Data Discovery in Biomedical Genomics and Cancer Research

Implementing a New Paradigm

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Professor of Bioinformatics
University of Zürich
Swiss Institute of Bioinformatics **SIB**
Member GA4GH Strategic Leadership Committee
GA4GH Workstream Co-lead *DISCOVERY*
Co-lead ELIXIR Beacon API Development
Co-lead ELIXIR hCNV Community

Universität Zürich[UZH]

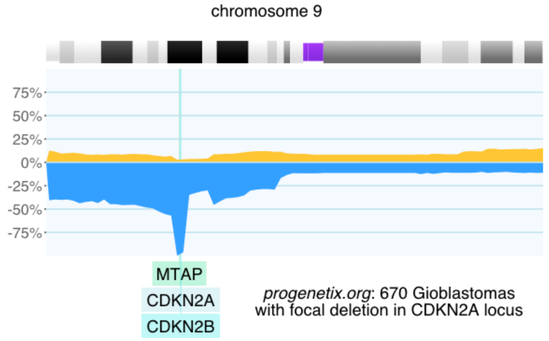
SIB Swiss Institute of Bioinformatics

Global Alliance for Genomics & Health
Collaborate. Innovate. Accelerate.

elixir

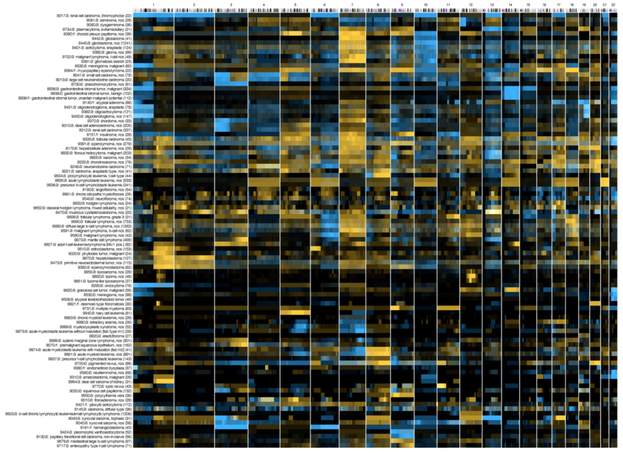
Genomics has seen massive and ongoing changes in technology

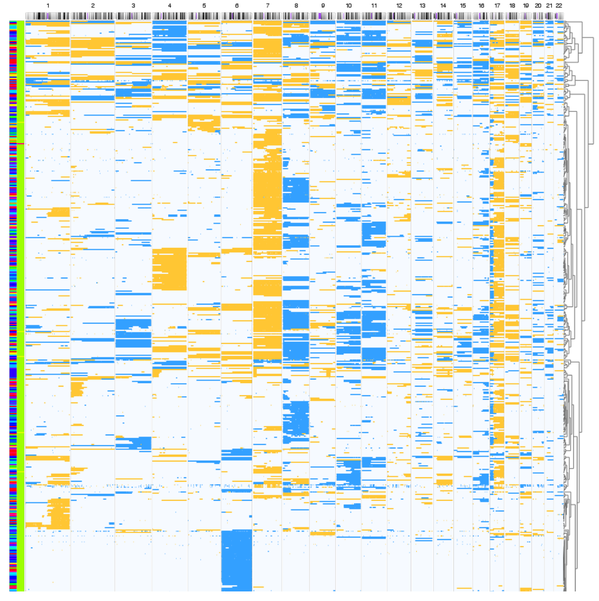
Theoretical Cytogenetics and Oncogenomics Research | Methods | Standards

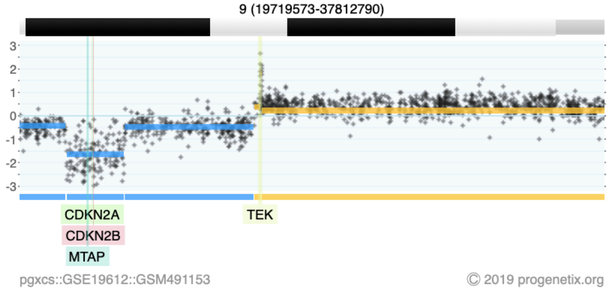


Genomic Imbalances in Cancer - Copy Number Variations (CNV)

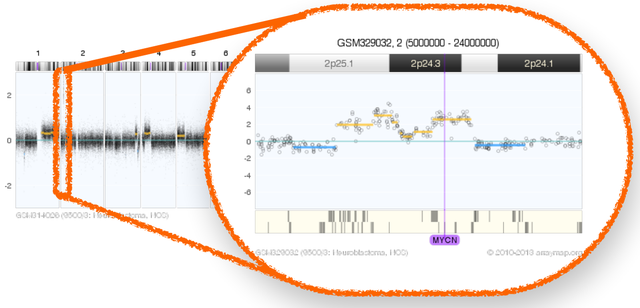
- Point mutations (insertions, deletions, substitutions)
- Chromosomal rearrangements
- **Regional Copy Number Alterations** (losses, gains)
- Epigenetic changes (e.g. DNA methylation abnormalities)





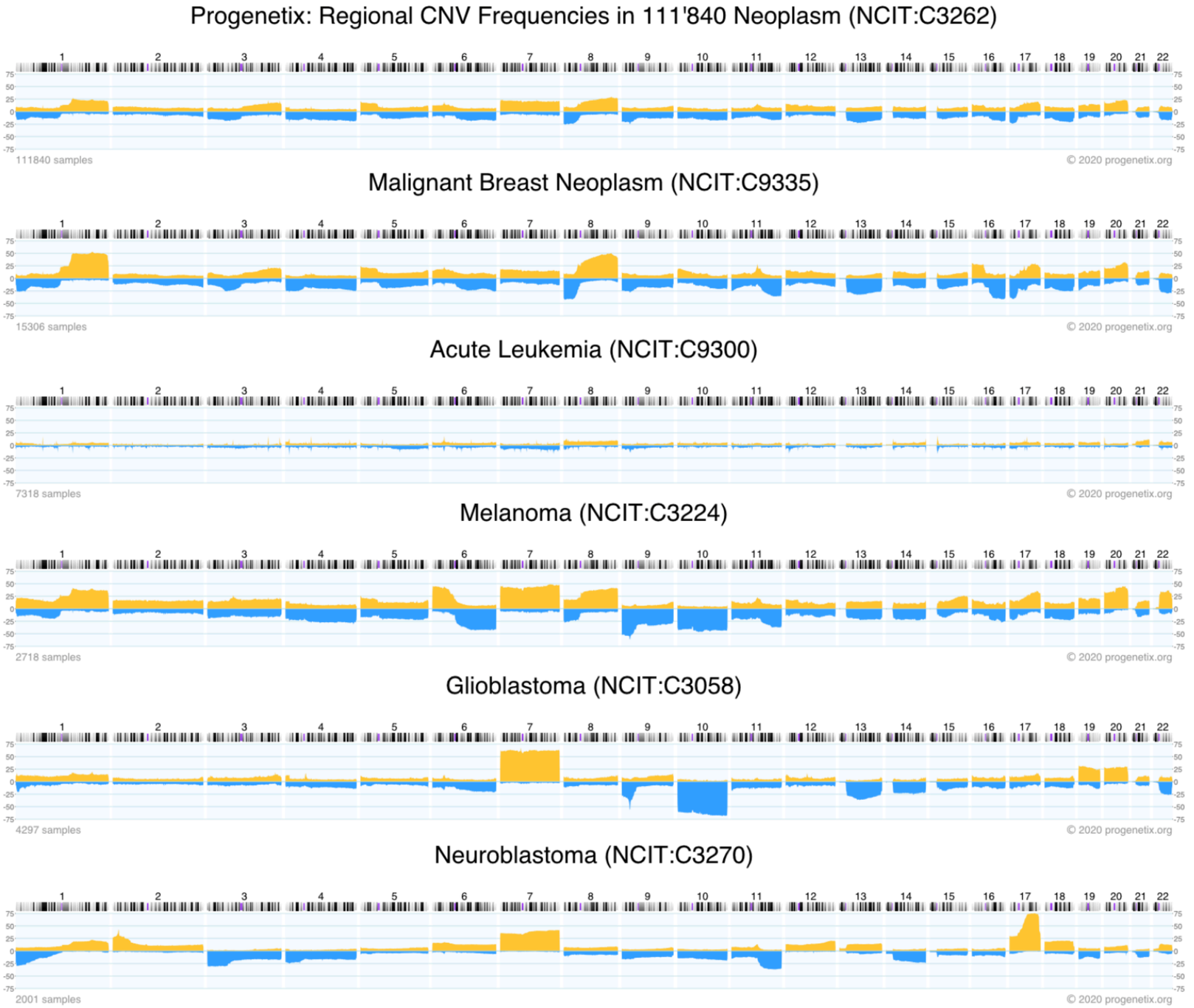


2-event, homozygous deletion in a Glioblastoma



MYCN amplification in neuroblastoma
(GSM314026, SJNB8_N cell line)

Somatic CNV in Cancer



progenetix

progenetix.org

Cancer Genomics Reference Resource

- ***open*** resource for oncogenomic profiles
- over **140'000 cancer CNV profiles**
- SNV data for some series (e.g. TCGA)
- more than **900 diagnostic types**
- inclusion of reference datasets (e.g. TCGA)
- standardized encodings (e.g. NCIt, ICD-O 3)
- identifier mapping for PMID, GEO, Cellosaurus, TCGA, cBioPortal where appropriate
- core clinical data (TNM, sex, survival ...)
- data mapping services

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Cancer CNV Profiles
- ICD-O Morphologies
- ICD-O Organ Sites
- Cancer Cell Lines
- Clinical Categories

Search Samples

arrayMap
- TCGA Samples
- 1000 Genomes Reference Samples
- DIPG Samples
- cBioPortal Studies
- Gao & Baudis, 2021

Publication DB
- Genome Profiling
- Progenetix Use

Services
- NCIt Mappings
- UBERON Mappings

Upload & Plot

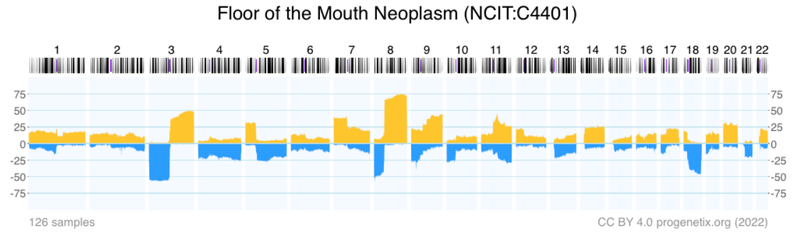
Beacon+

Documentation
- News
- Downloads & Use Cases
- Sevices & API

Baudisgroup @ UZH

Cancer genome data @ progenetix.org

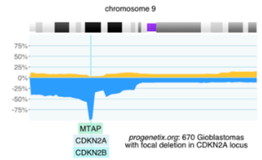
The Progenetix database provides an overview of mutation data in cancer, with a focus on copy number abnormalities (CNV / CNA), for all types of human malignancies. The data is based on *individual sample data* from currently **142063** samples.



Download SVG | Go to NCIT:C4401 | Download CNV Frequencies

Example for aggregated CNV data in 126 samples in Floor of the Mouth Neoplasm.
Here the frequency of regional copy number gains and losses are displayed for all 22 autosomes.

Progenetix Use Cases



Local CNV Frequencies

A typical use case on Progenetix is the search for local copy number aberrations - e.g. involving a gene - and the exploration of cancer types with these CNVs. The [Search Page] provides example use cases for designing queries. Results contain basic statistics as well as visualization and download options.

Cancer CNV Profiles

The progenetix resource contains data of **834** different cancer types (NCIt neoplasm classification), mapped to a variety of biological and technical categories. Frequency profiles of regional genomic gains and losses for all categories (diagnostic entity, publication, cohort ...) can be accessed through the [Cancer Types] page with direct visualization and options for sample retrieval and plotting options.

Cancer Genomics Publications

Through the [Publications] page Progenetix provides **4164** annotated references to research articles from cancer genome screening experiments (WGS, WES, aCGH, cCGH). The numbers of analyzed samples and possible availability in the Progenetix sample collection are indicated.

progenetix.org

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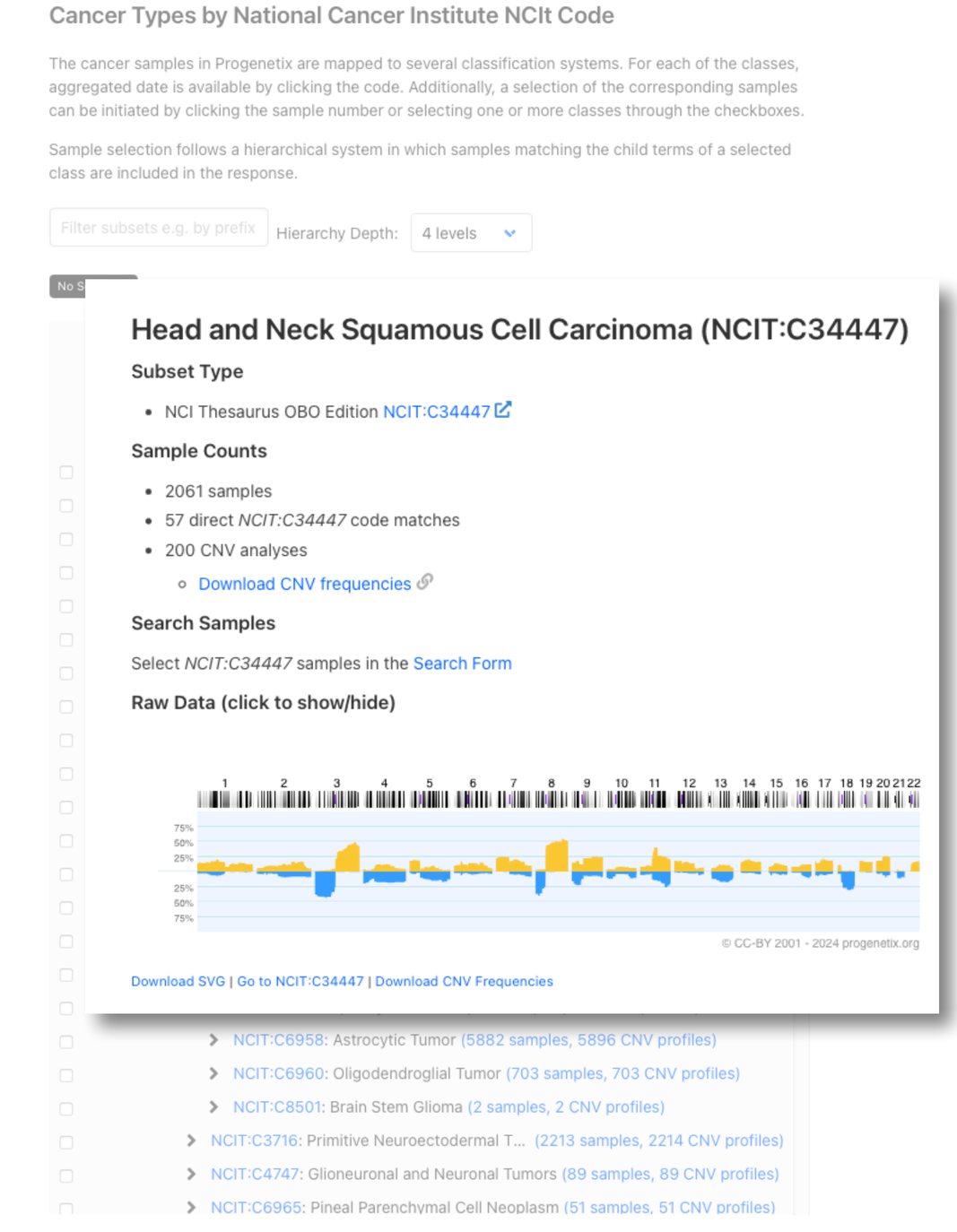

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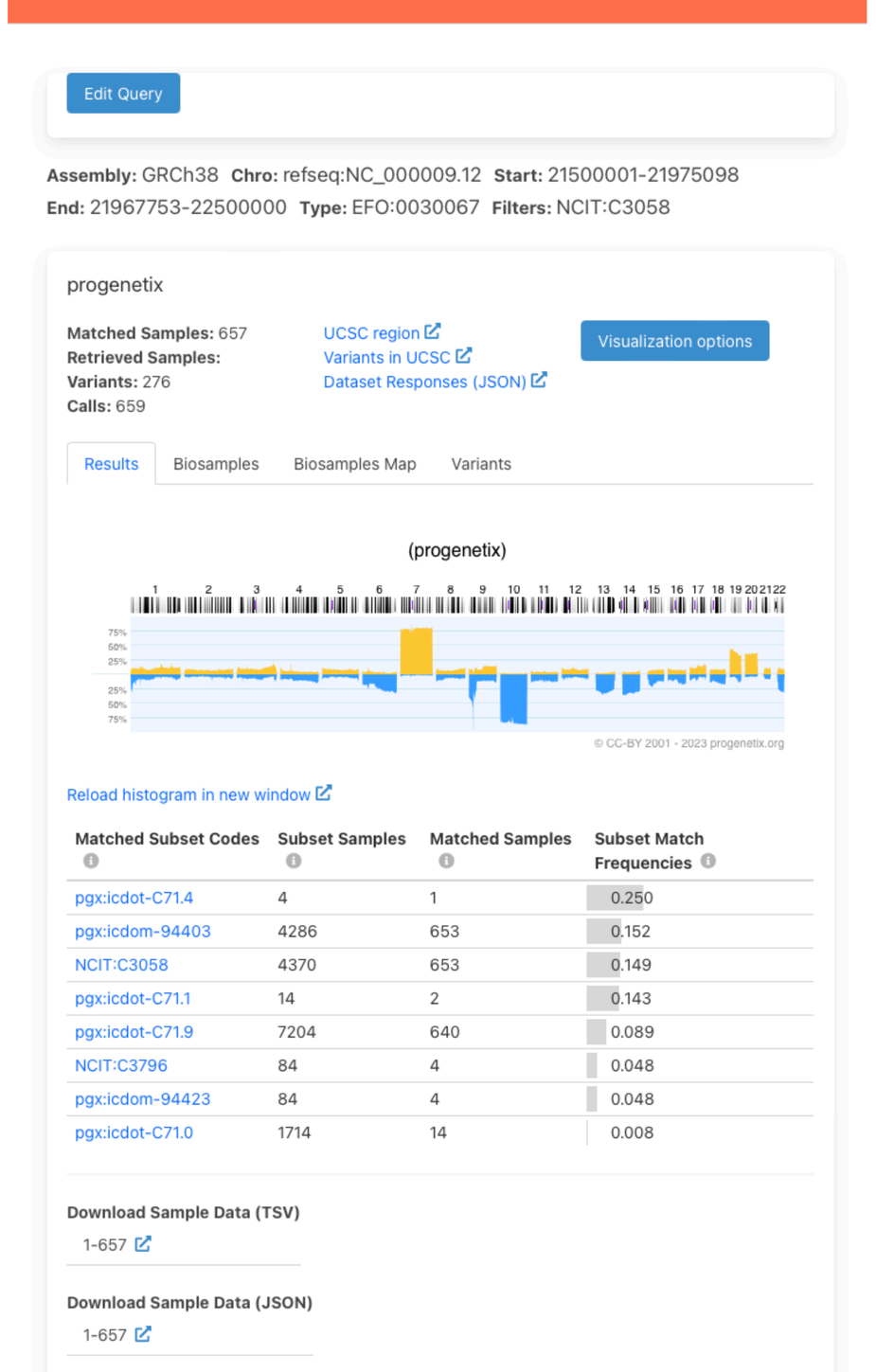

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Cancer Cell Lines

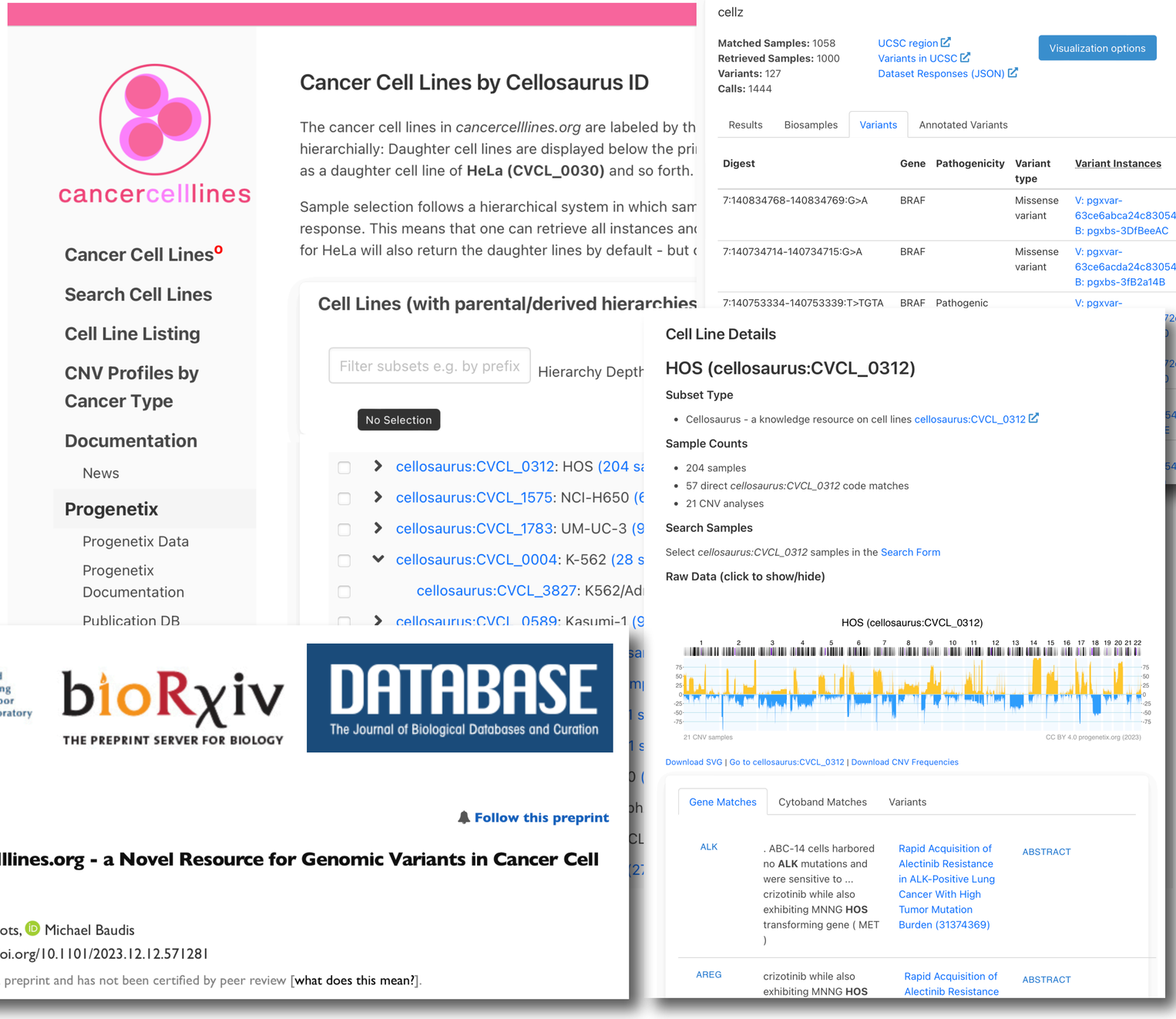
Cancer Genomics Reference Resource

- starting from >5000 cell line CNV profiles
  - 5754 samples | 2163 cell lines
  - 256 different NCIT codes
- genomic mapping of annotated variants and additional data from several resources (ClinVar, CCLE, Cellosaurus...)
  - 16178 cell lines
  - 400 different NCIT codes
- query and data delivery through Beacon v2 API

➡ integration in data federation approaches

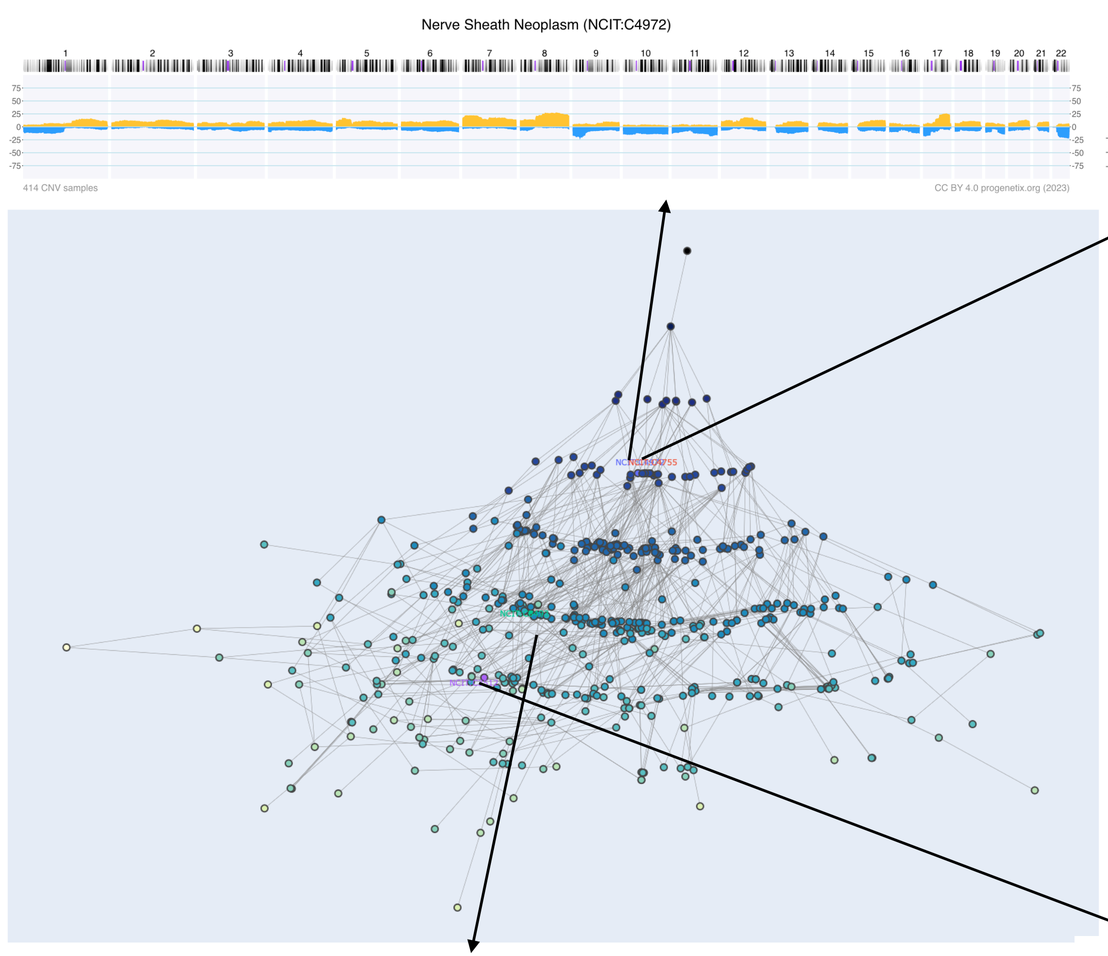
cancercelllines.org

Lead: Rahel Paloots



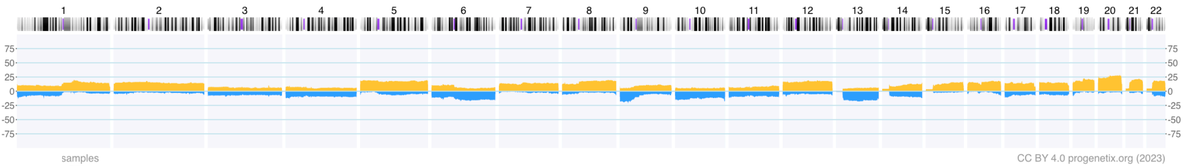
CNV profiles heterogeneity vs cancer classification

Correspondance of genomic profiles to NCIT cancer hierarchy

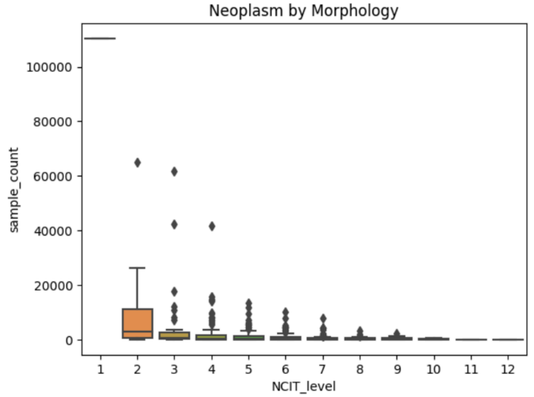


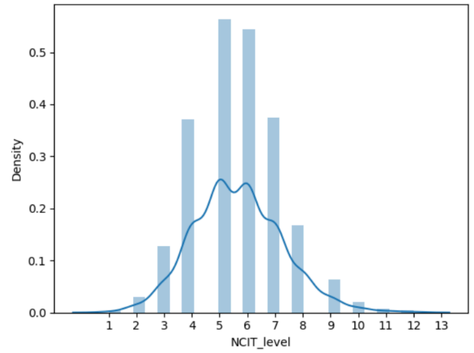
Nerve Sheath Neoplasm (NCIT:C4972)

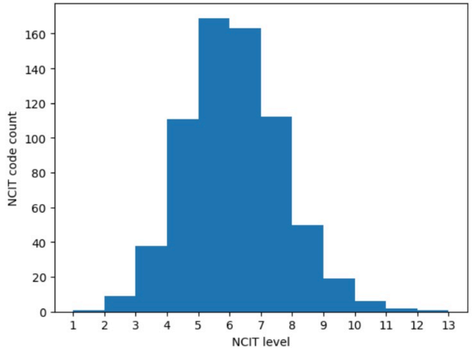
Chondrogenic Neoplasm (NCIT:C4755)



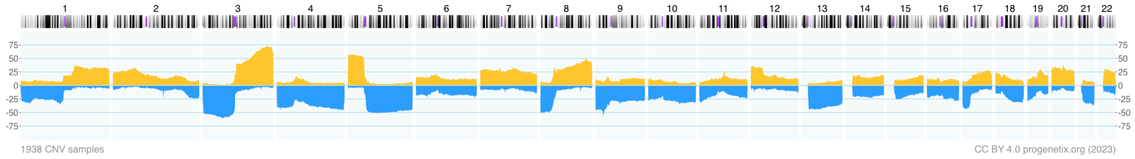
Neoplasm by Morphology



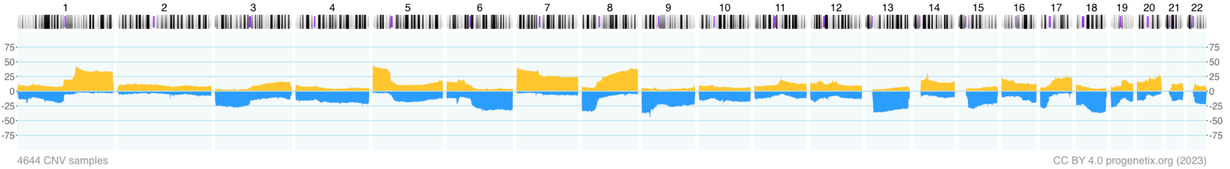




Lung Squamous Cell Carcinoma (NCIT:C3493)

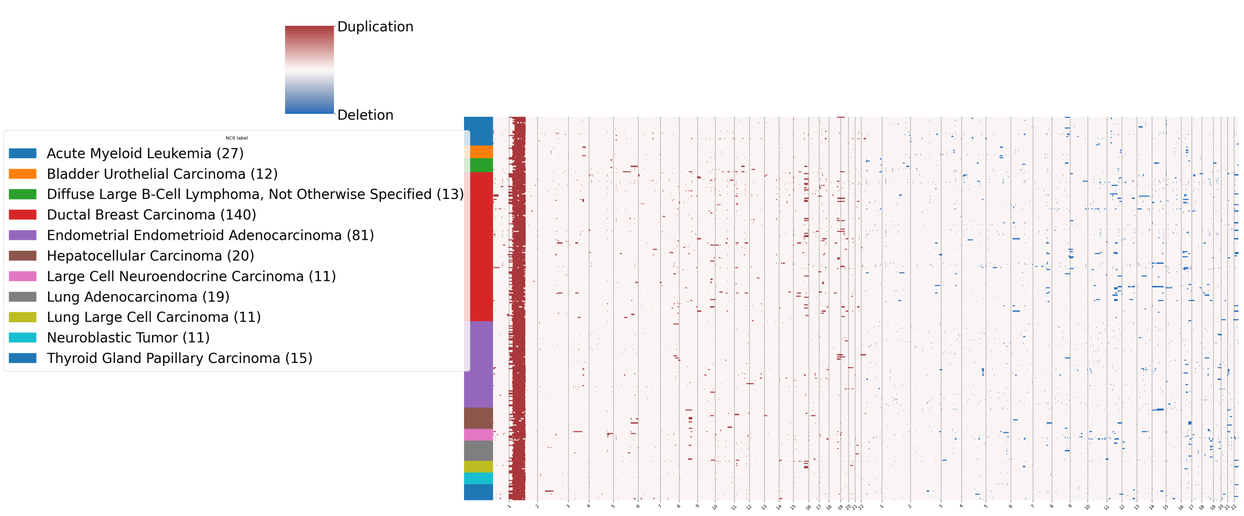


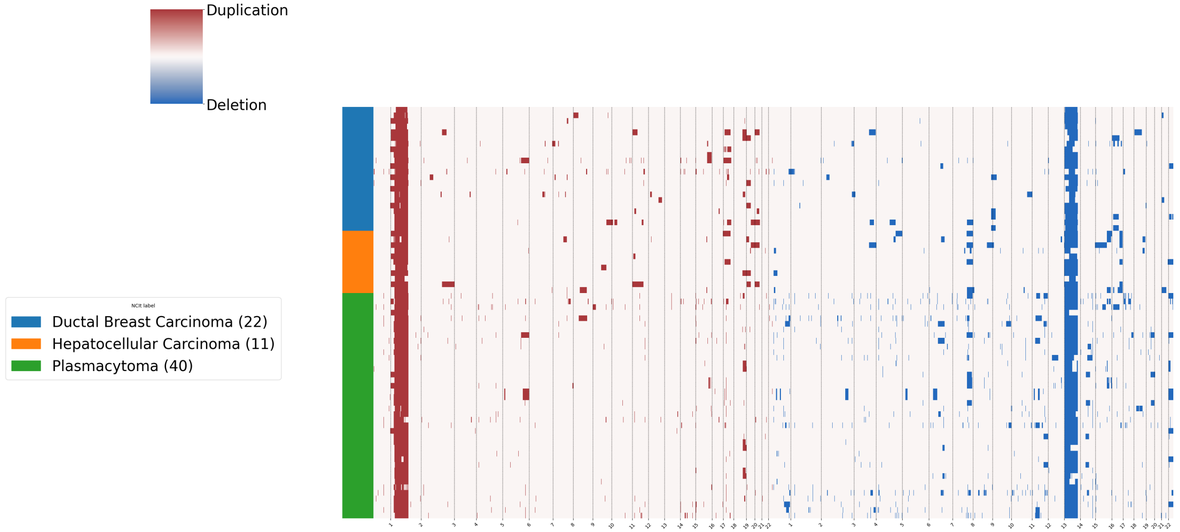
Lung Adenocarcinoma (NCIT:C3512)

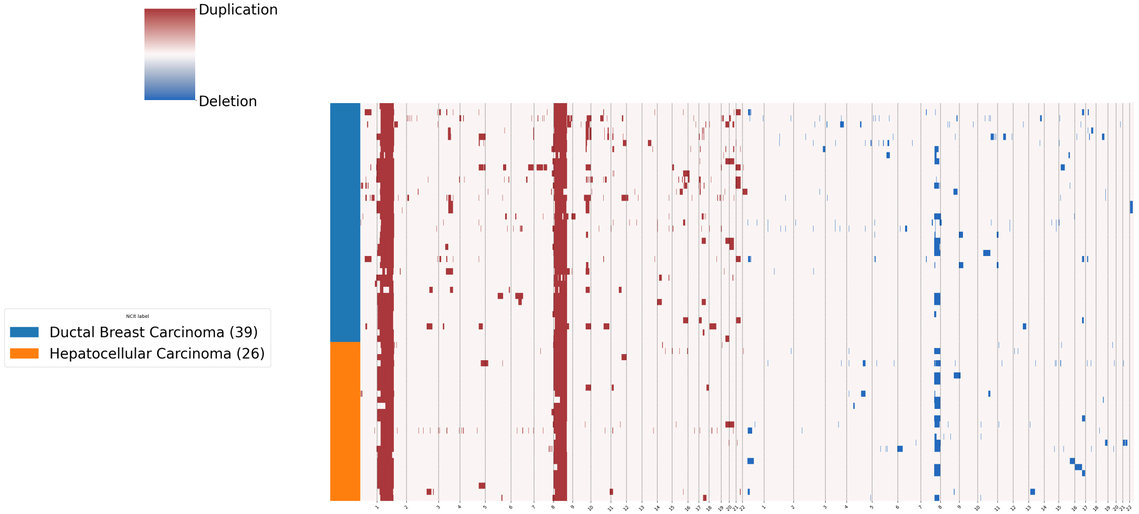


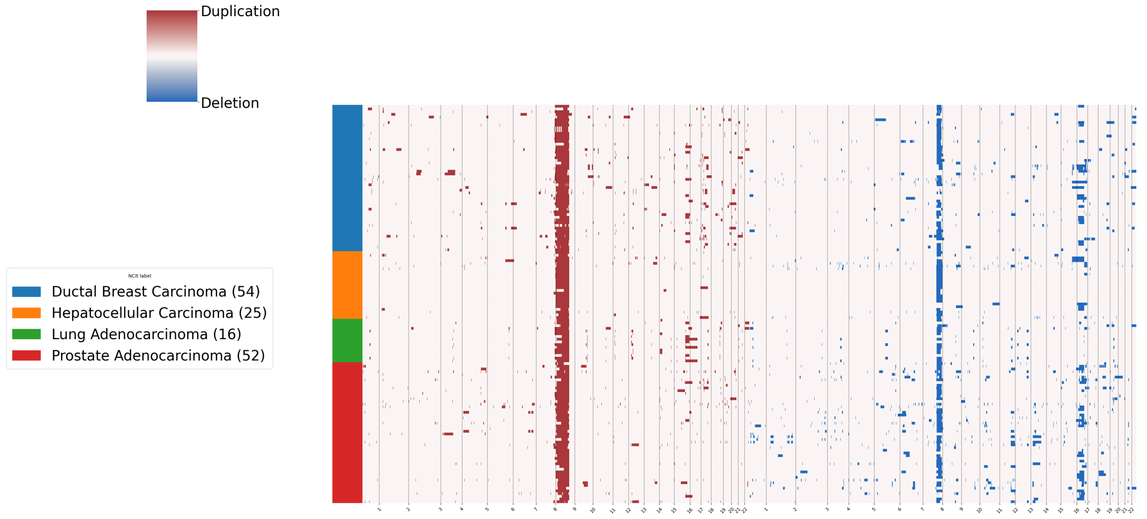
Example Use of Progenetix Data

Inter-tumoral CNV pattern similarity







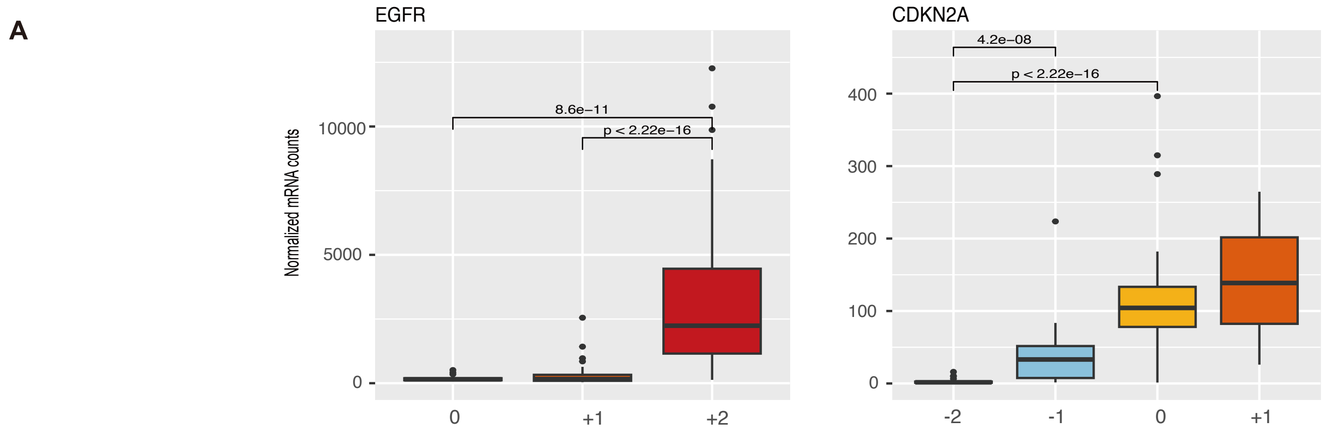


Mostly Carcinoma and Adenocarcinoma in different organs

labelSeg

Application

Strong relationship between copy-number dosage and messenger RNA expression



JOURNAL ARTICLE

labelSeg: segment annotation for tumor copy number alteration profiles

Hangjia Zhao, Michael Baudis

Briefings in Bioinformatics, Volume 25, Issue 2, March 2024, bbad541,
https://doi.org/10.1093/bib/bbad541
Published: 31 January 2024 **Article history**

Contributing to Standards Development: CNV Terms

in computational (file/schema) formats

GA4GH VRS1.3+	EFO	Beacon	VCF	SO
EFO:0030070 gain	**EFO:0030070** copy number gain	DUP or **EFO:0030070**	DUP SVCLAIM=D	SO:0001742 copy_number_gain
EFO:0030071 low-level gain	**EFO:0030071** low-level copy number gain	DUP or **EFO:0030071**	DUP SVCLAIM=D	SO:0001742 copy_number_gain
EFO:0030072 high-level gain	**EFO:0030072** high-level copy number gain	DUP or **EFO:0030072**	DUP SVCLAIM=D	SO:0001742 copy_number_gain
EFO:0030072 high-level gain	EFO:0030073 focal genome amplification	DUP or EFO:0030073	DUP SVCLAIM=D	SO:0001742 copy_number_gain
EFO:0030067 loss	**EFO:0030067** copy number loss	DEL or **EFO:0030067**	DEL SVCLAIM=D	SO:0001743 copy_number_loss
EFO:0030068 low-level loss	**EFO:0030068** low-level copy number loss	DEL or **EFO:0030068**	DEL SVCLAIM=D	SO:0001743 copy_number_loss
EFO:0020073 high-level loss	**EFO:0020073** high-level copy number loss	DEL or **EFO:0020073**	DEL SVCLAIM=D	SO:0001743 copy_number_loss
EFO:0030069 complete genomic loss	**EFO:0030069** complete genomic deletion	DEL or **EFO:0030069**	DEL SVCLAIM=D	SO:0001743 copy_number_loss

Different Approaches to Genomic Data Storage and Distribution

progenetix

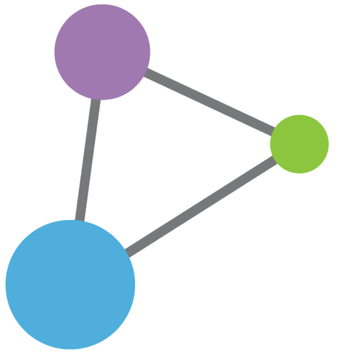
Centralized Genomic Knowledge Bases

European Genome-Phenome Archive

Data Commons
Trusted, controlled repository of multiple datasets

SPHN Swiss Personalized Health Network

Hub and Spoke
Common data elements, access, and usage rules



Linkage of distributed and disparate datasets

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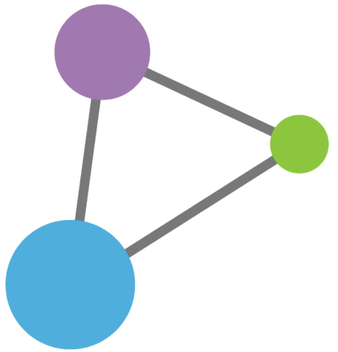


Linkage of distributed and disparate datasets

The EGA

European Genome-Phenome Archive

Long term secure archive for human biomedical research sensitive data, with focus on reuse of the data for further research (or "*broad and responsible use of genomic data*")

EUROPEAN GENOME-PHENOME ARCHIVE

CRG Centre for Genomic Regulation

EMBL-EBI

Global Alliance for Genomics & Health

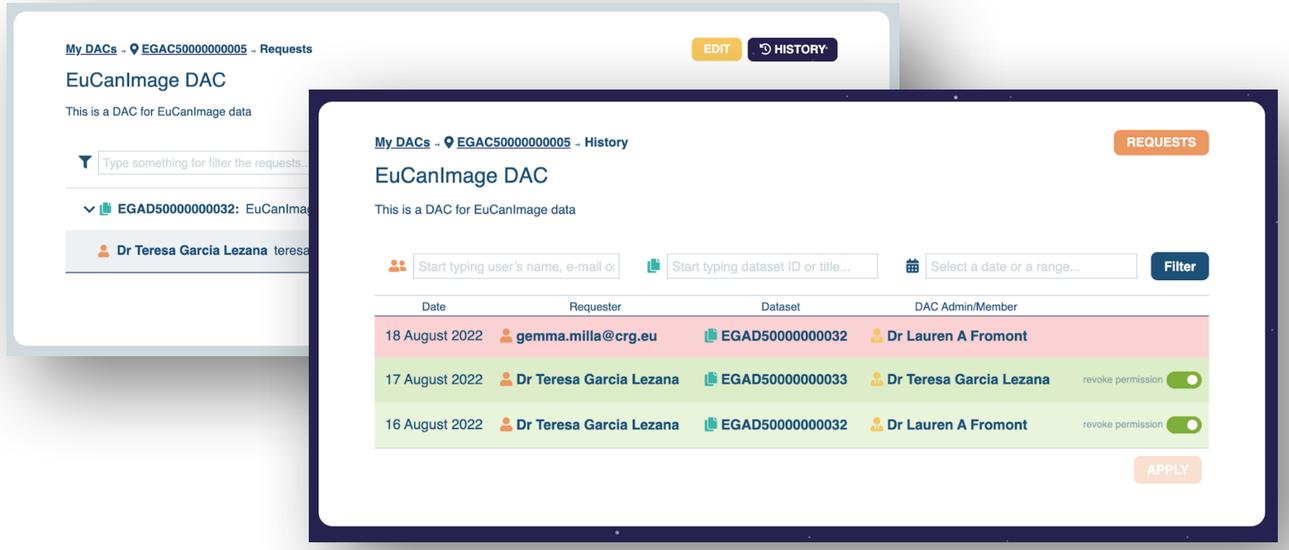
DRIVER PROJECT

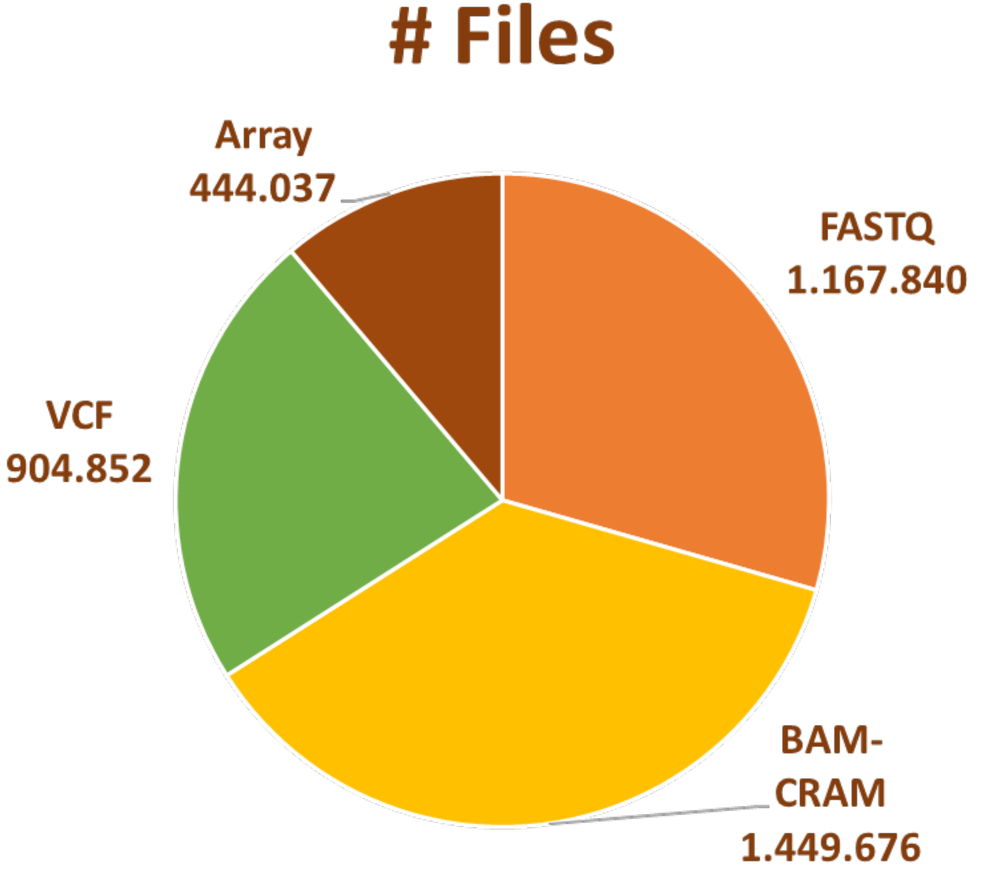
Slide: adapted from Jordi Rambla@ GA4GH 2023

The EGA

European Genome-Phenome Archive

- EGA “owns” nothing; data controllers tell who is authorized to access ***their*** datasets
- EGA admins provide smooth “all or nothing" data sharing process





4,328 Studies released
10,470 Datasets
2,309 Data Access Committees

Slide: adapted from Jordi Rambla@ GA4GH 2023

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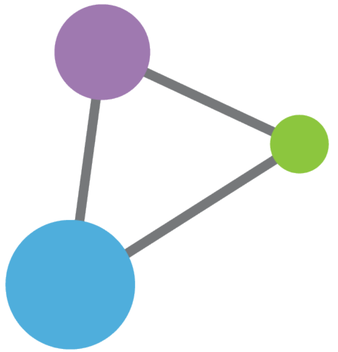
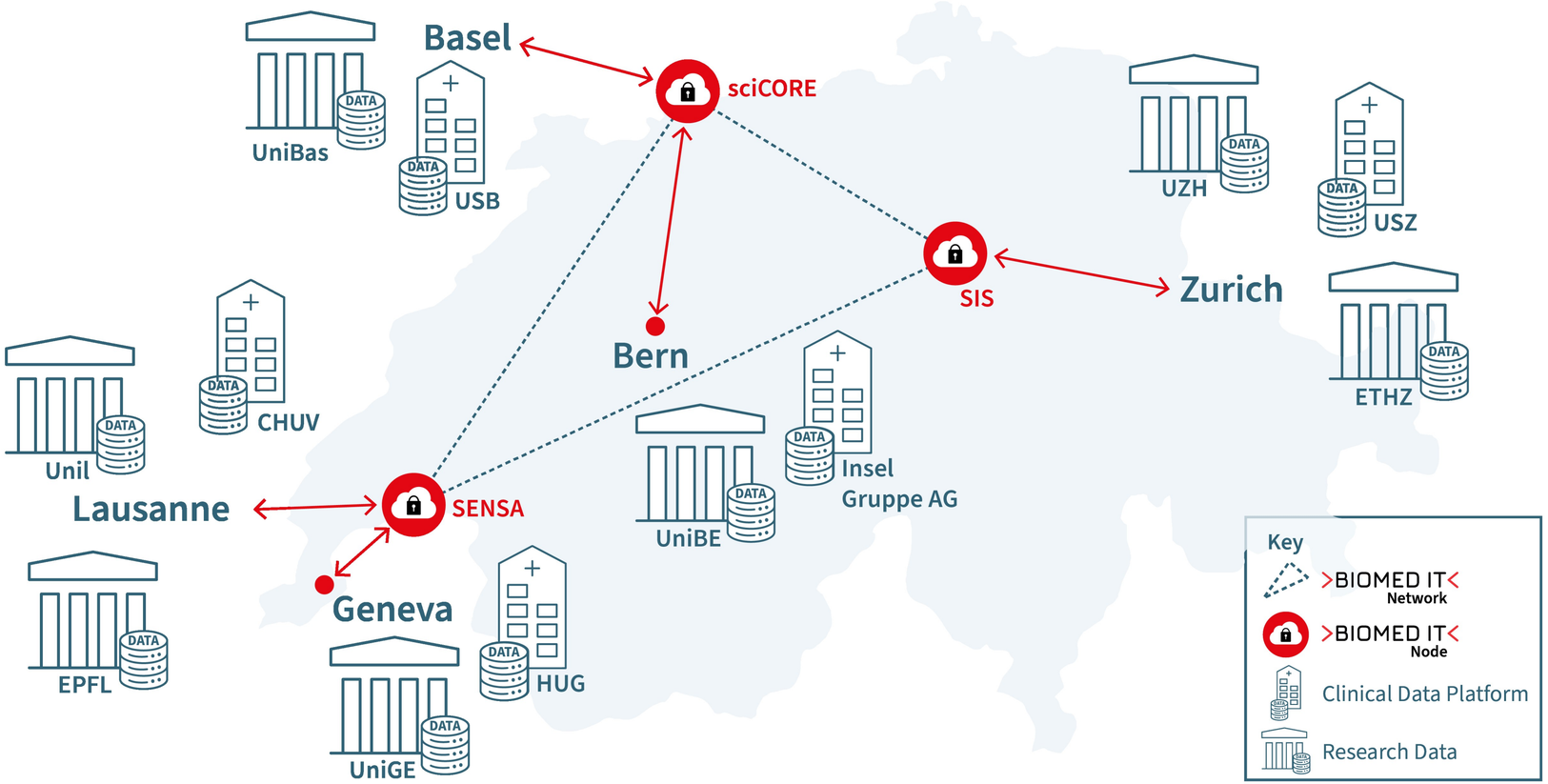


Linkage of distributed and disparate datasets

The Swiss Personalized Health Network



Strategic Focus Area
Personalized Health and Related Technologies

Personalized Health Informatics Group

SPHN Data Coordination Center (DCC)
BioMedIT Network

Swiss Personalized Health Network

ehealthsuisse

THE LOOP ZURICH MEDICAL RESEARCH CENTER

FNSNF Fonds national suisse Schweizerischer Nationalfonds Fondo nazionale svizzero Swiss National Science Foundation

Personalized Health Alliance Basel-Zurich

SWISS BIOBANKING PLATFORM

SCTO

SAKK

SSPH+ SWISS SCHOOL OF PUBLIC HEALTH

life sciences cluster basel

University Hospital Basel

USZ Universitäts Spital Zürich

HUG Hôpitaux Universitaires Genève

CHUV Centre hospitalier universitaire vaudois

INSELSPITAL UNIVERSITÄTSSPITAL BERN HOPITAL UNIVERSITAIRE DE BERNE BERN UNIVERSITY HOSPITAL

swissuniversities

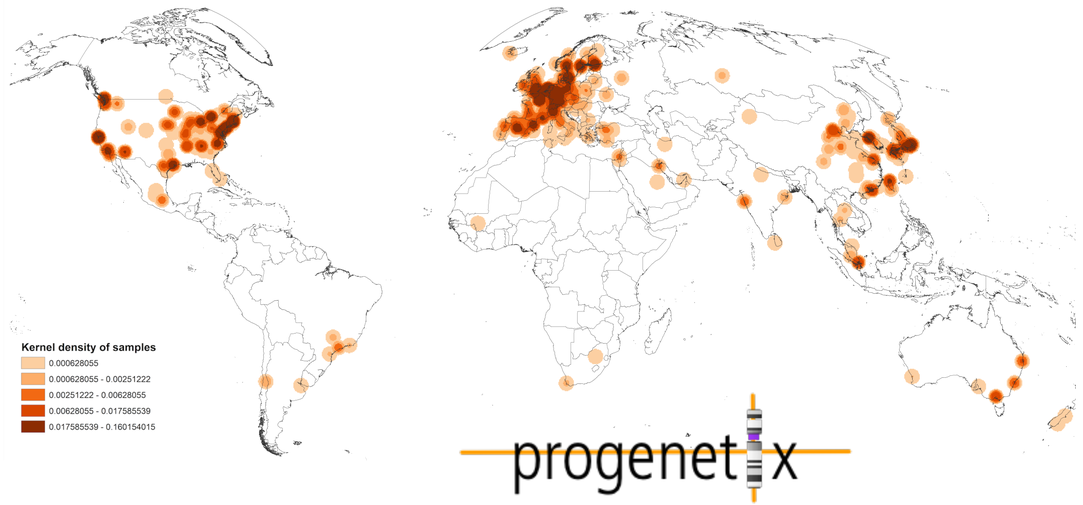
Universitäre Medizin Schweiz Médecine Universitaire Suisse

Cancer Studies Genomics Studies
Many *Potential* Access Points, Many Gaps Remaining...

Publication Landscape of Cancer CNV Profiling

Publication statistics for cancer genome screening studies. The graphic shows our as- sessment of publications reporting whole-genome screening of cancer samples, using molecular detection methods (chromosomal CGH, genomic array technologies, whole exome and genome sequencing).

For the years 1993-2018, we found 3'229 publications reporting 174'530 individual samples in single series from 1 to more than 1000 samples. Y-axis and size of the dots correspond to the sample number; the color codes indicate the technology used.



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Limited Population Diversity in Cancer Genomics

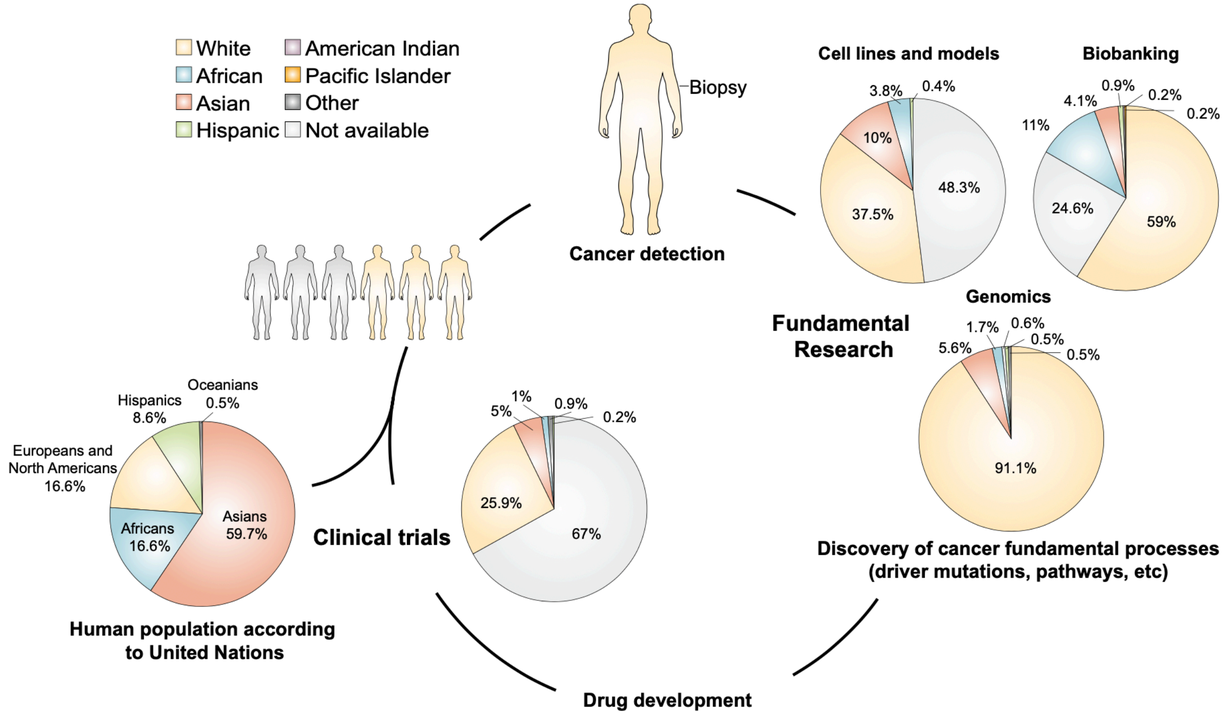


Figure 1. Racial/Ethnic disparities in cancer research. Racial/ethnic inclusion was studied in several aspects of oncological research, from cell lines and patient-derived xenografts to biobanking, genomics and clinical trials.

Guerrero S, López-Cortés A, Indacochea A, et al. Analysis of Racial/Ethnic Representation in Select Basic and Applied Cancer Research Studies. *Sci Rep*. 2018;8(1):13978.

When Dr. Anil Kapoor was diagnosed with stage four colon cancer in January his prognosis was positive, and his family was hopeful treatment would buy him several more years.

But weeks later, the 58-year-old Burlington, Ont., resident was dead — killed not by the cancer, say doctors, but by the commonly prescribed cancer drug Fluorouracil (5-FU) that was supposed to help save his life.

Studies favour white populations: expert

...

Anil was pre-screened and got the all clear to receive the drug.

...

Three weeks later, on Feb. 28, Anil died. More testing later revealed he had a genetic variant that wasn't included in the pre-screening.

www.cbc.ca/news/canada/toronto/cancer-drug-5fu-genetic-variant-testing-1.7039145

Toronto · GO PUBLIC

This commonly prescribed cancer drug was supposed to help save this doctor's life. Instead, it killed him

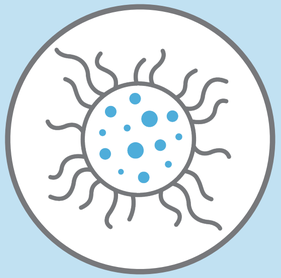
Some provinces pre-screen patients at risk of toxic reactions, but experts say tests don't go far enough

CBC NEWS

Rosa Marchitelli, Jenn Blair · CBC News ·
Posted: Nov 27, 2023 4:00 AM EST | Last Updated: November 28

Anil (Monty) Kapoor died on Feb. 28 after being prescribed a cancer drug that was toxic to him. From left, brothers Dr. Vimal (Scott) Kapoor, Dr. Sunil Kapoor and Anil's son, Akshay Kapoor. (Keith Burgess/CBC)

Global Genomic Data Sharing Can...



Demonstrate patterns in health & disease

Increase statistical significance of analyses

Lead to “stronger” variant interpretations

Increase accurate diagnosis

Advance precision medicine

Since data is distributed globally, we need interoperable standards to answer research questions

Global Alliance for Genomics & Health

Collaborate. Innovate. Accelerate.

GENOMICS

A federated ecosystem for sharing genomic, clinical data

Silos of genome data collection are being transformed into seamlessly connected, independent systems

The Global Alliance for Genomics and Health*

SCIENCE 10 JUNE 2016 • VOL 352 ISSUE 6291

Framework for Responsible Sharing of Genomics and Health-Related Data

ga4gh.org/framework

Translated into 14 languages

FOUNDATIONAL PRINCIPLES

- Respect Individuals, Families and Communities
- Advance Research and Scientific Knowledge
- Promote Health, Wellbeing and the Fair Distribution of Benefits
- Foster Trust, Integrity and Reciprocity

AIMS OF THE FRAMEWORK

- Foster responsible data sharing
- Protect and promote the welfare, rights, and interests of groups and individuals who donate their data
- Provide benchmarks for accountability
- Establish a framework for greater international data sharing, cooperation, collaboration, and governance

Universal Declaration of Human Rights (1948) **27(1)** **"The Right to Science"** **27(2)** **"The Right to Recognition"**

Executive team

HEIDI REHM

MASSACHUSETTS GENERAL HOSPITAL | BROAD INSTITUTE OF MIT AND HARVARD

Chair

Driver Project Champion for: Clinical Genome Resource (ClinGen) | Matchmaker Exchange

Community lead for: Clinical Genomics Laboratory Community

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Chair Emeritus

KATHRYN NORTH

MURDOCH CHILDREN'S RESEARCH INSTITUTE | AUSTRALIAN GENOMICS

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Interim Chief Standards Officer

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MICHAEL BAUDIS

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Product lead for: Beacon

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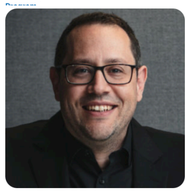
Work Stream lead for: Regulatory & Ethics Work Stream (REWS)

Product lead for: Clinical Data Sharing and Consent | Genetic Discrimination Toolkit



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SERENA SCOLLEN

ELIXIR

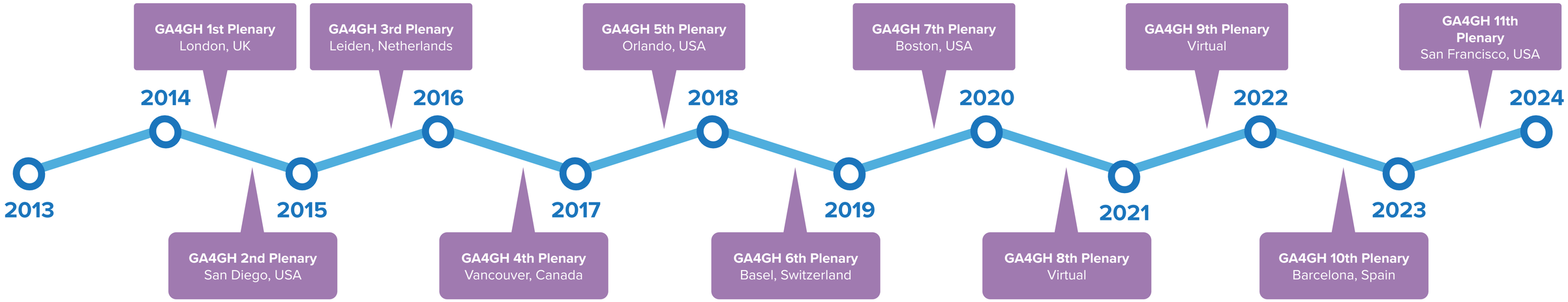
Strategic Partner Champion for: ELIXIR

HEIDI SOFIA

NIH NATIONAL HUMAN GENOME RESEARCH INSTITUTE (NHGRI)

GA4GH timeline

Global Alliance for Genomics & Health



Pre-launch

73 partners sign a letter of intent to form an alliance

Building momentum

Global Alliance for Genomics & Health

Collaborate. Innovate. Accelerate.

Formal launch of GA4GH

Published *Framework for Responsible Sharing of Genomic and Health-Related Data*

Formed four working groups

Developed three demonstration projects

GA4GH Connect

GA4GH CONNECT

Launch of **GA4GH Connect** and Strategic Roadmap

Formation of new organizational structure consisting of eight Work Streams and over twenty Driver Projects

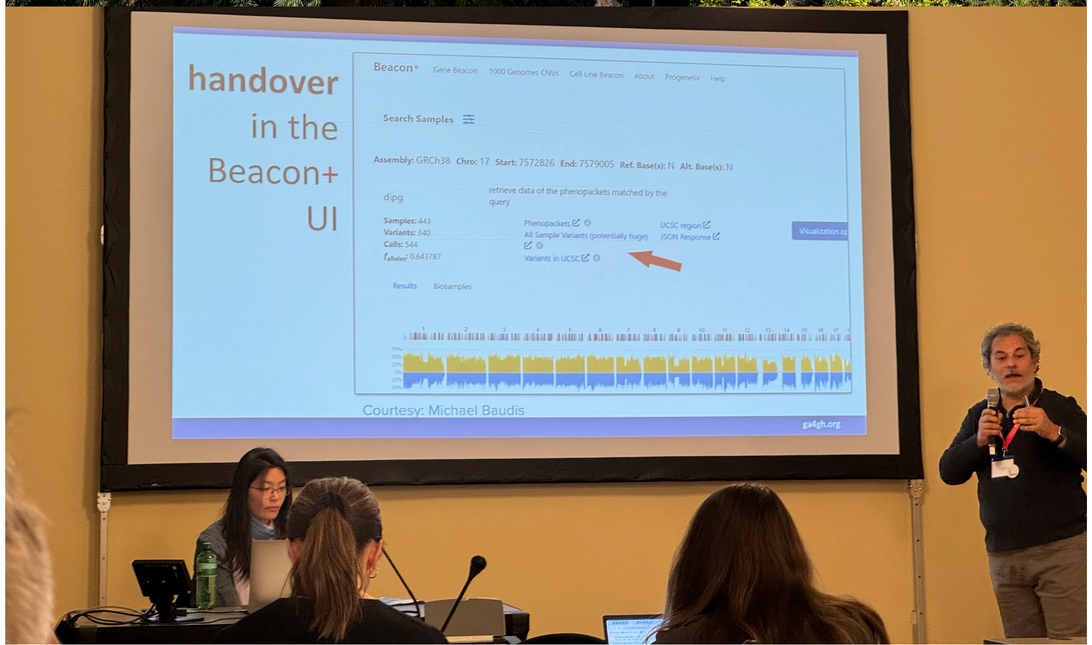
Gap analysis

Gap analysis identifies three community imperatives

- Interoperability and alignment
- Implementation support
- Engaging with healthcar and clinical standards

Strategic Refresh

Strategic refresh introduces updates to GA4GH to better meet the three community imperatives



The Global Alliance for Genomics and Health (GA4GH) gathered for the 2024 **April Connect meeting** in Ascona, Switzerland and online from 21 to 24 April. The GA4GH Connect meetings provide an opportunity for contributors to advance the GA4GH Road Map, showcase GA4GH standards and policies in action, and gather feedback on product development and community needs. The meeting brought together 103 in-person attendees and 312 virtual attendees for updates from Work Streams and Driver Projects, breakout sessions, and themed events.

Host Institutions

Global Alliance for Genomics & Health

OICR
Ontario Institute for Cancer Research

Toronto, Canada

OICR is a collaborative research institute that conducts and enables high-impact translational cancer research.

wellcome sanger institute

Hinxton, UK

The Wellcome Sanger Institute is a world leader in genome research delivering insights into human and pathogen biology.

BROAD INSTITUTE

Cambridge, USA

The Broad Institute seeks to narrow the gap between new biological insights and impact for patients by fulfilling the promise of genomic medicine.

EMBL-EBI

Hinxton, UK

EMBL-EBI provides the infrastructure needed to share data openly in life sciences to make discoveries that benefit humankind.

McGill
VICTOR PHILLIP DAHDALEH INSTITUTE OF GENOMIC MEDICINE AT MCGILL UNIVERSITY

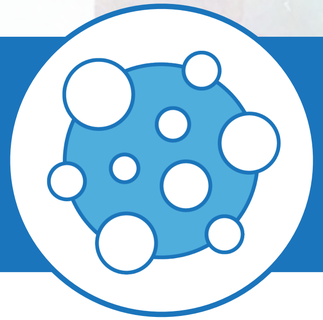
Montreal, Canada

The Victor Phillip Dahdaleh Institute of Genomic Medicine applies genomic innovation to pave the way towards a healthier, more sustainable, and informed future.

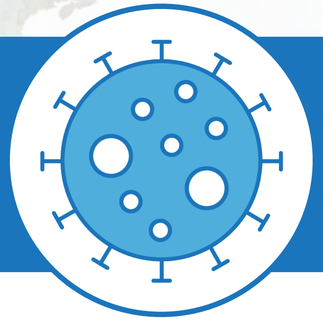
GA4GH Communities of Interest

Global Alliance for Genomics & Health

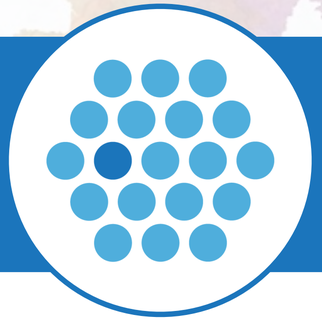
Domain-specific groups promoting global cooperation, data sharing and collaborative research through identifying the need for new standards, and implementing existing GA4GH standards.



Cancer

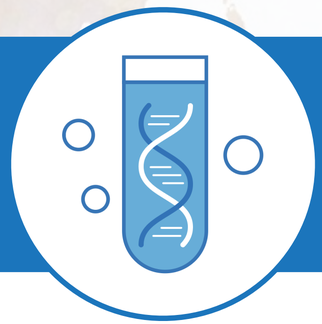


Infectious Disease



Rare Disease

Neuroscience



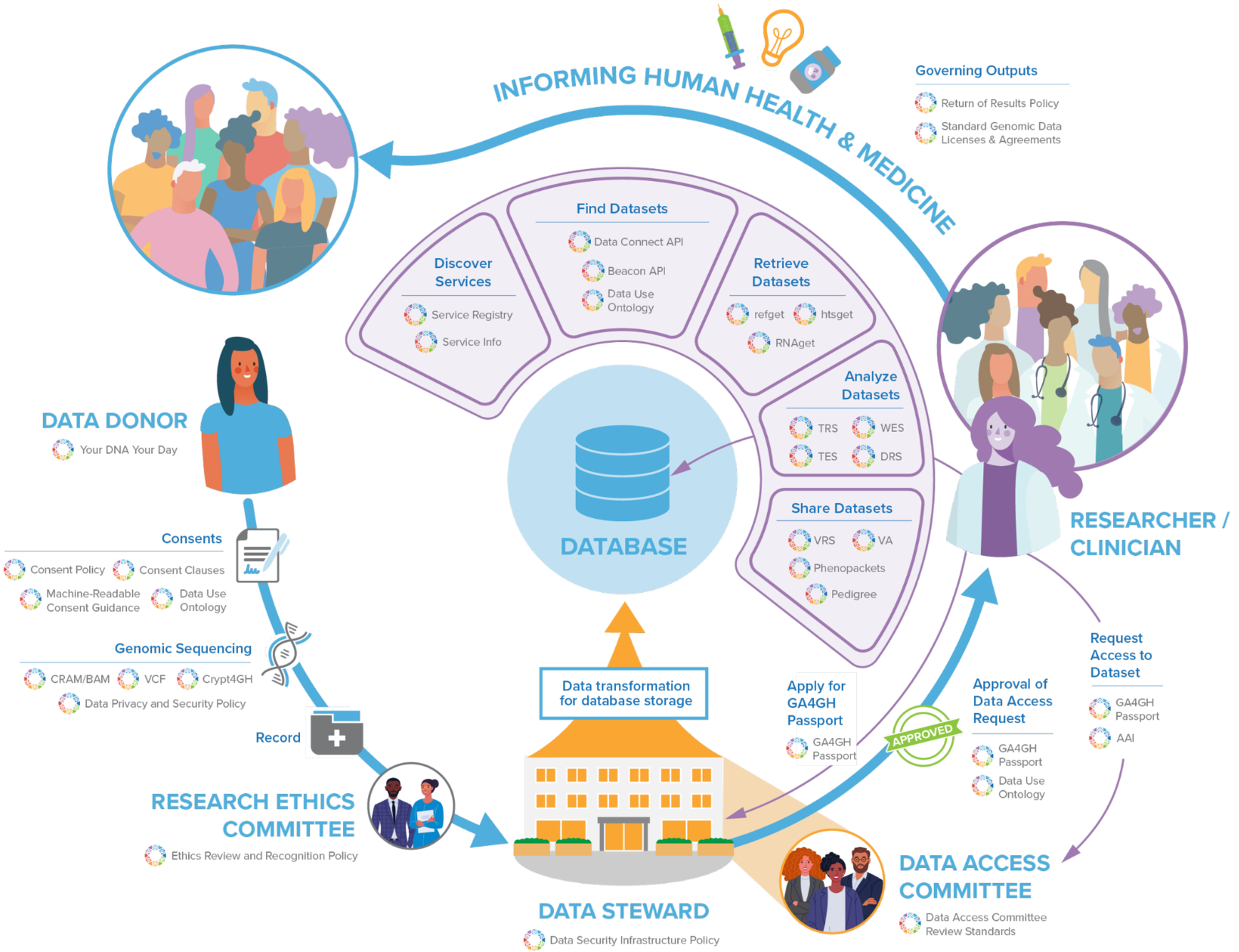
Clinical Laboratory

Opportunities for collaboration

Learn from others' implementations

Develop a study group

Propose a GIF project


INFORMING HUMAN HEALTH & MEDICINE
Governing Outputs
Return of Results Policy
Standard Genomic Data Licenses & Agreements
Find Datasets
Data Connect API
Beacon API
Data Use Ontology
Discover Services
Service Registry
Service Info
Retrieve Datasets
refget
htsget
RNAget
Analyze Datasets
TRS
WES
TES
DRS
Share Datasets
VRS
VA
Phenopackets
Pedigree
DATABASE
DATA DONOR
Your DNA Your Day
RESEARCHER / CLINICIAN
Consents
Consent Policy
Consent Clauses
Machine-Readable Consent Guidance
Data Use Ontology
Genomic Sequencing
CRAM/BAM
VCF
Crypt4GH
Data Privacy and Security Policy
Record
Data transformation for database storage
Apply for GA4GH Passport
GA4GH Passport
APPROVED
Approval of Data Access Request
GA4GH Passport
Data Use Ontology
Request Access to Dataset
GA4GH Passport
AAI
RESEARCH ETHICS COMMITTEE
Ethics Review and Recognition Policy
DATA STEWARD
Data Security Infrastructure Policy
DATA ACCESS COMMITTEE
Data Access Committee Review Standards

Alignment with other standards organizations

Global Alliance for Genomics & Health

Research → Clinical research → Clinical care

Different Approaches to Genomic Data Storage and Distribution

progenetix

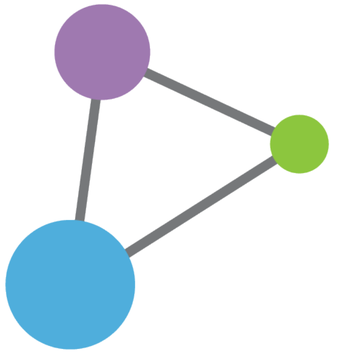
European Genome-Phenome Archive

SPHN Swiss Personalized Health Network

Centralized Genomic Knowledge Bases

Data Commons
Trusted, controlled repository of multiple datasets

Hub and Spoke
Common data elements, access, and usage rules



Linkage of distributed and disparate datasets

Federation

A New Paradigm for Data Sharing

FROM

TO

Data Copying

Data Visiting

A New Paradigm for Data Sharing

FROM

STANDARDS

TO

Data Copying

Data Visiting

Global Alliance
for Genomics & Health
Collaborate. Innovate. Accelerate.

INFORMATICS

Beacon v2 and Beacon networks: federated data discovery n biome

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Lauren A. Fromont[1] | Arcadi Navarro[1,5,6,7] | Rahel Paloots[3] |
Manuel Rueda[1] | Gary Saunders[8] | Babita Singh[1] | John D. Spalding[9] |
Juha Törnroos[9] | Claudia Vasallo[1] | Colin D. Veal[4] | Anthony J. Brookes[4]

Cell Genomics

CellPress
OPEN ACCESS

Commentary

International federation of genomic medicine databases using GA4GH standards

Adrian Thorogood,[1,2,*] Heidi L. Rehm,[3,4] Peter Goodhand,[5,6] Angela J.H. Page,[4,5] Yann Joly,[2] Michael Baudis,[7]
Jordi Rambla,[8,9] Arcadi Navarro,[8,10,11,12] Tommi H. Nyronen,[13,14] Mikael Linden,[13,14] Edward S. Dove,[15] Marc Fiume,[16]
Michael Brudno,[17] Melissa S. Cline,[18] and Ewan Birney[19]

Cell Genomics

OPEN ACCESS

Perspective

GA4GH: International policies and standards for data sharing across genomic research and healthcare

Heidi L. Rehm,[1,2,47] Angela J.H. Page,[1,3,*] Lindsay Smith,[3,4] Jeremy B. Adams,[3,4] Gil Alterovitz,[5,47] Lawrence J. Babb,[1]
Maxmillian P. Barkley,[6] Michael Baudis,[7,8] Michael J.S. Beauvais,[3,9] Tim Beck,[10] Jacques S. Beckmann,[11]
Sergi Beltran,[12,13,14] David Bernick,[1] Alexander Bernier,[9] James K. Bonfield,[15] Tiffany F. Boughtwood,[16,17]
Guillaume Bourque,[9,18] Sarion R. Bowers,[15] Anthony J. Brookes,[10] Michael Brudno,[18,19,20,21,38] Matthew H. Brush,[22]
David Bujold,[9,18,38] Tony Burdett,[23] Orion J. Buske,[24] Moran N. Cabili,[1] Daniel L. Cameron,[25,26] Robert J. Carroll,[27]
Esmeralda Casas-Silva,[123] Debyani Chakravarty,[29] Bimal P. Chaudhari,[30,31] Shu Hui Chen,[32] J. Michael Cherry,[33]
Justina Chung,[3,4] Melissa Cline,[34] Hayley L. Clissold,[15] Robert M. Cook-Deegan,[35] Mélanie Courtot,[23]
Fiona Cunningham,[23] Miro Cupak,[6] Robert M. Davies,[15] Danielle Denisko,[19] Megan J. Doerr,[36] Lena I. Dolman,[19]

(Author list continued on next page)

Cell Genomics

OP

Technology

The GA4GH Variation Representation Specification A computational framework for variation representation and federated identification

Alex H. Wagner,[1,2,25,*] Lawrence Babb,[3,*] Gil Alterovitz,[4,5] Michael Baudis,[6] Matthew Brush,[7] Daniel L. Cameron,[8,9]
Melissa Cline,[10] Malachi Griffith,[11] Obi L. Griffith,[11] Sarah E. Hunt,[12] David Kreda,[13] Jennifer M. Lee,[14] Stephanie Li,[15]
Javier Lopez,[16] Eric Moyer,[17] Tristan Nelson,[18] Ronak Y. Patel,[19] Kevin Riehle,[19] Peter N. Robinson,[20]
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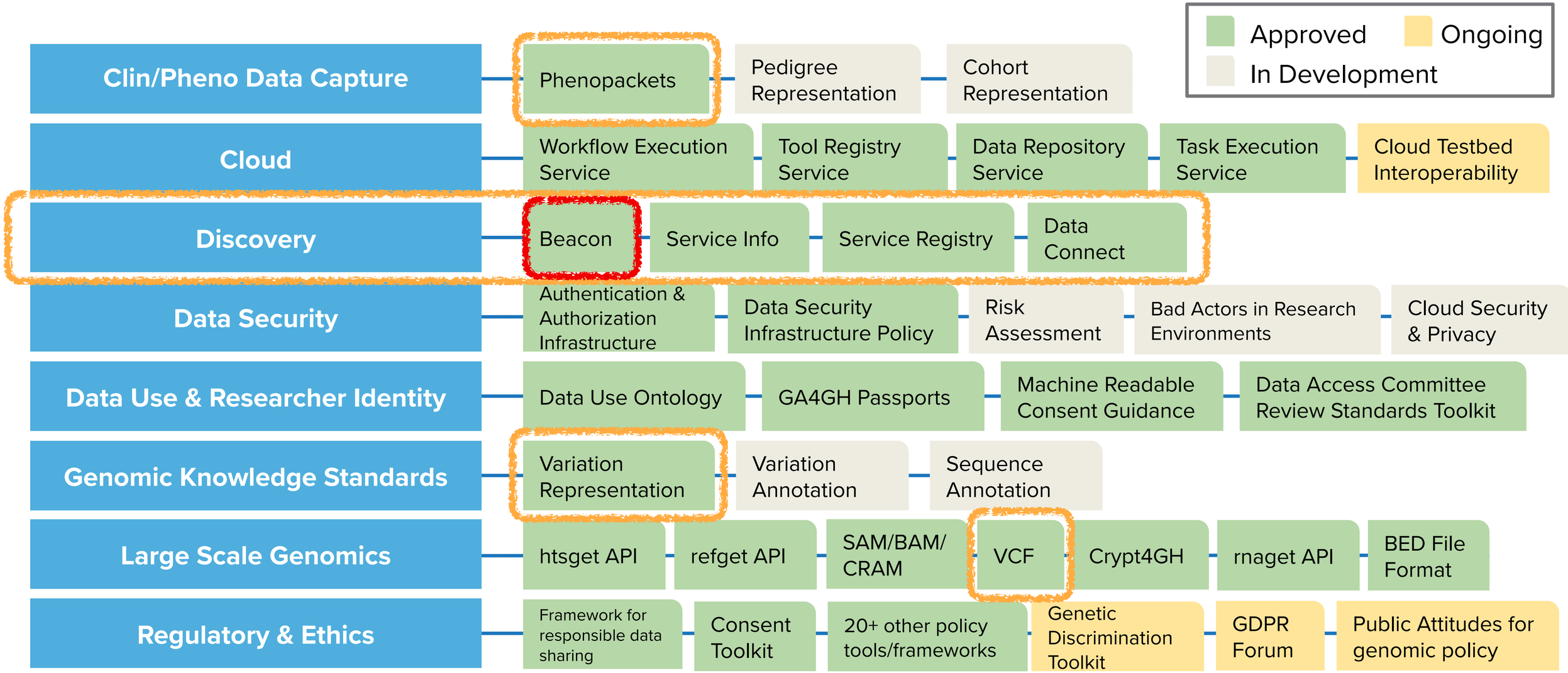
Andrew D. Yates,[12] Robert R. Freimuth,[23] and Reece K. Hart[3,24,*]

Overview of GA4GH standards and frameworks



Phenopackets v2

Phenopackets is a standard schema for sharing phenotypic information.

Approved: June 24, 2021

Example Users

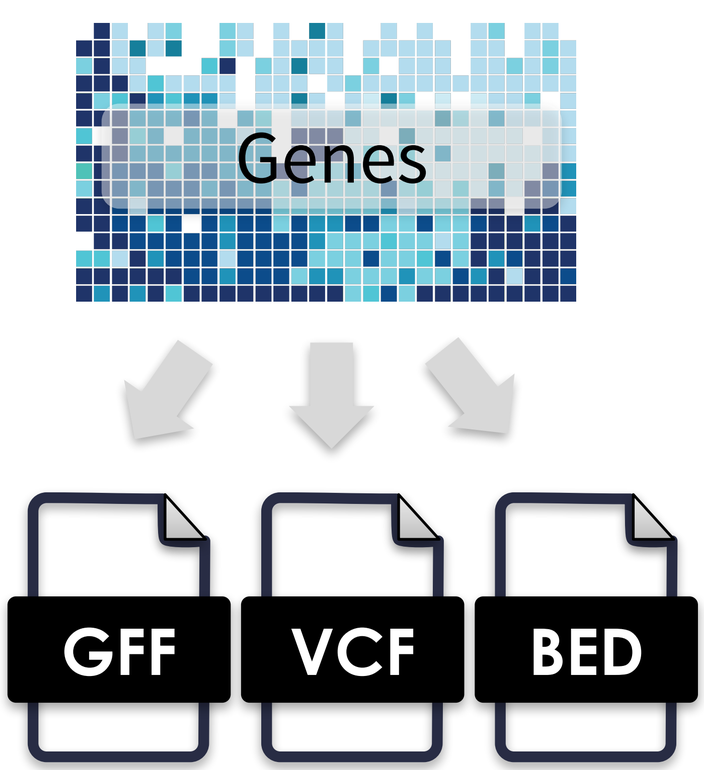
Cafe Variome

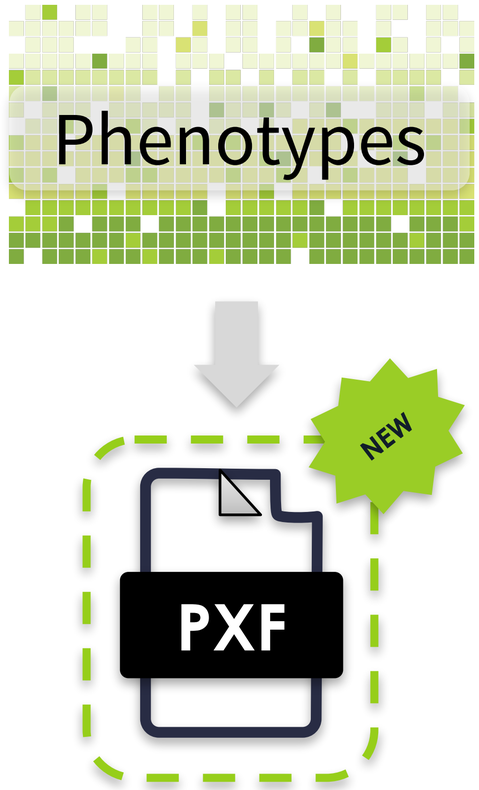
NIH

AMED

PHENOTIPS™

RD Connect





VCF/BCF

The Variant Call Format (VCF) specifies the format of a text file used in bioinformatics for storing gene sequence variations. The Binary Call Format (BCF) is the Binary equivalent, smaller and more efficient to process.

Software Libraries: htslib | htsjdk

Tools: Samtools | BCFtools

Databases: European Variation Archive (EVA) | dbGAP | dbSNP | 1000 Genomes Projects / IGSR

Genome Browsers: ENSEMBL | JBrowse | UCSC Genome Browser

Example Users

All of Us RESEARCH PROGRAM

BROAD INSTITUTE

elixir

EMBL-EBI

Genomics england

Concepts

VRS is a collection of data models or concepts that are used together to represent molecular and systemic variation. An inheritance view is available in the Class Diagram appendix. These models exist across several related domains:

- Molecular Variation: models that describe variation on a contiguous molecule
- Systemic Variation: models that describe variation in a system
- Sequence Location: a model that describes a location on a molecule sequence
- Sequence Expression: models that describe a molecule sequence
- Additional Data Types: additional data types that support the above models

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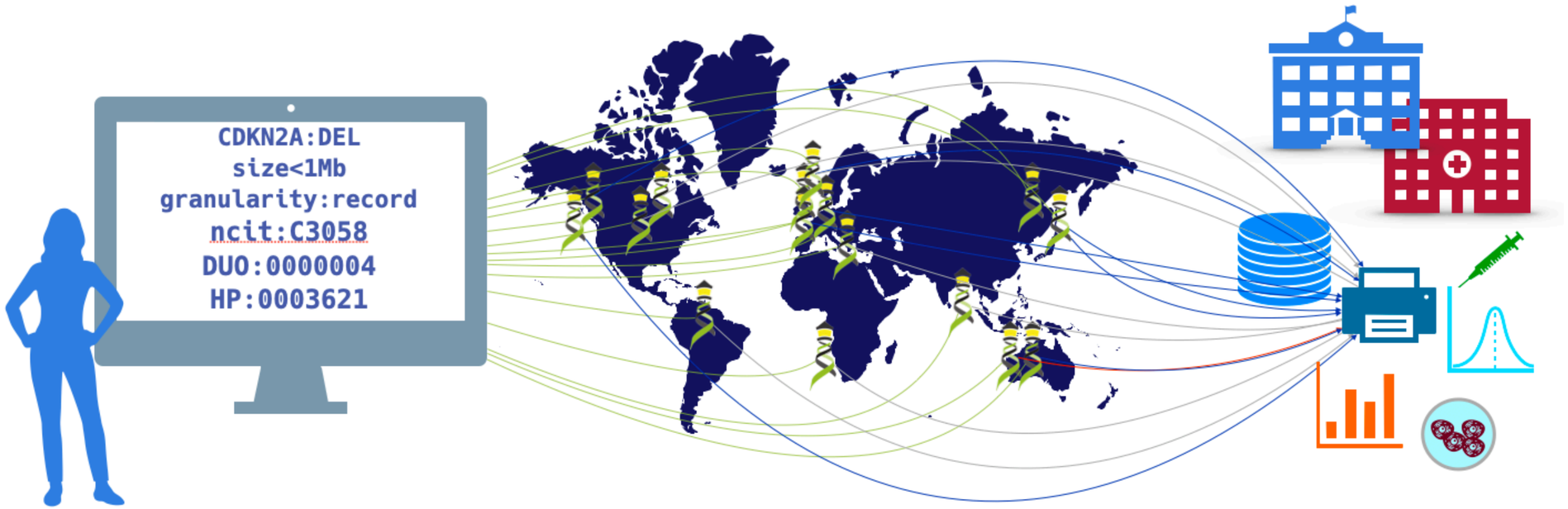
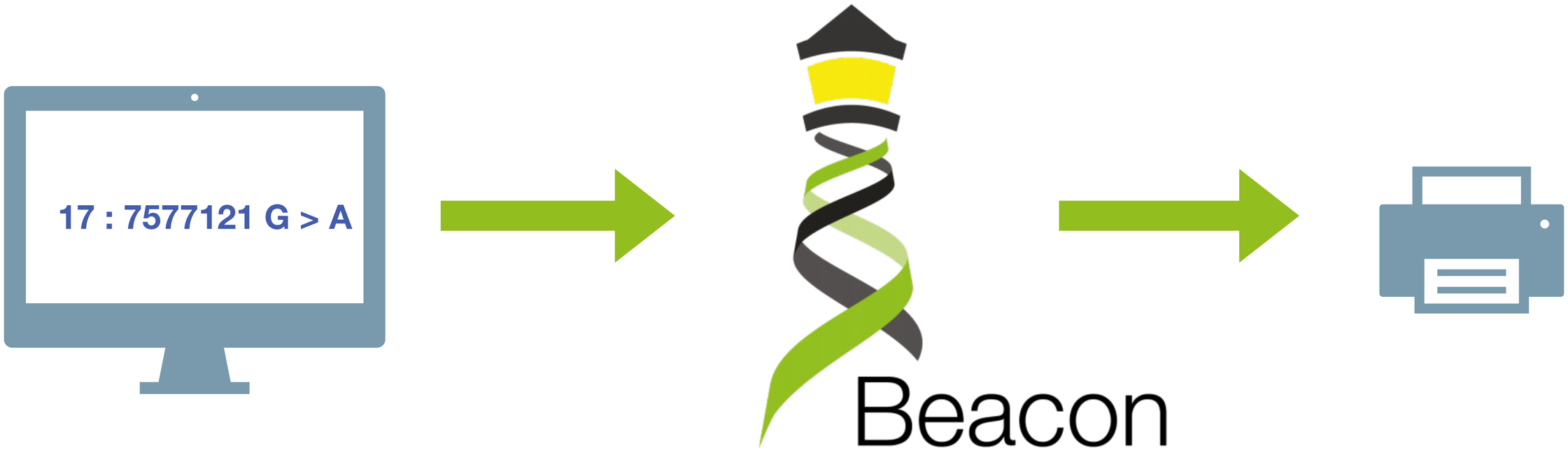


The GA4GH Beacon Protocol

Federating Genomic Discoveries



A ***Beacon*** answers a query for a specific genome variant against individual or aggregate genome collections

YES | **NO** | **\0**

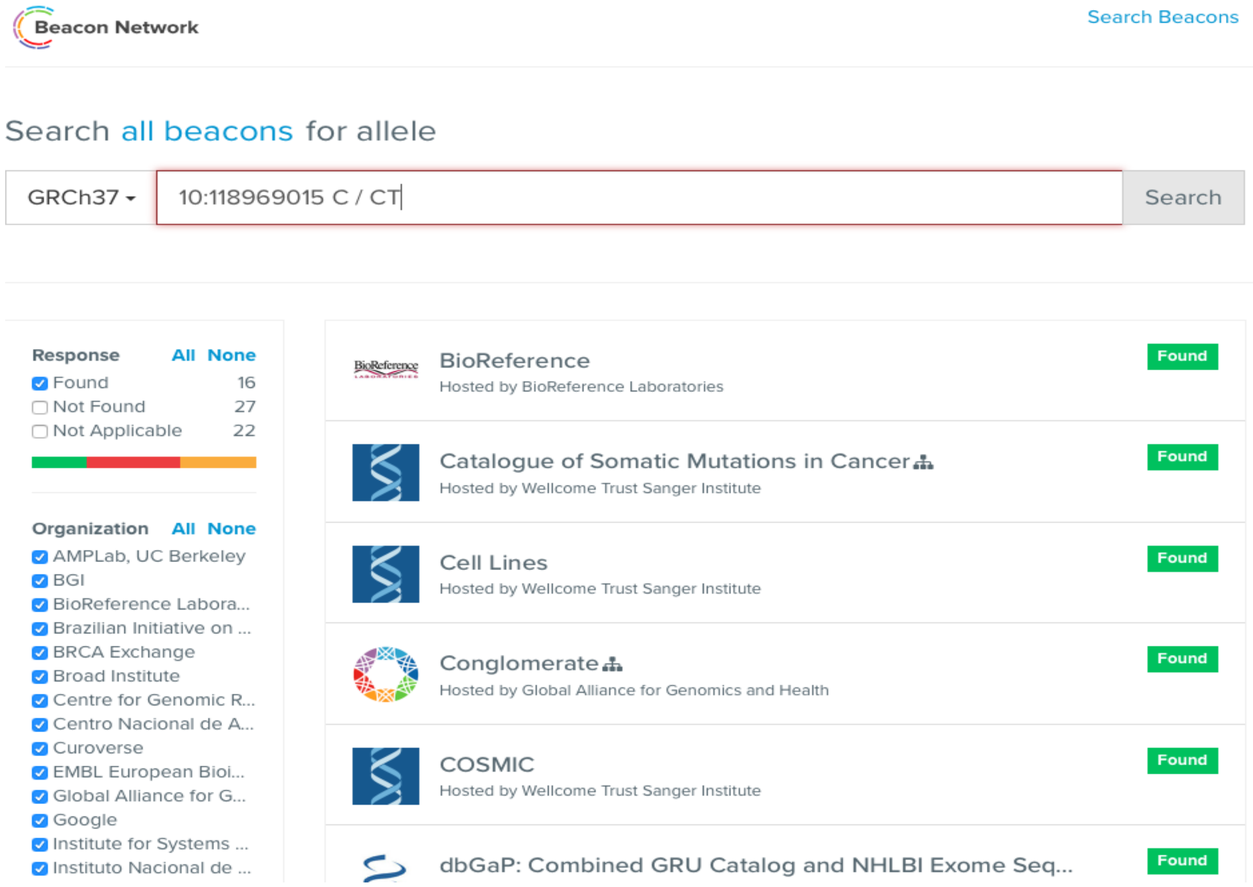
Have you seen this variant? It came up in my patient and we don't know if this is a common SNP or worth following up.

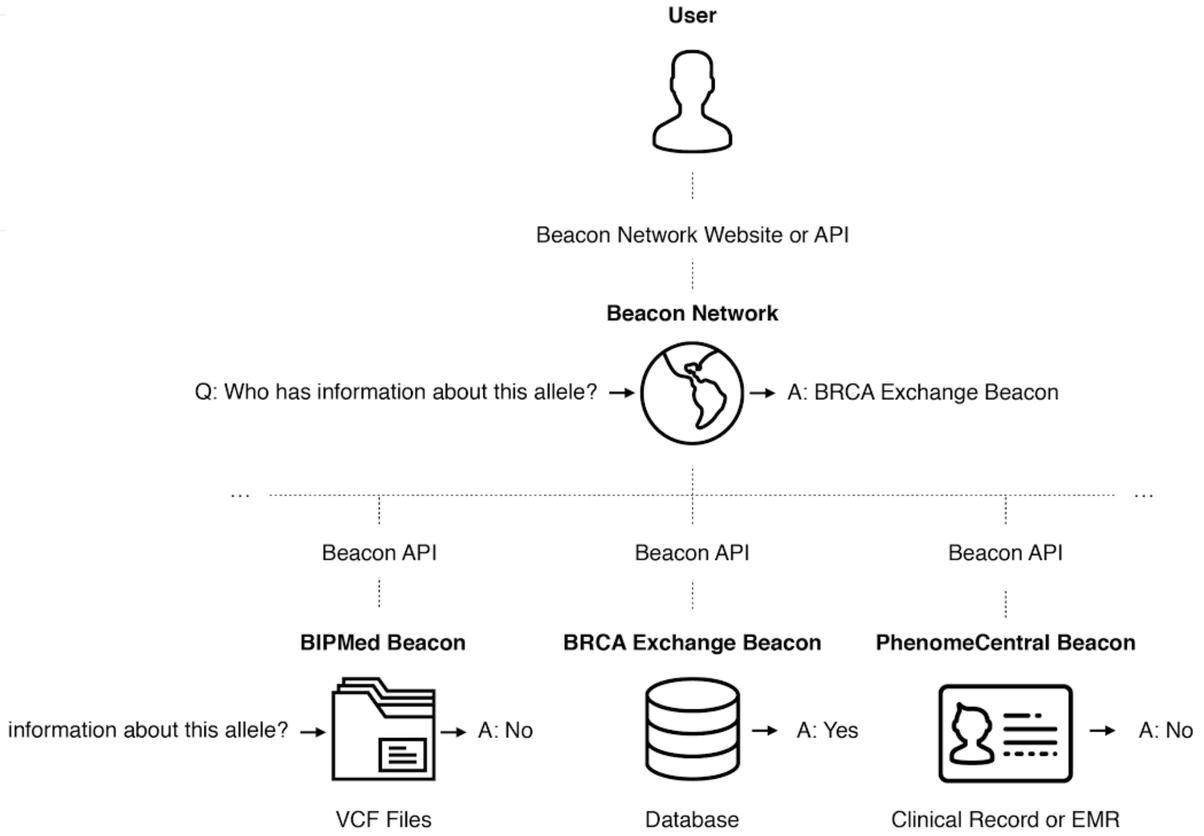
A Beacon network federates *genome variant queries* across databases that support the ***Beacon API***

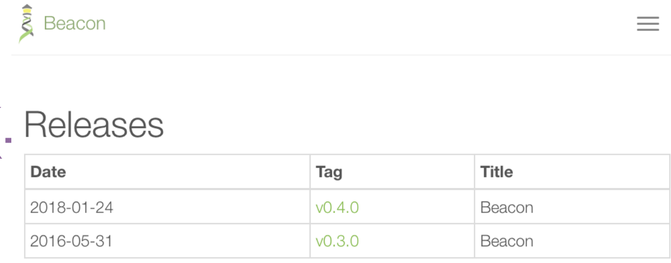
Here: The variant has been found in **few** resources, and those are from **disease** specific **collections**.

Beacon Project in 2016

An open web service that tests the willingness of international sites to share genetic data.







35+ Organizations

90+ Beacons

200+ Datasets

100K+

Global Alliance for Genomics & Health

Global Alliance “Beacon” - Jim Ostell, NCBI, March 7, 2014

Global Alliance for Genomics & Health

Introduction

… I proposed a challenge application for all those wishing to seriously engage in ***international*** data sharing for human genomics. …

1. Provide a public web service
2. Which accepts a query of the form “Do you have any genomes with an “A” at position 100,735 on chromosome 3?”
3. And responds with one of “Yes” or “No” …

“Beacon” because … people have been scanning the universe of human research for ***signs of willing participants in far reaching data sharing***, but … it has remained a dark and quiet place. The hope of this challenge is to 1) ***trigger the issues*** blocking groups … in way that isn’t masked by the … complexities of the science, fully functional interfaces, and real issues of privacy, and to 2) in ***short order*** … see ***real beacons of measurable signal*** … from ***at least some sites*** … Once your “GABeacon” is shining, you can start to take the ***next steps to add functionality*** to it, and ***finding the other groups*** … following their GABeacons.

Utility

Some have argued that this simple example is not “useful” so nobody would build it. Of course it is not the first priority for this application to be scientifically useful. …intended to provide a ***low bar for the first step of real*** … ***engagement***. … there is some utility in …locating a rare allele in your data, … not zero.

A number of more useful first versions have been suggested.

1. Provide ***frequencies of all alleles*** at that point
2. Ask for all alleles seen in a gene ***region*** (and more elaborate versions of this)
3. Other more complicated queries

"I would personally recommend all those be held for **version 2**, when the beacon becomes a service."
Jim Ostell, 2014

Implementation

1. Specifying the chromosome … The interface needs to specify the ***accession.version*** of a chromosome, or ***build number***…
2. Return values … right to ***refuse*** to answer without it being an error … DOS ***attack*** … or because …especially ***sensitive***…
3. Real time response … Some sites suggest that it would be necessary to have a ***“phone home” response*** …

Beacon v1 Development

Beacon v2 Development

Related ...

2014 — **GA4GH founding event; Jim Ostell proposes Beacon concept including "more features ... version 2"**

2015

- beacon-network.org aggregator created by DNAstack

- ELIXIR starts Beacon project support

2016

- Beacon v0.3 release
- work on queries for structural variants (brackets for fuzzy start and end parameters...)

- Beacon+ concept implemented on progenetix.org
- concepts from GA4GH Metadata (ontologies…)
- entity-scoped query parameters ("individual.age")

2017

- OpenAPI implementation
- integrating CNV parameters (e.g. "startMin, statMax")

- Beacon+ demos "handover" concept

- GA4GH re-structuring (workstreams...)
- Beacon part of Discovery WS

2018

- Beacon v0.4 release in January; feature release for GA4GH approval process
- GA4GH Beacon v1 approved at Oct plenary

- new Beacon website (March)

2019

- ELIXIR Beacon Network

- Beacon hackathon Stockholm; settling on "filters"
- Barcelona goes Zurich developers meeting
- Beacon API v2 Kick off
- adopting "handover" concept

- Beacon publication at Nature Biotechnology

2020

- "Scouts" teams working on different aspects - filters, genomic variants, compliance ...
- discussions w/ clinical stakeholders

2021

- framework + models concept implemented
- range and bracket queries, variant length parameters
- starting of GA4GH review process

- Phenopackets v2 approved

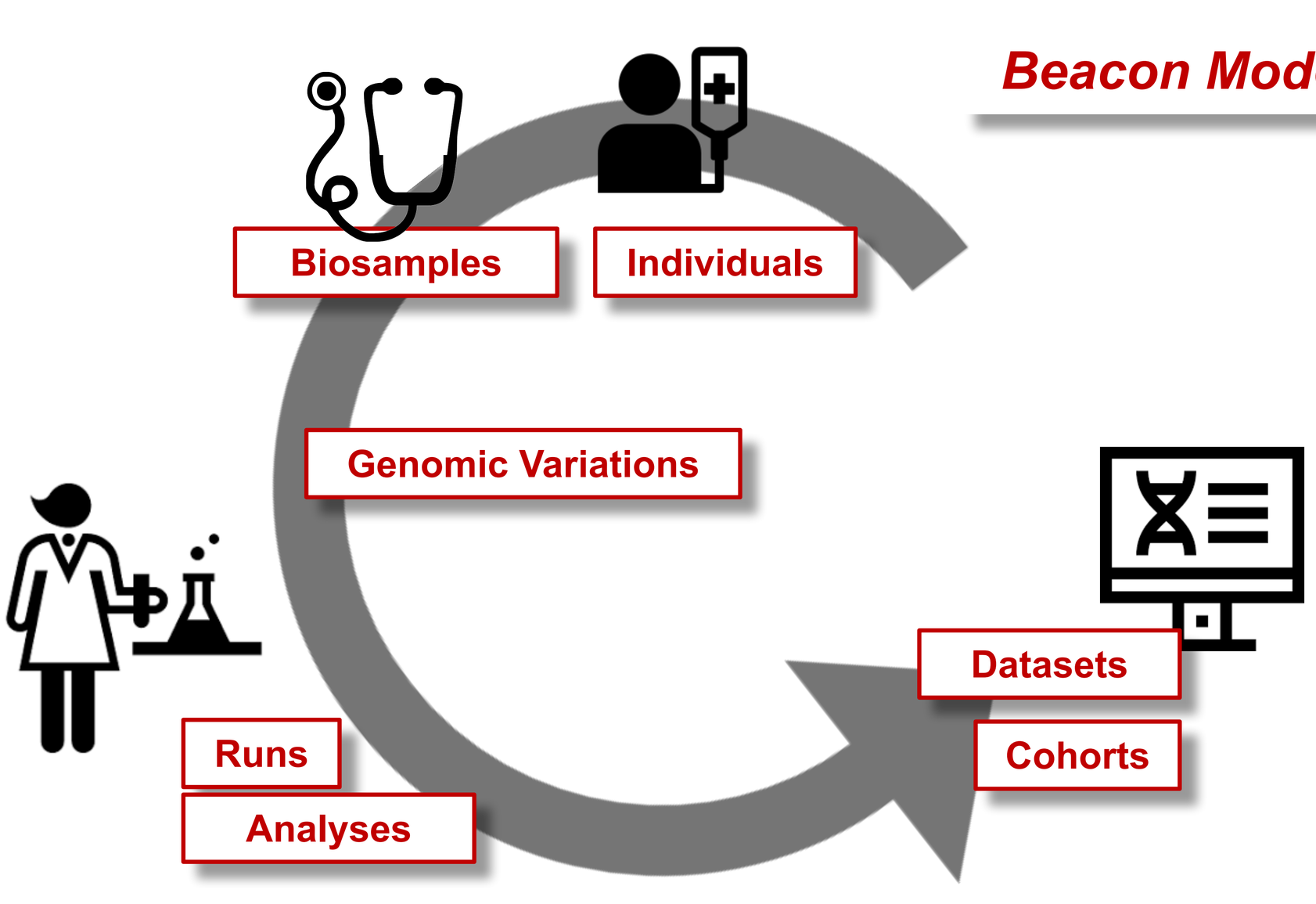
2022

- further changes esp. in default model, aligning with Phenopackets and VRS
- unified beacon-v2 code & docs repository
- Beacon v2 approved at Apr GA4GH Connect

- *docs.genomebeacons.org*

Beacon v2

docs.genomebeacons.org

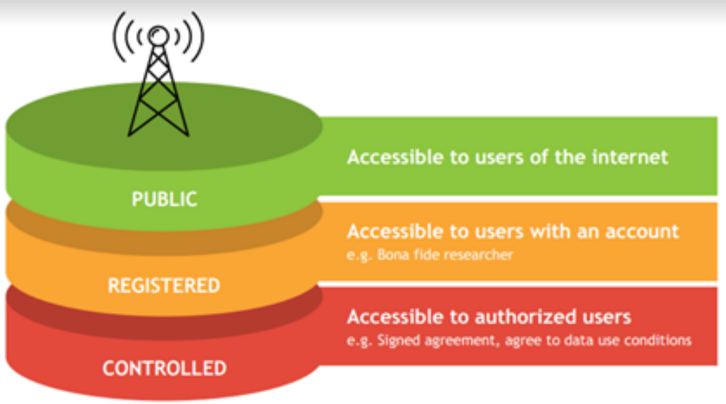


Beacon Model

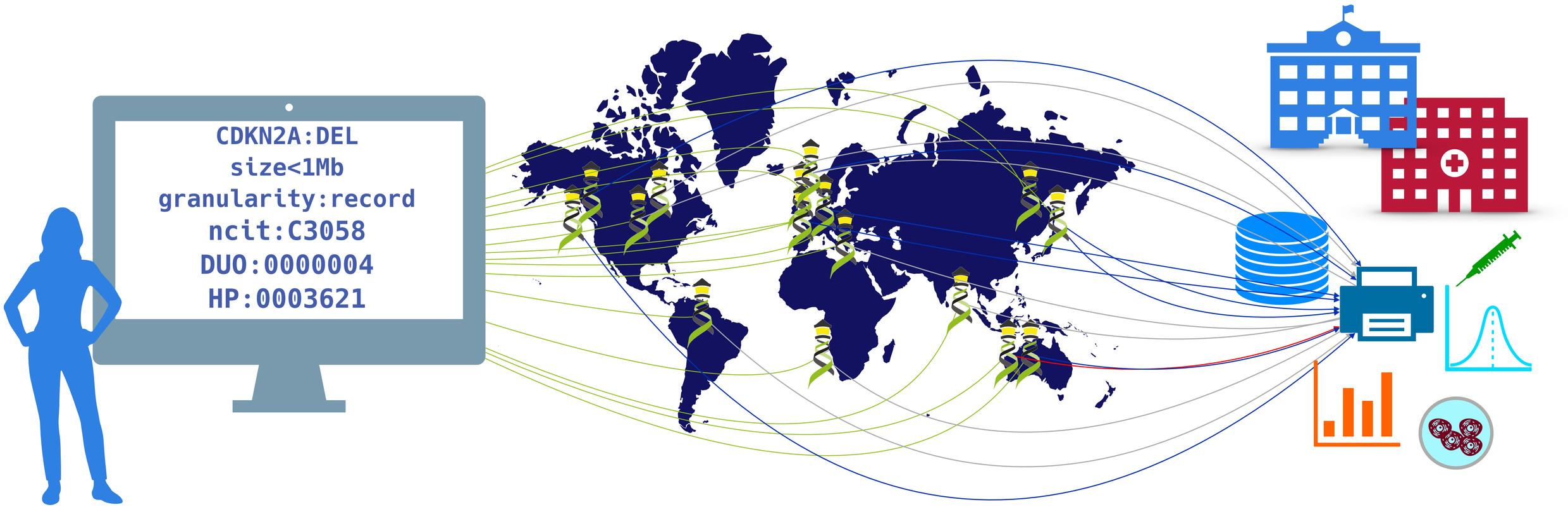
Beacon Framework (protocol)

Beacon Security

Security by Design ... if Implemented in the Environment



- the beacon API specification does not implement explicit security (e.g. checking user authentication and authorization)
- the framework implements different levels of response granularity which can be mapped to authorization levels (**boolean** / **count** / **record** level responses)
- implementations can have beacons running in secure environments with a **gatekeeper** service managing authentication and autorization levels, and potentially can filter responses for escalated levels
- the backend can implement additional access reduction, on a user <-> dataset level if needed



Can you provide data about focal deletions in CDKN2A in Glioblastomas from juvenile patients with unrestricted access?

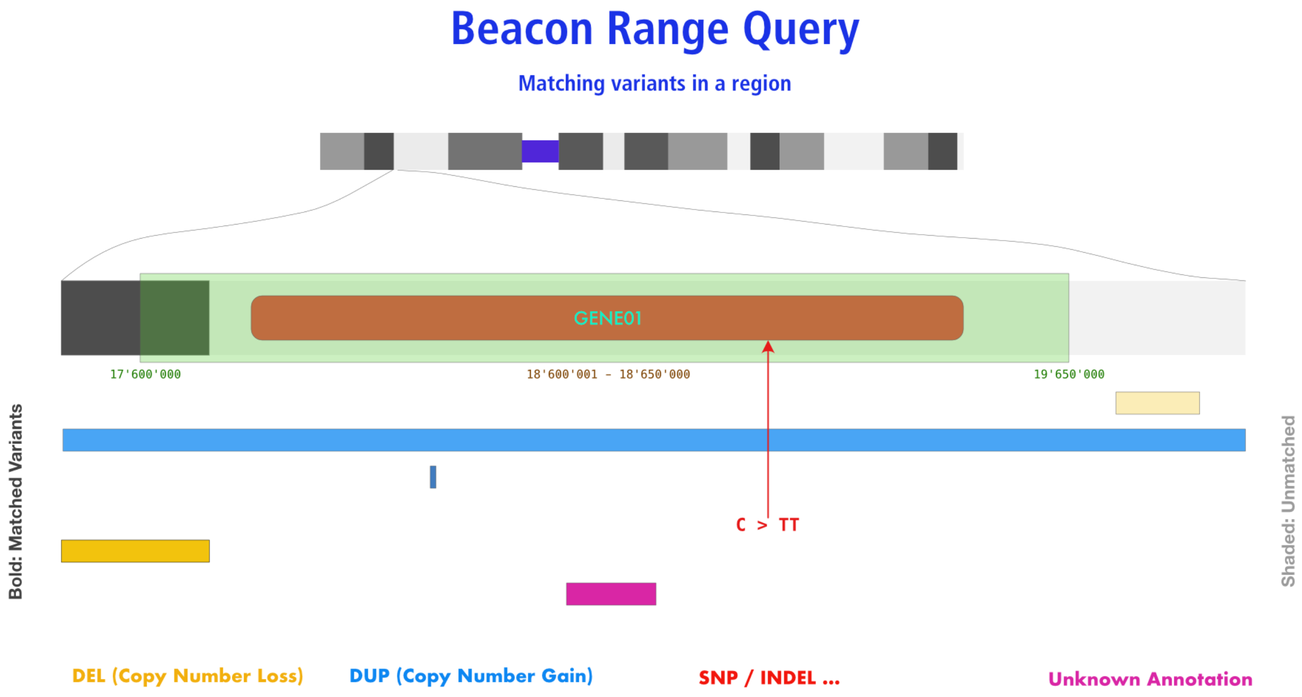
Beacon *v2* API

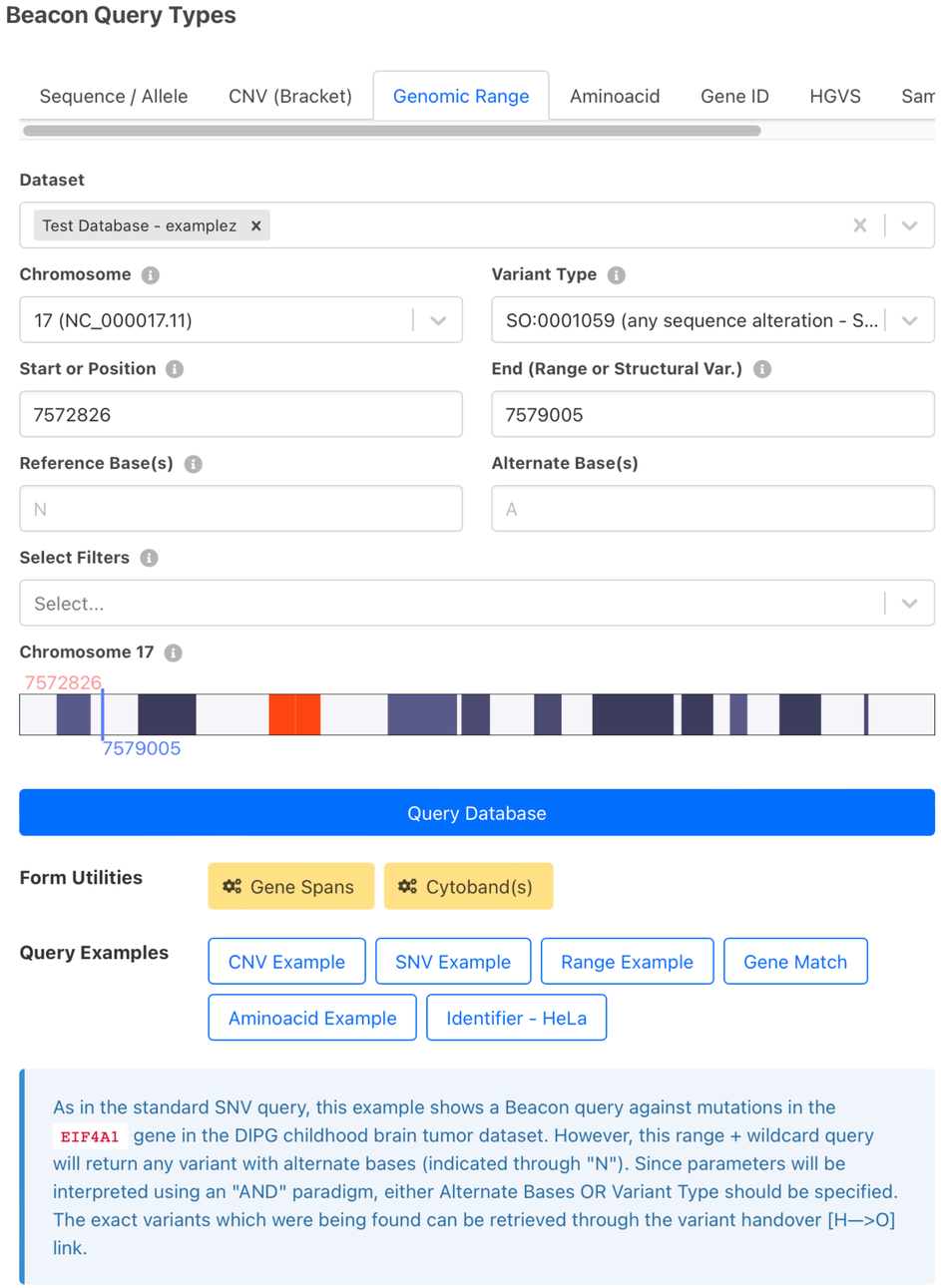
The Beacon API v2 represents a simple but powerful **genomics API** for ***federated*** data discovery and retrieval

Variation Queries

Range ("anything goes") Request

- defined through the use of 1 start, 1 end
- any variant… but can be limited by type etc.

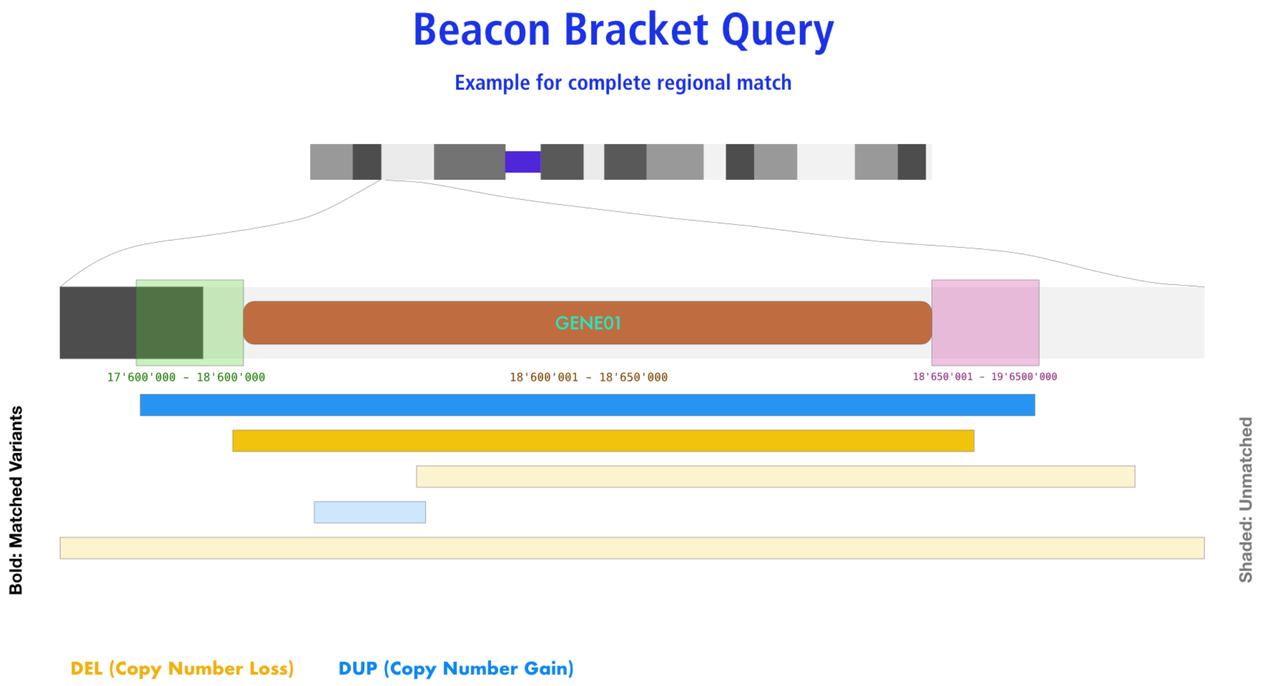


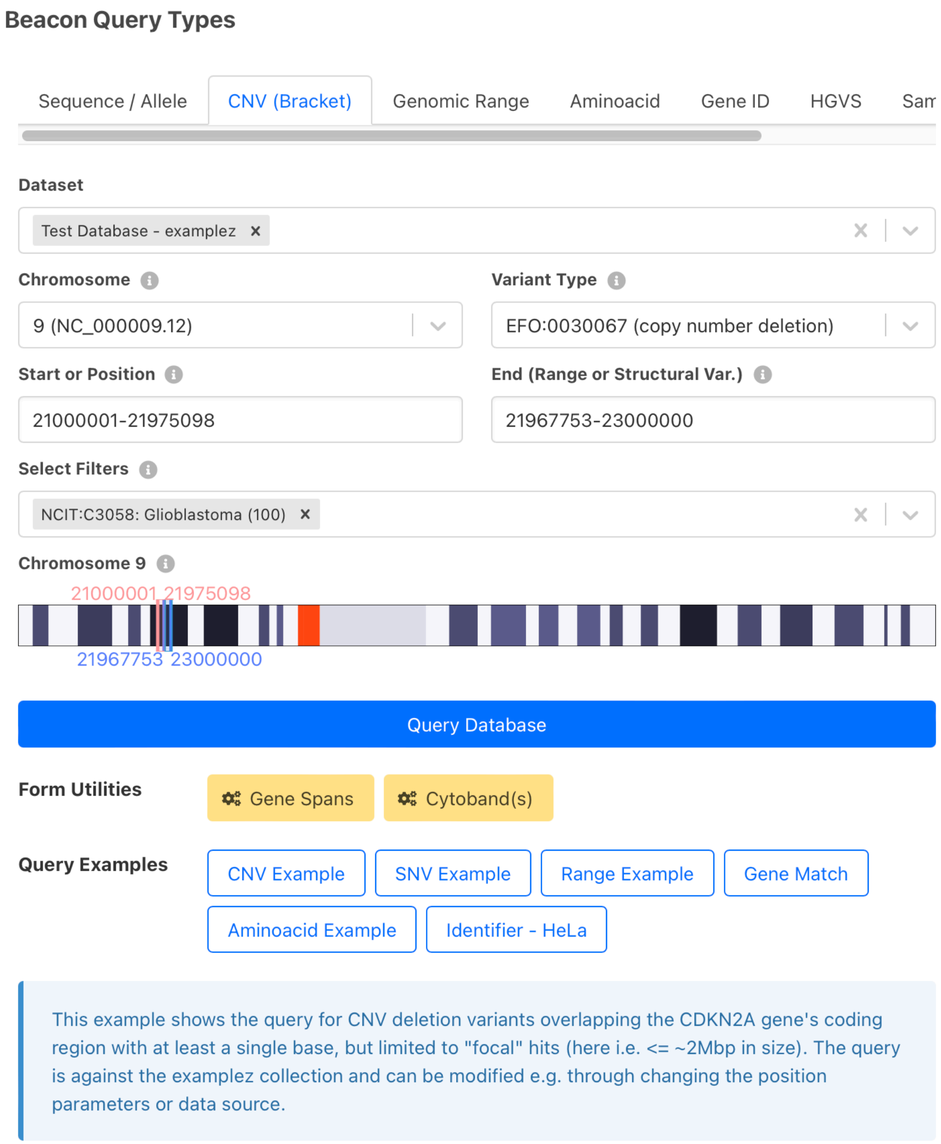


Variation Queries

Bracket ("CNV") Query

- defined through the use of 2 start, 2 end
- any contiguous variant...





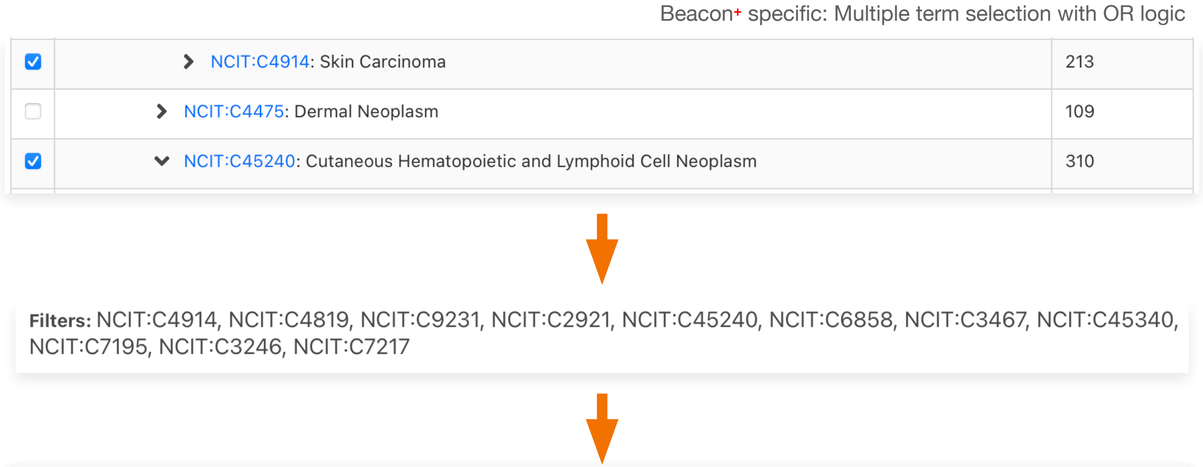
Beacon v2 Filters

Example: Use of hierarchical classification systems (here NCIt neoplasm core)

- Beacon v2 relies heavily on "filters"
  - ontology term / CURIE
  - alphanumeric
  - custom
- Beacon v2 "filters" assumes inclusion of child terms when using hierarchical classifications

  ➡ implicit *OR* with otherwise assumed *AND*
- implementation of hierarchical annotations overcomes some limitations of "fuzzy" disease annotations

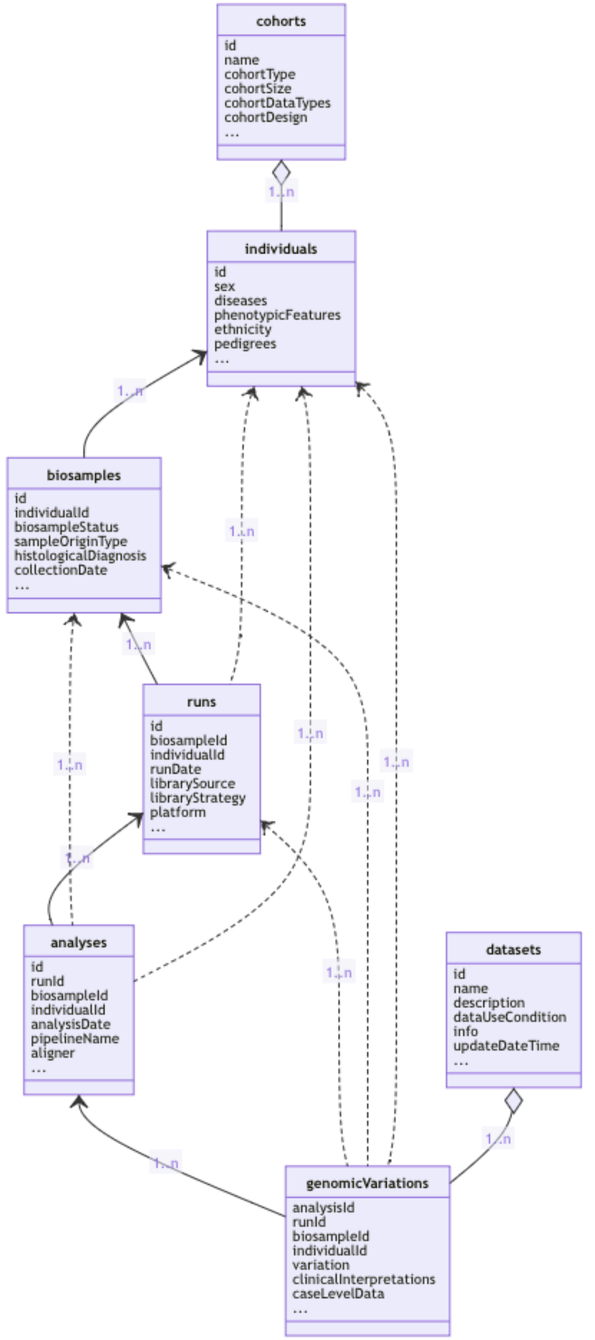
Beacon+ specific: Multiple term selection with OR logic



Id	Description	Classifications	Identifiers	DEL	DUP	CNV
PGX_AM_BS_MCC01	Merkel cell carcinoma	icdot-C44.9 Skin, NOS icdom-82473 Merkel cell carcinoma NCIT:C9231 Merkel Cell Carcinoma	PMID:9537255	0.116	0.104	0.22
PGX_AM_BS_MCC02	Merkel cell carcinoma	icdot-C44.9 Skin, NOS icdom-82473 Merkel cell carcinoma NCIT:C9231 Merkel Cell Carcinoma	PMID:9537255	0.154	0.056	0.21
PGX_AM_BS_MCC03	Merkel cell carcinoma	icdot-C44.9 Skin, NOS icdom-82473 Merkel cell carcinoma NCIT:C9231 Merkel Cell Carcinoma	PMID:9537255	0.137	0.21	0.347
PGX_AM_BS_MCC04	Merkel cell carcinoma	icdot-C44.9 Skin, NOS icdom-82473 Merkel cell carcinoma NCIT:C9231 Merkel Cell Carcinoma	PMID:9537255	0.158	0.056	0.214
PGX_AM_BS_MCC05	Merkel cell carcinoma	icdot-C44.9 Skin, NOS icdom-82473 Merkel cell carcinoma NCIT:C9231 Merkel Cell Carcinoma	PMID:9537255	0.107	0.327	0.434

Beacon Default v2 Model

- The Beacon ***framework*** describes the overall structure of the API requests, responses, parameters, the common components, etc.
- Beacon ***models*** describe the set of concepts included in a Beacon, like individual or biosample, and also the relationships between them.
- Besides logical concepts, the Beacon ***models*** represent the schemas for data delivery in “record” granularity
- Beacon explicitly allows the use of *other models* besides its *version specific default*.
- Adherence to a shared ***model*** empowers federation
- Use of the ***framework*** w/ different models extends adoption



Universität Zürich[UZH]

Global Alliance for Genomics & Health

bycon for GA4GH Beacon

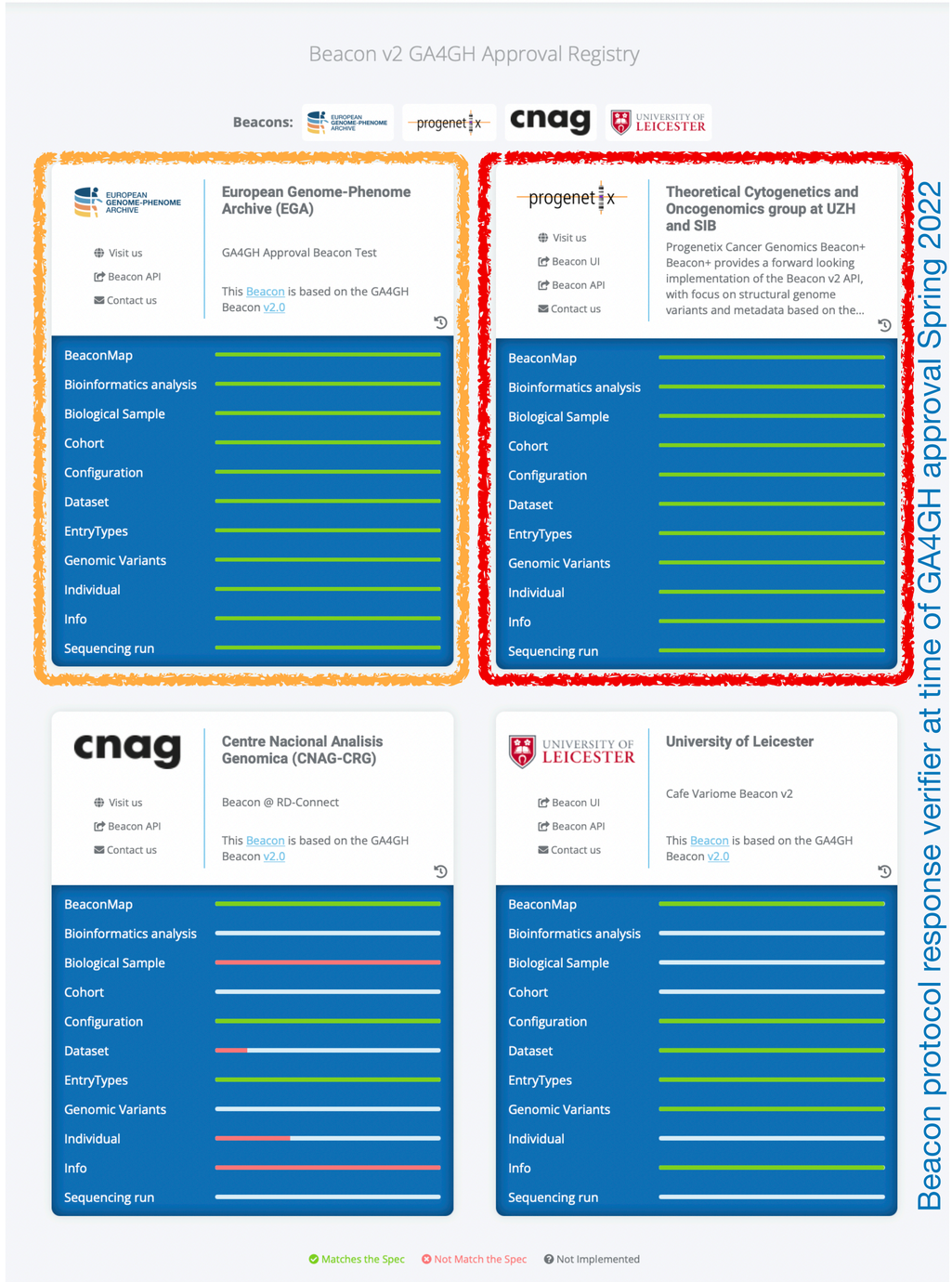
Implementation driven development of a GA4GH standard

progenetix

bycon Beacon

Implementation driven standards development

- Progenetix' Beacon+ has served as implementation driver since 2016
- the *bycon* package is used to prototype advanced Beacon features such as
  - ➡ structural variant queries
  - ➡ data handovers
  - ➡ Phenopackets integration
  - ➡ variant co-occurrences
  - ➡ ...



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bycon based Progenetix Stack

progenetix

- JavaScript front-end is populated for query results using asynchronous access to multiple handover objects
  - biosamples and variants tables, CNV histogram, UCSC .bed loader, .pgxseg variant downloads…
- the complete middleware / CGI stack is provided through the ***bycon*** package
  - schemas, query stack, data transformation (e.g. Phenopackets generation)…
- data collections mostly correspond to the main Beacon default model entities
  - no separate *runs* collection; integrated w/ analyses
  - *variants* are stored per observation instance

React

APACHE HTTP SERVER PROJECT

python™

mongoDB

- *collations* contain pre-computed data (e.g. CNV frequencies, statistics) and information for all grouping entity instances and correspond to **filter values**
  - PMID:10027410, NCIT:C3222, pgx:cohort-TCGA, pgx:icdom-94703…
- *querybuffer* stores id values of all entities matched by a query and provides the corresponding access handle for **handover** generation

```
_id: ObjectId("6249bb654f8f8d67eb94953b"),
id: '0765ee26-5029-4f28-b01d-9759abf5bf14',
source_collection: 'variants',
source_db: 'progenetix',
source_key: '_id',
target_collection: 'variants',
target_count: 667,
target_key: '_id',
target_values: [
  ObjectId("5bab578b727983b2e00ca99e"),
  ObjectId("5bab578d727983b2e00cb505"),
```

Entity collections

Utility collections

Beacon+: Phenopackets

Testing alternative response schemas...

http://progenetix.org/beacon/phenopackets/pgxind-kftx26j0

- the v2 default schemas are mostly aligned w/ Phenopackets v2
- creating phenopackets can be done mostly by re-wrapping of Beacon entities (individual, biosample)
- variants can be included through file resource URLs; in Beacon+ this is done through *ad hoc* handover URIs

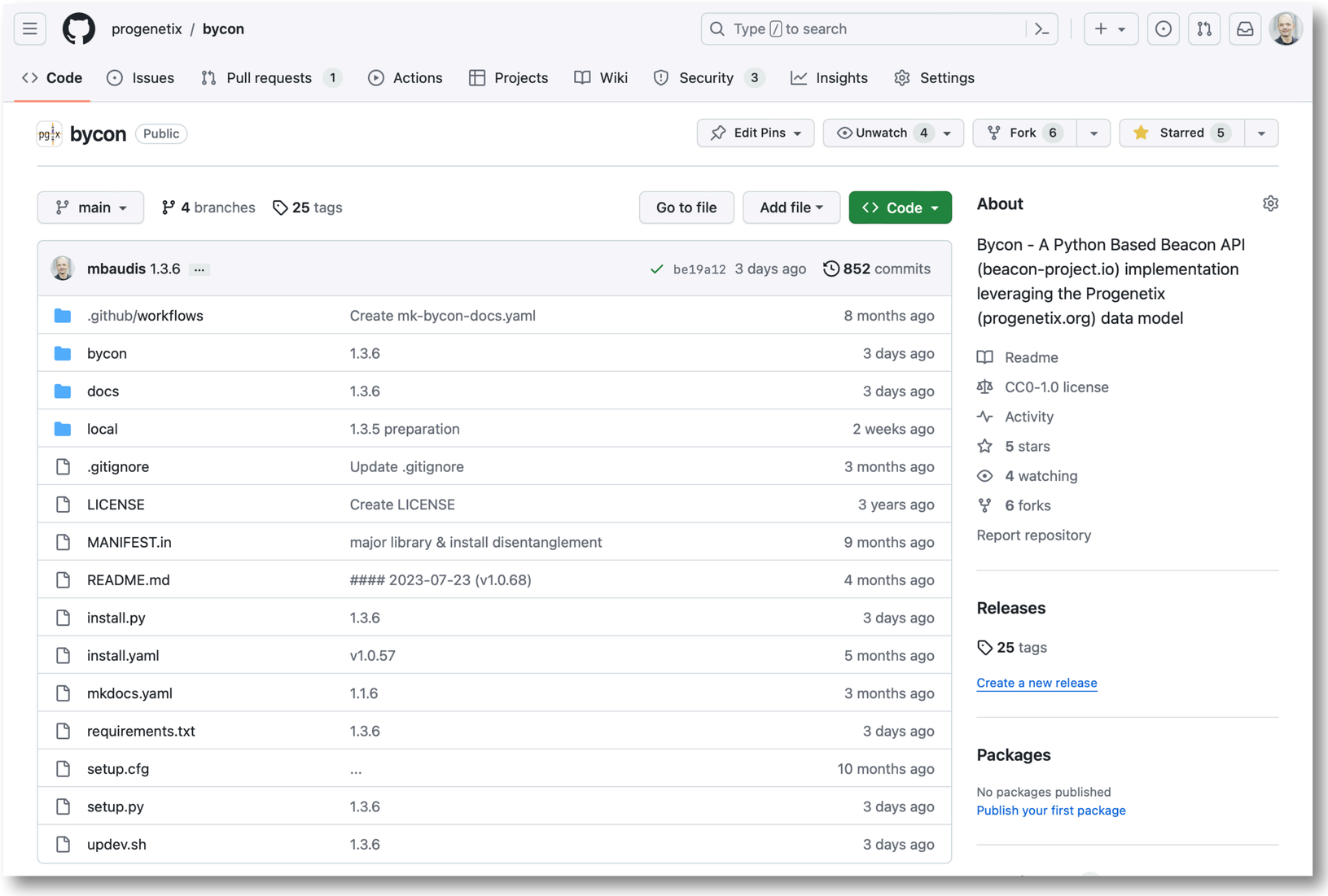

```
"id": "pgxpxf-kftx3tl5",
"metaData": {
  "phenopacketSchemaVersion": "v2",
  "resources": [
    {
      "id": "NCIT",
      "iriPrefix": "http://purl.obolibrary.org/obo/NCIT_",
      "name": "NCIt Plus Neoplasm Core",
      "namespacePrefix": "NCIT",
      "url": "http://purl.obolibrary.org/obo/ncit/neoplasm-core.c
      "version": "2022-04-01"
    },

"subject": {
  "dataUseConditions": {
    "id": "DUO:0000004",
    "label": "no restriction"
  },
  "diseases": [
    {
      "clinicalTnmFinding": [],
      "diseaseCode": {
        "id": "NCIT:C3099",
        "label": "Hepatocellular Carcinoma"
      },
      "onset": {
        "age": "P48Y9M26D"
      },
      "stage": {
        "id": "NCIT:C27966",
        "label": "Stage I"
      }
    }
  ],
  "id": "pgxind-kftx3tl5",
  "sex": {
    "id": "PATO:0020001",
    "label": "male genotypic sex"
  },
  "updated": "2018-12-04 14:53:11.674000",
  "vitalStatus": {
    "status": "UNKNOWN_STATUS"
  }
}

"biosamples": [
  {
    "biosampleStatus": {
      "id": "EFO:0009656",
      "label": "neoplastic sample"
    },
    "dataUseConditions": {
      "id": "DUO:0000004",
      "label": "no restriction"
    },
    "description": "Primary Tumor",
    "externalReferences": [
      {
        "id": "pgx:TCGA-0004d251-3f70-4395-b175-c94c2f5b1b81",
        "label": "TCGA case_id"
      },
      {
        "id": "pgx:TCGA-TCGA-DD-AAVP",
        "label": "TCGA submitter_id"
      },
      {
        "id": "pgx:TCGA-9259e9ee-7279-4b62-8512-509cb705029c",
        "label": "TCGA sample_id"
      },
      {
        "id": "pgx:TCGA-LIHC",
        "label": "TCGA LIHC project"
      }
    ],
    "files": [
      {
        "fileAttributes": {
          "fileFormat": "pgxseg",
          "genomeAssembly": "GRCh38"
        },
        "uri": "https://progenetix.org/beacon/biosamples/pgxbs-kftvhyvb/variants/?output=pgxseg"
      }
    ],
    "histologicalDiagnosis": {
      "id": "NCIT:C3099",
      "label": "Hepatocellular Carcinoma"
    },
    "id": "pgxbs-kftvhyvb",
    "individualId": "pgxind-kftx3tl5",
    "pathologicalStage": {
      "id": "NCIT:C27966",
      "label": "Stage I"
    },
    "sampledTissue": {
      "id": "UBERON:0002107",
      "label": "liver"
    },
    "timeOfCollection": {
      "age": "P48Y9M26D"
    },
```

Looking for implementers and contributors

- containerization
- data I/O ...
- standard library integration (VRSification of variants...)



bycon.progenetix.org
github.com/progenetix/bycon/

pgxRpi

An interface API for analyzing Progenetix CNV data in R using the Beacon+ API

GitHub: https://github.com/progenetix/pgxRpi

Bioconductor

README.md

pgxRpi

Welcome to our R wrapper package for Progenetix REST API that leverages the capabilities of Beacon v2 specification. Please note that a stable internet connection is required for the query functionality. This package is aimed to simplify the process of accessing oncogenomic data from Progenetix database.

You can install this package from GitHub using:

```
install.packages("devtools")
devtools::install_github("progenetix/pgxRpi")
```

For accessing metadata of biosamples/individuals, or learning more about filters, get started from the vignette Introduction_1_loadmetadata.

For accessing CNV variant data, get started from this vignette Introduction_2_loadvariants.

For accessing CNV frequency data, get started from this vignette Introduction_3_loadfrequency.

For processing local pgxseg files, get started from this vignette Introduction_4_process_pgxseg.

If you encounter problems, try to reinstall the latest version. If reinstallation doesn't help, please contact us.

pgxRpi

platforms all | rank 2218 / 2221 | support 0 / 0 | in Bioc devel only
build ok | updated < 1 month | dependencies 144

DOI: 10.18129/B9.bioc.pgxRpi
This is the **development** version of pgxRpi; to use it, please install the devel version of Bioconductor.

R wrapper for Progenetix

Bioconductor version: Development (3.19)

The package is an R wrapper for Progenetix REST API built upon the Beacon v2 protocol. Its purpose is to provide a seamless way for retrieving genomic data from Progenetix database—an open resource dedicated to curated oncogenomic profiles. Empowered by this package, users can effortlessly access and visualize data from Progenetix.

Author: Hangjia Zhao [aut, cre], Michael Baudis [aut]

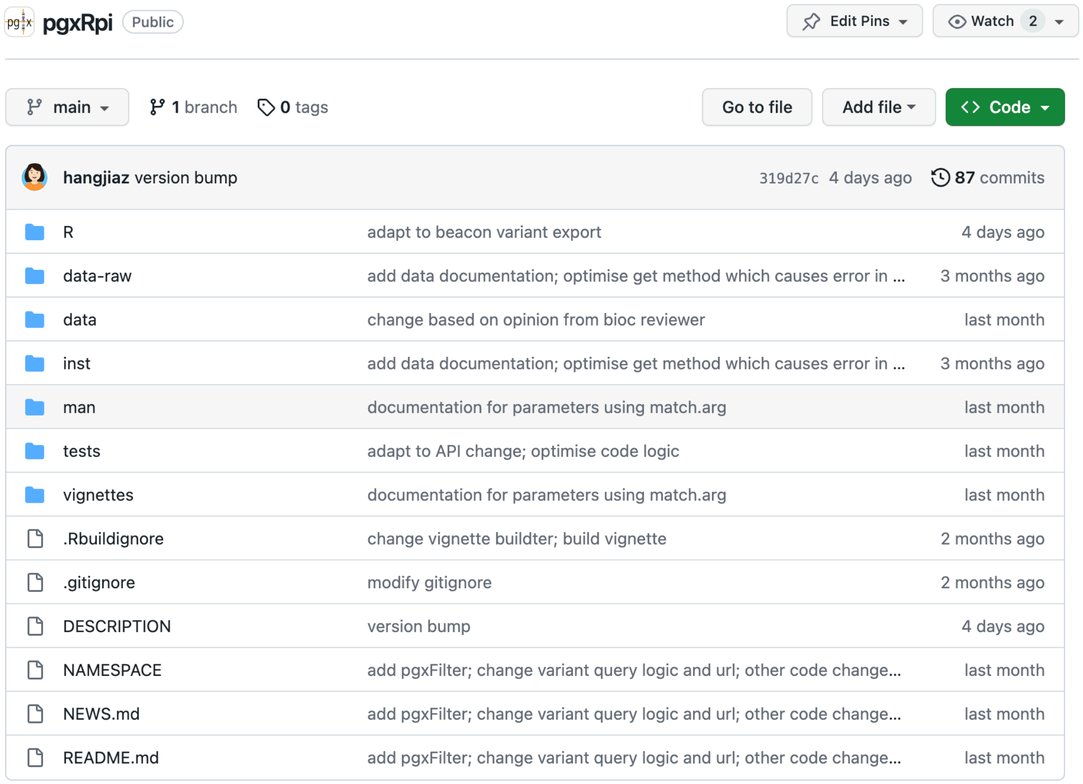
Maintainer: Hangjia Zhao <hangjia.zhao at uzh.ch>

Citation (from within R, enter `citation("pgxRpi")`):

Zhao H, Baudis M (2023). *pgxRpi: R wrapper for Progenetix*. doi:10.18129/B9.bioc.pgxRpi, R package version 0.99.9, https://bioconductor.org/packages/pgxRpi.

pgxRpi

An interface API for analyzing Progenetix CNV data in R using the Beacon+ API



pgxRpi Public

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main | 1 branch | 0 tags | Go to file | Add file | Code

hangjiaz version bump 319d27c 4 days ago 87 commits

R	adapt to beacon variant export	4 days ago
data-raw	add data documentation; optimise get method which causes error in ...	3 months ago
data	change based on opinion from bioc reviewer	last month
inst	add data documentation; optimise get method which causes error in ...	3 months ago
man	documentation for parameters using match.arg	last month
tests	adapt to API change; optimise code logic	last month
vignettes	documentation for parameters using match.arg	last month
.Rbuildignore	change vignette buildter; build vignette	2 months ago
.gitignore	modify gitignore	2 months ago
DESCRIPTION	version bump	4 days ago
NAMESPACE	add pgxFilter; change variant query logic and url; other code change...	last month
NEWS.md	add pgxFilter; change variant query logic and url; other code change...	last month
README.md	add pgxFilter; change variant query logic and url; other code change...	last month

2 Retrieve meatdata of samples

2.1 Relevant parameters

type, filters, filterLogic, individual_id, biosample_id, codematches, limit, skip

2.2 Search by filters

Filters are a significant enhancement to the Beacon query API, providing a mechanism for specifying rules to select records based on their field values. To learn more about how to utilize filters in Progenetix, please refer to the documentation.

The `pgxFilter` function helps access available filters used in Progenetix. Here is the example use:

```
# access all filters
all_filters <- pgxFilter()
# get all prefix
all_prefix <- pgxFilter(return_all_prefix = TRUE)
# access specific filters based on prefix
ncit_filters <- pgxFilter(prefix="NCIT")
head(ncit_filters)
#> [1] "NCIT:C28076" "NCIT:C18000" "NCIT:C14158" "NCIT:C14161" "NCIT:C28077"
#> [6] "NCIT:C28078"
```

The following query is designed to retrieve metadata in Progenetix related to all samples of lung adenocarcinoma, utilizing a specific type of filter based on an NCIt code as an ontology identifier.

```
biosamples <- pgxLoader(type="biosample", filters = "NCIT:C3512")
# data looks like this
biosamples[c(1700:1705),]
#>       biosample_id group_id group_label   individual_id    callset_ids
#> 1700 pgxbs-kftvjjhx       NA          NA pgxind-kftx5fyd pgxcs-kftwjevi
#> 1701 pgxbs-kftvjjhz       NA          NA pgxind-kftx5fyf pgxcs-kftwjew0
#> 1702 pgxbs-kftvjji1       NA          NA pgxind-kftx5fyh pgxcs-kftwjewi
#> 1703 pgxbs-kftvjjn2       NA          NA pgxind-kftx5g4r pgxcs-kftwjg5r
#> 1704 pgxbs-kftvjjn4       NA          NA pgxind-kftx5g4t pgxcs-kftwjg6q
#> 1705 pgxbs-kftvjjn5       NA          NA pgxind-kftx5g4v pgxcs-kftwjg78
```

Client for Accessing Progenetix

pgxRpi: an R/Bioconductor package

- **Query and export variants**

  https://progenetix.org/beacon/biosamples/pgxbs-kftvh94d/g_variants

  > variants <- pgxLoader(type="variant",biosample_id="pgxbs-kftvh94d")

- **Query metadata of biosamples and individuals by filters (e.g. NCIt, PMID)**

  http://progenetix.org/services/sampletable/?filters=NCIT:C3697

  > biosamples <- pgxLoader(type="biosample",filters="NCIT:C3697")

- **Query and visualize CNV frequency by filters**

  http://www.progenetix.org/services/intervalFrequencies/?filters=NCIT:C3512

  > freq <- pgxLoader(type="frequency",output="pgxfreq",filter
  > pgxFreqplot(freq)

- **Process local .pgxseg files**

  > info <- pgxSegprocess(file=file, show_KM_plot = T,
  return_seg = T, return_metadata = T, return_frequency = T)

pgxRpi

This is the **development** version of pgxRpi; for the stable release version, see pgxRpi.

R wrapper for Progenetix

platforms all | rank 2178 / 2266 | support 0 / 0 | in Bioc < 6 months | build unknown | updated < 1 month | dependencies 137

DOI: 10.18129/B9.bioc.pgxRpi

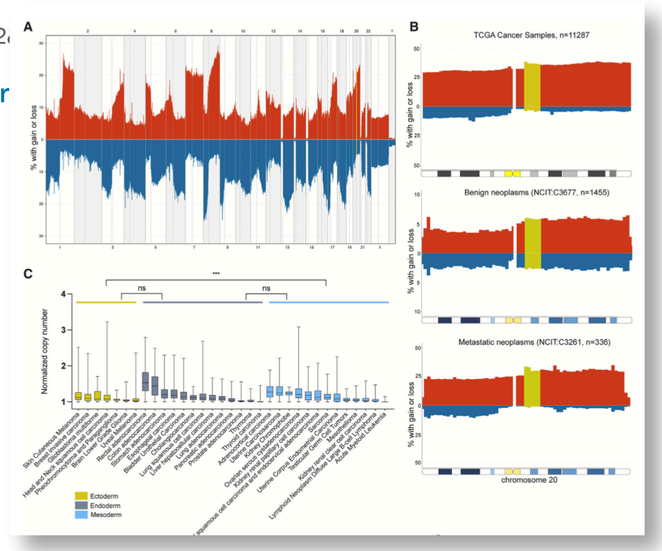
Bioconductor version: Development (3.20)

The package is an R wrapper for Progenetix REST API built upon the Beacon v2 protocol. Its purpose is to provide a seamless way for retrieving genomic data from Progenetix database—an open resource dedicated to curated oncogenomic profiles. Empowered by this package, users can effortlessly access and visualize data from Progenetix.

Author: Hangjia Zhao [aut, cre], Michael Baudis [aut]

Maintainer: Hangjia Zhao <hangjia.zhao at uzh.ch>

Use case: 2024 article using Progenetix' ***pgxRpi*** to retrieve & visualize 117'587 cancer CNV profiles for a study into pluripotent stem cells' genomics



Stem Cell Reports

Review

ISSCR

OPEN ACCESS

Gains of 20q11.21 in human pluripotent stem cells: Insights from cancer research

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https://doi.org/10.1016/j.stemcr.2023.11.013

Figure 2. Copy-number alterations of human chromosome 20q11.21 in cancers

(A) Aggregated copy-number variation (CNV) data of 117,587 neoplasms (NCIT: C3262) from the Progenetix database (Huang et al., 2021) were plotted using R library pgxRpi. The percentage of samples with aberrations (red, gain; blue, loss) for the whole chromosome are indicated on the y axis. Chromosomal regions are depicted on the x axis; the minimal region of interest at chr20:31216079-35871578 is marked in moss green. NCIT, National Cancer Institute Thesaurus.

(B) Top to bottom: Aggregated CNV data of 11,287 TCGA cancer samples, 336 metastatic neoplasms (NCIT: C3261), and 1,455 benign neoplasms (NCIT: C3677) from the Progenetix database (Huang et al., 2021), respectively, were plotted using R library pgxRpi. The percentage of samples with aberrations (red, gain; blue, loss) for the whole chromosome are indicated on the y axis. Chromosomal regions are depicted on the x axis; the minimal region of interest at chr20:31216079–35871578 is marked in moss green.

The Beacon team through the ages

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elixir

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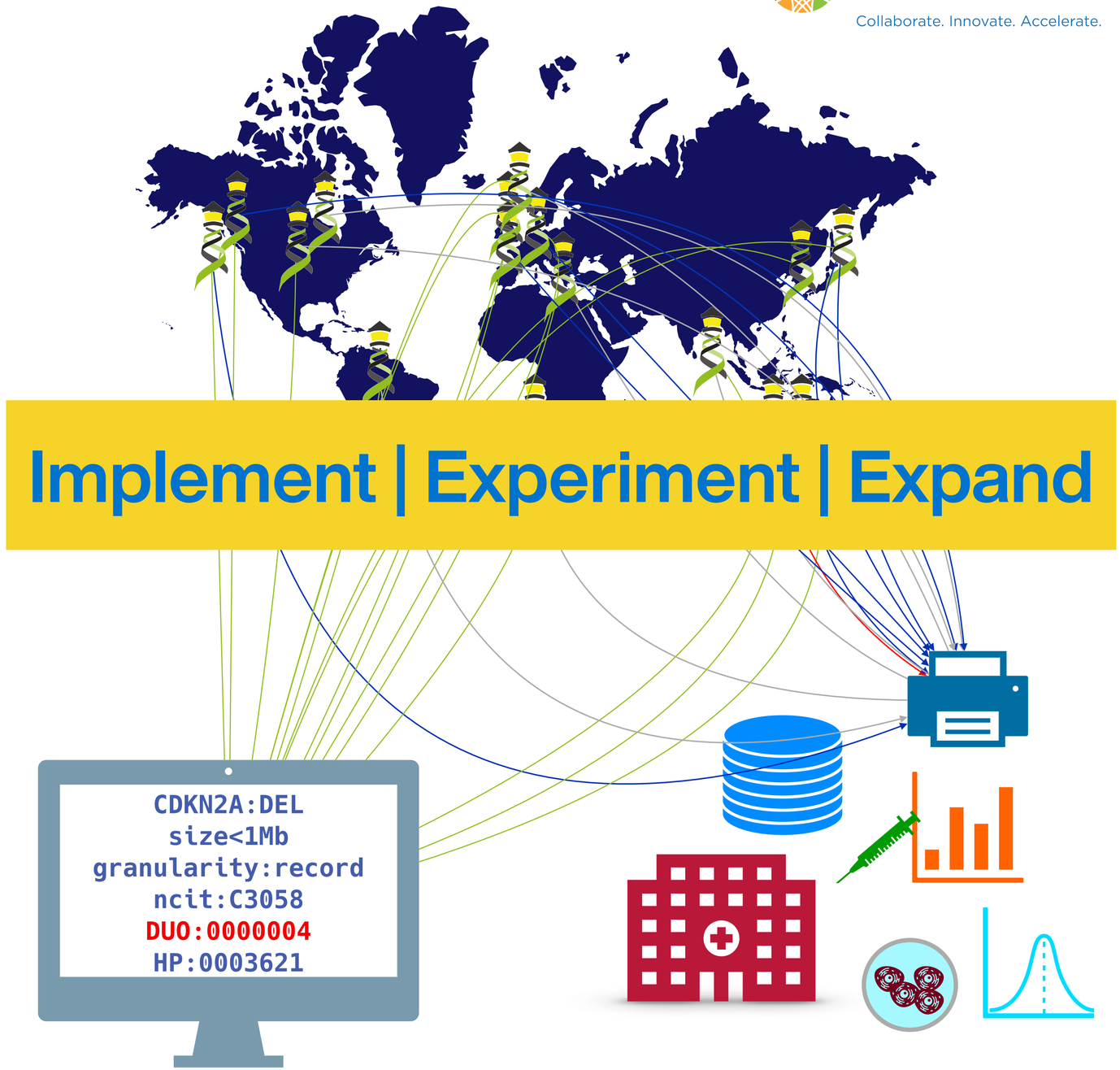
Collaborate. Innovate. Accelerate.

What Can You Do?

- find a way to make your (patients') **data discoverable** - through adding *at least* the relevant metadata to national or project centric repositories
- use forward looking consent and data protection models (**ORD** principle "*as secure as necessary, as open as possible*")
- **support** and/or get involved with international **data standards** efforts and projects

Beacon for Genomic Discovery Proxies

- Feature beacons for privacy protecting data discovery
  - ➡ privacy protection through aggregated data, cohorts
  - ➡ alternative is "horizontal gatekeeping": separate Beacons for discovery of e.g. genomic and phenotypic data and interleaving by data owner upon request
  - ➡ We'd love to help launching your beacon (especially as a bycon...)



Beacon for Genomic Discovery Proxies

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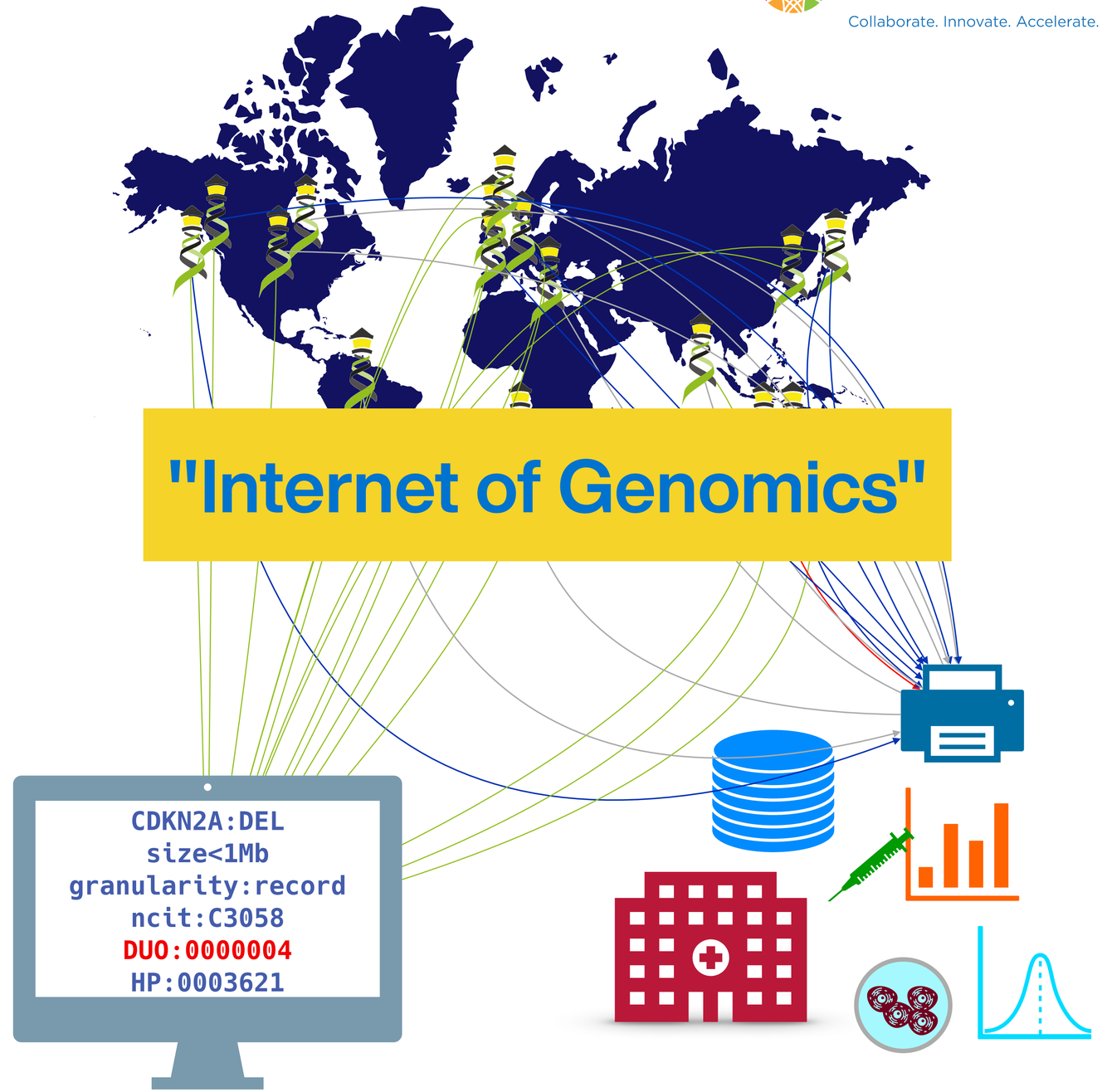

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Global Alliance for Genomics & Health

April Connect 2025

1 to 4 April 2025

Broad Institute, Cambridge, USA

Registration Open Now

13th Plenary

6 to 10 October

UKK, Uppsala, Sweden

Registration Opening Soon

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Swiss Institute of Bioinformatics