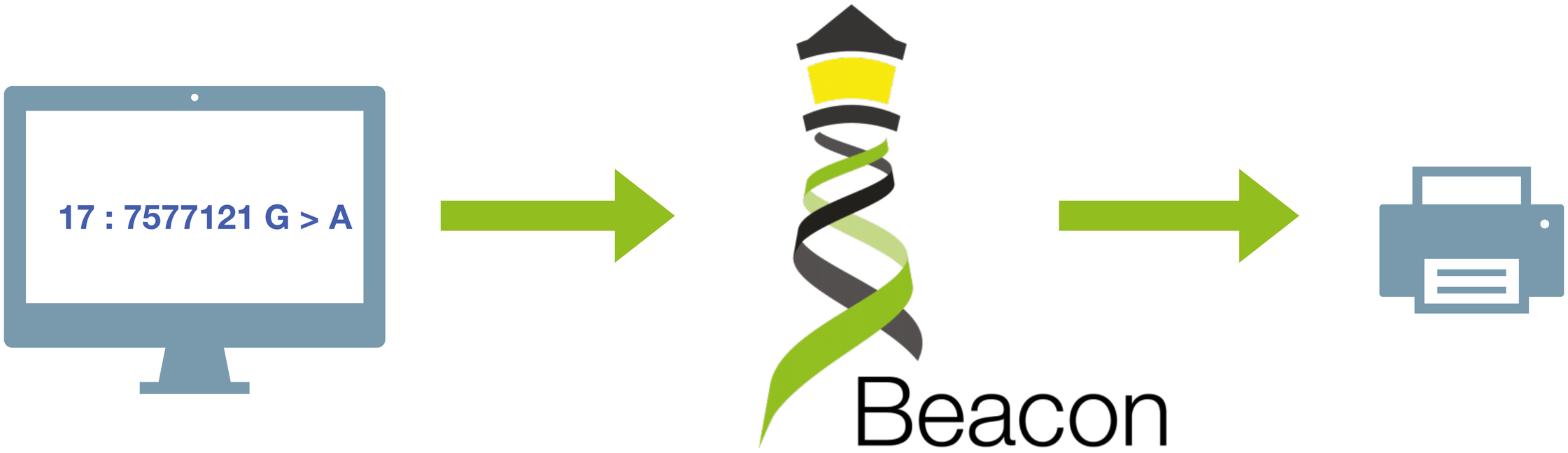
Driving oncogenomic and CNV reference resources through Beacon ~~v2~~

Data Discovery :: Data Sharing :: Analysis Support

Global Alliance for Genomics & Health

University of Zurich UZH

Michael Baudis :: ELIXIR AHM :: 2025-06-04



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**.

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

YES | **NO** | \0

Global Alliance "Beacon"

Jim Ostell, NCBI - March 7, 2014

Global Alliance for Genomics & Health

Why

... 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 ... research for ... ***signs of willing participants in far reaching data sharing***, … it has remained a dark and quiet place. [This] challenge is to 1) ***trigger the issues*** blocking groups … in way that isn't masked by the … complexities ... 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**. … provide a ***low bar for ... real*** … ***engagement***. … there is **some utility** in …locating a rare allele in your data … A number of more useful first versions have been suggested:

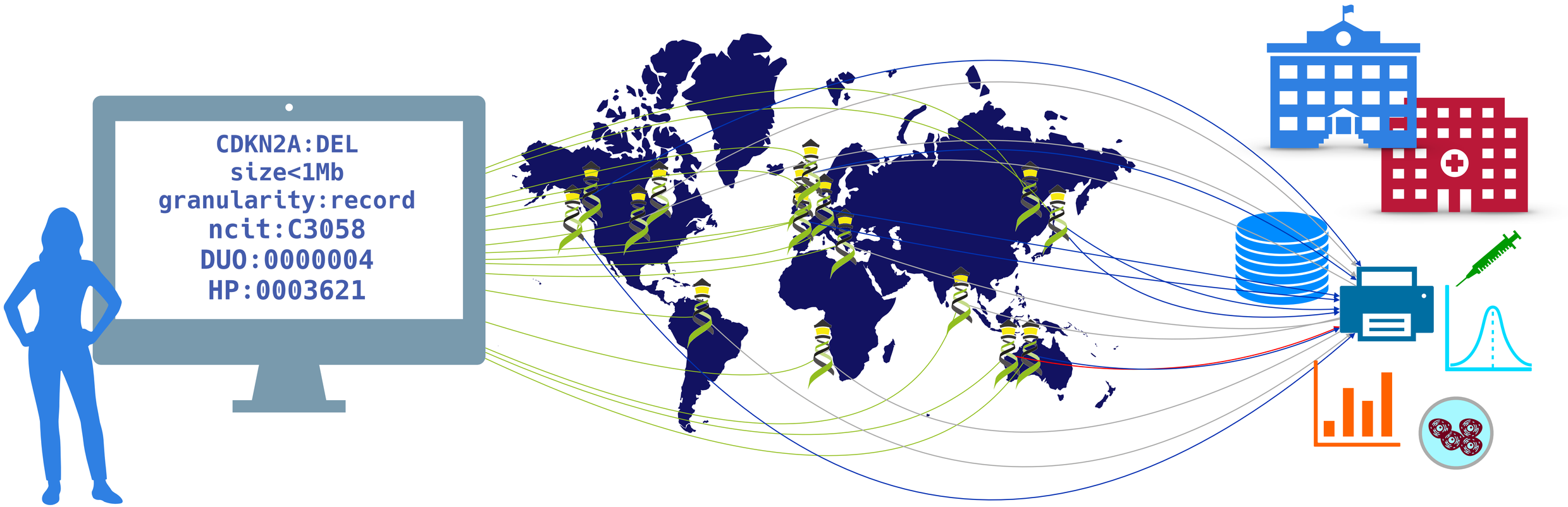
1. Provide ***frequencies of all alleles*** at that point
2. .. alleles seen in a gene ***region***
3. Other more complicated queries

"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 … [potentially including a] ***"phone home" response*** …

	Beacon v1 Development	Beacon v2 Development	Related ...
2014	**GA4GH founding event; Jim Ostell proposes Beacon concept including "more features ... version 2"**		
2015	• beacon-network.org aggregator created by DNAstack		• ELIXIR starts Beacon project support
2016	• Beacon v0.3 release • work on queries for structural variants (brackets for fuzzy start and end parameters...)	• Beacon+ concept implemented @ **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	• Beacon hackathon Stockholm; settling on **filters** • Barcelona goes Zurich developers meeting • Beacon API v2 Kick off • adopting "handover" concept	• new Beacon website (March)
2019	• ELIXIR Beacon Network		• Beacon publication at Nature Biotechnology
2020		• "**Scouts**" teams working on different aspects - filters, genomic variants, compliance ...	
2021		• **framework** + **models** concept implemented • range and bracket queries, variant length • starting of GA4GH review process	• Phenopackets v2 approved
2022		• changes in default model, aligning with Phenopackets and VRS • unified beacon-v2 code & docs repository • **Beacon v2 approved** at April GA4GH Connect	• *docs.genomebeacons.org*



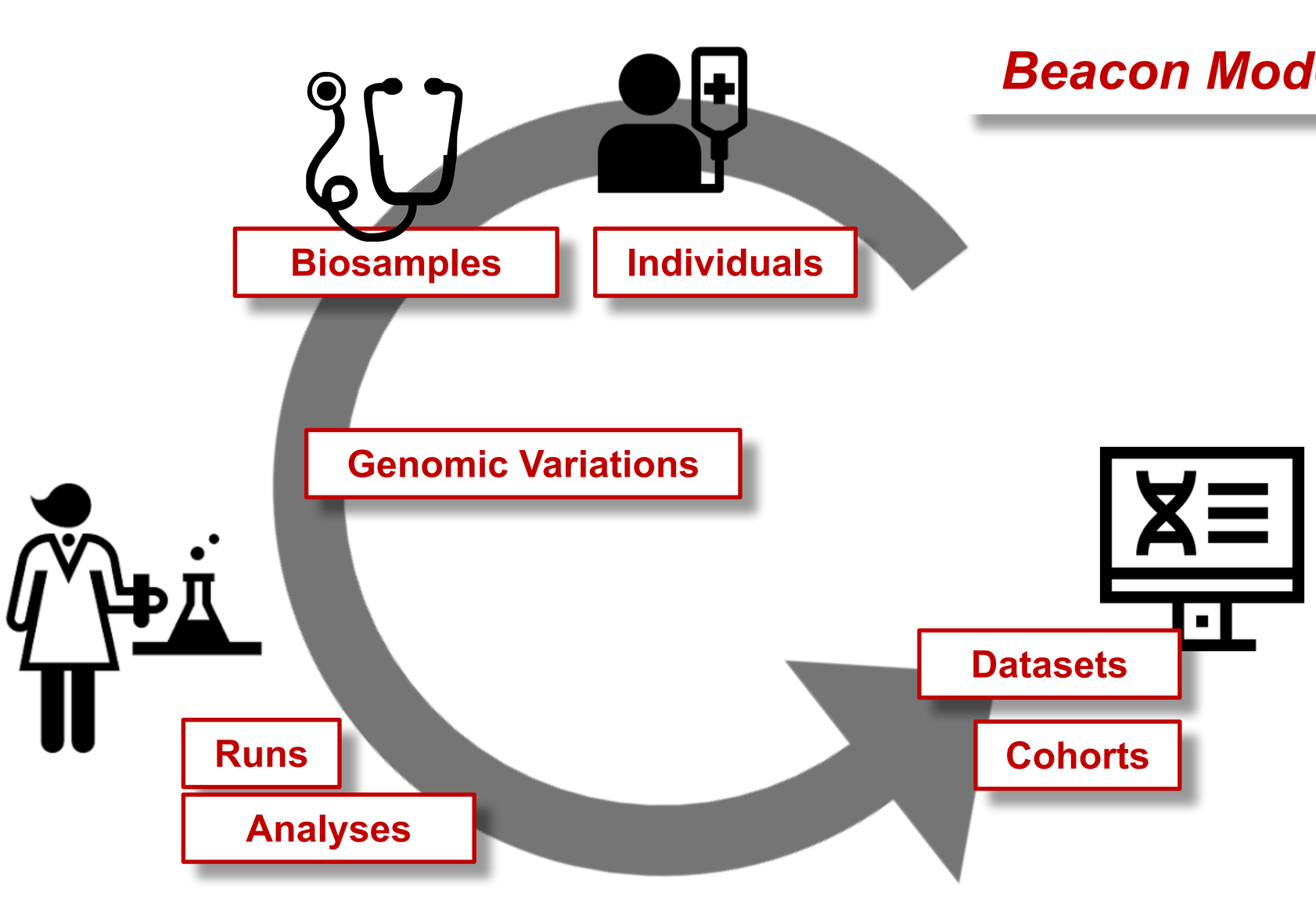
Can you provide data about focal deletions in CDKN2A in Glioblastomas from juvenile patients with unrestricted access?

Beacon API

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

Beacon v2

docs.genomebeacons.org

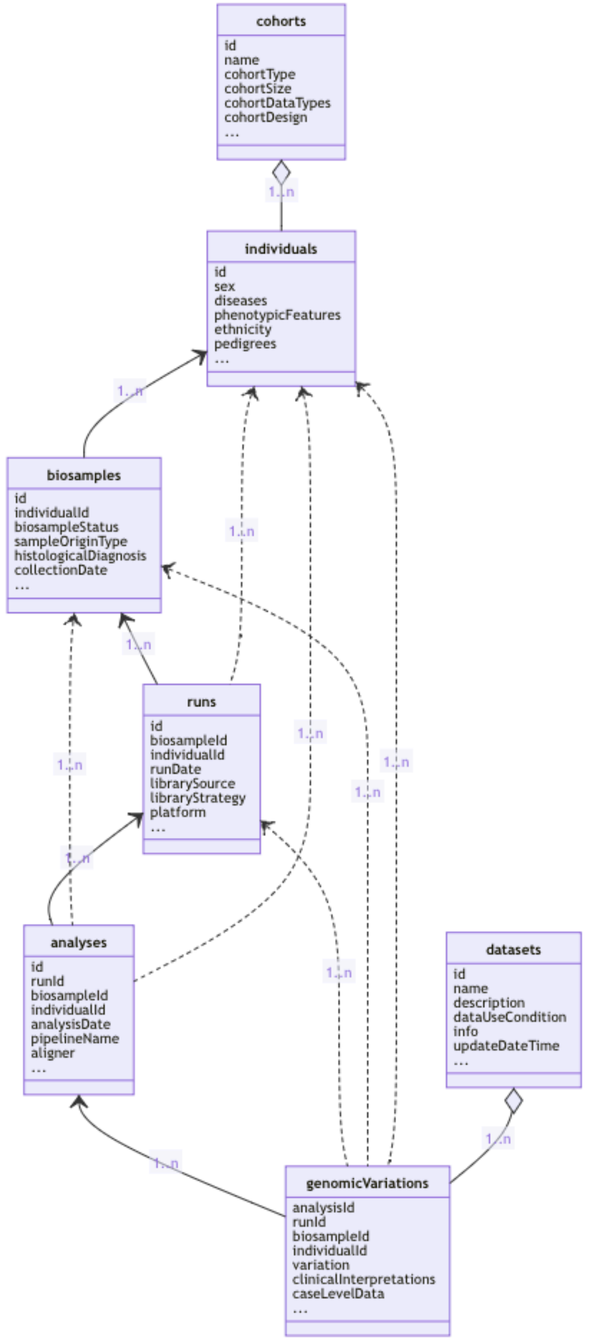


Beacon Model

Beacon Framework (protocol)

Beacon Default v2 Model

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



Standards Development & Implementation: CNV Terms

in computational (file/schema) formats

```
- EFO:0030064
- EFO:0030067
    |- EFO:0030068
    \- EFO:0020073
         \- EFO:0030069
- EFO:0030070
    |- EFO:0030071
    \- EFO:0030072
```

GA4GH VRS1.3+	Beacon v2	VCF v4.4	SO
EFO:0030070 gain	DUP or **EFO:0030070**	DUP SVCLAIM=D	SO:0001742 copy_number_gain
EFO:0030071 low-level gain	DUP or **EFO:0030071**	DUP SVCLAIM=D	SO:0001742 copy_number_gain
EFO:0030072 high-level gain	DUP or **EFO:0030072**	DUP SVCLAIM=D	SO:0001742 copy_number_gain
EFO:0030072 high-level gain	DUP or EFO:0030073	DUP SVCLAIM=D	SO:0001742 copy_number_gain
EFO:0030067 loss	DEL or **EFO:0030067**	DEL SVCLAIM=D	SO:0001743 copy_number_loss
EFO:0030068 low-level loss	DEL or **EFO:0030068**	DEL SVCLAIM=D	SO:0001743 copy_number_loss
EFO:0020073 high-level loss	DEL or **EFO:0020073**	DEL SVCLAIM=D	SO:0001743 copy_number_loss
EFO:0030069 complete genomic loss	DEL or **EFO:0030069**	DEL SVCLAIM=D	SO:0001743 copy_number_loss

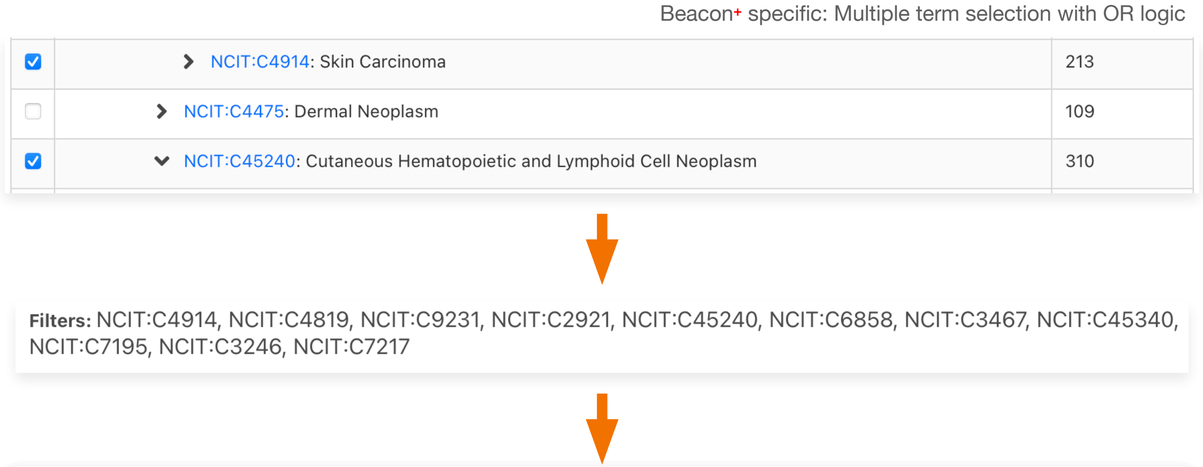
Beacon v2 Filters

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

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

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

Beacon+ specific: Multiple term selection with OR logic



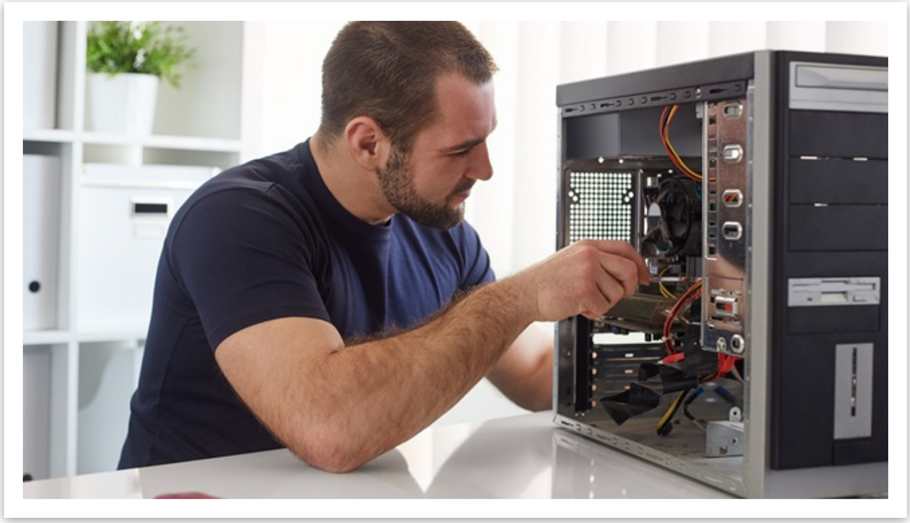
Begriffsbestimmung

The right expressions help to conceptualize...

- **Beacon**: The protocol/API, with framework and default model
- **beacon**: Implementation of Beacon
  - ➡ using the Beacon v2 framework & supporting at minimum boolean responses
  - ➡ suggested support of Beacon v2 default model but can choose other
- Beacon **Aggregator**: service distributes queries to beacons and aggregates responses into a single Beacon response
  - ➡ potential to liftover genomes, remap filtering terms, translate between protocol versions...
  - ➡ entry point to or potentially itself node in a ...
- Beacon **Network**: Set of beacons wit shared entry point for distributed queries and aggregated response delivery
  - ➡ "true" beacon networks should have managed aspects - scope, term use...
  - ➡ networks may combine mixes of internal (protected, rich data, additional extensions...) and external interfaces

Beacon v2 deployment

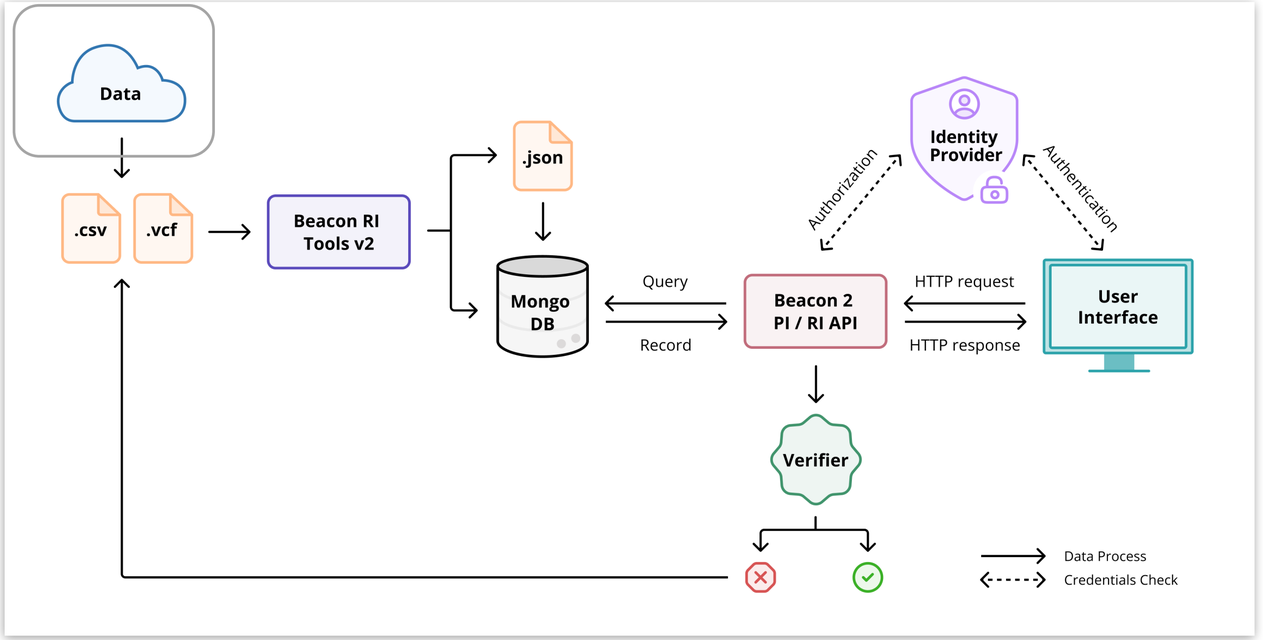
Build it yourself



GitHub

Beacon v2 API
https://github.com/ga4gh-beacon/beacon-v2

Toolkit for production environments



Beacon v2 Production Implementation (released Oct 2024)
https://github.com/ga4gh-beacon/beacon-v2

https://www.choice.com.au/electronics-and-technology/computers/desktop-and-laptop-computers/articles/is-building-your-own-pc-worth-it

bycon based Beacon+ Stack

progenetix

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

React

APACHE HTTP SERVER PROJECT

python™

mongoDB

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

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

Entity collections

GitHub github.com/progenetix/bycon

Utility collections

bycon based Beacon+ Stack

progenetix

- *collations* contain pre-computed data (e.g. CNV frequencies, statistics) and information for all grouping entity instances and correspond to **filter values**
  - `pubmed:10027410, NCIT:C3222, pgx:cohort-TCGA, pgx:icdom-94703…`
  - precomputed frequencies per collection informative e.g. in form autofills
- *querybuffer* stores id values of all entities matched by a query and provides the corresponding `accessid` for **handover** generation
- complete query aggregation; i.e. individual queries are run against the corresponding entities and ids are intersected
  - ➡ retrieval of any entity, e.g. all individuals which have queried variants analyzed on a given platform
  - ➡ allows multi-variant queries, i.e. all bio samples or individuals which had matches of all of the individual variant queries

React

APACHE HTTP SERVER PROJECT

python™

mongoDB

Entity collections

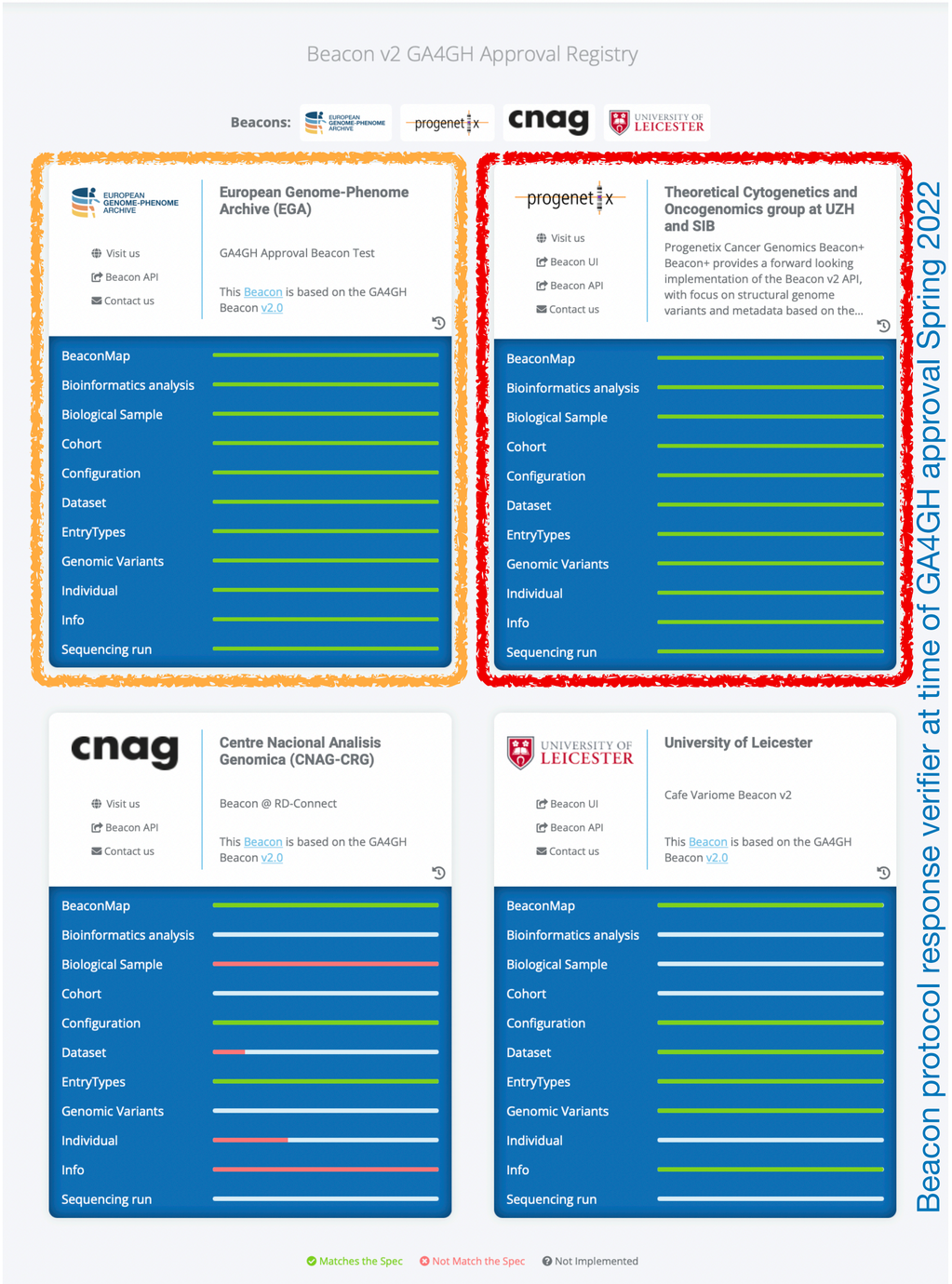
Utility collections

github.com/progenetix/bycon GitHub

bycon Beacon+

Implementation driven standards development

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



Global Alliance for Genomics & Health

progenetix

elixir

progenetix.org

Cancer Genomics Reference Resource

- ***open*** resource for oncogenomic profiles
- over **150'000 cancer CNV profiles**
- SNV data for some series (e.g. TCGA)
- more than **900 diagnostic types**
- inclusion of reference datasets (e.g. TCGA)
- standardized encodings (e.g. NCIt, ICD-O 3)
- identifier mapping for PMID, GEO, Cellosaurus, TCGA, cBioPortal where appropriate
- core clinical data (TNM, sex, survival ...)
- data mapping services

Universität Zürich[UZH]

progenetix

SIB Swiss Institute of Bioinformatics

Pushing the envelope...

Custom Beacon aggregation response for displaying CNV frequencies

progenetix

- **CNV Profiles**
  - ... by NCIT
  - ... by ICD-O Morphology
  - ... by ICD-O Site
  - ... by TNM & Grade
- **Search Samples**
- **arrayMap**
  - TCGA Data
  - cBioPortal Studies
- **Publication DB**
  - Progenetix Use
- **NCIT - ICD-O Mappings**
  - UBERON Mappings
- **Upload & Plot**
- **OpenAPI Paths and Examples**
- **Cancer Cell Lines**
- **Beacon+**
- **Documentation**
- **Baudisgroup @ UZH**

Select Summary Histograms

On this page you can combine one or multiple disease or other codes from one or more datasets frequencies). These based on pre-computed CNV frequencies for the given code; for a combina Page.

Dataset(s)

Progenetix cancer genome variants ×

Cancer Classification(s)

Select...

Various Subsets

pgx:TCGA-ACC: pgx:TCGA-ACC (180) × | pgx:TCGA-BLCA: pgx:TCGA-BLCA (810) × | pgx:TCGA-BRCA: pgx
pgx:TCGA-CESC: pgx:TCGA-CESC (586) × | pgx:TCGA-CHOL: pgx:TCGA-CHOL (85) × | pgx:TCGA-COAD:
pgx:TCGA-DLBC: pgx:TCGA-DLBC (94) × | pgx:TCGA-ESCA: pgx:TCGA-ESCA (373) × | pgx:TCGA-GBM: pg
pgx:TCGA-HNSC: pgx:TCGA-HNSC (1081) × | pgx:TCGA-KICH: pgx:TCGA-KICH (132) × | pgx:TCGA-KIRC:
pgx:TCGA-KIRP: pgx:TCGA-KIRP (594) × | pgx:TCGA-LAML: pgx:TCGA-LAML (285) × | pgx:TCGA-LGG: pg
pgx:TCGA-LIHC: pgx:TCGA-LIHC (767) × | pgx:TCGA-LUAD: pgx:TCGA-LUAD (1110) × | pgx:TCGA-LUSC:
pgx:TCGA-MESO: pgx:TCGA-MESO (173) × | pgx:TCGA-OV: pgx:TCGA-OV (1133) × | pgx:TCGA-PAAD: pgx:
pgx:TCGA-PCPG: pgx:TCGA-PCPG (363) × | pgx:TCGA-PRAD: pgx:TCGA-PRAD (1038) × | pgx:TCGA-READ
pgx:TCGA-SARC: pgx:TCGA-SARC (519) × | pgx:TCGA-SKCM: pgx:TCGA-SKCM (939) × | pgx:TCGA-STAD:
pgx:TCGA-TGCT: pgx:TCGA-TGCT (271) × | pgx:TCGA-THCA: pgx:TCGA-THCA (1025) × | pgx:TCGA-THYM:
pgx:TCGA-UCEC: pgx:TCGA-UCEC (1087) × | pgx:TCGA-UCS: pgx:TCGA-UCS (110) × | pgx:TCGA-UVM: pg

Plot Type

Select...

Gene Symbol(s) for Labeling

MYC (chr8:127735434-127742951) × | TP53 (chr17:7668421-7687490) × | CCND1 (chr11:69641156-69654
CDKN2A (chr9:21967752-21995324) × | EGFR (chr7:55019017-55211628) ×

Chromosomes to Plot

1,3,5,7,8,9,10,11,17

Plot Parameters

plot_axis_y_max:80;plot_area_height:40;plot_label_y_values:0,50

Retrieve CNV Profiles

B-Cell Lymphomas | TCGA Projects | Lung Cancers | Breast Cancers and Cell Lines

Beacon+: Phenopackets

Testing alternative response schemas...

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

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

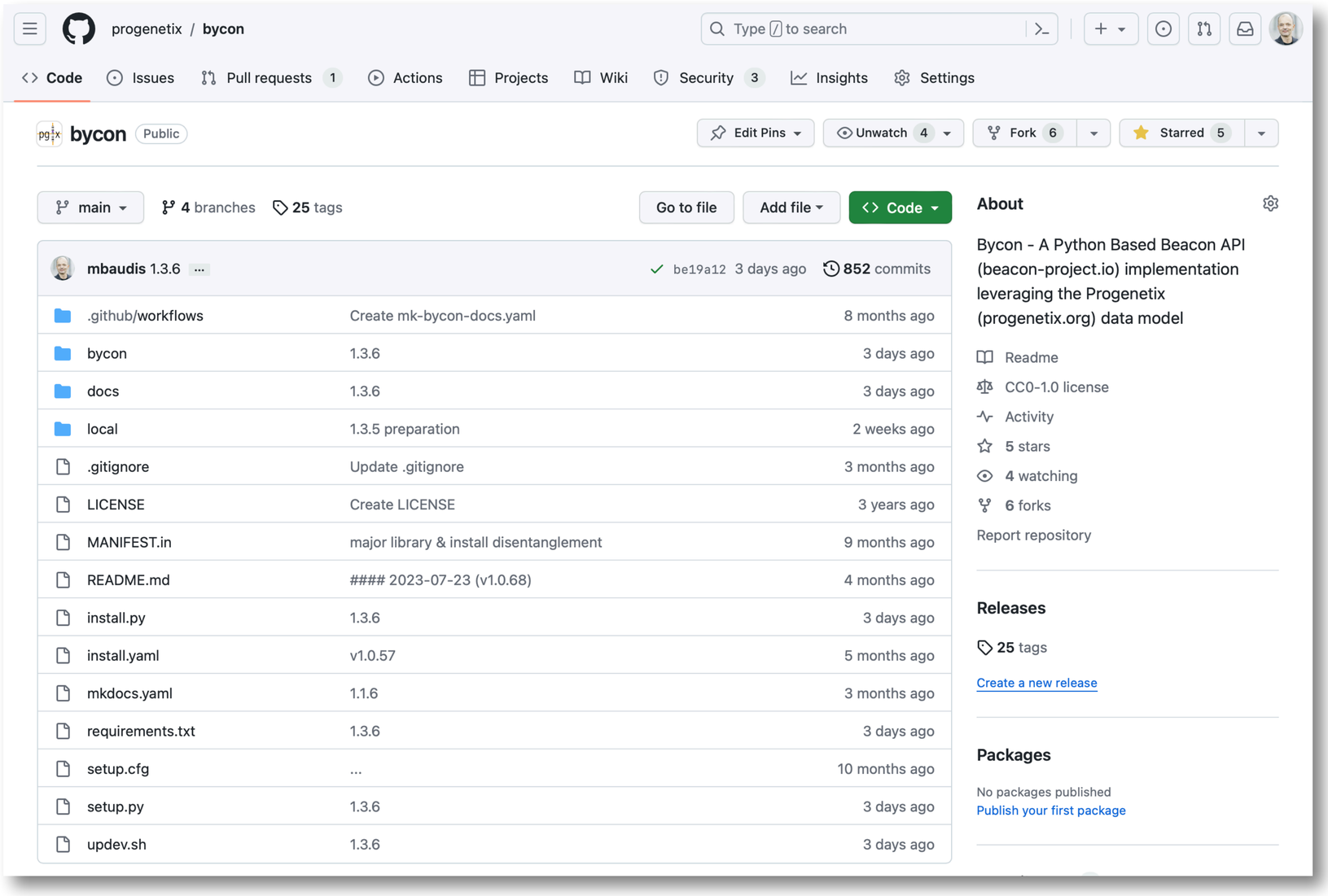

```
"id": "pgxpxf-kftx3tl5",
"metaData": {
  "phenopacketSchemaVersion": "v2",
  "resources": [
    {
      "id": "NCIT",
      "iriPrefix": "http://purl.obolibrary.org/obo/NCIT_",
      "name": "NCIt Plus Neoplasm Core",
      "namespacePrefix": "NCIT",
      "url": "http://purl.obolibrary.org/obo/ncit/neoplasm-core.c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


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

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

Looking for implementers and contributors

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



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

pgxRpi: an R/Bioconductor package

Client for Accessing Beaconized Data

pgxRpi

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

R wrapper for Progenetix

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

DOI: 10.18129/B9.bioc.pgxRpi

Bioconductor version: Development (3.20)

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

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

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

- **Query and export variants**

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

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

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

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

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

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

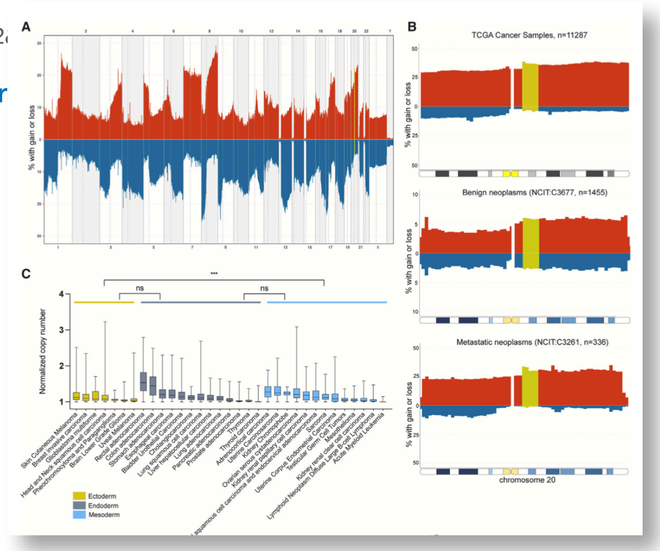
http://www.progenetix.org/services/intervalFrequencies/?filters=NCIT:C3512

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

- **Process local .pgxseg files**

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

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



Stem Cell Reports

Review

ISSCR

OPEN ACCESS

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

Nuša Krivec,[1,2] Manjusha S. Ghosh,[1,2] and Claudia Spits[1,2,*]

[1]Research Group Reproduction and Genetics, Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Brussels, Laarbeeklaan 103, 1090 Brussels, Belgium

[2]These authors contributed equally

*Correspondence: claudia.spits@vub.be

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

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

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

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

Beacon Security

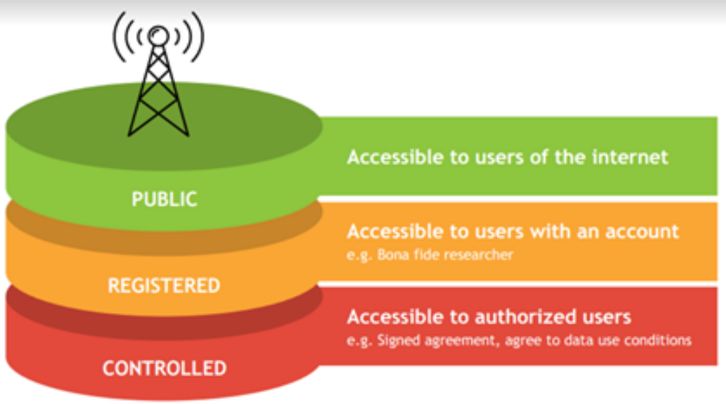
Making Beacons Biomedical - Beacon v2

- Scoping queries through "biodata" parameters
- Extending the queries towards clinically ubiquitous variant formats
  - cytogenetic annotations, named variants, variant effects
- Beacon queries as entry for **data delivery**
  - Beacon v2 permissive to respond with variety of data types
    - Phenopackets, biosample data, cohort information ...
  - handover to stream and download using htsget, VCF, EHRs
- Interacting with EHR standards
  - FHIR translations for queries and handover ...
- Beacons as part of local, secure environments
- Authentication to enable non-aggregate, patient derived datasets
  - ELIXIR AAI with compatibility to other providers (OAuth...)

Definitely breaks the "Relative Security by Design" Concept!

Beacon Security

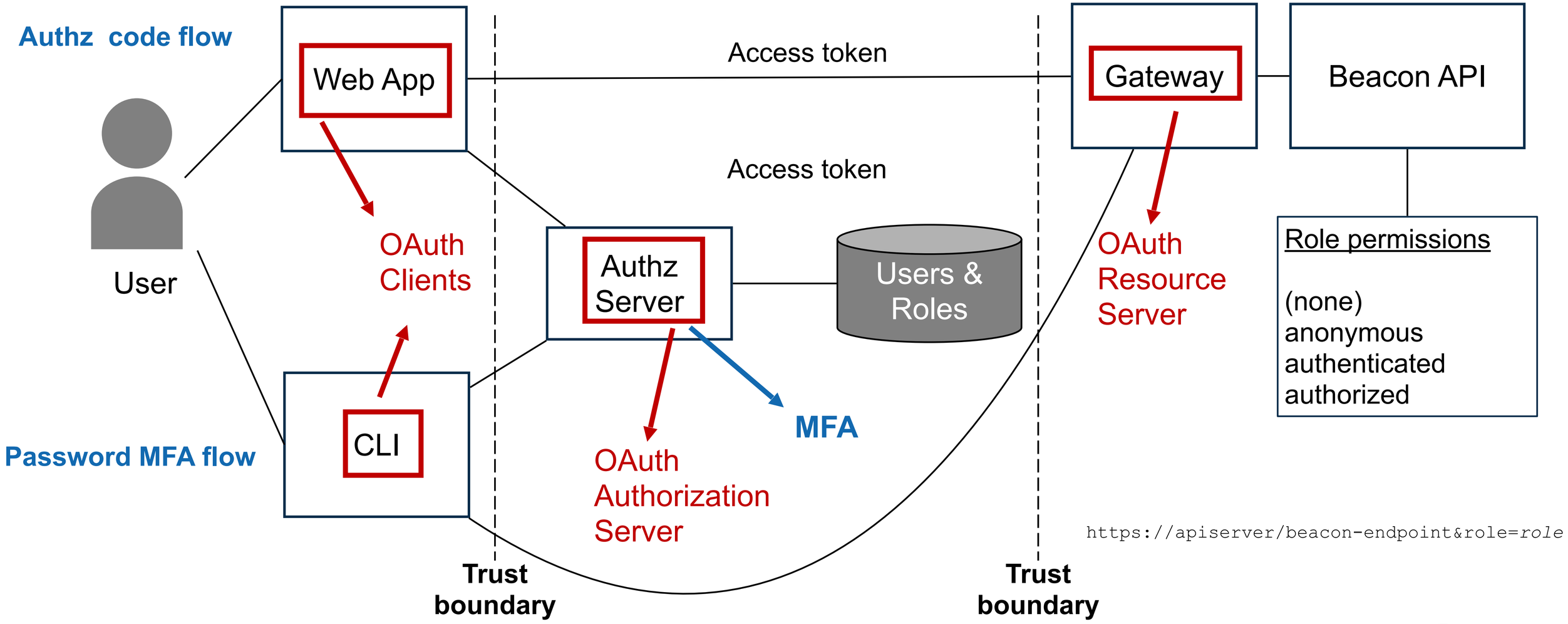
Security by Design ... if Implemented in the Environment



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

Architecture

Running the *bycon* stack in a secure environment



Architecture

Running the *bycon* stack in a secure environment

- The ***Beacon API*** implementation stack (e.g. bycon) is authentication procedure agnostic; i.e. it just accepts that a user has been authenticated and passed the general authorization gatekeeping
- The ***Beacon API*** server and the ***Gateway*** reside in a single VM, with only the ***Gateway***'s port exposed (with TLS). Beacon's port is not exposed by the VM and can only be reached through the ***Gateway***
- The ***Authentication Server*** can run on the same or separate VM; needs a database with user accounts.
- The ***Web Client*** can be in the same VM or a separate one.
- Separate ***Gateways*** (e.g. university firewall vs. public) can be configured to modify different roles, e.g. the public gateway may turn registered roles into anonymous, regardless of whether the user has registered status
- Users can write their own clients (web / command line) which are registered with the ***Authorization Server*** and are issued with a Client ID and Client Secret to use against the ***Authorization Server***.

Beacon as a global standard

Global Alliance for Genomics & Health
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Beacon Scouts

Real-world needs

Cancer

Common diseases

Rare Diseases

…

- **Beacon Filters** – improve current filter solutions
- **Beacon Cohorts** – develop aggregated request and response (e.g. counts by sex and age)
- **Beacon Variants** – expand specification to cover new use cases and typed queries
- **Beacon Dev** – improve API (cleaning code, GitHub issues)
- **Beacon Matchmaking** – implementation in matchmaking use cases

EUROPEAN GENOME-PHENOME ARCHIVE

Beacon v2 Variant Requests

Mix & Match?

- parameters allow positional and some identifier/classification based queries
  - ➡ genomic positions, sequences, variant types
  - ➡ no definition of allowed combinations so strange options possible…
    - genome assembly + versioned reference
  - ➡ patterns by convention/documentation
    - single start, end => range
    - 2 start, 2 end => bracket/CNV-style

g_variant Parameters

`assemblyId` : ./requestParameterComponents.yaml#/$defs/Assembly

`referenceName` : ./requestParameterComponents.yaml#/$defs/RefSeqId

`referenceBases` : ./requestParameterComponents.yaml#/$defs/ReferenceBases

`alternateBases` : ./requestParameterComponents.yaml#/$defs/AlternateBases

`variantType` : ./requestParameterComponents.yaml#/$defs/VariantType

`start` : ./requestParameterComponents.yaml#/$defs/Start

`end` : ./requestParameterComponents.yaml#/$defs/End

`geneId` : ./requestParameterComponents.yaml#/$defs/GeneId

`aminoacidChange` : ./requestParameterComponents.yaml#/$defs/AminoacidChange

`genomicAlleleShortForm` : ./requestParameterComponents.yaml#/$defs/GenomicAlleleShortForm

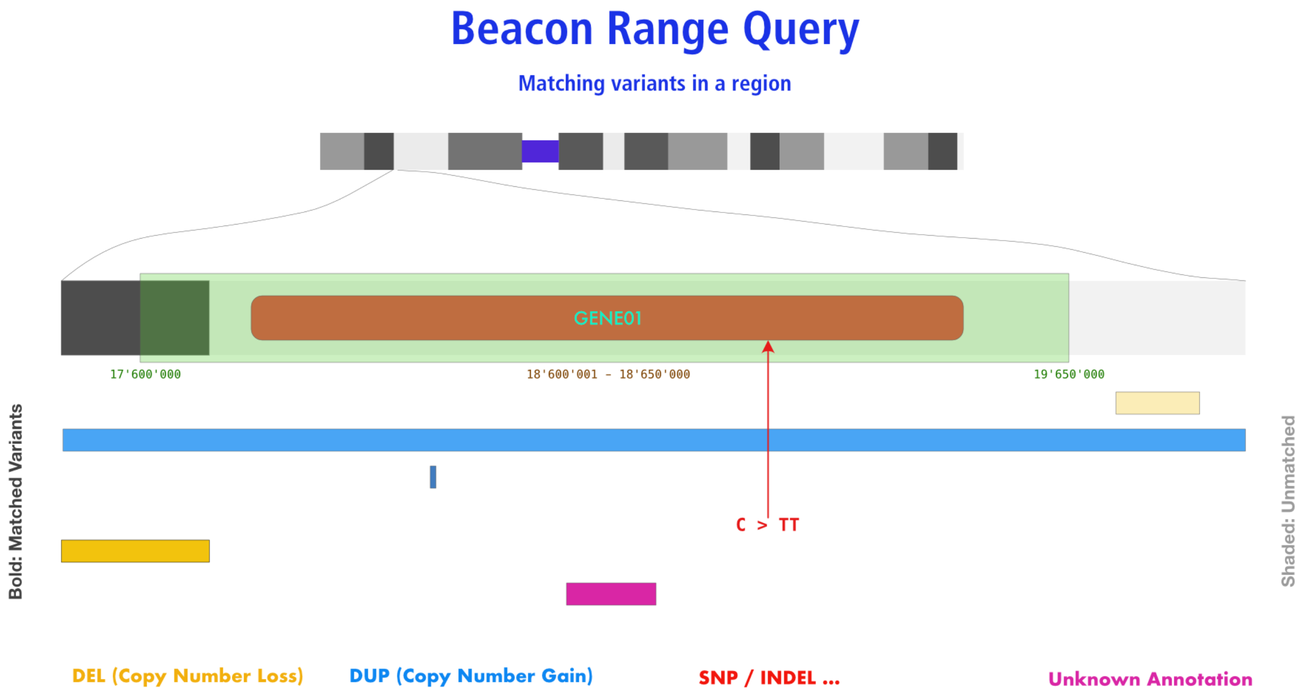
`variantMinLength` : ./requestParameterComponents.yaml#/$defs/VariantMinLength

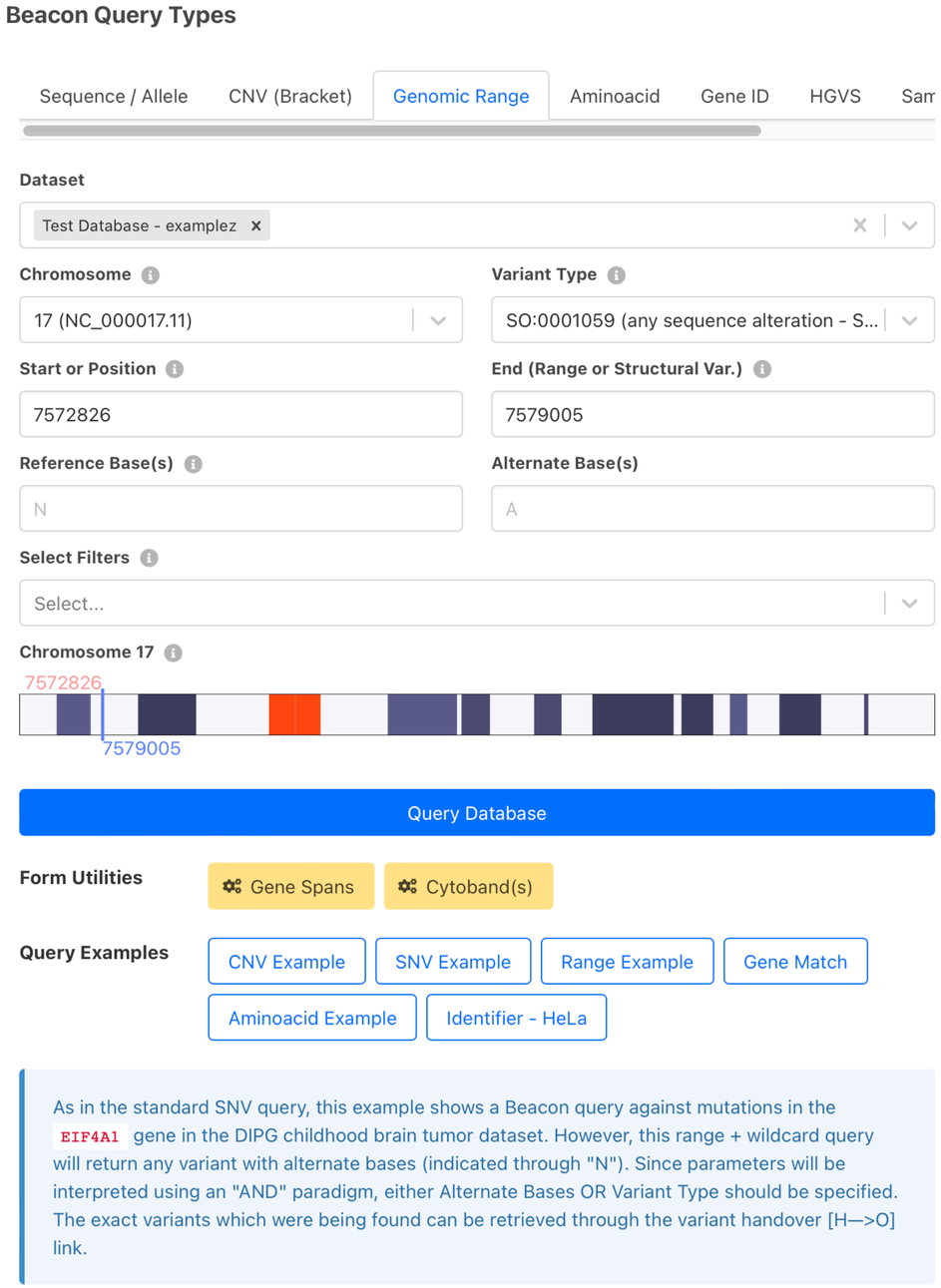
`variantMaxLength` : ./requestParameterComponents.yaml#/$defs/VariantMaxLength

Variation Queries

Range ("anything goes") Request

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

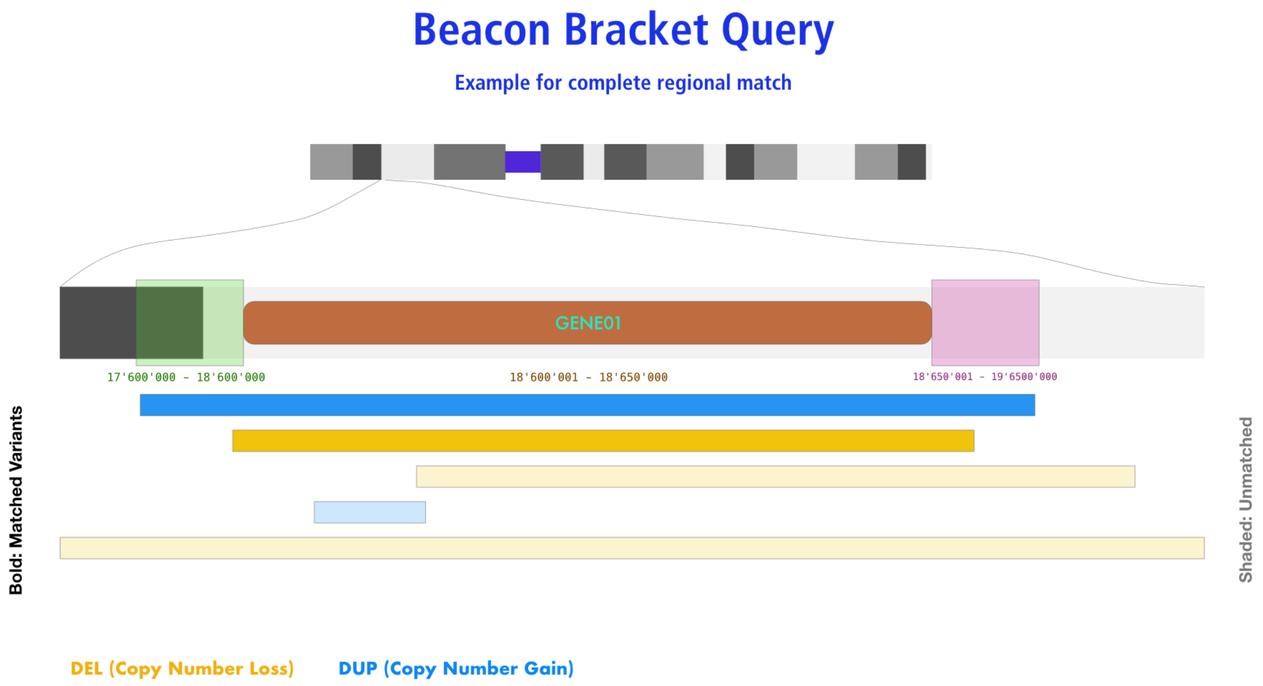


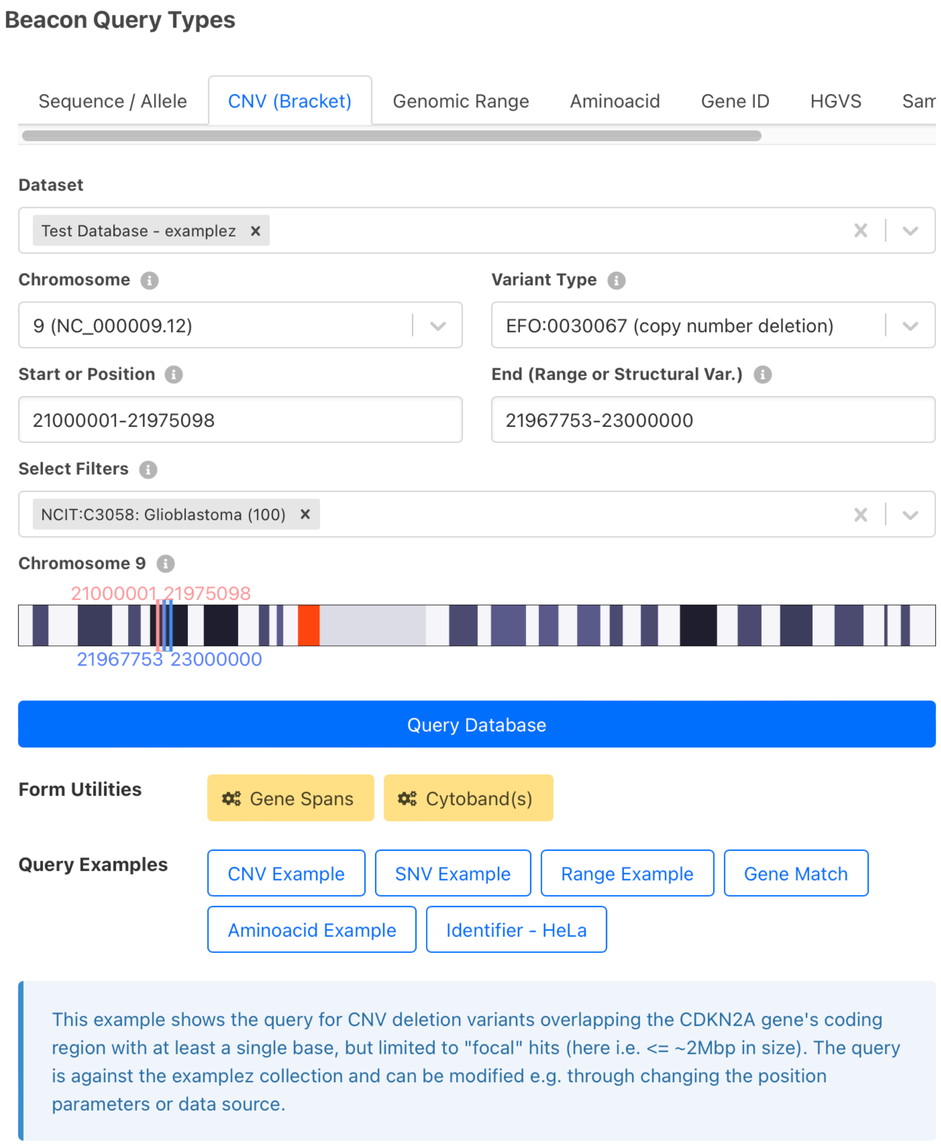


Variation Queries

Bracket ("CNV") Query

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

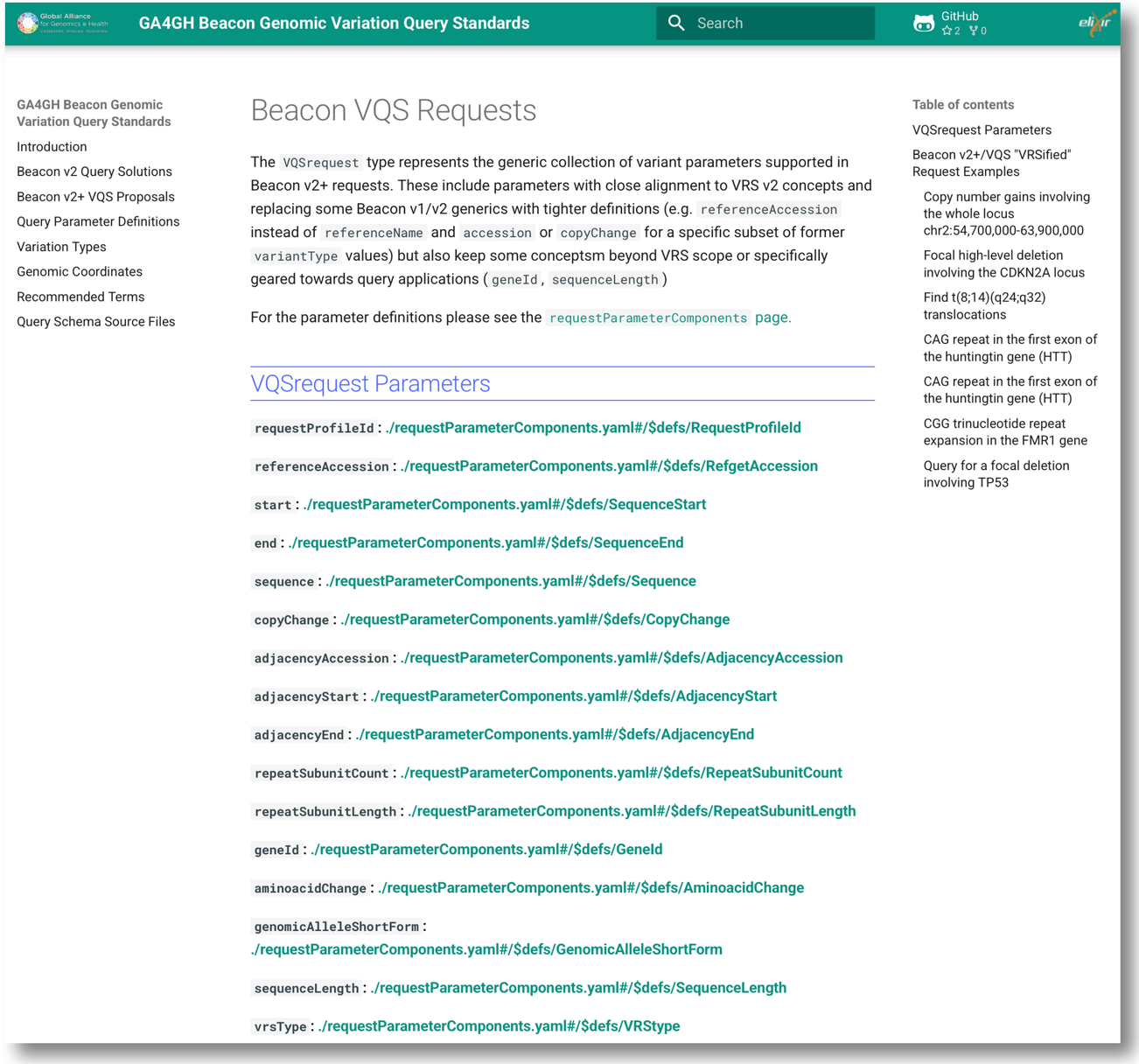




Beacon Scouts

Finding the Paths to Beacon's Future

- Genomic Variation Scouts
  - ➡ extension to the query model based on assessed needs
    - fusions/breakpoints, cytogenetic annotations, repeats, categorical variants...
  - ➡ adoption of evolving VRS... standards for variant representation
    - adjacency, repeats…
    - re-use of parameters where clear (e.g. **`sequenceLength`** instead of **`variantMinLength`** + **`variantMaxLength`**)

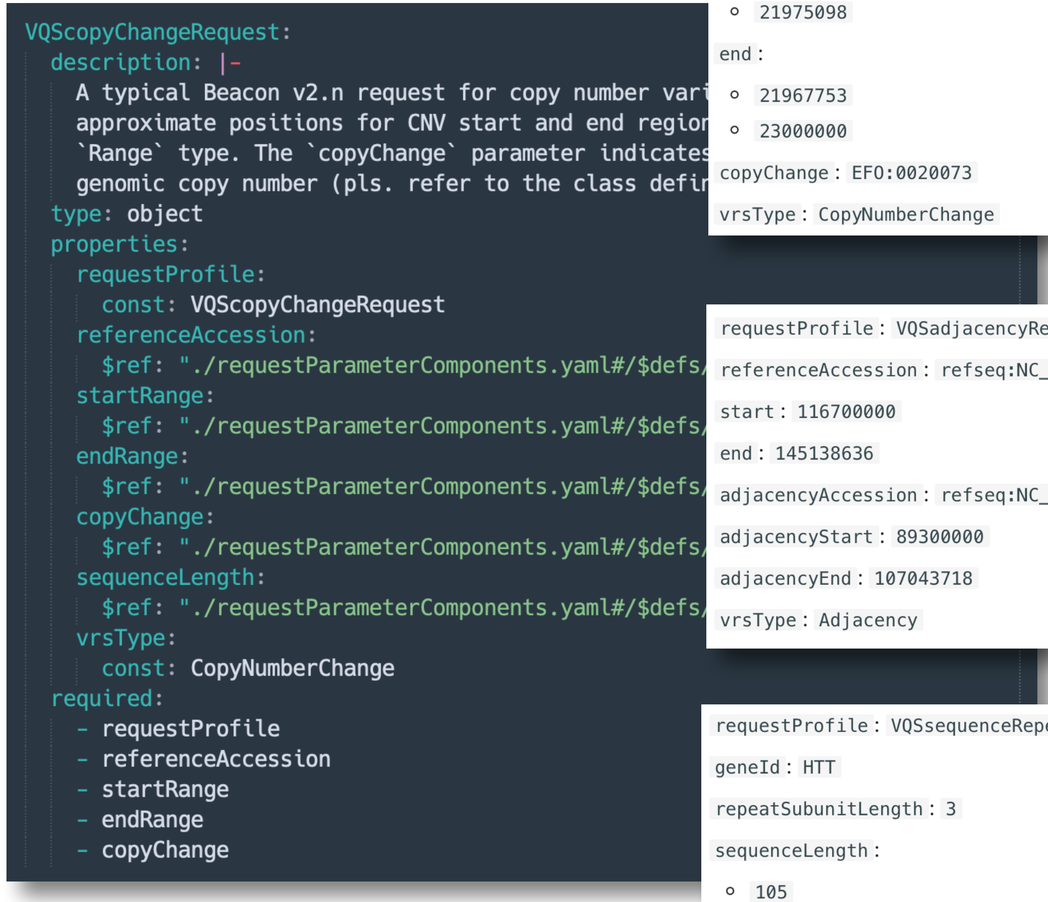


https://genomebeacons.org/variant-query-types/variant-scouts-home/

Variant Query Standard

VRS aligned typed queries

- Typed queries
  - ➡ query schemas with defined set of (required and optional) parameters
    - can be verified
    - profile ids can be advertised by beacons
- VRS aligned
  - ➡ explicit reference to VRS types
  - ➡ … but differ in (some) parameter use since query NE representation
- Expanding library
  - ➡ adjacency, repeats...



https://genomebeacons.org/variant-query-types/variant-scouts-home/

```yaml
VQSadjacencyRequest:
  description: |-
    A typical Beacon v2.n request for sequence adjacency queries, e.g. for
    the retrieval of chromosomal translocation events or sequence fusions.

    TODO: In VRS v2 there is an implicit sequence directionality from the use
    of either start or end parameters for either side of the adjacency. This
    might be problematic on the query side where in many instances just the
    approximate position of the (fused) breakpoints maight be of interest.

    This might need additional clarification (e.g. use of `startRange` or
    `endRange`, `adjacencyStartRange` and `adjecencyEndRange` parameters to
    indicate direction dependent matching).
  type: object
  properties:
    requestProfile:
      const: VQSadjacencyRequest
    referenceAccession:
      $ref: "./requestParameterComponents.yaml#/$defs/RefgetAccession"
    sequenceRange:
      $ref: "./requestParameterComponents.yaml#/$defs/Range"
    adjacencyAccession:
      $ref: "./requestParameterComponents.yaml#/$defs/AdjacencyAccession"
    adjacencyRange:
      $ref: "./requestParameterComponents.yaml#/$defs/Range"
    vrsType:
      const: Adjacency
  required:
    - requestProfile
    - referenceAccession
    - sequenceRange
    - adjacencyAccession
    - adjacencyRange
    - vrsType
```

```yaml
examples:
  VQSadjacency_01:
    description: |-
      ### Find  t(8;14)(q24;q32) translocations

      #### Solution for `VQSrequest` using genomic ranges (`VQSadjacencyRequest`)

      This is a query for translocations between the MYC and IgH loci, where the
      breakpoints are loosely defined through there well known cytogenetic bands.
      The query here follows the VRS adjacency model. In contrast to the VRS
      representational model, here:


      - VRS uses an array of 2 genomic locations while Beacon names the location
        parameters individually (using "adjacency..." for the second partner)
      - VRS explicitely encodes directionality by using either `start` or `end`
        position parameters (integers or ranges) while this query example creates
        non-directional ranges on both sides since directionality might not be known,
        the storage system might not encode this or all options could be of interest

    request:
      requestProfile: VQSadjacencyRequest
      referenceAccession: refseq:NC_000008.11
      start: 116700000
      end: 145138636
      adjacencyAccession: refseq:NC_000014.9
      adjacencyStart: 89300000
      adjacencyEnd: 107043718
      vrsType: Adjacency
```

Variant Query Standard

VRS aligned typed queries - Open Questions…

- Parameter Zoo?
  - ➡ Should we be explicit in parameters themselves
    - **`startRange`** vs. **`start`** and “requires 2 pos. in context of profile”
- Level of VRSification?
  - ➡ Queries don’t necessarily correspond to VRS objects (polymorphic matches) - is the use of VRS vocabularies appropriate?

```yaml
VQScopyChangeRequest:
  description: |-
    A typical Beacon v2.n request for copy number variations (CNVs) queries
    approximate positions for CNV start and end regions through use of the
    `Range` type. The `copyChange` parameter indicates the relative change in
    genomic copy number (pls. refer to the class definition.)
  type: object
  properties:
    requestProfile:
      const: VQScopyChangeRequest
    referenceAccession:
      $ref: "./requestParameterComponents.yaml#/$defs/RefgetAc
    startRange:
      $ref: "./requestParameterComponents.yaml#/$defs/Range"
    endRange:
      $ref: "./requestParameterComponents.yaml#/$defs/Range"
    copyChange:
      $ref: "./requestParameterComponents.yaml#/$defs/CopyCha
    sequenceLength:
      $ref: "./requestParameterComponents.yaml#/$defs/Sequence
    vrsType:
      const: CopyNumberChange
  required:
    - requestProfile
    - referenceAccession
    - startRange
    - endRange
    - copyChange
```

```
requestProfile : VQScopyChangeRequest
referenceAccession : refseq:NC_000002.12
start :
  - 21000001
  - 21975098
end :
  - 21967753
  - 23000000
copyChange : EFO:0020073
vrsType : CopyNumberChange
```

https://genomebeacons.org/variant-query-types/variant-scouts-home/

Progenetix Cancer Genomics Beacon+ v2.1.0-beaconplus OAS 3.0

/api

Beacon+ provides a forward looking implementation of the Beacon v2 API, with focus on structural genome variants and metadata based on the cancer and reference genome profiling data in the Progenetix resource (https://progenetix.org).

This page presents a prototype for an OpenAPI (Swagger) definition for the GA4GH Beacon API. The definitions are generated from the `entity_defaults` and `argument_definitions` in the bycon project. The complete. Please be aware that the whole capabilities of the project cannot be represented solely through the OpenAPI definitions and also involve features such as filtering terms logic and result aggregation entities. Additionally, the bycon project implements a number of data services beyong Beacon standards which again are only partially covered here.

`bycon` and Data Aggregation

The Beacon standard implements a REST style syntax - e.g. consistent id-based document retrieval for entities indicated through their framework provide full data aggregation; *i.e.* queries with parameters against **any** of the main data entities (g_variants, runs, analyses, intersection of the query results at the level of the response entity.

[Beacon v2 API] | [Example: Bv2 CNV / bracket] | [Proposal: VQS CNV / bracket] | [Proposal: VQS CNV by Gene ID] | [Proposa

Contact the developer

Servers

https://progenetix.org

Beacon

- GET /beacon/info Get info entries
- GET /beacon/datasets Get dataset entries
- GET /beacon/cohorts Get cohort entries
- GET /beacon/g_variants Get genomicVariant entries
- GET /beacon/g_variants/{id} Get genomicVariant entries
- GET /beacon/g_variants/{id}/analyses Get analysis entries
- GET /beacon/g_variants/{id}/biosamples Get biosample entries
- GET /beacon/g_variants/{id}/individuals Get individual entries
- GET /beacon/analyses Get analysis entries
- GET /beacon/analyses/{id} Get analysis entries
- GET /beacon/analyses/{id}/g_variants Get genomicVariant entries
- GET /beacon/analyses/{id}/biosamples Get biosample entries

Bv2minimalAlleleRequest

GET /beacon/g_variants Get genomicVariant entr

Get genomicVariant entries

Parameters

Name	Description
referenceName string (query)	Examples: Chromosome 17 17
start array<integer> (query)	Examples: Base position on chromosome 17 7577120 Add integer item
alternateBases string (query)	Examples: An `A` allele at the specified posit A
referenceBases string (query)	Examples: A reference `G` allele at the specif G
skip integer (query)	skip
limit integer (query)	limit
requestedGranularity string (query)	Examples: The minimal boolean response boolean

Bv2cnvbracketquery

GET /beacon/g_variants Get genomicVariant entries

Get genomicVariant entries

Parameters

Name	Description
filters array<string> (query)	Examples: Glioblastoma NCIT:C3058 Add string item
referenceName string (query)	Examples: Chromosome 9 (GRCh38) refseq:NC_000009.12
start array<integer> (query)	Examples: Range for start of CNV involving CDKN2A 21000001 21975098 Add integer item
end array<integer> (query)	Examples: Range for end of CNV involving CDKN2A 21967753 23000000 Add integer item
variantType string (query)	Examples: High-level copy number loss EFO:0020073

VQSadjacencyRequest

GET /beacon/g_variants Get genomicVariant entries

GET /beacon/analyses Get analysis entries

GET /beacon/biosamples Get biosample entries

Get biosample entries

Parameters

Name	Description
filters array<string> (query)	Examples: Malignant lymphoma, NOS (ICD-O 3 code 9680/3) pgx:icdom-95903 Add string item
referenceAccession string (query)	Examples: RefSeq ID for Chromosome 8 (GRCh38) refseq:NC_000008.11
breakpointRange array<integer> (query)	Examples: Range for band q24 on chromosome 8 116700000 145138636 Add integer item
adjacencyAccession string (query)	Examples: RefSeq ID for Chromosome 14 (GRCh38) refseq:NC_000014.9
adjacencyRange array<integer> (query)	Examples: Range for band q32 on chromosome 14 89300000 107043718 Add integer item
vrsType string (query)	Examples: Adjacency Adjacency

a menu

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

What Can You Do?

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

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

Beacon for Genomic Discovery Proxies

Global Alliance for Genomics & Health
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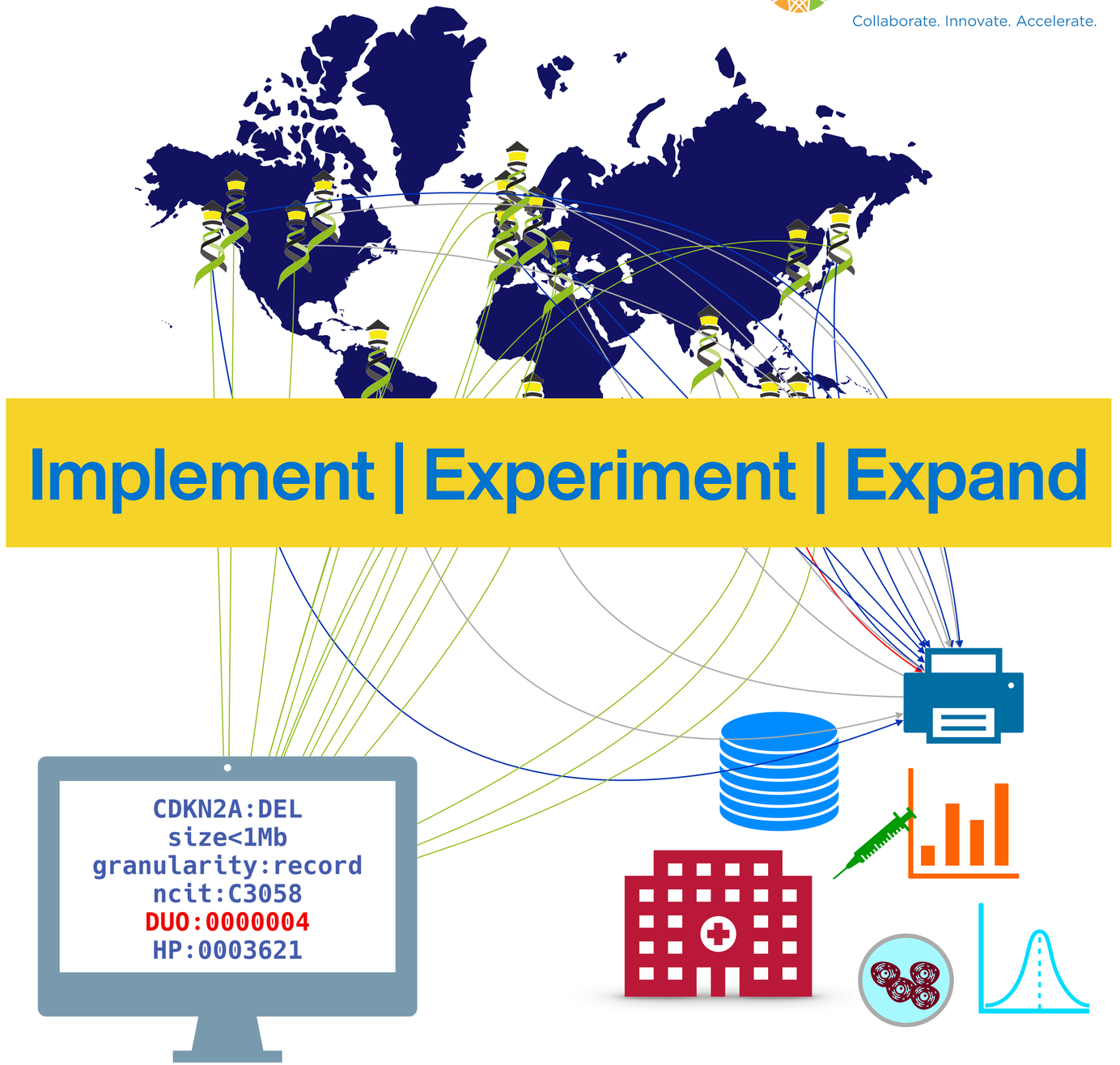
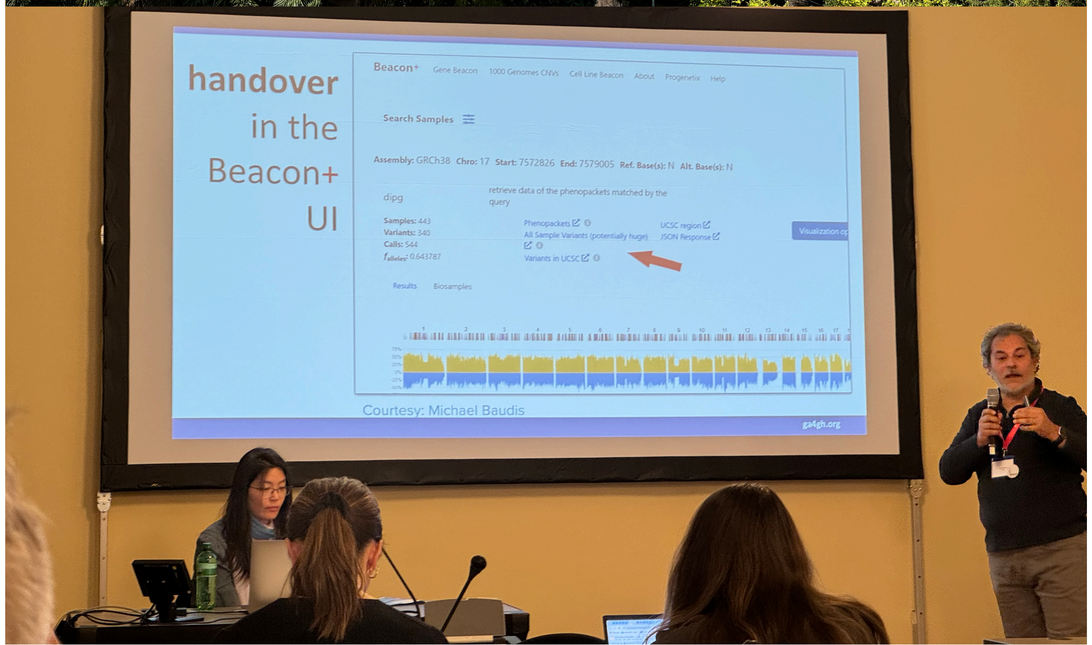
- Feature beacons for privacy protecting data discovery
  - ➡ privacy protection through aggregated data, cohorts
  - ➡ alternative is "**horizontal gatekeeping**": separate Beacons for ***discovery*** of e.g. genomic and phenotypic data and ***data delivery*** upon request / authentication
  - ➡ We'd love to help launching your beacon (especially as a **bycon**...)





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

The Beacon team through the ages

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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
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