

Theoretical Cytogenetics and Oncogenomics

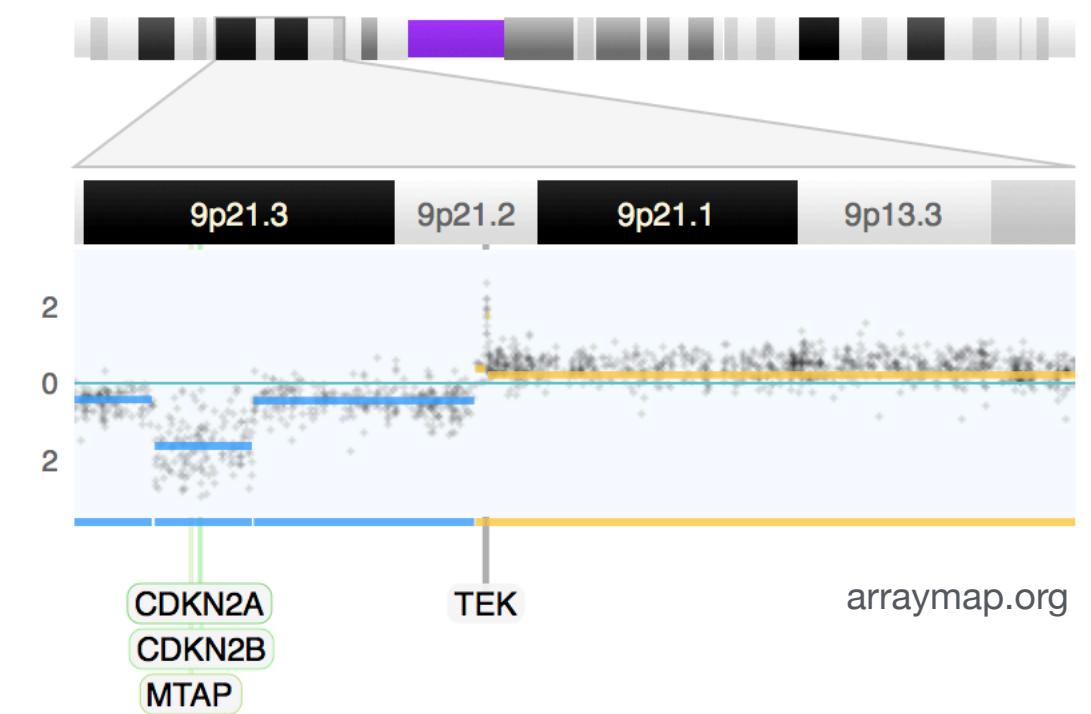
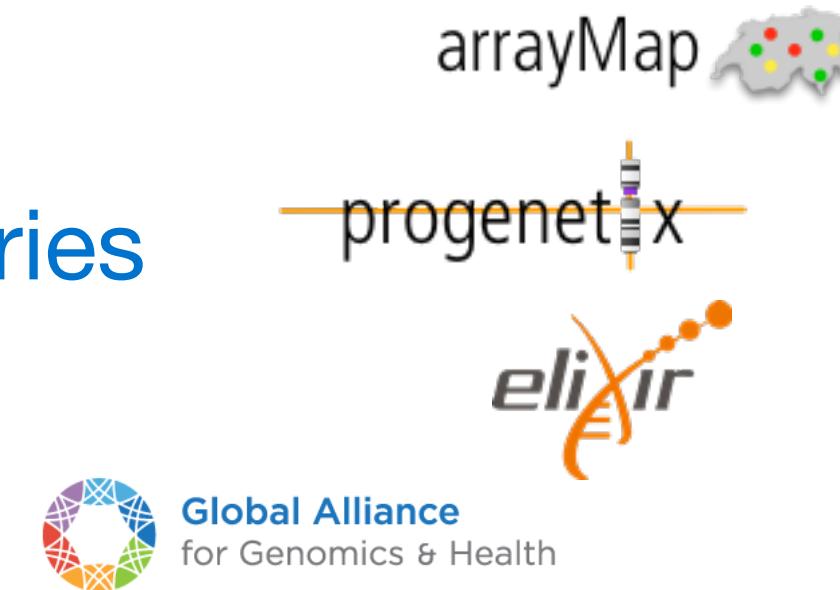
Cancer Genomics | Data Resources | Methods & Standards for Genomics and Personalized Health

Curators
~~Data Parasites~~

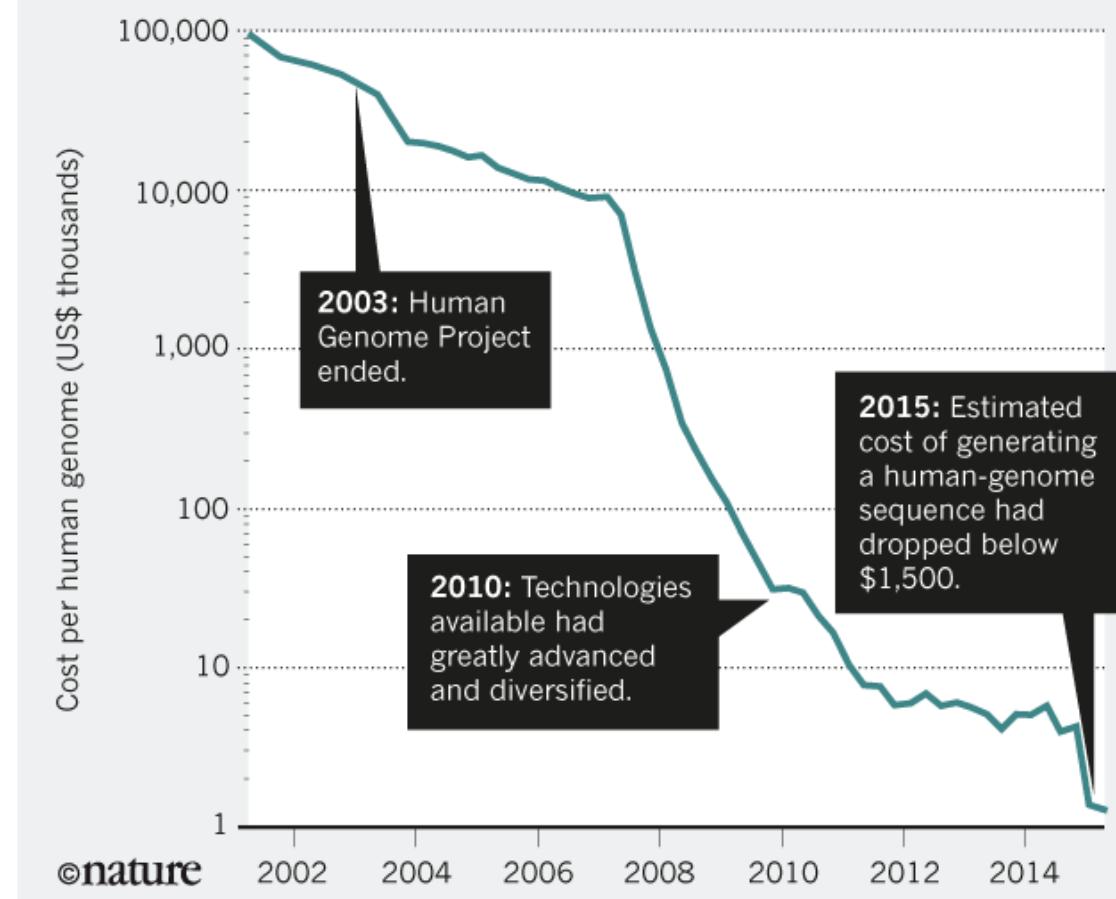


Department of Molecular Life Sciences

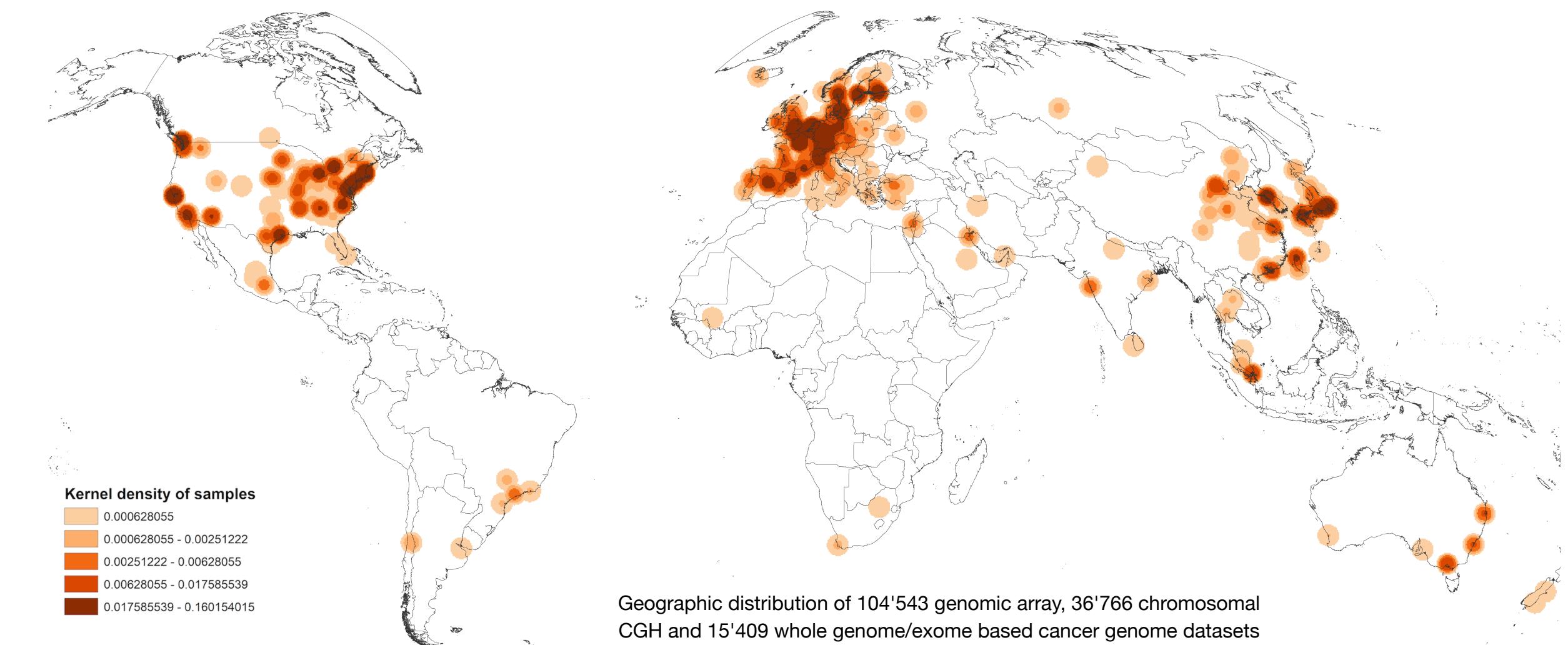
- ▶ **Genome analyses** (including transcriptome, metagenomics) are core technologies for Personalised Health™ applications
- ▶ The unexpectedly large amount of **sequence variants** in human genomes - germline and somatic/cancer - requires huge analysis efforts and creation of **reference repositories**
- ▶ **Standardized data formats** and **exchange protocols** are needed to connect these resources throughout the world, for reciprocal, international **data sharing and biocuration** efforts
- ▶ Our work @ UZH:
 - ▶ **cancer genome repositories**
 - ▶ **biocuration**
 - ▶ **protocols & formats**



BETTER, CHEAPER, FASTER
The cost of DNA sequencing has dropped dramatically over the past decade, enabling many more applications.



The future of DNA sequencing. Eric D. Green, Edward M. Rubin & Maynard V. Olson. Nature; 11 October 2017 (News & Views)

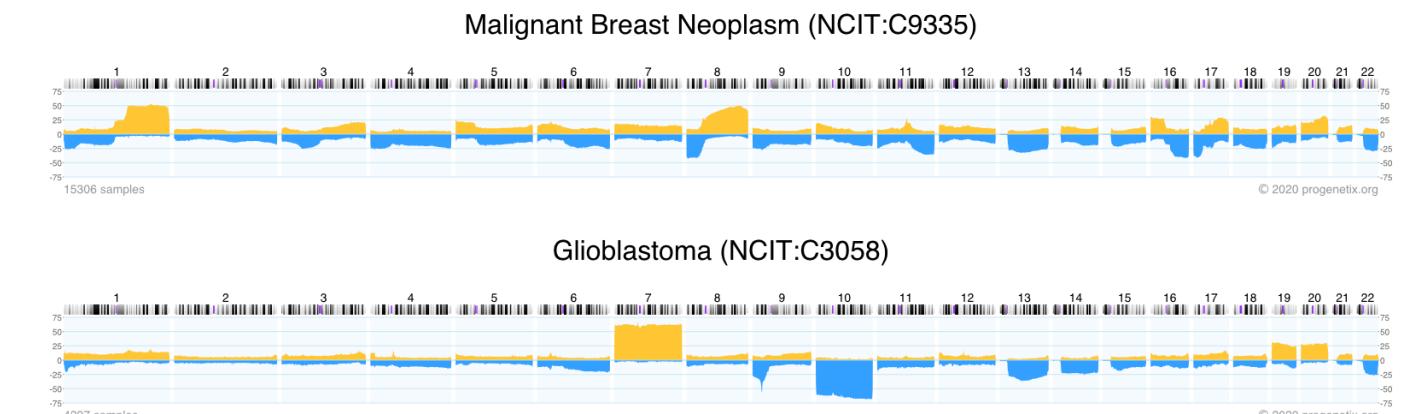


Geographic distribution of 104'543 genomic array, 36'766 chromosomal CGH and 15'409 whole genome/exome based cancer genome datasets

Theoretical Cytogenetics and Oncogenomics

... but what does this entail @baudisgroup?

- patterns & markers in cancer genomics, especially somatic structural genome variants
- bioinformatics support in collaborative studies
- reference resources for curated cancer genome variations
- bioinformatics tools & methods
- standards and reference implementations for data sharing in genomics and personalized health
- open research data "ambassadoring"

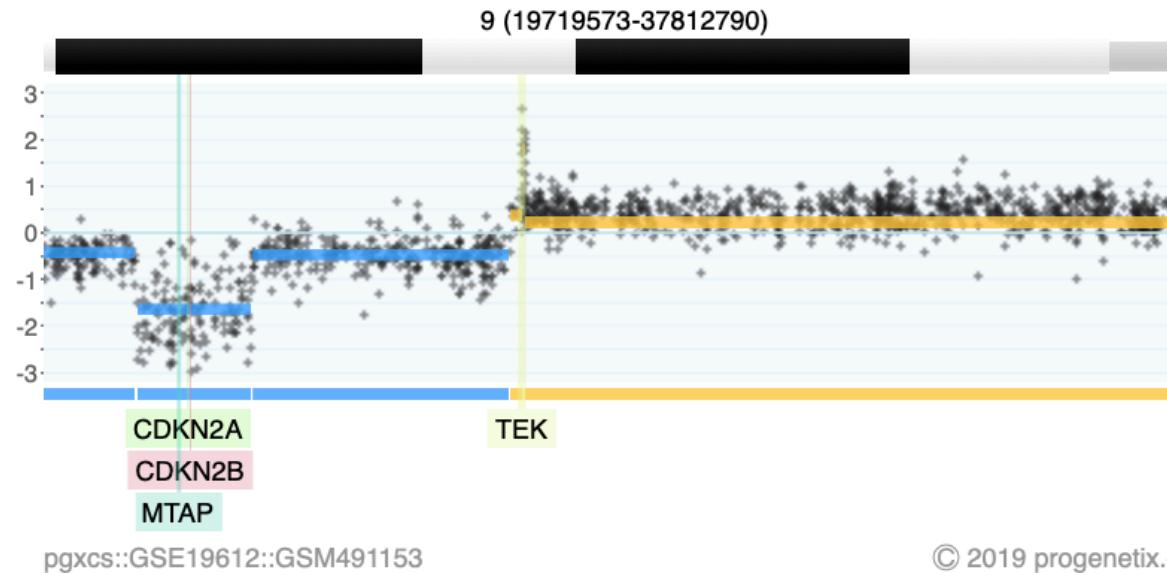


Theoretical Cytogenetics and Oncogenomics

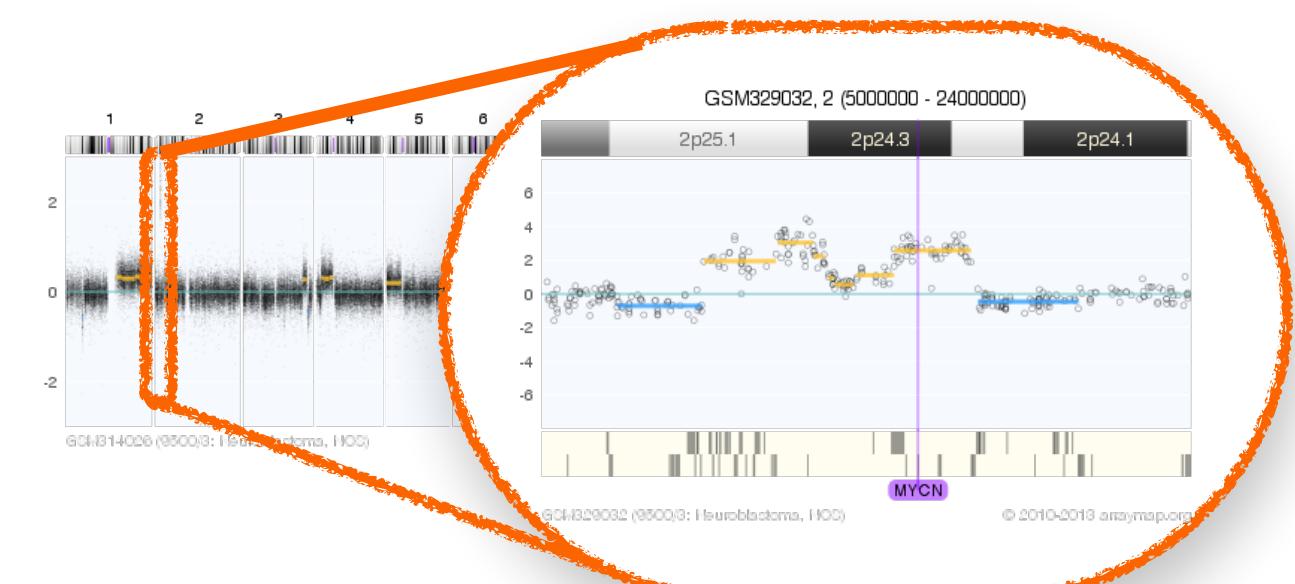
Research | Methods | Standards

Genomic Imbalances in Cancer - Copy Number Variations (CNV)

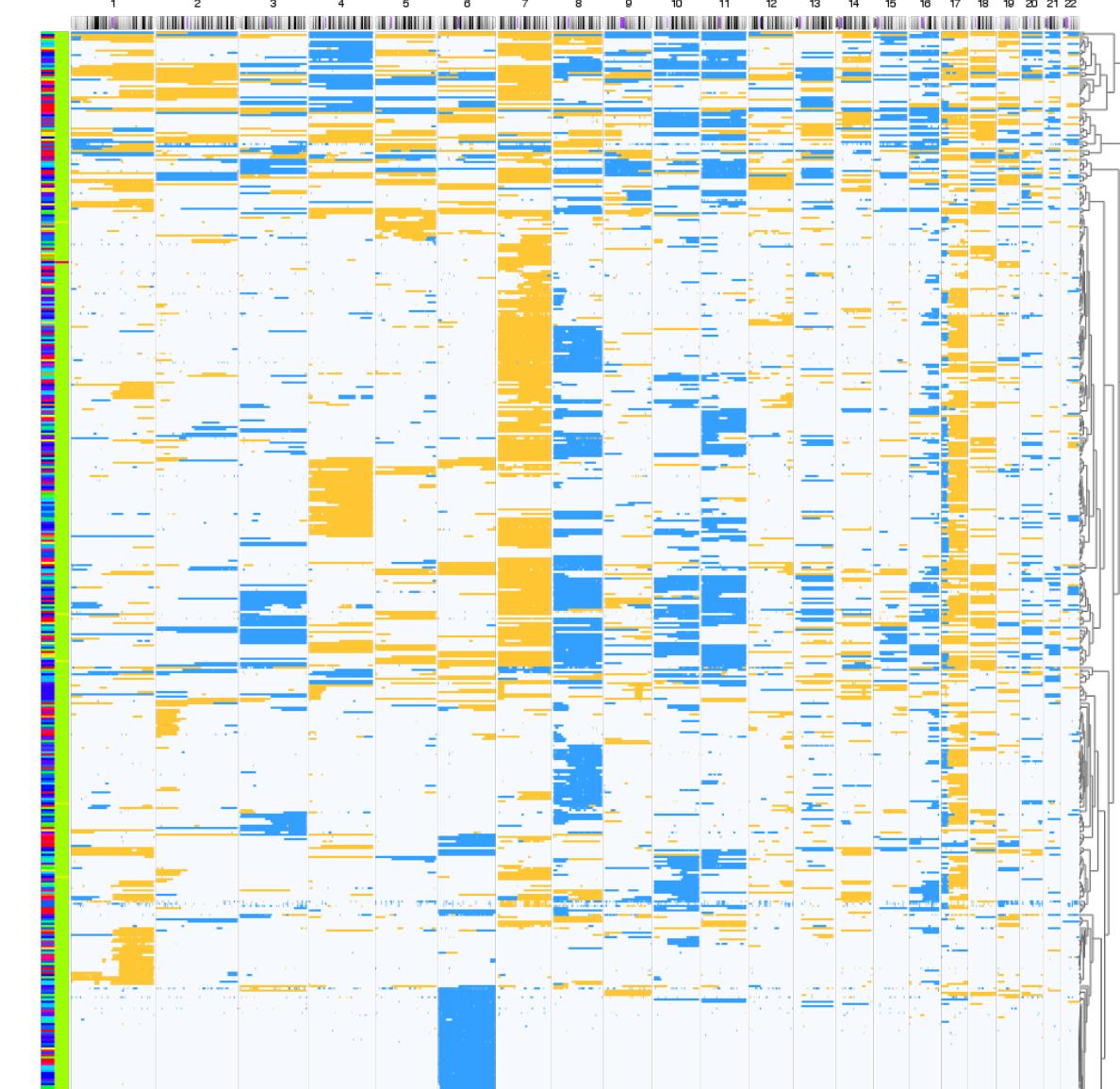
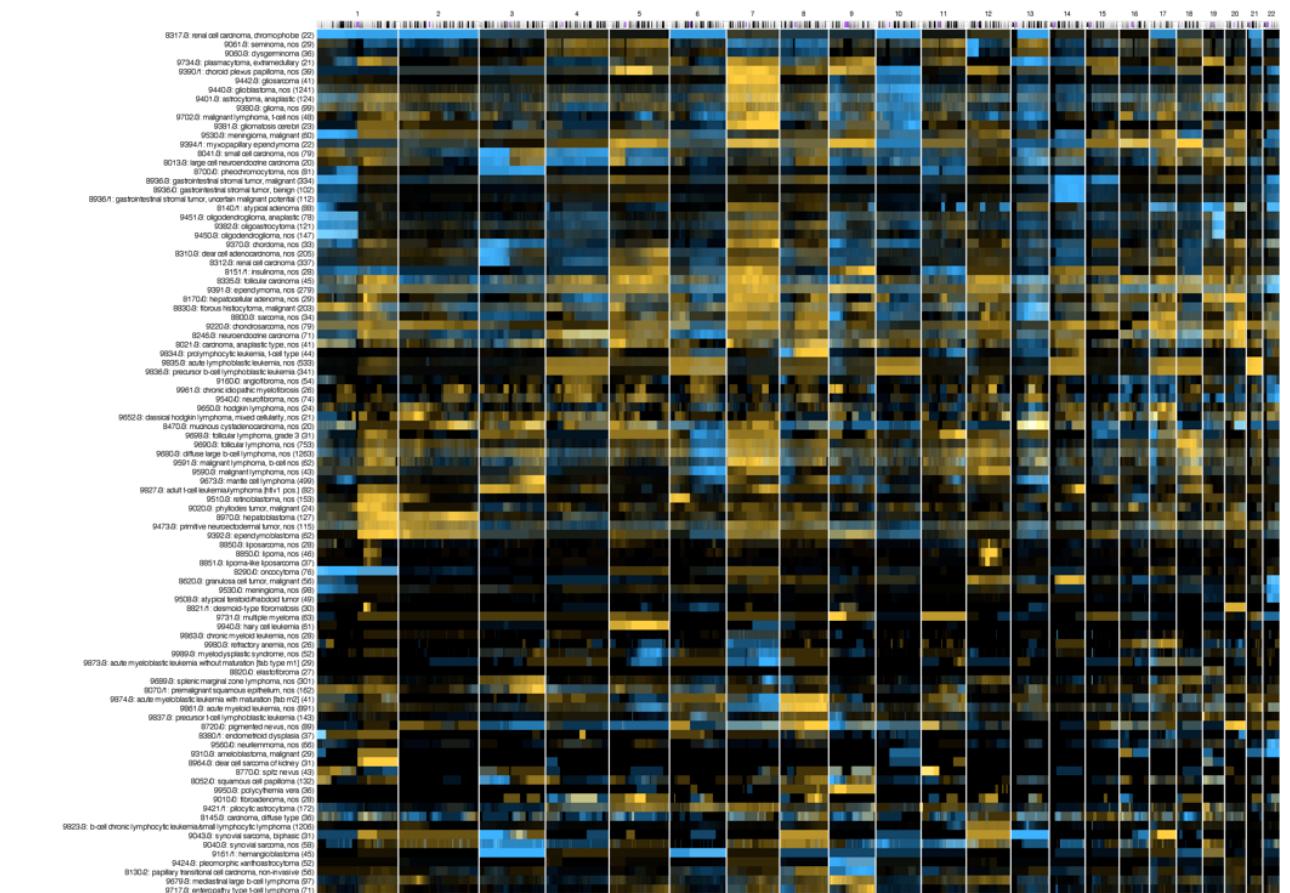
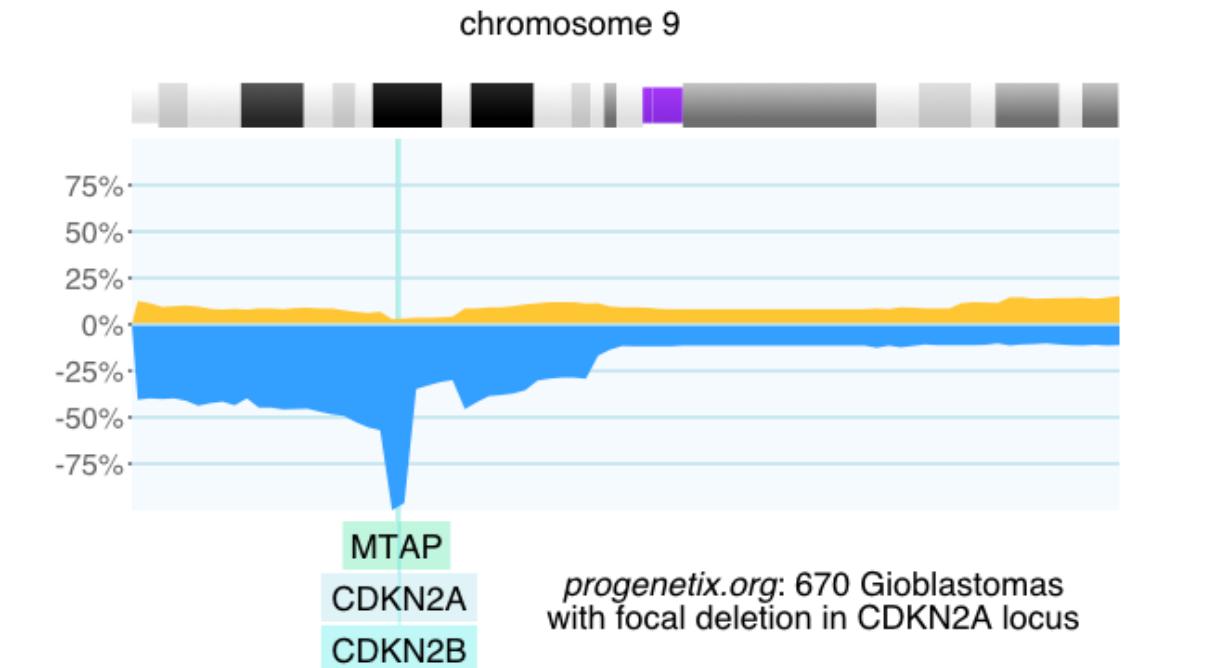
- Point mutations (insertions, deletions, substitutions)
- Chromosomal rearrangements
- **Regional Copy Number Alterations** (losses, gains)
- Epigenetic changes (e.g. DNA methylation abnormalities)



2-event, homozygous deletion in a Glioblastoma

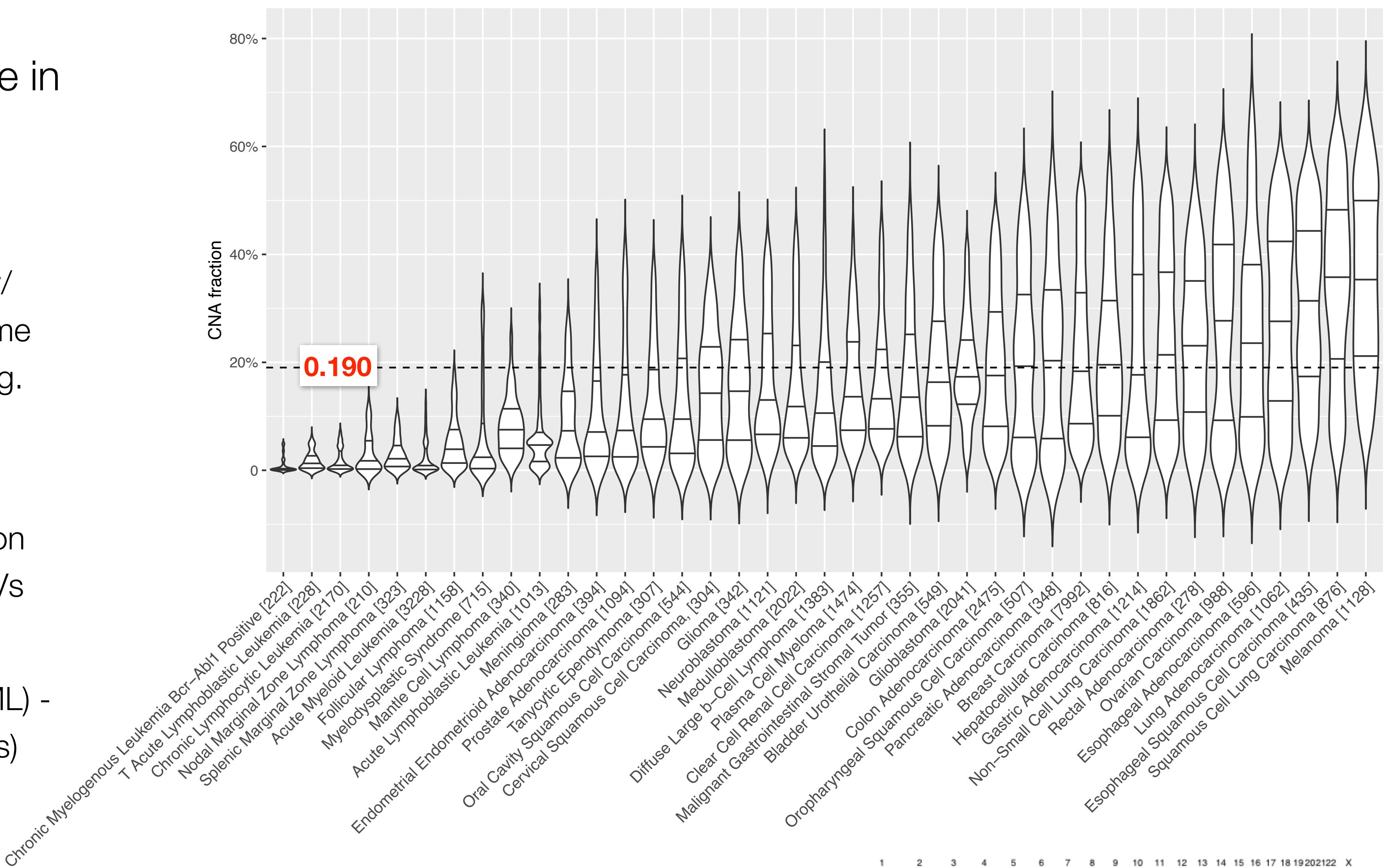


MYCN amplification in neuroblastoma
(GSM314026, SJNB8_N cell line)

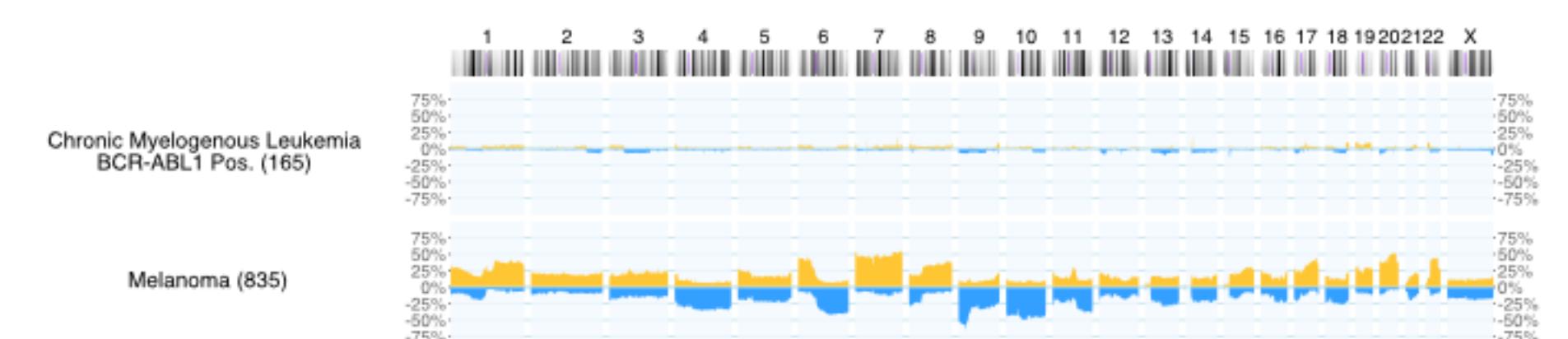


Genome CNV coverage in Cancer Classes

- 43654 out of 93640 CNV profiles; filtered for entities w/ >200 samples (removed some entities w/ high CNV rate, e.g. sarcoma subtypes)
- Single-sample CNV profiles were assessed for the fraction of the genome showing CNVs (relative gains, losses)
- range of medians 0.001 (CML) - 0.358 (malignant melanomas)



Lowest / Highest CNV fractions =>

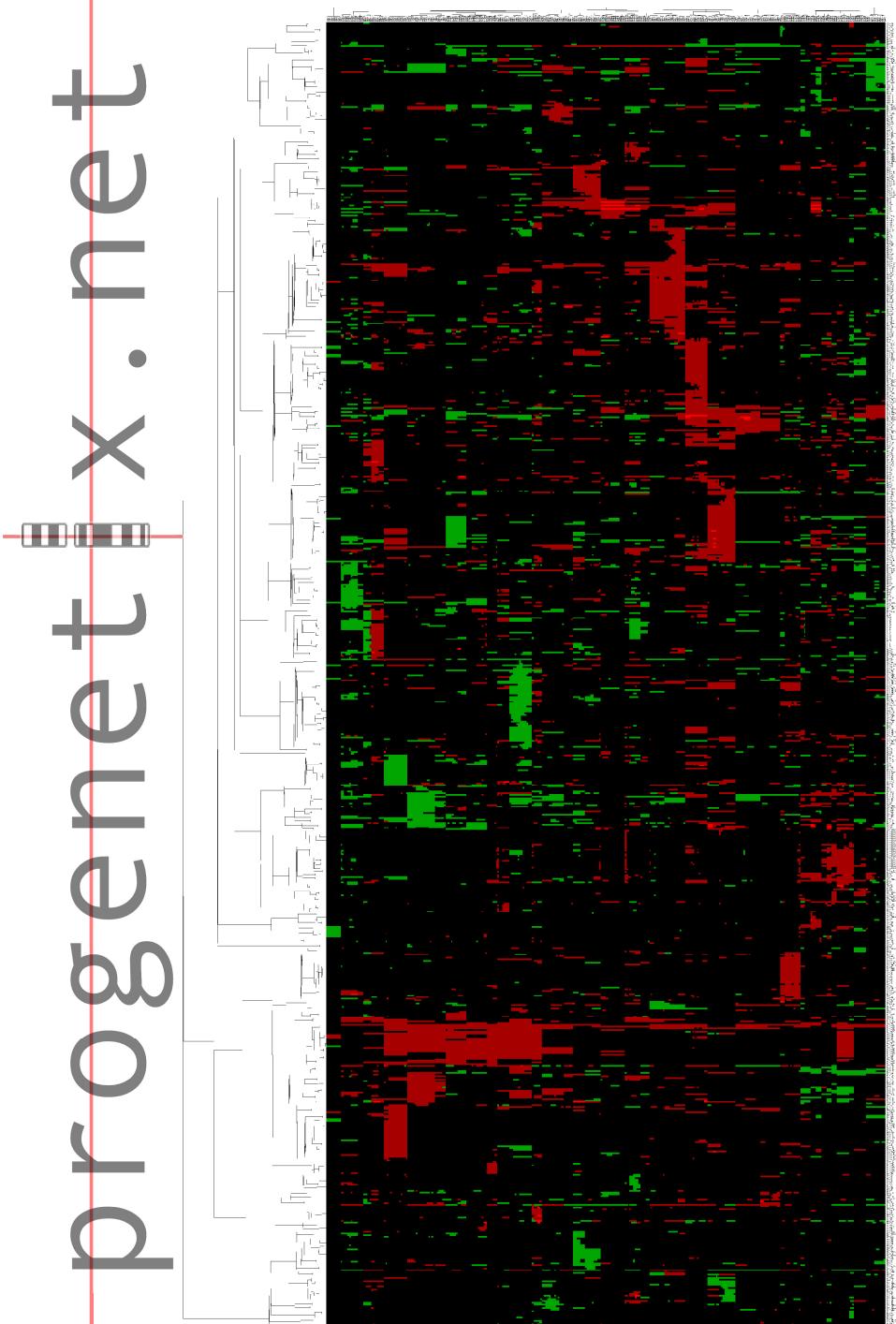


Over the last decade, techniques for the genome wide scanning for genomic imbalances in malignant neoplasia have been developed, e.g. Comparative Genomic Hybridization (CGH).

Currently, no comprehensive online source for CGH data with a standardized format suitable for data mining procedures has been made available for public access. Such a data repository could be valuable in identifying genetic aberration patterns with linkage to specific disease entities, and provide additional information for validating data from large scale expression array experiments.

A case and band specific aberration matrix was selected as most suitable format for the mining of CGH data. The [progenetix.net] data repository was developed to provide the according data to the research community for a growing number of human malignancies.

In the current implementation, two main purposes are being served. First, access to the band specific pattern of chromosomal imbalances allows the instantaneous identification of genomic "hotspots". Second, the band specific aberration matrices can be included in data mining efforts. As an example, the clustering off all informative cases from the current (September 2001) dataset is shown here (online source under www.progenetix.net/bcats/clustered.png).



Data selection

PubMed is searched for publications applying CGH to the analysis of malignant tumors. Articles are selected according to their online availability and the description of genomic imbalances on a per case basis.

Transformation of input data

Chromosomal aberration data is transformed via customized parsing commands to a common format adherent to ISCN 1995 recommendations. In some cases, aberration data was transcribed from graphical representations or provided by the authors.

Data storage

Currently, the primary data is stored in a dedicated "off-line" database. Besides case identifier and ISCN adapted chromosomal imbalance data, tumor classification and source information including the PubMed identifier is recorded. Disease entities are reclassified to ICD-O-3 codes.

Text parsing and generation of aberration matrix

For the generation of the case and band specific aberration matrix, a dedicated text pattern comparison model was developed using Perl. Briefly, for each chromosomal band, the aberration field of each case is searched for a variety of patterns containing aberration information applying to that band. A matrix with currently 324 band resolution is generated, annotating chromosomal gains with "1" and losses with "-1"; localized high-level gains are designated "2".

Website generation

For graphical representation of chromosomal imbalances, HTML pages containing different views of the underlying aberration matrices are generated using Perl. Graphics are implemented using HTML syntax. Besides band specific, whole genomic overviews, chromosome specific pages with links to all involved cases are generated for each ICD-O-3 entity as well as for each registered project. Additionally, those representations are available for several subsets combining related data (e.g. all lymphoid neoplasias, breast carcinoma cases). For each of the groups, the according aberration matrix is linked for download.

Hierarchical clustering of band specific chromosomal imbalances from 999 human neoplasias, contained in the [progenetix.net] collection. Cases without aberrations were excluded.

Progenetix.net: an online repository for molecular cytogenetic aberration data

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ABSTRACT

Summary: Through sequencing projects and, more recently, array-based expression analysis experiments, a wealth of genetic data has become accessible via online resources. In contrast, few of the (molecular-) cytogenetic aberration data collected in the last decades are available in a format suitable for data mining procedures. www.progenetix.net is a new online repository for previously published chromosomal aberration data, allowing the addition of band-specific information about chromosomal imbalances to oncologic data analysis efforts.

Availability: <http://www.progenetix.net>

Contact: mbaudis@stanford.edu

Neoplastic transformation and progression is the result of genetic defects arising in normal cells and giving rise to a malignant clone. During the process of oncogenesis, some of the usually multiple steps required for acquisition of the full neoplastic phenotype may represent themselves as numerical or structural abnormalities in the chromosomes of the transformed cells.

Over the last decades, the analysis of chromosomal abnormalities in malignant cells has gained importance in oncologic research as well as in clinical practice. A vast number of genetic abnormalities has been identified in the virtually complete range of human neoplasias. Several attempts have been undertaken for collection and classification of those abnormalities, the most widely recognized being the catalog by Mitelman and co-workers (Mitelman, 1994; online access through <http://cgap.nci.nih.gov/Chromosomes/Mitelman>).

In addition to metaphase analysis of short-term cultivated tumor cells or tumor cell lines, molecular cytogenetic techniques have recently been applied to the analysis of chromosomal abnormalities in primary tumor tissues. One of the more widely used screening techniques is Comparative Genomic Hybridization (CGH; Kallion-

iem et al., 1992; du Manoir et al., 1993). Briefly, this method is based on the competitive *in-situ* hybridization of differentially labeled tumor versus normal genomic DNA to normal human metaphase spreads. The calculation of the intensity ratios of the two fluorochromes gives an overview about relative gains and losses of DNA in the tumor genome with mapping to the respective chromosomal bands. The identification of frequently imbalanced regions in tumor entities may point towards tumor suppressor gene or proto-oncogenes mapping to the respective chromosomal bands. Usually, the result of those experiments is communicated either in text format according to the International System for Cytogenetic Nomenclature (Mitelman, 1995) or graphically, with aberration bars next to chromosomal ideograms for the representation of chromosomal gains and losses.

Because in each experiment CGH analysis covers the whole number of chromosomes, the comparision of data sets from related malignancies could lead to the delineation of common as well as divergent genetic pathways defining the respective malignant phenotypes. Although an extremely large number of malignant tumors has been analyzed using this technique, no comprehensive CGH database with band-specific chromosomal aberration information is publicly available[†].

A minimal requirement for such a database would be the conversion of the text or graphical information used in publications to data tables, representing the information about the aberration status of single chromosomal bands for each case. For the site discussed here, this process includes: (1) the transformation of the published results in a format adapted from the ISCN, and (2) the automatic generation of the band specific aberration table.

Due to format variations of the published data, step 1 consists of the manual conversion of the text data or evaluation and conversion of the graphical representations, respectively. Due to the (in computational terms) odd

[†]Links to a number of online CGH resources with different scopes can be found at www.progenetix.net.

*To whom correspondence should be addressed.

Cancer Genomics Reference Resource

- **open** resource for oncogenomic profiles
- over **116'000 cancer CNV profiles**
- more than **800 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
- recent addition of SNV data for some series



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

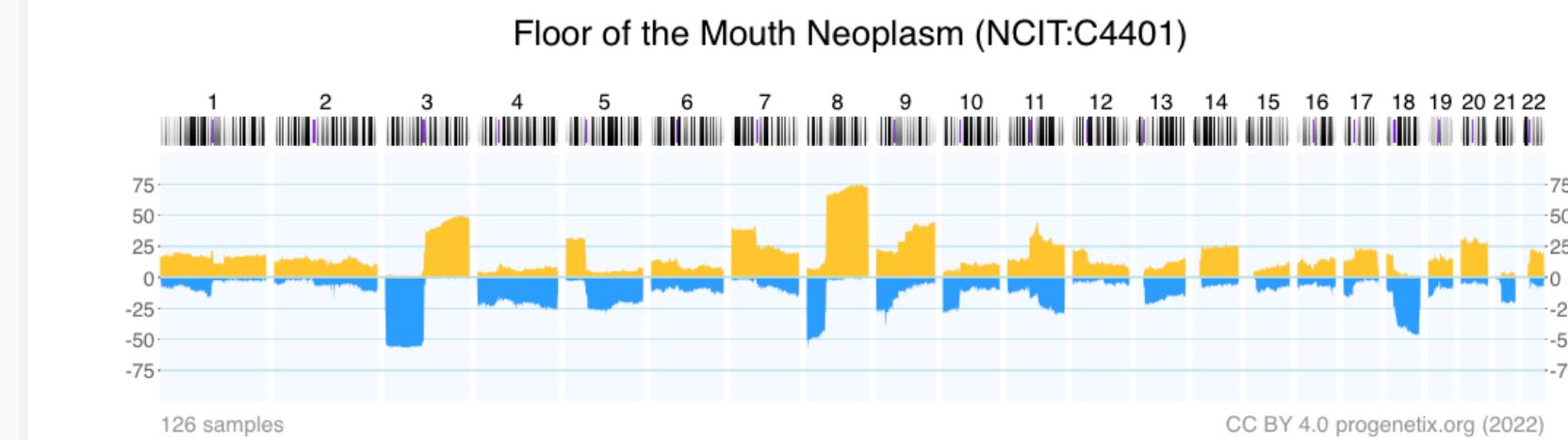
Beacon⁺

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.



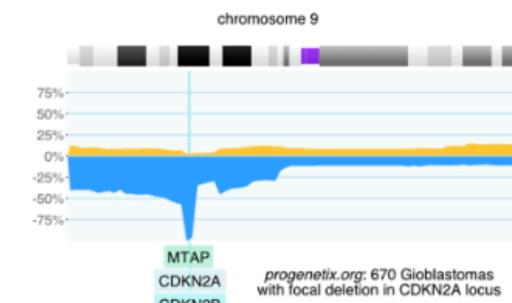
[Download SVG](#) | [Go to NCIT:C4401](#) | [Download CNV Frequencies](#)

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.

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Cancer Types by National Cancer Institute NCI Code

The cancer samples in Progenetix are mapped to several classification systems. For each of the classes, aggregated data is available by clicking the code. Additionally, a selection of the corresponding samples can be initiated by clicking the sample number or selecting one or more classes through the checkboxes.

Sample selection follows a hierarchical system in which samples matching the child terms of a selected class are included in the response.

Filter subsets e.g. by prefix Hierarchy Depth: 4 levels ▾

No Selection

- ▼ NCIT:C3262: Neoplasm (144956 samples, 118106 CNV profiles)
 - NCIT:C3263: Neoplasm by Site (112295 samples, 111637 CNV profiles)
 - NCIT:C000000: Unplaced Entities (27417 samples, 1219 CNV profiles)
 - ▼ NCIT:C4741: Neoplasm by Morphology (110745 samples, 110092 CNV profiles)
 - NCIT:C27134: Hematopoietic and Lymphoid C... (26137 samples, 26137 CNV profiles)
 - NCIT:C3422: Trophoblastic Tumor (49 samples, 49 CNV profiles)
 - ▼ NCIT:C35562: Neuroepithelial, Perineurial, and... (11770 samples, 11129 CNV profiles)
 - NCIT:C3787: Neuroepithelial Neoplasm (11356 samples, 10715 CNV profiles)
 - ▼ NCIT:C3059: Glioma (8825 samples, 8183 CNV profiles)
 - NCIT:C129325: Diffuse Glioma (6123 samples, 6137 CNV profiles)
 - NCIT:C182151: Diffuse Midline Glioma (2 samples, 2 CNV profiles)
 - NCIT:C3058: Glioblastoma (4370 samples, 4384 CNV profiles)
 - NCIT:C3288: Oligodendrogloma (500 samples, 500 CNV profiles)
 - NCIT:C3903: Mixed Glioma (391 samples, 391 CNV profiles)
 - NCIT:C4326: Anaplastic Oligodendro... (203 samples, 203 CNV profiles)
 - NCIT:C7173: Diffuse Astrocytoma (115 samples, 115 CNV profiles)
 - NCIT:C9477: Anaplastic Astrocytoma (542 samples, 542 CNV profiles)
 - NCIT:C132067: Low Grade Glioma (1503 samples, 1503 CNV profiles)
 - NCIT:C4324: Astroblastoma, MN1-Altered (12 samples, 12 CNV profiles)
 - NCIT:C4822: Malignant Glioma (5598 samples, 5418 CNV profiles)
 - NCIT:C6770: Ependymal Tumor (627 samples, 627 CNV profiles)
 - NCIT:C6958: Astrocytic Tumor (5882 samples, 5896 CNV profiles)
 - NCIT:C6960: Oligodendroglial Tumor (703 samples, 703 CNV profiles)
 - NCIT:C8501: Brain Stem Glioma (2 samples, 2 CNV profiles)
 - NCIT:C3716: Primitive Neuroectodermal T... (2213 samples, 2214 CNV profiles)
 - NCIT:C4747: Glioneuronal and Neuronal Tumors (89 samples, 89 CNV profiles)
 - NCIT:C6965: Pineal Parenchymal Cell Neoplasm (51 samples, 51 CNV profiles)

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No Selection

- NCIT:C3262: I
- NCIT:C326
- NCIT:C000
- NCIT:C474
 - NCIT:C2
 - NCIT:C3
 - NCIT:C3
 - NCIT:C3
 - N
- NCIT:C3058: Glioblastoma (NCIT:C3058)
 - Sample Counts
 - 4370 samples
 - 4286 direct NCIT:C3058 code matches
 - 4384 CNV analyses
 - Search Samples
 - Select NCIT:C3058 samples in the [Search Form](#)
 - Raw Data (click to show/hide)
- NCIT:C4822: Malignant Glioma (5598 samples, 5418 CNV profiles)
- NCIT:C6770: Ependymal Tumor (627 samples, 627 CNV profiles)
- NCIT:C6958: Astrocytic Tumor (5882 samples, 5896 CNV profiles)
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Glioblastoma (NCIT:C3058)

Download SVG | Go to NCIT:C3058 | Download CNV Frequencies

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Search Samples

CDKN2A Deletion Example MYC Duplication TP53 Del. in Cell Lines

K-562 Cell Line

Gene Spans

Cytoband(s)

This example shows the query for CNV deletion variants overlapping the CDKN2A gene's coding region with at least a single base, but limited to "highly focal" hits (here i.e. <= ~1Mbp in size). The query can be modified e.g. through changing the position parameters or diagnosis.

Dataset

Progenetix

Gene Symbol

Select...

Chromosome

NC_000009.12

Variant Type

EFO:0030067 (copy number deletion)

Start or Position

21500001-21975098

End (Range or Structural Var.)

21967753-22500000

Minimum Variant Length

Maximal Variant Length

Reference ID(s)

Select...

Cohorts

Cancer Classification(s)

NCIT:C3058: Glioblastoma (4...

Clinical Classes

Select...

Genotypic Sex

Select...

Biosample Type

Select...

Filters

Filter Logic

AND

Include Child Terms

Select...

Response Limit / Page Size

1000

Skip Pages

0

City

Select...

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Edit Query

Assembly: GRCh38 chro: refseq:NC_000009.12 Start: 21500001-21975098

End: 21967753-22500000 Type: EFO:0030067 Filters: NCIT:C3058

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Matched Samples: 657

Retrieved Samples:

Variants: 276

Calls: 659

UCSC region ↗

Variants in UCSC ↗

Dataset Responses (JSON) ↗

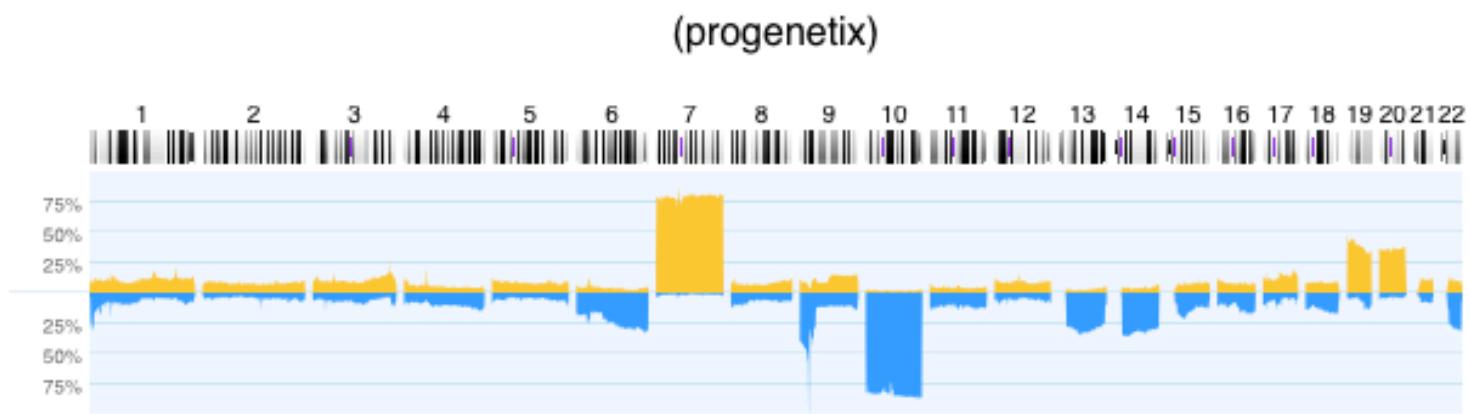
Visualization options

Results

Biosamples

Biosamples Map

Variants



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Reload histogram in new window ↗

Matched Subset Codes	Subset Samples	Matched Samples	Subset Match Frequencies
pgx:icdot-C71.4	4	1	0.250
pgx:icdom-94403	4286	653	0.152
NCIT:C3058	4370	653	0.149
pgx:icdot-C71.1	14	2	0.143
pgx:icdot-C71.9	7204	640	0.089
NCIT:C3796	84	4	0.048
pgx:icdom-94423	84	4	0.048
pgx:icdot-C71.0	1714	14	0.008

Download Sample Data (TSV)

1-657 ↗

Download Sample Data (JSON)

1-657 ↗

Ontologies and Classifications



Services: Ontologymaps (NCIt)

The **ontologymaps** service provides equivalency mapping between ICD-O and other classification systems, notably NCIt and UBERON. It makes use of the sample-level mappings for NCIT and ICD-O 3 codes developed for the individual samples in the Progenetix collection.

NCIT and ICD-O 3

While NCIT treats diseases as **histologic** and **topographic** described entities (e.g. [NCIT:C7700: Ovarian adenocarcinoma](#)), these two components are represented separately in ICD-O, through the **Morphology** and **Topography** coding arms (e.g. here [8140/3 + C56.9](#)).

More documentation with focus on the API functionality can be found on the [documentation pages](#).

The data of all mappings can be retrieved trough this API call: [{JSON ↗}](#)

Code Selection ⓘ

NCIT:C4337: Mantle Cell Lymphoma X | ▾

Optional: Limit with second selection | ▾

Matching Code Mappings [{JSON ↗}](#)

NCIT:C4337: Mantle Cell Lymphoma	pgx:icdom-96733: Mantle cell lymphoma	pgx:icdot-C77.9: Lymph nodes, NOS
NCIT:C4337: Mantle Cell Lymphoma	pgx:icdom-96733: Mantle cell lymphoma	pgx:icdot-C18.9: large intestine, excl. rectum and rectosigmoid junction
NCIT:C4337: Mantle Cell Lymphoma	pgx:icdom-96733: Mantle cell lymphoma	pgx:icdot-C42.2: Spleen

More than one code groups means that either mappings need refinements (e.g. additional specific NCIT classes for ICD-O T topographies) or you started out with an unspecific ICD-O M class and need to add a second selection.

In Progenetix all cancer diagnoses are coded to both NCIt neoplasm codes and ICD-O 3 Morphology + Topography combinations. The matched mappings are provided as lookup-service since neither an official ICD-O ontology nor such a "disease defined by ICD-O M+T" concept is codified anywhere.

List of filters recognized by different query endpoints

Public Ontologies with CURIE-based syntax

CURIE prefix	Code/Ontology	Examples
NCIT	NCIt Neoplasm ¹	NCIT:C27676
HP	HPO ²	HP:0012209
PMID	NCBI Pubmed ID	PMID:18810378
geo	NCBI Gene Expression Omnibus ³	geo:GPL6801, geo:GSE19399, geo:GSM491153
arrayexpress	EBI ArrayExpress ⁴	arrayexpress:E-MEXP-1008
cellosaurus	Cellosaurus - a knowledge resource on cell lines ⁵	cellosaurus:CVCL_1650
UBERON	Uberon Anatomical Ontology ⁶	UBERON:0000992
cBioPortal	cBioPortal ⁹	cBioPortal:msk_impact_2017

Private filters

Since some classifications cannot directly be referenced, and in accordance with the upcoming Beacon v2 concept of "private filters", Progenetix uses additionally a set of structured non-CURIE identifiers.

For terms with a `pgx` prefix, the [identifiers.org resolver](#) will

Filter prefix / local part	Code/Ontology	Example
pgx:icdom...	ICD-O 3 ⁷ Morphologies (Progenetix)	pgx:icdom-81703
pgx:icdot...	ICD-O 3 ⁷ Topographies(Progenetix)	pgx:icdot-C04.9
TCGA	The Cancer Genome Atlas (Progenetix) ⁸	TCGA-000002fc-53a0-420e-b2aa-a40a358bba37
pgx:pgxcohort...	Progenetix cohorts ¹⁰	pgx:pgxcohort-arraymap

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



Cold
Spring
Harbor
Laboratory

bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

New Results

cancercelllines.org - a Novel Resource for Genomic Variants in Cancer Cell Lines

Rahel Paloots, Michael Baudis

doi: <https://doi.org/10.1101/2023.12.12.571281>

This article is a preprint and has not been certified by peer review [what does this mean?].

The screenshot shows the cancercelllines.org website. At the top is a pink header bar. Below it is a navigation menu with the following items: cancercelllines (with a pink circular icon), Cancer Cell Lines (with a magnifying glass icon), Search Cell Lines, Cell Line Listing, CNV Profiles by Cancer Type, Documentation, News, and Progenetix (which is highlighted in grey). Under Progenetix are links for Progenetix Data, Progenetix Documentation, and Publication DB.

Cancer Cell Lines by Cellosaurus ID

The cancer cell lines in [cancercelllines.org](#) are labeled by their parentage hierarchically: Daughter cell lines are displayed below the primary cell line as a daughter cell line of HeLa ([CVCL_0030](#)) and so forth.

Sample selection follows a hierarchical system in which sample selection is done at the level of the parent cell line. For example, a search for HeLa will also return the daughter lines by default - but one can also search for a specific daughter line.

Cell Lines (with parental/derived hierarchies)

The screenshot shows a hierarchical tree view of cell lines under the HOS node. The tree starts with HOS (cellosaurus:CVCL_0312) and branches into cellosaurus:CVCL_0312: HOS (204 samples), cellosaurus:CVCL_1575: NCI-H650 (6 samples), cellosaurus:CVCL_1783: UM-UC-3 (9 samples), cellosaurus:CVCL_0004: K-562 (28 samples), cellosaurus:CVCL_3827: K562/Ad (1 sample), and cellosaurus:CVCL_0589: Kasumi-1 (9 samples). A 'Filter subsets e.g. by prefix' input field and a 'Hierarchy Depth' dropdown are visible at the top of the tree.

Assembly: GRCh38 Chro: NC_000007.14 Start: 140713328 End: 140924929

Type: SNV

cellz

Matched Samples: 1058
Retrieved Samples: 1000
Variants: 127
Calls: 1444

UCSC region ↗
Variants in UCSC ↗
Dataset Responses (JSON) ↗

Visualization options

Results Biosamples Variants Annotated Variants

Digest	Gene	Pathogenicity	Variant type	Variant Instances
7:140834768-140834769:G>A	BRAF		Missense variant	V: pgxvar-63ce6abca24c83054b B: pgxbs-3DfBeeAC
7:140734714-140734715:G>A	BRAF		Missense variant	V: pgxvar-63ce6acda24c83054b B: pgxbs-3fB2a14B
7:140753334-140753339:T>TGTA	BRAF	Pathogenic		V: pgxvar-72d54b

Cell Line Details

HOS (cellosaurus:CVCL_0312)

Subset Type

- Cellosaurus - a knowledge resource on cell lines [cellosaurus:CVCL_0312](#) ↗

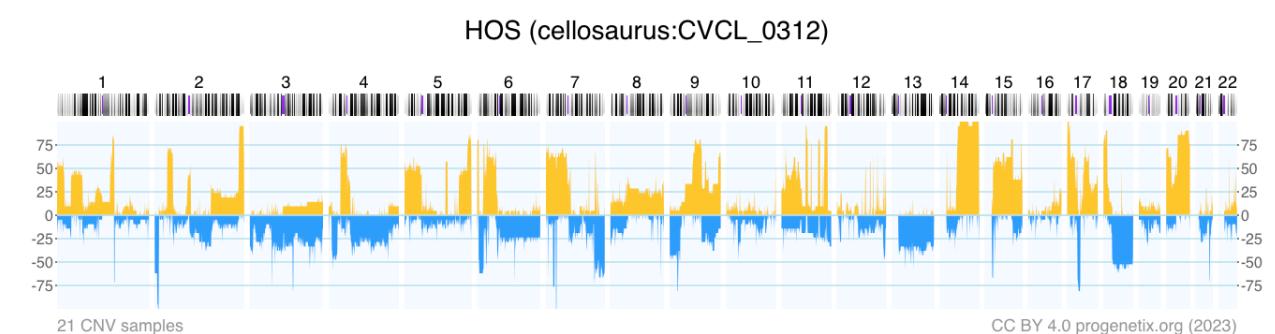
Sample Counts

- 204 samples
- 57 direct cellosaurus:CVCL_0312 code matches
- 21 CNV analyses

Search Samples

Select cellosaurus:CVCL_0312 samples in the [Search Form](#)

Raw Data (click to show/hide)



Download SVG | Go to cellosaurus:CVCL_0312 | Download CNV Frequencies

Gene Matches	Cytoband Matches	Variants	Abstract
ALK	. ABC-14 cells harbored no ALK mutations and were sensitive to ... crizotinib while also exhibiting MNNG HOS transforming gene (MET)	Rapid Acquisition of Alectinib Resistance in ALK-Positive Lung Cancer With High Tumor Mutation Burden (31374369)	
AREG	crizotinib while also exhibiting MNNG HOS	Rapid Acquisition of Alectinib Resistance	ABSTRACT

{Bio|informatics}Science}

```
for t in pars.keys():

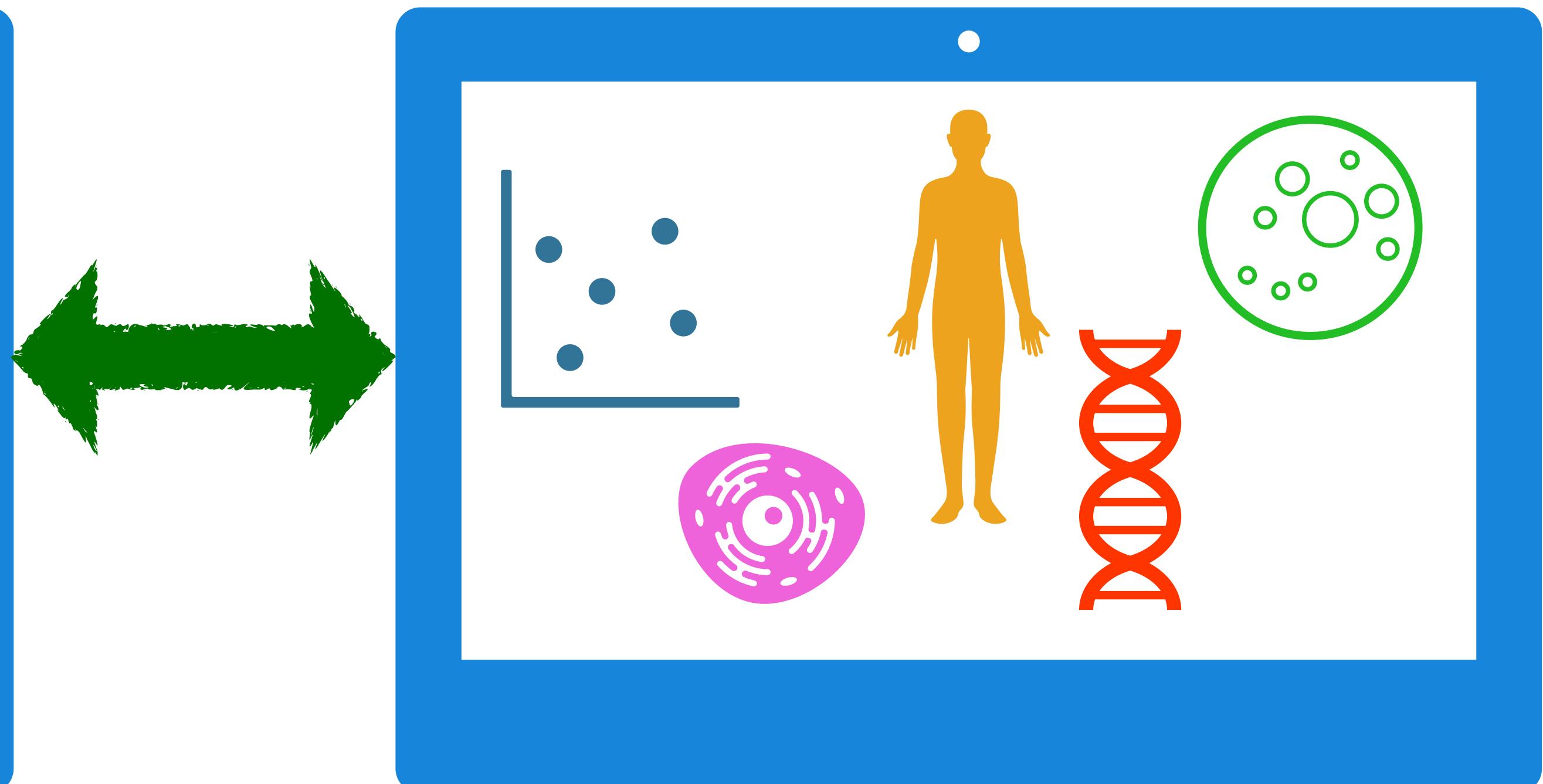
    covs = np.zeros((cs_no, int_no))
    vals = np.zeros((cs_no, int_no))

    if type(callsets).__name__ == "Cursor":
        callsets.rewind()

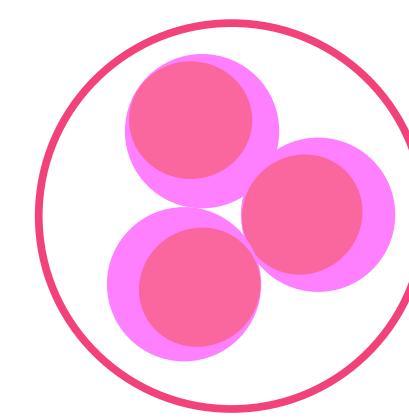
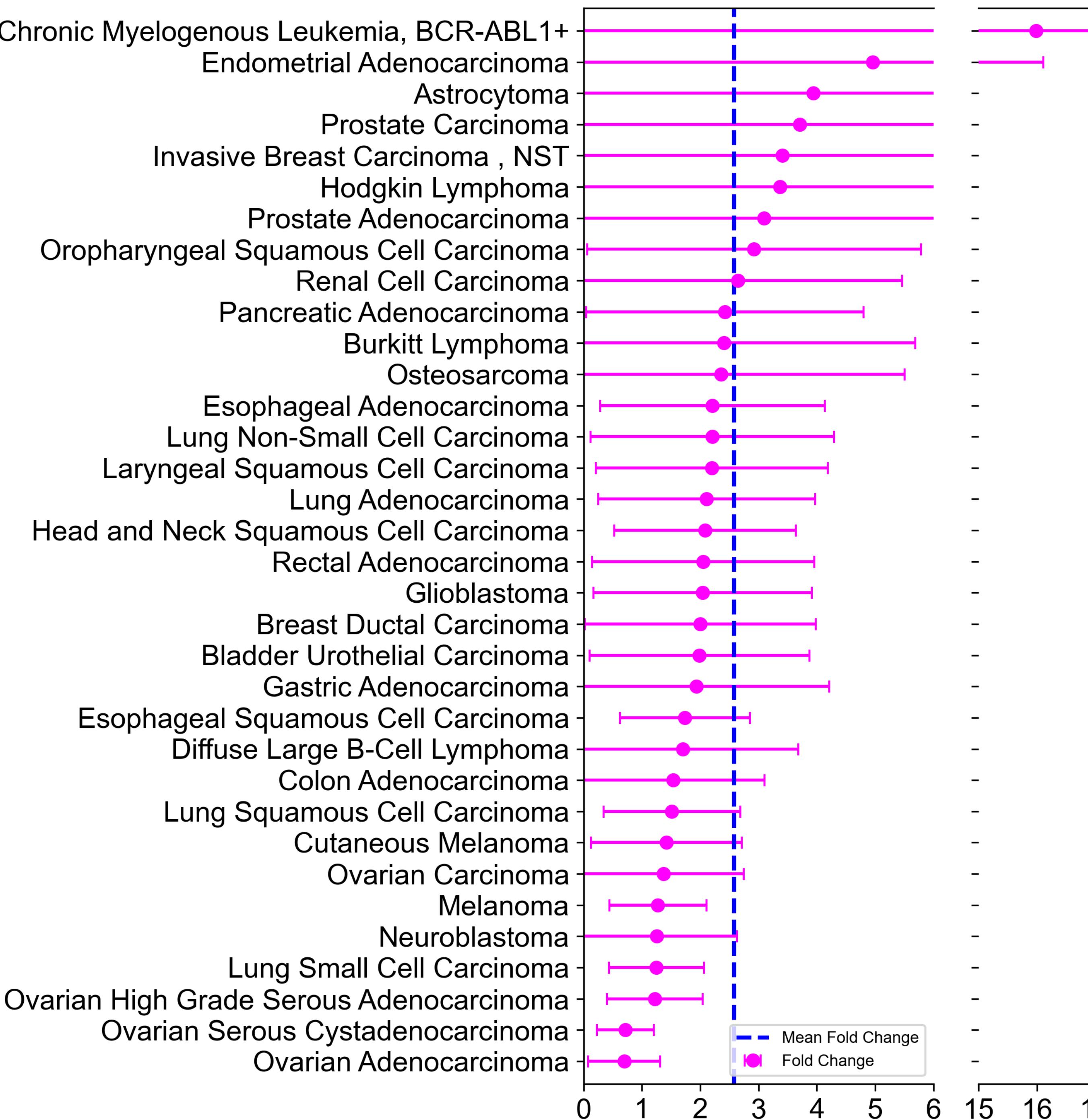
    for i, cs in enumerate(callsets):
        covs[i] = cs["cnv_statusmaps"][pars[t]["cov_l"]]
        vals[i] = cs["cnv_statusmaps"][pars[t]["val_l"]]

    counts = np.count_nonzero(covs >= min_f, axis=0)
    frequencies = np.around(counts * f_factor, 3)
    medians = np.around(np.ma.median(np.ma.masked_where(covs < min_f, vals), axis=0).filled(0), 3)
    means = np.around(np.ma.mean(np.ma.masked_where(covs < min_f, vals), axis=0).filled(0), 3)

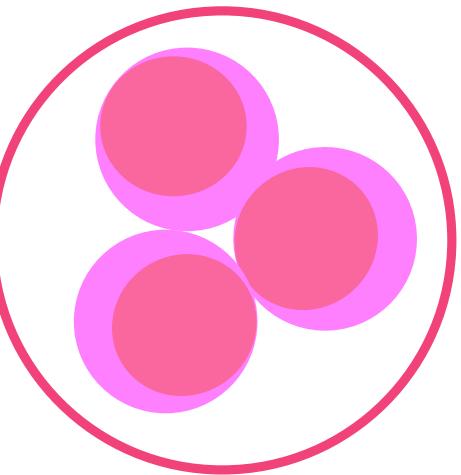
    for i, interval in enumerate(int_fs):
        int_fs[i].update({
            t + "_frequency": frequencies[i],
            t + "_median": medians[i],
            t + "_mean": means[i]
        })
```



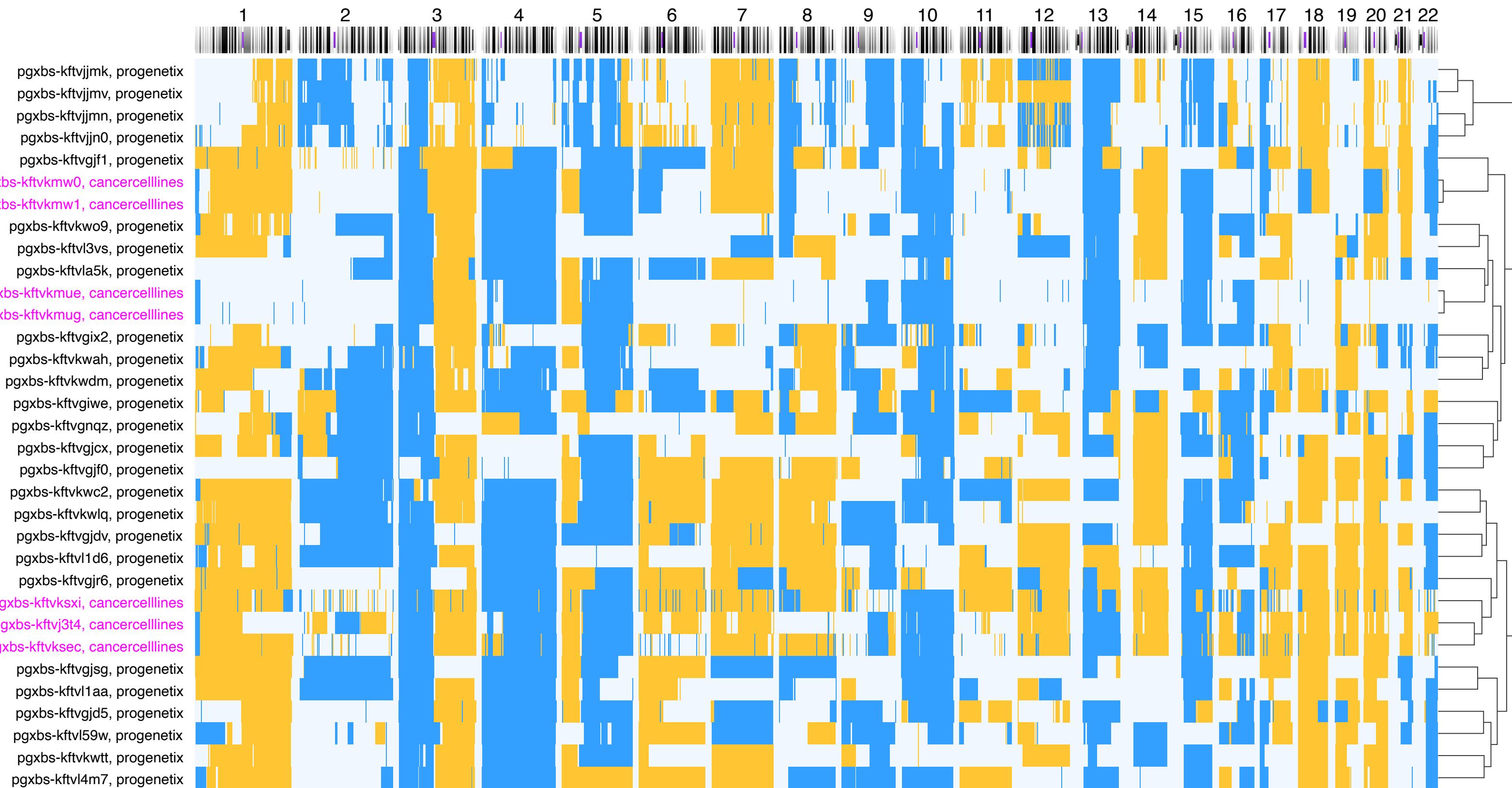
Higher level of CNV coverage of the genomes of cancer cell lines compared to their origins



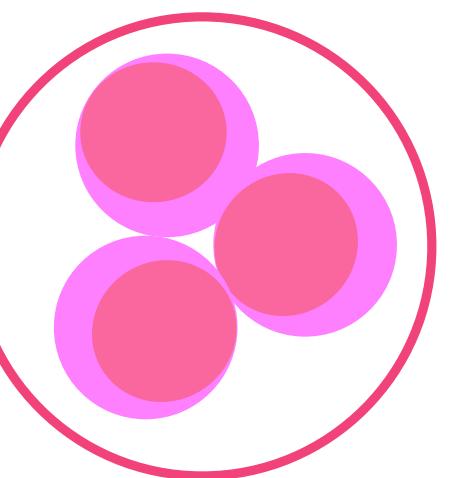
Tumor subpopulations can be matched with highly similar cell lines



- Lung Small Cell Carcinoma Subpopulation
- Cell Lines:
 - CVCL_1140: COR-L279
 - CVCL_1455: NCI-H1105
 - CVCL_1527: NCI-H2107



Tumor subpopulations can be matched with highly similar cell lines?!



Population stratification in cancer samples based on SNP array data

- Despite extensive somatic mutations of cancer profiling data, consistency between germline and cancer samples reached 97% and 92% for 5 and 26 populations
- Comparison of our benchmarked results with self-reported meta-data estimated a matching rate between 88 % to 92%.
- Ethnicity labels indicated in meta-data are vague compared to the standardized output from our tool



Lead: Qingyao Huang

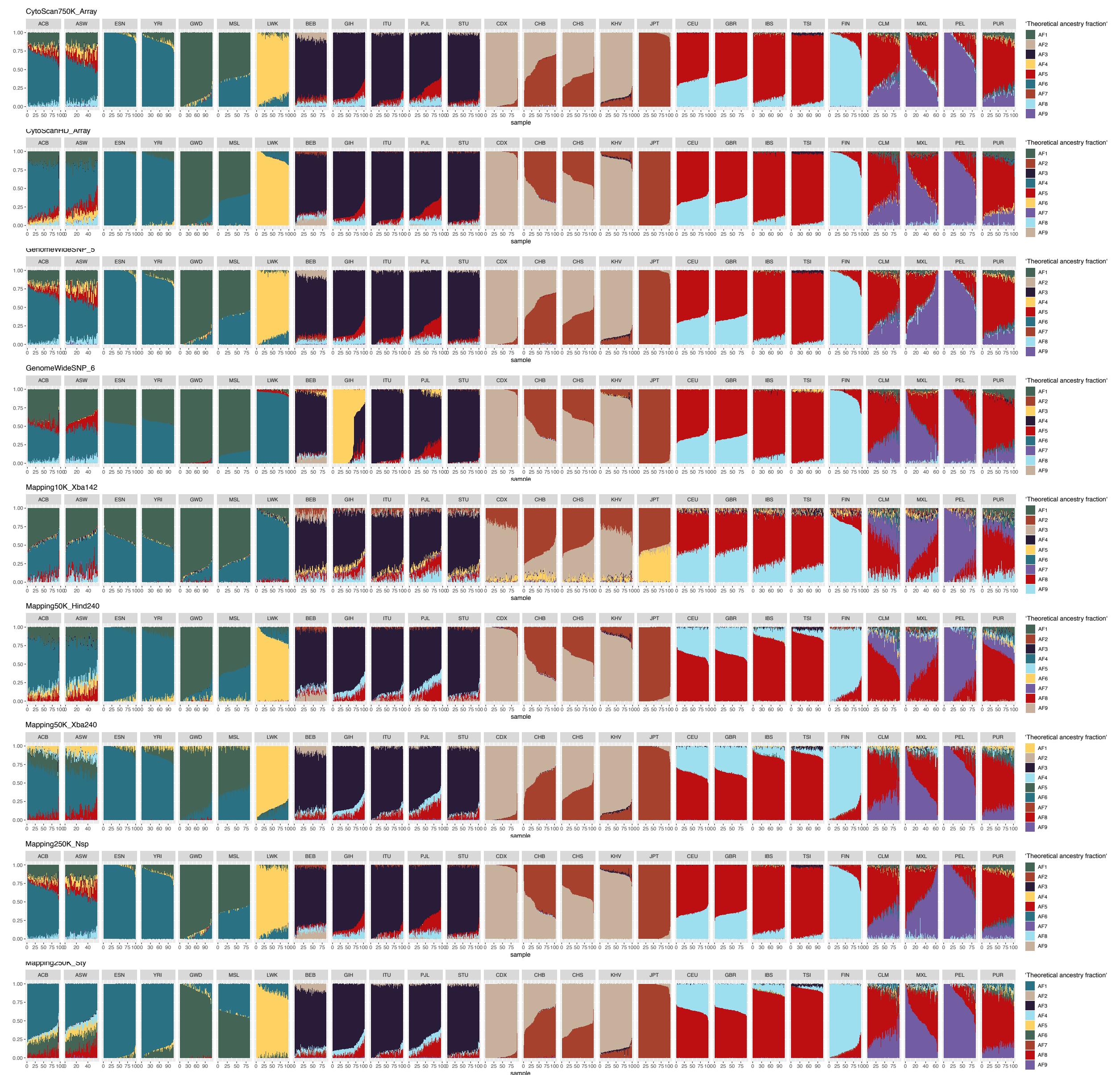
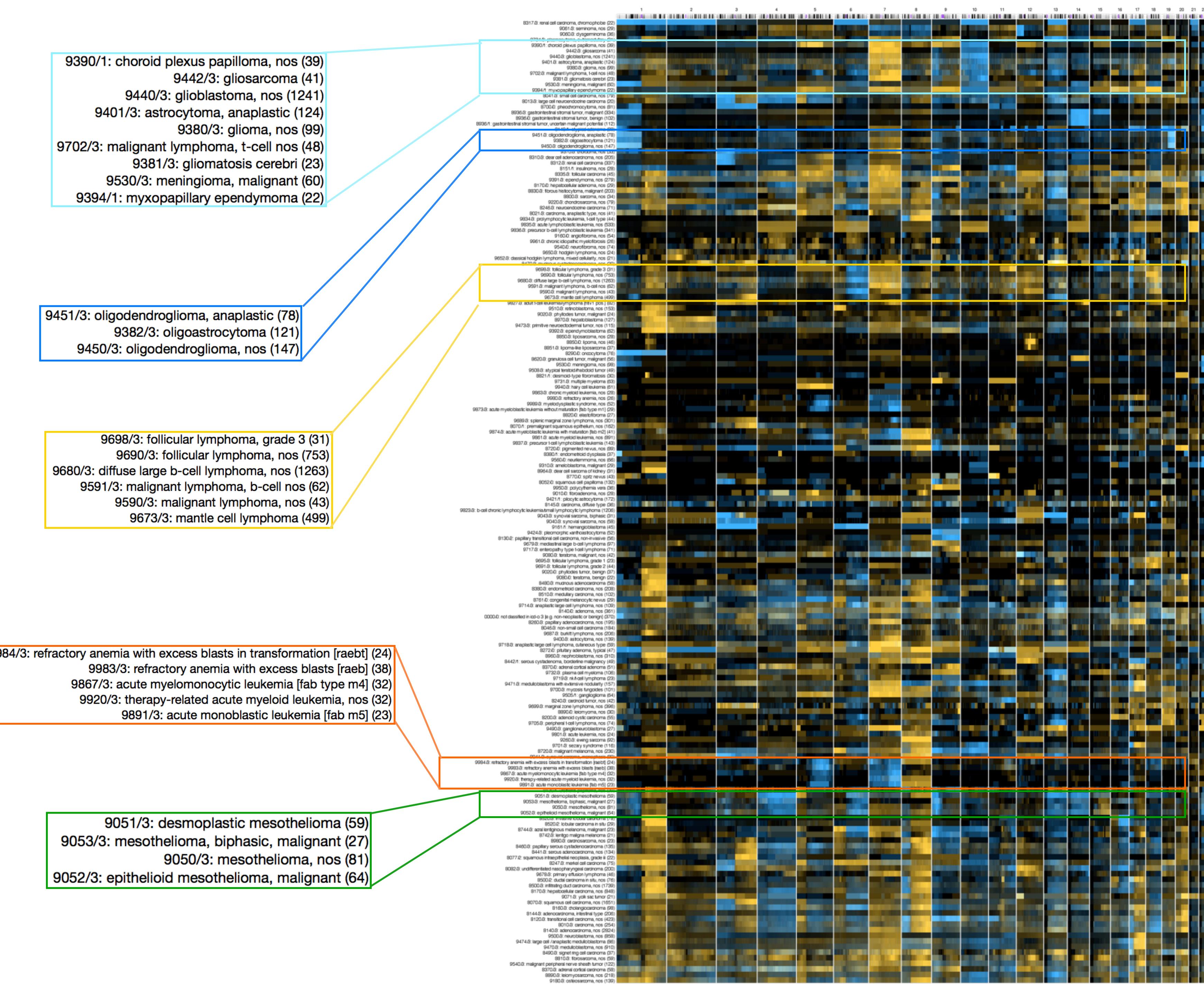


Figure S1 The fraction or contribution of theoretical ancestors ($k=9$) in reference individuals from 1000 Genomes Project with regard to nine SNP array platforms. The x-axis are individual samples, grouped by their respective population. Groups belonging to the same continent/superpopulation are placed neighboring to each other: AFR (1-7), SAS (8-12), EAS (13-17), EUR (18-22), AMR (23-26).

Somatic Mutations In Cancer: Patterns

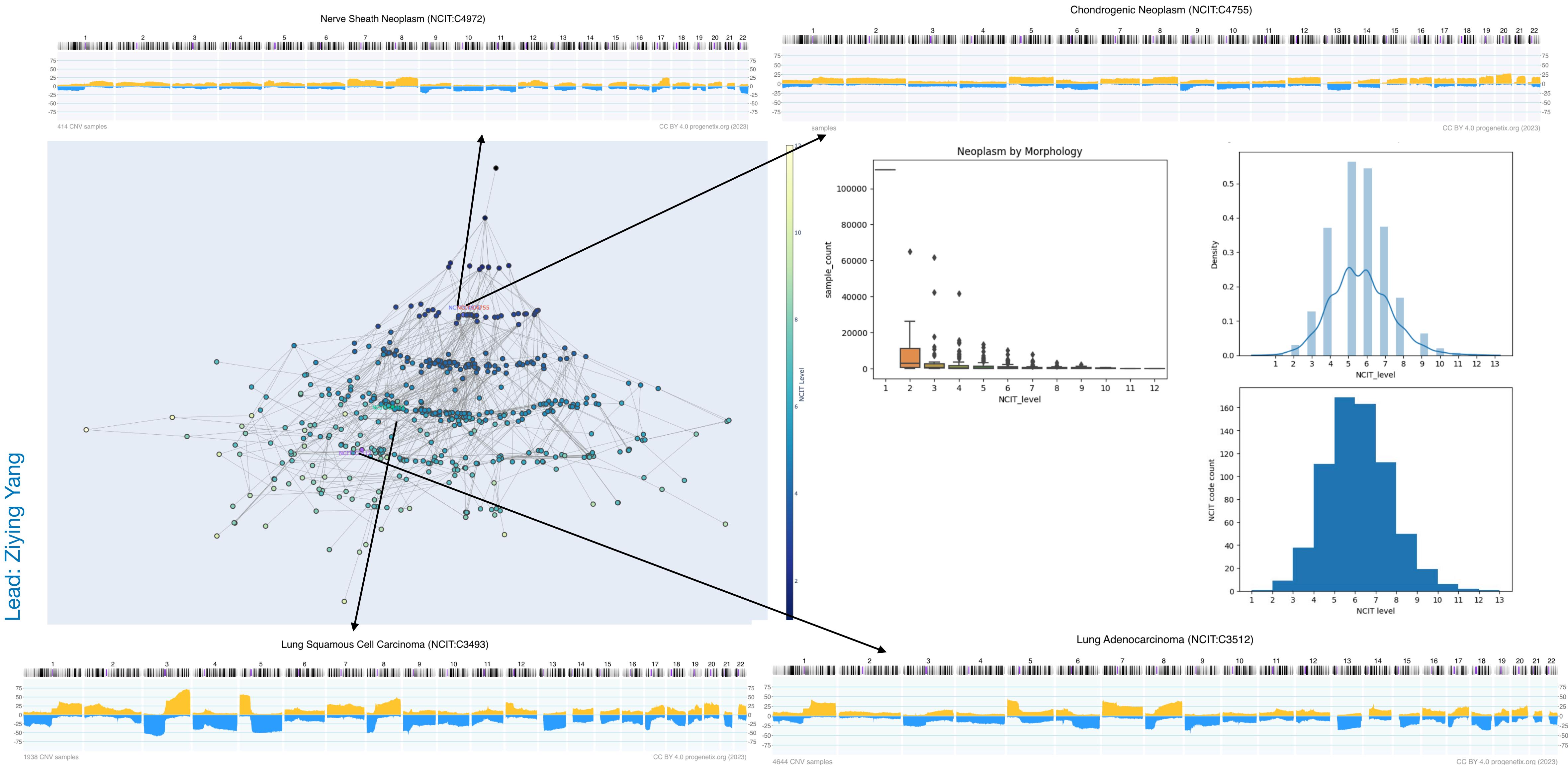
Making the case for genomic classifications

Some related cancer entities show similar copy number profiles



CNV profiles heterogeneity vs cancer classification

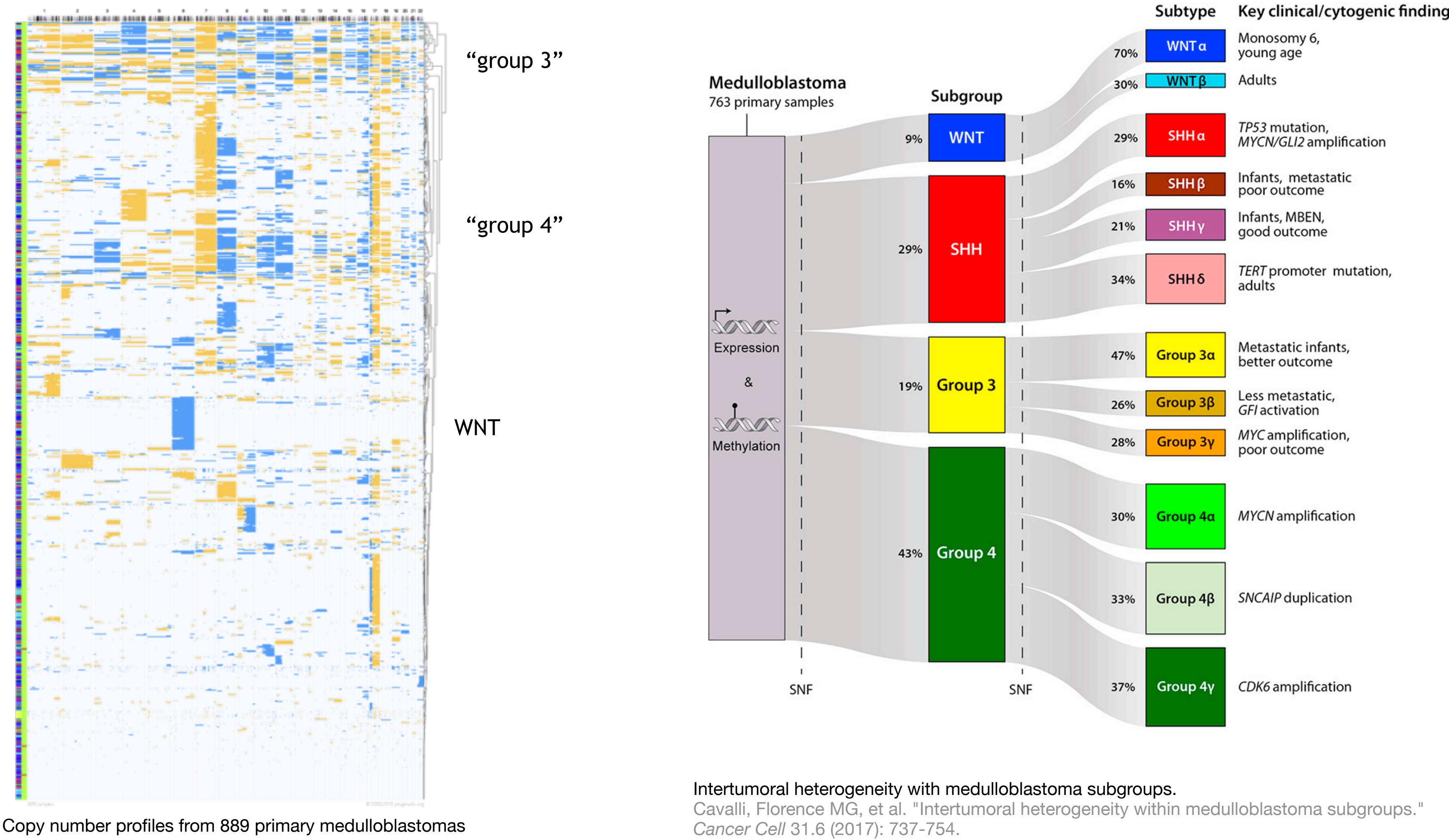
Correspondance of genomic profiles to NCIT cancer hierarchy



CNA & Cancer heterogeneity

Cancer type definitions can be improved by the addition of molecular parameters as subtype markers or even complete re-evaluation of entity definitions from molecular subtypes with distinct functional mechanisms and clinical trajectories.

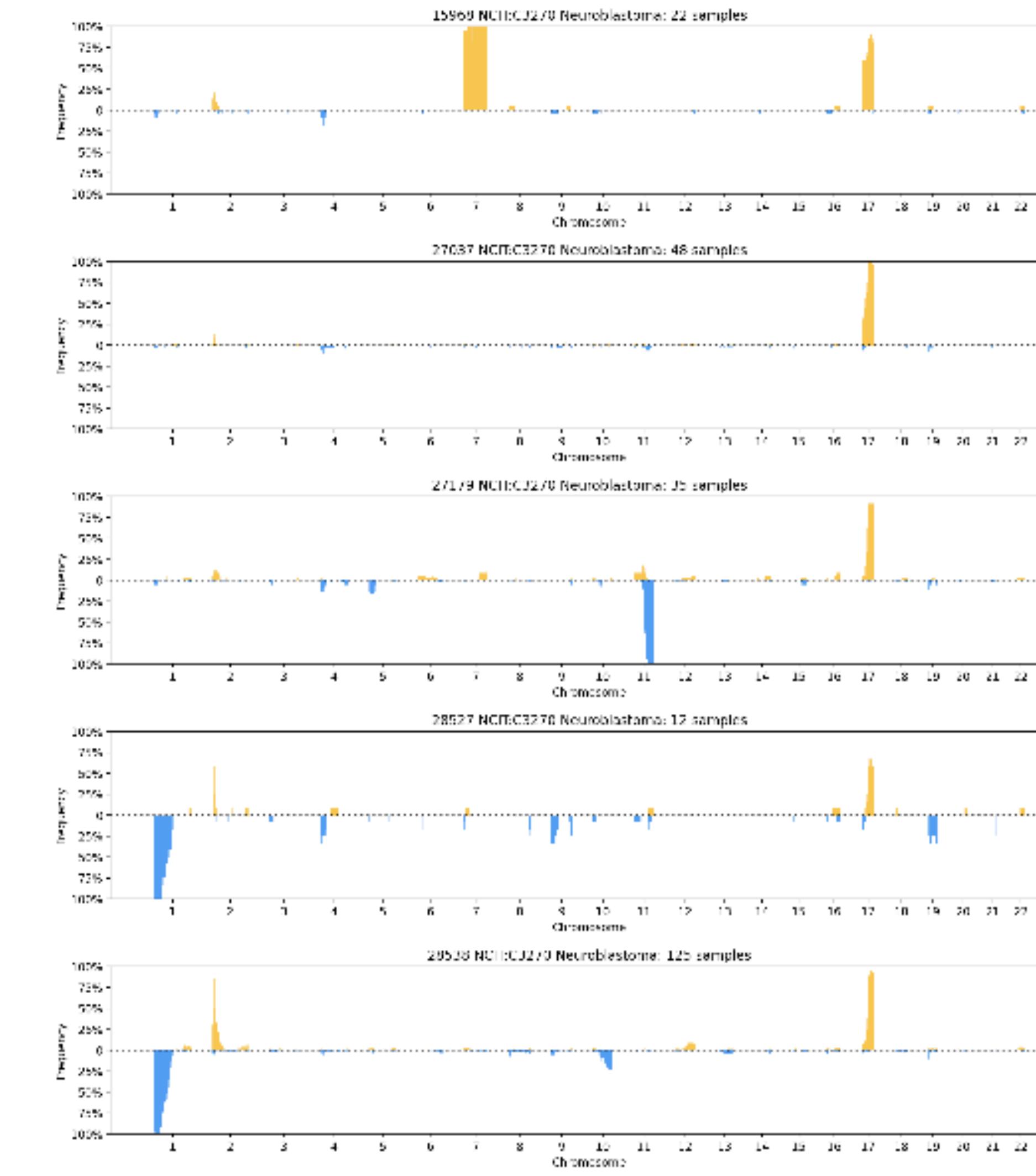
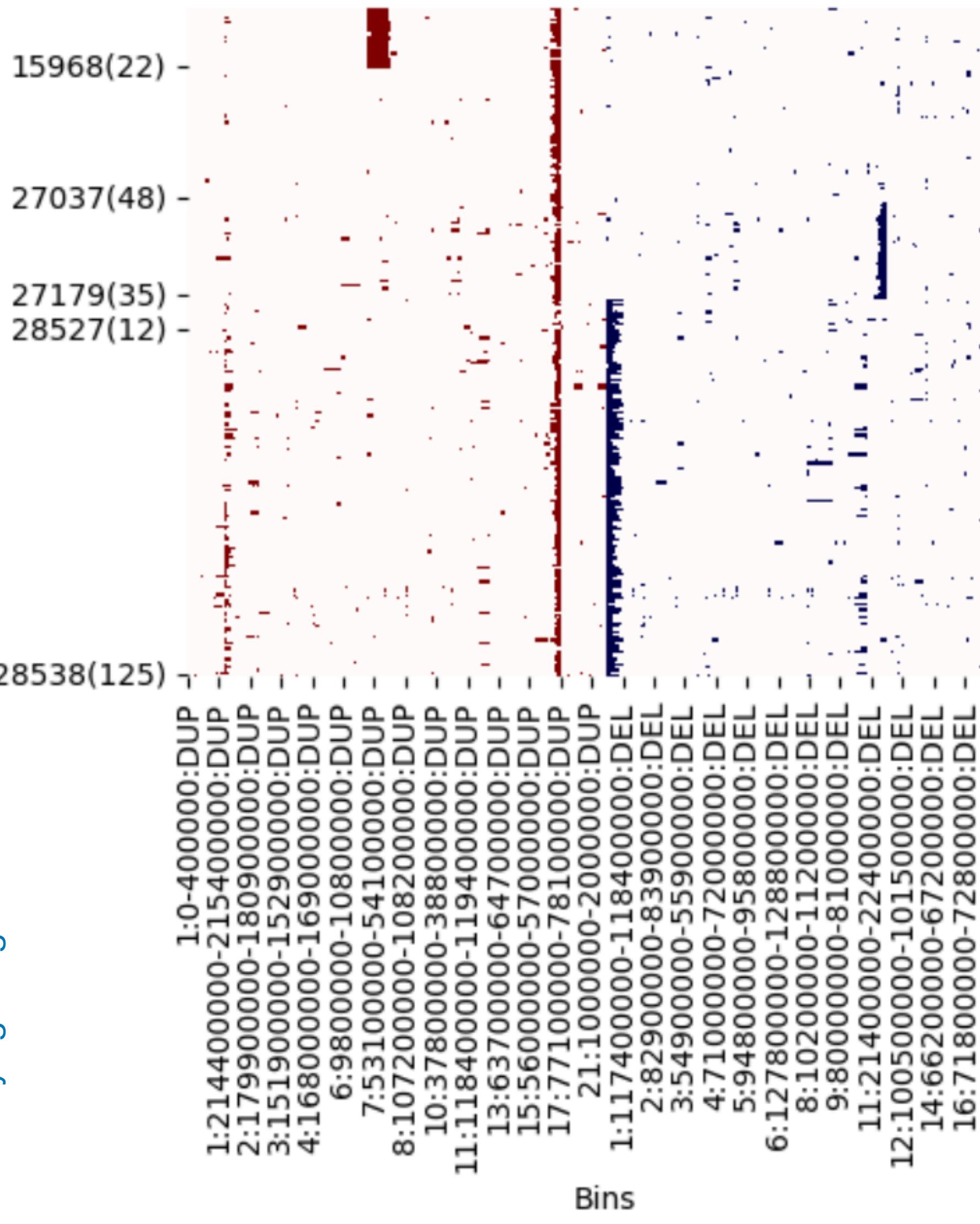
Lead: Ziyang Yang



Results

Entity CNV heterogeneity: Neuroblastoma

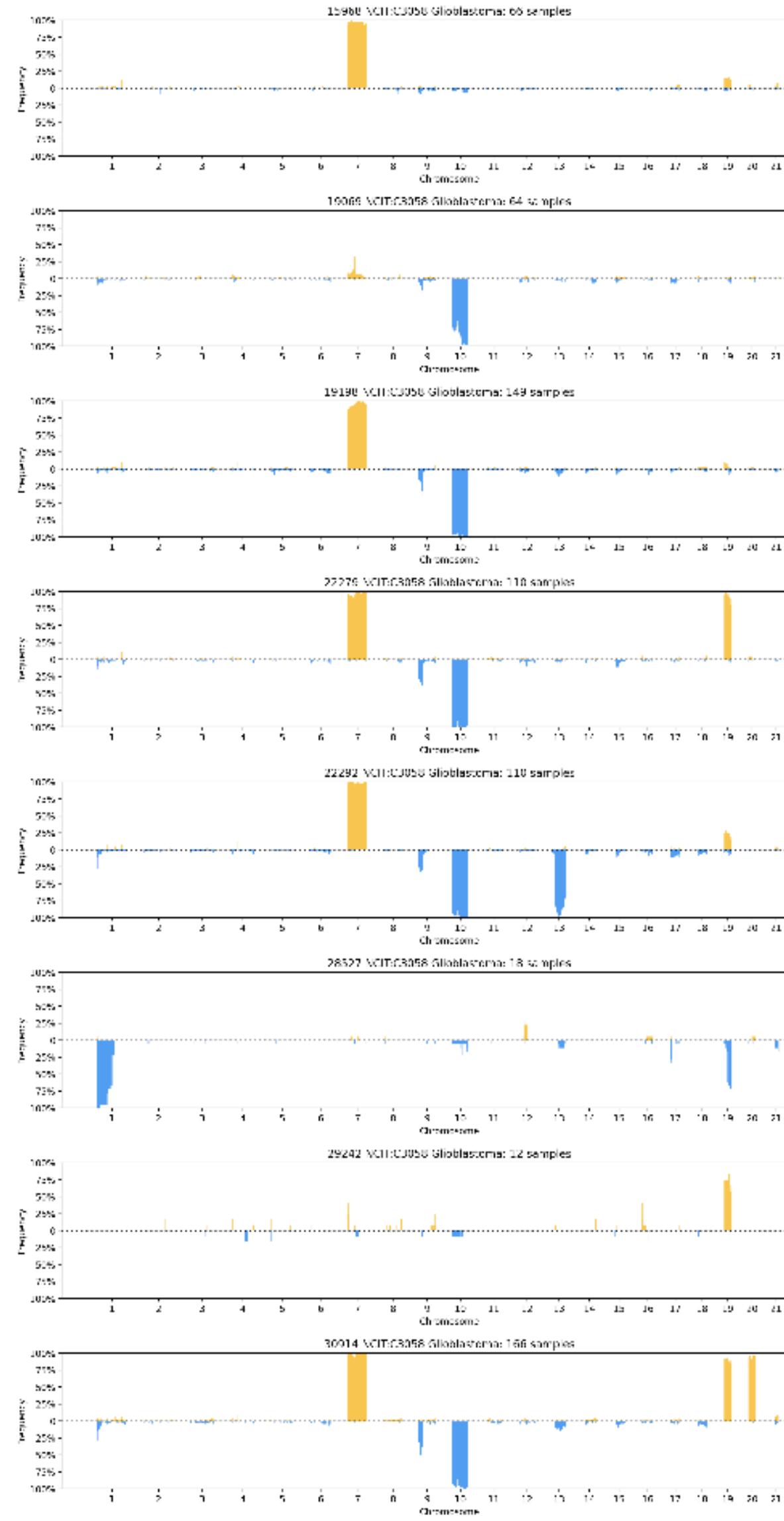
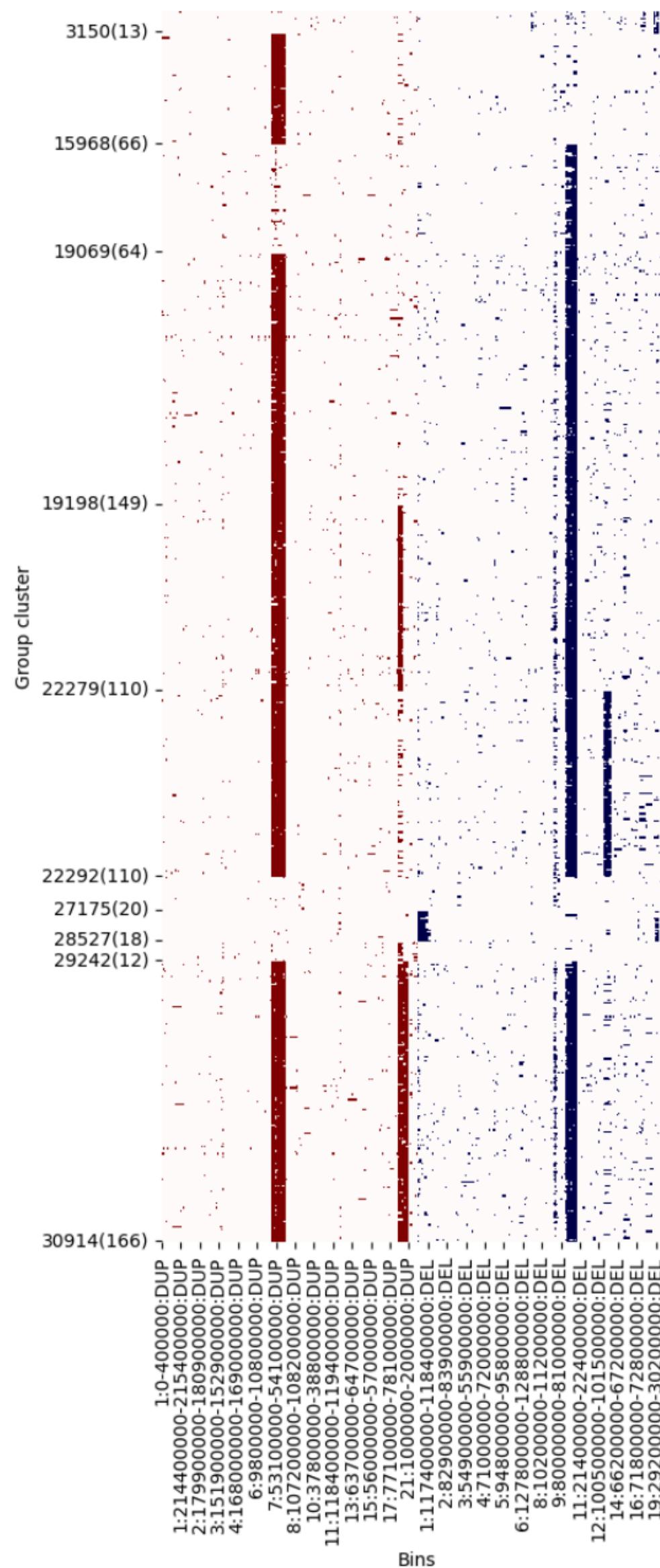
Lead: Ziyi Yang



group cluster	CNV features
15968	Dup 7
27037	Dup 17q
27179	Del 11q, Dup 17q
28527	Del 1p
28538	Del 1p, Dup 17q

Results

Entity CNV heterogeneity: Glioblastoma

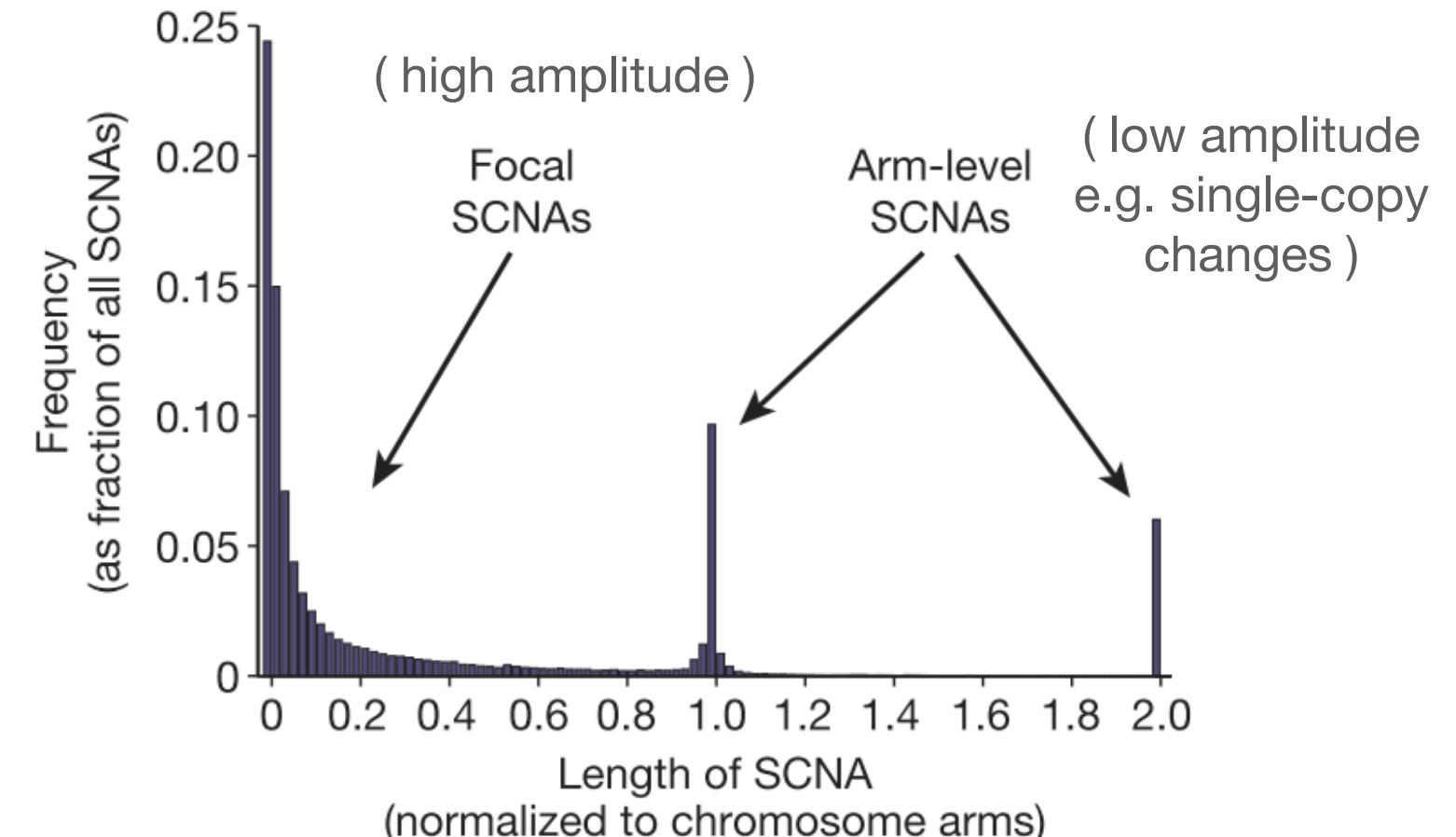


group cluster	CNV features
15968	Dup 7
19069	Del 10
19198	Dup 7, Del 10
22279	Dup 7, Del 10, Dup 19
22292	Dup 7, Del 10, Del 13
27175	Del 1p, Del 19q
28527	Del 1p, Del 19q
29242	Dup 19
30914	Dup 7, Del 10, Dup 19, Dup 20

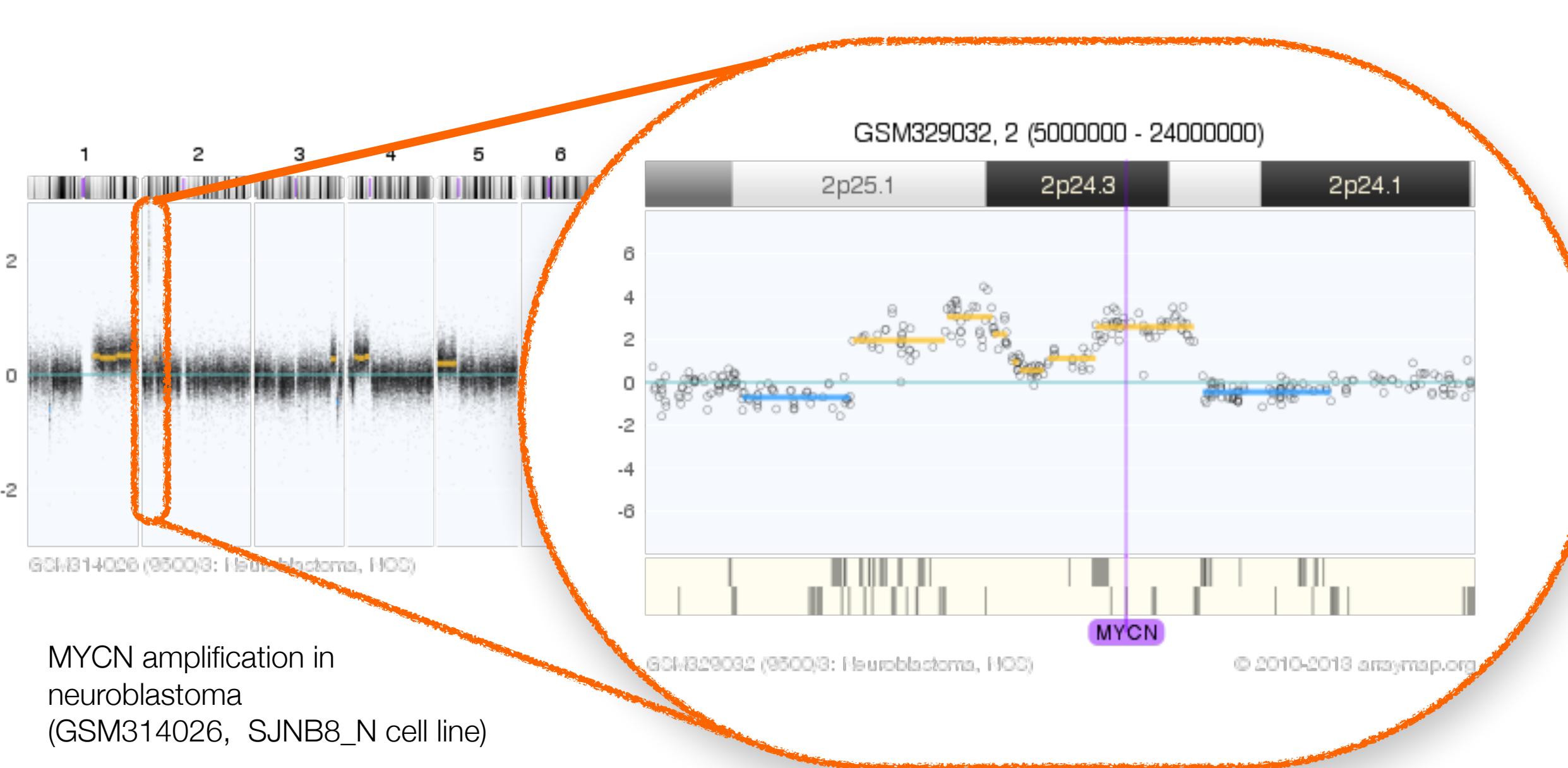


CNV Categorization

different levels of CNV



Rameen et al 2010 Nature



Lead: Hangjia Zhao

CopyNumberChange

Copy Number Change captures a categorization of copies of a molecule within a system, relative to a baseline. These types of Variation are common outputs from CNV callers, particularly in the somatic domain where integral **CopyNumberCount** are difficult to estimate and less useful in practice than relative statements. Somatic CNV callers typically express changes as relative statements, and many HGVS expressions submitted to express copy number variation are interpreted to be relative copy changes.

Computational Definition

An assessment of the copy number of a **Location** or a **Feature** within a system (e.g. genome, cell, etc.) relative to a baseline ploidy.

Information Model

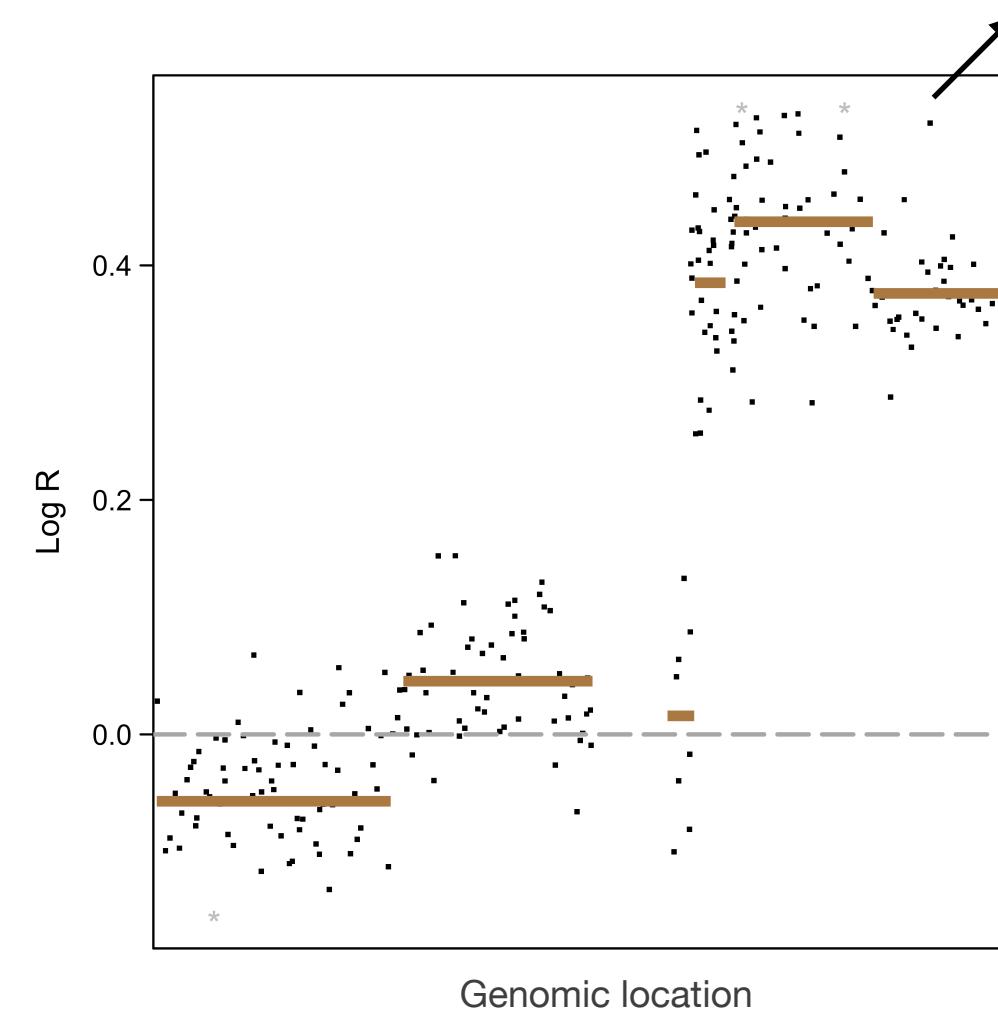
Some CopyNumberChange attributes are inherited from **Variation**.

Field	Type	Limits	Description
_id	CURIE	0..1	Variation Id. MUST be unique within document.
type	string	1..1	MUST be "CopyNumberChange"
subject	Location CURIE Feature	1..1	A location for which the number of systemic copies is described.
copy_change	string	1..1	MUST be one of "efo:0030069" (complete genomic loss), "efo:0020073" (high-level loss), "efo:0030068" (low-level loss), "efo:0030067" (loss), "efo:0030064" (regional base ploidy), "efo:0030070" (gain), "efo:0030071" (low-level gain), "efo:0030072" (high-level gain).

labelSeg

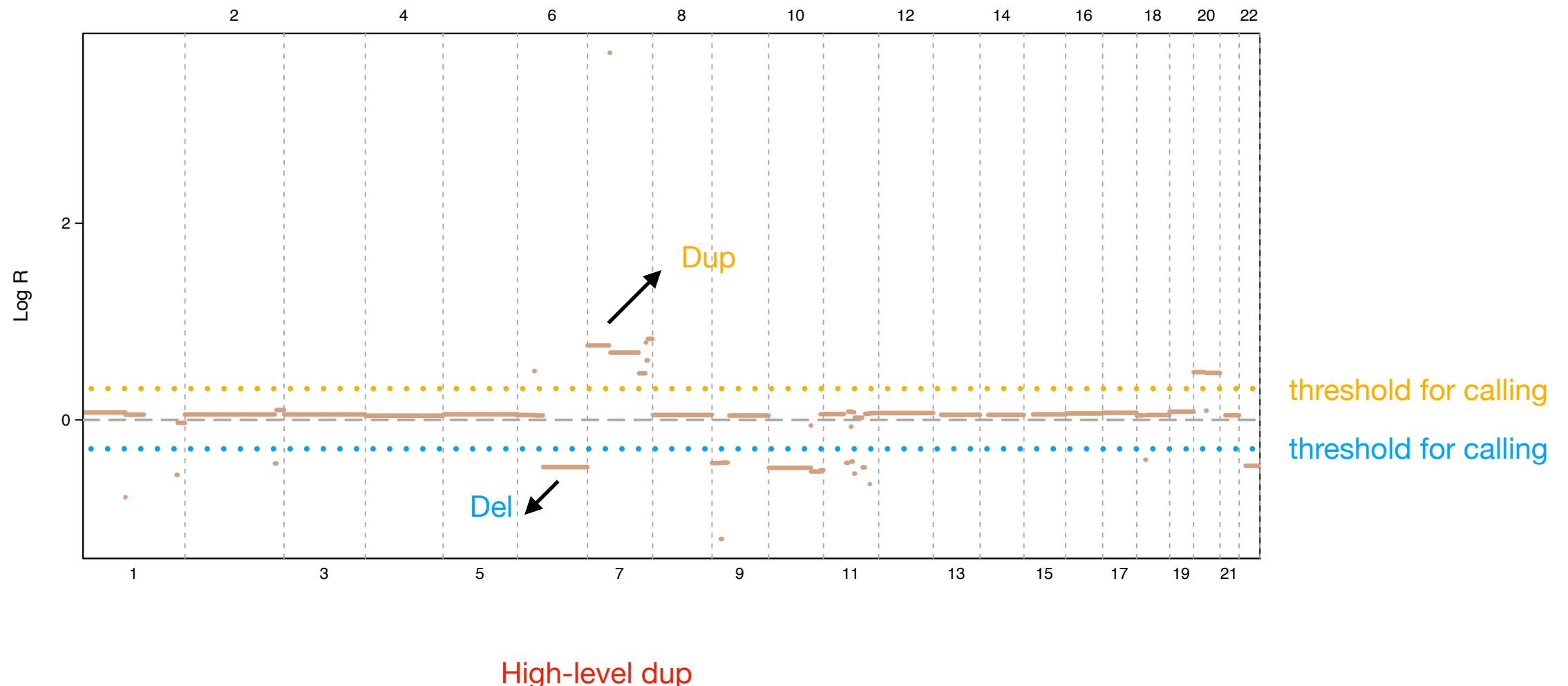
segment annotation for tumor copy number variation profiles

Signal from probes in microarray or from reads in NGS



Segmentation

a step to split the chromosomes into regions of equal copy number that accounts for the noise in the data.



README.md

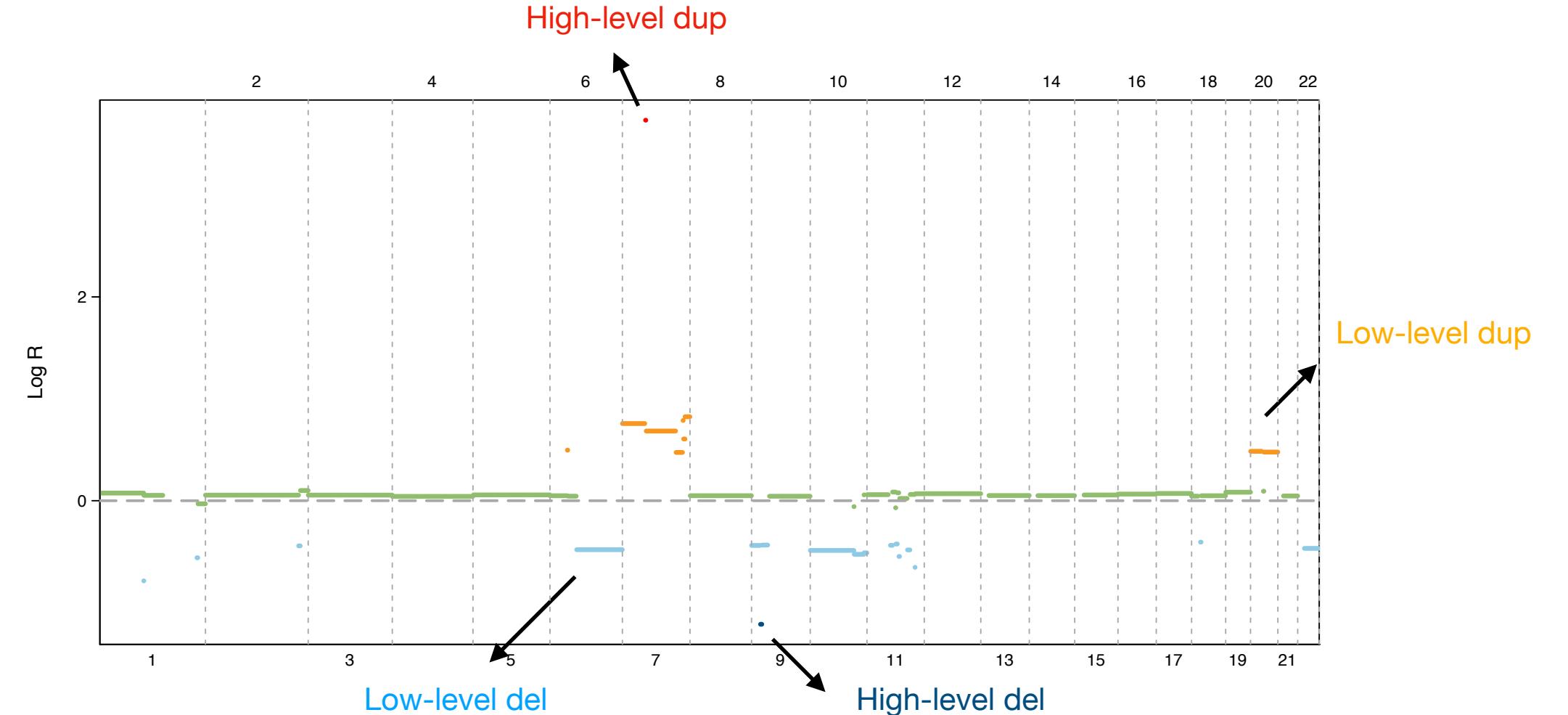
labelSeg

This is an R package designed to identify and label different levels of Copy Number Alterations (CNA) in segmented profiles.

Installation

To install the package, you can use the `devtools` package as follows:

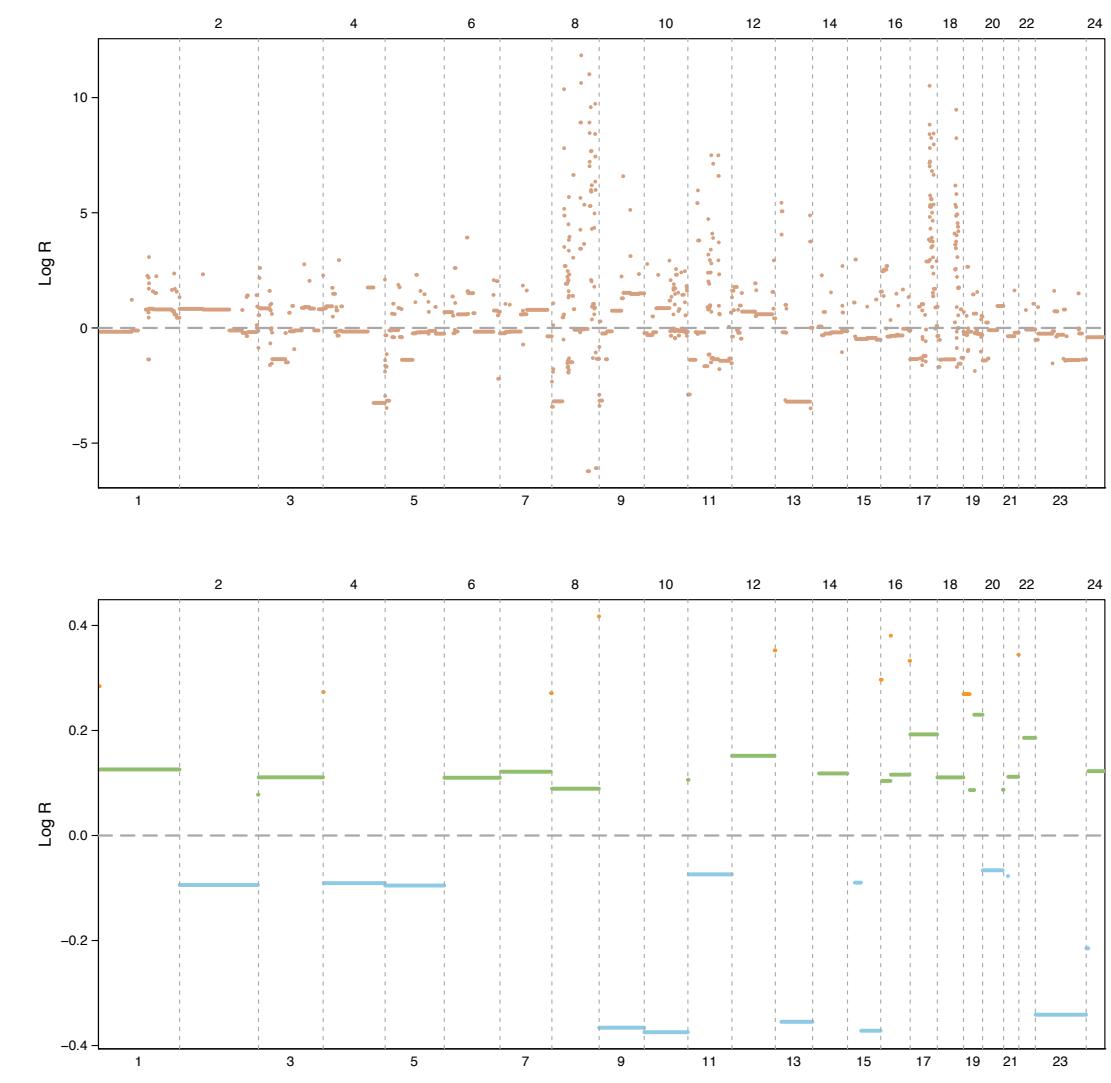
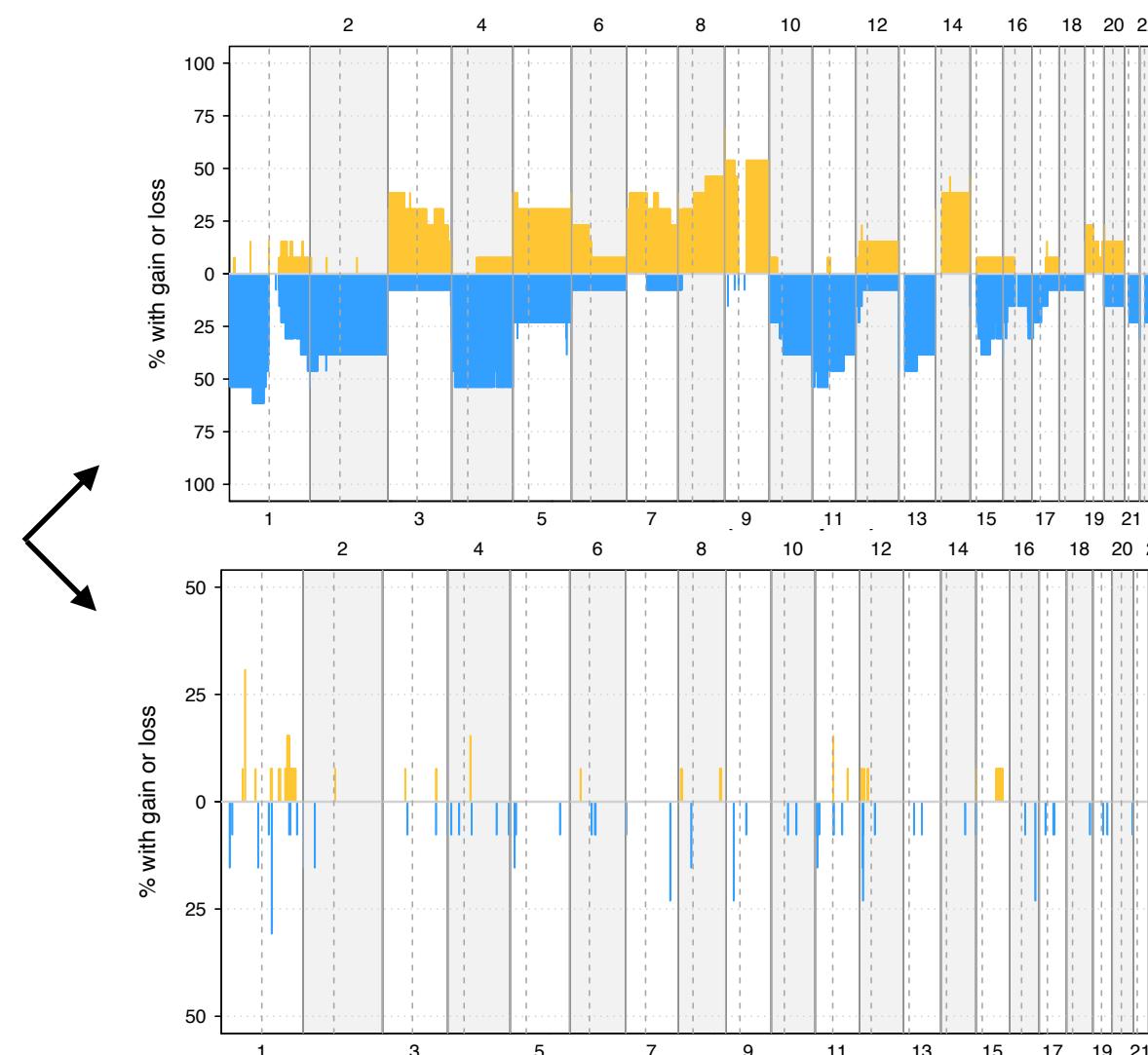
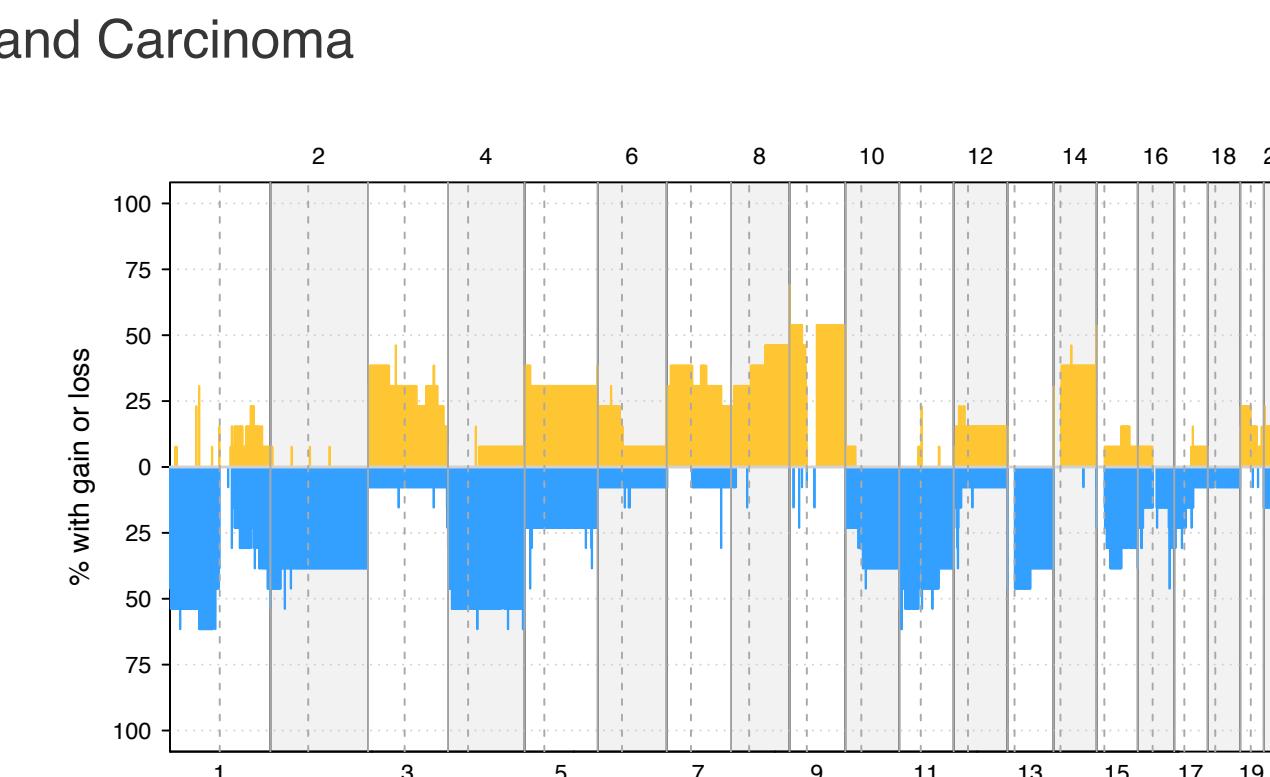
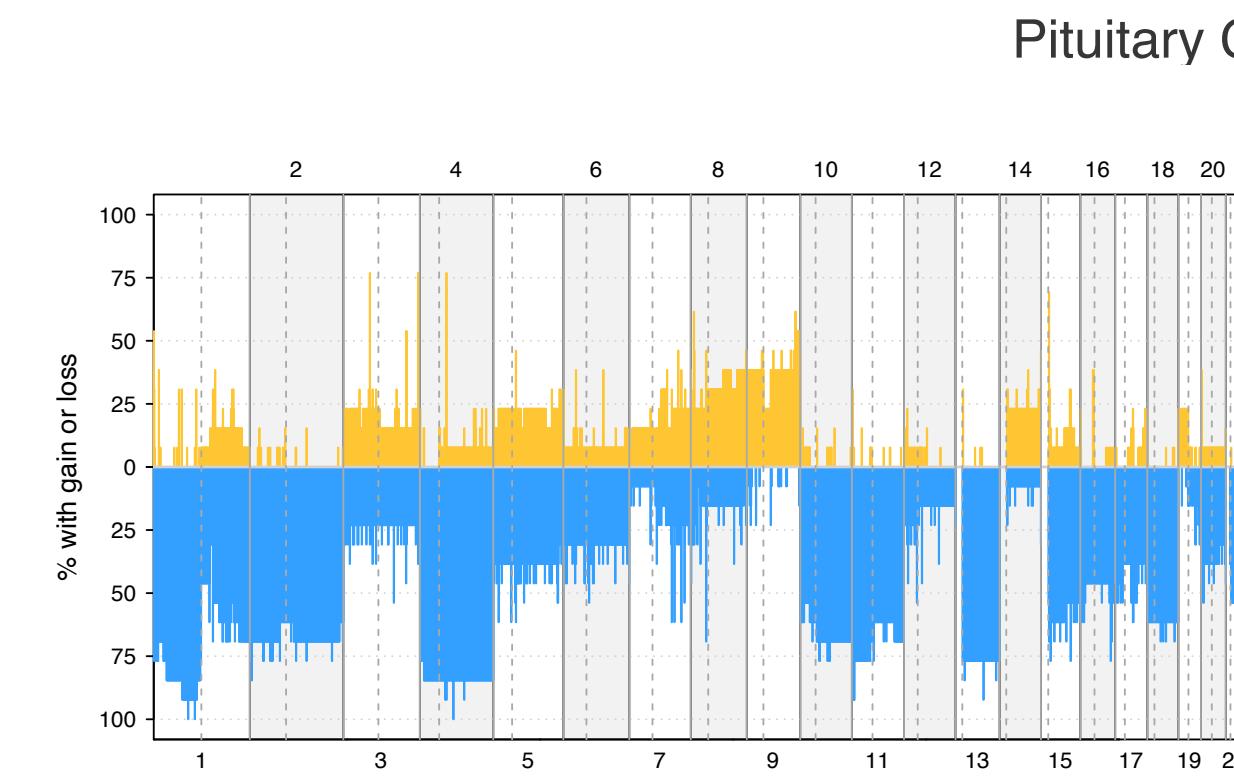
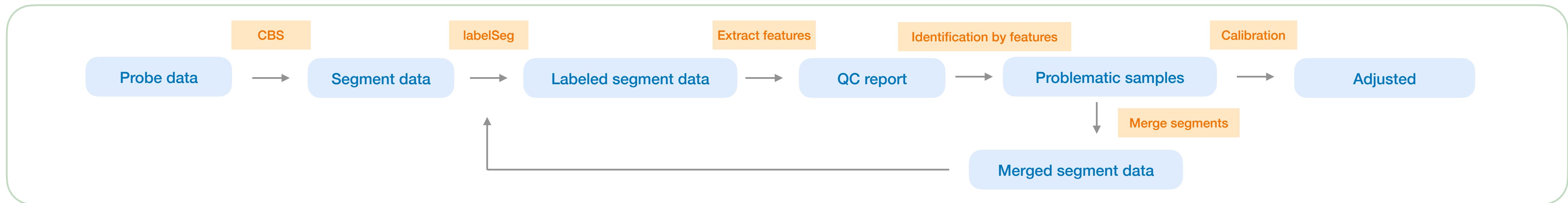
```
install.packages("devtools")
devtools::install_github("baudisgroup/labelSeg")
```



Pipeline Development

improve CNV calling in large numbers of heterogeneous cancer samples

nextflow





CNV Categorization

different levels of CNV



CopyNumberChange

Copy Number Change captures a categorization of copies of a molecule within a system, relative to a reference. It is more useful in practice than absolute statements, and many terms are interpreted to be relative copy numbers. A system (e.g. genome, cell, tissue, individual).

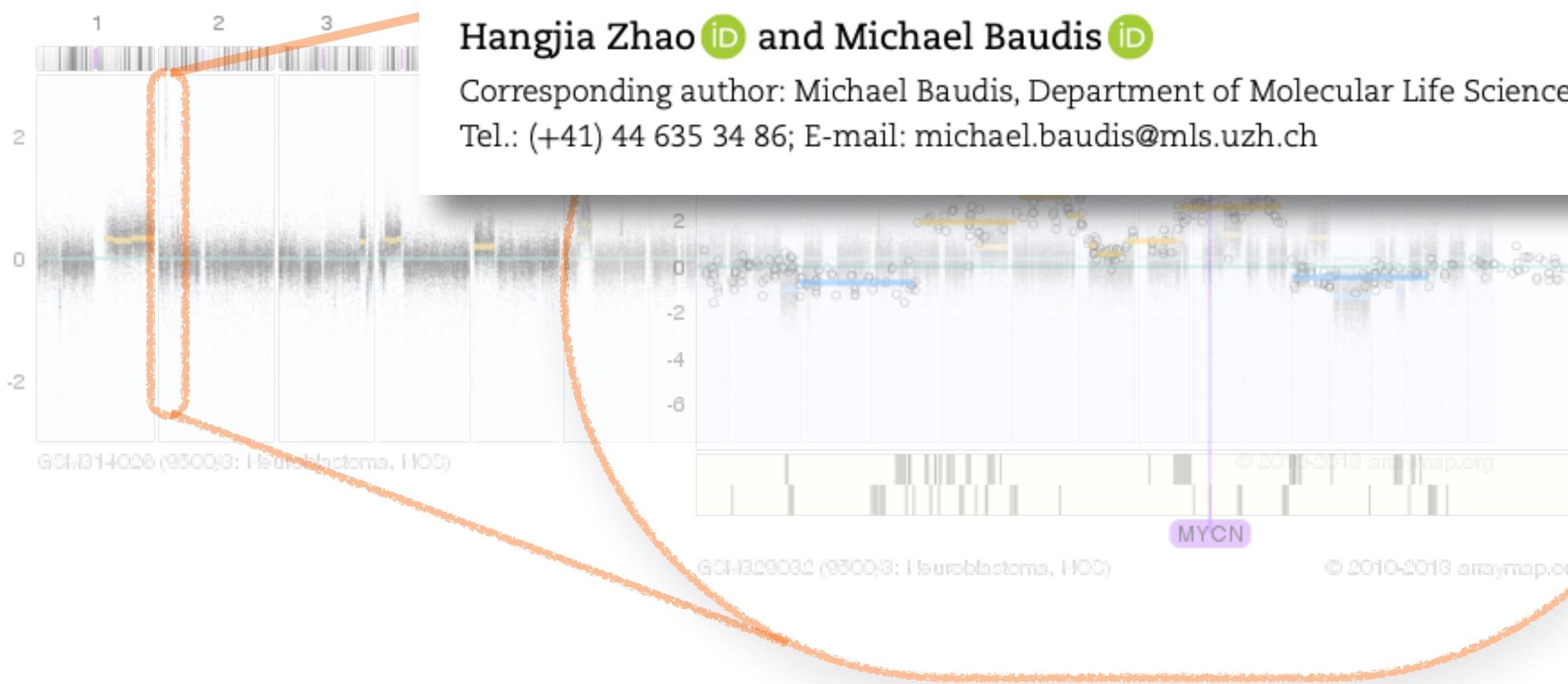
Briefings in Bioinformatics, 2024, 25(2), 1–12
<https://doi.org/10.1093/bib/bbad541>
Problem Solving Protocol

labelSeg: segment annotation for tumor copy number alteration profiles

Hangjia Zhao and Michael Baudis

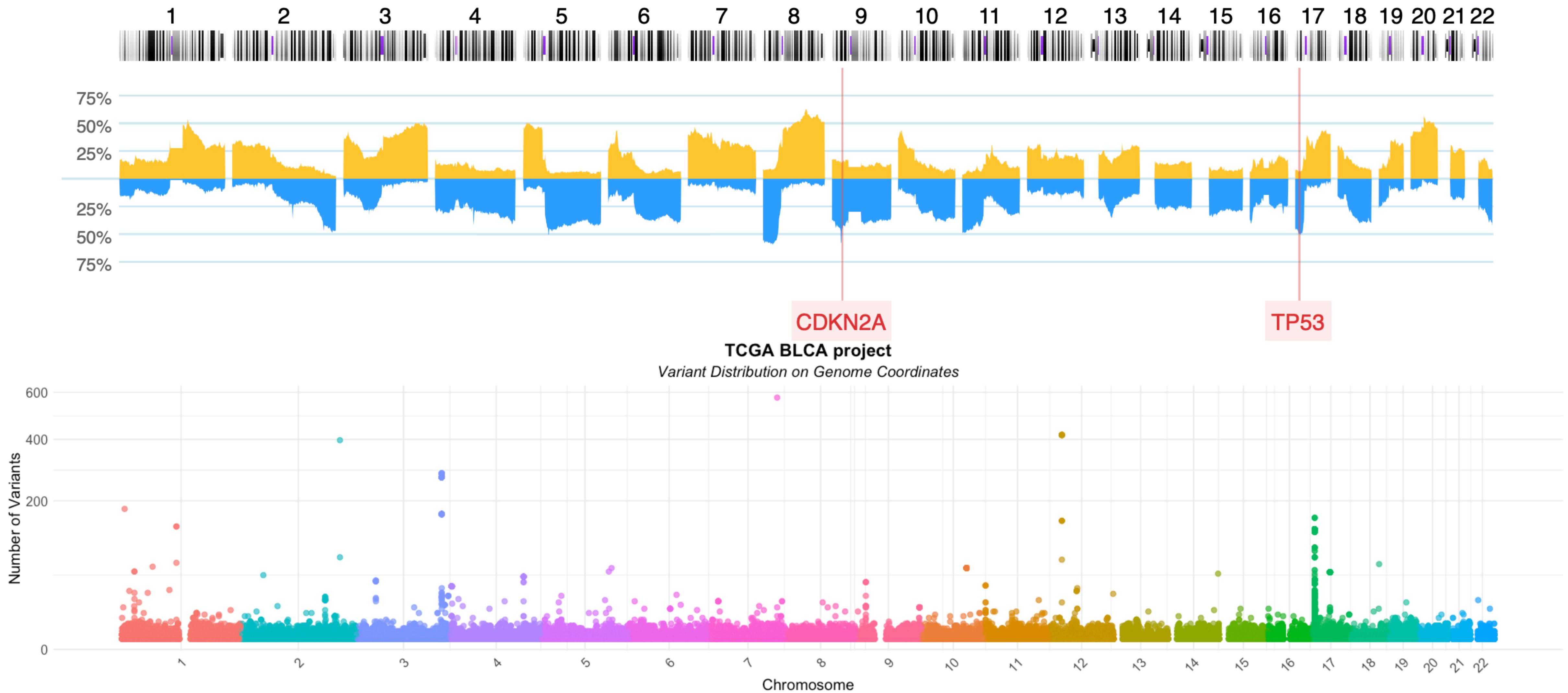
Corresponding author: Michael Baudis, Department of Molecular Life Sciences, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland.

Tel.: (+41) 44 635 34 86; E-mail: michael.baudis@mls.uzh.ch



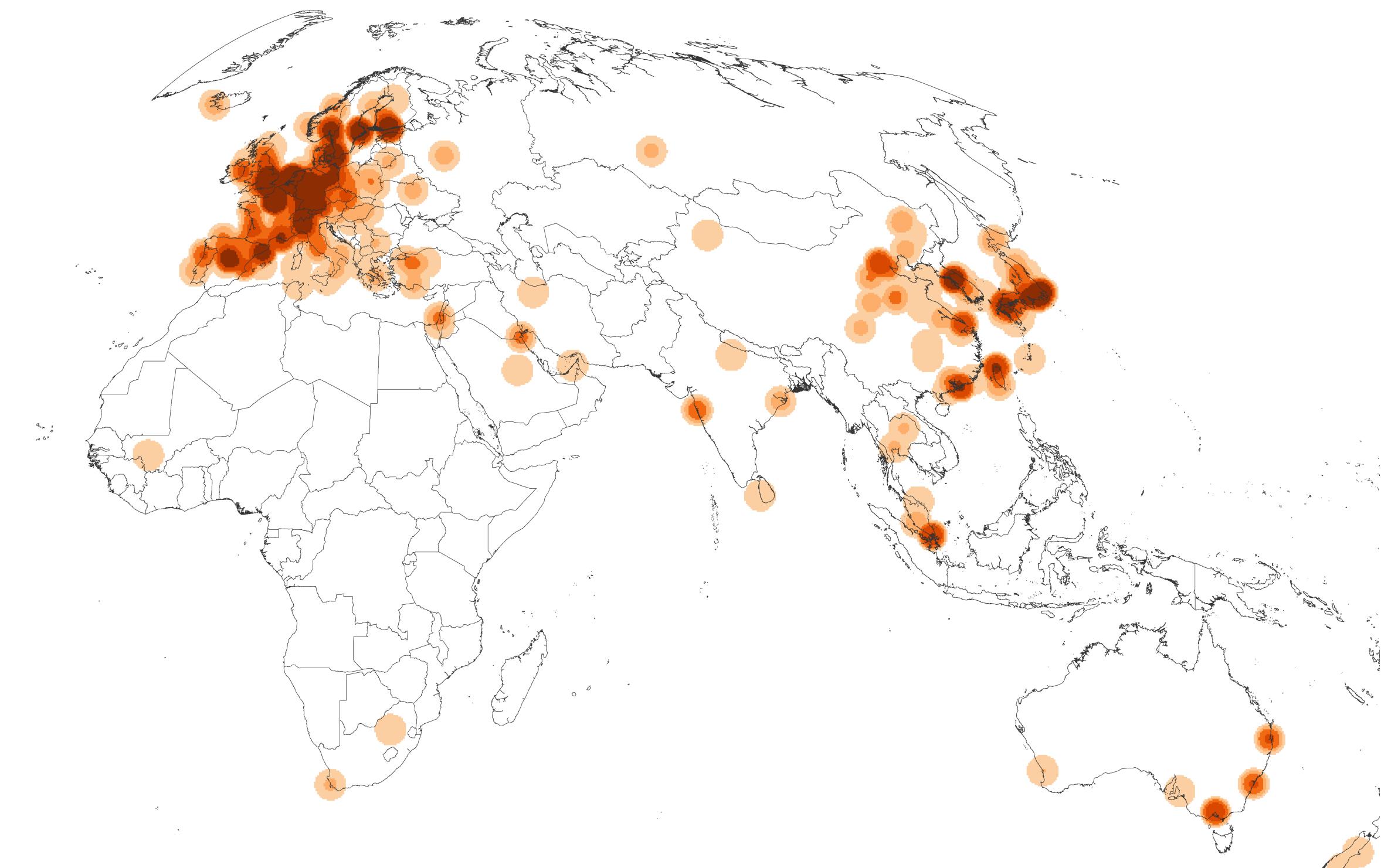
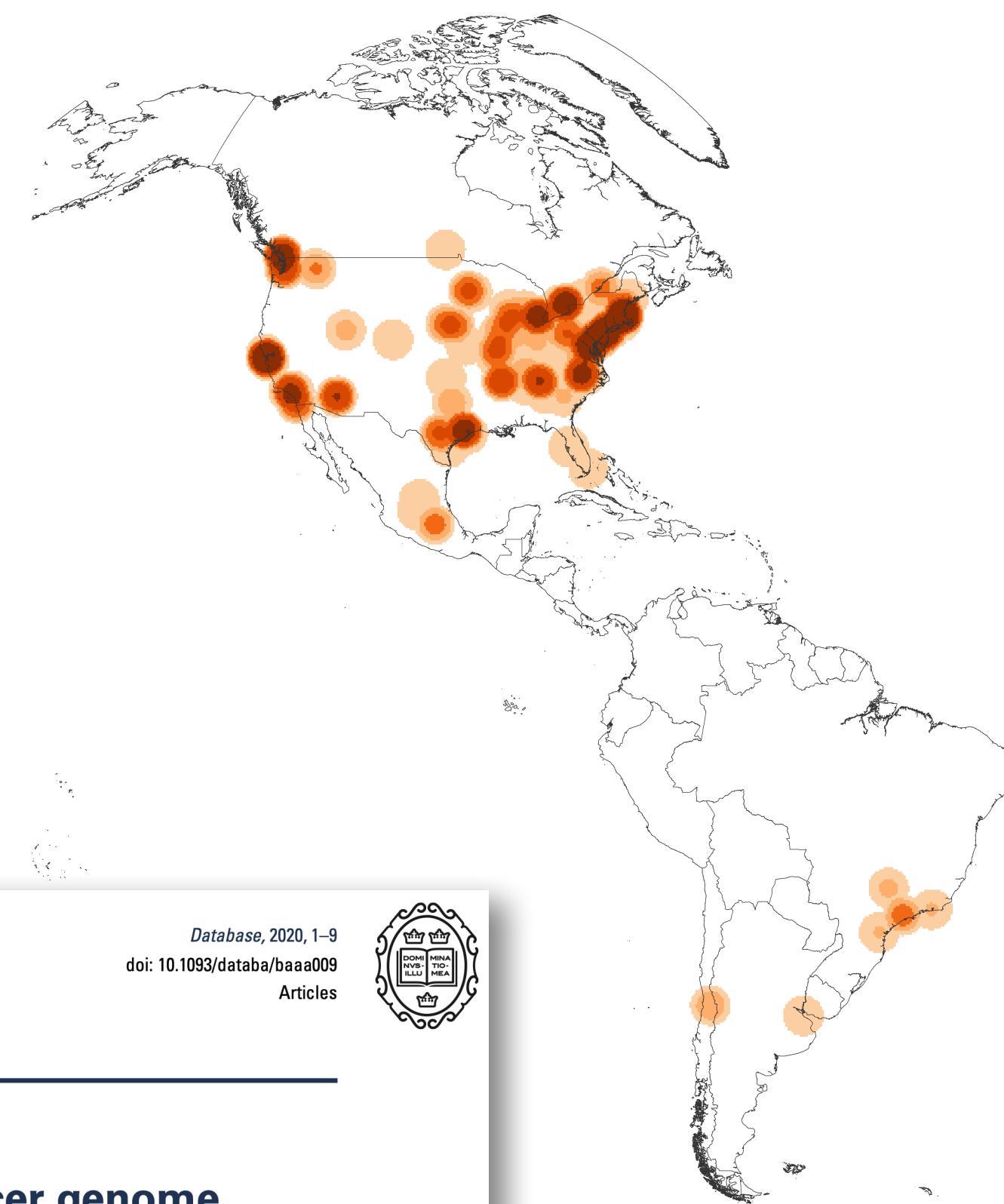
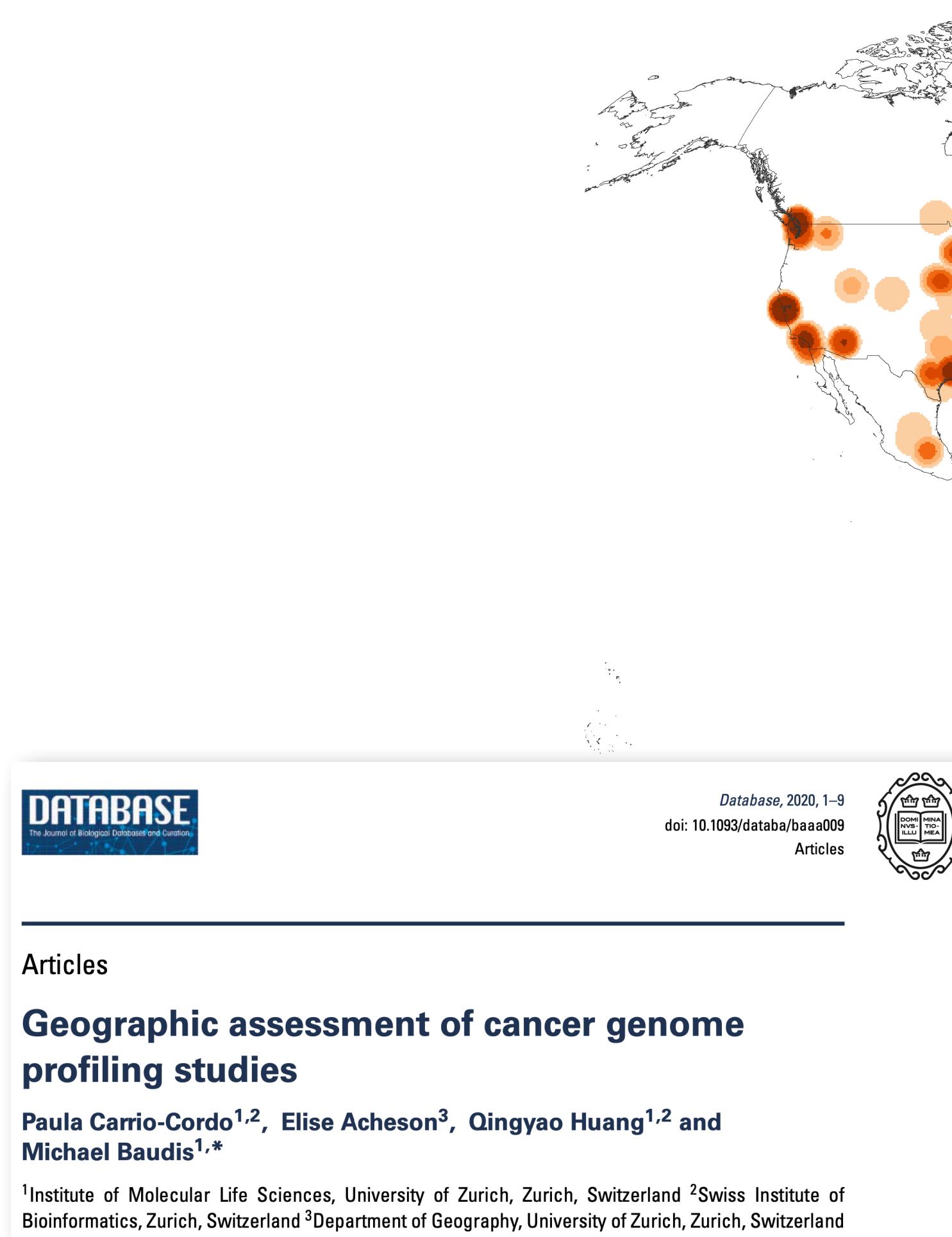
_id	CURIE	0..1	variation_id. MUST be unique within document.
type	string	1..1	MUST be "CopyNumberChange"
subject	Location CURIE Feature	1..1	A location for which the number of systemic copies is described.
copy_change	string	1..1	MUST be one of "efo:0030069" (complete genomic loss), "efo:0020073" (high-level loss), "efo:0030068" (low-level loss), "efo:0030067" (loss), "efo:0030064" (regional base ploidy), "efo:0030070" (gain), "efo:0030071" (low-level gain), "efo:0030072" (high-level gain).

TCGA BLCA project (pgx:TCGA.BLCA)



Where does Genomic Data Come From?

Geographic bias in published cancer genome profiling studies



Map of the geographic distribution (by first author affiliation) of the 104'543 genomic array, 36'766 chromosomal CGH and 15'409 whole genome/exome based cancer genome datasets. The numbers are derived from the 3'240 publications registered in the Progenetix database.



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

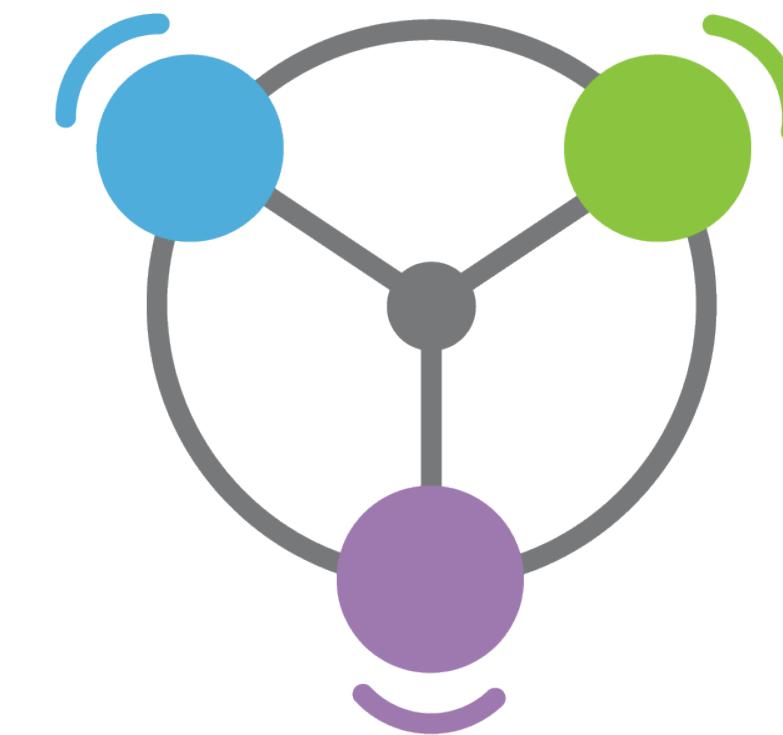
Different Approaches to Data Sharing



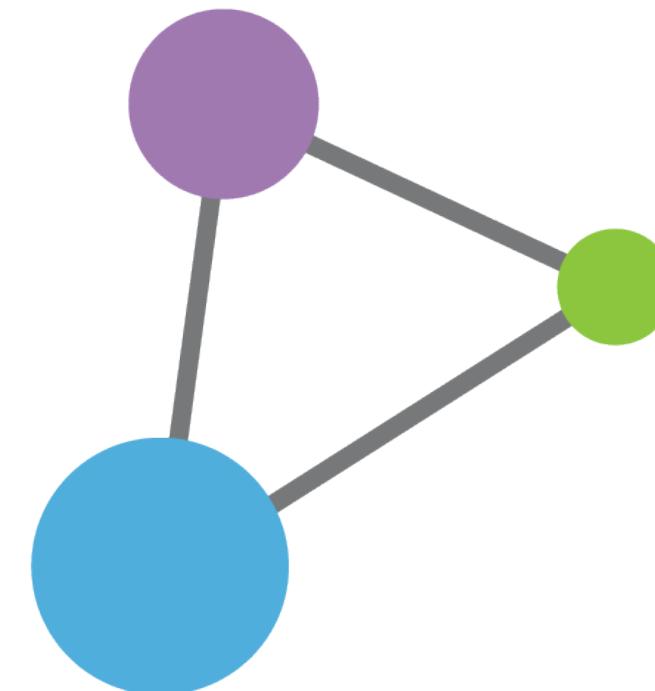
Centralized Genomic Knowledge Bases



Data Commons
Trusted, controlled repository of multiple datasets

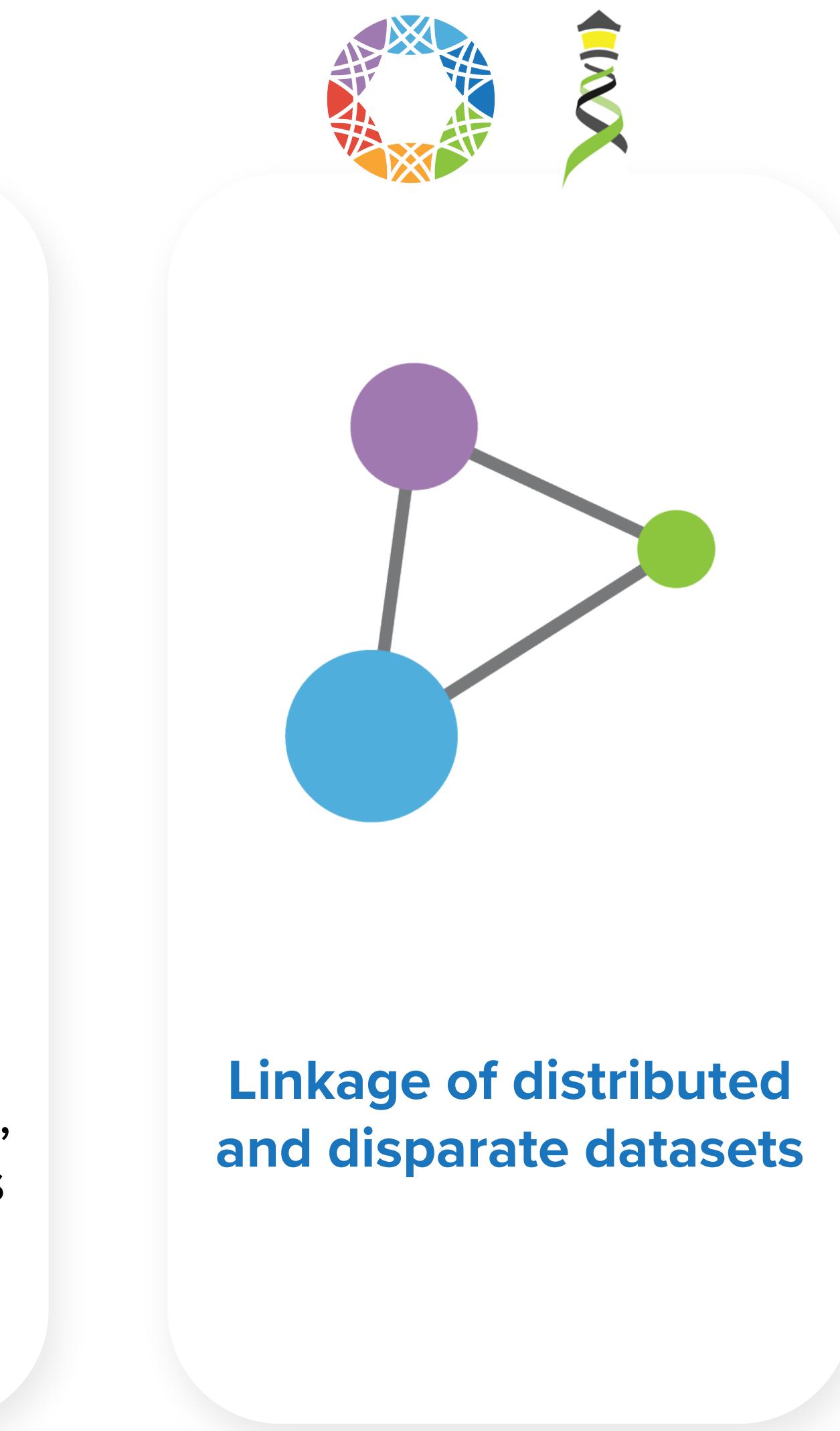
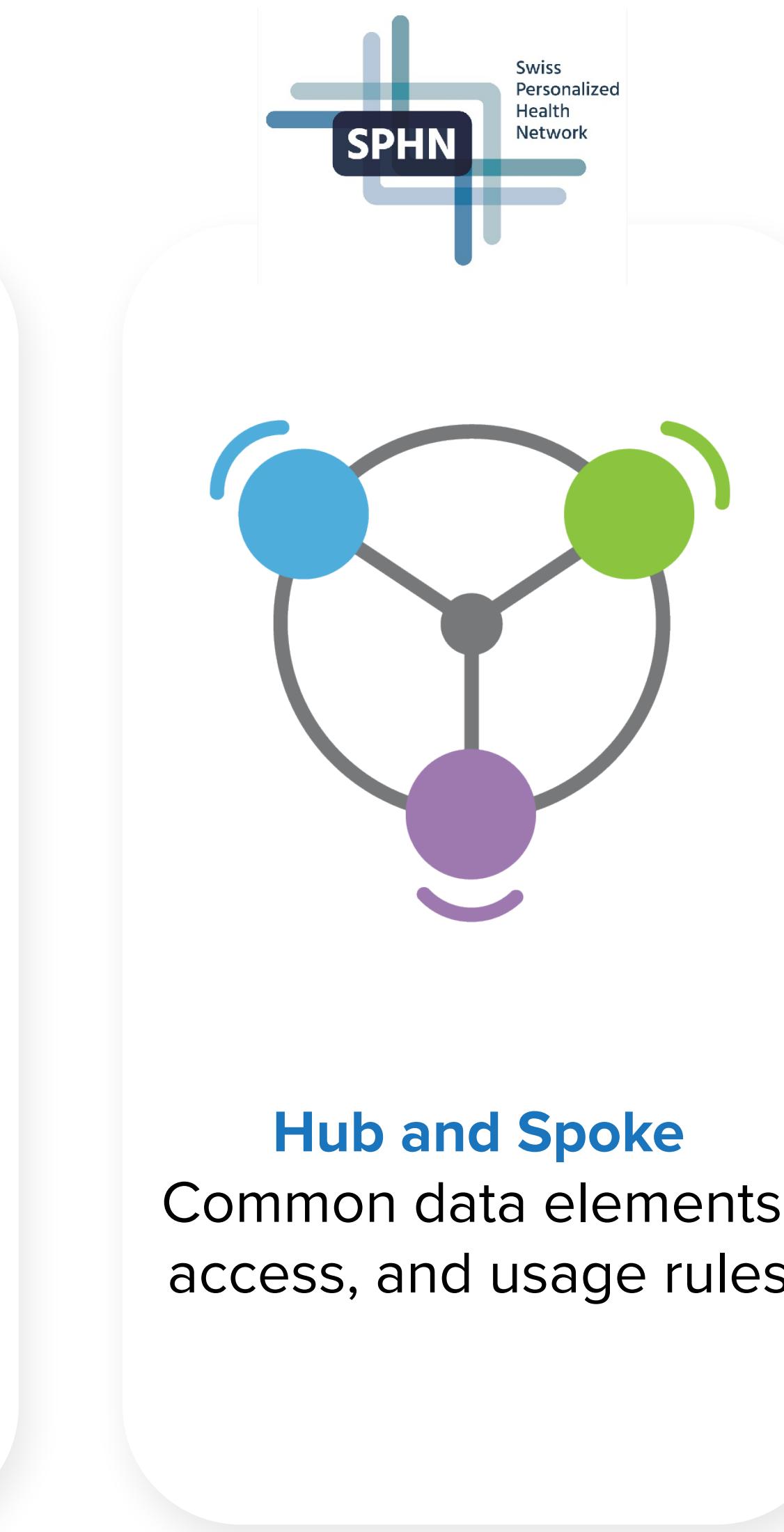
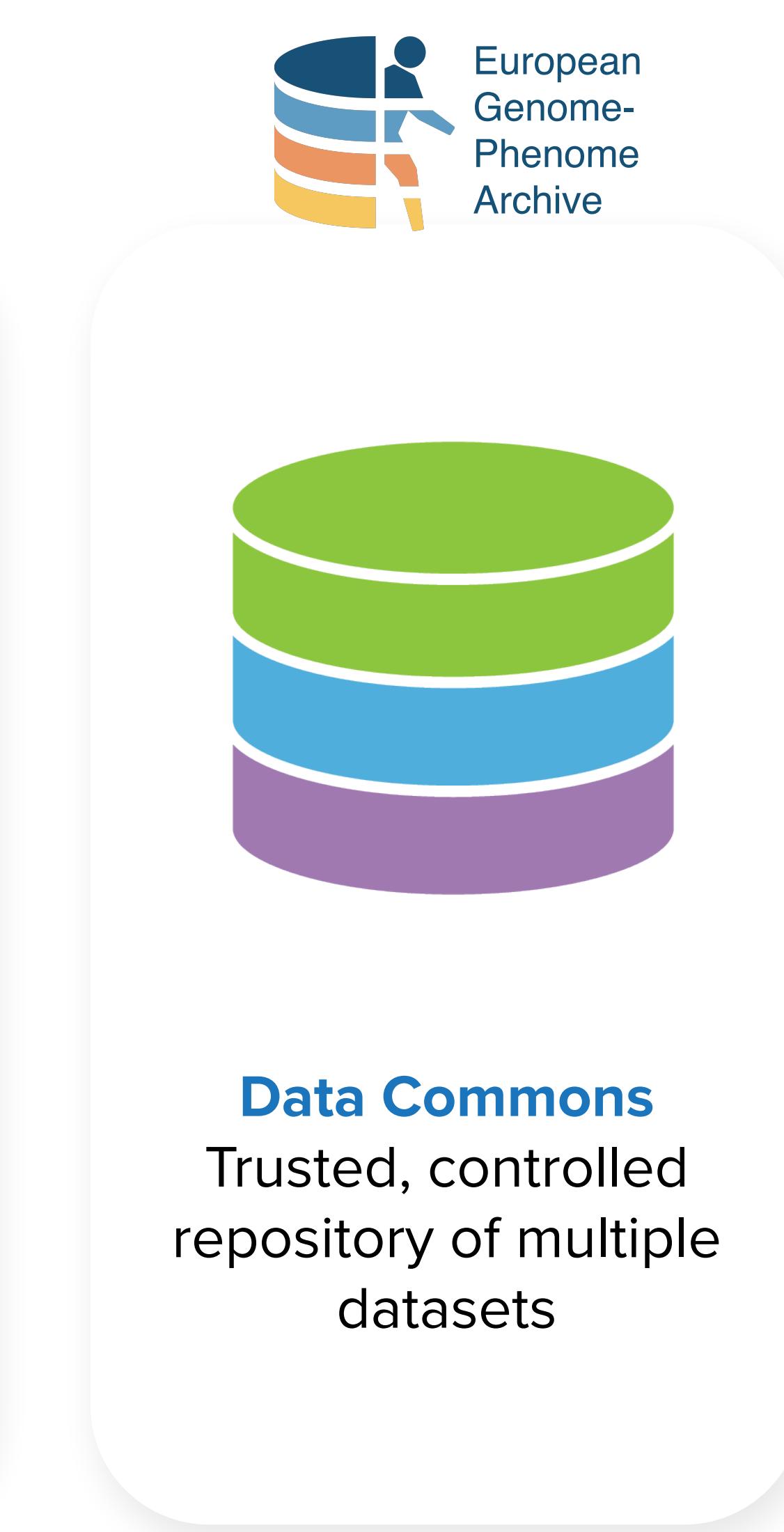
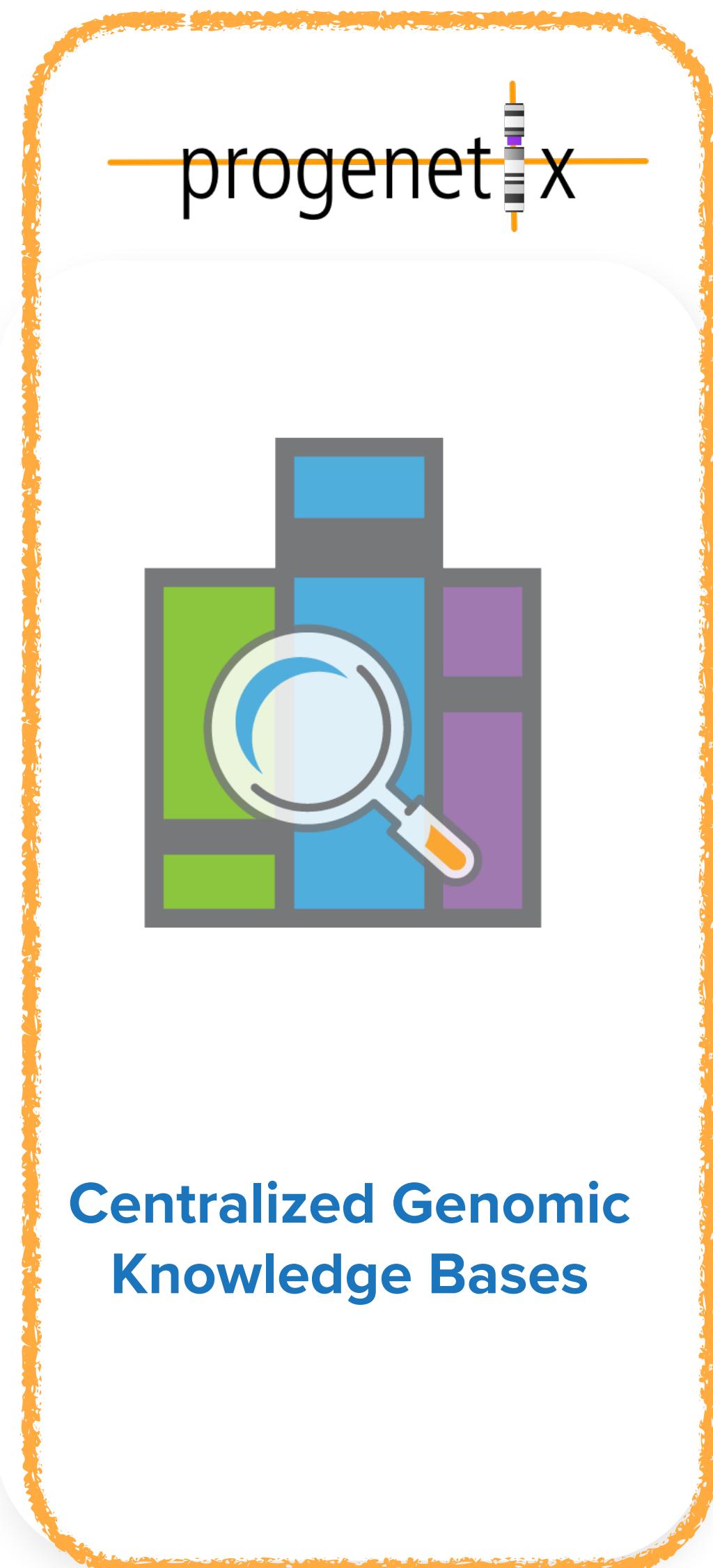


Hub and Spoke
Common data elements, access, and usage rules



Linkage of distributed and disparate datasets

Different Approaches to Data Sharing



Different Approaches to Data Sharing



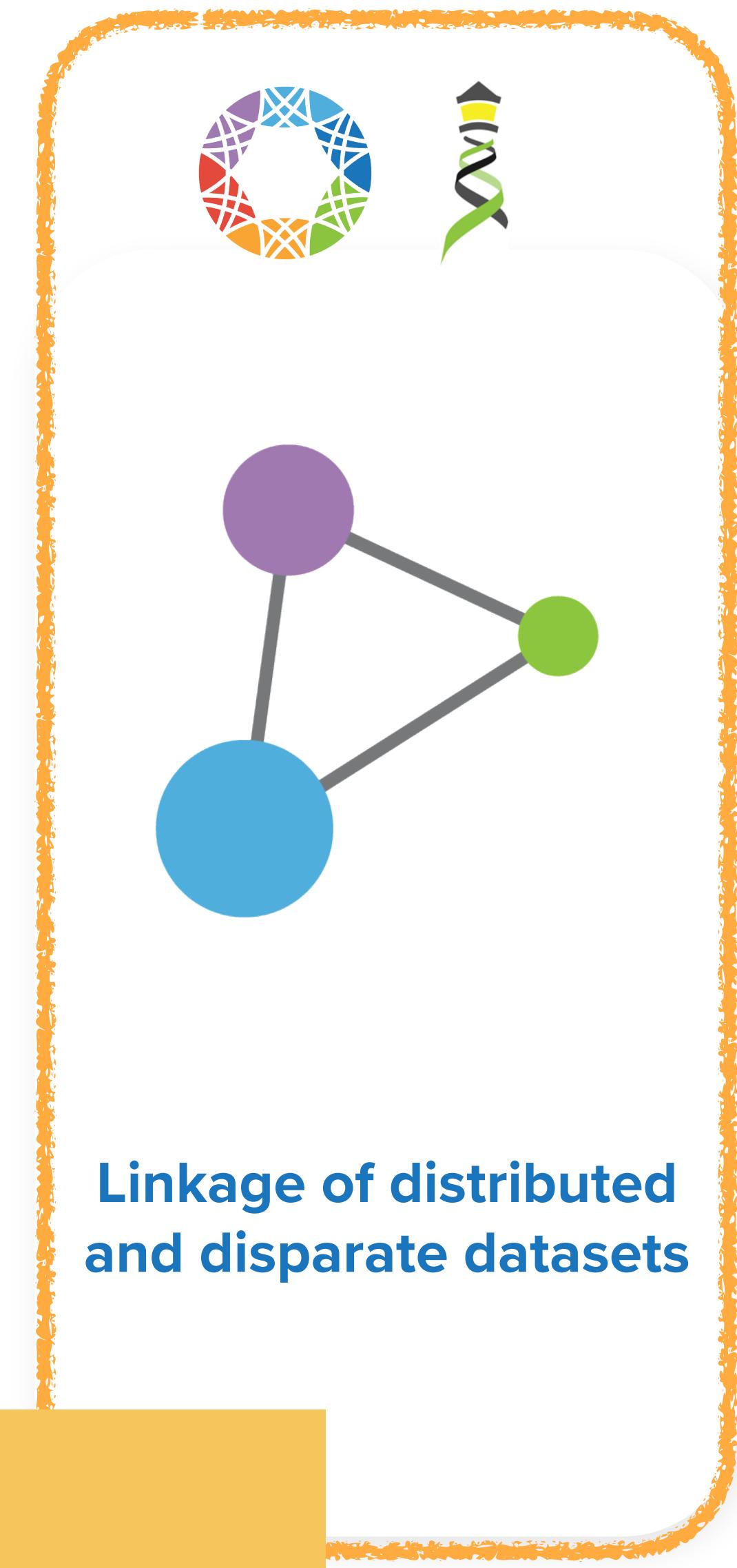
Centralized Genomic Knowledge Bases



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

INFORMATICS

Beacon v2 and Beacon networks: federated data discovery in biome

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 Birney¹⁹

Jordi Rambla^{1,2} | Michael Baudis³ | Roberto Ariosa¹ | Tim Beck⁴ |
 Lauren A. Fromont¹ | Arcadi Navarro^{1,5,6,7} | Rahel Paloots³ |
 Manuel Rueda¹ | Gary Saunders⁸ | Babita Singh¹ | John D. Spalding⁹ |
 Juha Törnroos⁹ | Claudia Vasallo¹ | Colin D. Veal⁴ | Anthony J. Brookes⁴

Cell Genomics

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 Shawn Rynearson,²¹ Helen Schuilenburg,¹² Kirill Tsukanov,¹² Brian Walsh,⁷ Melissa Konopko,¹⁵ Heidi L. Rehm,^{3,22} Andrew D. Yates,¹² Robert R. Freimuth,²³ and Reece K. Hart^{3,24,*}

Cell Genomics

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)

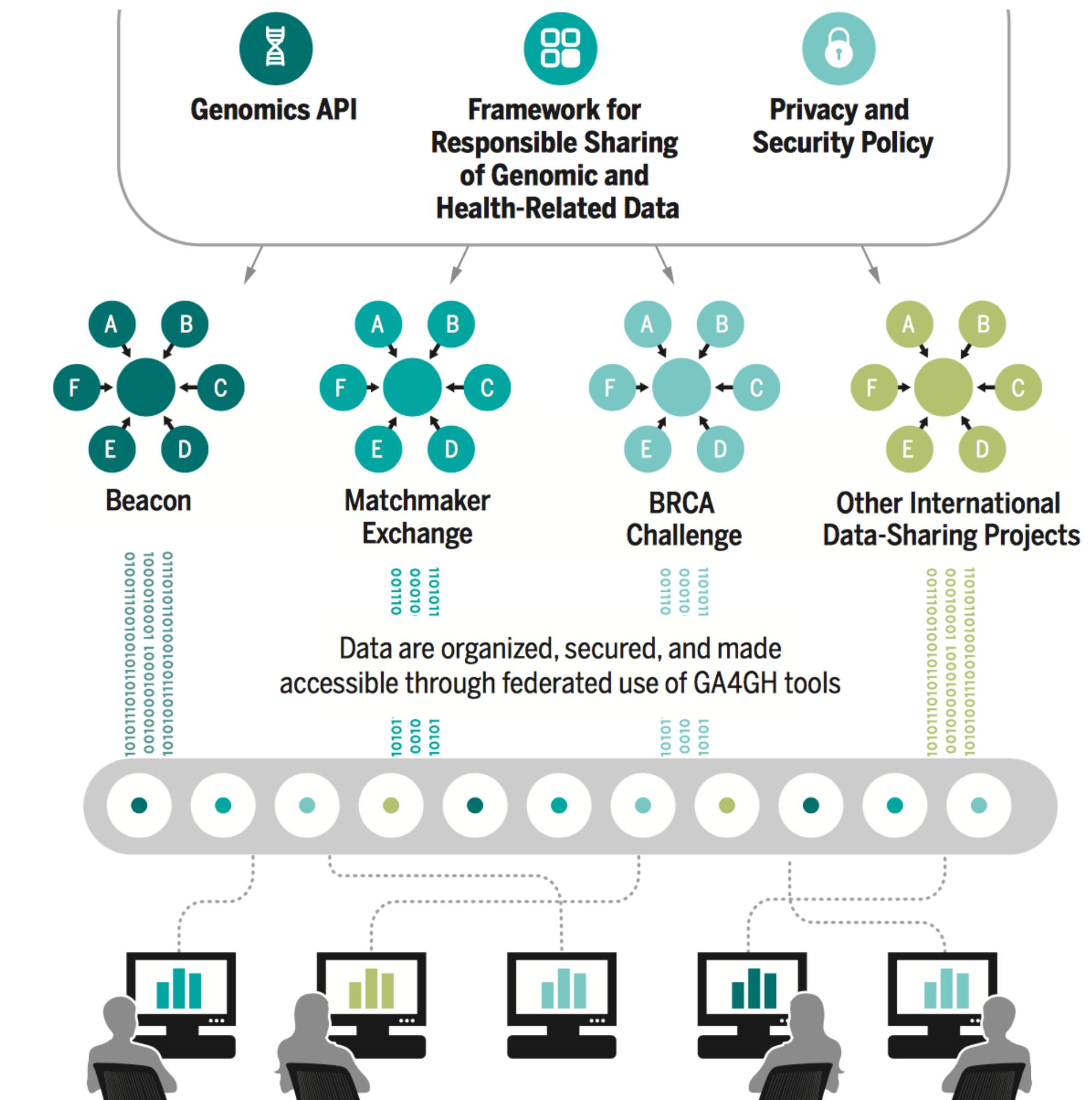


GENOMICS

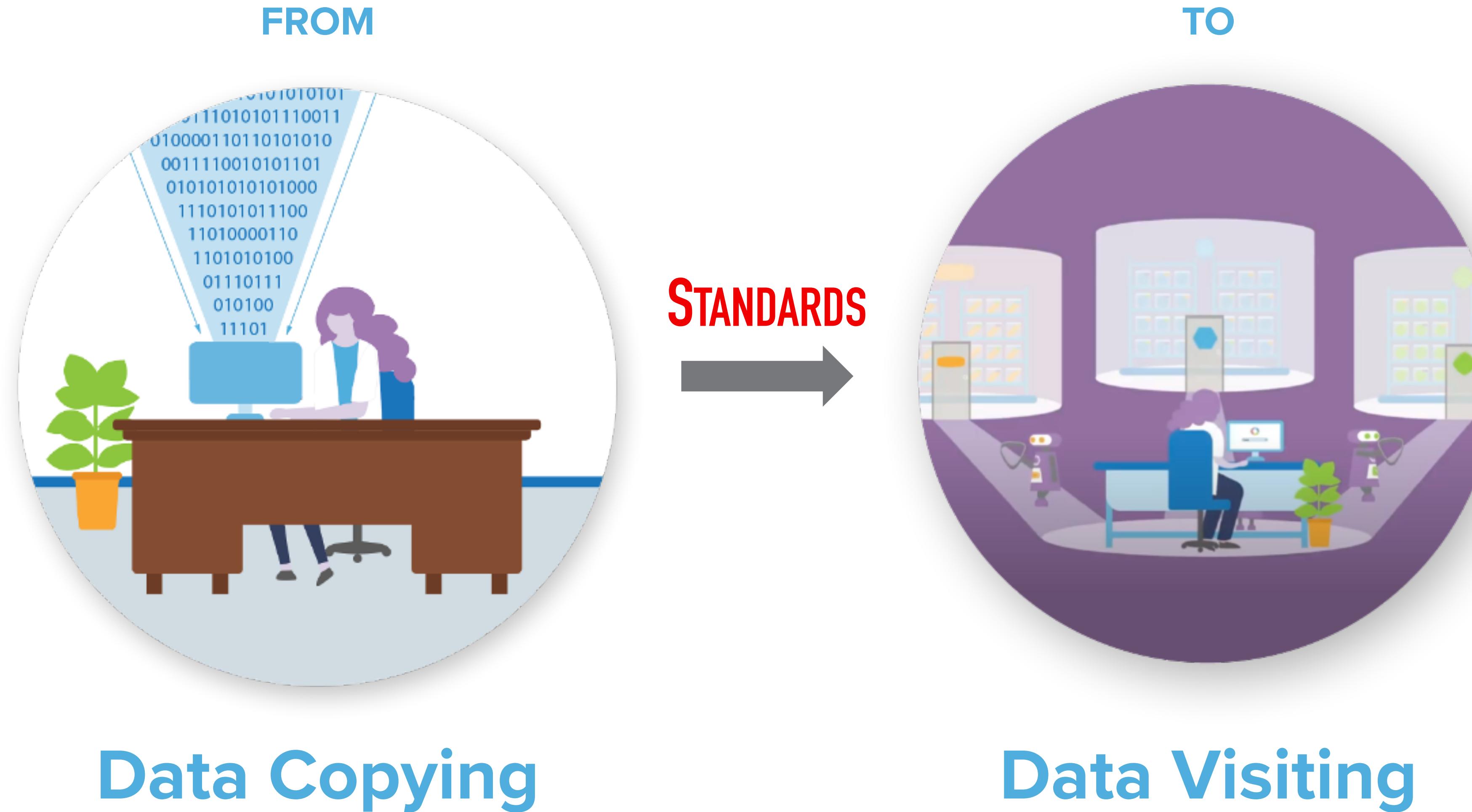
A federated ecosystem for sharing genomic, clinical data

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

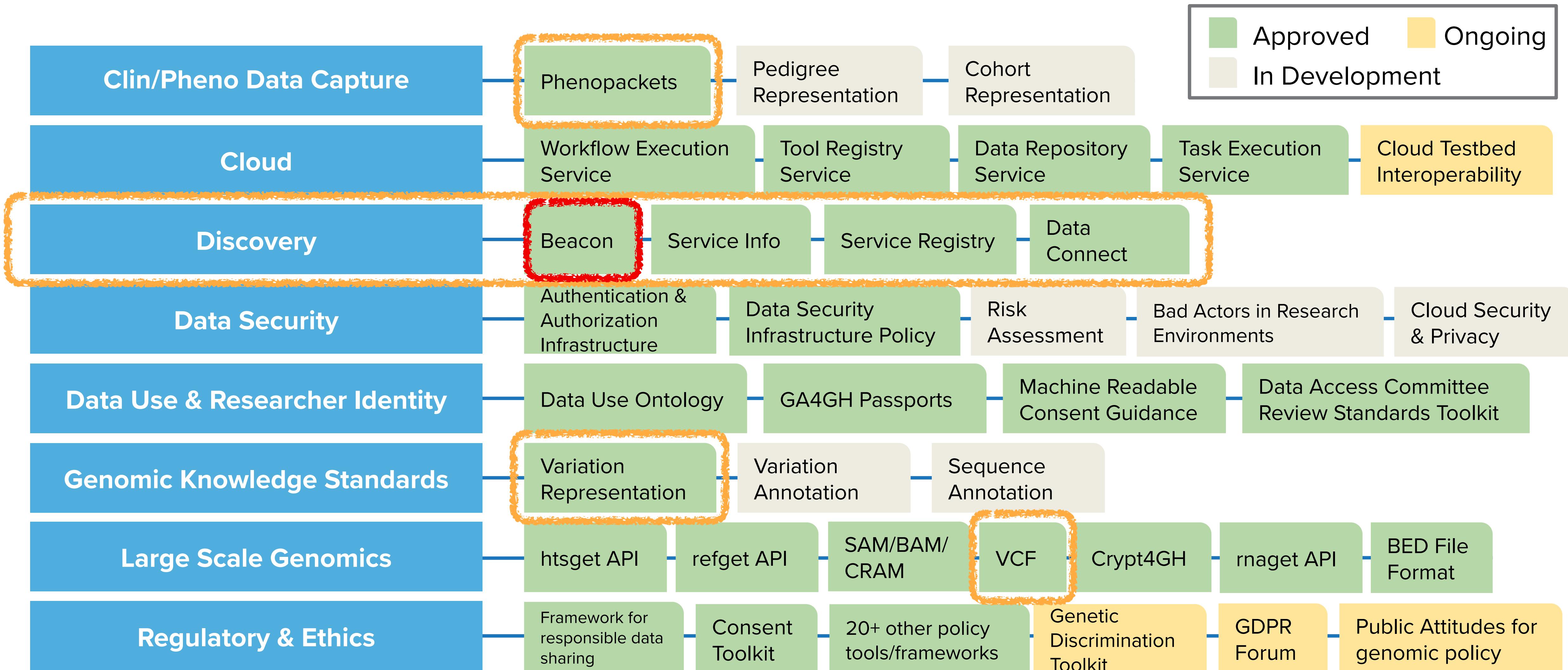
A federated data ecosystem. To share genomic data globally, this approach furthers medical research without requiring compatible data sets or compromising patient identity.

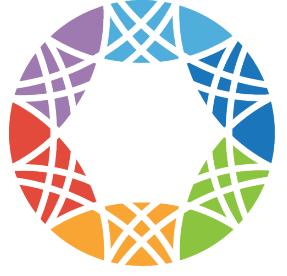


A New Paradigm for Data Sharing

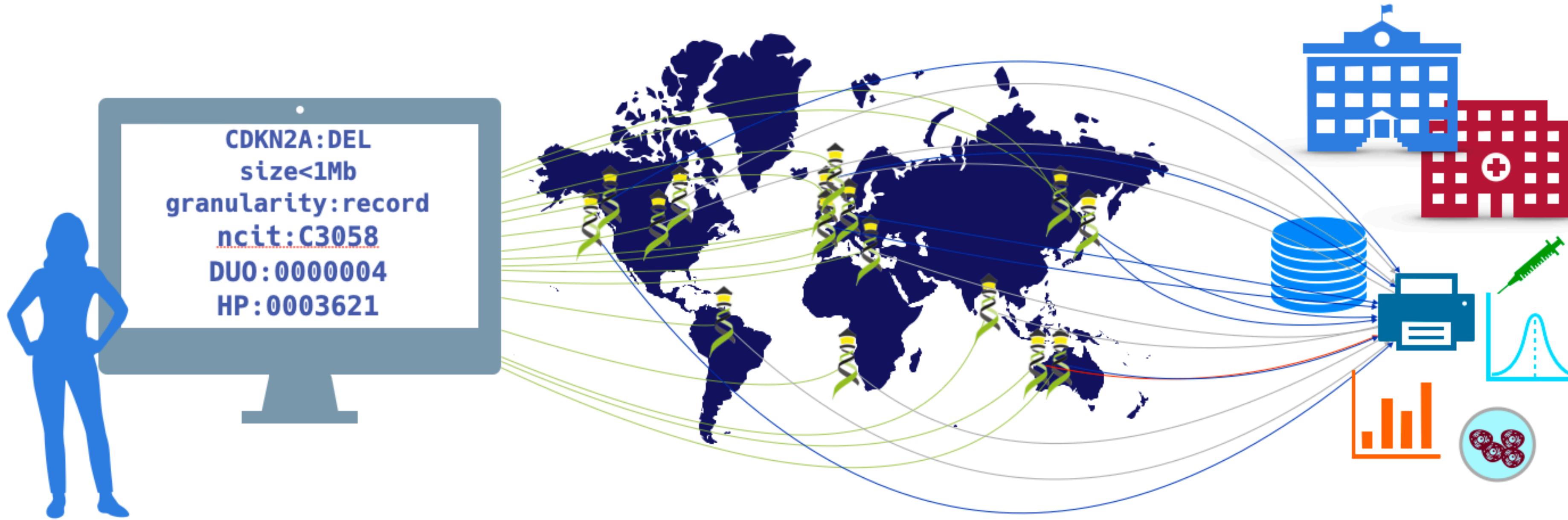


Overview of GA4GH standards and frameworks



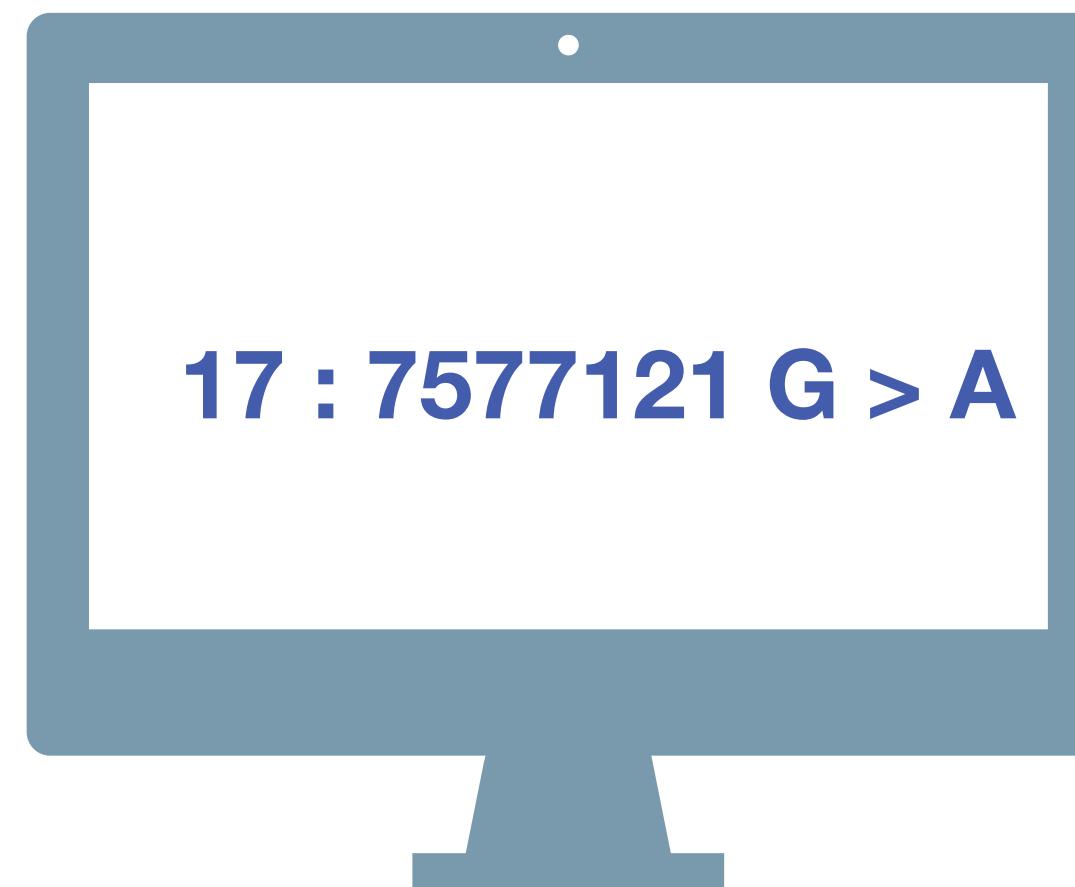


Global Alliance
for Genomics & Health
Collaborate. Innovate. Accelerate.



The GA4GH Beacon Protocol

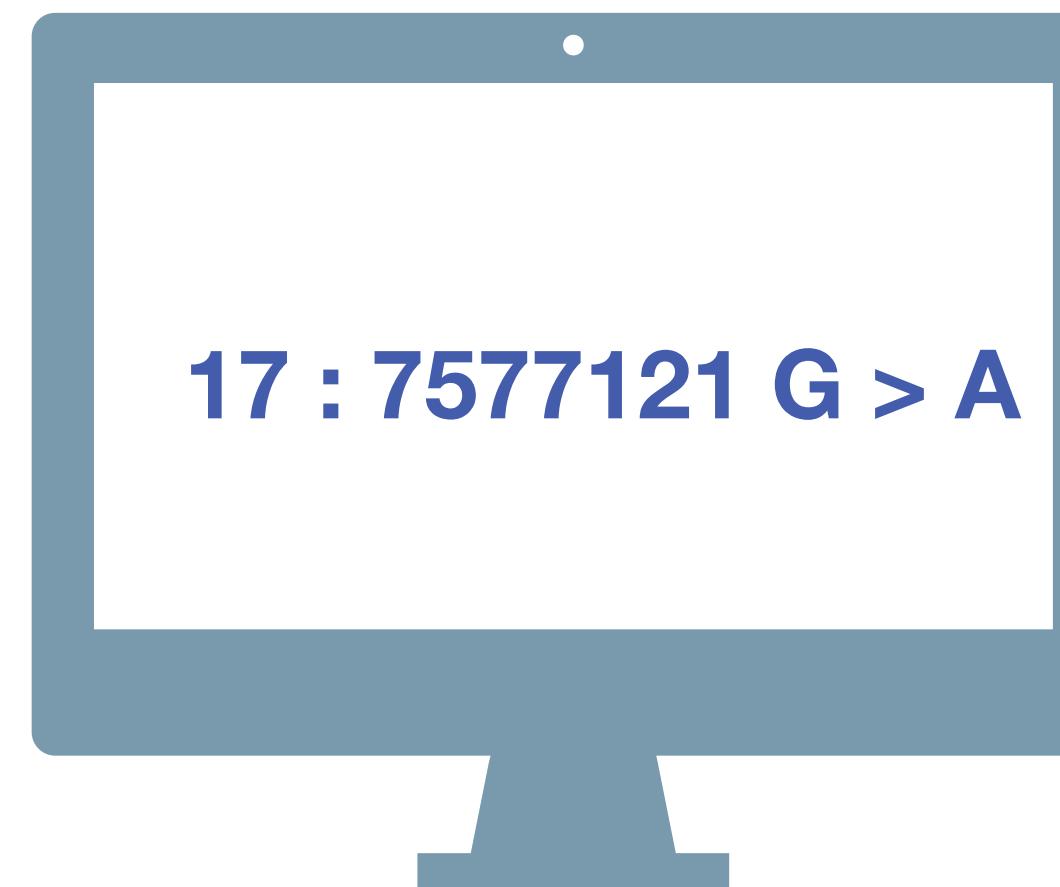
Federating Genomic Discoveries



Beacon

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**.

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.”

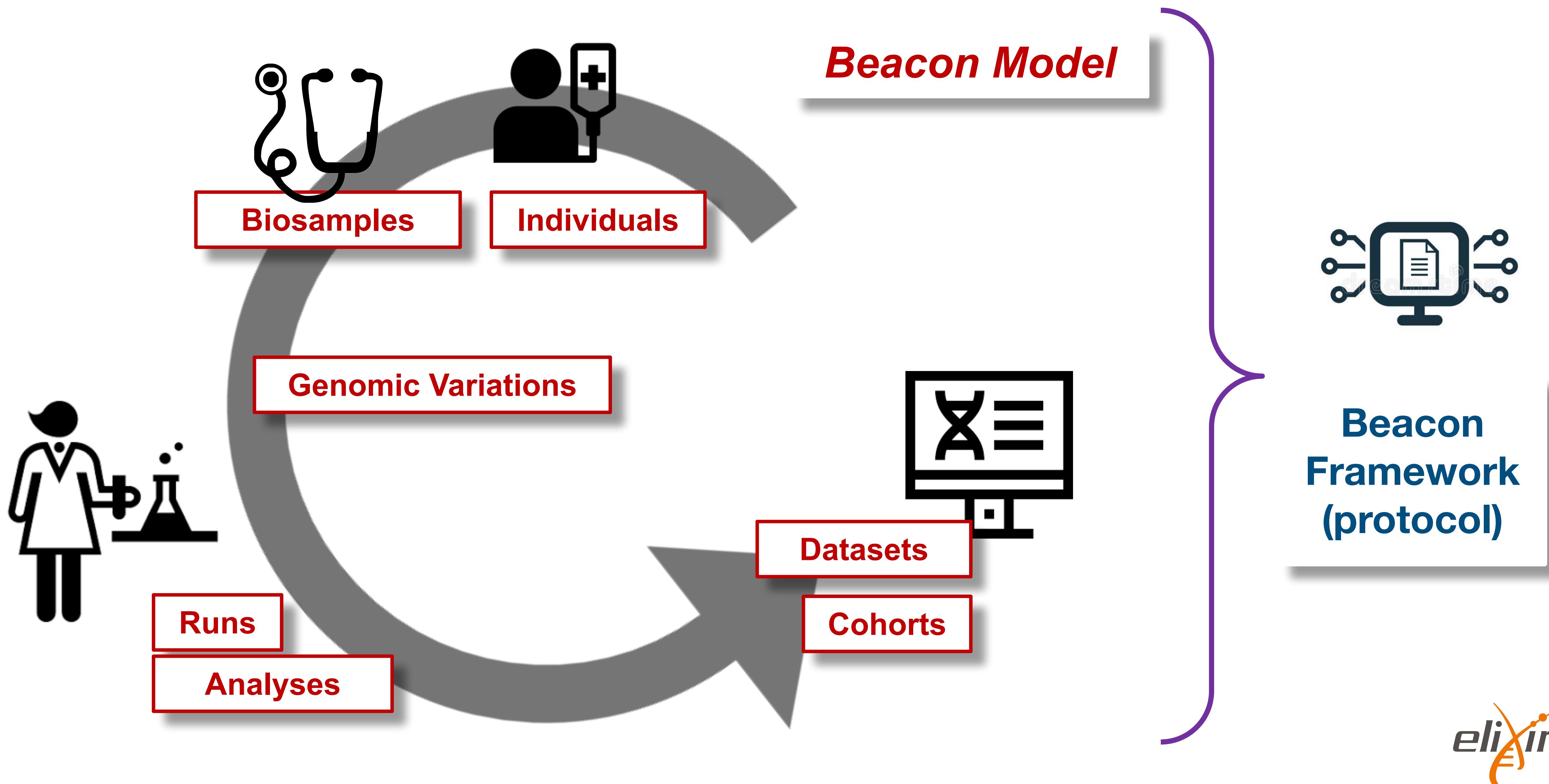
Jim Ostell, 2014

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 v2

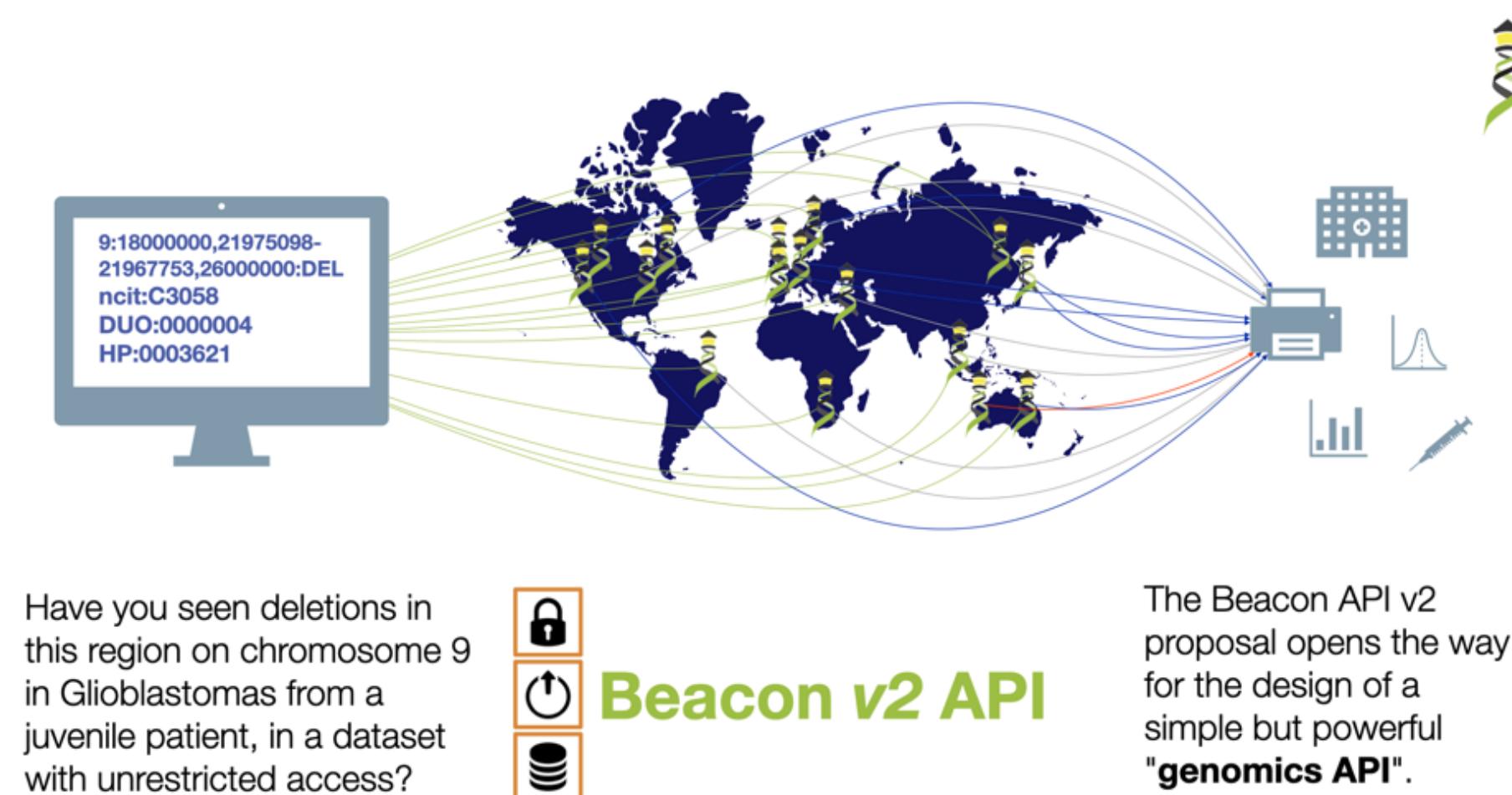
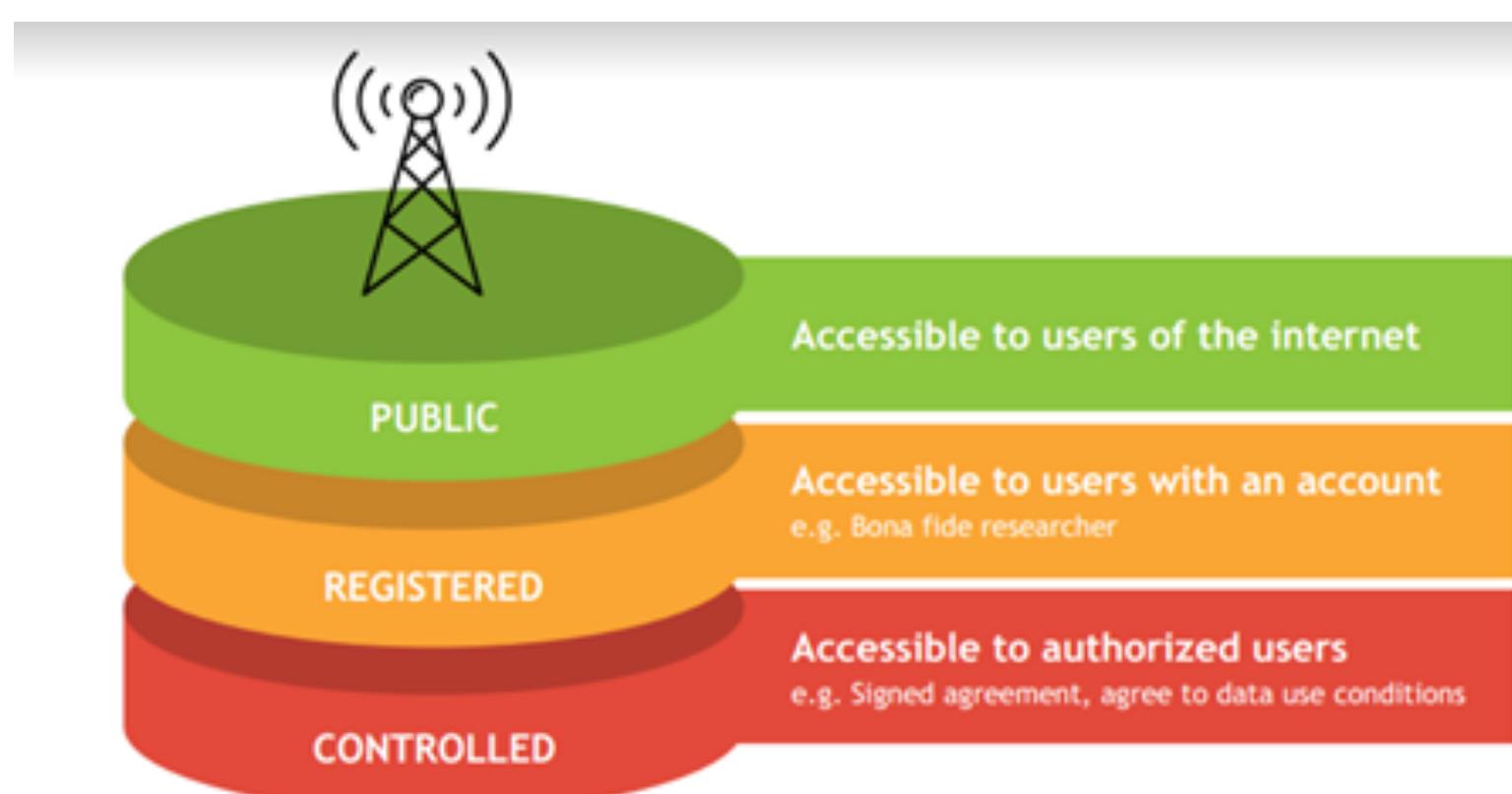
docs.genomebeacons.org



Beacon API v2

The Beacon API can be implemented as a web-accessible service that users may query for information about a specific allele.

Approved: April 21, 2022



Example Users



UNIVERSITY OF CALIFORNIA
SANTA CRUZ



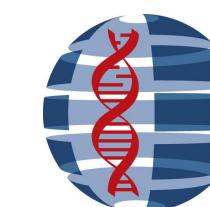
Australian
Genomics



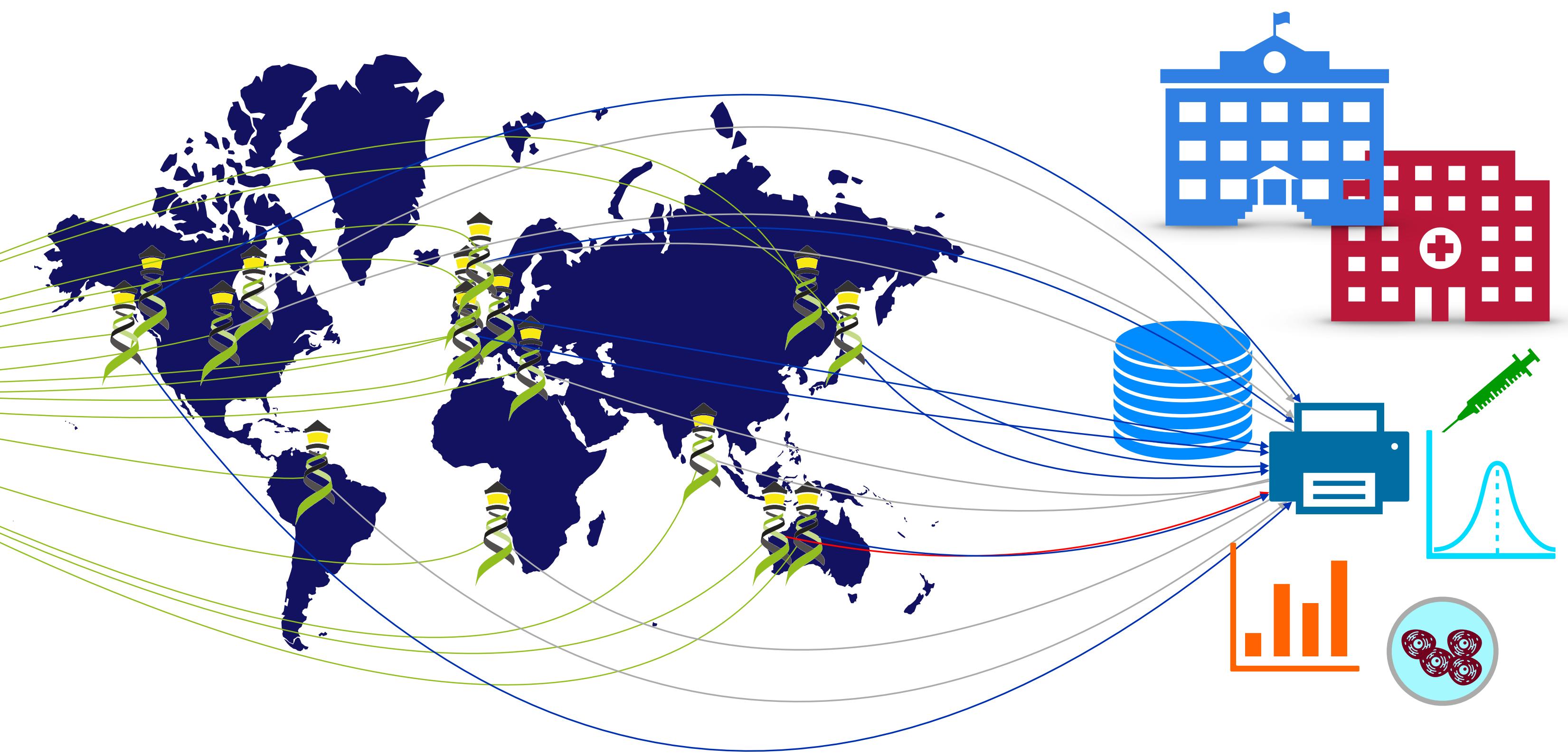
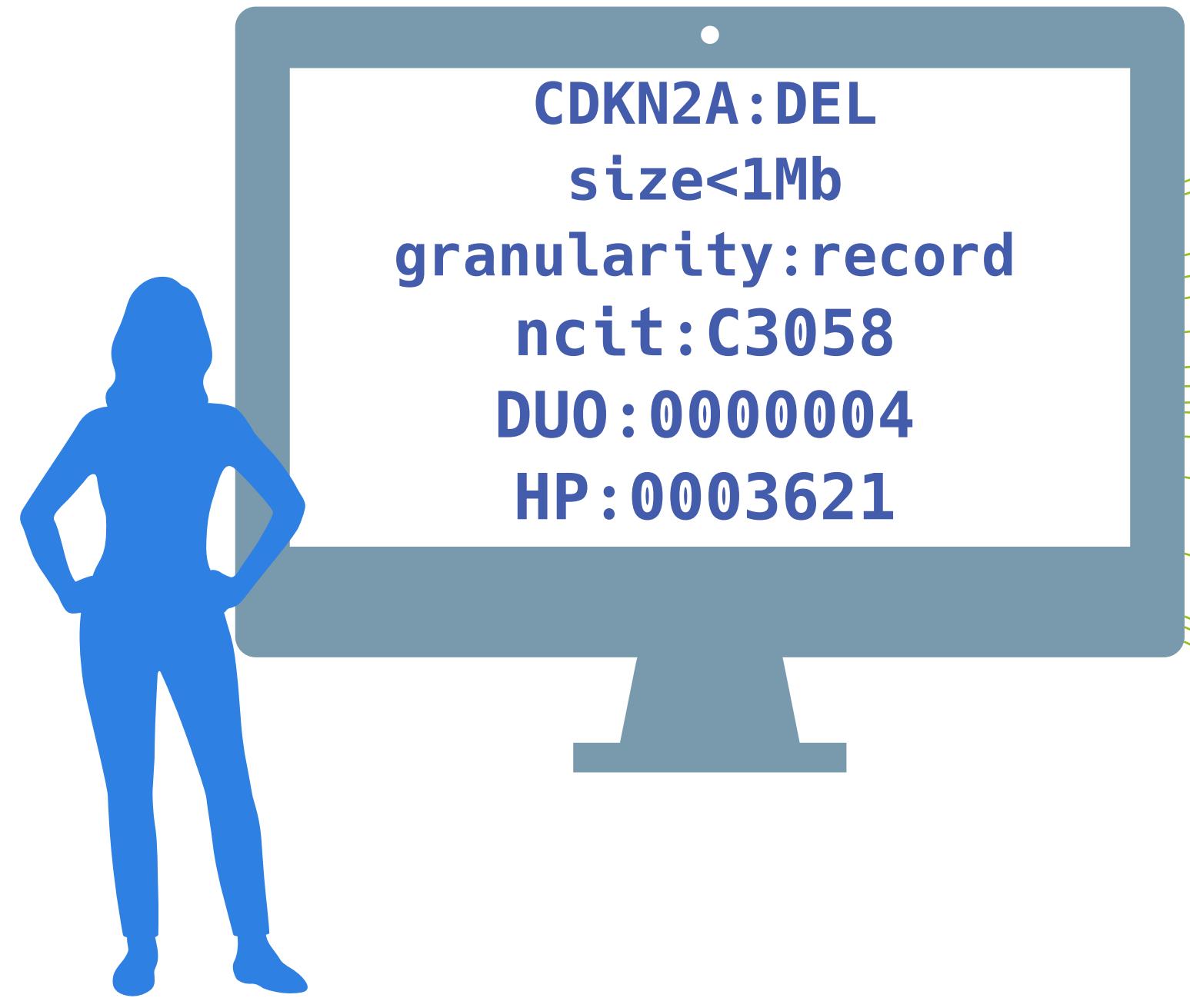
SciLifeLab



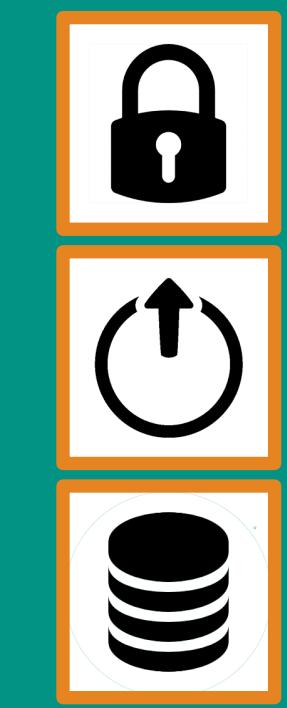
EUROPEAN
GENOME-PHENOME
ARCHIVE



International
Cancer Genome
Consortium



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

Progenetix and GA4GH Beacon

Implementation driven development of a GA4GH standard

Beacon v1 Development

2014

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

2015

- beacon-network.org aggregator created by DNAstack

2016

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

2017

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

2018

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

2019

- ELIXIR Beacon Network

2020

2021

2022

Beacon v2 Development

Related ...

- ELIXIR starts Beacon project support

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

- new Beacon website (March)

- Beacon publication at Nature Biotechnology

- Phenopackets v2 approved

- docs.genomebeacons.org

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

- Beacon+ demos "handover" concept

- Beacon hackathon Stockholm; settling on "filters"
- Barcelona goes Zurich developers meeting
- Beacon API v2 Kick off
- adopting "handover" concept
- "Scouts" teams working on different aspects - filters, genomic variants, compliance ...
- discussions w/ clinical stakeholders

- framework + models concept implemented
- range and bracket queries, variant length parameters
- starting of GA4GH review process
- further changes esp. in default model, aligning with Phenopackets and VRS
- unified beacon-v2 code & docs repository
- Beacon v2 approved at Apr GA4GH Connect

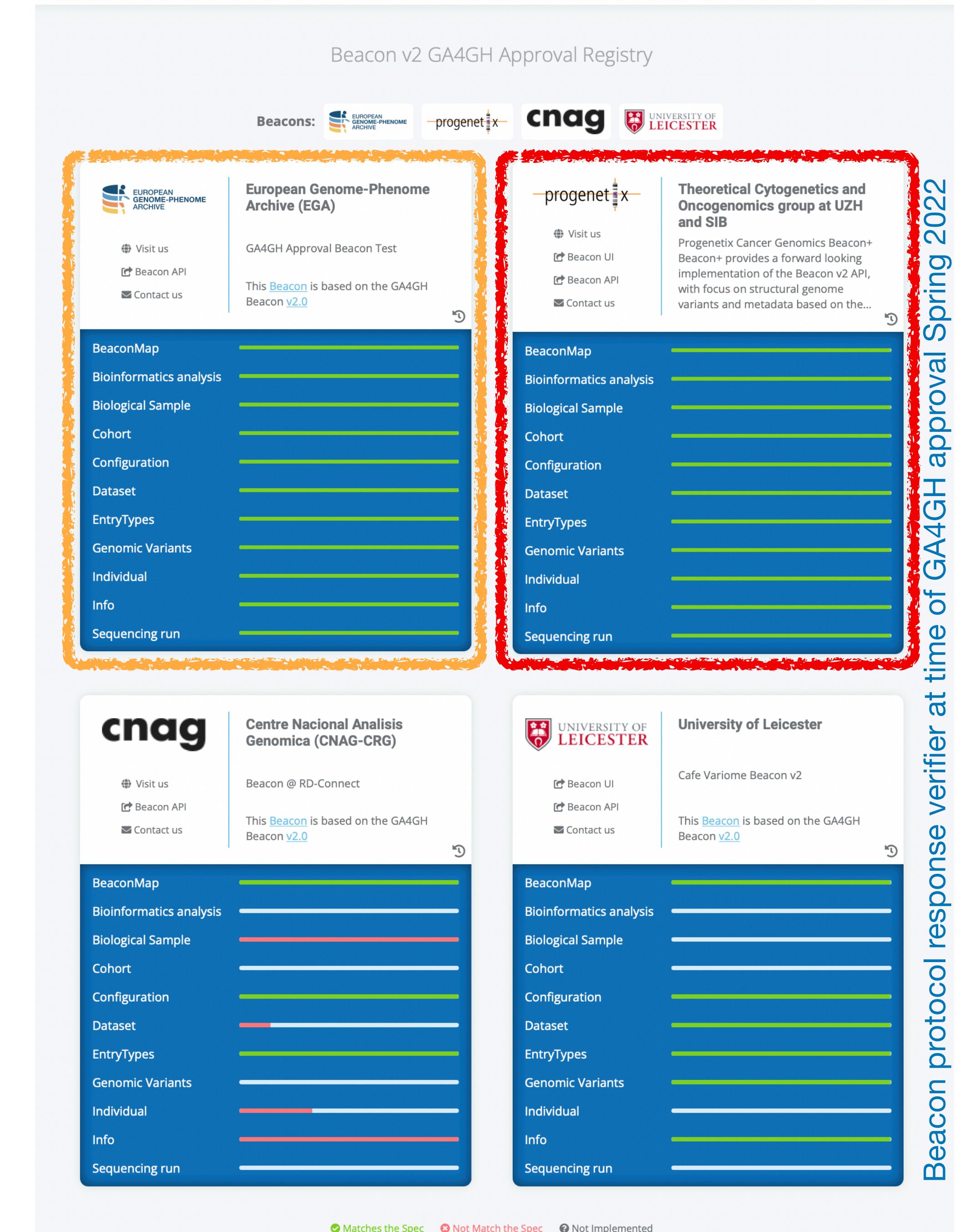
Progenetix & Beacon

Implementation driven standards development

- Progenetix Beacon+ has served as implementation driver since 2016
- prototyping of advanced Beacon features such as
 - structural variant queries
 - data handovers
 - Phenopackets integration

Beacon v2 GA4GH Approval Registry

Beacons: European Genome-Phenome Archive | progenetix | cnag | University of Leicester



The screenshot shows the Beacon v2 GA4GH Approval Registry interface. It displays four beacon responses from different organizations:

- European Genome-Phenome Archive (EGA)**: Beacon based on GA4GH Beacon v2.0. The response verifier is indicated by an orange box.
- progenetix**: Theoretical Cytogenetics and Oncogenomics group at UZH and SIB. Beacon+ provides a forward-looking implementation of the Beacon v2 API, with focus on structural genome variants and metadata based on the... The response verifier is indicated by a red box.
- cnag**: Centre Nacional Analisis Genomica (CNAG-CRG). Beacon @ RD-Connect. The response verifier is indicated by a white box.
- University of Leicester**: Cafe Variome Beacon v2. The response verifier is indicated by a white box.

Each response includes a list of beacon types (BeaconMap, Bioinformatics analysis, Biological Sample, Cohort, Configuration, Dataset, EntryTypes, Genomic Variants, Individual, Info, Sequencing run) with colored bars indicating the status: green for matches the spec, red for not match the spec, and grey for not implemented.

Beacon protocol response verifier at time of GA4GH approval Spring 2022

Beacon+ by Progenetix

From Beacon Query to Explorative Analyses of CNV Patterns

- Since 2016 the Progenetix resource has been used to model options for Beacon development
 - 138334 individual samples from 698 cancer types
- The consistent use of hierarchical diagnostic codes allows the use of Beacon "filters" for histopathological/clinically scoped queries
- Beacon's handover protocols can be utilized for data retrieval and, well, handing over to additional services, e.g.
 - downloads
 - visualization
 - use of external services (UCSC browser display...)



Search Samples

CNV Request Allele Request Range Query All Fields

CNV Example

This query type is for copy number queries ("variantCNVrequest"), e.g. using fuzzy ranges for start and end positions to capture a set of similar variants.

Dataset: progenetix

Cohorts: Select...

Genome Assembly: GRCh38 / hg38

Gene Symbol: Select...

Reference name: 9 **(Structural) Variant Type**: DEL

Start or Position: 19000001-21975098 **End (Range or Structural Var.)**: 21967753-24000000

Minimum Variant Length: **Maximal Variant Length**:

Cancer Classification(s): Select...

Filters:

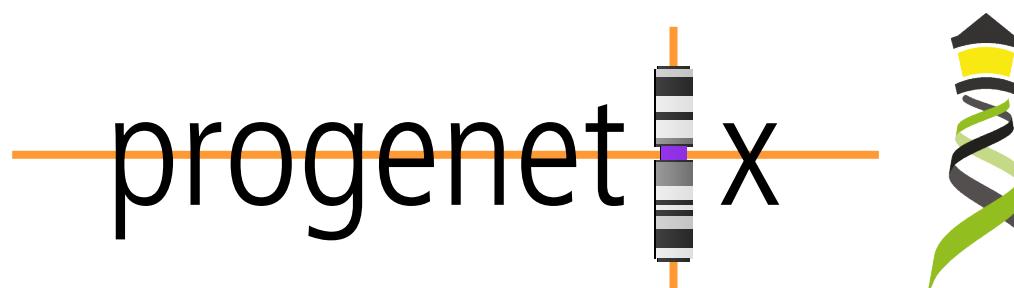
City: Select...

Query Database

Beacon v2 Filters

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

- 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

<input checked="" type="checkbox"/>	> NCIT:C4914: Skin Carcinoma	213
<input type="checkbox"/>	> NCIT:C4475: Dermal Neoplasm	109
<input checked="" type="checkbox"/>	> NCIT:C45240: Cutaneous Hematopoietic and Lymphoid Cell Neoplasm	310

Filters: NCIT:C4914, NCIT:C4819, NCIT:C9231, NCIT:C2921, NCIT:C45240, NCIT:C6858, NCIT:C3467, NCIT:C45340, NCIT:C7195, NCIT:C3246, NCIT:C7217



progenetix

Variants: 0 *f*alleles: 0 Callsets Variants ↗ UCSC region ↗ Calls: 0 Legacy Interface ↗ Samples: 523 [Show JSON Response](#)

Results **Biosamples**

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 Queries

Implementation of Current Options

- (so far) the Beacon model does not define explicit query types
- disambiguation of parameters is left to implementers
- implicit query types:
 - allele/sequence query
 - range query, w/ or w/o additional parameters
 - bracket query (e.g. sized CNVs)
 - aminoacid, HGVS, gene

Beacon+ Progenetix Help

Beacon Query Types

Sequence / Allele CNV (Bracket) Genomic Range Aminoacid Gene ID HGVS Sam

Dataset: Test Database - examplez

Chromosome: Select... Variant Type: Select...

Start or Position: 19000001-21975098

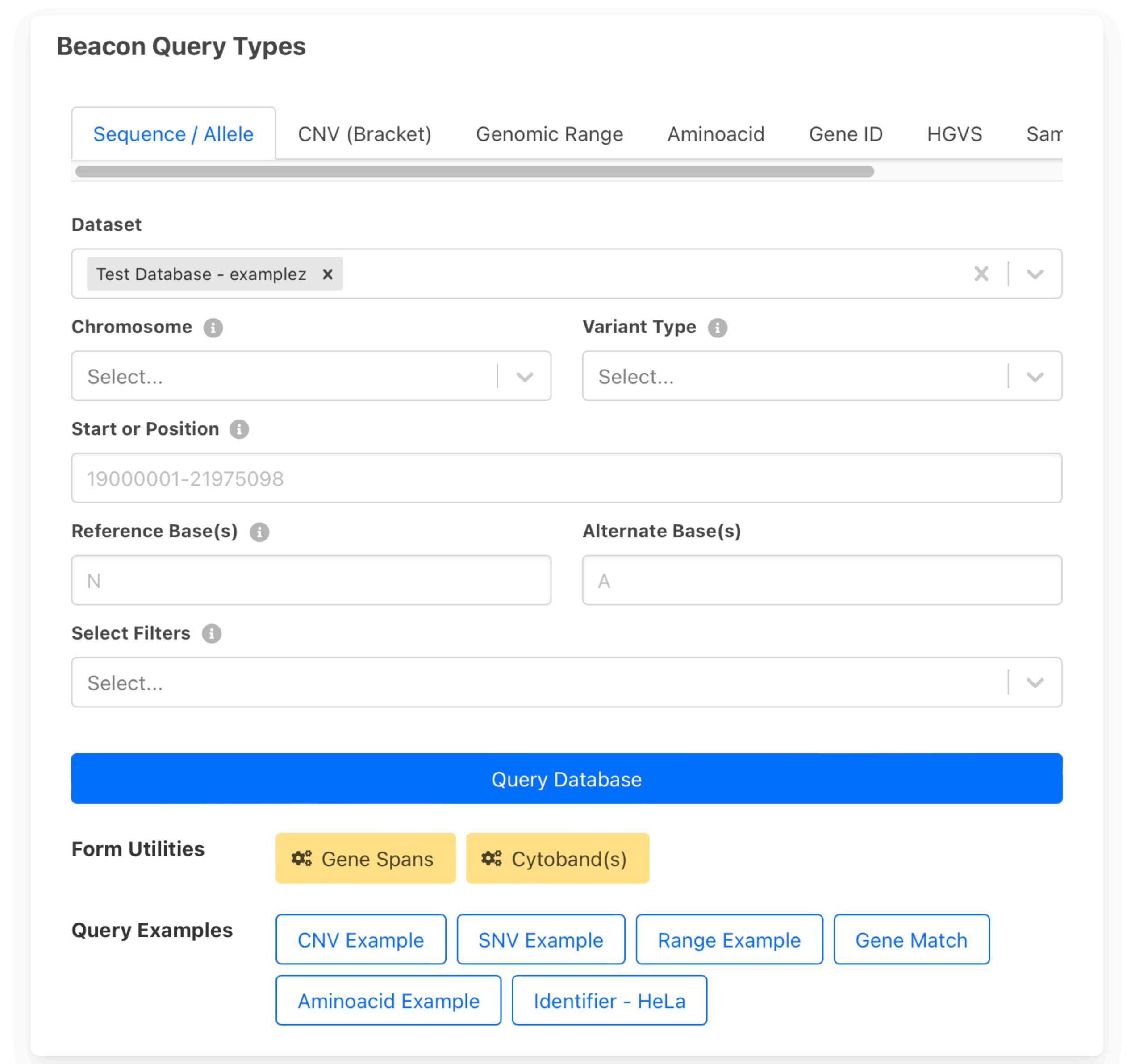
Reference Base(s): N Alternate Base(s): A

Select Filters: Select...

Query Database

Form Utilities: Gene Spans Cytoband(s)

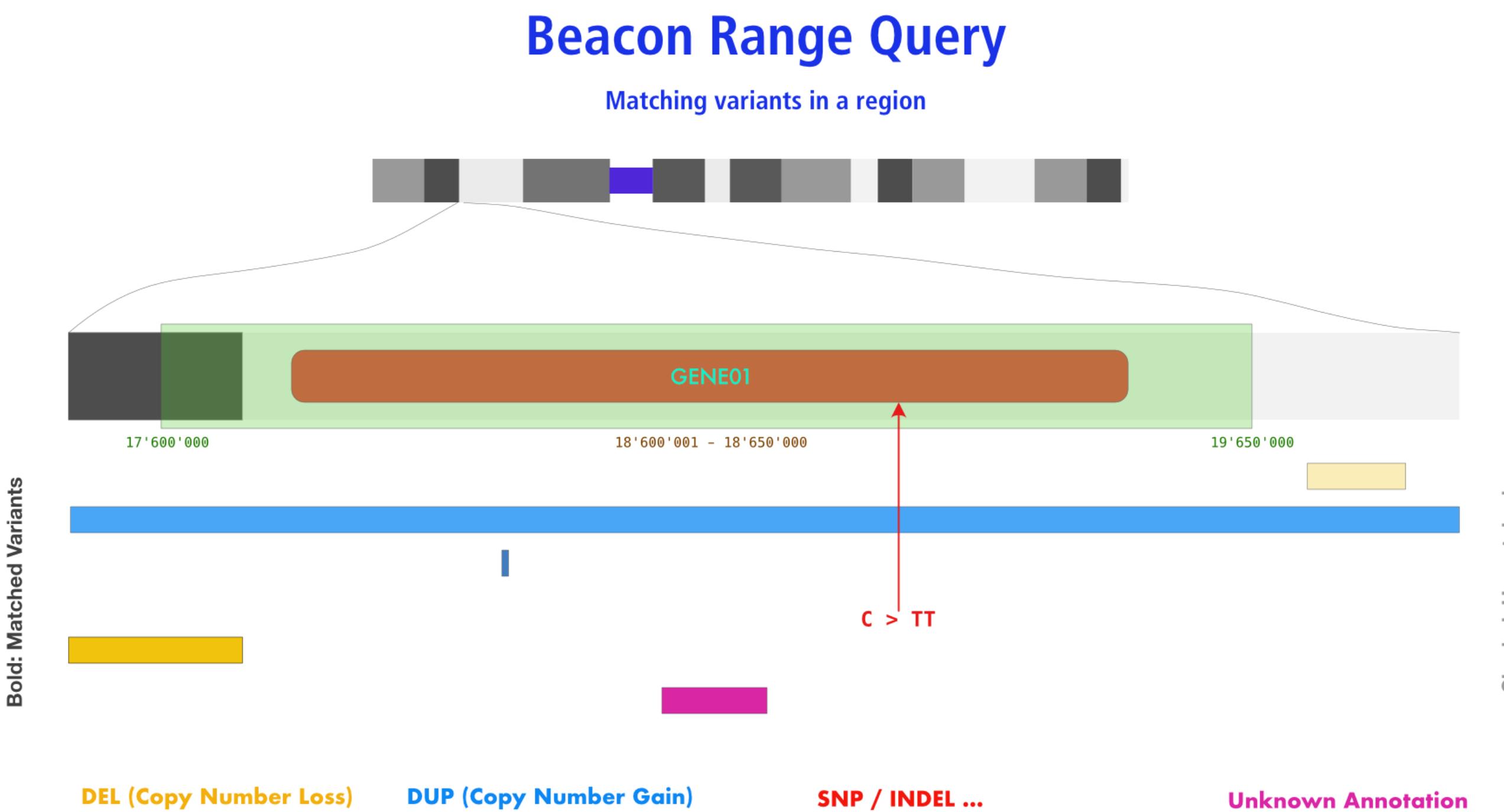
Query Examples: CNV Example SNV Example Range Example Gene Match Aminoacid Example Identifier - HeLa



Beacon Queries

Range ("anything goes") Request

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



Beacon Query Types

Sequence / Allele CNV (Bracket) **Genomic Range** Aminoacid Gene ID HGVS Sam

Dataset

Test Database - examplez X | ▼

Chromosome i **Variant Type** i

17 (NC_000017.11) | ▼ SO:0001059 (any sequence alteration - S...) | ▼

Start or Position i **End (Range or Structural Var.)** i

7572826 7579005

Reference Base(s) i **Alternate Base(s)**

N A

Select Filters i

Select... | ▼

Chromosome 17 i

7572826  7579005

Query Database

Form Utilities ⚙️ Gene Spans ⚙️ Cytoband(s)

Query Examples

CNV Example SNV Example Range Example Gene Match

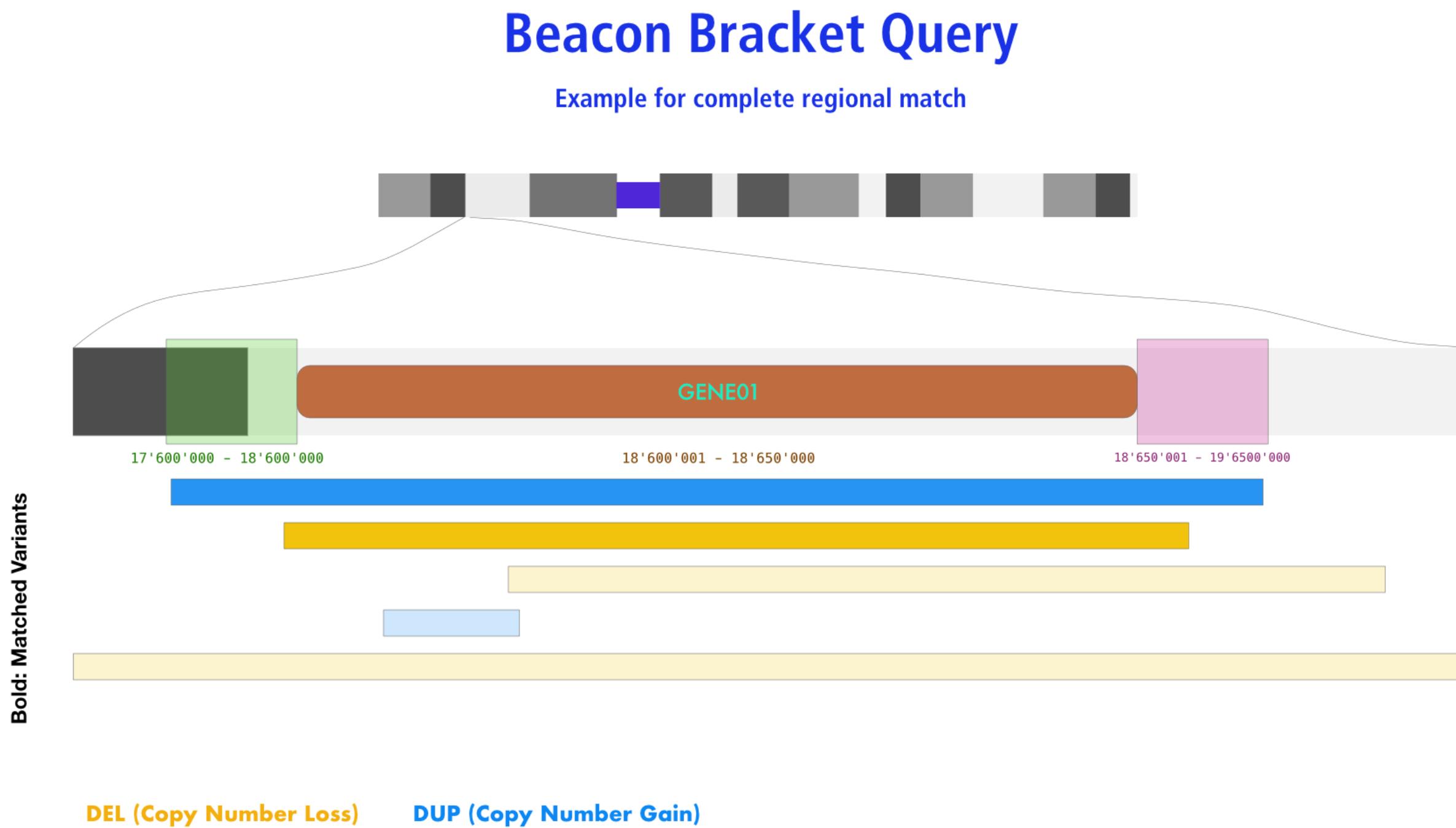
Aminoacid Example Identifier - HeLa

As in the standard SNV query, this example shows a Beacon query against mutations in the **EIF4A1** gene in the DIPG childhood brain tumor dataset. However, this range + wildcard query will return any variant with alternate bases (indicated through "N"). Since parameters will be interpreted using an "AND" paradigm, either Alternate Bases OR Variant Type should be specified. The exact variants which were being found can be retrieved through the variant handover [H→O] link.

Beacon Queries

Bracket ("CNV") Query

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



Beacon Query Types

Sequence / Allele **CNV (Bracket)** Genomic Range Aminoacid Gene ID HGVS Sam

Dataset

Test Database - examplez x | v

Chromosome

9 (NC_000009.12) | v

Variant Type

EFO:0030067 (copy number deletion) | v

Start or Position

21000001-21975098

End (Range or Structural Var.)

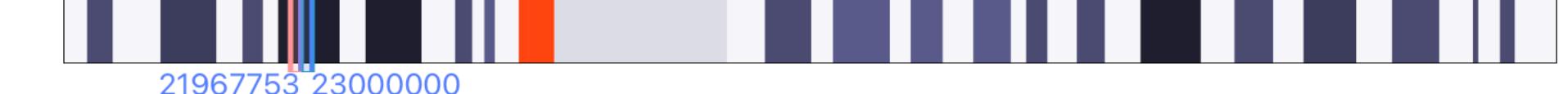
21967753-23000000

Select Filters

NCIT:C3058: Glioblastoma (100) x | v

Chromosome 9

21000001-21975098



21967753-23000000

Query Database

Form Utilities

Gene Spans

Cytoband(s)

Query Examples

CNV Example

SNV Example

Range Example

Gene Match

Aminoacid Example

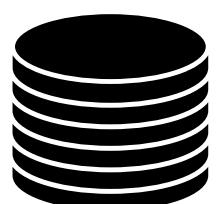
Identifier - HeLa

This example shows the query for CNV deletion variants overlapping the CDKN2A gene's coding region with at least a single base, but limited to "focal" hits (here i.e. <= ~2Mbp in size). The query is against the examplez collection and can be modified e.g. through changing the position parameters or data source.

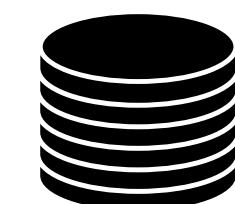
Beacon+ Stack



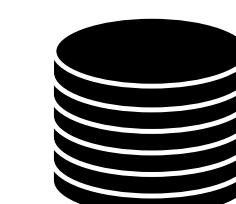
- JavaScript front-end is populated for query results using asynchronous access to multiple handover objects
 - ▶ biosamples and variants tables, CNV histogram, UCSC .bed loader, .pgxseg variant downloads...
- the complete middleware / CGI stack is provided through the *bycon* package
 - ▶ schemas, query stack, data transformation (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



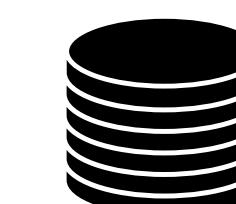
variants



analyses



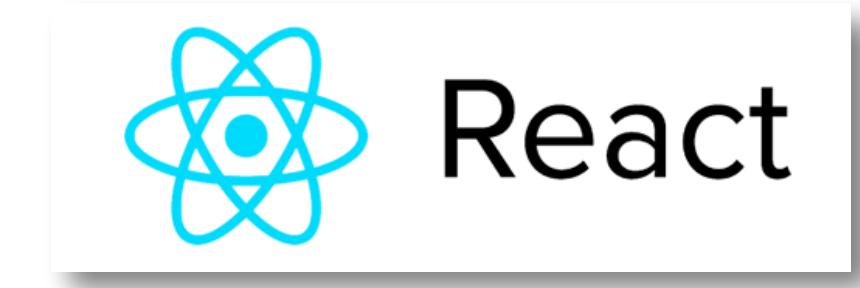
biosamples



individuals

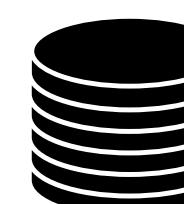


Entity collections

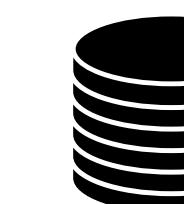


- *collations* contain pre-computed data (e.g. CNV frequencies, statistics) and information for all grouping entity instances and correspond to **filter values**
 - ▶ PMID:10027410, NCIT:C3222, pgx:cohort-TCGA, pgx:icdom-94703...
- *querybuffer* stores id values of all entities matched by a query and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

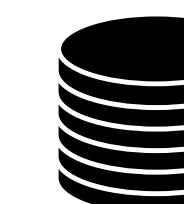
```
_id: ObjectId("6249bb654f8f8d67eb94953b"),
id: '0765ee26-5029-4f28-b01d-9759abf5bf14',
source_collection: 'variants',
source_db: 'progenetix',
source_key: '_id',
target_collection: 'variants',
target_count: 667,
target_key: '_id',
target_values: [
  ObjectId("5bab578b727983b2e00ca99e"),
  ObjectId("5bab578d727983b2e00cb505")]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



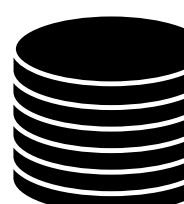
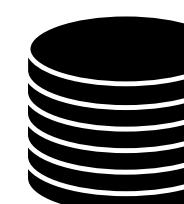
collations



geolocs



genespans publications



Utility collections

Beacon v2 Conformity and Extensions in *bycon*

Putting the ⁺ into Beacon ...

- support & use of standard Beacon v2 PUT & GET variant queries, filters and meta parameters
 - ➡ variant parameters, geneld, lengths, EFO & VCF CNV types, pagination
 - ➡ widespread, self-scoping filter use for bio-, technical- and id parameters with switch for descending terms use (globally or per term if using POST)
- extensive use of handovers
 - ➡ asynchronous delivery of e.g. variant and sample data, data plots
- + optional use of OR logic for filter combinations (global)
- + extension of query parameters
 - ➡ geographic queries incl. \$geonear and use of GeoJSON in schemas
- ↵ ↴ ↳ ↶ no implementation of authentication on this open dataset

bycon provides a number of additional services and output formats which are initiated over the /services path or provided as request parameters and are not considered Beacon extensions (though they follow the syntax where possible).



progenetix / byconaut

Type ⌘ to search

Code Issues Pull requests Actions Projects Wiki Security Insights Settings

byconaut Public

Edit Pins Unwatch 2 Fork 1 Star 0

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

progenetix / beaconplus-web

Type ⌘ to search

Code Pull requests Actions Projects Security Insights Settings

mbaudis get_plot_parameters

bin docs exports imports local rsrc services tmp .gitignore LICENSE README.md __init__.py install.py install.yaml mkdocs.yaml

2 branches

main

beaconplus-web Public forked from progenetix/progenetix-web

main 1 branch 0 tags

This branch is 44 commits ahead, 24 commits behind progenetix:main.

beaconplus.progenetix.org
.../progenetix/beaconplus-web/

progenetix / bycon

Type ⌘ to search

Code Issues Pull requests 1 Actions Projects Wiki Security 3 Insights Settings

bycon Public

Edit Pins Unwatch 4 Fork 6 Starred 5

main 4 branches 25 tags

Go to file Add file Code

mbaudis 1.3.6 ... be19a12 3 days ago 852 commits

File	Commit	Date
.github/workflows	Create mk-bycon-docs.yaml	8 months ago
bycon	1.3.6	3 days ago
docs	1.3.6	3 days ago
local	1.3.5 preparation	2 weeks ago
.gitignore	Update .gitignore	3 months ago
LICENSE	Create LICENSE	3 years ago
MANIFEST.in	major library & install disentanglement	9 months ago
README.md	#### 2023-07-23 (v1.0.68)	4 months ago
install.py	1.3.6	3 days ago
install.yaml	v1.0.57	5 months ago
mkdocs.yaml	1.1.6	3 months ago
requirements.txt	1.3.6	3 days ago
setup.cfg	...	10 months ago
setup.py	1.3.6	3 days ago
updev.sh	1.3.6	3 days ago

About

Bycon - A Python Based Beacon API (beacon-project.io) implementation leveraging the Progenetix (progenetix.org) data model

Readme CC0-1.0 license Activity 5 stars 4 watching 6 forks Report repository

Releases

25 tags Create a new release

Packages

No packages published Publish your first package

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>

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.

Bioconductor

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](https://doi.org/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] 

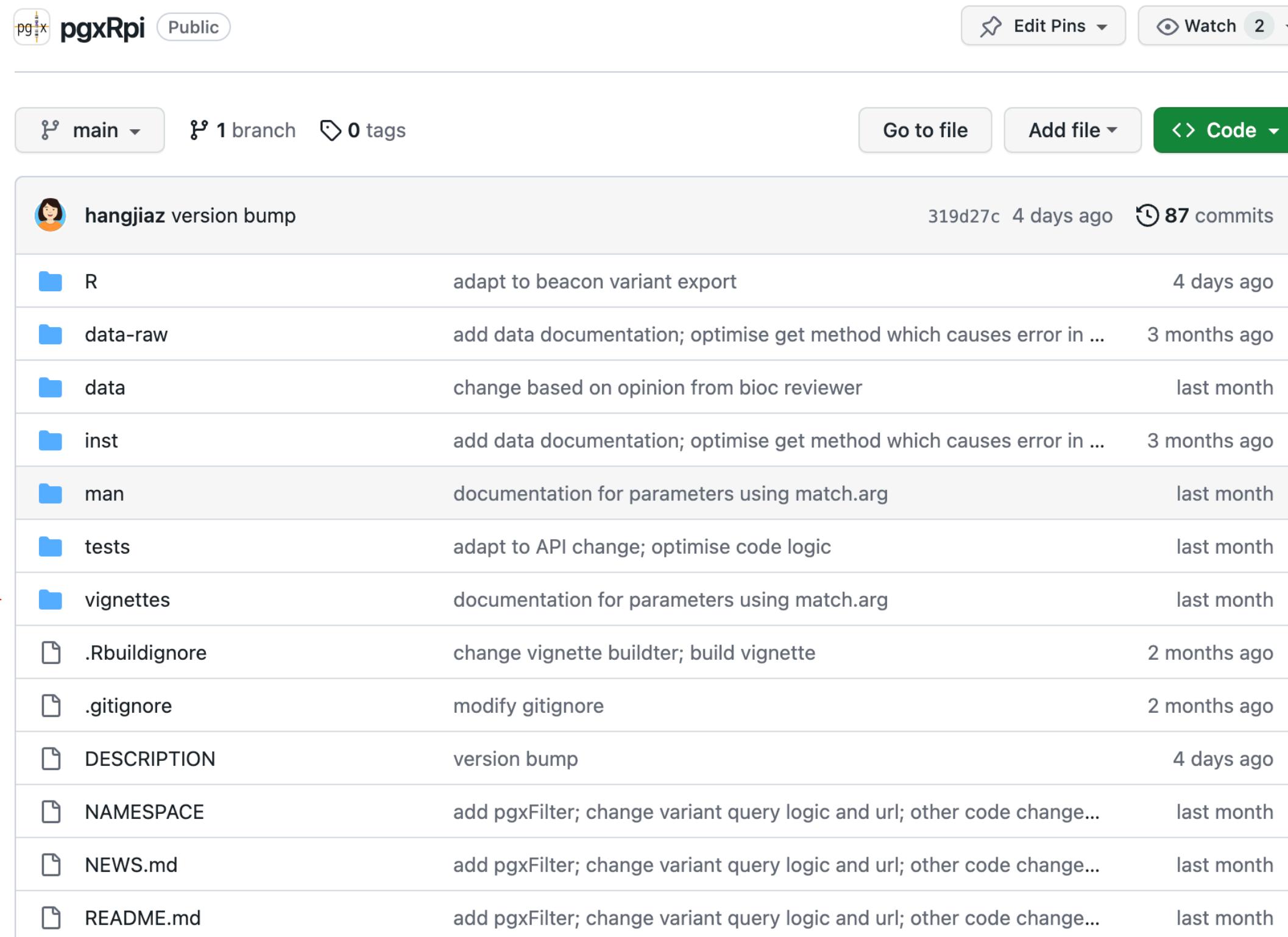
Maintainer: Hangjia Zhao <hangjia.zhao@uzh.ch>

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

Zhao H, Baudis M (2023). *pgxRpi: R wrapper for Progenetix*. [doi:10.18129/B9.bioc.pgxRpi](https://doi.org/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



The screenshot shows a GitHub repository page for 'pgxRpi'. At the top, there's a navigation bar with 'Edit Pins', 'Watch 2', and a 'Code' button. Below the navigation, there are buttons for 'main', '1 branch', '0 tags', 'Go to file', 'Add file', and another 'Code' button. The main content area displays a list of commits from a user named 'hangjiaz'. The first commit is highlighted with a red arrow pointing to it. The commit details are as follows:

Author	Commit Message	Date
hangjiaz	version bump	319d27c 4 days ago
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 builder; build vignette	2 months ago
.gitignore	modify gitignore	2 months ago
DESCRIPTION	version bump	4 days ago
NAMESPACE	add pgxFiler; change variant query logic and url; other code change...	last month
NEWS.md	add pgxFiler; change variant query logic and url; other code change...	last month
README.md	add pgxFiler; change variant query logic and url; other code change...	last month

2 Retrieve metadata 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 `pgxFiler` function helps access available filters used in Progenetix. Here is the example use:

```
# access all filters
all_filters <- pgxFiler()
# get all prefix
all_prefix <- pgxFiler(return_all_prefix = TRUE)
# access specific filters based on prefix
ncit_filters <- pgxFiler(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-kftvjjj1    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
```

Beacon Queries

Missing or ill defined options

- translocations are in principle possible (start bracket with "referenceName" and end bracket with "mateName") but not yet documented / battle tested
- functional elements?
- exon hits beyond specifying individual ones by sequence
- tandem dups ...

→ **Beacon & hCNV Scout Team**

The screenshot shows the Beacon+ query interface. At the top, there is a navigation bar with 'Beacon+' (highlighted in red), 'Progenetix', and 'Help' buttons. Below the navigation bar is a header titled 'Beacon Query Types' with tabs: 'Sequence / Allele' (selected), 'CNV (Bracket)', 'Genomic Range', 'Aminoacid', 'Gene ID', 'HGVS', and 'Sam'. Underneath the tabs is a 'Dataset' section containing a dropdown menu set to 'Test Database - examplez'. To the right of the dataset section are two dropdown menus for 'Chromosome' and 'Variant Type'. Below these are sections for 'Start or Position' (set to '19000001-21975098'), 'Reference Base(s)' (set to 'N'), and 'Alternate Base(s)' (set to 'A'). There is also a 'Select Filters' section with a dropdown menu. At the bottom of the form is a large blue button labeled 'Query Database'. Below this button are two yellow 'Form Utilities' buttons: 'Gene Spans' and 'Cytoband(s)'. At the very bottom are two rows of 'Query Examples' buttons: 'CNV Example', 'SNV Example', 'Range Example', 'Gene Match' in the first row, and 'Aminoacid Example', 'Identifier - HeLa' in the second row.



ELIXIR hCNV Community



www.elixir-europe.org

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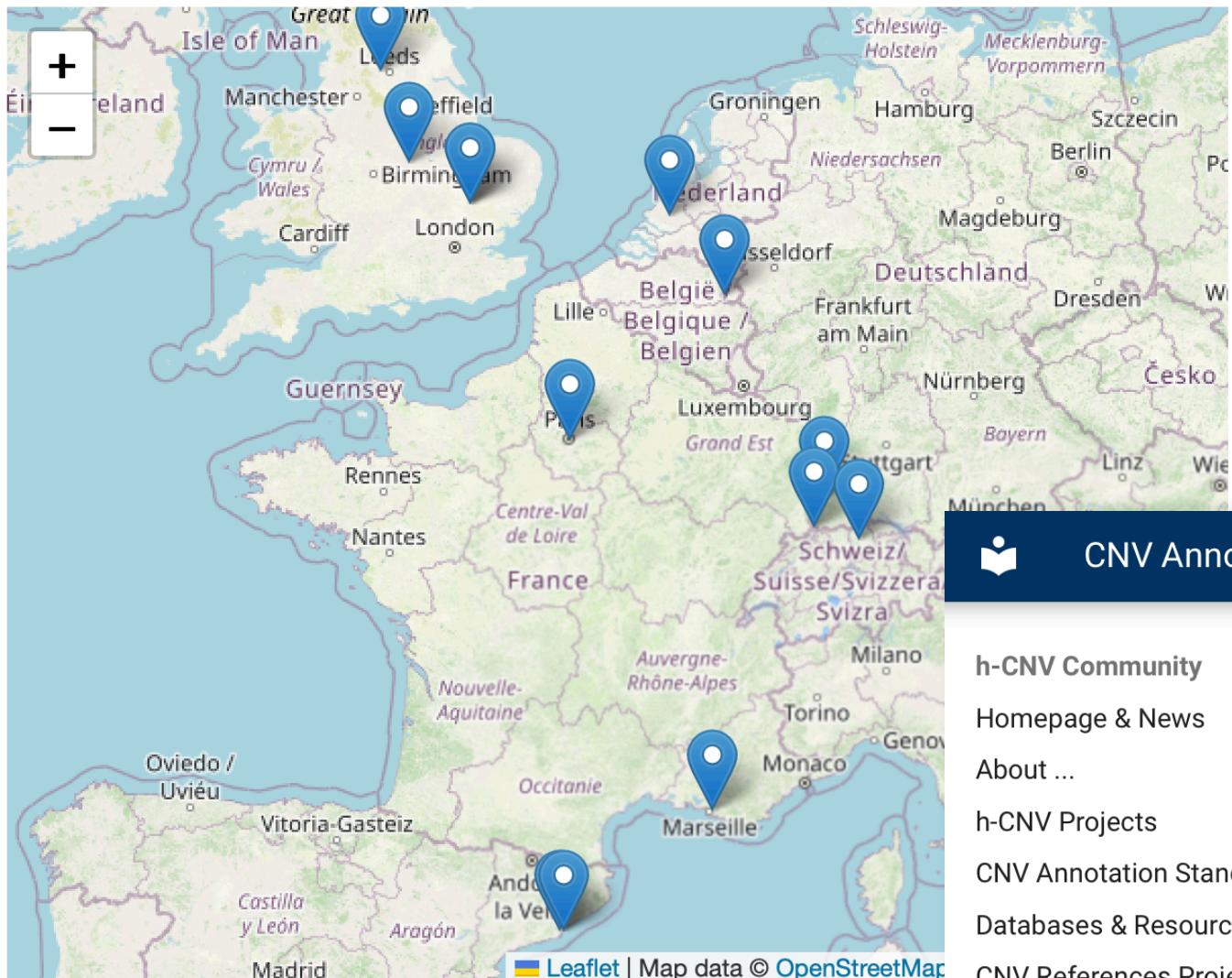
Beacon Project

ELIXIR Human Copy Number Variation community

Among the different types of inherited and acquired genomic variants, regional genomic copy number variations (CNV) contribute - if measured by affected genomic sequences - contribute by far the largest amount of genomic changes, contributing both to many syndromic diseases as well as the vast majority of human cancers. The [website](#) of the *Human Copy Number Variation*

Community (hCNV) is a resource originated in ELIXIR's h-CNV Community Implementation Study (2019-2021) with the aim to provide a resource hub and knowledge exchange space for scientists and practitioners working with - or being interested in - genomic copy number variations in health and diseases.

However, the scope of the community extends beyond CNVs and includes definition of and work with other types of genomic variations with a focus on structural variants.



ELIXIR hCNV Community

<https://cnvar.org/>

CNV Annotation Formats

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CNV Term Use Comparison in Computational (File/Schema) Formats

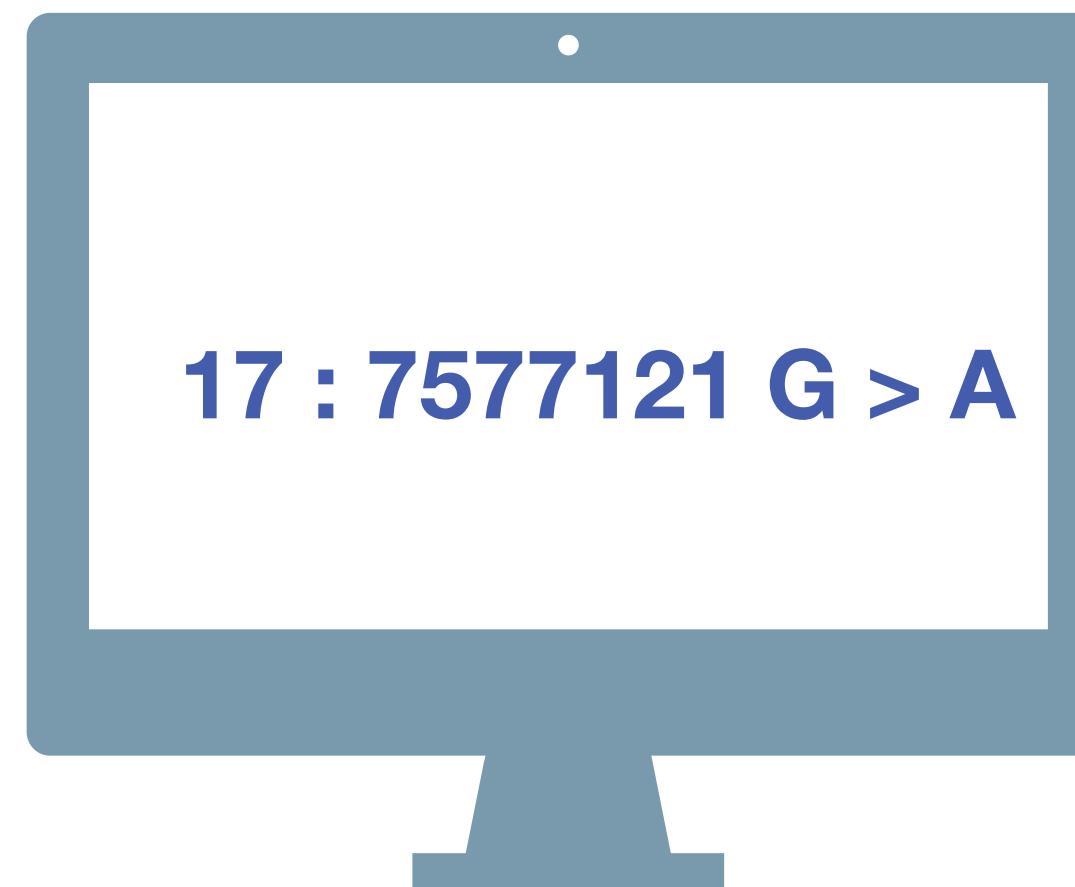
This table is maintained in parallel with the [Beacon v2 documentation](#).

EFO	Beacon	VCF	SO	GA4GH VRS ¹	Notes
EFO:0030070 copy number gain	DUP ² or EFO:0030070	DUP SVCLAIM=D ³	SO:0001742 copy_number_gain	EFO:0030070 gain	a sequence alteration whereby the copy number of a given genomic region is greater than the reference sequence
EFO:0030071 low-level copy number gain	DUP ² or EFO:0030071	DUP SVCLAIM=D ³	SO:0001742 copy_number_gain	EFO:0030071 low-level gain	
EFO:0030072 high-level copy number gain	DUP ² or EFO:0030072	DUP SVCLAIM=D ³	SO:0001742 copy_number_gain	EFO:0030072 high-level gain	commonly but not consistently used for >=5 copies on a bi-allelic genome region
EFO:0030073 focal genome amplification	DUP ² or EFO:0030073	DUP SVCLAIM=D ³	SO:0001742 copy_number_gain	EFO:0030072 high-level gain ⁴	commonly but not consistently used for >=5 copies on a bi-allelic genome region, of limited size (operationally max. 1-5Mb)
EFO:0030067 copy number loss	DEL ² or EFO:0030067	DEL SVCLAIM=D ³	SO:0001743 copy_number_loss	EFO:0030067 loss	a sequence alteration whereby the copy number of a given genomic region is smaller than the reference sequence
EFO:0030068 low-level copy number loss	DEL ² or EFO:0030068	DEL SVCLAIM=D ³	SO:0001743 copy_number_loss	EFO:0030068 low-level loss	
EFO:0020073 high-level copy number loss	DEL ² or EFO:0020073	DEL SVCLAIM=D ³	SO:0001743 copy_number_loss	EFO:0020073 high-level loss	a loss of several copies; also used in cases where a complete genomic deletion cannot be asserted

CNV Term Use Comparison

in computational (file/schema) formats

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



Beacon

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

YES | NO | \0



Genome Beacons Compromise Security?

Querying for thousands of specific SNV occurrences in a genomic data pool can identify individuals in an anonymized genomic data collection

Stanford researchers identify potential security hole in genomic data-sharing network

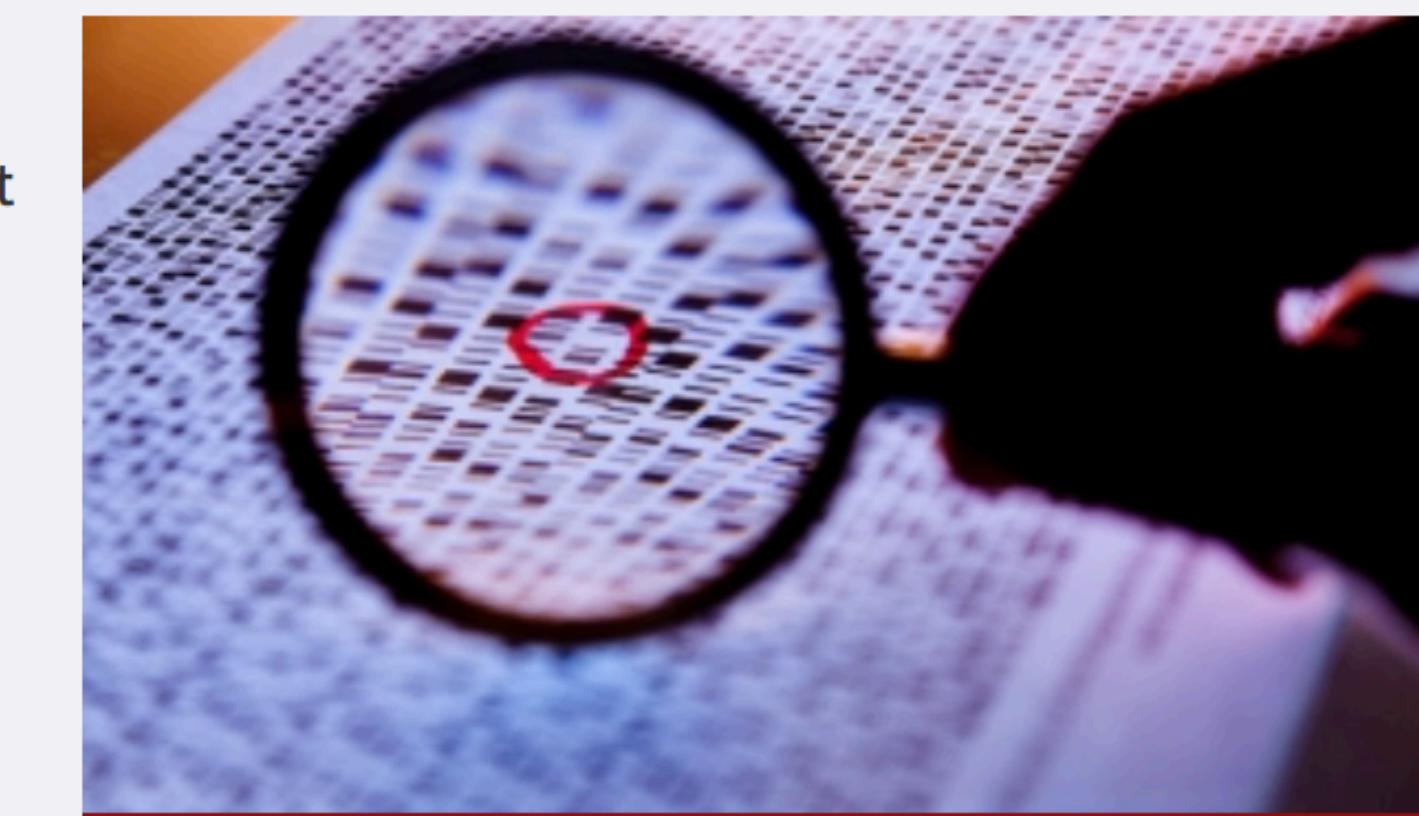
Hackers with access to a person's genome might find out if that genome is in an international network of disease databases.

OCT 29
2015

Sharing genomic information among researchers is critical to the advance of biomedical research. Yet genomic data contains identifiable information and, in the wrong hands, poses a risk to individual privacy. If someone had access to your genome sequence — either directly from your saliva or other tissues, or from a popular genomic information service — they could check to see if you appear in a database of people with certain medical conditions, such as heart disease, lung cancer or autism.

Work by a pair of researchers at the [Stanford University School of Medicine](#) makes that genomic data more secure. [Suyash Shringarpure](#), PhD, a postdoctoral scholar in genetics, and [Carlos Bustamante](#), PhD, a professor of genetics, have demonstrated a technique for hacking a network of global genomic databases and how to prevent it. They are working with investigators from the Global Alliance for Genomics and Health on implementing preventive measures.

The work, published Oct. 29 in *The American Journal of Human Genetics*, also bears importantly on the larger question of how to analyze mixtures of genomes, such as those from different people at a crime scene.



Stanford researchers are working with the Global Alliance for Genomics and Health to make genomic information in the Beacon Project more secure.
Science photo/Shutterstock



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