Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

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Biomarker Group Updates June 17, 2022

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Presenting: R. Taylor Sundby, MD

Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

REiNS Biomarker Group Members:

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- Edina Komlodi-Pasztor
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- Meena Upadhyaya
- Steven Rhodes
- Robert Soto
- Taylor Sundby
- Jaishri Blakeley
- Aerang Kim
- Onno Faber
- Vito Grasso
- Herb Sarnoff
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Current Projects

1. Centralized resource with NF1 biobanks and biorepositories
2. Manuscript with proposed common data language/model for NF1 biomarker research

NF1 Biorepository Resource

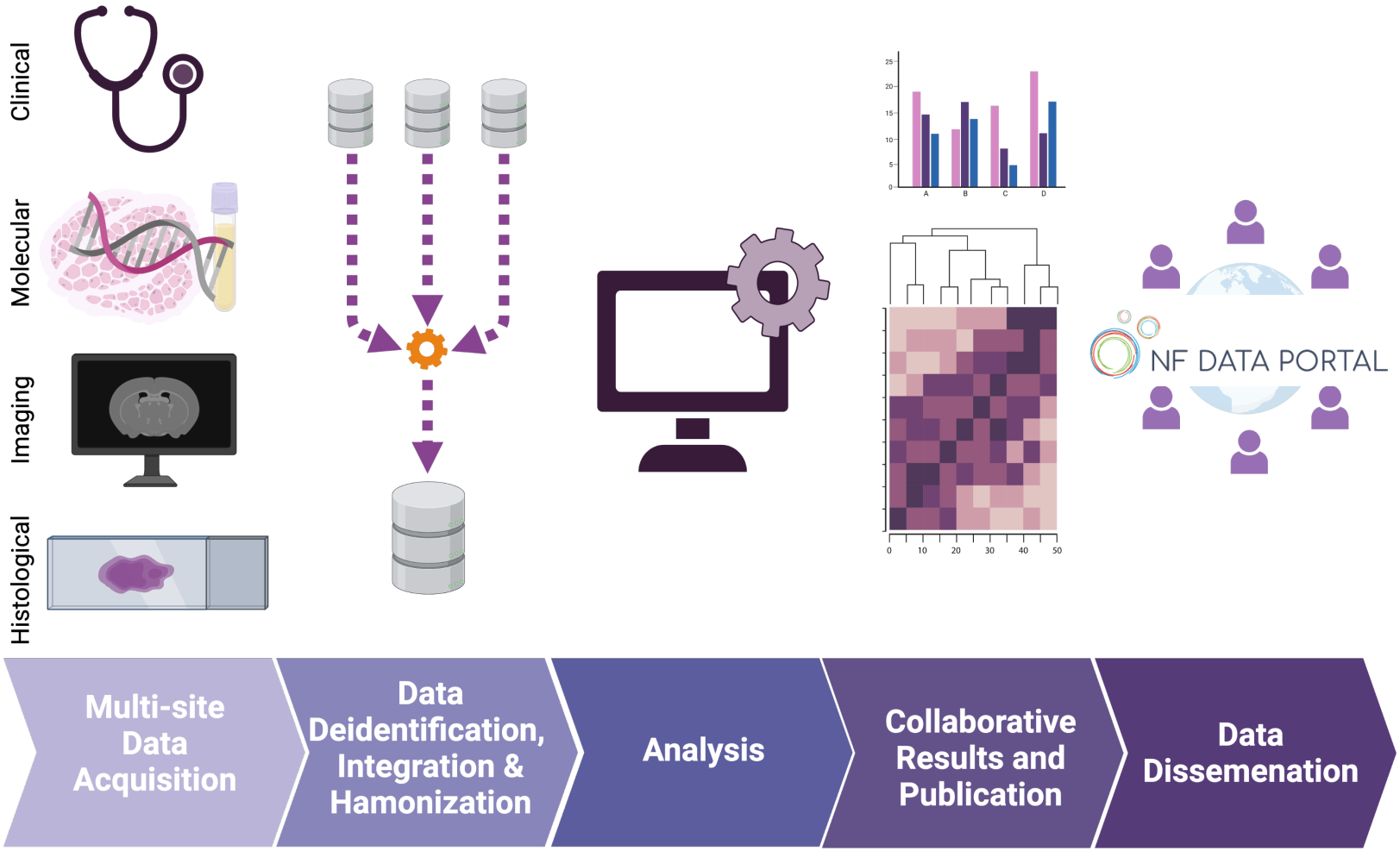
- List of international biobanks/biorepositories with NF1/2 and SWN samples
  - Tissue types, contact information
- List of NF Biomarker publications

- Currently limited to NF1, will expand to NF2, SWN
- Currently .csv, will publish to REiNS website

Manuscript:

Establishment of a common data language (CDL) and common data model (CDM) for neurofibromatosis biomarker research

Multi-institutional collaborations required to study rare diseases



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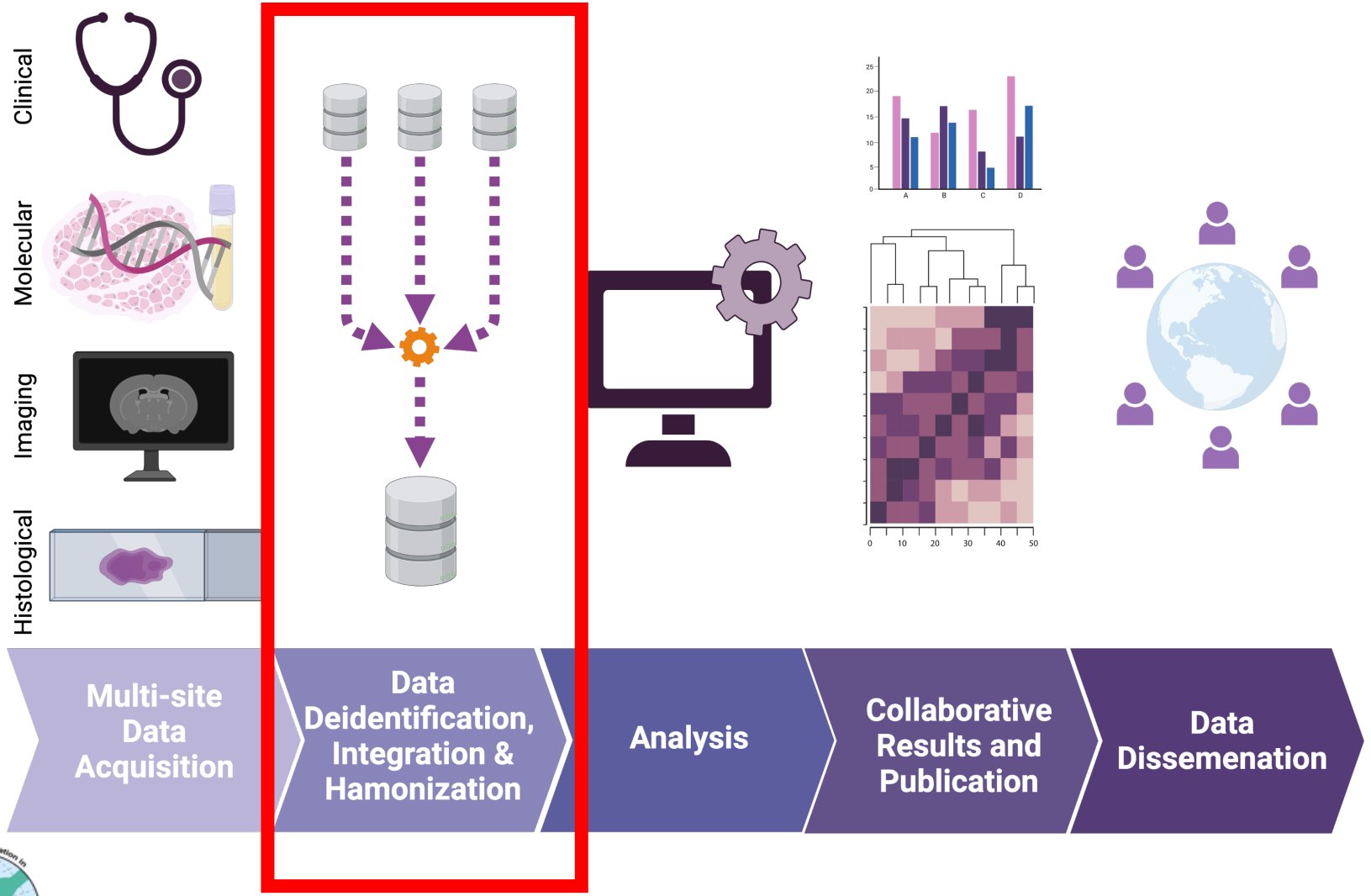

Challenge: Inter- (and intra-) institutional variation in sample collection and annotations complicate data harmonization

Neurology®
The most widely read and highly cited peer-reviewed neurology journal

August 16, 2016; 87 (7 Supplement 1) ARTICLE

Current status and recommendations for biomarkers and biobanking in neurofibromatosis

C. Oliver Hanemann, Jaishri O. Blakeley, Fabio P. Nunes, Kent Robertson, Anat Stemmer-Rachamimov, Victor Mautner, Andreas Kurtz, Michael Ferguson, Brigitte C. Widemann, D. Gareth Evans, Rosalie Ferner, Steven L. Carroll, Bruce Korf, Pierre Wolkenstein, Pamela Knight, Scott R. Plotkin, For the REiNS International Collaboration

First published August 15, 2016, DOI: https://doi.org/10.1212/WNL.0000000000002932

RECOMMENDATIONS FOR SAMPLE COLLECTION AND METHODOLOGY

The REiNS biomarker group discussed potential barriers to biomarker research for NF. These barriers include the low prevalence of NF1, NF2, and schwannomatosis, which makes coordinated studies technically difficult and expensive; the extreme variability of these conditions requires expert clinical researchers to accurately phenotype patients. Based on this discussion, the group endorsed the following goals to advance the study of biomarkers within the NF community:

1. Build a prospective biorepository of curated samples. The aim would be to collect longitudinal samples from each patient to facilitate the development of early detection and prognostic markers.
2. Standardize tissue collection at participating institutions. The aim would be to collect all tissues using an identical protocol that meets standards set forth by the American Association for Cancer Research–Food and Drug Administration–National Cancer Institute Cancer Biomarker Collaborative[4] and would be linked via a shared, anonymized registry (on a Web site). Participating sites would share common consent, SOPs, quality control (see supplemental data on the *Neurology*® Web site at Neurology.org), minimal clinical dataset, and database.
3. Annotate samples with an agreed minimal clinical dataset. The goal is to link anonymously the phenotypic data to deidentified samples in the biorepository. A proposed minimal clinical dataset developed at a consensus meeting in October 2014 is shown in **table 2**. The group anticipates that modifications of this dataset may be required in the future to optimize the utility of biomarker research.
4. Incorporate the decentralized biorepository into existing biorepositories that are used for diagnostic purposes. The biomaterial could thus be used for both diagnosis and research and is not necessarily restricted to an upfront definition of the amount of surplus tissue. Patient care takes preference when allocating the amount of samples used for biomarker investigations.
5. Provide open access to deposited biomarkers to facilitate research. The aim would be to have samples and data open to all qualified researchers with approval of an institutional review board. A biorepository council would govern database requests.
6. An operational and an executive committee will govern requests and audit implementation of SOPs and quality control measures.
7. Incorporate biomarker collection into clinical studies. When feasible, sample collection should be incorporated into prospective clinical trials and natural history studies to help develop pharmacodynamic and predictive biomarkers.
8. Incorporate biomarker collection into routine clinical visits. Patients receiving routine care should be invited to participate in prospective sample collection during routine clinic visits.

RECOMMENDATIONS FOR BIOMARKERS BASED ON EXISTING DATA

1. Validate individual biomarkers as well as cocktails/signatures of biomarkers.
2. For ongoing and planned NF trials, studies of drug metabolism/pharmacodynamic biomarkers should be drug-specific.
3. For malignant tumors such as MPNST, explore and validate cDNA, cRNA, and circulating tumor cells as biomarkers.
4. Validate use of extracellular vesicles (exosomes) based on encouraging preliminary data as biomarkers of cancer.[22]
5. Using candidate approach, focus on the clinically relevant questions, i.e., total tumor load, presence of plexiform neurofibroma, evidence of malignant transformation, and taking into account the statistical significance in published studies. We recommend validating the following biomarker candidates in patients with NF1: BIRC5/TK1/TOP2A immunohistochemistry, ADM, interferon-γ, IGFBP-1, and sAXL.
6. Complement candidate biomarker approach with systematic unbiased approach. Encourage well-powered studies using systematic unbiased approaches, including genomics (DNA, RNA, miRNA next-generation sequencing), metabolomics, and proteomics; that is, further screening with metabolomics, proteomics, expression arrays, and miRNA.

Common Data Model/Language Recommendations Manuscript

1

Review:
* **Variations in practice**
* **Examples of CDM** (OMOP, mCODE)

2

Provider Survey

3

Recommend:
* **Updated minimal clinical annotations**
* **Updated minimal sample collection**
* **NF and SWM specific CDM/L**

Part 2: Provider Survey

- Survey of NF1 Providers* covering:
  - Awareness of 2016 guidelines
  - Variation in current practice
    - Standardized clinical data forms?

**Proposed audience: CTF members (discussed with Salvo and Patrice)*

Table 2 Recommended minimal clinical dataset

Demographics						
Date:						
Sex	☐ male	☐ female				
Birth	☐ month	☐ year				
Diagnosis of NF1, NF2, or schwannomatosis	☐ infancy	☐ childhood	☐ adolescence	☐ adulthood	☐ unknown	
Inheritance	☐ parent affected	☐ parent not affected	☐ unknown			
Mosaicism	☐ patient is mosaic	☐ patient not mosaic	☐ unknown			
Germline mutation	☐ not tested	☐ tested + unknown	☐ determined: (specify __)			
Clinical status						
Status	☐ alive	☐ deceased				
WHO performance status	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
Pain	☐ not a problem	☐ occasional	☐ disabling			
Treatment directed at tumor	☐ no specific therapy	☐ chemotherapy	☐ surgery	☐ radiation	☐ targeted therapy (specify)	☐ clinical trial (specify)
NF1						
≥6 Café-au-lait macules	☐ absent	☐ present	☐ unknown			
Skin fold freckling	☐ absent	☐ present	☐ unknown			
Iris Lisch nodules	☐ absent	☐ present	☐ unknown			
Dermal neurofibromas	☐ absent	☐ scattered	☐ dense	☐ unknown		
Subcutaneous nodular neurofibromas	☐ absent	☐ scattered	☐ dense	☐ unknown		
Diffuse dermal neurofibromas	☐ absent	☐ scattered	☐ dense	☐ unknown		
Spinal neurofibromas	☐ not imaged	☐ absent	☐ 1-3 levels	☐ all levels (cervical, thoracic, lumbar, sacral)	☐ unknown	
Plexiform neurofibromas	☐ present	☐ absent by MRI	☐ absent clinically, but no MRI	☐ unknown		
Optic glioma	☐ unknown	☐ absent	☐ present, asymptomatic	☐ present, symptomatic, not treated	☐ present, symptomatic, treated	
Heart defect	☐ unknown	☐ absent	☐ present (specify)			
Vascular disease	☐ unknown	☐ absent	☐ present (specify)			
Puberty onset	☐ prepubertal	☐ precocious	☐ normal	☐ late	☐ unknown	
Stature	☐ <5th centile	☐ 5th-95th centile	☐ >95th centile	☐ unknown		
Peripheral neuropathy	☐ unknown	☐ absent	☐ present			
Aqueductal stenosis	☐ unknown	☐ absent	☐ present			
Long bone dysplasia	☐ unknown	☐ absent	☐ present			
Sphenoid dysplasia	☐ unknown	☐ absent	☐ present			
Scoliosis	☐ unknown	☐ absent	☐ present			
Intellectual disability	☐ unknown	☐ absent	☐ present			

Continued

Table 2 Continued

NF1					
Learning disability	☐ unknown	☐ absent	☐ present		
Attention deficit disorder	☐ unknown	☐ absent	☐ present		
Pheochromocytoma	☐ unknown	☐ absent	☐ present		
Glomus tumor	☐ unknown	☐ absent	☐ present		
MPNST	☐ unknown	☐ absent	☐ present		
Glioma (not optic glioma)	☐ unknown	☐ absent	☐ present		
GIST	☐ unknown	☐ absent	☐ present		
Leukemia	☐ unknown	☐ absent	☐ present		
Breast cancer	☐ unknown	☐ absent	☐ present		
Other tumors	☐ unknown	☐ absent	☐ present (specify ___)		
NF2					
Vestibular schwannoma	☐ MRI not done	☐ absent by MRI	☐ unilateral	☐ bilateral	☐ unknown
Meningioma	☐ MRI not done	☐ absent by MRI	☐ single	☐ multiple	☐ unknown
Glioma/ependymoma	☐ MRI not done	☐ absent by MRI	☐ present	☐ unknown	
Spinal schwannoma	☐ MRI not done	☐ absent by MRI	☐ single	☐ multiple	☐ unknown
Dermal schwannoma	☐ unknown	☐ absent	☐ present		
Nonvestibular cranial schwannoma	☐ MRI not done	☐ absent by MRI	☐ present (specify)	☐ unknown	
Lenticular opacity	☐ unknown	☐ absent	☐ present		
Schwannomatosis					
Schwannomas (nonvestibular)	☐ only by imaging evidence	☐ 1 pathologically confirmed	☐ 2 or more, at least 1 pathologically confirmed	☐ unknown	
Number of schwannomas	☐ single	☐ scattered	☐ dense	☐ unknown	
Vestibular schwannomas	☐ not imaged	☐ absent by imaging	☐ unilateral	☐ bilateral	☐ unknown
Meningiomas	☐ not imaged	☐ absent by imaging	☐ single	☐ multiple	☐ unknown
Other schwannomatosis-related tumors (please specify)	☐ not investigated	☐ absent	☐ present	☐ unknown	

Abbreviations: GIST = gastrointestinal stromal tumors; MPNST = malignant peripheral nerve sheath tumors; NF1 = neurofibromatosis 1; NF2 = neurofibromatosis 2.

Part 2: Provider Survey

- Survey of NF Providers* covering:
  - Awareness of 2016 guidelines
  - Current practice
    - Standardized clinical data forms?
    - Sample types collected
    - Sample frequency
    - Imaging type collected
    - Imaging Frequency
  - General attitude regarding data sharing
  - General attitudes regarding role of biomarkers in NF

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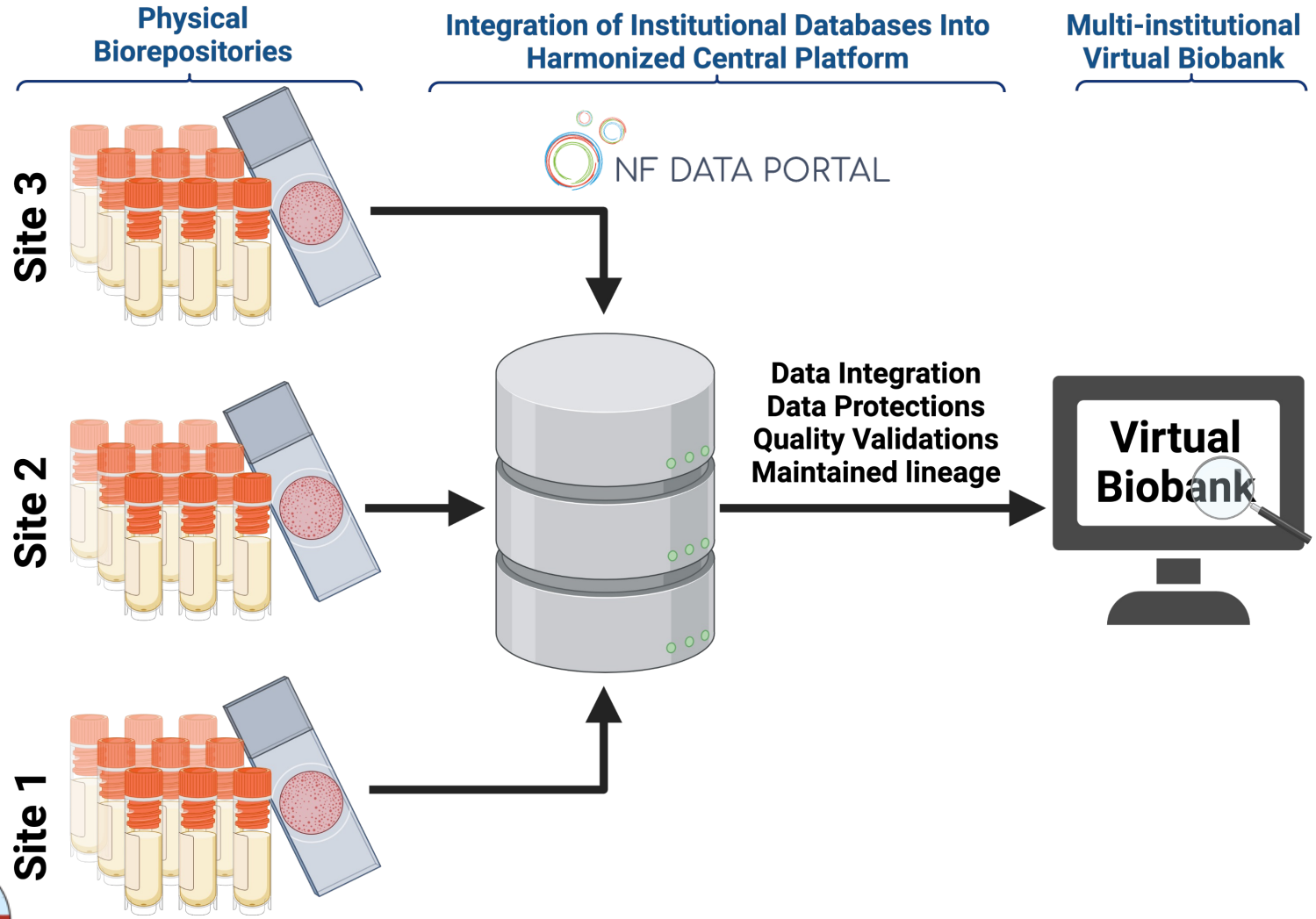
Future Directions: Establishment of a virtual biobank



Thank you!

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