## Title

# The Common Fund Data Ecosystem (CFDE)

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## Summary

The NIH Common Fund Data Ecosystem (CFDE) integrates data resources from 18 NIH Common Fund programs for discovery and integrative analysis. These programs generate valuable but heterogeneous datasets that can be difficult to discover, access, and reuse. CFDE aims to provide a collaborative, community-built infrastructure that links and enriches Common Fund programs. We describe the evolution, structure, and core technologies of CFDE, including practical approaches that support submission, integration, visualization, and public release of multimodal data. Training programs and workforce initiatives lower barriers to adoption. CFDE has devised solutions to critical issues facing cross-program initiatives, including data scale and heterogeneity, dataset integration, and long-term sustainability. We demonstrate the utility of linking Common Fund resources through integrative tools and cross-dataset queries to yield insights that would otherwise be infeasible. Collectively, CFDE shows that a standards-driven, federated approach enhances and unifies cross-disciplinary resources, fostering collaboration and data-driven discovery.

## Keywords

biomedical data integration, metadata harmonization, discovery, analysis workflow, data visualization, cloud computing, collaborative science, interoperability, sustainability, CFDE

## Introduction

The NIH Common Fund[1,2] supports ground-breaking, high-risk research programs that span multiple NIH institutes and that have the potential to accelerate discoveries across biomedical science. While these programs produce high-value datasets across a wide variety of projects and research consortia, their heterogeneity in formats, metadata, and access pathways has impeded data integration and reuse, a long-standing problem in the life sciences and other fields.[3–6] The Common Fund Data Ecosystem (CFDE) is a collaborative, NIH Common Fund-supported initiative designed to enable community-based standardization, integration, and enhanced accessibility of Common Fund data, thereby facilitating research and discovery (see companion paper; Kano et al.).[7,8] As of March 2026, CFDE offered access to 10,239,060 files, 2,101,705 biosamples, and 1,256,461 knowledge graph assertions from across 16 CFDE programs (https://data.cfde.cloud/processed). CFDE seeks to address interoperability challenges by connecting

communities centered on partially federated yet distinct data platforms. CFDE programs retain autonomy while contributing harmonized metadata to shared discovery platforms for use by the research community. Here, we provide an overview of CFDE and summarize challenges associated with data integration and reuse that necessitated the development of this initiative. We also outline the approach that CFDE has taken to address these challenges and provide examples from the effort.

The Common Fund's program portfolio encompasses multiple initiatives spanning common and rare disease phenotypes, clinical and basic data modalities, multiple species, and a multitude of biological processes. Data types include genetics and genomics, transcriptomics, epigenomics, proteomics, glycomics, metabolomics, drugs, imaging, and phenotyping, among others (Figure 1; interactive diagram available at https://cfde-sankey.github.io/). Collectively, Common Fund programs contribute to fundamental understanding of biological processes, clinical and translational science, generation of flagship reference maps and datasets, and development of standards for emerging areas such as artificial intelligence (Figure 2, Tables 1-2). Programs cover expansive ground in areas such as glycosylation, extracellular RNAs, the microbiome, molecular responses to exercise, rare disease genetics, bioelectronic medicine, signatures from massive perturbation studies, and illuminating understudied drug targets. Programs have independently developed their own Data Coordinating Centers (DCCs) as well as their own data models and portals, with the work of many spanning more than a decade. Since CFDE funding for each CFDE DCC is limited to 10 years, sustainability remains an ongoing challenge similar to that experienced by other federally funded efforts, despite various innovative approaches.[9–12]

Initially, CFDE programs were more inwardly focused with less emphasis on cross-program integration and interoperability. As CFDE matured and more programs were funded, CFDE sought to facilitate cross-disciplinary and collaborative data and code reuse across programs and projects. To enable this, CFDE developed the Cross-Cut Metadata Model (C2M2), a metadata standard that supports unified search across datasets.[7] CFDE has also adopted community standards for representing highly processed data such as knowledge graphs[13,14], gene regulatory information,[15] gene matrix transpose (GMT) files, and Croissant files,[16] with the goal of working toward FAIR (Findable, Accessible, Interoperable, and Reusable) principles.[17]

CFDE has undergone two phases in its development. During Phase I (2020-2022), CFDE was composed of Data Coordinating Centers (DCCs) from individual Common Fund programs and one CFDE Coordination Center.[18] The DCCs and CFDE Coordination Center collaborated via partnerships and working groups. Phase I focused on laying the groundwork for an ecosystem through development of community, infrastructure, and a few key products such as initial knowledge graphs, a preliminary portal for query of Common Fund data and information, and an initial cloud workspace. Phase II (2022-2027) aims to rapidly build upon the framework developed in Phase I, with the goal of demonstrating broad use of Common Fund data and tools for discovery. To achieve this goal, the NIH established five Centers to build awareness of CFDE resources and provide sufficient training and infrastructure for their use: the Data Resource Center (DRC), Knowledge Center (KC), Integration and Coordination Center (ICC), Cloud Workspace Implementation Center (CWIC), and Training Center (TC). The current structure of CFDE, comprising these 5 centers and 18 DCCs (Figure 2) along with multiple partnerships, directly enables new avenues of research and provides multiple entry points for users to access the ecosystem. Additionally, the NIH has developed other funding mechanisms (e.g., pilot projects; https://commonfund.nih.gov/dataecosystem/FundedResearch) to further demonstrate Common Fund data utility.

CFDE supports the biomedical research community by fostering cross-program collaborations across Common Fund programs,[13,14,19–21] illustrating the utility of developing and implementing standards for metadata harmonization, and lowering barriers to begin exploring the ecosystem. CFDE's approach is designed to promote interoperability and long-term impact of Common Fund resources by meeting research communities where they are with the capabilities to connect to broader resources, ultimately enabling a sustainable ecosystem that enhances and accelerates answering integrative research questions with best-in-class data resources.

## Results

### The CFDE approach to (meta)data

The Common Fund programs have produced data resources that offer a unique opportunity to observe and analyze biomedical processes at a scale and in a way that is often unattainable from other data resources. However, since Common Fund programs were established independently and asynchronously, each program created its own data types, data model, data elements, and

ontologies to represent its datasets. To realize the vision of easy access, integration, analysis, visualization, and exploration of data across publicly available Common Fund data resources, CFDE provides a thin layer of metadata harmonization through the C2M2 to enable integration and interoperability of multimodal datasets and exposes datasets ready to be merged for greater impact, as described below. Notably, some CFDE programs also rely on external repositories to house their data since they cannot be made accessible through CFDE. For example, human sequencing data from the Gabriella Miller Kids First Pediatric Research Program[22] must be maintained through controlled access repositories.

CFDE is not a true runtime federated query system. It creates a centralized, harmonized metadata catalog from periodic C2M2 data package submissions for cross-DCC discovery. The datasets remain distributed and under the autonomy of the participating DCCs. After datasets are discovered via a unified metadata search, they can be retrieved from DCCs using the provided persistent_id/access_url/drs links. Therefore, CFDE is a hybrid federated data ecosystem rather than either a fully centralized repository or a pure runtime federated query system.

## CFDE (meta)data formats & ontologies promote interoperability

A key output of CFDE interoperability initiatives is the Cross-Cut Metadata Model (C2M2; Table 3; Figure 3; https://data.cfde.cloud/img/C2M2_ERD_no_FKlabel_edited.png; https://info.cfde.cloud/documentation/C2M2). C2M2 standardizes metadata on experimental resources and products while promoting the harmonization and search integration of domain-specific data repositories.[7] Notably, C2M2 is a model of common CFDE metadata elements, not all metadata elements; it brings important shared attributes into the model but does not require all metadata elements across all projects to be aligned. This framework enables unified querying, aggregation, and integration of heterogeneous Common Fund datasets using harmonized metadata. C2M2 was initially designed for existing Common Fund datasets and has been adapted over time for data modalities from newer Common Fund projects, such as chromatin topology data from the 4D Nucleome project[23,24] and human clinical data from Bridge2AI.[25] C2M2 organizes metadata into core (Subject, Biosample, File), container (Collection, Project), and administrative (ID_Namespace, DCC) entities, enriched with ontology-driven attributes for taxonomy, anatomy, disease, assay, and data type (Figure 3). Figure 4 shows an

example of metadata in the C2M2 format for a single project, PR000663 (Biomarkers of NAFLD progression: a lipidomics approach to an epidemic), from the Metabolomics Workbench (MW) DCC.[26] Each piece of information in the C2M2 is accompanied by well-established ontologies, dictionaries, and mappings of DCC-provided namespaces to those defined by data providers. The DRC facilitates submission, ingestion and processing of C2M2 metadata to enable user queries for data discovery across the DCCs.[8]

The Acute to Chronic Pain Signatures (A2CPS)[27] project illustrates that C2M2 can be valuable as more than a downstream metadata exchange format. The program adopted the core C2M2 model internally because its primary entities and relationships matched much of what A2CPS needed to represent at a high level, including participants, biospecimens, assays, files, and study organization.[28] Where A2CPS required additional expressivity, particularly for longitudinal study events, perioperative milestones, and repeated clinical observations, the model was extended or adapted to capture those program-specific concepts while preserving compatibility with CFDE-aligned metadata practices. Using a C2M2-informed internal representation in this way both supported local harmonization and substantially simplified later submission to CFDE by reducing the amount of downstream remapping required.

Metadata coverage for C2M2 submissions over time is shown for one CFDE DCC, the Gabriella Miller Kids First Pediatric Research Program (Table 4).[22] These longitudinal C2M2 submission metrics reflect some variability due to two factors: firstly, variability driven by the standard ongoing data management activities of the Kids First DCC, including continuous maintenance and augmentation of study data; and secondly, variability driven by ongoing DCC C2M2 backend and pipeline improvements. For example, early incremental iterative testing and discovery in solidifying best data sharing practices and workflow improvements in transitioning from manual to automated pipelines led to initial fluctuations in metadata coverage. Data maintenance during Year 3 also led to a decrease in coverage for some entities during that time. However, results overall demonstrate progress in improving metadata coverage for certain aspects of C2M2 submissions over time and continuous improvement in the scope and scale of biosamples, files, projects, and subjects. Growth was driven by a combination of improved data measurement, tracking, and pipelines by the DCC, while data quality improved, in part, resulting from the validation and rigor introduced by the CFDE C2M2 manifest submission process.

A primary objective of CFDE was to develop standardized data and metadata formats, ontologies, and evidence attribution to enable interoperability.[7] A metadata model for experimental data was developed by two working groups approaching different aspects of interoperability. The CFDE Ontology Working Group selected the most appropriate ontology or controlled vocabulary for metadata in C2M2 (Table 3, Figure 3; https://data.cfde.cloud/img/C2M2_ERD_no_FKlabel_edited.png). Ontologies and controlled vocabularies were selected to be open access, stable but not static, community-endorsed, cross-mappable with other standards, and easily adoptable across existing databases. They themselves need to follow FAIR principles.[17] The CFDE Knowledge Graph Working Group assembled datasets and data products from eleven CFDE DCCs aligned with the ontologies and standards chosen by the Ontology Working Group into a unified analytic knowledge graph called the Data Distillery.

Additional standardized data and metadata formats have been developed primarily by individual CFDE DCCs with financial support from CFDE. These DCC initiatives promote broader integration of common data types across multiple CFDE DCCs and other non-CFDE programs. For example, in support of applications including multiscale reference atlas construction and exploration (Figure 5), a common coordinate framework (CCF) for Human Reference Atlas (HRA)[29] anatomical data was developed. The international HRA Working Group, led by HuBMAP and SenNet, created the CCF that captures the partonomy of 4,800+ anatomical structures (linked to UBERON ontology)[30] in more than 30 organs and the 1,300+ cell types located within them (linked to Cell Ontology), plus 2,070+ biomarkers (linked to HGNC) used to characterize those cell types.[29] The HRA CCF has been used to spatially register tissue data and to explore single-cell and anatomical data from HuBMAP, SenNet, HTAN, SPARC, Kids First, and many other projects (Figure 6).[31,32]

## Roles of standardized metadata formats in AI-readiness and lessons learned from the CFDE approach to metadata standardization

To build toward AI-readiness,[33] CFDE has more recently encouraged DCC adoption of Croissant,[16] a metadata format developed by an industry consortium to specify important information about datasets required for AI analytics. Thus far, Croissant has been

implemented by some DCCs (Bridge2AI, GTEx, LINCS, and MoTrPAC) for subsets of data and is expected to be applied to more datasets from these and other DCCs in the future. Beyond Croissant, AI-readiness includes specifying the provenance of datasets and software and detailed characterization of statistics, semantics, recommended and prohibited use cases, ethics, and computability. CFDE has not yet adopted an ecosystem-wide set of practices to address these additional facets of AI-readiness.

In large ecosystems like CFDE, two disparate approaches may be applied to metadata formatting requirements. An ecosystem may adopt few formats[34] or may alternatively adopt multiple formats.[35] Benefits of the first model include standardization of practices in a common framework and reusability of tools, but barriers exist to representing diverse multi-program data types, data models, data elements, and ontologies within a single framework. Benefits of the second model include the potential for increased community adoption, with a tradeoff of reduced interoperability. CFDE has favored the first approach, aligned with its goals of increasing interoperability across the ecosystem, but at times has engaged in judicious use of the second approach when the benefits of accessibility on disparate platforms outweigh the drawbacks (e.g., knowledge graph accessions, API definitions). Each of these formats is a “standard” within a specialized community and enables additional use cases and applications of the data.

## Knowledge graphs and infrastructure for data integration

A major goal of CFDE is to catalyze scientific hypothesis generation through integrative analyses that combine datasets generated by Common Fund programs with community-developed tools and data from other public resources. To achieve this goal, members of the CFDE community have developed infrastructure for data integration and hypothesis generation. The CFDE DRC, CWIC, and KC provide centralized locations to search, browse, and visualize high-level insights from datasets across DCCs and beyond, as described below.

To facilitate downstream analyses, datasets are processed into higher-order abstractions, such as knowledge graphs, gene set libraries, and attribute tables. CFDE knowledge graphs include the CFDE Data Distillery Knowledge Graph, ReproTox-KG, the BiomarkerKB Knowledge Graph, CFDE-GSE, Petagraph, and the HRA Knowledge Graph.[13,14,19,20,36] The CFDE Data Distillery

Knowledge Graph (DDKG; https://github.com/nih-cfde/data-distillery)[14] currently integrates over 180 ontologies and controlled vocabularies and data from 11 CFDE DCCs and several non-CFDE programs, enabling queries across disparate biomedical dataset types.[14] ReproTox-KG is (https://maayanlab.cloud/reprotox-kg) a knowledge graph that enables exploration of genetic or toxicologic mechanisms underlying structural birth defects.[13] By leveraging similarities in structures and gene expression signatures of small molecules, ReproTox-KG can be used to predict drugs' placental crossing capabilities and teratogenic risk. The BiomarkerKB (https://biomarkerkb.org) partnership has recently developed a standardized data model and controlled vocabulary for biomarkers, representing over 200,000 biomarkers and 1,000 phenotypes in multiple formats including a DDKG-integrated knowledge graph.[19] The CFDE Gene Set Enrichment (https://gse.cfde.cloud/) provides an integrated enrichment analysis from gene set libraries derived from eight Common Fund programs.[8]

Some of these knowledge graphs were designed with interoperability in mind, and integration of many is ongoing. DDKG-UI[14], ReproTox-KG[13], BiomarkerKG, ProKN, and CFDE-GSE[8] leveraged a generic KG user interface (KG-UI) template[37] that was developed by the DRC,[37] which uses Cytoscape as a main component for the frontend user interface and the Neo4j graph database platform (Neo4j, Inc.; https://neo4j.com/) for the backend KG database.

The Unified Biomedical Knowledge Graph (UBKG) serves as a base infrastructure that allows many assertions and entire graphs to be ingested for use across CFDE, with DDKG being the prime example that has used it (see use case section below). The CFDE Knowledge Graph Working Group is currently working on an exchange format standard consisting of a second version of UBKG with exchange in JSON, which will facilitate interoperable *ad hoc* assembly of assertions and knowledge graphs. CFDE's UBKG-based knowledge graphs include DDKG, Petagraph, and the BiomarkerKB Knowledge Graph. Petagraph is an early version of DDKG,[20] and the BiomarkerKB Knowledge Graph uses the same format and technology as DDKG and is integrated into DDKG in addition to a standalone format.[19] ASCT+B, a part of the HRA Knowledge Graph, is also integrated with DDKG.[36] The Protein Knowledge Network (ProKN; https://research.bioinformatics.udel.edu/ProKN) represents another UBKG-aligned knowledge graph, providing protein-centric data integration and use cases, leveraging the UniProt knowledgebase and associated resources. A

DDKG-compatible version of C2M2 is currently being explored. The DDKG, Petagraph, HRA Knowledge Graph, and other non-CFDE KGs have previously been visualized through a bimodal network to compare the ontologies imported and served by these KGs.[36] CFDE knowledge graphs have been interlinked to run novel queries and support multiscale data visualization and exploration (Figure 5), and machine learning analyses of CFDE knowledge graphs have generated new gene-disease association hypotheses across a dozen conditions.[38]

## CFDE collaborations with other consortia

CFDE frameworks for integration and analysis support cross-program analyses of CFDE data and, in some cases, enhance connections between CFDE and other large global repositories. For instance, the UniProt-CFDE partnership facilitates connections between protein-level data from UniProt[39] and other resources and genome-centric data from CFDE. This partnership is developing the Protein Knowledge Network (ProKN), a protein-centric multi-omic integration knowledge graph framework building on and complementing the DDKG. The ProKN combines CFDE and non-CFDE data at the genome, protein, drug, and phenotype levels to facilitate functional genomics discovery. Similar connections with the Knockout Mouse Phenotyping Program (KOMP2)[40,41] and the Bridge2AI Cell Maps for AI[25] project (CM4AI) and the Bridge2AI Bridge Center are enabling connection with additional modalities. Such partnerships also leverage new tools such as KSMoFinder,[42] a supervised neural network classifier that predicts kinases of human phosphosites at the motif and substrate levels for phosphoproteomic data analysis.

Partnerships between CFDE and non-CFDE teams can enrich the landscape for interoperable biomedical analyses. For example, the Metabotyping Humans partnership project spans the Metabolomics Workbench (MW),[26] Molecular Transducers of Physical Activity Consortium (MoTrPAC),[43,44] Human Health Exposure Analysis Resource (HHEAR),[45] and Nutrition for Precision Health (NPH)[46] programs and focuses on metabotyping. A metabotype defines a collection of metabolites or metabolite classes associated with a group of individuals based on the metabolome of humans conforming to a given phenotype. The project team is harmonizing metabolomics data across the three centers to identify metabotypes and facilitate functional interpretation. The team is developing

tools that will allow exploring how perturbations such as exercise, diet, or environmental exposures shift homeostatic metabolic states.

The Gene Regulatory Working group engaged the NHGRI Clinical Genome Resource (ClinGen) project to develop and implement a registry of regulatory elements and standards for sharing gene regulatory information. This two-way collaboration leveraged ClinGen infrastructure while harnessing information from CFDE projects to identify disease-causing gene regulatory variants revealed by genome sequencing, which is a core focus of ClinGen.[15]

## Documenting data, pipelines, and standards

Communities often develop internal practices that provide information necessary to understand the key variables of an experiment or analysis without becoming overly cumbersome. As a community-of-communities, CFDE has not adopted a single ecosystem-wide approach or platform for developing and running computational pipelines or experiments. However, CFDE has developed guidelines for how data resources and experimental methods are documented, and metadata collection is shareable, public, modular, and combinable.

CFDE itself has developed and centralized multiple publicly accessible user guides, protocols, and standards (https://data.cfde.cloud/documentation). Moreover, as of March 2026, the CFDE community has developed 11 distinct recommendations for policies, standards, and design principles pertinent to an array of needs within the ecosystem (https://github.com/nih-cfde/rfcs/blob/master/adoptionstatus.md). For example, the CFDE Playbook Partnership[21] was a two-year partnership project that involved the Data Resource Center and six DCCs. Together, partnership members created a visual platform to construct workflows from building blocks called metanodes. Each metanode can be an input form, an executable function like an API call, or an output such as a figure or a table. By combining metanodes, many workflows can be generated without the need for coding. The members of the partnership developed over 20 use cases that demonstrate how the system can perform on-the-fly analyses that integrate data from multiple Common Fund programs to form novel hypotheses or enrich users' input data. To support

this accomplishment, the partnership established standards for the development of interoperable APIs that could be used by multiple Common Fund DCCs in support of modular workflow development (https://github.com/nih-cfde/rfcs/blob/master/adoptionstatus.md).

Common Fund DCCs have also developed internal processes for documenting data and pipelines. While these are not CFDE products per se, CFDE does support the reuse and sustainability of these resources. Moreover, CFDE recognizes that some of these DCC-developed resources could be adopted more broadly across other resources to improve reproducibility and interoperability both within and outside of CFDE. Thus, a few examples are showcased here.

As one example, the GlyGen DCC approaches documentation of data and pipelines through the use of BioCompute Objects (BCOs).[47] All data ingested into GlyGen are stored as datasets at data.glygen.org. For each dataset, a BioCompute Object (BCO) is created that conforms to the IEEE BCO specification[48] and has been adapted for database and knowledgebase resources.[49] These dataset-level BCOs are generated from the perspective of the integration workflow, ensuring that every processing step and its associated metadata are captured. The resulting BCO serves as a “readme” for the dataset, providing precise details on how the data were integrated. By adopting the BCO standard, GlyGen ensures granular tracking of metadata, particularly provenance, which supports proper attribution, license compliance, workflow exchange between researchers, and reproducibility. All dataset BCOs are recorded in machine-readable JSON format and are available for viewing and download at the GlyGen data portal (data.glygen.org). As datasets are updated, their corresponding BCOs are also revised and versioned. Everything visible on the GlyGen frontend (glygen.org) is documented within BCOs. This extends beyond data provenance to include software provenance, input/output files, and where needed embedded workflow languages (e.g. CWL) that enable automated execution. Together, these practices not only enhance reproducibility and transparency but also support long-term sustainability, so that even if original resource providers can no longer maintain the resource, others can continue its use and development. Wider adoption of BCOs across resources both within and outside of CFDE could provide a robust standard for workflow documentation, transparency, reproducibility, and interoperability.

Among other DCCs, the MoTrPAC bioinformatics center harmonizes data across multiple submitters, projects, and -omics analysis approaches to facilitate downstream analyses. A series of quality control and metadata harmonization scripts (https://motrpac-data.org/code-repositories) prepare data for downstream normalization and analysis. HuBMAP (https://docs.hubmapconsortium.org/data-submission/Section6.html), SenNet (https://docs.sennetconsortium.org/data-submission/Section6.html), and SPARC[50] have established rich metadata and directory structure schemas with required and optional fields that all members of respective consortia must adhere to when submitting datasets. The metadata and directory schemas function as reference frameworks that allow for cross-program data findability and reuse. Datasets are validated against these schemas to promote data interoperability, reusability and compatibility with standardized pipelines. Central HuBMAP analysis pipelines are built with Docker containers in a Common Workflow Language (CWL) workflow to support reuse and reproducibility of these processing pipelines. KidsFirst uses CWL and Nextflow workflows and tools to enable reproducible bioinformatics. Currently, over 1000 community-sourced workflows are available for use via Cavatica (www.cavatica.org). Cavatica is also used by multiple DCCs across CFDE (e.g., LINCS, GlyGen, Kids First, exRNA)[51,52] in the CFDE Playbook Partnership (https://playbook-workflow-builder.cloud/playbooks).[15,21]

## Tools and interfaces for data analysis, visualization and discovery

Multiple CFDE initiatives target improving cross-program data harmonization and visualization within the ecosystem. One example is the Human Reference Atlas (HRA; https://humanatlas.io), which combines multiscale datasets and donor metadata from multiple CFDE programs (HuBMAP, SenNet, and GTEx; Figure 5). This supports construction of cell atlases, and harmonized reference data is available via the HRA Knowledge Graph (KG).[29,36] There are multiple tools for web-based access to the HRA, including the HRA KG Explorer (https://apps.humanatlas.io/kg-explorer), spatial examination via the Exploration User Interface (EUI; https://apps.humanatlas.io/eui; Figure 6c),[53] with cell distance distributions analyzable through the Cell Distance Explorer (CDE, https://apps.humanatlas.io/cde)[31] and immersive integration and visualization of healthy donor cell types available through the HRA Organ Gallery (https://humanatlas.io/hra-organ-gallery).[29]

Based in part on these integrative, collaboratively-developed tools, multiple CFDE Centers, in particular the Data Resource Center (DRC; https://info.cfde.cloud/)[8] and the the Knowledge Center (KC; https://cfdeknowledge.org), build toolkits for constructing integrative resources. The ultimate goal is to enable users who lack deep computational expertise to construct similar integrative analyses through intuitive web-based interfaces.

The DRC developed the tools GeneSetCart[54], GDLPA[55], CFDE-GSE, the Playbook Workflow Builder (PWB)[21], Rummagene[56], RummaGEO[57], and GSFM[58], all centered around the abstraction of omics datasets from over 10 Common Fund CFDE programs, and external resources, into gene sets, and the process of combining gene sets from multiple Common Fund programs for cross DCC knowledge discovery and hypothesis generation. Furthermore, the DRC's CFDE Workbench[8] provides an entry point for DCCs to submit processed data and metadata about their data, and a mechanism to search and discover data, processed data, knowledge graph assertions, and tools developed by the DRC and CFDE partnerships, applicable to items discovered on the workbench. The CFDE Workbench's search functions are exposed via an API and Model Context Protocol (MCP) server, leveraged by the CFDE Workbench chatbot to find DCC-submitted knowledge and trigger PWB workflows to respond to user queries.

The KC provides a centralized, user-friendly web entry point for the ecosystem and promotes novel disease-focused discoveries and integrative use cases. Users can gain a broad understanding of the ecosystem through curated summaries of each CFDE DCC, including its purpose, data, resources, and key publications. The KC routinely attends conferences and hosts a regular webinar series (https://cfdeknowledge.org/r/CFDE_webinars) to promote broader visibility into and integration of CFDE resources. A summary of flagship outreach activities by the KC and other centers is provided in Table 5.

Given the expansive range of data and information across CFDE, it is important to help users identify the data, information, or analytical results most relevant to them. To guide users toward datasets or analyses of interest, the KC has implemented large language model (LLM)-assisted workflows, CFDE-REVEAL and CFDE-DESIGN, whose current implementation leverages the OpenAI GPT5-mini LLM model. CFDE-REVEAL (https://cfdeknowledge.org/r/cfde_reveal) is an interface that converts users'

questions into mechanistic hypotheses. From user-supplied natural language queries, CFDE-REVEAL performs semantic search across statistical associations of gene sets and traits from the KC Gene Set Browser (https://cfdeknowledge.org/r/kc_gsb). An LLM then reveals candidate hypotheses and mechanisms derived from these associations. For example, a user might ask, “What are druggable targets for obesity?” REVEAL extracts search terms from the query, returns the top phenotype-gene signature associations across CFDE programs, and uses these associations to generate mechanistic hypotheses such as identifying a microRNA-mediated growth and extracellular remodeling axis that connects BMP/SMAD signaling to hip circumference. Specific candidate genes are proposed (e.g., *LTBP3, HMGA2, HSPG2*), and the underlying phenotype-gene signature associations and gene set clusters are provided that support each gene. These hypotheses or independent gene set-trait associations can then be supplied to a second KC workflow, CFDE-DESIGN (https://cfdeknowledge.org/r/cfde_design), to produce customized LLM-generated experimental protocols.

## Cloud computing infrastructure

Conducting integrative analyses can be challenging when the data reside in different environments. CFDE’s standardized metadata and tools aligned with community practices create the opportunity for a cloud computing environment capable of running analyses that integrate data from the underlying data repositories. The Cloud Workspace Implementation Center (CWIC) (https://cloudworkspace.org) provides a unified, scalable, and secure computational environment designed to aid interoperability among Common Fund resources to support a broad range of biomedical researchers and data scientists. Built on the Galaxy platform (https://usegalaxy.org),[59] CWIC offers a familiar interface that anchors a suite of integrated tools and environments. Users access CWIC using their free account that supports two-factor authentication and role-based access controls. This access is managed by the Texas Advanced Computing Center (TACC) application programming interface (Tapis).[60] Once logged in, users can access Common Fund datasets, tools, and workflows through the feature-rich, zero-code Galaxy graphical user interface and launch interactive sessions in Jupyter and RStudio. As TACC users, individuals can also directly access high-performance computing (HPC) resources using command-line interfaces. This direct access enables advanced customization, including the selection of compute

nodes, the installation of specialized packages, and the configuration of environment parameters tailored to specific workflows. Users access commercial cloud resources through CloudBank (https://www.cloudbank.org).

CWIC supports both CPU and GPU-based workloads, particularly for compute-intensive AI workloads. To minimize barriers to data-intensive research, CWIC minimizes data transfer and egress costs, aiming for seamless integration with external data repositories and services. Features such as workflow sharing, provenance tracking, and usage analytics enable users to effectively manage and optimize their computational resources. User dashboards enable usage, promoting transparency and supporting informed resource management. Furthermore, by leveraging several major GA4GH standards,[61] such as the Directory Registry Service (DRS) and Tool Registry Service (TRS), CWIC enables users to easily integrate with datasets and resources from other biomedical cloud resources such as the NHGRI AnVIL[62] or NHLBI BioDataCatalyst.[63] Overall, CWIC is developed as an open-source platform, leveraging existing investments in Galaxy and related projects to support long-term sustainability and community-driven innovation.

## Training and workforce development

The CFDE Training Center (TC) serves as a hub for developing and implementing training programs that bridge knowledge gaps, improve access to CFDE resources, and foster collaboration among CFDE community members and other researchers. Building the TC required a detailed assessment of the current training landscape to understand the needs and challenges of the CFDE community. Specifically, the landscape analysis assessed the effectiveness of existing CFDE training programs, identified barriers that impact researcher engagement and learning outcomes, evaluated best practices from bioinformatics and data science training models, and developed evidence-based recommendations to improve CFDE training strategies. Recommendations included improving access to resources through a centralized platform for CFDE resources; enhancing training structure through modular, hands-on, self-paced courses; strengthening mentorship programs through “train-the-trainer” programs that equip mentors with effective teaching and communication skills; and expanding evaluation methods with pre- and post-training assessments to measure

knowledge gains and real-time quizzes and coding exercises with instant feedback to reinforce learning (CFDE Training Team, personal communication).

The TC serves the CFDE community by building foundational and advanced omics analysis skills through a dynamic syllabus grounded in six aims for comprehensive development: understanding biological domains relevant to CFDE datasets; leveraging biological reference databases; automating computational tasks with scripting; using software and programming tools; applying appropriate statistical and visualization methods; and leveraging advanced computing and collaboration tools. Each aim includes clear learning outcomes structured around three cognitive levels—Remember, Understand, and Apply—to guide researchers from conceptual understanding to practical application (Figure 7a).

Together, the TC supports a cohesive and scalable learning framework for biomedical scientists. The TC has developed a wide range of resources and materials and hosted 10 events, such as the Decoding the Data Ecosystem podcast (https://podcast.show/3847772/) with over 900 views, the e-Learning Dashboard (which includes a How-To Seminar Series) (https://orau.org/cfde-trainingcenter/training/e-learning.html), a Digital Scavenger Hunt, and the Bio-IT World Hackathon (https://www.bio-itworldexpo.com/) (Figure 7b). By integrating these benchmarks into its initiatives, the TC has created an environment for the community that will empower researchers to leverage CFDE datasets and tools effectively while fostering collaboration and innovation. The TC has developed a robust program based on participant feedback to inform the development of new training resources and opportunities, while establishing partnerships with CFDE DCCs and other training and outreach efforts to adapt to changing needs.

## Coordination and Assessment

The CFDE Integration and Coordination Center (ICC) works across three core areas: administrative coordination, evaluation, and sustainability. ICC administers CFDE working groups and hosts semi-annual CFDE conferences, manages cross-CFDE

communications, defines evaluation metrics and creates dashboards to help monitor CFDE to identify best practices and areas for growth, and develops and supports sustainability strategies.

The CFDE evaluation strategy encompasses three temporal scales of outcomes. Short-term metrics focus on resource availability, tracking the deployment and accessibility of datasets, software tools, web-based platforms, and training materials such as webinars and tutorials. Mid-term assessments emphasize user engagement through usage statistics, user satisfaction surveys, trainee feedback, and early indicators of resource sustainability. For example, across CFDE web properties steady growth in usage was observed through mid-2025 (40-50% growth rates), at which point access patterns, potentially driven by AI-associated systems, drove substantial growth (1972 engaged sessions per day in 2024; 6953 engaged sessions per day in 2025). Long-term impact evaluation examines transformative outcomes, including peer-reviewed publications describing or leveraging CFDE resources, sustainment efforts and funding, and qualitative or quantitative changes in research practice or workforce. This multi-tiered, shared responsibility model provides a comprehensive framework for understanding how data ecosystem infrastructure translates into scientific advancement and community transformation.

The ICC's Evaluation Core has implemented automated workflows that supply NIH and stakeholders with standardized publication and citation metrics, social coding metrics (via GitHub), and Google Analytics. A centralized event and calendaring system forms the basis for the ongoing assessment of outreach activities, utilizing a shared survey approach. Automated collection of GitHub metrics, publication and citation metrics, Google Analytics, overall project budgets and funding timelines across funded CFDE projects, powers a dashboard that enables rapid examination of both ecosystem-wide and component-specific contributions.

The ICC Evaluation Core's automated collection of GitHub analytics for CFDE-developed source code from December 5, 2025, indicated 127 public repositories from CFDE-supported projects, which had garnered 861 stars. Open licensing is often key for sustainability. Across the public repositories, most had explicit open source licensing with 54 repositories using MIT licensing followed by 22 GPLv3 licensing. A README file, important for community engagement for open source software, was available for 85% of

repositories. Across all repositories, a total of 259 contributors had performed 108,614 commits and closed 14,767 pull requests. The TC utilized the Academic Analytics Research Insights database to examine research activities associated with 14 CFDE programs across 531 U.S. academic institutions. A total of 1,990 scholars from 195 academic institutions referenced at least one CFDE dataset in 4,438 publications. Finally, individual Common Fund programs demonstrate broad impact through their contributions to the scientific literature. For example, between 2013 and 2024, the exRNA Communication Program[64–66] alone produced 877 publications that were cited 79,442 times.[67]

## Sustainability

The ICC's Sustainability Core has developed a framework for improving the FAIRness, AI-readiness, and sustainable management of CFDE datasets through three guiding principles.[68] The current implementation is informational as opposed to evaluative. First, dataset collection and management must be ethically sourced, with data privacy, safety, and integrity safeguarded throughout every operational step, from acquisition to curation and dissemination. Second, building trust must be understood as a collaborative process involving both data contributors and users, embedding co-design and stewardship principles that cultivate transparency and accountability across the data lifecycle. Finally, achieving transparency, provenance, and explainability in all tools and resources is essential to rendering datasets reproducible and sustainable over time. Together, these components embody a commitment to ethical stewardship that enables CFDE to serve as a foundation for responsible and trustworthy biomedical AI integration.

Sustainability considerations for CFDE include data, computing, code, and funding. With respect to data, the DRC accepts quarterly submission of different datasets, metadata, and code assets from the DCCs. These include dataset assets and code assets. Dataset assets include C2M2 data packages,[7] knowledge graph assertions,[14] gene set libraries, and attribute tables. Code assets include APIs, ETLs, landing pages templates such as gene, drug, and disease pages, and models. As of March 2026, the Data Matrix on the Data Portal contains 70 assets that include 15 C2M2 packages submitted by 15 DCCs. Submissions are assessed for FAIRness using FAIRshake[69] (https://fairshake.cloud/) and vetted by both the DRC and the submitting DCCs. The FAIRshake evaluations are reported back to the submitter as feedback about what they can improve to make their assets more FAIR. FAIRshake evaluation

checks for data formatting errors in addition to FAIRness through a complex evaluation rubric (https://fairshake.cloud/rubric/) that is inspired by the universal FAIR metrics[70] but does not map to them precisely. While the DCCs have improved the FAIRness of their metadata, data, and code asset submissions over time, this is difficult to observe because over time new DCCs are introduced to the ecosystem and more assets are added to the Data Portal (Figure 8).

CFDE has not yet fully addressed the funding component of sustainability, and discussions of how to address this remain ongoing. As a partial solution, the ICC has mapped key CFDE data types to potential repositories available to host them at the conclusion of awards, with the idea that CFDE data could potentially be integrated into these external repositories for sustainability (Figure 1; interactive diagram available at https://cfde-sankey.github.io/). Some DCCs have already selected a subset of these repositories to host their data given the repositories' support of long-term sustainability. Sustainable access to computing is supported by the variety of computing resources available to users. TACC systems allow users access to 100K+ CPUs, 1K+ GPUs and 100s of petabytes of storage to allow for analysis and reproducibility of large-scale analysis. Additionally, users have access to commercial cloud computing tools via the Cloudbank partnership, which provides users access to all major cloud computing platforms. Collaborations between the KC, DRC, and CWIC enable users to identify datasets or construct workflows and then launch jobs directly onto the CWIC. The CWIC enables users to share their history, supporting the dissemination of workflows to easily reproduce analyses and validate data without having to re-conduct the underlying analyses.

## The value of an ecosystem: highlighted use cases and biological insights

Finally, CFDE aims to generate substantial community impact through three primary mechanisms: fostering cross-program collaborations among previously siloed Common Fund programs, establishing shared technical standards for metadata harmonization, and lowering barriers to entry for researchers unfamiliar with specific Common Fund program resources.

Use cases for cross-program collaborations arguably provide the most important insights for constructing analytical and data integration tools and demonstrating integrative data analysis. Most biomedical researchers develop hypotheses based on a

mechanistic, conceptual, or analytical model, embellishing it with additional data and evidence. Common Fund projects offer best-in-class datasets and tools that can aid a biomedical researcher in developing novel biological hypotheses and outcomes.

As a demonstration of this cross-ecosystem discovery, here we present a use case from the Data Distillery Knowledge Graph[14] using the Neo4j graph database platform (Neo4j, Inc.; https://neo4j.com/). We provide a Cypher query that captures mechanistic hypotheses that link genetic variation to disease through tissue-specific metabolic and transcriptional processes (Figure 9). The query follows a workflow initially proposed by the IDG Reactome Project (https://idg.reactome.org/) and was developed to extract a tightly constrained, semantically coherent subgraph from a biomedical knowledge graph by composing multiple relationship patterns across heterogeneous data sources. The query first anchors on a three-hop causal–correlational chain linking gene, metabolite, and condition concepts using source-qualified edges from Metabolomics Workbench (MW), then incrementally refines the result set by enforcing additional topological and semantic constraints. These include tissue-level provenance of metabolite production, independent evidence of gene expression from GTEx via intermediate expression entities, and shared or related tissue contexts connecting molecular activity to disease-relevant anatomy. After filtering the core graph pattern, we populate the resulting subgraph with low-cardinality annotations (preferred terms), upstream biochemical relationships from Illuminating the Druggable Genome (IDG) (gene–protein–compound), and quantitative expression metadata. This generated structure reflects a deliberate graph-querying strategy that balances expressiveness with performance while preserving provenance, semantic specificity, and interpretability of the extracted subgraph. The query is designed to use the information provided for tissue-specific diseases (utilizing content from the UMLS-based Unified Biomolecular Knowledge Graph (UBKG; https://ubkg.docs.xconsortia.org/))[20] as a means to filter the results and provide more meaningful relationships.

The results (Table 6) demonstrate sample outputs from this query, showing a candidate biological pathway in which a gene product (*MGAM*) influences a metabolite (sucrose) associated with a clinical condition (polycystic kidney disease). Both processes are grounded in a relevant tissue (kidney), where the sucrose levels may be influenced and *MGAM* is expressed. Finally, IDG suggests compounds associated with MGAM, thus highlighting candidate therapeutic targets for this pathway. While this example is

exploratory and would require additional downstream supporting evidence, it does show the power of this interface to rapidly generate initial hypotheses for future validation by leveraging information from multiple CFDE programs.

By integrating gene-metabolite-condition linkages from Metabolomics Workbench, expression evidence from GTEx, tissue anatomy from GTEx, and upstream chemical and protein interactions information from IDG, the extracted graph supports interpretation of how molecular regulation propagates across biological scales. This type of integrative representation is particularly valuable for elucidating disease mechanisms, prioritizing therapeutic targets, and identifying candidate biomarkers, as it contextualizes gene–disease associations within the metabolic, anatomical, and biochemical systems that underlie human pathophysiology. Because integrative tools from CFDE are still relatively new, efforts to disseminate these resources and demonstrate their uptake by the community are still ongoing.

## Challenges and solutions

CFDE shares certain challenges of its participating Common Fund-supported projects. These projects are ambitious, cross-disciplinary, and at the forefront of their fields. Therefore, nearly every project has elements that are both unique to CFDE and unique within their field. Across DCCs, priorities are often split between addressing the immediate needs of the project and the enabling work of the ecosystem, drawing focus away from generalizable solutions. CFDE Centers provide a mechanism to address this challenge by collaborating with DCCs on targeted initiatives. For instance, the CFDE KC and DRC are working with DCCs to develop and implement “The CFDE Navigation Wheel (Figure 1),” an interactive diagram of CFDE components that provides centralized access to the ecosystem across its many disparate web entry points. Finally, CFDE co-evolves alongside Common Fund programs to extend to broader data types, modeling, and simulations.

While CFDE aims to evaluate FAIR principles[71] systematically through FAIRshake[69] and to encourage the adoption of FAIR principles among DCCs, the uptake of FAIR principles across the ecosystem remains ongoing, and the ecosystem aims to balance promoting FAIRness with the timely sharing of data to encourage their uptake even if they are not yet completely FAIR. While this challenge is

not unique to the CFDE, each ecosystem has its own unique needs that require tailored approaches to improving FAIRness over time.[72,73] A previous study[74] analyzed the FAIRness of 28 major biomedical databases, 4 of which were CFDE programs (GTEx, HuBMAP, LINCS, and Metabolomics Workbench), using a 29-question rubric. For each of the 29 questions, one point was assigned if the information could be identified from the database to answer the question. Scores across the 28 databases ranged from 7 to 29 points, and the mean FAIRness score for CFDE databases was higher than for all databases (24.25 points for CFDE databases; 18.57 points for all databases), and the only database to score 29 points was the CFDE program HuBMAP. However, most CFDE databases had room for improvement across the FAIR spectrum.

Sustaining the large scale Common Fund data resources is nontrivial, as each DCC has developed its own architecture for consent and data access. The technical solutions used by individual DCCs often reflect the state of the art in their field at the time of DCC development, but many require engineering and informatic liftover to meet interoperability standards and best practices. Research objectives and data types also range across and within DCCs, and nearly any type of biomedical data referential to nearly any organ, tissue, molecule, disease, experimental approach, organism, or analytic approach may be part of a CFDE DCC. Thus, data harmonization is required across the same and distinct data modalities, but integration must focus on the practical to remain feasible, and many data elements may ultimately not be harmonized. Integrating data types across DCCs at different stages in the life cycle of a Common Fund project is difficult post-hoc but is supported by efforts including onboarding new data types, ontologies, and standardized metadata. Analysis workflows also partially address data integration challenges by building dynamic analytic strategies. For example, the Playbook Workflow Builder enables non-computational biologists to develop modular code-free analysis workflows that draw from multiple data sources and analysis pipelines to enable reproducible, cross-DCC discovery.[21] Workflow development is also supported through the generation of APIs by CFDE programs and centers. Visualization tools like Vitessce,[75] the Cell Distance Explorer,[31] the Exploration User Interface,[53] or the HRA Organ Gallery[76] support standard data formats and make it possible to display, explore, and download 2D and 3D data visualizations. However, they do not support all data formats, and multiscale data exploration and zoom, from the meter size human body to nm-scale biomarkers (e.g., 3D protein structures), is challenging (Figure 5).

Due to the 10-year limit of the legislation establishing Common Fund programs, many DCCs (e.g., GTEx) support 'legacy' datasets maintained through more limited versions of their data coordinating centers and/or deposited in data repositories but no longer supported by an underlying Consortium. Other DCCs (e.g., Metabolomics Workbench) overcome this challenge by serving as a perpetual knowledge center for particular data types. The CFDE Centers also support certain functions required for DCC sustainability. For example, the CWIC partially addresses sustainability concerns by providing computational infrastructure, lightweight long-term maintenance, multiple funding streams, and a model for data analysis that requires authentication. However, certain sustainability functions fall outside the purview of the Centers.

Finally, there are hurdles in establishing, broadening, and educating a user base for CFDE and in creating a unified experience for a wide array of user archetypes. The massive operational and domain-level scales of CFDE makes it difficult to define a single group of target users, and each CFDE DCC has its own unique consortia, which vary from one another and from other users outside of these consortia. Despite these challenges, CFDE has observed substantial increases in usage over time, as mentioned in the "Coordination and Assessment" section above. The COMPA (Communication and Outreach to Maximize Product Adoption) partnership was established to prototype market research of three test CFDE products in order to inform a CFDE-wide strategy to enhance the visibility and adoption of its range of products. The COMPA partnership studied three resources across the CFDE landscape and found the following problems across them: lack of user tracking, low awareness of CFDE resources, insufficient onboarding and training, undefined user personas, challenges in identifying and leveraging outreach and engagement venues, and concerns around sustainability. The report recommended developing a flexible toolkit of strategies and best practices in order to improve user identification, outreach and awareness, usability and support, programmatic API access, and user tracking and metrics. Additionally, new CFDE tools have been developed to identify the CFDE data or knowledge most pertinent to individual users, such as the KC tool CFDE-REVEAL (https://cfdeknowledge.org/r/cfde_reveal; see "Tools and interfaces for data analysis, visualization, and discovery").

## Discussion

CFDE was established to directly address fundamental challenges hindering biomedical discovery across NIH Common Fund programs: siloed repositories developed by specific projects, heterogeneous formats that impede cross-study analysis, and limited sustainability of data beyond individual program lifespans. The core of CFDE's success lies in its adoption of a hybrid federated data ecosystem model rather than a fully centralized repository or a pure runtime federated query system. This strategy avoids duplicating massive datasets by harmonizing the key elements of rich metadata while leaving the raw data in its original DCC repository, thereby respecting DCC autonomy and providing a unified discovery experience. Federation is facilitated in part by the C2M2 model, a flexible metadata schema that supports consistent search and integration across DCC resources. By integrating metadata from NIH Common Fund programs individually designed for transformational science and discovery and for re-engineering the research enterprise, CFDE provides a crucial infrastructure layer, enhancing the value of DCC resources.

Systematic cost-benefit analyses within other ecosystems outside of CFDE have shown that harmonized ontologies, tools, computational support, and training can save researchers time, streamline the research process, and lead to economic value.[77,78] Similar future cost-benefit analyses of CFDE resources will be useful to demonstrate the impact of CFDE on these outcomes and to inform broader recommendations for other large ecosystems. Other large biomedical consortia have additionally demonstrated the value of accessible platforms for reference datasets, standards, and interoperability (e.g,, The Encyclopedia of DNA Elements (ENCODE)[79], The Human Cell Atlas (HCA)[80], The Monarch Consortium[81], The International Cancer Genome Consortium[82], All of Us[83], and UK Biobank[84]), though these initiatives differ in their architecture (federated versus centralized) and data access models (open versus controlled).

In considering the challenge of integrative data reuse from the breadth of Common Fund programs, a single portal or commons is unlikely to be sufficient to drive transformative discoveries. CFDE is designed as an ecosystem with multiple specialized communities brought together alongside the software, skills, and data to enable success. This represents a shift in how biomedical data are managed and utilized and provides a blueprint for future efforts. By overcoming fragmentation through a rigorous and

community-driven approach, the ecosystem is supporting and enhancing the value of NIH Common Fund programs, positioning them for integrative analyses that support new discoveries.

## Methods

### Preparation of CFDE Review

This review was collectively assembled by members from across the CFDE community. A small Publication Working Group with representation from DCCs, partnerships, and centers outlined the key features of CFDE to be described and assigned individual manuscript sections to community members with domain expertise in them. For a subset of sections, a Publication Writing Sprint was held at the Fall 2025 CFDE Meeting, where ~60 members from across CFDE collectively contributed to brainstorming and drafting initial versions of the text. The text was further refined by the Publication Working Group, and then by all co-authors from across CFDE to produce the final version.

### Development of Aims for CFDE Omics Skills Development

The Training Center utilized a mixed-method approach including a review of existing CFDE trainings, key informant interviews with CFDE subject matter experts and learners, a systematic literature review, a CFDE trainer survey, a mentor survey, an analysis of CFDE datasets mentioned in academic research, and information gathering from CFDE stakeholders from Data Coordinating Centers (DCCs). Each aim includes clearly defined goals and outcomes to ensure a structured and effective learning experience. The aims are based on three core learning elements: Remember, Understand, and Apply.

### Metrics Collection

We developed software to collect metrics on resource usage on CFDE-developed software and web properties from GitHub and Google Analytics alongside publications that reference CFDE funding. For GitHub, awardees tag repositories with their grant identifier. We then use the GitHub API to find each tagged repository and gather total and over-time statistics on forks, stars, licenses, and the presence of key repository elements (README, CONTRIBUTING, and similar files). For Google Analytics, we use a similar mechanism. Awardees grant programmatic access to their existing website "properties" and tag them with grant identifiers.

We then use the Google Analytics API to list all properties we have access to, associate them with particular core projects, and gather total and over-time statistics on unique visitors, engaged interactions, most common geographic regions, and more. For publications, we gather grant-associated publications from NIH Reporter and obtain citation metrics for these publications using iCite. We present these data in a password-protected dashboard that is regularly updated, resulting in a holistic view of metrics across CFDE.

**FAIRshake Evaluation**

In March 2026, average FAIRshake scores were calculated across all submitted assets (n=70) from all DCCs (n=15) over time (years 2018-2026). These included dataset assets (C2M2 data packages, knowledge graph assertions, gene set libraries, and attribute tables) and code assets (APIs, ETLs, landing pages templates such as gene, drug, and disease pages, and models). FAIRshake scores were plotted relative to the total number of assets at each time point.

**Data Distillery Knowledge Graph Query Construction**

To demonstrate capabilities for cross-ecosystem discovery, we performed a query against the Data Distillery Knowledge Graph (DDKG), a biomedical knowledge graph developed from the Unified Biomedical Knowledge Graph (UBKG) and hosted through the Neo4j platform (Neo4j, Inc.; https://neo4j.com/). The DDKG incorporates multiple CFDE programs, including Metabolomics Workbench (MW), Genotype-Tissue Expression (GTEx), and Illuminating the Druggable Genome (IDG). The KG encodes provenance through a Source Abbreviation (SAB), which defines the original data source.

A Cypher query was developed to extract a mechanistically plausible subgraph. The query first uses Metabolomics Workbench annotations to generate a hypothesis for which a gene causally affects a metabolite, and the metabolite is connected with a disease. A secondary layer of constraints is then applied to require that a) the metabolite is generated within a specific tissue according to Metabolomics Workbench annotations, and b) the gene is expressed in the same tissue according to GTEx. Tissues were

harmonized across data sources using UBKG-derived controlled vocabularies. Finally, the query adds upstream relationships from IDG to connect compounds to proteins and gene products, thus nominating candidate drugs for targeting the associated pathway.

```
//Tabular Output Query
MATCH (compound_concept:Concept)-[r1:bioactivity
{SAB:"IDGP"}]->(protein_concept:Concept)-[r2:gene_product_of
{SAB:"UNIPROTKB"}]->(gene_concept:Concept)-[r3:causally_influences
{SAB:"MW"}]->(metabolite_concept:Concept)-[r4:correlated_with_condition
{SAB:"MW"}]->(condition_concept:Concept),(metabolite_concept:Concept)-[r5:produced_by
{SAB:"MW"}]->(tissue_concept_1:Concept),(tissue_concept_2:Concept)-[r6:expresses
{SAB:"GTEXEXP"}]->(gtexexp_concept:Concept)-[r7
{SAB:"GTEXEXP"}]->(gene_concept:Concept),(gtexexp_concept:Concept)-[r8:has_expression
{SAB:"GTEXEXP"}]->(exp_concept:Concept)-[:CODE]-(exp_code:Code),(condition_concept:Concept)-[]->(t
issue_concept_1:Concept),(tissue_concept_1:Concept)-[]->(tissue_concept_2:Concept) WITH *
MATCH (compound_concept:Concept)-[:PREF_TERM]-(compound:Term),
(protein_concept:Concept)-[:PREF_TERM]-(protein:Term),
(gene_concept:Concept)-[:PREF_TERM]-(gene:Term),
(condition_concept:Concept)-[:PREF_TERM]-(condition:Term),
(metabolite_concept:Concept)-[:PREF_TERM]-(metabolite:Term),
(tissue_concept_1:Concept)-[:PREF_TERM]-(tissue_1:Term),
(tissue_concept_2:Concept)-[:PREF_TERM]-(tissue_2:Term) RETURN DISTINCT
compound.name,protein.name,gene.name,metabolite.name,tissue_1.name,tissue_2.name,condition.name,ex
p_code.CODE limit 10
```

**Query Description:** we formulate a comprehensive Cypher query that conducts a dense, multi-branch graph traversal over biomedical **`Concept`** nodes by first establishing a primary causal chain in which a **`compound_concept`** is linked to a **`protein_concept`** via a **`bioactivity`** relationship constrained by IDG data through **`SAB:"IDGP"`**, the protein is connected to a **`gene_concept`** through **`gene_product_of`** with **`SAB:"UNIPROTKB"`**, the gene is propagated downstream to a

**metabolite_concept** via **causally_influences** (**SAB:"MW"**), and the Metabolomics Workbench metabolite is further associated with a **condition_concept** through **correlated_with_condition** (**SAB:"MW"**), thereby encoding a compound-to-phenotype mechanistic pathway. In parallel within the same **MATCH** clause, we populate this backbone by linking the **metabolite_concept** to a first tissue context **tissue_concept_1** using **produced_by** (**SAB:"MW"**), while independently introducing a second tissue context **tissue_concept_2** that **expresses** a **gtexexp_concept** (**SAB:"GTEXEXP**"), which is then connected via an additional GTEx-associated relationship (also filtered by **SAB:"GTEXEXP**", though without an explicit type) back to the same **gene_concept**, ensuring that the gene in the causal chain is the one whose expression is being measured. We further traverse from the **gtexexp_concept** to an **exp_concept** through **has_expression** (**SAB:"GTEXEXP**") and add an expression identifier via a **:CODE** relationship to an **exp_code:Code** node, capturing the measurable expression output. To maintain biological coherence across subgraphs, we also impose relationship constraints requiring that the **condition_concept** connects to **tissue_concept_1** and that **tissue_concept_1** connects to **tissue_concept_2**, thereby implicitly aligning disease relevance, metabolite production, and gene expression across anatomically or functionally related tissues. After this extensive pattern matching, we propagate all bound variables forward using **WITH ***, preserving the full intermediate result set for subsequent transformation. We then conduct a second **MATCH** clause that systematically resolves each **Concept** node (**compound_concept**, **protein_concept**, **gene_concept**, **condition_concept**, **metabolite_concept**, **tissue_concept_1**, **tissue_concept_2**) to its corresponding human-readable **Term** node via **PREF_TERM** relationships, effectively translating ontology-level identifiers into displayable names. Finally, we project a deduplicated (**RETURN DISTINCT**) tabular output consisting of **compound.name**, **protein.name**, **gene.name**, **metabolite.name**, **tissue_1.name**, **tissue_2.name**, **condition.name**, and the associated **exp_code.CODE**, and constrain the result cardinality with **LIMIT 10**, yielding a compact yet semantically rich integration of pharmacological activity, molecular biology, metabolic influence, disease association, tissue specificity, and transcriptomic expression measurements derived from multiple curated data sources.

**Visualization of Multi-Source Datasets Registered in the HuBMAP Human Reference Atlas**

A list of all CFDE and non-CFDE datasets registered in the HuBMAP Human Reference Atlas was obtained. These included datasets integrated through 3D registration of tissue into the CCF or through crosswalking cell type annotations via HRA-compatible transcriptomic tools (e.g., Azimuth) or spatial omics tools (e.g., DeepCellTypes). The top sources of these datasets were plotted against 30 anatomical structures from which they were derived, and the number of datasets and total cell counts within each was plotted (Figure 6d). Analyses and visualizations were generated using reproducible Python scripts accessible through a public GitHub repository (https://github.com/cns-iu/hra-cfde-marker-visualizations/blob/main/hra-pop-scatter-checkpoint.ipynb). Dataset-level metadata were mapped to standardized anatomical structures defined by the Human Reference Atlas to enable cross-consortium comparisons of organ coverage.

## Resource Availability

### Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact, Julie Jurgens (jjurgens@broadinstitute.org).

### Materials availability

This study did not generate new unique reagents.

### Data and code availability

This paper analyzes existing, publicly available data. Common Fund programs' metadata and processed datasets are available through https://data.cfde.cloud/. CFDE has developed a host of Standards, which are available at https://github.com/nih-cfde/rfcs/blob/master/adoptionstatus.md, and additional user guides, protocols, and standards available through https://data.cfde.cloud/documentation.

Data and original code for the HuBMAP analysis within this manuscript have been deposited at GitHub and are publicly available at https://github.com/cns-iu/hra-cfde-marker-visualizations/blob/main/hra-pop-scatter-checkpoint.ipynb as of the date of publication.

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## Declarations of interest

S.K.T. receives/d research funding from Incyte Corporation and Kura Oncology, serves/d on scientific advisory boards for Aleta Biotherapeutics, Amgen, AstraZeneca, Jazz Pharmaceuticals, Kura Oncology, and Syndax Pharmaceuticals, and received travel support from Amgen (all for unrelated studies). M.T.W. receives/d research funding from Astra Zeneca, Alexion, Bristol Myers Squibb, Salubris Bio, and Nihon Kohden, all outside the submitted work. T.I.O. is an advisor to InSilico Medicine, Chair of the Scientific Advisory Board for ExScalate, Dompé farmaceutici SpA, and CEO of Expert Systems, Inc. The remaining authors declare no competing interests related to this study.

## Consortia

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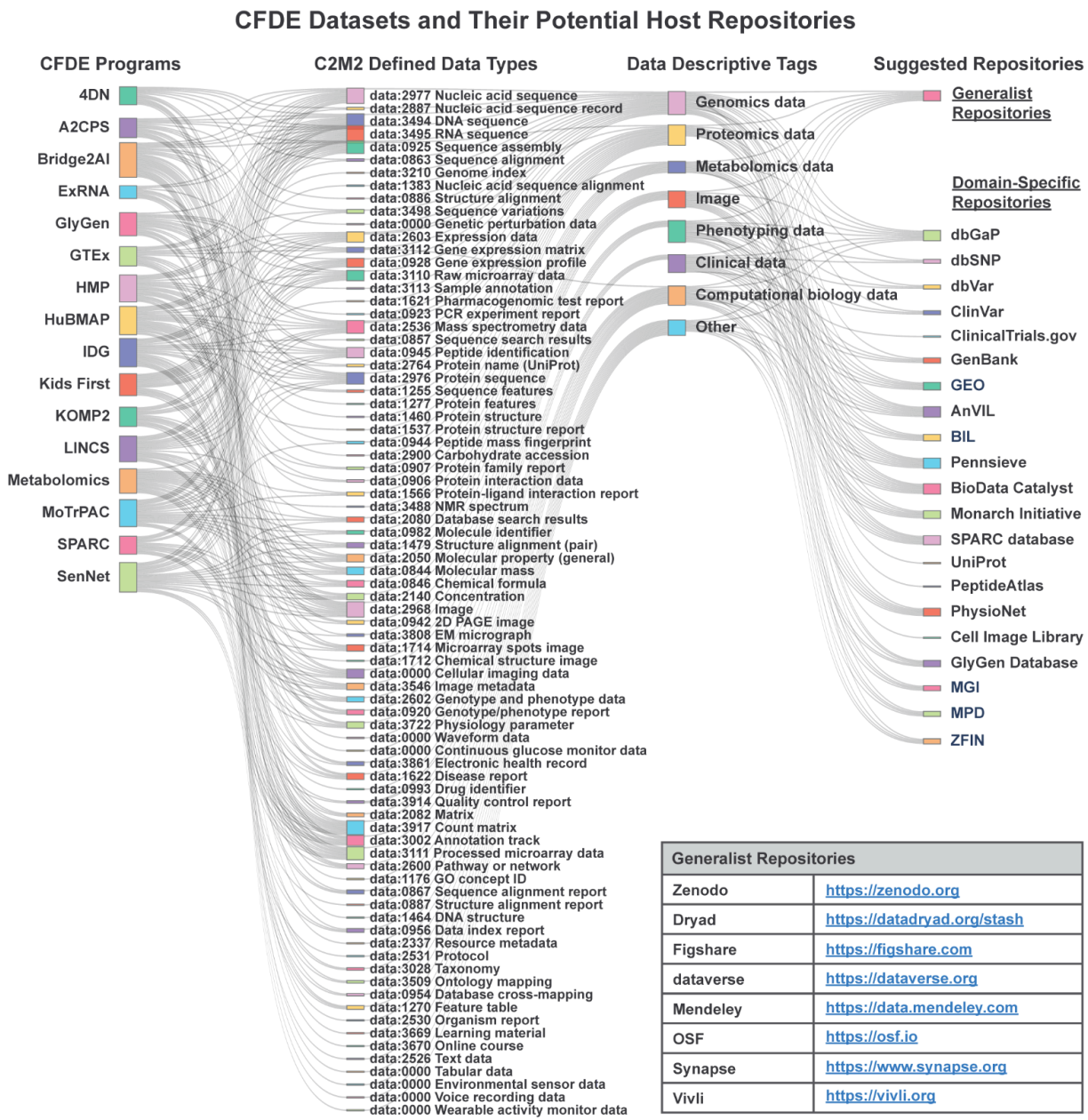
## Figure titles and legends

**Figure 1. Summary of CFDE digital assets.**

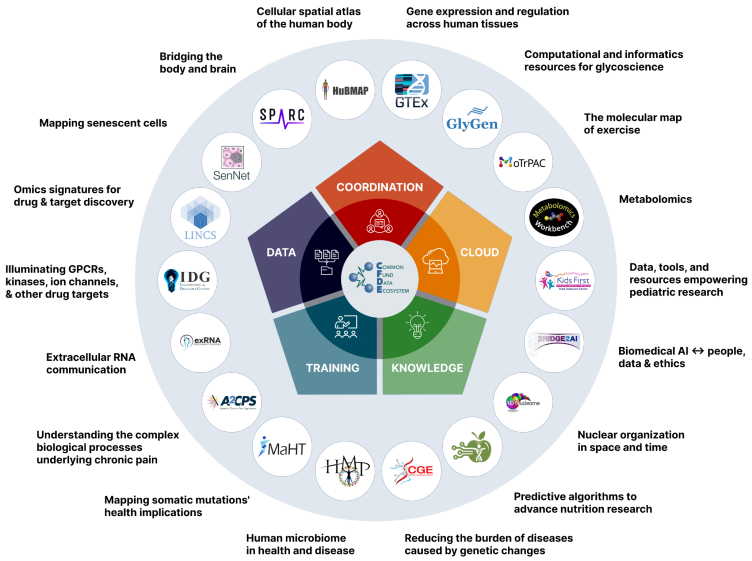
This Sankey diagram visualizes CFDE digital assets, which currently include datasets generated by 16 CFDE-participating programs (**Column 1**). These multimodal datasets were annotated with EDAM (EMBRACE Data and Methods Ontology)-supported data type terms based on each DCC's data classifications in their most recent C2M2 submissions (November 2025) and on their data portals. More than 80 data types (**Column 2**) were identified and further organized into eight higher-level categories (**Column 3**) using descriptors commonly adopted by the scientific community to support future data discovery and indexing. The diagram also incorporates 8 Generalist Repositories (**Table**, lower right) and 21 Domain-Specific Repositories (**Column 4**) as potential hosts for CFDE digital assets. An interactive version of the diagram is available at https://cfde-sankey.github.io/. This visualization represents a major CFDE ICC-SC effort supporting three core milestones: (1) assessing Common Fund program needs, (2) collaborating with DRCs to enhance the FAIRness of Common Fund digital assets, and (3) promoting outreach, reuse, and long-term sustainability of CFDE resources. Abbreviations: A2CPS-Acute to Chronic Pain Signatures, AnVIL-Analysis, Visualization, and Informatics Lab-space, BIL-Biomedical Imaging Library, BioData Catalyst-NHLBI BioData Catalyst Data Ecosystem, C2M2-Cross-Cut Metadata Model, CF-Common Fund, CFDE-Common Fund Data Ecosystem, ClinVar-Clinical Variation Database, dbGaP-Database of Genotypes and Phenotypes, dbSNP-Database of Single Nucleotide Polymorphisms, dbVar-Database of Genomic Structural Variation, DCC-Data Coordinating Center, EDAM-The EMBRACE Data and Methods (EDAM) Ontology, exRNA-The exRNA Research Portal, GEO-Gene Expression Omnibus, GTEx-The Genotype-Tissue Expression Project, HMP-The Human Microbiome Project, HuBMAP-The Human BioMolecular Atlas Program, IDG-Illuminating the Druggable Genome, Kids First-Gabriella Miller Kids First Pediatric Research Program, KOMP2-The Knockout Mouse Phenotyping Program, LINCS-Library of Integrated Network-based Cellular Signatures, Metabolomics-Metabolomics Workbench, MGI-Mouse Genome Informatics, Monarch Initiative-Monarch Initiative Integrative Biology Platform, MoTrPAC-The Molecular Transducers of Physical Activity Consortium, MPD-Mouse Phenome Database, OSF-Open Science Framework, Pennsieve-Pennsieve Data Platform, PeptideAtlas-Peptide Atlas Proteomics Resource, PhysioNet-Physiological Signal Archive Network, SenNet-Cellular Senescence Network, SPARC-Stimulating Peripheral Activity to Relieve Conditions, UniProt-Universal Protein Resource, ZFIN-Zebrafish Information Network, 4DN-The 4D Nucleome Program.



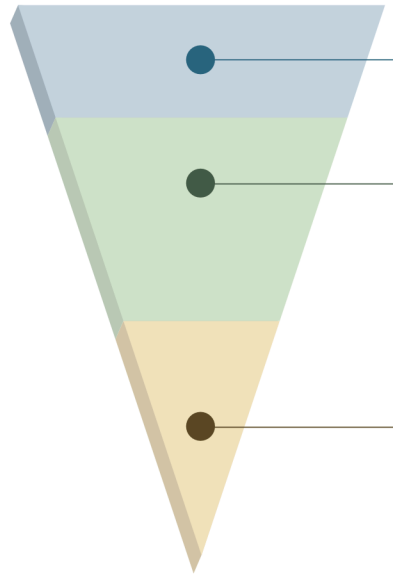

| Generalist Repositories | |
|---|---|
| Zenodo | https://zenodo.org |
| Dryad | https://datadryad.org/stash |
| Figshare | https://figshare.com |
| dataverse | https://dataverse.org |
| Mendeley | https://data.mendeley.com |
| OSF | https://osf.io |
| Synapse | https://www.synapse.org |
| Vivli | https://vivli.org |

**Figure 2. CFDE organization and scientific focus of individual programs.**

The CFDE consists of eighteen DCCs (circles; top layer of inverted pyramid) that are supported by five centers (spokes surrounding central hub; bottom layer of inverted pyramid). DCCs collaborate with one another and with non-CFDE entities to form partnerships (middle layer of inverted pyramid). Taglines summarize the major focus areas of each DCC. Abbreviations: A2CPS-Acute to Chronic Pain Signatures, B2AI-The Bridge2AI Consortium, CFDE-Common Fund Data Ecosystem, CWIC-Cloud Workspace Implementation Center, DCC-Data Coordinating Center, DRC-Data Resource Center, exRNA-The extracellular RNA Communication Program, GTEx-The Genotype-Tissue Expression Project, HMP-The Human Microbiome Project, HuBMAP-The Human BioMolecular Atlas Program, ICC-Integration and Coordination Center, IDG-Illuminating the Druggable Genome, KC-Knowledge Center, Kids First-Gabriella Miller Kids First Pediatric Research Program, KOMP-The Knockout Mouse Project, LINCS-Library of Integrated Network-based Cellular Signatures, MoTrPAC-The Molecular Transducers of Physical Activity Consortium, MW-Metabolomics Workbench, SCGE-Somatic Cell Genome Editing, SenNet-Cellular Senescence Network, SMaHT-The Somatic Mosaicism across Human Tissues Network, SPARC-Stimulating Peripheral Activity to Relieve Conditions, TC-Training Center, 4DN-The 4D Nucleome Program.




## CFDE Organizational Structure



**Common Fund DCC Projects**

A2CPS, Bridge2AI, exRNA, Kids First, GlyGen, GTEx, HuBMAP, HMP, IDG, KOMP, LINCS, Metabolomics Workbench, MoTrPAC, SCGE, SenNet, SMaHT, SPARC, 4DN

**U24 Partnerships**

BiomarkerKB, Data Distillery Knowledge Graph (DDKG), UniProt-CFDE / ProKN, Community Visualization Hub, Genetic Basis of Birth Defects & Childhood Cancer, Metabotyping Humans, Gene-Centric Prototype Dashboard, COMPA, Playbook Workflow Builder, ReproTox-KG, Standard RNA-Seq Pipeline, CIOvoc, Making Gene Regulatory Knowledge FAIR, Cloud Workspace Pilot

**Core Centers**

Data Resource Center (DRC), Knowledge Center (KC), Integration & Coordination Center (ICC), Cloud Workspace Implementation Center (CWIC), Training Center (TC)

**Figure 3. Ontologies/Controlled vocabularies used in the Cross-Cut Metadata Model (C2M2)**.

A simplified schema showing the C2M2 entities and their metadata encoding (green boxes) in corresponding ontologies/controlled vocabularies.

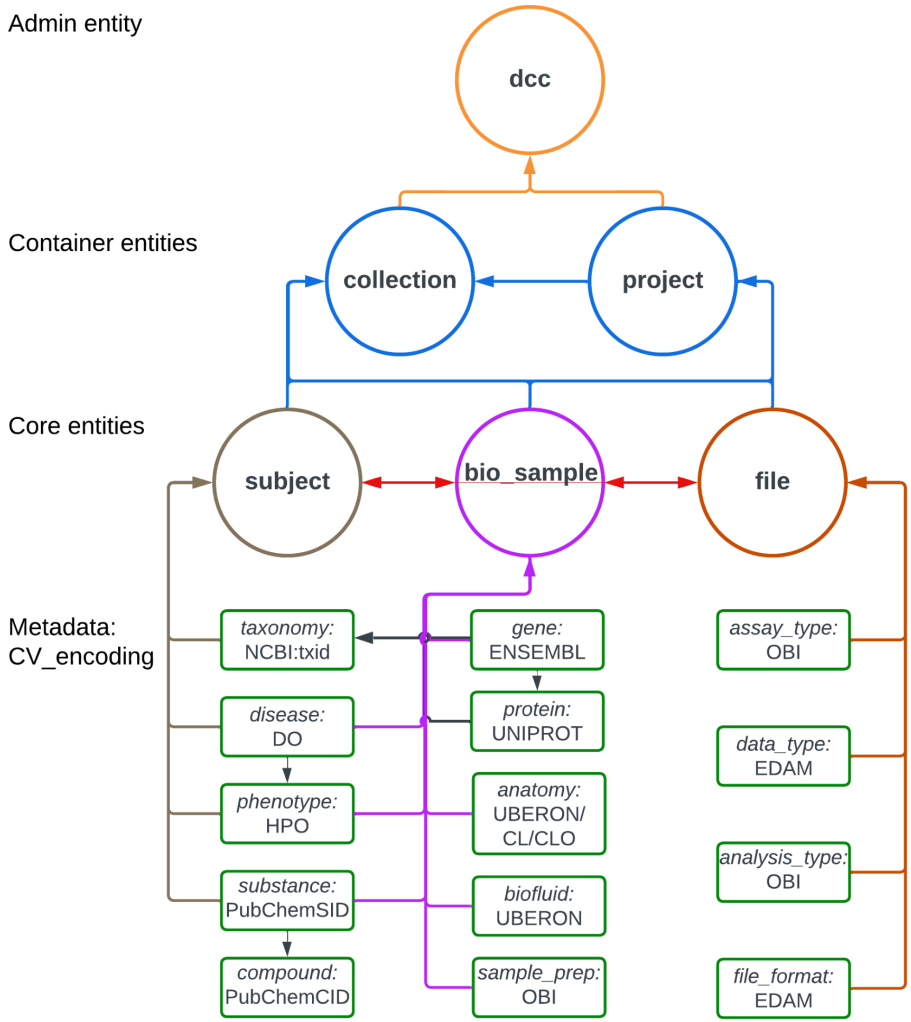


**Figure 4. Example of metadata in the C2M2 format.**

This figure shows an example of metadata in the C2M2 format, including the connections between the tables, for a single project, PR000663 (http://dx.doi.org/10.21228/M8ZX0W), from the Metabolomics Workbench (MW) DCC. It can be noted that this is only partial information, and some empty and id_namespace columns have been omitted. This project is about the study of Nonalcoholic Fatty Liver Disease (NAFLD) in humans (the project table). As per the information at MW, there are three studies under this project, each study with its own lumped subject ID. Thus, there are a total of 3 subject IDs associated with this project (the subject table). There are a total of 264 biosamples collected in the project, of which only three are listed due to space constraints (the biosample table). For the subjects, associated information such as disease, e.g., steatotic liver disease, is captured in the tables subject_disease and disease, and taxonomy for humans is captured in the tables subject_role_taxonomy and ncbi_taxonomy. For the biosamples, anatomy and biofluid information are listed in the respective tables. On the MW website, for this project, three files can be accessed and downloaded, and the relevant C2M2 information is listed in the file table. Details about the relevant data_type and assay_type for these files are captured in the tables data_type and assay_type. Depending upon the type of metadata information from a DCC, there can be additional tables with suitable information, such as those related to collections. A given DCC may have information on several projects and/or collections and the overall information in various tables will be the union of such information from different projects and/or collections.

## project

| local_id | persistent_id | name | description |
|---|---|---|---|
| PR000633 | http://dx.doi.org/10.21228/M8V961 | Biomarkers of NAFLD progression: a lipidomics approach to an epidemic | The spectrum of nonalcoholic fatty liver disease (NAFLD) includes steatosis, nonalcoholic steatohepatitis (NASH), and cirrhosis. Recognition and timely diagnosis of these different stages, particularly NASH, is important for both potential reversibility and limitation of complications. Liver |

## subject

| local_id | project_local_id | granularity |
|---|---|---|
| SU000953 | PR000633 | cfde_subject_granularity:0 |
| SU000954 | PR000633 | cfde_subject_granularity:0 |
| SU000955 | PR000633 | cfde_subject_granularity:0 |

## biosample_from_subject

| biosample_local_id | subject_local_id | age_at_sampling |
|---|---|---|
| SA053802 | SU000953 | |
| SA053890 | SU000954 | |
| SA053978 | SU000955 | |

## biosample

| local_id | project_local_id | persistent_id | anatomy | biofluid |
|---|---|---|---|---|
| SA053802 | PR000633 | https://www.metabolomicsworkbench.org/data/DRCCMetadata.php?Mode=Sample&MBSampleID=SA053802&StudyID=ST000915&StudyType=MS&ResultType=1 | UBERON:0002107 | |
| SA053890 | PR000633 | https://www.metabolomicsworkbench.org/data/DRCCMetadata.php?Mode=Sample&MBSampleID=SA053890&StudyID=ST000916&StudyType=MS&ResultType=1 | | UBERON:0001969 |
| SA053978 | PR000633 | https://www.metabolomicsworkbench.org/data/DRCCMetadata.php?Mode=Sample&MBSampleID=SA053978&StudyID=ST000917&StudyType=MS&ResultType=1 | | UBERON:0001088 |

## subject_disease

| subject_local_id | association_type | disease |
|---|---|---|
| SU000953 | cfde_disease_association_type:1 | DOID:9452 |
| SU000954 | cfde_disease_association_type:1 | DOID:9452 |
| SU000955 | cfde_disease_association_type:1 | DOID:9452 |

## subject_role_taxonomy

| subject_local_id | role_id | taxonomy_id |
|---|---|---|
| SU000953 | cfde_subject_role:0 | NCBI:txid9606 |
| SU000954 | cfde_subject_role:0 | NCBI:txid9606 |
| SU000955 | cfde_subject_role:0 | NCBI:txid9606 |

## ncbi_taxonomy

| id | clade | name | description | synonyms |
|---|---|---|---|---|
| NCBI:txid9606 | species | Homo sapiens | Human | ["Human"] |

## disease

| id | name | synonyms | description |
|---|---|---|---|
| DOID:9452 | steatotic liver disease | ["DOID:9451","alcoholic fatty liver","Fatty change of liver","fatty liver disease","hepatic lipidosis","hepatic steatosis","SLD","Steatosis of liver"] | A lipid storage disease characterized by the accumulation of large vacuoles of triglyceride fat in at least 5% of hepatocytes. |

## anatomy

| id | name | synonyms | description |
|---|---|---|---|
| UBERON:0002107 | liver | [] | An exocrine gland which secretes bile and functions in metabolism of protein and carbohydrate and fat, synthesizes substances involved in the clotting of the blood, synthesizes vitamin A, detoxifies poisonous substances, stores glycogen, and breaks down worn-out erythrocytes. |

## biofluid

| id | name | synonyms | description |
|---|---|---|---|
| UBERON:0001088 | urine | [] | Excretion that is the output of a kidney. |
| UBERON:0001969 | blood plasma | ["blood plasm","plasma","portion of blood plasma","portion of plasma"] | The liquid component of blood, in which erythrocytes are suspended. |

## file

| local_id | project_local_id | size_in_bytes | md5 | filename | file_format | data_type | assay_type | analysis_type |
|---|---|---|---|---|---|---|---|---|
| ST000915.zip | PR000633 | 29114694 | 07b18e154029c1b4cc4b4064486de8c9 | ST000915.zip | format:3987 | data:2536 | OBI:0000470 | OBI:0200085 |
| ST000916.zip | PR000633 | 29114694 | 9572dfc4dc230178838cd16bcb53e9a4 | ST000916.zip | format:3987 | data:2536 | OBI:0000470 | OBI:0200085 |
| ST000917.zip | PR000633 | 29114694 | d8b4e4511e67a31558c78b553bd5e4b5 | ST000917.zip | format:3987 | data:2536 | OBI:0000470 | OBI:0200085 |

## data_type

| id | name | synonyms | description |
|---|---|---|---|
| data:2536 | Mass spectrometry data | [] | Data concerning a mass spectrometry measurement. |

## assay_type

| id | name | synonyms | description |
|---|---|---|---|
| OBI:0000470 | mass spectrometry assay | [] | An assay that identifies the amount and type of material entities present in a sample by fragmenting the sample and measuring the mass-to-charge ratio of the resulting particles. |

**Figure 5. Multiscale data and user interfaces.**

The HRA Common Coordinate Framework (CCF)[85] makes it possible to register and explore data in three dimensions and across scales. The HRA Organ Gallery in virtual reality (VR)[76] supports multiscale exploration of 3D reference organs and HRA-harmonized single-cell datasets via head-mounted VR devices. VR supports interactions with HRA Digital Objects (DOs) via natural input using handheld VR controllers and enables the user to traverse the human body in an elevator-style system, from whole organs to anatomical structures, to functional tissue units (FTUS), to cell types, and down to sub-cellular structures, such as gene, protein biomarkers, see Figure 6. Abbreviations: CCF-Common Coordinate Framework, DO-digital object, HRA-Human Reference Atlas, FTUS-functional tissue units, VR-virtual reality.

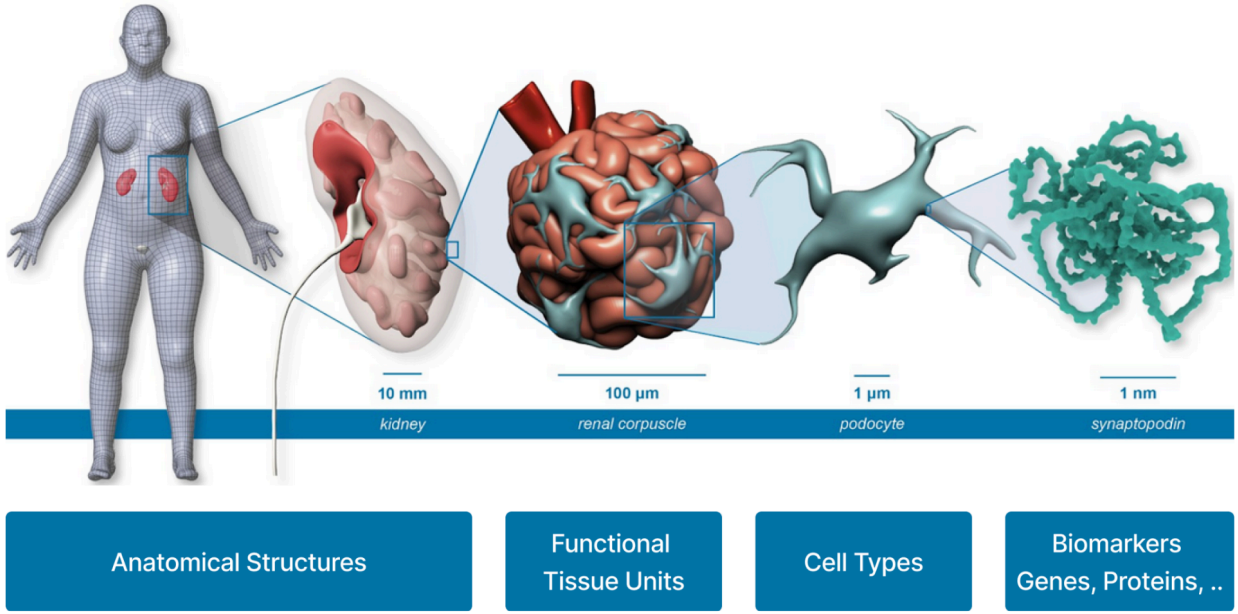


**Figure 6. Tissue registration using the HRA Registration User Interface (RUI).**

**a.** Tissue registration into kidney anatomical structures using the CCF. Using the Registration User Interface, the size, position, and rotation of the tissue block (yellow cube) are adjusted until they present the properties of the tissue (e.g., biopsy) extracted from a human donor. Tissue collides completely with one anatomical structure (here the 'outer cortex' of the female left kidney). **b.** Example of a tissue registration in which the virtual tissue block collides with two anatomical structures (here 'renal pyramid' and 'outer cortex' of the female left kidney). **c.** All registered tissue blocks and the more than 8,500 associated datasets can be explored in the HRA Exploration User Interface. **d.** This graph shows the number of CFDE and other datasets that have been registered into the Human Reference Atlas either via 3D registration of tissue into the CCF or via crosswalking cell type annotations via HRA-compatible transcriptomics tools (e.g., Azimuth) or spatial omics tools (e.g., DeepCellTypes). The horizontal axis lists 30 anatomical structures while the vertical axis lists CFDE and other projects. Circle size denotes the number of datasets and circle color (log scale) denotes total cell count. Abbreviations: CCF-Common Coordinate Framework, CFDE-Common Fund Data Ecosystem, DO-Digital Object, GTEx-The Genotype-Tissue Expression Project, HRA-Human Reference Atlas, HTAN-Human Tumor Atlas Network, HuBMAP-The Human BioMolecular Atlas Program, FTUS-Functional Tissue Units, RUI-Registration User Interface, SenNet-Cellular Senescence Network, SPARC-Stimulating Peripheral Activity to Relieve Conditions**,** VR-Virtual Reality.

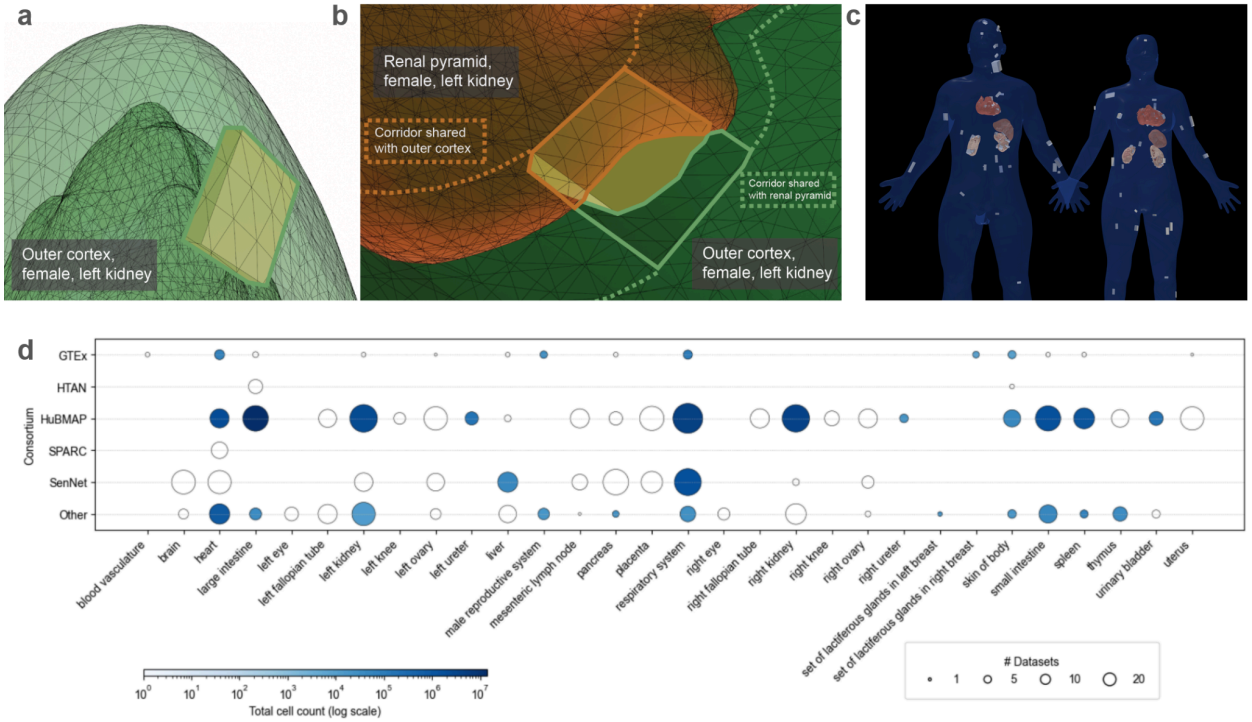

a
Outer cortex,
female, left kidney
b
Renal pyramid,
female, left kidney
Corridor shared
with outer cortex
Corridor shared
with renal pyramid
Outer cortex,
female, left kidney
c
d
Consortium
GTEx
HTAN
HuBMAP
SPARC
SenNet
Other
blood vasculature
brain
heart
large intestine
left eye
left fallopian tube
left kidney
left knee
left ovary
left ureter
liver
male reproductive system
mesenteric lymph node
pancreas
placenta
respiratory system
right eye
right fallopian tube
right kidney
right knee
right ovary
right ureter
set of lactiferous glands in left breast
set of lactiferous glands in right breast
skin of body
small intestine
spleen
thymus
urinary bladder
uterus
Total cell count (log scale)
# Datasets
1
5
10
20

**Figure 7. Training Center's Aims for Omics Skills Development**

**a.** The Training Center serves the CFDE community by building foundational and advanced omics analysis skills through a dynamic syllabus grounded in six comprehensive aims: understanding the specific areas of biology needed for CFDE datasets; leveraging biological reference databases; automating computational tasks; utilizing programming and software tools; applying appropriate statistical and visualization methods; and leveraging advanced computing and collaboration tools. **b.** In its first year, the TC has developed a wide range of resources and materials and hosted over 10 events. Events included Decoding the Data Ecosystem podcast (https://podcast.show/3847772/), the e-Learning Dashboard (which includes a How-To Seminar Series) (https://orau.org/cfde-trainingcenter/training/e-learning.html), a Digital Scavenger Hunt, and the Bio-IT World Hackathon (https://www.bio-itworldexpo.com/).

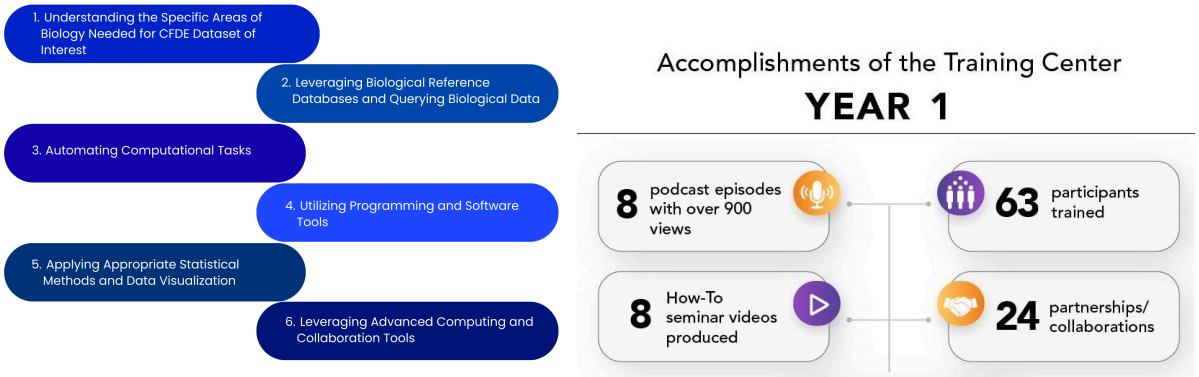


**Figure 8. Change in average FAIRshake scores across all submitted assets from all DCCs over time.**

In March 2026, average FAIRshake scores were calculated across all submitted assets (n=70) from all DCCs (n=15) over time (years 2018-2026). These included dataset assets (C2M2 data packages, knowledge graph assertions, gene set libraries, and attribute tables) and code assets (APIs, ETLs, landing pages templates such as gene, drug, and disease pages, and models). Blue-average FAIR score; green-number of assets assessed.

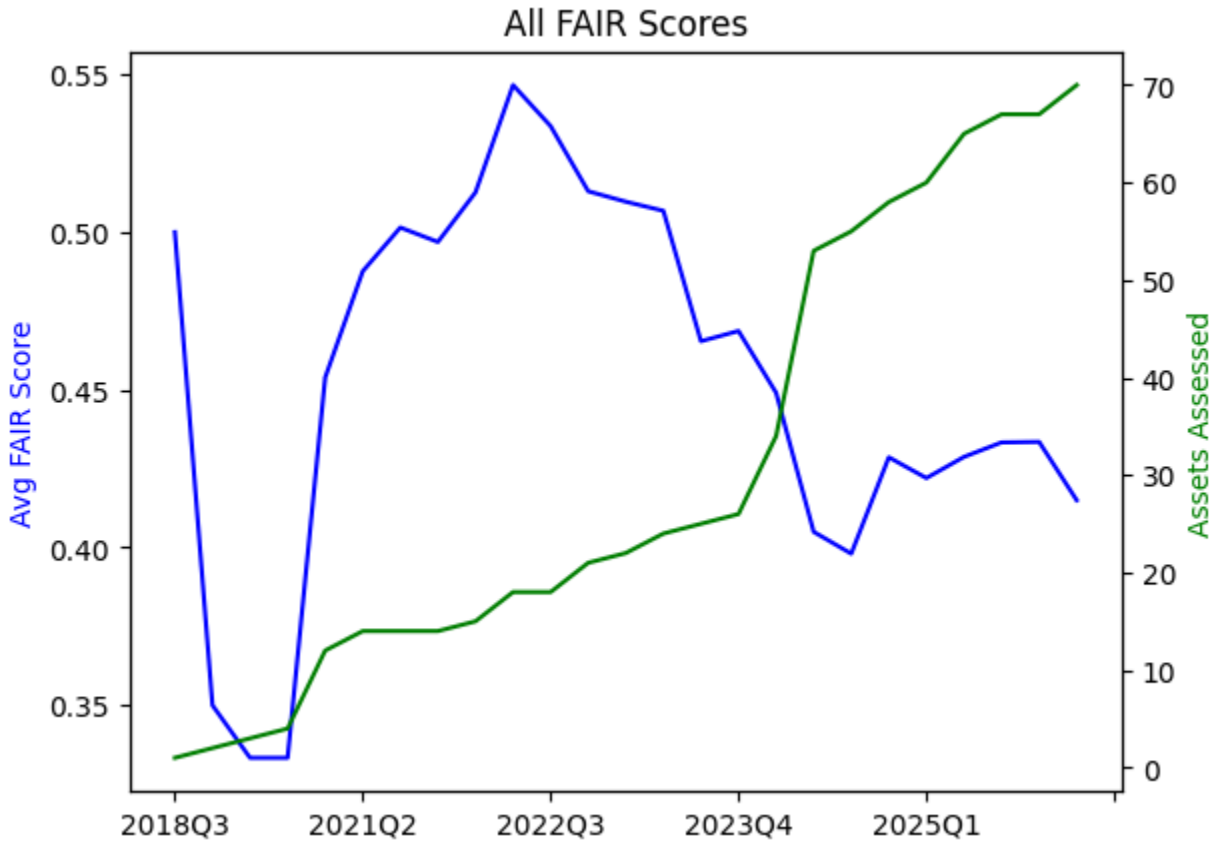
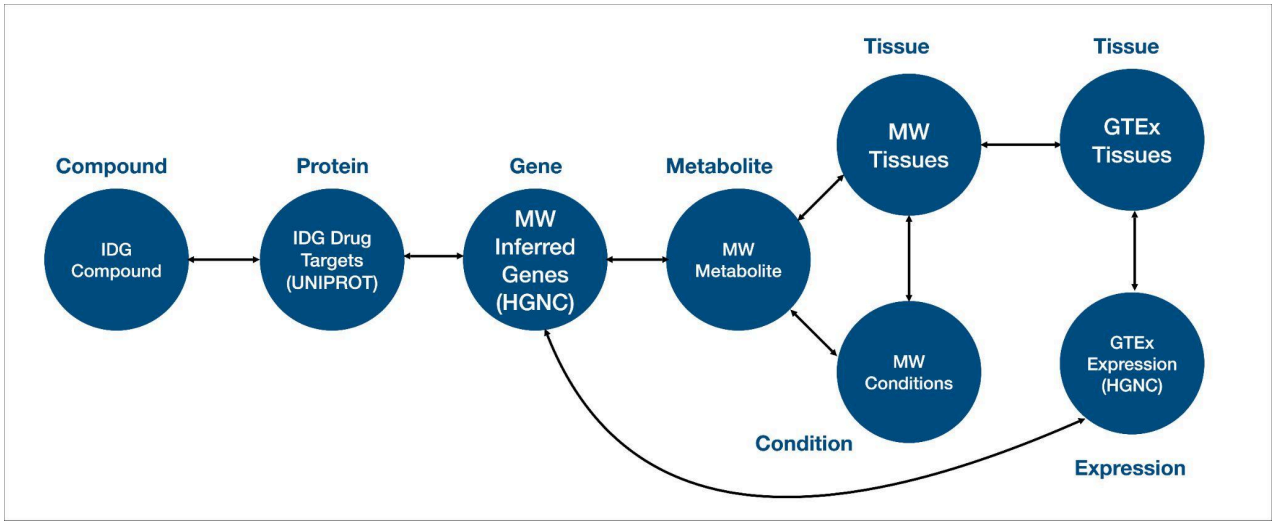


**Figure 9. Highlighted use case from the CFDE Data Distillery Knowledge Graph: sample Cypher query and schema intersecting data from three DCCs.**

Schema for the Cypher query from the Data Distillery Knowledge Graph developed to obtain novel biological insights using data from three CFDE DCCs (GTEx, IDG, and MW). Abbreviations: CFDE-Common Fund Data Ecosystem, DCC-Data Coordinating Center, GTEx-The Genotype-Tissue Expression Project, HGNC-HUGO Gene Nomenclature Committee, IDG-Illuminating the Druggable Genome, MW-Metabolomics Workbench.



## Tables

**Table 1. Overview of CFDE Centers, Data Coordinating Centers (DCCs), and Partnerships**

Names, descriptions, and weblinks are provided for CFDE Centers, DCCs, and Partnerships. Abbreviations: A2CPS-Acute to Chronic Pain Signatures, B2AI-The Bridge2AI Consortium, CFDE-Common Fund Data Ecosystem, CWIC-Cloud Workspace Implementation Center, DCC-Data Coordinating Center, DRC-Data Resource Center, exRNA-The extracellular RNA Communication Program, GTEx-The Genotype-Tissue Expression Project, HMP-The Human Microbiome Project, HuBMAP-The Human BioMolecular Atlas Program, ICC-Integration and Coordination Center, IDG-Illuminating the Druggable Genome, KC-Knowledge Center, Kids First-Gabriella Miller Kids First Pediatric Research Program, KOMP-The Knockout Mouse Project, LINCS-Library of Integrated Network-based Cellular Signatures, MoTrPAC-The Molecular Transducers of Physical Activity Consortium, MW-Metabolomics Workbench, SCGE-Somatic Cell Genome Editing, SenNet-Cellular Senescence Network, SMaHT-The Somatic Mosaicism across Human Tissues Network, SPARC-Stimulating Peripheral Activity to Relieve Conditions, TC-Training Center, 4DN-The 4D Nucleome Program

| Name | Type | Description |
|---|---|---|
| CFDE Knowledge Center (KC) | Center | The CFDE Knowledge Center (KC; https://cfdeknowledge.org/) has established the Knowledge Portal, a web-based resource that provides curated and precomputed analyses of data and knowledge generated within and across CFDE DCCs. |
| CFDE Data Resource Center (DRC) | Center | The CFDE Data Resource Center (DRC; https://info.cfde.cloud/) has developed two web-based portals: the CFDE Information Portal to share information about the CFDE, and the CFDE Data Portal to host harmonized metadata and processed data contributed by DCCs and other sources. These collectively comprise the CFDE Workbench, a comprehensive resource where users can obtain information, query, analyze, and visualize data from the CFDE participating Common Fund programs. A collection of tools, use cases, an AI assistant, and a workflow engine demonstrate how such data can be combined for |

| | | |
|---|---|---|
| | | hypothesis generation. |
| CFDE Cloud Workspace Implementation Center (CWIC) | Center | The CFDE Cloud Workspace Implementation Center (CWIC) (https://cfdeworkspace.org/) provides a secure, cloud-based platform that enables researchers to integrate and analyze data from the NIH Common Fund alongside their own datasets. This workspace is designed to remove technical and cost barriers by offering a freely accessible and scalable environment where scientists can perform complex, reproducible analyses without managing local infrastructure. The CWIC ensures data protection through robust authentication, controlled access, and compliance with established standards. |
| CFDE Training Center (TC) | Center | The CFDE Training Center (TC; https://www.orau.org/cfde-trainingcenter/index.html) provides training in basic and advanced computational and data analytics skills for learners interested in CFDE data, tools, and resources. We aim to enhance the confidence and complexity of CFDE dataset usage through training and community building engagement activities. |
| CFDE Integration and Coordination Center (ICC) | Center | The CFDE Integration and Coordination Center (ICC; https://cfdeconnect.org/) coordinates activities and facilitates collaboration across CFDE, enhancing CFDE's potential to revolutionize biomedical research. The ICC facilitates efficient operations, quality improvement, and sustainability to accelerate the impact of the CFDE. |
| Acute to Chronic Pain Signatures (A2CPS) | DCC | The Acute to Chronic Pain Signatures (A2CPS; https://a2cps.org/) project seeks to identify biomarkers and signatures of risk and resilience to the transition to chronic pain after surgery. |
| The Bridge2AI Consortium (B2AI) | DCC | The Bridge2AI Consortium (B2AI; https://bridge2ai.org/) is merging biomedicine with artificial intelligence (AI) and machine learning (ML) approaches. Bridge2AI will generate ethical guidelines, workforce development strategies, datasets, and tools that are findable, accessible, interoperable, and reusable (FAIR) and AI/ML-integratable. |
| The exRNA Communicati | DCC | The Extracellular RNA Communication Program (exRNA; https://exrna.org/) aims to elucidate the roles of extracellular RNAs |

| | | |
|---|---|---|
| on Program (exRNA) | | (exRNAs) and their carriers in order to uncover novel disease biomarkers and therapeutics. |
| Gabriella Miller Kids First Pediatric Research Program (Kids First) | DCC | The Gabriella Miller Kids First Pediatric Research Program (Kids First; https://portal.kidsfirstdrc.org/) aims to identify causes and commonalities among pediatric cancers and structural birth disorders. |
| GlyGen | DCC | GlyGen (https://glygen.org/) is a data integration and dissemination project for carbohydrate and glycoconjugate-related data. GlyGen retrieves information from literature, collaborates with individual laboratories and multiple international data sources, and integrates and harmonizes this data. The web portal allows exploring this data and performing unique searches that cannot be executed in any of the integrated databases alone. Key glycan function-relevant projects include the GlycoMotif collection, Glycan Dictionary, Sandbox, GlycoTree, and Glycan structure and function-related text mining. |
| The Genotype-Tissue Expression Project (GTEx) | DCC | The Genotype-Tissue Expression Project (GTEx; https://gtexportal.org/home/) is a comprehensive resource to study human tissue-specific gene expression and regulation, and its relationship to genetic variation across multiple diverse tissues and individuals. |
| The Human BioMolecular Atlas Program (HuBMAP) | DCC | The Human BioMolecular Atlas Program (HuBMAP; https://hubmapconsortium.org) is developing a framework for mapping the healthy human body at cellular resolution. HuBMAP developed the Human Reference Atlas (HRA) Portal (https://humanatlas.io) which serves data and code for the construction and usage of the multiscale, multimodal, 3D atlas of the anatomical structures and cells in the healthy human body linked to existing ontologies. |
| The Human Microbiome | DCC | The Human Microbiome Project (HMP) developed data and computational resources for the study of the human microbiome. |

| | | |
|---|---|---|
| Project (HMP) | | |
| Illuminating the Druggable Genome (IDG) | DCC | The Illuminating the Druggable Genome (IDG; https://druggablegenome.net/) program aims to understand the roles of unannotated “dark” proteins with high therapeutic potential, with a focus on the protein kinase, ion channel, and G-protein coupled receptor protein families. |
| The Knockout Mouse Project (KOMP) | DCC | The Knockout Mouse Project (KOMP) was responsible for generating and phenotyping knockout mouse models to enhance understanding of the role of genes in disease. |
| Library of Integrated Network-based Cellular Signatures (LINCS) | DCC | The Library of Integrated Network-based Cellular Signatures (LINCS) https://lincsproject.org/LINCS/) program utilized multi-omics and imaging technologies to catalog the molecular and cellular changes that occur when human cells are exposed to a large variety of perturbing agents and extracellular microenvironments. The aim was to create a Connectivity Mapping resource that would enable researchers to query the LINCS data to identify matching or reversing signatures for hypothesis generation. |
| Metabolomics Workbench (MW) | DCC | The Metabolomics Workbench (MW; https://www.metabolomicsworkbench.org/) serves as the portal for the National Metabolomics Data Repository (NMDR), and accepts data/metadata on metabolomics studies from across the world. Further, MW aggregates datasets, methods, resources, tools, and standards to accelerate metabolomics research. |
| The Molecular Transducers of Physical Activity Consortium (MoTrPAC) | DCC | The Molecular Transducers of Physical Activity Consortium (MoTrPAC; https://motrpac-data.org/) is the Consortium that studies exercise. MoTrPAC aims to identify and measure the molecular changes induced by acute and chronic exercise across multiple tissues and systems in both humans and animal models. |

| | | |
|---|---|---|
| Somatic Cell Genome Editing (SCGE) | DCC | The Somatic Cell Genome Editing (SCGE) aims to reduce the burden of diseases caused by genetic changes through enhanced performance and clinical translation of genome editing tools in somatic cells. |
| Cellular Senescence Network (SenNet) | DCC | The Cellular Senescence Network (SenNet; https://sennetconsortium.org/) Program aims to identify and spatiotemporally characterize senescent cells across multiple tissues and species in health and disease. The Human Reference Atlas (HRA) is used to register tissue data in the 3D human body and to explore SenNet data in its spatial (neighborhood) context and across scales. SenNet cell types and biomarkers are linked to existing ontologies. |
| The Somatic Mosaicism across Human Tissues (SMaHT) Network | DCC | The Somatic Mosaicism across Human Tissues (SMaHT) Network aims to characterize somatic mosaic variation across human tissues and understand its role in health and disease. SMaHT is generating omics datasets across 15–20 tissues from 150 post-mortem donors and analyzing mutational processes underlying somatic mosaicism. |
| Stimulating Peripheral Activity to Relieve Conditions (SPARC) | DCC | The Stimulating Peripheral Activity to Relieve Conditions (SPARC; https://sparc.science/) program is an open-science initiative dedicated to advancing understanding of the autonomic and peripheral nervous systems (ANS & PNS), related organ systems, brain-body connections and their role in health and disease with the goal of accelerating neuromodulatory therapeutic interventions. |
| The 4D Nucleome Program (4DN) | DCC | The 4D Nucleome program (4DN; https://www.4dnucleome.org/) aims to understand the 3D organization of DNA in the nucleus, how it varies over time and in different cell types, and its role in health and disease. |
| BiomarkerKB | Partnership | BiomarkerKB (https://biomarkerkb.org/) aims to develop a knowledgebase that integrates biomarker data from various public sources and to improve the harmonization and organization of biomarker data. This is being done by mapping biomarkers from public sources to, and across, Common |

| | | |
|---|---|---|
| | | Fund data elements. This mapping will bridge knowledge across multiple Data Coordinating Centers (DCCs) and biomedical disciplines. |
| Data Distillery Knowledge Graph (DDKG) | Partnership | The Data Distillery Knowledge Graph Partnership (DDKG; https://github.com/nih-cfde/data-distillery) aims to enable discovery by generating a knowledge graph that connects data from multiple CFDE DCCs. |
| UniProt-CFDE Partnership | Partnership | The UniProt-CFDE Partnership (Protein Knowledge Network, ProKN) aims to improve interoperability and connectivity between UniProt and CFDE through protein mapping and integration of protein-centric data, and systems biology and knowledge network-based analyses and visualization. |
| Community Visualization Hub | Partnership | The Community Visualization Hub aims to develop a cloud-based visualization platform that enables interactive exploration of omics and imaging data from CFDE and related sources. |
| Genetic Basis of Birth Defects and Childhood Cancer | Partnership | The Genetic Basis of Birth Defects and Childhood Cancer Partnership aims to develop novel predictive models to identify common genetic bases of pediatric cancers and structural birth defects. |
| Metabotyping Humans | Partnership | The Metabotyping Humans Partnership aims to identify the genetic and environmental determinants of human metabotypes in health and disease. |
| Gene Centric Prototype Dashboard | Partnership | The Gene Centric Prototype Dashboard (https://cfde-gene-pages.cloud/) aimed to develop methodologies for harmonizing variant, gene, protein, and drug/small molecule identifiers across DCCs, and landing pages that aggregate knowledge about single genes and drugs from across CF programs and external sources. |
| Communication and Outreach to Maximize | Partnership | The Communication and Outreach to Maximize Product Adoption (COMPA) Partnership developed a roadmap to maximize adoption of CFDE products. |

| | | |
|---|---|---|
| Product Adoption (COMPA) | | |
| Playbook Workflow Builder | Partnership | The Playbook Workflow Builder Partnership (https://playbook-workflow-builder.cloud/graph/extend) aimed to develop a user-friendly web platform to enable the creation of web-based interactive bioinformatics workflows from building blocks generated by the partners to explore CFDE data. |
| Reproductive Toxicology Screening Pipeline (Reprotox-KG) | Partnership | The Reproductive Toxicology Screening Pipeline Partnership (Reprotox-KG; https://maayanlab.cloud/reprotox-kg) developed a knowledge graph that connects genes and drugs to structural birth defects. |
| Standard RNA-Seq Pipeline | Partnership | The Standard RNA-Seq Pipeline Partnership developed standardized pipelines for RNA sequencing data across multiple CFDE DCCs. |
| Clinical Observations and Vocabularies (ClOVoc) | Partnership | The Clinical Observations and Vocabularies (ClOVoc) partnership illustrated a FAIR framework for the interoperability of clinical data across CFDE. |
| Making Gene Regulatory Knowledge FAIR | Partnership | The Making Gene Regulatory Knowledge FAIR Partnership aimed to improve the findability, accessibility, interoperability, and reusability of information about genetic regulatory elements. |
| Cloud Workspace Pilot | Partnership | The CFDE Cloud Workspace Pilot Partnership aimed to generate Appyters that integrate data from multiple CFDE DCCs and to support these analyses through the CAVATICA cloud-based platform. |

**Table 2. List of described CFDE products.**

Products described in the manuscript, listed alongside links to their websites and/or GitHub repositories and PMIDs or DOIs. Products are grouped based on their origination from CFDE Centers, U24 Partnership Projects, or DCCs. Abbreviations: A2CPS-Acute to Chronic Pain Signatures, C2M2-Cross-Cut Metadata Model, CDE-Cell Distance Explorer, CFDE-Common Fund Data Ecosystem, CFDE-GSE-Common Fund Data Ecosystem Gene Set Enrichment, CLI-Command Line Interface, CWIC-Cloud Workspace Implementation Center, DCC-Data Coordinating Center, DDKG-Data Distillery Knowledge Graph, DRC-Data Resource Center, DOI-digital object identifier, EUI-Exploration User Interface, exRNA-The exRNA Research Portal, GDLPA-Gene and Drug Landing Page Aggregator, GSFM-Gene Set Foundation Model, GTEx-The Genotype-Tissue Expression Project, HuBMAP-The Human BioMolecular Atlas Program, HRA-Human Reference Atlas, ICC-Integration and Coordination Center, IDG-Illuminating the Druggable Genome, KC-Knowledge Center, KG-Knowledge Graph, Kids First-Gabriella Miller Kids First Pediatric Research Program, KOMP-The Knockout Mouse Project, L2S2-LINCS L1000 Signatures Search, LINCS-Library of Integrated Network-based Cellular Signatures, MoTrPAC-The Molecular Transducers of Physical Activity Consortium, MW-Metabolomics Workbench, PMID-PubMed identifier, RUI-Registration User Interface, SCGE-Somatic Cell Genome Editing, SenNet-Cellular Senescence Network, SMaHT-The Somatic Mosaicism across Human Tissues Network, SPARC-Stimulating Peripheral Activity to Relieve Conditions, TC-Training Center, UI-user interface, 4DN-The 4D Nucleome Program.

| **Core CFDE Centers** | | | | |
|---|---|---|---|---|
| **CFDE Center** | **Product name** | **Type of product** | **GitHub repository or best link** | **PMID or DOI** |
| DRC | C2M2 | Metadata standard / schema | https://info.cfde.cloud/documentation/C2M2 | 41506317 |
| DRC | CFDE Information Portal | Web portal / UI | https://info.cfde.cloud/<br>https://github.com/MaayanLab/DRC-Portals | 41506317 |
| DRC | CFDE Data Portal | Web portal / workbench / database | https://data.cfde.cloud/<br>https://github.com/MaayanLab/DRC-Portals | 41506317 |
| DRC | GeneSetCart | Web application / data management | https://genesetcart.cfde.cloud/<br>https://github.com/MaayanLab/GeneSetCart/ | 40208796 |

| | | | | |
|---|---|---|---|---|
| DRC | GDLPA | Web application / aggregator | https://cfde-gene-pages.cloud/<br>https://github.com/MaayanLab/cfde_gene_pages | 35368424 |
| DRC | Rummagene | Web application / gene set search engine | https://rummagene.com/<br>https://github.com/MaayanLab/rummagene | 38643247 |
| DRC | RummaGEO | Web application / signature search engine | https://rummageo.com/<br>https://github.com/MaayanLab/rummageo | 39569206 |
| DRC | GSFM | Foundation model / model-backed web resource | https://gsfm.maayanlab.cloud/<br>https://github.com/MaayanLab/gsfm | 40501705 |
| DRC | CFDE-GSE | Gene set enrichment web application | https://gse.cfde.cloud/ | 41506317 |
| DRC | FAIRshake | FAIR assessment toolkit / web app | https://fairshake.cloud/<br>https://github.com/MaayanLab/FAIRshake | 31677972 |
| DRC | cfde-c2m2 | CLI / Python package | https://pypi.org/project/cfde-c2m2/ | 41506317 |
| DRC | KG-UI | UI template for hosting KG on web | https://github.com/MaayanLab/Knowledge-Graph-UI/ | 40956607 |
| KC | CFDE Knowledge Portal | Web portal / UI | https://cfdeknowledge.org/ | NA |
| KC | KC Gene Set Browser | Web application / browser | https://cfdeknowledge.org/r/kc_gsb | NA |
| KC | CFDE-REVEAL | LLM-assisted search interface | https://cfdeknowledge.org/r/cfde_reveal | NA |
| KC | CFDE-DESIGN | LLM-assisted protocol generation workflow | https://cfdeknowledge.org/r/cfde_design | NA |
| TC | e-Learning Dashboard | Training portal / dashboard | https://orau.org/cfde-trainingcenter/training/e-learning.html | NA |
| ICC | ICC Connect | Web portal / UI | https://cfdeconnect.org/ | NA |
| ICC | CFDE Sankey diagram | Interactive visualization / sustainability mapping | https://cfde-sankey.github.io/ | NA |

| | | | | |
|---|---|---|---|---|
| CWIC | CFDE Cloud Workspace | CFDE Cloud Workspace | https://cfdeworkspace.org/ | NA |
| **CFDE U24 Partnerships** | | | | |
| **U24 Partnership** | **Product name** | **Type of product** | **GitHub repository or best link** | **PMID or DOI** |
| DDKG | Data Distillery Knowledge Graph (DDKG) | Knowledge graph | https://github.com/nih-cfde/data-distillery | 40832351 |
| ReproTox-KG | ReproTox-KG | Knowledge graph / web application | https://maayanlab.cloud/reprotox-kg | 37460679 |
| Biomarker | BiomarkerKB Knowledge Graph | Knowledgebase / knowledge graph | https://biomarkerkb.org/ | 10.64898/2026.01.26.701395 |
| Metabotyping | Petagraph | Knowledge graph framework | https://github.com/TaylorResearchLab/Petagraph | 39695169 |
| UniProt | Protein Knowledge Network (ProKN) | Web portal / UI | https://research.bioinformatics.udel.edu/ProKN | NA |
| UniProt | KSMoFinder | Classifier / prediction tool | https://github.com/manju-anandakrishnan/KSMoFinder | 41279605 |
| Playbook | Playbook Workflow Builder | Workflow builder / web platform | https://playbook-workflow-builder.cloud/graph/extend | 40179105 |
| RNA-Seq Pipeline | Standard RNA-Seq Processing Pipelines | Standardized workflow / pipeline | https://github.com/hubmapconsortium/salmon-rnaseq | NA |
| Gene Centric Prototype Dashboard | Gene Centric Prototype Dashboard | Entity page dashboard | https://cfde-gene-pages.cloud/ | NA |
| **Individual Common Fund DCC projects** | | | | |
| **DCC** | **Product name** | **Type of product** | **GitHub repository or best link** | **PMID or DOI** |
| 4DN | 4D Nucleome Portal | Web portal / UI | https://www.4dnucleome.org/ | 28905911 |
| 4DN | 4D Nucleome Data Portal | Data portal / UI | https://data.4dnucleome.org/ | 35501320 |

| | | | | |
|---|---|---|---|---|
| A2CPS | Acute to Chronic Pain Signatures | Web portal / UI | https://a2cps.org/ | 35547202 |
| Bridge2AI | Bridge2AI | Web portal / UI | https://bridge2ai.org/ | 39484409 |
| exRNA | exRNA Research Portal | Web portal / UI / database | https://exrna.org/ | 26320938 |
| exRNA | exRNA Atlas | Data portal / UI | https://exrna-atlas.org/ | 30951672 |
| exRNA | CFDE Linked Data Hub | UI<br>API | https://ldh.genome.network/cfde/ldh/ui/<br>https://ldh.genome.network/cfde/srvc (https://ldh.genome.network/cfde/ldh/ui/api-docs) | 41557842 |
| exRNA | reGL Registry service | API | https://ldh.genome.network/ldh/alias/genereg/srvc (https://genboree.org/docs/ldh-alias/) | 41557842 |
| exRNA | Variant Dashboard | UI<br>API | https://genboree.org/gvi/vd-ui/app<br>https://genboree.org/docs/gvi/dst/ | 41557842 |
| exRNA | UCSC Tack Hub | UI | https://genboree.org/pub/genereg/ucsc_trackhub/hub.txt (for use in https://genome.ucsc.edu/cgi-bin/hgHubConnect) | 41557842 |
| GlyGen | GlyGen | Web portal / UI / database | https://glygen.org/ | 31616925 |
| GTEx | GTEx Portal | Web portal / UI | https://gtexportal.org/home/ | 23715323 |
| HuBMAP | HuBMAP Consortium Portal | Web portal / UI | https://hubmapconsortium.org/ | 31597973 |
| HuBMAP | Azimuth | Transcriptomic cell annotation tool | https://azimuth.hubmapconsortium.org/ | 31597973 |
| HuBMAP | Cell Distance Explorer (CDE) | Cell distance explorer | https://apps.humanatlas.io/cde | 10.1101/2025.09.23.678129 |
| HuBMAP | DeepCellTypes | Spatial omics cell type annotation tool | https://vanvalenlab.github.io/deepcell-types/ | 10.1101/2024.11.02.621624 |
| HuBMAP | Exploration User Interface (EUI) | Spatial exploration UI | https://apps.humanatlas.io/eui | 36513738 |

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|---|---|---|---|---|
| HuBMAP | HRA Knowledge Graph | Knowledge graph / web application | https://apps.humanatlas.io/kg-explorer | 10.1038/s41597-025-05183-6 |
| HuBMAP | HRA Organ Gallery | 3D organ gallery | https://humanatlas.io/hra-organ-gallery | 40082611 |
| HuBMAP | Registration User Interface (RUI) | Tissue registration user interface | https://apps.humanatlas.io/eui | 36513738 |
| HuBMAP | 3D Human Reference Atlas (HRA) | Web portal / UI | https://humanatlas.io/ | 40082611 |
| IDG | Illuminating the Druggable Genome (IDG) | Program portal / data resource | https://druggablegenome.net/ | 29472638 |
| IDG / Reactome | IDG Reactome Gene Pages | Gene entity pages / pathway-centric portal | https://idg.reactome.org/ | NA |
| Kids First | Kids First Data Resource Portal | Web portal / data resource | https://portal.kidsfirstdrc.org/ | 10.1158/1538-7445.AM2023-6576 |
| KOMP | KOMP Repository | Web portal / UI | https://www.komp.org/ | 27626380 |
| KOMP2 | Knockout Mouse Phenotyping Program (KOMP2) | | https://www.mousephenotype.org/ | 27626380 |
| LINCS | LINCS | Web portal / UI | https://lincsproject.org/LINCS/ | 29199020 |
| LINCS | L2S2 | Web application / gene set search engine | https://l2s2.maayanlab.cloud/ | 40308216 |
| Metabolomics Workbench | Metabolomics Workbench | Program portal / data repository | https://www.metabolomicsworkbench.org/ | 27352324 |
| MoTrPAC | MoTrPAC Data Hub | Web portal / UI | https://motrpac-data.org/ | 32269365 |
| SCGE | SCGE Program Portal | Web portal / UI | https://scge.mcw.edu/ | 33828315 |

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|---|---|---|---|---|
| SenNet | SenNet Consortium Portal | Web portal / UI | https://sennetconsortium.org/ | 10.64898/2026.02.06.704469 |
| SMaHT | SMaHT Network | Web portal / UI | https://smaht.org/ | 40604182 |
| SPARC | SPARC Portal | Web portal / UI | https://sparc.science/ | 34248680 |

**Table 3. List of Ontologies and Controlled Vocabularies used in the Cross-Cut Metadata Model (C2M2)**

The C2M2 model integrates standard ontologies and controlled vocabularies for a host of metadata fields, defined here. Abbreviations: C2M2-Cross-Cut Metadata Model, CL-Cell Ontology, CLO-Cell Line Ontology, DO-Disease Ontology, EDAM-The EMBRACE Data and Methods (EDAM) Ontology, HPO-Human Phenotype Ontology, MPO-Mammalian Phenotype Ontology, NCBI:txid-National Center for Biotechnology Information Taxonomy Identifier, OBI-The Ontology for Biomedical Investigations, PubChem-Public Chemical Information Resource, UniProtKB-UniProt Knowledgebase

| Metadata | Ontology/Controlled vocabulary |
|---|---|
| Analysis | OBI[86] |
| Anatomy | UBERON[30] |
| Assay | OBI[86] |
| Biofluid | UBERON[30] |
| Cell | CL[87] |
| Cell line | CLO[88] |
| Compound | PubChem[89] |
| Data Type | EDAM[90] |
| Disease | DO[91] |
| File Format | EDAM[90] |
| Gene | ENSEMBL[92] |
| Phenotype | HPO[93]/MPO[94] |
| Protein | UniProtKB[39] |
| Substance | PubChem[89] |
| Taxonomy | NCBI:txid[95] |

**Table 4. Tracked metadata coverage for C2M2 submissions over time for one CFDE DCC, the Gabriella Miller Kids First Pediatric Research Program.**

Metadata coverage for CFDE C2M2 submissions over time for the Gabriella Miller Kids First Pediatric Research Program DCC. CFDE C2M2 submissions were made on a quarterly basis for CFDE funding years beginning in January 2022 (Y2Q1) through the present (March 2026; Y6Q2). Counts are provided for each submitted metadata entity type. Some additional improvements have been planned but not yet deployed for the Year 6 Q2 submission; these are projected in the “Q2 Improved” column. Abbreviations: Q-quarter, Y-year.

| Entity Count | Y2Q1 | Y2Q2 | Y2Q3 | Y2Q4 | Y3Q1 | Y3Q2 | Y3Q3 | Y3Q4 | Y4Q1 | Y4Q2 | Y4Q3 | Y4Q4 | Y5Q1 | Y5Q2 | Y5Q3 | Y5Q4 | Y6Q1 | Y6Q2 | Y6Q2 (improved) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| anatomy | 21 | 21 | 15 | 16 | 16 | 14 | 16 | 16 | 16 | 18 | 18 | 18 | 17 | 18 | 20 | 20 | 20 | 105 | 118 |
| assay_type | 4 | 4 | 4 | 4 | 4 | 0 | 0 | 3 | 3 | 3 | 3 | 3 | 5 | 5 | 5 | 5 | 5 | 5 | 7 |
| biosample | 58601 | 58601 | 85555 | 85555 | 85555 | 93561 | 96683 | 41459 | 42208 | 37260 | 33621 | 89019 | 108029 | 108053 | 110390 | 110904 | 112229 | 112287 | 112287 |
| biosample_disease | 0 | 0 | 0 | 2157 | 92345 | 105744 | 106410 | 54386 | 55145 | 50647 | 43943 | 102403 | 121412 | 121436 | 123773 | 124287 | 125612 | 125670 | 119177 |
| biosample_from_subject | 58427 | 58427 | 85555 | 85555 | 85555 | 93561 | 96683 | 41459 | 42208 | 37260 | 33621 | 89019 | 108029 | 108053 | 110390 | 110904 | 112229 | 112287 | 112287 |
| biosample_in_collection | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 60016 |
| collection | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 60016 |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| collection_anatomy | NA | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 123994 |
| data_type | 7 | 7 | 7 | 7 | 7 | 12 | 12 | 10 | 9 | 9 | 8 | 10 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| disease | 0 | 0 | 0 | 2 | 20 | 20 | 20 | 27 | 28 | 28 | 27 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 27 |
| file | 114537 | 114537 | 213123 | 213123 | 213123 | 264384 | 285072 | 281223 | 273047 | 290423 | 274228 | 327791 | 1103456 | 1158044 | 1085407 | 1101617 | 1114261 | 1129821 | 1351623 |
| file_describes_biosample | 145140 | 145140 | 285783 | 285783 | 285783 | 362723 | 387414 | 389887 | 378109 | 409927 | 380787 | 470476 | 1574877 | 1668577 | 1547499 | 1570028 | 1592905 | 1606777 | 1961391 |
| file_describes_subject | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 318413 | 321724 | 378751 | 1270659 | 1325283 | 1237943 | 1253437 | 1276325 | 1291862 | 1539141 |
| file_format | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 15 | 15 | 15 | 15 | 15 | 14 | 15 |
| phenotype | NA | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1545 |
| project | 23 | 23 | 31 | 31 | 31 | 31 | 36 | 39 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 45 |
| project_in_project | 22 | 22 | 30 | 30 | 30 | 30 | 35 | 38 | 39 | 39 | 39 | 39 | 39 | 39 | 39 | 39 | 39 | 39 | 44 |
| subject | 17521 | 17521 | 28196 | 28196 | 28196 | 29882 | 32908 | 30560 | 31227 | 29662 | 25735 | 34364 | 35480 | 35480 | 37409 | 37411 | 38605 | 38605 | 38596 |
| subject_disease | 0 | 0 | 0 | 3362 | 35027 | 36828 | 36998 | 37814 | 38491 | 37247 | 30653 | 41715 | 42826 | 42826 | 44755 | 44757 | 45951 | 45951 | 40694 |
| subject_phenotype | NA | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 146665 |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| subject_race | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 26742 |
| subject_role_taxonomy | 17521 | 17521 | 28196 | 28196 | 28196 | 29882 | 32908 | 30560 | 31227 | 29662 | 25735 | 34364 | 35480 | 35480 | 37409 | 37411 | 38605 | 38605 | 38596 |

**Table 5. Flagship CFDE outreach and engagement activities**

Key outreach and engagement activities undertaken by CFDE centers since their activities began in earnest in 2024. Abbreviations: DRC-Data Resource Center, ICC-Integration and Coordination Center, KC-Knowledge Center, TC-Training Center.

| Event name | Type | Center(s) | Frequency | Target Audience | Brief Description | Hyperlink (if applicable) | Quantified outputs | Dates |
|---|---|---|---|---|---|---|---|---|
| CFDE Virtual Workshop | Workshop | KC, TC, ICC, DRC | N/A | Individuals looking to learn about CFDE | Navigating the Common Fund Data Ecosystem's (CFDE) Data & Resources to Empower Scientific Discoveries. | https://cfdeknowledge.org/r/kc_news_item?id=736 | Attendees | 2025 |
| CFDE Public Webinar Series | Webinar | KC | Monthly | CFDE, Center/DCC consortia members | CFDE Webinar Series brings the varied programs of the CFDE to the broad biomedical research community. | https://cfdeknowledge.org/r/CFDE_webinars | Attendees | 2024 to now |
| American Society of Human Genetics Booth | Conference Booth | KC | Yearly | Human geneticists | Attendees learn about CFDE and its applications to their research. | https://www.ashg.org/annual-meeting-2026/ | Attendees | 2024 to now |
| American Society of Human Genetics Ancillary Session | Conference Ancillary Session | KC | Yearly | Human geneticists | Attendees learn about CFDE and its applications to their research. | https://www.ashg.org/annual-meeting-2026/ | Attendees | 2024 to now |
| American Society of Human Genetics Networking Event | Conference Networking Event | KC | Yearly | Human geneticists | Attendees learn about CFDE and its applications to their research. | https://www.ashg.org/annual-meeting-2026/ | Attendees | 2024 to now |

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|---|---|---|---|---|---|---|---|---|
| Bio-IT World FAIR Data Hackathon | Hackathon | TC | Yearly | Leaders in biopharma, clinical research, healthcare, informatics, and technology | Guided by Open Source and FAIR Data principles, this two-day event fosters collaboration and innovation across multidisciplinary teams to solve real-world data challenges. | https://www.bio-itworldexpo.com/fair-data-hackathon | Attendees | 2019 to now |
| Bio-IT World FAIR Data Workshop | Workshop | DRC | N/A | Leaders in biopharma, clinical research, healthcare, informatics, and technology | This hands-on workshop introduces the Playbook Workflow Builder (PWB), guiding participants through step-by-step recipes to create reusable, transparent, and interoperable bioinformatics workflows using CFDE and other datasets. | https://www.bio-itworldexpo.com/workshops#1 | Attendees | 2026 |
| Decoding the Data Ecosystem | Podcast | TC | Monthly | Anyone passionate about the potential of omics research | Decoding the Data Ecosystem is a podcast series dedicated to unraveling the complexities and exploring the depths of omics research. | https://podcast.show/3847772/ | Number of streams | 2024 to now |
| Festival of Genomics Boston | Conference Booth | KC | Yearly | Omics researchers, pharma, biotech, healthcare, research and emerging tech | Attendees learn how to leverage omics, AI and advanced analytics to transform drug discovery, accelerate development, further research projects and enable precision medicine using CFDE. | https://festivalofgenomics.com/Boston | Booth attendees | 2025 to now |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Festival of Genomics Boston | Conference Ancillary Session | KC | Yearly | Omics researchers, pharma, biotech, healthcare, research and emerging tech | Attendees learn how to leverage omics, AI and advanced analytics to transform drug discovery, accelerate development, further research projects and enable precision medicine using CFDE. | https://festivalofgenomics.com/Boston | Genome Dome attendees | 2025 to now |
| Intelligent Systems for Molecular Biology | Conference | KC, TC, ICC, DRC | Yearly | Academics, bioinformatics and computational biology | Each year the Intelligent Systems for Molecular Biology hosts an academic conference centered around bioinformatics and computational biology. | https://www.iscb.org/ismb2026/home | Talk attendees | 2025 to now |
| Decoding the Data Ecosystem Virtual Symposium | Virtual Symposium | TC | N/A | Faculty, students, researchers, etc. | The Decoding the Data Ecosystem Virtual Symposium leverages collaboration between researchers, faculty, and students to explore how the Common Fund Data Ecosystem (CFDE) can support research, education, and discovery in omics-related research. | https://www.orau.org/cfde-trainingcenter/events/virtual-symposium.html | Attendees | 2025 |
| KDD (Knowledge Discovery and Data Mining) | Conference | ICC | Yearly | a broad range of professionals and students in the fields of data science, AI, machine learning, | The ICC will be hosting several events (Presentation, Booth, Ancillary Session, Invited Session) geared towards educating attendees on how the CDFE can help with data science. | https://kdd2026.kdd.org/ | Attendees | 2026 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | and data mining | | | | |
| National Association of Biology Teachers | Conference | TC | Yearly | Biology teachers, educators, trainers | | https://nabt.org/Events-2026-Conference | Attendees | 2026 |
| IEEE Vis | Conference | TC | Yearly | Visualization and Graphics Technical Community | IEEE VIS 2026 will be the year's premier forum for advances in theory, methods, and applications of visualization and visual analytics | https://www.ieeevis.org/year/2026/welcome/ | Attendees | 2026 |
| Omics Open House | Webinar | TC | Quarterly | Individuals looking to connect with CFDE technical experts and DCCs | Covers unique CFDE-related topics, offering live support, knowledge-sharing, and opportunities to ask questions. | | Attendees | 2025 to now |
| Decoding the Data Ecosystem (DeCoDE) Virtual Institute | Live training | TC | Bi-weekly | Researchers interested in exploring omics & enhancing skills | Gateway to mastering omics research, fostering collaboration, and building skills. | https://www.orau.org/cfde-trainingcenter/events/events.html | Attendees | 2025 to now |
| Broad Institute Medical and Population Genetics Departmental Retreat | Meeting | KC | Yearly | Genetics department at the Broad Institute | This retreat is designed to share scientific advances and promote future collaboration within the department. | | Attendees | 2025 to now |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Mount Sinai Center for Bioinformatics Webinar Series | Webinar | DRC | Bi-monthly | Researchers interested in exploring omics & enhancing skills | The webinar is geared towards omics tools and co-hosted by the Mount Sinai Center for Bioinformatics and the Ma'ayan Laboratory. | | Attendees | 2026 |
| American Association for Cancer Research (AACR) | Conference | DRC | Yearly | Cancer researchers from academia and industry | AACR's mission is to drive progress against cancer by advancing research, educating scientists and clinicians, strengthening collaboration, shaping science policy, advocating for patients, and funding innovative cancer research. | | Attendees | 2026 |
| CFDE Metabolomics Workbench Virtual Summer Workshop 2024 | Virtual workshop | DRC | N/A | Metabolomics/Omics researchers/educators/students | Summer Workshop on metabolomics and its integration with other omics data towards a better understanding of their role in health and disease. | https://www.youtube.com/watch?v=89VpLqR47aM | Attendees | 2024 |
| Metabolomics [Annual meeting by the Metabolomics Society] | Conference | DRC | Yearly | Metabolomics researchers | This conference is dedicated to technological advances, computational metabolomics, statistics, and bioinformatics. | https://metabolomicssociety.org/ | | 2024 |
| Spatial Omics Workshop | Virtual workshop | ICC | N/A | Faculty and research staff interested in spatial omics | This in-person workshop highlights spatial omics data for exploration and visualization, along with related tools for in-place computing on Bridges-2 and HuBMAP workspaces. | | Attendees | 2025 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Interoperable Workflows Using Workflow Management Systems and Singularity Containers | Virtual workshop | ICC | N/A | Faculty and research staff interested in automation | This workshop highlights how to build CWL workflows for big data pre- and post-processing, with a focus on HuBMAP data on Bridges-2. | | Attendees | 2024 |
| Data Exploration of HuBMAP data on Bridges-2 | Workshop | ICC | N/A | Faculty and research staff | This in-person workshop highlighted how to search HuBMAP data across multiple databases and portals, including using the CFDE portal as a starting point for data exploration. | | Attendees | 2024 |
| CFDE-GlyGen Summer Internship 2024 | Internship | GlyGen | N/A | Biolog Researhers Bioinformaticians, Data Scientists | The in-person summer internship offered hands-on experience in bioinformatics and biological data wrangling, focusing on CFDE and GlyGen data and tools to answer real-world biological questions. | https://wiki.glygen.org/GlyGen_Internships/GlyGen-CFDE_Summer_2024_Internship_Program_Announcement | 5 Inters | 2024 |
| CFDE-GlyGen Summer Internship 2025 | Internship | GlyGen | N/A | Biology Researhers Bioinformaticians, Data Scientists | The in-person summer internship offered hands-on experience in bioinformatics and biological data wrangling, focusing on CFDE and GlyGen data and tools to answer real-world biological questions. | https://wiki.glygen.org/GlyGen_Internships/GlyGen-CFDE_Summer_2025_Internship_Program_Announcement | 4 Interns | 2025 |

**Table 6. Highlighted use case from the CFDE Data Distillery Knowledge Graph: sample query results intersecting data from three CFDE DCCs**

Sample outputs from a Cypher query conducted on the Data Distillery Knowledge Graph that nominates candidate mechanistic hypotheses for future validation. The query first connects gene, metabolite, and condition concepts using edges from Metabolomics Workbench (MW), then refines the results through additional constraints. These include tissue-level provenance of metabolite production, independent evidence of gene expression derived from GTEx via intermediate expression entities, and shared or related tissue contexts connecting molecular activity to disease-relevant anatomy. After filtering the core graph pattern, the resulting subgraph was enriched with low-cardinality annotations, upstream biochemical relationships from IDG (gene-protein-compound), and quantitative expression metadata. Results demonstrate a candidate biological pathway in which a gene product (*MGAM*) influences a metabolite (sucrose), and the metabolite is associated with a clinical condition (polycystic kidney disease). Processes are grounded in a relevant tissue (kidney) where the *MGAM* gene is expressed. IDG suggests compounds that are associated with MGAM, thus highlighting candidate therapeutic targets for this pathway. Abbreviations: CFDE-Common Fund Data Ecosystem, DCC-Data Coordinating Center, GTEx-The Genotype-Tissue Expression Project, IDG-Illuminating the Druggable Genome, MW-Metabolomics Workbench.

| [IDG] | [UNIPROTKB] | [MW] | [MW] | [GTEx] | | [MW] | [GTEXEXP] |
|---|---|---|---|---|---|---|---|
| Compound | Enzyme | Gene | Metabolite | Tissue_1 | Tissue_2 | Condition | Expression |
| 1,4-Dideoxy-1,4-{(R)-[4-deoxy-3-O-(hept-1-yl)-D-erythritol-4-yl]episulfoniumylidene}-D-arabinitol chloride | MGA | MGAM | sucrose | Kidney | Set of outer region of renal pyramids | Polycystic Kidney Diseases | 0.5.0.6 |
| 1,4-Dideoxy-1,4-{(R)-[4-deoxy-3-O-isobutyl-D-erythritol-4-yl]episulfoniumylidene}-D-arabinitol chloride | MGA | MGAM | sucrose | Kidney | Set of outer region of renal pyramids | Polycystic Kidney Diseases | 0.5.0.6 |
| 1,4-Dideoxy-1,4-{(R)-[4-deoxy-3-O-neopentyl-D-erythritol-4-yl]episulfoniumylidene}-D-arabinitol chloride | MGA | MGAM | sucrose | Kidney | Set of outer region of renal pyramids | Polycystic Kidney Diseases | 0.5.0.6 |
| 1-Hydroxymethyl-5-[(pyridin-3-ylmethyl)-amino]-cyclohexane-1,2,3,4-tetraol | MGA | MGAM | sucrose | Kidney | Set of outer region of renal pyramids | Polycystic Kidney Diseases | 0.5.0.6 |
| 1-Hydroxymethyl-5-(3-phenyl-allylamino)-cyclohexane-1,2,3,4-tetraol | MGA | MGAM | sucrose | Kidney | Set of outer region of renal pyramids | Polycystic Kidney Diseases | 0.5.0.6 |
| 5-(3,5-Di-tert-butyl-4-hydroxy-benzylamino)-1-hydroxymethyl-cyclohexane-1,2,3,4-tetraol | MGA | MGAM | sucrose | Kidney | Set of outer region of renal pyramids | Polycystic Kidney Diseases | 0.5.0.6 |
| 1-Hydroxymethyl-5-[(thiophen-2-ylmethyl)-amino]-cyclohexane-1,2,3,4-tetraol | MGA | MGAM | sucrose | Kidney | Set of outer region of renal pyramids | Polycystic Kidney Diseases | 0.5.0.6 |
| 5-(3,7-Dimethyl-octa-2,6-dienylamino)-1-hydroxymethyl-cyclohexane-1,2,3,4-tetraol | MGA | MGAM | sucrose | Kidney | Set of outer region of renal pyramids | Polycystic Kidney Diseases | 0.5.0.6 |
| 1-Hydroxymethyl-5-phenethylamino-cyclohexane-1,2,3,4-tetraol | MGA | MGAM | sucrose | Kidney | Set of outer region of renal pyramids | Polycystic Kidney Diseases | 0.5.0.6 |
| 5-(4-Bromo-benzylamino)-1-hydroxymethyl-cyclohexane-1,2,3,4-tetraol | MGA | MGAM | sucrose | Kidney | Set of outer region of renal pyramids | Polycystic Kidney Diseases | 0.5.0.6 |

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