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Biomarkers in decentralized trials

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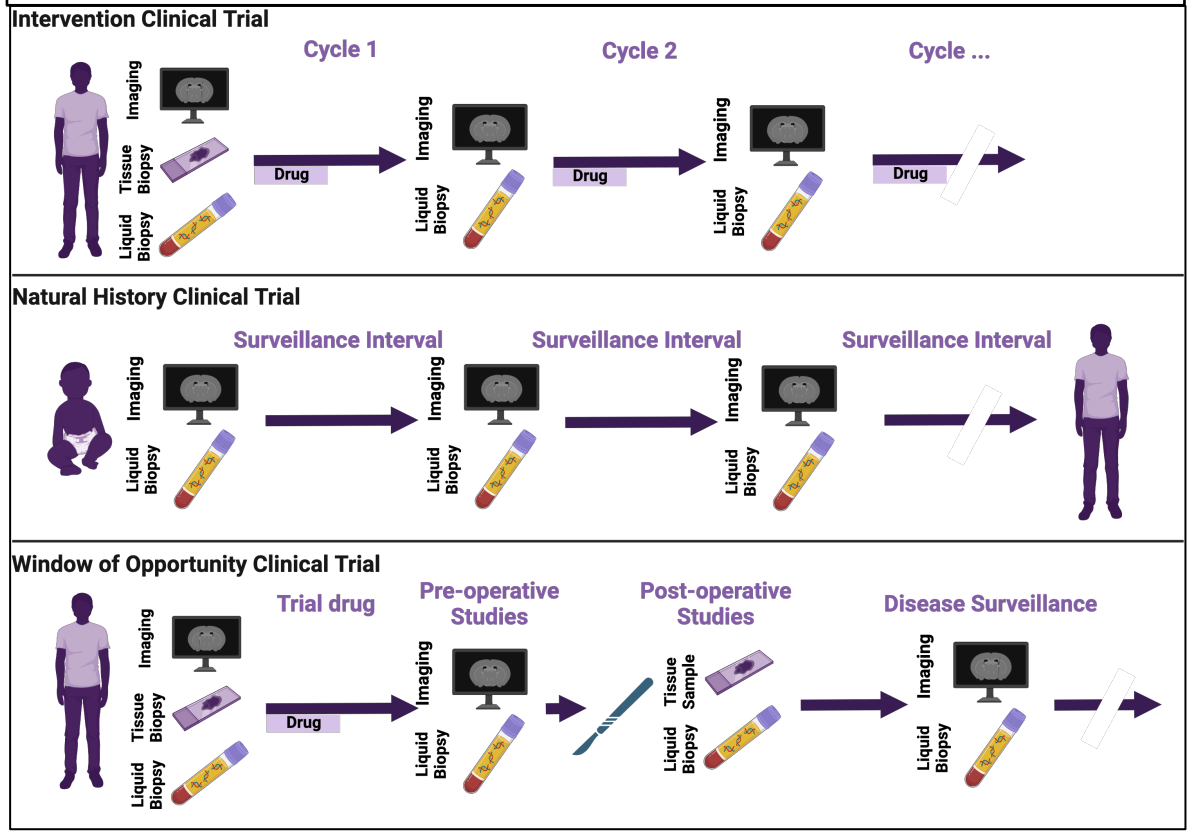
National Cancer Institute

December 3, 2023

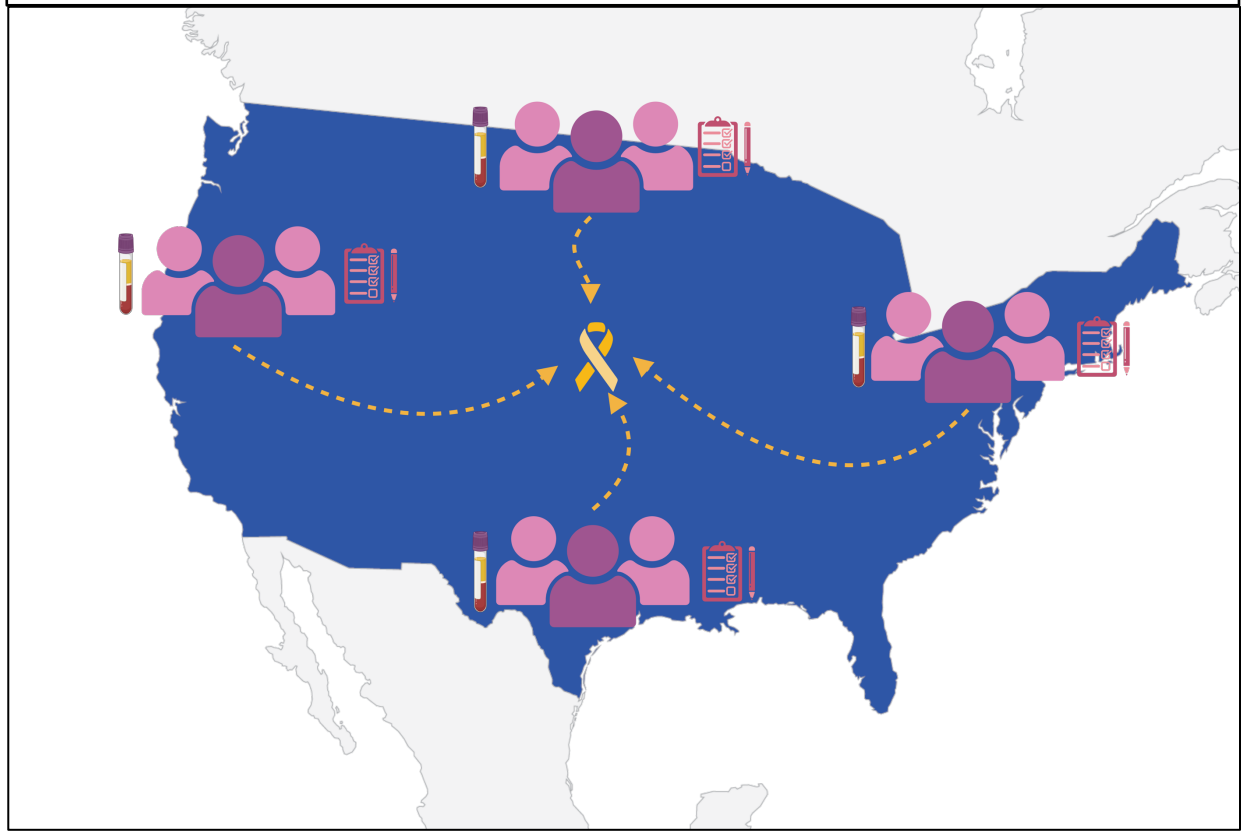
Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

Models of decentralized biomarker implementation

Clinical trial correlatives

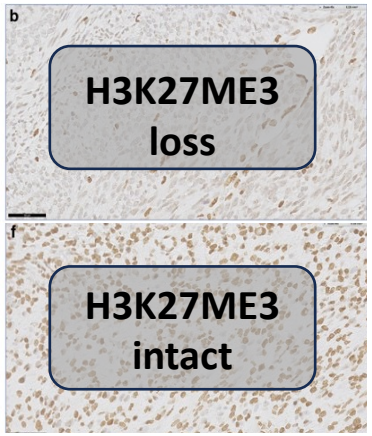


Patient initiated

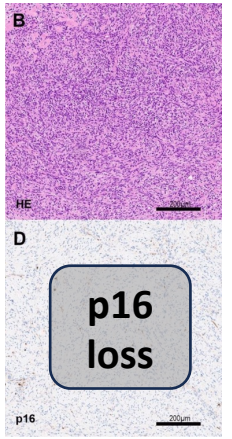


Currently available remote biomarker evaluations

- **Biopsy histology/immunohistochemistry**
  - Peripheral nerve sheath tumors:
    - p16: CDKN2A, potential marker of AN
    - H3K27me^3: MPNST and PRC2 status



(Cleven et al, 2016)



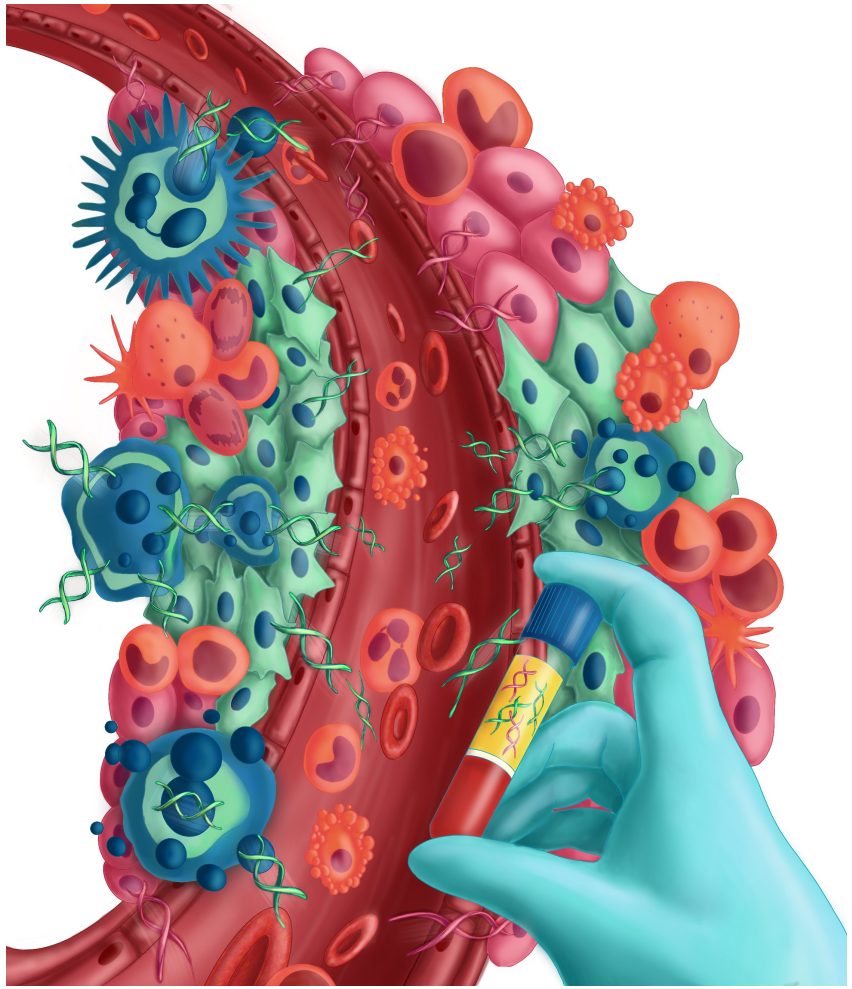
(Rosenbaum et al, 2023)

- **Examples in other settings**:
  - **Laboratory correlatives:**
    - "Web-based Methodology Trial to Evaluate the Efficacy and Safety of Tolterodine ER in Subjects With Overactive Bladder (REMOTE)" (2011, NCT01302938): community laboratory testing
  - **Patient-collected samples:**
    - Immunogenicity and Reactogenicity after SARS-CoV-2 mRNA Vaccination in Kidney Transplant Recipients Taking Belatacept: Blood samples collected by patient using home TAP II device
  - **DNA/RNA sequencing:**
    - "Pilot Decentralized Clinical Trial in Men and Pre and Post-menopausal Women With Breast Cancer and a Specific Mutation (PIK3CA) Treated With Alpelisib in Combination With Fulvestrant (TELEPIK)" (2022, NCT04862143): Decentralized pathology (ER+, PR +/-, HER2-), genetic characterization (PIK3CA, blood or tissue)

[redacted]

Promising technologies for NF1/SWN biomarkers

- **Tissue**
  - AI-assisted histology recognition
  - single cell RNAseq
- **Liquid Biopsy**
  - Circulating proteins
  - Cytokines
  - Cell free DNA



REiNS Biomarker Recommendations

Table 2. Summary of recommendations for incorporation of biomarker correlatives in NF1/SWN clinical trials.

- When feasible, unstained research tissue samples should be collected at study enrollment and all clinical tissue evaluations.
- Circulating biomarkers should be collected, at a minimum, with:
  - Study enrollment
  - Tissue biopsy or resection
    - Circulating biomarkers (cfDNA, cytokines, proteins): preoperatively, 72 h postoperatively, 4 weeks postoperatively
  - Suspected or confirmed disease progression
  - Imaging studies

REiNS Biomarker Recommendations

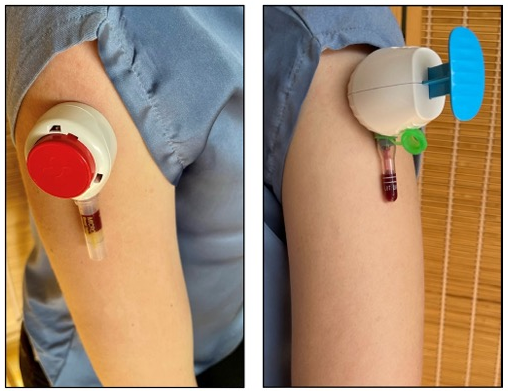
Table 3. Summary of recommended best practices for data annotation.

- Clinical minimal annotations per 2016 REiNS Biomarker guidelines
  - Standardized vocabulary using the Observational Medical Outcomes Partnership Oncology Module supplemented by 2016 REiNS Biomarker guideline terms
- Sample annotation should describe samples of interest as well as matched datapoints/studies
  - Time from sample collection to sample processing/storage
  - Minimal annotation of paired tissue should:
    - Detail timing relative to the candidate biomarker collection
    - Document timing relative to administration of last dose of therapeutic agent (if applicable)
    - Document timing from tissue collection to processing/storage
    - Address all criteria of consensus histologic or genomic guidelines
  - Minimal annotation of paired imaging should:
    - Detail timing relative to the candidate biomarker collection
    - Detail imaging modality and anatomic locations
    - Include ADC if DWI performed
    - Include SUV if PET performed
    - Include sum of the longest diameter and, if available, volumetrics
    - Include RECIST category, if relevant
- NF1/SWN experimental data should be annotated per the NF OSI metadata dictionary ontology and data structure.
- We recommend harmonization of existing NF1/SWN data through funding and maintenance of extraction, transformation and loading processes with disease-specific terms and dictionaries on a central NF1/SWN data repository.

Opportunities for remote blood collection

- **Current opportunities:**
  - LabCorp, Quest
  - Analyte stabilizing collection tubes
- **Emerging opportunities:**
  - "DIY" phlebotomy devices eg upper arm

Capillary blood sampling



Tasso+ TAP II

Figure 2 Capillary blood upper arm self-collection devices.

- Autoantibody and CRP detection in immune mediated rhematic disease (Simon et al, 2022)
  - 80% of participants able to collect on first attempt, 98.6% within two attempts
  - 94.7-99.5% concordance between capillary and venous samples
  - 48.6% (Tasso+), 62.9% (TAP II) patients preferred to venous blood collection
- Dried blood spots

Clinical Chemistry 66:5
697–705 (2020)

Cancer Diagnostics

Detection of ctDNA from Dried Blood Spots after DNA Size Selection

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Challenges

- Relatively rare histologies
  - Variability in institutions' experience with eg AN diagnosis
- “Ground truth” comparator
  - Biomarker discovery/validation requires accurate assessment of the endpoint to assure reliability
- Cost
  - EDTA tubes versus stabilizing tubes
    - EDTA tubes require immediate (~6h) processing: increased burden on collecting institution
    - Tubes with stabilizing preservatives cost more but can be processed at a central location and batched
  - Increased sample storage costs with patient initiated decentralized trial
  - Technologies for self collection currently increase cost
  - scRNAseq remains expensive

[redacted]

Solutions

Clinical Trials
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https://doi.org/10.1177/17407745231203330

Sage Journals

Article

Recommendations for the collection and annotation of biosamples for analysis of biomarkers in neurofibromatosis and schwannomatosis clinical trials

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- Guidelines for uniform times of collection and annotation: Improve "ground truth"
  - NTAP sponsored symposium planned to better define AN
- Current project outlining recommendations for sample processing and biobanking: Improve pre-analytic/pre-processing variability
- Histology/AI-assisted efforts: adoption of digital pathology platforms
- Cost: Anticipate decreasing costs with wider implementation. Consider negotiating costs at consortia/network level

[redacted]

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- Meena Upadhyaya
- AeRang Kim
- Gareth Evans
- Jaishri Blakeley
- Oliver Hanemann
- Stephanie Bouley

If you are interested in joining our working group please reach out!

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