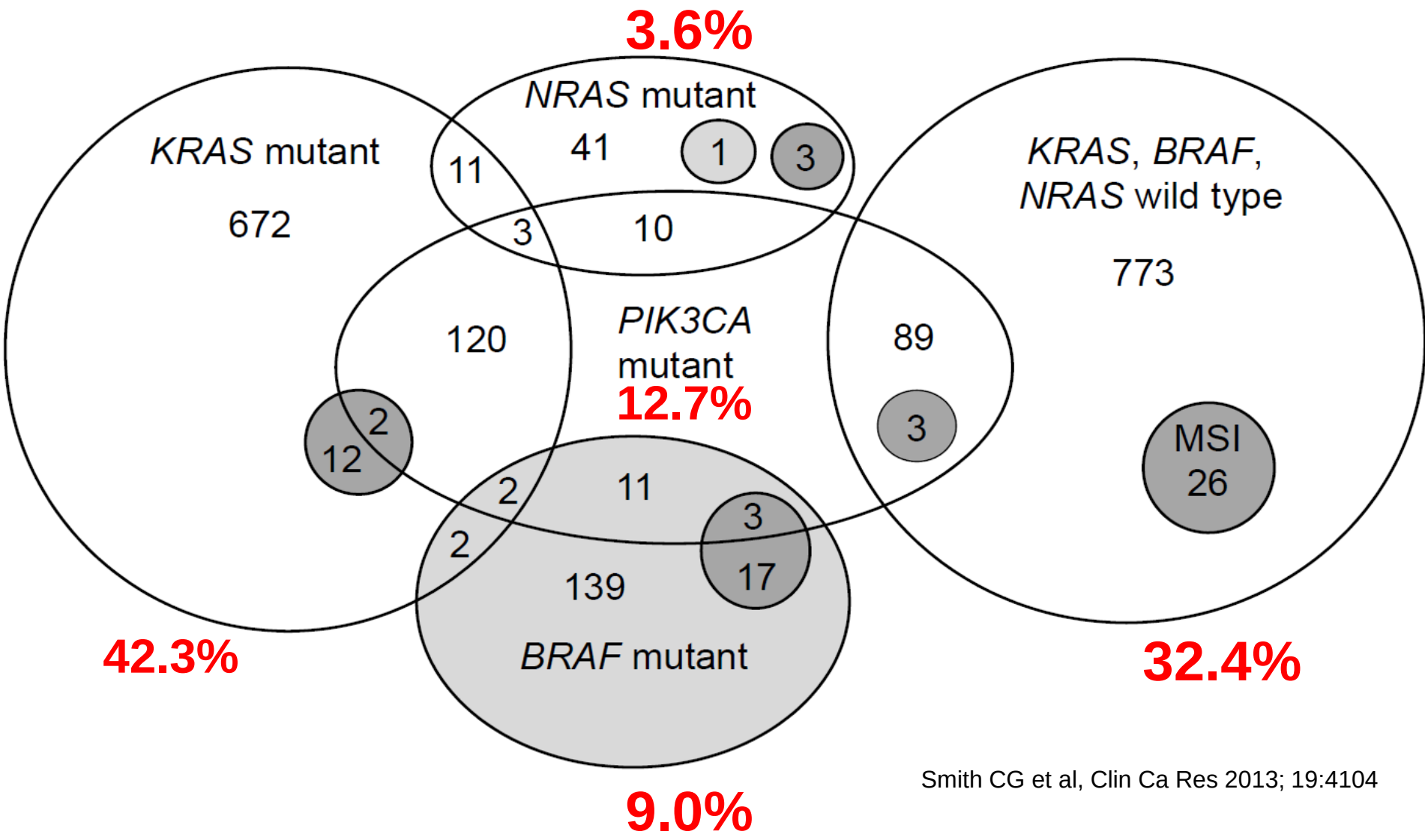



**aMOIs (actionable mutations of interest):**

- ALK translocations - (4%)
- BRAF fusions or non-V600E, non-V600K mutations - (2.79%)
- BRAF V600E or V600K - (1-12%)
- cKIT mutations - (4%)
- DDR2 mutations - (2%)
- EGFR activating mutations - (1-4%)
- EGFR T790M mutations - (1-2%)
- FGFR amplifications or FGFR mutations - (5%)
- GNA11 mutations - (1.6%)
- GNAQ mutations - (2%)
- HER2 activating mutations - (2-5%)
- HER2 amplifications - (5%)
- MET amplifications - (4%)
- mTOR mutations - (5%)
- NF1 mutations - (7.7%)
- NF2 loss - (2%)
- PIK3CA mutations or amplifications - (17-18%)
- PTEN mutations or deletions - (11%)
- ROS1 translocations - (5%)
- SMO or PTCH1 mutations - (2.63 and 3.76%)
- TSC1 or TSC2 mutations - (2.6-3.5%)

## COIN trial, approx. 1900 primary CRC

Supplementary Figure 1




Smith CG et al, Clin Ca Res 2013; 19:4104

# The roles of pathologists in oncologic management:

# The roles of pathologists in oncologic management:

# Chief Quality Officers for precision cancer medicine

Thanks for your attention.

# Resources for NCI-MATCH

- Main Webpages: cancer.gov/nci-match
  ecog-acrin.org/nci-match-eay131
- Protocol Documents: ctsu.org (password required)
- Spanish: cancer.gov/espanol/nci-match
- Email Inquiries: match@jimmy.harvard.edu
- Patient Brochure: EA website (above)
- Site Process Brochure: EA website (above)
- NCI's Cancer Information Service: 1-800-4-CANCER and cancer.gov/contact

*This slide presentation is updated regularly. For the latest version, visit ecog-acrin.org.*