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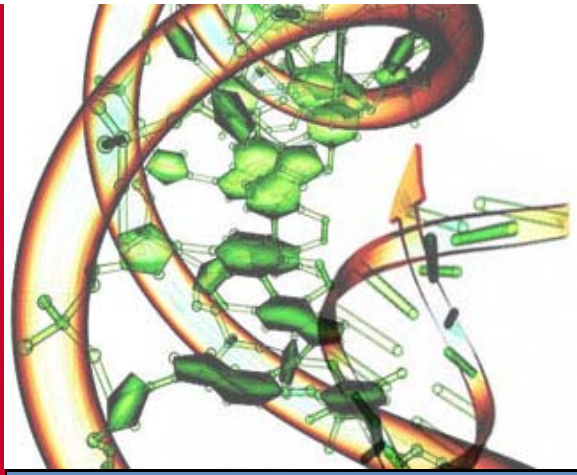

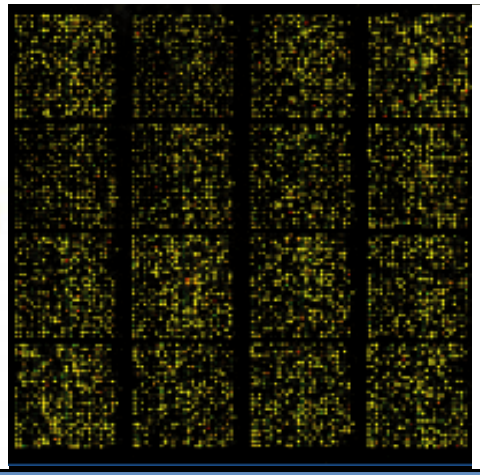

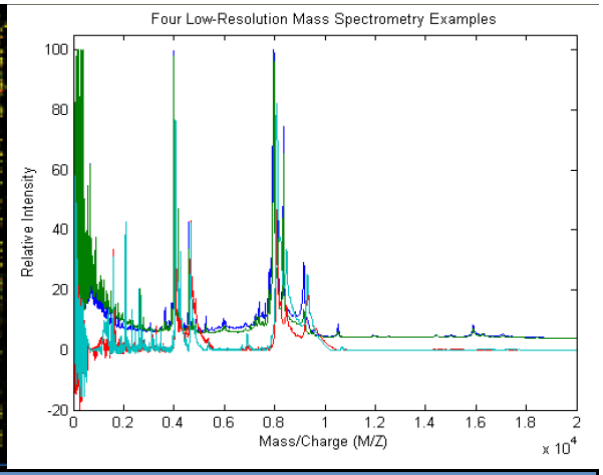

Opportunities and Challenges in Translating Novel Discoveries into Useful Clinical Tests

James H. Doroshow, M.D.
NCI Deputy Director for Clinical and Translational Research

NCI Workshop: Evidence Needed
To Support Clinical Utility of Molecular Diagnostics

Bethesda, MD
January 11, 2013

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Past, Present, Future

- Phase I-III drug testing, all-comers: generally small advances
- Classifiers to assist in decision making for some contexts (HER2/neu, oncotypeDx, EGFR mutation)
- Diagnostics as targets: GIST (c-kit); melanoma (BRAFv600), others
- Genomic profile of patient's tumor, then choose the treatment most likely to work

Scale?

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Opportunity/Challenges of Genomic Profiling

- Individual successes: ‘Exceptional Cases’
- Understand heterogeneity of ‘Resistance’
- Cost of technology decreasing while biologic information expanding but . . . . .

- $1000 whole genome sequence/$100,000 interpretation
  - Where is the data? Storage & Transport
  - Who can manage it? How does it get to the clinician?
- How do we know it benefits patients?

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Clinical Utility of a Test: Definition and Potential

Definition

- Context-dependent
- Result influences medical decision making
- Outcomes (which?) improved compared to not using the diagnostic (or to an antecedent diagnostic)

Potential

- Identify **prognostic** groups--can treatment be avoided?
- Identify **predictive** tests—who will benefit from specific treatment?
  - Selection criteria for agents
  - Optimize combinations
- Identify patients adversely affected by treatment: "**negative prediction**"
- Monitor patients for treatment success or progression

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Lessons Learned from Past Successes

- Classification of DLBCL
- Oncotype Dx

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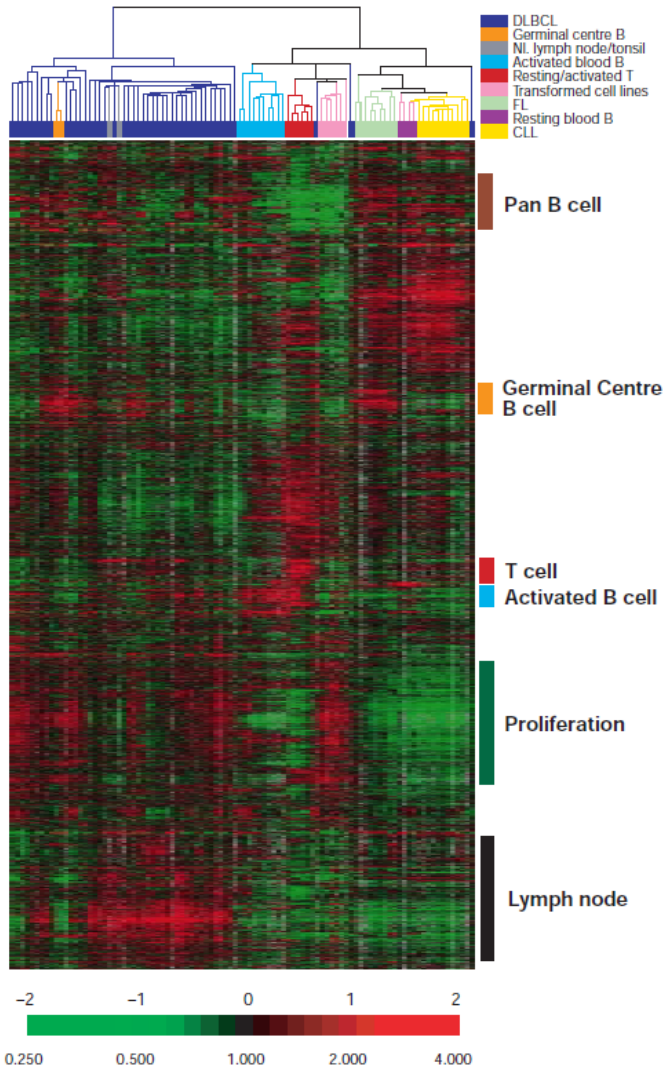
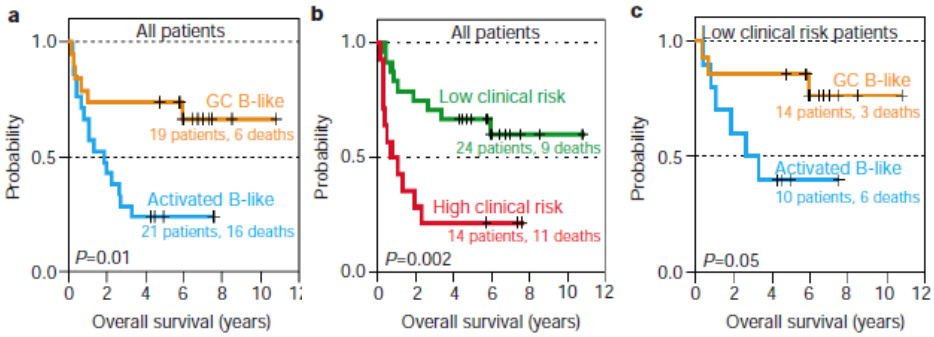
Discovery: ABC-GCB Subgroups in DLBCL



Alizadeh et al, *Nature* 2000

Initial intriguing finding:

Gene expression profiles separate DLCBL into two groups with distinct prognosis (Activated B-like, Germinal Center B-like) even within clinical low risk (IPI 0-2)



How can these profiles lead to better treatment for DLBCL patients?

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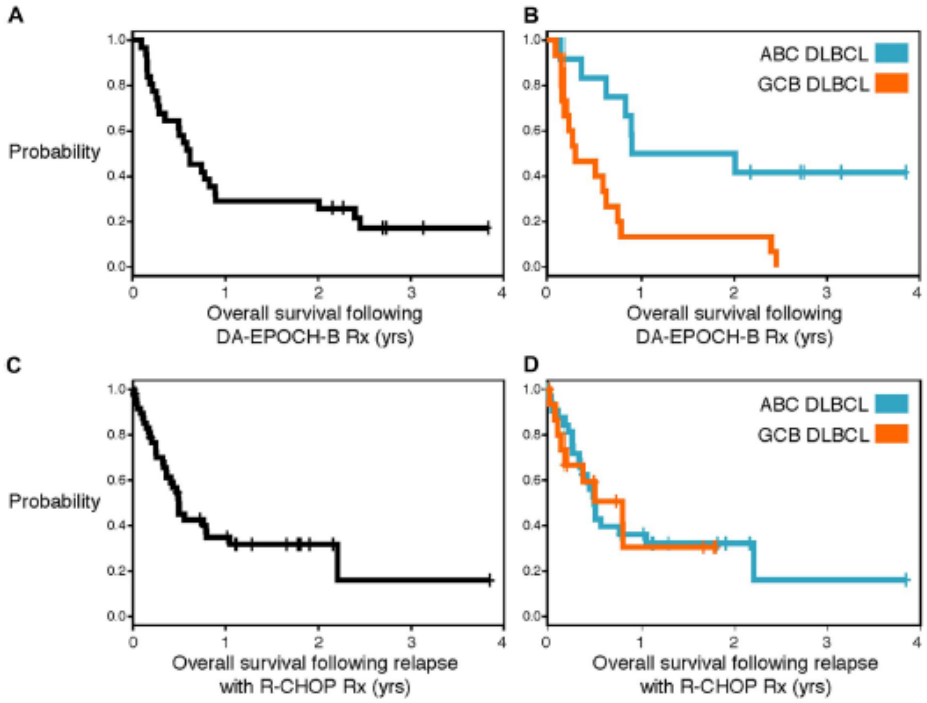
Clinical Potential: ABC-GCB DLBCL Subgroups



EPOCH+bortezomib

R-CHOP

(treatment not randomized; different patient groups; hypothesis generating only)

Figure 2 from Dunleavy et al, *Blood* 2009

- ABC DLBCL (worse prognosis) characterized by constitutive activation of NF-κB pathway
- Will inhibition of NF-κB sensitize ABC but not GCB to chemotherapy?
- Role of proteasome inhibitor bortezomib?

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Lessons Learned: DLBCL Subgroups

- Keep pace with changing treatment landscape
- Limited availability of fresh/frozen specimens for gene expression profiling
- Challenges of platform migration
  - In-house arrays
  - Affymetrix arrays
  - Platforms for FFPE specimens
- Importance of specimens from clinical trials
  - Contemporary treatments
  - Randomized treatment allocation
  - High quality clinical and pathological data annotation

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Oncotype DX Breast Cancer Recurrence Risk Score

- Recurrence Score (RS) development
  - Data mining
  - qRT-PCR assay developed for FFPE
  - Multiple patient sets
    - Rush (n=78, LN+, ER+/−, mixed systemic therapy)
    - Providence (n=136, LN+, ER+/−, mixed systemic therapy)
    - NSABP B-20 (n=233, all ER+, LN−, systemic therapy tamoxifen only)
- Risk calculation
  - Continuous (0-100) recurrence risk score (RS)
  - Low (<18), intermediate, high risk (≥31) classes
- NSABP B-14 Validation: Assay & classifier (RS & class cutpoints) locked down, blinded

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Lessons Learned: Oncotype DX

- Benefits of assays that can be performed on FFPE specimens (readily available, standard diagnostic material)
- Power of large specimen collections from randomized clinical trials
- Importance of optimization of assay performance
- Potentially enormous size and expense of prospective trials
- Risk of changing treatment landscape (entry of trastuzumab into adjuvant setting)
- Role of industry

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Clinical Utility: Regulatory Requirements

- Rigor in assay development and validation
- CLIA (CMS)
  - Necessary accreditation for the laboratory when test result will be returned to the patient or treating physician, whether in context of a clinical trial or in routine care
  - Relates to intra-lab procedures, not between labs or to clinical validation
- Investigational Device Exemption (IDE) Program for Human Subject Studies
  - Non-significant risk investigations
  - Application to FDA for approval of investigations

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Future: Overwhelmed by Data

- Data accumulating faster than we can interpret it
  - Genome sequencing faster, cheaper
  - Patients already having sequencing and other ‘omics profiling performed on their tumors; presenting data to their clinicians for interpretation and ACTION
- Associated high quality clinical data have not kept pace
- Often sparse evidence for appropriate actions to take based on profiles

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Future: Clinical Utility of Assigning Treatment by Molecular Information in Early Drug Development

- M-PACT: Molecular Profiling based Assignment of Cancer Therapeutics

  Pilot Trial to Assess the Utility of Genetic Sequencing to Determine Therapy and Improve Patient Outcome in Early Phase Trials

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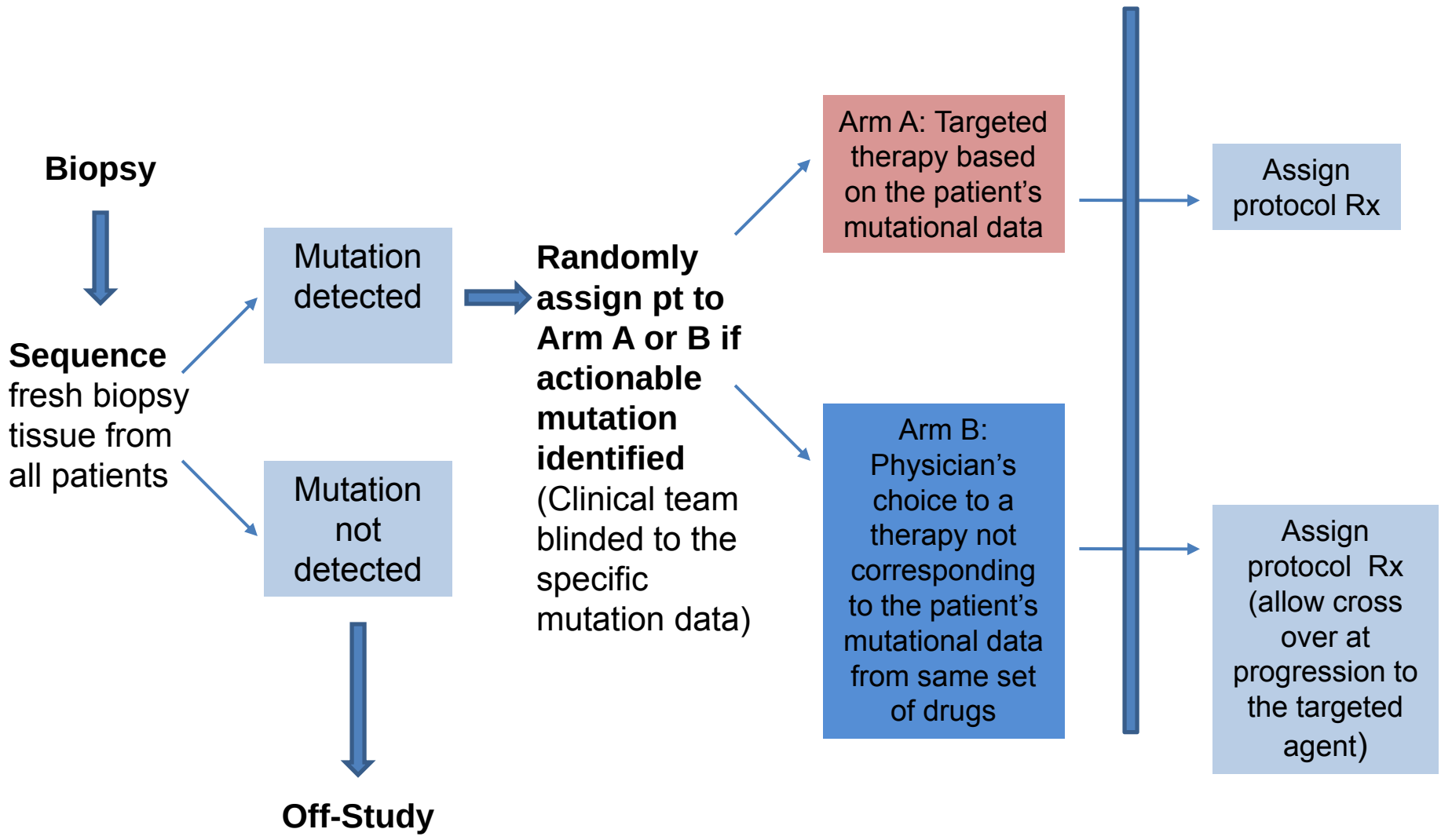
M-PACT Objectives

- Assess whether the response rate (CR+PR) and/or 4-month PFS is improved following treatment with agents chosen based on the presence of specific mutations in patient tumors versus not
  - Enter only patients with pre-defined mutations of interest
  - Study treatments, regardless of cohort, will be chosen from the list of regimens defined in the protocol
  - Arm A: Receive treatment based on an study agent prospectively identified to work on that mutation/pathway
  - Arm B: Receive treatment with one of the study agents in the complementary set (identified to not work on one of the detected mutations/pathways)
- LEARN how best to conduct a multisite trial of therapy choice driven by mutational analysis

Study Design



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M-PACT: Patient Population

- Patients with refractory solid tumors that have progressed on at least one line of standard therapy or for which no standard treatment is available that has been shown to improve survival.
- Adequate organ function (AST/ALT<3xULN, Bil < 1.5 xULN, S. Cr < 1.5 x ULN, platelets > 100K, ANC> 1500)
- Study regimens: As long as the same set of protocols are offered to a given set of patients, the number and actual treatments regimens can vary over time
- *Umbrella study of a variety of agents/mutational spectra*

Mutations in DNA repair pathways	Veliparib+ Temozolomide MK1775 + carboplatin
Mutations in the PI3K pathway; loss of PTEN, Akt amplification	mTOR inhibitor -Everolimus
Mutations in the RAS pathway	GSK 1120212 (MEK inhibitor)

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M-PACT: Matching Targeted Drugs to Molecular Lesions

- Utilize a validated targeted next-gen sequencing assay in clinically accredited laboratory for patient selection
  - Enhanced Ion Torrent PGM AmpliSeq Cancer Custom Panel (63 genes)
  - Minimal specimen (~50ng DNA)
  - Rapid turnaround time (<4 days)

- FFPET specimens
  - Adjacent H&E examined for tumor content and acceptability
  - Extraction method yields RNA (micro-RNA) and DNA simultaneously from each
  - FFPET Gene Expression Assays and Whole Exome Sequencing

Gene Name	*Pathways/Function*	*Gain or Loss of Function?*
BRAF	**RAS/RAF/ERK/MEK**	**Gain**
NF1	**RAS**	**Loss**
Kras	**RAS/RAF/ERK/MEK AKT/PI3K**	**Gain**
Nras	**RAS/RAF/ERK/MEK AKT/PI3K**	**Gain**
Hras	**RAS/RAF/ERK/MEKAKT/PI3K**	**Gain**
AKT1	**AKT/PI3K**	**Gain**
AKT2	**AKT/PI3K**	**Gain**
AKT3	**AKT/PI3K**	**Gain**
PIK3CA	**AKT/PI3K/RAS/RAF/ERK/MEK**	**Gain**
PTEN	**AKT/PI3K/RAS/RAF/ERK/MEK**	**Loss**
P53	**DNA Repair**	**Loss**
FBXW7	**DNA Repair**	**Loss**
ATM	**DNA Repair**	**Loss**
PARP1	**DNA repair**	**Loss**
PARP2	**DNA repair**	**Loss**
ERCC1	**DNA repair**	**Loss**
MLH1	**DNA repair**	**Loss**
MSH2	**DNA repair**	**Loss**
NBN	**DNA Repair**	**Loss**
ATR	**DNA repair**	**Loss**
MGMT	**DNA repair**	**Loss**

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Future: Greater Requirement for Multidisciplinary Expertise in Clinical Research & Practice

- Laboratory/basic scientists
- Pathologists
- Assay technology developers
- Clinicians
- Bioinformaticians
- Database developers & EHR translators
- Statisticians

How to bring interpretable data to the clinic?

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Clinical Utility: Summary of Issues

- Large screening population
- Which mutations/molecular characteristics are actionable? What is the evidence?
- Trials often “signal finding” – what comes next to demonstrate activity, clinical utility of this method of treatment?
- Standardization and validation of assays
- Versioning the assay
- Regulatory issues
- Participation of pharma, patients

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How Can NCI Promote Studies Addressing Clinical Utility of Diagnostics?

- Grants/cooperative agreements
- Clinical trials resources/groups
- Specimen resources funding
- Other resources
  - Technology development
  - Core facilities
  - Development of assay standards: authentic mutational calibrators, antibodies
- Facilitating Interactions with colleagues from industry, other government agencies, other countries