



Somatic Mosaicism across Human Tissues

Technical Assistance Webinar

April 29, 2022 – 12:00-1:00pm EDT

Please submit questions through the Q&A box
We will address questions at the end of the presentation

NIH SMaHT website <https://commonfund.nih.gov/smaht>

Contact: SMaHT@mail.nih.gov

Welcome!

Please put your questions in the Q&A.

We will address as many as possible at the
end of the talk.

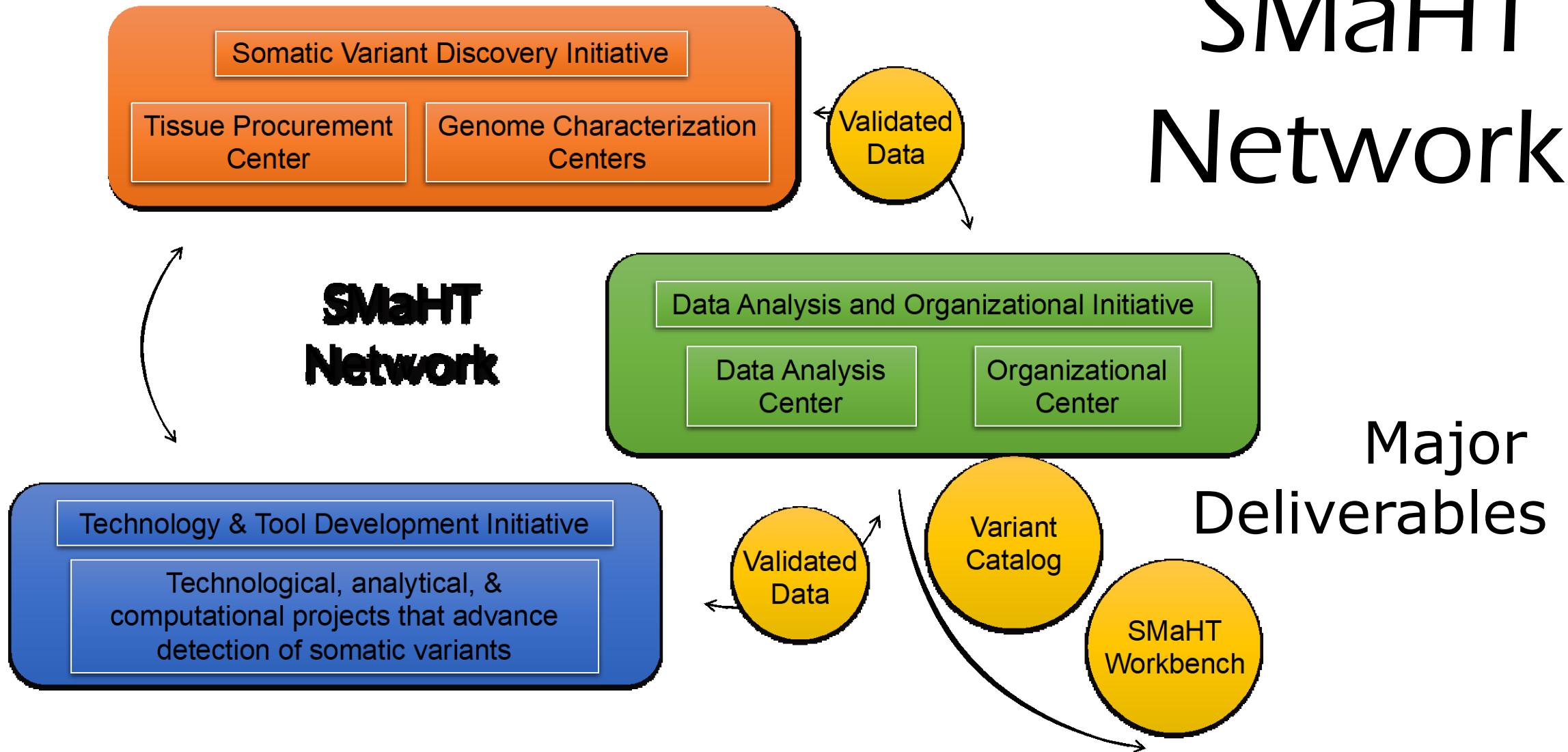
What is the NIH Common Fund?

- Supports **trans-NIH** scientific programs
- **Spurs biomedical advances** that require an initial strategic investment
- Funds short-term (5-10 year), **goal-driven** programs focused on developing specific deliverables (data, tools, technologies, etc.) to **catalyze future research**
- Managed by the **Office of Strategic Coordination** within the NIH Office of the Director, in partnership with the NIH Institutes and Centers

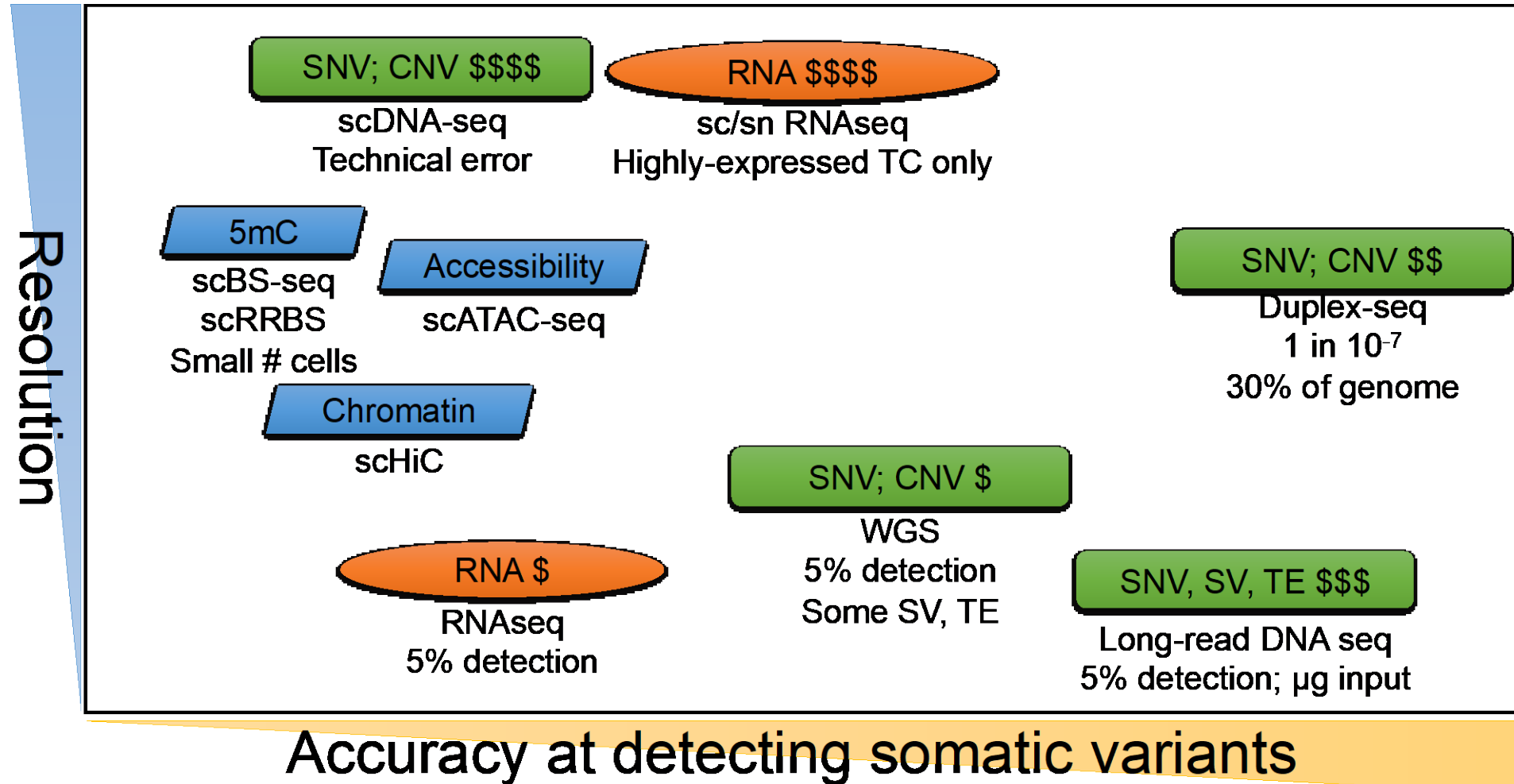


The purpose of the *S*MaHT Network is to enable discovery of new biology and disease mechanisms mediated by genomic variation in somatic tissues

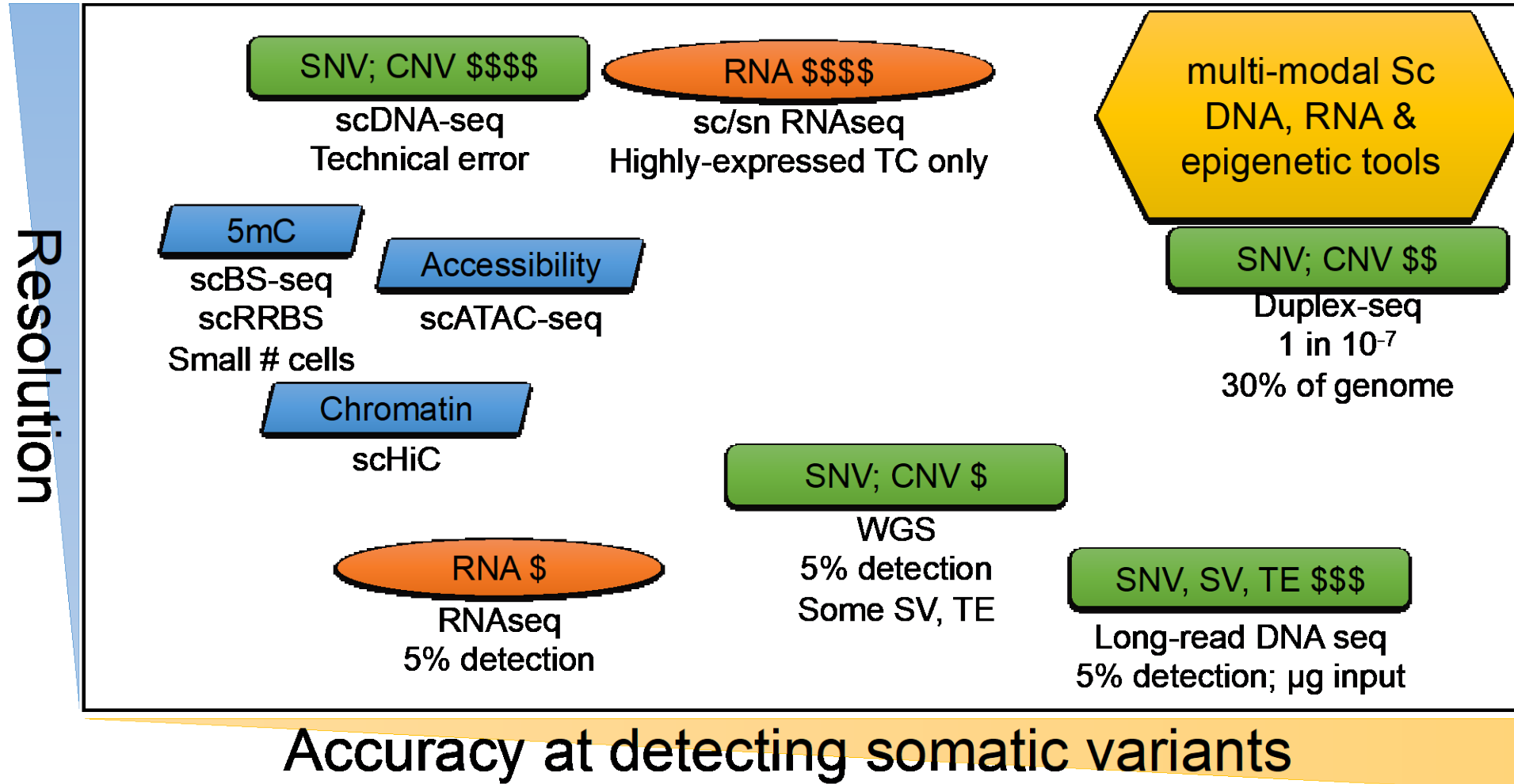
SMaHT Network



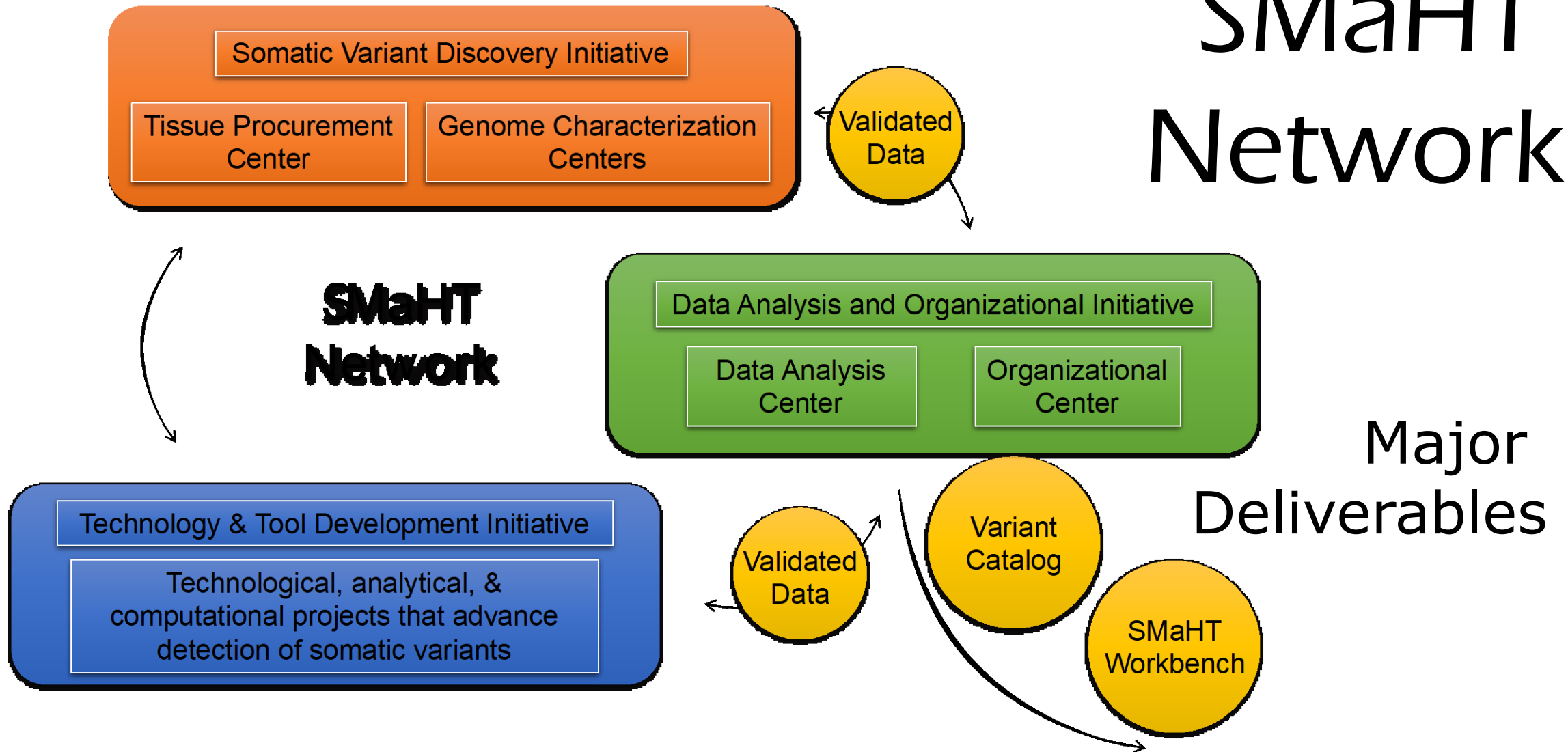
Barriers to Somatic Variant Detection



Vision for SMaHT Program



SMaHT Network



SMaHT Funding Opportunities

- Tissue Procurement Center ([RFA-RM-22-012](#))
 - Collect, process, and distribute a set of 10-15 high quality human tissues from a diverse set of 150 donors
 - FY2023 Total Budget: \$3M; 20% of budget for collaborations
 - One U24 Cooperative Agreement award
 - Geetha Senthil, Ph.D.

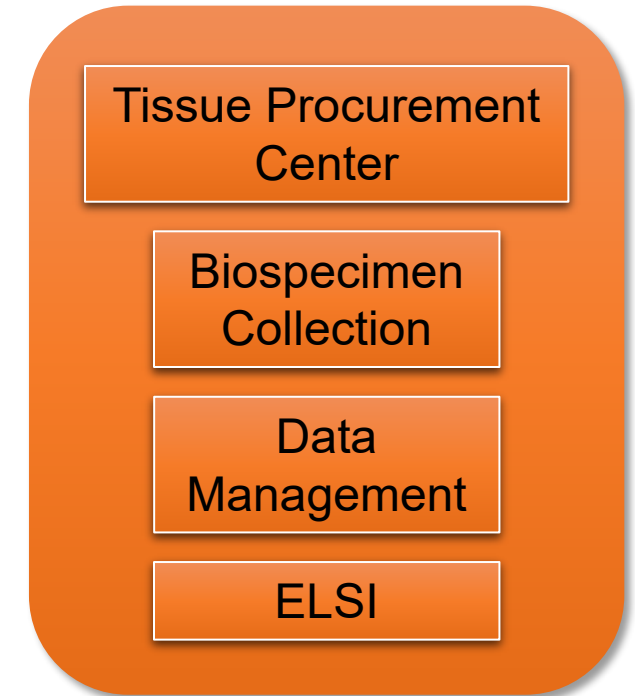
Tissue Procurement Center: Biospecimen Collection

Biospecimen Collection from 150 healthy donors

- 10-15 healthy tissues per donor across a diverse donor pool
- 3-5 Benchmark tissues (have at start of award)
- Bank, manage and coordinate tissue dissemination across SMAHT Network

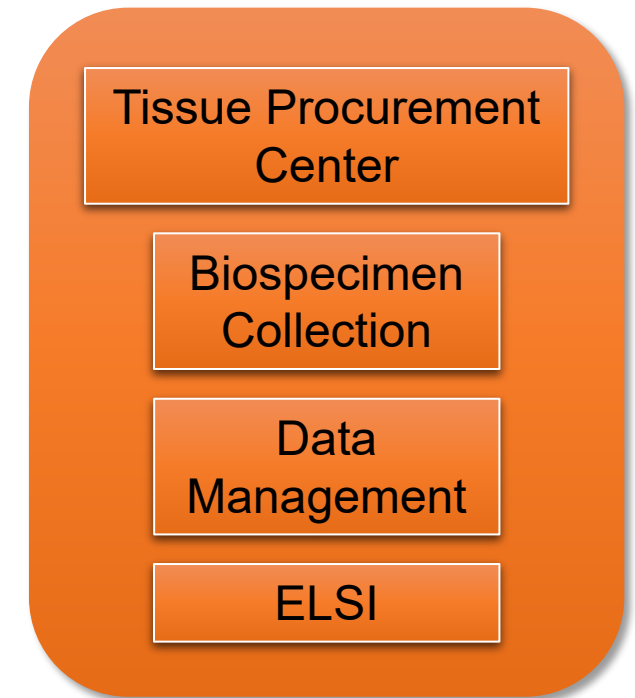
Considerations

- Tissues from 3 germ-layers for broad use, including long-read sequencing, single cell studies, iPSCs, etc.
- Broad Consent, create SOP for tissue collection
- Willingness to be flexible, based on fluid programmatic and scientific priorities



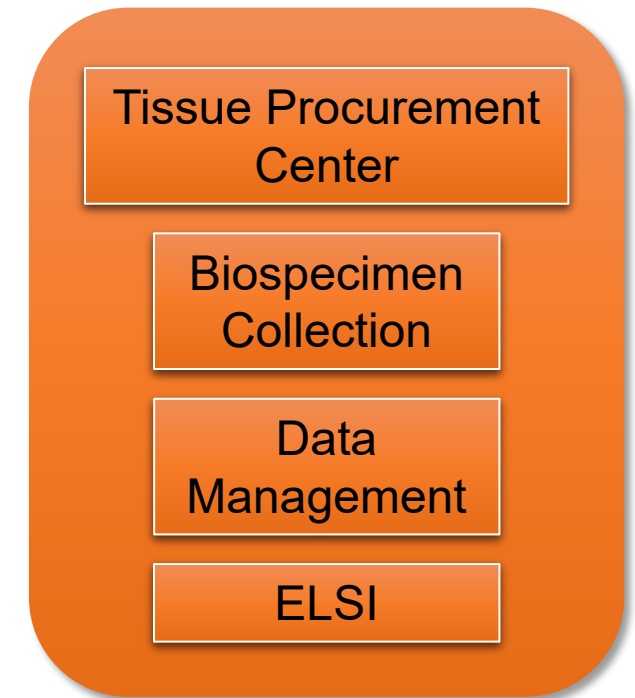
Tissue Procurement Center: Data Management

- Detail organizational structure and experience leading multi-institute projects (MTA, Single IRB, DUA, tissue distribution, etc.)
- Describe roles, responsibilities, internal decision-making, communication strategies, and conflict resolution
- Describe processes for Center operations and identification of problems in procurement, processing, and distribution pipelines (e.g. QC/QA metrics, Data security and stewardship, etc.)
- Define a clear set of semi-annual goals and quantitative milestones with metrics that will logically contribute towards the achievement of the ultimate goals of the SMaHT Network



Tissue Procurement Center: Ethical, Legal, and Social Implications

- Establish a Community Advisory Board
- Design community engagement strategies and metrics to recruit healthy donors from diverse backgrounds with broad consent for all 10-15 common tissues
- Assess implications of sharing results of known pathogenic variants in somatic tissues with families
- Conduct research on communication interpretation of somatic variant findings



SMaHT Funding Opportunities

- Genome Characterization Centers ([RFA-RM-22-013](#))
 - Use state-of-the-art sequencing technologies to identify all types of somatic variation in tissues from the biorepository.
 - FY2023 Total Budget: \$10M; 20% of budget for collaborations
 - 4-6 UM1 Cooperative Agreement awards
 - Amy C. Lossie, Ph.D.

Genome Characterization Centers: Data Production

Considerations

- Assume 30-50 donors with 10-15 tissues/donor (300 to 750 samples/Genome Characterization Center)
- Describe your strategy to complete the common core assays (short-/long-read DNA seq; RNA seq) and additional data modalities
- Justify ability of data modalities to meet SMaHT goals
- Document how you will generate reproducible data within the first year and meet data generation goals every six months
- Display a willingness to be flexible, based on fluid programmatic and scientific priorities

Data Production
67% of Budget

Data Processing
& Analysis
13% of Budget

Collaboration
20% of Budget

Genome Characterization Centers: Data Processing and Analysis

Coordinate data release with Data Analysis Center

- GCC works with TPC and DAC to establish Metadata standards, FAIR standards, data standards, and data processing pipeline
- GCC exports all production data to DAC
- DAC processes and harmonizes production data
- DAC creates a somatic variant catalog and data workbench

GCC Data Processing and Analysis

- Well-integrated data management processes
- Conduct GCC-specific data analysis and collaborate across all GCCs

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Collaboration
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Genome Characterization Centers: Collaboration

Considerations

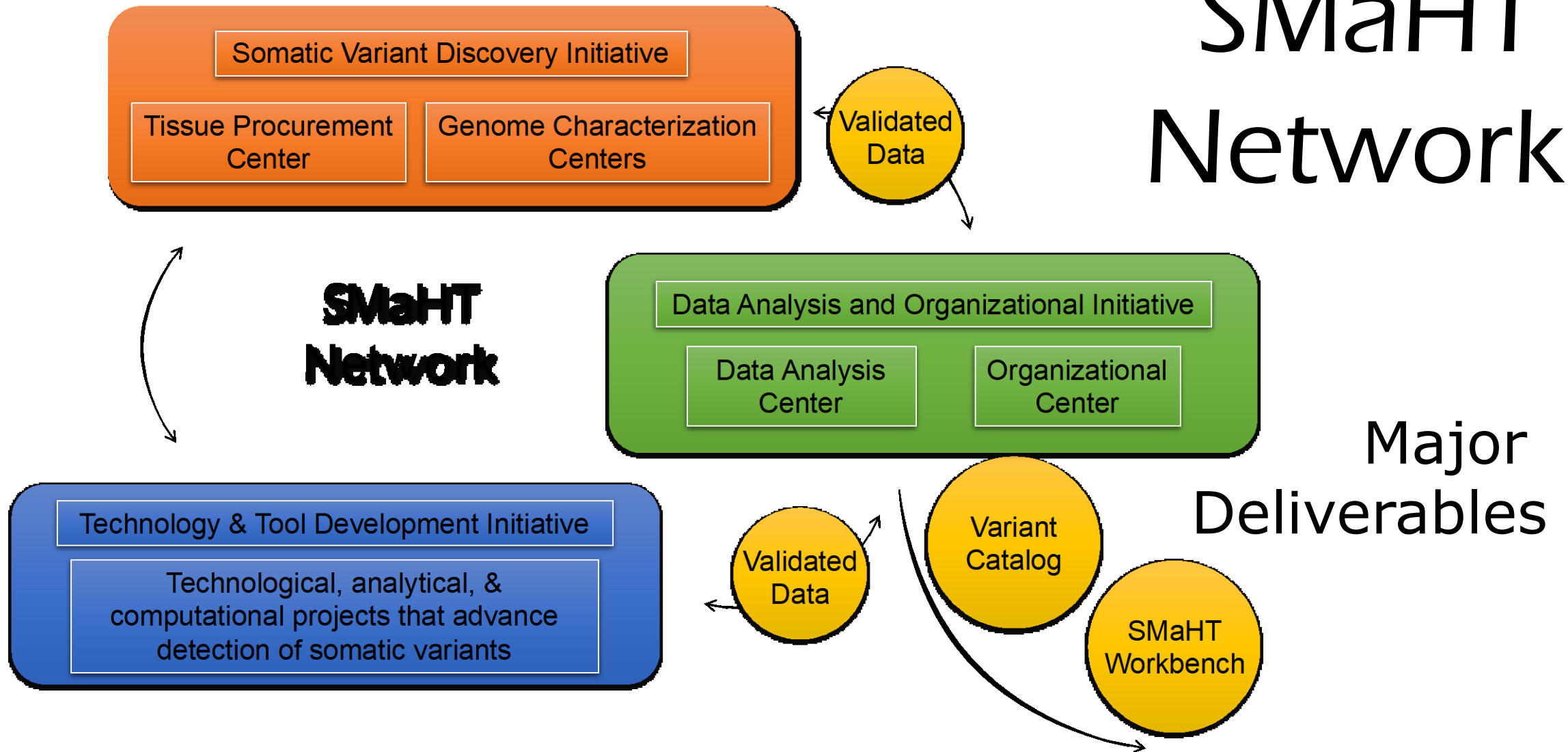
- Describe plans to adapt or adopt technologies for data-production quality assays (e.g. single cell studies, SV, TE, Indel, multi-omics/epigenomics, modalities from the Technologies and Tools Development RFA, etc.)
- Document plans to cross-validate benchmark tissues & your unique tools
- Describe the types of pilot projects you would conduct with other SMaHT Network teams
- Describe what makes you unique

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67% of Budget

Data Processing
& Analysis
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Collaboration
20% of Budget

SMaHT Network

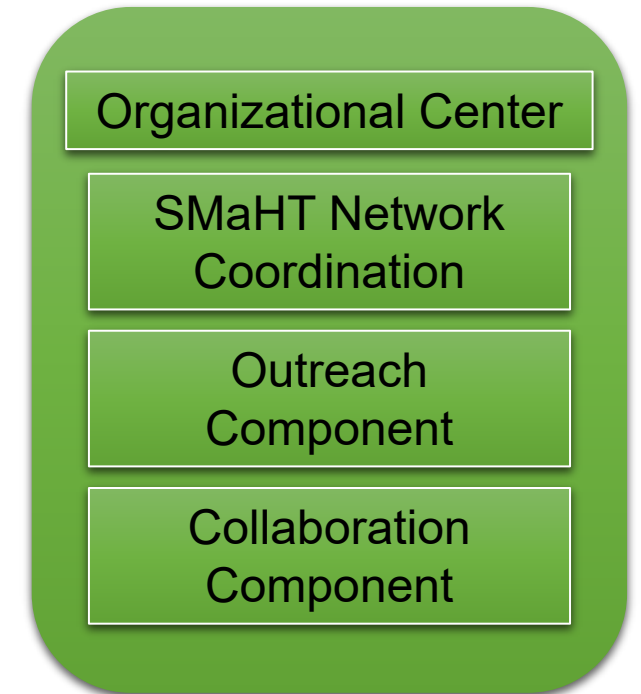


SMaHT Funding Opportunities

- Organizational Center ([RFA-RM-22-009](#))
 - Coordinate Network activities and establish strong links with related NIH and international programs
 - FY2023 Total Budget: \$1.5M; 20% of budget for collaborations
 - One U24 Cooperative Agreement award
 - Jill Morris, Ph.D.

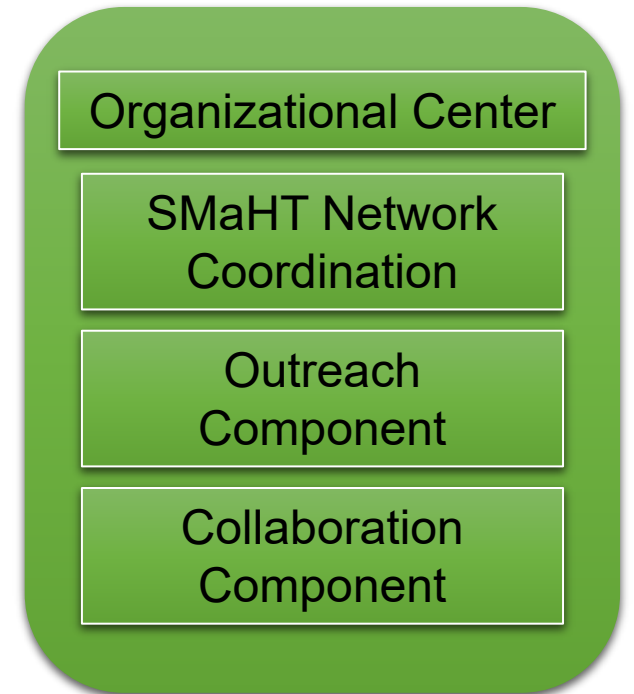
Organizational Center: SMaHT Network Coordination

- Coordinate all Network meetings and workgroups, including the Kick-Off Meeting
- Provide administrative support for Committees and Working Groups
- Develop an operations manual and common resources (protocols, etc.)
- Coordinate publications, branding, and data visualization efforts
- Coordinate progress reporting



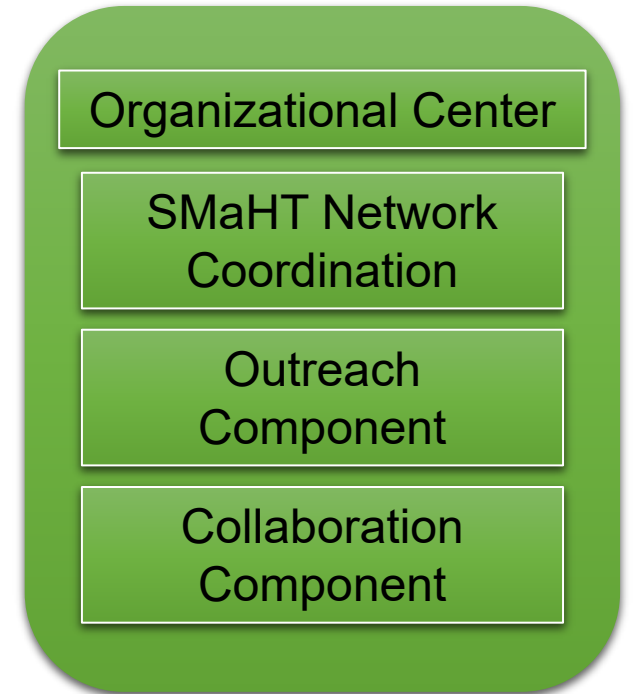
Organizational Center: Outreach Component

- Build and manage the SMaHT Network website
 - Internal Network website
 - External website for public engagement
- House communications and social media
 - Develop common design elements for communications
 - Coordinate dissemination of Network resources (workflows, training materials, etc.)
 - Write press releases, opinion and perspective pieces, social media content, newsletters
 - Track and report on publications and protocols
- Facilitate interactions with other NIH-supported research efforts and non-NIH partners



Organizational Center: Collaboration Component

- Provide administrative and budget support for developing and managing engagement and training
 - Satellite sessions as part of larger meetings
 - Regular public webinars on scientific findings from the Network
- Coordinate opportunities for researchers within and outside the Network
 - Cross-training awards for early-stage investigators
 - Pilot projects that test the feasibility of novel techniques, incorporate new techniques, and/or use the SMaHT Network data in new and innovative ways
 - Summer internships
 - Visiting researcher programs



SMaHT Funding Opportunities

- Data Analysis Center ([RFA-RM-22-010](#))
 - Integrate the data generated by the Network to build the variant catalog, web portal, and workbench
 - FY2023 Total Budget: \$2M; 20% of budget for collaborations
 - One UM1 Cooperative Agreement award
 - Amy C. Lossie, Ph.D.

Data Analysis Center: SMaHT Data Management

Create a framework for data ingestion and QC/QA

- Process for ingestion, quality control, processing, annotation, curation, documentation, and access
- Establish Metadata standards with TPC and GCC
 - Short-read/long-read DNA sequencing; RNA sequencing
 - Single cell, epigenomics, multi-omics,
 - Biospecimen data from Tissue Procurement Center

Establish security protocols

Ensure data follows FAIR Guidelines

Document sustainability plans

Data Analysis Center

SMaHT Data Management

Bioinformatics Tools & Data Workbench

Data Portal, Catalog & Browser

Data Analysis Center: Bioinformatics Tools and Data Workbench

Considerations

- Develop, adapt, and validate methods to improve the detection, characterization, and analysis of all types of somatic variants
- Create bioinformatics tools to integrate diverse data types
- Ensure data sharing protocols are interoperable with other NIH tools (e.g. Common Fund Data Ecosystem, etc.)
- Describe details for cloud deployment
- Provide documentation and training for new tools
- Collect and incorporate user feedback

Data Analysis Center

SMaHT Data
Management

Bioinformatics Tools
& Data Workbench

Data Portal, Catalog
& Browser

Data Analysis Center: SMaHT Network Data Portal, Variant Catalog, and Browser

Considerations

- Create the SMaHT Data Portal that houses the Somatic Variant Catalog and Data Browser
- Incorporate a multi-level data model, versioning, provenance-tracking, common ontologies with links to outside databases, and curation of collections
- Discuss plans to create a modern, dynamic portal with the ability to browse, search, visualize, and export data
- Detail plans to develop collaborative analysis strategies, integrate the datasets with other relevant datasets, and share useful information and insights about these data with the broader biomedical research community

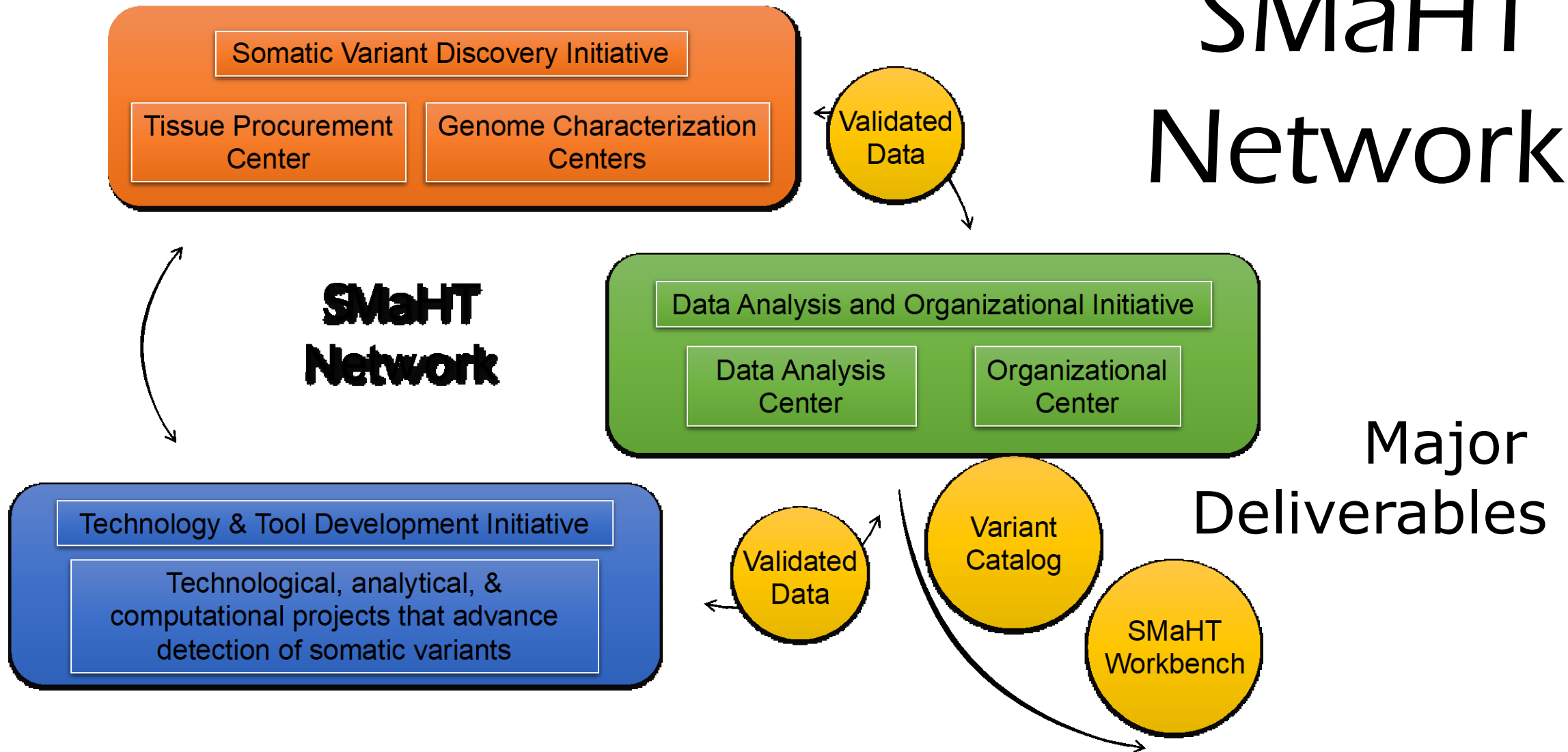
Data Analysis Center

SMaHT Data
Management

Bioinformatics Tools
& Data Workbench

Data Portal, Catalog
& Browser

SMaHT Network



SMaHT Funding Opportunities

Technology and Tool Development initiative ([RFA-RM-22-011](#))

- Develop next generation tools to improve detection and characterization of all types of somatic variants (SNVs, SV, TE, Indel, etc.)
- FY2023 Total Budget: \$6M; 20% of budget for collaborations
- 10 – 14 UG3/UH3 Exploratory/Developmental Phased Cooperative Agreement Awards
- Jill Morris, Ph.D.

Technology & Tool Development

Considerations and Gaps

- Improve the sensitivity, accuracy, and threshold of detection of all types of somatic variants
- Improve detection of rare variants, low-abundance transcripts, and at single cell resolution
- Develop new approaches for in situ analysis variant detection
- Improve base calling, read error correction, alignment and assembly, and base modification identification
- Create approaches to obtain high quality sequence from samples that range in quality
- Develop improved multi-omics techniques for correlating somatic variants with changes in the epigenome or transcriptome

Tool Development & Optimization

Improve detection threshold

Low-quality sample optimization

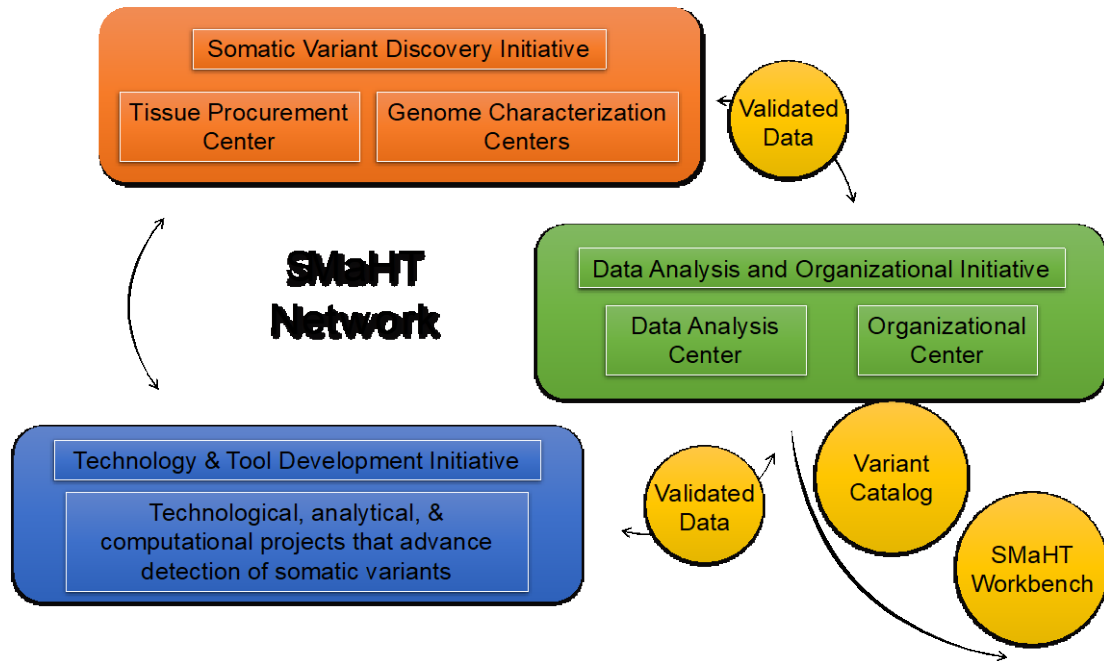
Variant detection in repetitive DNA

RNA/DNA base modifications

Reduce computing power

Single cell multi-omics analyses

SMaHT Network

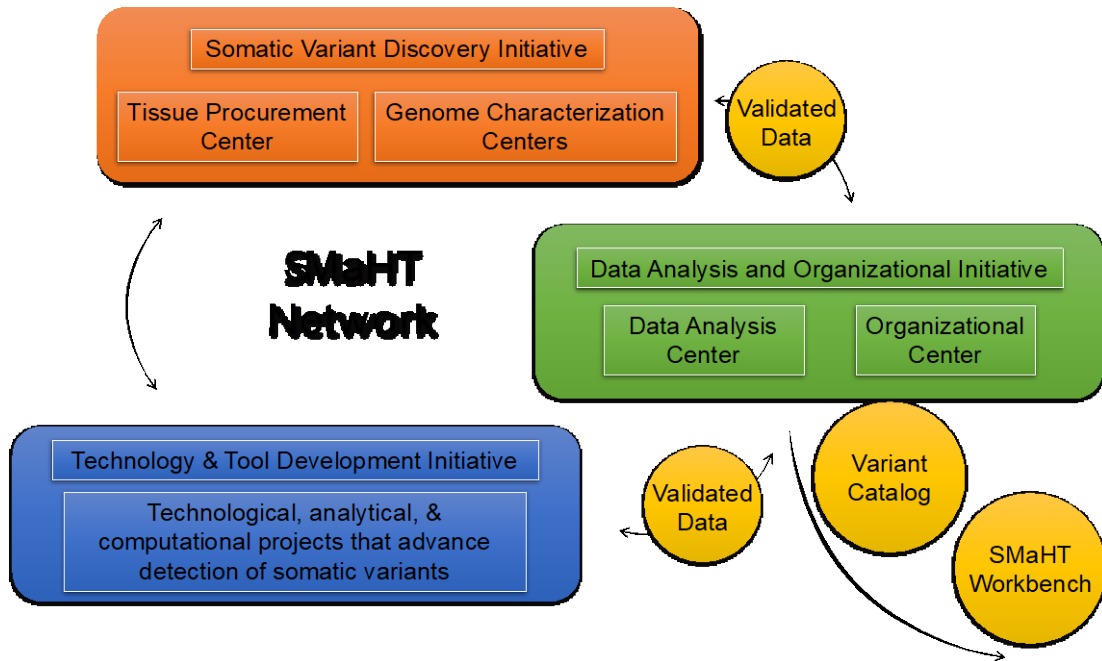


Network Expectations

- Common Goals across Network
 - PIs, NIH staff, and external advisors
 - Variant Catalog and Data Workbench
- Adopt a culture of sharing (e.g. methods, challenges, opportunities, data, methods and tech development, publication planning)
- 20% of budget for Network activities, resource sharing, outreach, and meeting attendance

SMaHT Network

NIH encourages applications from teams that include partnerships with minoritized people, people at primarily minority-serving institutes, and historically Black colleges and universities



Application Considerations

- Read ALL RFAs – What skills do you bring to the Network? How will you work within the Network?
- Read YOUR RFAs multiple times. Pay attention to review criteria. Ask us if you have ANY questions.
- Define clear, semi-annual quantitative **milestones** that logically contribute towards the achievement of SMaHT Network goals
- There are **no revisions or appeals**
- Check the RFA for **Eligibility**
- **LOIs** are not required, but strongly encouraged

SMaHT Network Considerations

- Adopt **SMaHT Network** policies for sharing, collaborative projects, regular meetings, changing goals, and milestones
- Expect **Substantial NIH Involvement** in individual projects & Network activities
- Prepare for **NIH modifications** to budgets, specific aims and milestones prior to award

Scientific Review Information

- Complete and responsive applications will be evaluated for scientific and technical merit by various Special Emphasis Panels (SEPs) convened by the Center for Scientific Review (CSR)
- Applications deemed unresponsive will be administratively withdrawn
- Reviews will likely take place between October – November 2022
- Meeting rosters will be posted online 30 days prior to the review meeting
- For further review information, read to **Section V** of the FOA – “**Application Review Information**” carefully
- **Pay special attention and address “Specific to this FOA” review questions under each criterion**

Important Dates and Information

Letter of Intent Due Date	June 8, 2022
Application Receipt Date	July 8, 2022
Scientific Merit Review Date	November 2022
Advisory Council Dates	January/February 2023
Earliest Start Date	April 2023

We strongly encourage you to talk with us prior to submitting an application by emailing us at SMaHT@nih.gov





Please send additional questions to SMaHT@mail.nih.gov

FAQs: <https://commonfund.nih.gov/smaht/faqs>

Slides will be available here: <https://commonfund.nih.gov/smaht>