

**Resources to Enhance
Biomarker Inclusion in Early
Phase Trials:**

***Clinical Assay Development
Program***

<http://cadp.cancer.gov>

Why CADP?

- Clinical trial protocols often include markers for determining eligibility, stratification, or treatment assignment (integral markers)
- The assays to be used to determine these markers usually do not meet standards that are required for clinical decision making.
- Predictive markers and robust means to measure them are urgently needed in the clinic

Definitions

- **Analytical performance (analytical validity)**: how accurately the test detects the analyte(s) of interest.
- **Clinical validity**: how well the test relates to the clinical outcome of interest, e.g., response to therapy, survival, etc.

Definitions

- **Clinical utility**: whether the results of the test provide information that can contribute to and improve current management of the patient's disease;
 - the test will lead to an improved outcome
 - Value of using the test versus alternatives
 - Ethical, legal and social implications of a test
- **Assay Qualification**: the process of linking a biomarker with biological processes and clinical endpoints to show it is "fit for purpose"
- These activities do require clinical trials.

Goal

- Not a grant: provides resources:
 - Process and services to efficiently develop diagnostic tests that address clinical needs, including co-development of targeted agents and predictive markers.
 - Develop clinical assays that:
 - Meet rigorous performance standards
 - Speed evaluation of molecularly guided therapy

CADP components

- Clinical Assay Development Network (CADN) *
- Specimen Retrieval System*
- Statistical Expertise (BRB: McShane, Polley)
- Program Expertise (Cancer Diagnosis Program)
- Project Management (Phillips Rohan) *

*Contracts

Clinical Assay Development Network

- Contracts (Basic Ordering Agreement 2010) – prequalification
- Function: assay optimization and validation
- CLIA certified labs: Expertise in one or more traditional assay platforms:
 - IHC
 - ELISA
 - ISH
 - qRT-PCR
 - qPCR
 - DNA sequencing

Clinical Assay Development Network (CADN)

- Molecular Characterization Laboratory: NCI-Frederick
- 8 Contracts: CLIA accredited labs
 - Dartmouth
 - MD Anderson
 - SeraCare
 - MolecularMD
 - U Colorado, Denver
 - Oregon Health Sciences Ctr
 - U Maryland
 - Midwest Research

Specimen Retrieval System

- Provides paraffin embedded and annotated specimens that closely reflect the type of cancers diagnosed and managed in the community setting
- NLP tool (Harvard) to scrub identifiable data
- Kaiser Permanente Northwest: Large health plan with stable membership, electronic medical records

2012 CADP dates and meetings

Open for Submission

- December 27, 2011
- April 23, 2012
- August 20, 2012

Submission Deadline

- February 15, 2012
- June 15, 2012
- October 15, 2012

Application receipt date	SEP *	Internal committee	SAC
February 15	April 10, 2012	April 27, 2012	June 14, 2012
June 15	July 31, 2012	Aug 23, 2012	Oct 19, 2012
October 15	November 27, 2012	Dec 14, 2012	Feb 13, 2013

* The dates for the SEPs will be confirmed according to the availability of participants.

CADP

- Earliest point of entry:
 - Working prototype assay has been developed
 - In human tissue
 - Intended clinical use for the assay is clearly defined
 - Prevalence data
 - Preliminary clinical validation data

CADP Marker Development Services

Biomarker discovery and initial assay development; biomarker prevalence data; potential clinical applications; preliminary data on human tissue demonstrating a clearly defined intended clinical use

Earliest entry point →

Transfer to quality environment

Analytic performance in intended-use context

Set preliminary cut-points

Clinical validity in a retrospective specimen set

Test cut-points in new set; retrospective test on new specimens; prospective study

Post-discovery

- Consultation, project management
- Begin matchmaking
- Platform migration
- Assay optimization
- SOP development
- Provide or help find specimens
- Reference sets, calibrators, reagent prep
- Statistical design advice

Pre-trial

- Check data that support earlier steps
- Provide or help find specimens
- Final validation in new specimen sets
- Statistical consultation
- Facilitate transportability

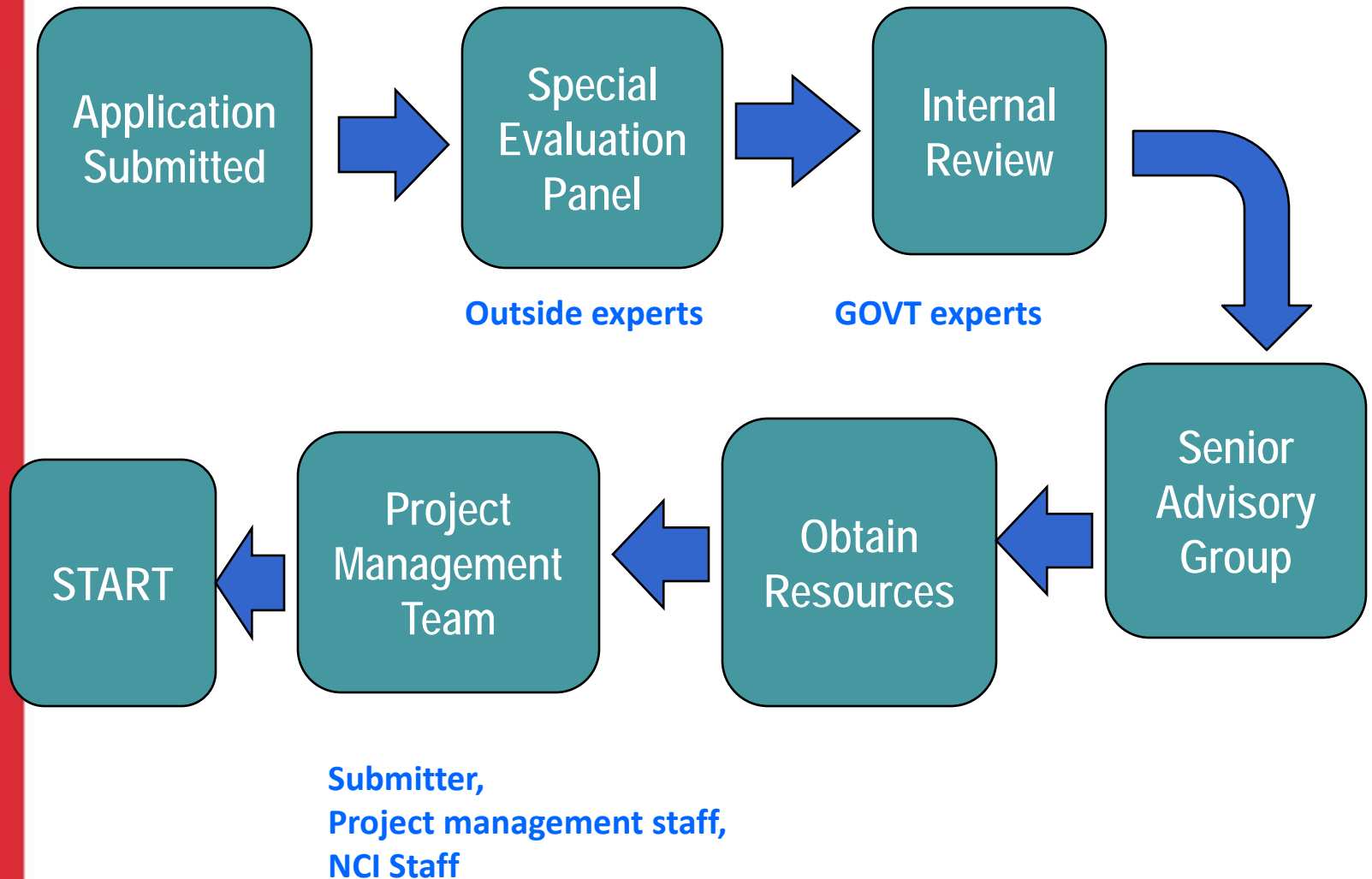
Requirements

- *Any working prototype assay*
 - clearly defined intended clinical use for cancer prognosis or prediction of treatment efficacy
- Assays that have progressed further but need additional validation are also eligible.

CADP

- Assays that have progressed further may need
 - Optimization
 - Transfer to quality environment
 - Platform migration
 - Validation of analytic performance
 - Statistical Consultation
 - Help with appropriate specimens to refine cutpoints
 - Assistance with transportability

Clinical Assay Development Program: Process



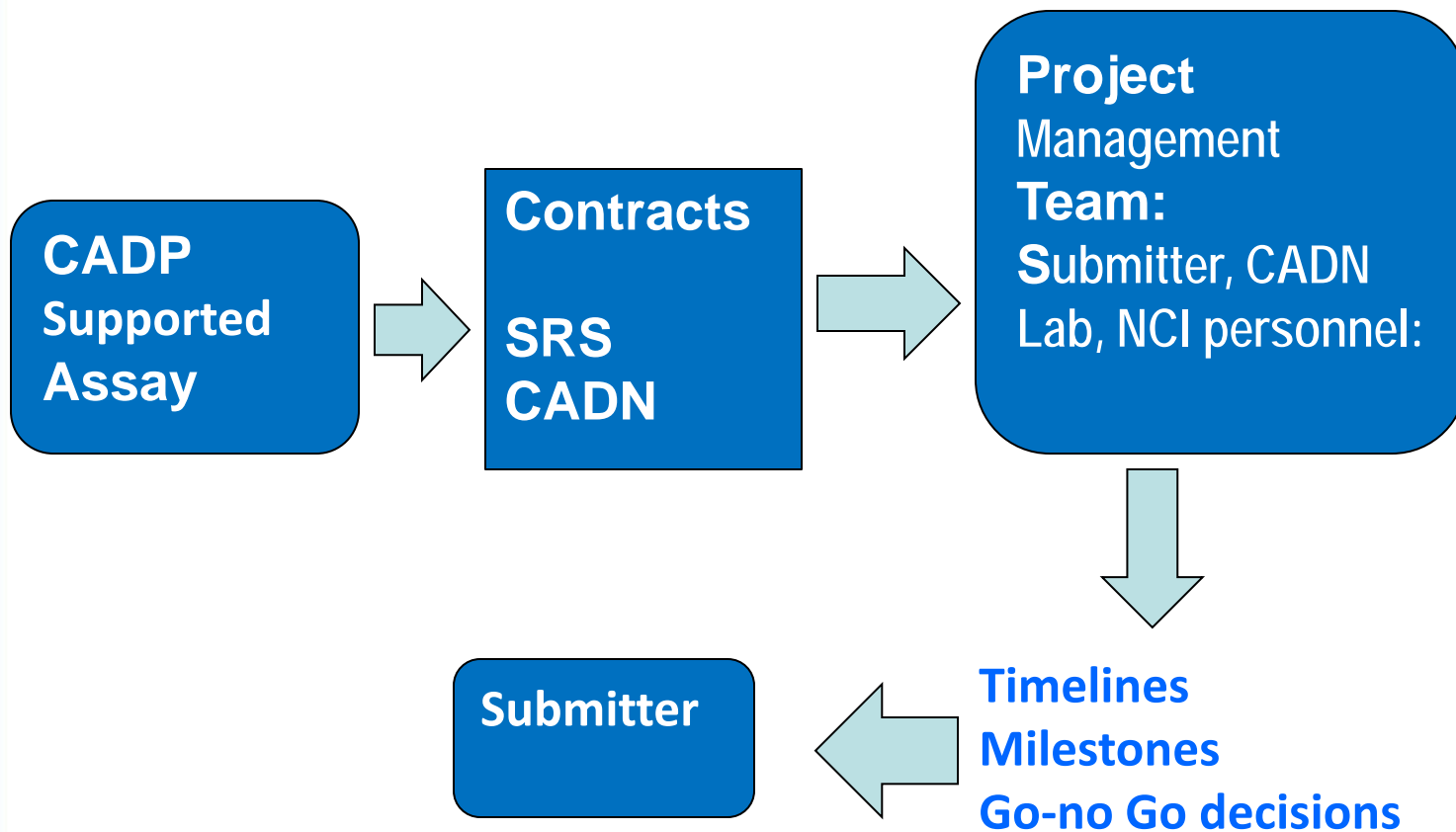
Special Emphasis Panel members

- Each round has different members
- About 2 from industry (diagnostic, pharma with biomarkers)
- Several (different fields) clinical research
- 1-2 patient advocates
- Pathologists (laboratorians)
- Statisticians (Coop group)

Evaluation

- **Scientific Merit**
 - Hypothesis sound; clinical utility
- **Feasibility**
 - Performance characteristics in context of intended clinical use
- **Impact/Clinical Need**
 - Intended Clinical Use
 - Novel insight; adds significantly to current clinical practice
- **Path to Clinical Implementation**

After assay receives support



Status: 3 rounds of applications

- 16 applications (15 applicants)
- 1 in project management (companion diagnostic)
- 1 ready for task order (predictive)
- 1 under consideration by SAC (predictive)
- 2 plans to resubmit

Ongoing educational need:

- Intended clinical use clearly stated: *usually no*
- Clinical need/impact: *Most can make a reasonable case*
- Biologic rationale: *Many too early*
- Prevalence data: *Many don't have*
- Specimens: *Need is great; current STS not adequate*
- Statistical expertise: *Many need this; confuse prognostic for predictive*
- Plan for development: *usually not much*

CADP adjustments

- Work with applicants prior to going to SEP
- Increase statistical consultation
- Acquire additional tissue resources

Current Activities

- Publicize to NCI supported Clinical Trialists
 - IDSC presentation
 - SPORE conference calls
 - Cancer Centers webinar March 2012
 - NCCN meeting presentation
 - AACR/ASCO/ENASCO presentations
 - Journal ads
 - Individually offer participation

Need input

- How could CADP better assist NCI's clinical trials efforts?
 - New/different resources?
 - New/different collaborations?
 - Other?

Useful Websites:

CADP

<http://cadp.cancer.gov>

Cancer Diagnosis Program

www.cancerdiagnosis.nci.nih.gov

QUESTIONS?