Beacon v2

Onboarding Strategies & Feature Examples

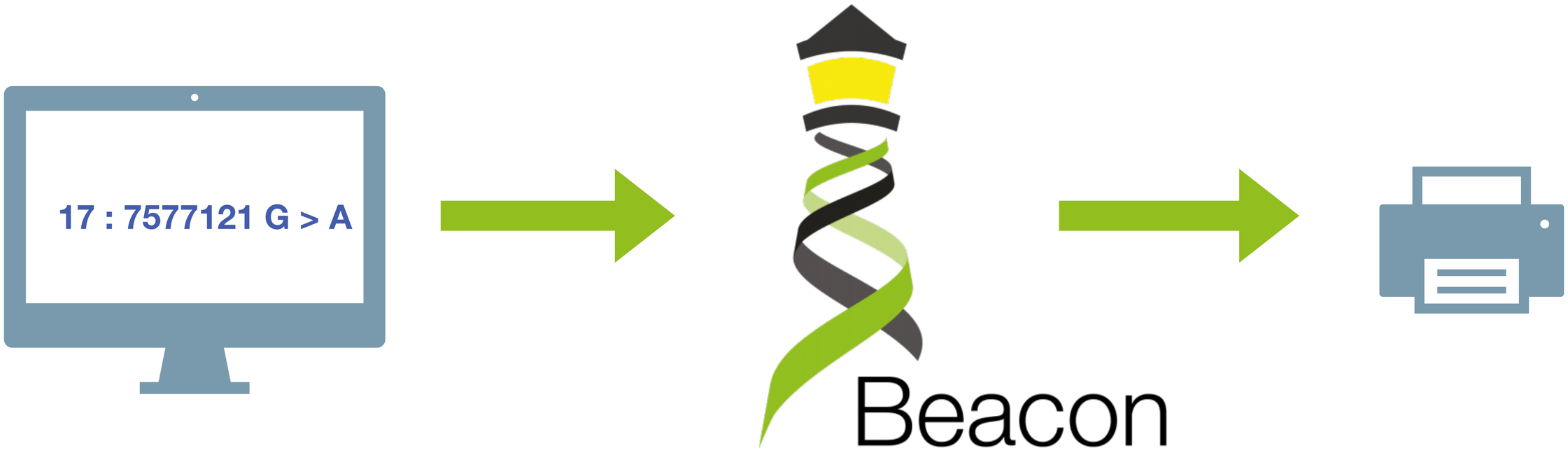
Michael Baudis | GA4GH Connect | 2022-11-16

Global Alliance
for Genomics & Health

Beacon v2

Migration Workshop

Global Alliance
for Genomics & Health



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

Introduction

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

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

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

Utility

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

A number of more useful first versions have been suggested.

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

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

Implementation

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

ELIXIR - Making Beacons Biomedical

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

	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	
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 v1 Development

Beacon v2 Development

Related ...

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- beacon-network.org aggregator created by DNAstack

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2016

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

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- concepts from GA4GH Metadata (ontologies…)
- entity-scoped query parameters ("individual.age")

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- further changes esp. in default model, aligning with Phenopackets and VRS
- unified beacon-v2 code & docs repository
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Beacon v1 => v2

Genomic variation queries

- Beacon v2 defines query schemas through JSON Schema documents for POST requests and REST paths in OpenAPI documents
- Additional variant parameters:
  - ➡ variantType, mateName (existing in v1)
  - ➡ geneId
  - ➡ variantMinLength, variantMaxLength
  - ➡ aminoacidChange
  - ➡ genomicAlleleShortForm

```
{
    "$schema":"beaconRequestBody.json",
    "meta": {
        "apiVersion": "2.0",
        "requestedSchemas": [
            {
                "entityType": "genomicVariation",
                "schema:": "https://
raw.githubusercontent.com/ga4gh-beacon/beacon-v2/
main/models/json/beacon-v2-default-model/
genomicVariations/defaultSchema.json"
            }
        ]
    },
    "query": {
        "requestParameters": {
            "g_variant": {
                "referenceName": "NC_000017.11",
                "start": [7577120],
                "referenceBases": "G",
                "alternateBases": "A"
            }
        }
    },
    "requestedGranularity": "record",
    "pagination": {
        "skip": 0,
        "limit": 5
    }
}
```

Beacon v1 => v2

Keep it simple - modifying GET query strings

0.3 `?ref=GRCh38&chrom=17&pos=7577121&referenceAllele=G&allele=A`

1.0 `?assemblyId=GRCh38&referenceName=17&start=7577120&referenceBases=G&alternateBases=A`

2.0 `?referenceName=refseq:NC_000017.11&start=7577120&referenceBases=G&alternateBases=A`

Beacon v1 => v2

Keep it simple - modifying GET query strings

0.3 `?ref=GRCh38&chrom=17&pos=7577121&referenceAllele=G&allele=A`

v1 switched for the API to 0-based coordinates (with 1-based representation in user facing forms - compare to UCSC genome browser)

1.0 `?assemblyId=GRCh38&referenceName=17&start=7577120&referenceBases=G&alternateBases=A`

v2 recommends using assembly-specific identifiers (refseq id) although *assemblyId* and alternative reference identifiers such as "chr17" are *in principle* permitted

2.0 `?referenceName=refseq:NC_000017.11&start=7577120&referenceBases=G&alternateBases=A`

Beacon v2

Boolean response example

- Beacon v2 is "chatty" regarding returned metadata, to disambiguate responses
- the response payload for ***Boolean*** and ***count*** responses is provided in the *responseSummary* object


```
{
  "meta": {
    "apiVersion": "v2.0.0",
    "beaconId": "org.progenetix.beacon",
    "receivedRequestSummary": {
     "apiVersion": "v2.0.0",
     "requestedGranularity": "boolean",
     "requestedSchemas": [
        {
          "entityType": "genomicVariant",
          "schema": "https://progenetix.org/services/schemas/genomicVariant/"
        }
      ],
      "variantPars": {
        "alternateBases": "A",
        "referenceBases": "G",
        "referenceName": "refseq:NC_000017.11",
        "start": [ 7577120 ]
      },
      "pagination": {
        "limit": 2000,
        "skip": 0
      },
    },
    "returnedGranularity": "boolean",
    "returnedSchemas": [
      {
        "entityType": "genomicVariant",
        "schema": "https://progenetix.org/services/schemas/genomicVariant/"
      }
    ]
  },
  "responseSummary": {
    "exists": true
  }
}
```

Beacon v2

Count response example

- Beacon v2 is "chatty" regarding returned metadata, to disambiguate responses
- the response payload for ***Boolean*** and ***count*** responses is provided in the *responseSummary* object


```
{
  "meta": {
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    "beaconId": "org.progenetix.beacon",
    "receivedRequestSummary": {
     "apiVersion": "v2.0.0",
     "requestedGranularity": "count",
     "requestedSchemas": [
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          "entityType": "genomicVariant",
          "schema": "https://progenetix.org/services/schemas/genomicVariant/"
        }
      ],
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      },
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        "skip": 0
      },
    },
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      {
        "entityType": "genomicVariant",
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      }
    ]
  },
  "responseSummary": {
    "exists": true,
    "numTotalResults": 2
   }
}
```

Beacon v2

So what would you need?

- Beacon v2 (as v1) for Boolean and count responses can be implemented w/o complex infrastructure
- compared to v1, some additional meta information is expected in the response (but this can be pretty static for individual instances)


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Beacon v2 - Migration Workshop

Reference Implementation (Manuel Rueda)

Global Alliance
for Genomics & Health

Progenetix & Beacon v2

A custom "full stack" implementation of a genomics resource around Beacon data model & API

progenetix

Progenetix in 2022

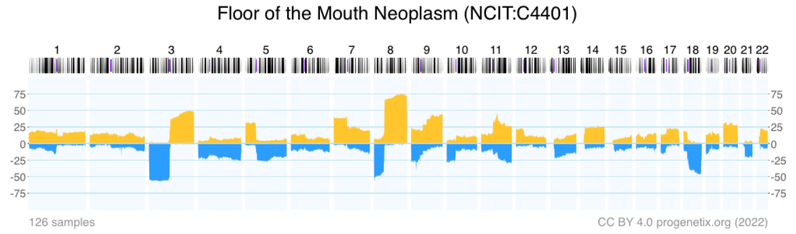
Cancer Genomics Reference Resource

- open resource for curated oncogenomic profiles
- >116'000 cancer CNV profiles, from >800 types
- majority of data from genomic arrays with ~50% overall from SNP platforms with original data re-processing
- standardized encodings (e.g. NCIt, ICD-O 3)
- identifier mapping for PMID, GEO, Cellosaurus, TCGA, cBioPortal where appropriate
- core biosample and technical metadata where accessible (TNM, sex, survival ...)
- publication database and code mapping services

progenetix

Cancer genome data @ progenetix.org

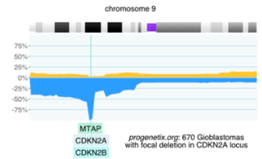
The Progenetix database provides an overview of mutation data in cancer, with a focus on copy number abnormalities (CNV / CNA), for all types of human malignancies. The data is based on *individual sample data* from currently **142063** samples.



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

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

Progenetix Use Cases



Local CNV Frequencies

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

Cancer CNV Profiles

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

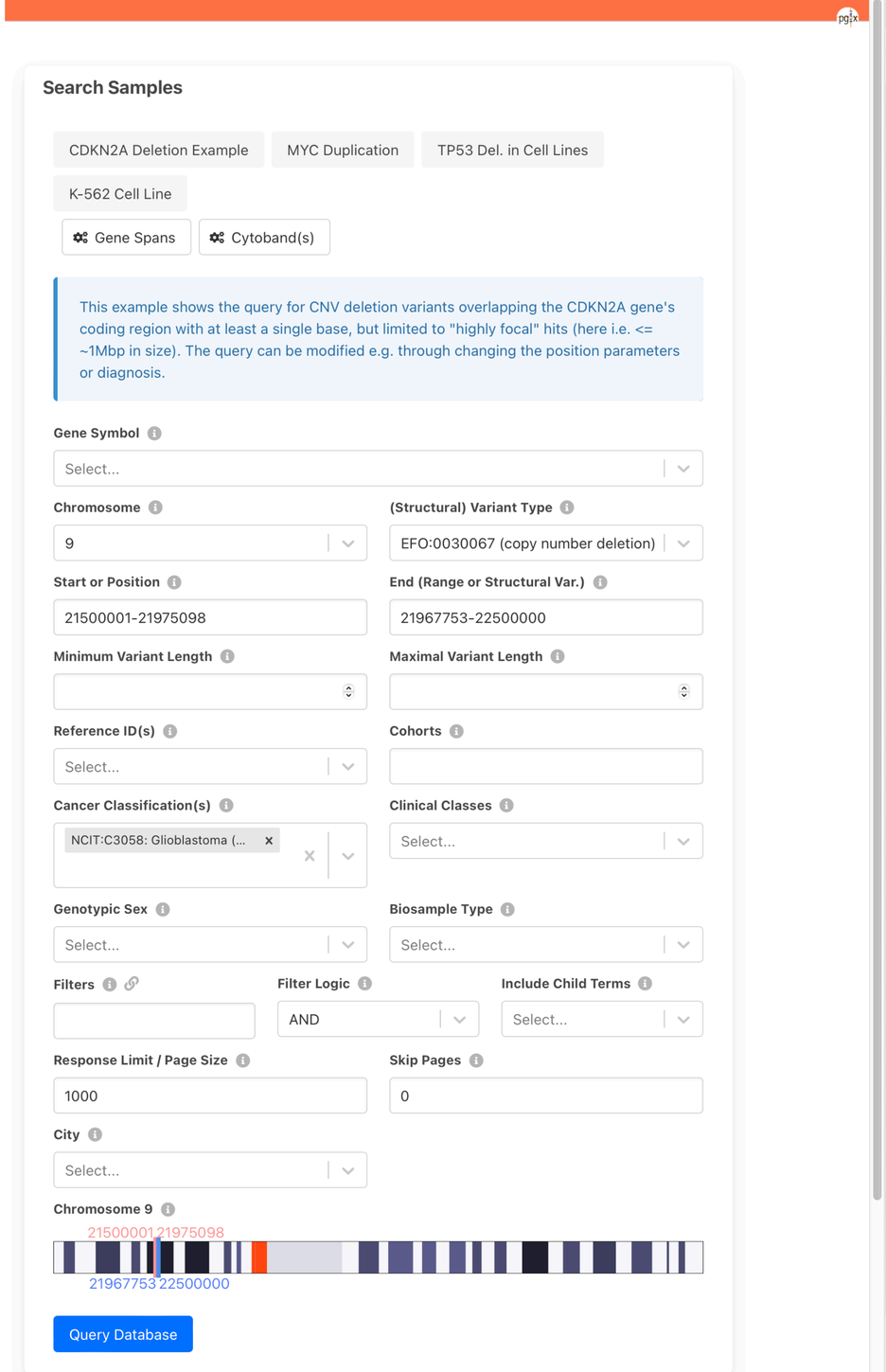
Cancer Genomics Publications

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

Progenetix

Genomic resource utilizing Beacon v2 calls

- Progenetix uses Beacon v2 queries to drive its UI
- all individuals, biosamples, variants, analyses matched by a given query are stored by their object ids
- handovers for variant purposes (e.g. to retrieve all matched variants) are returned in the original response and asynchronously retrieved by the front end app



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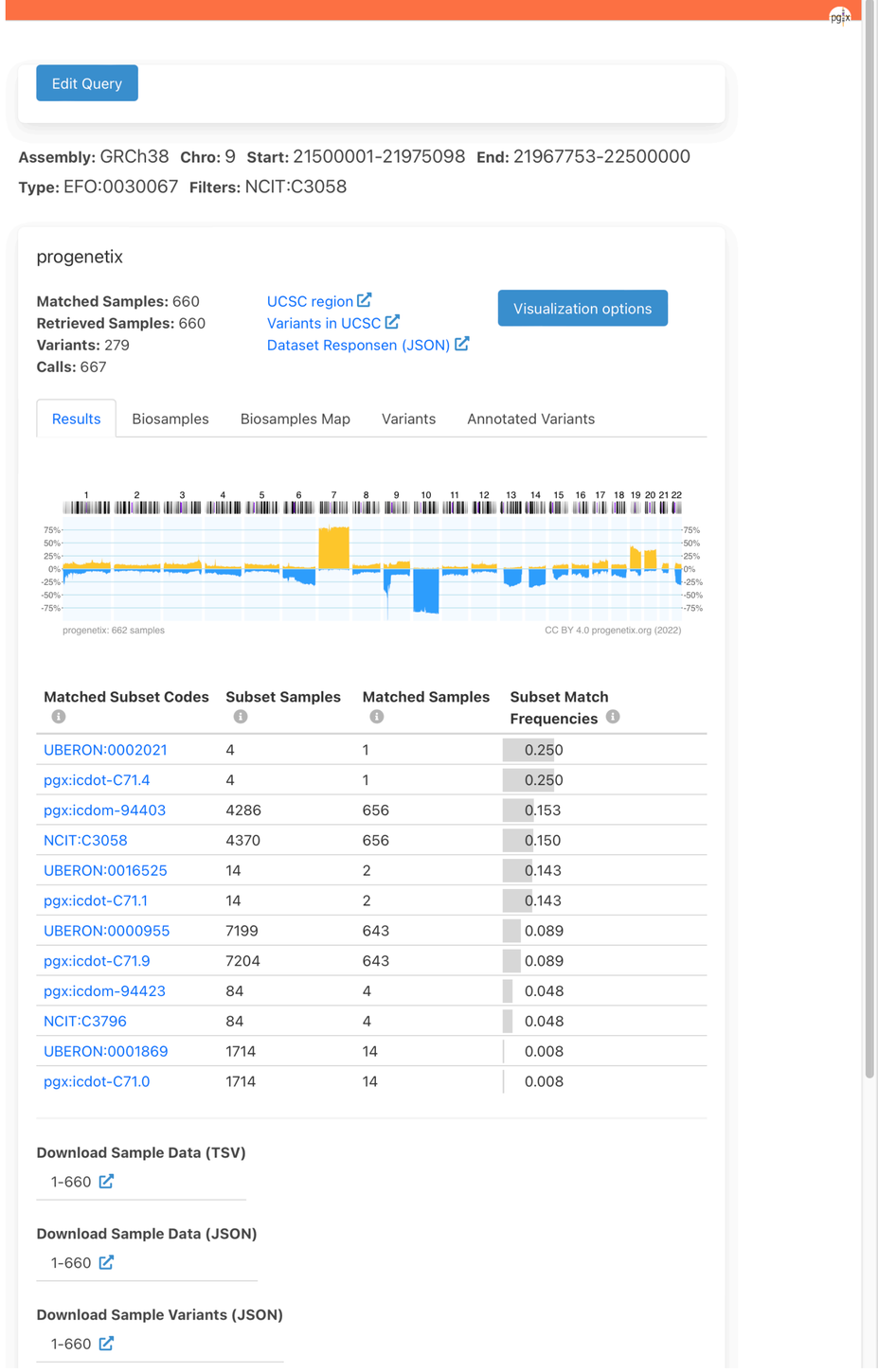

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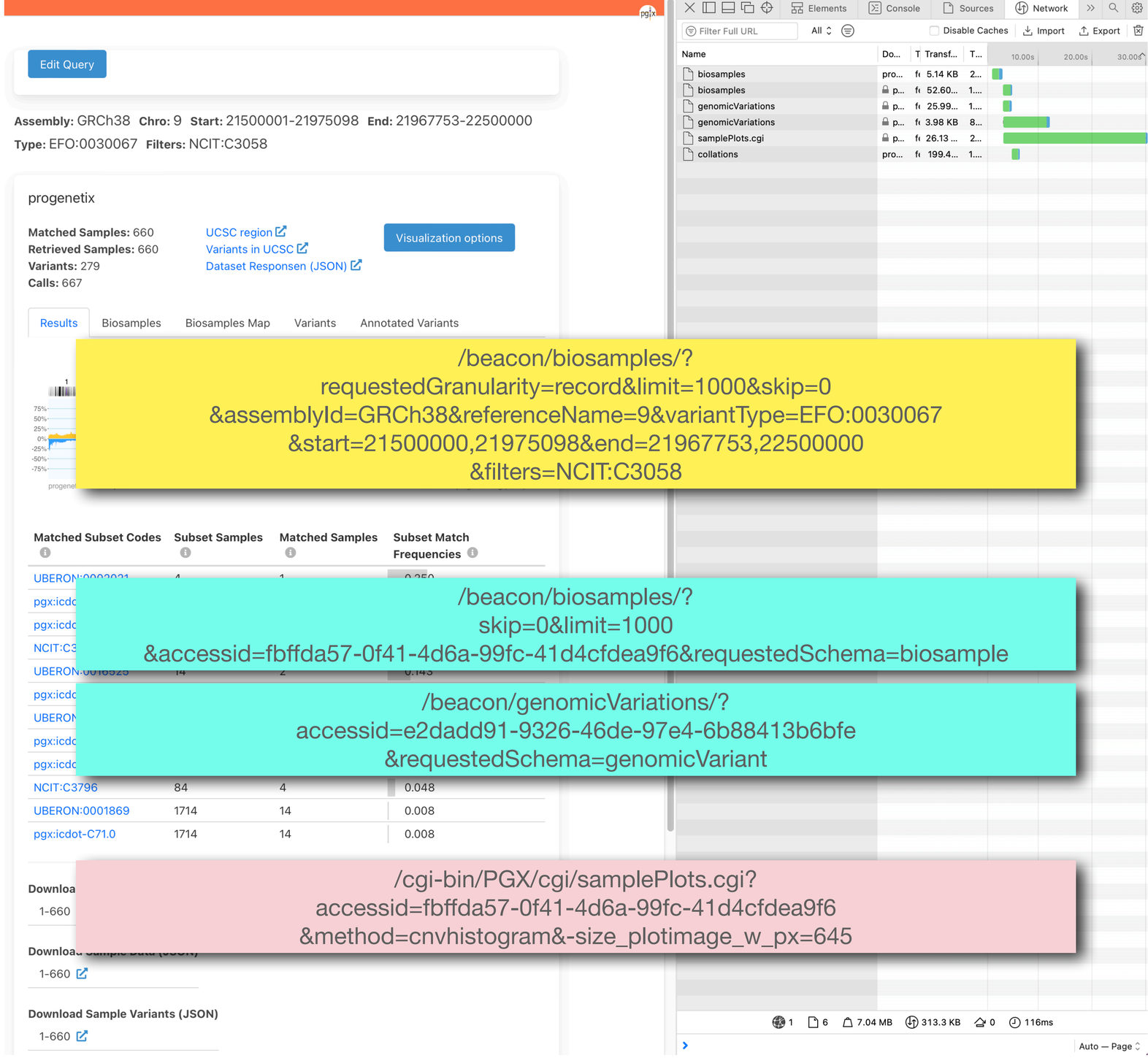


Progenetix Stack

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"),
```

variants analyses biosamples individuals

Entity collections

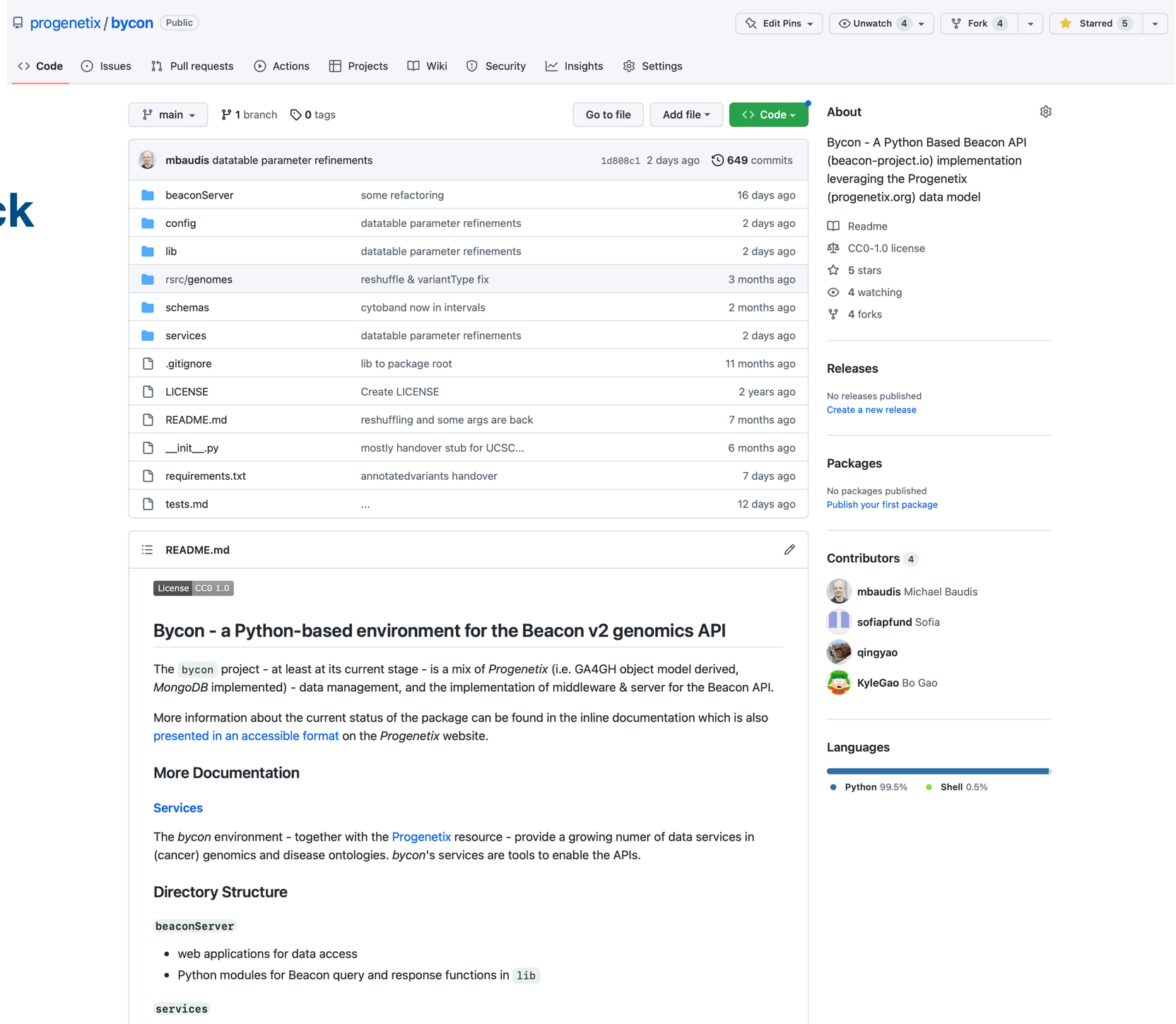
collations geolocs genespans publications qBuffer

Utility collections

bycon

Progenetix' Beacon Stack

- Python-based software stack
- developed for in-house use - not well documented etc.
- happy about adoption & contributions...



progenetix / bycon Public

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Code | Issues | Pull requests | Actions | Projects | Wiki | Security | Insights | Settings

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

mbaudis datatable parameter refinements 1d808c1 2 days ago 649 commits

beaconServer	some refactoring	16 days ago
config	datatable parameter refinements	2 days ago
lib	datatable parameter refinements	2 days ago
rsrc/genomes	reshuffle & variantType fix	3 months ago
schemas	cytoband now in intervals	2 months ago
services	datatable parameter refinements	2 days ago
.gitignore	lib to package root	11 months ago
LICENSE	Create LICENSE	2 years ago
README.md	reshuffling and some args are back	7 months ago
__init__.py	mostly handover stub for UCSC...	6 months ago
requirements.txt	annotatedvariants handover	7 days ago
tests.md	...	12 days ago

README.md

License CC0 1.0

Bycon - a Python-based environment for the Beacon v2 genomics API

The `bycon` project - at least at its current stage - is a mix of *Progenetix* (i.e. GA4GH object model derived, *MongoDB* implemented) - data management, and the implementation of middleware & server for the Beacon API.

More information about the current status of the package can be found in the inline documentation which is also presented in an accessible format on the *Progenetix* website.

More Documentation

Services

The *bycon* environment - together with the Progenetix resource - provide a growing numer of data services in (cancer) genomics and disease ontologies. *bycon*'s services are tools to enable the APIs.

Directory Structure

`beaconServer`

- web applications for data access
- Python modules for Beacon query and response functions in `lib`

`services`

About

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

Readme
CC0-1.0 license
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4 watching
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Releases

No releases published
Create a new release

Packages

No packages published
Publish your first package

Contributors 4

mbaudis Michael Baudis
sofiapfund Sofia
qingyao
KyleGao Bo Gao

Languages

Python 99.5% Shell 0.5%

Beacon v2

Beaconise your Data

Global Alliance
for Genomics & Health

Beacon v1 => v2

Genomic variation queries

- Beacon v2 defines query schemas through JSON Schema documents for POST requests and REST paths in OpenAPI documents
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        "requestParameters": {
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            }
        ]
    },
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                "start": [7577120],
                "referenceBases": "G",
                "alternateBases": "A"
            }
        }
    },
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    }
}
```

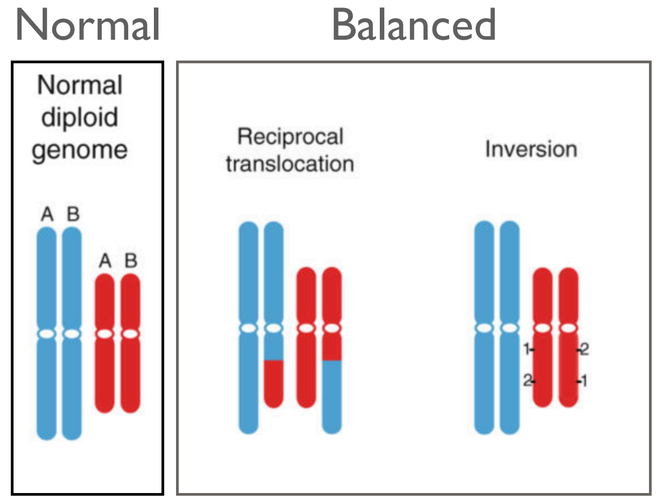
Types of genomic alterations in Cancer

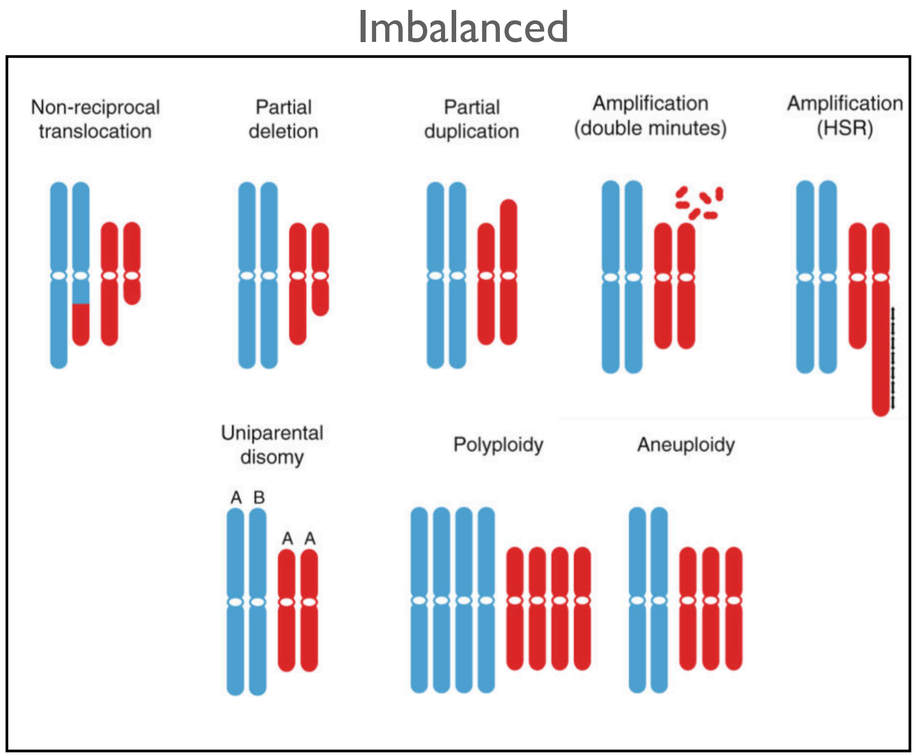
Imbalanced Chromosomal Changes: CNV

- Point mutations (insertions, deletions, substitutions)
- Chromosomal rearrangements
- Structural chromosomal Aberrations

➡ **Regional Copy Number Alterations** (losses, gains)

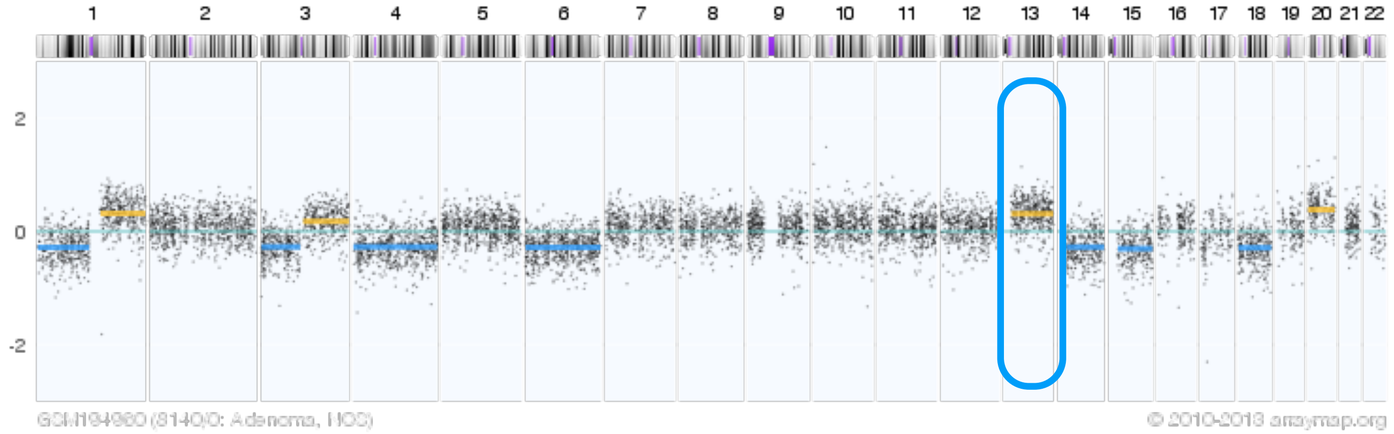
- Epigenetic changes (e.g. DNA methylation abnormalities)



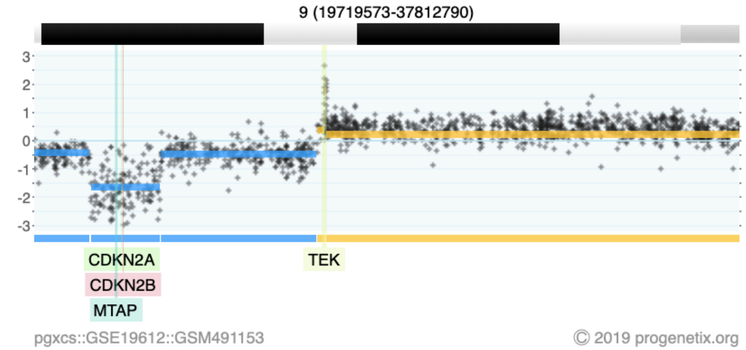


Grade et al., 2015 Recent Results Cancer Res

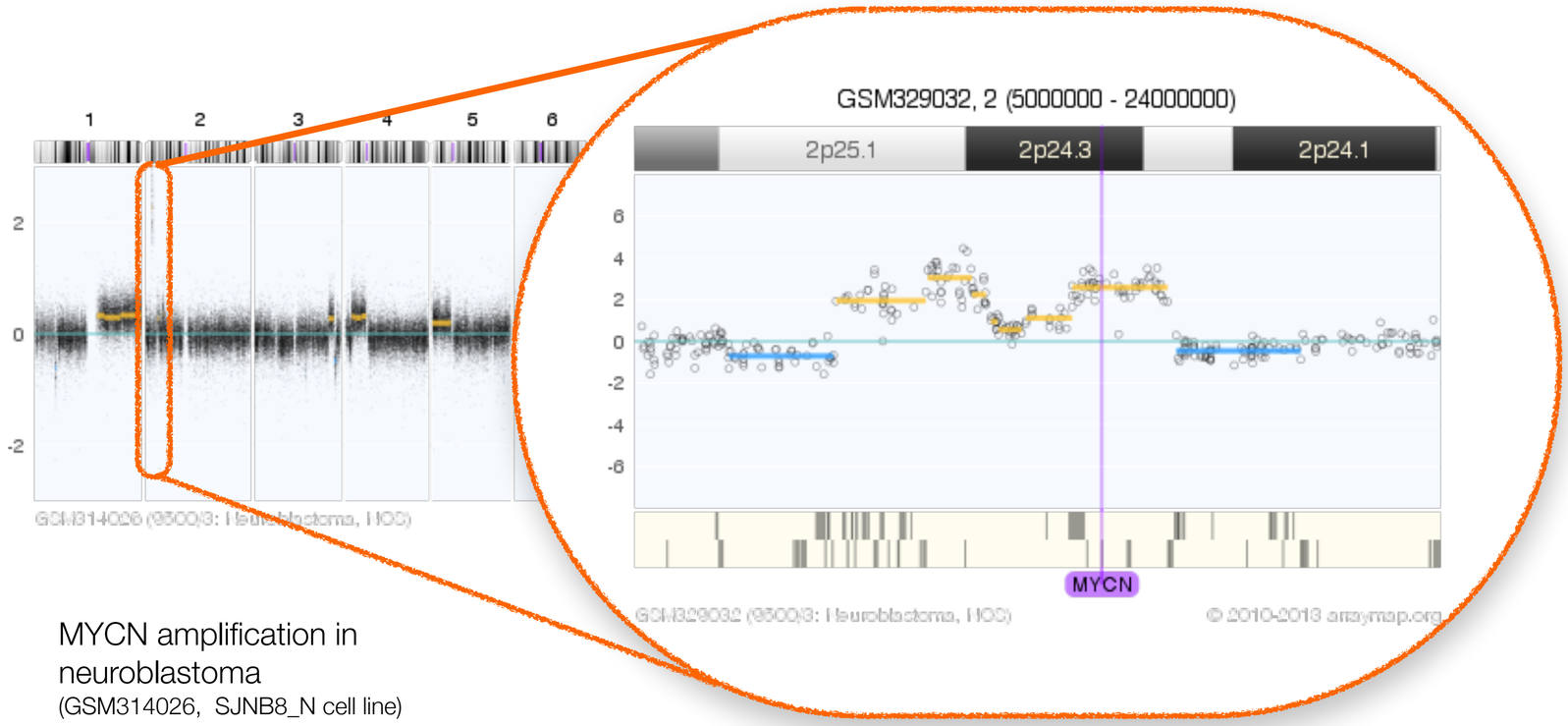
Somatic Copy Number Variations



Gain of chromosome arm 13q in colorectal carcinoma



2-event, homozygous deletion in a Glioblastoma



MYCN amplification in neuroblastoma
(GSM314026, SJNB8_N cell line)

low level/**high level** copy number alterations (CNAs)

arrayMap

CNVs Come in a Variety of Formats

Text conversion from ISCN

- articles and supplements with **cytoband-based** *rev ish* CGH results are a great source of CNV data
- conversion by mapping cytoband locations (e.g. UCSC annotation files) to genome coordinates and assigning CNV types (enh, dim, amp are standard)

progenetix

TABLE 3. Comparison of Primary Tumors and Metastases by CGH

Case	Gain in common	Loss in common	Primary tumor only	Metastasis only
108		18		
113	7, 8q24-qter, 13q11-qter, 20q11-qter, Xq11-Xter	1p33-pter, 2p21-pter, 4q24-qter, 15q11-q15, 17p11-pter, 18		
LM	12q22-qter, 15q23-qter, 17q11-ter, 20p11-p12, 20q11-ter, 22q11-ter	1p11-p32, 1q24-31, 4, 13q11-qter, 17p11-pter, 18, 20p11-ter	11p11-pter-	12+
145	4q26-q28, 6p11-p13, 8p11-p12, 920q11-qter	1p11-pter, 4q31-qter, 6q11-qter, 8p12-pter, 11, 15q11-qter, 16q11-qter, 17p11-pter, 18, 21q11-qter	13q21-qter+, 20p11-pter-	8q11-qter+,10-, 6p21-pter-
53	7, 8q11-qter, 9q33-qter, 13q11-qter, 20p11-p12, 20q11-qter	4p13-pter, 4q21-qter, 8p12-pter, 15q14-qter, 18q11-qter, 20p12-pter	5p11-pter-, 5q13-qter-, 14q11-qter-	11+, 16p11-pter+, 17q11-qter+, 19+, 21q11-qter+, 22q11-qter+
147	7, 13q11-qter, 20q11-qter	8p21-pter, 18	4p14-pter-, 4q28-qter+, 8p11-21-, 17q11-q2+, 21q11-qter-	11q22-qter+, 16+, 1p11-33-

TABLE 1. Clinical Data

Case number	Age	Sex	Site	Stage[a]	Grade[b]	Diagnosis of metastatic disease[c]
2	40	M	Transverse colon	IV	3	Synchronous
6	79	M	Ascending colon	IV	2	Synchronous
9	73	M	Transverse colon	II	2	N/A
11	56	M	Rectosigmoid	IV	2	Metachronous
12	70	F	Sigmoid colon	IV	2	Synchronous
13	65	M	Descending colon	II	9	Synchronous
14	60	M	Rectum	III	3	Metachronous
15	51	F	Rectum	III	2	Metachronous
19	63	M	Rectosigmoid Junction	III	2	Synchronous
20	63	M	Rectum	IV	9	Metachronous
21	64	F	Sigmoid colon	IV	2	Synchronous
35	71	M	Rectum	III	9	Metachronous
49	72	M	Cecum	IV	3	Synchronous
53	72	F	Sigmoid colon	IV	2	Synchronous
104	61	M	Sigmoid colon	IV	2	Metachronous
105	58	M	Ascending colon	II	2	Metachronous
107	77	F	Cecum	IV	2	Metachronous
108	53	F	Splenic flexure	IV	2	Synchronous
112	68	M	Rectum	III	3	Synchronous
113	41	M	Splenic flexure	IV	2	Synchronous
114	49	M	Splenic flexure	IV	3	Synchronous
116	73	M	Rectosigmoid	III	9	Metachronous
120	24	F	Descending colon	IV	2	Synchronous
123	62	F	Rectum	III	2	Metachronous
124	42	M	Rectum	IV	9	Synchronous
145	70	M	Rectosigmoid	IV	2	Synchronous
147	86	F	Cecum	IV	2	Synchronous

[a]AJCC/UICC staging system (Hutter and Sobin, 1986).
[b]Grade of primary tumor: 1–3, low, moderate, high grade; 9, grading unknown.
[c]Synchronous, diagnosis of metastatic disease within 12 months following diagnosis of primary tumor; metachronous, diagnosis of metastatic disease after 12 months or later.

GENES, CHROMOSOMES & CANCER 25:82-90 (1999)

Chromosome Arm 20q Gains and Other Genomic Alterations in Colorectal Cancer Metastatic to Liver, as Analyzed by Comparative Genomic Hybridization and Fluorescence In Situ Hybridization

W. Michael Korn,[1]* Toru Yasutake,[2] Wen-Lin Kuo,[1] Robert S. Warren,[3] Colin Collins,[1] Masao Tomita,[2] Joe Gray,[1] and Frederic M. Waldman[1]

CNVs Come in a Variety of Formats: VCF

Issue 1: There are two fields to specify SV/CNV

#CHROM	POS	ID	REF	ALT	QUAL	FILTER	INFO
1	2827694	rs2376870	CGTGGATGCGGGGAC	C	.	PASS	SVTYPE=DEL;END=28277(
2	321682	.	T	<DEL>	6	PASS	SVTYPE=DEL;END=321887
2	14477084	.	C	<DEL:ME:ALU>	12	PASS	SVTYPE=DEL;END=144773
3	9425916	.	C	<INS:ME:L1>	23	PASS	SVTYPE=INS;END=942591
3	12665100	.	A	<DUP>	14	PASS	SVTYPE=DUP;END=126862
4	18665128	.	T	<DUP:TANDEM>	11	PASS	SVTYPE=DUP;END=186652

1) Symbolic allele (SA) ↗ ↖ 2) SVTYPE

- DEL Deletion relative to the reference
- INS Insertion of novel sequence relative to the reference
- DUP Region of elevated copy number relative to the reference
- INV Inversion of reference sequence
- CNV Copy number variable region (may be both deletion and duplication)
- BND Breakend

The CNV category should not be used when a more specific category can be applied. Reserved subtypes include:

- DUP:TANDEM Tandem duplication
- DEL:ME Deletion of mobile element relative to the reference
- INS:ME Insertion of a mobile element relative to the reference

- DEL: Deletion relative to the reference
- INS: Insertion of novel sequence relative to the reference
- DUP: Region of elevated copy number relative to the reference
- INV: Inversion of reference sequence
- CNV: Copy number variable region (may be both deletion and duplication)
- BND: Breakend

VCF v4.4 deprecate SVTYPE

#CHROM	POS	ID	REF	ALT	QUAL	FILTER	INFO	FOR
chrA	2	.	TGC	T	.	.	EVENT=DEL_seq	
chrA	2	.	T	<DEL>	.	.	SVLEN=2;SVCLAIM=DJ;EVENT=DEL_symbolic;END=4	
chrA	2	delbp1	T	T[chrA:5[	.	.	MATEID=delbp2;EVENT=DEL_split_bp_cn	
chrA	2	delbp2	A	]chrA:2]A	.	.	MATEID=delbp1;EVENT=DEL_split_bp_cn	
chrA	2	.	T	<DEL>	.	.	SVLEN=2;SVCLAIM=D;EVENT=DEL_split_bp_cn;END=4	
chrA	5	.	G	GAAA	.	.	EVENT=homology_seq	
chrA	5	.	G	<DUP>	.	.	SVLEN=3;CIPOS=0,5;EVENT=homology_dup	
chrA	14	.	T	<INS>	.	.	IMPRECISE;SVLEN=100;CILEN=-50,50;CIPOS=-10,10;END=14	
chrA	14	.	G	.CCCCCCG	.	.	EVENT=single_breakend	

Symbolic allele (SA)

- DEL Region of lowered copy number relative to the reference, or a deletion breakpoint
- INS Insertion of novel sequence relative to the reference
- DUP Region of elevated copy number relative to the reference, or a tandem duplication breakpoint
- INV Inversion of reference sequence
- CNV Copy number variable region (may be both deletion and duplication)

The CNV category should not be used when a more specific category can be applied.
Implementations are free to define their own subtypes. The presence of a subtype does not change either the copy number or breakpoint interpretation of a symbolic structural variant allele. The following subtypes are recommended:

- DUP:TANDEM Tandem duplication
- DEL:ME Deletion of mobile element relative to the reference ← Reserved specific subtypes
- INS:ME Insertion of a mobile element relative to the reference

Note that the position of symbolic structural variant alleles is the position of the base immediately preceding the variant.

Use Subtype to define new structural variant

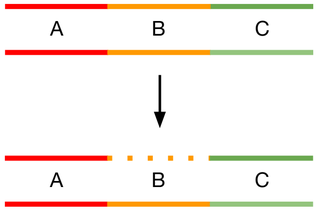
- <DUP:TANDEM> precise form of duplication
- <DEL:ME:LINE>

Subtypes do not change the meaning symbolic allele.

- using genome positions (POS, INFO.END) for start, end mappings
- treatment of markers for imprecision during matching is left to the implementer
- DUP, DEL are interpreted as indicators for the type of copy number change

CNVs Come in a Variety of Formats: VCF

Issue 2: two meanings of DEL and DUP



Usual interpretation of “DEL” (a deletion)

1. Copy number of B decreases from 2 to 1, **and**
2. Adjacency structure changes from (ABC, ABC) to (AC, ABC)

Both effects are important, for example...

- Copy number change can affect gene dosage
- Adjacency structure change can affect expression or disrupt a CDS

...but they do not necessarily happen at the same time.

The SVCLAIM field

New **SVCLAIM** INFO field to capture what the caller could ascertain

- **D** (abun**d**ance / read **d**epth) claim indicates that the call has been made based only on a measure of DNA abundance of the called region, with no evidence to support changes in breakpoint structure. This includes indirect claims of abundance made using SNV variant allele frequency.
- **J** (ad**j**acency / break **j**unction) claim indicates that the call has been made based on the detection of a non-reference DNA adjacency, with no evidence to support overall changes in DNA abundance.
- **DJ** indicates that there is evidence for both DNA abundance and adjacency changes, which are consistent with each other and suggest the structural variant of the type being reported.

- using genome positions (POS, INFO.END) for start, end mappings
- treatment of markers for imprecision during matching is left to the implementer
- DUP, DEL are interpreted as indicators for the type of copy number change ... unless there is an explicit INFO.SVCLAIM without a "**D**" label

Beacon & CNVs

Open types w/ some definitions

- Beacon supports structural variant queries through the ***variantType*** parameter
- The default model does not prescribe which types can be used (but documents VCF derived DUP & DEL)
- CNV values are not (yet) supported but EFO offers common classes
- Progenetix supports EFO *relative CN terms* (but accepts & interpolates DUP & DEL)

Beacon	VCF	SO	EFO	VRS	Notes
DUP	DUP[1]	SO:0001742 copy_number_gain	EFO:0030070 copy number gain	low-level gain (implicit)	a sequence alteration whereby the copy number of a given genomic region is greater than the reference sequence
DUP	DUP[1]	SO:0001742 copy_number_gain	EFO:0030071 low-level copy number gain	low-level gain	
DUP	DUP[1]	SO:0001742 copy_number_gain	EFO:0030072 high-level copy number gain	high-level gain	commonly but not consistently used for >=5 copies on a bi-allelic genome region
DUP	DUP[1]	SO:0001742 copy_number_gain	EFO:0030073 focal genome amplification	high-level gain	commonly but not consistently used for >=5 copies on a bi-allelic genome region, of limited size (operationally max. 1-5Mb)
DEL	DEL[1]	SO:0001743 copy_number_loss	EFO:0030067 copy number loss	partial loss (implicit)	a sequence alteration whereby the copy number of a given genomic region is smaller than the reference sequence
DEL	DEL[1]	SO:0001743 copy_number_loss	EFO:0030068 low-level copy number loss	partial loss	
DEL	DEL[1]	SO:0001743 copy_number_loss	EFO:0030069 complete genomic deletion	complete loss	complete genomic deletion (e.g. homozygous deletion on a bi-allelic genome region)

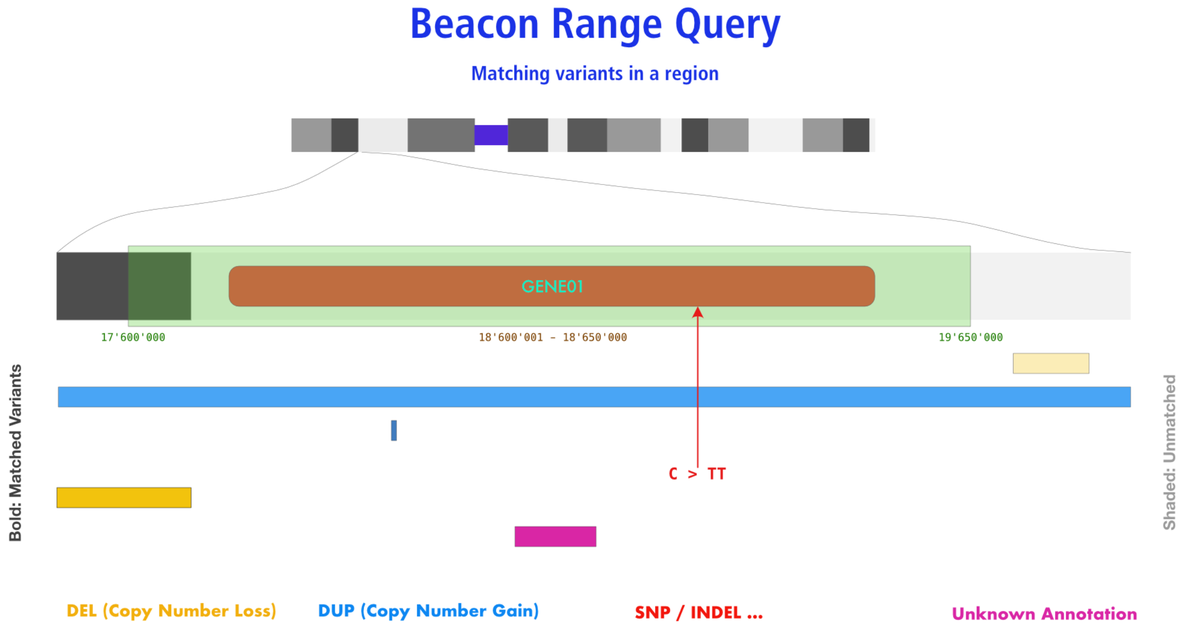
[1] VCFv4.4 introduces an SVCLAIM field to disambiguate between in situ events (such as tandem duplications; known adjacency/ break junction: SVCLAIM=J) and events where e.g. only the change in abundance / read depth (SVCLAIM=D) has been determined. Both J and D flags can be combined.

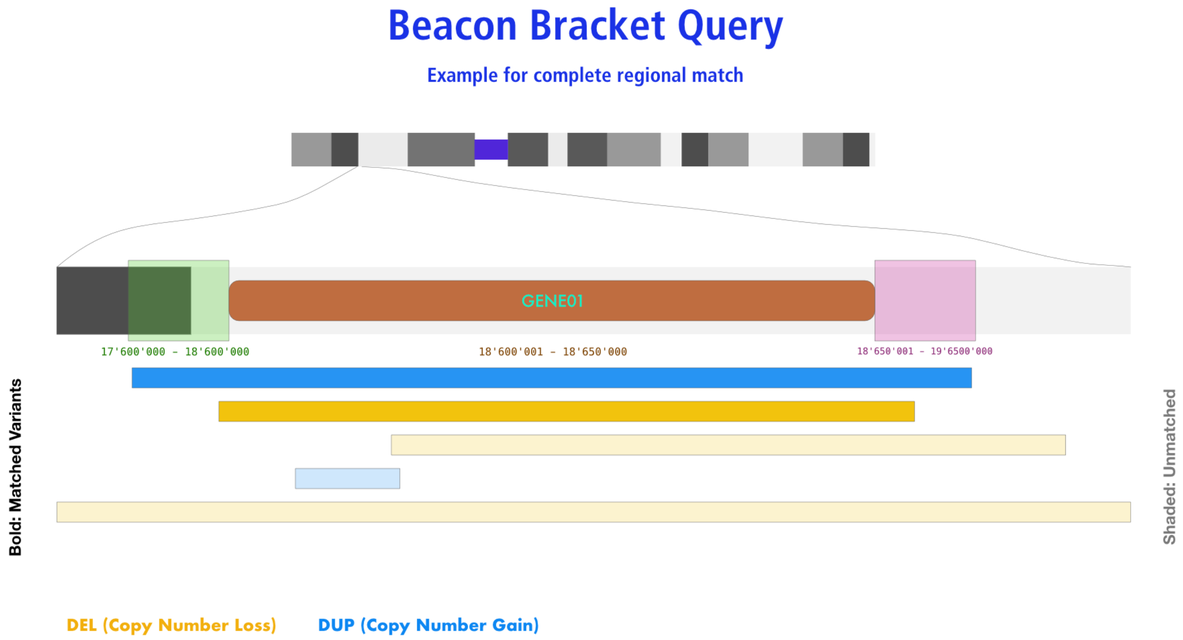
docs.genomebeacons.org/variant-queries/#term-use-comparison

Positional Queries

Going beyond single positions...

- Beacon v1 already provided support for "bracket" queries, e.g. for CNV queries - v2 improves documentation
- Use cases w/ focus on structural variants were evaluated by a Beacon "scout" team
- new "range" option
  - ➡ anything w/ overlap
  - ➡ matched variants can optionally be filtered by type, size, sequence
- query option are not hard defined but derived from parameters
  - ➡ Strong wish for defined types?





Beacon v2 - Beaconise your Data

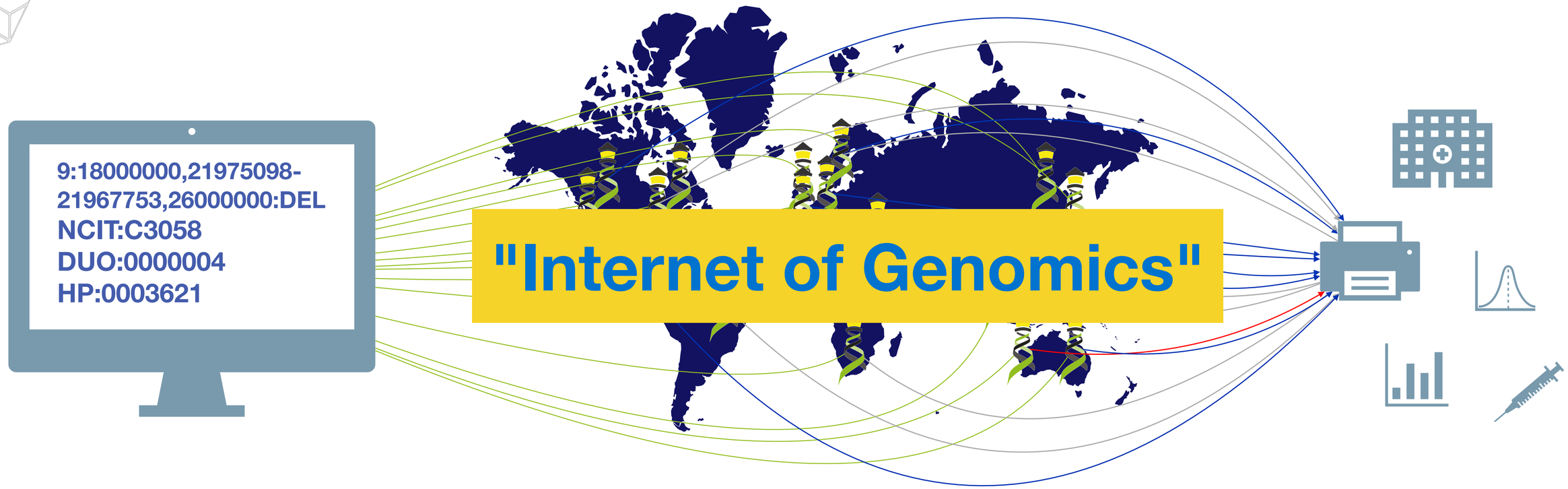
BANCCO (David Salgado)

Global Alliance
for Genomics & Health

Beacon v2 - Beaconise your Data

Filters (Vatsalya Maddi)

Global Alliance
for Genomics & Health



Have you seen deletions in this region on chromosome 9 in Glioblastomas from a juvenile patient, in a dataset with unrestricted access?

Beacon *v2* API

The Beacon API v2 proposal opens the way for the design of a simple but powerful "**genomics API**".

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Progenetix Documentation

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- Progenetix Data
- Baudisgroup @ UZH

Progenetix Source Code ¶

With exception of some utility scripts and external dependencies (e.g. MongoDB the software (from database interaction to website) behind Progenetix and Beac

`bycon`

- Python based service based on the GA4GH Beacon protocol
- software powering the Progenetix resource
- Beacon+ implementation(s) use the same code base

`progenetix-web`

- website for Progenetix and its Beacon+ implementations
- provides Beacon interfaces for the `bycon` server, as well as other Progenetix sevices (e.g. the publicat
- implemented as React / Next.js project
- contains this documentation tree here as `mkdocs` project, with files in the `docs` directory

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Base `/biosamples`

`/BIOSAMPLES/` + QUERY

- /biosamples?filters=cellosaurus:CVCL_0004
- this example retrieves all biosamples having an annotation for the Cellosaurus *CVCL_0004* identifier (K562)

es/pgxbs-kftva5c9

a single biosample

MODE=TRUE

es?testMode=true

some random samples

- for testing API responses

`/BIOSAMPLES/{ID}/G_VARIANTS`

- /biosamples/pgxbs-kftva5c9/g_variants/
- retrieval of all variants from a single biosample

Base `/individuals`

`/INDIVIDUALS` + QUERY ¶

/individuals?filters=NCIT:C7541

Rapidly evolving documentation of both the Beacon API itself and its use and technical implementation on
docs.genomebeacons.org
docs.progenetix.org

Shoutout to Laure(e)n Fromont & Manuel Rueda for being instrumental in the Beacon v2 documentation!

Beacon API

Beacon-style JSON responses

The Progenetix resource's API utilizes the `bycon` framework for data query and delivery and represents a custom implementation of the Beacon *v2* API.

The standard format for JSON responses corresponds to a generic Beacon v2 response, with the `meta` and `response` root elements. Depending on the endpoint, the main data will be a list of objects either inside `response.results` or (mostly) in `response.resultSets.results`. Additionally, most API responses (e.g. for biosamples or variants) provide access to data using *handover* objects.

Beacon v2 Documentation

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Progenetix & Beacon+

The Beacon+ implementation - developed in the Python & MongoDB based `bycon` project - implements an expanding set of Beacon v2 paths for the Progenetix resource.

Scoped responses from query object

In queries with a complete `beaconRequestBody` the type of the delivered data is independent of the path and determined in the `requestedSchemas`. So far, Beacon+ will compare the first of those to its supported responses and provide the results accordingly; it doesn't matter if the endpoint was `/beacon/biosamples/` or `/beacon/variants/` etc.

Below is an example for the standard test "small deletion CNVs in the CDKN2A locus, in gliomas" Progenetix test query, here responding with the matched variants. Exchanging the `entityType` entry to

- `{ "entityType": "biosample", "schema:": "https://progenetix.org/services/schemas/Biosample/"}`

would change this to a biosample response. The example ccan be tested by POSTing this as `application/json` to `http://progenetix.org/beacon/variants/` or `http://progenetix.org/beacon/biosamples/`.

```
{
    "$schema":"beaconRequestBody.json",
    "meta": {
        "apiVersion": "2.0",
        "requestedSchemas": [
            {
                "entityType": "genomicVariant",
                "schema:": "https://progenetix.org/services/schemas/genomicVariant"
            }
        ]
    },
    "query": {
        "requestParameters": {
```

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Future?

Some proposals for a stepwise Beacon protocol extension

- Query language expansion, e.g. Boolean options for chaining filters

  ➡use of heterogeneous/alternative annotations within and across resources

- **Phenopackets** support as a (the?) default format for biodata export
- **Phenopackets** as **request** documents
- Focus on service & **resource discovery**
- **ELIXIR Beacon Network**, including translations for federated queries to Beacon and Beacon-like resources