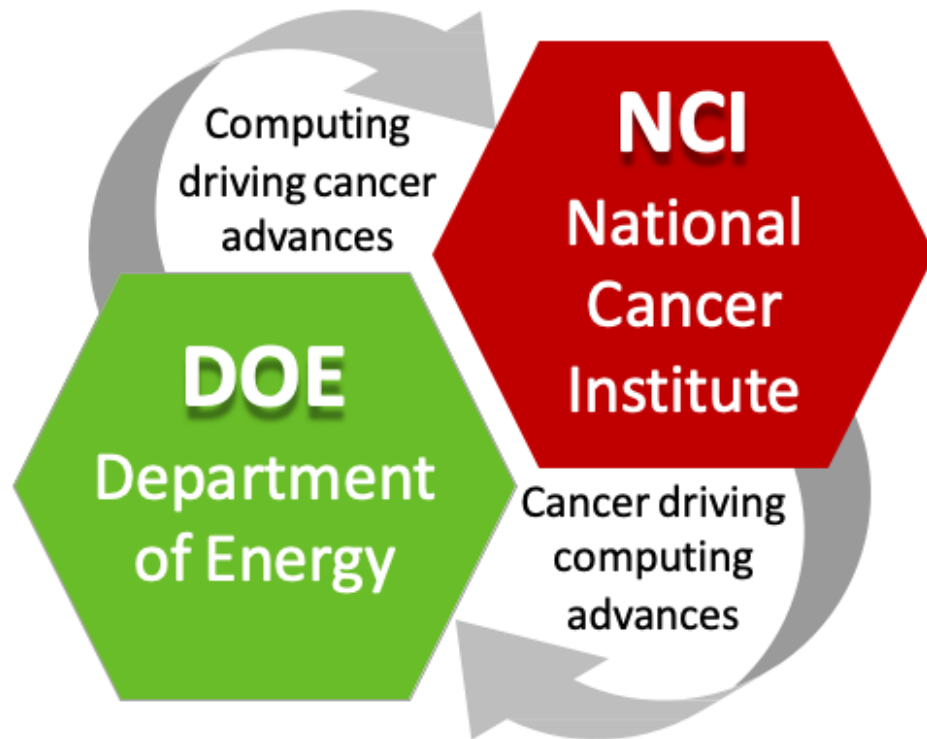


IMPROVE: Innovative Methodologies and New Data for Predictive Oncology Model Evaluation



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Frederick National Laboratory Advisory Committee
March 11, 2024

IMPROVE: Key Challenges & Goal of Partnership

Challenges

Huge Potential: The potential impact of AI on the biomedical community, including in the selection of cancer therapies, cannot be overstated

Underdeveloped: Yet, AI in oncology is still very much a novel and challenging undertaking in need of better *assessment of trustworthiness and reproducibility**

Goal

The Inter-Agency Agreement enables NCI-DOE to jointly ***leverage unique capabilities*** across the biomedical-computer science spectrum

The two Agencies will help establish stronger connections & ***standardized framework across the data science and clinical research communities***

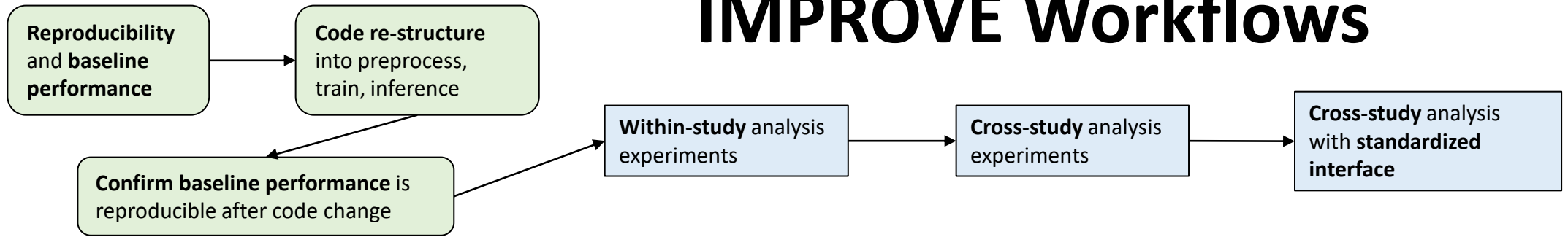
* ~100 papers of TDR models published in the last 4 years all claiming to be “state of the art”

The IMPROVE Project (phased in FY22)

- Two coupled aims targeting improving AI (deep learning) models for predicting tumor drug response
- **Aim 1 – Model Curation & Comparison:** Development of semi-automatic protocols for comparing deep learning models and identifying attributes that contribute to prediction performance
- **Aim 2 – Training & Testing:** Development of protocols for specifying drug screening experiments and to generate data explicitly aimed at improving model performance

IMPROVE Workflows

Model Curation



Data Curation

Original paper's data used to conduct experiments (features, responses, evaluation method)

IMPROVE benchmark data

- Features: pre-computed multiomics and drug features
- Response: single file combining responses from all cell line studies
- Splits: consistent train, validation, and test splits

Framework Development

- Conceptualize standardized interface (preprocess, train, infer)
- Core python modules
- HPO workflow (original paper's data)

- Data loaders
- Parameter parsing modules (CANDLE)
- Refine core modules
- Runtime stats (preprocess, train, infer)
- Identifying edge cases (long preprocess and training) – prep for HPC runs

- **Standardized interface** implemented
- Cross-study analysis workflow (python)
- Singularity containers
- HPO workflow (benchmark data)

Model Generalization Analysis: Leveraging DOE supercomputers

Three example models from over 60 models under curation

Models that lead within a single study do not lead in out of study generalization

GraphDRP

	CCLE	CTRP	gCSI	GDSC1	GDSC2
CCLE	0.76	0.50	0.06	0.48	0.05
CTRP	-0.64	0.83	-1.11	-0.15	-0.12
gCSI	-0.01	0.25	0.72	0.25	0.27
GDSC1	-0.15	0.16	-0.39	0.75	0.10
GDSC2	-0.25	0.28	-0.44	0.24	0.79

R² score

HiDRA

	CCLE	CTRP	gCSI	GDSC1	GDSC2
CCLE	0.69	0.54	-0.05	0.41	-0.03
CTRP	-0.33	0.82	-0.98	-0.10	-0.01
gCSI	-0.01	0.15	0.62	0.10	0.24
GDSC1	-0.06	0.12	-0.34	0.73	0.09
GDSC2	-0.05	0.24	-0.38	0.14	0.78



DeepTTC

	CCLE	CTRP	gCSI	GDSC1	GDSC2
CCLE	0.73	0.52	0.54	0.61	0.58
CTRP	-0.21	0.78	0.27	0.53	0.54
gCSI	-0.04	0.14	0.68	0.46	0.56
GDSC1	0.05	0.05	0.16	0.71	0.55
GDSC2	0.07	0.26	0.31	0.32	0.76



- **“Similar” models trained on the same data show radically different generalizability**
- Understanding these behaviors is key to making next generation AI algorithms more robust for clinical application
- Runs on Leadership computing resources are underway in preparation to expand testing of models to include PDO and PDX datasets along with clinical information

[Brief Bioinform.](#) 2022 Jan; 23(1): bbab356.

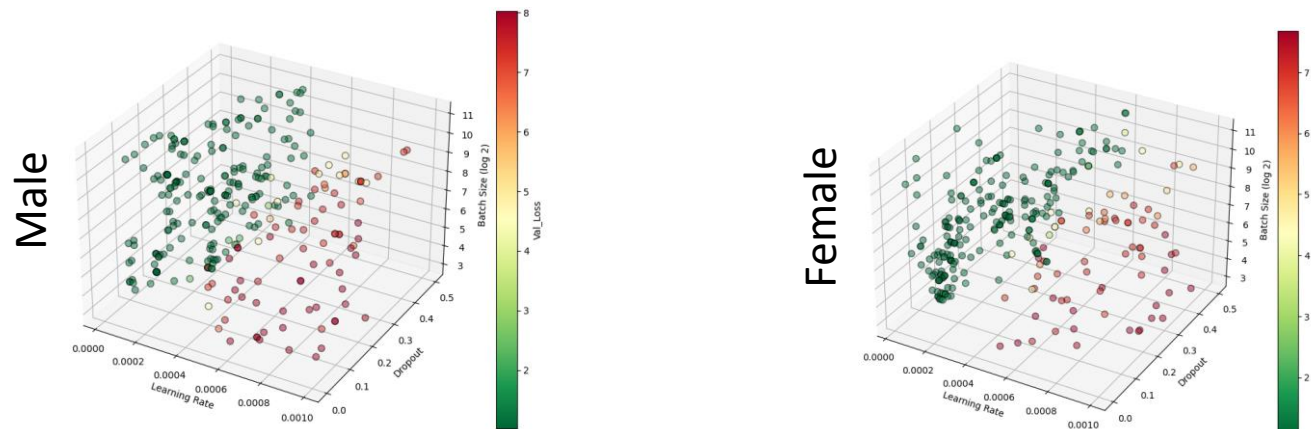
Published online 2021 Sep 14. doi: [10.1093/bib/bbab356](https://doi.org/10.1093/bib/bbab356)

PMCID: PMC8769697

PMID: [34524425](https://pubmed.ncbi.nlm.nih.gov/34524425/)

Hyperparameter Optimization (HPO) Uncovers Unintended Model Bias (gender bias in this example)

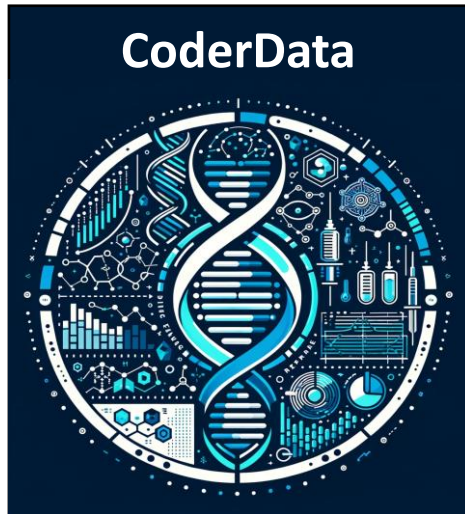
- To study the generality of IMPROVE community models across demographics, we structured a workflow to optimize models based on subsets of the training data
- We built a tool called Cell-GREP to slice the dataset based on metadata in the Cellosaurus encyclopedia, and compare the results of HPO runs on various demographic subsets



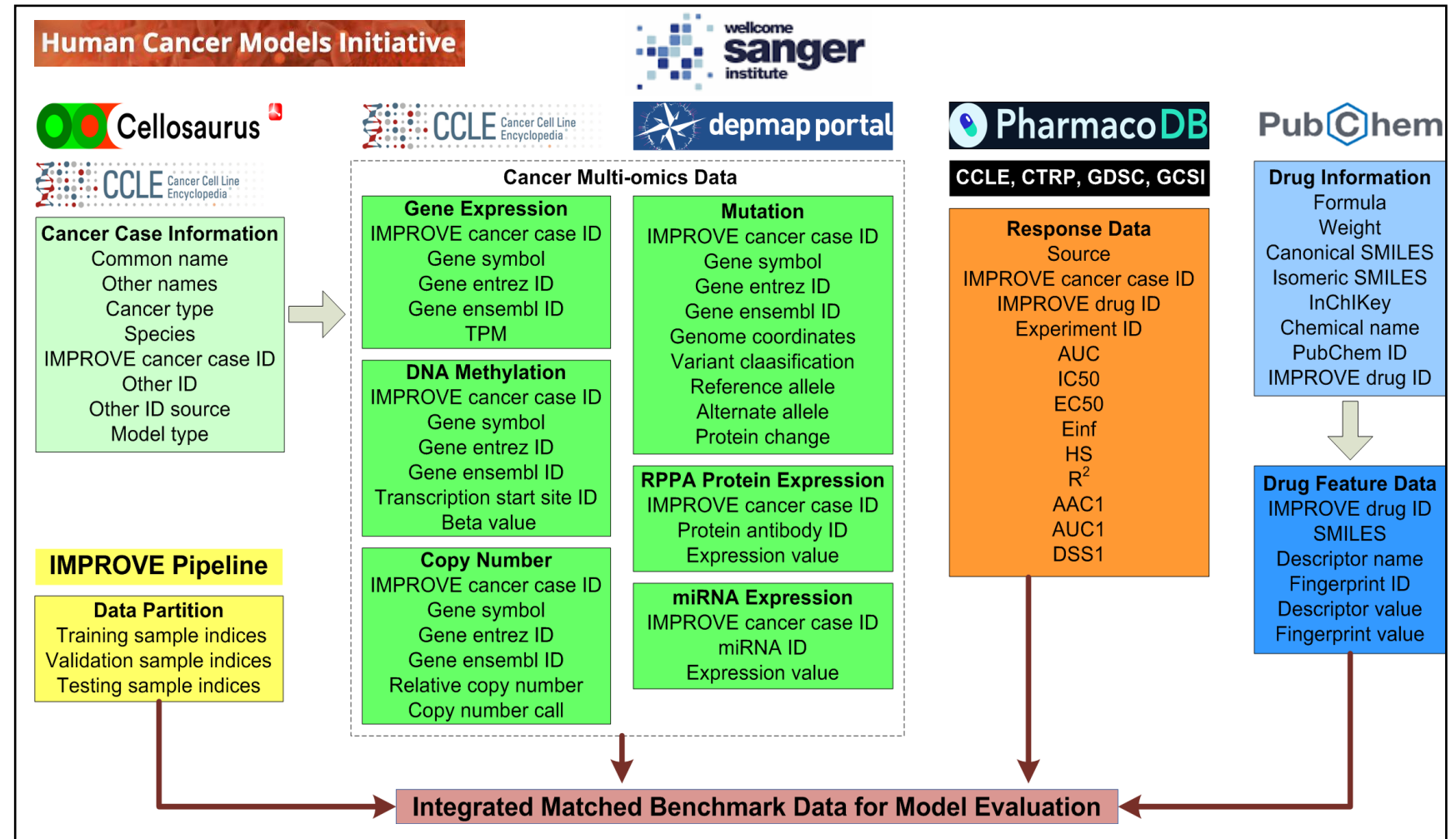
- The optimal parameters found by HPO by gender noticeably differ
- Other studies are underway to understand these effects more broadly

Cell-GREP: <https://github.com/ECP-CANDLE/Scratch/tree/master/cell-grep>
Demographic aware hyperparameter optimization for cancer
Rylie Weaver, PASC Student Research Competition, 2024 (under review).

IMPROVE's CoderData package: AI readiness for complex pan-cancer datasets



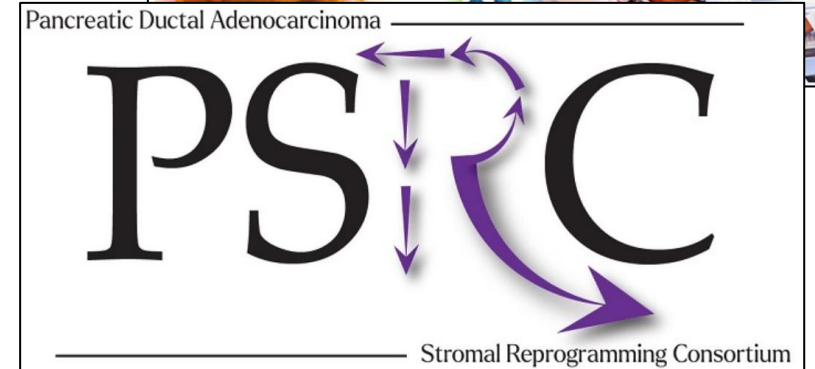
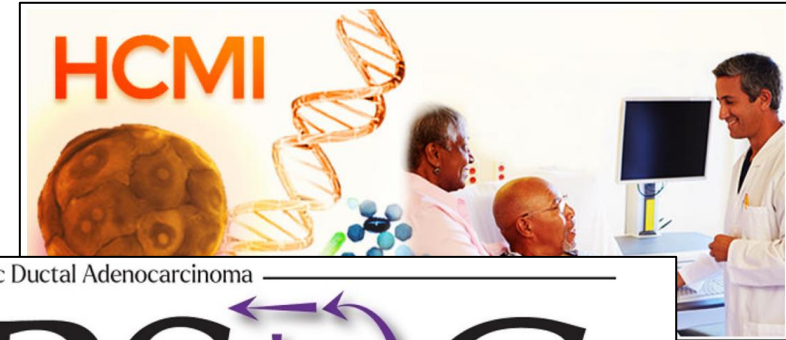
- **Launches** at AACR'24
- **Allows** developers to call IMPROVE's curated collection of AI ready data via standard software interface
- **Reduces** data management burden



IMPROVE's Collaboration with NCI Programs: Amplifies Existing Investments

IMPROVE has significant engagement in the community

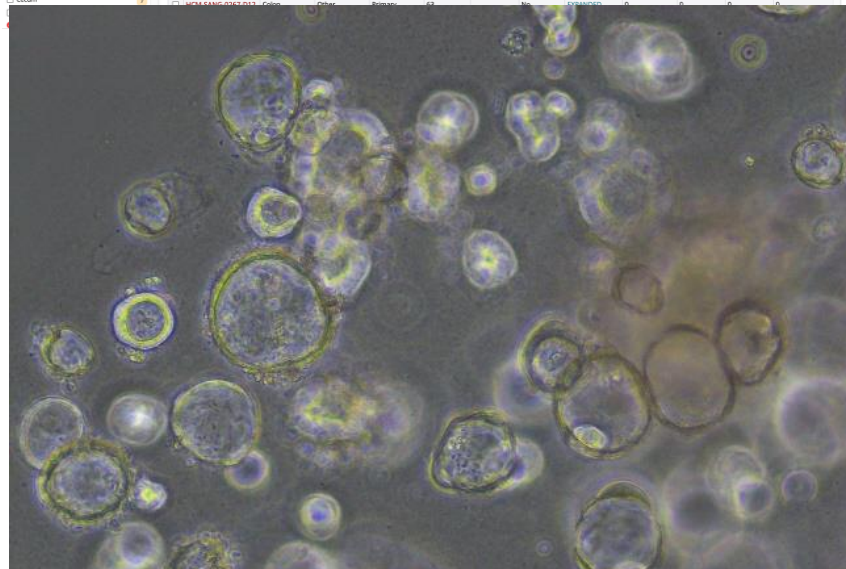
- Human Cancer Models Initiative (**HCMI**) provides multi-omic cancer molecular data, clinical data and matching organoids
 - **Collaborators: Broad/MIT/DFCRC**
- PDAC Stromal Reprogramming Consortium (**PSRC**) has committed to providing access to organoids, data and collaborative experiments
 - **Collaborators: MD Anderson, UCSD, DFCRC**
- Acquired Resistance to Therapy Network (**ARTNet**) ideally suited to help establish clinically-relevant resistance parameters
 - **Collaborators: ULCA, UAB, OHSU, OU-CM**
- Other NCI funded extramural collaborators
 - **Ideker Lab UCSD, Marth Lab UoU/SLC, Chiu Lab UPitt**



Generation of “nearer to patient” Datasets to Improve Models

- Gathering initial datasets for image-based response measures and assess how the models will need to adapt to data generated from PDO
 - The drugs being tested cover most of the MoAs needed for a pancreatic study and a selection of common bystander drugs.
- Concurrently IMPROVE is running studies with labs that have significant data sets for other cancer types to create a link between IMPROVE’s data and community data
 - **UCLA, MD Anderson/DFCRC/UCSD, and UChicago**
- IMPROVE will expand data generation focusing on pancreatic adenocarcinoma, GBM, AML and sarcoma, against an expanded repertoire of drugs
 - *Combination therapies are also being considered*

Name	Primary Site	Clinical Tumor Diagnosis	Tissue Status	Age At Acquisition (Years)	Age At Diagnosis (Years)	Has Multiple Models	Expansion Status	# Mutated Genes	# Research Somatic Variants	# Clinical Variants	# Histopathological Biomarkers
HCM.CSHL.0426.C18	Colon	Colorectal cancer Primary		73	72	No	EXPANDED	2701	3183	0	0
HCM.CSHL.0317.C18	Colon	Colorectal cancer Primary		65	64	No	EXPANDED	1502	1639	0	0
HCM.CSHL.0064.C18	Colon	Colorectal cancer Primary		75	75	No	EXPANDED	343	351	0	5
HCM.CSHL.0245.C18.A	Colon	Colorectal cancer Primary		73	72	Yes	EXPANDED	218	226	0	8
HCM.CSHL.0245.C18.B	Colon	Colorectal cancer Metastasis		76	76	Yes	EXPANDED	209	216	1	5
HCM.CSHL.0245.C18.C	Colon	Colorectal cancer Metastasis		73	73	Yes	EXPANDED	211	215	0	6
HCM.CSHL.0056.C18	Colon	Colorectal cancer Primary		75	75	No	EXPANDED	191	196	0	6
HCM.CSHL.0164.C20	Colon	Colorectal cancer Metastasis		52	51	No	EXPANDED	171	177	0	0
HCM.CSHL.0384.D32	Colon	Other Primary		51	51	No	EXPANDED	173	177	0	1
HCM.CSHL.0141.C18	Colon	Colorectal cancer Primary		67	67	No	EXPANDED	168	172	0	5
HCM.CSHL.0247.C18.A	Colon	Colorectal cancer Primary		76	76	Yes	EXPANDED	160	162	1	5
HCM.CSHL.0063.C18	Colon	Colorectal cancer Primary		75	75	No	EXPANDED	156	160	1	5
HCM.CSHL.0235.C18	Colon	Colorectal cancer Primary		71	71	No	EXPANDED	154	156	0	5
HCM.CSHL.0057.C18	Colon	Colorectal cancer Primary		59	58	No	EXPANDED	151	153	0	0
HCM.CSHL.0065.C20	Colon	Colorectal cancer Metastasis		63	63	No	EXPANDED	139	141	0	5
HCM.CSHL.0061.C18	Colon	Colorectal cancer Primary		61	60	No	EXPANDED	131	136	0	5
HCM.CSHL.0057.C18	Colon	Colorectal cancer Primary		68	68	No	EXPANDED	129	131	0	5
HCM.CSHL.0142.C18	Colon	Colorectal cancer Primary		61	61	No	EXPANDED	116	119	0	5
HCM.CSHL.0461.D12	Colon	Other Pre-malignant		54	54	No	EXPANDED	109	116	0	0
HCM.CSHL.0060.C18	Colon	Colorectal cancer Primary		50	50	No	EXPANDED	102	103	0	5
HCM.WCMC.0004.C18	Colon	Colorectal cancer Recurrent		58	58	No	EXPANDED	0	0	0	6



IMPROVE is an Open Community

UCSD Jamboree Dec'23

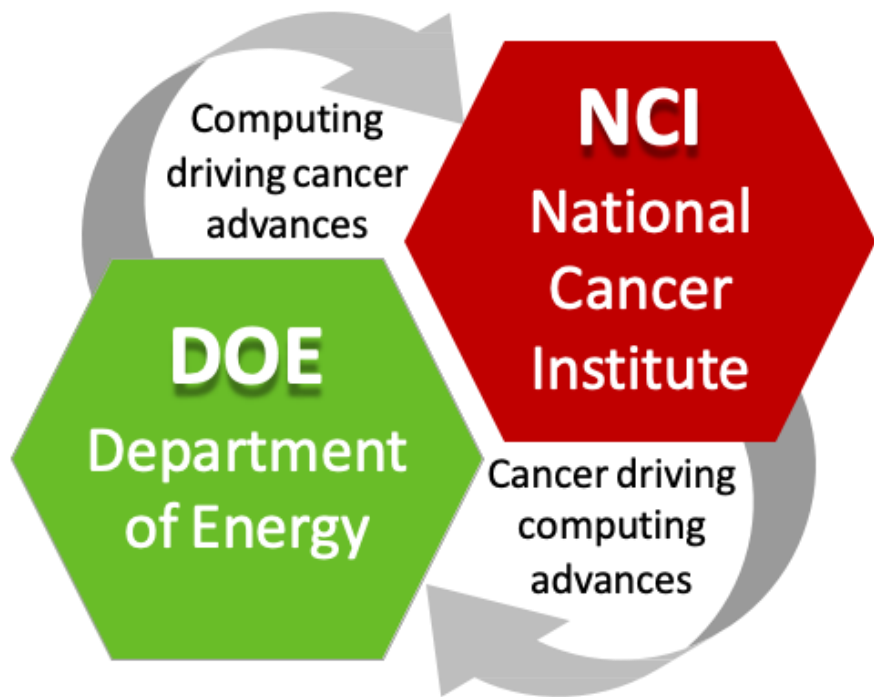
- Collaborative Core Modeling Groups (CCMG)
 - Mayo Clinic (Chen Wang)
 - Texas Tech University (Ranadip Pal)
 - Pacific Northwest National Laboratory (Sara Gosline)
- Events have been held at: ANL, U of Utah Salt Lake, UCSD and U Pitt (virtual)
- The next Hackathon is in Boston May 2024
 - Theme is data readiness for AI
 - Focused discussions on: Data collection, curation, and benchmark dataset preparation



CCMG Kickoff Jan'23

The IMPROVE Framework: All Resources Available to the Public

- **A GitHub project** (<https://github.com/JDACS4C-IMPROVE>), including repositories:
 - Drug response prediction models
 - Model evaluation workflows and APIs
 - Other relevant resources, e.g. data preprocessing scripts and documentation
 - Tutorial for making models compliant with the IMPROVE framework
 - Introduction and guidelines for curating models
- **Data & curated models** used by IMPROVE framework in MODAC (<https://modac.cancer.gov/>)
- **Project website:** (<https://datascience.cancer.gov/collaborations/nci-department-energy-collaborations/improve>)



Discussion