The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

Office of Data Science and Sharing (ODSS)

PRIVACY PRESERVING RECORD LINKAGE (PPRL) FOR PEDIATRIC COVID-19 STUDIES

FINAL REPORT

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NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Healthy pregnancies. Healthy children. Healthy and optimal lives.

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1 EXECUTIVE SUMMARY

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Office of Data Science and Sharing (ODSS) undertook a project to assess potential governance and technical approaches for implementing privacy preserving record linkage (PPRL) across pediatric COVID-19 (COVID hereafter) studies, with funding from the National Institutes of Health (NIH) Office of Data Science Strategy (ODSS) and support from Booz Allen Hamilton. The overall goal of the project is to inform an NIH-wide strategy on the use of PPRL for pediatric COVID studies, based on use cases from the Collaboration to Assess Risk and Identify LoNG-term outcomes for Children with COVID, known as CARING for Children with COVID—an initiative led by NICHD and the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID). CARING for Children with COVID is aimed at better understanding SARS-CoV-2 infection in children, including the multisystem inflammatory syndrome in children (MIS-C), a rare but serious multi-organ disease.

NIH rapidly mobilized the CARING for Children with COVID initiative by funding new and existing studies on pharmaceuticals for treatment, cardiovascular complications, immunologic pathway characterization, and the underlying risk factors that influence the full spectrum of symptomology in children infected with SARS-CoV-2. To align with the call for rapid data sharing in the January 2021 Executive Order on *Ensuring a Data Driven Response to COVID-19*[1], CARING for Children with COVID leveraged existing and new NIH data repositories to support data sharing with a broad community of researchers. Study investigators soon recognized that pediatric COVID patients were likely participating in multiple CARING for Children with COVID studies and saw value in linking the various data types for each child, yet they could not link participant data across studies because they were unable to share information about participant identities with one another. PPRL was identified as the most feasible approach to identifying which children are participating across CARING for Children with COVID studies.

PPRL is specifically designed to facilitate the linking of records associated with an individual represented across multiple datasets without exposing any personally identifiable information (PII). PPRL software uses cryptographic algorithms to generate irreversible, hashed codes (or "tokens") when PII, such as name and date of birth (DOB), are entered into the software. The hashed codes can then be compared across multiple datasets to match records from the same individual. In order to implement PPRL across multiple data repositories, rules (governance) must be defined including decisions regarding how the linkage is authorized, which datasets can be linked, which organization is trusted to create the linkage information, who can access linked datasets and how, and how reidentification risk can be mitigated as increasingly diverse data types are aggregated on a single research participant. Good governance is critical to protect research participant privacy and respect participant trust.

The overall goal of this project was to assess and analyze governance and technology approaches in diverse, existing record linkage implementations, to inform an NIH-wide approach to link data across pediatric COVID studies, and, more broadly, to inform approaches to linking individual-level datasets across pediatric research studies. The project achieved this goal through the following activities:

- Summarized information associated with PPRL feasibility for the CARING for Children with COVID studies
- Analyzed 13 existing record linkage implementations, both PPRL and non-PPRL, funded by NIH, other federal agencies, and non-government organizations, to fully document end-to-end governance decisions

- Evaluated the capabilities of seven PPRL vendors/organizations, including one NIH-developed tool, one university-developed tool, and five commercial vendor tools, by extending a recent technical assessment led by the National Cancer Institute (NCI) and adding facets specific to the pediatric COVID record linkage use cases

The project analyzed findings across these three activities to develop *governance and technology considerations* for a CARING for Children with COVID PPRL implementation, which could serve as a useful guidepost for the design of any new PPRL implementation. The project concluded that PPRL is a feasible approach for linking participant data across pediatric COVID studies so long as the involved parties *collaborate prior to implementation* to define the governance approaches, technical requirements, and the data elements required to ensure high-quality linkage.

Prior to implementing PPRL, funders, investigators, researchers, and data repositories should collaborate to make the following determinations:

- **Obtain approval or authorization to link:** Studies should consent research participants for the linkage of their data across studies and data repositories, if feasible, by clearly communicating the scope of the linkage and how the linked data will be shared. Since CARING for Children with COVID studies are subject to the NIH Genomic Data Sharing (GDS) Policy, it is appropriate to seek institutional approval for linkage, with input from an institutional review board (IRB) and/or equivalent Privacy Board, especially when re-consent is not feasible. It may be possible to link to data from typically unconsented sources, such as administrative datasets, if explicit consent for linkage and sharing the linked data is obtained in the context of the research studies (thereby changing the status of the administrative data to "consented").
- **Identify policies relevant to specific data types or participant populations:** Policies or procedures may apply to certain data types (e.g., genomic data that are subject to the NIH GDS Policy) or populations (e.g., tribal or international populations).
- **Collect and standardize a broad set of PII elements:** A broad set of PII elements are required to generate high-quality linkage, regardless of the PPRL technology used. These PII elements should be collected at the outset and in a standardized manner. Since certain PII elements are not typically collected in pediatric research, most, if not all, CARING for Children with COVID studies would need to collect new PII elements from their study participants.
- **Establish which party will link the data:** A three-party approach, where the PII is entered into the PPRL tool by the data originators, the hashed codes are matched by an honest broker or external server, and approved researchers link the data, offers researchers the flexibility to link and use datasets that are hosted in different data repositories. By separating the party that matches the hashed codes from the party that links the data, data use requirements and data provenance information are retained in all datasets.
- **Determine the scope of linkage:** All PPRL implementations should make up-front determinations regarding which datasets would be linked and whether the linkage would be specific to one study (study-specific) or would encompass multiple datasets from one or multiple repositories (linked database model), thereby supporting many studies. The linked database model is the most sustainable and reasonable approach for fostering reproducible research with CARING for Children with COVID data, as it could encompass multiple current and future NIH pediatric COVID datasets across multiple repositories, so long as the same PPRL technology is used.

- **Use a variety of controls for mitigating re-identifiability risk:** For CARING for Children with COVID, linkage information should be provisioned using access controls (approval from an NIH data access committee), while the original access tier status of unlinked datasets need not change. Additional policy controls include using a standard definition of "de-identified" (e.g., the NIH GDS Policy, which uses the Health Insurance Portability and Accountability Act [HIPAA] Safe Harbor and the Common Rule) and prohibiting re-identification by users. For certain implementations, re-identification risk assessments prior to and/or after linkage or applying modifications to certain data elements could also be considered.
- **Select PPRL software that meets basic requirements:** To support CARING for Children with COVID, the selected PPRL tool must accommodate a broad and flexible set of PII, support large scale implementations, prohibit vendor rights to the data, and appropriately protect PII. This project determined that nearly all PPRL tools assessed in this report can support these basic requirements. The PPRL tools diverge on certain desirable features associated with usability, functionality, and security, which may factor into deciding which software is best for a given implementation.
- **Consider PPRL software sustainability for long-term implementations:** Long-term implementations require that the hashed codes persist over time and may benefit from the use of NIH-owned software to avoid continual commercial vendor contracts, recurring or use-based costs, and risk associated with business model modifications.

This assessment represents a snapshot of the landscape of record linkage to support biomedical research, and additional work is required to assess linkage quality for a given PPRL tool, PII elements, and the configuration of matching algorithms that would be used for a PPRL implementation, by testing against a gold standard dataset that is appropriate for the implementation (e.g., pediatric data). Further investigation is warranted regarding participants' attitudes towards consent for linkage, as well as actual PPRL software vendor costs, cross-vendor interoperability capability, and challenges associated with vendor dependency for long-term implementations.

2 INTRODUCTION

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Office of Data Science and Sharing (ODSS) undertook a project to assess and analyze approaches for privacy preserving record linkage (PPRL) to meet the needs of pediatric COVID studies, with funding from the National Institutes of Health (NIH) Office of Data Science Strategy (ODSS) and support from Booz Allen Hamilton. The overall goal of the project is to inform an NIH-wide strategy on the use of PPRL for pediatric COVID studies, which could serve as a useful guidepost for the design of any new PPRL implementation.

This *public* NICHD ODSS report provides considerations regarding the use of PPRL for the pediatric COVID studies based on findings from the following:

- Summary of information associated with PPRL feasibility for pediatric COVID studies that are part of the Collaboration to Assess Risk and Identify LoNG-term outcomes for Children with COVID
- Analysis of governance frameworks for existing record linkage efforts implemented across NIH, other federal agencies, and non-government organizations
- Capability analysis and potential applicability of various PPRL vendors/organizations for pediatric studies

The intended audience of this *public* report is any stakeholder considering participating in or implementing PPRL to address research-based use cases.

3 INTRODUCTION TO NIH PEDIATRIC COVID STUDIES & THE CASE FOR RECORD LINKAGE

COVID in children

As evidenced by the COVID global pandemic, the novel SARS-CoV-2 virus can cause a broad spectrum of mild to severe disease, including death. Infection from this virus can also result in a rare but serious post-infectious hyperinflammatory condition affecting multiple organs called the multisystem inflammatory syndrome (MIS) in both children (MIS-C) and adults (MIS-A). Some features of MIS-C overlap with Kawasaki disease (KD), macrophage activation syndrome (MAS), and toxic shock syndrome (TSS)[2]—diseases that predate COVID.

The Collaboration to Assess Risk and Identify LoNG-term outcomes for Children with COVID, known as CARING for Children with COVID – an initiative led by NICHD and the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID) – was launched to better understand SARS-CoV-2 infection in children and includes the following studies:

- Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs Administered to Children per Standard of Care (POP02) focuses on understanding the treatment of children diagnosed with COVID or MIS-C with medicines that have shown promise in adults with COVID.
- Long-Term Outcomes after the MUltisystem Inflammatory Syndrome In Children (MUSIC) focuses on cardiovascular complications of MIS-C, but also collects data on all aspects of childhood and adolescent health in affected participants.
- Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM) aims to evaluate the short- and long-term health outcomes of SARS-CoV-2 infection in children, including MIS-C, and

to characterize the immunologic pathways associated with different disease presentations and outcomes.

- Eight studies that are part of the Predicting Viral-Associated Inflammatory Disease Severity in Children with Laboratory Diagnostics and Artificial Intelligence (PreVAIL kIds), which are part of the NIH Rapid Acceleration of Diagnostics Radical (RADx-rad) initiative, focus on developing cutting-edge approaches for understanding the underlying factors that influence the spectrum of possible conditions in children infected with SARS-CoV-2.

CARING for Children with COVID aims to answer the following questions:

- Why are some children more likely than others to get infected with SARS-CoV-2?
- Why do different children show different symptoms of COVID?
- Why do some children who become infected with SARS-CoV-2 have more severe illness, like MIS-C?
- What are the long-term outcomes for children who have become infected with SARS-CoV-2?

To help address these and other questions and to help develop public health strategies for prevention, diagnosis, and therapies, NIH is funding additional pediatric COVID studies across the U.S. and other countries as well. Including but not limited to CARING for Children with COVID, NIH funds approximately 2,966 active projects related to COVID and children, with 449 projects focused on MIS-C[3]. Data collected from these studies, including electronic health records (EHRs), pathology, laboratory, imaging, and genomic data, constitute a rich source of information that can be used to develop broad strategies to address the above questions. Given that MIS-C is a multi-organ disease, addressing these questions will require a multidisciplinary approach that involves pediatrics, genomics, immunology, cardiology, hematology, and other disciplines. This interdisciplinary approach towards understanding and treating MIS-C can best be served if the different types of datasets and records collected for a given patient—for example, EHRs collected at the various hospital systems, and -omics data generated by the various COVID studies funded by NIH—can be linked and integrated. Such linkage maximizes NIH's investments in research and advances clinical and scientific discoveries not only for MIS-C but also for other related pediatric conditions.

What is PPRL and how does it work?

Linking two or more records that correspond to the same individual (entity) is called *record linkage*, a term introduced in 1946 by Dunn[4] of the United States National Bureau of Statistics: "Each person in the world creates a Book of Life. This Book starts with birth and ends with death. Record linkage is the name of the process of assembling the pages of this Book into a volume." Linking records or datasets generated from multiple sources and stored in disparate data repositories facilitates creation of enriched datasets and/or longitudinal datasets for an individual that can then be used to address multifaceted research questions that a single dataset alone may not be able to answer. Currently two broad groups of methods exist for record linkage[a]:

- Traditional linkage uses information such as personally identifiable information (PII; for example, date of birth, Social Security number [SSN], address, which the Health Insurance Portability and Accountability Act[5] [HIPAA] classified as protected health information [PHI], if present in health records), or other direct information such as genetics to match records of an individual.

[a] Record linking and data linking are used interchangeably in this Final Report.

- Privacy preserving record linkage[6] (PPRL) encodes the PII to create one-way hashed codes (tokens), which are then encrypted and compared so that the resulting matches can be used to link data or records of an individual.

While both of the above methods use PII as the starting point, the traditional method exposes PII to the party charged with identifying matches, whereas in PPRL, the PII remains with the data originator and is not exposed to the party charged with matching the hashed codes/tokens (entity resolver) or linking the data (record linker).

Regardless of the method used for linking, two types of algorithms[7] are used: deterministic (exact) and probabilistic (approximate) matching.

- In the deterministic model, all PII elements must match exactly for the record to be considered to be belonging to the same individual. The model typically uses unique identifiers such as SSN or medical record number for matching and requires the PII elements in the records to be error-free, which is a challenge in real-world data.
- In the probabilistic model, the matches are based on the discriminatory power of the PII elements that are used and the degree of similarity between the elements, resulting in a likelihood ratio of the entities being a match, non-match, or possible match. This model tolerates errors and other quality issues often found in real-world data.

These two algorithmic models are routinely and widely used especially when linking administrative, survey, mortality, health, economic, social, and other types of data collected by various government agencies such as the Census Bureau[8], Centers for Disease Control (CDC)/National Center for Health Statistics (NCHS)[9], Agency for Healthcare Research and Quality (AHRQ)[10], and Administration for Children and Families (ACF)[11]. These agencies typically use the traditional method of linking, which exposes PII elements to the entity resolver, who typically uses PII elements to create a linked dataset. However, there are key constraints to utilizing the traditional method for linking patient or research study participant data, such as EHRs, clinical, non-clinical survey, genomic, image, and viral sequence data, collected by NIH researchers and stored in a federated data ecosystem:

- The PII elements from each data originator would need to be exposed or shared downstream, which could present non-compliance with various human subject protection and data privacy regulations such as the Federal Policy for the Protection of Human Subjects (known as the Common Rule)[12], HIPAA, and Privacy Act[13].
- Appropriate informed consents must be obtained from the study participants if the PII elements are to be shared beyond the data collector/originator. Participants are generally opposed to the idea of sharing their PII[14, 15, 16, 17] and usually require assurances that only de-identified data would be shared externally before agreeing to participate in a study.
- Records/data stored in the NIH data repositories follow a variety of de-identification standards, such as HIPAA Safe Harbor (de-identified of all 18 HIPAA identifiers), limited dataset (with 16 of the direct identifiers removed) as per HIPAA guidance[18], the Common Rule, and/or other determinations.

PPRL addresses several of these constraints and is specifically designed to facilitate the linking of records of an individual across multiple data originators without transferring any personal identifiers from the originating data source system. PPRL always involves at least two parties, the data originator and the entity resolver. In a "2-party data linkage model," the entity resolver is also the party that links the data

(records) for a given participant (entity) once that participant has been identified in multiple datasets. In a "3-party data linkage model," these two functions are performed by different parties. In the 3-party model, the entity resolver is often referred to as the honest broker as they handle only hashed codes/tokens (i.e., encoded PII) and are not exposed to any participant-level data.

An overview of the PPRL process using the 3-party data linkage model is illustrated in Figure 1. The data originator uses the PPRL software to process the PII elements and encode them to generate the hashed codes/tokens—this is the privacy preserving step. The data originator, via the software, then encrypts the tokens for transfer to the entity resolver, who then performs the matching of the tokens using deterministic and/or probabilistic algorithms, identifies the tokens that represent same participant/entity, and documents the matches using the participant IDs provided by the data originators and generates a linkage map. The matched IDs in the linkage map are then used to create a linked dataset by the data linker.

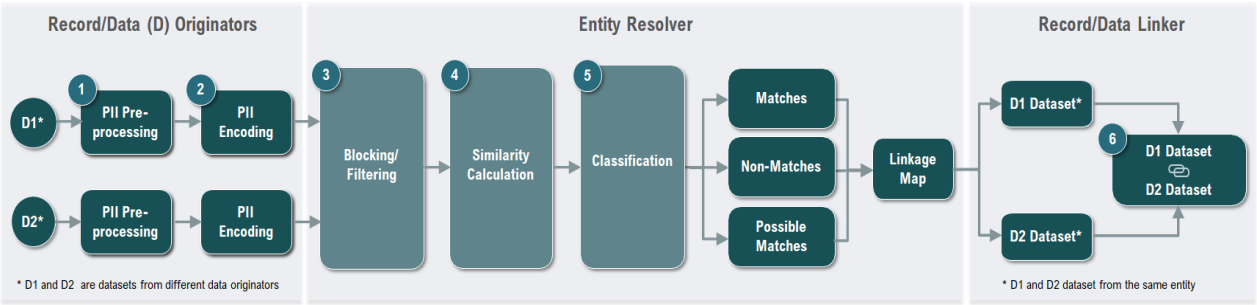


Figure 1: PPRL Process across Two Datasets (D1 and D2) in a 3-Party Data Linkage Model

The major steps in the PPRL process[19] as shown in Figure 1 include:

1. *Data Pre-processing (of PII elements)*: An essential step for generating high-quality linkages, pre-processing PII elements (sometimes referred to as data in this context) includes cleaning (handling missing, erroneous, incomplete values) and standardizing to ensure that the PII elements used for PPRL are transformed into a well-defined and consistent format. Pre-processing of PII elements (the input in the context of PPRL) is typically performed at the data originating sites and must be done consistently across sites to achieve the best linkage results.
2. *Data Encoding (Hashing)*: This is the privacy preserving step where the PII elements entered into the software are cryptographically encoded (hashed) using a *one-way* hashing algorithm so that the input of a set string of characters (generated from PII elements) for an individual will consistently produce a unique and repeatable fixed size output (a deterministic step), known as hashed codes or tokens. To further preserve privacy and mitigate the possibility of dictionary attacks aimed at breaking the hashed output and re-identifying the individual, a random known value known as salt or secret key, is often injected during the encoding process. The salt/secret key[20] is concatenated with the PII input string prior to hashing and all data originators participating in the linkage uses the same salt/secret key, which is typically provided by an external party such as the entity resolver. This ensures that a brute attack to reverse the hash codes or tokens will not reveal the PII elements or identify the individual. After the data originators generate the hashed codes/tokens, they are sent to the entity resolver.
3. *Blocking*: Blocking or filtering is the first step performed by the entity resolver when they receive the hashed codes/tokens. This process facilitates indexing the records prior to matching by

grouping the encoded inputs based on certain PII attributes (e.g., initial of last name and ZIP Code) to filter out, or reduce, the number of tokens that would need to be compared against each other. Blocking is critical for scaling up the number of records that can be linked efficiently, especially across large data sources and can significantly reduce the computational time required for matching tokens/records[21].

4. *Similarity/Matching Calculation*: This step involves comparing tokens either based on deterministic/exact or probabilistic/approximate matching of hashed codes/tokens. Deterministic/exact matching results in a similarity score of 1 (match) or 0 (null), whereas probabilistic/approximate matching is represented by a numerical value ranging from 0 to 1. Real world data often include errors and inconsistencies, and while data cleaning addresses it to a certain extent, PPRL algorithms generally use probabilistic matching with specific thresholds (based on which and the number of tokens that match) set to increase the likelihood of true positives while minimizing false positives.
5. *Classification*: The output of the matching process results in classifying two or more entities into matches, non-matches, and possible matches, based on the similarity scores. This step represents the actual process of entity resolution. The entity resolver develops a linkage map of matched participant IDs across data originating sites and may generate a new participant ID or a globally unique identifier (GUID) based on the matches to facilitate the linking of records across the data originating sites.
6. *Record/Data Linking:* The Data Linker uses the linkage map of matching participant IDs across data originating sites to link the datasets for research use.

Challenges to implementing PPRL in the NIH federated data ecosystem

PPRL has not yet been adopted widely at NIH for linking records across pediatric COVID projects due to various challenges associated with implementing it within NIH's federated data sharing ecosystem—these include:

- *Data are distributed across data repositories*: The urgent response that was required to address the COVID pandemic resulted in capturing and storing data for the same participant either in existing or newly established repositories that are primarily designed for sharing data with the broader research community. Linking data for the same individual across multiple repositories was not initially identified as a critical need and would have required more up-front coordination during the initial phases of the pandemic, when the focus was primarily on data collection and rapid analysis in line with international[22] and federal[1, 23] calls for rapid data sharing.
- *Data are shared without the required PII elements*: In keeping with de-identification standards and policies (e.g., the NIH Genomic Data Sharing Policy[24]), most, if not all, of the data repositories within NIH's data ecosystem hold de-identified data or limited datasets with many of the PII elements required for PPRL stripped from the data. This makes it difficult, if not impossible, to link data using information from the repositories alone. Instead, it requires working with the data originators to collect the required PII elements and assist with PPRL implementation—such retrofitting for PPRL is not always feasible, and when feasible, it is time consuming and costly.
- *Studies and data repositories follow a diversity of data governance models*: Data governance determines how data can be used at every step of the typical data lifecycle—collection,

linking/merging, and sharing—and data governance models vary greatly between NIH studies and repositories. Data governance models are dictated by regulatory requirements (such as the Common Rule), the study participant's informed consent, data submission and sharing policies and requirements outlined in data submission/sharing agreements, data access tiers (such as enclave, controlled or open[b]), and ethical considerations that may or may not be addressed by existing technical or policy frameworks[25]. While such governance controls are critical for data privacy and security and participant trust, it is not well understood how data governance models in different data systems can intersect to enable data linkage across a federated data ecosystem where a variety of technical and non-technical (e.g., policy, regulatory) controls are at play and effective governance approaches are needed for future data linkages to be defined in advance of data collection.

Nevertheless, the benefits and impact of using PPRL for health data (where privacy and confidentiality of PII/PHI are paramount), have led to the development of open source, government-owned, and commercial PPRL tools in use within a small number of NIH data repositories. One such PPRL tool is the Global Unique Identifier[26] (GUID) Tool that was developed by the National Institute of Mental Health (NIMH) to support the NIMH Data Archive. A second GUID tool developed by the Center for Information Technology (CIT) is being used for a limited number of projects by other NIH Institutes and Centers (ICs), including National Institute of Neurological Disorders and Stroke (NINDS), National Institute on Aging (NIA), National Eye Institute (NEI), and National Center for Advancing Translational Sciences (NCATS).

The case for linking pediatric study data

As of August 2022, pediatric COVID cases accounted for approximately 18.4% of the 78,513,599 cases in the U.S.[27] and among the 8,798 MIS-C cases, 71 children died due to MIS-C complications, as reported by the CDC [28]. Understanding the full spectrum of symptomology and risk factors underlying COVID in children is critical for the development or advancement of treatments, which require collecting and merging data from multiple sources.

Linkage of pediatric studies was identified as a need within the first year of the CARING for Children with COVID program when pediatric COVID and particularly MIS-C, was relatively rare (especially during the early phases of the pandemic when schools were closed), and it was strongly suspected that the same children were being enrolled across multiple studies. Since each study has a different focus (pharmaceutical data versus immune profiling versus cardiac imaging), the investigators saw value in the potential opportunity to link the various data types to the appropriate child; however, there was not a readily available mechanism for facilitating such linkages (i.e., studies were not allowed to share PII with each other).

Notwithstanding this and other challenges described above regarding linking data within a federated data ecosystem, an initial assessment conducted by NICHD identified the need to facilitate subject-level PPRL to support the following use cases across CARING for Children with COVID studies:

- Enable researchers to combine participant-level data collected from multiple studies to merge multiple data types for each participant and avoid working with inflated sample sizes
- Avoid duplicate data generation (primarily whole genome sequencing)

[b] Data access models – Open access: no access restrictions or registration required to access; Registration required: open to all, but users need to be signed in or registered with the resource to access; Controlled access: application and eligibility requirements need to be met to gain access (e.g., by a data access committee); Enclave: data cannot leave a specific system boundary (e.g., cannot be downloaded)

- Facilitate longitudinal data collection and analysis (e.g., understanding long COVID in children)

Furthermore, participant-level linkages and the subsequent responsible sharing of the linked data is expected to spawn new research studies and answer new questions long after the data collection has ended, thus enabling the research community to derive maximal impact from the data to ultimately benefit children's health. However, pediatric COVID researchers have identified specific record linking challenges that would need to be addressed, including:

- Misspellings of names or missing first or last names
- Missing certain commonly required elements such as city/municipality of birth or SSN
- The burden of supporting multiple PPRL tools at single sites
- Considerations for access and security procedures for both the data and the linkage information in a federated ecosystem where data are shared through multiple repositories (some that enclaves and others that are more open), and determining if new rules apply for access and use of linked datasets through these repositories

This project was undertaken to identify technology and governance approaches based on existing record linkage implementations that could address these challenges and form the basis of an appropriate PPRL approach for CARING for Children with COVID and other select pediatric COVID projects at NIH.

4 PROJECT GOAL, OBJECTIVES, AND APPROACH

The overarching goal of this PPRL assessment project was to inform an NIH-wide strategy on the use of PPRL for pediatric COVID studies. To effectively develop a strategy for implementing PPRL for pediatric COVID studies in NIH's federated ecosystem, the selection and establishment of two interrelated components are required:

- Appropriate *governance* for linking records using PPRL: This includes considerations such as what authorizations are required for creating linkages and sharing the linked data, whether the appropriate PII elements required to generate the hash codes or tokens are available at the data collection sites, who or what system will perform the entity resolution and data linkage, and which controls should be implemented to mitigate the risk of potential re-identification from data linkages.
- A *tool or technology* to implement PPRL: One PPRL tool must be selected to link across pediatric COVID studies because hashed codes from different tools cannot be matched. The selection of this tool will largely be determined by the tool's capabilities, including its flexibility to use various PII elements for hashing, data pre-processing capabilities, accuracy and other performance measures of the tool, computational and other resource requirements, ability to scale to accommodate increasing volumes of records, customization options, compliance with government security regulations, and flexibility to support the governance needs described above.

The project goal was achieved through the following three objectives and overall approach:

1. Summarized the current state of pediatric COVID studies selected for the project as related to PPRL implementation: The Project Team documented critical information such as the PII elements collected relevant consent language or other agreements potentially relevant to implementing PPRL, and the interoperability status of the data repositories used to share data from these studies.

2. Develop considerations for key governance components necessary for enabling PPRL for the selected pediatric COVID studies: The Project Team assessed existing record linkage governance models and best practices by performing an in-depth environmental scan of existing record linkage implementations and associated governance frameworks and interviewing relevant stakeholders to collect additional information, validate accuracy of the information collected, and fill in gaps.
3. Develop considerations for implementing potential PPRL tools for the selected pediatric COVID studies. The Project Team assessed available record linkage vendors/organizations against the needs of the pediatric COVID studies, building off a prior technology analysis performed by NCI—the *Landscape Analysis of Privacy Preserving Patient Record Linkage Software (P3RLS)*—Final Report Version 2 (2020)[29].

5 PEDIATRIC COVID STUDIES—PPRL FEASIBILITY

5.1 Studies Selected for the Project

NICHD ODSS identified a total of 11 NIH-funded pediatric COVID studies that are part of the CARING for Children with COVID initiative to assess the feasibility of implementing PPRL for linking data within and across these studies. An overview of the studies is shown in Table 1.

These studies aim to address a broad set of clinical questions related to diagnosing and treating COVID and MIS-C in children, including diagnostic methods for predicting disease severity, cardiological and immunological response profiles, and potential drug efficacy and safety. These multifaceted studies are expected to generate diverse types of data, including demographic, clinical, EHR, laboratory, genetic, imaging, other biomarkers, social, economic, and other survey data. These data present a rich source of information on an individual participant/patient and appropriate linkage of data across studies and data repositories using PPRL would enable the broader research community to derive answers beyond the initial set of questions posed by each of the respective primary studies.

Table 1: Pediatric COVID Studies Selected for the Project

	POP02	MUSIC	PRISM	PreVAIL kIds
Full Study Name	Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs Administered to Children Per Standard of Care (POPS or POP02)	Long-Term Outcomes after the MUltisystem Inflammatory Syndrome In Children (MUSIC)	COVID: Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM)	Predicting Viral-Associated Inflammatory Disease Severity in Children with Laboratory Diagnostics and Artificial Intelligence (PreVAIL kIds)
Study Description	The study investigators are interested in learning more about how drugs given to children by their health care provider act in the bodies of children and young adults in hopes to find the most safe and	The COVID MUSIC Study, funded by NIH and the National Heart, Lung, and Blood Institute, is an observational study that aims to understand cardiovascular	The primary objectives of this study are to determine: o The proportion of children with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) related death, rehospitalization, or major complications after	The PreVAIL kIds initiative funded eight studies that will evaluate genes, immune system proteins, and other biomarkers, and examine how the virus interacts with the body and how the immune system responds to it. These

	POP02	MUSIC	PRISM	PreVAIL kIds
	effective dose for children. The primary objective of this study is to evaluate the pharmacokinetics of understudied drugs currently being administered to children per standard of care (SOC) as prescribed by their treating provider[30].	outcomes after MIS-C, as well as other outcomes in children and adolescents[31].	infection with SARS-CoV-2 and/or Multisystem Inflammatory Syndrome in Children (MIS-C) ○ Immunologic mechanisms and immune signatures associated with disease spectrum and subsequent clinical course during the year of follow-up[32].	studies will rely on artificial intelligence and machine learning to interpret the data they acquire, to understand risk factors underlying the severity of COVID and MIS-C[33].
Years	2020-2024	2020-2025	2020-2023	2020-2024
Funding Agency	NICHD	NHLBI	NIAID	NIH
Program/ Network	Pediatric Trials Network	Pediatric Heart Network	Pediatric Research Immune Network	RADx-rad Program
Study Sites	U.S. 42 study sites	U.S., Canada 32 study sites	U.S., 20 study sites	U.S, U.K., Canada, Colombia 58+ study sites
Data Coordinating Center Name	The Emmes Company, LLC	HealthCore	Vanderbilt University Medical Center	University of California San Diego (UC San Diego) and the University of Texas Health Science Center at Houston (UTHealth)

5.2 Define Questions for PPRL Feasibility

In consultation with NICHD ODSS, the Project Team defined a set of questions for documenting PPRL feasibility for the CARING for Children with COVID studies, as shown in Table 2, given that these studies are underway and could have certain constraints around data linking (e.g., based on consents, IRB approved protocols, or other existing governance or logistical constraints).

Table 2: Analysis Questions for PPRL Readiness of CARING for Children with COVID Studies Selected for the Project

	PPRL Readiness Analysis Questions
1	Is there a broad set of **PII elements** collected by the study?
2	Does the **consent** obtained from study participants address the following? ○ Linking data across study sites within the study and with other pediatric COVID studies ○ Sharing the linked data If not, are other agreements in place for approval to link and share linked data?
3	Are there any **tribal or international data** collected in the study? If so, are the **agreements** required for linking and sharing data in place?
4	What technical and non-technical controls do the **data repositories** used for sharing study data have in place **to provide access** to the linked data?
5	Can each study's **repository interoperate** with other study repositories?

The project reviewed both public (study websites, funding announcements, clinicaltrials.gov, repository websites) and internal study documentation (study protocols, data dictionaries, informed consent

forms, and other study materials) as well as conducted stakeholder interviews with the Project Officers (POs) and data coordinating centers (DCCs) for each of the studies and their repositories.

5.3 Summarize Findings

The project summarized the current state of CARING for Children with COVID studies as it relates to feasibility for PPRL implementation using the questions listed in Table 2. Overall, the pediatric COVID studies all collected the PII elements first name, last name, date of birth, and sex while they rarely collected email, address, and SSN. Most studies also collected ZIP Codes.

The Project Team also documented language from the informed consent forms (ICFs) relevant to linking data and sharing linked data within a study and/or across multiple studies (see details of the language in the consent forms in Appendix Table 1). Since many of these studies are multi-site studies, the consent forms have language for linkage across study sites *within* a study. However, only two of the 11 studies include specific language regarding linkage of data *across* a broader network of studies that would encompass all of the CARING for Children with COVID studies. The study consents mainly focused on the broad sharing of de-identified data through NIH designated data repositories. Additionally, Institutional Certifications[34,35] used by these studies (which certify that data submissions to the repositories are appropriate) do not explicitly address record linkage and there are no additional agreements explicitly addressing PPRL that have been established for any of the CARING for Children with COVID studies.

Some studies that incorporate data from international sites specifically address sharing these data with organizations in the US in a manner consistent with the rest of the study data, while others use the same study documents to communicate consistent data sharing expectations regardless of whether the data are collected from non-tribal US, tribal, and international populations.

The data repositories for POP02, MUSIC, PRISM and PreVAIL kIds studies – the Kids First Data Resource, BioData Catalyst, ImmPort, and the RADx Data Hub – are planned to be interoperable so that CARING for Children with COVID data stored in one repository will be findable and accessible from any of the other repositories. The data access permissions for these repositories range from registered tier to controlled access. Genomic data, which has not yet been generated, will be shared through an NIH designated controlled data repository such as the Kids First Data Resource or BioData Catalyst. To access genomic data in these NIH controlled repositories, researchers must submit a Data Access Request and document their eligibility requirements in the NIH Database of Genotypes and Phenotypes Authorized Access System where requests are reviewed and approved by NIH Data Access Committees.

6 GOVERNANCE ASSESSMENT & FINDINGS

Governance as defined in this Report comprises of the policies, processes, and controls that address ethics, privacy protections, compliance, risk management, or other requirements for a given record linkage or PPRL implementation. PPRL governance is multifaceted—it involves the who (the people and organizations), the what (the policies, processes, and controls), the when (at what stage in the data lifecycle), and the how for implementation of processes and controls. Based on the recommendation from NICHD ODSS, the scope of the Governance Assessment included both PPRL and record linkage implementations not only in systems merging biomedical and healthcare data but also in other NICHD-prioritized systems where PPRL or record linkage has been employed successfully. The rationale behind expanding the scope to non-PPRL implementations and non-health data was to learn from the experience of those who have been performing record linking for an extended period of time (for

example, Census), to gather best practices, and to understand how they addressed various technical and non-technical challenges.

Gaining a detailed understanding of the critical governance elements necessary to implement PPRL, specifically within the NIH federated data ecosystem and with a pediatric focus, was fundamental to developing PPRL approaches for the selected pediatric COVID studies. The Project Team's overall approach for the Governance Assessment is described in Section 4. Briefly, team members defined assessment criteria, researched a variety of publicly available web pages and documentation, interviewed key stakeholders of 13 record linking and PPRL implementations, and, finally, analyzed and summarized the information to inform the development of considerations for PPRL in pediatric COVID studies. The sections below describe the various steps in more detail.

6.1 Define Criteria for Governance Assessment

The criteria examined the people, policies, processes, and controls along the data life-cycle continuum—from data collection through linking to data access—for record linkage/PPRL implementations that are currently operational and successful, paying particular attention to how linkage was operationalized in pediatric use cases. The criteria and the rationale for selecting the criteria are shown in Table 3. The key criteria included authorizations and controls in place for linking, sharing, and accessing the linked data, as well as the processes and methodologies in place to maintain participant privacy, data confidentiality, security, and other data use requirements.

Table 3: Criteria for Record Linkage/Governance Assessment

	Criteria	Rationale for Selection
1	**Sources and types of data used for linkage** ○ Where do the data originate and what types of data are linked?	○ Understand the breadth and scope of data linked, specifically if pediatric data were linked ○ Identify any limitations or constraints for data linking based on the type or source of data—for example, genomic, tribal data, international data, etc.
2	**Authorizations for linking** ○ Has the individual/participant given permission to link their records/data? ○ If not, who authorizes the linkage?	○ Addresses whether the participant was aware of and agreed to the linkage, and/or whether some other entity approved the linkage
3	**Record linking methodology** ○ What method was used for linking the records? ○ If PPRL methodology, what tool or software was used?	○ Determine if different methods used for matching records might dictate or limit how governance is implemented ○ Identify PPRL tools that are used in the NIH ecosystem and with healthcare and biomedical data
4	**PII elements used for the linking** ○ Which PII elements were used, if any, for linking the records?	○ Examines the breadth of PII elements, if used, for record linking, and identifies, if possible, the most common combinations used for matching *Note*: Although PII elements used for linking may be a technical component of PPRL implementation, this criterion is included in the governance assessment because policies and regulations could impact which PII elements are collected and/or used.

	Criteria	Rationale for Selection
5	**Entity resolving party/organization/system** ○ Who or which organization/system does the matching of the records?	○ Identifies the methodology and controls in place to access PII, hashed tokens based on PII, and/or other participant information to resolve entities ○ Examines whether there is physical separation between data generators who have access to PII and entity resolving processors
6	**Data linking party/organization/system** ○ Who or which organization/system does the actual matching of the records/data?	○ Identifies methodology and controls in place to link participant records/data ○ Examines whether there is physical separation among data generators who have access to PII, entity resolving processors, and record linking parties
7	**Data linkage model** What datasets are within the scope of the linkage? ○ Linked database model, where the linkage information created and/or provided encompasses all datasets in a given database ○ Study-specific model, where linkage information is created and/or provided for the purposes of a specific study	○ Identifies the scope of datasets linked—i.e., datasets associated with a database or datasets associated with a specific study
8	**Authorizations for sharing the linked data** ○ Has the individual/participant given permission to share their linked data? ○ If not, who authorizes the sharing of linked records?	○ Addresses whether the participant agreed to the sharing of linked data, and/or whether some other party approved the sharing of linked data
9	**Re-identification Risk Management** ○ Is deductive disclosure review of the linked data performed? If so, what is/are the process/criteria? ○ If not, what other re-identification risk management controls are in place?	○ Examines whether and which controls are in place for sharing the linked dataset, which may have a higher risk profile compared to an individual dataset alone
10	**Authorizations for accessing the linked data** ○ Who authorizes whether the linked records can be accessed by researchers?	○ Identify the controls in place for users to access the linked data and allowable use of that data
11	**Data access model** How are the data provisioned to the users? Data access models identified include: ○ Open access: no access restrictions or registration required to access ○ Registration required: open to all, but users need to be signed in or registered with the resource to access ○ Controlled access: application and eligibility requirements need to be met to gain access (e.g., by a data access committee) ○ Enclave: data cannot leave a specific system boundary (i.e., data cannot be downloaded locally)	○ Identify specific conditions under which users access the linked data

6.2 Select & Research Record Linkage Implementations

The overall process for selecting candidate record linkage implementations is shown in Figure 2. Briefly, the Project Team conducted an environmental scan of various record linkage examples across federal, academic, and commercial sectors using Google search[c] and PubMed search to gather an initial list and obtain an understanding of the breadth of record linkage implementations. The Project Team then conducted more comprehensive research of the resulting 21 implementations to gather available information from public sources, including web pages, documentation, research articles, publications, and white papers, and from NICHD ODSS Team based on their knowledge and experience of record linking. These 21 were further categorized into those using or not using PPRL tools/software for record linking.

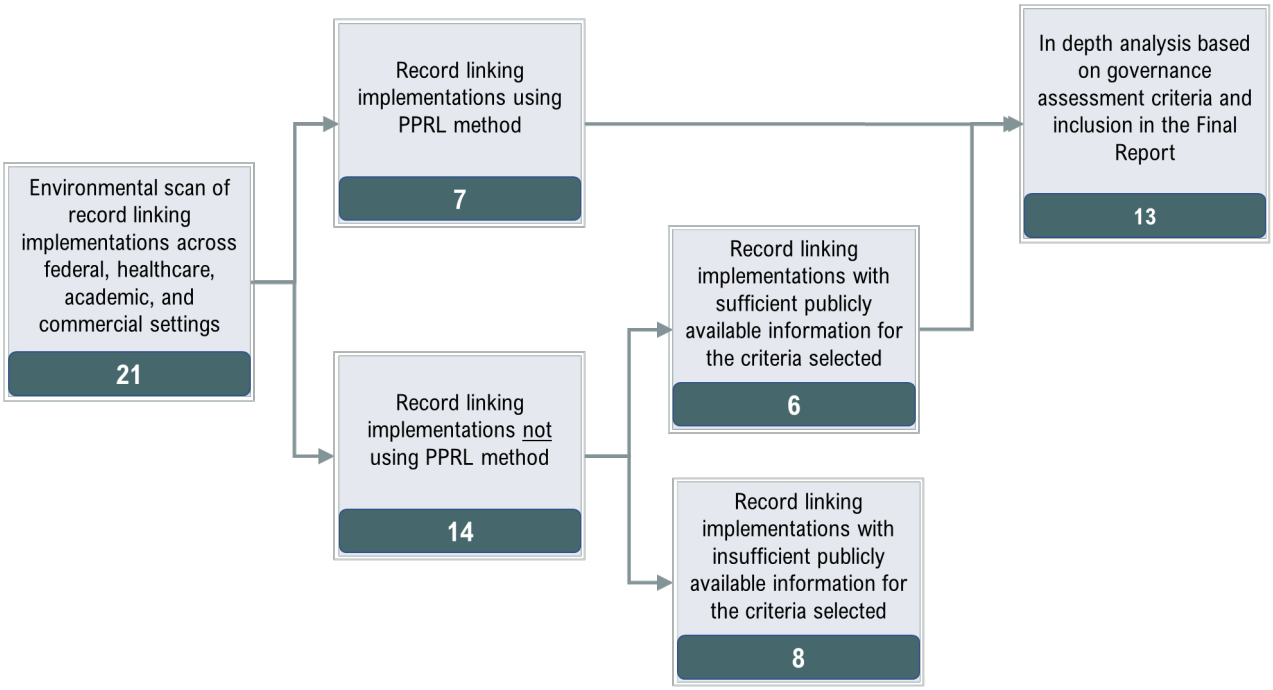


Figure 2: Process for selecting record linkage implementations for the assessment

A set of 13 PPRL and non-PPRL implementations were selected as the final set of candidates for in-depth analysis against the criteria listed in Table 3. The non-PPRL examples (often referred to as "clear text"[d] linkages, since direct PII are used) were also included to ensure that the project gains from the experiences of others with record linking in general and to collect broader best practices and lessons learned. The 13 included all seven of the record linking candidates using PPRL and six of the 13 non-PPRL implementations (the remaining eight were not selected due to lack of sufficient publicly available information). To facilitate a full understanding of the 13 record linkage implementations, the Project Team also prepared overview graphics to illustrate the flow of data from collection through linking to sharing to identify the various points of governance—two examples of data flow overview in the context of linking is shown in Appendix Figure 1 and Appendix Figure 2. After researching the 13 record linkage implementations, the Project Team identified gaps in the information needed to perform a thorough

[c] Major key words used for Google search included: record linking, data linking, data combining, data merging, entity resolution, identity resolution, identity management, PPRL, governance, and technology.

[d] Clear text: information that is not encrypted (https://csrc.nist.gov/glossary/term/clear_text)

assessment of the governance based on the criteria listed in Table 3 and reviewed them with NICHD ODSS to identify relevant stakeholders for interviews. The purpose of the interviews was to collect additional information, validate accuracy of the information collected, and fill in gaps. Ten of the 13 record linkage implementations were selected for the interviews (Table 4). All of the PPRL and non-PPRL implementations at NIH were selected for interviews.

Table 4: Record Linkage Implementations Included in Governance Assessment

	Record Linkage Implementations	System Type	Pediatric Focus	PPRL	Stakeholders Interviewed?
1	NIH Center for Information Technology (CIT)/ The Biomedical Research Informatics Computing System (BRICS) Instances[e]	Secondary Data Repository	No	Yes	Yes
2	National Institute of Mental Health (NIMH) Data Archive Repository (NDA)	Secondary Data Repository	No	Yes	Yes
3	National Center for Advancing Translational Sciences (NCATS)/National COVID Cohort Collaborative (N3C) – EHR Data Linkage	Clinical Data Infrastructure	No	Yes	Yes
4	National Center for Advancing Translational Sciences (NCATS)/National COVID Cohort Collaborative Class 0 (N3C) – EHR Data Linkage with Data from an external enclave	Clinical Data Infrastructure	No	Yes	
5	National Center for Advancing Translational Sciences (NCATS)/National COVID Cohort Collaborative Class 2 (N3C) – EHR Data Linkage with external datasets ingested into N3C	Clinical Data Infrastructure	No	Yes	
6	PEDSnet	Clinical Data Infrastructure	Yes	Yes	Yes
7	Centers for Disease Control and Prevention (CDC)/The Childhood Obesity Data Initiative (CODI)	Study	Yes	Yes	No
8	National Institute of Health National Center for Biotechnology Information (NIH NCBI)/Database of genotypes and phenotypes (dbGaP)	Secondary Data Repository	No	No	Yes
9	National Institute of Health (NIH) *All of Us* (AoU)	Study	No	No	Yes
10	The National Patient-Centered Clinical Research Network & Down Syndrome Connect (PCORnet-DS Connect)/DS-DETERMINED Study	Study	No	No	Yes
11	Georgetown University/Federal Statistical Research Data Center (FSRDC) – Census	Administrative Data Infrastructure	No	No	Yes
12	National Center for Health Statistics (NCHS) with National Death Index (NDI)	Study	No	No	No
13	The Administration for Children and Families (ACF) – The Child Maltreatment Incidence (CMI) Data Linkages project: Alaska Department of Health and Social Services/Oregon Health Sciences University (ADHHS/OHSU)	Study	Yes	No	No

[e] Includes implementations at the following institutes/programs (instances): *NINDS*/Parkinson's Disease Biomarker Program, NIA, *NEI*, NCATS/ Global Rare Diseases Data Repository (*GRDR*), NINR/Common Data Repository for Nursing Science (*cdRNS*), The Federal Interagency Traumatic Brain Injury Research (*FITBIR*).

6.3 Analyze & Summarize Findings

The initial governance analysis of the 13 record linkage implementations was based on publicly available information, and the subsequent deep dive of these for the project included distilling and documenting information collected from public sources and supplemental interviews to address each of the criteria shown in Table 3. Below are some high-level findings from the analysis:

- Only three of the 13 implementations selected for this project were focused on pediatric record linking (Table 4).
- Review of publicly available literature and documentation for the original 21 record linkage implementations, including the 13 that were chosen for this project, showed that publicly available information relating to governance is limited and not consistently documented or shared.
- Stakeholder interviews were a critical component of performing a comprehensive Governance Assessment—through these interviews, the Project Team identified discrepancies, gaps, and outdated information in the public documentation for the record linkage implementations.

A summary of the analysis for these 13 record linkage implementations categorized by PPRL vs non-PPRL examples are presented in Appendix Table 2 and Appendix Table 3. These tables summarize the assessment using the 11 criteria for each of the record linkage implementations, with additional descriptive details below the overview table. The Project Team identified the following key findings based on detailed governance analysis of these 13 record linkage implementations.

6.3.1 Types of Data Linked

Table 5 shows the types of data collected/linked in the 13 record linkage implementations—it is important to note that in all of these cases, while a specific type of data is collected, one cannot automatically infer that these data are *all* linked to each other. Further, the data types listed in the table may not be exhaustive. Nevertheless, the findings from the analysis show that a majority of the PPRL implementations collect and link EHR (or EHR-derived), clinical, and other types of data typically collected during clinical research, such as demographics, genetic, and imaging data. On the other hand, the majority of the non-PPRL record linkage implementations collect and link primarily administrative and survey data. A variety of other types of data are also collected and linked in these implementations—these range from data from mobile devices to disease registry data, vital statistics, geocoded data, longitudinal household records, economic data, and workforce data. Further details are available in Appendix Table 2 and Appendix Table 3.

Table 5: Types of Data Collected/Linked in the Record Linkage Implementations

[*Note: the list below may not be completely exhaustive*]

	Implementation	EHR	Clinical	Demographic	Genetic	Imaging	Mortality data	Administrative data	Survey data	Other
PPRL Implementations										
1	NIH BRICS Instances	X	X	X	X	X				
2	NIMH NDA	X	X	X	X	X				X[f]
3	N3C EHR Linkage	X	X	X						

[f] Neurosignal recordings data

	Implementation	EHR	Clinical	Demographic	Genetic	Imaging	Mortality data	Administrative data	Survey data	Other
4	N3C Class 0 Linkage	X	X	X		X				
5	N3C Class 2 Linkage	X	X	X			X			X[g]
6	PEDSnet	X	X	X		X				X[h]
7	CDC/CODI	X	X	X						X[i]
Non-PPRL Implementations										
8	dbGaP			X	X[j]	X				
9	*All of Us*	X		X	X			X	X[k]	X[l]
10	DS-DETERMINED	X		X					X[m]	
11	Georgetown FSRDC – Census							X	X[n]	X[o]
12	NCHS/NDI						X		X[p]	
13	ACF/CMI – ADHHS/OHSU			X			X		X[q]	X[r]

6.3.2 Authorization for Linking Data and Sharing Linked Data

Authorizations are an important and foundational element for appropriate data linking and sharing. Analysis of the 13 record linkage implementations showed the following mechanisms for authorization to link and share linked data; these authorizations were not mutually exclusive as some implementations used multiple mechanisms (Table 6):

- *Explicit consent from the participant for linking and sharing linked records*: Analysis of the 13 record linkage implementations showed that explicit consent for participant-level record linkage is verified in a minority (4/13) of implementations—*All of Us*, DS-DETERMINED, NCHS/NDI, and some, but not all, PEDSnet studies. When consent is obtained in PEDSnet, the consent language is broad and addresses sharing linked data. For some studies, PEDSnet also obtains consent for linkages using clear text. Available examples of consent language for some of these record linkage implementations that were available from various sources are in Appendix Table 4.
- *Waiver of consent from the data originator's IRB*: All three implementations of N3C and most of the PEDSnet studies operate under a waiver of consent.
- *Determination by an IRB or an equivalent Privacy Board*: Three implementations—CODI, Census/FSRDC, and ACF/CMI-ADHHS/OHSU—relied on the IRB of the institution or organization submitting participant data to provide authorization for linkage. CODI requires IRB approval for

[g] Viral variant summary data
[h] Data from health plans, disease specific registries, vital statistics, and geocoded data
[i] Community invention data including longitudinal household records
[j] Also, genome wide association (GWAS) data, Short Read Archive (SRA) data, and expression data
[k] Surveys topics include sociodemographic, overall health, lifestyle, and health care access and utilization
[l] Data from mobile devices
[m] Survey topics include the Initial Health Questionnaire (IHQ) from the DS-Connect Registry and the Self-Determination survey from the Self-Determination Inventory System Data Dashboard
[n] Survey topics include the American Community Survey (ACS), Population Survey, and the Survey of Income and Program Participation (SIPP)
[o] Also, health data, economic data, U.S. labor/workforce data, science and engineering and technology workforce data
[p] The linked dataset comprised of the following populated-based health surveys: National Health Interview Survey (NHIS): 1985-2014, Continuous National Health and Nutrition Examination Survey (NHANES): 1999-2014, NHANES III (1988-1994), NHANES II (1976-1980), NHANES I Epidemiologic Follow-up Study (NHEFS), Second Longitudinal Study of Aging (LSOA II), Supplement on Aging (SOA), National Home and Hospice Care Survey (NHHCS): 2007, National Nursing Home Survey (NNHS): 1985, 1995, 1997, 2004.
[q] Oregon Pregnancy Risk Assessment Monitoring System (PRAMS) survey data
[r] Child protective services record data

linking longitudinal patient records for research using PPRL. Record linking at Census/FSRDC is limited to statistical purposes only; while Census performs the linkage, the researcher requesting the linked data must certify and show proof (via the data sharing agreement with the data owner) that they have permission to link data from a specific agency or multiple agencies with Census data and with each other. Also, since the linkage is based on PII that must be shared with the FSRDC, an IRB from the organization contributing the data may need to make a determination regarding whether the intended use of the data is appropriate. Several NIH programs that use BRICS also require that an IRB and/or Privacy Board has verified that the submission and associated use of the GUID tool and data sharing is consistent with informed consent, that the data are de-identified according to the respective repository standards, risk to the study population has been considered, and the data were collected in a manner consistent with NIH/DOD regulations; however, the IRB is not asked to sign the submission request.

- *Data submitter authorization for linking and sharing the linked data*: Six of the record linkage implementations rely on data submitters to authorize linkage and sharing. For NDA and BRICS instances, the data submitters and their institutions must agree to linkage via the use of the GUID as part of the data submission requirements of each of the respective repositories, but whether the informed consent specifically addresses the use of the GUID is not confirmed by the repositories. dbGaP requires data submitters to submit an Institutional Certification and a subject consent file that describes various data use limitations based on consent, but it is up to the submitter to determine whether their subject IDs should be linked with existing dbGaP datasets. N3C, PEDSnet, and CODI allow data submitters/owners to participate or permit linkages for certain data sources (e.g., mortality data or viral variant data for N3C) or studies (PEDSnet and CODI sites can engage on a study-by-study basis).
- *Federal authorization*: Both Census/FSRDCs and NCHS/NDI operate under federal laws that authorize them to collect and link data with PII. The Census Bureau is authorized to collect and link data for statistical purposes based on Titles 13 and 26 of the United States Code and the Office of Management and Budget (OMB) Guidance M-14-06 (Guidance for Providing and Using Administrative Data for Statistical Purposes). In the case of NCHS/NDI linkage, specific federal laws authorize the National Health Interview Survey (NHIS) to ask for PII for linkage purposes. These include Section 308(d) of the Public Health Service Act (42 United States Code 242m(d)), the Confidential Information Protection and Statistical Efficiency Act (Title V of Public Law 107-347), and the Privacy Act of 1974 (5 U.S.C. § 552a). As noted above under consent, the NCHS survey data is deemed eligible to link based on whether a survey participant gives consent for data linkage in the survey and whether adequate PII is present for linkage.

Regardless of the mechanism for authorizing sharing, most of the data sharing approaches allow the withdrawal of data for a participant—in such instances, no future linking and sharing of the data for that participant will occur, but the data that have been already linked *and* shared will not be withdrawn. Further details on the authorizations for linking and sharing linked data are available in Appendix Table 2 and Appendix Table 3.

Table 6: Authorizations for Linking and Sharing for the 13 Record Linkage Implementations

	Record Linkage Implementations	Authorization for Linking Data (C/A: Consent/Assent, W: Waiver of Consent, I: IRB, S: Data Submitter Agreement, F: Federal Authorization)	Authorization for Sharing Linked Data (C/A: Consent/Assent, W: Waiver of Consent, I: IRB, S: Data Submitter Agreement, F: Federal Authorization)
PPRL Implementations			
1	NIH BRICS Instances	S	C or S
2	NIMH NDA	S	C or S
3	N3C EHR Linkage	W	W
4	N3C Class 0 Linkage	W + S	W + S
5	N3C Class 2 Linkage	W + S	W + S
6	PEDSnet	[W or C] + S	[W or C] + S
7	CDC/CODI	I + S	I + S
Non-PPRL Implementations			
9	dbGaP	S	C[s] or S
10	*All of Us*	C	C
11	DS-DETERMINED	C	C
12	Georgetown FSRDC – Census	F [+ I[t]]	F [+ I[17]]
13	NCHS/ NDI	F + C	F + C
14	ACF/CMI – ADHHS/OHSU	I	I

6.3.3 PII Elements Used in PPRL Implementations

The Project Team analyzed the PII elements used in the seven PPRL implementations and examined whether the pediatric PPRL implementations used a unique set of PII elements. The 25 PII elements utilized across these implementations are shown in Table 7 and can be summarized as follows:

- First name, last name, and date of birth are used in all seven implementations.
- All seven implementations use some form of geographical location information; five use ZIP Code, two use city of birth, and one uses household street address.
- Gender or sex is used in all seven implementations; three use gender, three use sex, and one uses "physical sex at birth."
- Cell/phone number is used in four of the seven implementations.
- SSN and email are used in all three N3C implementations, but not in other implementations.
- Combinations of five or more PII elements are used in all of the record linkage implementations.

Comparison of the PII elements used by the various PPRL tools showed the following:

- Two government-owned GUID tool implementations at NIH (BRICS instances and NIMH Data Archive) and an open source tool, Anonlink (used by CODI), use similar PII elements, including first name, last name, date of birth, and sex. Anonlink also uses ZIP Code and household street address and BRICS/NDA each use city of birth.
- The Datavant tool used by four of the seven record linkage implementations incorporated mostly the same PII elements: first name, last name, date of birth, gender/sex, SSN, email, cell phone number, and ZIP Codes.

[s] dbGaP obtains Study Consent files from submitters which denotes the consent groups.
[t] Linkages for statistical purposes only

The two pediatric-focused record linkage implementations, PEDSnet and CODI, did not use identical PII elements.

Table 7: PII elements used in PPRL based Record Linkage Implementations

	PII Elements	NIH BRICS Instances	NIMH NDA	N3C (3 Implementations)	PEDSnet	CODI	Total
	PPRL Tool Used	*BRICS GUID*	*NDA GUID*	*Datavant*	*Datavant*	*Anonlink*	
1	First name	X	X	X	X	X	7
2	First initial of first name				(X)[u]		(1)
3	Middle name	X	X				2
4	Last name	X	X	X	X	X	7
5	Date of birth	X[v]	X	X	X	X	7
6	Day of birth	(X)					1
7	Month of birth	(X)					(1)
8	Year of birth	(X)					(1)
9	City of birth	X	X				2
10	Country of birth	X					1
11	Place of birth	(X)	(X)				(2)
12	ZIP3				X		1
13	ZIP5			X			3
14	ZIP9			X			3
15	ZIP Code					X	1
16	Household street Address					X	1
17	Gender			X			3
18	Sex		X		X	X	3
19	Physical sex at birth	X					1
20	SSN			X			3
21	Email			X			3
22	Cell phone number			X		X[w]	4
23	Phone number					(X)	(1)
24	Government or national issued ID	X[x]					1
25	Country issuing government issued or national ID	X[x]					1

6.3.4 Two-Party or Three-Party Model for Entity Resolution and Data Linkage

The 13 record linkage implementations were analyzed for the separation of parties who perform entity resolution and who perform the data linking. In a two-party model, the entity resolution and the data linking are done by the same organization whereas in a three-party model, these two activities are

[u] (X): Derived PII elements
[v] Day, month, and year of birth used for BRICS instances were categorized as 'date of birth' in this table.
[w] Phone number was considered same as cell phone number for Anonlink in this table.
[x] PII field is not required for PPRL linkage.

performed by separate organizations (the first party is the PII holder). In three-party situations, often a trusted neutral party serves as the honest broker[y] who performs entity resolution.

Analysis of the 13 record linkage implementations show that six of them used the three-party model and the remaining seven used the two-party model, as shown in Table 8. The three-party model was used by a majority of the PPRL implementations (five of seven), whereas most of the non-PPRL implementations used two-party. Details of the data linkage approaches for all 13 record linkage implementations are in Appendix Table 2 and Appendix Table 3.

Table 8: Two-party or Three-party and Data Linkage Models used in the Record Linkage Implementations

	Record Linkage Implementations	Entity Resolution & Data Linkage			
		Two-Party (2) or Three-Party (3)	Entity Resolver	Data Linker	Data Linkage Model[z] (D: Linked database, S: Study-specific)
PPRL Implementations					
1	NIH BRICS Instances	3	GUID server	Researchers	D
2	NIMH NDA	3	GUID server	Researchers	D
3	N3C EHR Linkage	3	Regenstrief	Researchers	D
4	N3C Class 0 Linkage	3	Regenstrief	Researchers	D
5	N3C Class 2 Linkage	3	Regenstrief	Researchers	D
6	PEDSnet	2	PEDSnet Data Coordinating Center (DCC)	PEDSnet DCC	S
7	CDC/CODI	2	CODI DCC	CODI DCC	S
Non-PPRL Implementations					
8	dbGaP	3	dbGaP Data Curation Team	Researchers	D
9	*All of Us*	2	Raw Data Repository	Raw Data Repository	D
10	DS-DETERMINED	2	Study Team	Study Team	S
11	Georgetown FSRDC - Census	2	Census	Census	S
12	NCHS/NDI	2	NCHS Data Linkage Program	NCHS Data Linkage Program	D
13	ACF/CMI – ADHHS/OHSU	2	Integrated Client Services	Integrated Client Services	D

6.3.5 Data Linkage Model: Linked Database or Study-Specific Linkage

The data linkage model refers to the scope of the data that is linked and provisioned to users in the various record linkage implementations. For this project, two models were identified:

- *Linked database model*, where the linkage information that is created and/or provided encompasses all datasets in a given database

[y] A party that holds de-identified tokens ("hashes") and operates a service that matches tokens generated across disparate datasets to formulate a single Match ID for a specific use case.
[z] Linked database model: the linkage information is created and/or provided encompasses all datasets in a given database
Study-specific linkage model: linkage information is created and/or provided for the purposes of a specific study

- *Study-specific model*, where linkage information is created and/or provided for the purposes of a specific study

Table 8 shows that a majority (nine) of the 13 record linkage implementations operate as a linked database model by default and the remaining four are study-specific linkages. Details of the data linkage approaches for all 13 record linkage implementations are in Appendix Table 2 and Appendix Table 3 and a summary of the data linkage approaches for key record linkage implementations is included below.

BRICS and NDA use global unique identifier/s (GUID) servers/systems to perform the matching and entity resolution, where the PPRL tool automatically checks the database for existing GUID and returns an existing one (if a match is identified) or a new one (if no match is detected). Approved researchers receive access to the GUIDs for all of the data they are approved to access (no additional requests are needed); however, it is up to the researcher to use the GUID to link data in their analyses. Some instances[aa] of BRICS use a common GUID server, which means that users with approval to access data from multiple instances could use the GUIDs to link data across multiple instances. All three N3C PPRL implementations —internal EHR to EHR linkage and external Class 0 and Class 2 linkages —follow the linked database model where entity resolution occurs as the data are received by N3C and tokens are sent to the linkage honest broker from the data partners and the external sources. Only externally linked Class 2 data are currently available to users whereas the internal EHR data linkage and external Class 0 data linkages are in pilot phase. In all three cases, entity resolution is performed by a linkage honest broker (LHB), Regenstrief, based on matching the hashed tokens generated by N3C EHR data partners and external enclaves/data sources (for Class 0 and 2). The LHB then creates a linkage map with a new MATCH_ID mapping to the original de-identified subject IDs (Pseudo_IDs) provided by N3C data partners across all datasets that participate in PPRL. Once fully launched, the linkage map will be made available to researchers who have approval to access the HIPAA limited dataset (level 3) in the N3C enclave to use in their analysis. Entity resolution is performed across all participating EHR, Class 0, and Class 2 datasets, but linkage maps between EHR data and Class 0 or Class 2 will only be created for EHR data partners who have specifically approved linkage with a Class 0 or Class 2 dataset, and these linkage maps will only be shared with approved users of the specific Class 0 or Class 2 dataset.

dbGaP follows the linked database model by checking all incoming subject IDs provided by the submitter in the subject consent file against existing studies in the database using a custom string matching analysis. If the subject ID of the incoming data matches with the subject ID of existing datasets, dbGaP curators notify the incoming submitter to verify the origin of the matched subjects, and if there is a true match, dbGaP asks the submitter to *add* the existing study's IDs (in dbGaP) to the subject consent file and resubmit. When there is a match, dbGaP links the incoming data with the existing dbGaP Subject ID, and when there is no match, creates a new dbGaP Subject ID, which is openly available to all data users. Researchers can use the dbGaP Subject ID to find participants who are represented in multiple studies and link the data during analysis after approval to access the individual datasets from the respective data access committees. dbGaP also performs entity resolution *within* a study through the use of the Genetic Relationship and Fingerprinting (GRAF) tool, to assess inconsistencies between molecular data sample IDs and phenotype sample IDs, unintended data duplications, incorrect pedigree information, and subject relationships within a given data submission. DbGaP does not use GRAF to identify cross-study linkage, but GRAF could be leveraged for this purpose if approved for a specific implementation.

[aa] An instance is a collection of services for a managed data repository software platform; each instance is a distinct data repository in BRICS.

In the case of *All of Us*, all datasets collected from participants for the *All of Us* Research Program are assigned a participant identifier (PID) and are automatically linked using the PID when deposited into the raw data repository (RDR). The PID is an internal linking ID and is converted to a research ID for data users. *All of Us* is currently exploring linkage with external datasets, where the data linkage will be performed by *All of Us* across all *All of Us* participants and provisioned in the *All of Us* enclave.

PEDSnet, CODI, and FSRDC/Census use the study-specific linkage model where users must submit a research proposal detailing the proposed use of the linked data, and only after approval of the proposal does the study team or organization provide the linked data to the researchers. In PEDSnet and CODI implementations, their DCC performs the entity resolution using hashed codes and generates a new unique linking ID that is then used by the DCC to link across datasets for each study. In both these implementations, the linking ID is replaced with a study-specific ID for provisioning to the users. Census uses a study-specific linkage model within the FSRDC for linking Census data with data from other external sources for provisioning to approved users. The external data can be from other agencies (Agency for Healthcare Research and Quality, National Center for Health Statistics, Bureau of Economic Analysis, Bureau of Labor Statistics, etc.) or other sources that users bring into the FSRDC. Once the linkage is approved by both Census and the external source/s, Census links the data by generating a Personal Identification Key (PIK) for all data imported into Census or via a PIK bridge (provided by external agencies), after which the linked data is provisioned to the user.

6.3.6 Controls for Managing Re-Identification Risk with Linked Data

While the benefits of using linked data for addressing more complex and/or new research questions may be greater compared to the individual datasets, linking datasets at the individual record level raises the potential re-identification risk even if the data that are being linked are considered fully de-identified (e.g., stripped of all 18 HIPAA identifiers[18]). Therefore, managing re-identification risks is especially important when sharing linked data. While many controls typically used for sharing research data are also applicable when sharing linked data, there might be additional controls that are appropriate based on the nature of the datasets that are linked, such as whether they are pediatric data, the de-identification status of the data, the types of data (e.g., linkage with administrative data or social media data), the granularity of the data, and the sensitivity of the data (drug use, criminal record, etc.). Multiple controls—applied both prior to linking and after linking—can be used to manage the risk of re-identification. Two categories of re-identification risk management controls were examined in the 13 record linkage examples based on the information available publicly or gathered via stakeholder interviews.

***De-identification status of the data*:** De-identification of the linked data serves as a control mechanism *before* sharing the linked data. Methods typically used to de-identify datasets include masking, perturbing, suppressing variables, and collapsing small cell sizes; the method chosen will depend on whether the data can continue to be meaningfully used after it has been de-identified. While some implementations use other de-identification standards, the HIPAA Privacy Rule specifies the following standards for de-identifying PHI data and identifies two levels of de-identification:

- De-identified dataset: refers to Expert Determination or Safe Harbor (removal of all 18 identifiers enumerated at section 45 C.F.R. 164.514(b)(2) (the HIPAA Privacy Rule))
- Limited dataset: refers to PHI that excludes 16 of the direct identifiers but may include geographic information (city, state, ZIP Code), elements of dates, and other values that are not direct identifiers

The NIH Genomic Data Sharing Policy follows the definition for de-identified data in the HHS Regulations for Protection of Human Subjects (also known as the Common Rule) and the HIPAA Safe Harbor method.

An examination of the de-identification status of the *linked* data that are shared in the 13 record linkage implementations shows that a majority (9 of 13) share exclusively de-identified datasets whereas all three N3C implementations share linked data only as limited datasets, and one (CODI) shares a mix of limited and de-identified linked datasets (Table 9). Additional details for all 13 record linkage implementations are in Appendix Table 2 and Appendix Table 3.

Disclosure review and other re-identification risk management controls: Disclosure "relates to inappropriate attribution of information to a data subject, whether an individual or an organization"[36], and a disclosure review is designed to prevent potential disclosures. Disclosure reviews and other re-identification risk management protocols and procedures serve as controls that can be implemented before or after data linkage, prior to sharing linked data. Disclosure review usually comprises some combination of an expert review of variable combinations and statistical analysis of potential re-identifiability. Other controls include requiring a letter of determination (LOD) from the data user's IRB and including specific terms in the data use agreement/certification established with the user's institution that explicitly prohibit re-identification of study participants and limit the period of data use.

The Project Team assessed disclosure reviews and other re-identification risk management controls in place for sharing linked data in 12 of the 13 record linkage implementations (Table 9) and drew the following conclusions (*Note*: DS-DETERMINED is not sharing the linked data beyond the study team yet):

- Six of the 12 record linkage implementations—N3C Class 0 and Class 2 linkages, PEDSnet, *All of Us*, Census and NCHS/NDI—have some form of re-identification assessment process in place. In some of these implementations, special committees perform a formal re-identification risk analysis—these committees include the Tools and Resources Review Committee for N3C Class 0 and Class 2, the PEDSnet Steering Committee for PEDSnet, the Committee on Access, Privacy, and Security (CAPS) for *All of Us* internal datasets, and a Disclosure Review Board for Census. These assessments may result in the exclusion of sharing certain datasets or data elements or modifying specific data elements to share less detailed information.
- PEDSnet Policy also requires masking cell counts <11 in reports and manuscripts. However, smaller cell counts can be reported if five or more institutions contributed to the dataset and these institutions agree to allow the small cell sizes to be revealed.
- Of the 12 implementations, an LOD from the user's IRB is required for all three N3C implementations. There are specific datasets in dbGaP, NDA, and BRICS that require IRB approval as a component of the data access request, but this is based on consent-based data use limitations and not related to record linkage, nor is it standard practice across all datasets that reside in these repositories. Finally, NDA and BRICS data access guidance advises that data submitters who still have access to PII for the datasets they shared, may need to update their IRB approved protocol because access to additional data obtained through use of the GUID increases the amount of data they are accessing for their participants.
- All 12 record linkage implementations require the user and their institution to execute a Data Use Agreement/Certification, which explicitly prohibits re-identification of study participants.

Additional details for these 12 record linkage implementations are in Appendix Table 2 and Appendix Table 3.

Table 9: Disclosure and Re-identification Risk Management of Linked Data

	Record Linkage Implementations	De-identification Status of the Linked Data[bb] (Limited Dataset, De-identified, Synthetic)	Disclosure Review/ Other Re-Identification Risk Management Controls	IRB Letter of Determination[cc]	Data Use Agreement/ Certification[dd]
PPRL Implementations					
1	NIH BRICS Instances	De-identified data	No	No	Yes
2	NIMH NDA	De-identified data	No	No	Yes
3	N3C EHR Linkage	Limited dataset (retains dates and ZIP Codes)	No	Yes	Yes
4	N3C Class 0 Linkage	Limited dataset (retains dates and ZIP Codes)	Re-identification risk assessed by the Tools and Resources Review Committee	Yes	Yes
5	N3C Class 2 Linkage	Limited dataset (retains dates and ZIP Codes)	Re-identification risk assessed by the Tools and Resources Review Committee	Yes	Yes
6	PEDSnet	De-identified	Risk review is conducted for each proposed study, but no separate deductive disclosure review of the linked data is performed	No	Yes
7	CDC/CODI	De-identified or Limited dataset	No	No	Yes
Non-PPRL Implementations					
8	dbGaP	De-identified (HIPAA Safe Harbor + Common Rule per NIH Genomic Data Sharing Policy)	No	No	Yes
9	*All of Us*	De-identified	Risk of re-identification is routinely assessed by the *All of Us* Committee on Access Privacy and Security (CAPS)	No	Yes
10	DS-DETERMINED	De-identified	Linked data sharing process yet to be defined	Linked data not yet shared outside of study team	Linked data not yet shared outside of study team

[bb] *Limited dataset* refers to PHI that excludes 16 categories of direct identifiers; *De-identified data* refers to removal of all 18 identifiers enumerated at section 45 C.F.R. 164.514(b)(2) (the HIPAA Privacy Rule); *Synthetic data* refers to data that are computationally derived from the limited dataset and that resemble patient information statistically but are not actual patient data.

[cc] Determination that an activity IS NOT Human Subject Research: the project does not meet either the definition of "research" as defined in 45 CFR 46.102(l) or 21 CFR 56.102(c); or the definition of "human subject" at 45 CFR 46.102(e)(1) or 21 CFR 56.102(e) – or – Determination that an activity IS Human Subject Research: proposed activity is human subject research because it meets the DHHS definition of research [45 CFR 46.102(l).

[dd] Data Use Agreement or Certification established with the user's institution explicitly prohibiting re-identification of participants

	Record Linkage Implementations	De-identification Status of the Linked Data[bb] (Limited Dataset, De-identified, Synthetic)	Disclosure Review/ Other Re-Identification Risk Management Controls	IRB Letter of Determination[cc]	Data Use Agreement/ Certification[dd]
11	Georgetown FSRDC – Census	De-identified	Approval from the Disclosure Review Board (DRB) prior to disseminating statistical products or publications derived from the analysis	No	Yes
12	NCHS/NDI	De-identified	NCHS Research Data Center (RDC) reviews research proposals from users requesting access to restricted use linked mortality files (LMFs) to identify potential disclosure risks	No	Yes
13	ACF/CMI – ADHHS/OHSU	De-identified	No	No	Yes

6.3.7 Authorizations and Controls for Accessing the Linked Data

As mentioned earlier, linked data might present a higher risk profile than the individual datasets. It is critical therefore to ensure that such data are provisioned to users in a manner by which participant confidentiality and data privacy are protected and maintained. Two criteria were used to examine the mechanisms established by the 13 record linkage implementations to provision the linked data to users:

- *Authorization for data access*: Analysis of the 12 record linkage implementations that are currently sharing linked data showed that a majority (10 out of 12) relied on an internal group—a Data Access Committee, Steering Committee, Governance Board, or a Resource Access Board (Table 10) (*Note*: DS-DETERMINED is not sharing the linked data beyond the study team yet). These committees were responsible for reviewing the proposed research plan from data users or requestors to ensure it is consistent with data use limitations if any, imposed by the consent or by the submitter, or other requirements. For accessing linked data within N3C, which is considered level 3 (limited dataset), users must attest to the N3C Code of Conduct, IT security training, and human subjects protection training. In the case of Census/FSRDCs, users requesting access to the linked data via FSRDCs are required to obtain Special Sworn Status[37], complete background check and training, and sign an agreement prohibiting attempts to re-identify the participants and requiring using the data only for statistical purposes. A Census Bureau data access team confirms that all researchers have completed required trainings and then provides access within a secure computing environment. Use of data provisioned by Census through the FSRDCs are governed by laws and policies from agencies that supplied data. For example, Titles 13 and 26 of the U.S. Code protect the privacy and confidentiality of the participants and their data. Violation of these laws are federal crimes are punishable by serious penalties including prison time and fines.
- *Data access models*: The four types of access options examined in the record linkage implementations included open, registration required, controlled, and enclave (Table 10). All 12 of the implementations that are currently sharing individual-level linked data provision those data either in a controlled manner or through an enclave. For linkage of EHR data with external

datasets that are categorized as Class 0, N3C provisions the linked data in an ephemeral workbench, which is a temporary extension of the N3C enclave. *All of Us* provisions data in the secure curated data repository (CDR) via three tiers of access—an open tier where summary statistics and aggregate information are provided, and registered and controlled tiers, where data with differing levels of granularity are provided. Re-identification risk analysis is performed before provisioning the *All of Us* data through the registered and controlled tiers. Although the controlled tier (with genomic and more granular demographics, EHR, and survey data) tolerates a higher level of risk than the registered tier, both the registered and controlled tiers within *All of Us* also function as enclaves (i.e., data cannot be downloaded or analyzed in other systems).

Table 10: Authorizations and Controls for Accessing the Linked Data

	Record Linkage Implementations	Authorization for Data Access	Data Access Model[ee] (O: Open, R: Registration required, C: Controlled, E: Enclave)
PPRL Implementations			
1	NIH BRICS Instances	Respective Program's Data Access Committee (DAC)	C
2	NIMH NDA	NDA DAC	C
3	N3C EHR Linkage	N3C DAC	E
4	N3C Class 0 Linkage	N3C DAC	E[ff]
5	N3C Class 2 Linkage	N3C DAC	E
6	PEDSnet	PEDSnet Steering Committee	E
7	CDC/CODI	CHORDS Governance Committee	C
Non-PPRL Implementations			
8	dbGaP	Respective Dataset's DAC	C[gg]
9	*All of Us*	*All of Us* Resource Access Board	O, R/E, C/E[hh],
10	DS-DETERMINED	N/A[20]	N/A[ii]
11	Georgetown FSRDC – Census	Census Bureau's Data Access Team	E
12	NCHS/NDI	NCHS Research Data Center (RDC)	E
13	ACF/CMI – ADHHS/OHSU	Project specific approving authority including an advocate from one state agency (Oregon Health Authority)	C

7 TECHNOLOGY ASSESSMENT

In support of the overall project goal to inform an NIH-wide strategy on the use of PPRL for pediatric COVID studies, a third objective was to develop considerations for implementing potential PPRL tools in support of the selected use cases identified by the pediatric COVID studies. To meet this objective, the Project Team assessed the landscape of broadly used PPRL vendors/organizations, with a focus on those used within the NIH data ecosystem. To further understand the existing tools, the Project Team expanded upon a prior technology analysis conducted by NCI—the *Landscape Analysis of Privacy*

[ee] Data access models–Open access: no access restrictions or registration required to access; Registration required: open to all, but users need to be signed in or registered with the resource to access; Controlled access: application and eligibility requirements need to be met to gain access (e.g., by a data access committee); Enclave: data cannot leave a specific system boundary (e.g., cannot be downloaded).
[ff] Ephemeral Work Bench (A temporary extension of the N3C Enclave)
[gg] Controlled Data but Public dbGAP IDs
[hh] Both the registered and controlled tiers of access are within *All of Us*'s enclave environment.
[ii] Linked data sharing process yet to be defined

Preserving Patient Record Linkage Software (P3RLS)[jj]*—Final Report Version 2 (2020)*[29]. The high-level approach for performing the analysis is further discussed in the sections below.

7.1 Define Criteria for Technology Assessment

The Project Team developed a PPRL technology survey questionnaire based off the NCI Landscape Analysis to address the pediatric data linkage use cases presented in Section 3. The survey comprised 57 questions organized into seven capability categories. The categories and descriptions can be found in Table 11. A subset of these questions was designated as essential as they address pediatric-specific needs and are related to the ability to implement PPRL governance models.

Table 11: Technology Capability Categories for Survey Questions

	Capability Category	Category Description
1	Hash Generation and Record Linkage	Describes the overall process required in the generation of hashes from one or more combinations of input data fields.
2	Operating Environment and Licensing Model	Describes deployment considerations such as the ability to deploy to the cloud, availability on different operating systems, and licensing parameters such as what software or features the license is for, how long it is valid for, how many users can use the software, the computers on which the software can be used.
3	Usability & Security Features	Describes the difficulty or ease for users to become proficient in using the software effectively, quality of the user interface, robustness for error handling, accessibility, installation and maintenance. In addition, this category captures requirements for protection of information such as confidentiality, integrity, non-repudiation, and accountability.
4	External System Integration	Describes the ability of the software to interface with other systems (such as the ability to ingest data).
5	Data Cleaning/Pre-Processing Features	Describes the ability of transforming data into consistent formats and performing semantic cleanups (e.g., phonetic spellings of names and substitution of nicknames) to enable more consistent generation of identifiers and improving matching performance.
6	Performance and Scalability	Describes whether processing times and resources fall within specified constraints and whether the software scales to the required data sizes.
7	Use Cases, Applications, and Future Capabilities (Informational Questions)	Describes current use cases and applications that the vendor has supported/is currently supporting as well as any future capabilities that are being planned.

7.2 Select & Research Candidate PPRL Technologies

The Project Team defined the scope for the Technology Assessment to include only vendors/ organizations with products that are widely used, able to support large use cases (greater than 1 million records), and/or currently used within NIH data systems. Based on these criteria, a total of seven vendors/organizations were included in the Technology Assessment (Table 12). An eighth product, Anonlink, which is an open source tool used in the federal space for PPRL linkage (for example in the CDC/CODI governance example) was also contacted for the survey but was not included in this assessment due to lack of response. The tools identified are or have been used for record linkage implementations within health systems, academic medical centers, research institutions, commercial data aggregators, biopharma stakeholders, population health analytic platforms, medical device vendors, registries, government entities, national clinical laboratories, Electronic Medical Record (EMR)

[jj] This report uses the term privacy preserving record linkage (PPRL) to refer to the concept of P3RL in the NCI report.

vendors, retailers, Prescription Benefit Managers (PBMs), health information technology companies, pharmaceutical manufacturers, health insurers, health services providers, and healthcare suppliers.

Table 12: PPRL Vendors and Tools

Number	PPRL Vendor/Tool	Prior/Current Use at NIH/Other Federal Agencies
1	HealthVerity	Used by NIH, NCI, CDC, and FDA
2	Datavant	Used by N3C and for NIH funded studies in PEDSnet
3	Senzing	Currently being assessed for use at NIH
4	Crossix	Unknown
5	IQVIA	Identified during the N3C stakeholder interview as another vendor that NIH is using for certain projects
6	BRICS GUID	Used by many NIH institutes/program data repositories, including NINDS, NIA, NCATS, NEI, NINR, and DOD/FITBIR
7	NHash	A hashed subject ID generator that is being used by the RADx-rad PreVAIL Kids Initiative to generate subject IDs for data submission to the RADx-rad Data Hub

The Project Team sent the capability questions to the seven vendors/organizations. The vendors who had participated in the NCI Landscape Analysis were given the opportunity to update any original answers to the NCI request. All vendors/organizations completed the questionnaires by self-assessing their capabilities in the seven question categories.

The Project Team received the survey responses and reviewed all responses and explanations provided by the vendors/organizations to summarize their key capabilities to address the pediatric PPRL use cases.

7.3 Summarize Findings

Results of the complete and detailed analysis of survey responses performed by the Project Team are not shared in this *public* report as they are intended to inform internal NIH decision making. General observations and findings are documented in the sections below. In general, most PPRL tools responded favorably to a majority of the essential capabilities criteria. The tools that fulfilled the majority of these criteria differentiated themselves by offering data cleaning and pre-processing capabilities and by their superior security certifications in their array of features. Tools that did not address the essential capabilities criteria primarily were hard-coded with inflexible hash generation and little additional functionality.

7.3.1 Hash Generation and Record Linkage

Hash generation capabilities, such as the ability for the user to specify which variables are used in the hashes and the ability to link on multiple hashes, are crucial for accurate record linkage without sharing PII. All vendors/organizations generally responded favorably to the evaluation questions in the hash generation and record linkage category. All tools support two-party and three-party protected linkage. To support three-party protected linkage, each tool handles the transmission of additional information to an honest broker (sometimes also referred to as a trusted broker) differently, including sending a metadata file that provides a data quality profile of the tokenizing site, sharing a list of the top candidates of matches, allowing a third party to generate confidence scores to map matches, or sending metadata about the match. The majority of PPRL tools allow for linking based on multiple concatenated input variable hashes that are generated from different arrangements of concatenated input PII

elements, with no limit on the number of these variable combinations. However, some tools require certain PII elements for generating a hash, such as first name, last name, DOB, location elements, and/or gender.

Each tool also has its own unique tunable characteristics for identifying matches between hashes. Some allow for all matching parameters to be tuned through different matching designs or plugins and configurations, whereas others only permit the adjustment of certain parameters, such as risk ratios, error rates, and/or toggling between close match checking.

7.3.2 Operating Environment and Licensing Model

All PPRL tools assessed are implementable in a variety of operating environments, including all major platforms (Windows, MacOS and Linux). Although the vendors/organizations assessed utilize various licensing models, all tools demonstrated vendor-rights policies that align to NICHD ODSS requirements (i.e., vendors do not have rights to the data ingested). This includes PII, metadata, derivative software data, and hashes along with the associated metadata.

7.3.3 *Usability and Security Features*

Several vendors/organizations responded favorably in the Usability and Security Features category, as their tools met various security certification thresholds (e.g., SOC 2, NIST) while providing a low technology barrier for non-technical users. With regard to usability, several vendors/organizations have implemented numerous features to improve usability such as Graphical User Interfaces (GUIs) while others are configurable from the start. These tools can be configured to automate a significant portion of the PPRL operations and include a default configuration to be used "out of the box."

In terms of security, several PPRL tools have or are in the process of obtaining a U.S. government security certification like the Federal Information Security Modernization Act (FISMA) or the Federal Risk and Authorization Management Program (FedRAMP), although not all tools that are being used by the government have FISMA or FedRAMP status. Additionally, all the PPRL vendors/organizations ensure that unencrypted PII elements are not exposed. The most common hash generation algorithm was SHA-256 followed by SHA-512. A couple of tools incorporate AES-128 encryption, a two-way encryption algorithm which can both encrypt and decrypt, within its hash generation pipeline.

7.3.4 External System Integration

Only a limited number of tools offer the capability to easily customize and flex input and output formats. Among the assessed vendors/organizations, the CSV file format was the most popular usable format for providing PII elements followed by JSON file format. Other supported formats include flat/gzipped delimited/positional files, input files encoded in UTF-8 delimited by pipe, comma, tab, or semicolon, and delimited or fixed width text files.

7.3.5 Data Cleaning/Pre-Processing Features

Data cleaning and pre-processing improve the quality of the PII data elements used to generate hashes. Since real world data are messy, data that are cleaned and standardized prior to hashing returns more consistent hashes and in return, higher quality record linkages[38].

A couple of the tools included in the technology assessment are currently only intended for hashing and linking and therefore did not have data cleaning/pre-processing features. Of the vendors/organizations

with capabilities beyond hashing and linking, additional data cleaning/pre-processing features include handling cases of data abnormalities, phonetic encoding of names (Soundex), international naming, metadata cleaning, substitution name expansion, noise detection, and collision scores. Certain tools also allow for the specification of data cleaning by field. In addition to data cleaning, probabilistic matching, aggregation techniques, bloom filters, and frequency tables and other statistical analysis features have been implemented by a couple of tools to ensure the quality of the data linkages.

7.3.6 Performance and Scalability

All tools have little to no restrictions for handling large quantities of data for PPRL. Significant advances in software development in the last decade have enabled scalable and high-performance software for PPRL applications. Several of the assessed vendors/organizations can handle an uncapped maximum number of records (up to tens of billions), with the limiting factor instead being hardware performance.

7.3.7 Informational Questions

A few tools currently support or have previously supported initiatives with pediatric data. Additionally, one vendor/organization reported that they are developing the ability for their tools to interoperate with other PPRL vendors/organizations' tools. However, technical documentation was not provided for review. Any interoperability approaches between different vendors/organizations' PPRL tools warrant careful analyses, given the complexity of the technical challenge.

8 CONSIDERATIONS

The NIH CARING for Children with COVID initiative was established to better understand SARS-CoV-2 infection in children who display a broad spectrum of the symptomology, with some infected children exhibiting a serious multi-organ disease called MIS-C. CARING for Children with COVID study investigators identified the need to link data from these studies early in the pandemic when the cases were relatively rare due to school closures and it was suspected that the same children were being enrolled across multiple studies. The investigators recognized the potential value and impact of linking different types of data collected for an individual child across these studies, given the multi-organ nature of the disease and each study having a different focus (pharmaceutical data versus immune profiling versus cardiac imaging). PPRL was identified as the most feasible approach to address this need, given that the studies are unable to share PII with one another or with the data repositories used for sharing the de-identified study data and while genetic matching was another possibility, study investigators wanted to reduce the number of times the same child underwent genetic sequencing.

The overall goal of this project was to assess and analyze governance and technology approaches in diverse, extant record linkage implementations to inform an NIH-wide approach to using PPRL to link data across pediatric COVID studies and, more broadly, to inform approaches for linking individual-level datasets across pediatric research studies. The project achieved this goal by:

- Summarizing the status of the CARING for Children with COVID studies for PPRL feasibility
- Analyzing 13 record linkage implementations—both PPRL and non-PPRL—funded by NIH, other federal agencies, and non-government organizations, to fully document end-to-end governance decisions, including authorization for linking and sharing, data linkage models, re-identification risk management, and access controls

- Evaluating the capabilities of seven PPRL vendors/organizations, including one NIH-developed tool, one university-developed tool, and five commercial vendor tools, by extending a recent Technology Assessment led by NCI[29] and adding facets specific to the pediatric COVID record linkage use cases

The Project Team considered the current state and context of the CARING for Children with COVID studies when identifying and evaluating existing record linkage implementation approaches, including the following:

- The CARING for Children with COVID studies selected for the project—POP02, MUSIC, PRISM, and PreVAIL kIds—are already underway, and participant enrollment has closed for some studies.
- The studies are depositing data to multiple NIH data repositories that are or will be interoperable (data will be findable and accessible across multiple repositories) and use multiple access tiers to share data.
- None of the studies currently uses a PPRL tool to link data within the study or across studies.

The Project Team determined that PPRL is a feasible approach for linking participant data across pediatric COVID studies so long as the involved parties *collaborate prior to implementation* to define the governance approaches, technical requirements, and the data elements required to ensure high-quality linkage. The Project Team developed eight key considerations for governance and technology implementations derived from the findings presented in three sections of this report: Pediatric COVID Studies – PPRL Feasibility (Section 5), Governance Assessment & Findings (Section 6), and Technology Assessment (Section 7). Based on these key considerations, the Project Team identified potential approaches for PPRL implementation across the CARING for Children with COVID studies. Most of these key considerations are generalizable to other record linkage implementation efforts. These considerations and approaches are primarily targeted to NIH and HHS agency staff, who are considering implementation of PPRL to address research-based use cases. They are also applicable to stakeholder communities that might participate in or implement PPRL, including investigators conducting pediatric research and their institutions, and data repositories and data centers. Other audiences for these considerations may include PPRL software vendors and IRBs, privacy boards, or equivalent bodies.

8.1 Key Considerations Based on Governance and Technology Assessment

8.1.1 Key consideration 1: Authorization for linking and sharing linked data should be based on informed consent or approval from the data originator's institution and/or their IRB or an equivalent Privacy Board

Authorization for record linkage and sharing linked data is a foundational element of a record linkage governance model. The 13 record linkage implementations revealed a wide range of authorization mechanisms that are sometimes employed in combination, including:

- Informed consent from participants (and assent in the case of children, where applicable)
- Waiver of consent
- Data originator/submitter authorization
- Approval/determination from an IRB or an equivalent Privacy Board
- Federal authority

8.1.1.1 Informed Consent from Participants

Federally funded human subjects research in general must abide by the informed consent requirements of the Common Rule[39]. However, record or data linkage activities involving de-identified data that do not qualify as "human subjects research" are not subject to the requirements[40] of the Common Rule. A majority of the record linkage implementations analyzed in this project share data that are considered de-identified. Nevertheless, it is ideal to obtain explicit consent for record linkage from study participants to foster transparency of data use and to honor participant trust[25,41,42,43]. Where feasible, such consent should address the scope of linkage—that is, which datasets will be linked—and how the linked data will be shared without overly restricting the scope in a way that could pose challenges for answering future unanticipated valuable scientific questions.

In the record linkage implementations analyzed in this project for which data were collected under the auspices of consent, consent language often does not explicitly address record linkage. Further, while data sharing often is addressed in consent, there is usually no separate language for sharing of *linked* data. In examples where the consent does address record linkage, the language is sometimes very specific to a particular study or linkage. For example, the DS-DETERMINED study consent describes linking to associated EHR data and DS-Connect surveys, and in the NCHS/NDI implementation, the NCHS survey data are deemed eligible to link with NDI based on whether a survey participant gives consent for data linkage in the survey. Consent language for some implementations, such as the recommended language from NDA, anchors the scope of linkage to the use of a specific PPRL tool (i.e., the NDA GUID tool) and covers sharing of linked data across all studies hosted within one data repository (NDA). While *All of Us* participants consent for linking to data from "other sources," the linked data are shared specifically through the *All of Us* Research Workbench, which includes two tiers that both function as enclaves and do not allow data exchange with external data systems.

The CARING for Children with COVID study datasets span multiple repositories, and as additional pediatric COVID studies generate and share data, the desired scope of linkage could grow beyond the datasets and repositories known today. The two CARING for Children with COVID studies that do address record linkage in their consents (MUSIC and one of the PreVAIL kIds studies) do so in a broad manner anchoring the scope of linkage to "multiple projects and databases" or "other research studies" (Appendix Table 1).

Pediatric COVID research highlights the value of this broad manner of consent when it is difficult to anticipate the scope of studies and data repositories to be incorporated into a record linkage implementation. Additionally, rather than naming a specific data repository for future sharing, consent language could describe baseline expectations for sharing data in repositories designated or controlled by NIH from which those data might be shared for future use, as has been done in several of the consent examples shared in this report.

There are also distinct considerations for linking consented data with data collected without consent, such as data from health care systems or public health surveillance and other administrative sources. The Project Team documented an approach to authorizing this type of linkage by specifically obtaining consent for linkage to unconsented/administrative data sources. The *All of Us* consent process explicitly describes planned linkage with "other sources" and lists specific administrative data sources as examples (e.g., pharmacy records, health insurance records, or cancer registries) and an additional form[44] is required to obtain and link with EHR records (Appendix Table 4). Another example not fully

assessed in this report is the Health and Retirement Survey, for which participants consent specifically for linkage with CMS records (Appendix Table 5).

For pediatric studies that require consent, in addition to obtaining consent from a legal guardian, the minor should be given age-appropriate information and included in the permission/assent process to the greatest extent possible[45]. Reconsent is required when the minor reaches the age of majority if the protocol is still active and the study team continues to hold the personal information (e.g., PII) of the study participants. This multi-level consent adds an additional layer of consideration to obtaining consent for immediate linkages, and more so when the scope includes potential linkages in the future. However, a record linkage implementation with pediatric data would not require reconsent to continue linking to new data that are submitted to a repository if all data in the repository(ies) are de-identified and the longitudinal linkages are derived from PPRL-based hashed codes rather than PII itself. While the Project Team did not analyze it as part of this project due to limited information available publicly, the National Survey of Child and Adolescent Well-Being (NSCAW) administered by the Administration for Children and Families (ACF) provides language that addresses the various consent/assent scenarios for linking and sharing linked data, including reconsenting as an adult[46]. Consents for both *All of Us* and NSCAW also address the option for participants to withdraw their consent/assent and prevent future data sharing, with the caveat that data that have already been linked and shared with users will not be withdrawn (Appendix Table 5).

Based on the analysis of existing implementations, the Project Team developed example consent (for the legal guardian, the language refers to "your child") and assent language (for the child, the language refers to "you") to address broadly scoped linkage and sharing of linked data that could be used for studies like CARING for Children with COVID. Note that the scope of this example language is limited to other *studies* that the child may participate in, meaning this language may not be appropriate for linkage with data that are collected for other *purposes* (e.g., unconsented administrative data sources), which may warrant additional data source-specific language. Additionally, example language should be considered in the context of other key elements and requirements of consent[47,48].

> *If [you/your child] join this study, we will gather data about [you/your child]. What we learn in this study will be put in a secure NIH-designated storage location, called a data repository, where these data would be shared for future research. Information about [you/your child] will be "de-identified," which means it will not include anything that identifies [you/your child]. [NIH] will approve researchers from all over the world to access information from the repository. Researchers will agree not to attempt to identify [you/your child]. It is possible that if [you/your child] participate[s] in more than one study, researchers may be able to combine de-identified data from multiple studies to ease the burden on researchers and participants alike. The purpose of sharing this information is to make more research possible that may improve children's and everyone's health. This sharing of information will be done without obtaining additional permission from [you/your child].*
>
> *If [you/your child] no longer want [your/your child's] de-identified data to be shared with researchers and combined with other data about [you/your child], you can request [your/your child's] data to be withdrawn from the data repository and destroyed. Please note that any data that has already been shared with researchers cannot be withdrawn.*

If [you/your child] turns 18 years old while taking part in this study, [you/your child] will be asked to review and sign an informed consent form as an adult if [you/your child] wants to continue to be in the study.

Across all the record linkage implementations, the Project Team observed that the governance frameworks for linking and sharing linked data are often more complex when consent for data collection is lacking such that additional controls are needed. Examples include restricting access to a specific enclave (N3C) or a physically restricted area (Census and administrative datasets accessed at the FSRDC), or creating the linked dataset only for a specific research project and then destroying the linkages and dataset after use (PEDSnet).

8.1.1.2 Data Originator/Submitter and/or IRB or an Equivalent Privacy Board Determination

For data that are collected under the auspices of consent for research, but for which the consent may not necessarily include explicit language addressing record linkage, other mechanisms have been employed to authorize the record linkage. These mechanisms include authorization from the data originator/submitter and/or their institution, which may include approval or determination from an IRB or an equivalent Privacy Board. In many cases, the authorization to share *linked data* is addressed by the general requirements for data sharing for a given implementation; therefore, this discussion focuses on the linkage-specific authorizations.

BRICS and NDA require record linkage (via the use of the GUID) for all data submissions. This requirement is clearly described in data submission agreements and associated policies, although exceptions are reviewed case-by-case[49]. The NDA Data Submission Agreement requires an Authorized Organizational Representative to sign on behalf of the data originator/submitter's research institution, confirming that the data submission is consistent with informed consent. By agreeing to the terms of the submission agreements, the data submitter and their institution authorize the GUID-based record linkage. Several NIH programs that use BRICS also expect that an IRB and/or an equivalent Privacy Board has verified that the data submission is consistent with informed consent. This expectation means that the submitter's IRB and/or an equivalent Privacy Board weighs in on the decision to link data as part of the submission. An IRB and/or an equivalent Privacy Board could, in theory, then require updates to the informed consent or administer a waiver of consent for the linkage; however, such behind-the-scenes procedures are typically not tracked by these NIH data repositories.

While dbGaP does not implement PPRL, it does implement some cross-dataset linkage based on submitted subject IDs that are detected to likely represent the same participant in an existing study. In such cases, it is up to the submitter to decide whether the linkage should be incorporated into the dbGaP data repository. While under the NIH GDS Policy[50], the Institutional Certification[34] used for dbGaP expects that an IRB and/or an equivalent Privacy Board has ensured that the data submission is consistent with the informed consent, cross-study record linkage is not an element of this agreement. In fact, the topic of data linkage was raised in a recent *Request for Information (RFI) on Proposed Updates and Long-Term Considerations for the NIH GDS Policy[51],* specifically, whether data linkage should be addressed when obtaining consent for sharing and future use of data under the GDS Policy, as well as in IRB consideration of risks associated with submission of data to NIH genomic data repositories.

For datasets that are collected under a waiver of consent and use PPRL, the waiver of consent is often combined with approval from the data originator/submitter (e.g., N3C data partner, PEDSnet site, CODI data partner) and/or some other governing body (e.g., PEDSnet Data and Steering Committees, CODI's

CHORDS Research Council) to authorize the linkage on behalf of the participants. In the CODI implementation, for example, the linkage also requires approval from the data originator's IRB or an equivalent Privacy Board or a designation as non-human subject research.

While institutional oversight is a critical component of making decisions regarding sharing data[52] and data linkage (as described above), the Secretary's Advisory Committee on Human Research Protections (SACHRP) response[40] to the above-mentioned RFI on the NIH GDS Policy suggests that IRB or an equivalent Privacy Board approval may not be an appropriate path when making determinations about de-identified (i.e., non-human subjects) data submissions that fall outside the scope of an IRB's jurisdiction. However, for both consented and unconsented scenarios, this report uncovered several potential reasons why it might be appropriate for an IRB or an equivalent Privacy Board to engage in the decision to link data:

- While a given data submission (and downstream secondary use of the data) may not qualify as "human subjects research," data linkage could result in the data originator obtaining access to additional information about participants for whom identities are known, if the data originators still hold PII for their study. Therefore, when the IRB protocol for a given study is still active, it is appropriate for the IRB or an equivalent Privacy Board representing the data originator/ submitter to weigh in on the decision to link because the breadth and depth of the data collected under the protocol could be expanded through linkage to additional data accessible in the repository. The NDA Data Use Certification (DUC) describes this situation for researchers accessing data from NDA who may have also submitted data to the NDA (Appendix Table 2).
- IRB approval is often appropriate for non-PPRL record linkage approaches where the direct PII are sent to other locations to identify matches (e.g., FSDRC/Census). In addition to explicit consent regarding record linkage that occurs within the *All of Us* system boundary, the consent informs participants that if PII is shared with an outside entity to link records from external sources, *All of Us* will file an amendment with the *All of Us* IRB.
- For PPRL implementations where the PPRL software is installed locally on the data originator's server, PII does not leave the boundary of the data originator's organization. Studies that are not able to use or install PPRL software locally at the data source may need local IRB approval to send the PII to another location such as a DCC to generate the information needed for PPRL.
- Data that are subject to the NIH GDS Policy require an IRB and/or an equivalent Privacy Board to ensure that the data sharing is consistent with the informed consent and to determine whether the use of the data are limited to certain purposes (i.e., data use limitations). Therefore, it may also be appropriate for the IRB to weigh in on the decision to link de-identified genomic data with other datasets.
- Finally, even for implementations that follow the HIPAA Safe Harbor method[18] of de-identification, linkage of individual datasets comprising multiple data types may alter the status, whereby the "identity of the human subjects cannot readily be ascertained" as defined in the Common Rule, is no longer applicable[53,54,55]. This report did not uncover any scenarios where a record linkage implementation evidently crossed this threshold based on the richness and/or diversity of data types that were linked, but the implementations already have multiple re-identifiability risk mitigation processes in place (see Section 8.1.6). Providing an IRB or an equivalent Privacy Board the opportunity to weigh in on the decision to link for a given implementation affords the opportunity for them to assess potential re-identification risk. In scenarios where the planned scope of the linkage is known, this review may provide the IRB or

equivalent Privacy Board an opportunity to determine the appropriateness of linkages with specific datasets (e.g., similar to when an N3C data partner can opt out of linking with specific external datasets such as mortality data); however, potential re-identification risks can be difficult to predict and determine when the scope of data linkage is constantly expanding through the addition of new datasets.

8.1.1.3 Federal Authority

Federal authorizations based on U.S. Code laws and regulations may permit the unconsented collection and linkage of individual-level datasets containing PII for statistical use, public health surveillance, or public health emergency response. Of the 13 record linkage implementations assessed, two non-PPRL implementations—Census/FSRDC and NCHS/NDI—use PII matching for data linkage under federal authority for statistical use. However, any external data sources that are ingested to be linked to these federally authorized datasets are expected to be authorized for linking and sharing based on informed consent and/or IRB approval. The federal authorization mechanism and PII-based record linkage approach is not applicable to the CARING for Children with COVID studies.

8.1.2 Key consideration 2: Linkage of certain types of data or data from certain populations may be subject to additional policies or governance

The analysis of the 13 record linkage implementations did not uncover many specific considerations for addressing unique linkage requirements for certain data types or modalities (e.g., EHR, survey, imaging, genomic), as for the most part, the rules that govern a given implementation or repository apply to all data modalities represented in that implementation. However, the NIH GDS Policy[50] and the recent RFI[51] contain two conditions for sharing NIH-funded genomic data that relate to data linkage:

- "For studies initiated after the effective date of the GDS Policy, NIH expects investigators to obtain participants' consent for their genomic and phenotypic data to be used for future research purposes and to be shared broadly."
- "(D)ata should be de-identified to meet the definition for de-identified data in the HHS Regulations for Protection of Human Subjects[12] and be stripped of the 18 identifiers listed in the HIPAA Privacy Rule[5]."

While the current GDS policy does not explicitly address record linkage, sharing genomic data that are linked with a HIPAA limited dataset would result in a violation of the GDS definition of "de-identified." This topic warrants further consideration pending the outcomes of the RFI[51].

The Project Team sought to understand how various implementations address record linkage for data from participants from U.S. tribal and international settings. The Project Team's findings indicate that for the 13 record linkage implementations assessed, either: 1) the scope of the implementation was limited to data from the United States and non-tribal populations, or 2) the implementation did not have unique requirements for these populations (i.e., they would be subject to the same data submission and data access/use agreements and policies as all other datasets represented in the implementation). Some tribal or international data requirements may not be consistent with the linkage and data sharing policies of a given implementation[56]. Such cases may require additional agreements and governance approaches or may preclude data from inclusion in any type of data linkage or data sharing activities.

8.1.3 Key consideration 3: A broad set of PII elements are required to generate high quality linkage regardless of the tool used, and these PII elements should be collected early and in a standardized manner

To successfully implement PPRL, certain PII elements must be collected by the data originator/submitter based on both software requirements and linkage quality considerations. IRB approval is generally required to collect the PII needed for generating record linkage in the research setting. This requirement for IRB review may constrain the PII elements available for linking if the study is already underway and the protocol has already been approved (i.e., submitting protocol modifications to an IRB to collect additional PII elements could place study timelines at risk).

While some of the PPRL tools assessed in this report are extremely flexible in terms of the PII elements they can use for record linkage (i.e., they do not require specific PII elements to use their products for PPRL), the Project Team observed that most tools typically rely on first name, last name, date of birth, and sex or gender. Most tools also use some sort of "location" information, either in the form of city/municipality of birth or household address or ZIP Code. In the seven PPRL implementations the Project Team reviewed for governance approaches, first name, last name, date of birth, and gender or sex were common to all seven. Four out of seven PPRL implementations the Project Team reviewed also relied on cell or phone numbers, including one of the pediatric-focused studies (CODI), although the initial NICHD-led pilot assessment identified phone number as a potential challenge for linking data from children. The CARING for Children with COVID studies all collected first name, last name, date of birth, and sex that are used by most tools.

8.1.3.1 PII Element Standardization

For any PPRL implementation, standardization of all PII elements, including clear definitions, should improve linkage quality[57,58]. For example, gender or sex are collected in all 11 of the CARING for Children with COVID studies and gender *or* sex is used in all seven PPRL implementations the Project Team assessed. However, the definitions of gender versus sex were not assessed in this Report and there is evidence that these elements are used interchangeably in studies such as RADx ("sex" is a common data element for RADx-rad and "gender" is used in its NHash tool). In general, sex and gender are often conflated, and a majority of current studies/systems use "Birth Sex," "Administrative Gender," or just "Sex." The HL7 Gender Harmony Project[59] recommends expanding the elements to include: gender identity, recorded sex or gender ("used to more accurately identify sex values or gender values that are specified in a particular source or documents such as identity cards or insurance cards"), sex for clinical use (defined as "a summary sex classification element based on one or more clinical observations such as an organ survey, hormone levels, and chromosomal analysis"), name to use, and pronouns. Given that the CARING for Children with COVID studies are already collecting sex or gender, using both sex *and* gender as distinct PII elements might be preferable when implementing PPRL for these studies.

Of the 11 CARING for Children with COVID studies included in this project, only two collect city/municipality of birth (required for BRICS and NDA GUIDs). An alternative to city/municipality of birth is to use either ZIP Code or address. Eight CARING for Children with COVID studies collect and four of the seven PPRL implementations use some iteration of ZIP Code and one study used household street address. The Project Team assumes, but could not confirm, that these refer to the participants' current home ZIP Code and address.

For the use case "facilitate longitudinal data collection and analysis," using current home location information could be challenging given that people move an average twice before turning 18 and 11.7 times across their lifetime[60]. As records of home location information are collected at various time points, this information could be unreliable for longitudinal data linkage. If the ZIP Code collected refers to the location of study enrollment rather than home address, it would not enable linking data from multiple studies and sources. ZIP Codes that refer to the location of birth may be more stable, but this element is not significantly different from city/municipality of birth (used in NDA and BRICS), which may in fact be easier for a participant or their parent/guardian to remember and easily provide when enrolling in a study.

Pediatric data may not contain some of the PII elements typically available for adult linkage, such as phone number and email address. Phone number was noted as a challenge with the CARING for Children with COVID studies. For the youngest research participants, hospital record naming conventions such as "Baby Girl Jones" are yet another limitation to PPRL. Researchers have proposed collecting additional PII elements to facilitate pediatric record linkages, such as mother's maiden name[61].

8.1.3.2 PII Element Preprocessing

Preprocessing of PII elements prior to using PPRL software is a common practice to account for data entry errors or misspellings in study datasets. Some PII elements useful for PPRL are truncated or derived versions of PII elements already collected, such as first three characters of first name, Soundex of first and/or last name, and a less specific ZIP Code (e.g., ZIP2 or ZIP3). Of the seven PPRL implementations the Project Team reviewed, only PEDSnet and the three N3C implementations reported using Soundex to account for possible name misspellings. Although not documented in this assessment, PEDSnet anecdotally expressed that Soundex introduces and raises the noise levels leading to increased false positives. Some of these results may be due to the fact that PEDSnet used populations that included families (i.e., multiple people with similar last names) for PPRL. Similarly, N3C indicated that email address and SSN led to high match failure rates.

8.1.3.3 PII Element Combinations for Tokenization

The Project Team compared the PII elements that are collected and those that can be derived in the CARING for Children with COVID studies to the PII elements required for existing NDA, BRICS, N3C and PEDSnet PPRL implementations assessed in the Governance Assessment (Section 6). The Project Team found that none of these PPRL implementations could be leveraged for CARING for Children with COVID as many of these studies lack location information like ZIP Code and municipality of birth/country. Furthermore, tools that currently require use of email, phone number, and/or SSN, would not work for CARING for Children with COVID as these elements are generally not collected by the studies. In general, analysis of the seven PPRL implementations showed that combinations of five or more PII elements are used in all of them. While the existing PII elements collected in the CARING for Children with COVID studies could enable linkage in PPRL tools that allow for flexible PII element inputs, the currently available PII may not be robust enough to support high-quality linkage. The CARING for Children with COVID studies will likely have to revise their IRB protocols to obtain additional PII elements, possibly including city/municipality of birth or some sort of location at birth information, or possibly other elements (mother's name) to yield high-quality record linkage, regardless of the PPRL tool adopted.

Prior to any PPRL implementation, the selected PII elements, data standardization and preprocessing approaches, and matching algorithms should undergo rigorous statistical assessments using relevant

gold standard datasets to identify the configuration that delivers an acceptable threshold for false positive and false negative matches. In the case of pediatric studies, an adult-focused dataset would not serve as a sufficient gold standard.

8.1.4 Key consideration 4: The three-party linkage approach offers researchers the flexibility to link and use datasets hosted in different data systems

For each record linkage implementation, the Governance Assessment documented which parties have access to the PII needed to generate hashed tokens in PPRL, which parties use the hashed codes/tokens (that typically do not qualify as "PII" but are often treated as sensitive) to identify matches (entity resolution), and which parties use the resulting linkage information (either in the form of GUIDs or linkage maps) to create a linked and de-duplicated dataset (data linking). In a two-party model, the entity resolution and the data linking are performed by the same organization whereas in a three-party model, these two activities are performed by separate organizations (the first party is always the PII holder). PPRL implementations that use a three-party model utilize either an honest broker or a separate GUID server to perform entity resolution (i.e., match hashed codes/tokens) and generate GUIDs or linkage maps for repositories and researchers. The GUID server or honest broker does not share the matched hash codes/tokens with the repositories or the researchers using the data.

The Project Team observed that the record linkage implementations using a three-party linkage model (e.g., dbGaP, NDA, BRICS, N3C) typically do so by providing researchers access to individual datasets alongside either GUIDs or linkage maps. This approach means that linking of data (i.e., merging and deduplicating) is not performed centrally, but the information needed to "link" is made available to researchers who are then responsible for linking and de-duplicating the data as part of their analysis approach. Each individual dataset is treated separately, which enables the user to:

- Make decisions about potentially conflicting data from multiple sources (e.g., different diagnoses from different data originators)
- Track new data that are added for a given participant over time (and determine which studies have long-term follow-up information)
- Attribute the data to the original studies
- Follow requirements of any specific data use limitations that may be associated with a given dataset (e.g., a dbGaP dataset that has a disease specific data use limitation for the study of COVID is more constrained than a dataset that is approved for General Research Use, even if the same participant is represented in both)

In two-party linkage implementations the entity resolver is also the data linker. For several of the two-party linkage implementations the Project Team reviewed, the entity resolver and data linker creates a merged and deduplicated dataset without providing researchers any provenance information for the original records nor any decisions made regarding deduplication (e.g., PEDSnet, CODI, *All of Us,* Census/FSDRC). In these cases, a common data access governance approach is applied to the merged data product. For example, in CODI, all data contributors agree that the merged dataset is the property of the DCC—the dataset provided is stripped of information linking specific participants to the data sources/original sites and it can be used by approved data requestors (both within and outside of CODI).

This two-party approach could be difficult to accommodate in a federated ecosystem designed to share many study datasets in a manner that is consistent with consent-based data use limitations, where such limitations should travel with the data such that two separate datasets have different approved uses

even if the same participants are represented in both[52]. Consent-based data use limitations, such as those described in the NIH GDS Policy[24] can require very specific research use for a given dataset and should be conveyed to end users to reduce risk for data management incidents.

8.1.5 Key consideration 5: The linked database model encompasses a broad scope of datasets and should be paired with additional controls to protect participant privacy

The majority of the PPRL implementations the Project Team reviewed utilize a linked database model, meaning the scope of linkages created and made available to researchers is defined by the datasets associated with a given database. The linked database model can also span one or multiple data repositories (e.g., multiple BRICS instances that use the same GUID server, N3C linking with Class 0 datasets like MIDRC) or encompass only a subset of datasets within a given repository. For example, N3C EHR data partners choose to participate in PPRL and can opt out of linkage with specific external datasets; however, the hashed codes/tokens generated are designed to link all participating N3C datasets.

Study-specific linkages are typically created as needed for a specific research study or scientific question. In PEDSnet and CODI, for example, each data contributor chooses whether to participate in a specific study and associated linkage. Study-specific linkage provides data originators the opportunity to choose on a case-by-case basis whether to contribute their data to a given research study. However, such study-specific linkage presents scaling challenges given the time to review/approve each request and to re-run linking processes. Further, this approach introduces reproducibility challenges, as linkage information is only recreated in response to each study request and is not maintained over time.

The linked database model approach of maintaining a persistent database of GUIDs or linkage maps fosters reproducibility and continuous tracking of longitudinal data without having to recreate the linkage information for every use. Further, the linkage information in a linked database model can be shared using a variety of access controls. For example, while most dbGaP data are controlled-access, dbGaP shares cross-study dbGaP subject IDs in an open manner, whereas BRICS and NDA provide GUIDs as part of an approved data access request. N3C requires an additional approval (Letter of Determination from the requester's IRB) to access PPRL-generated linkage maps across participating EHR datasets. While the scope of the N3C linkage encompasses external (Class 2/Class 0) datasets, access to those datasets and associated linkage information must be specifically requested and combined analysis with data from other repositories (e.g., MIDRC/Class 0) must be performed in an ephemeral workbench.

PPRL implementations could take similar modular approaches by generating linkage information that spans a broad scope of datasets while requiring that the researchers who would like to obtain the GUIDs or linkage maps specifically apply for and/or request this information. Controlling access to GUIDs or linkage maps could be a component of a data access request for each dataset; however, rather than generating a unique set of linkage information on-demand for every request, the linkage information that is provided would be the same for all approved requesters. Regardless of the method chosen, the scope of the linkage should be clear from the beginning of a project so it can be communicated to study participants (via consent) and/or to data originators/submitters, and so a plan for making the linkage information available to users can be strategized with the parties sharing the data (i.e., data repositories).

8.1.6 Key consideration 6: Re-identification risk management controls can be implemented both prior to and after linkage

While all record linkage implementations the Project Team reviewed shared data that are considered de-identified, six of the 12 implementations that are currently sharing linked data (DS-DETERMINED is currently not sharing the linked data) also used some form of re-identification risk assessment (where the datasets that are to be linked are assessed for potential re-identification when combined) or other risk management controls at various stages in the linking and sharing process. Some of these risk re-identification assessments/controls take place prior to data linkage or data submission to a repository, which may result in excluding the dataset or modifying the data to reduce the potential for re-identifiability (e.g., N3C Tools and Resources Committee classification of linkage with external datasets).

Other assessments are performed after the data have been linked but prior to sharing (e.g., *All of Us*, FSDRC/Census) and may result in modifications to the linked dataset prior to research use or data export. In the case of N3C, for example, an internal Tools and Resources Review Committee reviews the linkage of the EHR data from within N3C to external datasets (Class 0 and Class 2) for any potential re-identification risks, and data may be modified for certain datasets (e.g., using zip3 instead of zip5 for tribal reservations). *All of U*s takes multiple steps to fully strip all data of PII prior to sharing, and additionally performs a number of transformations on data that are shared in their registered tier versus the controlled tier (e.g., share more detailed demographic information and genomic data in the controlled tier). In contrast to other data repositories, however, *All of Us*'s registered tier functions more like an enclave and currently the requirements for accessing data from *All of Us* are not different between the registered and controlled tier. The FSDRCs only allows users to access read-only de-identified versions of approved files and further require the application of "Disclosure Avoidance[kk]" techniques prior to removing analytical results and statistical products from the FSDRC workspaces and approval from the Disclosure Review Board prior to publishing or disseminating findings.

While the NICHD-funded Data Sharing for Demographic Research (DSDR) [62] repository was not included in this assessment, DSDR reviews all data for disclosure risk from both direct identification and inferential re-identification. DSDR also checks data for sensitivity and special populations such as children. When possible, DSDR remediates the data sufficiently (e.g., by masking direct identifiers, suppressing certain variables, collapsing categories, and perturbing responses) to allow public access via download from the DSDR website. For data that still have inferential disclosure risk (e.g., geographic identifiers and detailed personal histories) or sensitive information (e.g., drug abuse and sexual activity), DSDR provides controlled access via its restricted tiers. DSDR considers data linkage projects as restricted. For access to restricted data, researchers must submit a research plan, IRB or Ethics Panel review and pledges to protect the confidentiality of the data. Restricted access requires the execution of a data use agreement (DUA) with the researcher's organization to cover any mishandling of the data. While this approach is extremely robust, it may not be scalable or feasible to implement a full disclosure review for all linkage scenarios or requests to access or download linked data across a federated ecosystem.

[kk] At the U.S. Census Bureau, disclosure avoidance is defined as a process used to protect the confidentiality of respondents' personal information.

In addition to these specific re-identification risk mitigation procedures, the Project Team identified several broader approaches that have been implemented across the 13 record linkage implementations that serve to manage re-identification risk. These include:

- Using a controlled or enclave data access model, and requiring approval from a data access committee, steering committee, or some other governing body prior to accessing the linked data
- Setting a clear definition of de-identified for all data shared from a repository or for all data shared in each access tier (e.g., the Genomic Data Sharing Policy currently requires adherence to the Common Rule and HIPAA Safe Harbor definition of de-identified, PEDSnet has specific masking rules, *All of Us* uses different thresholds for each of its tiers, N3C requires additional rules for HIPAA-limited and PPRL-linked data, and other implementations require removal of the 18 HIPAA identifiers)
- Prohibiting re-identification through Data Use Agreements or terms of access
- Where feasible, performing a broader risk assessment to determine which (if any) data elements require more data access controls than others

8.1.7 Key consideration 7: All PPRL tools assessed for this Project meet a basic set of capability requirements, but vary on certain desirable features

A PPRL implementation for the CARING for Children with COVID studies requires certain essential capabilities in the PPRL tool selected: (1) the PPRL tools must accommodate a broad set of PII (see Section 8.1.3) and be scalable, (2) the vendors should have no rights to the data (including PII elements, associated metadata), and (3) the tool must have appropriate protections for the source data/PII elements. All seven vendors/organizations assessed met these essential capabilities.

The PPRL tool selected must be able to accommodate hashed codes/tokens from many participants and sites because there are already at least 150 sites contributing data to the CARING for Children with COVID studies. As new pediatric COVID studies are launched[63], it would be valuable to link records with existing CARING for Children with COVID studies that have been enrolling participants since the start of the pandemic, to increase data richness and track data collected over time.

The PPRL Technology Assessment conducted in this project examined the largest use case with real world data as a proxy for the scalability of each product. All tools supported scaling in upwards of a million records, which is more than sufficient for the number of records generated in CARING for Children with COVID studies. For many of these tools, the limiting factor on how many records can be processed is not the software itself but the computational power available, such as memory, central processing unit (CPU) and random access memory (RAM), so scalability will be dependent on the set up of the application server/environment.

Most tools use proprietary algorithms for their PPRL products, which raises a concern about whether the vendors have any right to the PII elements, the hashes/tokens generated from the PII elements, or other data that may be sent to or used by the software (e.g., metadata or derivative software data). Vendors/organizations for all assessed tools indicated in their survey that they do not retain rights to these data or metadata. Additionally, all the vendors/organizations indicated the source data never leave the data originator's computer/server; therefore, no unhashed PII elements are ever accessible to anyone other than the data originator. Several of the vendors surveyed do offer services that allow data originators to link their data to external commercial datasets in a "data-as-a-service marketplace"

model. This assessment did not review the governance models for these arrangements and the topic merits further review.

All seven tools assessed meet the required criteria for the CARING for Children with COVID studies. The Project Team identified additional features that are desirable, but not required, that differentiate the tools assessed. These features include pre-processing/data cleaning, tuneability of matching algorithm, ease of use, and federal security certification.

Prior to generating the hashes, the data cleaning and/or pre-processing of PII elements step standardizes and recodes the PII to reduce data entry errors and generate more consistent hashes. This preprocessing can improve the ability to resolve potential linkage matches and substitution of nicknames (e.g., “Jim” to “James"). While manipulation of PII elements must be consistently applied across all CARING for Children with COVID studies for the best quality linkage[38], such pre-processing and standardization could be performed prior to using the PPRL software; hence, it is not a required criterion for a PPRL tool.

Soundex is a type of phonetic encoding that occurs during PII pre-processing and was considered to be a desirable characteristic to accommodate name misspellings in children. Only some tools have this feature, and it may introduce risk of high false positive matching rates[64]. For example, some PPRL implementations, such as PEDSnet, indicated that Soundex yields an inflated number of false positives when performing linkage that includes families and its use should therefore be considered carefully.

Tunable matching criteria/algorithms (e.g., comparison/classification parameters that can be configured) for entity resolution is another capability that is a “nice to have,” as PII elements may contain fields with potential errors and such errors can be accommodated by accepting certain imperfect matches. Examples of adjusting hash matching criteria include choosing a matching design with either a higher false positive rate or a higher false negative rate and changing the number of match parameters. The ability to adjust the linkage schema and associated weights of each combination of PII elements provides the flexibility needed to improve the ability to detect true matches based on the availability of certain PII elements when using pediatric data. There may also be certain use cases for which a different ratio of false negatives to false positive is desirable. For example, a conservative approach (reducing the number of false positives) better supports the data generation and analysis goals of the CARING for Children with COVID use cases, while a higher rate of false positives could be tolerated in use cases that involve contacting sites to potentially recruit participants to a new study (this approach is currently being explored by N3C[65]). Some tools allow tuning/configuration of their linkage algorithm for a specific PPRL implementation. Tuning the algorithm and adjusting the linkage schema does impact all linkages in a given implementation, so the final matching algorithm configuration should be based on an assessment utilizing a gold standard dataset that closely matches the data sources for the given implementation.

Similarly, making linkage performance reports available to the data originator (e.g., number of matches, number of possible matches, number of duplicates) that describe the performance of a software also helps adjust for and identify errors in the data, such as name misspellings and other reasons potential linkages should be identified and reviewed. For example, a PPRL tool may provide the data originator the option to create matches with the option of indicating “With Close Match Checking” (provides some fault tolerance for PII entry errors) or “No Close Match Checking" (only matches the PII entered) but do not otherwise have the flexibility to adjust the matching threshold.

Six of the seven tools the Project Team surveyed generate linkage performance reports. While useful for informing real-time linkage decisions, these reports should not be used as proxies for rigorous data linkage quality assessments for a given hashing/matching protocol.

FISMA/FedRAMP certifications are rigorous federal authorization processes that are tailored to ensure an Information Technology system has an adequate plan for security, clear security responsibilities, periodic review, and authorization to operate in a Federal IT environment. Although a FISMA/FedRAMP certification is not a requirement for a PPRL tool for use with the CARING for Children with COVID studies, these certifications demonstrate compliance with federally approved system security controls for managing sensitive data. Some tools the Project Team assessed either have or are in the process of achieving FISMA and/or FedRAMP status. All PPRL tools the Project Team assessed have basic security features (e.g., encrypted data transfer, database encryption) and security certifications (such as FISMA certification, SOC 2) in place and are considered truly "privacy preserving" in the sense that PII does not leave the data originator's environment.

If PPRL technology is to be implemented at study sites, the ease of use of a product is a "nice-to have" characteristic for the CARING for Children with COVID study investigators who are generally constrained for resources and time. Therefore, product usability features such as the presence of a GUI may be a priority. Having a GUI to enter/upload the PII elements for hashing, instead of requiring the study sites/researchers to programmatically ingest the data, simplifies the PPRL process for users. Most of the tools have GUIs, whereas implementing those PPRL products that do not have GUIs would require additional development efforts, which would result in increased budget and prolonged timelines. Researchers with more technical experience/knowledge of PPRL have indicated that they would appreciate the ability to use web services and scripts to automate token generation. All the tools the Project Team assessed include this feature of automated token generation.

8.1.8 Key consideration 8: Certain PPRL tool features better serve robust implementation approaches and sustainability

Although all PPRL tools assessed for this project meet a basic set of capability requirements (see Section 8.1.7), tool features such as the ability to persist hashes over time, software ownership, the cost of maintenance, and potential interoperability with other PPRL tools impact a tool's utility for long-term implementation of record linkage for NIH pediatric studies.

Some of the CARING for Children with COVID studies are longitudinal, and as new studies are rolled out in the future, it would be ideal to utilize a PPRL tool that can persist hashes and the associated metadata such that new hashes can be matched with existing hashes without needing to regenerate them from PII elements. Regenerating hashes may not be feasible for past data submissions (e.g., the investigator may no longer be engaged or have access to the PII) and could result in additional run time and effort for entity resolution, increased budget, and other resource considerations when implementing PPRL for longitudinal data collection. Six of the seven tools the Project Team assessed are able to persist hashes.

Once a PPRL tool is selected for a record linkage implementation, the program/initiative is generally "locked-in"[ll] to using that product for the duration of the record linkage implementation. A few commercial PPRL vendors self-reported that they are developing interoperability solutions, but their methodologies have not been published nor implemented at the time of this assessment. Although

[ll] Locked-in, as used here, refers to the operational algorithms and configurations that are distinct and are not interoperable.

BRICS is not interoperable with other vendors, BRICS does have a robust network of NIH institutes that use its Centralized GUID Server approach for PPRL linkages. As long as the proper approvals are in place (authorizations, research plan approvals, data use agreements, etc.), BRICS is able to link data from 250+ studies across NIH institutes.

The overall cost to NIH to maintain a PPRL implementation over multiple years factors into the sustainability of the PPRL solution. The tools the Project Team assessed use different cost models. These cost models include an annual licensing fee in addition to pricing based on the number of sites generating tokens, a one-time configuration fee plus a licensing fee per site, a fee based on the number of sites and the scale of the linkage, a fee based solely on the number of records ingested, and only upfront costs relating to initial setup and any desired customizations to the product. The differences in these cost models emphasize the differences between commercial vendors (Crossix, Datavant, HealthVerity, Senzing, and IQVIA) and the government-owned PPRL product (BRICS) and the university-owned product (NHash):

- The commercial PPRL products have per site or per record costs in addition to some products with annual licensing fees.
- The government/university owned products only charge for initial configuration.

While assessing the overall implementation cost of these tools was not within the scope of this Project, these variations in cost models impact consideration for long-term sustainability. Over time, cost models with only initial set-up costs could be more cost effective than the annual, per site, and/or per record commercial cost models.

Additionally, commercial vendors are subject to fluctuations in the private market. During the analysis performed by NCI, the number of candidate software products shrank from eleven to eight as companies merged or went out of business and products were deprecated.

The NCI report assessed Anonlink, which is an open source PPRL tool used by CODI for pediatric linkage. This assessment does not include Anonlink as they did not respond to Project Team inquiries. Since Anonlink has been adopted by CDC's CODI, further evaluation may be warranted for the tool.

In order to generate a direct comparison of overall costs for each of the PPRL tools in this report, the CARING for Children with COVID studies would need to finalize technical details of the PPRL implementation model (requirements for customization, the number of study sites, estimated number of records generated in the CARING for Children with COVID studies, and specifications/desired architecture for a GUID server or honest broker).

8.2 Considerations for CARING for Children with COVID

Prior to moving forward with record linkage across the CARING for Children with COVID studies, the collaborators should agree on an overall approach and the planned scope for the record linkage. A three-party approach, where approved researchers link the data themselves, should be adopted to maintain separation between the entity resolver and the data repositories that share the data and associated linkage information (e.g., GUIDs and/or linkage maps). This approach will enable maintaining provenance of individual datasets (e.g., tracking which data are from PRISM versus MUSIC, attribution, which datasets are modified over time) and will allow data access and use requirements (e.g., consent-based data use limitations[52]) to "travel" with individual datasets. The three-party approach could use either an NIH GUID tool-based approach (where the GUID server is the entity resolver) or leverage a

commercial or open source tool and identify a separate party to play the role of the honest broker and create linkage maps.

A linked database model is likely the most sustainable and reasonable approach to foster reproducibility and could encompass many datasets across multiple repositories as long as the same PPRL tool and entity resolver are used by all repositories. The collaborators should define up front the general scope of datasets to be included in the implementation, so the linkage (and associated benefits and risks) can be communicated during the informed consent process to participants and/or data submitters. A relatively broad scope is required given that CARING for Children with COVID data spans multiple programs (including RADx) and data repositories (RADx Data Hub, BioData Catalyst, the Kids First Data Resource, and ImmPort), and there could be a desire to include in the PPRL implementation additional pediatric COVID studies funded by other programs. One way to establish a clear but broad scope of linkages is to define the scope of linkage to data associated with NIH-designated or NIH-controlled repositories and/or other NIH studies. An NIH-defined scope could be too limiting for certain research use cases but would address the current CARING for Children with COVID use cases.

The CARING for Children with COVID initiative plans to perform whole genome sequencing to understand inherited risks associated with SARS-CoV-2 infection in children; therefore, these studies are subject to the requirements of the NIH GDS Policy. Under the current GDS Policy, it may be possible to link to data from typically "unconsented" sources such as administrative datasets if explicit consent for linkage and sharing the linked data is obtained in the context of the research studies (thereby changing the status of the administrative data to "consented"). However, certain administrative datasets (e.g., Census) may prohibit re-distribution of their data through other repositories.

If the outcome of the GDS RFI determines that explicit consent is not required for linking consented genomic data to unconsented data sources, and re-consent is not feasible, thoughtful consideration and possibly further governance analysis should go into determining whether linkage with unconsented data sources is appropriate for the CARING for Children with COVID studies. If this type of linkage is agreed upon by the collaborators, it should be explicitly communicated to all other data contributors who participate in the linkage scope. Additionally, the collaborators could consider an approach where data contributors can "opt in" or "opt out" of linkage with a specific unconsented dataset (similar to what has been done with administrative datasets that are "external" to but linked with N3C EHR data).

The current GDS definition of "de-identified" prohibits linkage with HIPAA limited datasets; however, adhering to both the Common Rule definition of "de-identified" and HIPAA Safe Harbor, which excludes certain dates and location information, helps mitigate some re-identification risk that may be introduced when linking across multiple studies and data types. If the outcomes of the GDS RFI changes the definition of de-identified under the GDS Policy, additional de-identification standards (e.g., expert determination[18]) or re-identification risk assessments (e.g., those done by *All of Us*) could also be considered.

CARING for Children with COVID study datasets vary in terms of controlled and registered tier data access requirements. Linkage between datasets of any tier introduces potential re-identification risk, and this risk can be mitigated through an NIH approval process. For a CARING for Children with COVID record linkage implementation, the linkage information (e.g., GUIDs, linkage maps) should be maintained in a controlled access tier, which incorporates an NIH review process and institutional oversight[66]. With this approach, the original tier status of all unlinked datasets need not change, and researchers who obtain approval to access the controlled data and linkage information will be able to

deduplicate participant data in their analyses. This proposed implementation is similar to the approach N3C is planning for the EHR-EHR linkage, where level 2 (de-identified) data will not include the PPRL-generated linkage maps, but users can update their data use request and provide the required LOD from their IRB to access the level 3 (HIPAA limited dataset), which includes the linkage maps across all participating EHR datasets.

For the CARING for Children with COVID studies, this approach will require determining which system(s) will be responsible for maintaining and distributing the linkage information (created by the GUID server or honest broker) and how it will be operationalized. This approach should be feasible with minimal development work, given the current authentication/authorization framework of the data repositories involved. Its implementation will also require determining which data access committees should provide oversight over the approval to access the linkage maps and how that oversight will be incorporated into the dbGaP data access request process used by the Kids First Data Resource, BioData Catalyst, and the RADx Data Hub for managing controlled access data.

Researchers should be able to receive linkage maps that encompass all datasets they are authorized to access, in line with all of the three-party models reviewed in the assessment. However, for datasets that are available only in the registered tier and are not associated with a controlled access dataset, a mechanism needs to be established for users to request that portion of the linkage map as well. To reduce unnecessary data linkage access requests, each of the repositories could display whether a given study has common participants with other CARING for Children with COVID studies and list those studies. This approach should be reviewed by the CARING for Children with COVID program leadership to ensure there are no edge cases that would introduce reidentification risk to study participants.

Only two CARING for Children with COVID studies currently address record linkage in their informed consent forms. MUSIC includes language that implies broad linkage with “other research studies” and one of the PreVAIL kIds has already consented for broad use of a “GUID” approach (Appendix Table 1). While the consents from the other studies do not prohibit linkage activities, it would be ideal to explore the feasibility of re-consenting participants to include explicit record linkage information (drawing from the example language developed in this report) or seeking institutional approval for linkage, when re-consent is not feasible.

Since these studies use the GDS Institutional Certifications to certify that the data sharing is appropriate and consistent with the consent and as record linkage is not addressed in these documents, it is appropriate to provide submitting institutions the opportunity to certify whether the planned linkage is appropriate, with input from their IRB and/or equivalent Privacy Board. As part of this certification process, information should be provided outlining the planned scope of the linkage and how the linked data will be shared through the data repositories (i.e., linkage information will be available to “approved researchers” via controlled access only).

There may be data collected from tribal and/or international participants for the CARING for Children with COVID studies. If there are tribal or international laws, regulations, or policies that conflict with the proposed process or outcomes of a record linkage implementation and cannot be addressed by additional agreements, certain participants may need to be excluded from the PPRL implementations. Additionally, it may be appropriate to consider sharing pediatric COVID data associated with tribal nations through the forthcoming Tribal Data Repository[67].

The selection and implementation of a specific PPRL tool could constrain the scope of linkage to a particular set of data originators that are able to use that tool with their studies. This assessment demonstrates that nearly all PPRL tools can support the basic requirements for pediatric record linkage, including a three-party linked database model, as well as the proposed governance considerations. The primary technological limitation is the minimal common subset of PII elements collected across the CARING for Children with COVID studies. However, as additional PII is likely needed to yield high-quality linkages with pediatric data (e.g., standardized location information, even new elements like mother's maiden name), essentially any PPRL tool in this assessment would be acceptable. Using an NIH-owned software for a long-term and large-scale implementation strategy may preclude the need for new vendor contracts, avoid vendor-associated costs, and reduce risk of vendor business model modifications (e.g., mergers/acquisitions, bankruptcy) that could adversely affect tool maintenance and longitudinal linkage.

Finally, a long-term pediatric-wide approach to record linkage may look different than responding to the urgent needs of the pandemic, CARING for Children with COVID, and other pediatric COVID use cases. If possible, it may be appropriate to leverage existing record linkage implementations that already include some pediatric COVID studies and expand the scope to encompass the CARING for Children with COVID and other relevant studies. Further discussions would be needed to ensure the generation of high-quality linkages for children and that a robust governance approach is configured to share the linkage information across multiple repositories charged with sharing pediatric COVID data in the federated NIH data ecosystem.

8.3 Limitations of this Assessment & Future Directions

This assessment represents a snapshot of the landscape of record linkage to support biomedical research. The findings and considerations in this assessment will serve as a useful guidepost for the design and implementation of new PPRL implementations. The Project Team identified and prioritized several additional topics that merit further investigation as they were either outside the scope of this report or were not uncovered in the specific implementations assessed, including:

- Linkage quality assessments must be performed prior to selecting and implementing any PPRL tool. These assessments should be based on combinations of PII input elements, matching algorithms that are relevant to the features of a given record linkage implementation, and acceptable error rates based on the purpose of a given implementation. In parallel, the feasibility of collecting relevant PII elements across data submitters should be assessed. In this assessment, the Project Team surfaced challenges associated with PII elements currently used by various implementations but uncovered the potential opportunity for using additional and novel elements such as mother's maiden name. The Project Team also collected some anecdotal information from interviews and some quality-relevant information from vendors; however, performing a linkage quality assessment requires rigorous testing against a relevant gold standard dataset, the development of which is time and cost intensive. Such efforts are currently being taken on by research teams within NCI, ONC[68], and N3C. Ideally, these efforts should make available gold standard datasets for future quality assessments.
- While this report highlights the importance of transparent yet flexible consent, participant attitudes towards explicitly consenting for linkage, transparency in how data are used in future research, and linkage with unconsented data were out of scope for this project and should be assessed further. The discussion from the NIH Policy and Ethics of Record Linkage Workshop[25]

which was convened by the NIH Office of Data Science and Sharing, should be the starting point for these assessments.

- While many vendors publicly share some cost information, actual costs of PPRL are nearly impossible to determine without first making key decisions for a new record linkage implementation, including whether an honest broker will be needed, the duration of the desired linkage, the PII combinations or "tokens" that will be used, the number of sites, and the number of linkages.
- Multiple PPRL vendors purport to solve the lock-in challenge through development of interoperability methods such as the "token bridging" approach. This solution appears to be nascent technology that warrants rigorous analysis before any PPRL implementation includes this feature as a dependency.
- Finally, as technology rapidly evolves, there could be unforeseen nuances not captured or fully addressed in this report.

Researchers and other stakeholders can learn from existing record linkage implementations, as well as the key considerations and observations documented in this report, taking into account the specific requirements for a given implementation. While technology continues to advance rapidly, there is nearly an endless number of ways it can be used and it is critical for policy and governance approaches to be planned in advance of and inherently incorporated in its implementation, especially when sharing data from human participants.

9 GLOSSARY

Table 13: Glossary of Terms

Term	Definition
Aggregate data	Summary statistics compiled from multiple sources of individual-level data. (NIH)
Authorization	The function of specifying access rights/privileges to resources. (HHS)
Authorized users	Any appropriately provisioned individual with a requirement to access an information system. (NIST)
Blocking (or indexing)	Blocking or indexing "splits each database into smaller blocks according to some blocking criteria." It identifies a smaller set of potential candidate pairs without having to compare every single pair in the full comparison space. (NCHS)
Bloom filters	A data structure that can be used for efficiently checking membership to a set and whether two sets approximately match. (Schnell, R., Bachteler, T., Reiher, J.: Privacy-preserving record linkage using Bloom filters. BMC Med Inform Decis Mak 9(1) (2009) DOI: 10.1186/1472-6947-9-41)
Common data model (CDM)	A CDM standardizes the definition, format and model content of data across participating data partners so that standardized applications, tools and methods can be applied. (PCORnet)
Controlled access	Application and eligibility requirements need to be met and approved (e.g., by a data access committee) to gain access. (NIH) "Controlled access" and "access controls" refer to measures such as requiring data requesters to verify their identity and the appropriateness of their proposed research use to access protected data. (NIH) [*see also data access model*]
Clear text	Information that is not encrypted. (NIST)
Data access committee (DAC)	The DAC is responsible for reviewing all requests for access to datasets from external requestors and is composed of individuals with expertise in science, policy, or bioinformatics resources. (NIH)
Data access models	Four types of data repository access models (NIH): ○ Controlled access: Application and eligibility requirements need to be met to gain access ○ Registration required: Open to all, but users need to be signed in or registered with the resource to access ○ Open access: No access restrictions or registration required to access ○ Mixed: Has both controlled and open access.
Data coordinating center (DCC)	The DCC is an organization that coordinates large multi-site clinical research programs/trials and can provide common questionnaires, data collection forms and data management; statistical analysis; overall study training, coordination and quality assurance; support of ancillary study activities; support of websites or online resources for the program; and more. (NIH)
Data linkage model	Describes the scope of the datasets that are part of the linkage implementation. As defined in this Report: ○ Linked database model—where the linkage information that is created and/or provided encompasses all datasets in a given database ○ Study-specific model—where linkage information is created and/or provided for the purposes of a specific study

Term	Definition
Data originator/ contributor/submitter	Institutions/organizations/researchers that collect data from patients or study participants or that collect administrative data; they may also be the party to submit the data to a repository for sharing.
Data steward	A formal position or an assigned accountability with responsibility for the following areas: ○ Adherence to an appropriately determined set of privacy and confidentiality principles and practices ○ Appropriate use of information from the standpoint of good statistical practices (such as by not implying cause and effect when the data only point to correlation) ○ Limits on use, disclosure, and retention ○ Identification of the purpose for a specific use of the data ○ Application of "minimum necessary" principles ○ Verification of receipt by the correct recipient, wherever possible ○ Data de-identification (HIPAA-defined and beyond) ○ Data quality, including integrity, accuracy, timeliness, and completeness (NCVHS)
Data use agreement (DUA)	A DUA establishes who is permitted to use and receive data, and the permitted uses and disclosures of such information by the recipient. (HHS modified)
Data user	A person who is authorized by the Data Access Committee (DAC) or equivalent to access and/or analyze data. (N3C)
Disclosure	Disclosure relates to inappropriate attribution of information to a data subject, whether an individual or an organization. Disclosure occurs when a data subject is identified from a released file (identity disclosure), sensitive information about a data subject is revealed through the released file (attribute disclosure), or the released data make it possible to determine the value of some characteristic of an individual more accurately than otherwise would have been possible (inferential disclosure).(HHS)
De-duplication	The process of removing redundant patient records from a database. (CDC)
De-identification	De-identified patient data is patient information that has had personally identifiable information (PII; e.g., a person's name, email address, or SSN), including protected health information (PHI; e.g., medical history, test results, and insurance information) removed. This is normally performed when sharing the data from a registry or clinical study to prevent a participant from being directly or indirectly identified. (NIH)
Dictionary attack	An attack where an attacker uses pre-computed tables to reverse engineer the inputs to the hash. For example, if some possible contents are known to be contained in the inputs to the hashing function (such as name, date of birth, etc.), an attacker can construct rainbow lookup tables by producing hashes from the complete set of potentially valid input values. (Dong X, Randolph DA, Rajanna SK. Enabling Privacy Preserving Record Linkage Systems Using Asymmetric Key Cryptography. AMIA Annu Symp Proc. 2020 Mar 4;2019:380-388. PMID: 32308831; PMCID: PMC7153159)
Electronic health records (EHRs)	EHRs are electronic versions of the paper charts in your doctor's or other health care provider's office. An EHR may include your medical history, notes, and other information about your health including your symptoms, diagnoses, medications, lab results, vital signs, immunizations, and reports from diagnostic tests such as x-rays. (HHS)
Enclave	A data enclave is a secure network through which confidential data, such as identifiable information from census data, can be stored and disseminated. In a virtual data enclave, a researcher can access the data from their own computer but cannot download or remove it from the remote server. Higher security data can be accessed through a physical data enclave where a researcher is required to access the data from a monitored room where the data is stored on non-network computers. (NNLM) [*see also data access model*]

Term	Definition
Encoding/Hashing	Encoding: Using a system of symbols to represent information, which might originally have some other representation. Example: Morse code, phonetic encoding, hashing. (NIST) Hashing: A method of calculating a relatively unique output (called a hash digest) for an input of nearly any size (a file, text, image, etc.) by applying a cryptographic hash function to the input data. (NIST)
Encryption	Cryptographic transformation of data (called "plaintext") into a form (called "ciphertext") that conceals the data's original meaning to prevent it from being known or used. If the transformation is reversible, the corresponding reversal process is called "decryption," which is a transformation that restores encrypted data to its original state. (NIST)
Encryption key	A cryptographic key that has been encrypted using an approved cryptographic algorithm in order to disguise the value of the underlying plaintext key. (NIST)
Entity Resolution	Process of joining or matching records from one data source with another that describe the same entity. (Census) In PPRL, hash codes/tokens are used to match individual records without using PII/PHI. (N3C)
Federal Information Security Modernization Act (FISMA)	The Federal Information Security Modernization Act of 2014 requires that agencies maintain programs that provide adequate security for all information collected, processed, transmitted, stored, or disseminated in general support systems and major applications. FISMA requires an annual independent evaluation to determine effectiveness of information security programs. (HHS)
Federal Risk and Authorization Management Program (FedRAMP)	FedRAMP is a government-wide program that provides a standardized approach to security assessment, authorization, and continuous monitoring for cloud products and services. (HHS)
Geocoding	The process of inputting an address and receiving back latitude/longitude coordinates calculated along an address range. (Census)
Global Unique Identifier (GUID)	The GUID is a subject ID that allows researchers to share data specific to a study participant without exposing personally identifiable information (PII). The GUID is made up of random alpha-numeric characters and is NOT generated from PII/PHI. (NIH)
Governance	Governance, as defined in this Report, comprises of the policies, processes, and controls that address ethics, privacy protections, compliance, risk management, or other requirements for a given record linkage or privacy preserving record linkage (PPRL) implementation.
Hash codes/tokens	An encrypted value created by an irreversible conversion algorithm and any underlying Protected Health Information that has been de-identified using the expert determination method as described under HIPAA regulations at 45 CFR 164.515(b)(1). (N3C) The string of bits which is the output of a hash function. A hash function maps a bit string of arbitrary length to a fixed-length bit string using an algorithm that computes a numerical value (called the hash value) on a data file or electronic message that is used to represent that file or message and depends on the entire contents of the file or message. A hash function can be considered to be a fingerprint of the file or message. (NIST)

Term	Definition
Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule	The Standards for Privacy of Individually Identifiable Health Information are codified in 45 C.F.R. Parts 160 and 164 promulgated by the U.S. Department of Health and Human Services under the Health Insurance Portability and Accountability Act (HIPAA) of 1996. The HIPAA Privacy Rule establishes national standards to protect individuals' medical records and other individually identifiable health information (collectively defined as "protected health information") and applies to health plans, health care clearinghouses, and those health care providers that conduct certain health care transactions electronically. The Rule requires appropriate safeguards to protect the privacy of protected health information and sets limits and conditions on the uses and disclosures that may be made of such information without an individual's authorization. The Rule also gives individuals rights over their protected health information, including rights to examine and obtain a copy of their health records, to direct a covered entity to transmit to a third party an electronic copy of their protected health information in an electronic health record, and to request corrections. (HHS Health Information Privacy)
Honest broker	A party that holds de-identified tokens ("hashes") and operates a service that matches tokens generated across disparate datasets to formulate a single Match ID for a specific use case. (N3C)
Individual-level de-identified data	Health information that is not individually identifiable (if it does not identify an individual and if the covered entity has no reasonable basis to believe it can be used to identify an individual). (HHS)
Institutional Review Board (IRB)	An IRB is the institutional entity charged with providing ethical and regulatory oversight of research involving human subjects, typically at the site of the research study. (NIH) An Institutional Review Board is an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects. An IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects. FDA)
Interoperability	According to section 4003 of the 21st Century Cures Act, the term 'interoperability,' with respect to health information technology, means such health information technology that— "(A) enables the secure exchange of electronic health information with, and use of electronic health information from, other health information technology without special effort on the part of the user; "(B) allows for complete access, exchange, and use of all electronically accessible health information for authorized use under applicable State or Federal law; and "(C) does not constitute information blocking as defined in section 3022(a)." (HIT)
Key escrow	The system responsible for storing and providing a mechanism for obtaining copies of private keys associated with encryption certificates, which are necessary for the recovery of encrypted data. (NIST)
Letter of determination (LOD)	An LOD documents an IRB decision on the status of research. (HHS)
Limited dataset (LDS)	Datasets containing protected health information but excludes the following 16 HIPAA direct identifiers: names, postal address information, other than town or city, State, and ZIP Code, telephone numbers, fax numbers, electronic mail addresses, SSNs, medical record numbers, health-plan beneficiary numbers, account numbers, certificate and license numbers, vehicle identifiers and serial numbers, including license plate numbers, device identifiers, and serial numbers Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, Biometric identifies including fingerprints and voice prints, Full-face photographic images and any comparable image. (HHS)
Linkage Map	As defined in this Report: A linkage map is a crosswalk between participant-level IDs across disparate datasets and repositories.

Term	Definition
Metadata	Information describing the characteristics of data including, for example, structural metadata describing data structures (e.g., data format, syntax, and semantics) and descriptive metadata describing data contents (e.g., information security labels). (NIST)
Non-technical controls	Non-technical security and privacy controls and activities include such actions and things as: administrative controls (policies, training, risk management, risk assessment, workforce security and privacy) and physical controls (facility access controls, maintenance records, work area use, work are security and privacy, and contingency operations) (NIST)
Open Access	Data within this category presents minimal risk of participant identification. Access to these data does not require user certification, and researchers may explore data content without restriction. (NCI) No access restrictions or registration required to access (NIH) [*see also data access model*]
Patient Identifier	Unique data used to represent a person's identity and associated attributes. (NIST)
Personally identifiable information (PII)	Any information that can be used to distinguish or trace an individual's identity, either alone or when combined with other information that is linked or linkable to a specific individual. (NIST and CODI)
Privacy preserving record linkage (PPRL)	A technique identifying and linking records that correspond to the same entity across several data sources held by different parties without revealing any sensitive information about these entities (UK Office for National Statistics)
Protected Health Information (PHI)	Individually identifiable health information that is transmitted or maintained in any form or medium (electronic, oral, or paper) by a covered entity or its business associates, excluding certain educational and employment records. (NIH)
Pseudo Global Unique Identifier	A Pseudo-GUID is a unique ID that is not based on PII. This is a random ID that can be used as a placeholder when PII is not available, and "promoted" to a real GUID when the information is obtained at a future date.(NDA)
Record Linkage	Combining information from a variety of data sources for the same individual. (AHRQ)
Registered Tier	Registration required; open to all, but users need to be signed in or registered with the resource to access the system, tool or data. Sometimes requires a "click-through" agreement first. NIH) [*see also data access model*]
Repository	A repository is a place to store and make available data that includes research results, publications, and scientific data for usage. (NIH)
Salt	Random data used to modify the input of a hash function to guarantee a unique output. This adds another hashing layer on top of an encryption algorithm, increasing the difficulty of reversing the encryption of the data. (UK Office for National Statistics)
Secret key	A cryptographic key, used with a secret key cryptographic algorithm, that is uniquely associated with one or more entities and should not be made public.(NIST)
Soundex	Soundex is a phonetic index/encoding that codes names based on the way a name sounds rather than on how it is spelled. (NIST)
Study_ID	An arbitrary, study-specific, site-agnostic, unique identifier that identifies a patient in a Project dataset. (CODI)
Subject ID	As defined in the Report: Refers to a de-identified subject/participant identifier that can be generated by hashing or non-hashing methods. If hashing is used, it is different from a hash code/token (hashed ID) generated using a PPRL tool (as in RADx-rad PreVAIL kIds projects and PEDSnet).

Term	Definition
Technical controls	The security controls for an information system are primarily implemented and executed by the information system through mechanisms contained in the hardware, software, or firmware components of the system. (NIST)

10 ACRONYMS

Table 14: Acronyms

Acronym	Expansion
ABCD	Adolescent Brain Cognitive Development
ACF	Administration for Children and Families
ACS	American Community Service
ACS	American Community Survey
ADHHS	Alaska Department of Health and Social Services
AES	Advanced Encryption Standard
AHRQ	Agency for Healthcare Research and Quality
ALCAN	Alaska Longitudinal Child Abuse and Neglect Linkage
AMIA	American Medical Informatics Association
AoU	*All Of Us*
API	Application Programming Interface
BAM	Binary Alignment Map
BEA	Bureau of Economic Analysis
BRICS	Biomedical Research Informatics Computing System
CAPS	Committee on Access, Privacy, Security
CARING for Children with COVID	Collaboration to Assess Rick and Identify LoNG-term outcomes for Children with COVID
CDC	Centers for Disease Control and Prevention
CDR	Curated Data Repository
cdRNS	Common Data Repository for Nursing Science
CHORDS	Colorado Health Observation Regional Data Service
CIT	Center for Information Technology
CMI	Child Maltreatment Incidence
CMS	Centers for Medicare & Medicaid Services
CODI	Childhood Obesity Data Initiative
CPU	Central Processing Unit
DA	Disclosure Avoidance
DAC	Data Access Committee
dbGAP	Database of Genotypes and Phenotypes
DBMS	Database Management Systems
DCC	Data Coordinating Center
DHDN	Distributed Health Data Network
DMR	Data Management Resource
DOD	Department Of Defense
DRC	Data and Research Center
DSA	Data Sharing Agreement
DSC	Down Syndrome Connect

Acronym	Expansion
DSDR	Data Sharing for Demographic Research
DUA	Data User Agreement
DUCC	Data User on Code Conduct
DUR	Data Use Request
EHR	Electronic Health Record
EMR	Electronic Medical Record
EPA	Environmental Protection Agency
ERB	Ethics Review Board
ETL	Extract Transformation and Load tool
FedRAMP	Federal Risk and Authorization Management Program
FISMA	Federal Information Security Management Act
FITBIR	Federal Interagency Traumatic Brain Injury Research Informatics System
FSDRC	Federal Statistical Research Data Center
GDS	Genomic Data Sharing
GIID	Government Issued ID
GRAF	Genetic Relationship and Fingerprinting
GRDR	Global Rare Diseases Data Repository
GUI	Graphical User Interface
GUID	Global Unique Identifier
GWAS	Genome Wide Association Studies
HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HPO	Healthcare Provider Organizations
ICF	Informed Consent Form
ICS	Integrated Client Services
ID	Identifier
IHQ	Immunization History Questionnaire
IKDR	International Kawasaki Disease Registry
IRB	Institutional Review Board
IT	Information Technology
JAAMH	Joint Addiction, Aging, and Mental Health
JDBC	Java Database Connectivity
JSON	Javascript Object Notation
JWT	JSON Web Token
KD	Kawasaki Disease
KUMC	University of Kansas Medical Center
LHB	Linkage Honest Broker
LOD	Letter of Determination
LSOA	Longitudinal Study of Aging

Acronym	Expansion
MAS	Macrophage Activation Syndrome
MIDRC	Medical Imaging and Data Resource Center
MIS	Multisystem Inflammatory Syndrome
MIS-A	Multisystem Inflammatory Syndrome in Adults
MIS-C	Multisystem Inflammatory Syndrome in Children
MRN	Medical Record Number
MSUA	Master Sharing and Use Agreement
MUSIC	Multisystem Inflammatory Syndrome In Children
N3C	National COVID Cohort Collaborative
NCATS	National Center for Advancing Translational Studies
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NCSES	National Center for Science and Engineering Statistics
NDA	National Institute of Mental Health Data Archive
NDI	National Death Index
NEI	National Eye Institute
NHANES	Continuous National Health and Nutrition Examination Survey
NHEFS	NHANES 1 Epidemiologic Follow-Up Study
NHGRI	National Human Genome Research Institute
NHHCS	National Home and Hospice Care Survey
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute of Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism Data Archive
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Development
NIDA	National Institute on Drug Abuse
NIH	National Institute of Health
NIH ODSS	National Institute of Health Office of Data Science Strategy
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NIST	National Institute of Standards and Technology
NNHS	National Nursing Home Survey
NSCAW	National Survey of Child and Adolescent Well Being
OAI	Osteoarthritis Initiative
ODBC	Open Database Connectivity
ODSS	Office of Data Science and Sharing
OHA	Oregon Health Authority

Acronym	Expansion
OHRP	Office for Human Research Protections
OHSU	Oregon Health Sciences University
OMB	Office of Management and Budget
PCORnet	The National Patient-Centered Clinical Research Network
PDBP	Parkinson's Disease Biomarkers Discovery
PHI	Personal Health Information
PID	Participant Identifier
PII	Personally Identifiable Information
PIK	Personal Identification Key
PO	Project Officer
POP02 or POPS	Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs Administered to Children per Standard of Care
PPI	Patient Provided Information
PPRL	Privacy Preserving Record Linkage
PRAMS	Pregnancy Risk Assessment Monitoring System
PreVAIL kIds	Predicting Viral-Associated Inflammatory Disease Severity in Children with Laboratory Diagnostics and Artificial Intelligence
PRISM	Pediatric Research Immune Network on SARS-CoV-2 and MIS-C
PTSC	Participant Technology System Center
PVS	Person Identification Validation System
RAB	Resource Access Board
RADx	Rapid Acceleration of Diagnostics
RADx-ATP	Rapid Acceleration of Diagnostics Advanced Technology Platforms
RADx-rad	Rapid Acceleration of Diagnostics Radical
RADx-UP	Rapid Acceleration of Diagnostics Underserved Populations
RAM	Random Access Memory
RDC	Research Data Committee
RDR	Raw Data Repository
RECOVER	Researching COVID to Enhance Recovery
RFI	Request for Information
SC	Subject Consent
SDI	Self Determination Inventory from the Self-Determination Inventory System (SDIS) Data Dashboard
SDOH	Social Determinants of Health
SHA-2	Secure Hash Algorithm 2
SIPP	Survey of Income and Program Participation
SOA	Supplement on Aging
SOC 2	Service Organization Control 2
SRA	Short Read Archive
SSA	Social Security Administration
SSM	Subject Sample Matching

Acronym	Expansion
SSN	Social Security Number
SSTR	Sample Status Telemetry Report
TSS	Toxic Shock Syndrome
U.K.	United Kingdom
VCF	Variant Cell Formula

11 APPENDIX

11.1 CARING for Children with COVID Studies – Supplemental Information

Appendix Table 1: Informed Consent Forms from Pediatric COVID Studies Selected for the Project

Study	Consent for Linking Data		Consent for Sharing (Linked) Data	Dynamic Consent Language (unenroll/withdraw)	Reconsent Language (for reaching age of majority)
	Across Sites Within a Study	Across Studies			
POP02	"If your child is seen at another location, we may ask you to sign a form to allow us to get those records. Examples include medical history, physical exam, recent laboratory test results, and evaluations over the course of your child's hospitalization or clinic visits. If these evaluations are not already noted in the medical record, they may be performed for this study and will be recorded as study data. Additionally, we will collect whether your child has or is participating in other research studies"	Not available	*Linked data sharing*: Not included in the consent form *General data sharing*: "What we learn in this study will be put in a database run by the National Institutes of Health (NIH) to be shared for future research. This information will not include anything that identifies your child. All participants' de-identified study data and any remaining de-identified study samples will be submitted to a NIH-designated storage location, such as the NICHD Data and Specimen Hub or DASH (https://dash.nichd.nih.gov) or the NIH database of Genotypes and Phenotypes or dbGaP (https://www.ncbi.nlm.nih.gov/gap/) from which the data will be shared with other researchers. Individual level genomic data will be managed in a controlled-access manner. Controlled access means that only researchers who apply for and get permission to use the information and samples for a specific research project will be able to access the information. Your child's genetic data, study samples and health information, stored in these databases, will not be labeled with your child's name or other information that could be used to identify them. Researchers approved to access information in these databases will agree not to attempt to identify your child. De-identified samples may also be used by other researchers in the future to conduct tests separate from those being done in the current study. These researchers may conduct whole genome sequencing; by doing WGS, these researchers may have information that is unique to your child. The purpose of sharing this information is to make more research possible that may improve children's health. This will be done without obtaining additional permission from you.	"You have the right to stop this Authorization at any time. Your decision to stop your Authorization will not involve any penalty or loss of access to treatment or other benefits to which you/ your child is otherwise entitled. If you decide you no longer want your child to participate in this study, but do not stop your Authorization, new health information may be collected until this study ends. To stop this Authorization, you should inform the site investigator, as named on the first page of this form, of your decision in writing. Stopping your Authorization will prevent sharing of PHI in the future but will not affect any PHI that has already been gathered or shared."	"I have been told that if I become an adult while enrolled in this study, I will be asked to sign the consent form."

Study	Consent for Linking Data		Consent for Sharing (Linked) Data	Dynamic Consent Language (unenroll/withdraw)	Reconsent Language (for reaching age of majority)
	Across Sites Within a Study	Across Studies			
			The data and samples collected in this study may be kept forever. We may publish the results of this study. However, we will not include your or your child's name or any other identifying information."		
MUSIC	"Study information sent outside of this institution will be linked to your [name] through a study identification (ID) number. The link between your name and this study ID number will be kept in a locked, secure area that only the study team can get to."	"If you participated in other research studies, we may collect and share information and lab data between studies to ease the burden on research staff and participants alike. Data and samples will be available to researchers within the PHN as well as researchers from other national and international institutions for the study of MIS-C and other diseases."	*Linked data sharing*: Not included in the consent form *General data sharing*: "I agree to have my data and samples shared in a central biobank after PHN funding ends for future studies in heart disease and other diseases. 'Biobanking' is storing health information and/or blood, saliva, or tissue for future research studies. A 'bank' is the place where it is stored. We would like your permission to bank your blood (or saliva) sample for future research. In the future, your data (clinical and genetic) and sample might be placed in a central data or biobank to make it easier for researchers to use your samples and data for research."	"If you choose to provide a blood (or saliva) sample for the biobank and later want to withdraw your sample from the biobank, it is important that you contact study staff and tell them in-person or in writing. You will have the choice to have the study ID number removed from the sample and leave the sample and existing data in the biobank for future research. Or, you may ask to have the unused samples and data destroyed. If your sample is placed in a central biobank, your personal information was already removed so it cannot be identified as you and therefore cannot be removed. We will also not be able to destroy samples and data that have already been used or distributed for research.	"If your child turns 18 years old while taking part in this study, he/she will be asked to review and sign an informed consent form as an adult if he/she wants to continue to be in the study"
PRISM	"Information about you/your child and samples collected for this study may be shared with other PRISM researchers. We will not ask you for additional permission before sharing the information with other PRISM researchers."	Not available	*Linked data sharing*: Not included in the consent form *General data sharing*: "Once the data and samples have been stripped of all personal information identifying you/your child, they can be shared without your consent. As a NIH-sponsored clinical study, we serve the public by sharing research information (data) that is collected during a study with the scientific community to advance science and health. We will keep the information resulting from this study in a safe place, controlled by the NIH, called a central data repository. The scientific information will be available for future studies that may help future patients. Your/your child's data may be stored for a very long time. The information in the central data repository will not contain personal information that would identify you/your child, such as name, birthdate, address, etc. We will not	Once samples have been stripped of all identifiers, or have been sent to another laboratory, or have been used for a research test, you will not be able to change your mind about giving permission for their use."	Not available

Study	Consent for Linking Data		Consent for Sharing (Linked) Data	Dynamic Consent Language (unenroll/withdraw)	Reconsent Language (for reaching age of majority)
	Across Sites Within a Study	Across Studies			
			ask you for additional permission before sharing the information in the central data repository."		
RADx-rad PreVAIL kIds Studies					
AICORE-ids: Artificial Intelligence COVID-19 Risk AssEssment for kids (PI: Dr. Ananth Annapragada)	Not available	Not available	*Linked data sharing:* Not included in the consent form *General data sharing*: "Information that identifies you may be removed from your identifiable private information collected as part of this research, and after such removal, your information may be used for future research studies or distributed to another investigator for future research studies without additional consent/authorization from you. Sharing and Future Research Studies with Identifiable Biospecimens Information that identifies you may be removed from your identifiable biospecimens collected as part of this research, and after such removal, your biospecimens may be used for future research studies or distributed to another investigator for future research studies without additional consent/authorization from you."	"Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study. If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights."	Not available
Diagnosing and Predicting Risk in Children with SARS-CoV-2 Related Illness (PI: Dr. Jane Burns)	Not available	Not available	*Linked data sharing*: Not included in the consent form *General data sharing*: "Your child's blood sample, body fluids, or swabs may be used in additional research related to Kawasaki disease to be conducted by the University of California personnel for an unlimited period of time. These samples may be shared with other investigators at other institutions."	"If you decide later that you do not want the specimens collected from your child to be used for future research, you may tell this to Dr. Burns, who will use her best efforts to stop any additional studies. However, in some cases it may be impossible to locate and stop such future research once the materials have been shared with other researchers."	"When your child turns 18 years of age, he /she will not be re-consented for the continued use of banked specimens."
Discovery and Clinical Validation of Host Biomarkers of Disease Severity and Multi-System Inflammatory Syndrome in Children (MIS-C) with COVID-19 (PI: Dr. Charles Yen Chiu)	Not available	Not available	*Linked data sharing*: Not included in the consent form *General data sharing*: "Your information, blood, and saliva will be sent to scientists in several laboratories. After our study is over, your information and any leftover blood and saliva will be sent to a central data repository at the National Institute for Health (NIH) and will be available for other scientists who are studying COVID to use in their research. Any information that could be used to identify you from your medical records or clinical samples will be removed before it is given to scientists outside of UCSF."	"If you decide later that you do not want your sample and information to be used for future research, you can tell us, and we will destroy any remaining identifiable sample and information if it is no longer needed for your care."	Not available
COVID-19 Network of Networks Expanding Clinical	"The research team may use or share your or your child's information	Not available	*Linked data sharing:* Not included in the consent form	"You may also withdraw your consent/permission for the use of data already collected about you or your child,	Not available

Study	Consent for Linking Data		Consent for Sharing (Linked) Data	Dynamic Consent Language (unenroll/withdraw)	Reconsent Language (for reaching age of majority)
	Across Sites Within a Study	Across Studies			
and Translational Approaches to Predict Severe Illness in Children (CONNECT to Predict Sick Children) (PI: Dr. Lawrence Kleinman)	collected or created for this study with the following people and institutions: Rutgers University Investigators involved in the Study, Non-Rutgers Investigators on the Study Team: National Institute of Health, our study sponsor; Yale University, partner study sites; New York Medical College, partner study sites. Those persons or organizations that receive your or your child's information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by the laws governing them."		General data sharing: "The research team is interested in advancing the science to improve the diagnosis and treatment of COVID for children, adolescents, and young adults. Therefore, we may share remaining data and biospecimens with other collaborators, including companies after removal of all personal identifiers that could be linked to your identity without obtaining additional informed consent from you." "We may share your or your child's health and genetic information through databases at the National Institutes of Health (NIH), including the database of Genotypes and Phenotypes (dbGaP). By sharing this information, the hope is to maximize the chance for researchers to use and learn from your or your child's information to better understand the effects of the coronavirus that causes COVID-19 in children, adolescents, and young adults. The NIH team will work with Dr. Kleinman and the study team from Rutgers to coordinate the secure transfer, storage, and access of your or your child's information. The NIH team will make sure that this information cannot be used to identify you or your child and that it remains password-protected and available only to qualified researchers studying the coronavirus that causes COVID-19."	but you must do this in writing to Lawrence Kleinman, M.D., M.P.H. at Children's Health Institute, 89 French Street, Room 1338, New Brunswick, NJ 08901, 732-235-7906. Any data that has already been sent to NIH or its designee, such as another organization that integrates data from across studies at several institutions (also known as a Data Coordinating Center) or data that has been published cannot be withdrawn because there may not be any identifiers with the data." "You may change your mind and not allow the continued use of your or your child's information (and to stop taking part in the study) at any time. If you take away permission, your information will no longer be used or shared in the study, but we will not be able to take back information that has already been used or shared with others. If you say yes now but change your mind later for use of your or your child's information in the research, you must write to the researcher and tell him or her your decision."	
A Data Science Approach to Identify and Manage Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 Infection and Kawasaki Disease (KD) in Pediatric Patients	"De-identified study data (information that does not allow anyone to determine your child's identity by removing all names, contact information, medical record number and any other information that can be linked directly to you/you child) will be combined with data from all other sites participating in this study. All IKDR	"As part of this study, a Global Unique Identifier (GUID) will be created. A Global Unique Identifier (GUID) is a secure one-of-a-kind code that is assigned to your child so we can securely track your child participating in multiple projects and databases.	*Linked data sharing*: Not included in the consent form *General data sharing*: "External researchers can get data directly from the IKDR. They will first obtain REB approval and sign an agreement with the Hospital for Sick Children (where the IKDR data coordinating center is located). These agreements will control how your child's study data will be used. They will not be permitted to disclose or to transfer study data to anyone else. They will also not be permitted to use study data for purposes other than those included in the agreements. Researchers will also agree that they will not attempt to re-identify your child from their study data. The information from this registry will be	"It is your choice, and your child's, to decide to take part in this study, and participation is voluntary. You and your child can change your mind at any time during the research study. The study team may ask why you are withdrawing your child for reporting purposes, but you do not need to give a reason to withdraw your child from the study if you do not want to. Withdrawal from the study will not have any effect on the care your child or your	Not available

Study	Consent for Linking Data		Consent for Sharing (Linked) Data	Dynamic Consent Language (unenroll/withdraw)	Reconsent Language (for reaching age of majority)
	Across Sites Within a Study	Across Studies			
(PI: Dr. Cedric Manlhiot)	investigators are required to have an agreement with the Hospital for Sick Children in Toronto to participate in this study and will be allowed to access de-identified data. Data might be accessed by IKDR investigators for approved research or to participate in IKDR research activity (e.g., helping with result interpretation)."	Please let the study team know if you have any questions or if you do not want multiple studies that your child is participating in to be linked through a GUID."	available only to researchers who have received REB approval for their research. Data will be deposited in an approved National Institutes of Health (NIH) data registry in the United States after they undergo a process called anonymization where some information such as dates are modified to further reduce the possibility of re-identification. The information will be merged with the information from other patients across the world. The NIH has a strict process to ensure the security and privacy of research data it makes available through NIH-approved registries. Researchers will be required to enter into an agreement with the NIH to obtain access to the data. This agreement stipulates that researchers will not be permitted to disclose or to transfer study data to anyone else. They will also not be permitted to use study data for purposes other than those included in the agreements. Researchers will also agree that they will not attempt to re-identify your child from their study data. Only researchers from academic institutions may obtain access to data through this mechanism."	family will receive at SickKids. If you decide to have your child leave the study, you can contact a member of the study team to let them know. If you no longer want your child's study information to be used in this research, you can request your child's data to be withdrawn and destroyed. Please note that any study data that has been included as part of the analysis or that has been shared cannot be withdrawn."	
Diagnosis of MIS-C in Febrile Children (PI: Dr. Audrey Odom John)	Not available	Not available	*Linked data sharing*: Not included in the consent form *General data sharing*: "We will use and may share data and/or specimens for future research. They may be shared with researchers/institutions outside of CHOP. This could include for profit companies. We will not ask for your consent before using or sharing them. We will remove identifiers from your data and/or specimens, which means that nobody who works with them for future research will know who you are. The NIH repository stores genetic information and phenotypic data from many studies. The NIH then shares that information with researchers. We will send the information about you and the other participants to a repository at the NIH. The information will be de-identified (no names or other direct information about you will be included). The NIH will not be able to re-identify you or any other individual. The NIH intends to share the collected information with other researchers. The researchers who receive data must	"You may change your mind and withdraw your permission to use and disclose your health information at any time. To take back your permission, it is preferred that you inform the investigator in writing. In the letter, state that you changed your mind and do not want any more of your personal information collected. The personal information that has been collected already will be used if necessary for the research. No new information will be collected. If you withdraw your permission to use your personal health information, you will be withdrawn from the study."	Not available

Study	Consent for Linking Data		Consent for Sharing (Linked) Data	Dynamic Consent Language (unenroll/withdraw)	Reconsent Language (for reaching age of majority)
	Across Sites Within a Study	Across Studies			
			promise to keep the data confidential and to use it only for the purpose approved by NIH. They must also promise to not try to re-identify anyone."		
Identifying Biomarker Signatures of Prognostic Value for Multisystem Inflammatory Syndrome in Children (MIS-C) (PI: Dr. Juan Salazar)	Not available	Not available	*Linked data sharing*: Not included in the consent form *General data sharing*: "At the end of the study, your information, survey answers, and any leftover blood and saliva will be shared with the National Institute of Health's Rapid Acceleration of Diagnostics (RADx) Data Coordinating Center. The RADx is a NIH program that funds studies researching ways to use technology for COVID testing. All studies that are funded will share their data and samples with the Data Coordinating Center to create a research resource for everyone to use. This study is funded by the RADx program. All data and samples that are shared with the Data Coordinating Center will be completely de-identified by removing all of your private information. The Data Coordinating Center can store your information and samples indefinitely." *Genomic data sharing*: "In order to allow researchers to share results, the NIH has developed special sample/data "banks" that collect the results and analyze samples/data from research studies, including genetic studies. For example, there is a database called The NIH Database of Genotypes and Phenotypes (DbGaP). Some of your genetic, genomic or health information might be placed into one or more of these banks so other qualified and approved researchers can do more studies. We do not think that there will be further risks to your privacy and confidentiality by sharing your health information, samples and/or genetic information with these banks. However, we cannot predict how genetic information will be used in the future. The samples and data will be sent with only your research code number attached. Your name or other directly identifiable information will not be given to these central banks. There are many safeguards in place to protect your privacy."	"You can leave any time after you start. To leave, email Dr. Salazar at: jsalaza@connecticutchildrens.org. The file linking your code to your private information will be destroyed. Any remaining blood or saliva samples will be destroyed. All of your information will be kept and still used, but it won't have any of your private information."	"If the research subject reaches the age of 18 prior to the close of the study, we will attempt to contact them and re-consent them as adults. If we are unable to contact them, they will not be discontinued from study. However, their data and specimens will be completely de-identified including the destruction of any link to identifiers from coded data."

Study	Consent for Linking Data		Consent for Sharing (Linked) Data	Dynamic Consent Language (unenroll/withdraw)	Reconsent Language (for reaching age of majority)
	Across Sites Within a Study	Across Studies			
Severity Predictors Integrating Salivary Transcriptomics and Proteomics with Multi Neural Network Intelligence in SARS-CoV2 Infection in Children (SPITS MISC) (PI: Dr. Usha Sethuraman)	Not available	Not available	*Linked data sharing*: Not included in the consent form *General data sharing*: Your identifiable information in the research study records may also be shared with, used by or seen by collaborating researchers, the sponsor of the research study (National Institutes of Health), the sponsor's representatives including the Data Coordinating Center assigned by the NIH, and certain employees of the Central Michigan University and Pittsburgh University if needed to oversee the research study."	"However, you can withdraw your permission to allow the research team to review your medical records in writing to Dr. Usha Sethuraman, Children's Hospital of Michigan, Central Michigan University at any time. Any identifiable research or medical information recorded for, or resulting from, your participation in the study prior to the date that you formally withdrew your consent may continue to be used and disclosed for the purposes described above. You may also withdraw your permission at any time through a written request. Any identifiable research or medical information recorded for, or resulting from, your participation in the study prior to the date that you formally withdrew your consent may continue to be used and disclosed for the purposes described above."	Reconsent form language: "I understand that I am currently participating in a research study. I further understand that consent for my participation in this research study was initially obtained from my authorized representative since I was unable to provide direct consent at the time that this initial consent was requested. I have now turned age 18 and I am able to provide direct consent for continued participation in this research study."

11.2 Governance Assessment Supplemental Information

11.2.1 Governance Summary For Record Linkage Implementations Using PPRL

Appendix Table 2: Governance Summary for Record Linkage Implementations Using PPRL

	Record Linkage Implementation	Datasets Linked	Authorization (Consent/IRB/Other) for			PPRL Tool	PII Elements Used for PPRL	Entity Resolution (Matching) Performed by	Data Linking Performed by	Data Linkage Model[mm]	Data Access Model[nn]	Additional Information Link
			Record Linkage	Sharing Linked Data	Accessing Linked Data							
1	The Biomedical Research Informatics Computing System (BRICS) Instances: ○ NINDS/Parkinson's Disease Biomarker Program/NIA ○ NEI ○ NCATS/Global Rare Diseases Data Repository (GRDR) ○ NINR/ Common Data Repository for Nursing Science (cdRNS) ○ The Federal Interagency Traumatic Brain Injury Research (FITBIR)	Data within BRICS instances: clinical, genetic, phenotypic, specimen, and medical imaging	User and their institution agree to the terms of data submission, which specifically addresses linkage via use of the GUID; no explicit language for linking or use of GUID in the informed consent	User and their institution agree to the terms of data submission, which specifically addresses linkage via use of the GUID; no explicit language for linking or use of GUID in the informed consent	Data Access Committee approval; all approvals include access to the GUIDs	BRICS GUID tool	○ Complete legal given (first) name of the subject at birth ○ Middle name (if available) ○ Complete legal family (last) name of subject at birth ○ Day of birth ○ Month of birth ○ Year of birth ○ Name of city/ municipality in which subject was born ○ Country of birth [Optional PII elements in Section 11.2.1.1]	GUID server for each BRICS instance *or* a BRICS instance can connect to the Centralized GUID server. Presently BRICS instances: PDBP, NEI, NCATS, NINDS, NIA, cdRNS connect to the centralized GUID server.	Researchers who have approval to access the data	Linked database model	Controlled	Section 11.2.1.1
2	NIMH Data Archive (NDA) Repository	Phenotypic, clinical, genomic/ pedigree, neuroimaging, and other neurosignal recordings data	○ Example consent language describes GUID but use of language in studies is not verified by NDA	Data submitters agree that informed consent from participants aligns to "broad data use" by signing the NDA	Data Access Committee approval; all approvals include access to the GUIDs	NDA GUID tool	○ First Name ○ Middle Name ○ Last Name ○ Sex ○ Date of Birth ○ City/ Municipality of Birth	NDA GUID server	Researchers who have approval to access the data	Linked database model	Controlled	Section 11.2.1.2

[mm] Two types of linkage models: Linked database model, where the linkage information that is created and/or provided encompasses all datasets in a given database; Study-specific model, where linkage information is created and/or provided for the purposes of a specific study

[nn] Data access models: Open access = no access restrictions or registration required to access; Registration required = open to all, but users need to be signed in or registered with the resource to access; Controlled access = application and eligibility requirements need to be met to gain access (e.g., by a data access committee); Enclave = data cannot leave a specific system boundary (e.g., cannot be downloaded)

	Record Linkage Implementation	Datasets Linked	Authorization (Consent/IRB/Other) for			PPRL Tool	PII Elements Used for PPRL	Entity Resolution (Matching) Performed by	Data Linking Performed by	Data Linkage Model[mm]	Data Access Model[nn]	Additional Information Link
			Record Linkage	Sharing Linked Data	Accessing Linked Data							
			○ Data submitters agree to data linkage by signing the NDA Data Submission Agreement.	Data Submission Agreement								
3	National COVID Cohort Collaborative (N3C) EHR data linkage [*Linked data not yet available to users*]	EHR data of COVID-19 patients from N3C participating institutions (=data partners) *who have opted in for PPRL*	○ Data partners must agree to linking data by signing the Linkage Honest Broker Agreement ○ Informed consent not collected from patients ○ NCATS obtained a waiver of consent from NIH IRB	○ Informed consent not collected from patients ○ NCATS obtained a waiver of consent from NIH IRB	○ Local IRB letter of determination for HIPAA limited dataset ○ N3C Data Access Committee approval for data use, which includes access to linkage map with MATCH_ID and Pseudo IDs (generated by the Honest Broker for the specific use case)	Datavant	Combinations of PII elements to generate 18 tokens *per record* (last name, first name, DOB, gender, SSN, email, zip5/9, cell phone)	Third-party honest broker: Regenstrief	N3C Enclave	Linked database model	Enclave	Section 11.2.1.3
4	N3C – Class 0: N3C EHR data linkage with data from an external enclave Example: Linkage with data from the Medical Imaging and Data Resource Center (MIDRC) [*Linked data not yet available to users*]	○ EHR data from N3C data partners ○ Data stored in an external enclave — imaging data (currently)	○ N3C data partners must agree to linking their EHR data by signing the Linkage Honest Broker Agreement, and provide permission to link EHR data with individual external datasets ○ Informed consent not collected from N3C patients; NCATS obtained a waiver of consent from NIH IRB ○ Interconnect Agreement established with	○ Informed consent not collected from patients; NCATS obtained a waiver of consent from NIH IRB ○ Interconnect Agreement established with N3C and the external enclave (the interconnect agreement is being developed and not yet live)	○ Local IRB letter of determination ○ N3C Data Access Committee approval for data use, which includes access to linkage map with MATCH_ID and Pseudo IDs (generated by the Honest Broker for the specific use case)	Datavant	Combinations of PII elements to generate 18 tokens *per record* (last name, first name, DOB, gender, SSN, email, zip5/9, cell phone)	Third-party honest broker: Regenstrief	N3C Enclave	Linked database model	Enclave; Ephemeral work bench (a temporary extension of the N3C enclave)	Section 11.2.1.4

	Record Linkage Implementation	Datasets Linked	Authorization (Consent/IRB/Other) for			PPRL Tool	PII Elements Used for PPRL	Entity Resolution (Matching) Performed by	Data Linking Performed by	Data Linkage Model[mm]	Data Access Model[nn]	Additional Information Link
			Record Linkage	Sharing Linked Data	Accessing Linked Data							
			N3C and the external enclave (the interconnect agreement is being developed and not yet live)									
5	N3C – *Class 2:* N3C EHR data linkage with external datasets Examples: Linkages with viral variant data and mortality data ingested into N3C	EHR data from N3C data partners linked to external data for COVID-19 patients; current sets of external data linkages include: ○ Viral variant data (submitted to NCBI repository by data partners) ○ Mortality data (from government mortality sources and obituary sites)	○ Data partners must agree to linking their EHR data by signing the Linkage Honest Broker Agreement, and must provide permission to link EHR data with external data ○ Informed consent not collected from patients ○ NCATS obtained a waiver of consent from NIH IRB ○ Mortality data sources – no authorization required as the data are purchased by N3C from various private sources	Informed consent not collected from N3C patients; NCATS obtained a waiver of consent from NIH IRB	○ Local IRB letter of determination ○ N3C Data Access Committee approval for data use, which includes access to linkage map with MATCH_ID and Pseudo IDs (generated by the Honest Broker for the specific use case)	Datavant	Combinations of PII elements to generate 18 tokens *per record* (last name, first name, DOB, gender, SSN, email, zip5/9, cell phone)	Third-party honest broker: Regenstrief	N3C Enclave	Linked database model	Enclave (private user workspace within the N3C enclave)	Section 11.2.1.5
6	PEDSnet	EHR data from the 11 participating PEDSnet institutions, including demographic data, outpatient encounters, inpatient admissions, ER encounters, anthropometrics, vital signs, providers, diagnoses,	○ Large observational studies operate under waiver of consent ○ Consent for data linking is embedded in the broad study consent ○ PEDSnet Data and Steering Committees approve linkage for a study;	○ Broad study consent ○ PEDSnet Steering Committee	PEDSnet Data Committee	Datavant	○ Last name ○ First name ○ First initial of first name ○ Sex ○ DOB ○ Zip3 ○ Soundex of first name ○ Soundex of last name	PEDSnet Data Coordinating Center (DCC) as the honest broker The honest broker may be an external entity for out-of-network linkages, depending on the study	PEDSnet DCC	Study-specific linkage model	Enclave	Section 11.2.1.6

	Record Linkage Implementation	Datasets Linked	Authorization (Consent/IRB/Other) for			PPRL Tool	PII Elements Used for PPRL	Entity Resolution (Matching) Performed by	Data Linking Performed by	Data Linkage Model[mm]	Data Access Model[nn]	Additional Information Link
			Record Linkage	Sharing Linked Data	Accessing Linked Data							
		treatments, visit payer, lab test results, and medications. Several linkages have been done with health plans, disease specific registries, vital statistics, and geocoded data.	PEDSnet sites decide whether to participate in linkage on a study-by-study basis.									
7	CDC/The Childhood Obesity Data Initiative (CODI)	Colorado child health data from: ○ Denver Public Health & Hospital Authority ○ Children's Hospital Colorado ○ Kaiser Permanente Colorado ○ Girls on the Run of the Rockies ○ Hunger Free Colorado CODI expanded in 2020 to include a North Carolina cohort including clinical and community data in the Triangle region from health care, local/state health departments, and community-based organizations in North Carolina.	○ Data partners agree to linking data within the CODI network via the Master Sharing and Use Agreement (MSUA) ○ IRB approval ○ CHORDS Research Council approves data linkage study request.	○ Data partners agree to share linked data within CODI network via the Master Sharing and Use Agreement (MSUA)	○ Master Sharing and Use Agreement (MSUA)	AnonLink	○ First name ○ Last name ○ Date of birth ○ Sex ○ Phone number ○ Household street address ○ Zip code	CODI Data Coordinating Center (DCC)	CODI Data Coordinating Center (DCC)	Study-specific linkage model	Controlled	Section 11.2.1.7

11.2.1.1 The Biomedical Research Informatics Computing System (BRICS) Instances: NINDS/Parkinson's Disease Biomarker Program, NIA, NEI, NCATS/GRDR, NINR/cdRNS, FITBIR

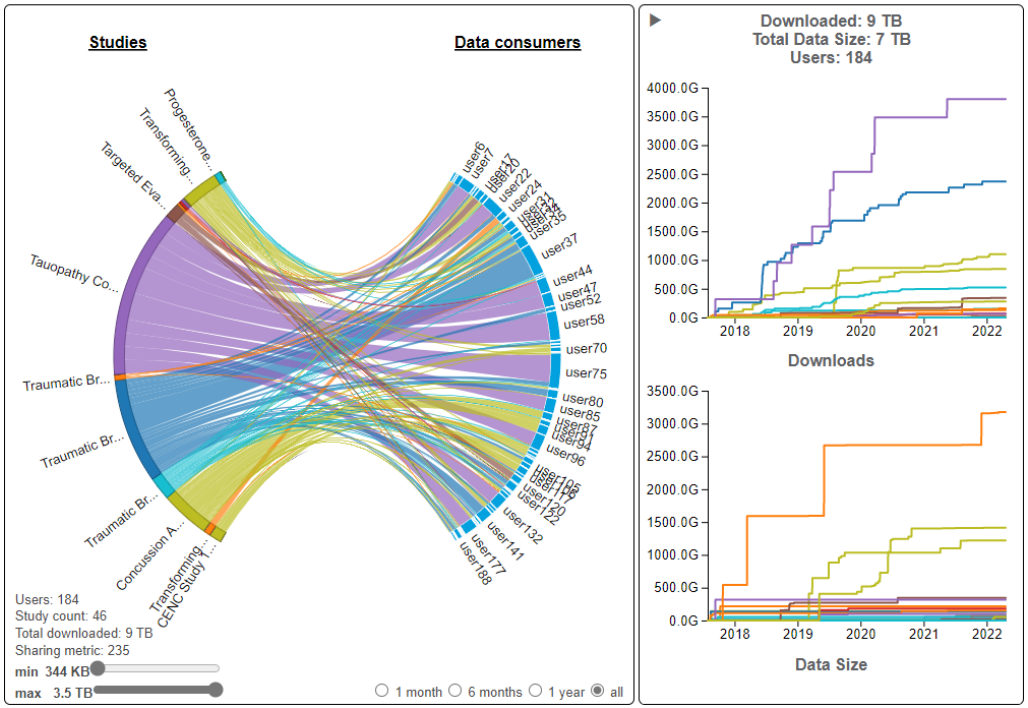
- ***Description***[69]: The NIH Biomedical Research Informatics Computing System (BRICS) is a collaborative and customizable bioinformatics repository designed to efficiently collect, validate, harmonize, and analyze research datasets. BRICS was designed to address the wide-ranging needs of several biomedical research programs[70]. The overall concept was to develop services that could be integrated and deployed as instances for individual research programs. De-identification of each patient within a research study is supported by the use of a Global Unique Identifier (GUID). It is a de-identification tool developed for researchers to use prior to submission of data to a specific BRICS instance. With the implementation of the BRICS GUID tool[71], researchers can have access to data across studies, without revealing personally identifiable information (PII), while correlating study data across different studies and uniquely sorting across distinct and redundant datasets. At this time, BRICS does not link with external genomic data repositories such as the database of Genotype and Phenotype (dbGaP), but it does link with the NINDS biorepository, Biospecimen Exchange for Neurological Disorders (BioSEND).
- ***Data sources***[72]: Data sources depend on the instances.
    - In the BRICS Centralized GUID server solution[71,73] used by multiple instances below, the source of data is from studies conducted by the respective institutes/program:
        - The National Institute of Neurological Disorders & Stroke (NINDS), Parkinson's Disease Biomarkers Program (PDBP), and the National Institute of Aging (NIA)[74]
        - The National Eye Institute (NEI)[75]
        - The Global Rare Diseases (Patient Registry) Data Repository (GRDR) at the National Center for Advancing Translational Sciences (NCATS)[76]
        - The Common Data Repository for Nursing Science (cdRNS) at National Institute of Nursing Research (NINR)[77]
    - In the Federal Interagency Traumatic Brain Injury Research (FITBIR) instance[78], the source of data is from the traumatic brain injury (TBI) studies funded by the DoD and NIH.
- ***Data types***[69]: Variety of data from BRICS instances which includes clinical, genetic, phenotypic, biospecimen, and medical imaging data.
- ***Linkage agreements***:
    - *Submission*: Each data submitter must agree to linkage via the use of GUID as part of the data submission requirements of each of the respective repository. For example: the NINR cdRNS[79] and the FITBIR[80] data sharing policies states the GUID is a unique code that allows linkage of all submitted information on a single participant, giving researchers access to information that may have been collected elsewhere. Both programs also expect that an Institutional Review Board (IRB) and/or Privacy Board has verified that the submission is consistent with informed consent, that the data are de-identified according to the respective repository standards, risk to the study population has been considered, and the data were collected in a manner consistent with NIH/DOD regulations, but the IRB is not asked to sign the Submission Request.
    - *Access/Use*: Linkage of data between the data sources are performed by the researchers who are interested in using the data[81]. They must first obtain approval from the Data Access Committee (DAC) of the respective study/program to access the data, and then they perform the linkage using the subject-level GUID[72].

- ***Entity resolution***: Performed by each instance's GUID server.
    - *Standardization/pre-processing of PIIs*[82]: Instructions regarding *required* PII elements to ensure that a valid GUID is created include:
        - The "Last Name" field must contain the family name given at birth, prior to legal name change, or marriage. If there is any doubt as to the original legal name at birth, refer to the information on the birth certificate. Name suffixes such as "Jr.," "Sr.," "III," etc. should be ignored.
        - If the participant's "First Name" is a compound name, such as Anne Marie, or Jose- Luis, it may be unclear whether the second part of the compound is a first name or a middle name. In such cases, use the first name as you would report it on other records, such as school transcripts, or credit card billing statements. If in doubt, refer to the birth certificate.
        - If the participant does not have a "Middle Name" (known not to have a middle name at birth), leave this field blank and respond "No" when asked if the individual has a middle name. The GUID Software has a selection to accommodate this possibility. If in doubt, refer to the birth certificate.
        - If the "City or Municipality of Birth" has undergone a name change during a participant's lifetime, use the name of the city at the time of the participant's birth. Examples of this are Peking / Beijing, or Bombay / Mumbai. Again, if there is any doubt, refer to the birth certificate.

      The following PII fields are optional:
        - Physical sex of subject at birth
        - Government-issued or National ID (i.e., SSN) (No one has provided government issued ID to date.)
        - Country issuing government-issued or National ID
        - Organization/cohort association (for example, PDBP)
    - *GUID generation process*[73]: Each instance of BRICS is connected to a BRICS GUID server to generate GUIDs. An instance of BRICS either uses a centralized GUID server called the Multi-tenant GUID Solution (example: NINDS) or has its own GUID server (example: FITBIR). Each instance of the GUID server has a different salt. The centralized GUID server salt is consistent across studies within that instance.
        - Researchers within BRICS instances log into the GUID client on their local computers and enter in subject PII.
        - The GUID client (on local computers) uses PII to derive a series of one-way hashes which securely encrypt PII information.
        - The one-way hashes are sent to the GUID server for reference and storage. No PII is sent to the server.
        - The GUID server returns a GUID identifier. If the one-way hashes match an existing GUID identifier, an existing GUID will be returned. If this is a new subject, a new GUID will be returned.
    - *GUID quality assessment*[73]: Some hash codes leave out one PII element which allows the GUID system to determine if there is a close match. If the hashes are the same other than the one PII element, the system can notify the user to check if the PII was entered incorrectly. The quality is also validated during the data entry at the client site, which includes practices such as checking that the months are between 1-12 and day is between 1-31. In the GUID interface, data has to be entered twice to confirm validation. Currently, data pre-processing in BRICS does not include breaking out syllables within names prior to hashing to facilitate "fuzzy matching" of names (e.g., Soundex).
    - *Hash/GUID storage and destruction procedures*[73]: The one-way hashes are sent from the BRICS instances to the NIH GUID server for reference and storage. The hashes are stored in an encrypted database. The hashes are not shared and cannot be accessed except potentially by BRICS developers. Withdrawal of consent leads to the destruction of hashes and GUIDs. If subjects no longer consent to their data being shared, the

GUID and the associated hashes are removed from system. The study or program officers must inform BRICS to remove the GUIDS associated with the patient and the associated hashes will be removed.

- ***Data Linkage***[73,75]: BRICS facilitates the linkage of data by adding the GUID to the records associated with each subject, which allows researchers to distinguish between unique subjects and recurrent subjects across datasets. BRICS databases can support data queries (cohort discovery) and link data with GUIDs both within a study (by linking the data from different forms/datasets) or between different studies (such as between different FITBIR studies). The BRICS system does not track all queries since they are often refined. However, all downloads of data from the query tool are audited and recorded (e.g., Visualization | FITBIR (nih.gov); see figure below). In this example usernames are masked but the System Administrators can identify actual users as well as metrics including what data was download from each study. In addition, each owner of a study can download a report of who has accessed their study data.



Presently, the instances do not directly communicate with each other; a GUI/interface can only query within an instance of BRICS. However, when a common GUID server is used between two instances, a user could manually see if participants match. They would first have to get DAC approval and download the data from the two different instances. There are programmatic ways of doing this, but presently the GUI/interface does not provide the

ability to query across different instances. However, the foundational infrastructure has already been developed (query and download APIs) and is included in the BRICS system. Extending the BRICS query tool to query across instances is very possible and is not a massive level-of-effort.

- *Process*:
  1. Once the researcher has a GUID, they may submit data associated with this subject. No data may be submitted to the system without a GUID.
  2. Once data are in the database, a researcher may query this data. The GUID allows researchers to distinguish between unique subjects and recurrent subjects across all datasets (i.e., studies).
  3. Researchers access data across different studies from within their instances, without revealing PII, while correlating study data across different studies *and* uniquely sorting between distinct and redundant datasets.

- ***Sharing and accessing linked data—authorizations/agreements/approvals***:
  - *De-identification status of shared data*: As per NINR/cdRNS policy[79] and FITBIR[80] policy, data submitted to BRICS/NINR or FITBIR will be de-identified such that the identities of data subjects cannot be readily ascertained or otherwise associated with the data by the BRICS/cdRNS or FITBIR staff or secondary data users.
  - *Authorization for sharing linked data*[72]: User and their institution agree to the terms of data submission, which specifically addresses linkage via use of the GUID; no explicit language for linking or use of GUID in the informed consent.
  - *Deductive disclosure review*[81]: Deductive disclosure review of linked data is not currently done by the programs. The researcher links the datasets after obtaining approval for access from the respective program's data access committees. The programs do not track the linkage. However, each program requires that approved users agree to a Data Use Certification (DUC), which explicitly prohibits re-identification of study participants. For example, the FITBIR DUC[83] states, "Recipient agrees that data will not be used, either alone or in conjunction with any other information, in any effort whatsoever to establish the individual identities of any of the subjects from whom data were obtained." Also, the DUC states the potential requirement for an IRB approval from the user's institution: "If Recipients request access to data on individuals for whom they themselves have previously submitted data to FITBIR, they may gain access to more data about an individual participant than they themselves collected. Consequently, these research activities may be considered "human subjects research" and may require that they obtain institutional IRB approval of their Research Project."
  - *Approvals/agreements for accessing linked data*[72]: Approval for access from the respective program's data access committees.

11.2.1.2 National Institute of Mental Health (NIMH) Data Archive (NDA)

- ***Description***[84]: The National Institute of Mental Health Data Archive (NDA) provides infrastructure for sharing human subjects research data, tools, methods, and analyses, enabling collaborative science and discovery. The NDA is a collection of research data repositories including the NIMH Data Archive (NDA), the Osteoarthritis Initiative (OAI), the Adolescent Brain Cognitive Development (ABCD) data repository, and the National Institute on Alcohol Abuse and Alcoholism Data Archive ($NIAAA_{DA}$). The NDA infrastructure was established initially to support autism research but has grown into an informatics platform that facilitates data sharing across all of mental health and other research communities, making data available from each of these repositories combined into a single resource with a single process for gaining access to all shared data.

- ***Data sources***[85]: NDA accepts human subjects research data related to mental health and other NIH-funded scientific domains. All NIMH-funded researchers performing human subjects research are required to submit data to NDA as per the 2019 NIMH Data Sharing Policy[86]. In addition, any researchers who have acquired high-quality research data appropriate to an NDA-supported research cluster may request to submit data, regardless of funding source and location.
- ***Data types***[85]: Clinical, phenotypic, genomic/pedigree, neuroimaging, and other neurosignal recordings data on human subjects.
- ***Linkage agreements***[87]: All data submitters to the NIMH Data Archive must agree to the following as per the NIMH Data Archive Data Submission Agreement:
    - "Submitter agrees to collect the information required to generate a Global Unique Identifier (GUID) for all research participants, using software provided by the NIMH Data Archive (https://nda.nih.gov/s/guid/nda-guid.html),"
    - "Submitter may use the NIMH Data Archive GUID Tool to generate pseudoGUIDs if their IRB determines that the information required to create a GUID may not be collected from research participants. Submitter agrees to submit all subject data to the NIMH Data Archive with a GUID or pseudoGUID."
    - "Submitter acknowledges that data are submitted to the NIMH Data Archive in accordance with informed consent of research participants and/or with the approval of the IRB."
    - The Agreement specifies linkage via GUID: "NDA GUID allows the NIMH Data Archive to link together all submitted information on a single participant, giving authorized researchers access to information even if the data were collected at different locations or through different studies".
    - "Submitter agrees that data and Supporting Documentation submitted to the NIMH Data Archive may be accessed and *used broadly* by approved users for research and other activities as authorized by and consistent with law."
    - The Policy[88] for the NIMH Data Archive (NDA) also expects that the data submission is consistent with consent where feasible:
        - "For prospective studies, in which data sharing through the NDA is conceived within the study design at the time research participants provide their consent, the NIMH expects specific discussion within the informed consent process and documentation that participant's data will be shared for research purposes through the NDA. For retrospectively collected data, the NIMH anticipates considerable variation in the extent to which data sharing and future research have been addressed within the informed consent documents; therefore, the NIMH expects the submitting institution to determine whether a retrospective study is appropriate for submission to the NDA (including an IRB and/or Privacy Board review of specific study elements, such as participant consent)."
- ***Entity resolution***:
    - *Standardization/pre-processing of PIIs*[89]: The following information is required to create a GUID and should be recorded exactly as it appears on the birth certificate, to ensure that it does not change over the course of the participant's life:
        - First Name
        - Middle Name
        - Last Name
        - Sex

- Date of Birth
- City/Municipality of Birth

If adequate information is not available to fully create a valid GUID, a pseudoGUID[90] can be created. This is a random ID that can be used as a placeholder where this information is not available, and "promoted" to a real GUID when the information is obtained at a future date.

- *GUID generation process*[89]: Performed by the GUID system at NDA:
  1. An authorized member of the research project team (user) with an active Data Submission Agreement may request access to and then download the NDA GUID Tool on a local computer[91]. Third-party NDA GUID Tool requests must be submitted by an NDA user with an active NDA account and an authorized Signing Official (SO) from that user's institution and are reviewed on a case-by-case basis. All NDA GUID Tool users must agree to the terms of use for the tool.
  2. The user enters participant PII into the tool.
  3. The tool generates a series of one-way hash codes based on the PII entered, without the PII ever leaving the computer.
  4. The one-way hash codes are encrypted and securely sent to the GUID system at NDA.
  5. If the hash codes match an existing hash code, the GUID associated with that existing hash code is sent back to the researcher. The GUID is an alphanumeric code that is randomly and persistently linked to the hash codes within the secure NDA GUID system and cannot be traced back to the PII entered by the research project team member.
  6. If the hash codes do not match an existing hash code in the NDA GUID system, a new GUID is created and sent back.
- *GUID quality assessment*[92]: The hash codes generated by the algorithm depend on the spelling of the words (PII) entered, so there's no way to account for/predict typos or data entry errors. To address possible data entry errors, it is possible to reconcile GUIDs at a later date[93]. Occasionally, the submitted hashes will closely (but not exactly) match the hashes of an existing GUID subject. This situation primarily occurs when working with twin research subjects who have differing first names beyond the first letter. When this happens, the tool will prompt the user (data originator) to indicate whether it should use the existing GUID or create an entirely new GUID. Generally, unless the user knows for certain that the subject is truly a different person, e.g., as in the twin example, they should choose to "Create New GUID."[92]
- *Hash/GUID storage and destruction procedures*[89]: The hashing algorithm is run inside the NDA GUID Tool software that researchers must run on their own computer. The PII input into the NDA GUID Tool never leaves the researcher's local environment. Instead, one-way hashes are securely transmitted to the NDA cloud database, which uses the same secure transmission protocol (via a secure web service) to return random alphanumeric strings called GUIDs. GUIDs and their matched hash codes are stored in the secure database maintained by NDA's security team in the Amazon cloud. Additional information is available at GUID Tool Terms of Use.

- ***Data linkage***[94]: NDA facilitates the linkage of data by adding the GUID to the records associated with each subject, which allows the NDA to associate a single research participant's genomic, imaging, clinical assessment, and other information even if the data were collected at different locations or through different studies. The GUID is then used as the primary participant identifier in data submissions. The GUID allows researchers to distinguish between unique subjects and recurrent subjects across all datasets. Linkage of data is performed by researchers who have approval from the NDA Data Access Committee to access the datasets.

- ***Sharing and accessing linked data—authorizations/agreements/approvals***:
    - *De-identification status of shared data*[88]: As per NDA policy, data submitted to NDA will be de-identified such that the identities of data subjects cannot be readily ascertained or otherwise associated with the data by the NDA staff or secondary data users.
    - *Authorization for sharing linked data*[87]: Based on the required data submission agreement provided by the submitter: "Submitter agrees that data and Supporting Documentation submitted to the NIMH Data Archive may be accessed and *used broadly* by approved users for research and other activities as authorized by and consistent with law." Example informed consent language that addresses the use of the GUID is available; however, it is not confirmed whether such language is used as part of the data submission.
    - *Deductive disclose review*: Deductive disclosure review of linked data is not currently done by the program. The researcher links the datasets after they obtain approval for access from NDA. The approved users must agree to a Data Use Certification (DUC) [95], which explicitly prohibits re-identification of study participants. The DUC states, "Recipient agrees that data will not be used, either alone or in conjunction with any other information, in any effort whatsoever to establish the individual identities of any of the subjects from whom data were obtained that data will not be used to attempt to establish the individual identities of any of the study participants from whom data were obtained (or their relatives)."
    - *Approvals/agreements for accessing linked data* [93,95] : Access to linked data require approval from the Data Access Committee and may require IRB approval of the Research DUC. The NDA DUC prohibits users from re-identifying the study participants from whom data were obtained. Researchers who submitted data to NDA may have access to personal identifying information for research participants in the original study at their institution and therefore their use of NDA data from other studies with the same participants may be considered "human subjects research" and subject to IRB approval. The NDA DUC states: "If Recipients access data on individuals for whom they, themselves, have previously submitted data to the NIMH Data Archive, Recipients may gain access to more data about an individual participant than they, themselves, collected. Consequently, these research activities may be considered "human subjects research" within the scope of 45 C.F.R. 46. Recipients must comply with the requirements contained in 45 C.F.R. 46, as applicable, which may require IRB approval of the Research Data Use Statement."

11.2.1.3 National COVID Cohort Collaborative (N3C) EHR Data Linkage

[*Linked data from this implementation is not yet available to users*]

- ***Description***[96]: The N3C Data Enclave is a centralized, secure, national clinical data resource with powerful analytics capabilities that the research community can use to study COVID-19, including potential risk factors, protective factors, and long-term health consequences. The N3C collects data derived from the electronic health records (EHRs) of people who were tested for COVID-19 or who had related symptoms, as well as data from individuals infected with pathogens that can support comparative studies, such as SARS1, MERS and H1N1. *EHR to EHR data linkages are not yet available to users*.
- ***Data sources***[96]: Participating institutions (also called "N3C data partners") release EHR data to N3C under the HIPAA Privacy Rule that allows medical and health care institutions to release data for research without obtaining an individual's authorization if direct identifying information is removed and appropriate oversight and agreements are in place. Under the HIPAA Privacy Rule requirements, these institutions can release what is called a limited data set to N3C. As of September 2022, the N3C enclave hosts EHRs from over 15.5 million patients.

- ***Data types***[97]: The EHR data in N3C include demographics, symptoms, lab test results, procedures, medications, medical conditions, physical measurements.
- ***Linkage agreements***[65]: Participation in PPRL is voluntary for N3C data partners. Data partners who choose to participate in PPRL must do the following:
    - Agree and sign the Datavant software license agreement
    - Agree and sign the Linkage Honest Broker (LHB) Agreement (LHBA)[98]. The LHB for N3C is Regenstrief and the LHBA provides terms and conditions for data linkage and outlines the general terms of data use. Institutions do not need to sign the LHBA (i.e., participate in PPRL) in order to contribute data.
    - Send the de-identified tokens and Pseudo ID[oo] to the LHB and the Pseudo ID to the N3C along with data payload.
- ***Hashed token generation by data partners using Datavant tool***:
    - *Standardization/pre-processing of PIIs*[99]: Data partners collect data in various data models (OMOP, TRINETX, PCORnet, ACT, FHIR etc.); hence, the PII elements collected by individual data partners are standardized.
    - *Hash/token generation*[100]: Performed by N3C data partners who have signed the LHBA and installed Datavant at their institutions. Datavant tokens are generated using cryptographic hash functions, specifically with SHA-256, one-way, irreversible cryptographic hash function from identifiable information. Datavant tokens are certified under the Expert Determination Standard in the HIPAA Privacy Rule.
    - *Token storage and destruction procedures*[65]: The N3C de-identified tokens are held separately from data residing within the N3C data enclave. The LHB is a neutral entity located outside of the N3C enclave that serves as an escrow for the cryptographic hash codes (tokens). Token storage and destruction is defined by the agreement between LHB and N3C[101]. The destruction agreement assures a standard process for receiving, reviewing, authorizing, executing, and confirming a token data destruction request for the LHB system. The requesting party must submit a written request to an authorized NCATS official who will first verify that the request is appropriately scoped to the token data pertaining to the requesting party and will then honor the party's request and will submit an LHB Token Destruction Form to the LHB to execute the destruction. Once destroyed by the LHB, the authorized NCATS official will inform the requesting party.
- ***Entity resolution & data linkage***[100]: Entity resolution is performed by the LHB, and data linkage is done within N3C enclave by requesting researchers. Entity resolution/deduplication across all participating EHR datasets is a requirement for any institution that participates in the LHBA because of its importance to the data quality of the N3C data enclave and its scientific mission. However, *access to deduplicated EHR records across N3C is not yet available*.
    - *Process*[100]: N3C performs entity resolution builds on a weekly basis.
        1. Data partners send a randomly generated Pseudo ID (=PAT_ID = Source ID) and the cryptographic hashes/tokens to LHB (Regenstrief).
        2. N3C enclave receives EHR data payload with the Pseudo IDs (=PAT_ID = Source ID) from data partners.
        3. When the N3C enclave receives the data payload from a data partner, an N3C_ID is assigned.
        4. The N3C_ID together with the site's randomly generated ID for a specific record (=Pseudo ID = PAT_ID = Source ID) are sent by the N3C data enclave to LHB.

[oo] Pseudo ID is the de-identified subject ID used in the data by the data partners for sharing. It is also referred to as PAT_ID or Source ID.

5. LHB runs Datavant matching algorithms and generates a MATCH_ID[pp] which represents the records that should be linked (linkage map).
6. When a user is approved for access to the Limited Data Set level, the N3C enclave provides the linkage map (with MATCH_ID, N3C_ID, Site ID, and Pseudo ID) and data in the researcher's private workspace in the N3C enclave. The user accesses the datasets for an individual participant based on the linkage map. [Note: N2C provides *all* of the EHR data available in N3C to the users along with the linkage map; no removal of duplicate records across sites is performed.]

- *Linkage/matching quality assessment*[101]: A linkage quality assessment report is being prepared by N3C. In general, the linkage quality measures will depend on the linkage use case—for example: the linkage quality for EHR data linkage is stringent to support academic research but could be less stringent for recruitment use cases (what N3C calls "cohort discovery")

- ***Sharing and accessing linked data—authorizations/agreements/approvals***:
  - *De-identification status of shared data*[102]: PPRL-linked data are Level 3 (limited dataset), where 16 of 18 HIPAA identifier have been removed; data retains dates and zip codes.
  - *Authorization for sharing linked data*[103]: N3C participating institutions do not obtain consent from individual patients for the data they send to the N3C. The 1996 HIPAA Privacy Rule allows medical and health care institutions to release data for research without obtaining an individual's authorization if direct identifying information is removed and appropriate oversight and agreements are in place. Under the HIPAA Privacy Rule requirements, data partners can release what is called a limited dataset. This is what participating health sites send to the N3C.
  - *Deductive disclosure review* currently not being done at N3C[101]; however, access to PPRL-linked EHR data will be made available for users who have approval for accessing HIPAA Limited Data Set (which is a Level 3). Accessing the HIPAA limited dataset requires a letter of determination from the data requestor's IRB in addition to and other requirements for access (see below).
  - *Agreements/approvals for accessing linked data*[102]:
    - Technical data privacy controls: Linked data is provisioned in a private workspace within the N3C enclave
    - Non-technical data privacy controls: The following non-technical controls are in place for accessing the linked level 3 data:
      - Data Use Request (DUR) with justification to access the linked data, approved by N3C Data Access Committee
      - Signed institutional Data Use Agreement (DUA) executed with NCATS
      - Institutional IRB Letter of determination (LOD)
      - Attestation to: N3C Code of Conduct, IT security training, and human subjects protection training

11.2.1.4 N3C Class 0—External Data Linkage

[*Linked data from this implementation is not yet available to users*]

- ***Description***[96]: The N3C Data Enclave is a centralized, secure, national clinical data resource with powerful analytics capabilities that the research community can use to study COVID-19, including potential risk factors, protective factors and long-term health consequences. The N3C collects data derived from the EHRs of people who were tested for COVID-19 or who had related symptoms, as well as data from individuals infected with pathogens

[pp] Also referred to as N3C_GUID, N3C_HDB_MATCH_ID, Linked_ID

that can support comparative studies, such as SARS 1, MERS and H1N1. N3C facilitates the linking of external datasets with EHR data available in the N3C enclave using PPRL to generate a richer dataset that can answer new questions about COVID-19. The details below specifically pertain to PPRL linkage with external Class 0 datasets that originate from *different* enclaves and allows for a temporary extension of the N3C Data Enclave in the form of an ephemeral workbench to accommodate this requirement[65]. A current example of a Class 0 linkage is with imaging data from the Medical Imaging and Data Resource Center (MIDRC). Class 0 data linkage is not yet available to users.

- ***Data sources***[97]: EHR data in the N3C enclave (submitted by N3C data partners) and imaging data from external data repositories, such as imaging data in MIDRC
- ***Data types***[97]: EHR data in N3C (including demographics, symptoms, lab test results, procedures, medications, medical conditions, physical measurements) and external individual-level data, such as imaging data.
- ***Linkage agreements***[65]: Authentication of Class 0 data linking is at the NIH level. An interconnect agreement is required between N3C and the enclave from where the external datasets are used for Class 0 linkage. For N3C data partners—participation in PPRL is voluntary, and linkage of EHR data with external datasets is limited to only those N3C data partners who are participating in PPRL[100]. Each PPRL participating data partner has the option to choose which type of data linkage they want to participate in—that is, they can choose whether or not to permit linking their EHR data with external data such as imaging data. Participating sites can, at any time, update their participation in linkage of multiple datasets by changing their setting of institutional parameters within N3C via a web interface dashboard[100]. Individual data partners can only see their linkage permissions in the dashboard. N3C data partners who choose to participate in PPRL with external datasets must comply with the following:
    - Agree and sign the Datavant software license agreement
    - Agree and sign the Linkage Honest Broker (LHB) Agreement (LHBA)
    - Send the Pseudo_ID to the LHB and N3C (along with the data payload)
    - Agree to link to the given external dataset via the PPRL Site Permissions Dashboard
- ***Hashed token generation***:
    - *Standardization/pre-processing of PIIs*[99]: N3C data partners collect data in various data models (OMOP, TRINETX, PCORnet, ACT, FHIR etc.); hence, the PII elements collected by individual data partners are standardized.
    - *Hash/token generation*[100]: Both the N3C data partners (who are participating in PPRL) and external data stewards, such as MIRDC, generate hashed tokens using the Datavant tool installed on a local server. Datavant tokens are generated using cryptographic hash functions, specifically with SHA-256, one-way, irreversible cryptographic hash function from identifiable information. Datavant tokens are certified under the Expert Determination Standard in the HIPAA Privacy Rule.
    - *Token storage and destruction procedures*[65]: The N3C de-identified tokens are held separately from data residing within the N3C data enclave. The LHB is a neutral entity located outside of the N3C enclave that serves as an escrow for the cryptographic hash codes (tokens). Token storage and destruction is defined by the agreement between LHB and N3C. The destruction agreement assures a standard process for receiving, reviewing, authorizing, executing, and confirming a token data destruction request for the LHB system. The requesting party must submit a written request to an authorized NCATS official who will first verify that the request is appropriately scoped to the token data pertaining to the

requesting party and will then honor the party's request and will submit an LHB Token Destruction Form to the LHB to execute the destruction. Once destroyed by the LHB, the authorized NCATS official will inform the requesting party.

- ***Entity resolution/data linkage***[100]:
    - Entity resolution performed by the LHB, based on tokens received from the N3C data partners and external data stewards, and when requested by N3C enclave based on two criteria:
        - The data partner whose EHR data are being linked has provided the permission to link with imaging data
        - The 'linkage requesting researcher' has been approved by N3C enclave to access the linked data
    - Linked database model: Data linkage performed by N3C enclave encompasses all participating datasets.
    - *Process*[101]:
        1. Data partners send the Pseudo ID and the hashed tokens to LHB for EHR data
        2. External data steward (MIRDC) also sends their MIRDC Pseudo ID and the hashed tokens to the LHB
        3. When the N3C enclave receives the EHR data payload from a data partner, an N3C_ID is assigned
        4. The N3C_ID and the Pseudo IDs for the EHR data and the Class 0 data are sent by the N3C enclave to LHB. The LHB runs Datavant matching algorithms and generates a MATCH_ID[qq] (unique de-duplicated ID) that maps to N3C Pseudo ID and external (MIRDC) Pseudo ID; the linkage map represents the records that should be linked.
        5. When a user is approved for access to the Limited Data Set level, the N3C enclave provides the linkage map (with MATCH_ID, N3C_ID, Site ID, and Pseudo IDs) and the respective data in a secure ephemeral workbench, which is a temporary virtual workspace. The workbench is ephemeral because it is short-lived for a specific task and then destroyed when the user's work is completed. [Note: N3C provides all of the EHR and Class 0 data available in N3C to the users along with the linkage map; no removal of duplicate records across sites is performed.]
    - *Linkage/match quality assessment*: A linkage quality assessment report is being prepared by N3C.
- ***Sharing and accessing linked data—authorizations/agreements/approvals***:
    - *De-identification status of linked data*[102]: PPRL linked N3C and external data such as imaging data are classified by N3C as Level 3 limited dataset (LDS), which consists of patient data that retain the dates of service and patient ZIP code.
    - *Authorization for sharing linked data*[103]: Participating institutions do not obtain consent from individual patients for the data they send to the N3C. The 1996 HIPAA Privacy Rule allows medical and health care institutions to release data for research without obtaining an individual's authorization if direct identifying information is removed and appropriate oversight and agreements are in place. Under the HIPAA Privacy Rule requirements, data partners can release what is called a limited data set. This is what participating health sites send to the N3C. For external Class) data, an interconnect agreement must be established for (linking and) sharing data.
    - *Deductive disclosure review*[104]: Prior to approving each external dataset, re-identification risk is assessed during the technical integration call by the Tools and Resources Review Committee comprised of federal employees from NCATS, the N3C community, and the Information Systems Security Officer.

[qq] Also referred to as N3C_GUID, N3C_HDB_MATCH_ID, Linked_ID

- *Agreements/Approvals for accessing linked data*[100]:
  - Technical data privacy controls: Linked data are provisioned in a temporary ephemeral workbench within N3C
  - Non-technical data privacy controls: The following non-technical controls are in place for accessing the linked level 3 data:
    - DUR with justification to access the linked data, approved by N3C Data Access Committee
    - Signed institutional DUA
    - Institutional IRB Letter of determination (LOD)
    - Attestation to: N3C Code of Conduct, IT security training, and human subjects protection training
    - Interconnect agreement between N3C and the external data system

11.2.1.5 N3C Class 2 External Data Linkage

- ***Description***[96]: The N3C Data Enclave is a centralized, secure, national clinical data resource with powerful analytics capabilities that the research community can use to study COVID-19, including potential risk factors, protective factors and long-term health consequences. The N3C collects data derived from the EHRs of people who were tested for COVID-19 or who had related symptoms, as well as data from individuals infected with pathogens that can support comparative studies, such as SARS 1, MERS and H1N1. N3C facilitates the linking of external datasets with EHR data available in the N3C enclave using PPRL to generate a richer dataset that can answer new questions about COVID-19. The details below specifically pertain to PPRL linkage with two examples of external data linkages that fall under Class 2 and are currently performed within N3C—viral variant data and mortality data[100].
- ***Data sources***[100]: EHR data in the N3C enclave (submitted by N3C data partners) and the following external datasets:
  - *Viral variant data*: Collected by N3C data partners but stored in NIH's National Center for Biotechnology Information (NCBI) Sequence Read Archive (SRA); currently only viral variant summary data provided by the N3C data partners are linked. When the viral variant sequence data use case is ready, it will be imported into N3C.
  - *Mortality data*: The mortality data sources include government mortality sources (death certificates and person-reporting), ObituaryData.com, and private obituary sites
- ***Data types***[100]: EHR data in N3C (including demographics, symptoms, lab test results, procedures, medications, medical conditions, physical measurements), viral variant summary data (currently; sequence data will be available later), and mortality/death date
- ***Linkage agreements***[65]: N3C authorizes the linkage of Class 2 datasets. For N3C data partners, participation in PPRL is voluntary, and linkage of EHR data with external datasets is limited to only those N3C data partners who are participating in PPRL[65]. Each PPRL participating data partner has the option to choose which Class 2 datasets their EHR data can link to—for example: they can choose to permit linking their EHR data with viral variant and/or mortality data. Participating sites at any time can update their participation in linkage of multiple datasets by changing their setting of institutional parameters within N3C via a web interface dashboard[100]. Individual data partners can only see their linkage permissions in the dashboard. Data partners who choose to participate in PPRL with external datasets must agree to the following:
  - Agree and sign the Datavant software license agreement
  - Agree and sign the Linkage Honest Broker (LHB) Agreement (LHBA)

- Agree to send the de-identified tokens and Pseudo ID[rr] to the LHB and the Pseudo-ID along with the EHR data to N3C
- Agree to link to the given external dataset PPRL Site Permissions Dashboard

- ***Hashed token generation***:
  1. *For viral variant summary data linkage*[105]: Because the viral variant summary data are collected by N3C data partners for their cohort of COVID-19 patients, hashing is performed by the N3C data partners who are participating in PPRL using the Datavant tool. The details are, therefore, similar to what is described above in N3C EHR data linkage section (11.2.1.3).
  2. *For mortality data linkage*: N3C data partners who are participating in PPRL generate the hashed tokens for EHR data as described in N3C EHR data linkage section (11.2.1.3). An external party engaged by N3C aggregates mortality data from government and private sources and generates hashed tokens using PII elements.
- ***Entity resolution***[100]:
  - *Process*: Performed by LHB based on (1) tokens received from the N3C data partners for viral variant summary data linking and from N3C for mortality data linking, and (2) when requested by N3C enclave based on two criteria:
    - The data partner whose EHR data are being linked has provided the permission to link with viral variant and/or mortality data
    - The linkage-requesting researcher has been approved by N3C enclave to access the linked data
  - *Linkage/match quality assessment*: A linkage quality assessment report is being prepared by N3C.
- ***Data Linkage***[100]: Linked database model encompassing all participating datasets. Performed by N3C enclave; below is the process:
  1. Data partners send Pseudo ID along with their EHR data payload to N3C and set permissions for EHR data linkages with external datasets within N3C dashboard (web interface).
  2. When the N3C enclave receives the EHR data payload from a data partner, an N3C_ID is assigned.
  3. For viral variant data: Data partners send the following to N3C for viral variant data[105]: a crosswalk between the local specimen ID and the N3C_ID, and the viral variant summary data.
  4. N3C data partners send the Pseudo ID and the hashed tokens for the EHR data to the LHB. For mortality data: The external party engaged by N3C sends the hashed tokens to the LHB.
  5. N3C enclave sends the N3C_ID and the Pseudo ID for the EHR data to LHB.
  6. LHB runs Datavant matching algorithms and generates a MATCH_ID that maps to Pseudo IDs; the linkage map represents the records that should be linked
  7. When a user is approved for access to the Limited Data Set level, the N3C enclave provides the linkage map (with MATCH_ID, N3C_ID, Pseudo ID, and Site ID) and the respective data in a secure private workspace. [*Note*: N3C provides *all* of the EHR and Class 2 data available in N3C to the users along with the linkage map; no removal of duplicate records across sites is performed.]

[rr] Pseudo ID is the de-identified subject ID used in the data by the data partners for sharing. It is also referred to as PAT_ID or Source ID.

- ***Sharing and accessing linked data—authorizations/agreements/approvals***:
  - *De-identification status of the shared data*[102]: Linked viral variant data and mortality data are classified as Level 3 limited dataset, which consists of patient data that retain the dates of service and patient ZIP code.
  - *Authorization for sharing linked data*[103]: Participating institutions do not obtain consent from individual patients for the data they send to the N3C. The 1996 HIPAA Privacy Rule allows medical and health care institutions to release data for research without obtaining an individual's authorization if direct identifying information is removed and appropriate oversight and agreements are in place. Under the HIPAA Privacy Rule requirements, data partners can release what is called a limited dataset. This is what participating health sites send to the N3C.
  - *Deductive disclosure review*[104]: Prior to accepting Class 2 datasets into the N3C enclave, re-identification risk associated with Class 2 (external) datasets is assessed during the technical integration call by the Tools and Resources Review Committee comprised of federal employees from NCATS, the N3C community, and the Information Systems Security Officer. Additional methods are evoked for certain datasets such as using zip3 instead of zip5 or removal of zip for data from tribal reservations.
  - *Agreements/approvals for accessing linked data*[100]:
    - Technical control: Linked data are provisioned in the researcher's private workspace within N3C
    - Non-technical controls: The following non-technical controls are in place for accessing the linked level 3 data:
      - DUR with justification for to access the linked data, approved by N3C Data Access Committee
      - Signed institutional DUA
      - Institutional IRB Letter of Determination (LOD)
      - Attestation to: N3C Code of Conduct, IT security training, and human subjects protection training

11.2.1.6 PEDSnet

- ***Description***: PEDSnet[106], a national pediatric learning health system, is a large national community of hospitals and healthcare organizations, researchers and clinicians, and patients and families. The PEDSnet community works together to identify the most important research questions that can reduce children's suffering and support their health and well-being.
- ***Data sources***[107]: EHR data from the 11 PEDSnet participating institutions. The sites include Children's Hospital of Philadelphia (lead), Ann & Robert H. Lurie Children's Hospital of Chicago, Children's National Hospital, Children's Hospital Colorado, Cincinnati Children's Hospital Medical Center, Nationwide Children's Hospital, Nemours Children's Health System (both the Delaware and Florida health systems), Riley Children's Hospital, St. Louis Children's Hospital, Seattle Children's Research Institute, Stanford Children's Health, and Texas Children's Hospital.
- ***Data types***[108]: Demographic data, outpatient encounters, inpatient admissions, ER encounters, anthropometrics, vital signs, providers, diagnoses, treatments, visit payer, lab test results, and medications; access to physician notes and other unstructured data such as operative, imaging, and pathology reports.
- ***Linkage agreements***[109]: Linkage is determined by the PEDSnet sites based on the particular use case/research study. When sites sign up to be part of the PEDSnet network, they must agree to hash their data; however, individual PEDSnet study sites can decide whether to participate in data linkages on a

study-by-study basis once the PEDSnet Steering Committee approves the data linkage as part of a specific study research plan. PEDSnet also uses Datavant technology to create deduplicated reports of their data on an annual basis.

- ***Hash/token generation***[109]: Hashes are only generated when a patient is enrolled in a research study conducted by two or more PEDSnet institutions (they are not generated for routine patient care, and they are not stored in a persistent fashion).
    - *Standardization/pre-processing of PIIs*: Study sites collect data in the PEDSnet Common Data Model which is harmonized to the PCORnet Common Data Model; therefore, the PIIs collected by individual data partners are standardized.
    - *Hash/token generation*: Performed by the 11 participating institutions using Datavant.
    - *Hash/token generation success rate*: Hashing success rate is calculated by the Data Coordinating Center (DCC). The success rate is dependent on the PII elements used. The tokens that use last name, first name, sex, and DOB generate the best match with over 93% success rate.
    - *Hash/token storage and destruction procedures*: Hash codes/ tokens are stored at the DCC and destroyed at the end of each specific study; the study sites never access them.
- ***Entity resolution and data linkage***[109,110]: Performed by the PEDSnet DCC for in-network study linkages and annual reports.
    - *Process*:
        1. PEDSnet study sites install Datavant software which uses various PII elements to generate de-identified cryptographic hash codes for each patient.
        2. Study sites send the hash codes and site-level patient IDs to the DCC along with the limited dataset (with dates, zip codes and Census block groups). The DCC never accesses the PII/PHI.
        3. The DCC uses the hash codes to perform entity resolution and generates a Master Patient Index (MPI) for the specific study.
        4. The DCC links data based on the MPI and distributes the linked dataset to the study team using another DCC-assigned patient identifier that is unique for that specific study only; study researchers access the linked data within the PEDSnet enclave.
        5. The MPI is destroyed after the study is completed; there is no persistent PEDSnet wide MPI.
    - *Linkage quality assessment*[109]: For smaller projects: The DCC has validated the linkage in the past by identifying the relevant patient for the study, assembling the case report forms from multiple sites, and sending the patient and case report form information to the respective PEDSnet sites, who will then perform a chart review to ensure the patient is the same. For larger projects: chart review is not feasible; so, linkages must be done more stringently (such as stringent hashing parameters) to ensure quality.
- ***Sharing and accessing linked data—authorizations/agreements/approvals***[34,46]:
    - *De-identified status of shared data*: PII elements are eliminated from data prior to linking. The sites send the hashed codes generated from PII elements to the DCC which securely stores the hashed codes and performs entity resolution. The DCC then assigns a study specific study ID to the participant which is only known by the DCC and the study. The study researchers never see the hashed code. The study handles a de-identified dataset in which the participants are assigned a unique study specific ID.
    - *Sharing/accessing linked data*[109]: PEDSnet Steering Committee approval is required for linking data based on review of the study research plan. Much of PEDSnet's work involves large observational studies and operates under waiver of consent, but when consent is obtained, the consent language is broad and addresses sharing linked data.

- *Deductive disclosure review*[109]: A risk review is done for each proposed study, but no separate deductive disclosure review of the linked data is performed. Data use agreement prohibits reidentification and re-use for other studies. All members must agree to the PEDSnet standard policies when joining the Network; additional terms of data use are stipulated on a case-by-case basis. Policy also requires masking cell counts <11 in report and manuscripts. However, smaller cell counts can be reported if five or more institutions contributed to the dataset and institutions agree to allow the small cell sizes to be revealed.
- *Agreements/approvals for accessing linked data*: Investigators, data analysts, and statisticians who need to access the database will first apply to be an authorized user. Approval for access is required from the PEDSnet Data Committee. For approved PEDSnet studies, the Data Coordinating Center will set up a workspace within the PEDSnet database environment and transfer the minimum necessary data for the research project to the workspace. The workspace will support database and statistical applications allowing the team to conduct data analyses.

11.2.1.7 CDC/The Childhood Obesity Data Initiative (CODI)

- ***Description***[111,112]: The Centers for Disease Control and Prevention (CDC) designed CODI to integrate clinical and community longitudinal data for childhood obesity research, evaluation, and surveillance. The goals of the initiative were to demonstrate enhanced data capacity to conduct childhood obesity research and surveillance within an existing distributed health data network (DHDN), and to develop and share reusable tools/resources to encourage similar work. CODI brings together data stored across different sectors and organizations to create individual-level, linked longitudinal records that include SDOH, clinical and community interventions, and health outcomes. CODI also creates longitudinal household records, linking individual longitudinal records within the same household. Five Colorado-based organizations collaborated to expand an existing DHDN, Colorado Health Observation Regional Data Service (CHORDS) network, to include community-generated data and assemble longitudinal patient records for research. (CODI expanded in 2020 to include a North Carolina cohort for individual and household level data. Data linkage and standardization and infrastructure optimization are currently in progress. CODI is a demonstration project of the CHORDS network and operates within the CHORDS governance framework. The CHORDS Governance Committee, which meets regularly and represents all CHORDS participants, is the decision-making body for both the CODI project and the CHORDS network.)
- ***Data sources***[112]: CODI Data Partners share de-identified linked data outside their institutional boundaries based on HIPAA Privacy Rule 45 C.F.R. 164.514 (b). Current data sources include:
  - Colorado child health-related data from:
    - Three health systems (Denver Public Health & Hospital Authority, Children's Hospital Colorado, and Kaiser Permanente Colorado)
    - Two community-based organizations (Girls on the Run of the Rockies and Hunger Free Colorado)
  - North Carolina:
    - Clinical and community data in the Triangle region from health care, local and state health departments, and community-based organizations
- ***Data types***[112]: Social determinants of health data, clinical interventions (EHR), community interventions, health outcomes, and geographic data
- ***Linkage agreements***[111]:

- The Master Sharing and Use Agreement (MSUA) is a multiparty reciprocal agreement which defines the roles of each party, general network functionality relationship between DCC and Data Partners, and tasks the DCC is permitted to carry out for the CODI network. The MSUA designates and empowers the DCC to conduct PPRL activities, create and distribute queries for data, process and aggregate site-specific datasets, share study datasets with data users, and delegate authority to the DCC to sign DUAs on behalf of Data Partners.

- ***Hashed token generation***[111]: Anonlink, an open source PPRL software, modified such that data from more than two organizations could be matched at the same time.
  - *PII elements*[113]: Given name, family name, date of birth, sex, phone number, household street address, and household ZIP Code
  - *Anonlink schema*[114]: Name-sex-DOB-phone, name-sex-DOB-ZIP, name-sex-DOB-parents, name-sex-DOB-address
- ***Entity resolution***[115]: Performed by the DCC, which the MSUA designated as the University of Colorado.
  - Process:
    1. The DCC shares with each Data Partner configuration information which contains information on how to normalize PII before hashing. This ensures a consistent representation of PII which serve as the inputs for hashing.
    2. Data Partners input PII along with a randomly generated encryption key to compute specific hash values for each individual. Because a given individual corresponds to multiple hash values, the Data Partner also includes a HASHEDID, which is the hash of that site's arbitrary patient identifier from the CODI warehouse (this ID is not PII).
    3. The Data Partners send the hashed values and the HASHEDID to the DCC.
    4. After receiving the collections of hashed values from Data Partners, the DCC builds a hash index from these values to identify any matches. By combining hash values and the HASHEDIDs, the DCC can determine all of the hashes that correspond to the same individual. The DCC then assigns a unique network wide ID, known as the LINK_ID, for each unique individual.
    5. The DCC then sends the mapping between the HASHEDID and the globally unique LINK_ID to the Data Partner. Each Data Partner stores its patients' LINK_IDs in its local CODI warehouse for use in future research queries. Sharing of the LINK_ID is prohibited with any research dataset.
- ***Data linkage***[115]: Study-specific linkage model; the DCC performs the data linkage.
  - Process:
    1. Researchers query data across multiple CODI sites after an agreement has been established with the DCC.
    2. Once the agreement is in place, the DCC distributes queries to Data Partners. Data Partners execute the agreed upon query and review site-specific results before returning results to the DCC.
    3. The DCC then combines site-specific results to build a longitudinal record in accordance with the applicable protocol and returns the research dataset to the researcher/data requester. The DCC replaces the LINK_ID with a study-specific STUDY_ID, unique to the query, before distributing the data to the requester.
- ***Sharing and accessing linked data—authorizations/agreements/approvals***[111]:
  - *Governance structure*:
    - CODI DCC works with data requesters to develop and submit local IRB protocols for approval.

- CHORDS Research Council oversees research reviews and makes recommended approvals for studies to the Governance Committee.
- CHORDS Governance Committee and Research Council handle the decision-making, creating guiding principles, and maintaining the governance plan which documents policies and procedures for data request initiation, Data Partner approval and participation, regulatory requirements, security, privacy and confidentiality, and publication and presentation guidelines.
- Multi-organizational DCC-merged datasets with site identifiers removed is owned by the DCC, who then acts as the data steward.

- *De-identification status of shared data*: Longitudinal records are stripped of site and patient identifiers (i.e., the unique ID resulting from PPRL) and are temporarily provisioned for analysis to researchers on a study-specific basis. For recipients of longitudinal records who are CODI Data Partners, stripping identifiers ensures that patients from the receiving Data Partner cannot be reidentified. Policies prohibit data users from reidentifying patients.
- *Authorization for data sharing*:
  - Researchers complete a CHORDS Project Intake Form which is then sent to the data partners via email by the Research Project Manager.
  - The CHORDS Research Council provides a recommendation to the CHORDS Governance Committee. At the subsequent CHORDS Governance Committee meeting, the study is presented, and the Committee votes on formal approval for the study to proceed. Once approved, Data Partner participation is formally requested, and written participation responses are required.
  - CODI Data Use and Transfer Agreement requirements pertaining to receipt of a limited dataset or individual-level de-identified dataset differ, dependent upon the data user:
    - For a study led by a Non-Data-Partner Data User, a study-specific Data Use and Transfer Agreement is required.
    - For a study led by a Data-Partner Data User, a study-specific Data Use and Transfer Agreement is not required.
  - The MSUA is a multiparty reciprocal agreement which defines the parameters of data exchange, approved uses of CODI data, and expectations of end-users. The reciprocal nature of the MSUA allows it to act as a DUA for a project initiated by a CODI Data Partner. The MSUA also allows the DCC to create and distribute queries, process, and aggregate site-specific datasets, share study datasets with data users, and delegated authority to the DCC to sign DUAs on behalf of Data Partners.
  - All CODI studies require approval or designation as non-human subjects research by the requesting researcher's IRB.
- *Deductive disclosure review*: Deductive disclosure review is not performed for datasets that are linked for CODI studies. Additionally, the Working Group determined that garbled information (PPRL identifiers) did not require added governance protections to maintain privacy. Data Partners would be notified of any unapproved use or breach of garbled information or the unique identifier. The governance plan establishes guidelines for data destruction at a study's conclusion.
- *Agreement/approvals for accessing linked data*:
  - The MSUA includes a reciprocity provision that allows sharing of limited or de-identified datasets among CODI Data Partners without an additional DUA. For researchers from organizations not participating in CODI, a study specific DUA is required. MSUA appendices include a template DUA approved by CODI Data Partners for use in research studies and a Responsible Use of Data Agreement that defines the responsibilities of researchers receiving CODI longitudinal records.

- CODI data users are required to sign a Responsible Use of CODI Data Agreement and return the signed agreement to the DCC. The Responsible Use of CODI Data Agreement defines the expectations of a data user, as a recipient of a CODI research dataset from DCC, and the limitations on the use of that research dataset. When a data user receives a research dataset containing individual-level data from the DCC, the Responsible Use of CODI Data Agreement functions in concert with the specific terms detailed in the Data Use and Transfer Agreement.

11.2.2 Governance Summary for Record Linkage Implementations Not Using PPRL

Appendix Table 3: Governance Summary for Record Linkage Implementations Not Using PPRL

	Record Linkage Implementation	Datasets Linked	Authorization for			Linkage Methodology	PII Elements Used for Linking	Entity Resolution (Matching) Performed by	Data Linking Performed by	Data Linkage Model[mm]	Data Access Model[nn]	Additional Information Link
			Record Linkage	Sharing Linked Data	Accessing Linked Data							
1	Database of Genotypes and Phenotypes (dbGaP)	Genotype data, phenotype data, genome wide association (GWAS) data, Short Read Archive (SRA) data, expression data, image data, etc.	Data Submitter	Data Submitter	NIH Data Access Committee approval	Genetic Relationship and Fingerprinting (GRAF) analysis within studies and Subject ID (string) matching across studies	Not applicable	dbGaP Data Curation Team	Requesting investigators	Linked database model for matches across studies and study-specific linkage model for within study	Controlled data but public dbGaP IDs	Section 11.2.2.1
2	*All of Us* (AoU)	○ EHR data, genomic data via biospecimens, physical measurements, patient provided information (PPI) via surveys (topics include sociodemographic, overall health, lifestyle, and health care access and utilization), data from mobile devices, biosamples ○ Future external datasets: mortality data, EPA, USDA, health registry, pharmacy data, etc.	Consent from participants and IRB approval to use PII for linkages with external datasets	Consent from participants	Approval from the AoU Resource Access Board (RAB) for access to individual level data via the registered and controlled tiers	Internal AoU data linkages: using a common Participant ID (PID, a unique random 10-character string) External data linkages: two current pilot/ assessment projects via Datavant	Internal AoU data linkages: Not applicable For two external data linking projects: Unknown	Internal AoU data linkages: AoU Data and Research Center (DRC) For two external data linking projects: third party	AoU Data and Research Center (DRC)	Internal AoU data linkages: Linked database model For two external data linking projects: Study-specific linkage model	○ Public Tier ○ Registered Tier (Enclave) ○ Controlled Tier (Enclave)	Section 11.2.2.2

	Record Linkage Implementation	Datasets Linked	Authorization for			Linkage Methodology	PII Elements Used for Linking	Entity Resolution (Matching) Performed by	Data Linking Performed by	Data Linkage Model[mm]	Data Access Model[nn]	Additional Information Link
			Record Linkage	Sharing Linked Data	Accessing Linked Data							
3	PCORnet-DS Connect/DS-DETERMINED Study	○ EHR data of PCORnet patients with Down Syndrome who were recruited to DS-DETERMINED for linkage with external data which include: ○ DS-Connect demo-graphic and Initial Health Questionnaire (IHQ) data ○ Self Determination Inventory (SDI) survey data	Informed consent	Informed consent for sharing with study team and with a NIH designated data repository	Access requirements to be defined based on the NIH designated repository used for sharing the data.	Linked using unique patient specific referral code, which is a combination of de-identified pat_id generated at the PCORnet sites and the study_id generated by REDCap for the study	Study Referral Code (=study id+ pat_id)	Study Team	Study Team	Study-specific linkage model	Controlled	Section 11.2.2.3
4	Georgetown Federal Statistical Research Data Center (FSRDC)	○ Survey data from American Community Survey (ACS), Population Survey, Survey of Income and Program Participation (SIPP) ○ Administrative data from Social Security Administration (SSA) and the Centers for Medicaid and Medi-care Services (CMS) ○ Other types of data from 5 agencies: Agency for Healthcare Research and Quality (AHRQ), Bureau of Economic Analysis (BEA), Bureau of Labor Statistics (BLS), National Center for Health Statistics (NCHS), and National Center for Science and Engineering Statistics (NCSES) ○ Data provided by researchers	○ Data owners (per their data collection authorities and/or IRBs) and Census requirements ○ For statistical purposes only	○ Data owners (per their data collection authorities and/or IRBs) and Census requirement ○ For statistical purposes only	○ Data owners and Census requirements, including Special Sworn Status to access the FSRDC data enclave ○ For statistical purposes only	Probabilistic matching software (Multi-Match) to generate a Protected Identification Key (PIK)	○ SSN ○ Date of birth ○ Name ○ Gender ○ Address/es	Census	Census	Study-specific linkage model	Enclave	Section 11.2.2.4

	Record Linkage Implementation	Datasets Linked	Authorization for			Linkage Methodology	PII Elements Used for Linking	Entity Resolution (Matching) Performed by	Data Linking Performed by	Data Linkage Model[mm]	Data Access Model[nn]	Additional Information Link
			Record Linkage	Sharing Linked Data	Accessing Linked Data							
5	National Center for Health Statistics (NCHS) with National Death Index (NDI)	○ National Center for Health Statistics (NCHS) survey data ○ Mortality data from the National Death Index	○ Consent from participants ○ NCHS Research Ethics Review Board (ERB)	○ Consent from participants ○ Public version has been cleared for public distribution by CDC.	○ Access to restricted-use files is reviewed by the NCHS Research Data Center (RDC)	○ Combination of probabilistic and deterministic data linkage.	○ First name ○ Middle initial ○ Last name ○ Date of birth ○ State of birth ○ State of residence ○ Race ○ Sex ○ Marital status ○ SSN9 or SSN4	Data Linkage Program at NCHS	Data Linkage Program at NCHS	Linked database model	Enclave	Section 11.2.2.5
6	The Child Maltreatment Incidence (CMI) Data Linkages project, Alaska Department of Health and Social Services/ Oregon Health Sciences University (ADHHS/ OHSU) Project	○ 2009-2011 Pregnancy Risk Assessment Monitoring System (PRAMS) survey data from Oregon Health Authority (OHA), Oregon Public Health Division ○ 2009 birth and death Records from OHA, Center for Health Statistics ○ Child welfare data from Oregon Department of Human Services	IRB approvals from OHA and Oregon Health and Science University	IRB approvals from OHA and Oregon Health and Science University	Access is restricted to staff listed in the DUA and IRB protocol	Combination of probabilistic and deterministic matching method that leveraged ALCANLink technology, which was created for a similar previous project	○ First name ○ Last name ○ Middle name ○ Date of birth ○ Birth certificate number	Trusted third party: Integrated Client Services (ICS)	Trusted third party: Integrated Client Services (ICS)	Linked database model	Controlled	Section 11.2.2.6

11.2.2.1 Database of Genotypes and Phenotypes (dbGaP)

- ***Description***[116]: The database of Genotypes and Phenotypes (dbGaP) was developed to archive and distribute the data and results from studies that have investigated the interaction of genotype and phenotype in humans. When dbGaP was established in 2007, data that were uploaded originated from studies that used different subjects, but with time, newer studies began submitting data that used subjects from previous studies. To link the same subjects from the newer studies to the previous studies, dbGaP developed a method to match the study provided subject IDs while generating a unique dbGaP subject ID, which serves as the primary key for all data in dbGaP[117].
- ***Data sources***[118]: Genotype, phenotype, GWAS, SRA, expression, and image data generated by NIH funded studies.
- ***Data types***[119]: The types of data distributed through the dbGaP include phenotype data, GWAS data, summary level analysis data, SRA data, reference alignment (BAM) data, VCF (Variant Call Format) data, expression data, imputed genotype data, image data, etc.
- ***Linkage authorization/agreement/approval***[118]: Based on decisions made by the data submitter. The GDS Institutional Certification[34] does not address record linkage or require explicit consent for record linkage.
- ***Entity resolution***[117]: Linked database model
    1. Study submitters are required to provide the following along with the de-identified study data:
        - *Subject Consent (SC) file*: Comprehensive list of all unique de-identified subject IDs, their assigned consent group, and biological sex value. [Each subject should be submitted with a single, unique, de-identified subject ID. Subject IDs should be an integer or string value.]
        - *Subject Sample Mapping (SSM) file*: File mapping SUBJECT_IDs (consented subjects and their phenotype data) to molecular SAMPLE_IDs. Has explicit list of samples from each subject. A Sample ID is a biological aliquot from a person and is the primary key for the molecular data.
        - *Subject Phenotypes file*: Includes any number of measured data and/or descriptive traits per individual and is how the demographic, clinical and exposure variables for a person are submitted. The primary ID in this file is the SUBJECT_ID. All SUBJECT_IDs must be listed in the SC file.
        - *Pedigree file*: Lists the genealogical relationships of subjects within a study. If there are no known relationships, this file does not need to be submitted.
        - *Sample Attributes file*: Includes sample level variables such as body site, analyte type, etc. The primary ID in this file is the SAMPLE_ID. All SAMPLE_IDs in this file must be listed in the SSM file.
        - *Data Dictionary*: Table that defines and describes the variables in the corresponding dataset (DS) file. If the DS file contains coded values, the code meanings need to be included in the DD file. Each of the above listed files also have a data dictionary defining the variables and coded values.
    2. Once dbGaP receives the above files, the dbGaP Curator performs entity resolution *within* and *across* studies:
        - *Within studies*: Genetic Relationship and Fingerprinting (GRAF)[120,ss] analysis is used to assess inconsistencies between molecular data sample IDs and phenotype sample IDs, phenotypic and genotypic sexes, and self-described races/ethnicities and populations inferred from

[ss] Per Mike Feolo, Staff Scientist at NCBI and Team Lead for dbGaP: GRAF has been incorporated into the dbGaP automated curation pipeline to check for relatedness within a study as a data curation and quality measure. It is not typically used to check for relatedness or similarity across studies. GRAF is efficient and accurate at identifying the same subjects across datasets. It could be useful for data linkage; however, dbGaP policy is that subject linking across studies using GRAF is not performed unless the PI approves it or unless there is a "good reason" to do so. One example of using GRAF as a data linkage tool is NHLBI's TopMed project, where GRAF was used to prove subjects are exact matches in these large cohorts.

genotypic data, unintended data duplications, incorrect pedigree information, and subject relationships. GRAF ensures that the relatedness status between samples correspond to what are being reported by submitters, by inferring the sexes, ancestry backgrounds, and relationships between samples using the fingerprint genotypes.

- *Across studies*: Incoming subject ID is checked against existing studies using a custom string matching analysis. If the subject ID of the incoming data potentially matches with existing data, curators notify the submitter to verify the origin of the matched subjects.
  - If the submitter wishes to confirm that the incoming subject ID matches with an existing subject ID in dbGaP, the Subject Consent File is sent back to the submitter to add the existing study's Subject_Source and Source_Subject_ID and resubmit to dbGaP. (The source is the source repository, consortium, institute, or other study where the existing subject originated[121].)
  - Once resubmitted, dbGaP will assign the unique *dbGaP subject ID for each individual*. Submitters will have access to the dbGaP subject IDs via a Sample Status Telemetry Report (SSTR) provided by dbGaP once the IDs and consents have been loaded into the dbGaP database.

- ***Sharing and accessing linked data—authorizations/agreements/approvals***:
  - *Authorization for sharing linked data*:
    - *Consent* [122]: As of 2015, the Genomic Data Sharing Policy requires that data submitted to dbGaP be consented for sharing to a public database. All subjects must be assigned a single consent group in the Subject Consent files upon submission. Consent groups correspond with the data use limitations on the Institutional Certification, which include: General research use, Health/Medical/Biomedical, Disease-Specific, and other. Data use limitation modifiers that can be added, if applicable, are local IRB approval required, Publication required, Collaboration required, Not-for-profit use only, Methods, and Genetic studies only.
    - *Consent withdrawal* [123]: Consent versioning is a dbGaP feature which allows for the termination of distribution of datasets with participant data who wish to retract their consent for sharing. Since dbGaP is not the primary study site, but instead is an archive and distribution point for data supplied by primary study sites, withdrawal of data from an individual participant in the original study requires the submission of a new version of data tables to dbGaP by the primary study site. The dbGaP study accession number (for example phs000001.v1.p1) will change to account for these versioning changes. If any participants have withdrawn consent or changed into a different consent group, then the "v" version and the "p" participant set will increment, and *only* the most recent version of the data will remain accessible.
    - *Institutional certification*[34]: The institution, in consultation with its IRB or equivalent body, assures NIH that the study data being submitted is consistent with the NIH GDS Policy, and with the informed consent of the original study participants. Data use limitations (and modifiers) should be based on language in informed consent forms.
  - *De-identification status of shared data*: To comply with the Genomic Data Sharing Policy[24], data should be de-identified to meet the definition for de-identified data in the HHS Regulations for Protection of Human Subjects (Common Rule) and also be stripped of the 18 identifiers listed in the HIPAA Privacy Rule, e.g., names, cities, dates, telephone numbers, social security numbers, and any other potentially identifying information, characteristic, or code. Additionally, submitter-provided subject IDs must be two steps removed from PII in study records; therefore, the dbGaP subject IDs are also at least two steps removed from PII.
  - *Deductive disclosure review*: A formal deductive disclosure review is not conducted.

- *Agreements/approvals for accessing linked data*:
  - *Consent*[34]: The informed consent under which the data or samples were collected determines whether the submitted data should be available in an unrestricted or a controlled access manner. Controlled access data are available to investigators only after review of their proposed research use. Unrestricted access data are publicly available to anyone.
  - *Data Access Committee (DAC) approval*[124]: Access to individual-level controlled access data is dependent upon approval by the data access committees. NIH DACs review all requests for access to datasets distributed through dbGaP. Some DACs are specific to a single NIH IC, such as the National Human Genome Research Institute (NHGRI) and review only Data Access Requests (DARs) funded by and/or submitted to dbGaP through that IC. Other DACs represent multiple ICs with similar research goals, such as the Joint Addiction, Aging, and Mental Health (JAAMH) DAC, which includes the National Institute on Drug Abuse (NIDA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute on Aging (NIA), and National Institute of Mental Health (NIMH). Users must sign dbGaP's DUC Agreement, including agreement not to use the requested datasets, either alone or in concert with any other information, to identify or contact individual participants from whom data and/or samples were collected, unless they have specific IRB approval to do so. Additionally, the NIH GDS Policy prohibits investigators who download unrestricted-access data from NIH designated data repositories from attempting to identify individual human research participants from whom the data were obtained[24].
  - *IRB approval*[125]: Some datasets require additional local IRB approval for use, if required per the Institutional Certification.

11.2.2.2 All of Us (AoU)

- ***Description***[126,127]: The *All of Us* (AoU) Research Program is a historic effort to collect and study data from one million or more people living in the United States. The program aims to reflect the diversity of the United States and to include participants from groups that have been underrepresented in health research in the past. Unlike research studies that focus on one disease or group of people, AoU is building a diverse database that can inform thousands of studies on a variety of health conditions. The program began national enrollment in 2018 and is expected to last at least 10 years.
- ***Data sources***:
  - *AoU data*[128]: From direct volunteers (DV) collected through the AoU Participant Portal or from participants enrolled through participating healthcare provider organizations (HPO) collected through the Data and Research Center (DRC) at Vanderbilt.
  - *External data*[129]: Sources for linkage of AoU data with external data vary. AoU has linked to Census American Community Survey (ACS) data and anticipates linking with mortality data, Census, Environmental Protection Agency (EPA), U.S. Department of Agriculture Food Access Research Atlas, private and public claims data, health registry data, private pharmaceutical data, etc.
  - *PPRL projects*: Thus far, AoU PPRL projects have only been performed for the purposes of evaluation and experimentation, but not for releasing linked data through the workbench, and include:
    - A collaboration among AoU, N3C, and NHLBI BioData Catalyst (a project within the NIH COVID Jumpstart initiative[130]) to identify common participants across the three programs and internally report results at the aggregate level; no individual-level data was exchanged across or linked between systems

  - An EHR/claims data linkage project to assess the completeness of the AoU EHR data by linking with external claims data from a claims aggregator
- ***Data types***[131]: EHR data, genomic data via biospecimens, physical measurements, patient provided information (PPI) via surveys (topics include sociodemographic, overall health, lifestyle, and health care access and utilization), data from mobile devices, measurements, biosamples.
- ***Linkage authorizations/agreements/approvals***[132, 133]:
  - *Consent*: Consent for data linkage is collected from participants at the time of enrollment. AoU is not currently enrolling participants under 18 years of age. The informed consent for AoU is modular. Each module requires an electronic signature from the participant. Module 1 (Primary Consent)—Consent to Join the *All of Us* Research Program—gives an overview of all program activities. Signing the primary consent indicates general understanding of the research program and approval to take part in the PPI, Data Linkage, Physical Measurements, Biospecimen Collection, Biobanking, Biomarker assays, Genomic Testing, and Sensor/Wearable Technology activities if invited. The Consent to Join the *All of Us* Research Program has the following language:
    - "If you join, we will gather data about you. We will combine it with data from other people who join. Researchers will use this data for lots of studies. By looking for patterns, researchers may learn more about what affects people's health."
    - "If you decide to join *All of Us*, we will gather data about you. We will gather some of the data from you directly. We will gather some of the data from elsewhere."
    - "Data about your health from other sources: We will add data from other sources to the data you give us. For example, environmental data and pharmacy records. This will give researchers more data about factors that might affect your health.... We will use data that identifies you like your name and date of birth to add data that is specific to you. For example, we may add data from pharmacy records or health insurance records. If you have had cancer, we may add data from cancer registries..."
    - "These other sources can contain sensitive data. For example, they may tell us about your mental health, or use of alcohol or drugs. They may contain sexual or infection data, including HIV status. Because of this, we will ask the *All of Us* ethics committee to review and approve each data source before we add it."
  - *HIPAA Authorization:* Participants must specifically consent to AoU accessing and linking to data from their EHR by signing the "All of Us Research Program HIPAA Authorization for Research EHR/Part 2 Supplement[134]"
    - "We will access your whole EHR. That means we will take a copy of all the tests, results, and images in your EHR. This includes data about your diagnoses, medications, symptoms, allergies, and treatments."
    - "We will add your EHR to your All of Us record. Your record will be part of the All of Us scientific database"
  - *IRB approval*[133]: While the primary consent encompasses data linkage, it is anticipated that prior to linking participant data with external sources, an amendment will be filed with the IRB for any linkages to "health registries" or "claims data" that require the DRC to share participant-identifying information to an outside entity. Such submissions would detail the data to be linked and the general methods for doing so. No additional participant consent will be undertaken. The consent discusses that identifying information may be shared in this process.
- ***Entity resolution/data linkage***: Linked database model

- *Internal AoU data linkage*[133]: AoU data are linked upon arrival to the raw data repository (RDR) using a common participant ID (PID) to create the AoU Core Dataset:
  - Participants are assigned a PID, a unique random 10-character string (format P000000000), upon registration with the AoU Program. The PID generation is not based on PII elements.
  - Individual level participant data collected through the Participant Portal (PPI, mobile device data, fitness tracker data, biosample, etc.) and via the DRC (EHR, physical measurements, biosample) is linked using the common PID. This Core Dataset is stored in the RDR, maintained by the DRC.
  - New individual-level datasets are merged with existing participant study record in the RDR using PIDs.
- *External data linkage*[129]: AoU has performed linkages with external data sources using PPRL tools only for evaluation and experimentation and plans to perform geocoding methods.
  - For the two PPRL projects, AoU is exploring Datavant's PPRL tool.
    1. For the collaboration project among AoU, N3C, and NHLBI BioData Catalyst (the COVID Jumpstart initiative[130]), hashed tokens based on first name, last name, date of birth, SSN, gender, zip, email, and cell (18 tokens) are generated by each collaborator and matched via a trusted third-party honest broker to identify how many participants are represented in both programs. No data transfer has occurred between the organizations.
    2. For the EHR/claims data linkage project, AoU DRC has engaged an external party to generate tokens for the participants and identify matches with the claims data. No data transfer has occurred yet.
  - AoU program is still deciding which PPRL tool to officially use moving forward. AoU has established a Working Group focused on science, policy and technology of data linkages; this Working Group is developing criteria and governance for data linkages and will develop criteria for data linkages in 2022.
  - Geocoding based linkages have not yet occurred. When a participant registers, they provide their address, which will be used for linking their data using geocoding. AoU would like to perform data linkages based on geospatial location, for example with EPA data, environment exposure data, or other county level data, but would need to determine the acceptable level of geolocation information to use without the risk of deductive disclosure. AoU is in discussions with NIEHS to explore geocoding.
- *Linkage quality assessment*[129]: AoU is still in a very early stage of exploring data linkages and has limited experience with assessing the quality of the linkages.
  - Internal AoU data linkages: AoU evaluates quality for internal data linkages by detecting duplicated data (via PID) to prevent data duplication in the RDR.
  - External data linkages: AoU is using gold standard external datasets to ensure high quality and trustworthy data sources (for example: the American Community Survey (ACS)/Census are gold standard sources as Census is collecting data at the geographical level. For the EHR/claims data linkage project, the team is still determining how to assess the quality of the matches.

- ***Sharing and accessing linked data—authorizations/agreements/approvals***:

- *De-identification status of the linked data*[135]: AoU does not release data that directly identifies participants (i.e., data that can be linked to specific individuals by users either directly or indirectly through coding systems), even to users with access to controlled data. These inaccessible data elements include, but are not limited to, personal names, addresses of residence or employment, medical record numbers, and social security numbers. Furthermore, these individual-level data will be coded, and authorized users will not be given the key to this code.
- *Deductive disclosure review*:
  - *Internal AoU data linkages*[133]: AoU currently does not have a disclosure review board in place, however, all internal dataset linkages are reviewed for disclosure risk prior to release. Additionally, direct identifiers are removed from structured and unstructured data streams, and the data gets organized and curated into a Curated Data Repository (CDR). A de-identified Core Dataset made available as registered tier or controlled tier via the AoU Research Program Research Portal/Research Workbench. AoU will use a variety of approaches to remove explicit personal identifiers such as name, email, phone number, street address, medical record number (MRN) and Social Security number (SSN) from the datasets made available for research purposes, including from free text data sources such as open response fields and EHR notes. As part of this process, personally identifiable information (PII) is removed from participant data as follows: PII from structured fields (e.g., Yes/No questions, selecting a birthdate, rating an experience from 1 to 10) will be replaced with code. The Committee on Access, Privacy, and Security (CAPS) will evaluate these approaches prior to release and routinely control their quality to minimize the risk of inappropriate re-identification.
  - *External data linkages*[129]: AoU currently does not have a disclosure review board in place, however, datasets / assets are reviewed for disclosure risk prior to release. [Note: the Working Group is expected to develop governance around this type of data linkage.]
- *Authorization for sharing linked data*[132]: Authorization to share AoU data, including linked data, via the CDR is based on informed consent:
  - "The scientific database will have individual-level data and samples. This includes your DNA data. Access to this database will be controlled. Researchers will have to be approved by *All of Us* to use this database. They will have to have special training before they can be approved. Their research may be on nearly any topic. They may look for patterns in DNA. This may help them discover different ways that DNA affects people. These researchers may be from anywhere in the world. They may work for commercial companies, like drug companies. They may be citizen or community scientists. Citizen and community scientists are people who do science in their spare time."
  - "The data researchers get from studying your samples and DNA may be added to the *All of Us* scientific database."
  - "Except if you withdraw (quit) or there are limits imposed by law, there is no limit on the length of time we will store your samples and data. Researchers will use your samples and data for research long into the future."
  - "In order to work with your health data, researchers must sign a contract stating they will not try to find out who you are."
  - "Once your information is shared with *All of Us*, it may no longer be protected by patient privacy rules (like HIPAA). However, it will still be protected by other privacy rules. These include the rules that researchers must follow to access the *All of Us* scientific database."
- *Agreements for accessing linked data*[133]: De-identified individual level (linked) data stored in the CDR is made available for querying by the research community through a dedicated analysis platform, the AoU Research Program Research Portal/Research Workbench, for research. The PID is converted to a research ID before releasing it for access, and the research ID maintains the linkage of the de-identified data. Qualified researchers who wish to access the data must agree to not remove data (registered and controlled tier—see definitions below) from the Research Portal without

approval. The AoU will bring researchers to the data rather than allowing researchers to download data to their own machines. The CAPS serves as the stewards of the data. The Research Portal has three levels of data access: public tier, registered tier, and controlled tier. The registered tier includes participant-level data with a number of transformations to protect participant privacy (re-identification risk analysis performed). The controlled tier contains data elements that may not, in their own right, readily identify individual participants, but may increase the risk of unapproved re-identification when combined with other data elements; data is pre-processed to minimize risk by domain experts. Data is at the more granular level (zip 3 vs state) in the controlled tier than in the registered tier. The requirements for access vary between the public vs registered and controlled tiers (*note*: access requirements are subject to change):

  - *Public Tier*: No individual participant level information included. It contains only summary statistics and aggregate information (bin size set at 20 individuals). No login required to access public tier data.
  - *Registered and Controlled Tier*: While the two tiers may have different requirements in the future, the current requirements for access include:
    - Institutional Data Use Agreement
    - Registration and eRA Commons Account Validation
    - Responsible Conduct of Research Training
    - Signing the Data User Code of Conduct
    - Approved access by the Research Access Board (RAB)
- *Approvals for accessing linked data*[135]: The research that occurs within the CDR Workbench accessible via the registered or controlled tiers are not subject to IRB review or approval. Users may be bound by institutional policies governing research, which may include local IRB review. Data user's institution must enter into *an institutional data use agreement* with AoU for an individual to become an authorized user. Review of the research proposal and approval from the AoU Resource Access Board (RAB) is also required.

11.2.2.3 PCORnet-DS Connect/DS-DETERMINED Study

- ***Description***[136]: The DS-DETERMINED study supports and enhances Down Syndrome research and the DS-Connect® registry by leveraging PCORnet, the National Patient-Centered Clinical Research Network. This study links PCORnet to the DS-Connect® Registry and tests capability in three dimensions: 1) increase DS-Connect® enrollment, 2) extract of clinical observations, treatments, and outcomes from PCORnet patients, and 3) conducting cognitive assessment survey of self-determination in the PCORnet Down Syndrome population.
- ***Data sources***[137]:
  - PCORnet, the National Patient-Centered Clinical Research Network. PCORnet partners of this study include University of Missouri, University of Kansas Medical Center, Allina Health System, and University of Pittsburgh.
  - DS-Connect Registry. A resource for people with Down Syndrome and their families to connect to researchers and health care providers, express interest in participating in certain clinical studies, and take confidential health-related surveys.
  - Self-Determination Inventory System (SDIS) Data Dashboard, a platform for measures related to self-determination.

- ***Data types***[138]: EHR data from PCORnet will be linked to demographic and Initial Health Questionnaire (IHQ) data from DS-Connect Registry and the survey data from the SDIS Data Dashboard. The PCORnet common data model is used to encode and organize the EHR data.
- ***Linkage agreements***[137]: PCORnet sites agree to become a recruiting site for the study; DS-DETERMINED does not have a separate agreement with the SDI website because the site is created and operated by the University of Kansas, which is a PCORnet site. Although DS-Connect does create NDA GUIDs for participants, the GUIDs are not shared with PCORnet as part of this study.
- ***Entity resolution/data linkage***[137]: Linked database model. Study participants are tracked using a unique referral code, which is a combination of the study ID and patient ID; the referral code links the participants across PCORnet/REDCap, DS-Connect and the SDI website. The software for DS-Determined linkage is available on GitHub (https://github.com/kumc-bmi/ds-determined-tools).
    - *Process for tracking participants*:
        1. Eligible participants (with a pat_id) are recruited from PCORnet and are sent a unique trial invite ID
        2. When the patient clicks on the link in the invite, they are directed to REDCap where they log in with their trial invite ID to complete their consents for the study. Once registered for the study, REDCap generates a unique referral code which is a combination of pat_id + study_id, and the participant is sent the link to the DS-Connect.
        3. Participants then register at DS-Connect and SDI using the unique referral codes. The referral code is used to link across PCORnet/REDCap, DS-Connect and the SDI website, while keeping the participant's PII elements private.
        4. Participant data from DS-Connect and SDI are sent to PCORnet/REDCap for linkage via the referral code. PCORnet sites store the mapping of trial invite codes to pat_id, which allows for linkage to EHR data.
    - *Quality assessment*[137]: The linkage quality is assessed in terms of maintaining the linkage process rather than the matching rate because linkage is performed via explicit referral codes that were tracked and matched automatically. The team receives raw files at a weekly cadence from both SDI and DS-Connect that report on which patient has completed the study and how far they have progressed. The DS-Connect files report how far the patient has progressed in filling out the DS-Connect surveys. The SDI report only states whether the participant has completed the survey (yes or no).
- ***Sharing and accessing linked data—authorizations/agreements/approvals***:
    - *De-identification status of shared data*[137]: The study is currently in progress, and the data has not been shared to external researchers; however, when shared it will be shared through the INCLUDE Data Hub and de-identified of 18 HIPAA identifiers.
    - *Authorization for sharing linked data*[138]: DS-DETERMINED Consent Forms include sharing data with the Kansas University Medical Center (KUMC) research team and with a NIH designated data repository. There is also a disclaimer that de-identified research results will be shared outside of KUMC for research purposes. Participants may contact Evan Dean, Ph.D., if they would like to have their data removed from future use in the study.
    - *Deductive disclosure review*[137]: Deductive disclosure review is not conducted on the linked data.
    - *Agreements/approvals for accessing linked data*[137]: NIH will have to determine how the linked data should be shared via the new INCLUDE Data Hub. The INCLUDE Data Hub has a multi-tiered access approach with controlled and registered tiers. Participants and families have access to the registered tier data. Access to both registered tier and controlled-access data require agreeing to not attempt to re-identify or contact

participants represented in INCLUDE Data Hub. The agreements for accessing the registered tier[139] is available through the INCLUDE Data Hub and for accessing the controlled tier via dbGaP[66].

11.2.2.4 Georgetown Federal Statistical Research Data Center

- ***Description***[140]: The Census Bureau operates 31 open Federal Statistical Research Data Center (FSRDC) locations, including at the Massive Data Institute at Georgetown University. The FSRDCs partner with over 50 research organizations including universities, non-profit research institutions, and government agencies[141]. Federal and state statistical agencies collaborate with the Census Bureau to provide microdata to approved researchers in the secure FSRDC environment. At FSRDCs, qualified researchers can access restricted-use microdata from a variety of statistical agencies to address important research questions.
- ***Data sources***[140]: American Community Survey (ACS), Population Survey, and Survey of Income and Program Participation (SIPP), Social Security Administration (SSA), Centers for Medicare & Medicaid Services (CMS), Agency for Healthcare Research and Quality (AHRQ), Bureau of Economic Analysis (BEA), Bureau of Labor Statistics (BLS), National Center for Health Statistics (NCHS), National Center for Science and Engineering Statistics (NCSES) and data provided by researchers
- ***Data types***[140]: Survey data, administrative data, health data, economic data, U.S. labor/workforce data, science and engineering and technology workforce data
- ***Linkage agreements***[142]: Census determines whether datasets they have acquired for agency use can be linked. For linkages involving researcher-provided data, the researcher must certify and show proof (via the data sharing agreement) from the data owner that they have permission to link data from a specific agency or multiple agencies with Census data and with each other. Since the linkage is based on PII, an IRB from the organization contributing the data may need to make a determination regarding whether this use of the data is appropriate. Depending on how the data were collected, other federal authorities may dictate the data linkage.
- ***PIK generation process***[143]: The Person Identification Validation System (PVS) at Census uses probabilistic matching software (Multi-Match) to assign a unique Census Bureau identifier called Protected Identification Key (PIK) for each person that matches a reference file of government administrative data.
- ***Entity resolution/data linking***: Study-specific model. Data linkage is done by Census for a fee ($19,000 per linkage/join request; one request can include linkages across multiple datasets). Linkage is only allowed for statistical purposes.
    - *Process*[142]:
        - The PVS matches incoming files to reference files created with data from the Social Security Administration (SSA) Numerical Identification file (= SSN master file/Numident) and SSA data with addresses obtained from federal files. The reference files used for the matching includes federal data for generally the same time period as the incoming files.
        - Reference file contains one record for each SSN, and is based on SSN, the Census Bureau assigned PIK, date of birth, name, gender, and addresses where the person may have resided (within a specified time frame).
        - When a linkage can be made between an incoming file and the reference file, the PIK is appended to the incoming file.
        - The PIK serves as a person deduplication key within files.

- *Linkage quality assessment*[142]: The Census attempts to assign a PIK to all files; the success rate of assigning the PIK varies on the quality of the completeness of the PII in the files. The most robust linkages are with social security number (SSN), name, and date of birth.
  - Data from CMS and SSA are very high quality and generally produce PIKs that are almost 100%.
  - National change of address files from Postal Service only contains name and address which results in a lower PIK rate (40-60%).
  - Parameters defining matches and non-matches affect the PIK rate.
  - Additional information can improve the match rates (e.g., parent names or place of birth).

- ***Sharing and accessing linked data—authorizations/agreements/approvals***[144]:
  - *De-identification status of shared data*: Users can access read-only, de-identified versions of approved files. Use of data provisioned by Census through the FSRDCs are governed by laws and policies from agencies that supplied data. For example, Title 13 and 26 of the U.S. Code that protects the privacy and confidentiality of the subjects and their data. Violation of the laws are federal crimes and punishable by serious penalties including prison time and fines.
  - *Deductive disclosure review*: Census uses the term "disclosure" as privacy protection—this includes:
    - Redacting the PII and adding the PIK before provisioning the data to the researcher in the FSRDC[142]
    - Prior to removing the analytical results and statistical products from the FSRDC workspaces, applying Disclosure Avoidance (DA) techniques to ensure that the products do not disclose the confidentiality of the subjects or their data[145]
    - Approval from the Disclosure Review Board (DRB) prior to disseminating statistical products or publications derived from the analysis
  - *Authorization for sharing the linked data*: FSRDCs receive authorization via the data sharing agreement provided by the researcher when requesting linkage of Census data with data from other agencies.
  - *Agreements/approvals for accessing linked data*: Linked data can only be access in restricted physical and IT infrastructure (enclave). Researchers must obtain Special Sworn Status[37], complete background check and training, and sign an agreement in order to use the FSRDCs. In those agreements, they vow to:
    - Not attempt to reidentify
    - Only use the data for statistical purposes
    - Not misuse affiliation or PIV card
    - Understand there is no guarantee of privacy when using the FSRDC lab
    - If the researcher is bringing in their own cohort of data, they agree for Census to take possession of that data and be the steward of the data.

11.2.2.5 National Center for Health Statistics (NCHS) with National Death Index (NDI)

- ***Description***[146]: A linkage between the National Center for Health Statistics (NCHS) survey on health outcome data and health care utilization information with the National Death Index (NDI) to maximize the scientific value of the NCHS survey data without increasing respondent reporting burden.
- ***Data sources***[147]: Death record information from the NDI for each person dying in the United States or a U.S. territory from 1979 through 2015. The NCHS data being used in this linkage were from the following populated-based health surveys and years:

- National Health Interview Survey (NHIS): 1985-2014
- Continuous National Health and Nutrition Examination Survey (NHANES): 1999-2014
- NHANES III (1988-1994)
- NHANES II (1976-1980)
- NHANES I Epidemiologic Follow-up Study (NHEFS)
- Second Longitudinal Study of Aging (LSOA II)
- Supplement on Aging (SOA)
- National Home and Hospice Care Survey (NHHCS): 2007
- National Nursing Home Survey (NNHS): 1985, 1995, 1997, 2004

- ***Data types***[147]: The data types were comprised of national population and provider surveys and mortality data from death certificates.
- **Linkage authorizations/agreements/approvals**[147]:

  Linkage authorization[148]: The specific federal laws that authorize the National Health Interview Survey (NHIS) to ask for PII for linkage purposes are the Section 308(d) of the Public Health Service Act (42 United States Code 242m(d)), the Confidential Information Protection and Statistical Efficiency Act (Title V of Public Law 107-347), and the Privacy Act of 1974 (5 U.S.C. § 552a). Furthermore, the NCHS survey data are deemed eligible to link based on whether a survey participant gives consent for data linkage in the survey and whether adequate PII is present for linkage.

  - ***Entity resolution/Data linkage***[146]: Linked database model. Performed by the NCHS Data Linkage Program. The linkage algorithm was developed with custom code (using SAS 9.4) and was tailored to perform these specific linkages.
    - The primary identifiers used in the linkages were: SSN9 or SSN4 (depending on the survey year or cycle of the survey), first name, middle initial, last name or father's surname, month of birth, day of birth, year of birth, state of birth, state of residence, race, and sex.
    - Process:
      1. Participants with exact SSNs matches were joined via a deterministic linkage. Matches were joined and validated by a comparison of other identifying fields.
      2. Probabilistic linkage was then conducted to identify likely matches, or links, between all records, including those where SSN was missing. All deterministic matched pairs (from Step 1) were assigned a probabilistic match probability of 1; other records were linked and scored as follows:
         - Pairs were formed via blocking.
         - Potential matches were scored based on the concurrence of first name, middle initial, last name or father's surname, year of birth, month of birth, day of birth, state of birth, state of residence, race, and sex.
         - Match probabilities were estimated through a model which assigned the estimated probability that pairs are matches.
      3. Pairs with the highest estimated match probability were selected which were believed to represent the same individual between the data sources.
    - *Linkage quality assessment*[146]: To account for changes in the data collection process for some NCHS surveys and potential demographic shifts among survey participants, an enhanced linkage methodology was adopted in order to produce high quality matches with a low degree of linkage error. The

change in data linkage quality is due to the fact that NHIS traditionally collected full 9-digit Social Security Numbers (SSN9) from survey participants; however, there was increased refusal to provide SSN and consent for linkage, thus in the 2007 surveys, NHIS began to collect only the last four digits of SSN (SSN4) and added an explicit question about linkage for those who refused to provide SSN. The linkage algorithm that was previously used to create the 2015 linked mortality files had to be enhanced to account for the changed PII collected. Specifically pertaining to the NHIS, from 2007-2014 (the years when the collection of SSNs changed) the 2019 Linked Mortality Files (LMF) captured 83.3% of the previously linked records. However, in the prior years when SSN9 was collected, 1986-2006 NHIS, the 2019 LMF captured 94.0% of the previously linked records. Of note, for the 1999-2014 NHANES where the collection of SSN9 continued to be part of the data collection process, the 2019 LMF captured 92.5% of the previously linked records.

- Sharing and accessing linked data—authorizations/agreements/approvals[146]:
    - *De-identification status of the linked data*[146]: NCHS removes all direct personal identifiers from both the restricted-use and the public-use linked mortality files. Only select geographic variables are available in the restricted-use datasets.
        - Public-use Linked Mortality Files (LMFs) are made available for selected surveys and will include a limited set of mortality variables for adult participants only. The public-use versions of the 2019 LMFs will be subjected to data perturbation techniques including synthetic data substitution for follow-up time and underlying cause of death for select records to reduce the participant disclosure risk. Current public use linked files are available for: 1986-2014 NHIS, 1999-2014 NHANES, and NHANES III surveys.
    - *Authorization for sharing linked data*[146]: Authorization is obtained through informed consent. Participation to NCHS surveys is voluntary and participants consent to data linkages and sharing their de-identified data to health professionals and to the public.
    - *Deductive disclosure review*[150,147]: To prevent the possibility of re-identification, the NCHS-NDI LMFs are not available as public-use files. Researchers who want to obtain the NCHS-NDI LMFs must submit a research proposal to the NCHS Research Data Center (RDC) to obtain permission to access the restricted use files. All researchers must submit a research proposal to determine if their project is feasible and to gain access to these restricted data files. The proposal provides a framework which allows RDC staff to identify potential disclosure risks.
        - Restricted-use Linked Mortality Files are accessible only through the NCHS Research Data Center (RDC). Data access is reviewed by the NCHS Research Data Center (RDC). To avoid risk of participant re-identification researchers are not allowed to use public-use and restricted-use Linked Mortality Files, together, in the RDC.
        - Additionally, no outputs will leave RDC facilities without first being reviewed by an RDC Analyst for possible disclosures of confidential information.[149]
    - *Agreement/approvals for accessing linked data*[146]: The linked data files are made available in secure facilities for approved research projects at NCHS RDCs. Researchers must submit a proposal to use the restricted LMFs as well as sign the NCHS Data Use Agreement[150] which states that the researcher will:
        1. Use the data in this dataset for statistical reporting and analysis only.
        2. Make no attempt to learn the identity of any person or establishment included in these data.
        3. Not link this dataset with individually identifiable data from other NCHS or non-NCHS datasets.
        4. Not engage in any efforts to assess disclosure methodologies applied to protect individuals and establishments or any research on methods of re-identification of individuals and establishments

11.2.2.6 ACF/The Child Maltreatment Incidence (CMI) Data Linkages—Multiple projects

- ***Description***[151]: Child Maltreatment Incidence Data Linkages (CMI Data Linkages) program identified five research sites with experience linking administrative data to examine child maltreatment incidence and related risk and protective factors and supported these sites to enhance their approaches to administrative data linkage through acquisition of new data sources, use of new methods, or replication of existing methods. The ADHSS/OHSU project was conducted as part of the CMI Data linkages work as a replication study of the Alaska Longitudinal Child Abuse and Neglect Linkage project (ALCANLink). ALCANLink was developed to examine over time the incidence of maltreatment, predictive and etiologic factors, and disparities related to child maltreatment in Alaska. ALCANLink partnered with the Oregon Health Authority and Oregon Health Sciences University to replicate the ALCANLink methods for the state of Oregon.
- ***Data sources***[151]: Oregon Health Authority (OHA), Oregon Department of Human Services (OHSU), and ALCANLink.
- **Data types**[151]:
    - Oregon Pregnancy Risk Assessment Monitoring System (PRAMS) survey data (2009– 2011)
    - Oregon birth and death records data for 2009
    - Child protective services record data (2009–2018) for children born in 2009 and child protective services record data for children born in 2009–2011 whose mothers responded to the PRAMS survey
    - ALCANLink data which linked Alaskan 2009–2011 PRAMS cohort to vital records and child welfare records
- **Linkage authorizations/agreements/approvals**[151]: IRB approval is required from OHA and Oregon Health and Science University
- ***Entity resolution/data linkage***[151]:Linked database model. Performed by Integrated Client Services (ICS), an Oregon State operated data warehouse, as required by IRB approval. Much of the linking and processing of data was programmed in a software called RedPoint.
    - *Process*: ICS used a combination of probabilistic, deterministic, and manual matching each month to make/maintain the individual-level links. Each month, each "class" of probabilistic matching components (one class might be Names-DOB, another might be Names-SSN, etc.) went through iterations in which the matching criteria gradually loosened. With some exceptions, most of the matching components were a mix of deterministic matching on some fields and probabilistic matching on others. Records went through multiple matching components, and the highest-scoring match was chosen at the end.
        1. A state agency, Integrated Client Services (ICS), completed data linkages on behalf of the research team, as per IRB requirements from data partners. This agency receives and links data from multiple state programs and agencies on a monthly basis. As an intermediary, the unit provided a structured process for executing data use agreements, accessing data, and completing linkages.
        2. Annual data was first processed through an Extract Transformation and Load (ETL) tool called Pentaho®. This tool systematically identifies and merges in new information for cases that have already been linked using unique project IDs (using ID Keys and Foreign Keys).
        3. Next, a deterministic match based on the birth certificate number was used to link PRAMS and vital records data.
        4. A probabilistic match using a weighted Jaro-Winkler edit distance scoring based on names and date of birth was used to link vital records to CPS data.

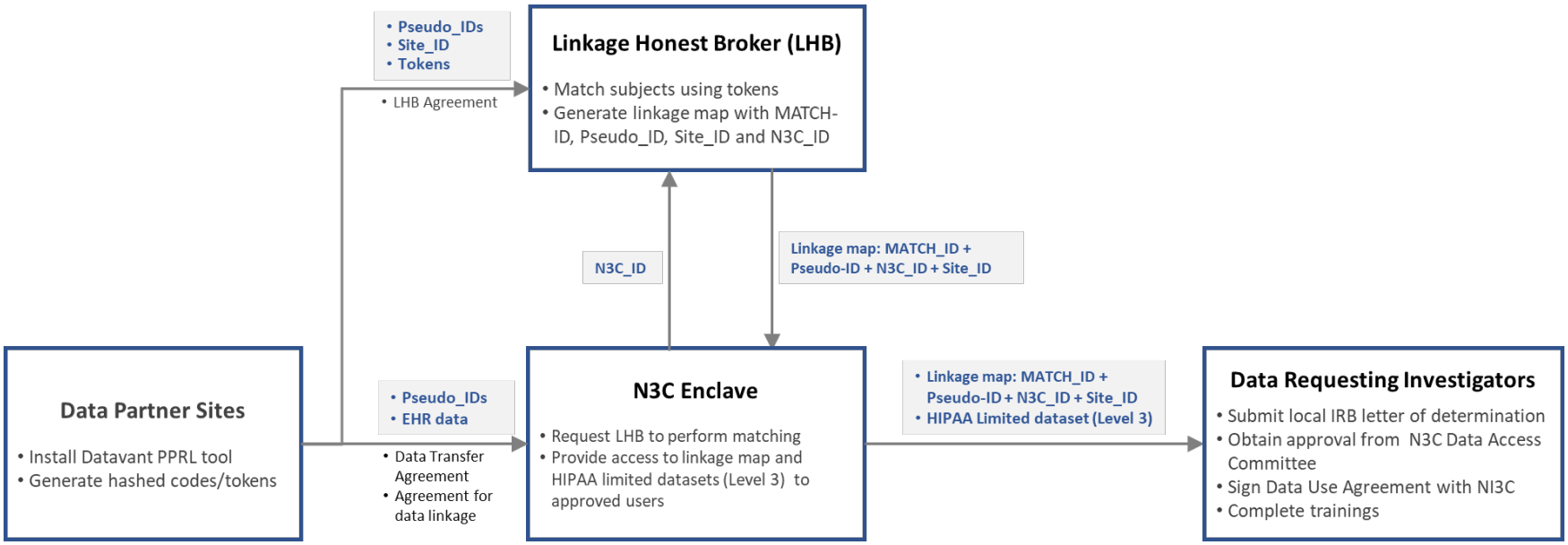
5. Data are stored on secure servers maintained by OHSU's Advanced Computing Center. The servers are physically located at an off-site facility with emergency power, weekly backup, multiple firewalls, and physical security. Only staff listed on the DUA and in the IRB protocol for this study have access to the data

- *Linkage quality assessment*[151]: Involving a separate agency in data linkage meant that the research team was not able to monitor the quality and completeness of linkages during that process. It was therefore important to establish a high level of confidence and trust in the linkage approach from the outset. The site team held an in-person meeting with representatives from ICS to discuss the basic approach and linkage flow for each data source. The team then documented this flow in project materials and its IRB application. Ultimately, it was determined that ICS's linkage approach was close enough to the ALCANLink method.

- Sharing and accessing linked data—authorizations/agreements/approvals[151]:
  - *De-identification status of shared data*[151]: The dataset is stripped of all direct identifiers, leaving only the encrypted unique identifier
  - Deductive disclosure review: Information not available.
  - Authorizations for sharing data:
    - Data Use Agreement for the PRAMS data was approved by Oregon Health Authority (OHA), Oregon Public Health Division, Section of Maternal and Child Health
    - DUA for vital record data was approved by the OHA, Center for Health Statistics
    - Data Sharing Agreement (DSA) for child welfare data was approved by Oregon Department of Human Services, Children, Adults and Family Division.

    ADHSS/OHSU site had permission to use child welfare data for the CMI Data Linkages project specifically; it is not a broad authorization
    - DSA was approved by Integrated Client Services
  - *Agreements/approvals for accessing linked data*[151]: Data are stored on secure servers maintained by OHSU's Advanced Computing Center. The servers are physically located at an off-site facility with emergency power, weekly backup, multiple firewalls, and physical security. Only staff listed on the DUAs and in the IRB protocol for this study have access to the study data.

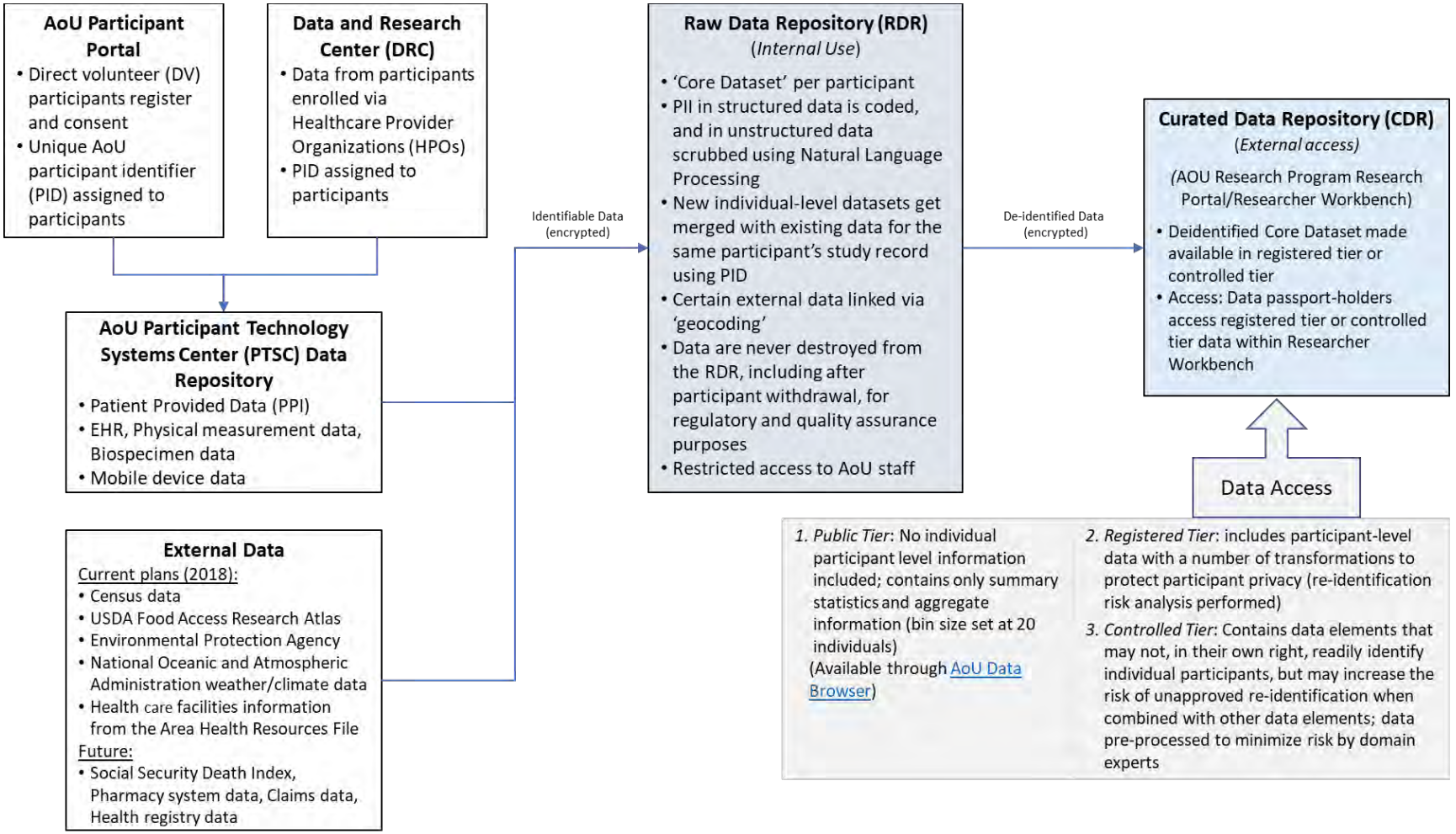
11.2.3 Example Data Flow Schematic for Record Linkage Implementations



Appendix Figure 1: Example Data Flow Schematic for PPRL Linkage: N3C (EHR to EHR Linkage)

Sources:

1. https://covid.cd2h.org/PPRL
2. https://ncats.nih.gov/n3c/about/data-overview
3. N3C Privacy-Preserving Record Linkage and Linked Data Governance: https://doi.org/10.5281/zenodo.5165212



Appendix Figure 2: Example Data Flow Schematic for Non-PPRL Linkage: All of Us

Sources:

1. AoU Protocol: https://allofus.nih.gov/sites/default/files/aou_operational_protocol_v1.7_mar_2018.pdf
2. Framework for Access to *All of Us* Data Resources v1.1: https://www.researchallofus.org/wp-content/themes/research-hub-wordpress-theme/media/data&tools/data-access-use/AoU_Data_Access_Framework_508.pdf

11.2.4 Consent Language for the Record Linkage Implementations Assessed in the Project

Appendix Table 4: Consent Language for the 13 Record Linkage Implementations (If available)

	Record Linkage Implementations	Consent for Linking Data	Consent for Sharing (Linked) Data	Dynamic Consent Language (unenroll/withdraw)	Reconsent Language (for reaching age of majority)
PPRL IMPLEMENTATIONS					
1A	BRICS Instance – NINDS/ PDBP	No explicit language on Data Linkage	Data Management Resource (DMR) Consent Language: ○ The data will be submitted to a database, with all identifying information removed (it will be anonymous). ○ No personal identifiers will be sent to the Repository or the database. ○ Samples and data will be distributed to scientists for use in research and teaching only. ○ The sample and unidentified data will be available to researchers at hospitals, universities, and commercial organizations. ○ There is a risk that someone could use information from the sample you submitted, via DNA, to identify you if it were matched with another DNA sample provided by you. However, any user of this sample must agree not to use it for that purpose, and the risk, while real, is small. https://pdbp.ninds.nih.gov/policy#dmr-consent-language	DMR Consent Form: "You have the right to withdraw from this research project at any time. If possible, any samples and data you have contributed will be discarded if you request this; however, because of the sample and data-masking, we may not always be able to identify which samples were donated by you. Your withdrawal from the study will in no way affect access to medical care for which you are otherwise eligible." https://pdbp.ninds.nih.gov/policy#dmr-consent-language	No explicit language on reconsent
1B	BRICS Instance – FITBIR	No explicit language on Data Linkage	"All links with your identity will be removed from the data before they are shared. Only de-identified data which do not include anything that might directly identify you will be shared with FITBIR users and the general scientific community for research purposes." https://fitbir.nih.gov/sites/default/files/inline-files/FITBIR_Data_Sharing_Policy_final.pdf	No explicit dynamic consent language	No explicit reconsent language

	Record Linkage Implementations	Consent for Linking Data	Consent for Sharing (Linked) Data	Dynamic Consent Language (unenroll/withdraw)	Reconsent Language (for reaching age of majority)
2	NIMH NDA	Sample consent language provided on the NDA website (below), but it is not verified by the NDA repository: "It is possible that you will participate in more than one study that sends data to NDA. NDA can connect your data from different studies by matching the code number on your deidentified data from each study. This data matching helps researchers who use NDA data to count you only one time. It also helps researchers who use NDA to better understand your health and behavior without knowing who you are." https://nda.nih.gov/contribute/contribute-data.html#infocon	"NDA is a large database where deidentified study data from many NIH studies are stored and managed. Sharing your deidentified study data helps researchers learn new and important things about brain science more quickly than before." "Deidentified study data means that all personal information about you (such as name, address, birthdate and phone number) is removed and replaced with a code number. The study researchers will have to collect your personal information from you in order to make that code number. The code number cannot be used to identify you. The study researchers will never send your personal information to NDA." "During and after the study, the study researchers will send deidentified study data about your health and behavior to the NDA. Other researchers across the world can then request your deidentified study data for different research projects. Every researcher (and the institution to which they belong) who requests your deidentified study data must promise to keep your data safe and promise not to try to learn your identity. Experts at the NIH who know how to keep your data safe will review each request carefully to reduce risks to your privacy. Sharing your study data does have some risks, although these risks are rare. Your study data could be accidentally shared with an unauthorized person who may attempt to learn your identity. The study researchers will make every attempt to protect your identity." https://nda.nih.gov/contribute/contribute-data.html#infocon	"You may decide now or later that you do not want your study data to be added to NDA. You can still participate in this research study even if you decide that you do not want your data to be added to NDA. If you know now that you do not want your data in NDA, please tell the study researcher before leaving the clinic today. If you decide any time after today that you do not want your data to be added to NDA, call or email the study staff who conducted this study, and they will tell NDA to stop sharing your study data. Once your data is part of NDA, the study researchers cannot take back the study data that was shared before they were notified that you changed your mind." https://nda.nih.gov/contribute/contribute-data.html#infocon	No explicit reconsent language

	Record Linkage Implementations	Consent for Linking Data	Consent for Sharing (Linked) Data	Dynamic Consent Language (unenroll/withdraw)	Reconsent Language (for reaching age of majority)
3-5	N3C EHR Linkage N3C Class 0 Linkage N3C Class 2 Linkage	Participating institutions do not obtain consent from individual patients for the data they send to the N3C. NCATS obtained a waiver of consent from NIH IRB	Participating institutions do not obtain consent from individual patients for the data they send to the N3C. NCATS obtained a waiver of consent from NIH IRB	Participating institutions do not obtain consent from individual patients for the data they send to the N3C. NCATS obtained a waiver of consent from NIH IRB	Participating institutions do not obtain consent from individual patients for the data they send to the N3C. NCATS obtained a waiver of consent from NIH IRB
6	PEDSnet	Much of PEDSnet's work involves large observational studies and operates under waiver of consent, but when consent is obtained, the consent language is broad and addresses sharing linked data.	Much of PEDSnet's work involves large observational studies and operates under waiver of consent, but when consent is obtained, the consent language is broad and addresses sharing linked data.	Much of PEDSnet's work involves large observational studies and operates under waiver of consent, but when consent is obtained, the consent language is broad and addresses sharing linked data.	All sites have policies to reobtain consent when the participant turns 18. It is specified in the policy as to whether the data cuts off or is removed entirely if they do not reconsent.
7	CDC/The Childhood Obesity Data Initiative (CODI)	No consent found	No consent found	No consent found	No consent found
NON-PPRL RECORD LINKING IMPLEMENTATIONS					
1	dbGaP	Based on submitter provided Subject Consent file	"Genomic and phenotypic data, and any other data relevant for the study (such as exposure or disease status) will be generated and may be shared broadly and used for future research in a manner consistent with the participant's informed consent and all applicable federal and state laws and regulations." https://sharing.nih.gov/sites/default/files/flmngr/NIH_Guidance_on_Elements_of_Consent_under_the_GDS_Policy_07-13-2015.pdf	"Participants may withdraw consent for research use of genomic or phenotypic data at any time without penalty or loss of benefits to which the participant is otherwise entitled. In this event, data will be withdrawn from any repository, if possible, but data already distributed for research use will not be retrieved." https://sharing.nih.gov/sites/default/files/flmngr/NIH_Gui2dance_on_Elements_of_Consent_under_the_GDS_Policy_07-13-2015.pdf	No explicit reconsent language

	Record Linkage Implementations	Consent for Linking Data	Consent for Sharing (Linked) Data	Dynamic Consent Language (unenroll/withdraw)	Reconsent Language (for reaching age of majority)
2	*All of Us* (AoU)	"If you join, we will gather data about you. We will combine it with data from other people who join. Researchers will use this data for lots of studies. By looking for patterns, researchers may learn more about what affects people's health." "If you decide to join *All of Us*, we will gather data about you. We will gather some of the data from you directly. We will gather some of the data from elsewhere." "Data about your health from other sources: We will add data from other sources to the data you give us. For example, environmental data and pharmacy records. This will give researchers more data about factors that might affect your health. ... We will use data that identifies you like your name and date of birth to add data that is specific to you. For example, we may add data from pharmacy records or health insurance records. If you have had cancer, we may add data from cancer registries... These other sources can contain sensitive data. For example, they may tell us about your mental health, or use of alcohol or drugs. They may contain sexual or infection data, including HIV status. Because of this, we will ask the *All of Us* ethics committee to review and approve each data source before we add it." . https://allofus.nih.gov/sites/default/files/Consent_to_Join_AoU_English.pdf	"Researchers can also ask to study your samples or DNA directly. We may send them a small amount of your samples or DNA so that they can do this. Before we send researchers your samples or DNA, they will have to take special training and sign a contract stating that they will not try to find out who you are. They will have to tell us what they want to study. *All of Us* will have to approve it. Their research may be on nearly any topic. They may look for patterns in DNA. This may help them discover different ways that DNA affects people. These researchers may be from anywhere in the world. They may work for commercial companies, like drug companies. They may be citizen or community scientists. Citizen and community scientists are people who do science in their spare time." "The data researchers get from studying your samples and DNA may be added to the *All of Us* scientific database." "In order to work with your health data, researchers must sign a contract stating they will not try to find out who you are." "Once your information is shared with *All of Us*, it may no longer be protected by patient privacy rules (like HIPAA). However, it will still be protected by other privacy rules. These include the rules that researchers must follow to access the *All of Us* scientific database." https://allofus.nih.gov/sites/default/files/Consent_to_Join_AoU_English.pdf	"If you decide to join *All of Us*, you can change your mind at any time. If you decide you want to withdraw (quit), you need to tell us. You can tell us through the app or website or use the contact information at the end of this form to call or write to us. If you withdraw, your samples will be destroyed. Your data will not be used for new studies. However, if researchers already have your data or samples for their studies, we at *All of Us* cannot get it back. Also, we will let researchers check the results of past studies. If they need your old data to do this work, we will give it to them." https://allofus.nih.gov/sites/default/files/Consent_to_Join_AoU_English.pdf	No explicit reconsent language (currently not enrolling children)

	Record Linkage Implementations	Consent for Linking Data	Consent for Sharing (Linked) Data	Dynamic Consent Language (unenroll/withdraw)	Reconsent Language (for reaching age of majority)
3	PCORnet-DS Connect/DS-DETERMINED study	"You will be asked to share your information from your Electronic Health Record with the KUMC study team. We will only access data on diagnosis, procedures, condition, medications, vital signs, and provider. We will combine your survey results (DS-Connect completed IHQ and the SDI results) with your medical information. [DS-DETERMINED consent form from ODSS]	"You will be asked to share your information from your Electronic Health Record with the KUMC study team. We will only access data on diagnosis, procedures, condition, medications, vital signs, and provider. This information will be shared with members of the KUMC research team."	No explicit dynamic consent language	No explicit reconsent language
4	Georgetown Federal Statistical Research Data Center (FSRDC) – Census	No explicit consent language on sharing linked data	No explicit consent language on sharing linked data	No explicit dynamic consent language	No explicit reconsent language
5	National Center for Health Statistics (NCHS) with National Death Index (NDI)	"We take your privacy very seriously. We combine your answers with other people's answers in a way that keeps everyone's identity secret. As required by federal law, your identity can be seen only by those NCHS employees and specially designated agents (such as the U.S. Census Bureau) who need that information for a specific reason." "Once you complete the survey, your confidential data will be combined with information from thousands of other survey participants. The combined data are then analyzed and shared with health professionals and the public to raise awareness about progress and needs, and as a means for inspiring positive change." https://www.cdc.gov/nchs/nhis/participants/images/English-Letter-Generic-508.pdf	"Everything you tell us is confidential. Your information is ONLY used for statistical purposes. We remove all personally identifying information from the data. After that, the data is posted on the NHIS website for future research or to guide public health decisions." https://www.cdc.gov/nchs/nhis/participants/images/English-Letter-Generic-508.pdf	No explicit dynamic consent language	No explicit reconsent language
6	The Administration for Children and Families (ACF) -- The Child Maltreatment Incidence (CMI) Data Linkages project-Alaska Department of Health and Social Services/Oregon Health Sciences University (ADHHS/OHSU)	No explicit consent language for data linkage	No explicit consent language on sharing linked data	No explicit dynamic consent language	No explicit reconsent language

11.2.5 Consent Language for the Record Linkage Examples Not Used in the Project

Appendix Table 5: Consent Language from Record Linkage Examples Not Used in the Project

	Record Linking Examples	Consent for Linking Data	Consent for Sharing (Linked) Data	Dynamic Consent Language (unenroll/withdraw)	Reconsent Language (for reaching age of majority)
1	National Survey of Child and Adolescent Well-Being NSCAW[46]	**Legal Guardian/Caregiver Permission for Child Data Linkage form language**: "The NSCAW interview data we collect from the child can be even more valuable to researchers when combined with other data. This includes information that exists now as well as future information. We also ask the child's current caregiver to offer permission to combine interview data with other information about them. This form requests your approval to add other sources to the child's interview data. We would add three types of information to the child's interview data. • We would add records collected from child welfare services agencies taking part in the study. Adding this information will help us to learn about foster care, adoption, or other services the child receives. • We would add information about the child's household, such as wages and other benefits from the Social Security Administration and from data available to the Administration for Children and Families—the agency funding the study. • Researchers interested in NSCAW data may wish to add other types of information in the future. For example, in the past, data on county or state child welfare policies have been added to NSCAW interviews." **Youth Age 13-17 Data Linkage Assent Forms**: "The NSCAW interview with you can be even more useful when we combine your answers with other data. This includes information available now as well as future information. We want to ask for your okay to add other types of information to your survey answers.	**Legal Guardian/Caregiver Permission for Child Participation Consent form language**: "This research is covered by a federal protection called a Certificate of Confidentiality. This means the researchers cannot share the information they gather that may identify the child. The Certificate prevents researchers from revealing this information even if it is subpoenaed by a court." "However, the Certificate does allow researchers to share information in some situations. For example, researchers must follow reporting laws about child and adult abuse. Also, as a part of agreeing to be in this study, you are giving permission for researchers to share information in the rare circumstance that it is needed to prevent serious risk to the child or others. In addition, the agency that funds this research (the Administration for Children and Families) is permitted to access information to confirm that the research is being conducted properly." "In the future, information from this study may be securely shared with qualified individuals to help learn more about the experiences of children and families with the child welfare system. The information that is shared will only include a study ID number and not the child's name." **Youth Age 13-17 Data Linkage Assent Forms**: "We do many things to make sure your answers stay private. I am going to enter your answers into a laptop computer. We have a paper from the government that promises that we do not have to give your information to anyone. We will not tell anyone your answers unless we are worried about you or someone else's safety. For example, if you tell us you might hurt yourself or someone else,	**Legal Guardian/Caregiver Permission for Child Data Linkage form language**: "If in the future should you decide you no longer want the child's interview data combined with other records, you can opt out of this request and stop further collection from outside sources. Please contact Jennifer Keeney at RTI International (toll-free at 800-334-8571 extension 23525) or RTI's Office of Human Research Protections at 1-866-214-2043 (a toll-free number) to record your request." **Youth Age 13-17 Data Linkage Assent Forms**: "You have the right to say yes or no to this request. Your okay also allows us to share it with researchers for other approved research studies. If you change your mind, please call Jennifer Keeney at RTI International (RTI) (toll-free at 800-334-8571, extension 23525) or RTI's Office of Human Research Protections at 1-866-214-2043 (a toll-free number) to record this request." https://www.reginfo.gov/public/do/PRAViewDocument?ref_nbr=202109-0970-003	**Legal Guardian/Caregiver Permission for Child Data Linkage form language**: "Your permission allows us to add these other types of information to the child's interview data. We will add this information to the child's interview data until the child becomes an adult (turns 18 years old). We can add some information about the child now. Some of the information we will add in the future. "Your permission to add other information will stop when the child turns 18 years old. When the child turns 18 years old, we will ask the child's permission to add new information. The child's permission will allow us to add information about the child's adult life. " **Youth Age 13-17 Data Linkage Assent Forms**: If you give your okay now, we will collect these other kinds of information to combine with your interview data. Your okay to link your interview data to other information will last until you turn 18 years old unless you change your mind before then. Your okay means we can start adding information about you now or in the future.

	Record Linking Examples	Consent for Linking Data	Consent for Sharing (Linked) Data	Dynamic Consent Language (unenroll/withdraw)	Reconsent Language (for reaching age of majority)
		We would add three types of information to your interview data. • We would add records collected from child welfare services agencies taking part in the study. Adding this information will help us learn about foster care, adoption, or other services you receive. • We would add information about your household's income, such as wages and disability benefits from the Social Security Administration and from data available to the Administration for Children and Families—the agency funding the study. • Researchers interested in NSCAW data may wish to add other information in the future. This could include data on county or state child welfare policies. " https://www.reginfo.gov/public/do/PRAViewDocument?ref_nbr=202109-0970-003	we may tell someone. If you tell us someone hurts you, we may tell authorities to keep people safe." https://www.reginfo.gov/public/do/PRAViewDocument?ref_nbr=202109-0970-003		When you turn 18 years old, we will ask if it is okay to collect information about you as an adult. If you say no then, we will stop adding information about you as an adult and only keep and share the information collected before you turned 18 years old. https://www.reginfo.gov/public/do/PRAViewDocument?ref_nbr=202109-0970-003
2	LunaPBC	"By sharing any Personal Data or Shared Data into this platform, you agree to and consent to the use of that data as set forth in this LunaDNA Agreement and in our Privacy Policy. The Privacy Policy contains further detail on many of the concepts in this LunaDNA Consent, and we urge you to read it in full." https://support.lunadna.com/support/solutions/articles/43000076335-lunadna-consent	"To protect your privacy, we separate your Shared Data from your Personal Data. We refer to the separation of your Personal Data from your Shared Data as de-identifying your Shared Data. Your Shared Data is then combined, or aggregated, with the entire pool of de-identified Shared Data of our community, to create a searchable database to power research and discovery. LunaDNA and researchers (including our manager, LunaPBC) may perform population-level searches based on a pre-defined and approved study design. We refer to these searches as queries. The results of a study-linked query will include a list containing de-identified data file identification numbers of members whose Shared Data is a match for the query. Based on these results, a subset of aggregated, de-identified Shared Data is populated in a private, secured compute environment controlled by LunaDNA, which we refer to as a sandbox, in order to	"Your data is owned by you. You may revoke your consent at any time. At any time after you provide Shared Data or Personal Data to LunaDNA, you can decide to revoke your consent, purge some or all of your data, and even delete your account completely from our databases. If you revoke your consent or delete your account, your data will be permanently removed, or purged, from our database (subject to retaining an archival copy if, and for so long as, required by law), and this Consent Agreement relating to that data will automatically terminate. If you choose to purge some or all of your data, LunaDNA will immediately prevent that data from being found in any new queries for researchers. LunaDNA will also determine if your Shared Data is at	No explicit reconsent language

	Record Linking Examples	Consent for Linking Data	Consent for Sharing (Linked) Data	Dynamic Consent Language (unenroll/withdraw)	Reconsent Language (for reaching age of majority)
			complete the analysis required by the study design." https://support.lunadna.com/support/solutions/articles/43000076335-lunadna-consent	that time available to any researchers in a sandbox." https://support.lunadna.com/support/solutions/articles/43000076335-lunadna-consent	
3	Health and Retirement Survey – CMS data linkage (NIA)	"We would like to understand how people's medical history affects their financial status, and how use of health care may change as people age. To do that, we need to obtain information about health care costs and diagnoses for statistical purposes. The best place to get this information without taking up a lot more of your time is in the (Medicaid/State name for Medicaid) files.) Could you give me your Medicaid number for this purpose?" https://g2aging.org/?section=item&itemid=361791			

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