National Cancer Institute
Patient Derived Models Repository (PDMR)
An NCI Precision Oncology Initiative℠ Resource

Presentation to the FNLAC: June 27, 2019

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National Cancer Institute, NIH

https://pdmr.cancer.gov

Ad Hoc Working Group on Cancer Models and Therapeutics Development: First Teleconference 6/17/2019

FNLAC Members

- Nilsa C. Ramirez-Milan, M.D., FCAP, Ohio State University College of Medicine
- Kevin Cullen, M.D., Univ. of Maryland
- Lisa Coussens, Ph.D., Oregon Health Sciences University

Extramural Members

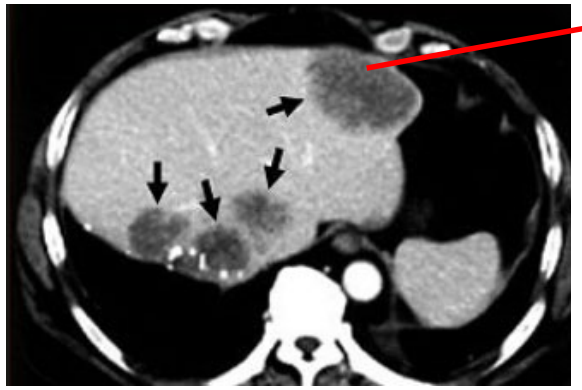
- Meenhard Herlyn, D.V.M., D.Sc., Wistar Institute
- Michael Lewis, Ph.D., Baylor College of Medicine
- Peter Houghton, Ph.D., Univ. of Texas San Antonio

Overview

- Overview of Model Development Efforts for the PDMR
- Issues/Challenges Reviewed with the WG
- PDMR Activities for Further Discussion with the WG

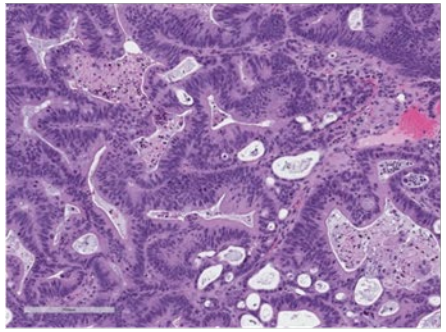
NCI's Patient-Derived Models Repository

- A national repository of Patient-Derived Models (PDMs) to serve as a resource for academic discovery efforts and public-private partnerships for drug discovery
- Clinically-annotated & early-passage models with comprehensive molecular-characterization and quality control metrics
- Complements existing PDM collections and focuses on under-represented model types such as rare cancers and models representing racial and ethnic minorities
- Provides models to the research community at modest cost compared to other distributors
- Provides all related metadata including: de-identified patient clinical history and outcomes, model histology, WES and RNASeq of models, and SOPs through a public website: https://pdmr.cancer.gov

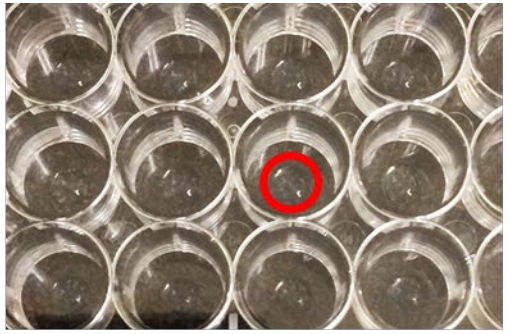


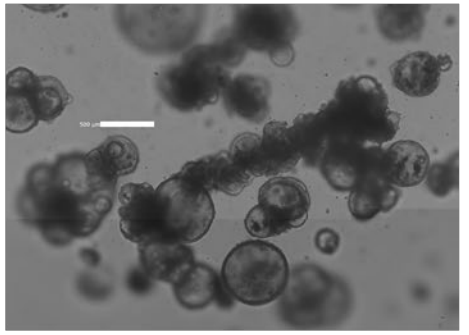
Tumor biopsies or surgical samples shipped overnight from clinical sites to FNLCR:
Multiple patient-derived model types initiated when sufficient material available

PDX

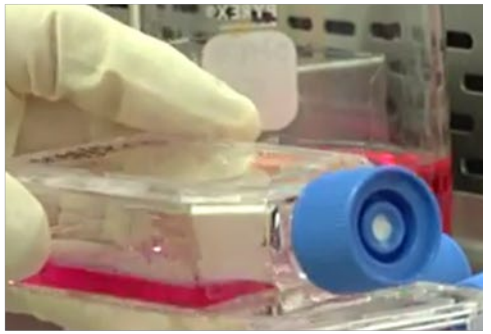


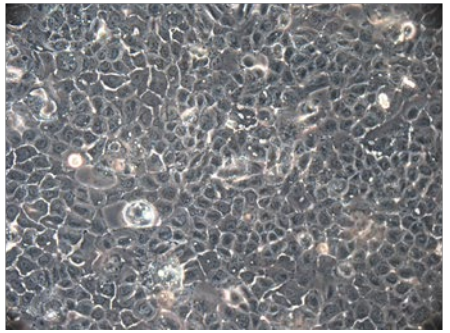
PDOrg Culture





PDC/CAF Culture





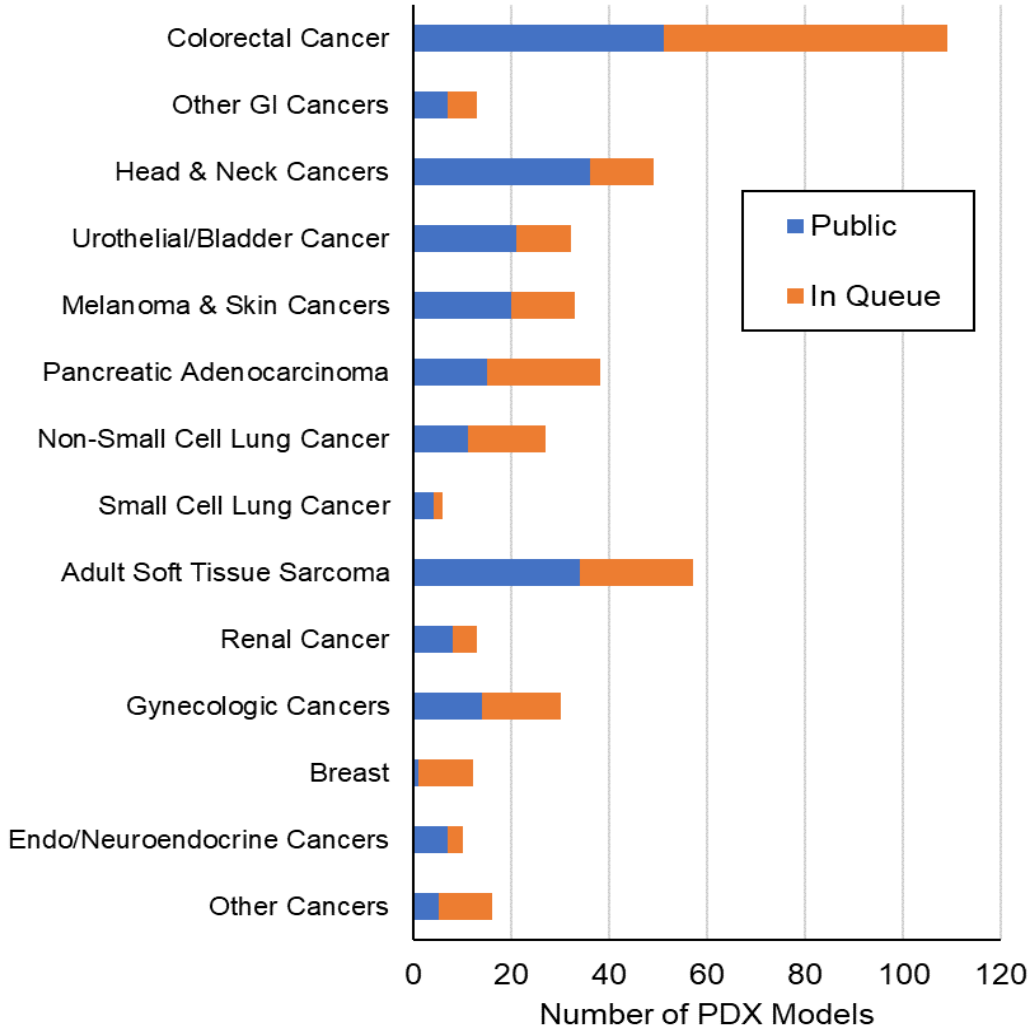
PDMR NCI Patient-Derived Models Repository
An NCI Precision Oncology Initiative℠ Resource

Multi-laboratory Effort to Develop & Characterize Models

- DCTD (NCI, NIH), James H. Doroshow, MD – leadership, scientific/technical oversight
- PDMR (FNLCR), Yvonne A. Evrard, PhD – scientific/technical oversight, contract management, clinical interface
- Biological Testing Branch (DCTD, NCI, NIH), Melinda Hollingshead, DVM, PhD – scientific/technical oversight, in vivo (PDX development) efforts, in vitro efforts, preclinical efficacy studies
- In Vitro Evaluation Group (FNLCR), Dianne Newton, PhD – cell line and organoid development
- Molecular Characterization Laboratory (FNLCR), P. Mickey Williams, PhD – NextGen Sequencing, bioinformatics

Model Development and Characterization

Patient-Derived Xenografts (PDXs)



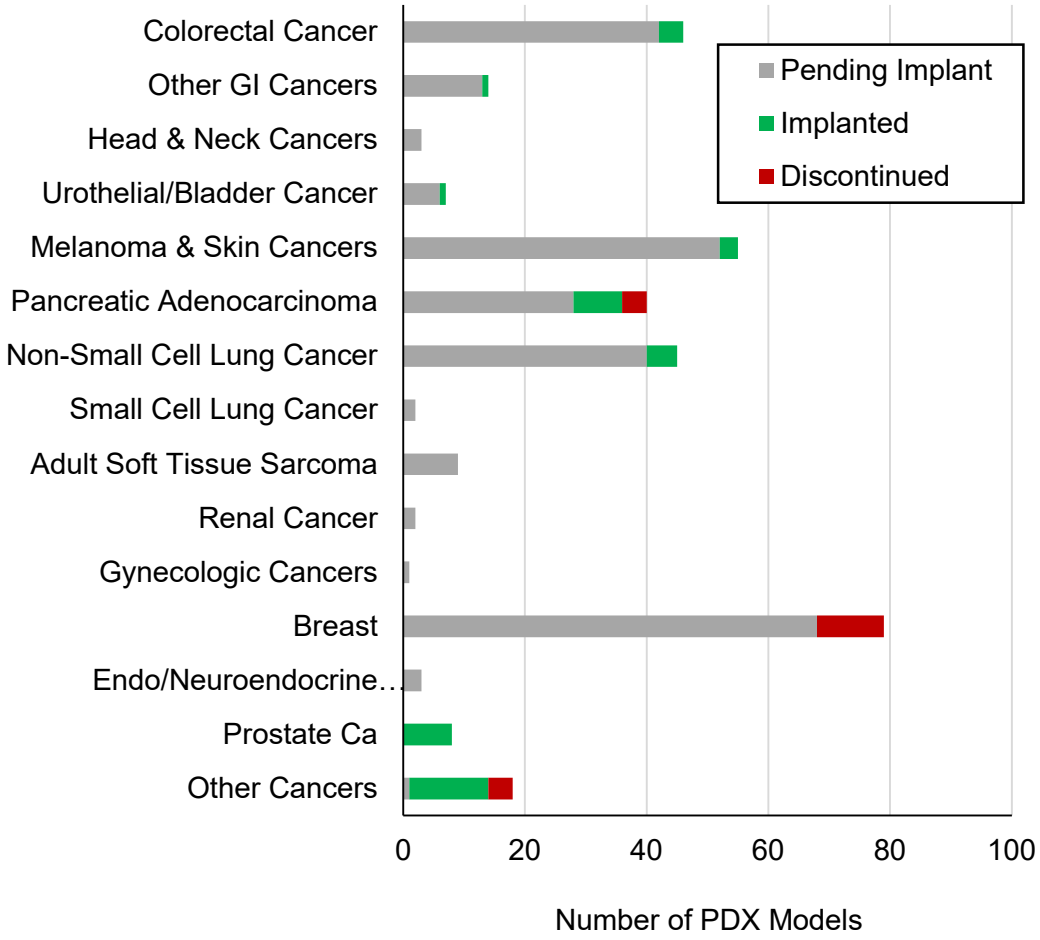
233 PDX models *publicly* available (pdmr.cancer.gov)

- 211 additional models (***in queue***) going through final QC (final pathology, NGS, STR, regrowth from freeze,…)
- >300 models in Passage 1-4 expansion
- ~400 models in Passage 0

Distribution Material

- Median Passage = 2
  - ✓ Range for NCI-generated models: 1-7
- Clinically-annotated, molecularly-characterized
- Specimens from patients with both primary and metastatic disease, ranging from treatment-naïve to heavily pre-treated backgrounds
- Current distribution within the US (pdmr.cancer.gov).
  - ✓ Model information also available through PDX Finder at www.pdxfinder.org

Externally Deposited PDX Models



Contributor Sources

- PDXNet Consortium: 179 models
- DCTD Administrative Supplement grantees: 126 models
- Extramural Academic Centers: 27 models

Process

- Required implantation & expansion within mouse isolators to minimize any chance of pathogen contamination
- Implanted in batches by Contributing Center and monitored for growth

Issues

- Limited Isolator Space, one Contributor per Isolator
- Pathogens:
  - One site: Mouse Kidney Parvovirus (MKPV) positive; One site: *Achromobacter* xylosoxidans positive; and One site had several LDEV+ models from contaminated Matrigel; NOT from PDXnet sites
  - Sites notified of issues
  - 2 models submitted were 100% mouse tumor

PDX Take-Rate from Tumor Tissue Implantations

Body Location	Total Specimens Received	Total Assessable Specimens	%Take-Rate of Assessable Specimens	Histology-Confirmed Tumor	Discontinued	*Not Yet Assessable: P0 tumors*
Breast	263	**203**	**14%**	**28**	175	60
Digestive/ Gastrointestinal	633	**559**	**44%**	**244**	315	74
Endocrine/ Neuroendocrine	174	**154**	**8%**	**12**	142	20
Genitourinary	453	**392**	**19%**	**75**	317	61
Germ Cell	4	**4**	**0%**	**0**	4	0
Gynecologic	335	**243**	**36%**	**87**	156	92
Head and Neck	175	**162**	**52%**	**84**	78	13
Hematologic	8	**3**	**38%**	**3**	0	5
Musculoskeletal	370	**333**	**26%**	**86**	247	37
Neurologic	9	**6**	**0%**	**0**	6	3
Respiratory/Thoracic	189	**160**	**32%**	**51**	109	29
Skin	77	**74**	**58%**	**43**	31	3
Unknown Primary	18	**17**	**18%**	**3**	14	1
Totals	2708	**2310**	**31%**	**716**	1594	398

All tumor material collected and shipped priority overnight in CO2-independent media for next-day implantation into NSG host mice

PDX Take-Rate Assessments by Tumor Source

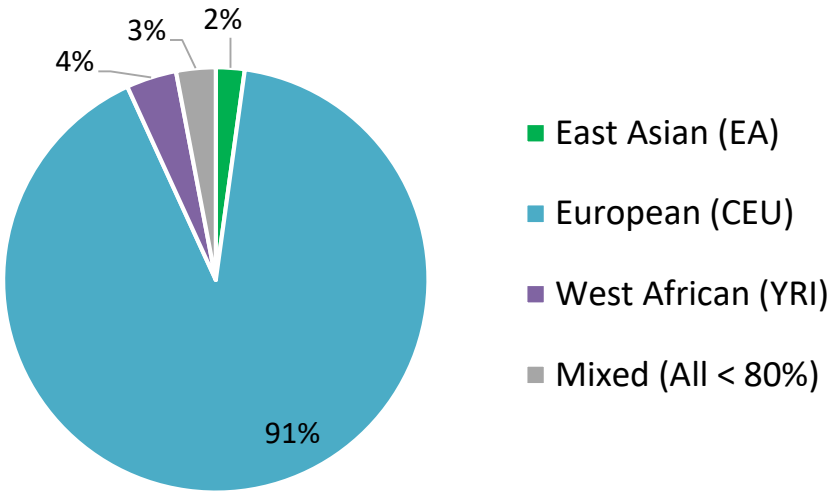
Collection Type	Total Specimens Received	Total Assessable Specimens	%Take-Rate of Assessable Specimens	Histology-Confirmed Tumor	Discontinued	*Not Yet Assessable: P0 tumors*
Resection (R)	2464	2090	30%	629	1470	373
Tumor biopsy (T)	230	207	40%	83	122	23
Malignant Effusion (M)	14	13	33%	4	2	2
Totals	**2708**	**2310**	**31%**	**716**	**1594**	**398**

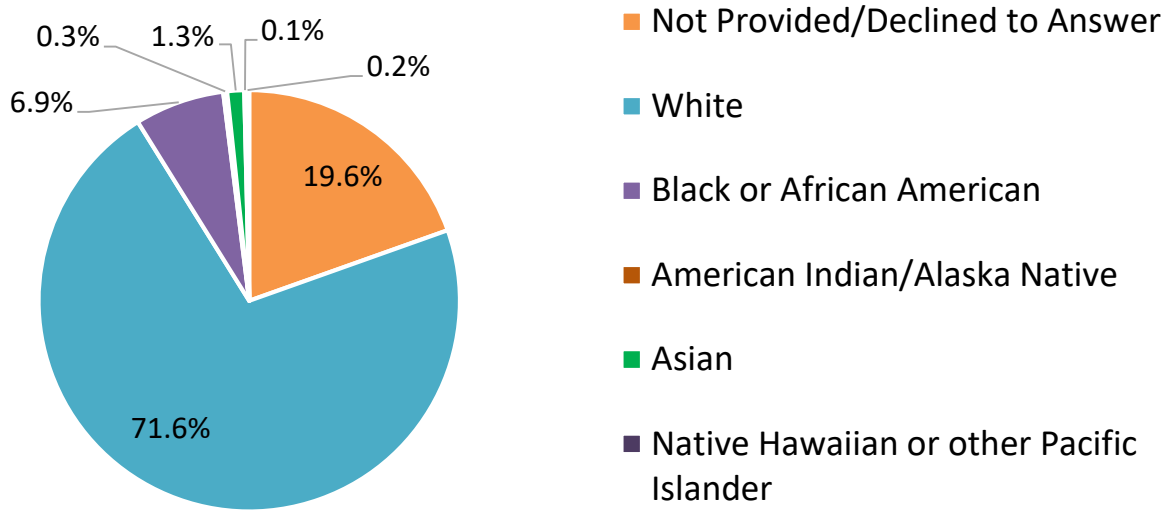
RAPID Autopsy Material	Total Specimens	Total Assessable Specimens	%Take-Rate of Assessable Specimens	Passageable Tumor	Discontinued	Not Yet Assessable
Breast	5	0		0	0	5
Digestive/Gastrointestinal	196	168	23%	39	129	28
Endocrine/Neuroendocrine	27	21	10%	2	19	6
Genitourinary	34	24	0%	0	24	10
Gynecologic	2	2	0%	0	2	0
Head and Neck	5	5	20%	1	4	0
Hematologic/Blood	2	0		0	0	2
Musculoskeletal	22	22	0%	0	22	0
Respiratory/Thoracic	13	3	0%	0	3	10
Skin	10	10	60%	6	4	0
Totals	**316**	**255**	**19%**	**48**	**207**	**61**

Understudied Cancer Histologies: PDX Models Available

- Merkel Cell Carcinoma
- Mesothelioma
- Hurthle Cell Neoplasm of the Thyroid
- Malig. Periph. Nerve Sheath Tumor
- Salivary Gland SCC
- Pharyngeal SCC
- Nasopharyngeal SCC
- Laryngeal SCC
- Vaginal Cancer
- Cervical SCC
- Carcinosarcoma of the Uterus
- Synovial Sarcoma
- Liposarcoma
- Leiomyosarcoma – uterine and non-uterine
- Rhabdomyosarcoma
- Osteosarcoma
- Chondrosarcoma
- Malignant fibrous histiocytoma
- Fibrosarcoma – not infantile
- Ewing sarcoma/Peripheral PNET

Inferred Ancestry for PDMR Models





Inferred Ancestry

- 336 PDMR models with WES SNP data available

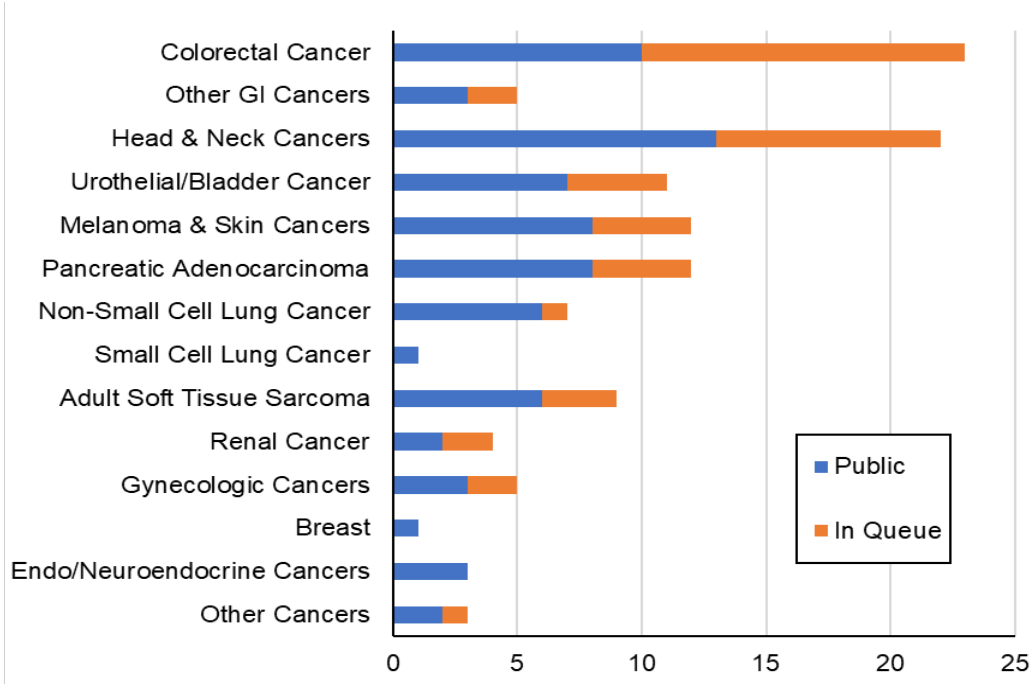
Self-Reported Race from Patient Enrollments

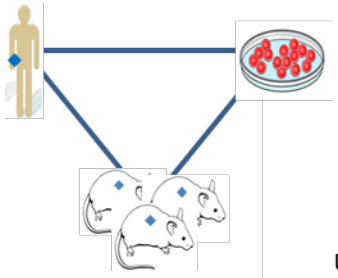
- Self-Reported Race above, of these 4% self-reported as Hispanic or Latin American

2 Minority-Based PDXnet sites funded 8 months ago; Minority-Based NCORP sites now enrolling

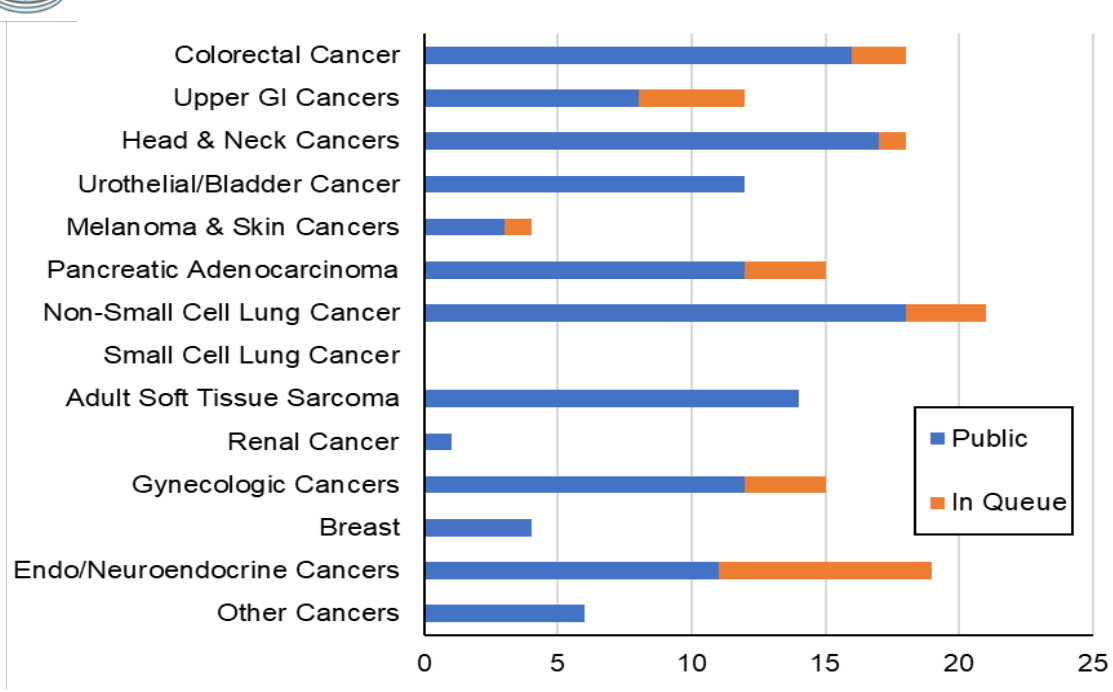
Patient/PDX-Derived Cancer Cell Lines (PDCs) and Cancer Associated Fibroblast Cultures (CAFs)

PDCs: 73 Public





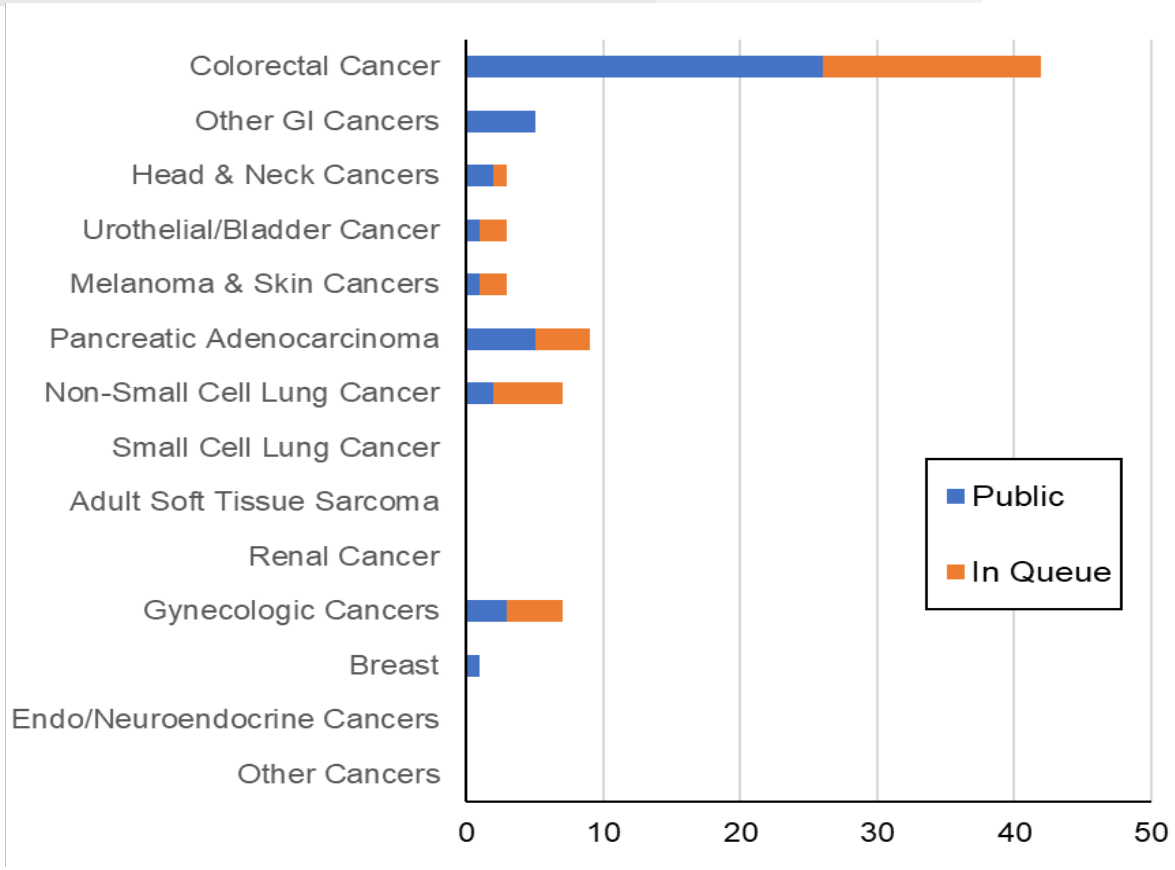
CAFs: 134 Public



- **Adherent & Suspension Cultures**
- **Requires use of defined media**
- **Distribution Material**
  - ✓ Median Passage = 20
    - Range : 12-51

- **Not Transformed - Limited Lifespan**
- **Requires use of defined media**
- **Distribution Material**
  - ✓ Median Passage = 14
    - Range: 9-18

Patient/PDX-Derived Organoids (PDOrg)



- **Requires use of defined media**
- **Distribution Material**
  - ✓ Median Passage = 10
    - Range : 6-30

- First 46 models now publicly available with another 30 going through QC (NGS, tumorgenicity verification, STR, etc)
- Major developmental effort for new SOPs for H & N, NSCLC, melanoma, cervix Orgs
- Provide all related metadata and SOPs through the PDMR website and public database: pdmr.cancer.gov

Goal:
Wherever possible develop a PDX, 2D *in vitro* PDC, and PDOrg culture for comparative preclinical studies

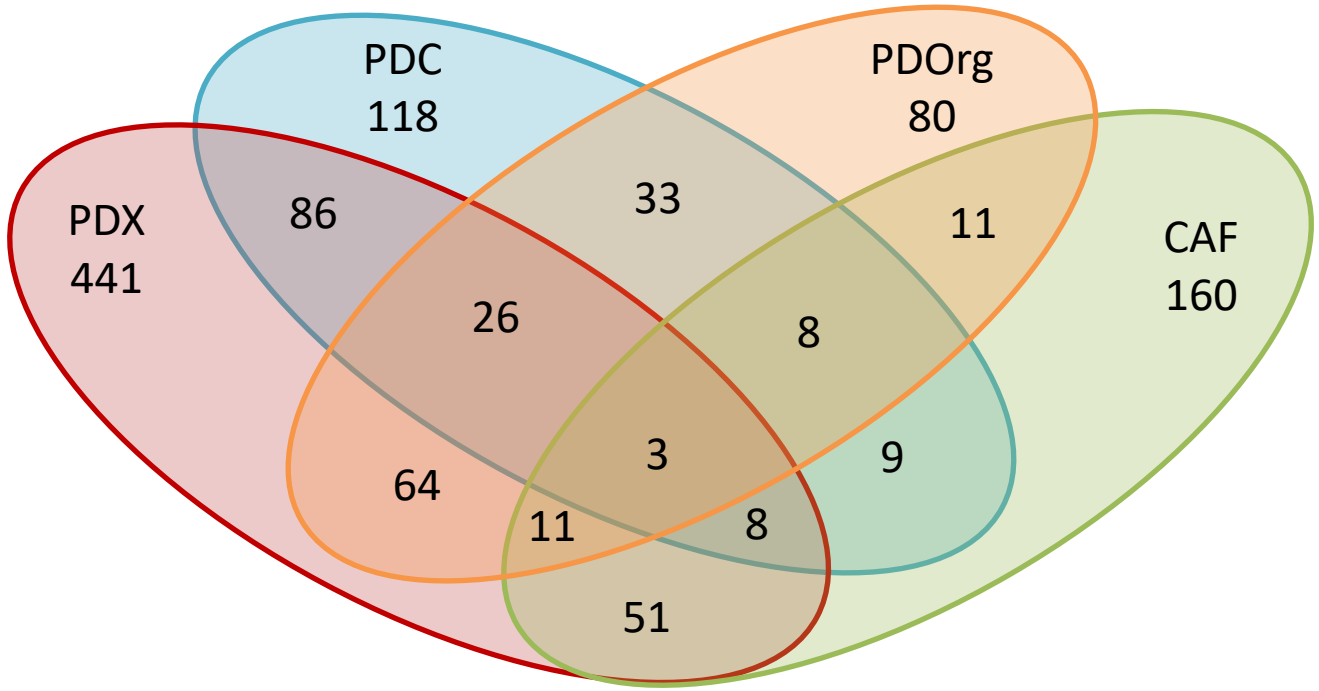
Matched PDX, PDOrg, PDC, and CAF Models

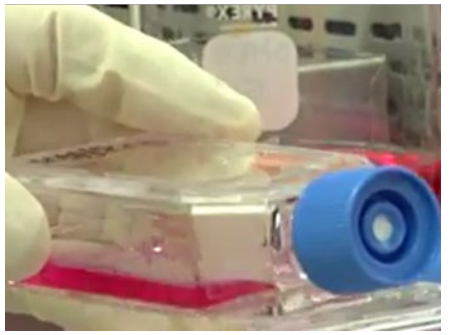
Includes models that are either

(1) Publicly Available or

(2) Going through final QC for Public release (pathology confirmation of all contributing material, NGS, STR, regrowth from cryopreservation, etc)

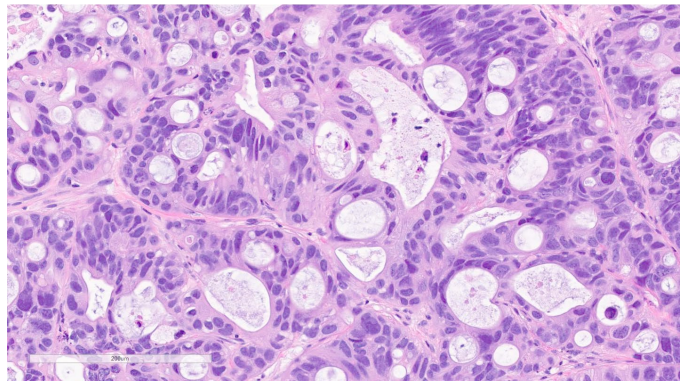
PDX	441
PDC	118
PDOrg	80
CAF	160





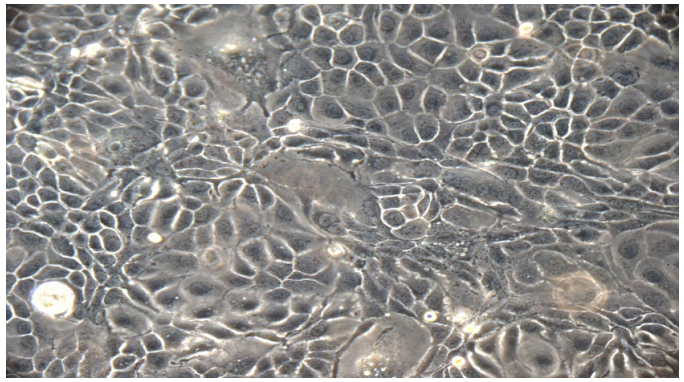
521955-158-R2, Adenocarcinoma - pancreas

PDX

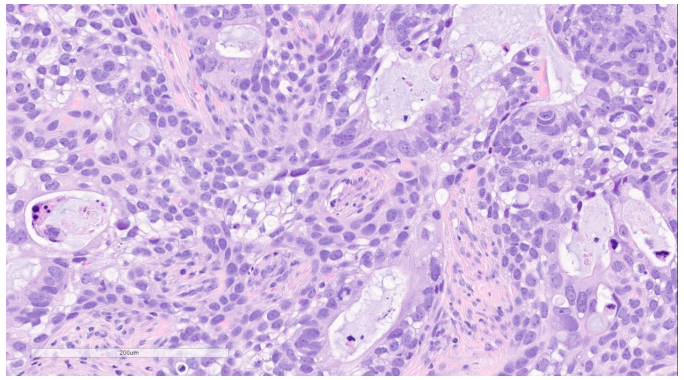


Glandular architecture is present with nests of glands with areas of back to back gland formation

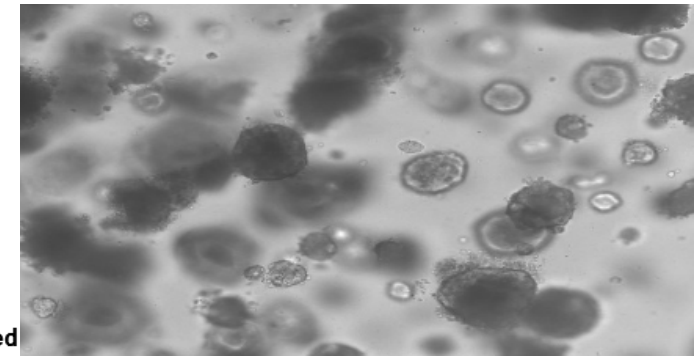
PDC Culture



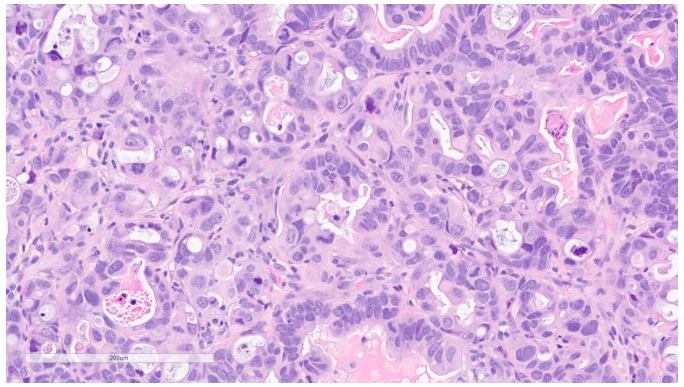
PDC Xenograft



PDOrg Culture



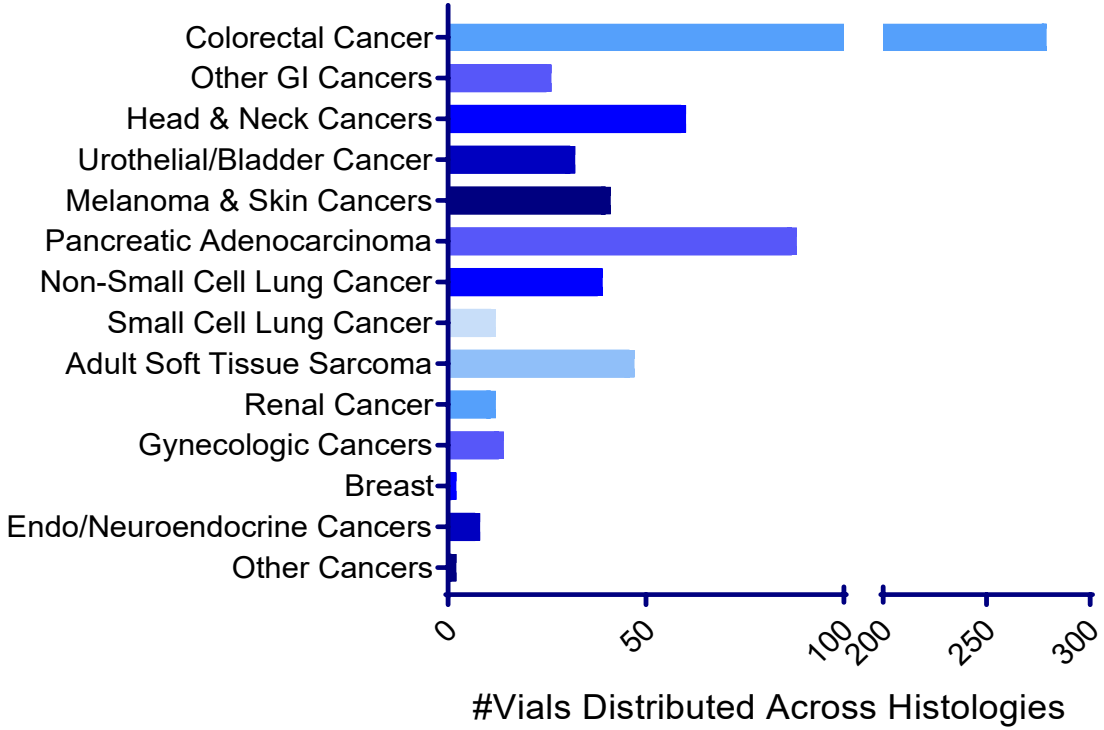
PDOrg Xenograft



Distribution of Models

- Academic, Commercial, and Intramural PIs

Material	Number of Vials Distributed
PDX Fragments – Viably Cryopreserved	277
DNA from PDX Fragment (Solution)	3
RNA from PDX Fragment (Solution)	20
Fresh-Frozen PDX Fragment for Extraction	257
In Vitro PDCs – Viably Cryopreserved	101
In Vitro CAFs – Viably Cryopreserved	10
PDOrgs – Viably Cryopreserved	20
Total	688



USES:

- ✓ Methylome assessment
- ✓ Target-specific inhibitors matched to molecular phenotypes
- ✓ Small molecule agents
- ✓ Angiogenesis
- ✓ Proteogenomics
- ✓ Radiotherapy
- ✓ Small animal imaging studies
- ✓ Biomarker assessment matched to molecular phenotypes
- ✓ Academic preclinical core services
- ✓ Commercial investigational agent validation

Institutions/Companies Receiving PDMR Resources

- Emory University
- Fred Hutchinson Cancer Research Center
- Georgetown University Medical Center
- Huntsman Cancer Institute, Univ Utah †
- Indiana University School of Medicine
- Johns Hopkins University
- MD Anderson Cancer Center * †
- Ohio State University Medical Center †
- Roswell Park Cancer Institute
- Stanford University *
- University of Texas at Dallas
- Thomas Jefferson University
- University of California at Los Angeles *
- University of California – Irvine *
- University of Maryland * †
- University of Michigan * †
- University of Pittsburgh *
- University of Texas - Southwestern Medical Center
- Virginia Commonwealth University * †
- Wake Forest Baptist Comprehensive Cancer Center
- University of Georgia
- Frederick National Laboratory for Cancer Research * †
- Center for Cancer Research, NCI * †

<u>Biotech/Pharma</u>

- Dicerna Pharmaceuticals, Inc †
- Merrimack Pharmaceuticals
- SRI International

*** Multiple PI's have requested material**

† The same PI has made >1 request

Continuing to communicate regularly to extramural PI's to enhance awareness

Working Group Discussion & Input

Issues / Challenges Discussed: Input

- Recent challenges
  - ✓ Newly identified Mouse Kidney Parvovirus (MKPV); first described in Fall of 2018 as cause of murine nephropathy.
    - --We now have changed all aspects of how externally derived PDX deposits are handled within the Biological Testing Branch (DCTD/NCI).
    - --As discussed with WG, all PDMR model recipients notified, as well as PDXnet members; new SOPs posted on PDMR website with details of commercial testing availability for MKPV (now routine at PDMR)
  - ✓ PDMR has stopped routinely accepting colon adenocarcinomas for model development (>100 models in hand). Cases with unique histologies or mutational status are reviewed on a case-by-case basis so that something like Lynch Syndrome would still be accepted.

- Advice from WG
  - ✓ How to improve knowledge of model availability for the research community?
    - --Increase blast emails to DCB grantees as well as DCTD grantees each time a group of new models released
    - --Announced on NCI Treatment twitter account
  - ✓ Organoids
    - --Attempting to make organoids from tumor types that traditionally are not thought to make organoids: Mel's; Sarcomas
    - --Will promote new SOP's for non-traditional organoid propagation

Issues / Challenges Discussed: Input (2)

- Advice from WG
  - ✓ CAFs
    - --How do we best use them/market them?
    - --Of note: we often develop a CAF line from patient material when no PDX or PDC develops
  - ✓ Preclinical Assessment
    - --Finding additional metrics for preclinical response; we need to assess multiple ways to get a better picture of response
  - ✓ Uses for EBV-transformed DLBCL-like models (Xenograft-associated lymphoproliferative disease; effect of Rituximab)?

- Other Recommendations
  - ✓ Expand PDMR with pediatric tumors—ALL samples from Dr. Houghton
  - ✓ GBM and other brain tumors from NCI Neuro-oncology program
  - ✓ Expand RPPA and other proteomic characterization studies

Other PDMR Activities for Discussion with WG

PDMR-Related Activities

- PDX (patient-derived xenograft) Development and Trial Centers Research Network (PDXNet)—Moonshot effort
  - ✓ Perform preclinical studies at PDX centers to accelerate translation to ETCTN trials; PDMR is the Hub
- NCI-DOE Collaboration – Moonshot effort
  - ✓ Joint Design of Advanced Computing Solutions for Cancer (JDACS4C)
  - ✓ Develop predictive models, both computational and experimental, to improve pre-clinical therapeutic drug screening
- Preclinical Assessment of PDX Models
  - ✓ Rare Tumor PDXs: 40 models x 60 novel therapeutic combinations. Goal: to identify new therapies for rare cancers
  - ✓ Standard of care: 72 models x 6 single agent SoC. Goal: to determine if PDX models respond similarly to Phase II trials
  - ✓ Support for ongoing DCTD efforts for NExT program (preclinical, pharmacodynamics, in vitro screening etc)
  - ✓ Genomic assessment of PDX 'drift"
- Imaging studies (Cancer Imaging Program)
  - ✓ Future portal on TCIAA

The NCI expresses its deepest thanks to the patients, families, and clinical teams that make this effort possible.

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