The Association of Biomolecular Resource Facilities

A Comprehensive Guide to Using Your Institutional Shared Resources Effectively
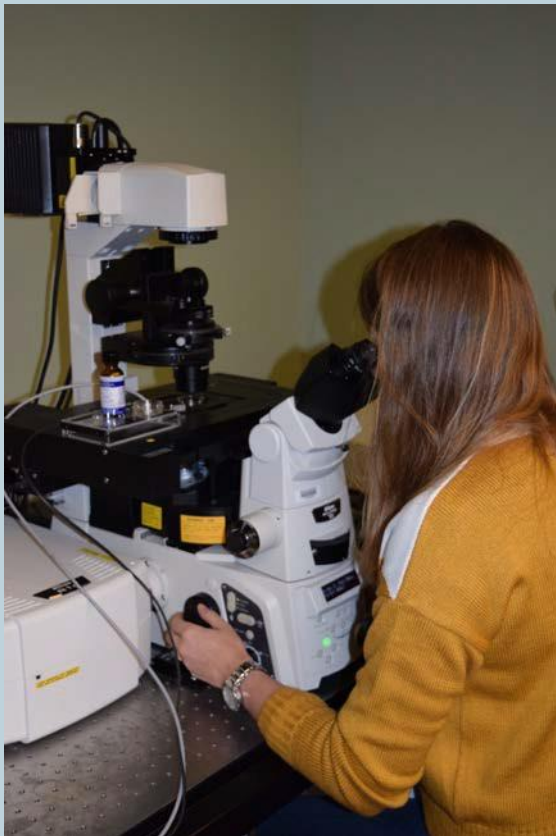
An online seminar for ASHG

Who is ABRF?

The Association of Biomolecular Resource Facilities

An international scientific society dedicated to advancing technologies, education, communication and reproducible research in the operations of shared research resources, aka core facilities.

- A non-profit professional membership organization and member of the Federation of American Societies of Experimental Biology (FASEB)

- Founded in 1989, ABRF currently includes over **2500** members from more than **400** institutions across **17** countries representing academia, government and industry

- A **member-driven** society that relies on volunteers for ongoing activities which promote research, technology, communication and education

- Members access unique resources & professional opportunities specific for Share Research Resource scientists

https://abrf.org

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- Sheenah Mische, PhD

- Nicholas Ambulos, PhD

- Laboratory Director, DNA Services Group, Genetic Resources Core Facility, Johns Hopkins University School of Medicine, ABRF Executive Board member

- Director of Research Operations, Cincinnati Children's Hospital, ABRF Chair of the Core Administrators Network Committee

- Director, Center for Functional Genomics, University of Albany, ABRF Executive Board member

- Senior Director, Division of Advanced Research Technologies (DART), Assistant Director for Shared Services, Perlmutter Cancer Center, NYU Grossman School of Medicine

- Director, Center for Innovative Biomedical Resources, Associate Director For Shared Services, Marlene and Stewart Greenebaum Cancer Center Director, Translational Genomics Lab, University of Maryland, Baltimore

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- The NIH has defined a Core or Shared Research Resource as:
  A centralized shared research resource that provide access to instruments, technologies, services, as well as expert consultation and other services to scientific and clinical investigators.

- The typical core is a discrete unit within an institution and may have dedicated personnel, equipment, and space for operations.
- In general, core facilities recover their costs, or a portion of their costs, of providing service in the form of user fees that are charged to an investigator's funds, often to NIH or other federal grants.
  (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-13-053.html)

Shared Research Resources are…

- A nexus between basic discovery and the application of new groundbreaking technologies, including multidisciplinary -omic tools (e.g. transcriptomics, proteomics, metabolomics, and the microbiome), single cell sequencing and systems biology approaches for phenotyping single cell populations using systems-biology approaches.

- Scientists with expert resources who can help you refine your experimental design and methodology in grant proposals by discussing all aspects of your proposed research. These scientists are often critical grant co-PIs.

- Links to other SRRs which may provide ancillary services, creating a collaborative hub for project synergy.

Getting Started

Most research proposals can be broken down into three components:
1) Sample Collection
2) Data generation
3) Analysis

(And let's not forget the thing that ties them all together…the budget.)

Working with your Cores can help assure that all components work together.

Before you reach out to your Cores, it can be helpful to think through some details.

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Samples Checklist

Scan QR to download checklists

- ❏ How many samples do I need?
- ❏ Is there publicly available data that I leverage to run fewer controls?
  - ❏ dbGAP
  - ❏ All of US
  - ❏ H3Africa
  - ❏ UKBioBank
  - ❏ Etc
- ❏ Are my consents appropriate for the future uses of the samples?
- ❏ What type of sample do I need?
- ❏ How much sample do I need?

Samples Checklist Continued
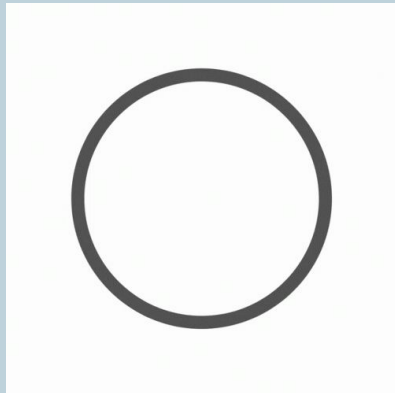
❏ Does the method of collection affect what I can do with the samples after collection?

❏ Does the method of storage affect what I can do with the samples after collection?

❏ How long will I store the samples?

❏ How will I pay for storage of the samples?

❏ What is the eventual disposal plan for the samples?

❏ If I use a public database, what kind of controls do I need?

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Data Checklist
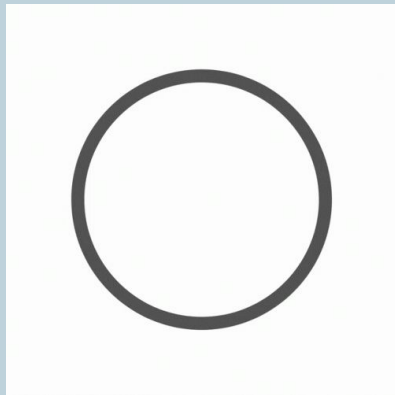
❏ How much data is appropriate for the question I am asking?

❏ What controls (samples and QC) do I need?

❏ Am I looking at specific genes, regions or pathways?

❏ Do I need the whole genome?
  ❏ What would the whole genome give me that a narrower focus won't?

❏ Are my questions narrow and focused, or broad?

❏ How does the amount of data generated affect my study power?
  ❏ Your answer to this question may make you circle back to the samples questions

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Technology Checklist
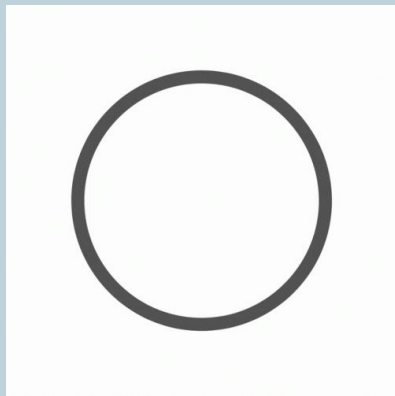
❏ What is the most appropriate technology to generate the data I need?
  - ❏ Genotyping? Low or high throughput?
  - ❏ Sequencing? Targeted, Exome, Whole?
  - ❏ Single cell? Spatial?
  - ❏ Gene Expression?
  - ❏ Methylation?

❏ How much does any of this cost?

❏ Do you need one core or several that work together?

❏ Are there references citing similar workflows? What are the pros and cons in those references?

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Analysis Checklist
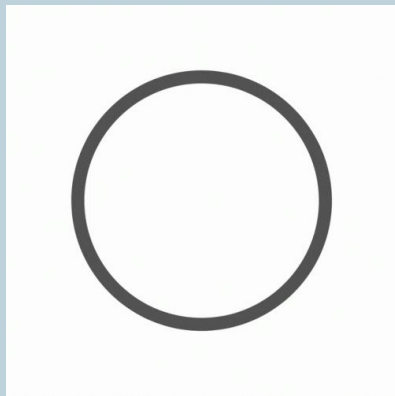
- ❏ Do I understand the data generated by the technology I am considering?
- ❏ Am I am able to analyze the data myself?
- ❏ Can I collaborate with someone for data analysis, or do I need to hire a data analyst?
- ❏ How much does it cost to analyze the data?
- ❏ How long will it take to analyze the data?
- ❏ What are the reporting/sharing requirements for the type of data I am generating and the granting agency?
- ❏ What are the data storage requirements?
- ❏ What are your institutional data management requirements?

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Budget Checklist
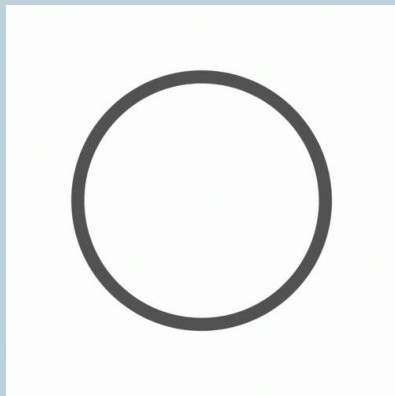
❏ Read the NOF and follow the guidelines.
❏ Be reasonable with your budget needs and make sure they are clearly justified and relate to your research needs in the grant.
❏ Do not pad or overinflate your budget.
❏ Do plan for some error in methods development and experimental error.
❏ Validate and walk through your resource needs
❏ Make sure you are clearly explaining your needs to guarantee the best estimated quote.

- Internal resources:
  - Institutional Core Management Software such as:
    - iLAB, Stratacore, home grown
  - Dean of Research website
  - Your internal institutional Core/Shared Resources website
  - Your favorite search engine
  - Your local sales rep from your favorite company

- External resources:
  - Core Marketplace (https://coremarketplace.org/)
  - ABRF (https://www.abrf.org/)
  - iLab
  - Stratacore

- Potential funding/collaboration opportunities:
  - Chan Zuckerberg (https://chanzuckerberg.com/grants-ventures/grants/), CIDR (https://cidr.jhmi.edu/), GREGoR (https://gregorconsortium.org/), Rare Disease Consortium (https://rarediseases.info.nih.gov/), Simons Foundation (https://www.simonsfoundation.org/funding-opportunities/), etc.
  - NIH institutionally sponsored Core facilities
  - Institutional vouchers/Startup credits?

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You should:

- **Provide a written draft of your aims**
- Provide as much specific detail as possible (including references)
- Understand budget constraints
- Make an attempt to understand the technology prior to the meeting, if possible
- If you don't think you understand the technology, prepare a list of questions to help clarify what you don't understand
- Ask if they work with other facilities that might be linked to your study process
- Provide your timeline

Your Core Director should:

- Take time to consider the proposal aims
- Provide information on the best uses of the technology
- Provide information on the best sample types for the technology
- Connect you to other cores, if appropriate
- Analyze your project for strengths and weakness from the technological perspective
- Provide language for methods to address research aims
- Possibly make suggestions for alternative technologies
- Possibly provide language for data management plan
- Provide advice on budgeting for the project
- Provide quotes and letters of support in a timely manner

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What do cores bring to the table?


❏ Experienced scientists who are experts in advanced technologies and services that enhance research and maximize efficiencies

❏ Trained staff who have a broad range of expertise across technologies and connections to others in their field

❏ Maximizing usage while minimizing cost to you

Spatial Transcriptomics

Cores needed:
- Histology/Pathology
- Imaging
- Genomics
- Data analysis

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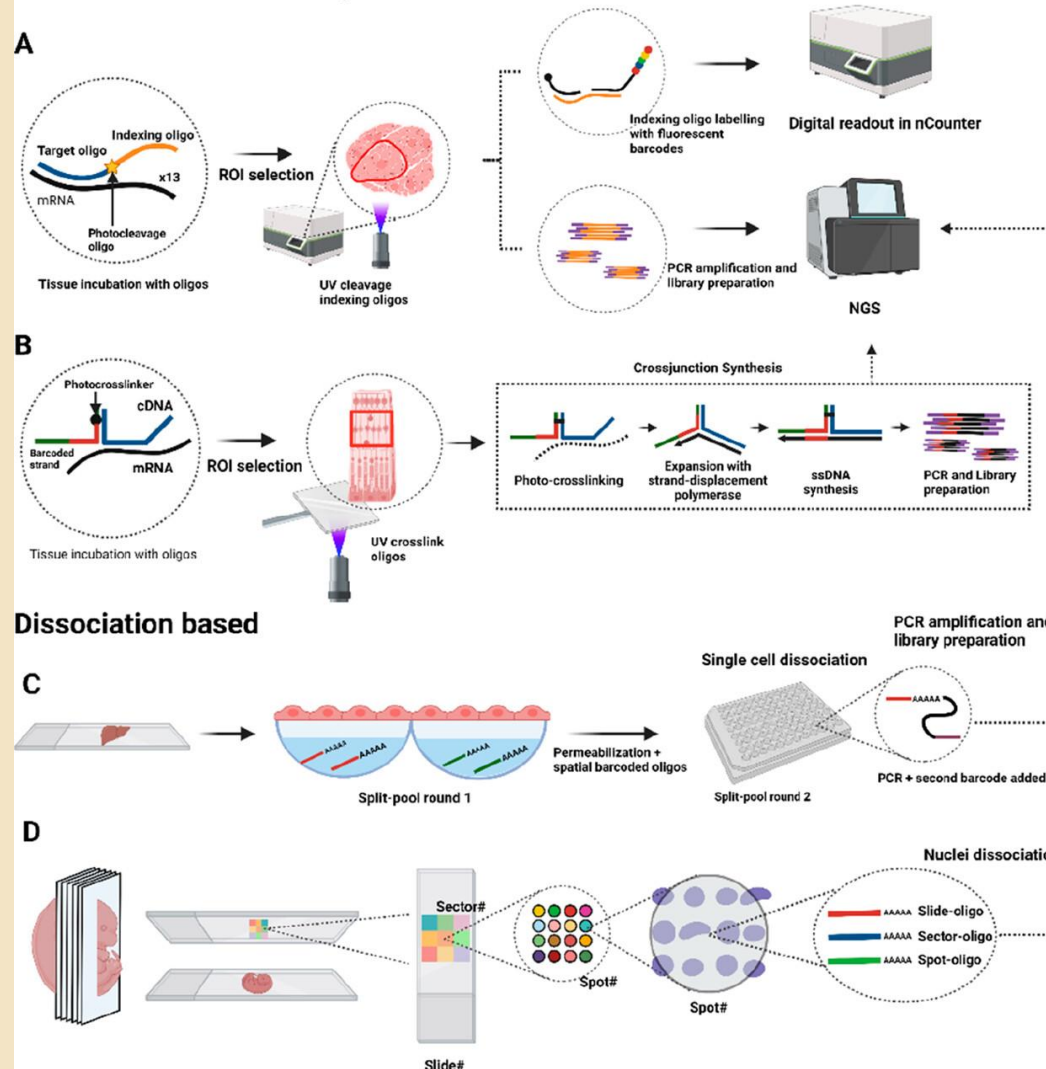
Spatial Transcriptomics

Seems like it went well. So why is she screaming?
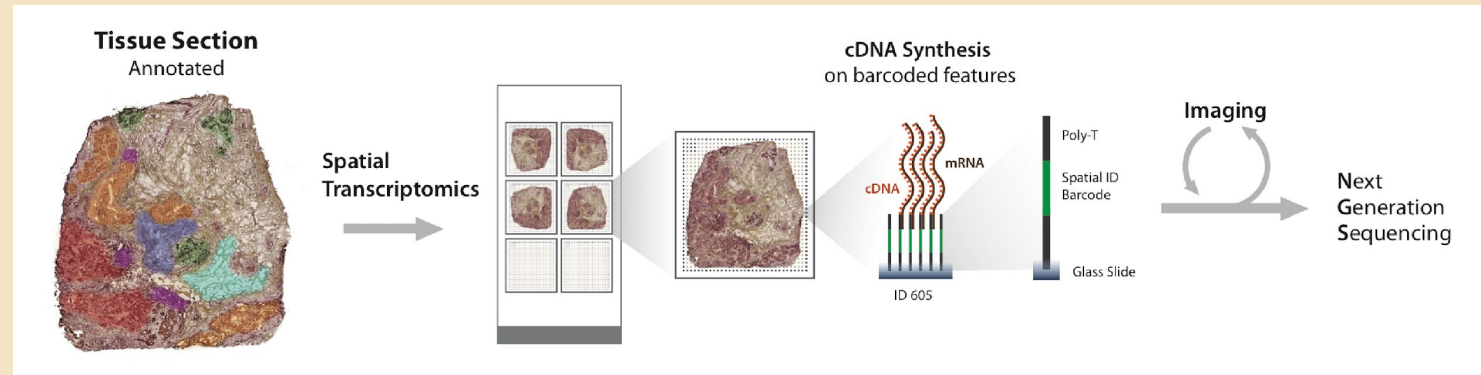
- PI wants to try out spatial transcriptomics. Talks to their genomics core lab who has expertise in the genomics but not histology. They recruit the histology lab for the sectioning process.
- Genomics core purchases the Visium slides and hands them to histology tech…..
- Histology tech cuts sections on 3 slides and chooses best one for NGS…………..

- Genomics core finishes the process and produces the data

Choosing the appropriate technology:

- A PI working on salivary gland development has utilized microarray technology for many years. One of their grant applications was criticized by a reviewer who said RNAseq was the way to go. PI decided to present preliminary data demonstrating RNAseq in their revised grant application due in a few weeks

- Salivary glands in mice were harvested and processed for RNAseq
- No surprises in RNA extraction, library prep or sequencing……

- BUT!!!

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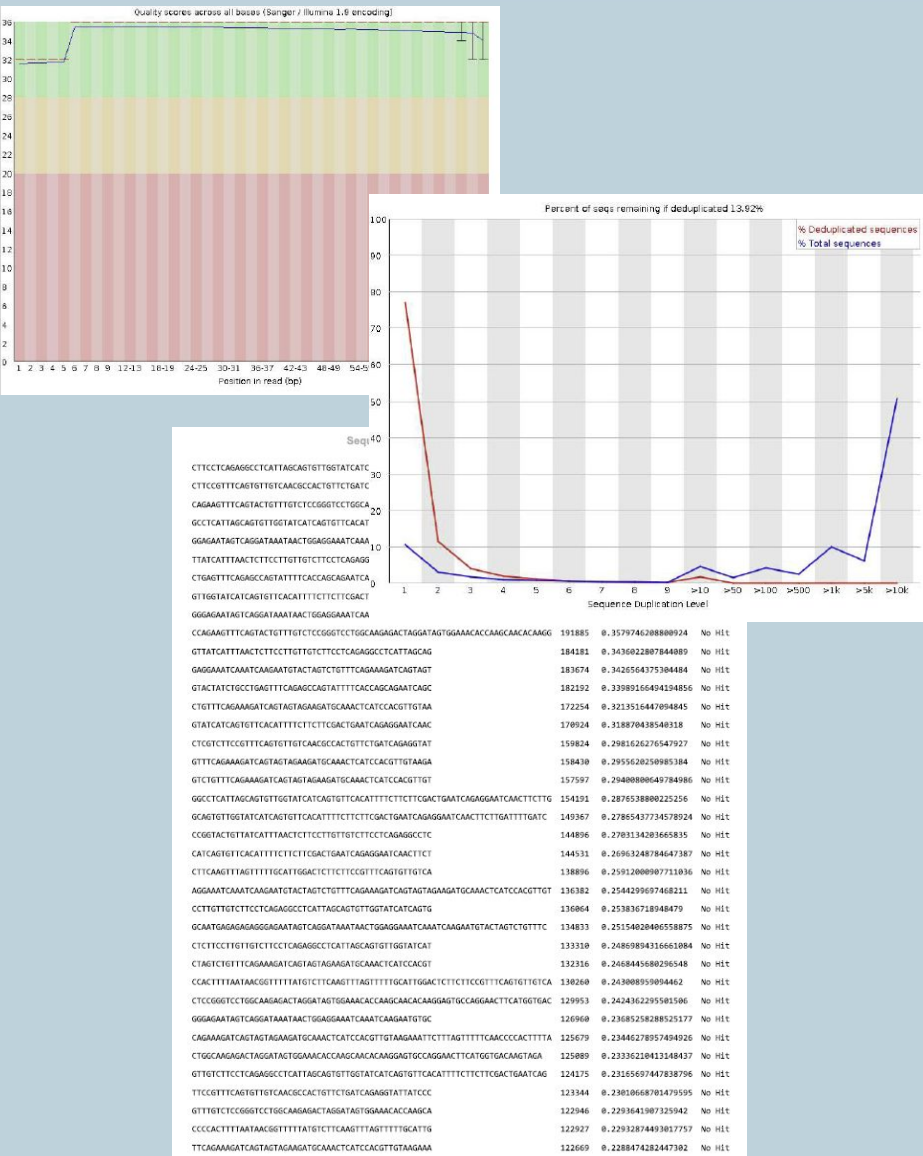
- Lots of reads attributed to overrepresented sequences…..MUCIN transcripts!!!

- Core recommended use of the Clariom S arrays for gene expression
- Data generated over next 2 days and used as preliminary info for the grant submission
- Grant funded subsequently

- Since then:
  - Dissociation protocols optimized
  - RNAseq and scRNAseq data successfully generated

- Miniaturization of reaction volumes to decrease costs

- Choosing best solutions for ribosomal reduction depending on sample input amounts

- Best practices for sample collection, isolation, processing
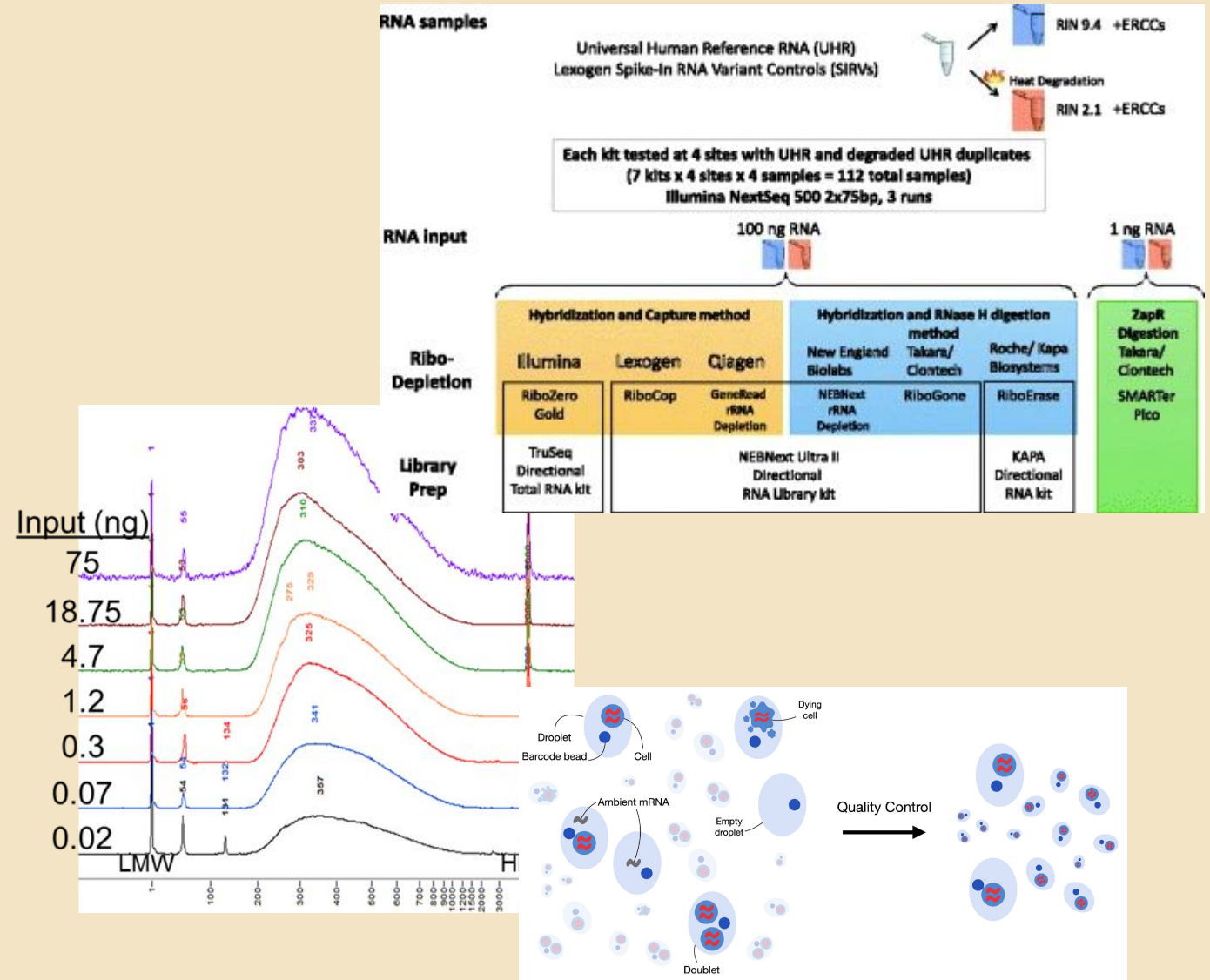
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Taking the Big Leap:

Translating Your Discovery into Clinical Utility

You've now discovered a potential new biomarker that is predicted to have an association with a disease.

Now what?

Cores can accelerate the clinical translation process

Stages of Translational Research

- Basic Research
  - Discovery Science
- Preclinical Research
  - Optimizing an assay and associated data analysis and informatics and identifying an appropriate platform
- Clinical Research
  - Obtain data to support regulator approval
- Clinical Implementation
  - Demonstrating utility in patient populations
- Clinical Care
  - The ultimate goal

Basic Research:

Identification of over 12 specific CYP2C19 alleles associated with clopidogrel response.

Those with highest frequencies include *2, *3, and *17.

Clopidogrel (Plavix): Most commonly prescribed anti-platelet Therapy

- Genome-wide Association Study: Identifying a genetic association with clopidogrel (Plavix) response
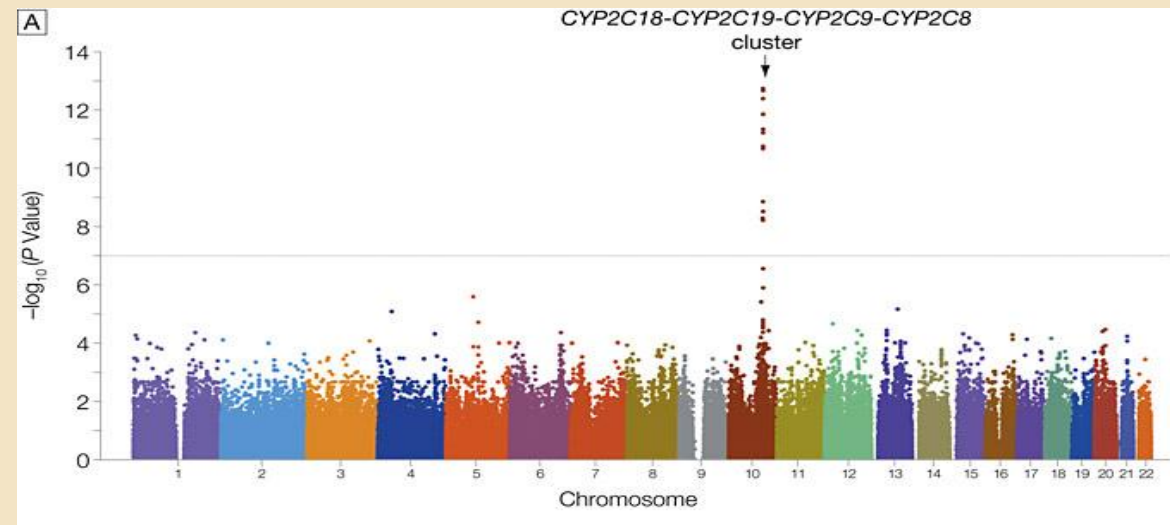
Shuldiner et al (2009) JAMA

Preclinical Research

- Platform optimization
  - Taqman
  - Verigene
  - Spartan
  - GenMark
    - Speed and accuracy
- Identification of positive and negative controls
  - Coriell (comprehensive panel of controls)
- Racial bias towards specific alleles?
- Data analysis

Each aspect can be facilitated in your core

Clinical Research:

Pharmacogenomics of the Anti-Platelet Intervention (PAPI) with Clopidogrel (Plavix)

- Defining response in humans
- Assessment of safety and effectiveness
- Demonstrate optimized assay/platform

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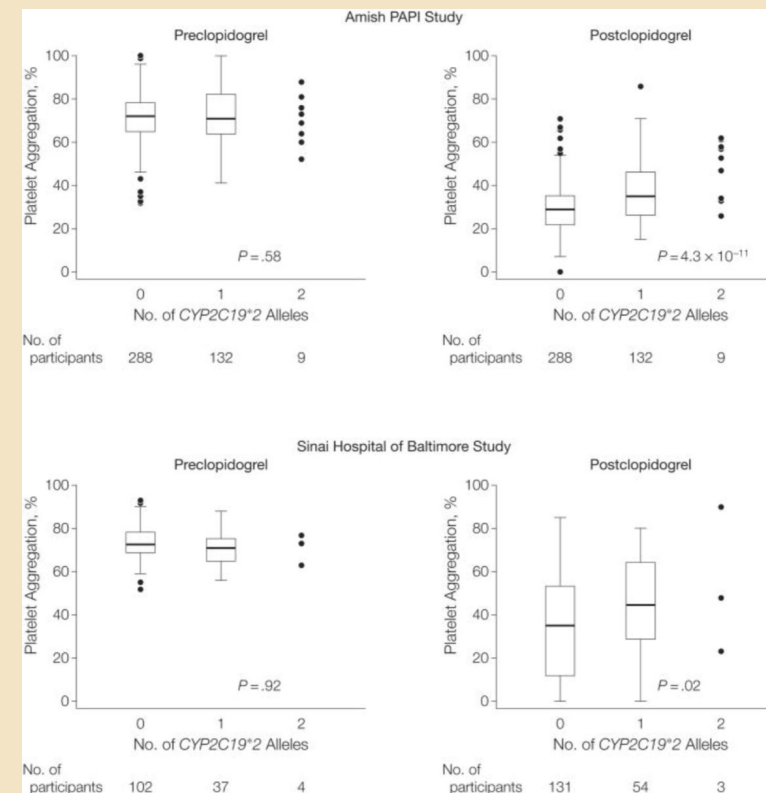
Clinical Implementation:

Multi-Site Study

Clinical Implementation of *CYP2C19* Genotype-Guided Antiplatelet Therapy after PCI at 7 U.S. Institutions

MACE: Major Adverse Cardiovascular Event (myocardial infarction, stroke, death)

Kaplan-Meier Survival Estimates of MACE in Relation to *CYP2C19* Genotype and Antiplatelet Therapy

LOF: Loss of Function allele

Log-rank p=0.016
Log-rank p=0.15

LOF-Clopidogrel
Non-LOF
LOF-Alternative

No. at risk							
LOF-Clopidogrel	226	112	89	76	63	39	3
Non-LOF	1243	759	636	577	451	293	28
LOF-Alternative	346	245	221	195	161	112	9

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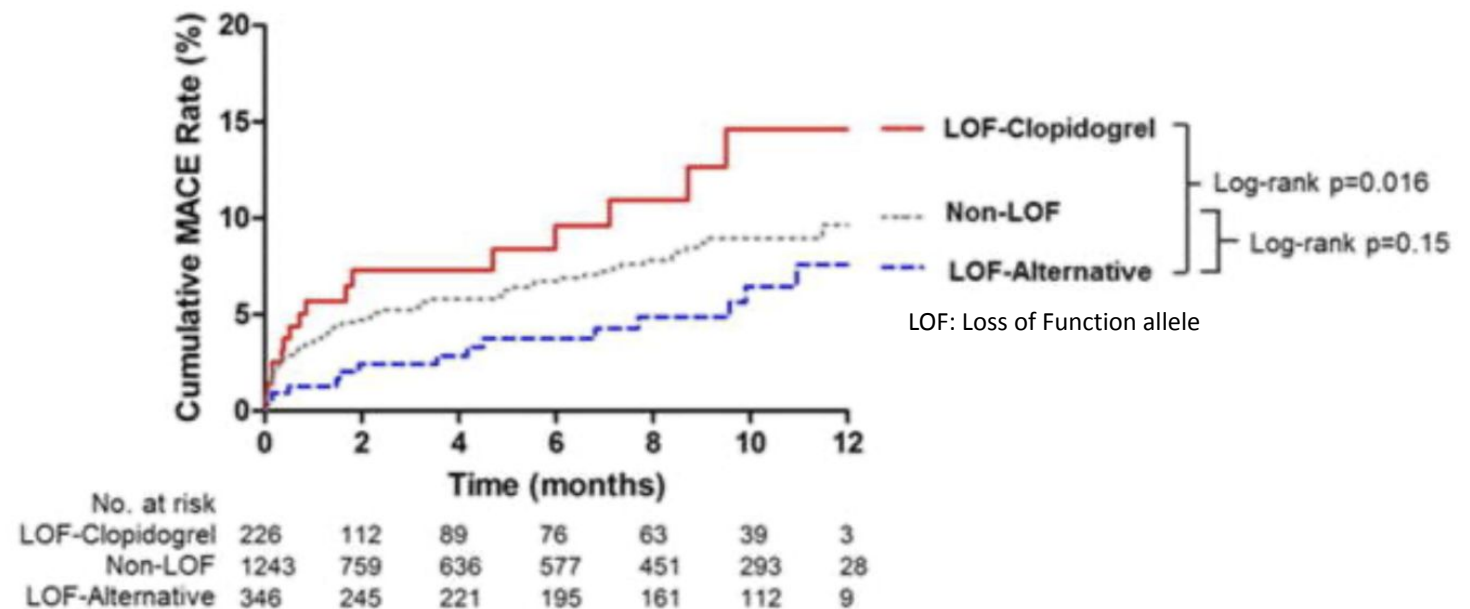
Impact on Clinical Care

Metabolizer phenotype	Genotype	U.S. population	Response to clopidogrel
Ultra-rapid (UM)	2 increased function alleles (*17/*17)	1-5%	Normal or increased antiplatelet response to clopidogrel
Rapid (RM)	1 increased function and 1 normal function allele (*1/*17)	20-30%	Normal or increased antiplatelet response to clopidogrel
Normal (NM)	Absence of any tested increased function or LOF alleles (*1/*1)	35-50%	Normal antiplatelet response to clopidogrel
Intermediate (IM)	1 LOF allele (*1/*2, *1/3, *2/17, *3/*17)	20-30%	Reduced antiplatelet response to clopidogrel
Poor (PM)	2 LOF alleles (*2/*2, *2/3, *3/*3)	1-5%	Significantly reduced antiplatelet response to clopidogrel

WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE

The effectiveness of Plavix results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*. Plavix at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed "CYP2C19 poor metabolizers"). Tests are available to identify patients who are CYP2C19 poor metabolizers *[see Clinical Pharmacology (12.5)]*. Consider use of another platelet P2Y$_{12}$ inhibitor in patients identified as CYP2C19 poor metabolizers.

Sanofi package insert

Translation of Genomic Discovery into Clinical Utility

Cores can support many of these stages of Translational Research.

At some stages, there is a requirement for a Core to operate as a **clinically-regulated lab**, but many institutions do have these labs, which can collaborate with genomic cores to transfer assays and methodologies to simplify the process.

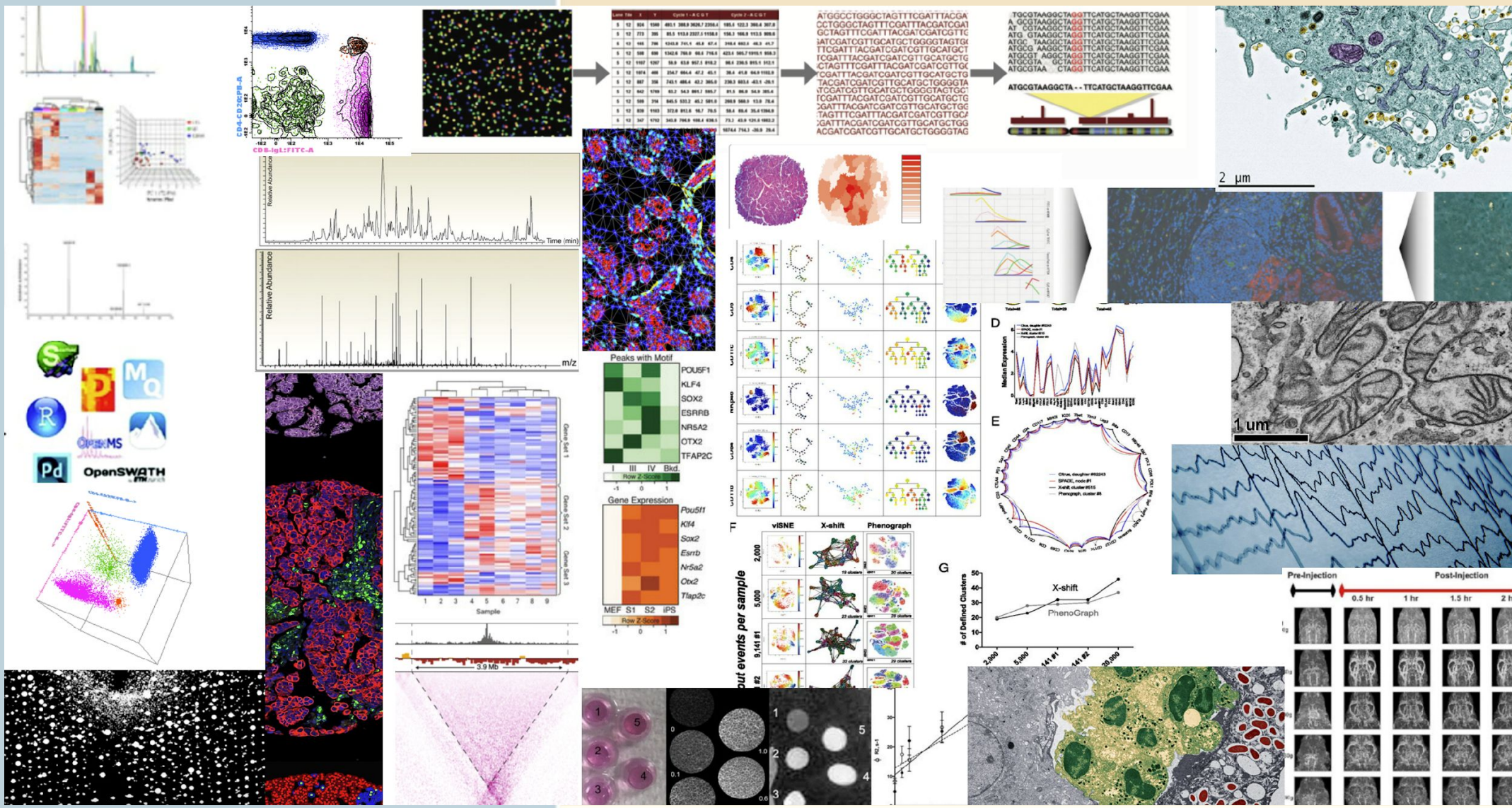The Association of Biomolecular Resource Facilities

For Shared Resource core labs, **Data is our key deliverable**

Our mandate is to support F.A.I.R. data principles to ensure data sharing and future data re-use across disciplines through data annotation with essential descriptive information – metadata

Data Accumulation/ Generation → Metadata Management → Data Migration → Data Architecture → Data Filtering/QC → Data Analysis
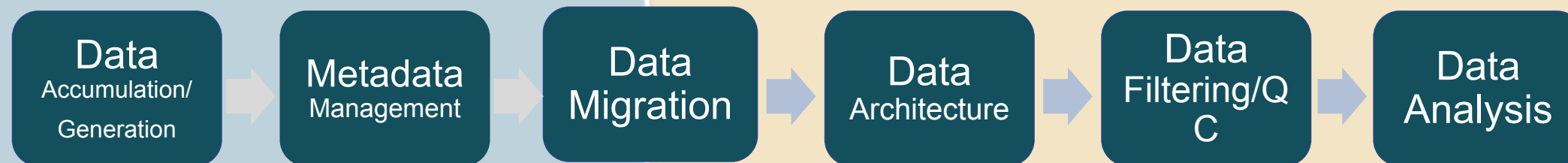
Good data management is not a goal in itself, but rather is the key conduit leading to knowledge discovery and innovation, and to subsequent data and knowledge integration and reuse by the community after the data publication process.

FAIR Principles

In 2016, a global consortium of researchers published "The FAIR Guiding Principles for scientific data management and stewardship" in *Scientific Data*:

- Findable
  - Data is described with rich metadata; data is assigned globally unique and persistent identifiers
- Accessible
  - Data and metadata are retrievable
- Interoperable
  - Data can be integrated with other data; data can be used in multiple applications or workflows
- Reusable
  - Data and metadata are well-described so they can be replicated

Wilkinson, M., Dumontier, M., Aalbersberg, I. et al. (2016) Sci Data 3, 160018. https://doi.org/10.1038/sdata.2016.18

ABRF members support FAIR Data Principles and ensure data provenance

- Instrument Standardization
- SOPs
- QA/QC
- Unbiased data acquisition
- Unbiased data analysis
- Documentation
- Source data | metadata | shared data
- Transparent reporting

Experimental Design Acquisition Details

Raw Data

Analyses & Workflows

Derived Data

Publications

Data Repositories

DATA PROVENANCE

Jianwu Wang et al., Proc IEEE Int Conf Big Data. 2015 ; 2015: 2509–2516. doi:10.1109/BigData.2015.7364047
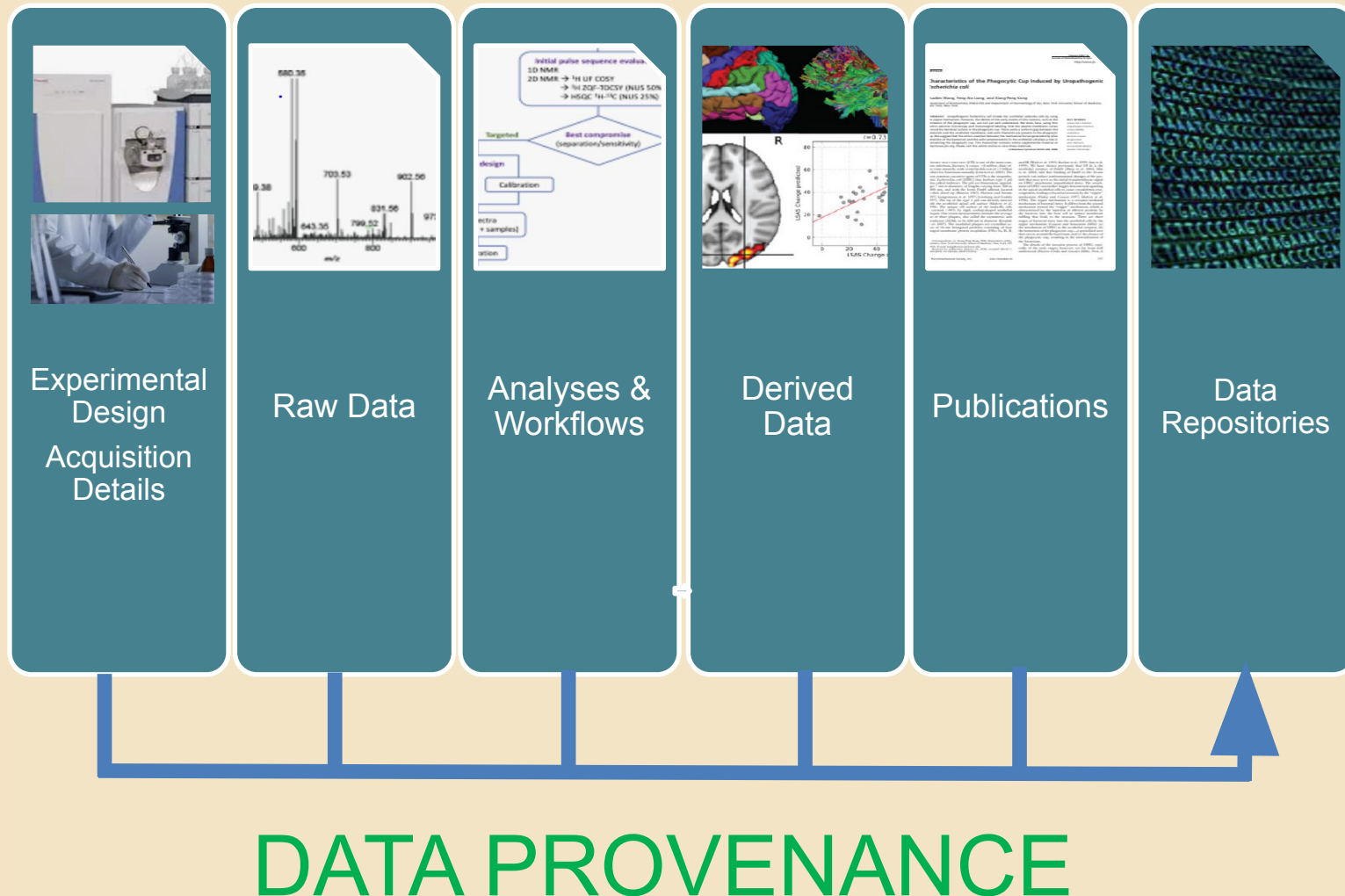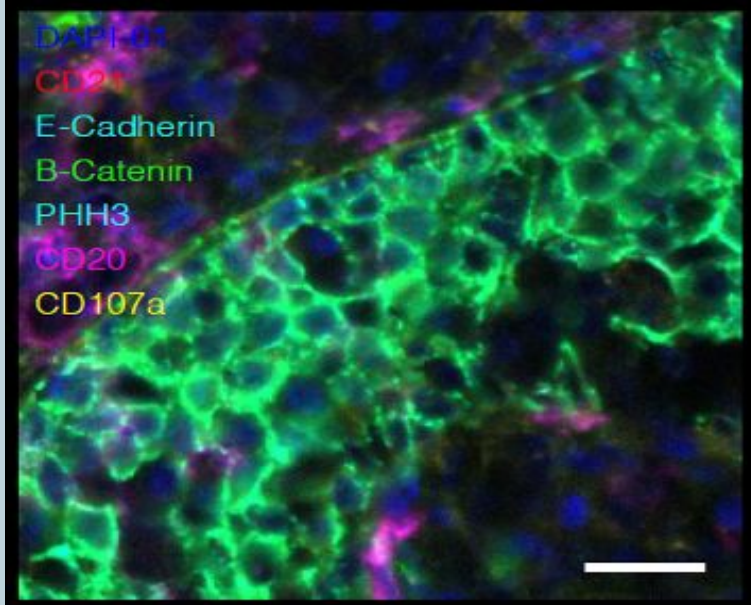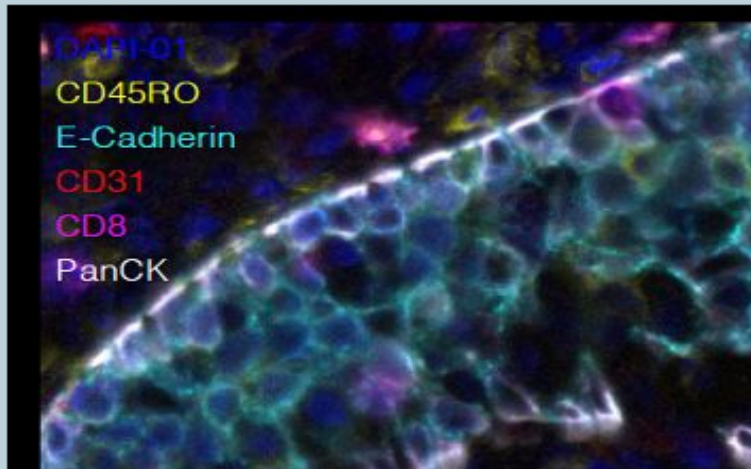
"Typically, the FAIRification process begins when a *community of practice* *considers its* *domain-relevant metadata requirements* and other policy considerations, and formulates these considerations as machine-actionable metadata components."

Wilkinson, M. Sci Data 3, 160018 (2016)

PERSPECTIVE
https://doi.org/10.1038/s41592-021-01316-y

nature | methods

Check for updates

Spatial mapping of protein composition and tissue organization: a primer for multiplexed antibody-based imaging

John W. Hickey[1,26], Elizabeth K. Neumann[2,3,26], Andrea J. Radtke[4,26]✉, Jeannie M. Camarillo[5], Rebecca T. Beuschel[4], Alexandre Albanese[6,7,25], Elizabeth McDonough[8], Julia Hatler[9], Anne E. Wiblin[10], Jeremy Fisher[11], Josh Croteau[12], Eliza C. Small[13], Anup Sood[8], Richard M. Caprioli[2,3,14], R. Michael Angelo[1], Garry P. Nolan[1], Kwanghun Chung[6,7,15,16,17,18], Stephen M. Hewitt[19], Ronald N. Germain[4], Jeffrey M. Spraggins[3,14,20], Emma Lundberg[21], Michael P. Snyder[22], Neil L. Kelleher[5] and Sinem K. Saka[23,24]✉

Hickey JW, et al Nat Methods Vol 19 p284 (2022)

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1. Determine Sponsor Requirements
2. Identify the Data to Be Collected
   Types | Sources | Volume | Data and file formats
3. Define How Data Will Be Organized
4. Explain How Data Will Be Documented
5. Describe How Data Quality Will Be Assured
6. Data Storage and Preservation Strategy
7. Define Project's Data Policies
8. Describe Data Sharing
9. Assign Roles and Responsibilities
10. Prepare a Realistic Budget

A. Research Cycle

B. Data Life Cycle

A.
4. Publish & Disseminate Findings
1. Formulate Ideas & Hypotheses
3. Analyze, Visualize & Interpret
2. Acquire Data

B.
1. Plan (1,7 9,10)
8. Share the Data (7,8)
3. Collect & Organize New Data (2,3)
2. Discover Existing Data (2,3, 7)
7. Preserve the Data (6,8)
4. Assure Data Quality (5)
6. Use the Data (4)
5. Describe the Data (4)
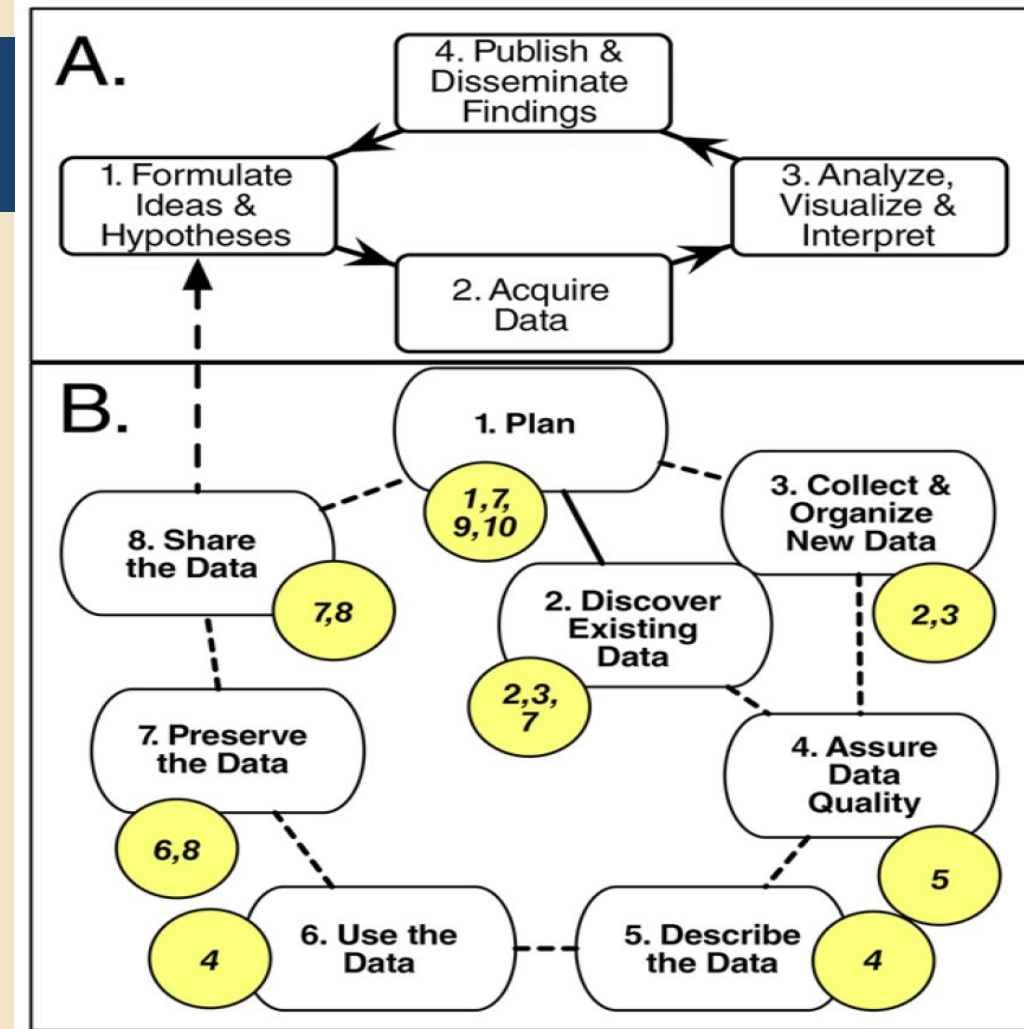
NIH Policy for Data Management and Sharing
- effective date January 2023

Scope:
All research that will generate scientific data with any NIH funding must include a plan for data sharing (*or state what sharing is not possible)*
Includes
- Competing grant applications submitted to NIH
- Contract proposals
- NIH Intramural Research Projects
- Other funding agreements with NIH (e.g., Other Transactions)

Persistent Unique Identifiers: Assigns datasets a citable, persistent unique identifier (PUID), digital object identifier (DOI) or accession number, to support data discovery, reporting (*e.g.,* of research progress), and research assessment (*e.g.,* identifying the outputs of Federally funded research).

- ***Best practices include using RRID for cores that have provided data for your grant, publication, presentation.***

Reuse: Enables tracking of data reuse (*e.g.,* through assignment of adequate metadata and PUID).
Provenance: Maintains a detailed logfile of changes to datasets and metadata, including date and user, beginning with creation/upload of the dataset, to ensure data integrity.
Metadata: Ensures datasets are accompanied by metadata sufficient to enable discovery, reuse, and citation of datasets, using a schema that is standard to the community the repository serves.
Curation & Quality Assurance: Provides expert curation and quality assurance to improve the accuracy and integrity of datasets and metadata.
Common Format: Allows datasets and metadata to be downloaded, accessed, or exported in a standards-compliant, and preferably non-proprietary, format.
Long-term sustainability: Has a long-term plan for managing data, including guaranteeing long-term integrity, authenticity, and availability of datasets; building on a stable technical infrastructure and funding plans; has contingency plans to ensure data are available and maintained during and after unforeseen events.
Retention: Data is maintained in accordance with this Policy for the longer of (i) three (3) years after the final project close-out or (ii) six (6) years after any reporting, publication, presentation, or use in any grant application by the researcher of such Research Data.
Research Data relating to a student project must be retained at least until the degree is granted or it is clear that the student has abandoned the work.
Secure: Provides documentation of meeting accepted criteria for security to prevent unauthorized access or release of data, (i.e., ISO 27001 (*https://www.iso.org/isoiec-27001-informationsecurity.html*) or NIST 800–53 controls (*https://nvd.nist.gov/800-53*)
Privacy: Provides documentation that administrative, technical, and physical safeguards are employed in compliance with applicable privacy, risk management, and continuous monitoring requirements.

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Data Collection:	• What data will you collect or create? • How will the data be collected or created?
Documentation and Metadata:	• What documentation and metadata will accompany the data?
Ethics and Legal Compliance:	• How will you manage any ethical issues? How will you manage copyright and Intellectual Property Rights (IP/I)
Storage and Backup:	• How will the data be stored and backed up during the research? • How will you manage access and security?
Selection and Preservation:	• Which data are of long-term value and should be retained, shared, and/or preserved? • What is the long-term preservation plan for the dataset?
Data Sharing:	• How will you share the data? • Are any restrictions on data sharing required? • Does it need to be placed in a funding agency sponsored repository?
Responsibilities and Resources:	• Who will be responsible for data management? • Do you understand what the metadata means?

Budgeting in Research Centers/Cores/Facilities for Grants

What is a Budget?

It is a Plan   a forecast   an informed estimate

"An estimate, often itemized, of expected income and expenses for a given period of time."

Your financial roadmap

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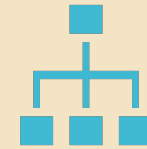Biomolecular Resource
Facilities

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Expenses

What is a Budget?

Operating costs

Continuous costs: Salary, lab supplies,
conferences, overhead

Dependent Costs: One-time large expenses
(capital, service contracts, etc.)

Qualitative Adjustments

Meta/Macro/Meso Influences:
Policy
Culture

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Preparing your Budget

★ Read the NOF or Required format for the funder.

★ Walk through your Specific Aims and identify the resources you would need to complete the work.

★ Identify the costs and obtain quotes and fiscal information for each component.

★ Ensure your expenses can be justified in the context of the proposal.

Things not to do

★ Do not pad your budget.

★ Do not assume every cost will be understood as a need by the reader. Explain it.

★ Do not give broad estimates of costs. Itemize it.

★ Do not list cost covered by your organization.

★ Do not list costs the funder clearly states they will not fund.

★ Do not wait until the last minute to put together your budget your organization will most likely want to review this prior to your submission – allow for that time.

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Compiling the information

Software	Analysis	Services
Study Support	Salaries	Grant Writing Support
Conferences and Travel	Collaborators	Resources for New PIs

Gathering Information will build accuracy

Budget Building Blocks

Building your Budget

Keep it on target: Justify and adequately explain all your expenses for your research project

Description of line item	How it related so the activities in your work plan	Budget Amount
Recruit Research Participants	Provide $50 Compensation to 100 Research Participants	$5,000
Sequence and Library Prep for 100 samples.	Conduct sequencing for each research participant	$100,000
SPSS Software	To conduct Statistical Analysis	$300
Publication Costs	To publish discovered works	$5000
Data Storage Costs	Costs of storing Data	$100

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Working with Core Facilities

★ Be clear with your needs

★ Request an actual quote

★ Project for rate increases over the future years

★ Review the quote with the Shared Resource and your Mentor

★ Make sure your expenses line up with your research objectives

★ Do not budget for items you do not need in your study

★ Predict for unexpected repeats needed in experiments

★ Predict for methods development

★ Review your research proposal and needs to ensure all resources are covered in your budget assessment.

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Considerations For Building your Budget

★ Keep it on target: Justify and adequately explain all your expenses for your research project

★ Plan for what you can do and can afford

★ Include Personnel Costs with appropriate amounts of effort.

★ Compare past award to outline what has been funded

★ Do not forget to include your effort

★ Focus on your scope of research and keep your expenses aligned with your project needs.

★ Be specific, not broad.

Example of Budget Building Exercise for a Grant Application

Build the Budget

	Justification	Year 1	Year 2	Year 3	Year 4
Personnel					
Person A	PI Effort @ 25%	$XXX	$XXX	$XXX	$XXX
Person B	Graduate Assistant @ 10%	$XXX		$XXX	
Fringe	Fringe – 23.5 %	$XXX	$XXX	$XXX	$XXX
Equipment	Need Cell Counter, PCR Machine, and Gel Reader		$XXX		
Materials and Supplies	Reagents, consumables, cell dye, office supplies.	$XXX	$XXX	$XXX	$XXX
Travel	Travel to one Conference Year 1 and 3	$XXX		$XXX	
Contractual Agreements	Subcontract agreement	$XXX	$XXX	$XXX	
Other Direct Costs	Publication Fees, Data Storage Costs,			$XXX	$XXX
Shared Research Resource	Data Analysis and Informatics Support, Flow Cytometry Services, DNA Sequencing.	$XXX	$XXX	$XXX	$XXX
F&A	60.5%	$XXX	$XXX	$XXX	$XXX
TOTAL		$XXXXX	$XXXXX	$XXXXX	$XXXXX

The Association of Biomolecular Resource Facilities

Why Budgeting Does not Work

Poor information sources

Inaccurate Quoting

Making the process too complex

Research Aims do not line up with Resources in Budget

Not accounting for all costs

Blissful ignorance

Not talking to your institutional resources

Inflating Costs

- Trust your core director (but verify, to quote a dead president)
- Use your core director to strengthen your application
- Advantages of a core over a commercial company
  - The core cares about your science, not the profit margin
  - They are on-site and available
  - Or are academic and understand you, even if at another institution
  - Many core staff are ABRF members and collectively have a vast amount of experience to tap into through collaboration

Remember: your cores need funding too. We depend on acknowledgments and authorship (when appropriate) to justify our existence both to institutional leadership and the NIH.