NCI's Patient-Derived Models Repository: Generating Models from Racial and Ethnic Minorities

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https://pdmr.cancer.gov

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

Disclosure Information

AACR Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved
Yvonne A. Evrard, PhD

I have the following financial relationships to disclose:

    Employee of: Leidos Biomedical Research, Inc.

I will not discuss off label use and/or investigational use in my presentation.
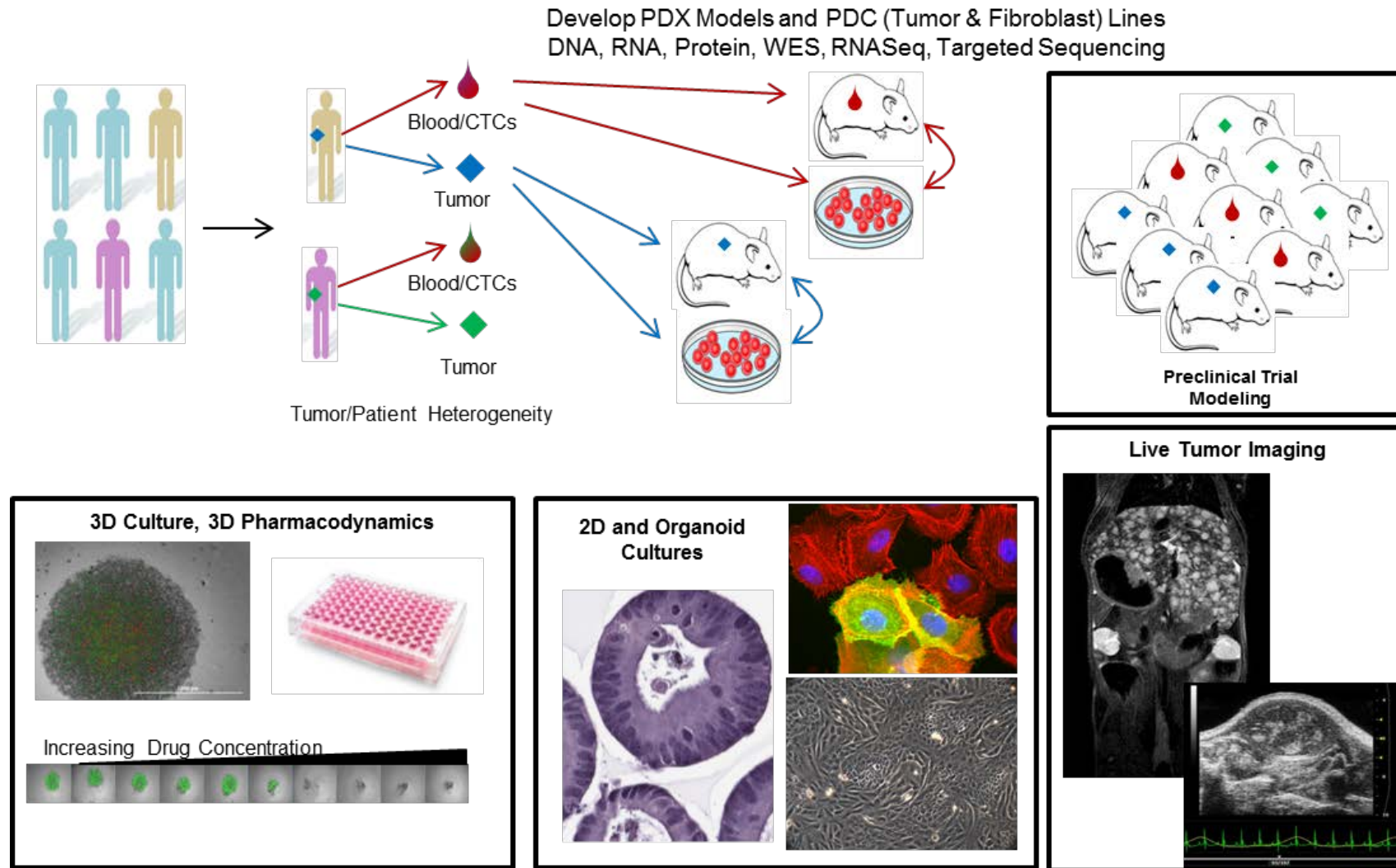
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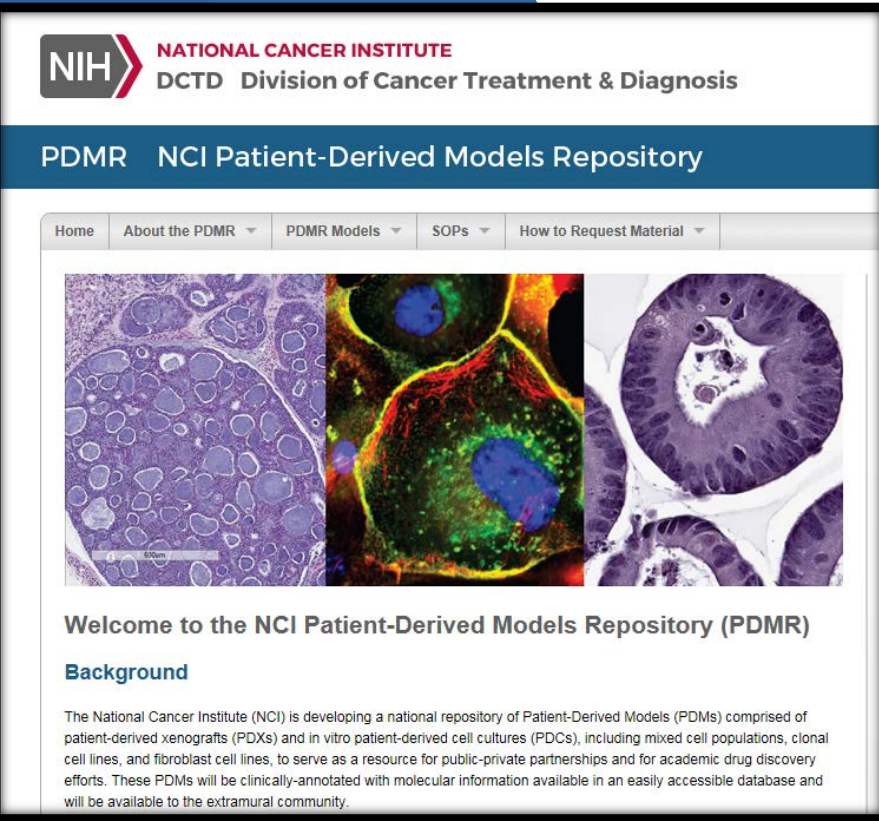
NIH | NATIONAL CANCER INSTITUTE

NCI Patient-Derived Models Repository (PDMR)

- A national repository of Patient-Derived Models (PDMs) to serve as a resource for academic discovery efforts and public-private partnerships for drug discovery comprised of:
  - Clinically-annotated, Early-passage, Molecularly-characterized Patient-derived Xenografts (PDXs),
  - Patient-derived tumor cell cultures and cancer-associated fibroblast cultures (PDCs) developed from primary or metastatic tumors and/or PDXs,

- NCI to provide long-term home for >1000 PDX models and develop matched in vitro and organoid models wherever possible

- Goals:
  - ~50 unique patient models/disease (minimum) with sufficient size of each molecularly-characterized subgroup to power validation and/or efficacy studies
  - Comprehensive pre-competitive molecular characterization of samples and earliest passage PDXs: NCI Cancer Gene Panel, WES, RNAseq, histology, growth curves, and preclinical drug responses
  - All models and associated data made available through a publicly available website

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NCI Patient-Derived Models Repository: Multiple Avenues for Discovery

Develop PDX Models and PDC (Tumor & Fibroblast) Lines
DNA, RNA, Protein, WES, RNASeq, Targeted Sequencing

Blood/CTCs

Tumor

Blood/CTCs

Tumor

Tumor/Patient Heterogeneity

Preclinical Trial Modeling

Live Tumor Imaging

3D Culture, 3D Pharmacodynamics

Increasing Drug Concentration

2D and Organoid Cultures

NCI's Patient-Derived Models Repository (PDMR)

https://pdmr.cancer.gov

- Distribute Early-Passage, Clinically-Annotated, and Molecularly-Characterized patient-derived models at a minimal cost to researchers.
- Provide all related metadata and SOPs through a publicly available website.

NCI Patient-Derived Models Repository (PDMR)
Initial Distribution Types

Pie chart — Initial Distribution Types:
- Colorectal Adenocarcinoma, 21
- H&N SCC, 19
- Urothelial/Bladder, 15
- Melanoma, 11
- Pancreatic Adenocarcinoma, 9
- Lung SCC, 5
- Adult Soft Tissue Sarcoma, 11
- Renal, 5
- Upper GI, 5
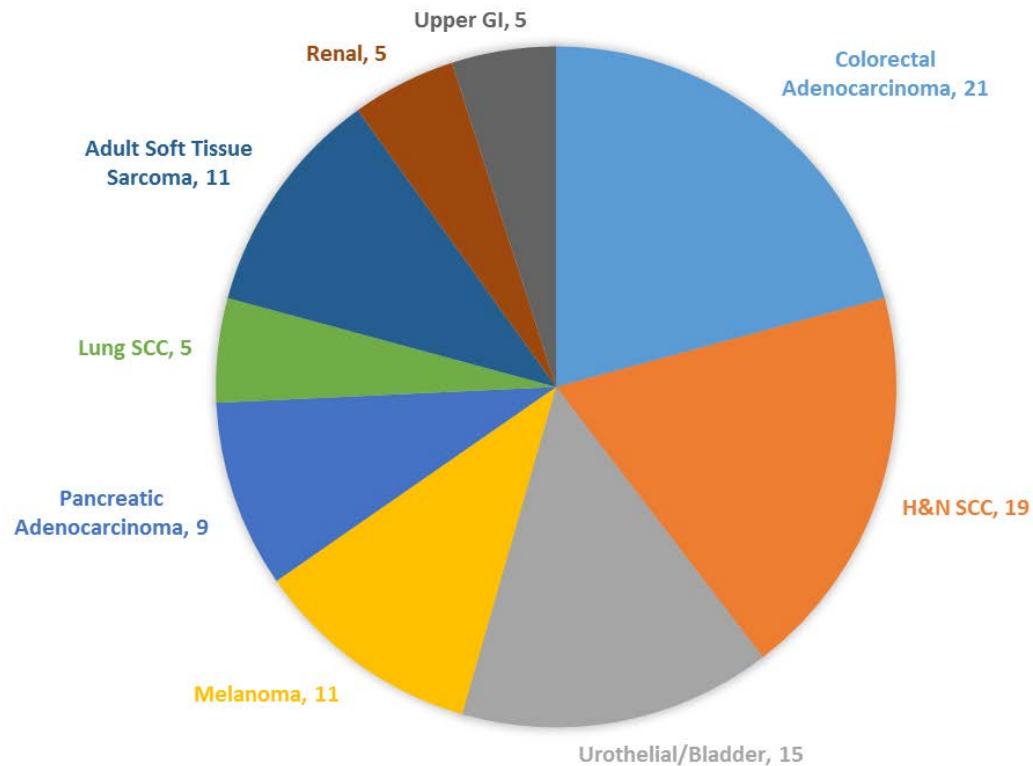
- Currently have 100 PDX models available for request through the public website.

- Every model has associated patient limited medical history and representative PDX histopathology, whole exome sequence, and RNASeq data publicly accessible and available for download for metadata analysis and model selection

- Specimens are from patients with both primary and metastatic disease from treatment naïve to heavily pre-treated.

- PDX Pathology Confirmed
- Whole Exome Sequence, RNASeq, and an NCI Cancer Gene Panel Available (4-6 representative PDXs per model)
- Human Pathogen Screening and STR Profile Available
- Confirmed Re-growth from Cryopreserved Fragments

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NCI Patient-Derived Models Repository (PDMR)
Initial Distribution Types
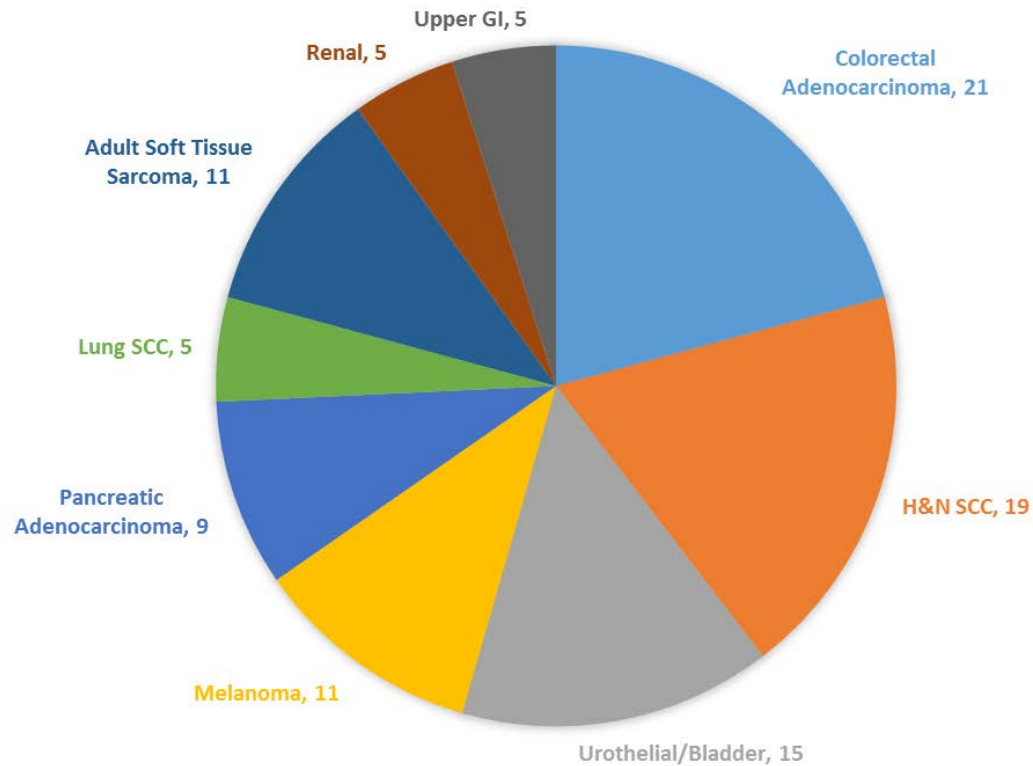
| Disease Distribution Groups |
| --- |
| **Colorectal Adenocarcinoma** |
| **Head & Neck Squamous Cell Carcinoma**
• Pharyngeal, Laryngeal, Lip/oral cavity, NOS |
| **Urothelial/Bladder Ca** |
| **Melanoma** |
| **Pancreatic Adenocarcinoma** |
| **Lung Squamous Cell Carcinoma** |
| **Adult Soft Tissue Sarcoma**
• Ewings, Leiomyosarcoma, Malignant fibro. histiocytoma, Fibrosarcoma, Non-Rhabdosarcoma NOS, Rhabdosarcoma NOS |
| **Renal Ca** |
| **Upper GI Ca**
• Stomach, Sm. Intest, GIST, Appendiceal |

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Patient Information and Limited Medical History
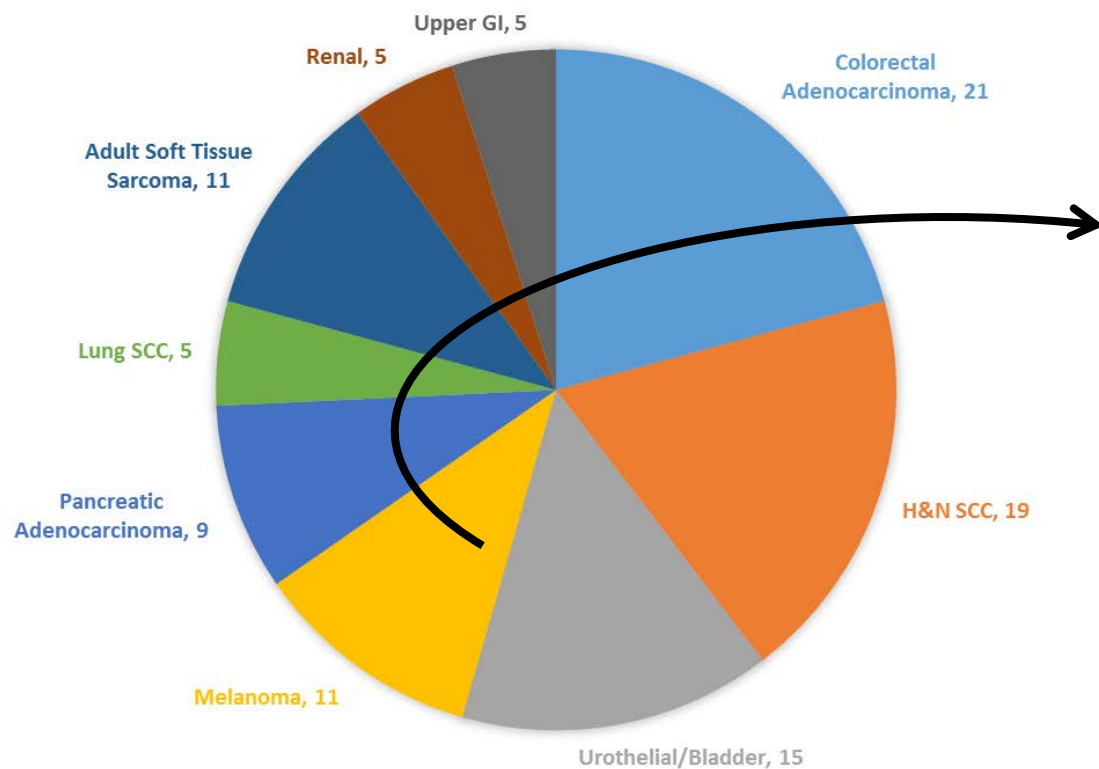
CTEP SDC Code   10053571 - Melanoma
Diagnosis Subtype
Date of Diagnosis   06/2013
Age at Diagnosis   61

Grade/Stage Information Available   • None Provided
Patient Notes
STR Profile   Download

Pie chart categories:
- Upper GI, 5
- Renal, 5
- Adult Soft Tissue Sarcoma, 11
- Lung SCC, 5
- Pancreatic Adenocarcinoma, 9
- Melanoma, 11
- Urothelial/Bladder, 15
- H&N SCC, 19
- Colorectal Adenocarcinoma, 21

⌄ Limited Medical Information (provided after delinking)

Current Therapy

View	Date Regimen Started	Standardized Regimen	Best Response	Number of Cycles	Date of Progression or Off Therapy	Comments	Reason for Off Therapy
🔍		No Current Therapy	NA				

Export

Prior Therapies and Response

View	Date Regimen Started	Standardized Regimen	Best Response ▾	Duration Months	Comments
🔍	04/2014	Decitabine, Vemurafenib	Disease Progression	1	All other disease sites responded except left forearm
🔍	06/2013	TVEC, Ipilimumab	PR	3	left forearm did not respond, all other disease sites responded

Export

Additional Patient History

Known Genetic Mutations and Tumor Markers   V600E-BRAF

Additional Medical History   Est diagnosis date from first prior therapy.

⌄ Social History (provided after delinking)

Social History

View	Ethnicity	Race	Occupation	Has Smoked 100 Cigarettes	Total Pack Years	Tobacco Use History ▾
🔍	Not Provided	Not Provided	-	Not Provided	-	-

Pathology and Molecular Characterization of PDX Models

Pathology Data

View	Tumor Grade	Tumor Content	Necrosis	Stromal	Inflammatory Cells	Low Magnification Image	High Magnification Image
🔍	Intermediate grade or moderately differentiated	65%	5%	30%	1+ (Low)		

Sample (PDX)

View	PDM Type ▼	Sample ID	Patient/Originating Specimen	PDX Passage	Sample Images Avail	NCI Cancer Gene Panel Data	Whole Exome Sequence Avail	RNASeq Avail
🔍	PDX	JI5	No	0	Yes	Yes	Yes	Yes
🔍	PDX	JI5M632	No	1	Yes	Yes	Yes	Yes
🔍	PDX	JI5M633KB9	No	2	Yes	Yes	Yes	Yes
🔍	PDX	JI6	No	0	Yes	Yes	Yes	Yes
🔍	PDX	JI6K88	No	1	Yes	Yes	Yes	Yes
🔍	PDX	JI6_RG-KD3	No	1	Yes	Yes	Yes	Yes

Race/Ethnicity Reporting was an Early Recognized Limitation of the PDMR Models

Self-reported Race

2 HA

1%

2%

40%

57%

- American Indian/ Alaska Native
- Asian
- Black or African American
- Native Hawaiian or Other Pacific Islander
- White
- Multi-Racial (>1 Selection)
- Unknown
- Declined to Answer
- Not Provided
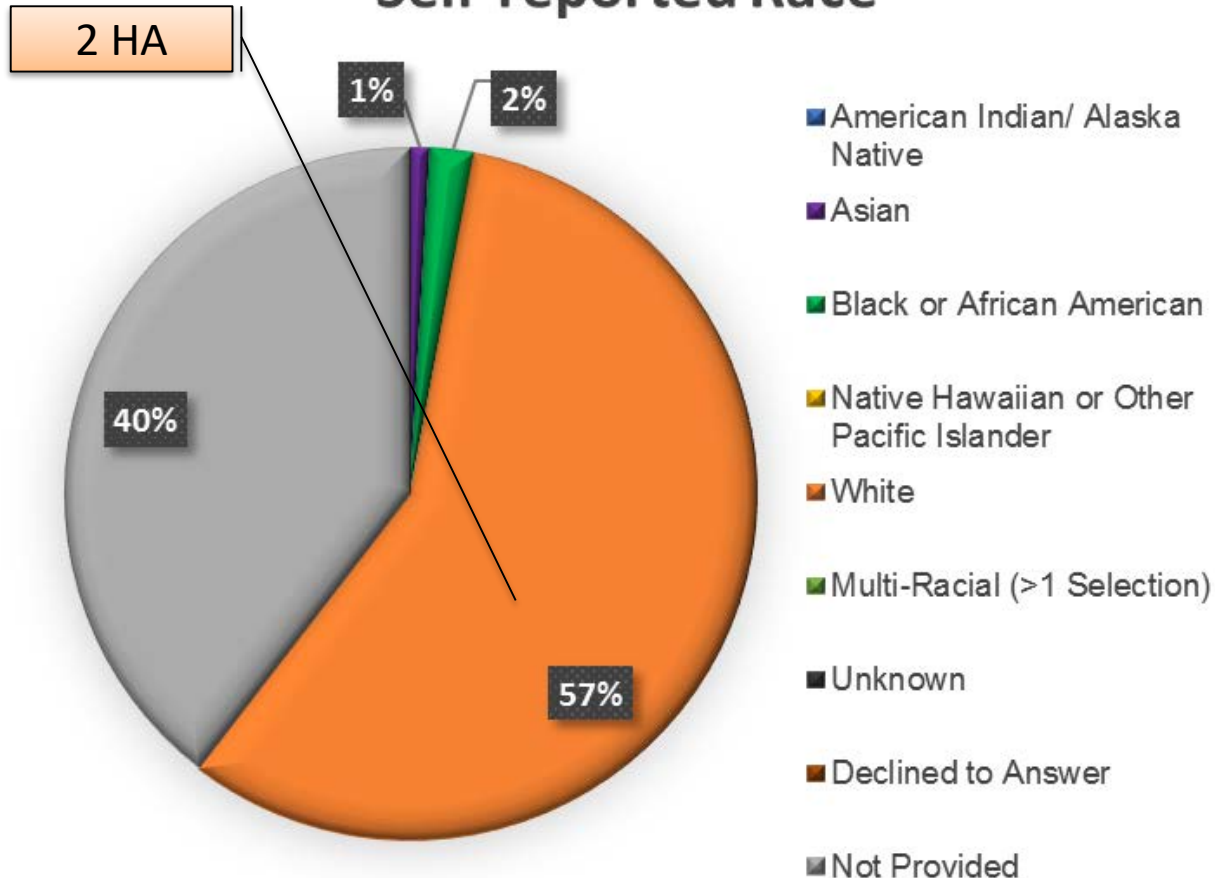
Assessment of patient data from 454 PDX models with confirmed pathology from at least one passage 0 tumor

- During the first two years of patient recruitment, race and ethnicity were not part of the required minimal patient information requirements.
- In addition, from those that were reported there was an obvious gap in racial and ethnic minority patient recruitment
- Solutions
  - Perform ancestry assessment on all PDX models to provide the research community with additional information on patient inferred genetic ancestry
  - Increase the number of patient specimens and/or PDXs coming into the PDMR from racial and ethnic minorities

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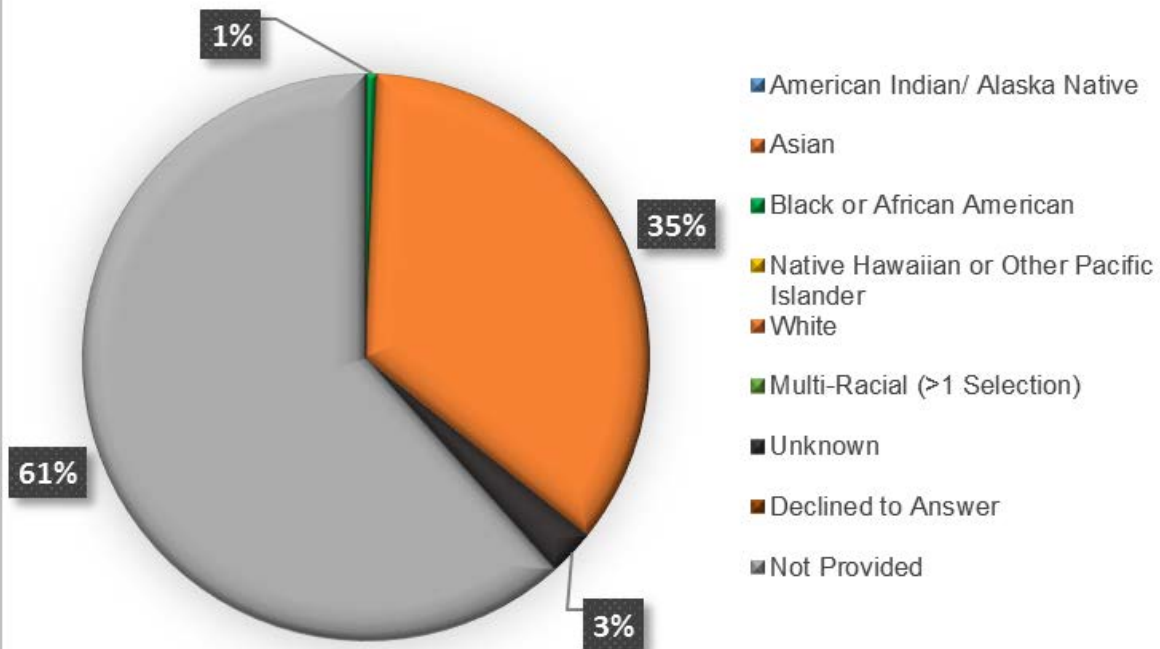
Genetic Ancestry Assessment

- Genetic ancestry assessment using the whole exome sequencing that is performed on all of our models.
- SNPweights Reference Panels
  - "Improved ancestry inference using weights from external reference panels" (Chen et al., Bioinformatics, 2013)
  - West African (YRI), European (CEU), East Asian (EA) and Native American (NA) from HapMap 3
  - 364,458 SNPs
- Reporting criteria
  - When available, patient material ("originator") used for ancestry assessment
  - …Else the average genetic ancestry of all sequenced PDX samples (4-6) is reported
  - If all ancestry assignments are <80%, inferred ancestry reported as "Mixed – All <80%"
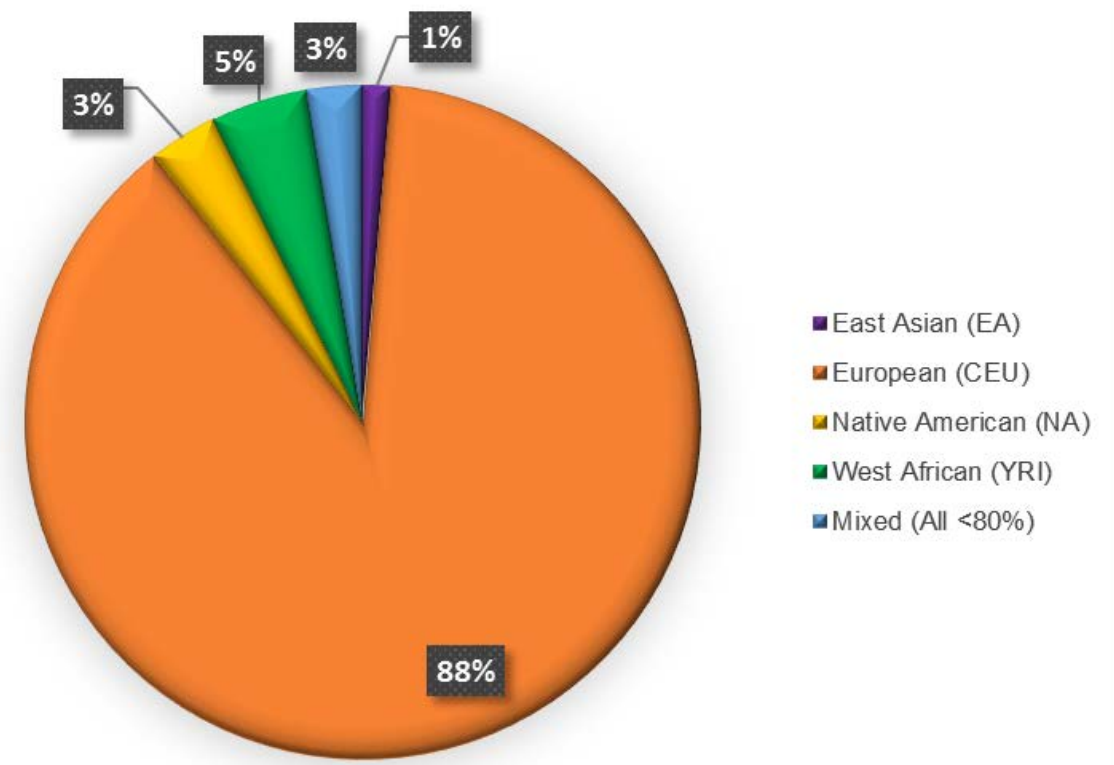
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Genetic Ancestry Assessment

| Gender | Diagnosis | Self-Reported Race | Genetic Ancestry (SNPweights) | | | | 80% cut-off Inferred Ancestry Assignment | Source Material |
			% YRI	% CEU	% EA	% NA		
Female	Adenocarcinoma - cervix	Not Provided	1%	1%	98%	0%	East Asian	PDX
Male	Adenocarcinoma - colon	Not Provided	84%	16%	0%	0%	West African	PDX
Male	Adenocarcinoma - colon	Not Provided	0%	100%	0%	0%	European	PDX
Female	H & N squamous cell car., NOS	White	5%	95%	0%	0%	European	Originator
Female	Leiomyosarcoma - uterus	Not Provided	11%	46%	0%	43%	Mixed (All <80%)	PDX
Male	Melanoma	White	0%	100%	0%	0%	European	Originator
Male	Melanoma	Black or African American	1%	99%	0%	0%	European	PDX
Male	Non-Rhabdo. soft tissue sarcoma	White	5%	95%	0%	0%	European	Originator
Male	Pharyngeal squam. cell carcinoma	White	0%	100%	0%	0%	European	Originator
Female	Salivary gland cancer	Not Provided	83%	17%	0%	0%	West African	PDX

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# Genetic Ancestry Assessment for 151 PDX Models with WES

Increasing Racial/Ethnic Minority Representation in PDMR Models

- Minority-Underserved NCORP sites (RFP Awarded, Leidos Biomedical Research – funding in support of the DCTD/NCI)
  - o Goal: Enroll patients with cancer from predominantly racial and ethnic minorities to provide research specimens to the PDMR for patient-derived models development
  - o Proposed specimen provision includes: Breast (incl. TNBC), Prostate, Pancreatic, Renal, Lung, and Hepatic cancer from patients of Hispanic and African-American descent; Ovarian, Cervical and Endometrial Cancers from patients of African-American descent
- NEW: S17-199 - Acquisition of Biological Samples for the Development of NCI's Patient-Derived Models (PDM) Repository (LBR RFP funding in support of the DCTD/NCI)
  - o Posted to: FedBizOpps and Leidos Biomedical Research website
  - o Date Issued: Sept 25, 2017
  - o Response Due: October 13, 2017
- PENDING: Minority PDX Development and Trial Centers (M-PDTCs) RFA (U54) to participate as part of the PDXNet
  - o Goal to perform large-scale, multicenter preclinical PDX studies

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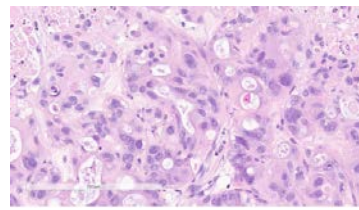An NCI Precision Oncology Initiative[SM] Resource

PDMR In Development

- Ancestry SNP Assessment
- Consensus Genomic Variants: list of variants that are 100% represented in WES data
- Germline Whole Exome Sequence
- Designation of Metastatic PDX Models (spontaneous, post-debulking)
- Preclinical Drug Study Results
- Whole Mouse Imaging (e.g., MRI, US)
- In vitro Early-Passage Tumor and Cancer-Associated Fibroblast Cultures
- Models Developed from Rapid Autopsy Procedures:
  - Current focus is on Pancreatic and Prostate Cancer
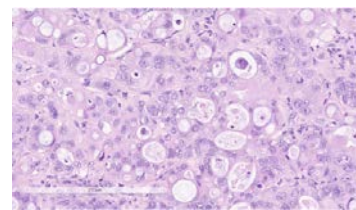 - PDX Models from Primary and Metastatic Pancreatic Adenocarcinoma
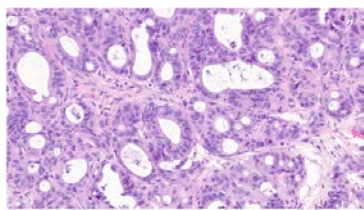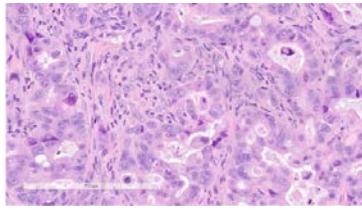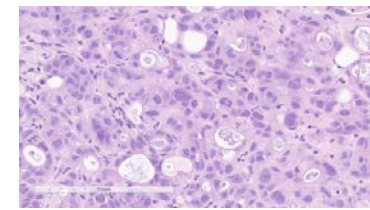
1°: Pancreas	Met: Liver	Met: Colonic Fat	Met: Myometrium	Met: Colon

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