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

Universität Zürich[UZH]

Structural Genome Variations in Cancer
and the
Case for Open Data Standards

Michael Baudis
Professor of Bioinformatics
University of Zürich
Swiss Institute of Bioinformatics **SIB**
GA4GH Workstream Co-lead *DISCOVERY*
Co-lead ELIXIR Beacon API Development
Co-lead ELIXIR hCNV Community

SIB
Swiss Institute of
Bioinformatics

elixir

Theoretical Cytogenetics and Oncogenomics

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

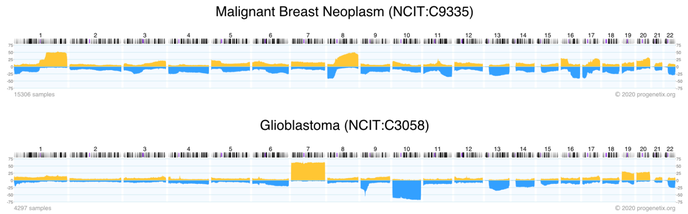
Curators

Data ~~Parasites~~

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"



progenetix

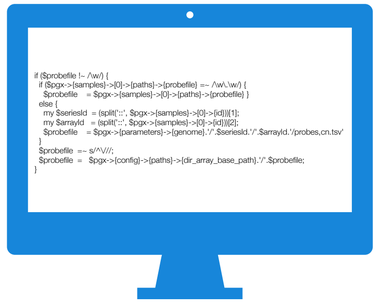
Bioinformatics & Bioinformaticians are …

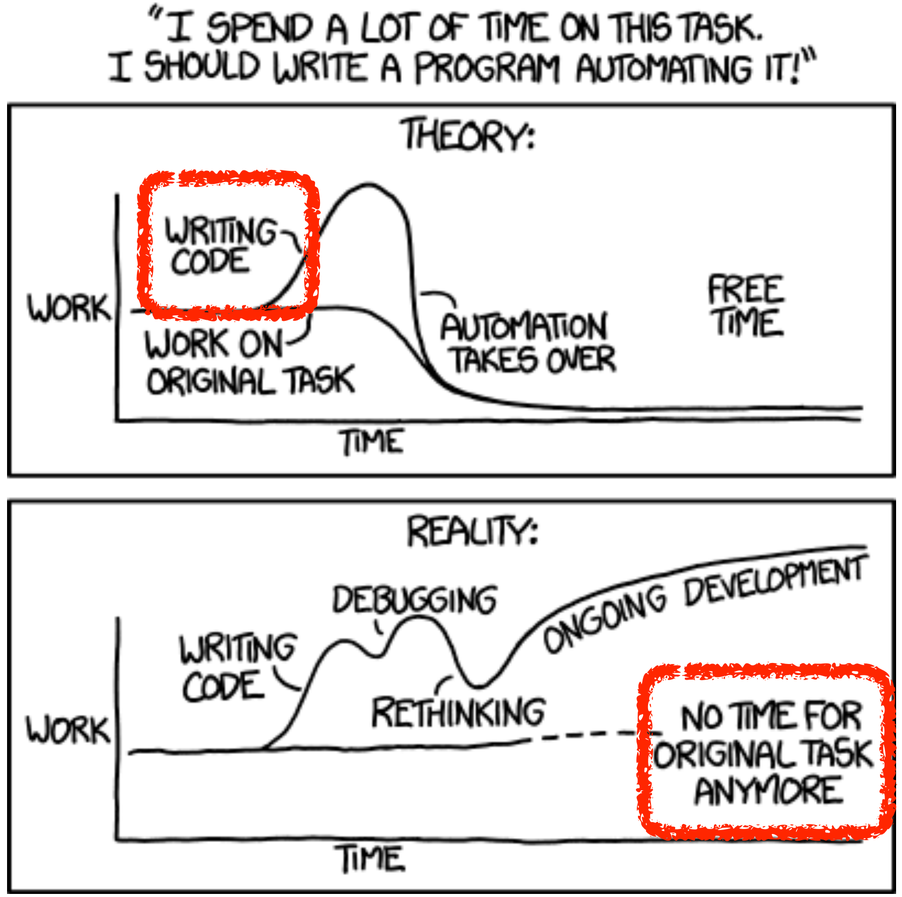
Bioinformatician	Bio**informatician**
strong biological knowledge	sufficient biological background
provides hypothesis and / or dataset	provides statistical, analysis methods
sufficient statistical and **computational** expertise to correctly use bioinformatics tools & develop workflows (scripting …)	**sufficient biological** or **medical** background to understand problems presented and identify pitfalls and hidden biases arising from data generation
expert **user** of informatics tools	**developer** of informatics tools
may get a Nobel	may get rich

Bioinformatics & Bioinformaticians are ...

Bioinformatician	Bio**informatician**
strong biological knowledge	sufficient biological background
provides hypothesis and / or dataset	provides statistical, analysis methods
sufficient statistical and **computational** expertise to correctly use bioinformatics tools & develop workflows (scripting ...)	**sufficient biological** or **medical** background to understand problems presented and identify pitfalls and hidden biases arising from data generation
expert **user** of informatics tools	**developer** of informatics tools
may get a Nobel	may get rich

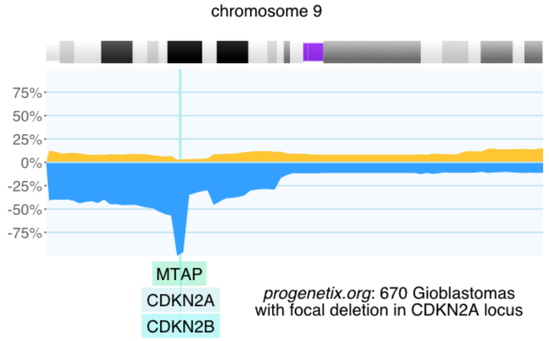
{bio_informatics_science}





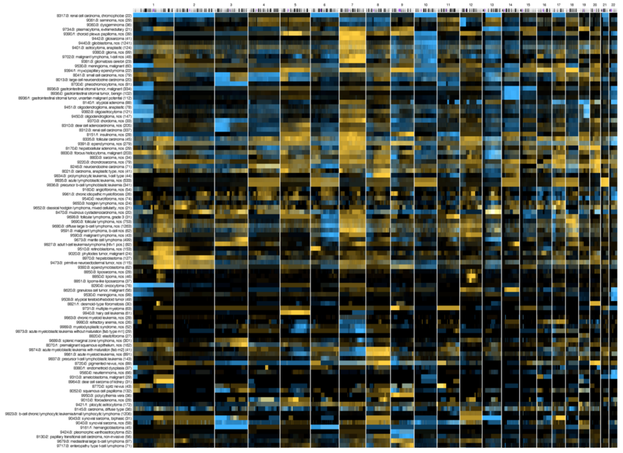
Randall Munroe - XKCD
https://xkcd.com/1319/

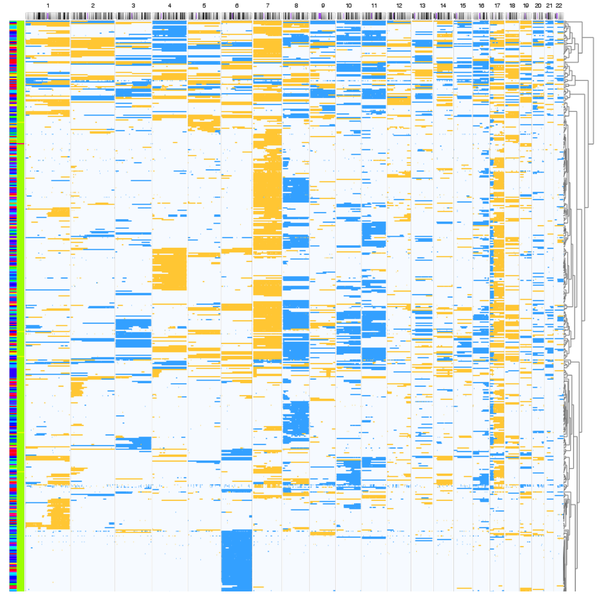
Theoretical Cytogenetics and Oncogenomics Research | Methods | Standards

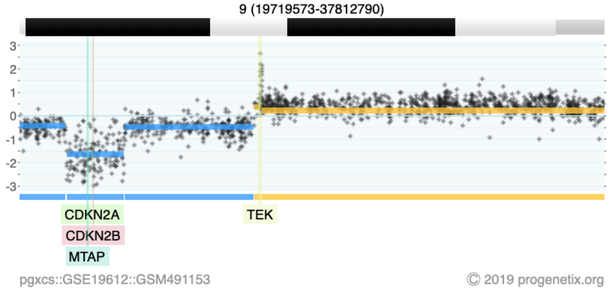


Genomic Imbalances in Cancer - Copy Number Variations (CNV)

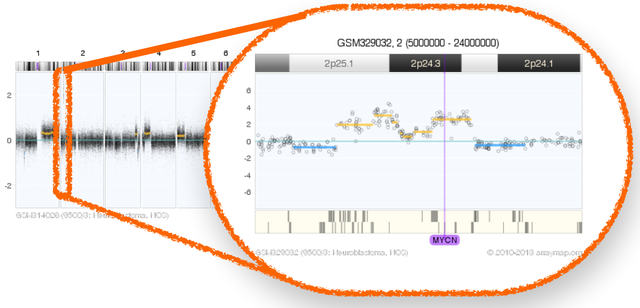
- Point mutations (insertions, deletions, substitutions)
- Chromosomal rearrangements
- **Regional Copy Number Alterations** (losses, gains)
- Epigenetic changes (e.g. DNA methylation abnormalities)







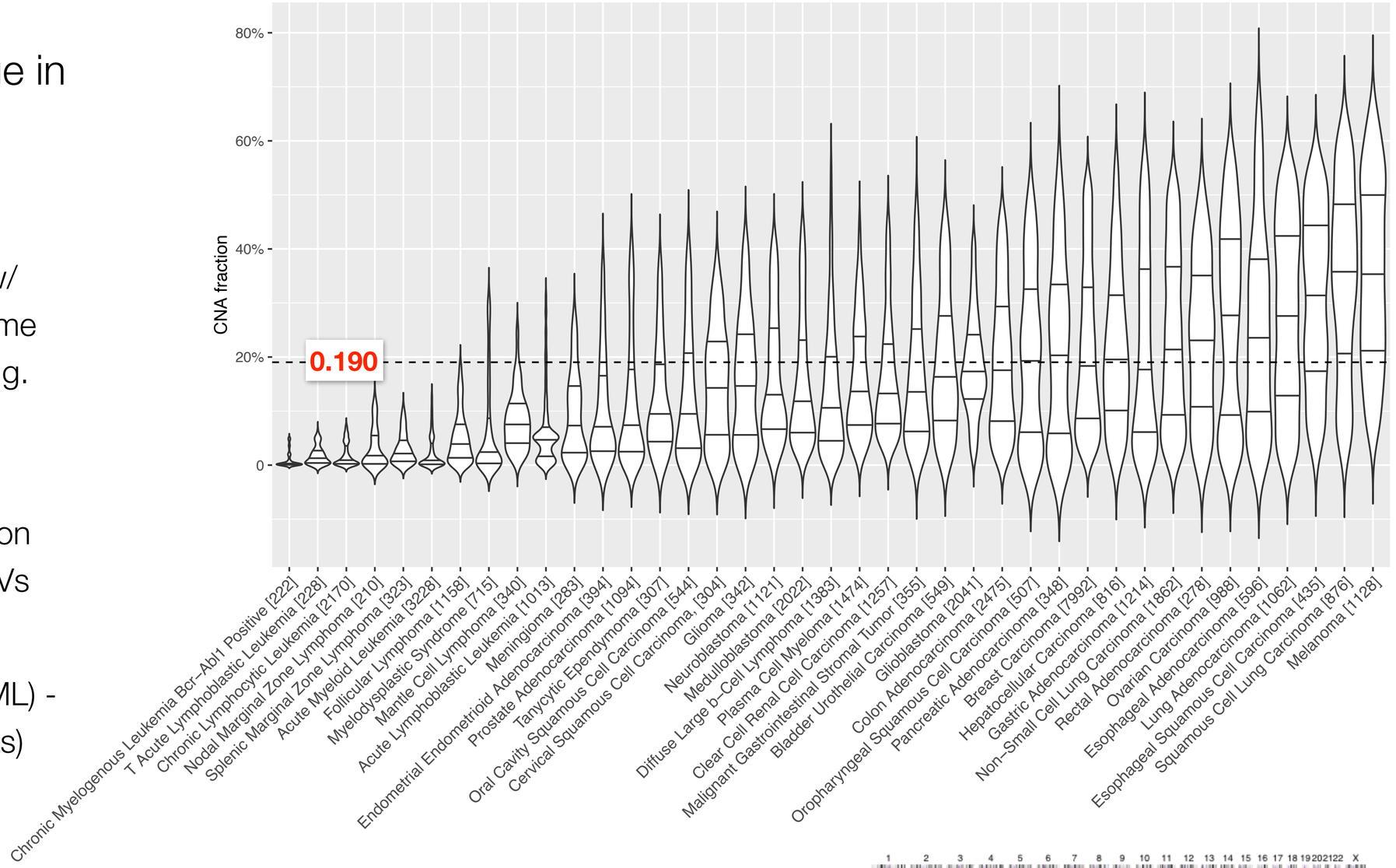
2-event, homozygous deletion in a Glioblastoma



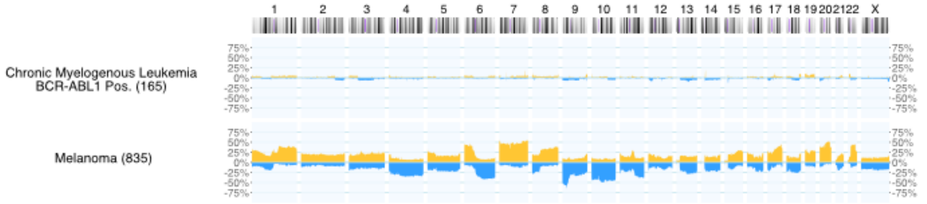
MYCN amplification in neuroblastoma
(GSM314026, SJNB8_N cell line)

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 =>



progenetix.net: storage and visualization of genomic aberration data in human malignancies

michael baudis, md

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

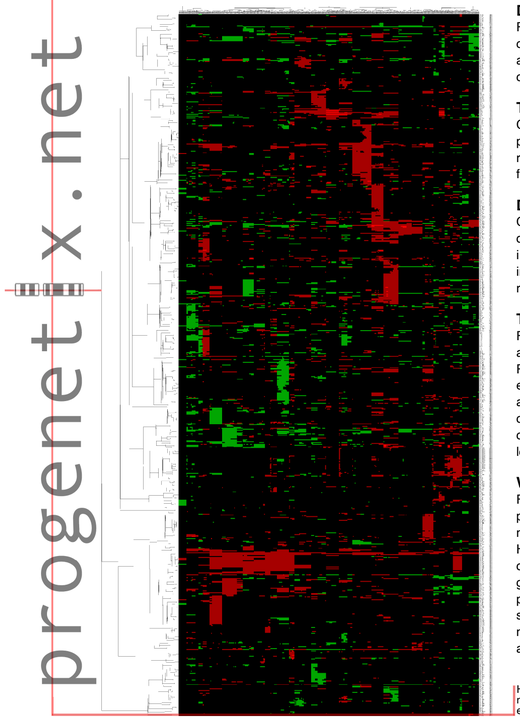
Currently, the primary data is stored in a dedicated “off-line” database. Besides case identifier and ISCN adapted chromosomal imbalance data, tumor classification and source information including the PubMed identifier is recorded. Disease entities are reclassified to ICD-O-3 codes.

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.

BIOINFORMATICS **APPLICATIONS NOTE** *Vol. 17 no. 12 2001*
Pages 1228–1229

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

Michael Baudis [1, 2,] and Michael L. Cleary [2]*

[1]Medizinische Klinik und Poliklinik V der Universität Heidelberg, Germany and [2]Department of Pathology, Stanford University Medical Center, Stanford, CA 94305, USA

Received on July 5, 2001; revised on July 9, 2001; accepted on July 16, 2001

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; Kallioniemi *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

*To whom correspondence should be addressed.

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

progenetix.org

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

Universität Zürich[UZH]

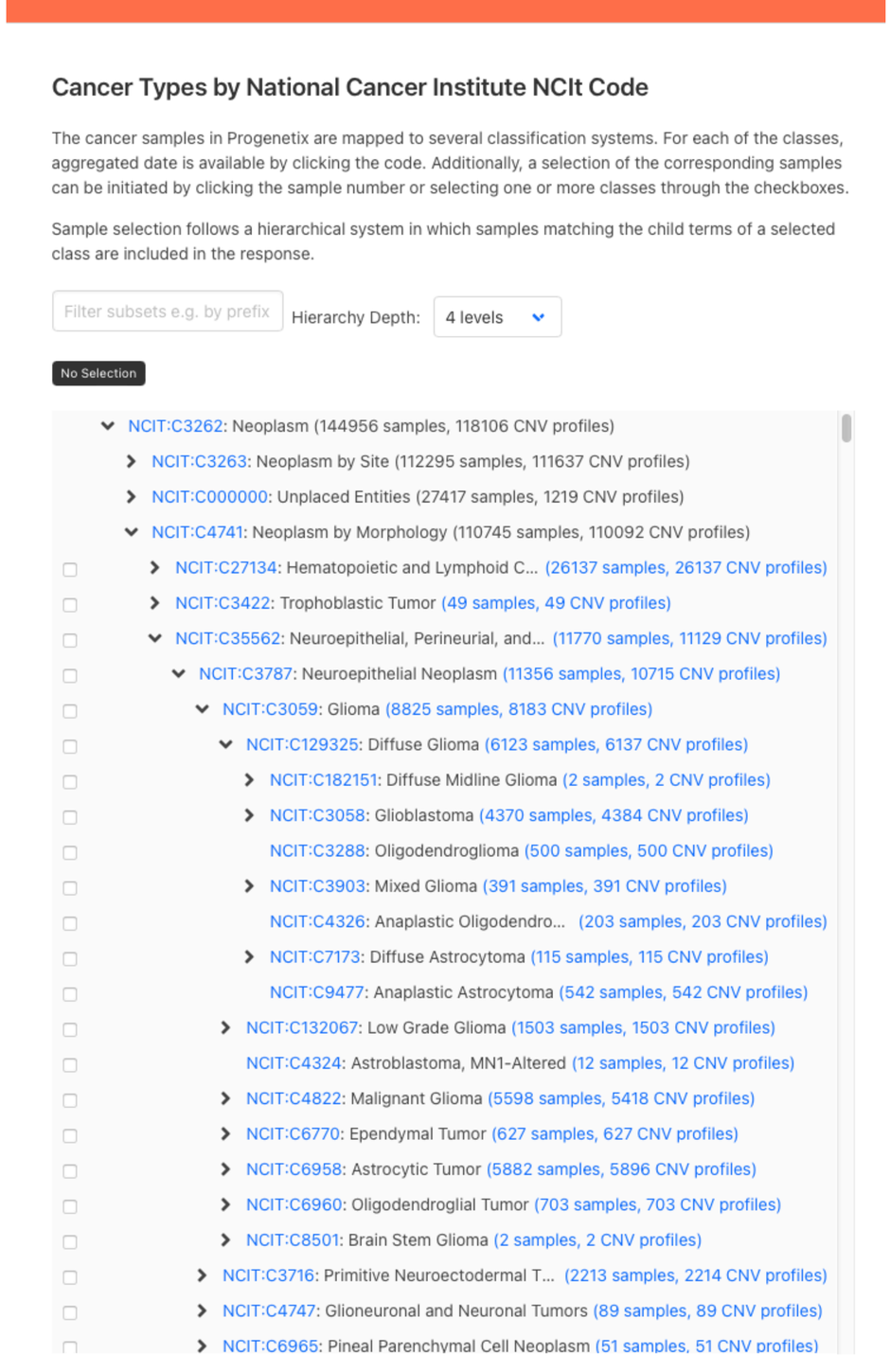
progenetix

SIB Swiss Institute of Bioinformatics

progenetix.org

Cancer Genomics Reference Resource

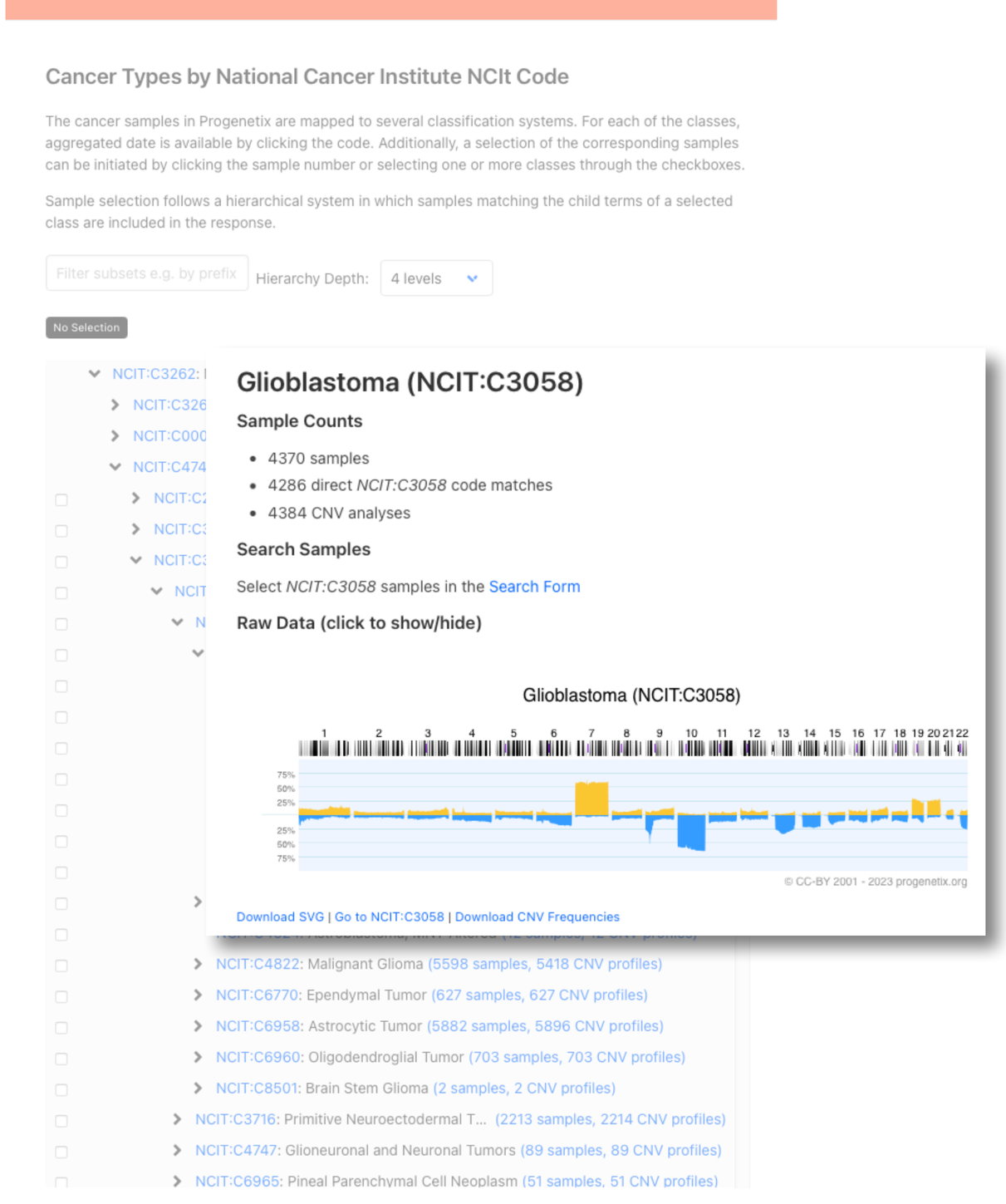
- ***open*** resource for oncogenomic profiles
- over **116'000 cancer CNV profiles**
- more than **800 diagnostic types**
- inclusion of reference datasets (e.g. TCGA)
- standardized encodings (e.g. NCIt, ICD-O 3)
- identifier mapping for PMID, GEO, Cellosaurus, TCGA, cBioPortal where appropriate
- core clinical data (TNM, sex, survival ...)
- data mapping services
- recent addition of SNV data for some series



progenetix.org

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



Universität Zürich[UZH]

progenetix

SIB Swiss Institute of Bioinformatics

progenetix.org

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

Universität Zürich[UZH]

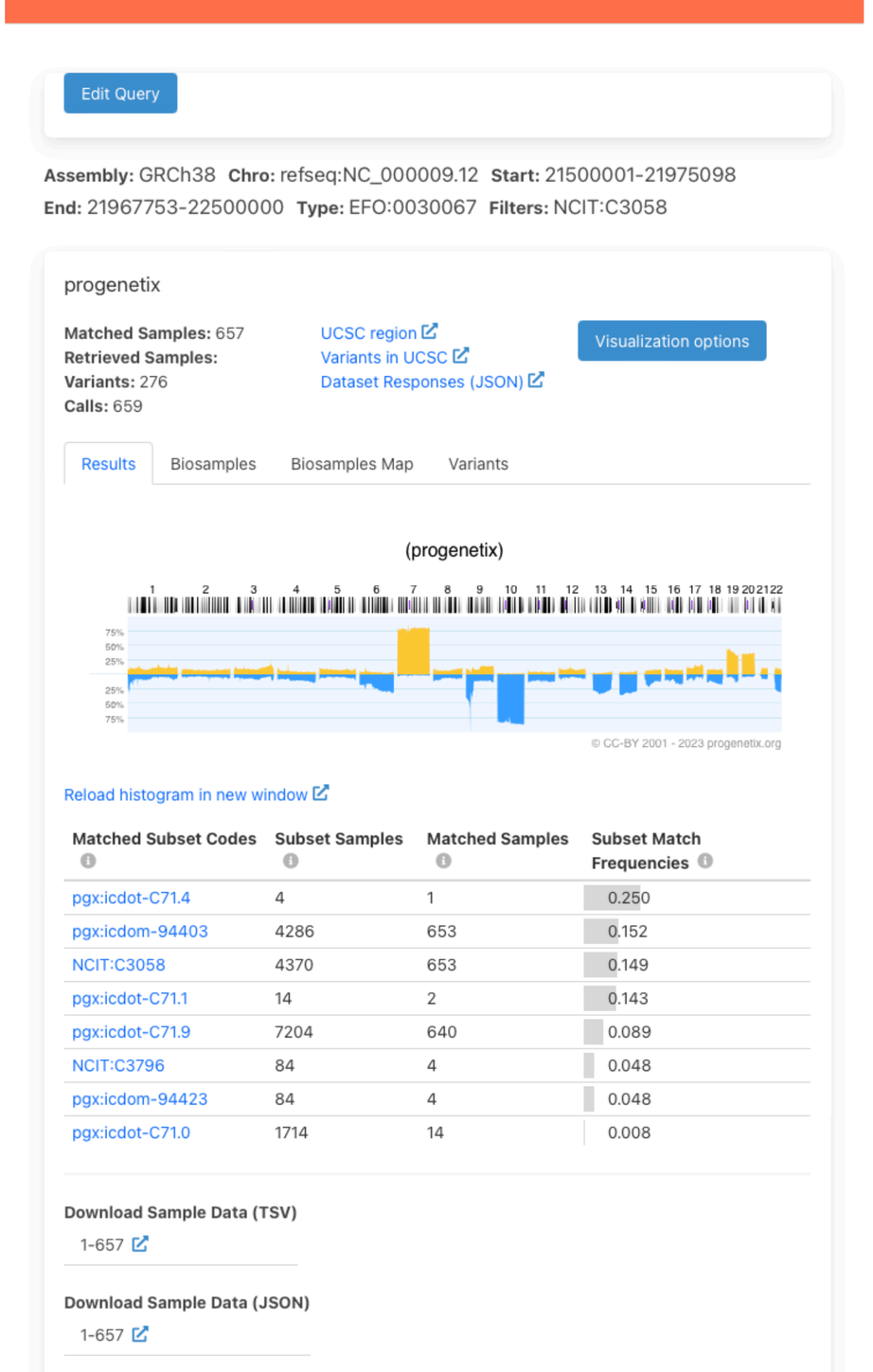
progenetix

SIB Swiss Institute of Bioinformatics

progenetix.org

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



Universität Zürich[UZH]

progenetix

SIB Swiss Institute of Bioinformatics

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

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

progenetix.org

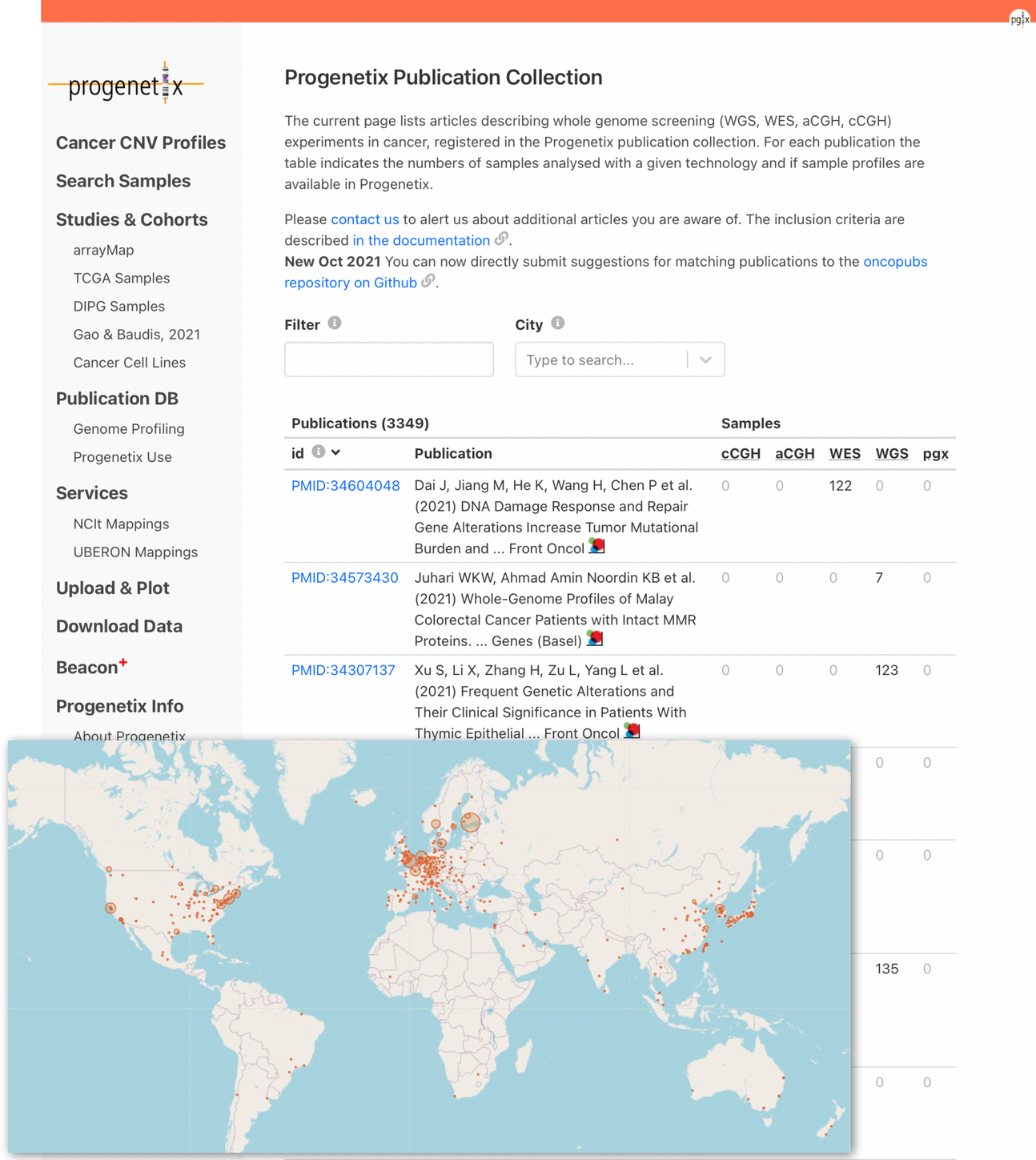
Cancer Genomics Reference Resource

- ***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

Universität Zürich[UZH]

progenetix

SIB Swiss Institute of Bioinformatics



Cancer Cell Lines

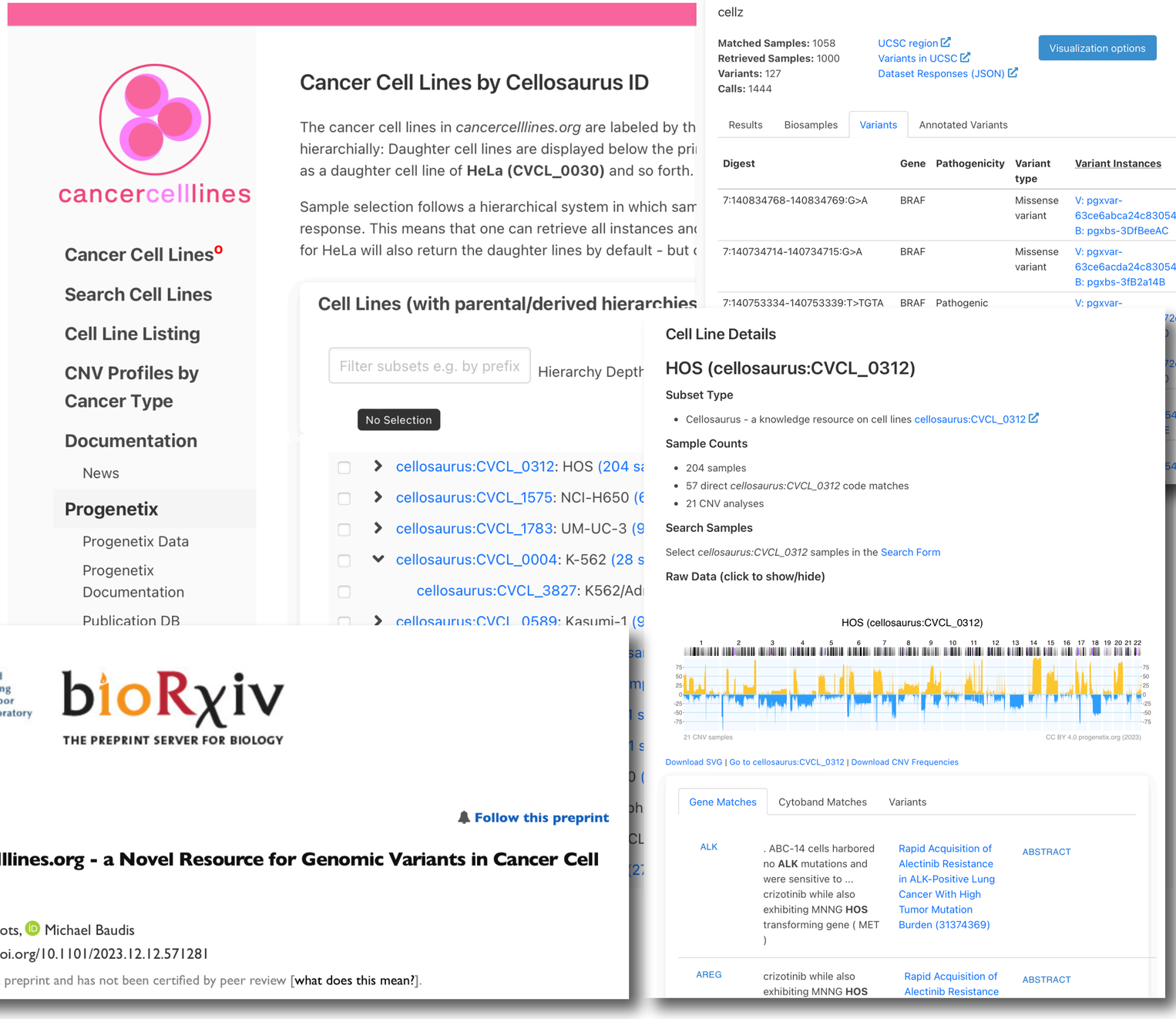
Cancer Genomics Reference Resource

- 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

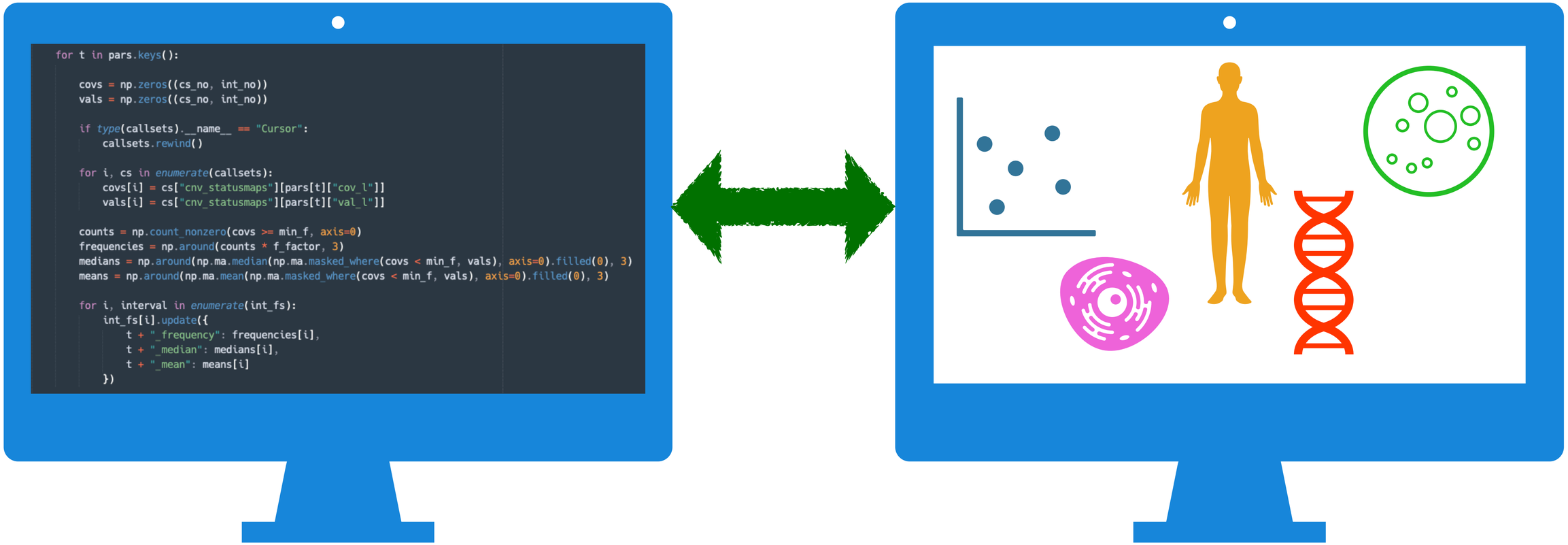
➡ integration in data federation approaches

cancercelllines.org

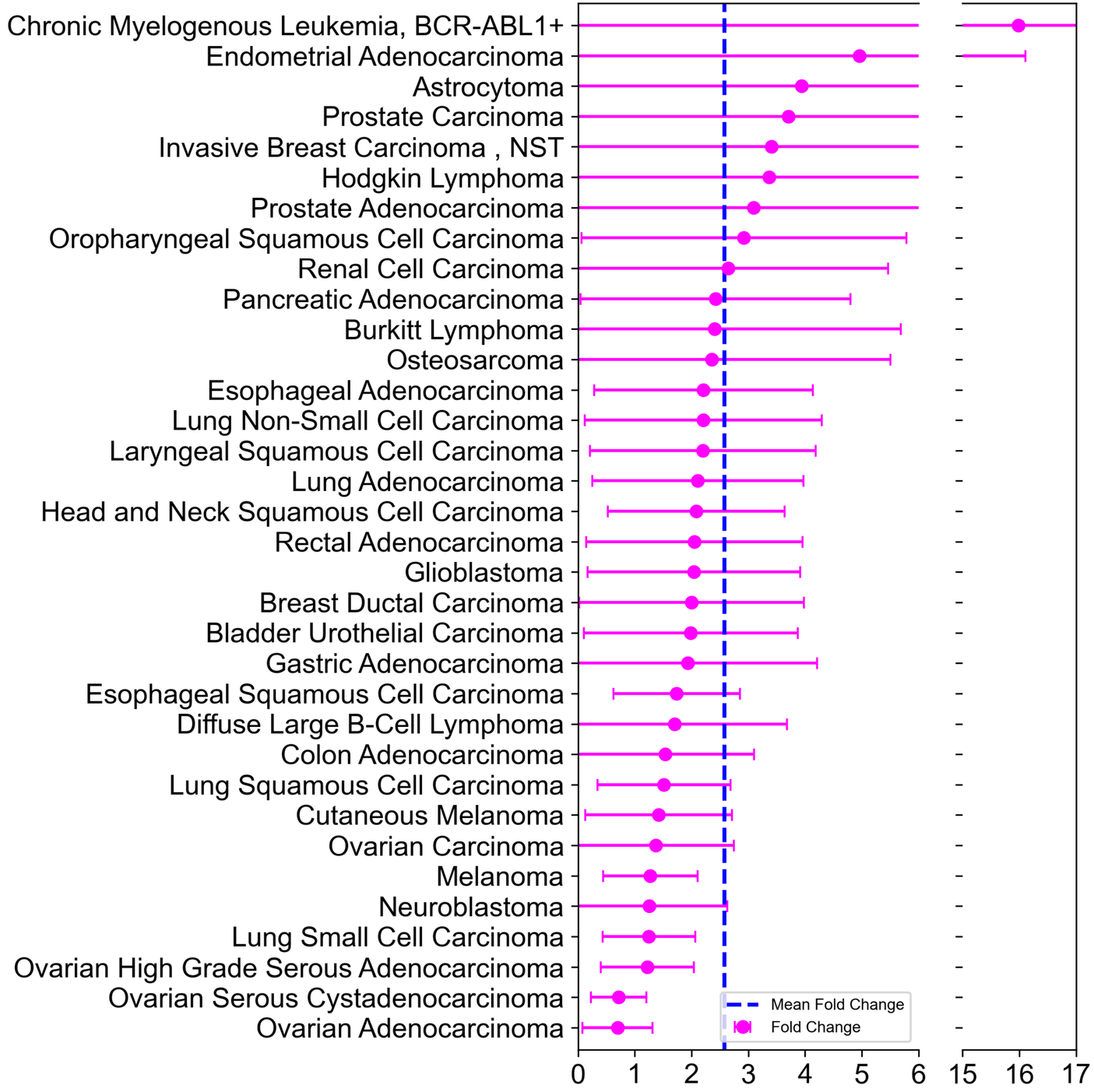
Lead: Rahel Paloots



{BioInformaticsScience}



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

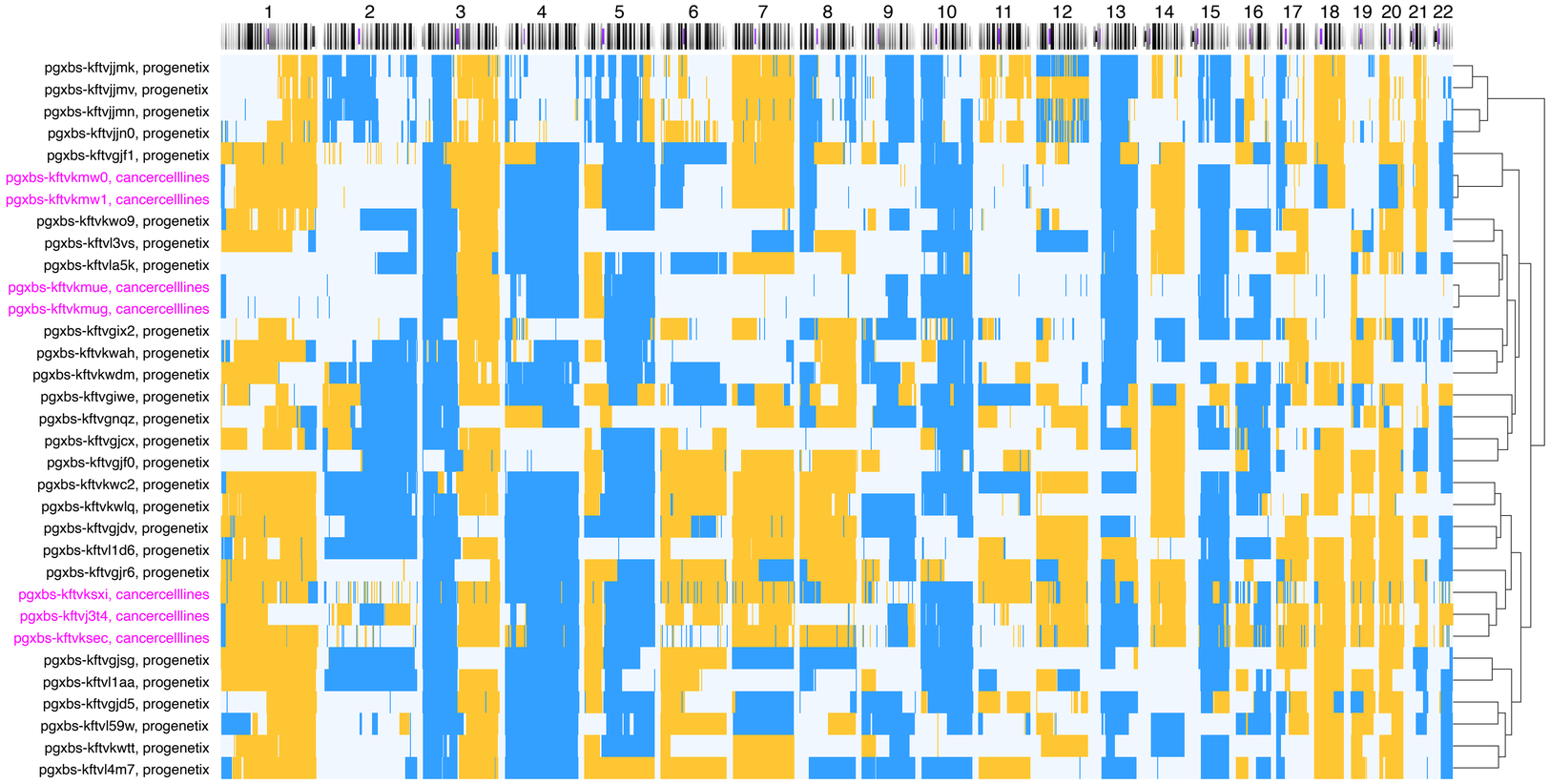


Fold changes between genome CNV coverages of cell lines and tumors

Lead: Rahel Paloots

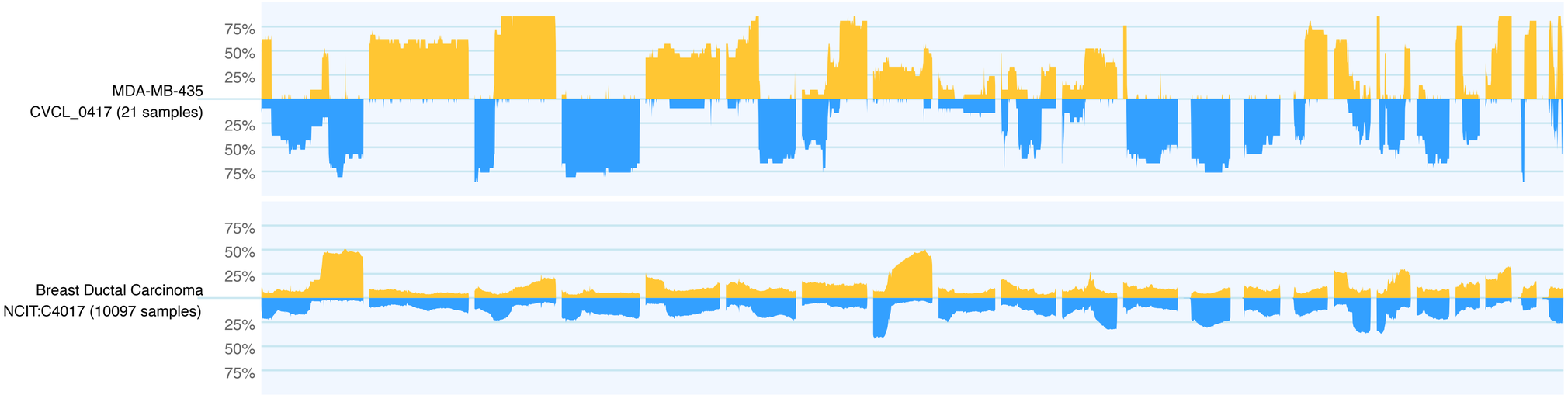
Tumor subpopulations can be matched with highly similar cell lines

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



Lead: Rahel Paloots

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

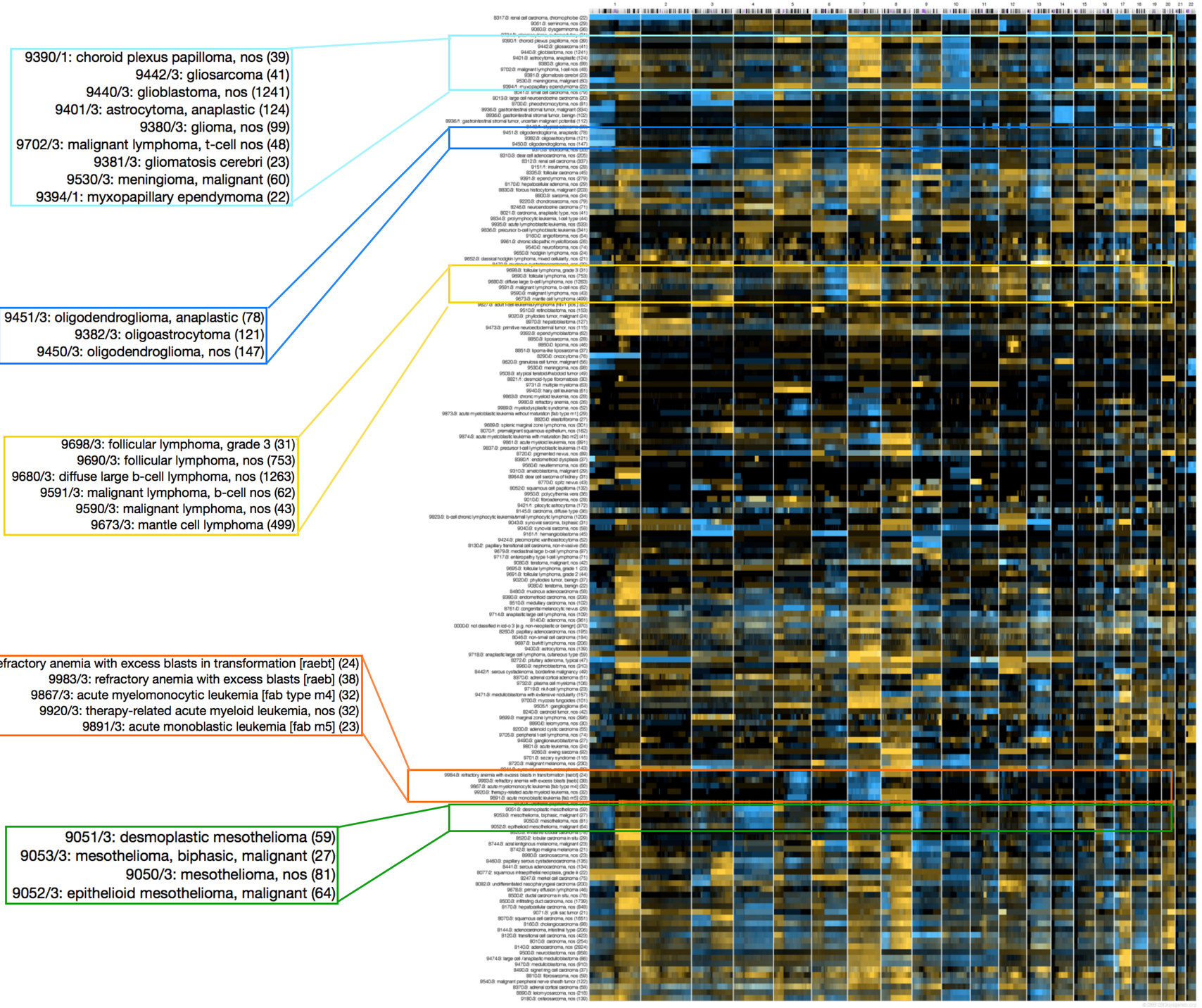


Lead: Rahel Paloots

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

Lead: Rahel Paloots

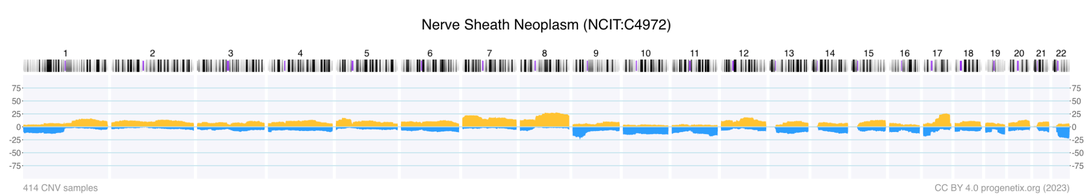
Somatic Mutations In Cancer: Patterns
Making the case for genomic classifications
Some related cancer entities show similar copy number profiles

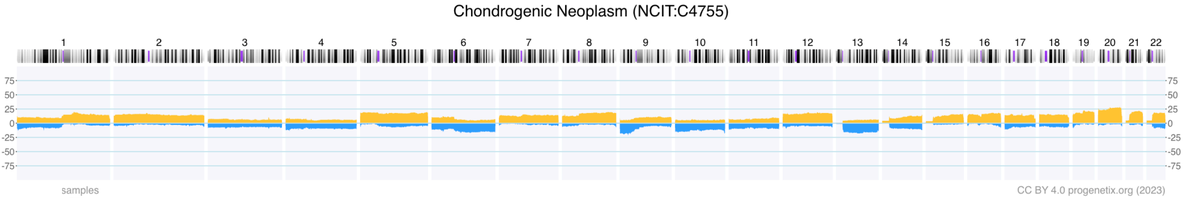


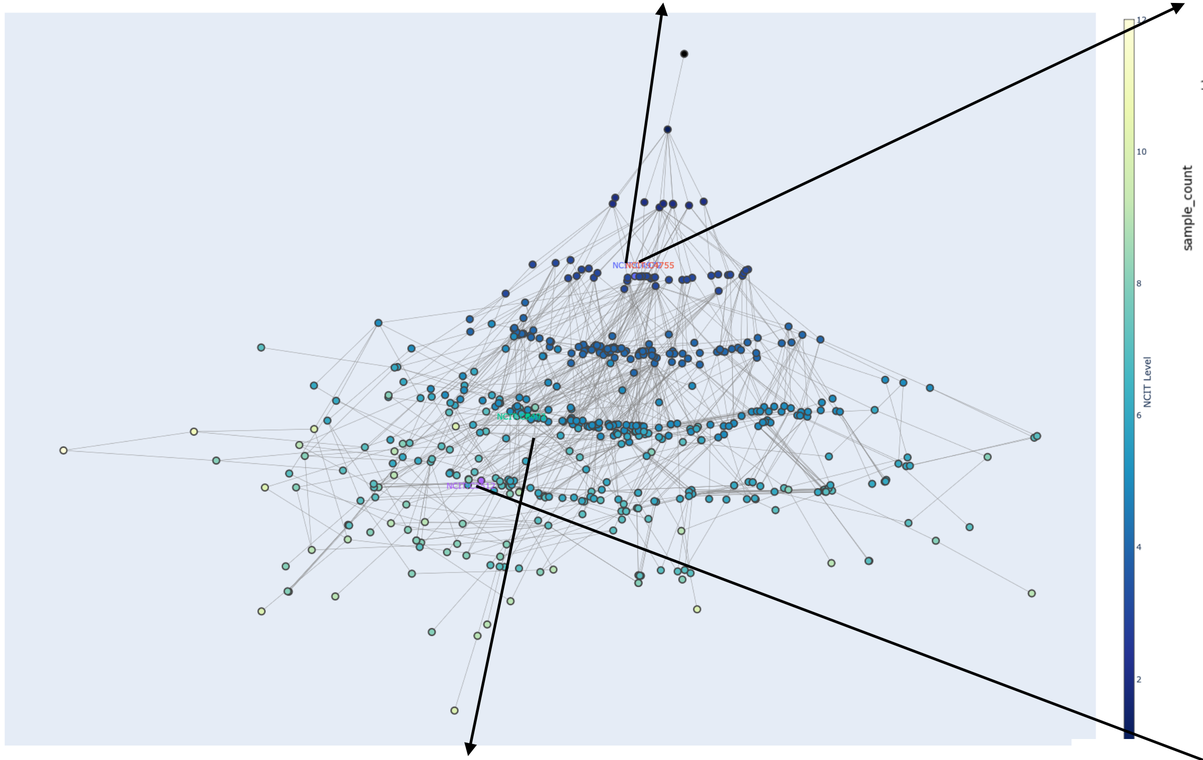
arrayMap

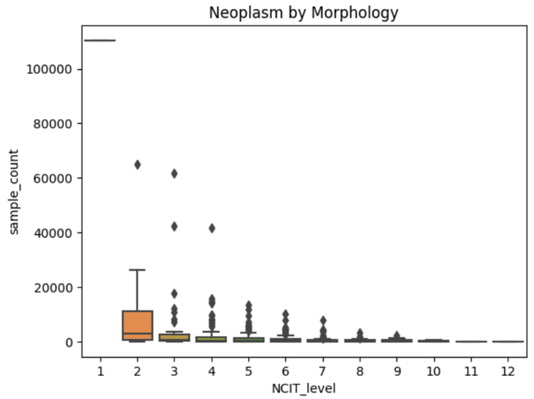
CNV profiles heterogeneity vs cancer classification

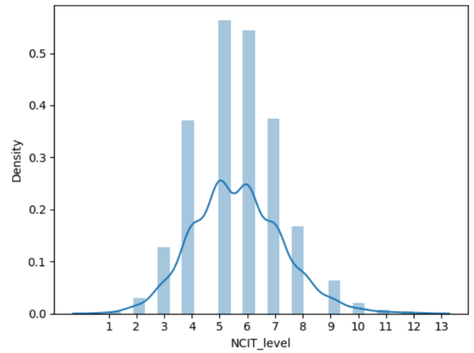
Correspondance of genomic profiles to NCIT cancer hierarchy

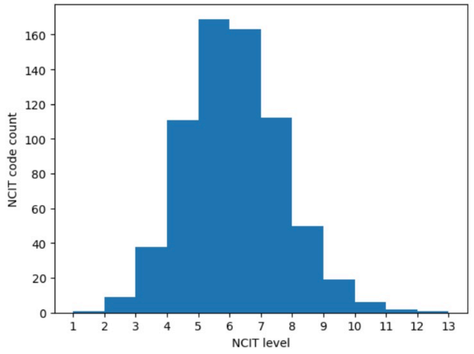


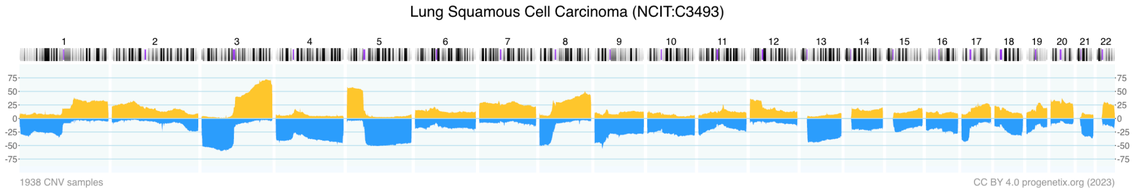


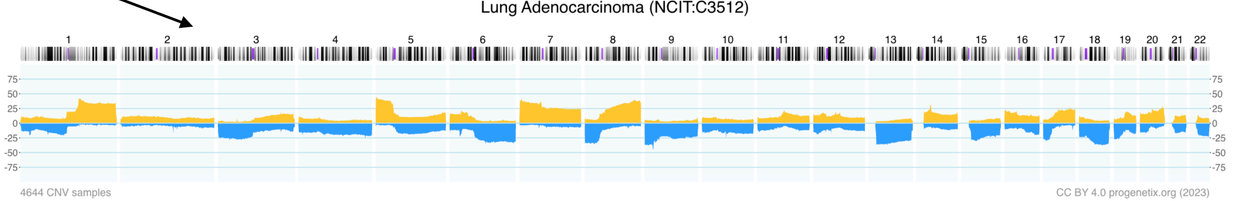








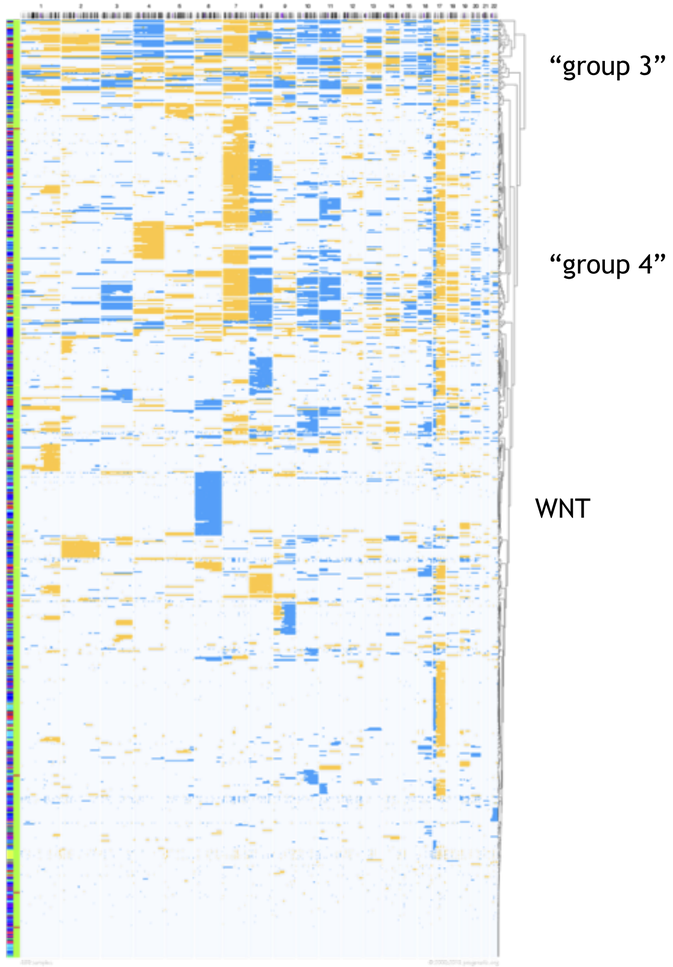




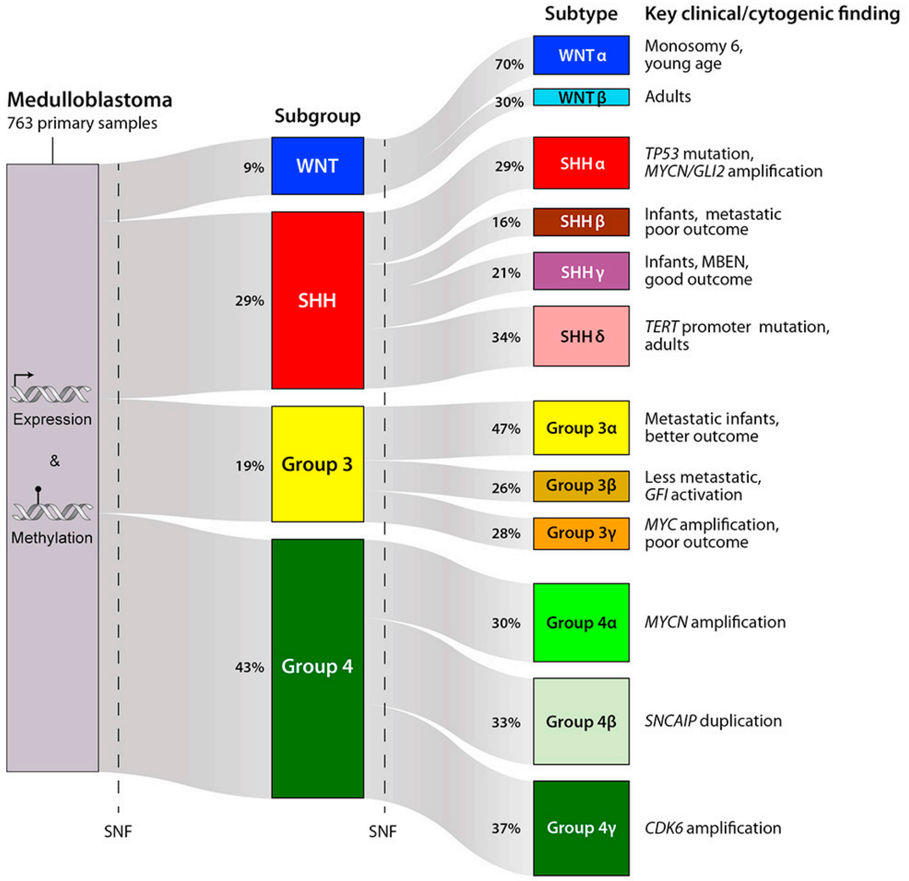
Lead: Ziying Yang

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.



Copy number profiles from 889 primary medulloblastomas

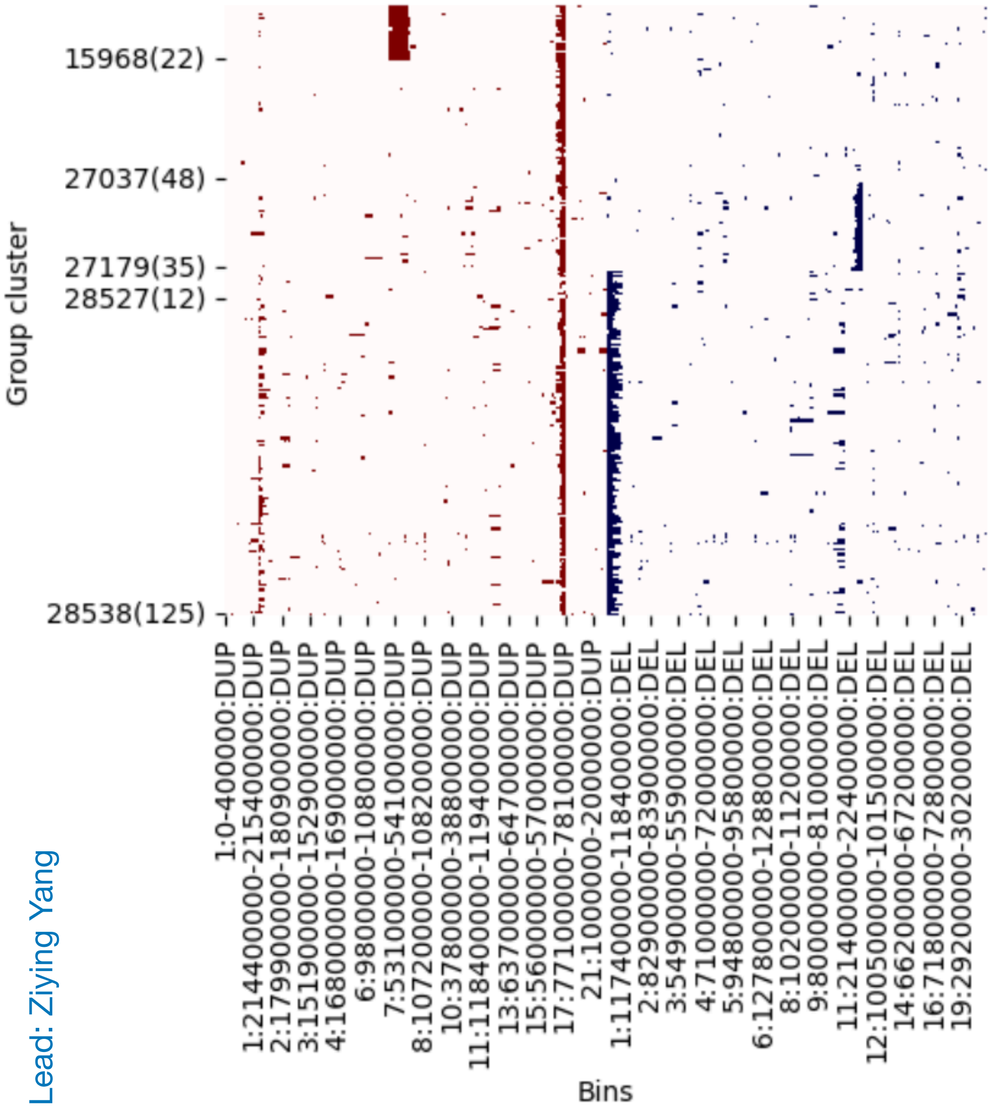


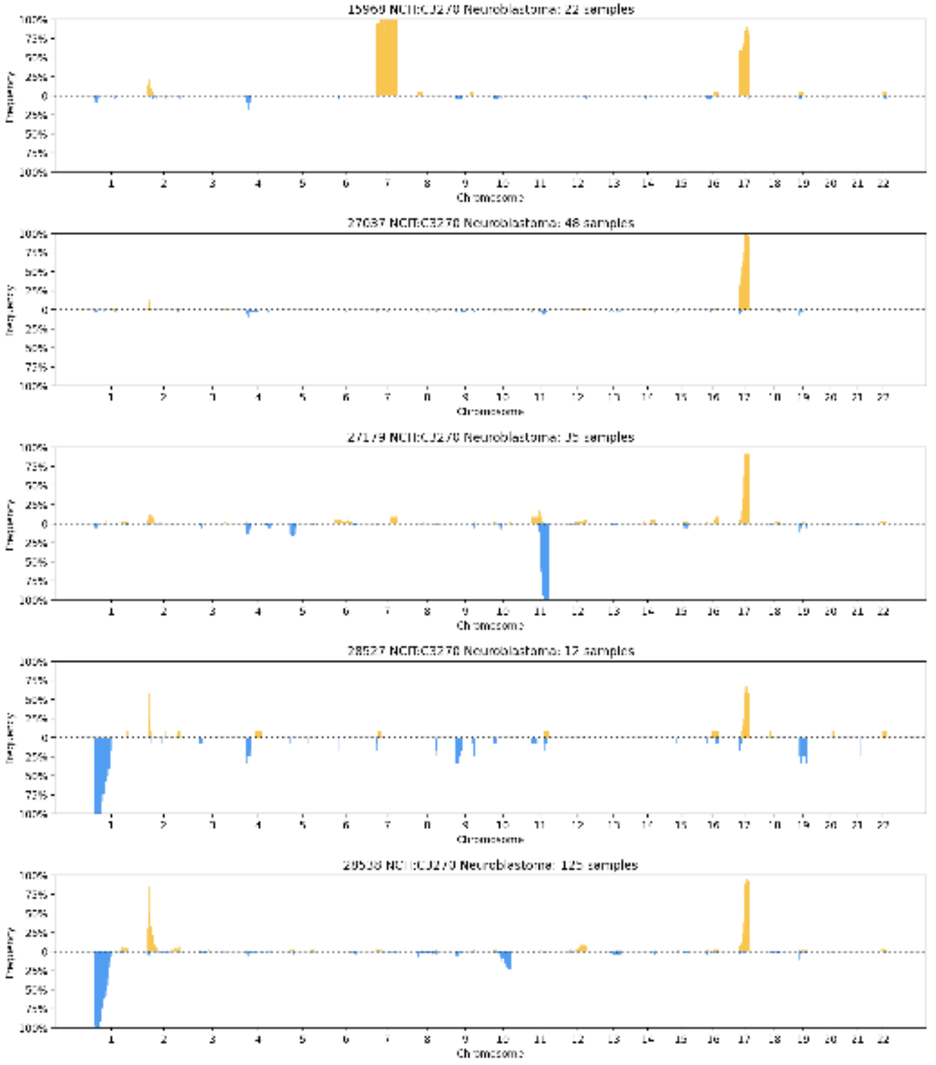
Intertumoral heterogeneity with medulloblastoma subgroups.
Cavalli, Florence MG, et al. "Intertumoral heterogeneity within medulloblastoma subgroups." *Cancer Cell* 31.6 (2017): 737-754.

Lead: Ziying Yang

Results

Entity CNV heterogeneity: Neuroblastoma



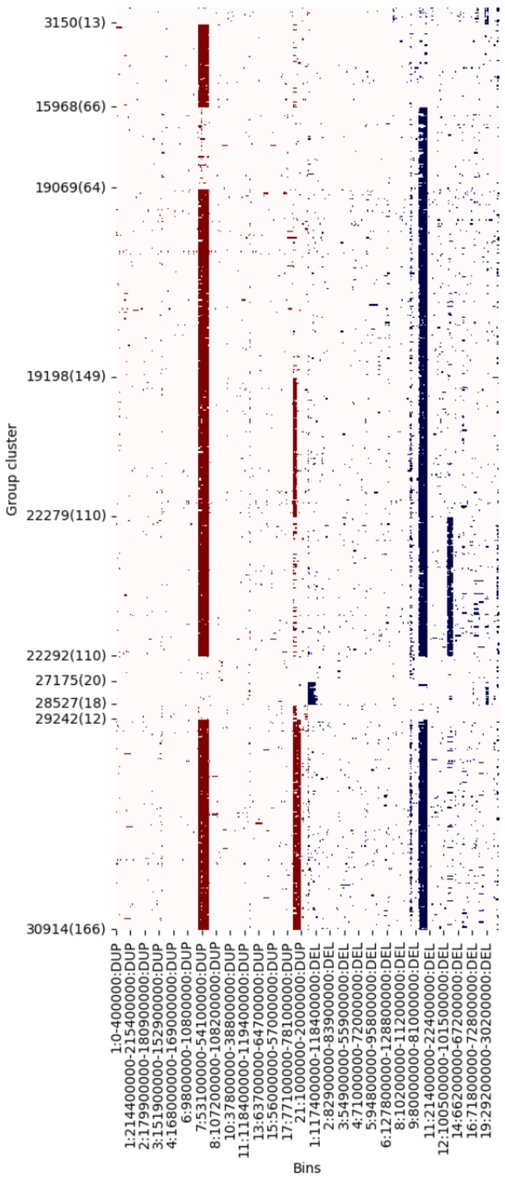


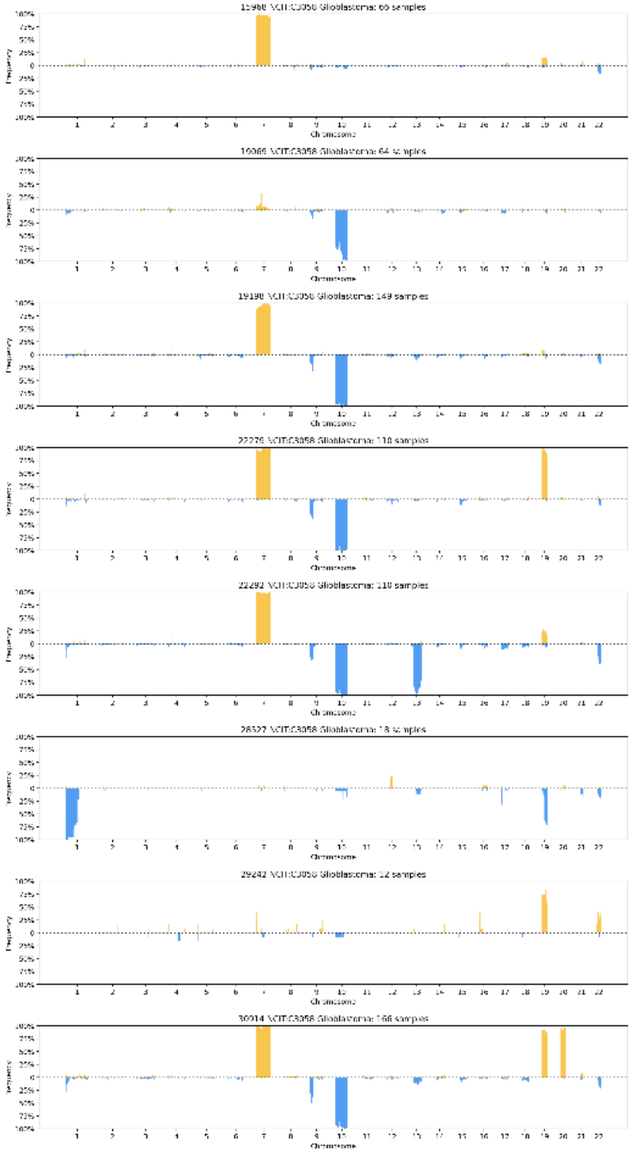
group cluster	CNV features
15968	Dup 7
27037	Dup 17q
27197	Del 11q, Dup 17q
28527	Del 1p
28538	Del 1p, Dup 17q

Lead: Ziying Yang

Results

Entity CNV heterogeneity: Glioblastoma



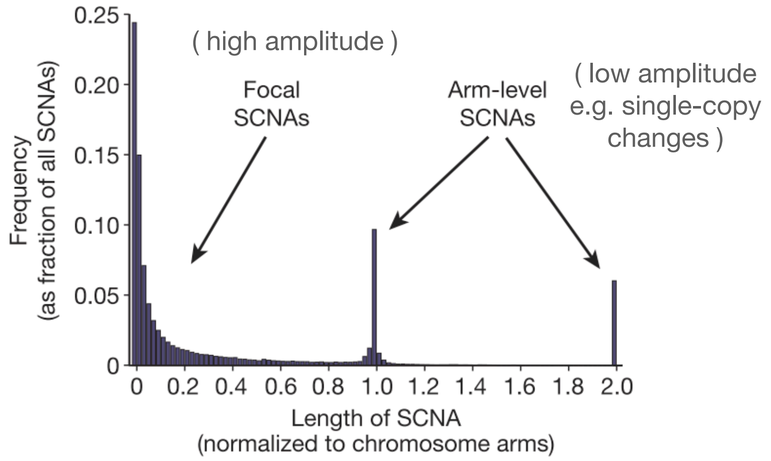


group cluster	CNV features
15968	Dup 7
19069	Del 10
19198	Dup 7, Del 10
22279	Dup 7, Del 10, Dup 19
22292	Dup 7, Del 10, Del 13
28527	Del 1p, Del 19q
29242	Dup 19
30914	Dup 7, Del 10, Dup 19, Dup 20

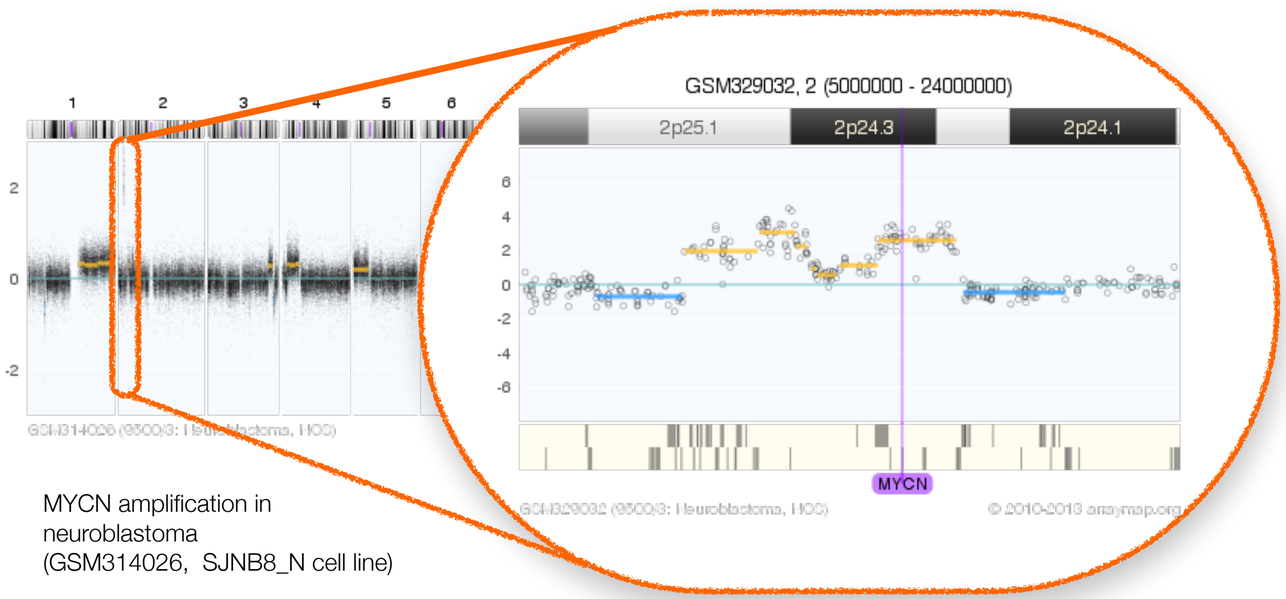
Lead: Ziying Yang

CNV Categorization

different levels of CNV



Rameen et al 2010 Nature



MYCN amplification in neuroblastoma (GSM314026, SJNB8_N cell line)

Lead: Hangjia Zhao

GA4GH Variation Representation Specification

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

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).

CNV Term Use Comparison

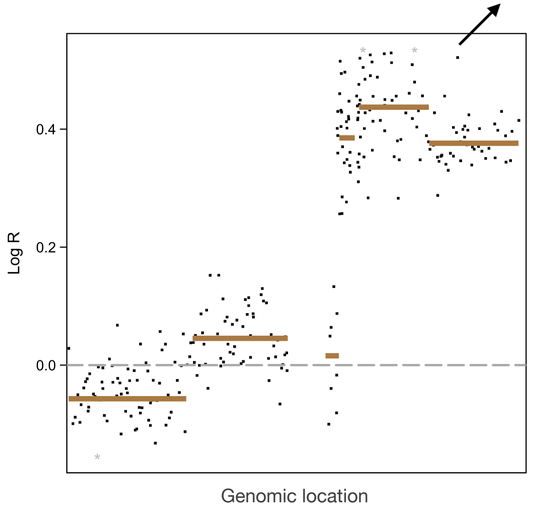
in computational (file/schema) formats

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

labelSeg

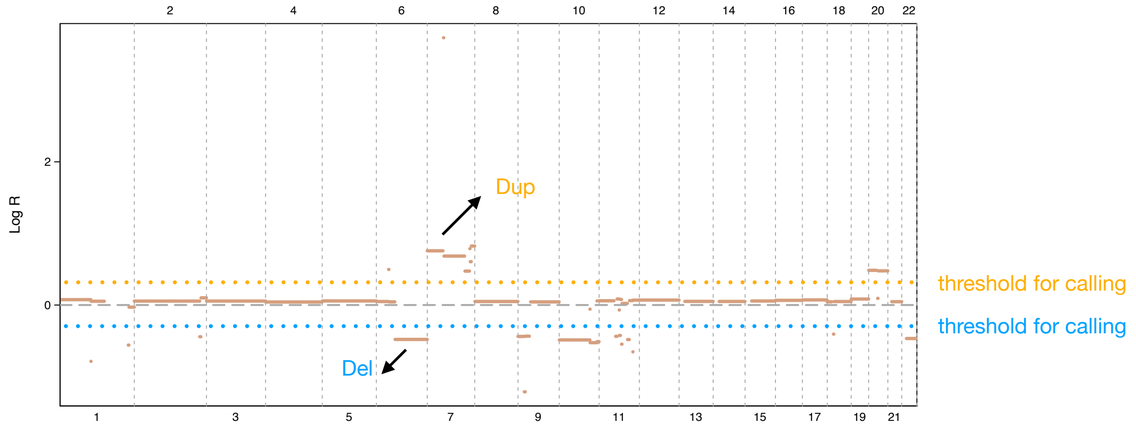
segment annotation for tumor copy number variation profiles

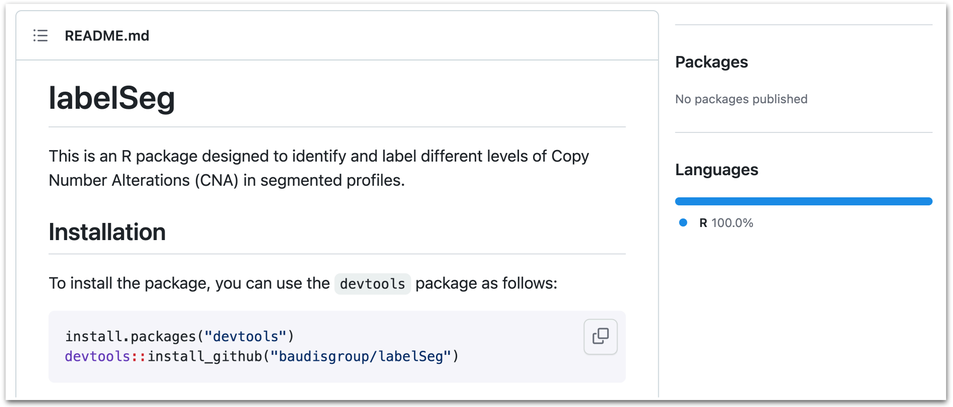
Signal from probes in microarray or from reads in NGS

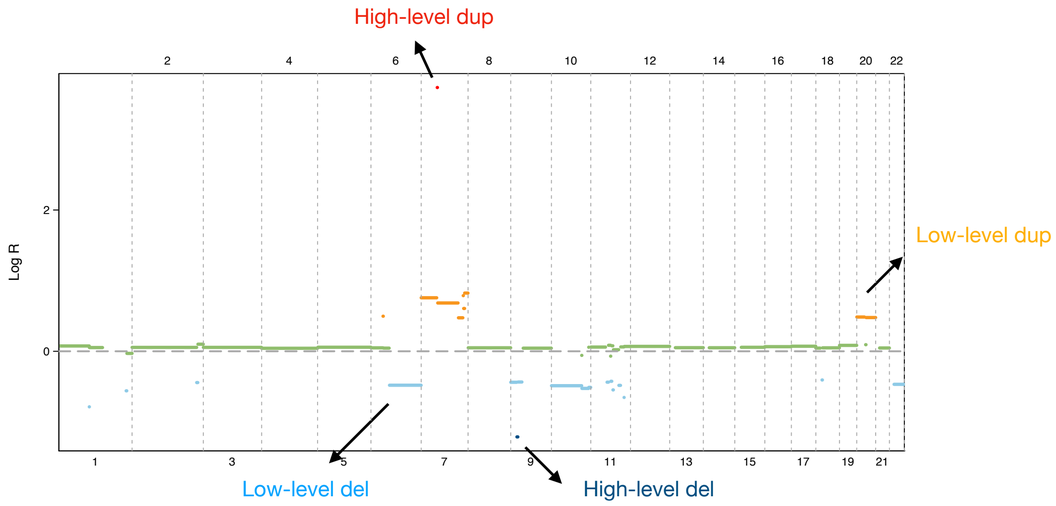


Segmentation

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







Lead: Hangjia Zhao

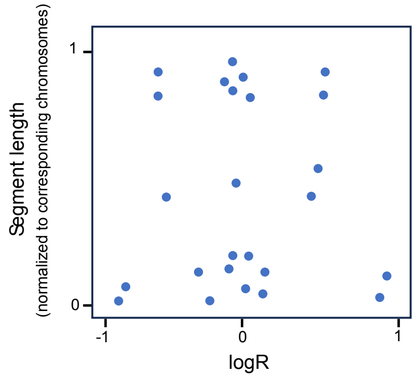
labelSeg

segment annotation for tumor copy number variation profiles

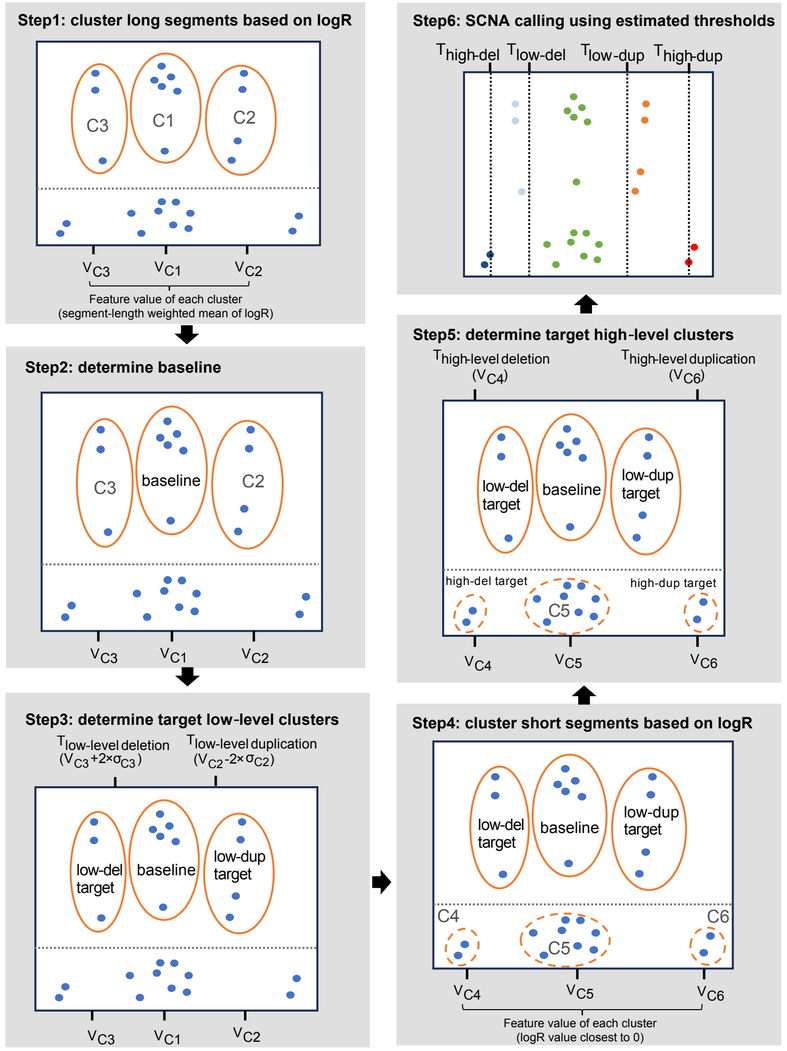
A

INPUT: individual .seg files

Smaple ID	Chr	Start	End	#Marker	logR
S1	1	9965785	10911995	450	0.306
…	…	…	…	…	…
S1	X	3236359	155677414	63741	0.005



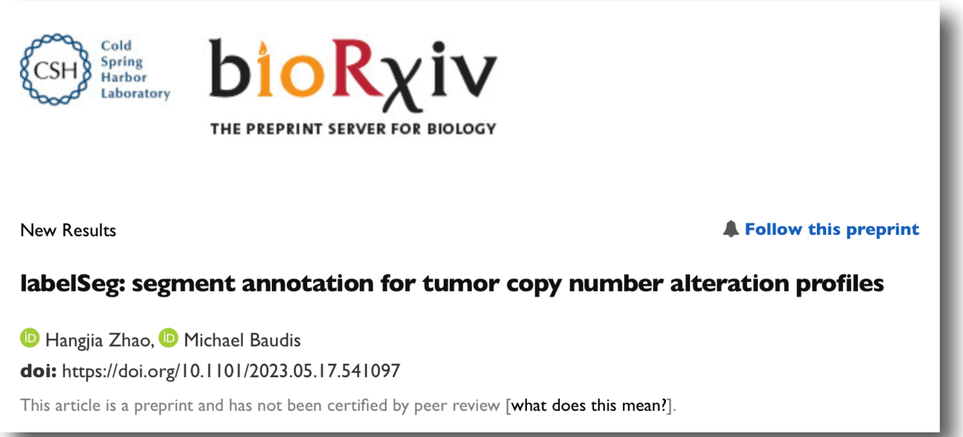
B



C

OUTPUT: individual .seg files with SCNA labels

Smaple ID	Chr	Start	End	#Marker	logR	Label
S1	1	9965785	10911995	450	0.306	+1
…	…	…	…	…	…	
S1	X	3236359	155677414	63741	0.005	0

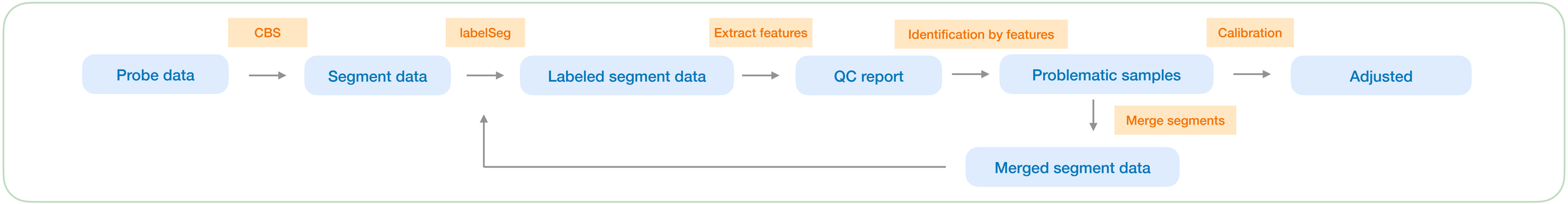


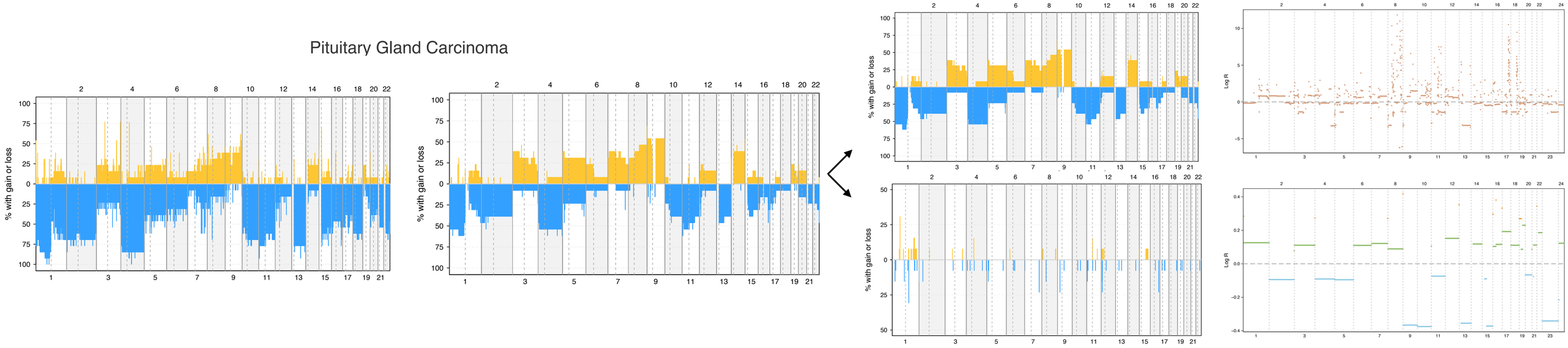
Lead: Hangjia Zhao

Pipeline Development

improve CNV calling in large numbers of heterogeneous cancer samples

nextflow





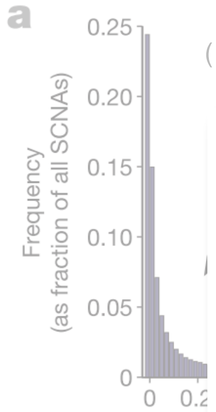
Lead: Hangjia Zhao

CNV Categorization

different levels of CNV

GA4GH Variation Representation Specification

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



(high amplitude)

Focal

Arm-level

(low amplitude

OXFORD

Briefings in Bioinformatics, 2024, **25(2)**, 1–12

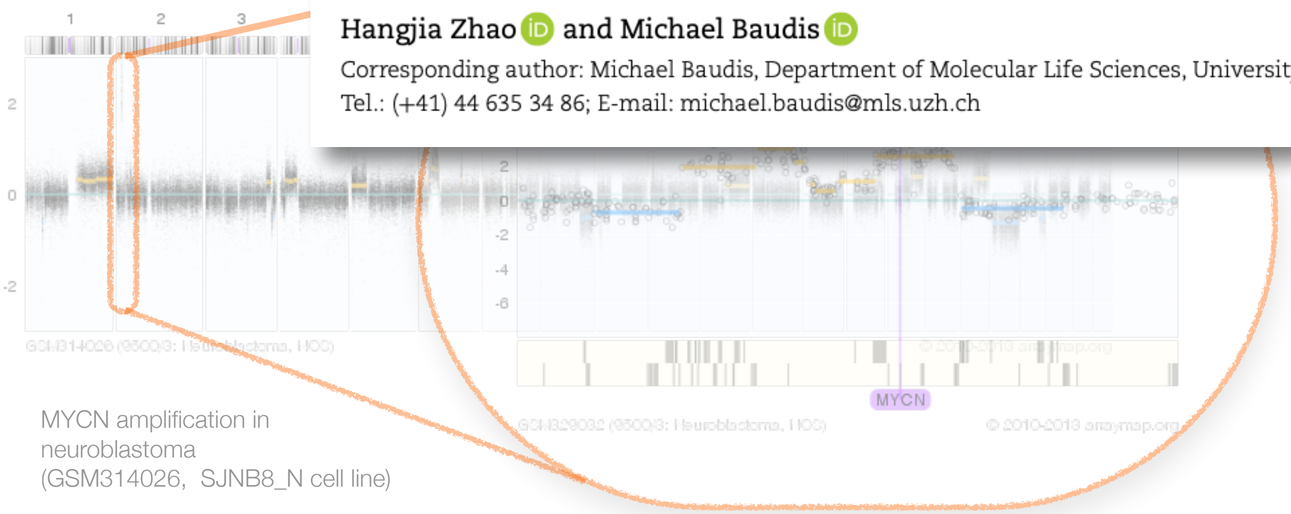
https://doi.org/10.1093/bib/bbad541

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



MYCN amplification in neuroblastoma (GSM314026, SJNB8_N cell line)

CopyNumberChange

Copy Number Change captures a categorization of copies of a molecule within a system, relative to a
allers, particularly in the somatic
nd less useful in practice than
s relative statements, and many
nterpreted to be relative copy

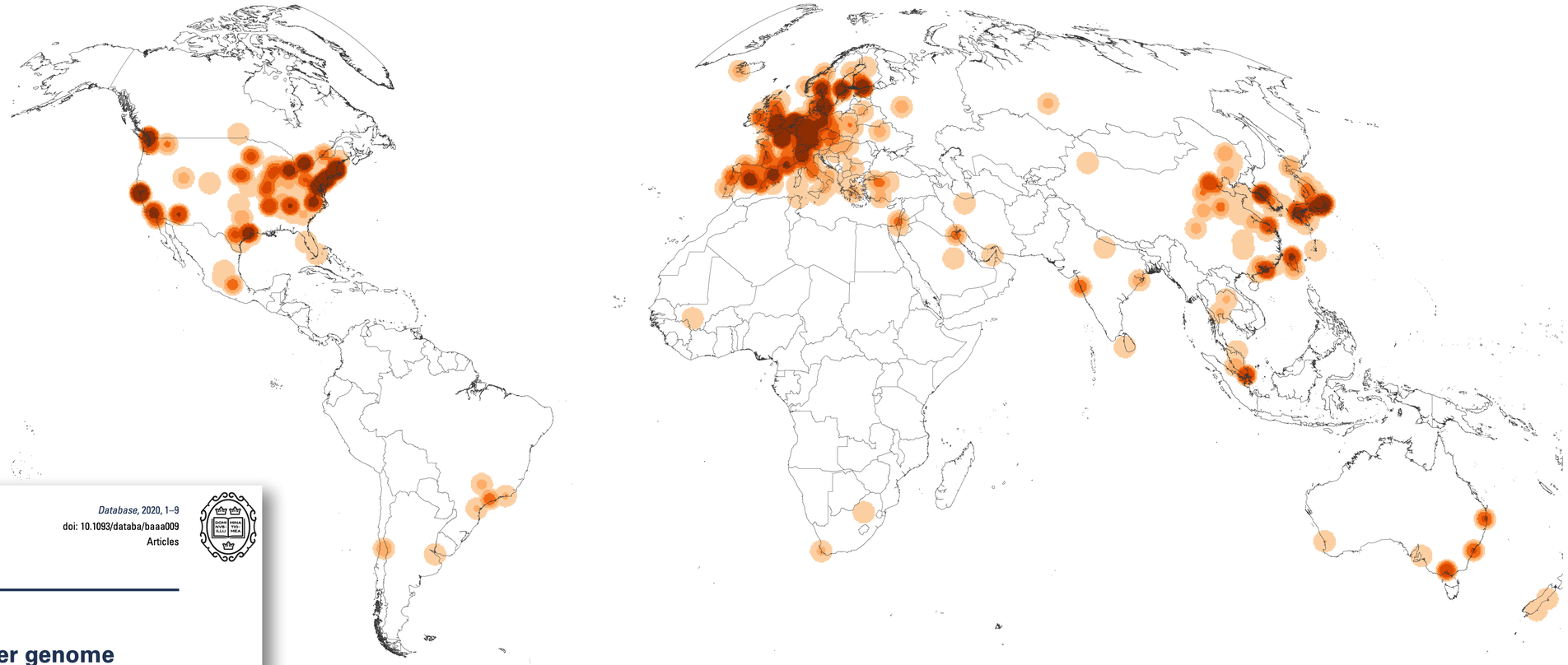
a system (e.g. genome, cell,

_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).

Lead: Hangjia Zhao

Where does Genomic Data Come From?

Geographic bias in published cancer genome profiling studies



DATABASE
The Journal of Biological Databases and Curation

Database, 2020, 1–9
doi: 10.1093/databa/baaa009
Articles

Articles

Geographic assessment of cancer genome profiling studies

Paula Carrio-Cordo[1,2], Elise Acheson[3], Qingyao Huang[1,2] and Michael Baudis[1,*]

[1]Institute of Molecular Life Sciences, University of Zurich, Zurich, Switzerland [2]Swiss Institute of Bioinformatics, Zurich, Switzerland [3]Department of Geography, University of Zurich, Zurich, Switzerland

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

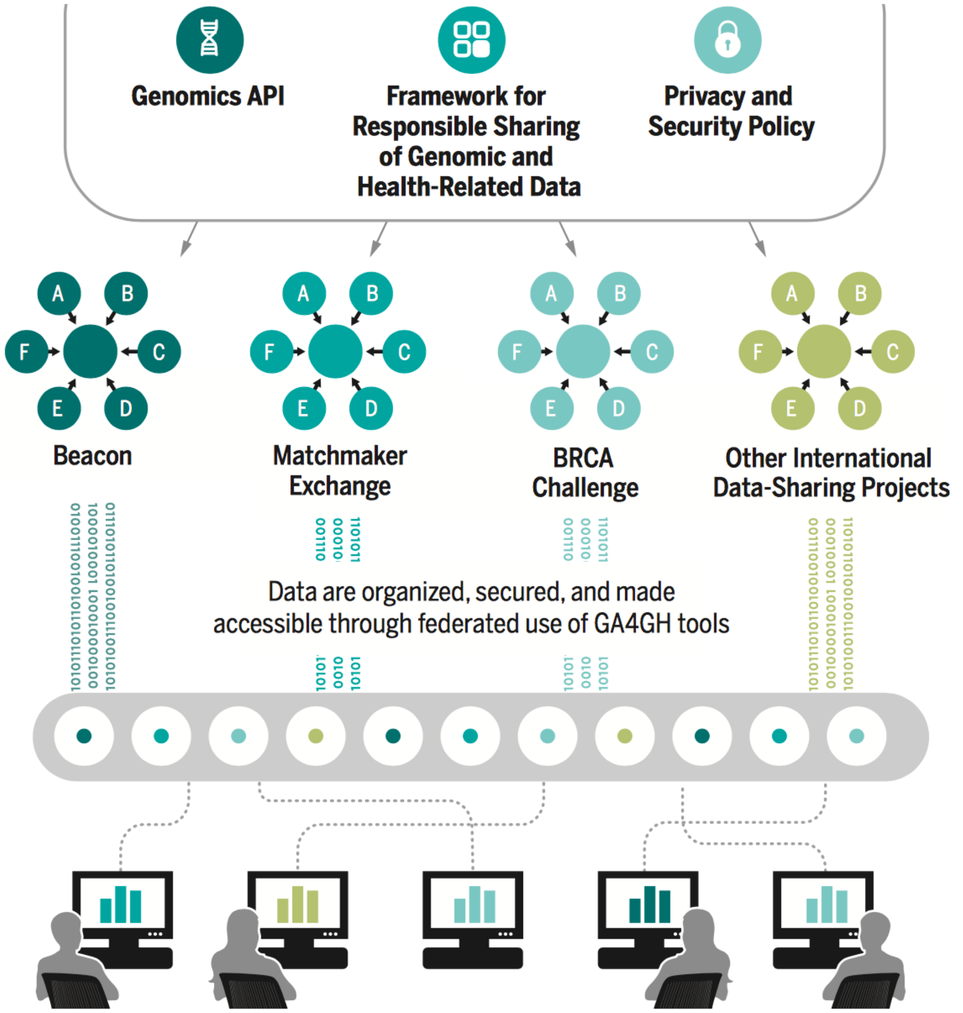
A federated ecosystem for sharing genomic, clinical data

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

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



Global Alliance for Genomics & Health

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

INFORMATICS

Beacon v2 and Beacon networks: federated data discovery n biome

Jordi Rambla[1,2] | Michael Baudis[3] | Roberto Ariosa[1] | Tim Beck[4] |
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

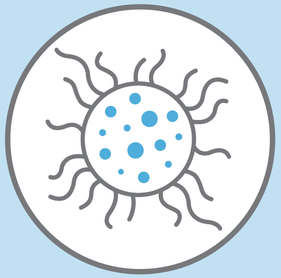
OP

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]
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,*]

Global Genomic Data Sharing Can…



Demonstrate patterns in health & disease

Increase statistical significance of analyses

Lead to “stronger” variant interpretations

Increase accurate diagnosis

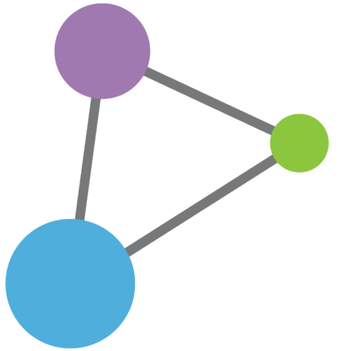
Advance precision medicine

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

progenetix

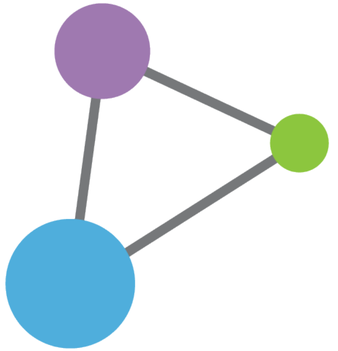
European Genome-Phenome Archive

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

Different Approaches to Data Sharing

progenetix

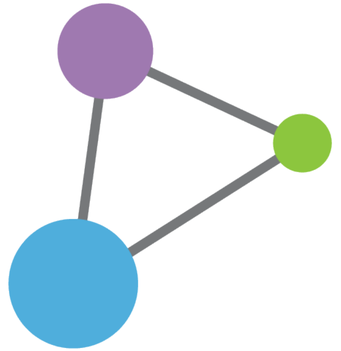
Centralized Genomic Knowledge Bases

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

Different Approaches to Data Sharing

progenetix

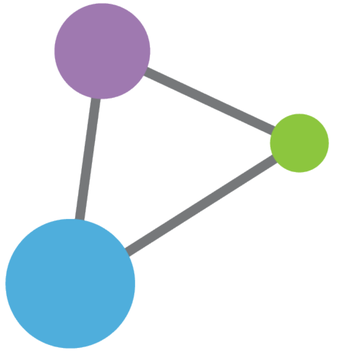
Centralized Genomic Knowledge Bases

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

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

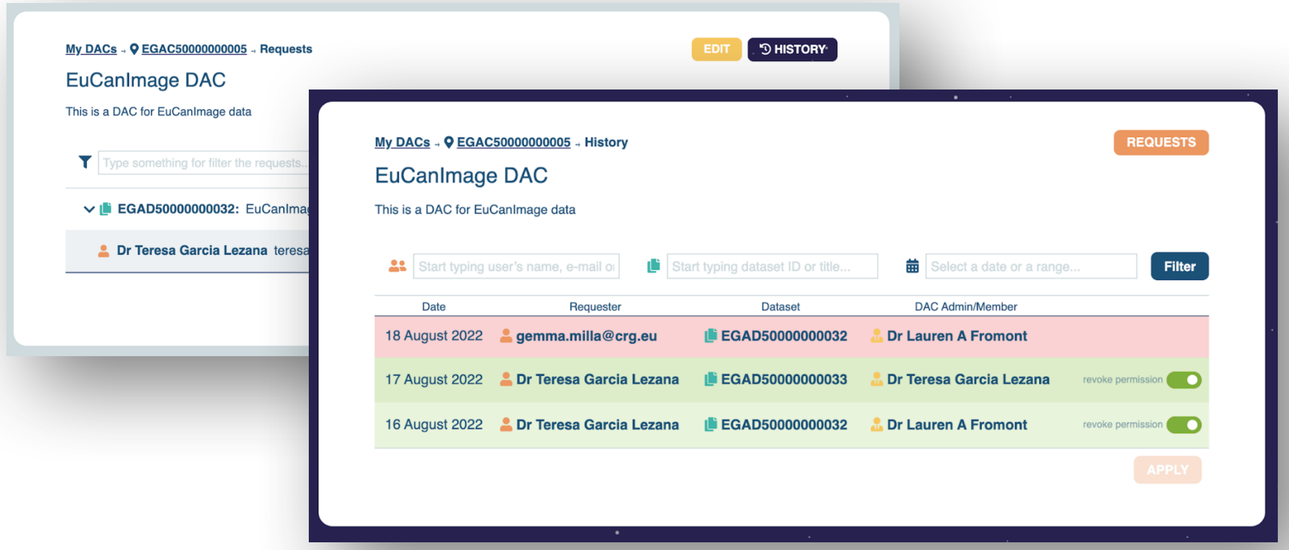
DRIVER PROJECT

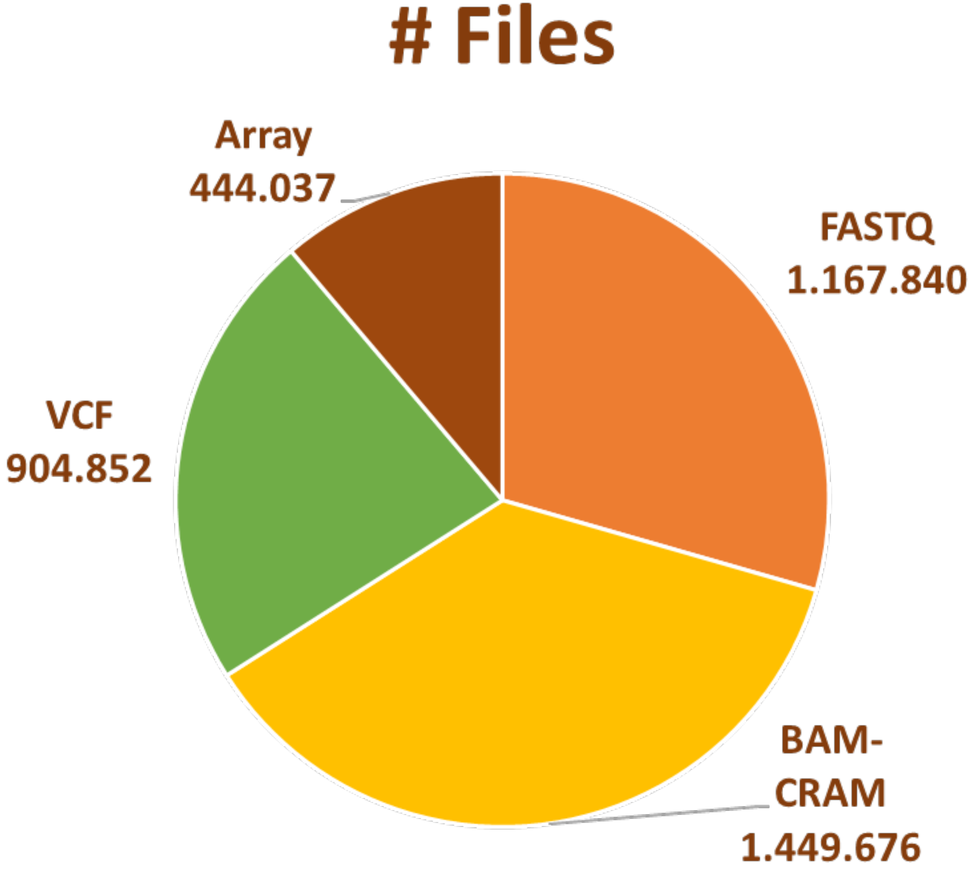
Slide: adapted from Jordi Rambla@ GA4GH 2023

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

Different Approaches to Data Sharing

progenetix

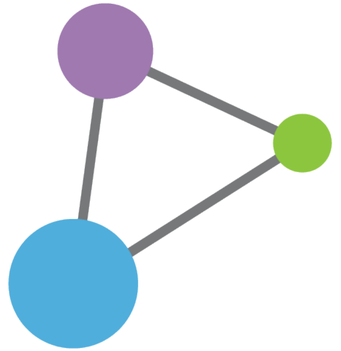
Centralized Genomic Knowledge Bases

European Genome-Phenome Archive

Data Commons
Trusted, controlled repository of multiple datasets

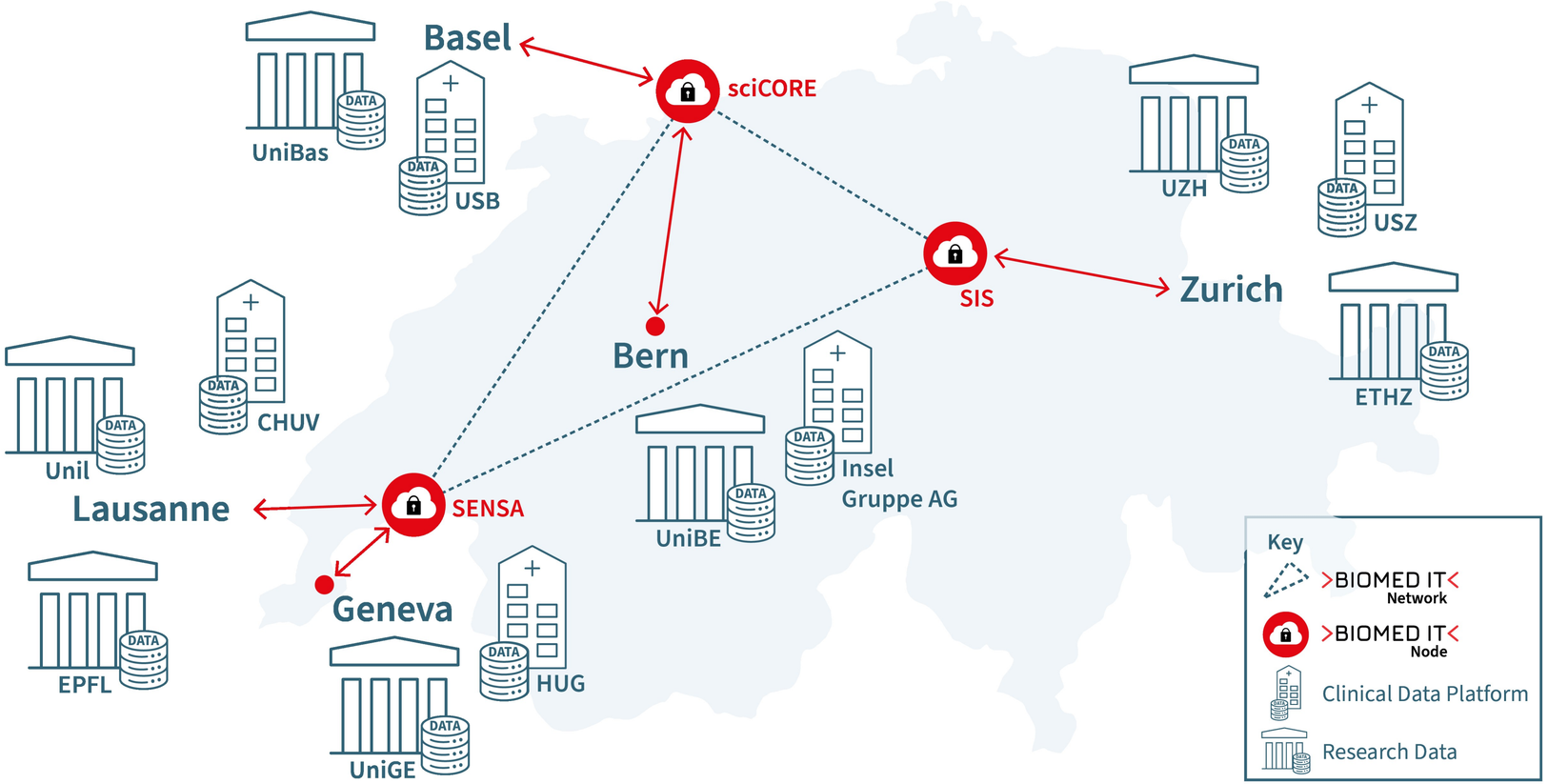
SPHN Swiss Personalized Health Network

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



Linkage of distributed and disparate datasets

The Swiss Personalized Health Network



Swiss Personalized Health Network

Strategic Focus Area
Personalized Health and Related Technologies

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
WE BRING PROGRESS TO CANCER CARE

SSPH+
SWISS SCHOOL OF PUBLIC HEALTH

life sciences cluster basel

Personalized Health Informatics Group

SPHN Data Coordination Center (DCC)
BioMedIT Network

University Hospital Basel

USZ Universitäts Spital Zürich

HUG Hôpitaux Universitaires Genève

Centre hospitalier universitaire vaudois

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HOPITAL UNIVERSITAIRE DE BERNE
BERN UNIVERSITY HOSPITAL

swissuniversities

Universitäre Medizin Schweiz
Médecine Universitaire Suisse

Different Approaches to Data Sharing

progenetix

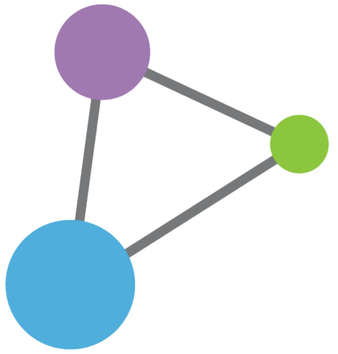
European Genome-Phenome Archive

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

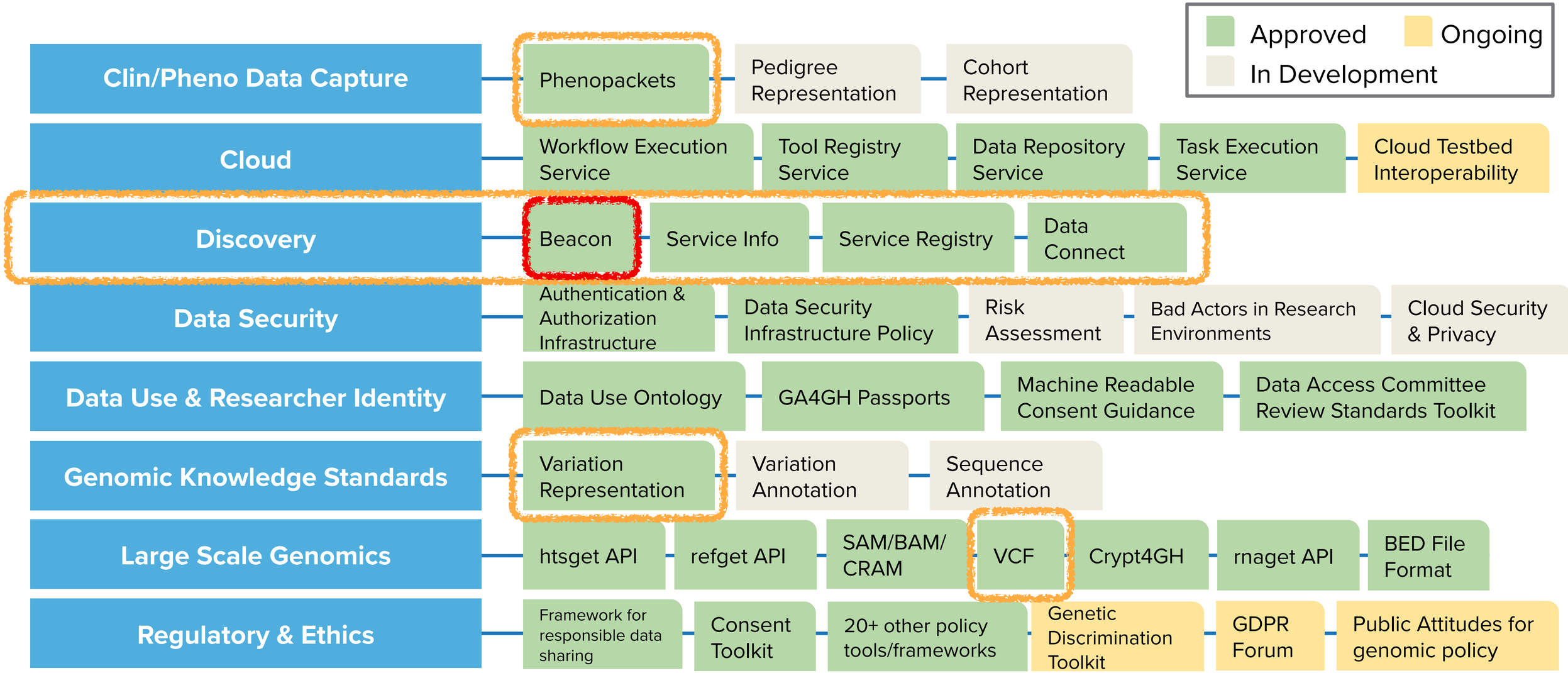
STANDARDS

TO

Data Copying

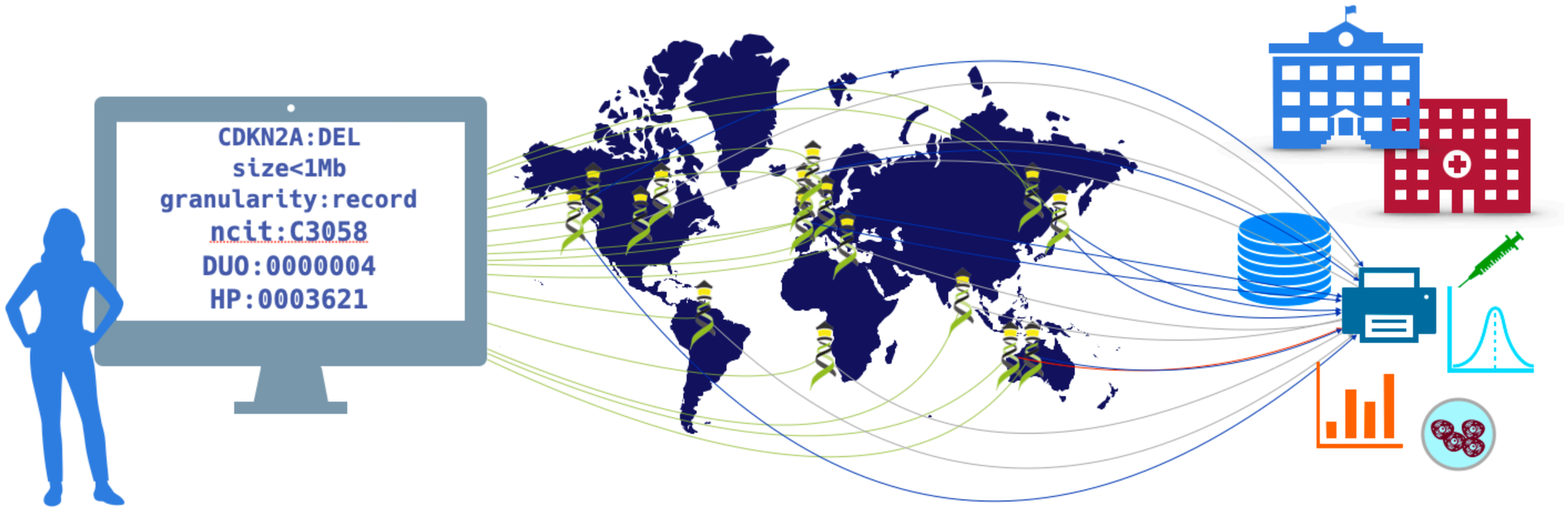
Data Visiting

Overview of GA4GH standards and frameworks



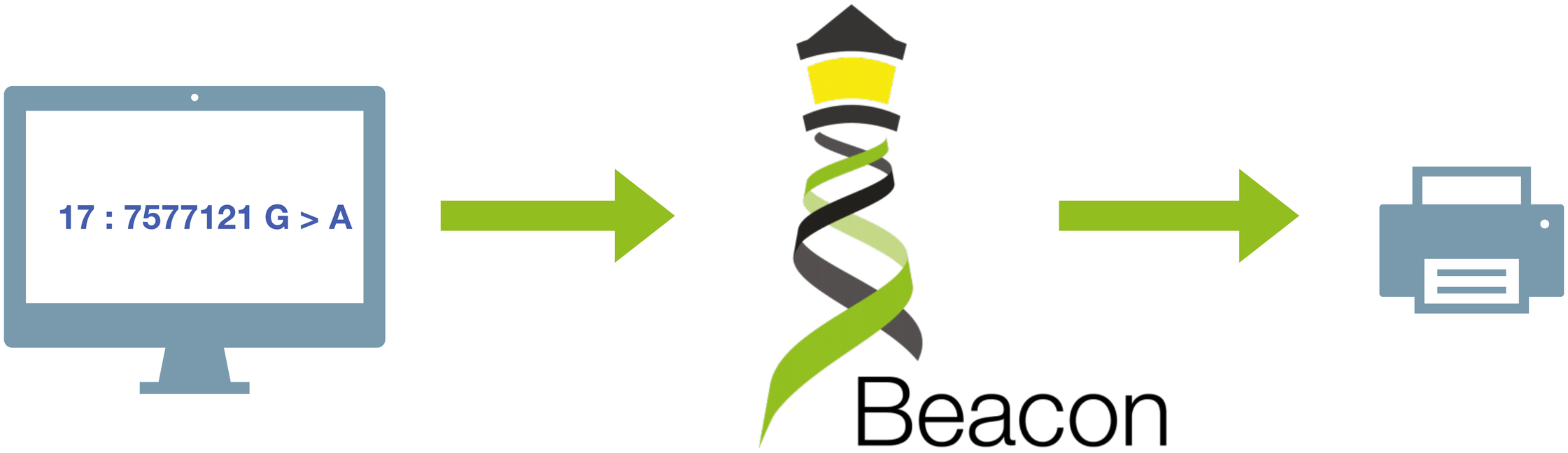
Global Alliance
for Genomics & Health

Collaborate. Innovate. Accelerate.



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**

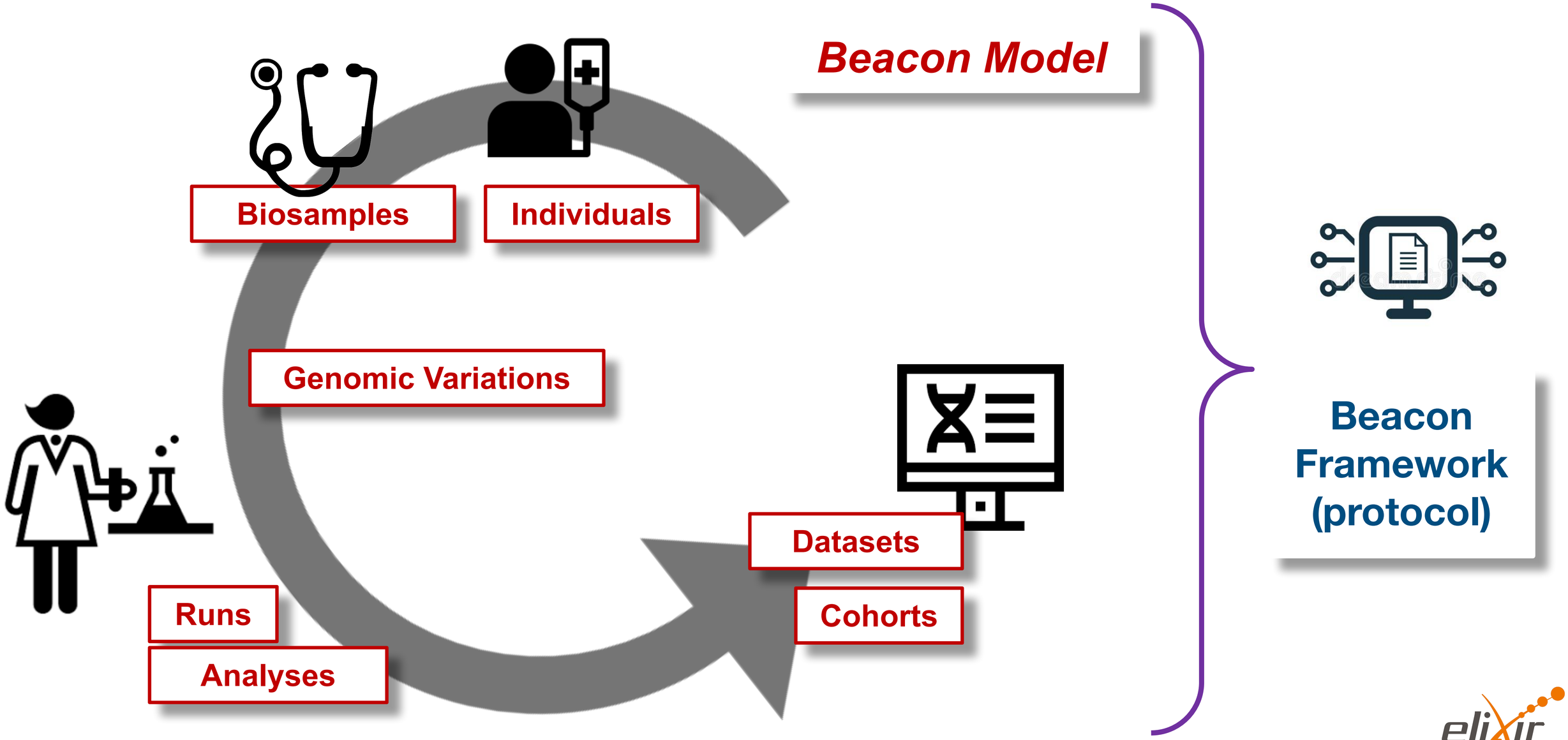
Have you seen this variant? It came up in my patient and we don't know if this is a common SNP or worth following up.

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 v2

docs.genomebeacons.org



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

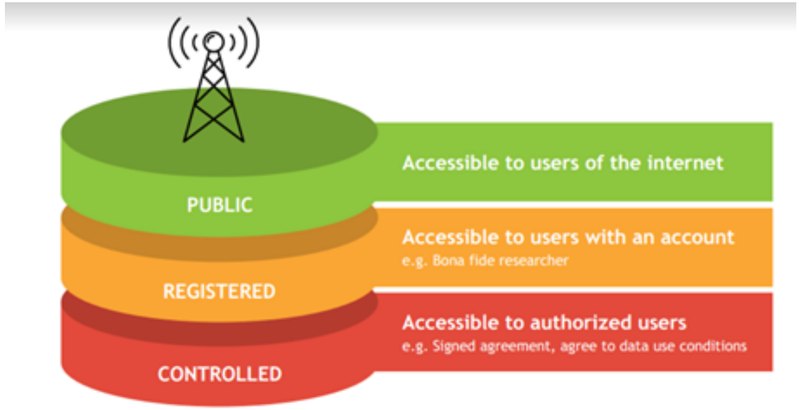
- further changes esp. in default model, aligning with Phenopackets and VRS
- unified beacon-v2 code & docs repository
- Beacon v2 approved at Apr GA4GH Connect

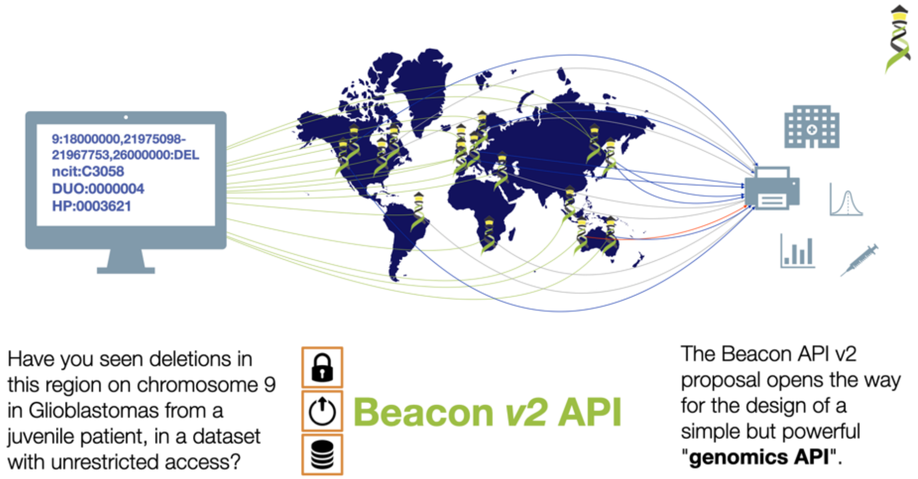
- *docs.genomebeacons.org*

Beacon 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

EMBL-EBI

Australian Genomics

SciLifeLab

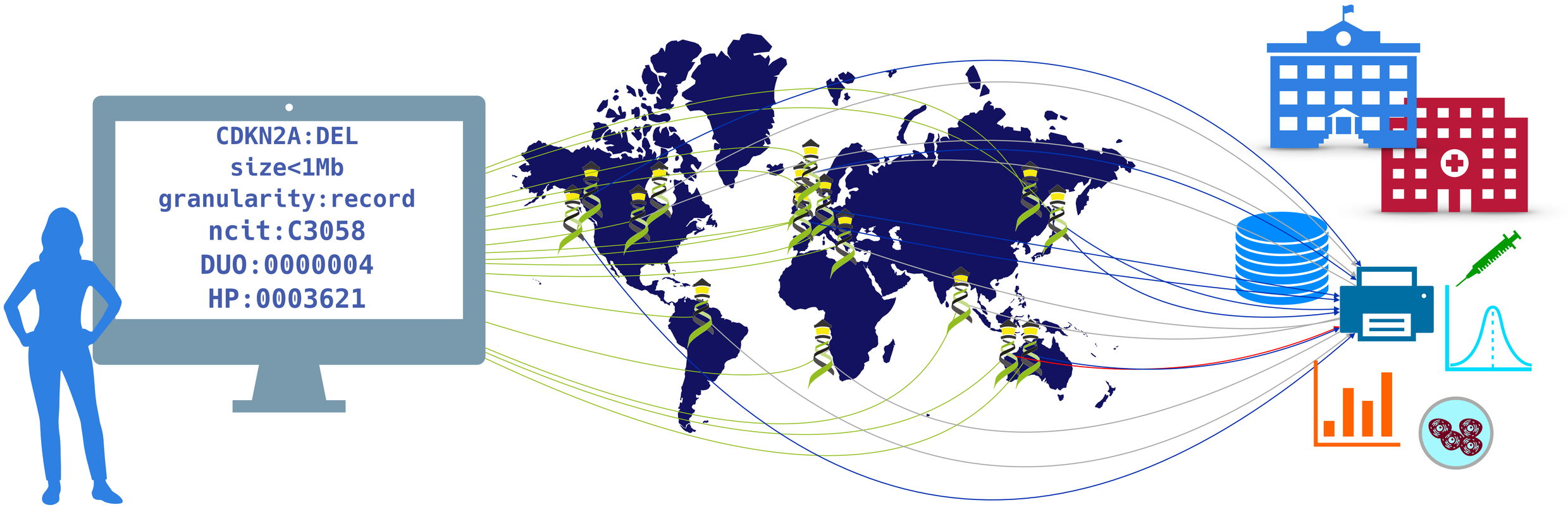
elixir

UNIVERSITY OF CALIFORNIA SANTA CRUZ

BROAD INSTITUTE

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

Universität Zürich[UZH]

Global Alliance for Genomics & Health

Progenetix and GA4GH Beacon

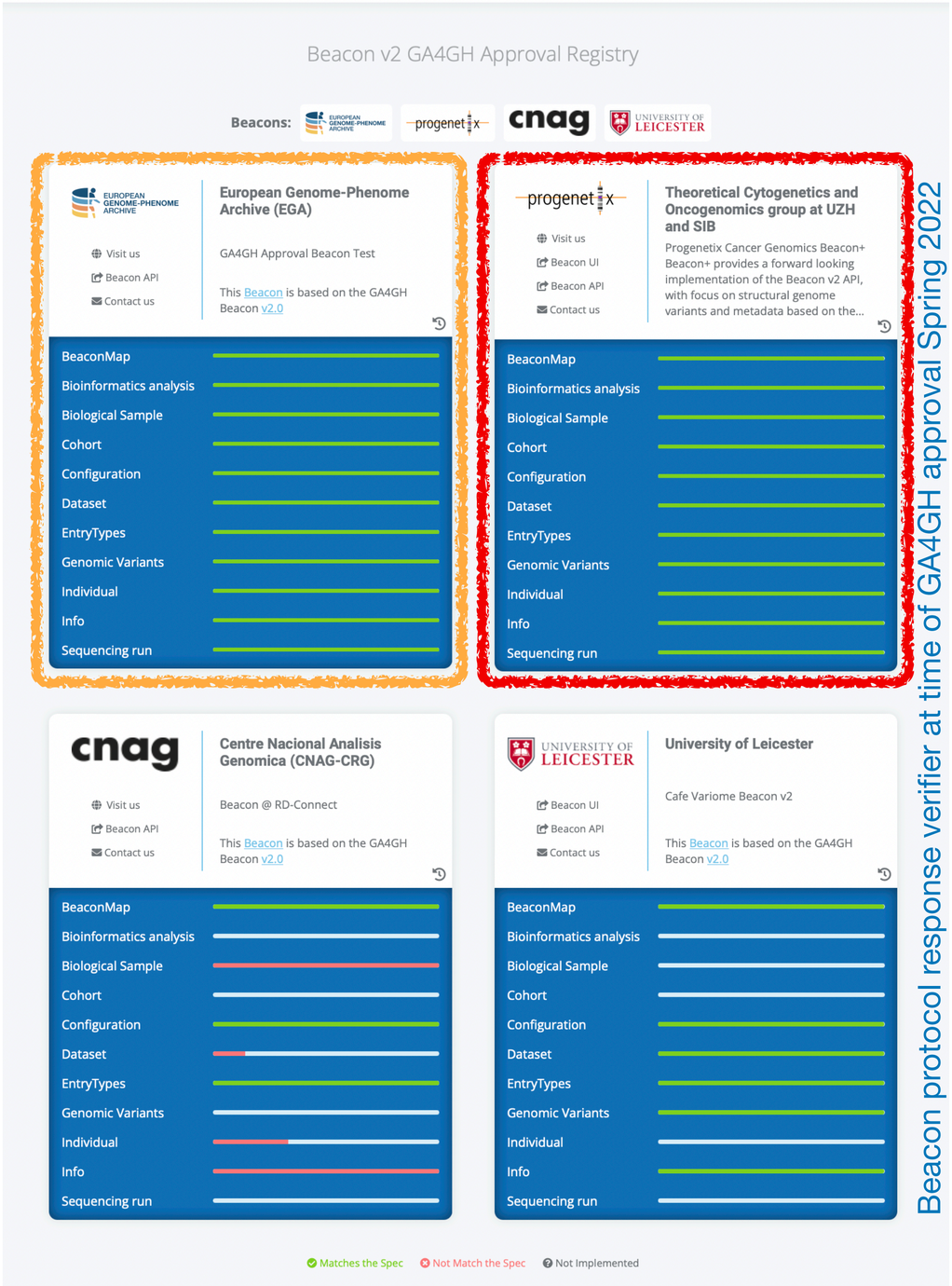
Implementation driven development of a GA4GH standard

progenetix

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



Global Alliance for Genomics & Health

progenetix

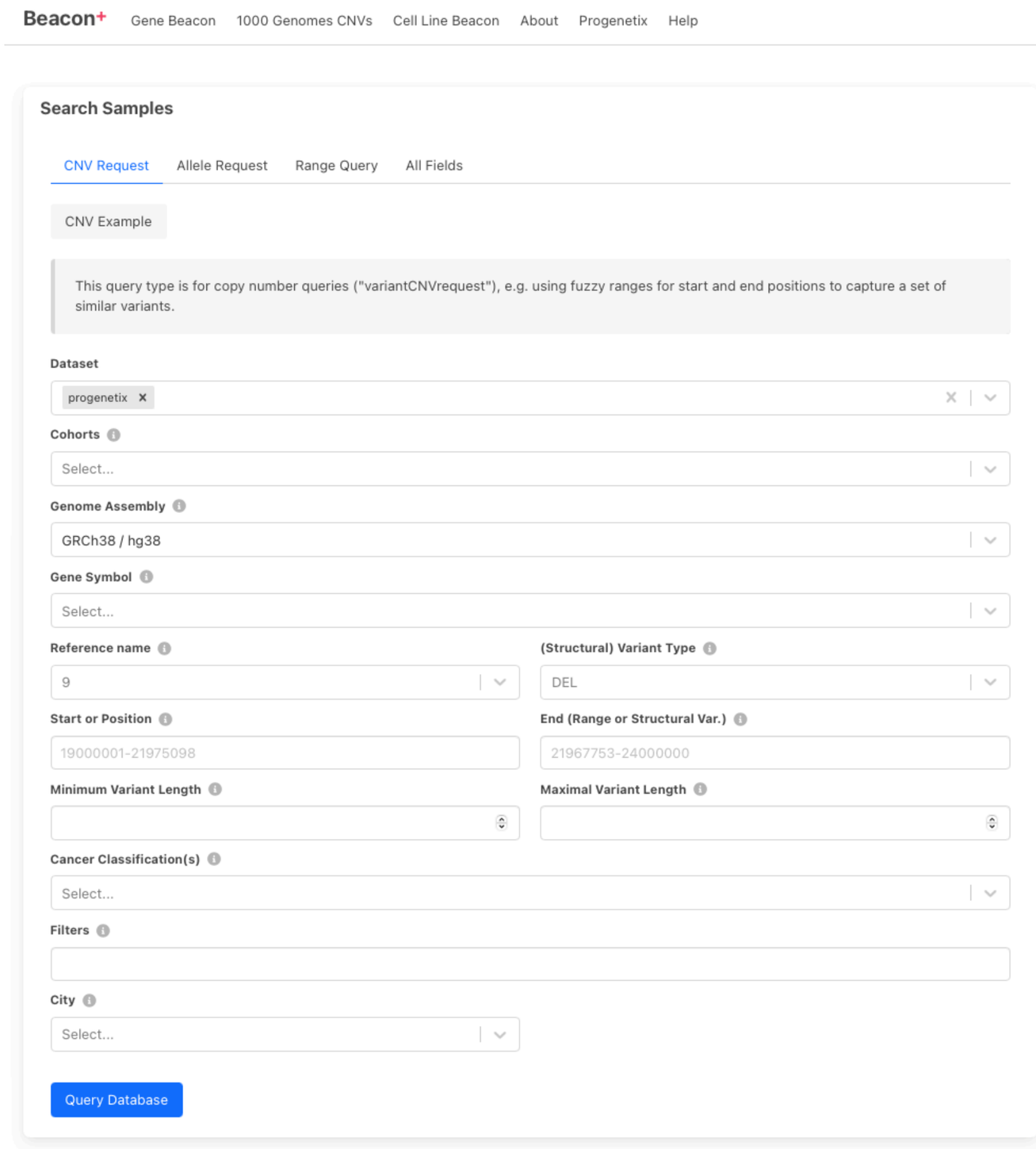
elixir

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...)

progenetix



Beacon v2 Filters

Example: Use of hierarchical classification systems (here NCIt 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 limitatiions of "fuzzy" disease annotations

Beacon+ specific: Multiple term selection with OR logic

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
Calls: 0
Samples: 523

$f_{alleles}$: 0

Callsets Variants | Legacy Interface | UCSC region

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

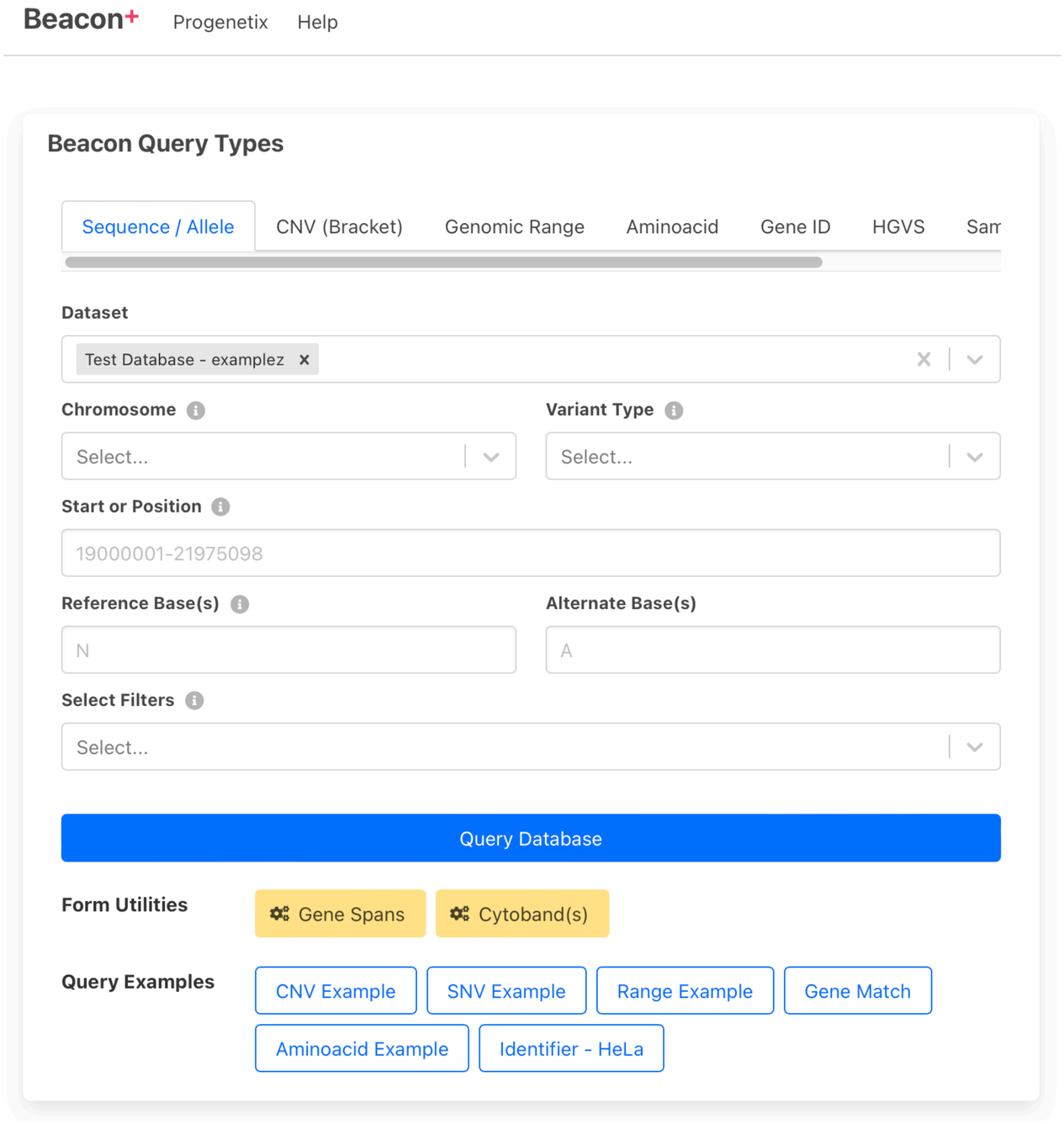
Page **1 of 105**

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

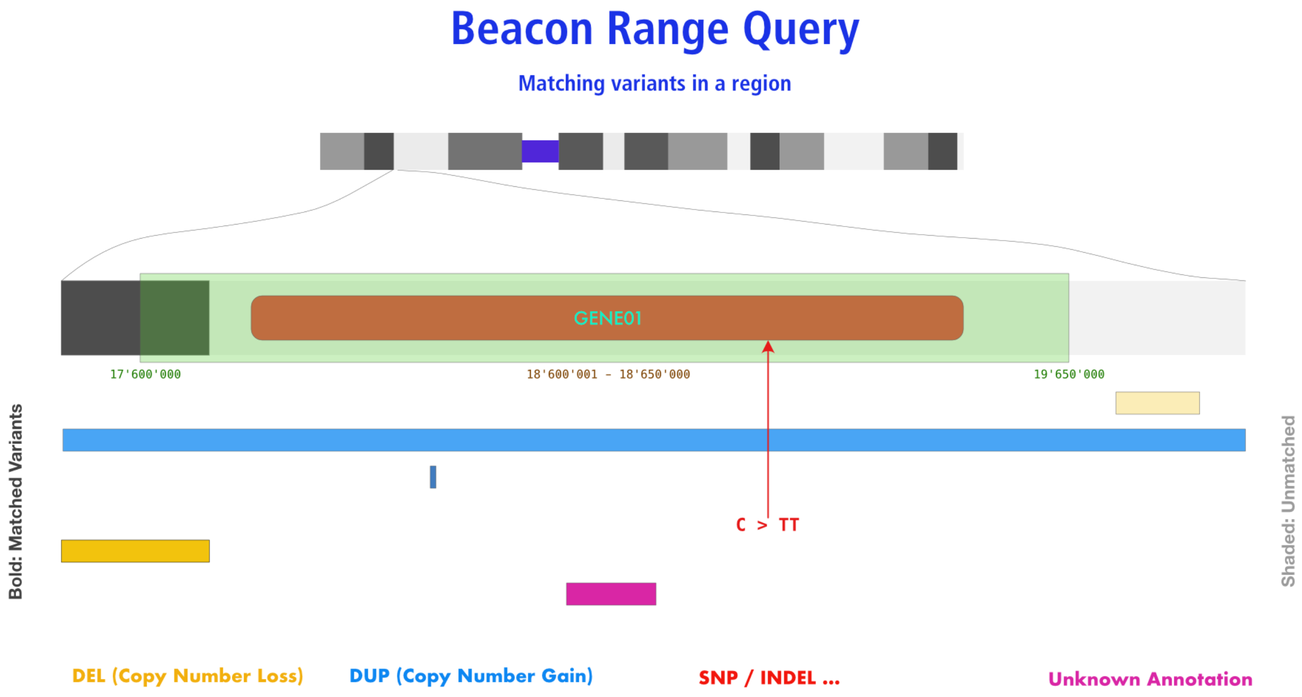
beaconplus.progenetix.org

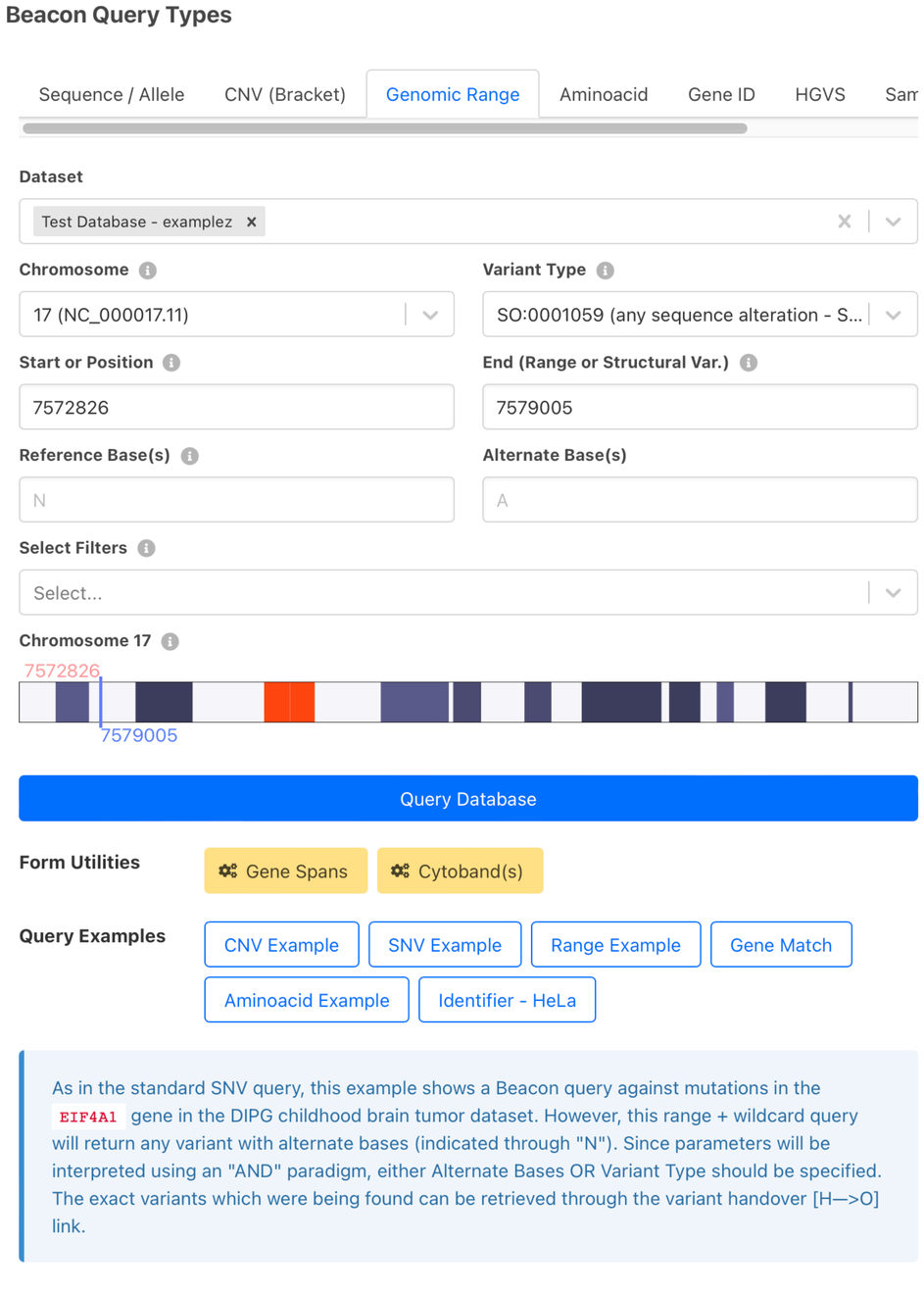


Beacon Queries

Range ("anything goes") Request

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

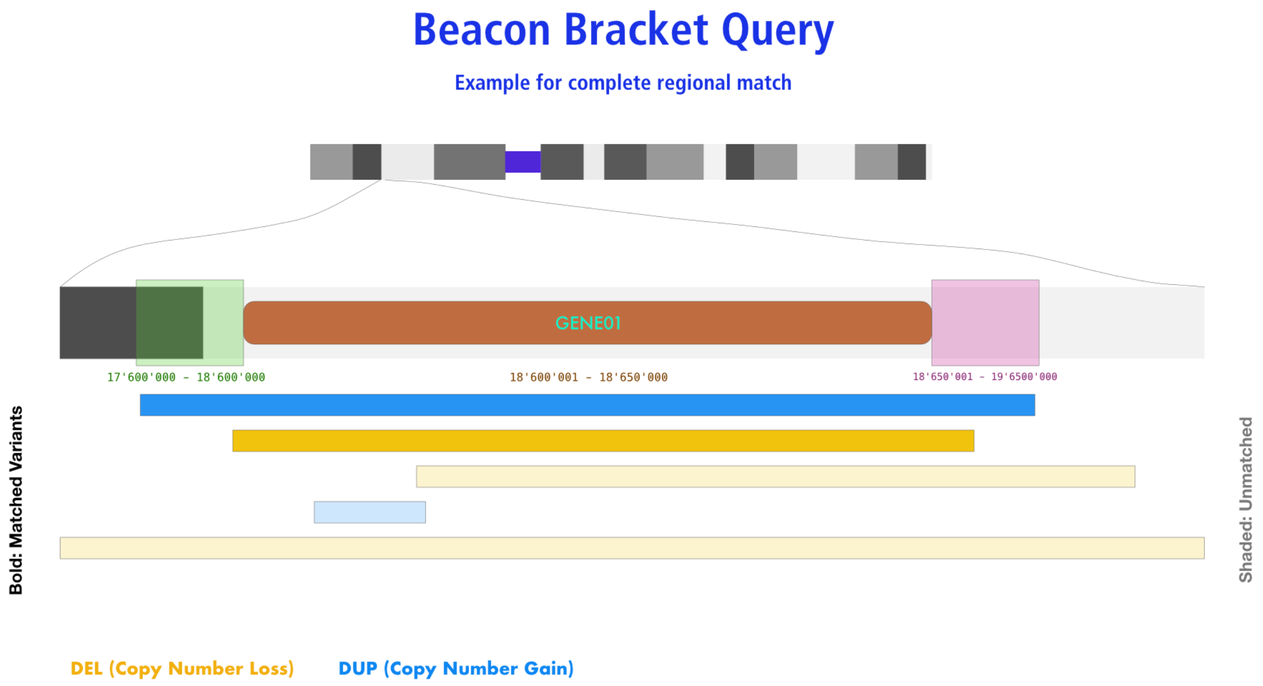


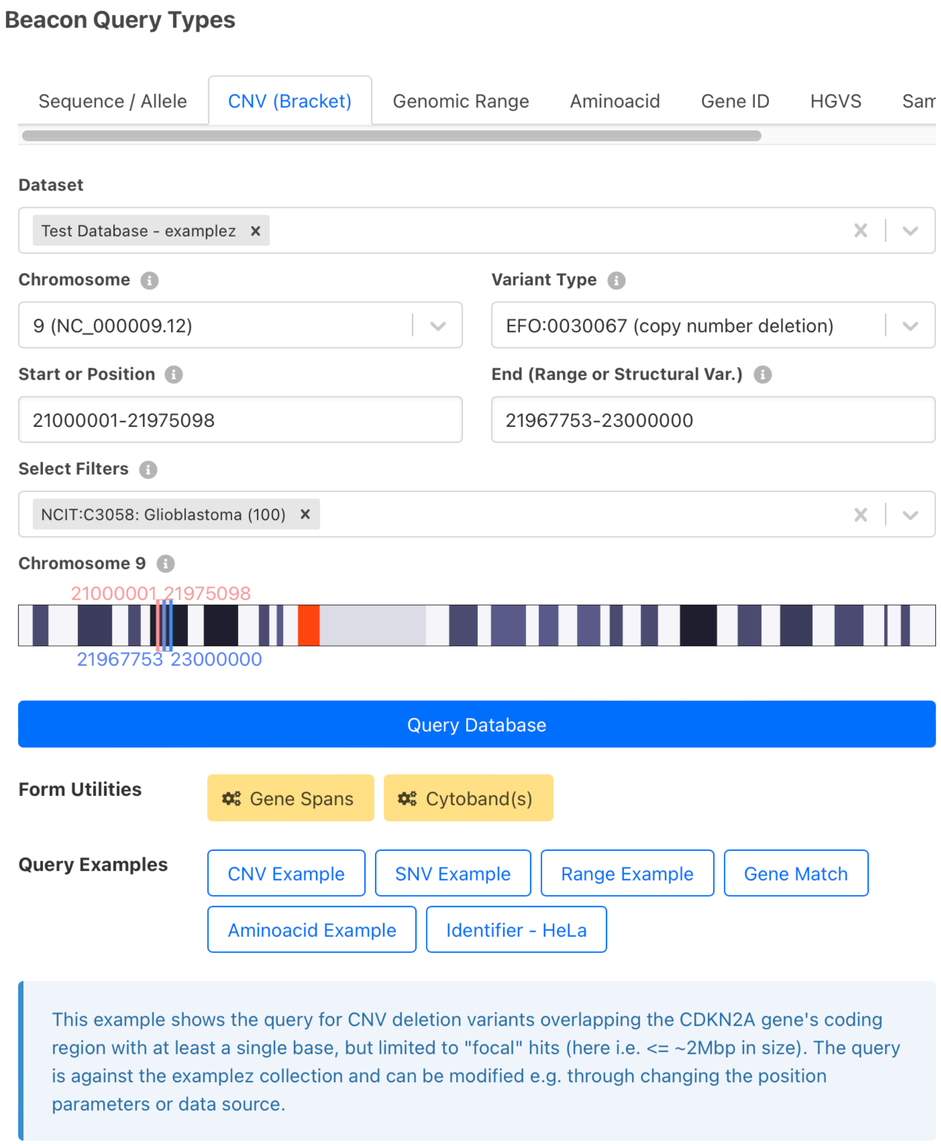


Beacon Queries

Bracket ("CNV") Query

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





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"),
```


variants


analyses


biosamples


individuals

Entity collections


collations

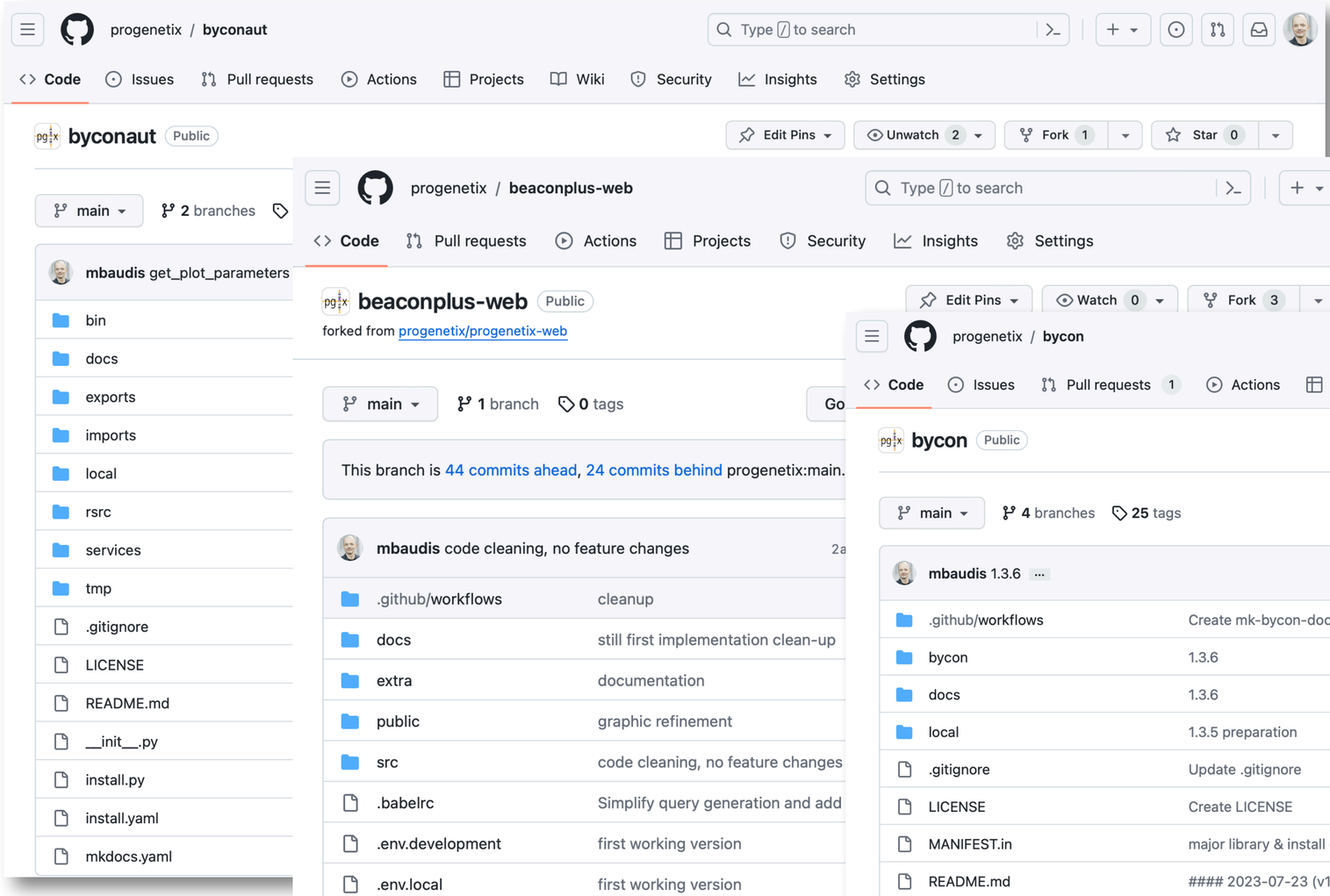

geolocs


genespans


publications

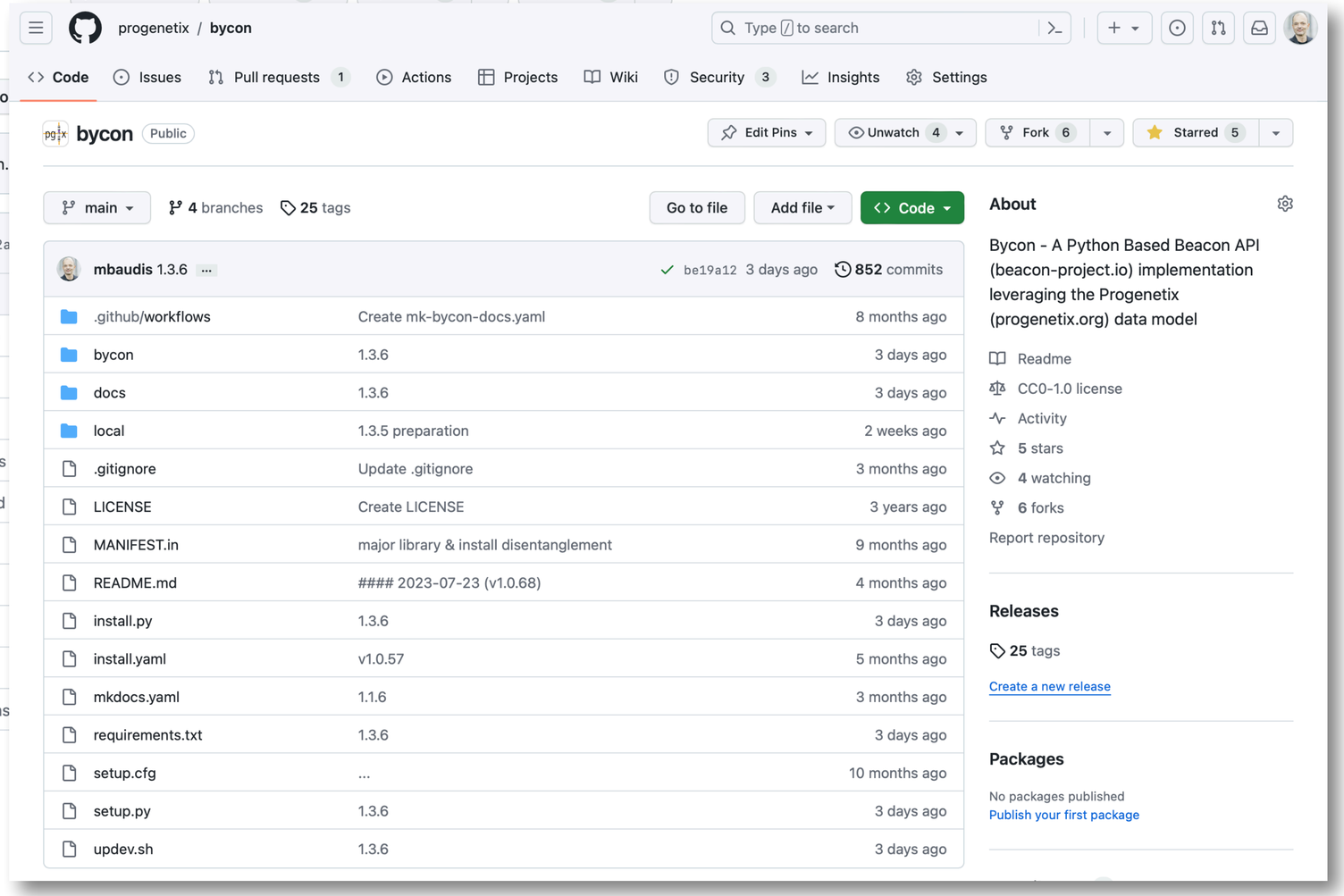

qBuffer

Utility collections



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

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



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]

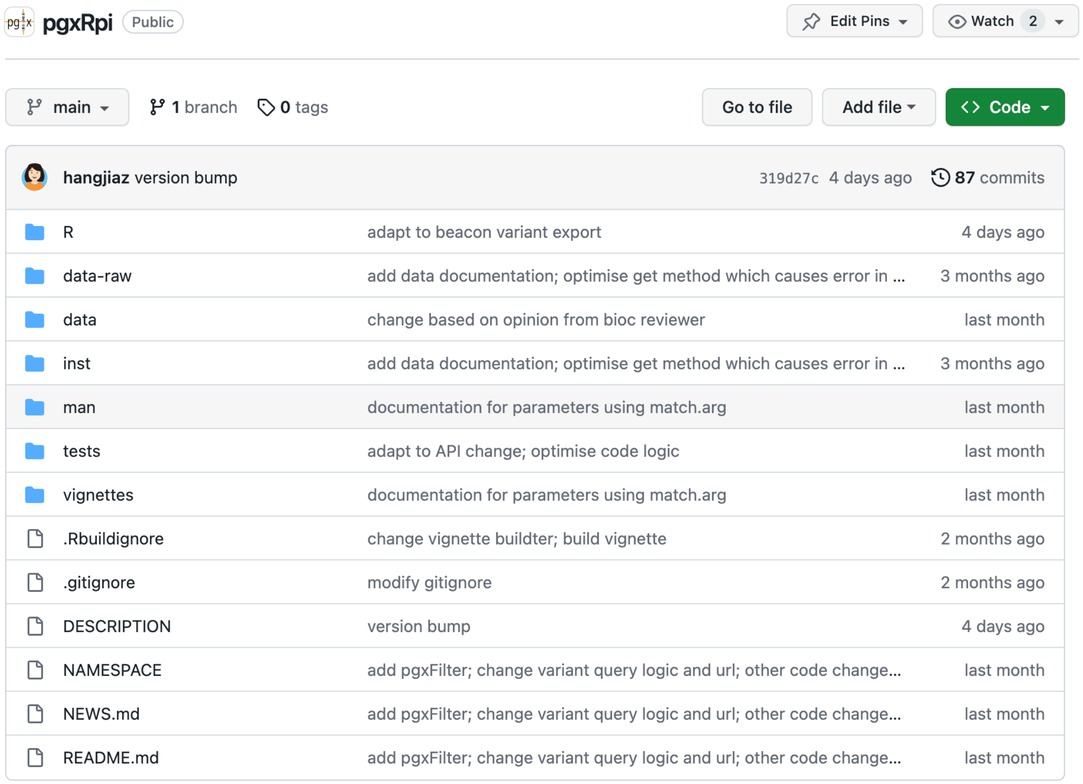
Maintainer: Hangjia Zhao <hangjia.zhao at uzh.ch>

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

Edit Pins | Watch 2

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
```

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

What Can You Do?

- implement procedures and standards supporting **data discovery** (FAIR principles) and federation approaches
- forward looking consent and data protection models adhering to **ORD** principles ("*as secure as necessary, as open as possible*")
- **support** and/or get involved with international **data standards** efforts and projects

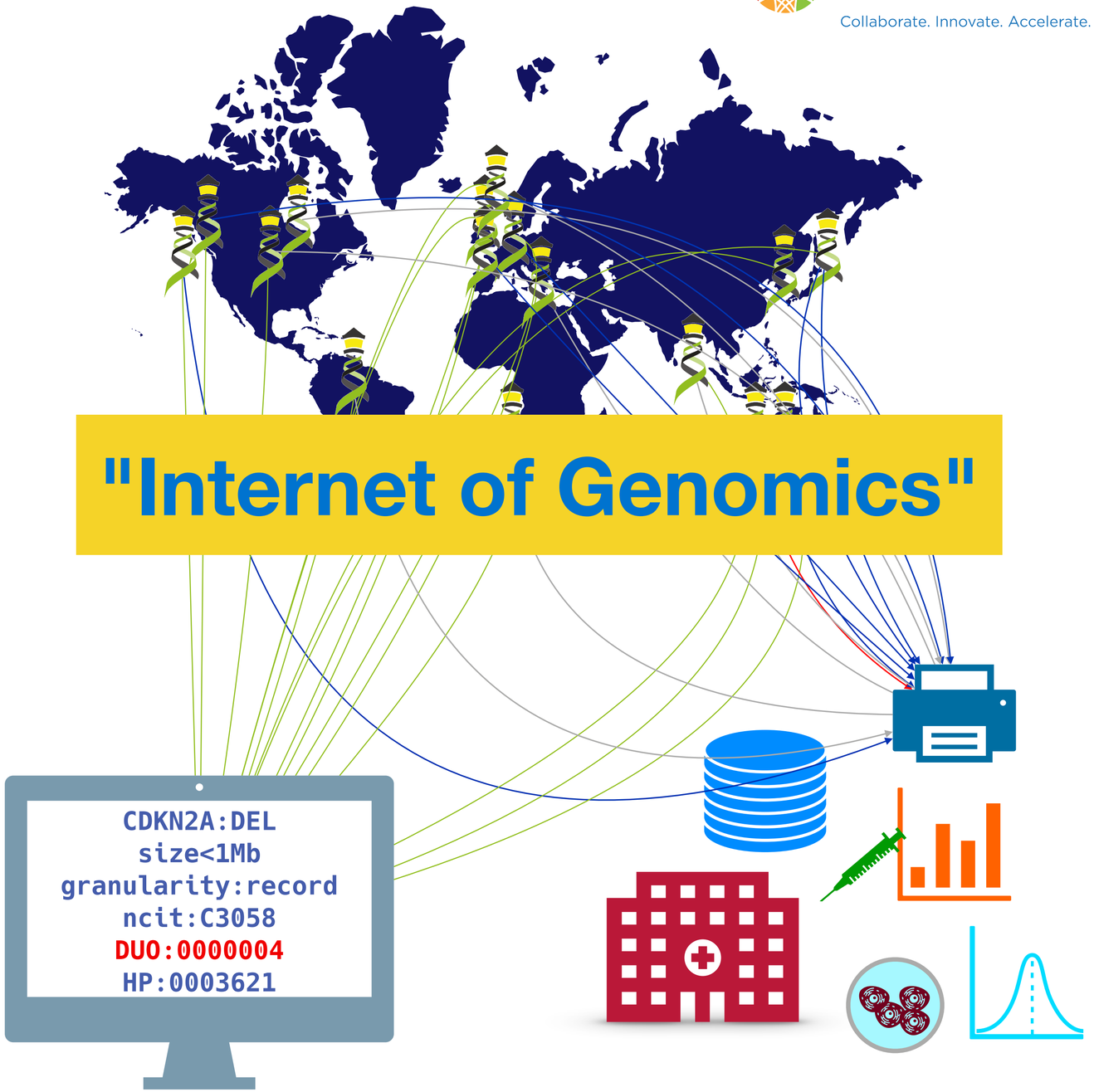
➡ **Collaborate!**

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

What Can You Do?

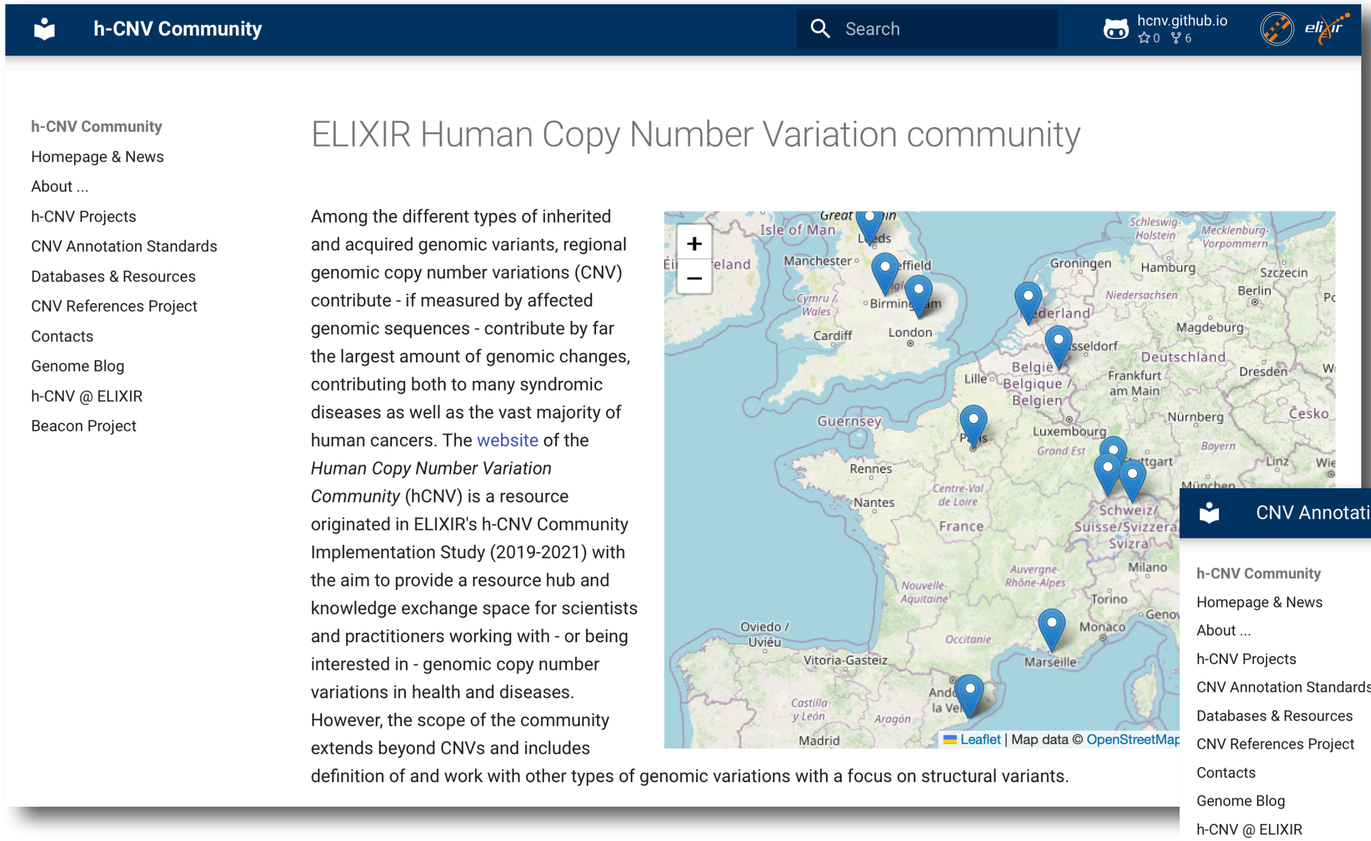
- implement procedures and standards supporting **data discovery** (FAIR principles) and federation approaches
- forward looking consent and data protection models adhering to **ORD** principles ("*as secure as necessary, as open as possible*")
- **support** and/or get involved with international **data standards** efforts and projects

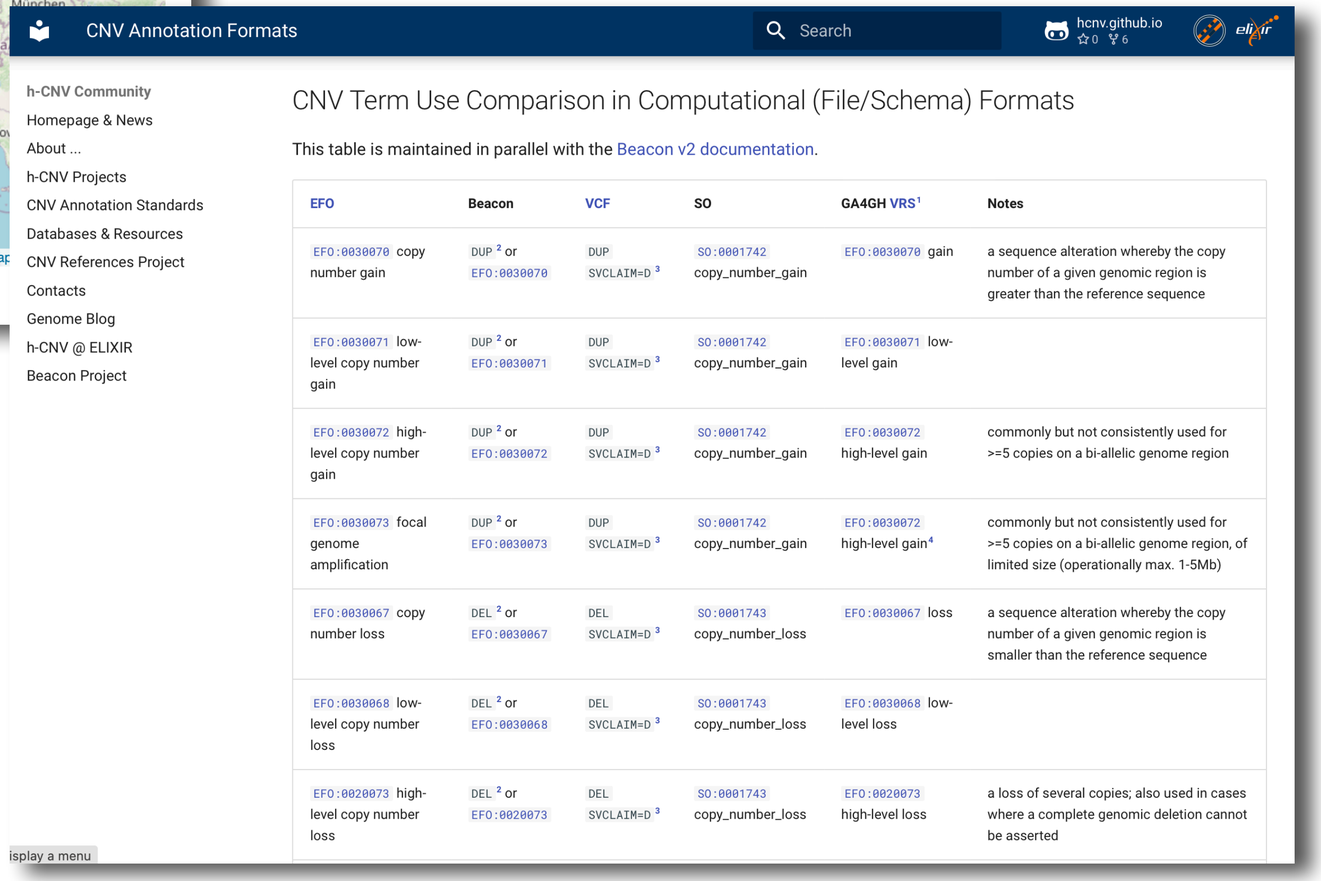
➡ **Collaborate!**



ELIXIR hCNV Community

https://cnvar.org/





The Beacon team through the ages

EUROPEAN GENOME-PHENOME ARCHIVE

CRG Centre for Genomic Regulation

Jordi Rambla
Arcadi Navarro
Roberto Ariosa
Manuel Rueda
Lauren Fromont
Mauricio Moldes
Claudia Vasallo
Babita Singh
Sabela de la Torre
Marta Ferri
Fred Haziza

CSC

Juha Törnroos
Teemu Kataja
Ilkka Lappalainen
Dylan Spalding

UNIVERSITY OF LEICESTER

Cafe Variome Central

Tony Brookes
Tim Beck
Colin Veal
Tom Shorter

Swiss Personalized Health Network (SPHN)

University of Zurich[UZH]

Michael Baudis
Rahel Paloots
Hangjia Zhao
Ziying Yang
Bo Gao
Qingyao Huang

Genomics england

Augusto Rendon
Ignacio Medina
Javier López
Jacobo Coll
Antonio Rueda

cnag
centre nacional d'anàlisi genòmica
centro nacional de análisis genómico

Sergi Beltran
Carles Hernandez

Inserm
Institut national de la santé et de la recherche médicale

David Salgado

BSC Barcelona Supercomputing Center
Centro Nacional de Supercomputación

Salvador Capella
Dmitry Repchevski
JM Fernández

DisGeNET

Laura Furlong
Janet Piñero

elixir

B1MG

Serena Scollen
Gary Saunders
Giselle Kerry
David Lloyd

H3Africa
Human Heredity & Health in Africa

Nicola Mulder
Mamana Mbiyavanga
Ziyaad Parker

EU Can CAN.

David Torrents

AUTISM SPEAKS

Dean Hartley

JUNTA DE ANDALUCIA
Fundación Progreso y Salud
CONSEJERÍA DE SALUD

Joaquin Dopazo
Javier Pérez
J.L. Fernández
Gema Roldan

CINECA

Thomas Keane
Melanie Courtot
Jonathan Dursi

Heidi Rehm
Ben Hutton

GEM Japan

Toshiaki Katayama

Stephane Dyke

DNASTACK

Marc Fiume
Miro Cupak

BRCA EXCHANGE

Melissa Cline

ENA

EMBL-EBI

Diana Lemos

EUROPEAN JOINT PROGRAMME RARE DISEASES

VICC Variant Interpretation for Cancer Consortium

GA4GH Phenopackets
Peter Robinson
Jules Jacobsen

GA4GH VRS
Alex Wagner
Reece Hart

Beacon PRC
Alex Wagner
Jonathan Dursi
Mamana Mbiyavanga

Alice Mann
Neerjah Skantharajah

elixir

Genomic Data & Privacy

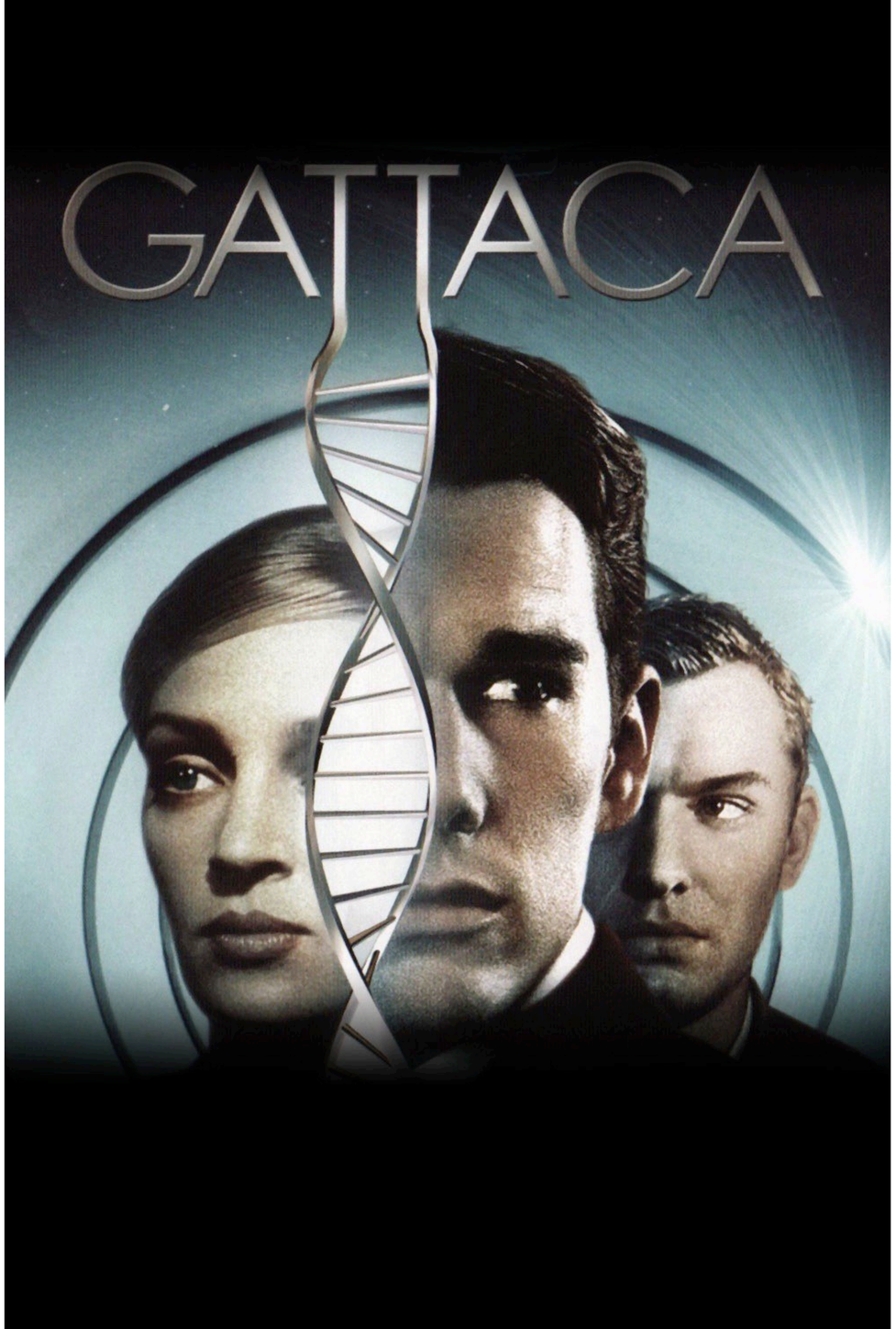
Risks & opportunities

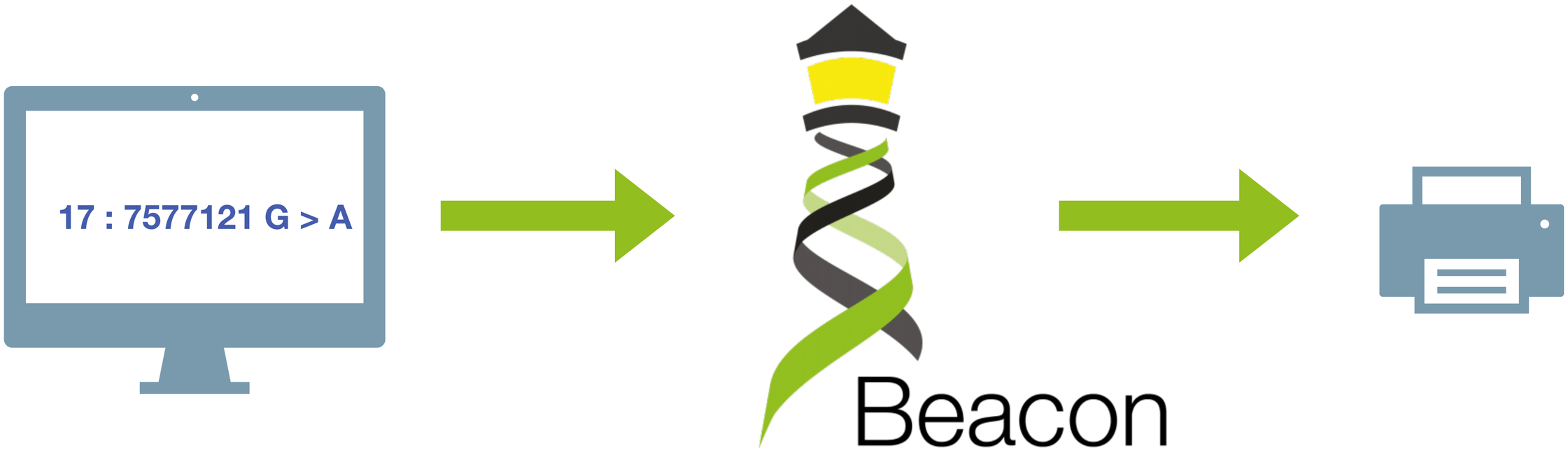
Gattaca (1997)

A genetically inferior man assumes the identity of a superior one in order to pursue his lifelong dream of space travel.

- genetic determinism
  - main character has been determined to be unsuitable for complex jobs based on genetic analysis
- genetic identification
  - the use of genetic sampling for personal identification is daily routine

With information from https://www.imdb.com/title/tt0119177/





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

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

Genome *Beacons* Compromise Security?

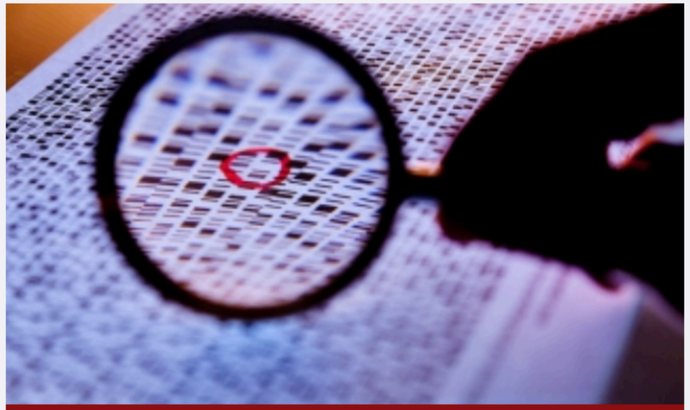
Querying for thousands of specific SNV occurrences in a genomic data pool can identify individuals in an anonymized genomic data collection

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.



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

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.

IDENTIFICATION OF INDIVIDUALS FROM MIXED COLLECTIONS USING RARE ALLELES

The American Journal of Human Genetics *97*, 631–646, November 5, 2015

Privacy Risks from Genomic Data-Sharing Beacons

Suyash S. Shringarpure[1,*] and Carlos D. Bustamante[1,*]

The human genetics community needs robust protocols that enable secure sharing of genomic data from participants in genetic research. Beacons are web servers that answer allele-presence queries—such as "Do you have a genome that has a specific nucleotide (e.g., A) at a specific genomic position (e.g., position 11,272 on chromosome 1)?"—with either "yes" or "no." Here, we show that individuals in a beacon are susceptible to re-identification even if the only data shared include presence or absence information about alleles in a beacon. Specifically, we propose a likelihood-ratio test of whether a given individual is present in a given genetic beacon. Our test is not dependent on allele frequencies and is the most powerful test for a specified false-positive rate. Through simulations, we showed that in a beacon with 1,000 individuals, re-identification is possible with just 5,000 queries. Relatives can also be identified in the beacon. Re-identification is possible even in the presence of sequencing errors and variant-calling differences. In a beacon constructed with 65 European individuals from the 1000 Genomes Project, we demonstrated that it is possible to detect membership in the beacon with just 250 SNPs. With just 1,000 SNP queries, we were able to detect the presence of an individual genome from the Personal Genome Project in an existing beacon. Our results show that beacons can disclose membership and implied phenotypic information about participants and do not protect privacy a priori. We discuss risk mitigation through policies and standards such as not allowing anonymous pings of genetic beacons and requiring minimum beacon sizes.

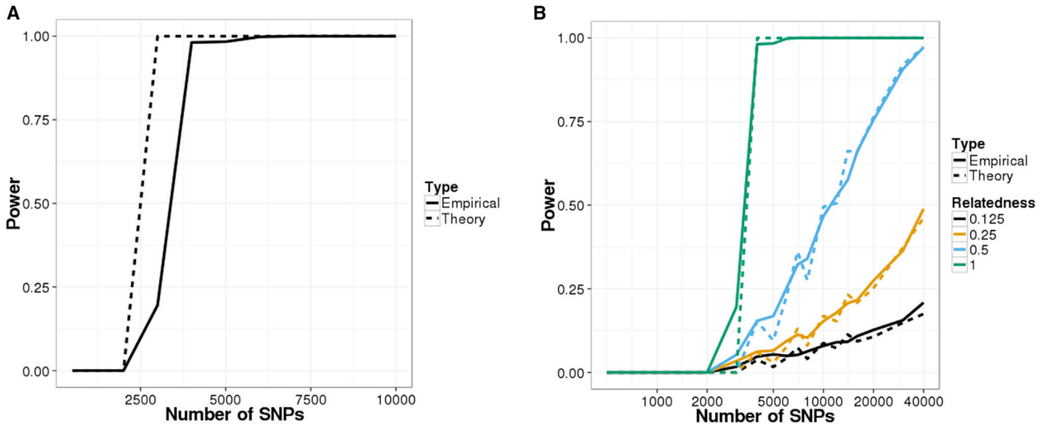
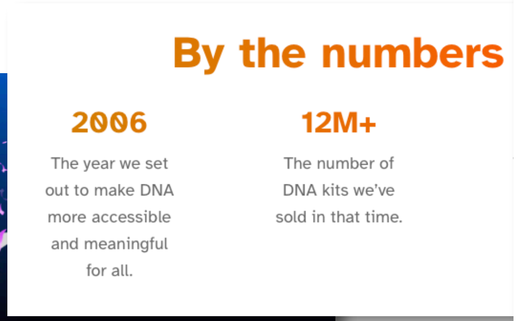


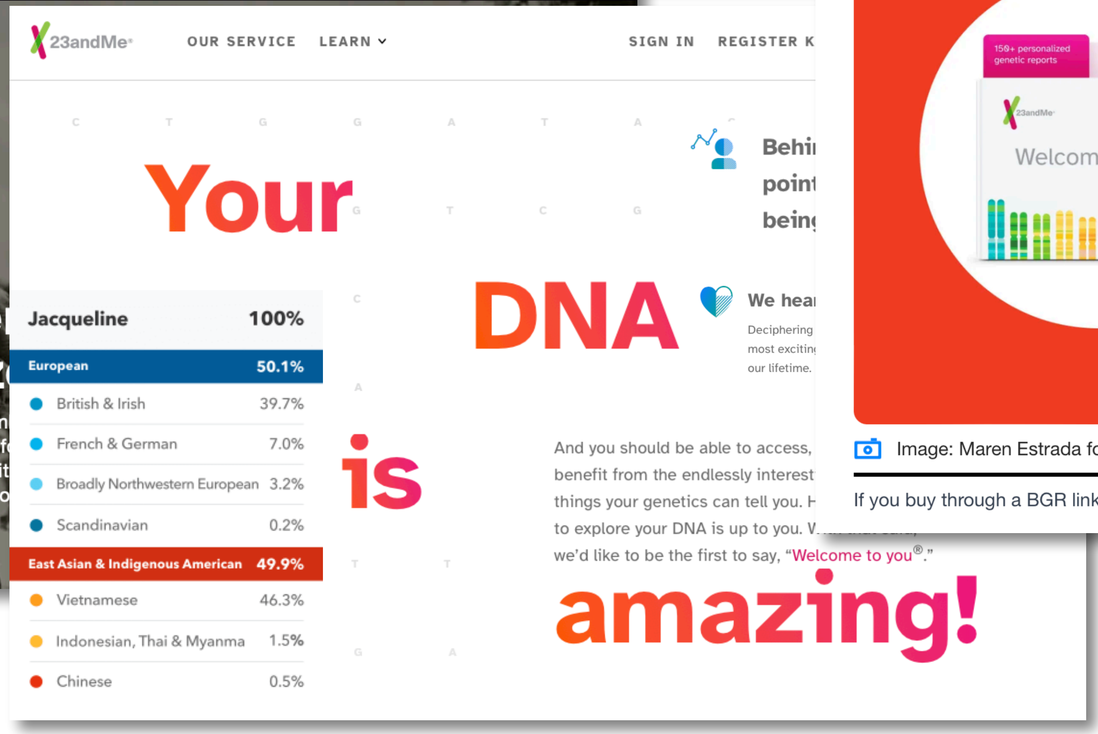
Figure 1. Power of Re-identification Attacks on Beacons Constructed with Simulated Data
Power curves for the likelihood-ratio test (LRT) on (A) a simulated beacon with 1,000 individuals and (B) detecting relatives in the simulated beacon. The false-positive rate was set to 0.05 for all scenarios.

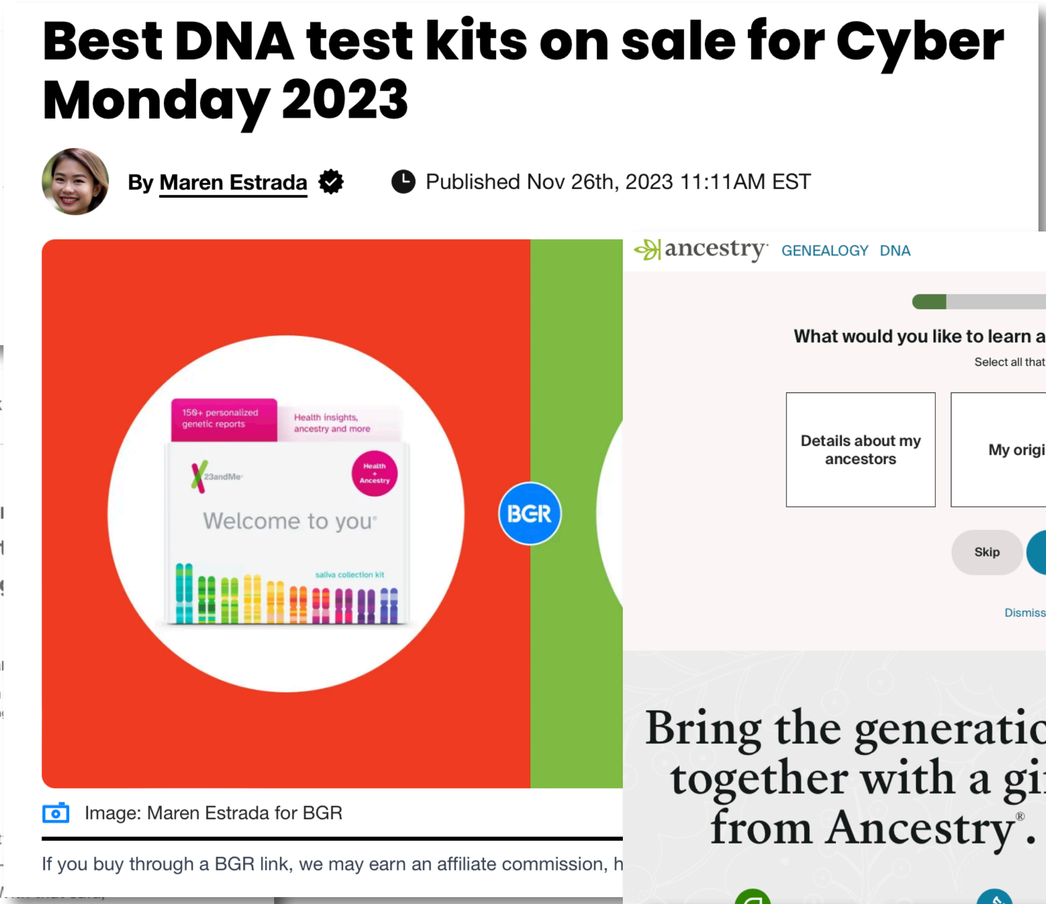
- rare allelic variants can be used to identify an individual (or her relatives) in a genome collection without having access to individual datasets
- however, such an approach requires previous knowledge about the individual's SNPs

Direct to Consumer DNA Analyses

Population Background, Family Trees, Traits & Disease Risks...







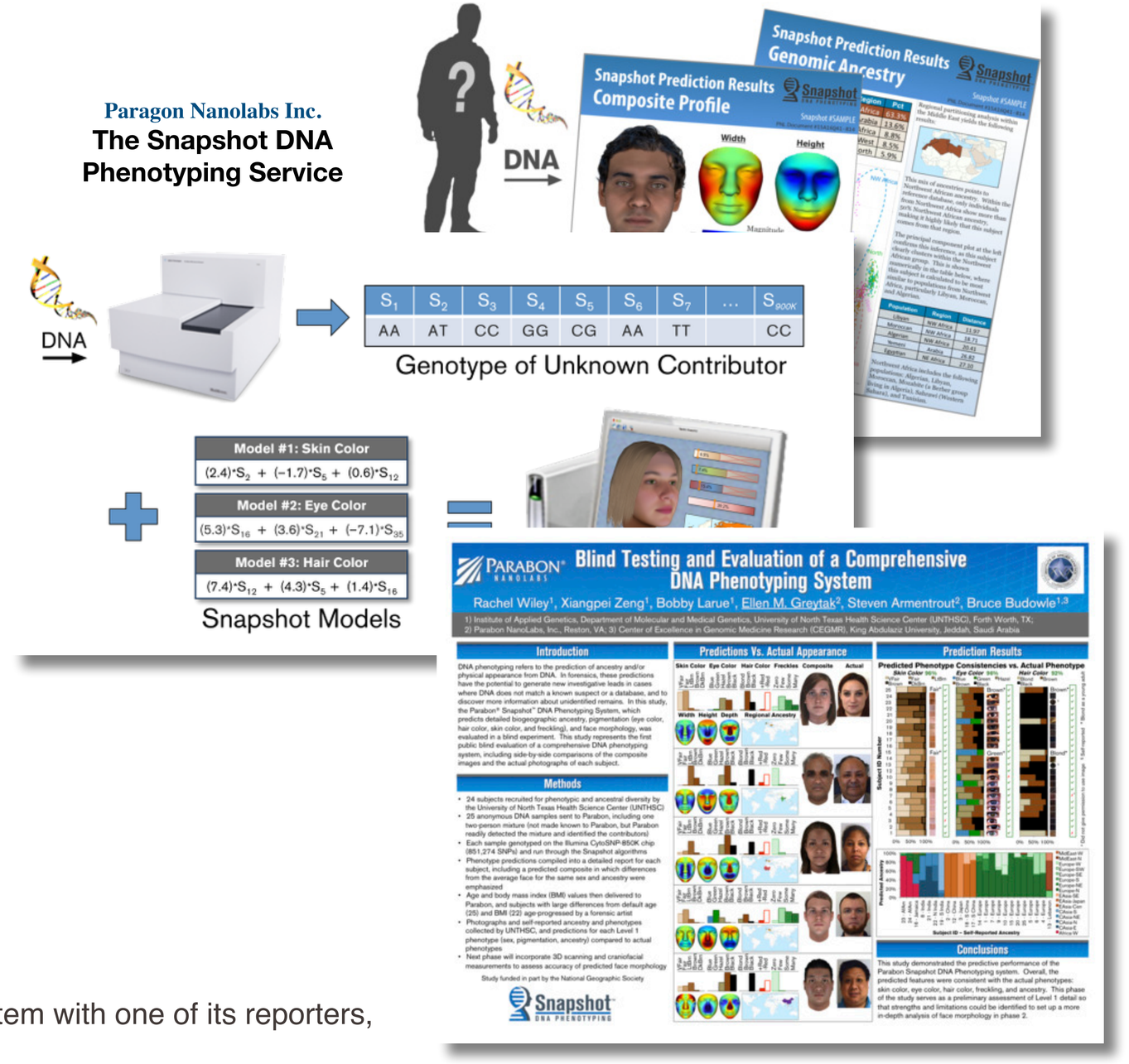
“We’re an information economy. They teach you that in school. What they don’t tell you is that it’s impossible to move, to live, to operate at any level without leaving traces, bits, seemingly meaningless fragments of personal information. Fragments that can be retrieved, amplified . . .”

–William Gibson in "Johnny Mnemonic" (1986)

Phenotyping from DNA

From DNA to "Wanted" Posters?

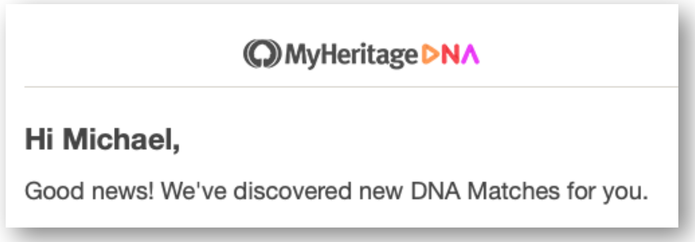
- association of genomic variants with phenotypic data collection
- while hair, eye color are easy targets not useful for relevant phenotypic features especially if large environmental component
- huge biases based on input/collection data
- Belgium and Germany do not allow forensic DNA phenotyping
- Switzerland: Bundesrat decision on 2020-12-04 to allow phenotyping for law enforcement purposes



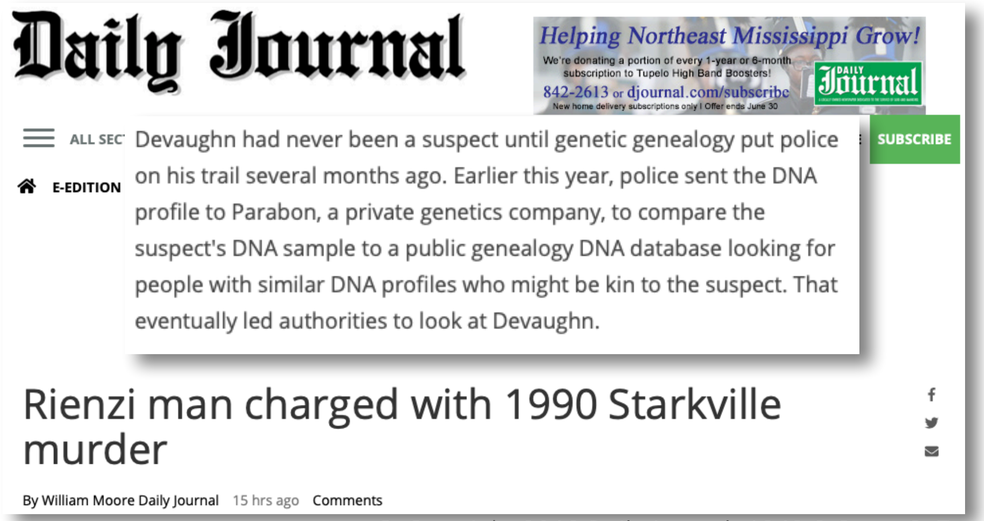
"When the New York Times ran an informal test of the Parabon system with one of its reporters, it failed badly." (ACLU.org)

https://snapshot.parabon-nanolabs.com/phenotyping

Long-Range Familial Searches



- Commercial, "Direct to Customer" DNA analyses are provided through independent sites and such affiliated to genealogy services (MyHeritage, Ancestry.com, 23andMe...)
- Genealogy sites identify individuals with matching haplotype blocks & provide a prediction about degree of genetic relation
- Law enforcement agencies (and who else?!) can send individual SNP profiles (e.g. recovered from evidence many years after a crime) using a *Jane Doe* identity, to identify relatives of the suspect - **long range familial search**



DNA & Law Enforcement

Legal minefields, hard to avoid?

- "...when police in Edmonton, Canada, released a suspect's image, the **crude graphic** ... came **from the suspect's DNA**."
- "...every time a **family member** sends in their swab, they're sending in your data too..."
- "...**many players** in this growing movement offer to translate our genetic code into phenotypes (that is, observable features like eye color), often with **scant commitment to scientific accuracy**..."
- "...Veering into **pseudoscience**, they are a modern **sales pitch for** the long-discredited **phrenology** of the past. They wrongly treat race as a biological fact, rather than the social construct that it is. And in the process, they open all the **flaws of facial recognition** to new realms..."
- "...we first have to change our focus from preventing DNA collection to **preventing misuse** and managing access..."
- "The answer is simple: **Ban DNA searches** ... beyond the types of one-to-one DNA tests that are subject to judicial oversight..."

Cops Might Already Have Your DNA, Without Your Consent

FAREWELL PRIVACY

We've entered the era of genetic surveillance and nothing—not even our own cells—is off-limits.

Albert Fox Cahn | Ayesha Rasheed

Published Nov. 14, 2022 4:51AM ET

"The unchallenged expansion of DNA collection and law enforcement misuse of the data has also spurred a surge in DNA surveillance startups."

thedailybeast.com/cops-might-already-have-your-dna-without-your-consent

But genotyping itself is for professional labs, right?

Rapid re-identification of human samples

...

We developed a rapid, inexpensive, and portable strategy to re-identify human DNA using the MinION. Our strategy requires only ~60 min preparation and 5-30 minutes of MinION sequencing, works with low input DNA, and enables familial searches using Direct-to-Consumer genomic reference datasets. This method can be implemented in a variety of fields:

Forensics

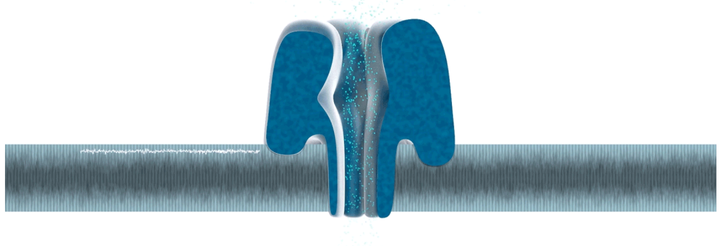
Identification of abandoned meterial using DNA fingerprinting is a common practice. The main challange currently being: time. Our method allows rapid sample preparation at the crime scene (see movie). We envision that the method can be adopted in the field for rapid checks, after a mass disaster, and can be adopted in border control to fight human traffacking.

Clinic

Clinics procces many samples, either for analysis or, for example, organ donations. These samples are DNA fingerprinted to prevent sample mix-up mistakes. Our method can be implemnted in the clinic for rapid sanitiy-check of all incoming samples.

Cell line identification

Cross contamination of cell lines in science is a major problem. It results in unreproducible data, and clinical trails based on inaccurate findings. This problem costs billions of dollars per year. We envision labs can adopt our identification method to ensure the purity of the cell line, and detect contamination.



The MinION (Oxford Nanopore)
Source: Sophie Zaaijer

DEMOCRATIZING DNA FINGERPRINTING

Sophie Zaaijer, Assaf Gordon, Robert Piccone, Daniel Speyer, Yaniv Erlich, 2016

ddf.teamerlich.org

MinION by Oxford Nanopore Technologies

The MinION is the smallest DNA sequencer currently around. Its the size of a Mars bar, and can be simply plugged into a laptop with a USB3.0 port.

For more information about the MinION please click:

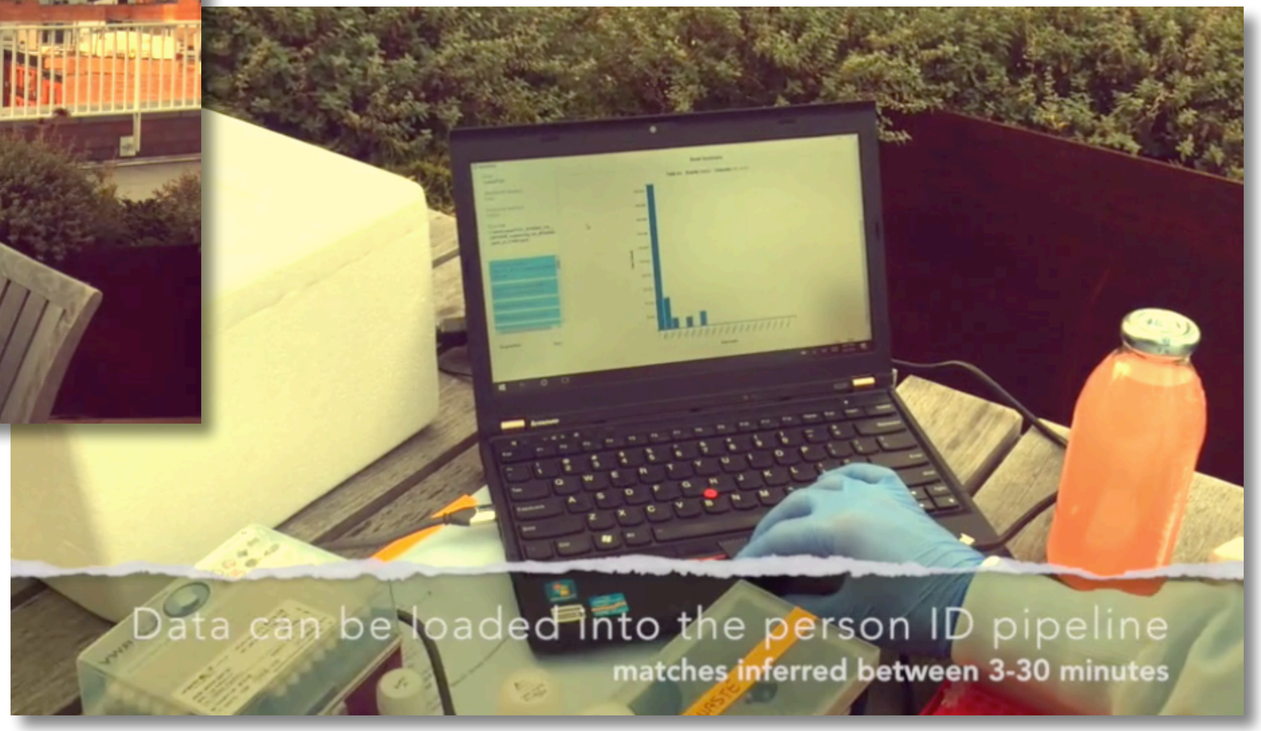
Oxford Nanopore Technologies

Bento Lab

The Bento lab is a miniature lab with a centrifuge, thermocycler and a electrophoresis compartment.

For more information about the Bento-lab please click:

Bento Lab



DNA sequencing for identification/fingerprinting soon “commodity” technology (in contrast with technological/data challenges in “precision medicine”)

Generalkonsent

BENEFIT

BLOCKCHAIN

HEALTH

PRIVACY

SECURITY

CONSENT

ACCESS

Right to Research

HACKERS

LAWS

Genetic
Information
Nondiscrimination
Act

Health
Insurance
Portability and
Accountability
Act

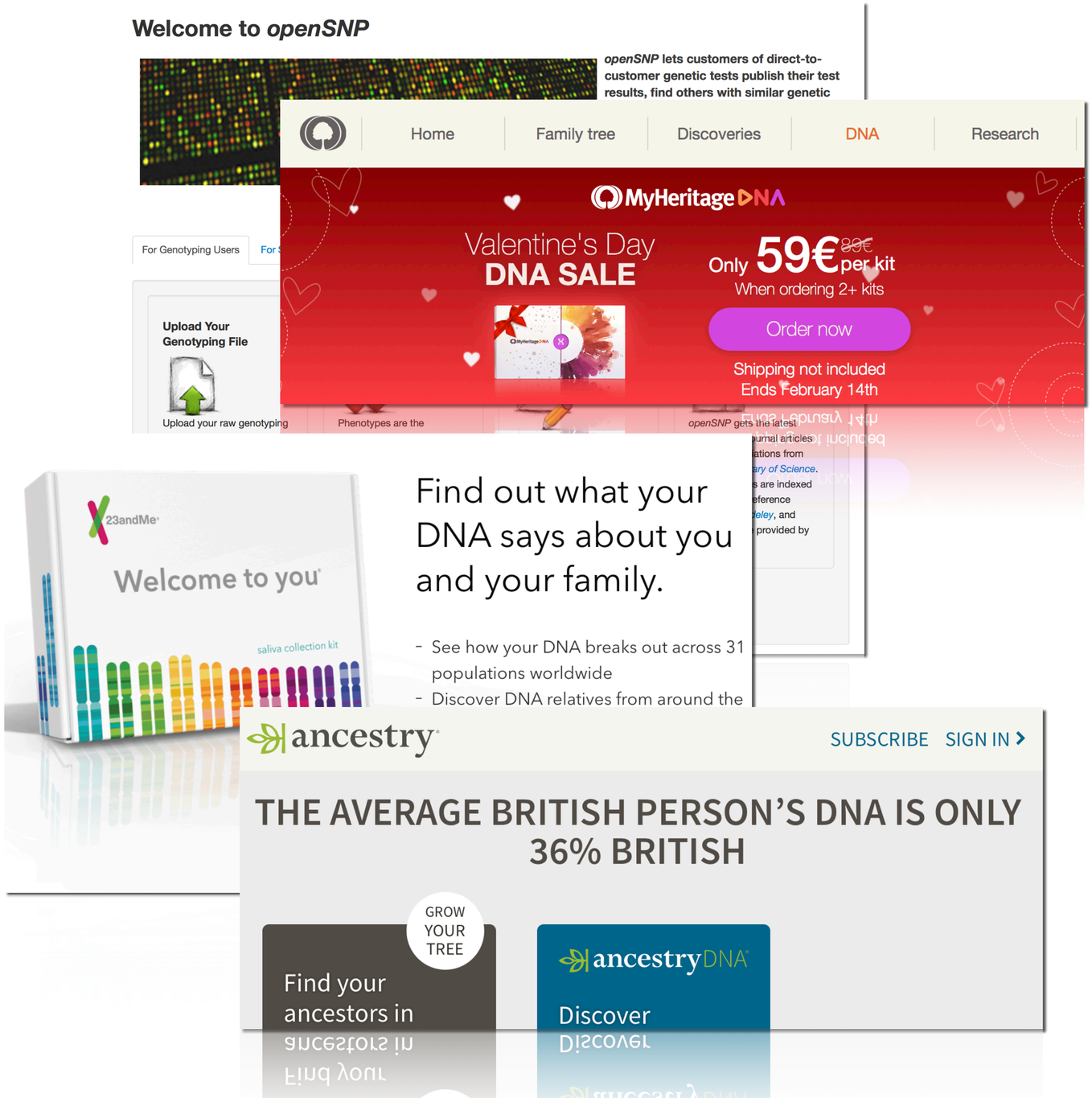
SAFETY

CRYPTOGRAPHY

Share *YOUR* Genome data?

- The Beacon concept - balanced approach for accessing genome variant data from internationally distributed resources
- However: Genome data has the inherent “risk” of being identified and linked to a person

Solutions from Technology or Society? Discourse!



THE SUNDAY TIMES

TECHNOLOGY

How can a DNA firm lose half its users' data to 'Jew-hating' hackers?

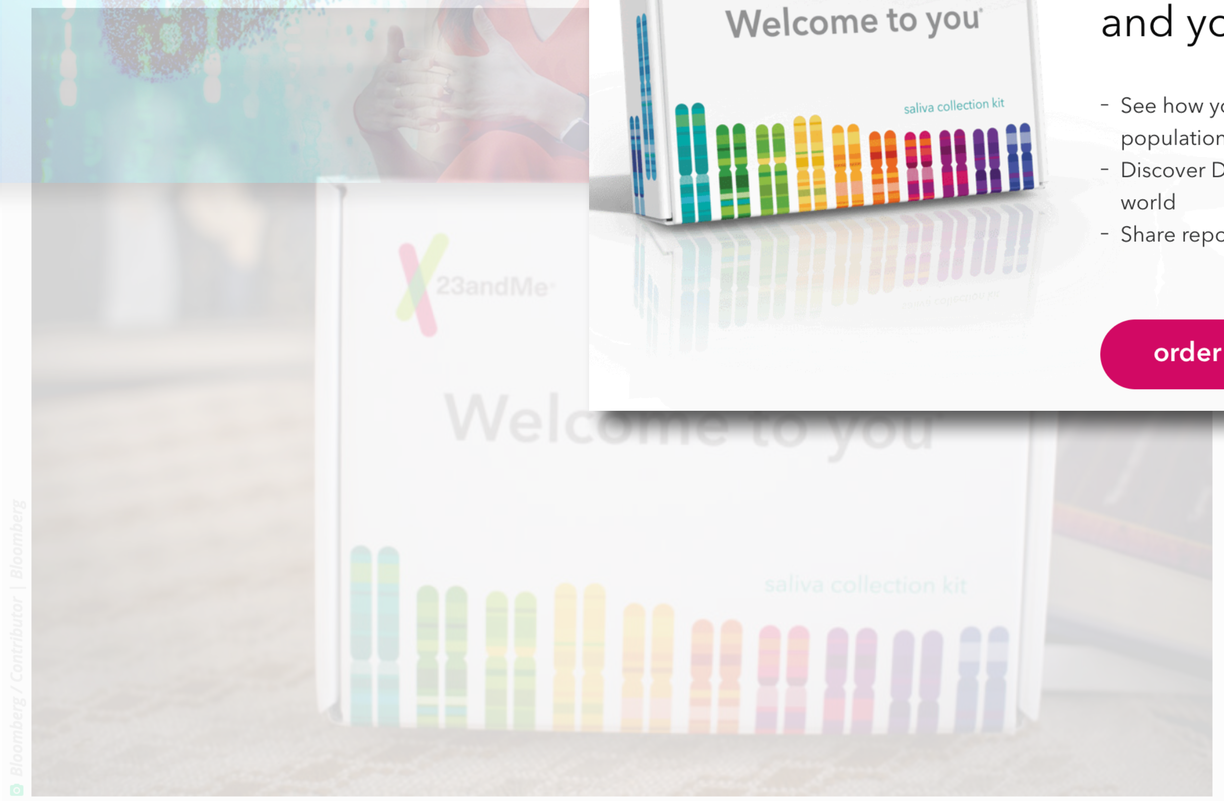
Dark-web criminals cited the head of 23andMe's faith after a raid on the details of 6.9 million people — including her Google-founding ex. Now the lawsuits are coming

FAMILY MATTERS

Hackers stole ancestry data of 6.9 million users, 23andMe finally confirmed

Majority of impacted users are now being notifie

ASHLEY BELANGER - 12/4/2023, 11:48 PM



Bloomberg / Contributor | Bloomberg

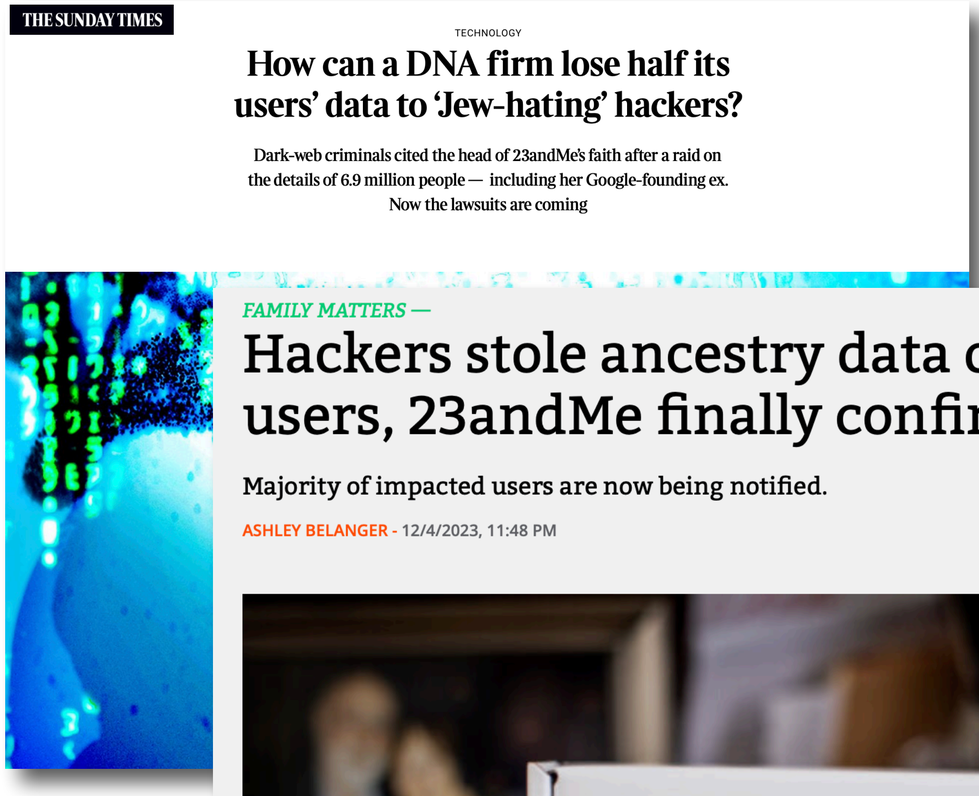
It has now been confirmed that an additional **6.9 million 23andMe users had ancestry data stolen** after hackers accessed thousands of accounts by likely reusing previously leaked passwords.

... Wired estimated that "at least a million data points from 23andMe accounts" that were "exclusively about Ashkenazi Jews" and data points from "hundreds of thousands of users of Chinese descent" seemed to be exposed.

a spokesperson to confirm that two groups of
pted into the **DNA Relatives feature** had their
a stolen.

scribes the DNA Relatives feature as ...
to find and connect with genetic relatives and
bout your family." By **opting in**, users hope to
ly members by **willingly** giving others access to
ike their birth year, current location, and
ames and birth locations. Users can opt out at

... about 5.5 million users, was hacked after opting in to automatically sharing information with DNA Relatives, including their "**name, birth year, relationship labels, the percentage of DNA shared with relatives, ancestry reports, and self-reported location**," TechCrunch reported.
... about 1.4 million users, shared "Family Tree profile information" ... including display names, relationship labels, birth year, and self-reported location, TechCrunch reported.



It has now been confirmed that an additional **6.9 million 23andMe users had ancestry data stolen** after hackers accessed thousands of accounts by likely reusing previously leaked passwords.

... Wired estimated that "at least a million data points from 23andMe accounts" that were "exclusively about Ashkenazi Jews" and data points from "hundreds of thousands of users of Chinese descent" seemed to be exposed.

... prompting a spokesperson to confirm that two groups of users who opted into the **DNA Relatives feature** had their personal data stolen.

23andMe describes the DNA Relatives feature as ... "allowing you to find and connect with genetic relatives and learn more about your family." By **opting in**, users hope to find lost family members by **willingly** giving others access to information like their birth year, current location, and ancestors' names and birth locations. Users can opt out at any time ...

... about 5.5 million users, was hacked after opting in to automatically sharing information with DNA Relatives, including their "**name, birth year, relationship labels, the percentage of DNA shared with relatives, ancestry reports, and self-reported location**," TechCrunch reported.
... about 1.4 million users, shared "Family Tree profile information" ... including display names, relationship labels, birth year, and self-reported location, TechCrunch reported.

THE SUNDAY TIMES

TECHNOLOGY

How can a DNA firm
users' data to 'Jew-ha

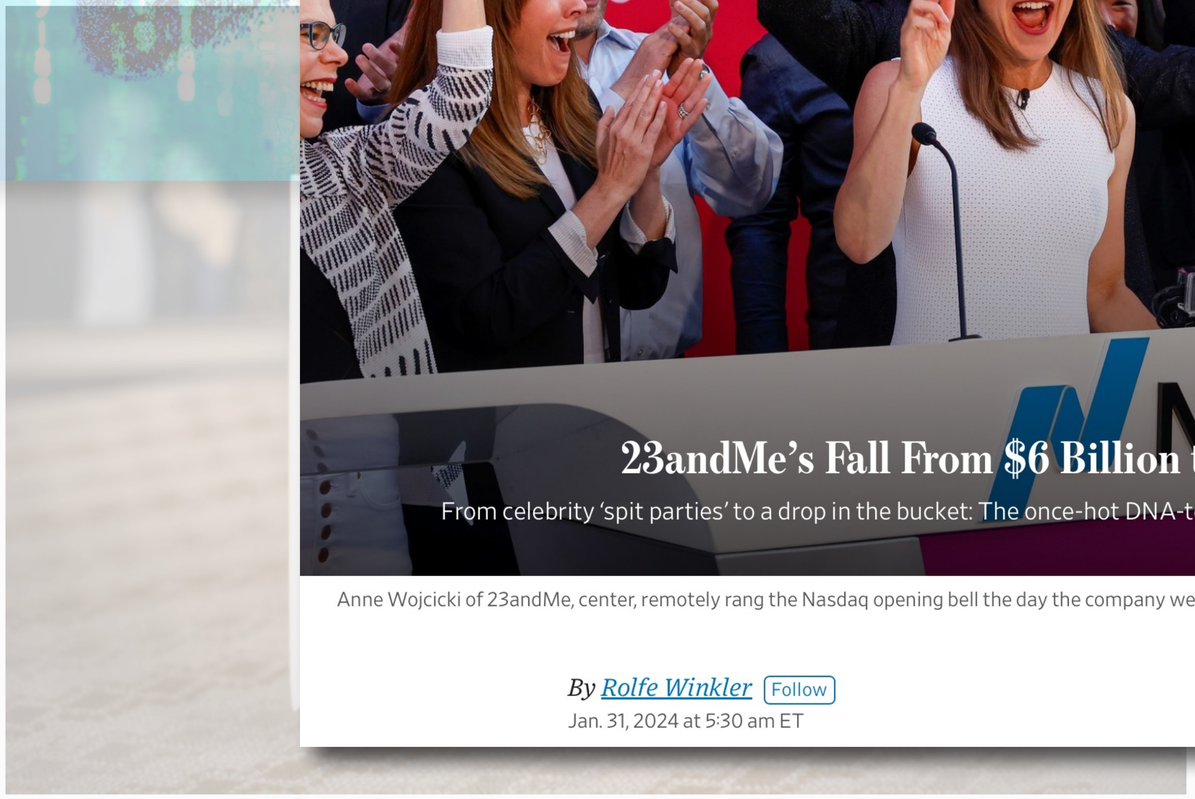
Dark-web criminals cited the head of 23a
the details of 6.9 million people — includi
Now the lawsuits are

FAMILY MATTERS —

Hackers sto
users, 23an

Majority of impacted use

ASHLEY BELANGER - 12/4/2023, 11:48



Bloomberg / Contributor | Bloomberg

WSJ Barron's MarketWatch IBD

THE WALL STREET JOURNAL.

SIGN IN SUBSCRIBE

23andMe's Fall From $6 Billion to Nearly $0

From celebrity 'spit parties' to a drop in the bucket: The once-hot DNA-testing company is struggling to profit

Anne Wojcicki of 23andMe, center, remotely rang the Nasdaq opening bell the day the company went public in 2021. PETER DASILVA/REUTERS

By *Rolfe Winkler* Follow

Jan. 31, 2024 at 5:30 am ET

It has now been confirmed that an additional **6.9 million**
ry data stolen after hackers
unts by likely reusing previously

ast a million data points from
e "exclusively about Ashkenazi
hundreds of thousands of users
to be exposed.

to confirm that two groups of
A Relatives feature had their

Relatives feature as ...
nect with genetic relatives and
." By **opting in**, users hope to
villingly giving others access to
ar, current location, and
ocations. Users can opt out at

s hacked after opting in to
ation with DNA Relatives,
ear, relationship labels, the
with relatives, ancestry
ocation," TechCrunch reported.
ared "Family Tree profile
lay names, relationship labels,
birth year, and self-reported location, TechCrunch reported.

Universal Declaration of Human Rights (1948)

27(1) "The Right to Science"

"Everyone has the right freely to participate in the cultural life of the community, to enjoy the arts and **to share in scientific advancement and its benefits.**"

27(2) "The Right to Recognition"

"Everyone has the right to the protection of the moral and material interests resulting from any scientific, literary or artistic production of which he is the author."

Universität Zürich[UZH]

SIB Swiss Institute of Bioinformatics

elixir