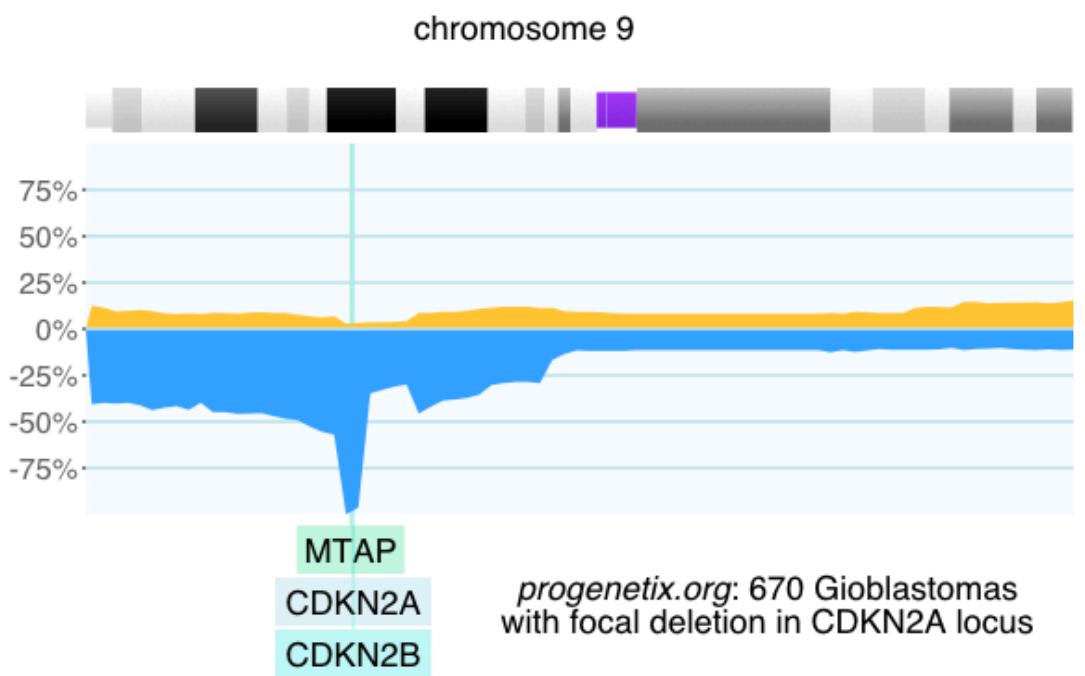


# ELIXIR hCNV

## Updates and future plans

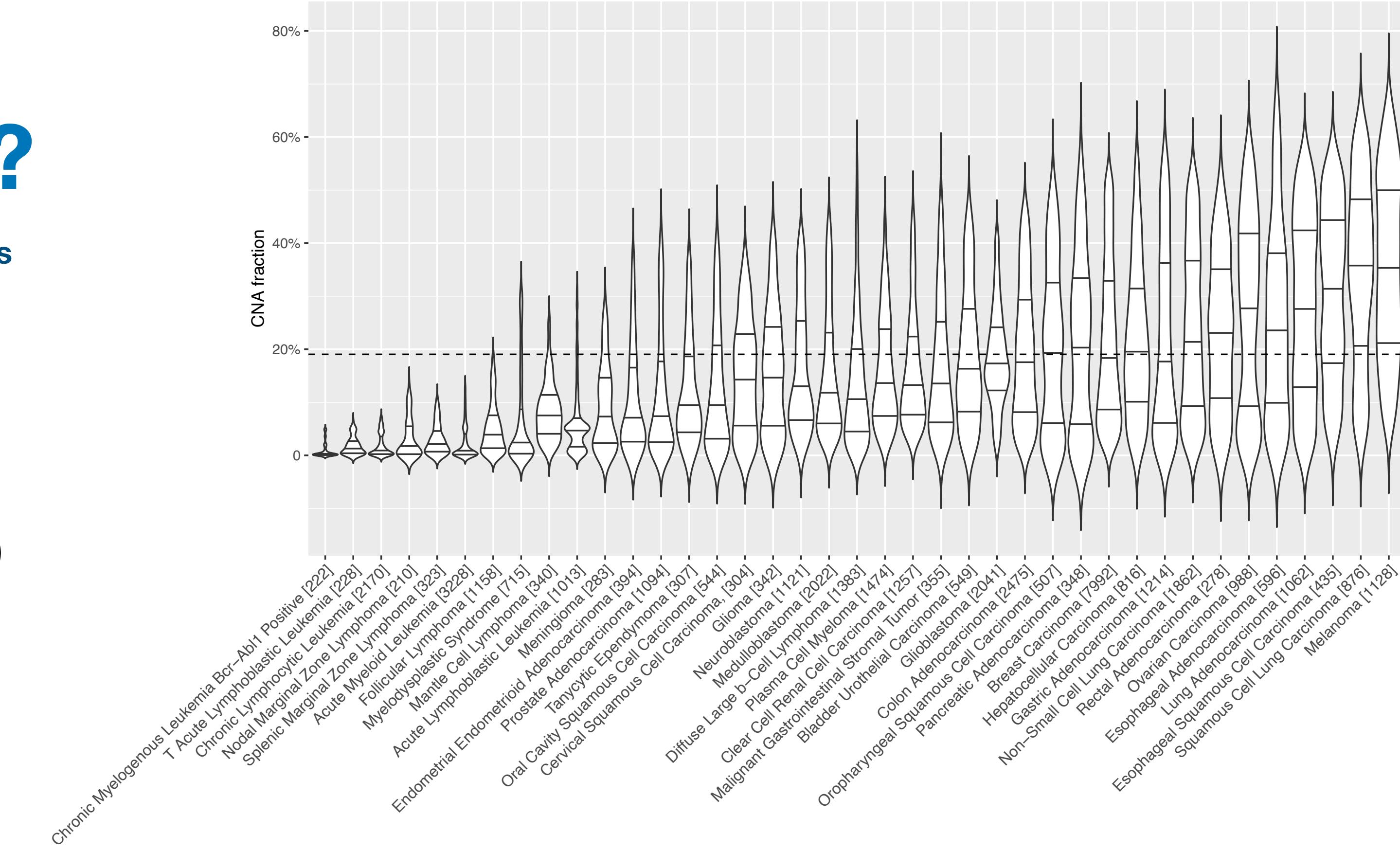
Michael Baudis | ELIXIR Human Data Day | 2021-06-11



# Why hCNV Community?

## Structural Genome Variation Data :: Resources and Technologies

- structural genome variations are a major contributor to genetic diseases and cancer
- knowledge about and standards for copy number variations / aberrations (CNV/CNA) has not been in step with NGS & GWAS driven SNV/SNP assessment



## Mission statement

Despite the fact that **Copy Number Variations** are the **most prevalent genetic mutation type**, identifying and interpreting them is still a major challenge. The ELIXIR human Copy Number Variation (hCNV) Community aims to implement processes to make the **detection**, **annotation** and **interpretation** of these variations easier

### Genome CNV coverage in Cancer Classes

- 43654 out of 93640 CNV profiles; filtered for entities w/ >200 samples
- 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)
- knowledge about and standards for copy number variations / aberrations (CNV/CNA) has not been in step with NGS & GWAS driven SNV/SNP assessment



# ELIXIR hCNV Community

## Structural Genome Variation Data :: Resources and Technologies

- First meeting of group in 2018
- ELIXIR Human Copy Number Variation (hCNV) approved in 2019
- initial implementation study (2019-2021) for community set-up, gap analysis and exploration of technical deliverable

### Mission statement

Despite the fact that **Copy Number Variations** are the **most prevalent genetic mutation type**, identifying and interpreting them is still a major challenge. The ELIXIR human Copy Number Variation (hCNV) Community aims to implement processes to make the **detection**, **annotation** and **interpretation** of these variations easier

### Purpose

The human CNV community (h-CNV) has been officially created in December 2018. It aims to address the major challenge of NGS data interpretation in the era of whole genome sequencing for the most frequent mutation type: Copy Number Variation. Seven topics have been identified during the kick-off meeting and further refined with all h-CNV partners. This ultimately led to the proposal described in this implementation study.

Node	Name of PI
ELIXIR-FR	Christophe Béroud, David Salgado, Marc Hanauer, Victoria Dominguez
ELIXIR-CH	Michael Baudis
ELIXIR-DE	Jan Korbel
EMBL-EBI	Thomas Keane, Fiona Cunningham
ELIXIR-ES	Joaquin Dopazo, Alfonso Valencia, Salvador Capella, Sergi Beltran, Steven Laurie, Gemma Bullich, Laura I. Furlong, Janet Piñero
ELIXIR Hub	John Hancock, Gary Saunders, Kathi Lauer, Leyla Garcia
ELIXIR-NL	Bauke Ylstra, Daoud Sie, Leon Mei, Morris Swertz (UMCG), Lennart Johansson
ELIXIR-NO	Eivind Hovig, Pubudu Samarakoon
ELIXIR-HU	Attila Gyenessei ,Katalin Monostory
ELIXIR-SI	Brane Leskošek, Polonca Ferk, Marko Vidak
ELIXIR-UK	Krzysztof Poterlowicz
Delivery	Starting from June 2019 for a period of 24 months.



Christophe Béroud  
(ELIXIR France)



David Salgado  
(ELIXIR France)



Gary Saunders  
(Human Data Coordinator,  
ELIXIR Hub)



Michael Baudis  
(ELIXIR Switzerland)



# hCNV Implementation Study 2019-2021

## Setting the Scope | Solidifying the Community | First Deliveries

- challenge participants and define the wider landscape as well as future directions
- set of 7 work packages
  - landscape analysis
  - technical products
  - resource improvement
  - community building & outreach
- regular meetings, website, hackathons...
  - ▶ WP1 - Optimal CNV detection pipelines for research and diagnostics
  - ▶ WP2 - Definition of reference datasets
  - ▶ WP3 - Improvement of community formats for CNV exchange
  - ▶ WP4 - Enabling CNV data discovery in diagnostic and phenotypic context
  - ▶ WP5 - Creation of innovative tools
  - ▶ WP6 - FAIRification of h-CNV databases and datasets
  - ▶ WP7 - Dissemination



# hCNV Implementation Study 2019-2021

## Setting the Scope | Solidifying the Community | First Deliveries

- highly ambitious goals, beyond available support
  - especially reference / benchmarking dataset generation and pipeline development
- emerging interactions and collaborations with ELIXIR platforms & communities and beyond
  - Galaxy
  - GA4GH / ELIXIR Beacon project
- ▶ WP1 - Optimal CNV detection pipelines for research and diagnostics
- ▶ WP2 - Definition of reference datasets
- ▶ WP3 - Improvement of community formats for CNV exchange
- ▶ WP4 - Enabling CNV data discovery in diagnostic and phenotypic context
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- ▶ WP6 - FAIRification of h-CNV databases and datasets
- ▶ WP7 - Dissemination



# hCNV Implementation Study 2019-2021

## Some Achievements and Deliveries

- HGVS satellite meeting – Human CNV – June 14th 2019 – Göteborg Sweden
- hCNV community workshop ELIXIR All-Hands Lisbon – June 2019
- survey of data annotation formats, including comments on VCF development
- start FAIRification of CNV national / reference databases (BANCCO, Progenetix)
- Community white paper published
- Biohackathon Paris 2019
- in 2021 start of shared meetings of subgroup with Beacon variants scout team

F1000Research

F1000Research 2020, 9(ELIXIR):1229 Last updated: 01 JUN 2021



OPINION ARTICLE

**The ELIXIR Human Copy Number Variations Community: building bioinformatics infrastructure for research [version 1; peer review: 1 approved]**

David Salgado <sup>1</sup>, Irina M. Armean<sup>2</sup>, Michael Baudis <sup>3</sup>, Sergi Beltran<sup>4,5</sup>, Salvador Capella-Gutierrez <sup>6,7</sup>, Denise Carvalho-Silva <sup>8,2,8</sup>, Victoria Dominguez Del Angel <sup>9</sup>, Joaquin Dopazo <sup>10</sup>, Laura I. Furlong <sup>11</sup>, Bo Gao <sup>12</sup>, Leyla Garcia <sup>12,13</sup>, Dietlind Gerloff<sup>14</sup>, Ivo Gut<sup>4,5</sup>, Attila Gyenessei<sup>15</sup>, Nina Habermann<sup>16</sup>, John M. Hancock <sup>13</sup>, Marc Hanauer<sup>17</sup>, Eivind Hovig <sup>18,19</sup>, Lennart F. Johansson<sup>20</sup>, Thomas Keane<sup>2</sup>, Jan Korbel<sup>16</sup>, Katharina B. Lauer <sup>13</sup>, Steve Laurie<sup>4</sup>, Brane Leskošek<sup>21</sup>, David Lloyd <sup>13</sup>, Tomas Marques-Bonet<sup>22</sup>, Hailiang Mei<sup>23</sup>, Katalin Monostory<sup>24</sup>, Janet Piñero <sup>11</sup>, Krzysztof Poterlowicz <sup>25</sup>, Ana Rath<sup>17</sup>, Pubudu Samarakoon<sup>26</sup>, Ferran Sanz<sup>11</sup>, Gary Saunders <sup>13</sup>, Daoud Sie<sup>27</sup>, Morris A. Swertz<sup>20</sup>, Kirill Tsukanov <sup>12</sup>, Alfonso Valencia<sup>6,7,28</sup>, Marko Vidak<sup>21</sup>, Cristina Yenyxe González<sup>2</sup>, Bauke Ylstra<sup>29</sup>, Christophe Béroud<sup>1,30</sup>

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<sup>25</sup>Centre for Skin Sciences, University of Bradford, Bradford, UK



# hCNV Implementation Study 2019-2021

## Some Achievements and Deliveries

- Close interaction with Beacon "scout" teams
  - use case driven (BANCCO - RD && Progenetix - cancer) development of essential query standards for the upcoming Beacon v2

**Beacon Scouts: Genomic Variants Use Cases & Examples**

This document develops a set of genomic variant types and associated query formats to be supported by the Beacon protocol. The initial development focuses on the possibly limited, but unambiguous definition of query formats, driven and documented through real-world use cases.

References	1
Conventions Followed in the Document	1
Use of Positional Parameters	2
Variant Types, Documentation and Example Queries	2
INS (Insertion)	2
DEL (Deletion)	3
DUP (Duplication)	5
Amp (DUP more than 2) CN type of approach	8
LOH (loss of representation of second allele, with or without copy number change)	8
INV (inversion)	8
TL (Translocation)	9
Proposal: BRK (Breakpoint)	9
ME (Mobile elements insertion /deletion)	10
CNV - (non directional CNVs) - do we allow cnv queries? / complex CNVs	10
Tandem Duplication	11

**DUP (Duplication)**

**Definitions:**

- SO:0001742 - A sequence alteration whereby the copy number of a given region is greater than the reference sequence (copy number gain).
- CNV query resolves to DUP or DEL or CNV (and their equivalents -> see DUP, DEL), tandem dups?
- CNV loss / CNV gain

Examples below based on a specific study (<https://doi.org/10.1016/j.tjog.2018.06.018>)

**Example:** Find duplications involving the whole locus (chr2:54,700,000-63,900,000)

Provided by: David Salgado & Michael Baudis  
Notes:

- This is an application of a **Bracket Query**.
- Here, matched duplication events start 5' to the gene.
- Besides the positions, this requires knowing the size of the gene (or use of a very large one exceeding the size of chr2" value).

Query structure:

```
referenceName: "2"  
start: [0, 54700000]  
end: [63900000, 242193529]  
variantType: "SO:0001742"  
  
?referenceName=2&start=0, 54700000&end=63900000&variantType=SO:0001742
```

Genomic region:<----->

**Query Range**

Start pars:	<=====??=====>	End pars:	<=====????=====>
Match1:	<=====*****=====>	Match2:	<=====*****=====>
Match3:	<=====*****=====>	Match4:	<=====*****=====>

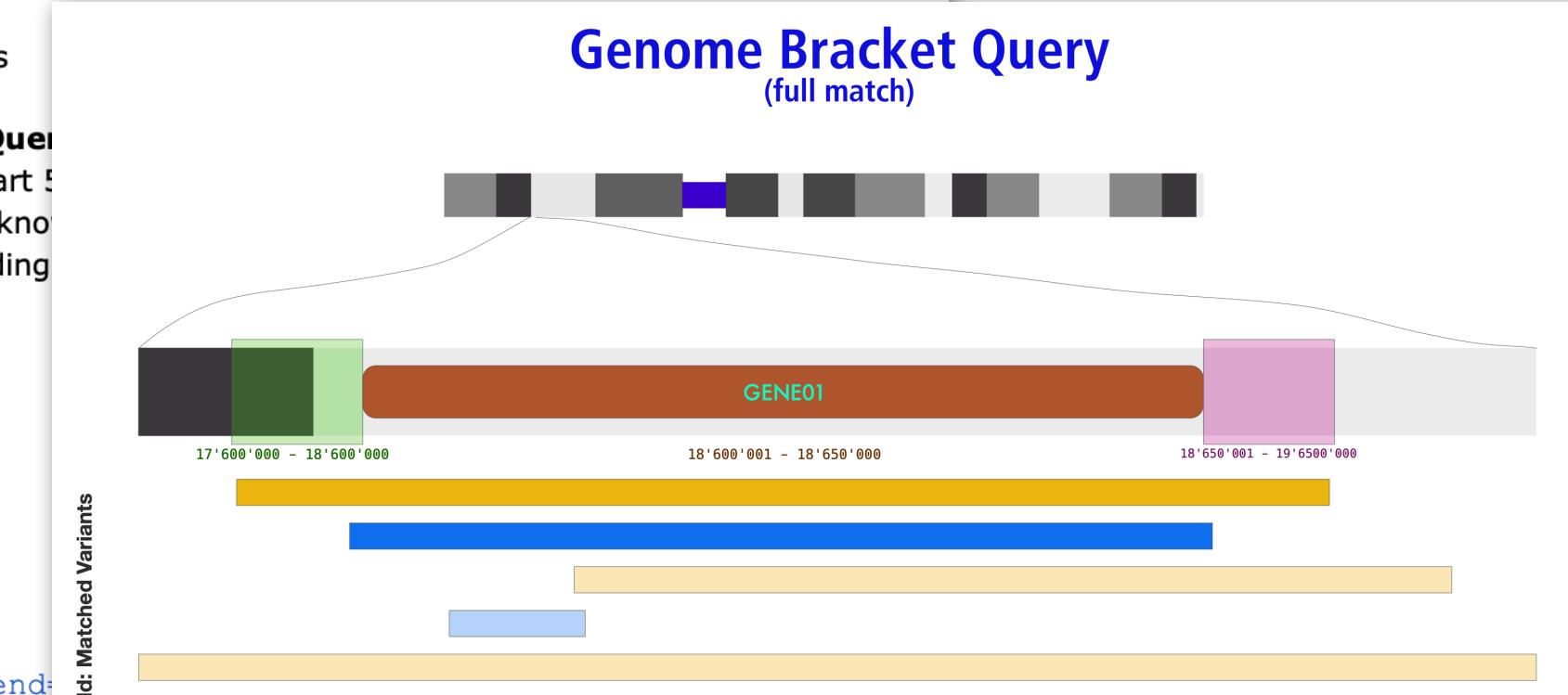
**Matched variants**

Match1:	<=====*****=====>	Match2:	<=====*****=====>
Match3:	<=====*****=====>	Match4:	<=====*****=====>

**Not Matched**

No Match1:	<=====!!!!=====>	No Match2:	<=====!!!!=====>
No Match3:	<=====!!!!=====>	No Match4:	<=====!!!!=====>

**Genome Bracket Query (full match)**



# 2x hCNV Implementation Studies 2021-2023

## Reference hCNV datasets, use-case workflows and benchmarking

The ELIXIR human CNV Community (hCNV) was created in December 2018. In two years contributions to the field have been numerous (ELIXIR IS, Rare Diseases, Federated Human Data, Beacons, GA4GH, EJP-RD and Beyond 1 Million Genomes - B1MG). The Community now aims to address the major challenge of NGS data interpretation in the era of whole genome sequencing: Copy Number Variation. During the first commissioned service offered as a starting grant, the Community has identified various gaps to proceed with CNV tools benchmarking and in particular for Exome and targeted sequencing, which are by far the most widely used technologies in diagnostic laboratories and in research. Within this implementation study we want to provide solutions and bioinformatic infrastructure solutions to fill identified gaps, and to make these biomedical reference materials available (i.e. via Open Science) to the various communities and platforms.

### Interactions and utility to other projects

#### ELIXIR platforms:

Data, Tools, Interoperability, Training

#### ELIXIR Communities:

hCNV, Galaxy, Rare diseases, Federated Human Data

#### National and International projects:

EJP-RD, B1MG, EOSC-Life, EOSC-Pillar

## Beacon and beyond – Implementation-driven standards and protocols for CNV discovery and data exchange

The initial 2019-2021 hCNV community implementation study employed a set of perceived needs to a) deliver first community standards and procedures; b) identify intersections with other ELIXIR communities and stakeholders in ELIXIR connected organizations, such as GA4GH; and c) to streamline priorities for relevant, achievable deliveries of hCNV community projects.

This proposal for an hCNV implementation study focuses on those potential high-value targets for data access and delivery, using reference resources and community stakeholder engagement to directly implement and test hCNV resources aligned with ELIXIR ecosystems.

The main target here will be the empowerment of the Beacon protocol, to act as standard for federated hCNV discovery and data delivery, in conjunction with additional GA4GH derived standards.

#### Intersecting ELIXIR Platforms, Communities and Projects:

- ELIXIR Galaxy Community
- ELIXIR AAI Infrastructure Service
- ELIXIR Compute Platform
- ELIXIR Training Platform
- ELIXIR FHD Community
- ELIXIR Health Data Focus Group
- ELIXIR Beacon Strategic Implementation Study
- ELIXIR Interoperability Platform

#### External Projects and Partners:

- EJP-RD
- GA4GH (Discovery, Genomic Knowledge Standards, Phenopackets)



# **hCNV Implementation Studies 2021-2023 No. 1**

## **Reference hCNV datasets, use-case workflows and benchmarking**

- only limited datasets exist to test and benchmark tools for the analysis of CNV and structural variations
  - recent datasets focused on high-quality Whole Genome Sequencing (WGS) analyses but not on the most commonly used Whole Exome Sequencing (WES) or genomic array technologies
  - generation of publicly accessible reference sets (raw and interpreted CNV data) for a variety of technological platforms will allow the hCNV community to generate the mandatory material
  - creation of “control datasets” required by many detection tools
  - complement standardization and benchmarking efforts such as the “Genome in a Bottle” initiative
  - integrate with Galaxy community & platforms
- ▶ WP1 - Dataset selection and generation
  - ▶ WP2 - Analyse and Compare CNV with other Benchmarking initiatives
  - ▶ WP3 - Exploitation of the datasets by the Galaxy Community
  - ▶ WP4 - Training and dissemination



# hCNV Implementation Studies 2021-2023 No. 2



## Beacon and beyond – Implementation-driven standards and protocols for CNV discovery and data exchange

- reinforce work on priority areas established in the current hCNV Implementation Study
- extend collaborations with the Rare Diseases and Galaxy Communities, EJP-RD and GA4GH
- Expected outcomes
  - ▶ shared CNV resources testing advanced versions of the Beacon protocol
  - ▶ integration of GA4GH standards such as Phenopackets in such resources
  - ▶ tools for data ingestion and export for standard formats (e.g. VCF, Phenopackets) and CNV-specific improvements of such standards
  - ▶ ELIXIR AAI demo on clinical and research hCNV resources
  - ▶ demonstration of Galaxy pipeline adoption for real-world hCNV data analysis projects
- connecting to international partners, e.g. Cancer Genomics Consortium (U.S.)

- ▶ WP1 - hCNV community reference resources
- ▶ WP2 - hCNV Resources and Beacon
- ▶ WP3 - Galaxy Community Intersection and Data Exchange
- ▶ WP4 - Workflows and Tools for hCNV Data Exchange Procedures
- ▶ WP5 - Training and dissemination



# hCNV Implementation Studies 2021-2023 No. 2



Beacon and beyond – Implementation-driven standards and protocols for CNV discovery and data exchange

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 **139448** samples.

Sezary syndrome (icdom-97013)

CC BY 4.0 progenetix.org (2021)

Download SVG | Go to icdom-97013 | Download CNV Frequencies

Example for aggregated CNV data in 166 samples in Sezary syndrome.  
Here the frequency of regional **copy number gains** and **losses** are displayed for all 22 autosomes.

BANCCO

Accueil Statistique Contact Inscription

Email Mot de passe Connexion  Se rappeler de moi

Importer vos données et partager les avec les partenaires du réseau

BANCCO - Banque Nationale de CNV Constitutionnelles



- ▶ WP1 - hCNV community reference resources
- ▶ WP2 - hCNV Resources and Beacon
- ▶ WP3 - Galaxy Community Intersection and Data Exchange
- ▶ WP4 - Workflows and Tools for hCNV Data Exchange Procedures
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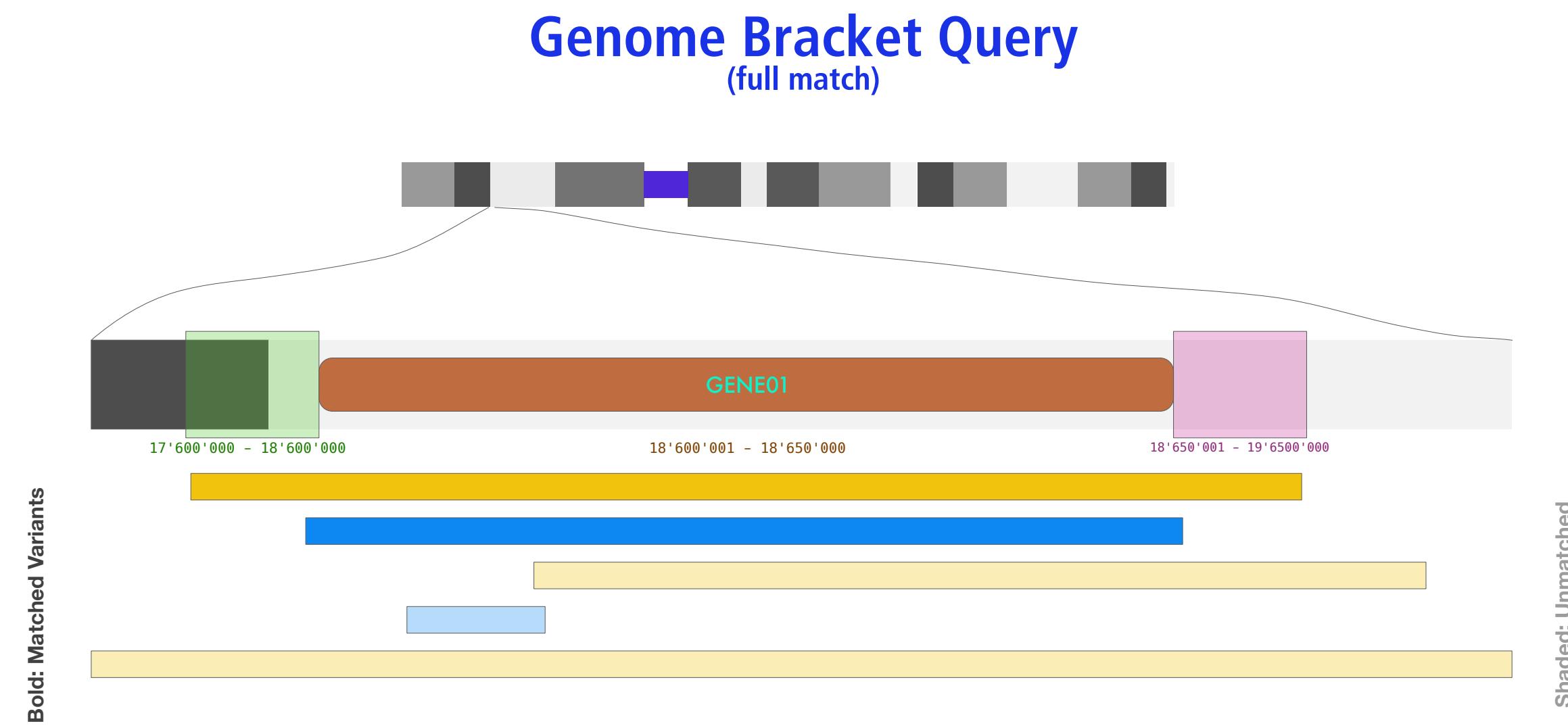
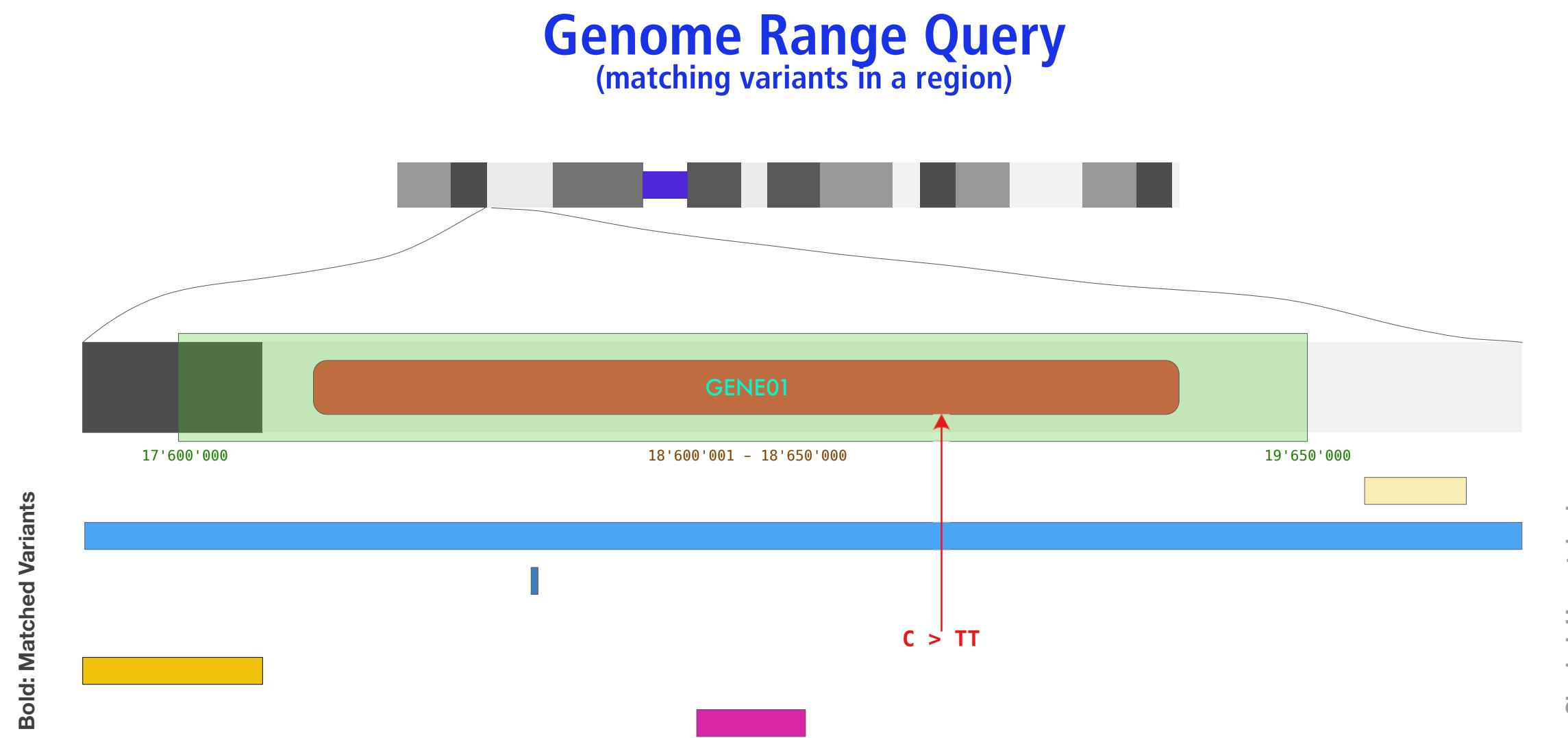
"Galaxify", "Beaconize" & "Phenopack"  
Progenetix & RD-CNVdb prototypes



# Beacon v2: Extended Variant Queries



## Range and Bracket queries enable positional wildcards and fuzziness



- Genome Range Queries provide a way to "fish" for variants overlapping an indicated region, e.g. the CDR of a gene of interest
- Additional parameters (e.g. variant type, reference or alternate bases) limit the scope of the responses
- new Beacon v2 size parameters to limit structural variants (e.g. "focal" CNVs)

- Genome Bracket Queries allow to search for structural variants with start and end positions falling into defined sequence ranges
- allows to query any contiguous genomic variant (and in principle also can step in for range queries)
- typical use case is e.g. the query for variants such as duplications covering the whole CDR of a gene, while limiting the allowed start or end regions

# Beacon & Phenopackets

**Data *discovery* and *delivery* using standardized GA4GH formats and schemas**

- modern standards and protocols such as Beacon & Phenopackets are essential for federation and exchange of biomedical data
  - emerging / established principles are the use of hierarchical coding systems and with widespread use of CURIEs
  - other formats based on international standards, e.g.
    - ISO (ISO 8601 time & period, ISO 3166 country codes ...)
    - IETF (GeoJSON ...)
    - W3C (CURIE ...)
  - these standards become pervasive throughout GA4GH's ecosystem
- Beacon query **filters** correspond well to Phenopackets data
- Phenopackets as supported protocol for Beacon data delivery

```
"data_use_conditions" : {  
    "label" : "no restriction",  
    "id" : "DUO:0000004"  
},  
"material" : {  
    "id" : "EF0:0009656",  
    "label" : "neoplastic sample"  
},  
{  
    "ageAtDiagnosis": "P25Y3M2D"  
},  
"sampled_tissue" : {  
    "id" : "UBERON:0002037",  
    "label" : "cerebellum"  
},  
"histological_diagnosis" : {  
    "id" : "NCIT:C3222",  
    "label" : "Medulloblastoma"  
},
```



# hCNV Implementation Studies 2021-2023

## Focus on Integration with ELIXIR Platforms and Communities - and beyond

- original 2019-2021 implementation study provided visibility and established connections for new studies
- instrumental were Biohackathons, use case & standards surveys and co-participation of group members
- future work plans to leverage the resources of participants through pre-established interactions and synergies
- 2 independent studies provide clearer definitions of deliverables and individual scopes



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