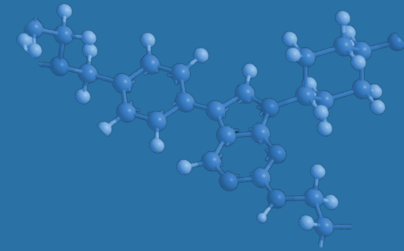# Role of FNLCR in NCI's New Precision Medicine Initiatives

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NIH) NATIONAL CANCER INSTITUTE

FNLAC Meeting

October 24, 2019
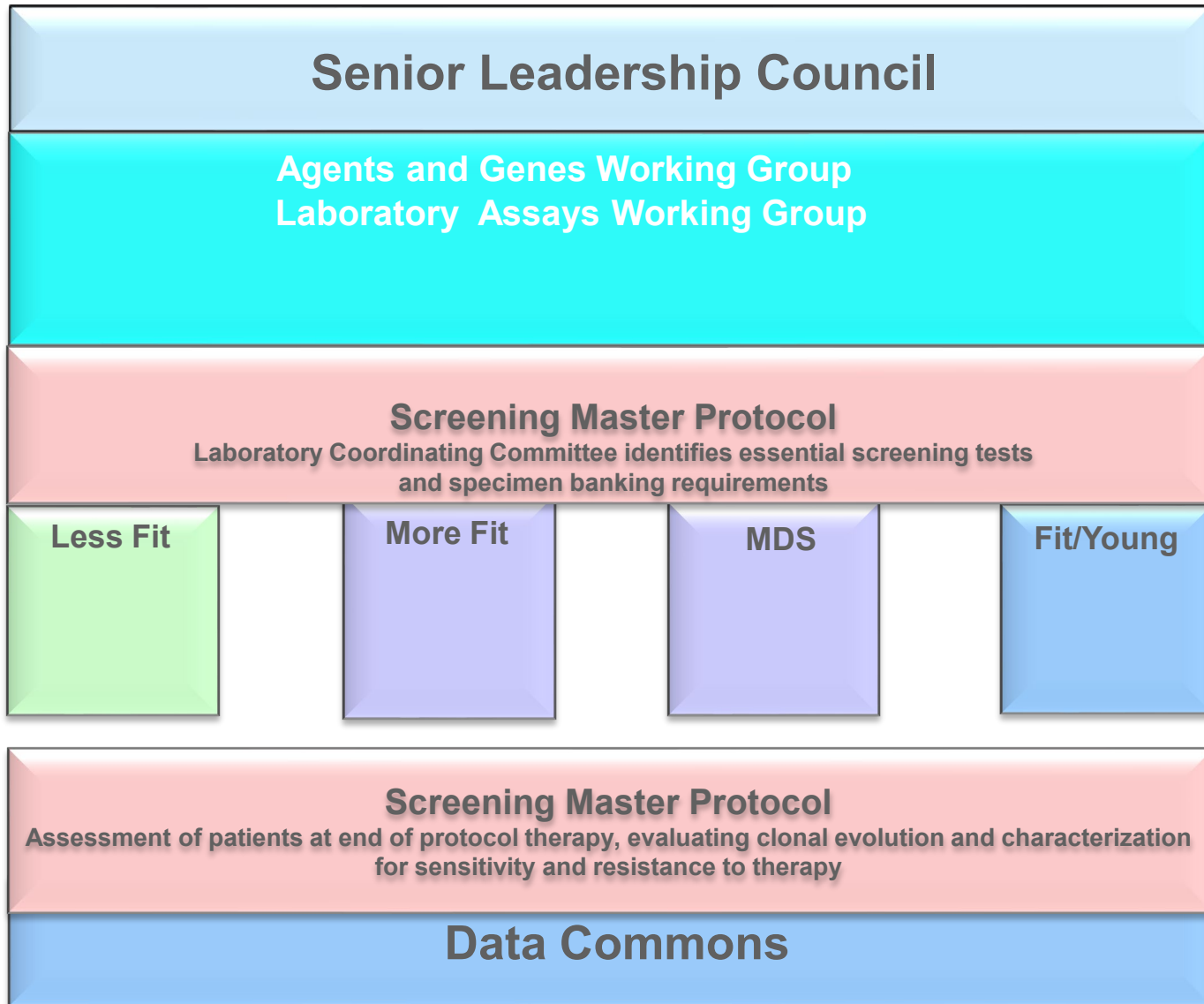
NATIONAL PRECISION MEDICINE TRIALS TO SUCCEED NCI-MATCH: PRELIMINARY PLANS

- **MATCH** trial has stopped accepting new arms; eventually all arms will close [Successful application of voluntary biomarker lab network; 30 institutions; 5-7 patients per week enrolling in MATCH based on NGS by vetted outside labs]

- Three successor trials are in development:

  - ✓ **AML/MDS basket trial--**focus on matching AML molecular subtypes to targeted therapies in different age/fitness groups

  - ✓ **ComboMATCH**--focus on drug combinations vs single agents in MATCH

  - ✓ **iMATCH**--focus on providing prospective immunologic profiling to feed IO study arms defined by histology or biomarkers

- All trials will be structured with a master protocol run by one of the cooperative groups with the ETCTN employing substudies performed by all of the NCTN or ETCTN members
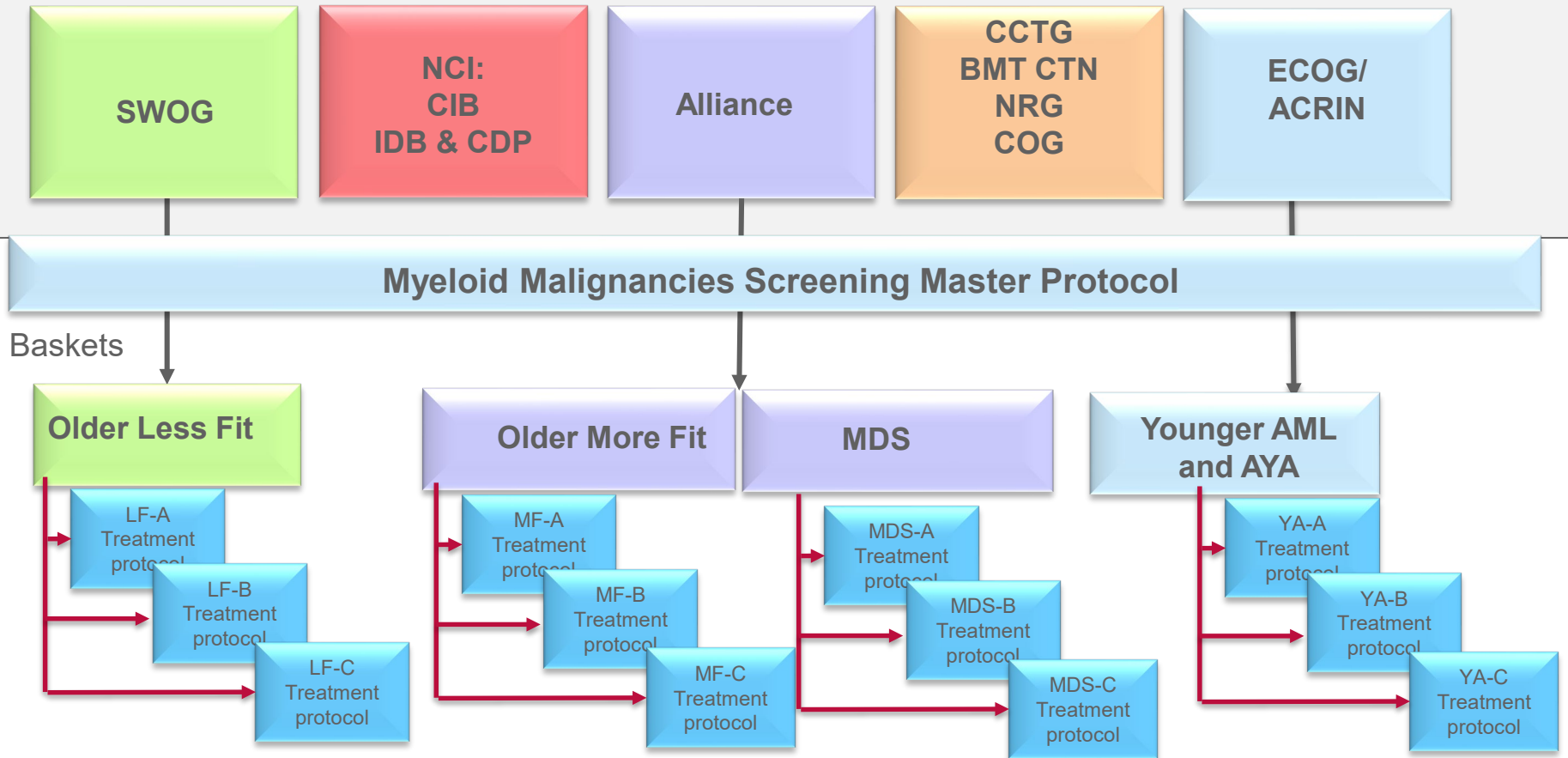
AML/MDS Basket Trial

- Extramural co-leads: Harry Erba and Mark Litsow; SWOG screening

- NCI co-leads: Richard Little, Percy Ivy

- **Premise**: Prospective genotyping can identify optimal populations for targeted therapy investigations; characterize leukemia biology at time of relapse, long term remission and refractoriness and develop data commons for longitudinal studies through the entire disease course

- **Hypothesis**: Since AML therapy must be age and performance status appropriate, distinct and complementary biomarker-driven therapeutic research questions can be addressed in these different contexts

- **Requires**: 48-72 hr turnaround in CLIA labs for initial screening studies: FLT3-ITD, NPM1 (nucleophosmin), CEPBA indels, IDH1/2 mutations, rapid karyotyping following rapid DNA/RNA extraction, cfDNA, buccal swab germline sequencing; **subsequent** dsNGS for targeting patients with MRD, Nanostring and AML specific NGS panels for patients at relapse; automated eligibility assignment through standardized algorithms—**MDNet & PMACC**

Myeloid Malignancies PMI Structure

Senior Leadership Council

Agents and Genes Working Group
Laboratory Assays Working Group

Screening Master Protocol
Laboratory Coordinating Committee identifies essential screening tests and specimen banking requirements

| Less Fit | More Fit | MDS | Fit/Young |

Screening Master Protocol
Assessment of patients at end of protocol therapy, evaluating clonal evolution and characterization for sensitivity and resistance to therapy

Data Commons

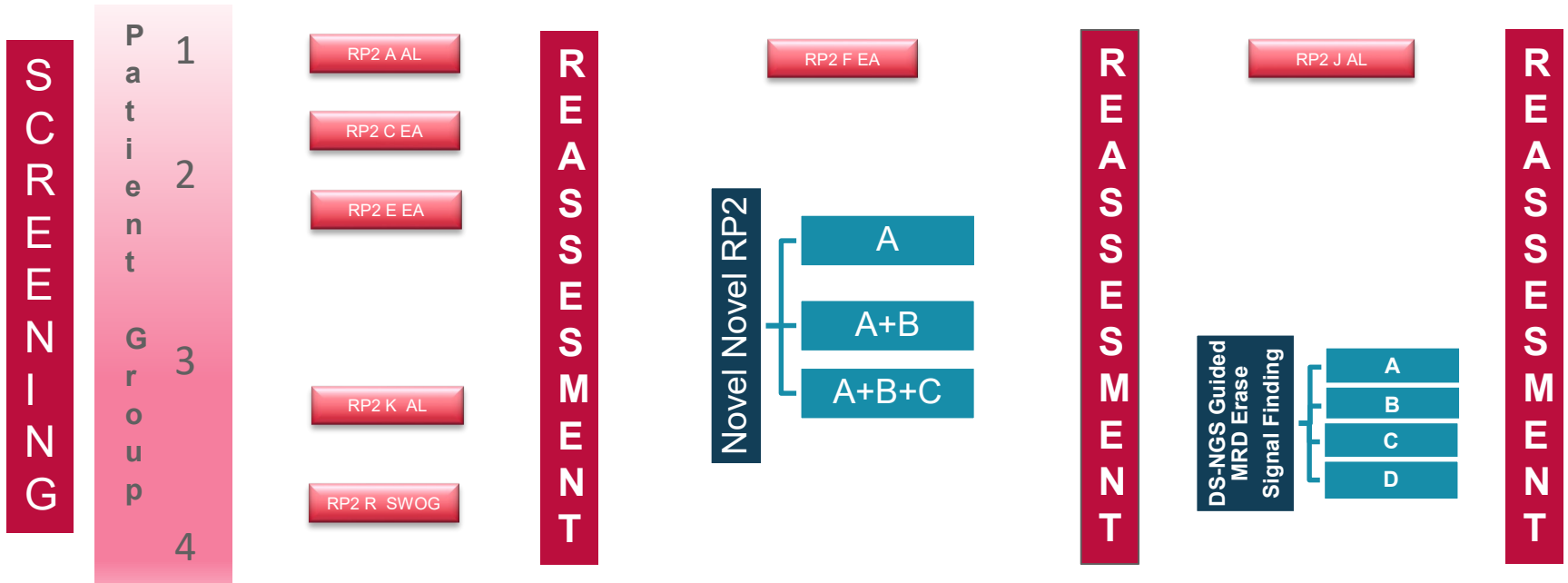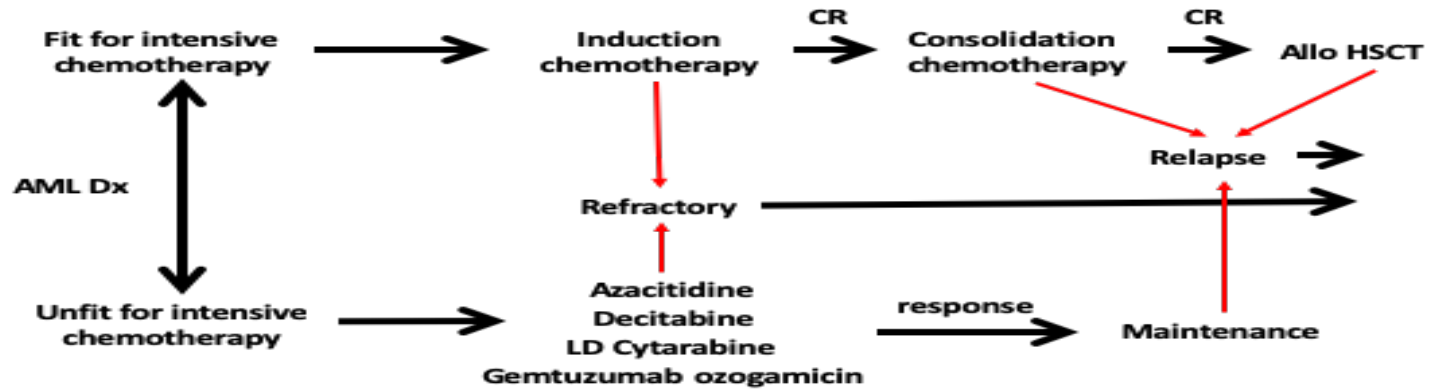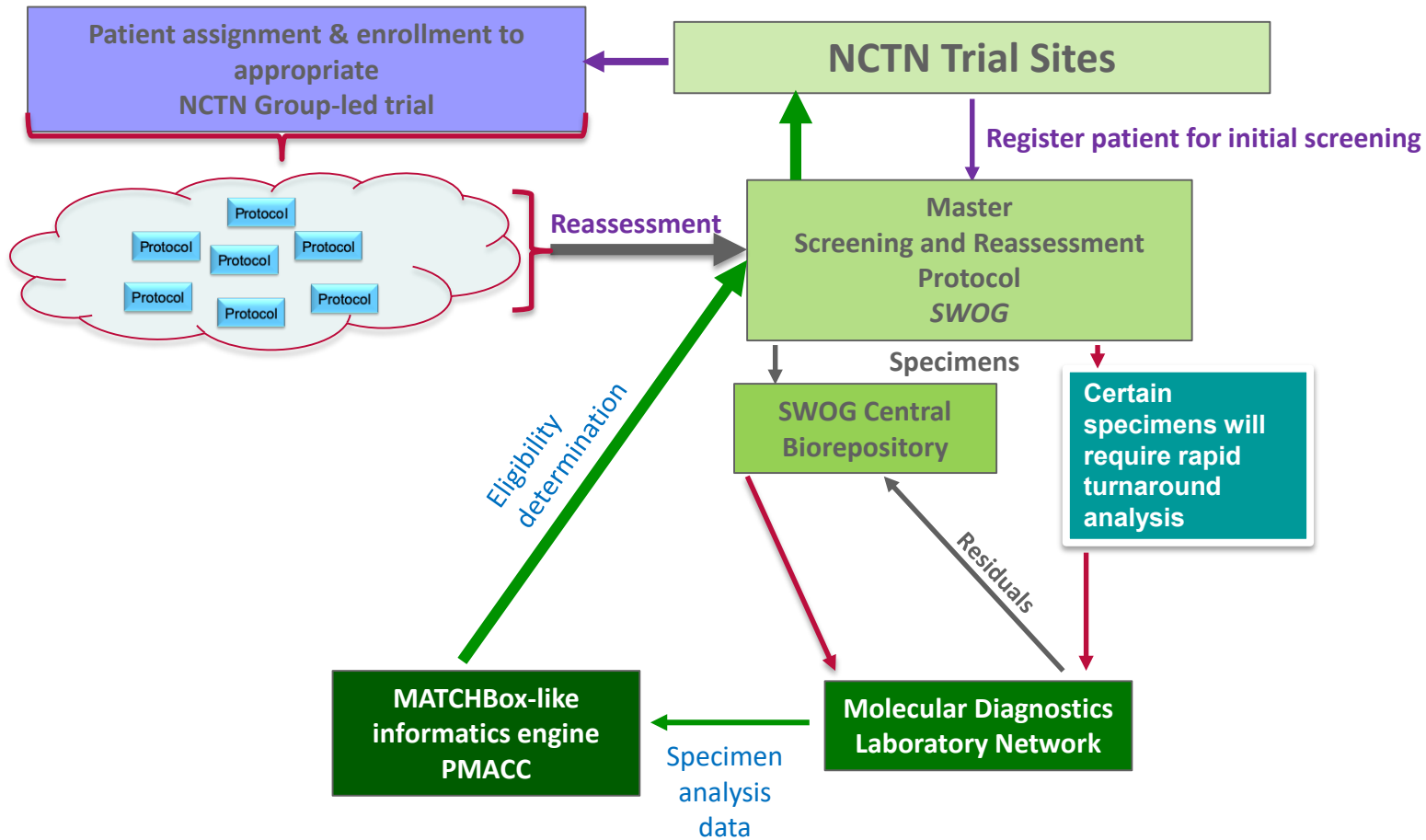# AML/MDS Basket Trial – Organization

Clinical Trials Mirror AML/MDS Rx Sequence Paradigm
Patient Allocation via a Master Screening and Reassessment Protocol (MSRP)

MDNet Screening and Reassessment for AML MDS Basket Trial

ComboMATCH

- **Premise:** Drug combinations are more likely to provide clinical benefit than single agents in most scenarios, so successor trial to MATCH will focus on therapeutic combinations

- **Hypothesis:** Pre-clinical data from *in vivo* models demonstrating drug synergy (and prolonged tumor regressions) for combinations can predict clinical benefit in defined patient groups; data from FNLCR & PDXnet

- ComboMATCH is a **signal seeking study**, like MATCH. The definition of a signal must be defined in the context of a drug combination. A positive signal will not be definitive, but would constitute sufficient evidence for further exploration of the combination; can be histology specific or agnostic

- Umbrella screening study led by ECOG-ACRIN

- Extramural co-leads: Funda Meric-Bernstam, David Hyman and Jim Ford; NCI co-leads: Lyndsay Harris, Jeff Moscow

- **Requires**: Initial ComboMATCHbox algorithms for interpreting commercial NGS testing for eligibility; subsequent cfDNA assessments before and during treatment—**MDNet & PMACC**

ComboMATCH Protocol Organization

ECOG-ACRIN administrative coordination

EA ComboMATCH master protocol
(Contains rules for assignment of patients to treatment arms)

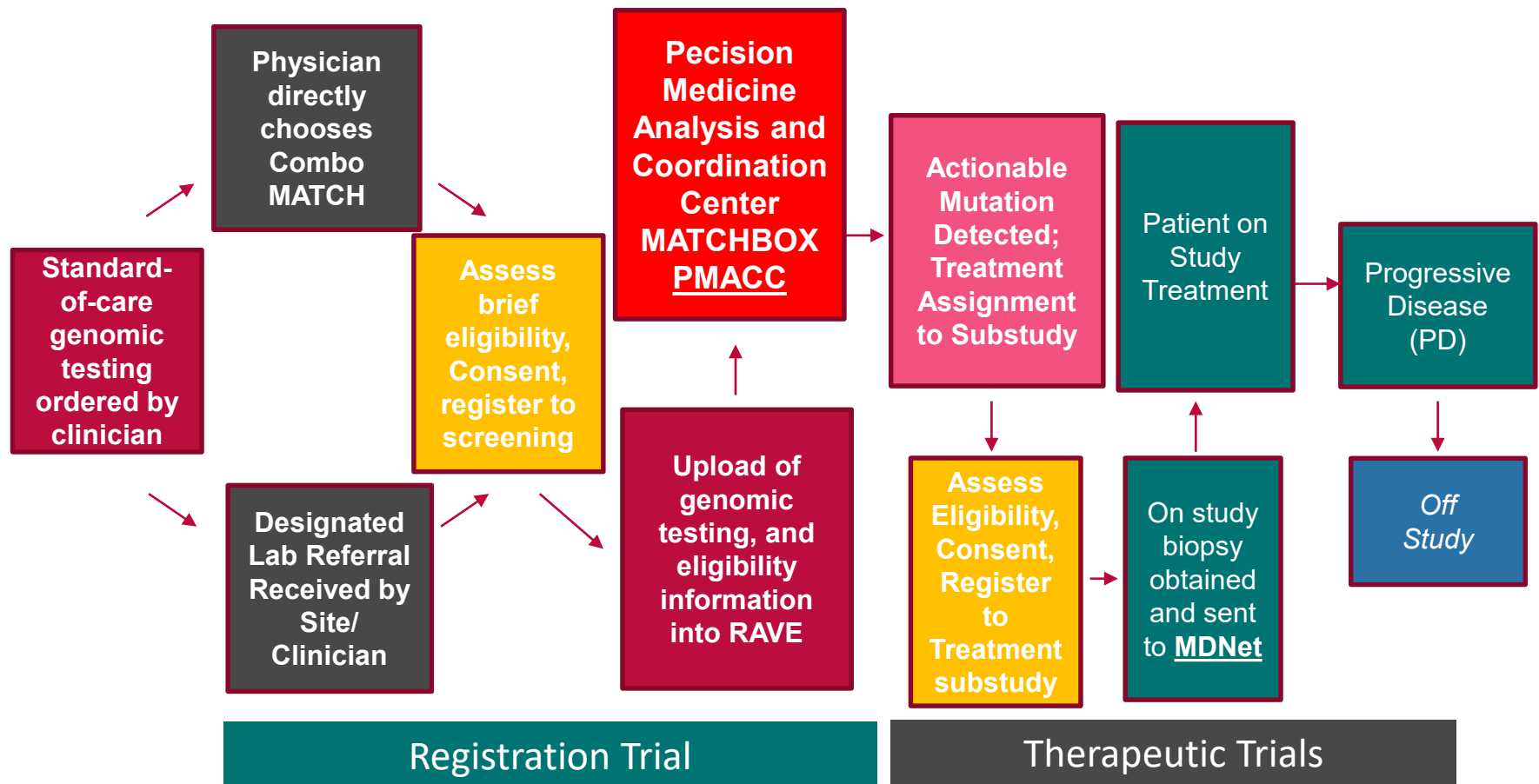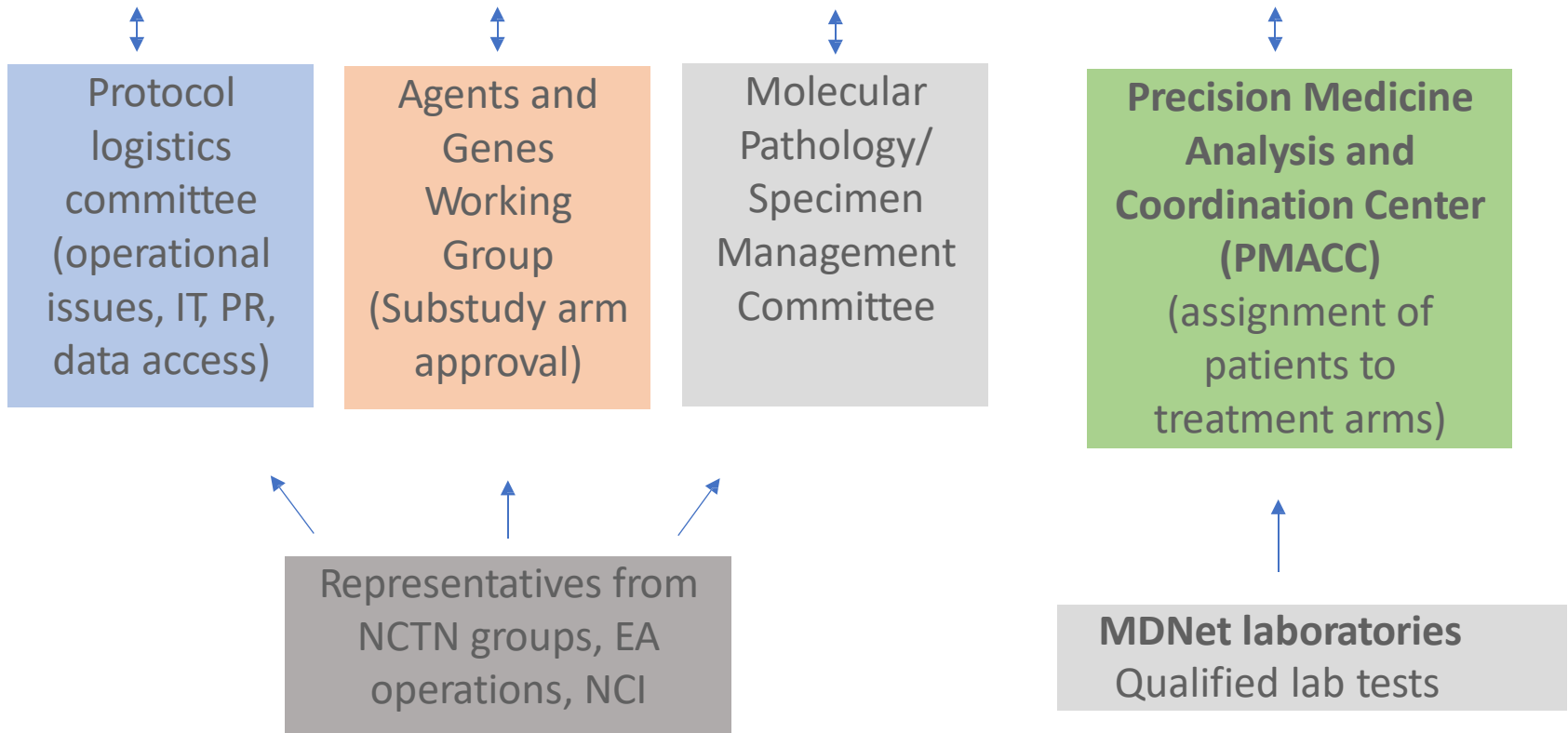| ECOG ACRIN cassette	Alliance cassette	SWOG cassette	NRG cassette
Substudy 1	Substudy 1	Substudy 1	Substudy 1
Substudy 2	Substudy 2	Substudy 2	Substudy 2
Substudy 3	Substudy 3	Substudy 3	Substudy 3
Substudy 4	Substudy 4	Substudy 4	Substudy 4

ComboMATCH Patient Flow

- Two paths to screening step – lab referral and direct patient referral, both require consent—differs from current NCI-MATCH approach
- Eligibility for screening and eligibility for treatment assessed separately
- Will have arms open for patients without eligible molecular abnormalities
- Archival tissue to be sent with on-study biopsy tissue to MDNet

ComboMATCH Administrative Organization

ComboMATCH Steering Committee: Overall PI's – (Drs Meric-Bernstam, Hyman and Ford), EA operations, NCTN representatives, NCI)

Protocol logistics committee (operational issues, IT, PR, data access)

Agents and Genes Working Group (Substudy arm approval)

Molecular Pathology/ Specimen Management Committee

Precision Medicine Analysis and Coordination Center (PMACC) (assignment of patients to treatment arms)

Representatives from NCTN groups, EA operations, NCI

**MDNet laboratories** Qualified lab tests

ISSUES REGARDING LEVELS OF EVIDENCE (LOE)

- LoE for targeting genomic alterations
  - ✓ Can we adopt MATCH rules without creating new ones?

- LoE for supporting anticancer activity of a drug combination in a given setting
  - ✓ Clinical evidence of benefit of combined activity over single agent activity in other settings
  - ✓ <u>Pre-clinical evidence of greater than additivity using genomically relevant *in vivo* models; at least 2 positive models</u>

- LoE for supporting clinical <u>tolerability</u> of a drug combination
  - ✓ Prior phase 2 study of the combination
  - ✓ Prior phase 1 study of the combination
  - ✓ Anticipated drug-drug interactions
  - ✓ Will phase 1 study, or safety lead-in, be required for a given drug combination?

LEVEL OF EVIDENCE

Model ID	Diagnosis
692163-330-T	Leiomyosarcoma, uterine
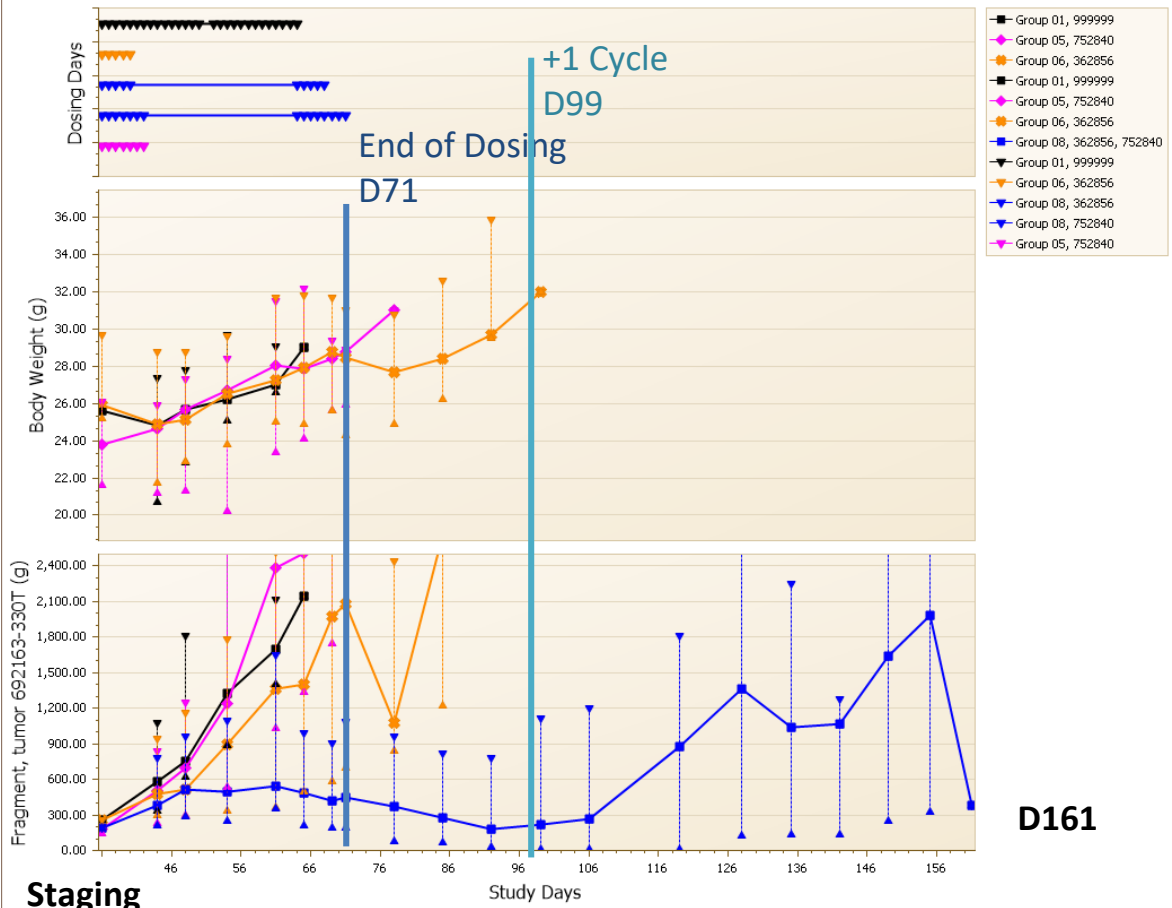
Agent	RMEFS	Regression: consecutive days Group Median
Veliparib	0.9	None
Temozolomide	1.1	None
Veliparib + Temozolomide	2.1	None

Agent	Kaplan Meier, % Increase in Life Span (ILS)
Veliparib	8%
Temozolomide	30%
Veliparib + Temozolomide	106%

P value	
Veh v Velp	0.1900
Veh v Tmz	0.0160
Veh v V+T	<0.00001
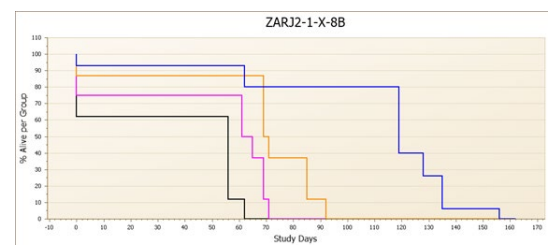
iMATCH

To establish an immuno-oncology precision medicine framework for immunotherapy trials, capitalizing on NCI's infrastructure for precision medicine and "platform" trials, and CRADA mechanisms for collaboration with industry partners

- A **central assay and informatics platform (MDNet & PMACC)** will be established to provide **prospective** tumor/immune profiling and patient triage for trials or treatment arms
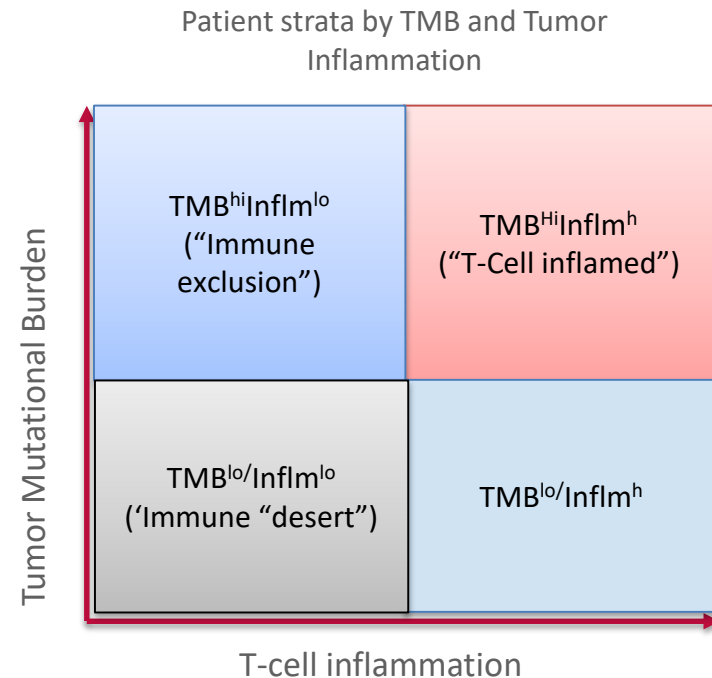 - ✓ Patient stratification based on currently available markers (CLIA labs for WES for TMB, T cell Inflammation score, γIFN signatures, actionable variants, Nanostring IO panel, IHC (CD8/PD-L1), RNAseq myeloid signatures
  - ✓ Flexibility to incorporate new markers from the rapidly evolving IO field
  - ✓ Data coordination lab and clinical/laboratory data sharing across NCTN
- **Therapeutic trials** will be developed to evaluate IO regimens in pre-defined molecular subgroups; patients progressing on checkpoint inhibitors the major focus
- Retrospective studies with deeper immune profiling will be integrated for marker discovery for future trials
- **iMATCH will be a cross-NCTN effort**, with SWOG leading the central protocol, and all NCTN groups developing subprotocols under the "central screening" platform

iMATCH (2)

- **iMATCH is different from MATCH trial (for targeted agents) … currently no marker-regimen matches for IO combinations**

- **Key prospective markers are biology-based and will stratify patients by categories of TME and potential mechanisms of immune evasion**
  - √ **Tumor mutational burden (TMB)**
  - √ **Tumor inflammation "inflammation markers** (Gene Expression Profiles (GEP); and/or PD-L1, CD8)
  - √ **Specific genomic variants or other markers that are potentially actionable**

- **Current classifiers may not be optimal …** stratification vs. enrichment will be considered in trial designs, depending on qualification of the markers, MOA of the drugs, and purpose of the trial

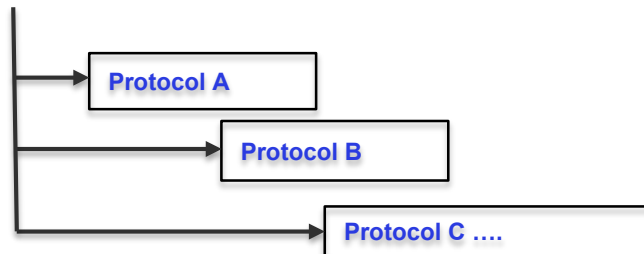Patient strata by TMB and Tumor Inflammation

$TMB^{hi}Inflm^{lo}$ ("Immune exclusion")

$TMB^{Hi}Inflm^{h}$ ("T-Cell inflamed")

$TMB^{lo}/Inflm^{lo}$ ('Immune "desert")

$TMB^{lo}/Inflm^{h}$

Tumor Mutational Burden

T-cell inflammation

iMATCH Central Screening Protocol

I. CLIA Assay Platforms

NGS - TMB
(Also → Oncogene; HLA, ..)

Tumor Inflammation

IHC
(PD-L1, CD8)

And/ OR

GEP
(e.g. T-cell inflammation signature)

New Assays or new markers when relevant

II. Markers and classifiers

High TMB   **Low TMB**

Oncogene alterations

Genes associated Immune evasion.

Genes associated with ICI sensitivity (e.g. SWF/SNF)

GEP high Or CD8/PD-L1+   **GEP low Or CD8/PD-L1-**

III. Potential subgroups

TMB/Inflm strata

"INFLAMED"
High TMB/hi-inflammation

Hi TMB/Lo-inflammation

Lo-TMB/Hi-inflammation

"IMMUNE DESERT"
Low TMB/ Non-inflamed

Specific variants

Oncogene alterations
- (e.g. PI3CA, PTEN; BRAF/MAPK; LKB1, HRD/BRAC ....)

Immune evasion.
E.g. APM defects, B2M loss, JAC1/2 etc

Variants sensitive to ICI
(E.g. PD-L1 amplification; SWF/SNF defect; MSI, POLE, etc)

iMATCH subprotocols for therapeutic trials

Protocol A
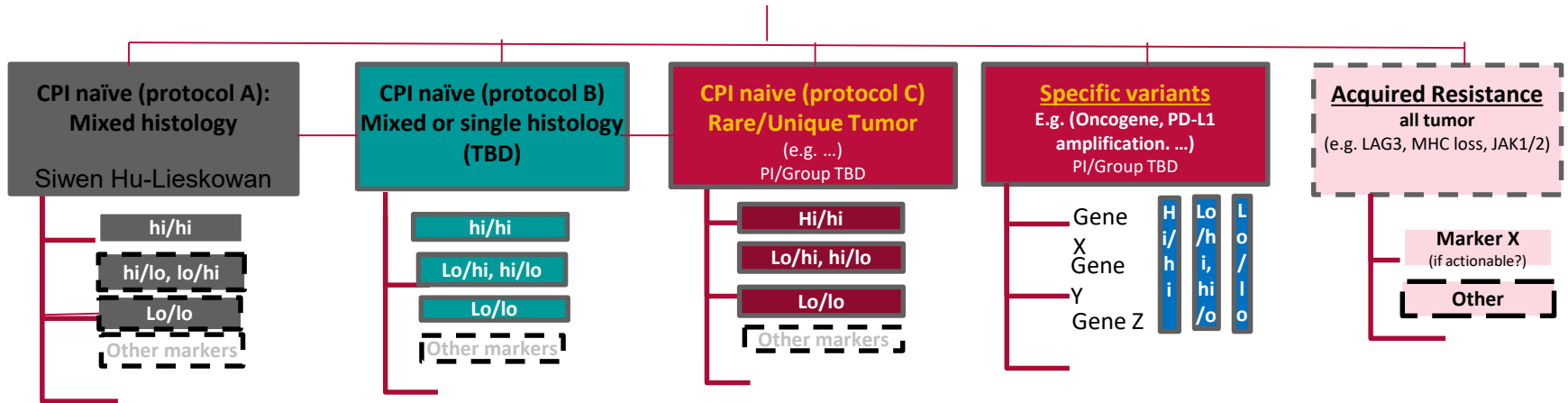
Protocol B

Protocol C ….

- The Master protocol will provide central assays for prospective molecular profiling on recent/new specimens

- Assay results will be used to define patient subgroups by TMB and T-cell inflammation as well as specific variants if actionable

- Therapeutic trials can be developed to evaluate IO regimens in pre-defined subgroups (by enrichment or stratification)

- Each trial can be multi-cohort or multi-arm, for select clinical settings, molecular groups, or experimental arms.

iMATCH Potential Organizational Structure

iMATCH Central Screening Protocol - SWOG
- Katie Politi PhD/Ken Grossmann MD/PhD

CPI naïve (protocol A): Mixed histology
Siwen Hu-Lieskowan
- hi/hi
- hi/lo, lo/hi
- Lo/lo
- Other markers

CPI naïve (protocol B) Mixed or single histology (TBD)
- hi/hi
- Lo/hi, hi/lo
- Lo/lo
- Other markers

CPI naive (protocol C) Rare/Unique Tumor (e.g. …) PI/Group TBD
- Hi/hi
- Lo/hi, hi/lo
- Lo/lo
- Other markers

Specific variants E.g. (Oncogene, PD-L1 amplification. …) PI/Group TBD
- Gene X
- Gene Y
- Gene Z
- Hi/hi
- Lo/hi, hi/lo
- Lo/lo

Acquired Resistance all tumor (e.g. LAG3, MHC loss, JAK1/2)
- Marker X (if actionable?)
- Other

Potential combination partners or novel approaches - Top regimens by mechanism?
- CPI/T-reg depleting: e.g. CTLA-4, LAG3 …
- Costim/cytokine: 41BB/CD137, PEG IL-2, CD40 ..
- TME/macrophage: IDO, CD47, VEGF ..
- Other …
- Vaccine/onco-virus/endogenous adj: TLR-9, T-VEC, vaccines …
- Epigenetics (HDACi , BET..)
- Beyond CPI – Bispecific mab,

Potential regimens for specific variants?
- Oncogene/suppresser gene alterations (e,g, PTEN, DDR, LKB1)
- PD-L1 amplified, SWF/SNF, etc

- **For CPI-naïve patients**, there may be 2-3 protocols for mixed histology or single histology. Each may include 4-5 arms for novel regimens in pre-defined TMB/inflam strata (2, 3, or 4, strata depending on regimen) and other actional markers

- Protocol(s) for <u>rare variants</u> will test regimens targeting actionable variants identified from central screening

- Protocol(s) <u>for acquired resistance</u> will be considered if there are sufficient hypothesis for marker-based treatment assignment

NCI Centralized Biomarker Resources

- Local investigator-developed biomarker assays frequently do not meet necessary laboratory standards for analytical validation

  ✓ Laboratory research techniques such as Western blot are not amenable for use as reproducible PD analysis of biopsy specimens

  ✓ Research labs not equipped or trained to develop validated biomarker assays

  ✓ Use of grant funding to help investigators develop analytically validated assays led to mixed results

- Evolution to centralized laboratories for biomarker assays for patient specimens

  ✓ Assays developed by research pathologists with expertise in assay development

  ✓ Centralized assays allow cross-trial comparison

 ✓ SOPs developed for each assay that include pre-analytic SOPs for sites collecting specimens

NCI's New Centralized Biomarker Resource: NCLN—National Clinical Lab Network

Objectives

- Establish a US laboratory network capable of providing centralized, robust assays for ETCTN (early phase) clinical trials that will provide:
  - ✓ Genomic characterization
    - ➤ FNLCR Molecular Characterization Lab (MoCha)
    - ➤ MD Anderson Cancer Center-subcontracted network lab

  - ✓ Pharmacodynamic biomarkers
    - ➤ FNLCR Clinical Pharmacodynamics Program (PADIS/NCTVL) as hub
    - ➤ Molecular Pathology Laboratory Network, Inc. for multiplexed sandwich immunoassays (Luminex platform)
    - ➤ MD Anderson Cancer Center for multiplexed quantitative immunofluorescence microscopy assays (Aperio and Axio Scan platforms)

- Labs will offer robust assays following harmonized and locked SOPs that are analytically validated and performed in CLIA accredited facilities
    - ➤ Implement uniform assay workflow, instrumentation & data analysis pipeline across network labs

- Centralized specimen biorepository (Nationwide)
- Tools for genomic data visualization

National Clinical Laboratory Network for Precision Medicine
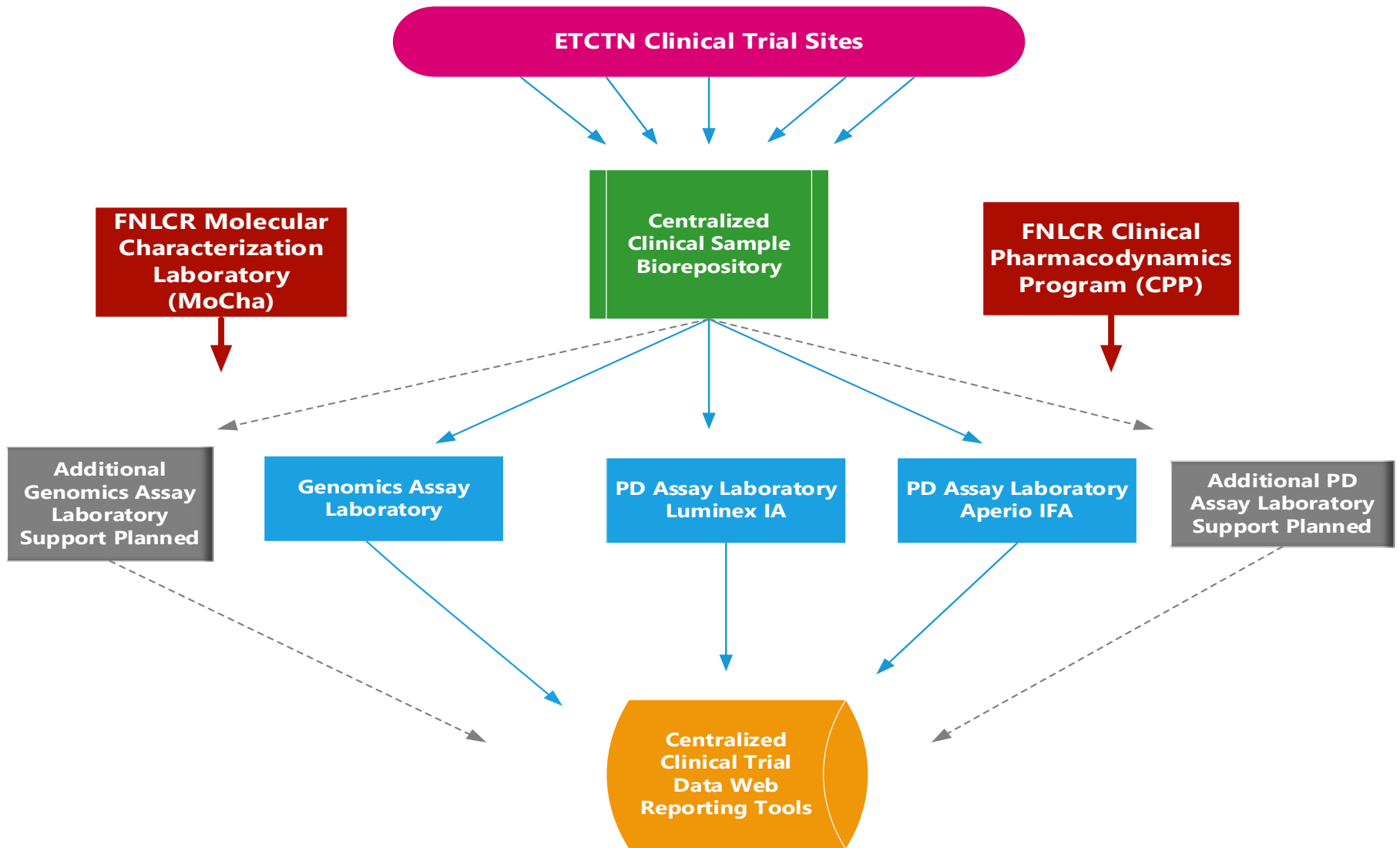
Core Technologies Supported by the NCLN

- Oncomine pan-cancer targeted gene panel (OCAv3)
  - ✓ *Ready now*

- Whole Exome Sequencing (WES) & RNA Sequencing (RNA-Seq)
  - ✓ *Ready now at MoCha; Expect to be validated in network and ready by Fall 2019 at MDACC*

- TSO500 targeted gene panel for ctDNA
  - ✓ *Expected to be validated in network and ready by end of 2019*

- Broad range of PD assays: DDR, apoptosis, EMT

ctDNA Assay

523-gene targeted panel (TSO500)

- Reports SNVs, Indels, clinically relevant fusions, CNVs and TMB
- Upcoming version will include MSI status
- *Technology*: Hybrid capture; incorporates unique molecular indices (UMIs) and error correction algorithms
- *Status*: completed first stage of validation and currently undergoing final validation; available in the NCLN by end of 2019
- *Blood collection requirements*: 2 Streck tubes (preferred)

➤ TSO500 will be a CLIA laboratory test at MoCha and will be used as an integral or integrated assay in ETCTN trials and in new NCI-supported precision medicine studies

NCLN Pharmacodynamic Assay Support

- **Initial Multiplexed Immunofluorescence Microscopy Assays**

  ✓ **Network Lab is <u>M.D. Anderson Cancer Center (Principal Investigator: Dr. Stan Hamilton, MD)</u>**

  ✓ **Initial Priority Assay for Transfer:** *γH2AX, pNBS1 Immunofluorescence Assay with β-Catenin Segmentation for Tumor Biopsy Slides; RAD51 coming*

  ✓ *EMT markers; $pY^{1235}MET$;*

  ✓ *ImmunoPD: CD8, CD3-pY142 zeta, ZAP70-pY493*
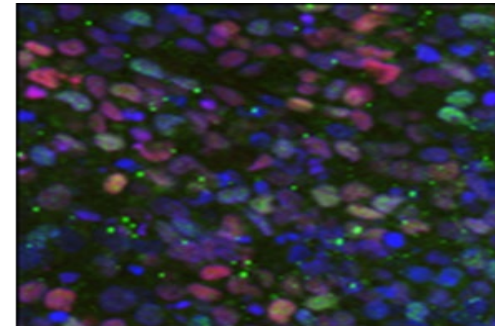
pS343-Nbs1   γH2AX   DAPI

- **Initial Multiplexed PD Immunoassays on Luminex**

  ✓ **Network Lab Selected is <u>Molecular Pathology Laboratory Network, Inc.</u> (Principal Investigator: Dr. Roger Hubbard, Ph.D.**

  ✓ **Initial Priority Assay has been Transferred:** *Intrinsic Apoptosis Multiplex Assay – measurement of 13 cytosolic and membrane associated proteins indicative of the induction, onset and commitment to apoptosis in tumor biopsies*

    - Panel-1: BAK, BAX, Lamin-B, SMAC
    - Panel-2: BIM, BAD, BAX—Bcl-2, Bcl-xL, Mcl-1
    - Panel-3: BAK —Mcl-1, BAK —Bcl-xL, Cleaved Caspase-3, Survivin

NCI CENTRAL SUPPORT FOR MATCH SUCCESSOR TRIALS

- **MDNet**--(Molecular Diagnostics Network)--a network of laboratories that will provide both CLIA and non-CLIA lab support for all three new precision medicine trials: **NCI with FNLCR**

  - ✓ Molecular characterization of myeloid malignancies

  - ✓ Genomic characterization for investigational combinations

  - ✓ Immunologic characterization for next generation IO trials

  - ✓ Tissue repository, Q/C, distribution

  - ✓ Expanded version of NCLN

- **PMACC**--(Precision Medicine Analysis and Coordination Center) a data center that will provide data coordination and warehousing, decision-making, and communications support for the trials **through FNLCR**

  - ✓ IT infrastructure to support molecular screening algorithms, automated treatment assignment, data sharing and integration across NCI clinical trials networks

- NCI now actively engaged with FNLCR in developing these new centralized resources

MDNet
Molecular & Immunologic Diagnostics Network of Laboratories

(NCI) Central Molecular Screening Protocol(s)

NCTN Protocols

Patient Groups

- **AML/MDS (newly Dx) (progressing)**

- **ComboMatch Solid Tumor (newly Dx) (progressing)**

- **iMATCH IO eligible**

→ Pt Specimens →

MDNet (FNL) (molecular testing)

MDS/AML
TP53, FLT3, NPM1, IDH1/2, blast profiling, karyotype, CEBPA, FISH (-5p/q, -7(q), tris8, MLL, t(8;21), t(15;17), inv(16)

MRD assessment
NGS for clonal evolution

solid tumor
aMOI by NGS (tumor, cfDNA)
WES/RNASeq confirmed aMOI
re-assessment at PD/EoT

solid tumor
TMB by NGS (tumor, cfDNA)
tumor inflammation by GES, IHC

→ Test Results →

PMACC (FNL) FNL "Matchboxes"

MDS/AML treatment assignment

solid tumor matched combo treatment

solid tumor IO subgroup assignment

→ Trial Assignment →

Alliance

CNG

COG (ped)

ECOG-ACRIN

NRG Onc

SWOG

NCORP

www.cancer.gov