FNLCR and NCI's New Precision Medicine Initiatives

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NIH NATIONAL CANCER INSTITUTE

Frederick National Laboratory Advisory Committee

October 19, 2023

Overview

- Overview—J. Doroshow, M.D.
- Clinical Laboratory Support of NCI's Precision Medicine Trials—
  M. Williams, Ph.D.
- iMATCH (immunotherapyMATCH)—H. Chen, M.D.
- ComboMATCH—L. Harris, M.D.
- MyeloMATCH—R. Little, M.D.

Frederick National Laboratory for Cancer Research

Clinical Laboratory Support of NCI's Precision Medicine Trials

P. Mickey Williams, PhD

Director of the Molecular Characterization Lab,
Frederick National Laboratory for Cancer Research

February 27, 2023

MOCHA

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The Beginning: NCI-MATCH

- **NCI-MATCH opened to enrollment in November 2015**
- **NCI-MATCH, a multi-treatment arm trial relied on NGS to detect actionable somatic mutations with evidence of predicting treatment response**
- **The Trial was tumor histology agnostic**
- **The use of NGS as a clinical assay was relatively new (no FDA approved tests)**
- **A decision was made to develop a clinical laboratory network and standardize a novel targeted NGS assay insuring consistent realtime tumor screening results**
  - The NCI-MATCH NGS Assay*:
    - Produced near identical results in each of 4 laboratories
    - Required minimal amounts of nucleic acids, therefore compatible with core needle biopsies
    - Performed well with formalin fixed core needle biopsies
    - Provided results within 15 days of biopsy
    - * The same assay supported PedsMATCH and currently supports Moonshot Biobank

NCI-MATCH Designated Laboratory Network 2017

- **A decision to change to a Designated Laboratory Network (DLN) was made after screening ~6000 patient tumors**
  - Some actionable somatic variants were very rare in the enrolling population, requiring excessive screening to identify the variants
  - FDA approved Foundation One and MSK-IMPACT (2017) and clinical NGS had become more widely available
- **NCI recruited clinical laboratories by posting in the Federal Register**
- **11 laboratories were selected, initially after a successful vetting process:**
  - Review of analytical validation report
  - Cross laboratory performance testing, comparing results to the original central laboratory assay
- **DLN assays are performed prior to trial enrollment as part of routine patient management**

Overview of MDNet at FNLCR

- **MDNet Goals: Building upon NCI-MATCH/PedsMATCH and NCLN experience, establish an assay network for support of NCI's Precision Medicine Trials Initiative**
  - iMATCH
  - ComboMATCH
  - MyeloMATCH
- **Utilizing:**
  - Designated laboratory networks for standard of care assays (ComboMATCH)
  - Sub-contracts with external laboratories OR FNLCR laboratories for new and novel assays

iMATCH Assay Support

Assay	Laboratory	Biomarker
cWES	MoCha MD Anderson	**TMB**; full clinical report for 675 cancer related genes; MSI; HLA-LOH
IO360 Gene Expression Panel Tumor Inflammation Score (TIS)	Almac	**TIS**; other inflammation signatures
IFA CD8, PDL-1	MD Anderson	Immune related protein markers
RNAseq	MoCha MD Anderson	Research gene expression signatures
ctDNA NGS	MoCha MD Anderson	Somatic mutation profile, correlation of ctDNA to treatment response
Black = Integral*; Red = Integrated*	Red = subcontract	**Bold underline are current stratification biomarkers**

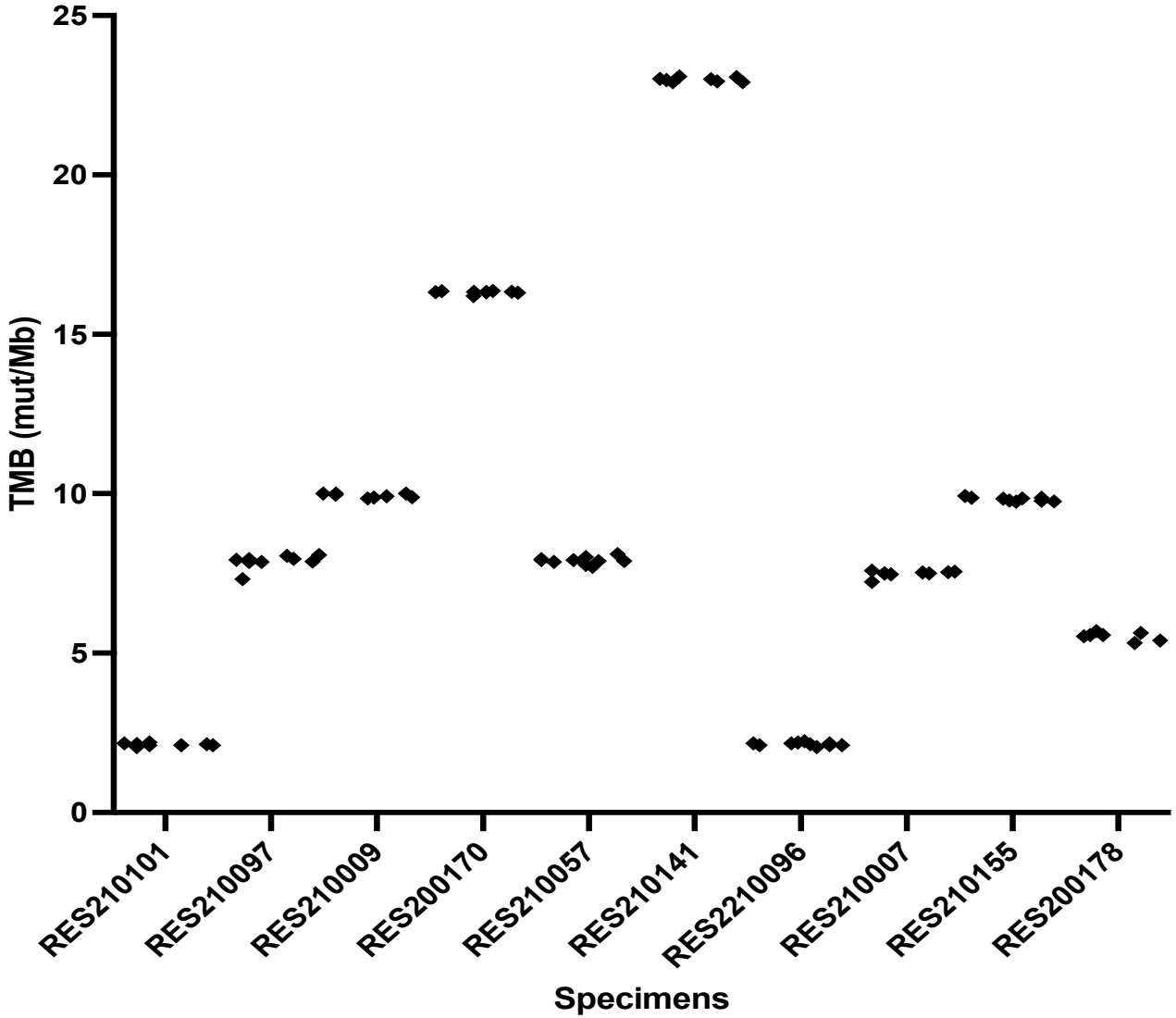
cWES, RNAseq & ctDNA leverage NCLN activities

*Integral assay ~ Results in a clinical report performed in an accredited clinical lab, used for enrollment/treatment

*Integrated ~ Specimens collected; assay is used for research purposes. No clinical report returned for patient management

Precision of cWES TMB

- **Precision of TMB values across the reportable range of 5-20 mut/Mb is high (% CV <2.87)**



ComboMATCH Assay Support

Assays	Laboratory	Biomarker
Designated Lab Network (NGS) ctDNA under consideration w/FDA discussion beginning	38 Clinical Laboratories and growing (NCI research agreement)	**All required somatic mutations for all treatment arms**
cWES	MoCha MD Anderson	Research, snv's, indels, CNV, LOH, MSI, TMB
RNAseq	MoCha MD Anderson	Research gene expression signatures
ctDNA NGS	MoCha MD Anderson	Somatic mutation profile, correlation of ctDNA to treatment response
Black = Integral Red = Integrated	Red = subcontract	**Black underline are required biomarkers for enrollment and treatment selection**

MyeloMATCH Assay Support

Assay	Laboratory	Biomarker
Cytogenetics/FISH*	Fred Hutchinson Cancer Center	**Translocations for ELN Risk**
MyeloMATCH NGS*	MoCha Fred Hutchinson Cancer Center	**Somatic mutations for ELN Risk and treatment selection**
FLOW*	Children's Hospital Los Angeles	Disease stratification and **MRD**
Duplex NGS	TwinStrand MoCha	Initially research comparison to FLOW, if adequate performance is observed will be moved into **MRD and treatment selection**
• *Initial integral assays requiring 72-hour turn-around time at diagnosis, IDE • Initially performed as integrated assay	Red = subcontract	**Bold underline are integral biomarkers with assays requiring IDE**

MDNet Trials: Determining the Assay & Defining the Assay Intended Use

- **FNLCR staff work with NCI and Trial Investigators to identify predictive biomarkers and appropriate assays.**
  - Defining the assay intended use:
    - Integral assays require a clinical report which determines eligibility for enrollment, treatment selection or treatment stratification; this requires an analytically validated assay performed in an accredited clinical lab
    - Integrated assay are for research only, but still require documentation of analytical performance and locked protocols
    - Define specific biomarkers and thresholds and detail the assay platform
    - Specimen pre-analytics:
      - Method of collection, shipment, central pre-analytic lab versus assay lab processing, specimen processing requirements
    - Required turn-around time for results (i.e., 72 hours for MyeloMATCH)

Finding the Laboratories- Designated Lab Network ComboMATCH

- Designated Lab Network for ComboMATCH
  - RFI posted in Federal Register to add labs to the Designated Lab Network
  - Assays vetted for acceptable analytical performance
  - Assay analytical validation report reviewed, and cross lab comparability studies performed
    - If approved, NCI signs a research contract for assay support
- Designated lab assays performed prior to patient enrollment
  - If enrollment biomarkers are detected, the lab will notify physician of potential match for our trial
  - Request made by physician to enroll on ComboMATCH trial site
  - Assay data and patient pathology reports are reviewed for possible enrollment
  - Acceptance is sent to physician
- During the trial:
  - Assay performance monitored by periodic proficiency testing or comparability studies
  - CAPA's related to the trial are documented (with appropriate follow up)
  - Any major assay changes are vetted for acceptable performance
- We are continuing to add labs for ComboMATCH focusing on labs with 30% or greater underserved populations
- We intend to work with FDA to request inclusion of ctDNA assays

Finding the Laboratories- Highly Subjective or New & Novel Assays

- **Highly subjective assays include non-standardized LDT IHC's**
- **New and novel examples include: 72-hour turn-around MyeloMATCH NGS, Myeloid double strand NGS assay for MRD**
- **Depending on expertise and status of the technology, RFP's are opened to all applicants or focused on a few with unique expertise (TwinStrand: dsMyeloid NGS)**
- **The MoCha lab develops novel assays via CRADA's and as appropriate can be utilized**
  - TSO500ctDNA (Illumina)
  - MyeloMATCH NGS (Thermo Fisher)
- **MoCha staff write the technical statements of work, evaluate the RFP's, monitor sub-contract performance, approve invoicing, participate in lab audits, monitoring of chain of custody, CAPA's, and working with NCI to collect and upload data to public databases**

IND and IDE Discussions with FDA

- **Assay details are included in the trial IND**
- **MoCha attends discussions with CDRH when needed to address assay related questions**
- **Risk determination is agreed upon**
  - ComboMATCH and iMATCH integral assays required abbreviated IDE's determined by non-significant risk
  - MyeloMATCH assays require a full IDE determined by significant risk
- **During the trial, we partner with NCI in lab monitoring and audit's**

Reference Materials, Quality Control Materials and Diagnostic Harmonization Efforts

- **Precision Medicine efforts require Dx assays for cancer patient management**
- **Difficult to judge accuracy and comparability of these complex assays**
- **MoCha engaged in:**
  - Genome in a Bottle; human genome RM (NIST)
  - Developed and Implemented Oncology RM (SeraCare CRADA)
  - Co-Developed Copy Number RM (NIST)
  - Developing **ctDNA** QCM (FNIH, NIST)
  - FOCR **TMB** Comparability Study
  - FOCR HRD Comparability Study
  - Contributed to CIMAC genomic assay harmonization effort
  - SRS Somatic Reference Samples (MDIC & NIST, based on Genome in a Bottle RM)

Summary

- **We have built upon our efforts for NCI-MATCH and added additional laboratories and expertise to continue our support of MDNet**
- **The focus remains on providing accurate, “fit for the intended use” and well-documented assays, such that data is reproducible and available in the public domain**

Acknowledgements to MANY!!

- **NCI (Dr. Lyndsay Harris, Dr. Rich Little, Dr. Helen Chen, CTEP Regulatory and Dr. Doroshow)**
- **Our many subcontractors and collaborators**
- **Many non-MoCha collaborators within Leidos: FNLCR (Ralph Parchment & Christy Young)**
- **All of the staff at MoCha**
  - Chris Karlovich PhD, Associate Director
  - Lily Chen PhD, BioInformatic/Computational Biology
  - Bishu Das PhD, R&D
  - DJ Jiwani MD PhD, CLIA Lab Director/Histology
  - Corrine Camalier
  - Andi Zak

- **OPEN TO COMMENTS AND QUESTIONS AT THE END OF PRESENTATION**

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iMATCH
(Immunotherapy "MATCH")

Helen Chen, M.D., IDB, CTEP

Aiming for Precision Immunotherapy – *a step-wise approach*

Premise:

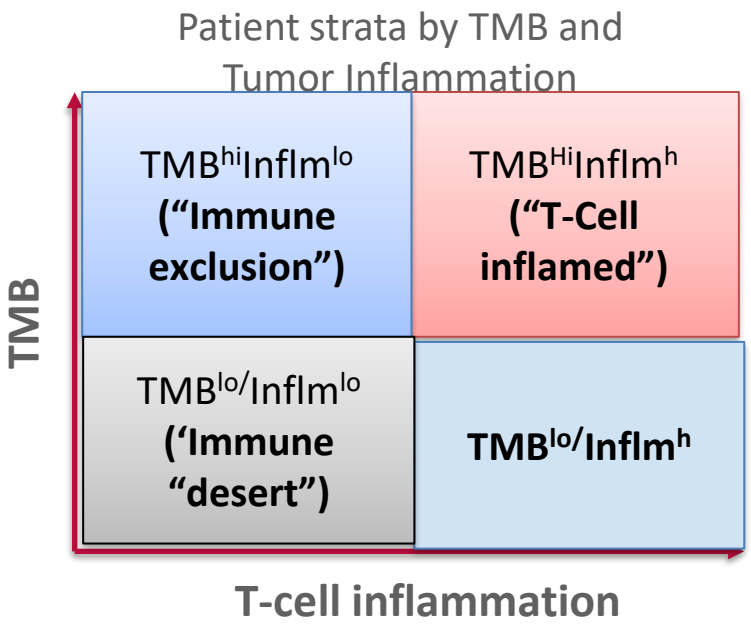
- A major impediment to further development of immunotherapy is **lack of patient selection markers for combination regimens** designed to overcome the complex mechanisms of resistance

- Clinical testings, esp. signal seeking trials in “all comers”, are often negative or difficult to interpret.
  - Retrospective studies often noninformative due to small subsets and high specimen attrition

- ***However*****,** some ”clinical grade” markers can be used prospectively to define **“biological” subgroups with** underlying MORs that may be relevant (or not) to certain agents

  - **Tumor mutation burden (TMB)** … c/w neoantigen/immunogenic:
  - **T-Cell Inflammation markers** (INFγ signature, PD-L1, CD8) … c/w presence of T effector in TME

Composite biomarker



Aiming for Precision Immunotherapy – *a step-wise approach (2)*

The iMATCH concept:

Current

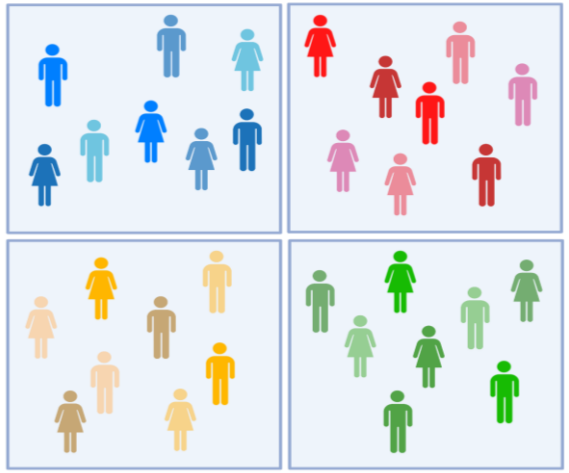
- No upfront patient/tumor characterization in most IO trials

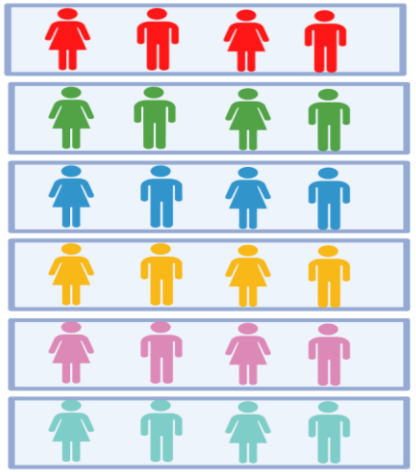
iMATCH Initiative

- Prospective use of TMB and Inflammation markers for "biological" stratification or enrichment in signal seeking trials

Future

- True precision biomarkers for specific regimens and combinations





Created with BioRender.com

The iMATCH Concept

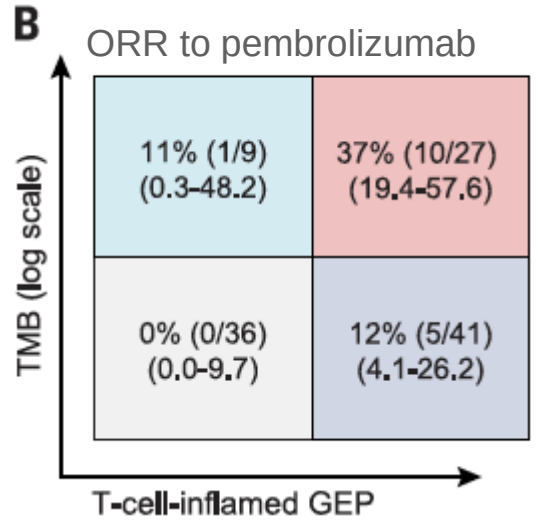
iMATCH aims to enhance clinical evaluation of novel IO agents or combinations by providing a central assay platform for both prospective and retrospective molecular characterizations

- **The integral markers will characterize "molecular subgroups"**
  - Tumor mutation burden (TMB) and potentially actionable variants
  - Tumor inflammation Score (TIS) .. An 18-gene expression signature
  - Potential to incorporate new markers and adapt to interim biomarker findings
- **Comprehensive retrospective analysis will be performed for further marker optimization and discovery.**
- **Independent treatment protocols will be developed, with a focus on signal seeking trials for IO combinations**
- iMATCH will be a cross-NCTN effort. SWOG will lead the central protocol, and all NCTN groups can develop subprotocols using the "central assay" protocol

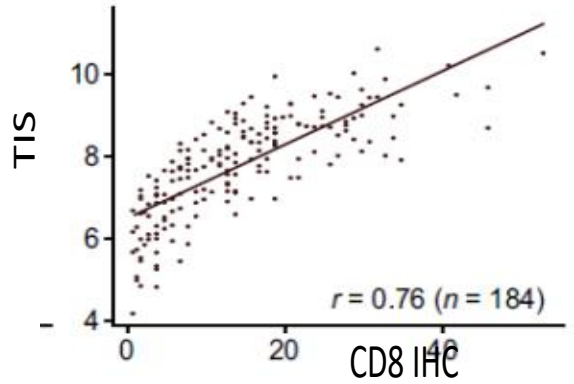
Selection of integral markers and Cutoffs

Tumor Inflammation Signature (TIS), a NanoString 18-gene signature**,** was selected as integral markers for Tumor Inflammation

- TIS assay is quantitative, robust and more likely histology-agnostic (compared with CD8, PD-L1 IHC)
- TIS cutoffs were tested for correlation with response to anti-PD-1 monotherapy (… reflect presence of presence of adaptive immunity)
- TIS scores correlated closely with CD8 IHC and an RNA-based CD8 signature (>180 patients with various tumor types)



TIS vs. CD8 IHC



Cristescu et al, Science 2018
Szabo et al, J Mol Diagnostic, 2022

iMATCH Concept - Schema

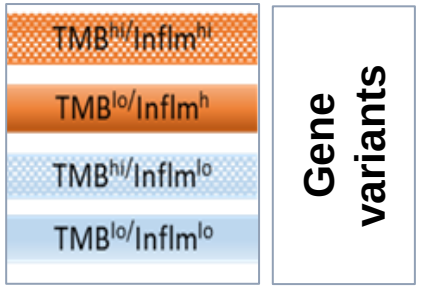
Recent biopsy or new biopsy

iMATCH Central Testing Platform
(Upfront **WES** AND **IO 360)**

Retrospective studies
- Integrated:
  - Deeper WES and IO360 analysis
  - RNASeq, PD-L1, CD8 IHC
  - ctDNA;
- Exploratory: mIF and others

Integral markers
- TMB
- TIS
- Specific variants

Therapeutic protocols
(using integral biomarkers to define subgroups for enrichment or stratification)

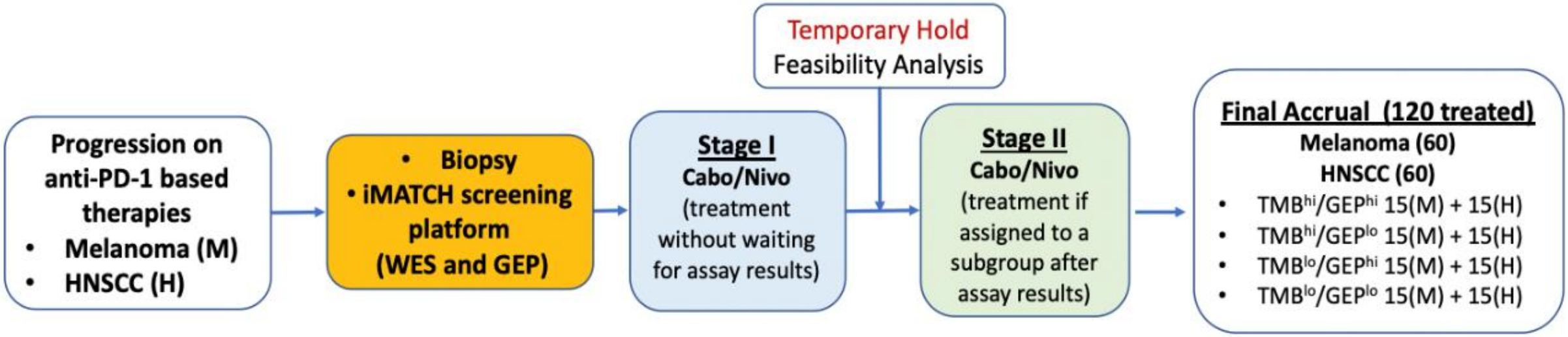


- Unlike other PMI trials, iMATCH integral markers are biology-, not target-based.
- Cutoffs will be pre-defined based on best available data, but may be adjusted in different stages or follow up trials
- A given regimen may be tested in all subgroups, but each will have a pre-defined sample size

iMATCH Pilot Trial:

SWOG 2101: BiCaZO – (Biomarker Stratified CaboZantinib and NivOlumab in pts with CPI-refractory melanoma or HNSCC)

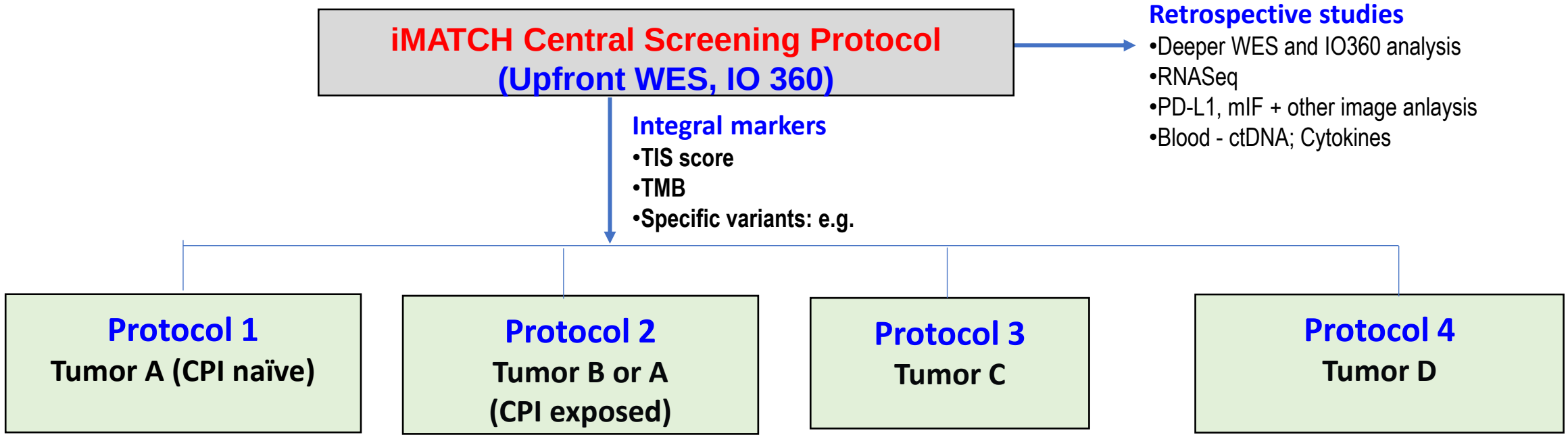
PIs: Siwen Hu-Lieskovan; Katie Politi; Paul Sweicki;



- **Primary Goals -**
  - Feasibility – Turnaround time for both TMB and TIS within 21 days
  - Preliminary efficacy assessment by subgroups
- **Interim analysis** will be performed after Stage I (60 patients), for assay turnaround time and subgroup distribution
- **The pre-defined TMB and TIS cutoffs** may be adjusted in Stage II

Status: 30 patients tested and treated

Potential therapeutic trials



- Each protocol will be standalone using the same central screening platform
- Each protocol will be in a specified clinical setting (single or limited histology, CPI-naïve or exposed)
- Each protocol will use integral markers (TMB, TIS +/- gene alternations) to define "Molecular" cohorts"
- Depending on the clinical setting and treatment regimen, integral markers could be used upfront or in second stage of a trial

IMATCH Summary….

iMATCH is developed to enhance signal seeking trials for IO combinations, by providing a central assay platform for both prospective and retrospective molecular characterizations

- Ensure adequate representation of potentially relevant biology
- Ensure adequate sample size with biomarkers for meaningful retrospective analysis

A robust and reliable biomarker infrastructure is essential to realizing the vision

- Need complex assay platforms and analytic pipelines
- Rapid turnaround to enable upfront patient enrichment and inform interim analysis and adaptive designs
- Flexibility and capacity to add or develop new markers

FNL is a unique resource with the experience and expertise necessary for developing complex PMI platforms like iMATCH

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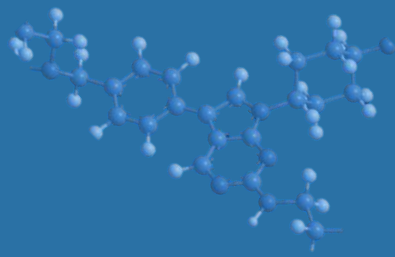
ComboMATCH

Lyndsay Harris, M.D.

Jeffrey Moscow M.D.

Funda Meric-Bernstam M.D.

James Ford M.D.



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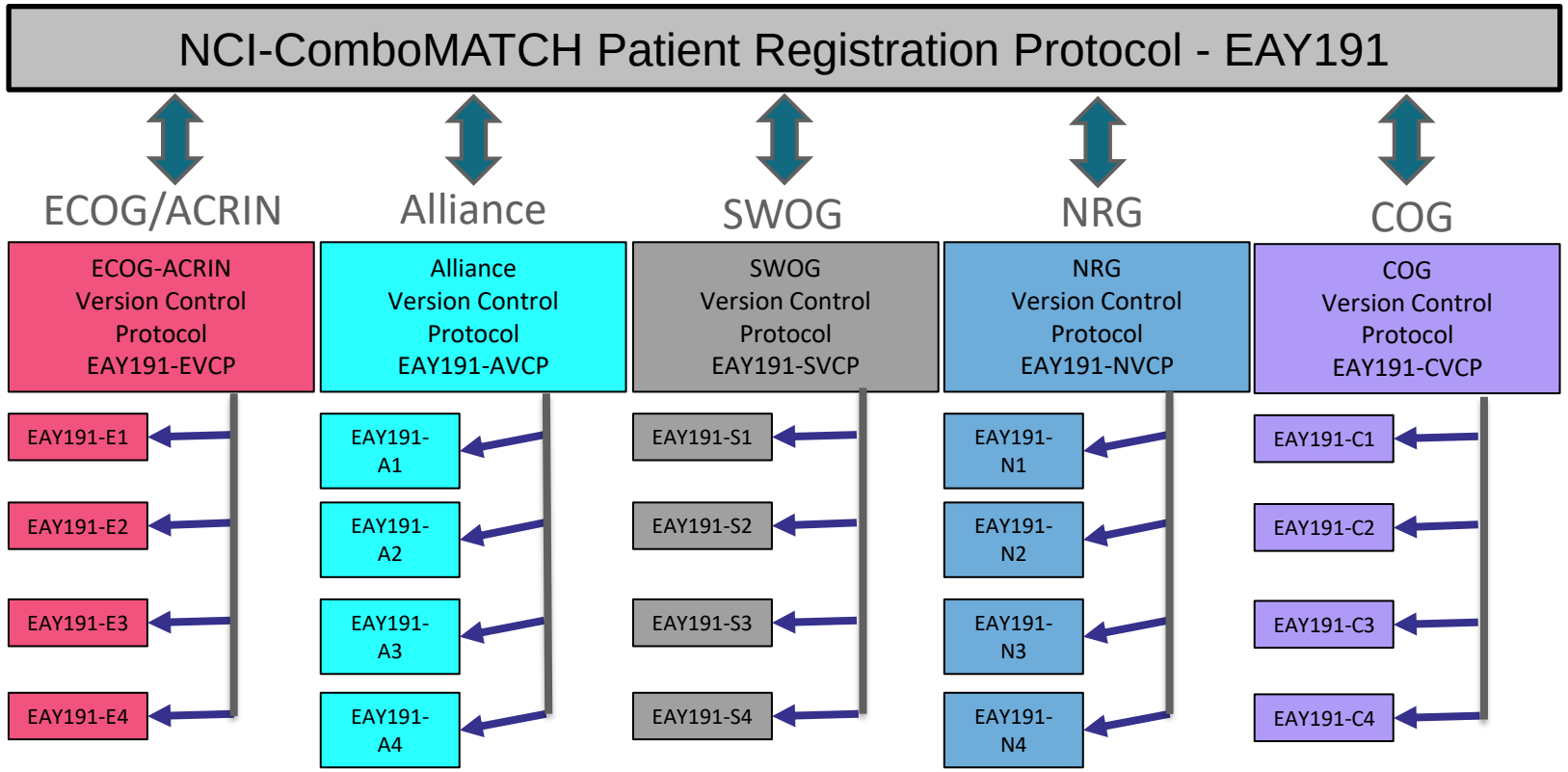
FNLAC Meeting

October 19, 2023

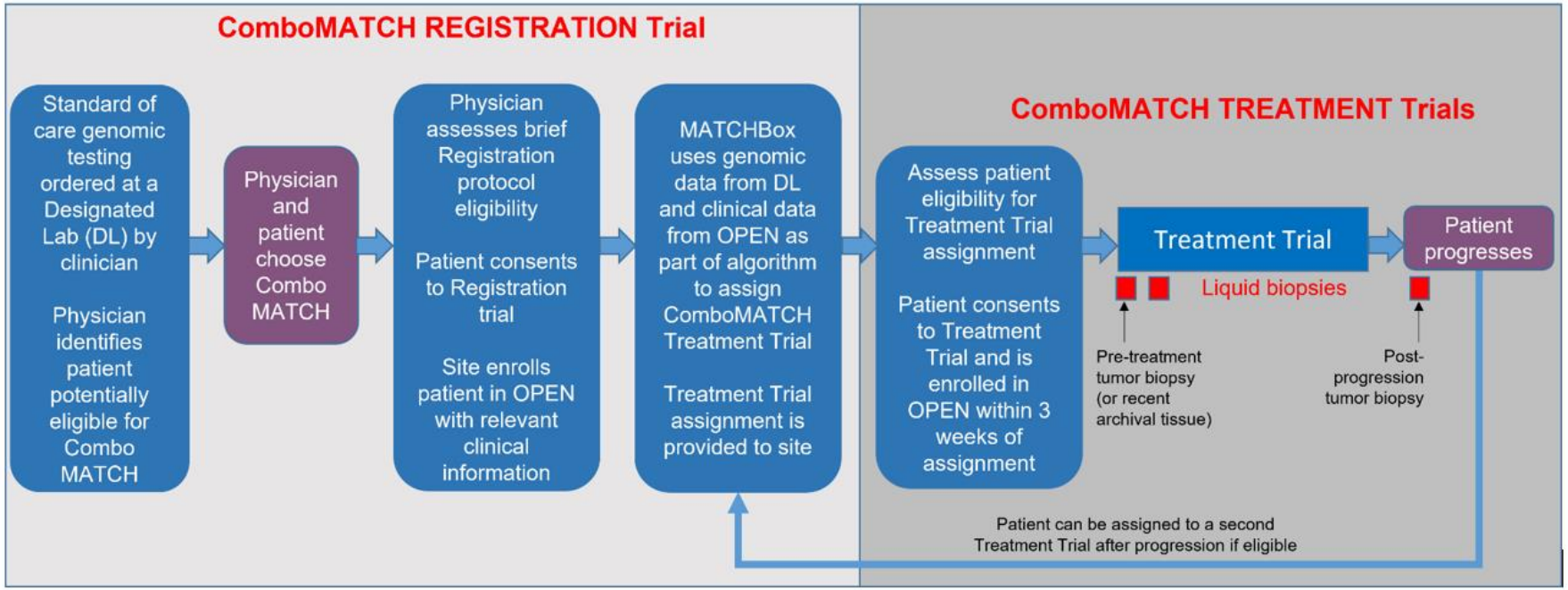
ComboMATCH

- **Premise:** Drug combinations are more likely to provide clinical benefit than single agents in most situations, so the successor trial to NCI-MATCH focuses on therapeutic combinations
- **Hypothesis:** Pre-clinical data from *in vivo* models of combinations demonstrating drug synergy and prolonged tumor regressions can predict clinical benefit in defined patient groups
- **ComboMATCH** will use both single arm studies and Phase II randomized trials in both histology-agnostic and -specific patient cohorts
- **Umbrella** screening study led by ECOG-ACRIN
- **Extramural co-leads**: Funda Meric-Bernstam, Jim Ford; **NCI co-leads**: Lyndsay Harris, Jeff Moscow
- **Requires**: Initial ComboMATCHbox algorithms for interpreting commercial NGS testing for eligibility **(Designated Lab Network)**; subsequent ctDNA assessments before, during and after treatment **(MDNet)**

ComboMATCH Protocol Organization

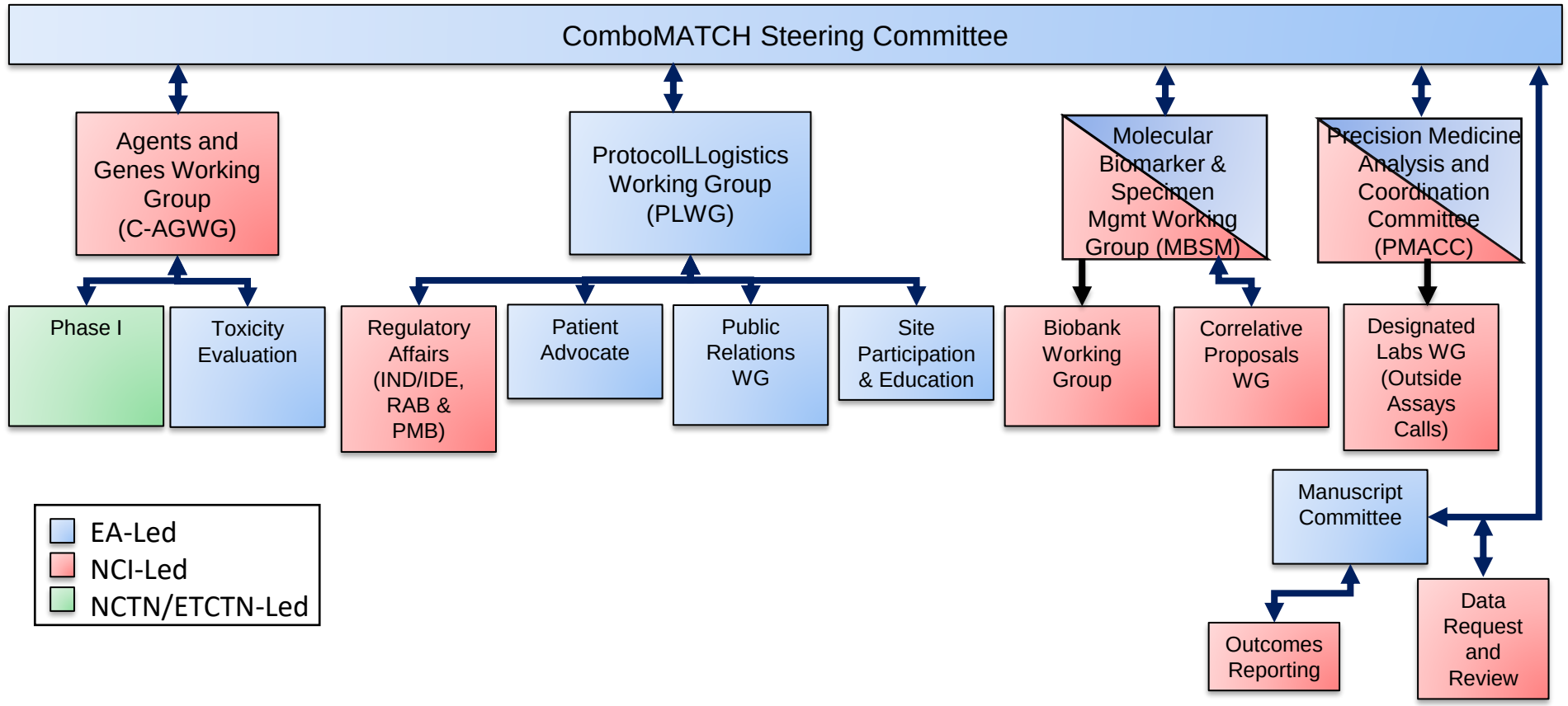


ComboMATCH Steps for Patients

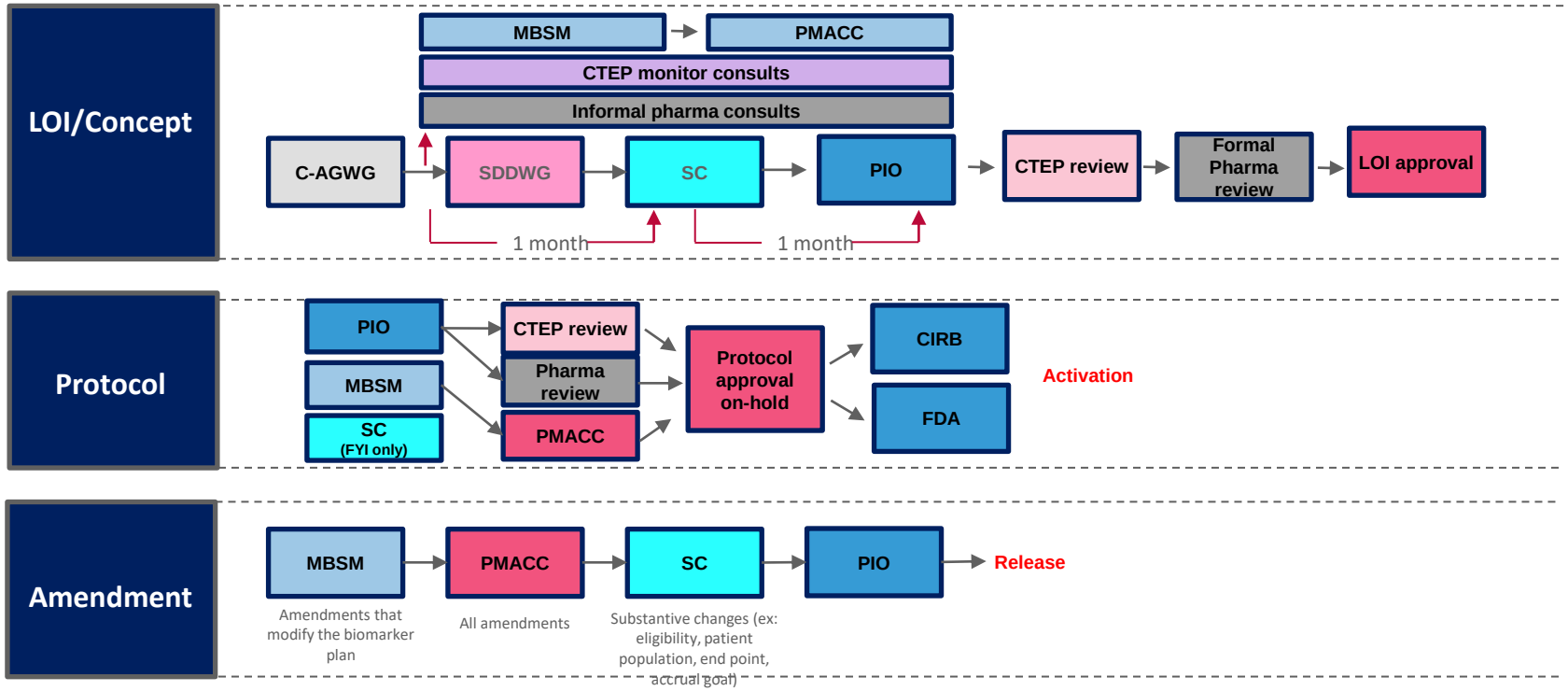


Meric-Bernstam, *CCR*, 2023

ComboMATCH Committee Structure



ComboMATCH Protocol Review



C-AGWG: ComboMATCH Agents and Genes Working Group
SDDWG: Sub-Protocol Design Development Working Group (SDDWG)
SC: Steering Committee
MBSM: Molecular Biomarker and Specimen Management Committee
PMACC: Precision Medicine Analysis and Coordination Committee

Designated Laboratory Network

- Screening for ComboMATCH
- Vetted network of academic and commercial CLIA labs performing NGS as part of standard of care
- Whole exome and targeted panel DNA sequencing will detect snvs, indels, CNVs and fusions
- Variants that match listed on CLIA report
- Physician can directly refer based on CLIA report

Designated Commercial Labs

- BostonGene
- Caris Life Sciences
- CellNetix
- Exact Sciences
- Foundation Medicine
- Genomic Testing Cooperative
- GenPath Diagnostics
- Intermountain Precision Genomics
- Neogenomics Labs
- Quest Diagnostics
- siParadigm Diagnostic Informatics
- Strata Oncology
- Tempus
- The Jackson Laboratory

Designated Academic Labs

- Cedars-Sinai
- Children’s Hospital of Philadelphia
- City of Hope
- Columbia
- Johns Hopkins
- Knight/Oregon HSU
- Memorial Sloan-Kettering
- Molecular Characterization Lab at Frederick National Lab
- NCI
- Providence
- Stanford
- Texas Children’s Hospital
- UT MD Anderson Cancer Center
- U California San Francisco
- U Chicago
- U Colorado
- U Illinois Chicago
- U Michigan
- U Washington
- Weill Cornell

MD Net

- Whole exome sequencing*
- RNA Sequencing*
- IHC assays
- TSO500 ctDNA Assay (Illumina)*
- Tissue Processing, Biobanking*
- Other assays as needed

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myeloMATCH

Myeloid Malignancies Molecular Analysis for Therapy Choice

NCI National Clinical Trials Network

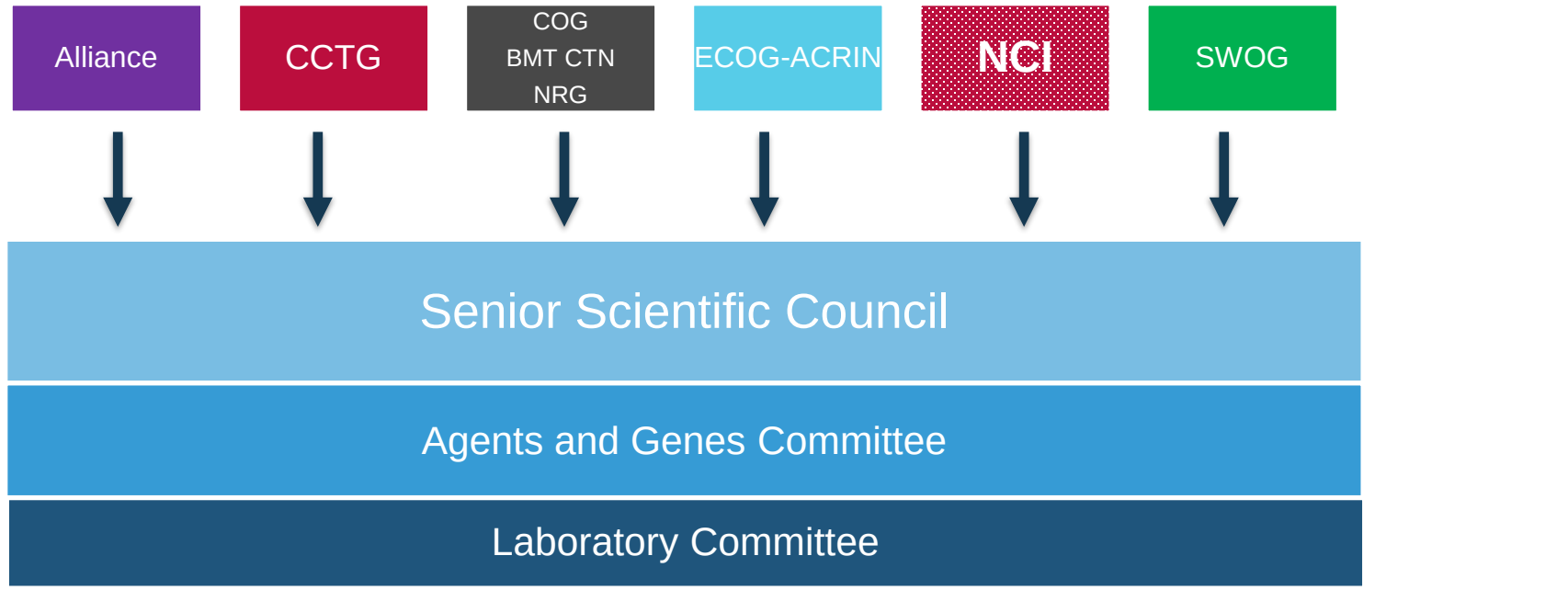
MyeloMATCH AIMS

- To create a portfolio of rationally designed treatment substudies onto which patients sequentially enroll over their entire treatment journey. As increasingly lower remaining tumor burden is achieved, the focus will be to target residual disease more effectively.

- Create an efficient operational model attractive to industry partners and NCTN sites to accelerate therapeutic advances for myeloid malignancies.
  - One IND
  - One IDE

- Develop the careers of young investigators by promoting leadership throughout the clinical trial portfolio and laboratory program.

Administrative components of myeloMATCH



Five Clinical Basket Working Groups

Older AML

Younger AML

MDS

Transplant Cell-based therapy

NGS Directed Rx

Assays for Treatment Assignment in myeloMATCH

Patient

Basket Assignments in Each Tier

Master Screening and Reassessment Protocol

Initial treatments for newly diagnosed patients

Tier 1 Treatment Trials

Older Adult MDS Young Adult

MSRP Reassessment 1

or

Trials designed to evaluate patients in CR using MRD-based assignments

Tier 2 Treatment Trials (MRD)

Older Adult MDS Young Adult

MSRP Reassessment 2

or

Trials designed to evaluate patients using MRD-based assignments

Tier 3 Treatment Trials (Transplant/Cellular Therapy)

Transplant/ Cellular Therapy

MSRP Reassessment 3

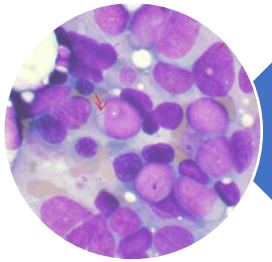
Participants with low disease burden states: trials designed to validate clinical utility of NGS and other assays

Tier 4 Treatment Trials (NGS)

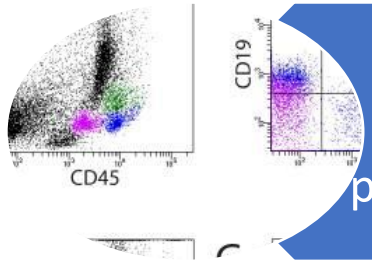
Clinical Utility Assay Validation studies

High Disease Burden

Low Disease Burden



Genexus, Cytogenetics, FISH for targeted treatments or risk based assignments



Flow MRD for response and next protocol assignment

Error Corrected Duplex Sequencing to target surviving clones

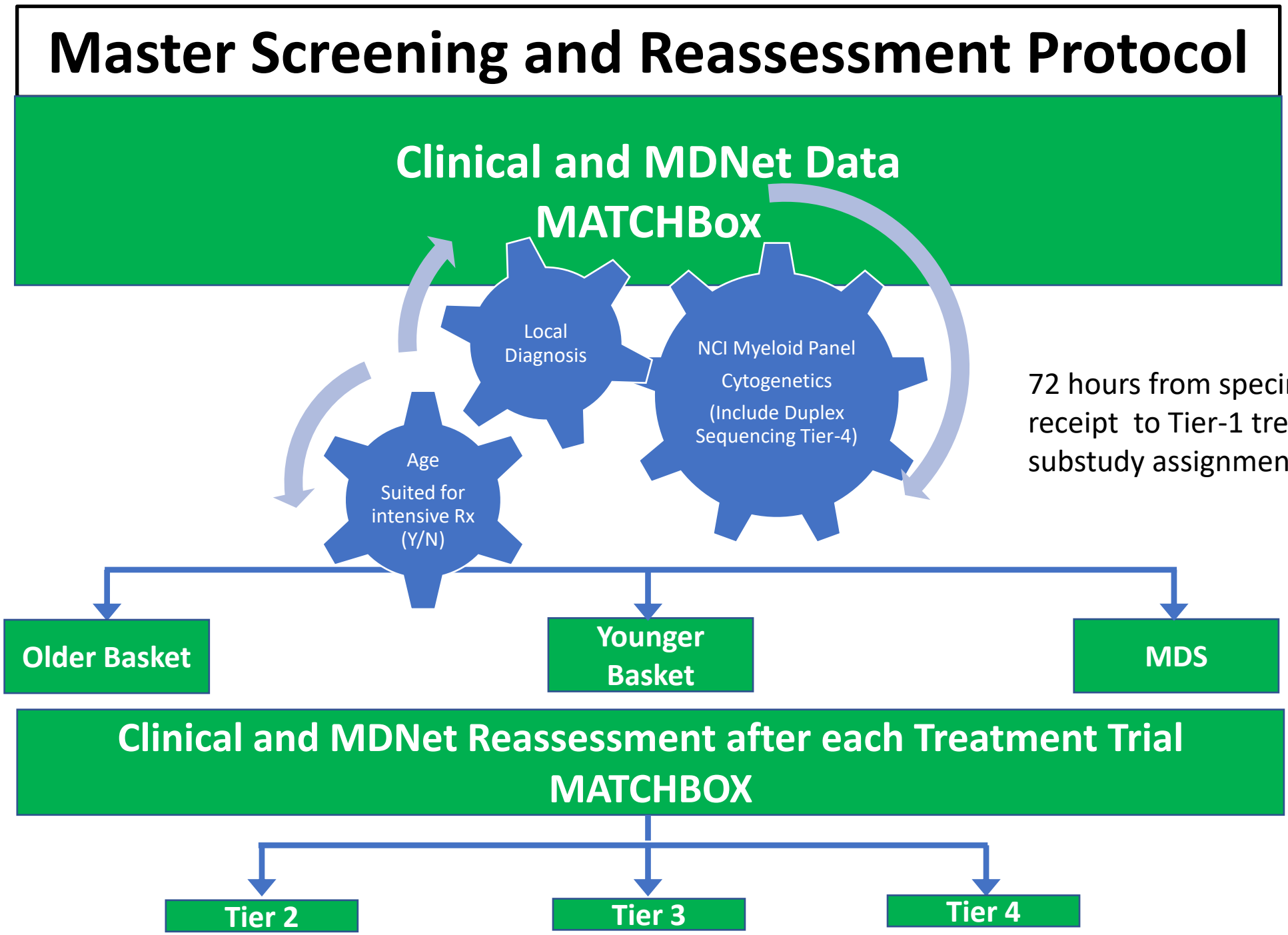
Molecular Diagnostics Laboratory Network (MDNet)
Integral Assays Under NCI IDE

72 Hours for Initial Patient Assignment and
10 Days for Subsequent Assignment

- NCI Myeloid Assay version 2
- Cytogenetics and FISH
- Flow Cytometric Analysis
- Duplex Sequencing to be added to IDE for tier 4 assignments

Integrated assays not subject to IDE include Whole Exome Sequencing, RNA Sequencing

Master Screening and Reassessment Protocol



NCI Myeloid Assay Gene List
Genexus platform with less than 72 hour turnaround for patient assignment

Hotspot

ABL1
BRAF
CBL
CSF3R
DNMT3A
FLT3
GATA2
HRAS
IDH1
IDH2
JAK2
KIT
KRAS
MPL
MYD88
*NPM1**
NRAS
PTPN11
SETBP1
SF3B1
SRSF2
U2AF1
WT1

Full Gene

ASXL1
BCOR
CALR
*CEBPA**
ETV6
EZH2
IKZF1
NF1
PHF6
PRPF8
RB1
*RUNX1**
SH2B3
STAG2
TET2
TP53
ZRSR2

Fusion

*ABL1**
ALK
BCL2
BRAF
CCND1
CREBBP
EGFR
ETV6
FGFR1
FGFR2
FUS
HMGA2
JAK2
*KMT2A**
(MLL)
*MECOM**
MET
MLLT10
*MLLT3**
MYBL1
*MYH11**
NTRK3
*NUP214**
PDGFRA
PDGFRB
RARA
*RBM15**
*RUNX1**
TCF3
TFE3

Expression

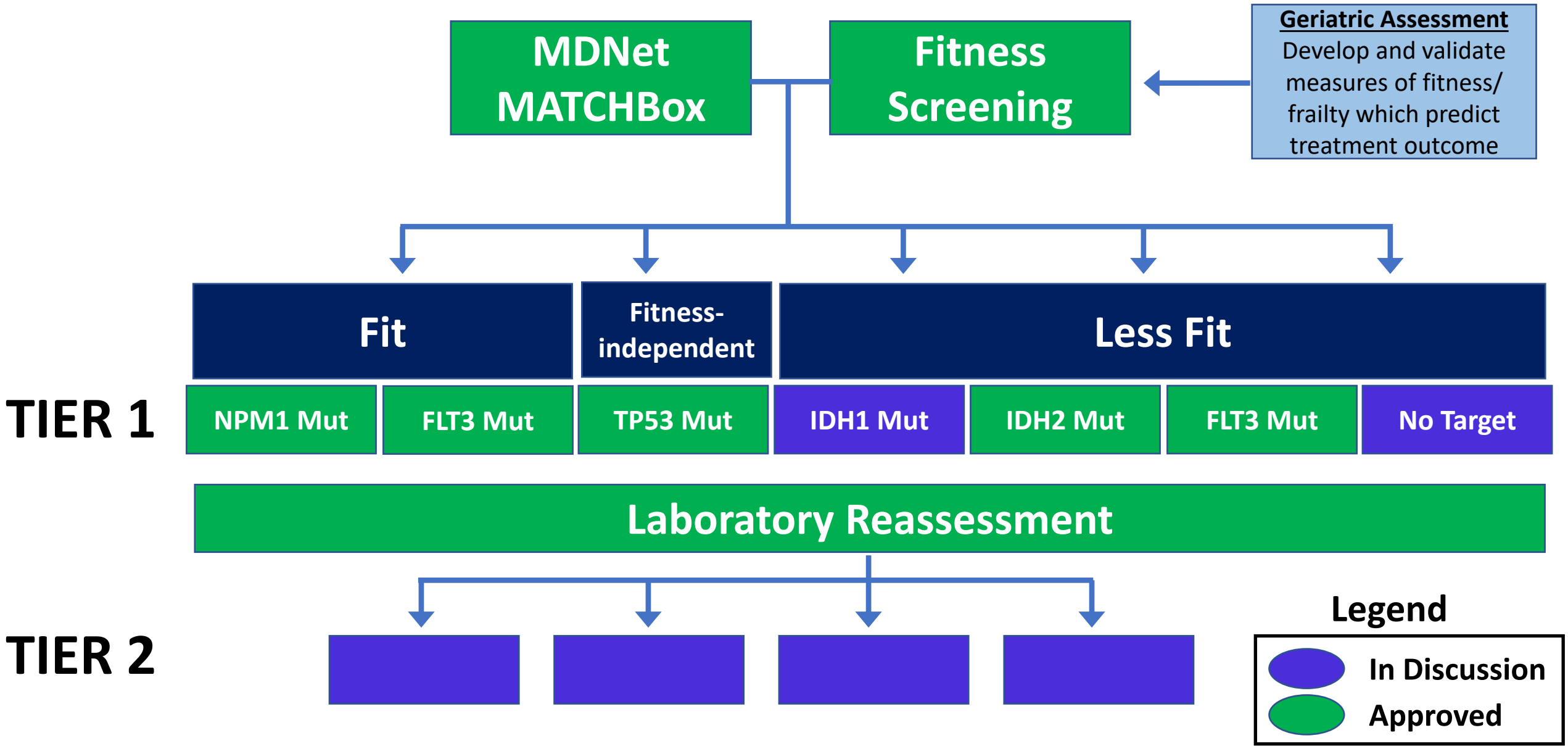
BAALC
MECOM
MYC
SMC1A
WT1

Control

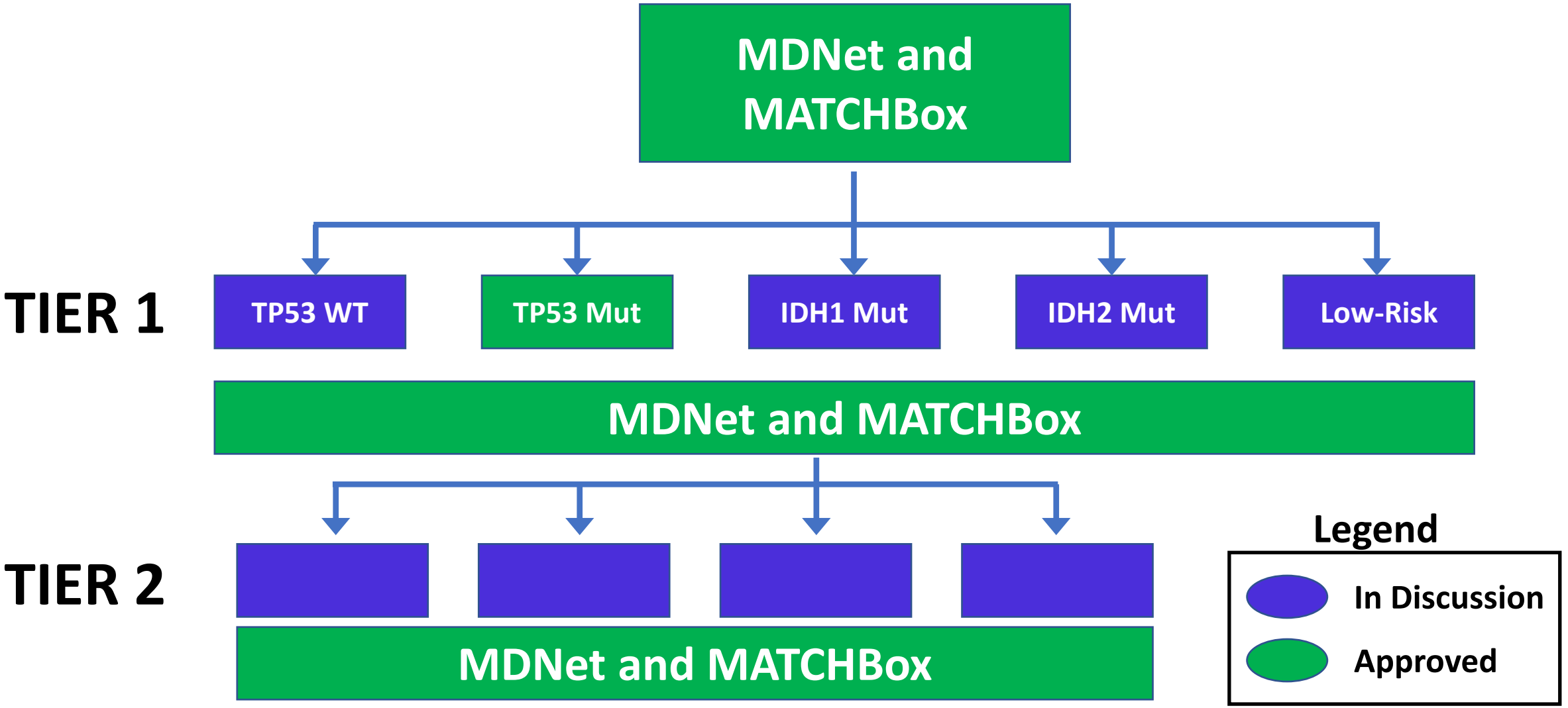
EIF2B1
FBXW2
PSMB2
PUM1
TRIM27

Additional targets can be added to above panel, if needed

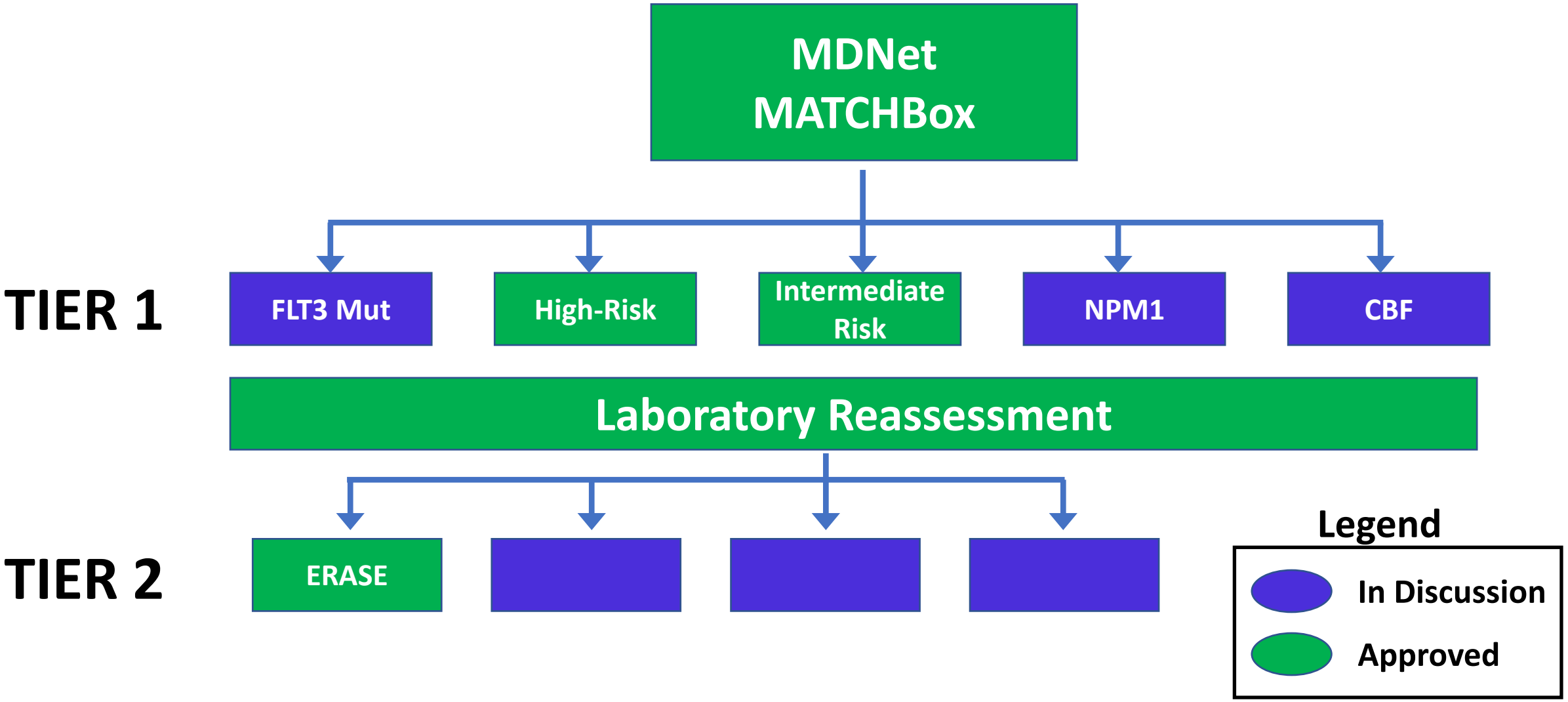
First Generation Studies in the Older Basket



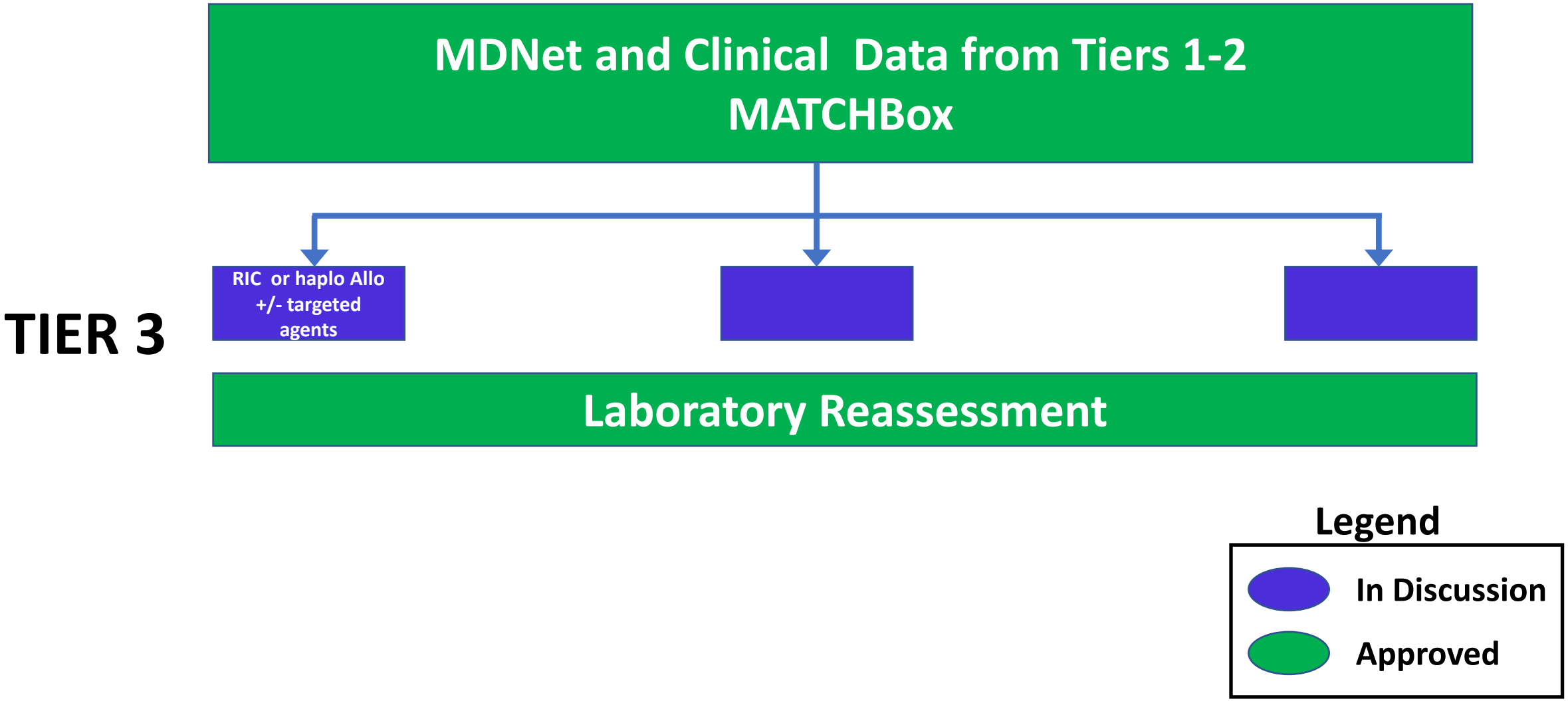
First Generation Studies in the MDS Basket



First Generation Studies in the Younger Basket

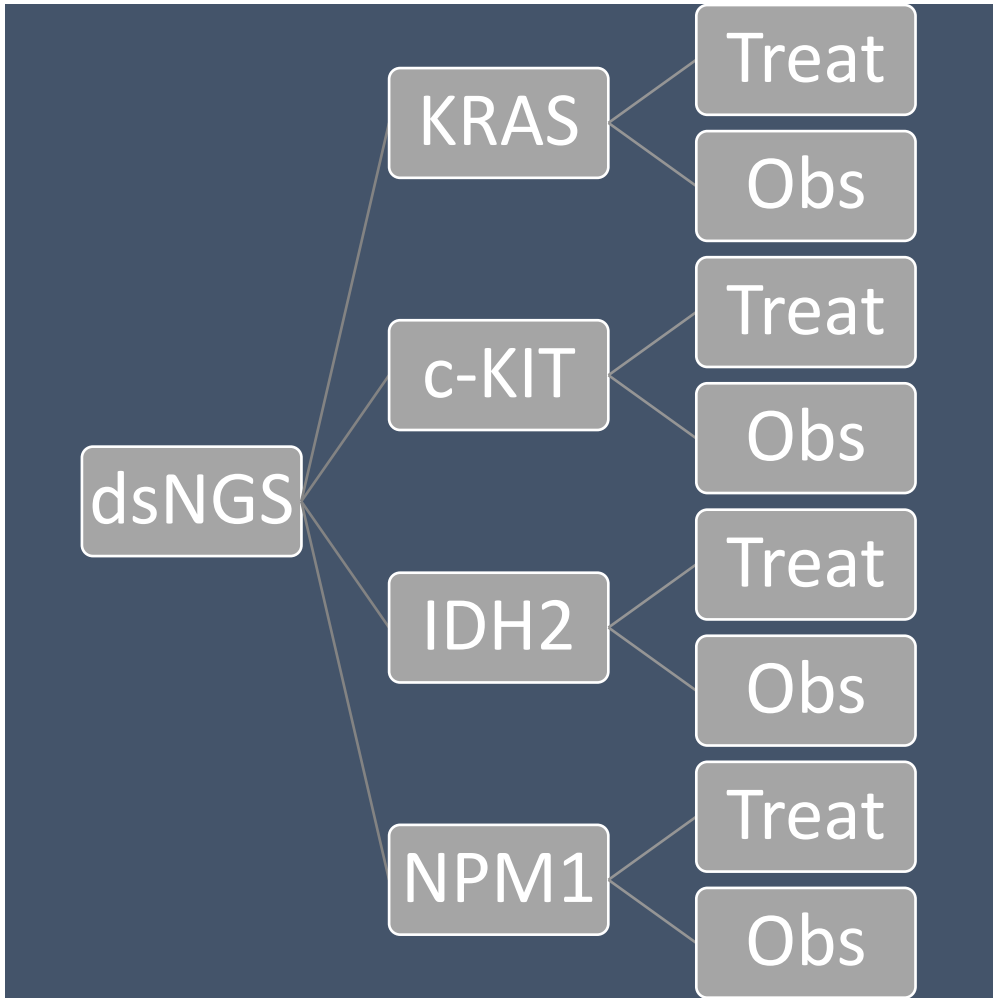


First Generation Studies in the Transplant/Immuno/Cellular Therapy Basket



Clinical Utility Validation for DS NGS Assay—Example Trial Design

Flow undetectable cohort



Primary Readout:

- **NGS: increase or decrease**
- **Flow: increase or remain uMRD**

Secondary objectives

- **EFS, DFS, OS**

Observation arm: treat when Flow +

If in the treatment arm NGS decreases and FLOW remains uMRD,
AND in the observation arm NGS is shown to be reproducible and consistent with the baseline values or increasing compared to baseline
then dsNGS validated as predictive endpoint

MyeloMATCH and Frederick National Lab

- DCTDs largest most complex trial in a single disease area treating patients through sequential treatment substudies from initial diagnosis until progression or death
- Assay data will promote rapid treatment assignment and inform clonal evolution and provide insights into treatment sensitivity and resistance
- May provide insights toward changing AML and MDS treatment paradigm
- Trial would not be feasible without DCTD infrastructure and FNL

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