Building a Genomics Resource

Progenetix - From Experiments to APIs

Michael Baudis | UZH BIO390 HS23

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Building a Genomics Resource

A (personal) journey through time...

- Genomic Copy Number Variations in cancer (CNA / CNV)
- Comparative Genomic Hybridization (CGH) as the original CNV screening technique
- CNVs differ between cancer (sub)types and may correlate to clinical outcome
- single studies are limited in understanding disease-specific changes - **let's build a database**
- databases should be accessible - **let's move online**
- **more data** - data parsers & text mining
- **visualization** - graphics libraries and data formatting
- large datasets - access through **APIs**

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University of Zurich[UZH]

Department of Molecular Life Sciences

Genome screening at the core of “Personalised Health”

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

arrayMap

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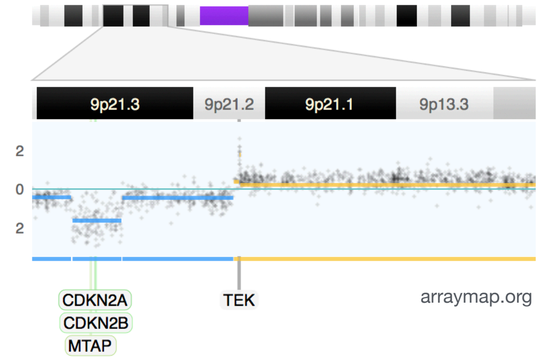
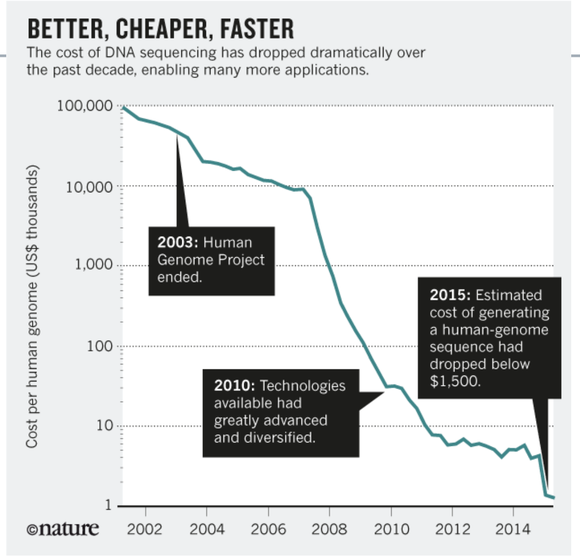
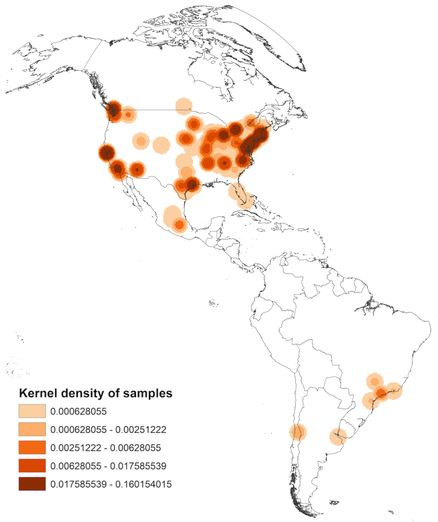
elixir

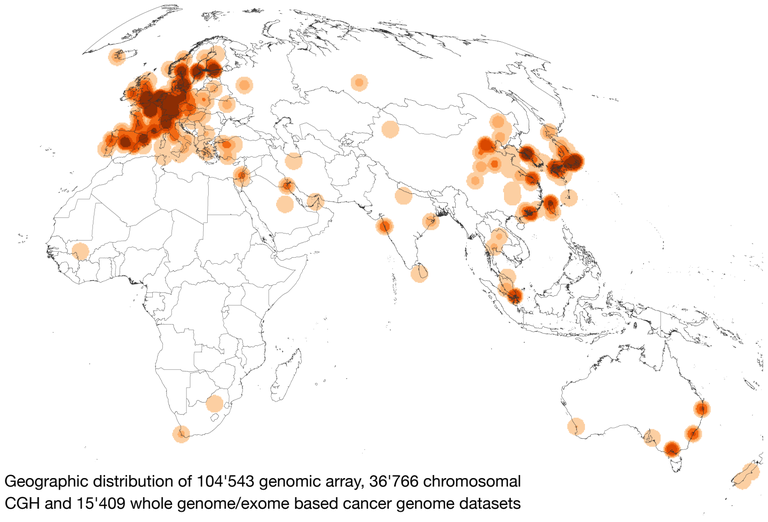
Global Alliance for Genomics & Health



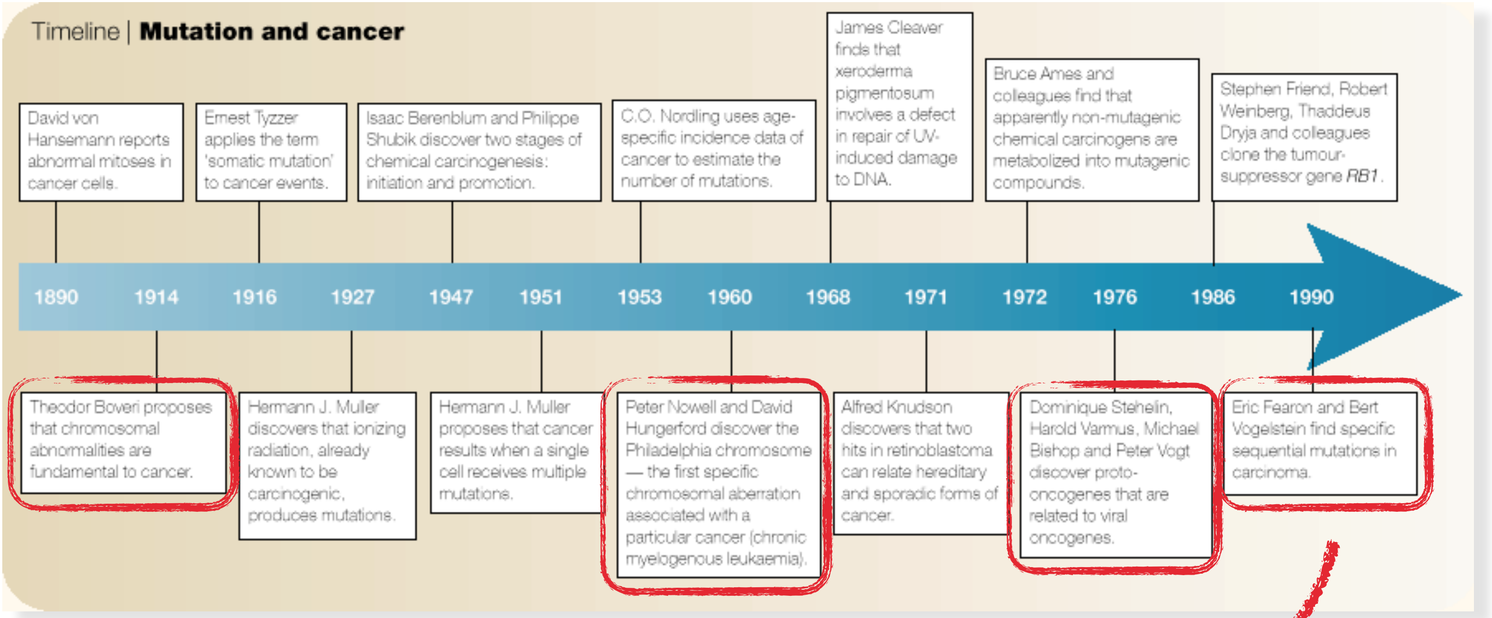


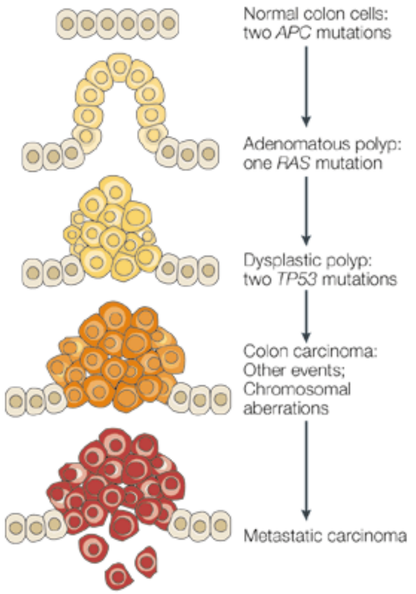
The future of DNA sequencing. Eric D. Green, Edward M. Rubin & Maynard V. Olson. Nature; 11 October 2017 (News & Views)





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





Cancers are based on acquired and inherited genomic mutations

Knudson, A. G. (2001). Two genetic hits (more or less) to cancer. Nature Reviews Cancer, 1(2), 157–162.

Theodor Boveri (1914)

Observations in sea urchin eggs

- **Cell-cycle checkpoints** (“Hemmungseinrichtung”)
- **Tumour-suppressor genes** (“Teilungshemmende Chromosomen”), which may be overcome by external signals, and can be eliminated during tumour progression
- **Oncogenes** (“Teilungsfoerdernde Chromosomen”) that become amplified (“im permanenten Übergewicht”)
- **Progression** (benign to malignant), w/ sequential changes of chromosomes
- Clonal origin & Genetic mosaicism
- Cancer **predisposition** through inheritance of “chromosomes” that are less able to suppress malignancy
- Inheritance of the same 'weak chromosome' from both parents leads to **homozygosity** and, consequently, to high-penetrance cancer syndromes - (e.g. xeroderma pigmentosum)
- Wounding and inflammation in tumour promotion; loss of cell adhesion in metastasis; sensitivity of malignant cells to radiation therapy (based on Hertwig *et al.*)

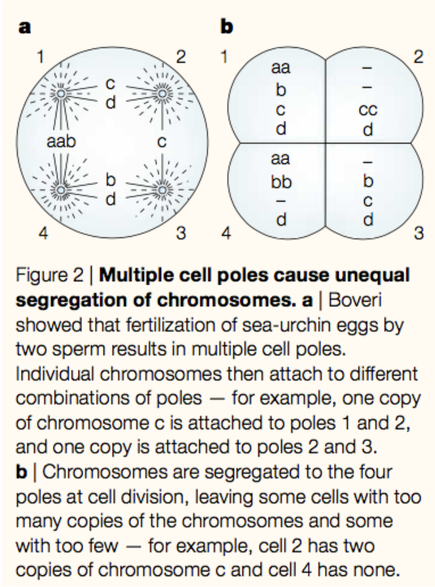


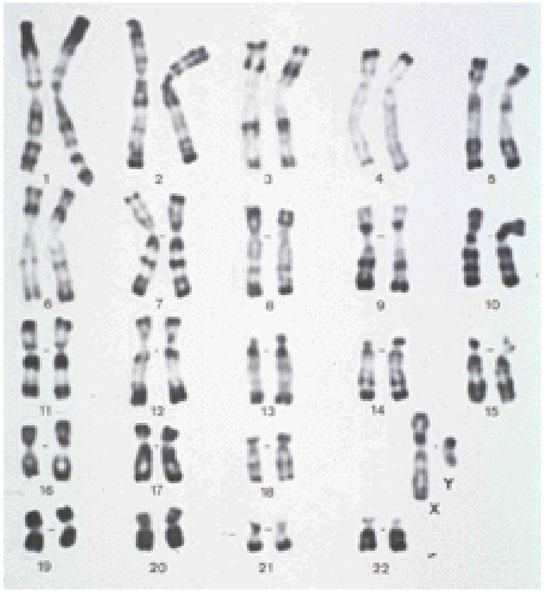
Figure 2 | **Multiple cell poles cause unequal segregation of chromosomes. a** | Boveri showed that fertilization of sea-urchin eggs by two sperm results in multiple cell poles. Individual chromosomes then attach to different combinations of poles — for example, one copy of chromosome c is attached to poles 1 and 2, and one copy is attached to poles 2 and 3. **b** | Chromosomes are segregated to the four poles at cell division, leaving some cells with too many copies of the chromosomes and some with too few — for example, cell 2 has two copies of chromosome c and cell 4 has none.

Allan Balmain
Cancer genetics: from Boveri and Mendel to microarrays.
NatRev Cancer (2001); 1: 77-82

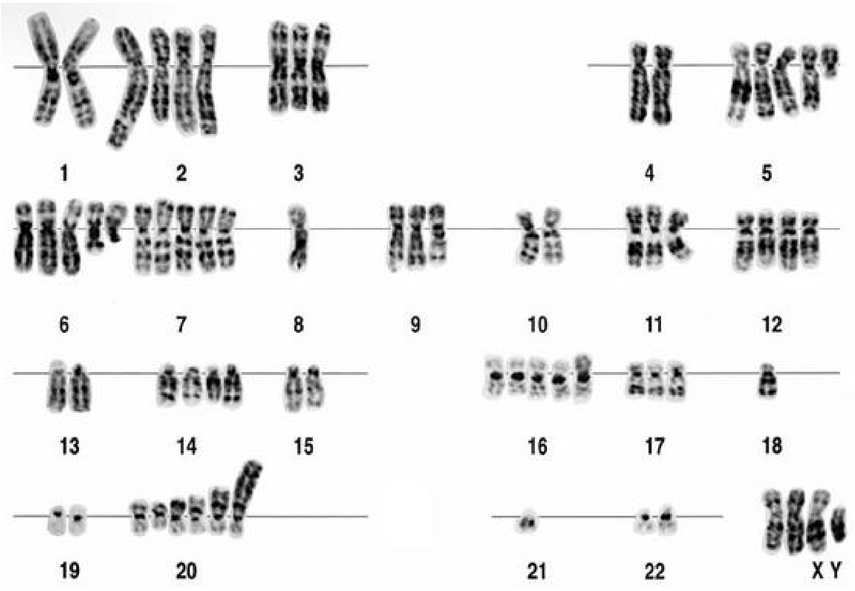
Anna Di Lonardo , Sergio Nasi , Simonetta Pulciani
Cancer: We Should Not Forget The Past
Journal of Cancer (2015), Vol. 6: 29-39
(for book cover & summary)

Genomic changes at the DNA level are hallmarks of cancer

We inherited 23 paternal and 23 maternal chromosomes, mostly identical.



Normal karyotype



Tumor karyotype

Our goal: identify CN changes to improve characterization, classification, and treatment of cancers

Janet Rowley (1972/73)

Chromosomal translocations in cancer

- Recurrent chromosomal translocations in leukemias /lymphomas
- "Philadelphia chromosome" in CML (Nowell & Hungerford, 1960) represents a reciprocal translocation between chromosomes 9 and 22
- 1972: t(8;21) ALL manuscript rejected by NEJM
- 1973: t(9;22) manuscript rejected by *Nature* "*with some reasonable comments and some truly wrong*"
- Clinical implications: **Tyrosine Kinase inhibitors** as standard first-line therapy in CML
  - first trials in 1998 (STI-571; Imatinib/Gleevec)
  - cf. Druker BJ, Lydon NB (2000). Lessons learned from the development of an Abl tyrosine kinase inhibitor… J Clin Invest 2000;105:3-7)

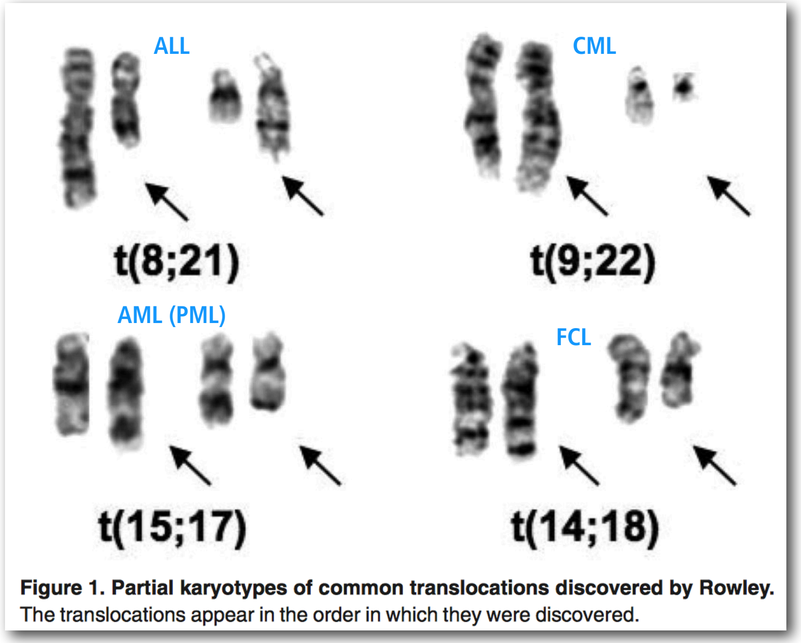
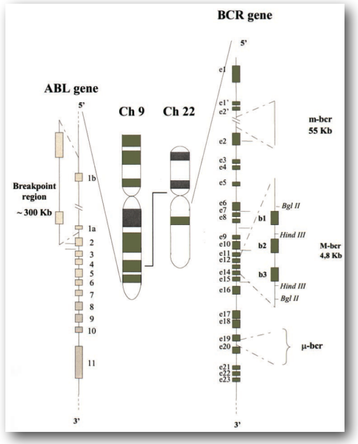
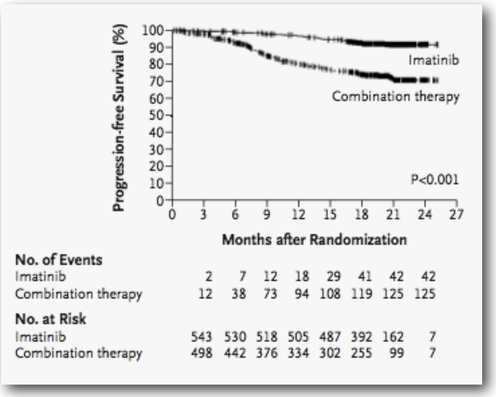


Figure 1. Partial karyotypes of common translocations discovered by Rowley. The translocations appear in the order in which they were discovered.

Janet D Rowley. Chromosomal translocations: revisited yet again Blood (2008), 112(6)



Pane et al. BCR/ABL genes …. Oncogene (2002), 21 (56)



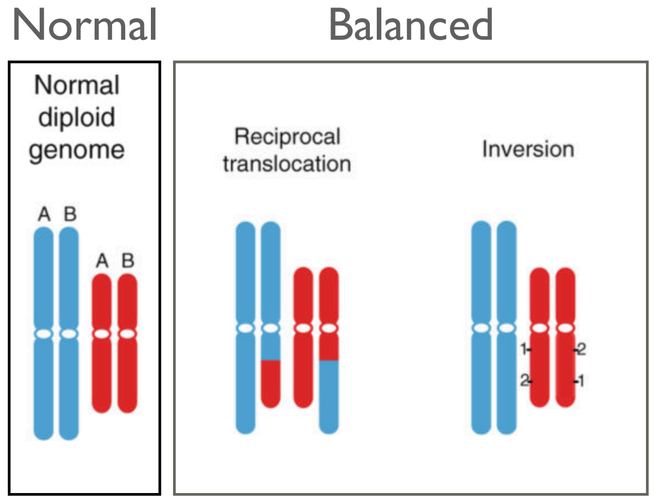
Event free Survival in first large Imatinib Trials

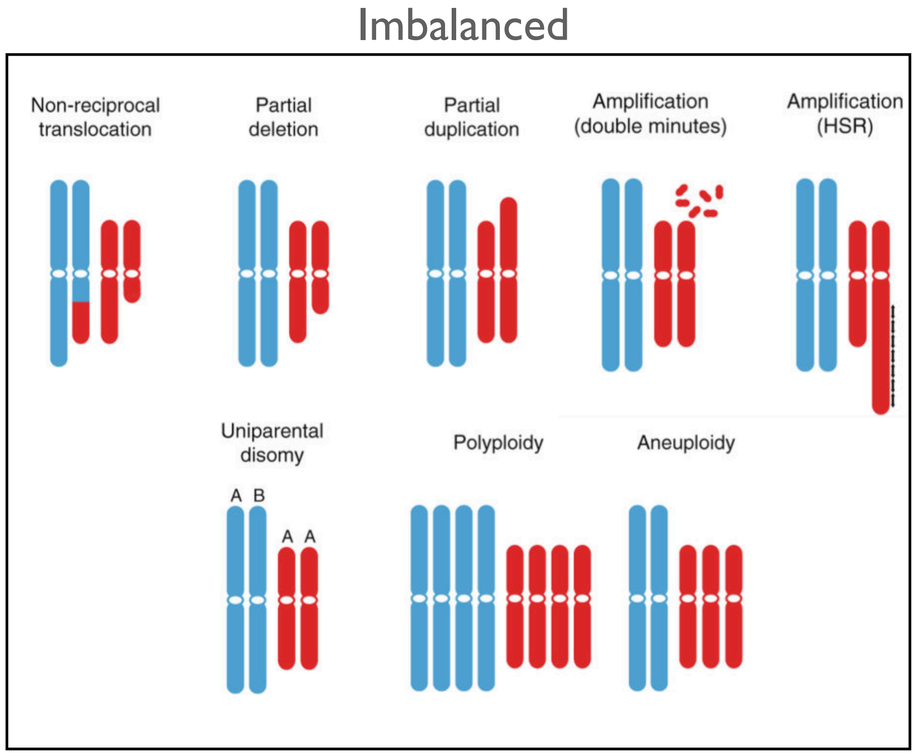
O'Brien et al. Imatinib compared with interferon and low-dose cytarabine… NEJM (2003) vol. 348 (11)

Types of genomic alterations in Cancer

Imbalanced Chromosomal Changes: CNV

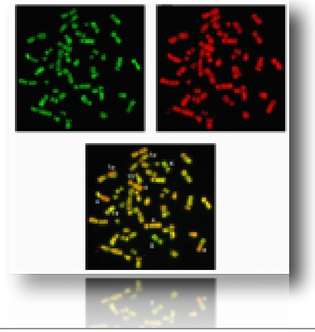
- Point mutations (insertions, deletions, substitutions)
- Chromosomal rearrangements
- Structural chromosomal Aberrations
  - ➡ **Regional Copy Number Alterations** (losses, gains)
- Epigenetic changes (e.g. DNA methylation abnormalities)

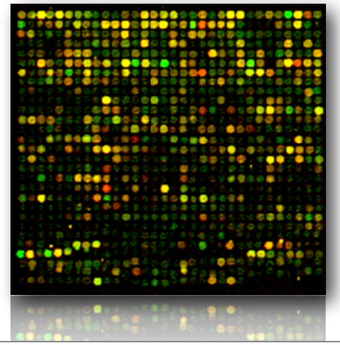


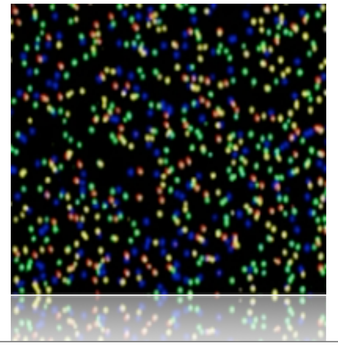


Grade et al., 2015 Recent Results Cancer Res

WHOLE GENOME SCREENING IN CANCER

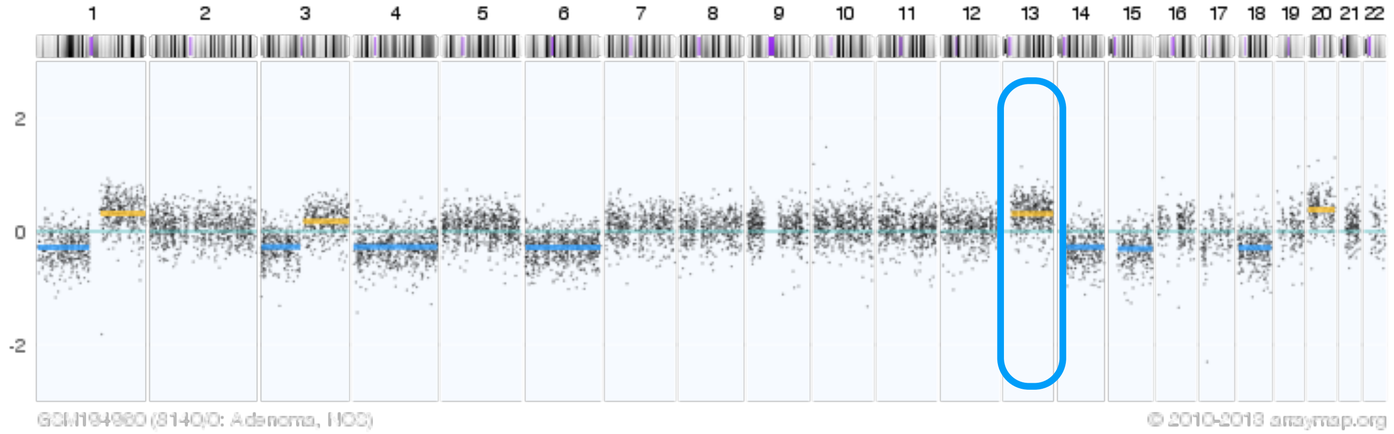




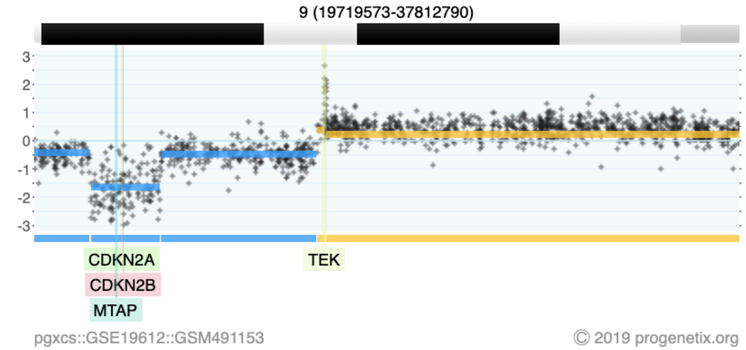


	chromosomal CGH	genomic arrays	"NGS" genome sequencing (WES, WGS)
1st application report	**1992**	**1997**	**2010**
source	DNA (paraffin, micro-dissected ...)	DNA (paraffin, micro-dissected ...)	DNA (paraffin, micro-dissected ...)
main source problems	mixed/degraded source tissue	mixed/degraded source tissue	mixed/degraded source tissue
resolution	chromosomal bands = few megabases	mostly in the 100kb range, but tiling possible	single bases
target identification	surrogate (position)	"semidirect" (segmentation spanning probes)	direct quantitative and qualitative
structural	no	depending on type	yes
available data	>24,000 cases (57%) through **Progenetix**	raw data repositories (GEO, EMBL, SMD), **Progenetix**	Limited for rax data (BAMs ...); variant call data in dbgap, clinvar; selected studies with called CNV segments
predominant data format	ISCN = static	raw => depends on bioinformatics	mostly annotated variant calls or SNVs

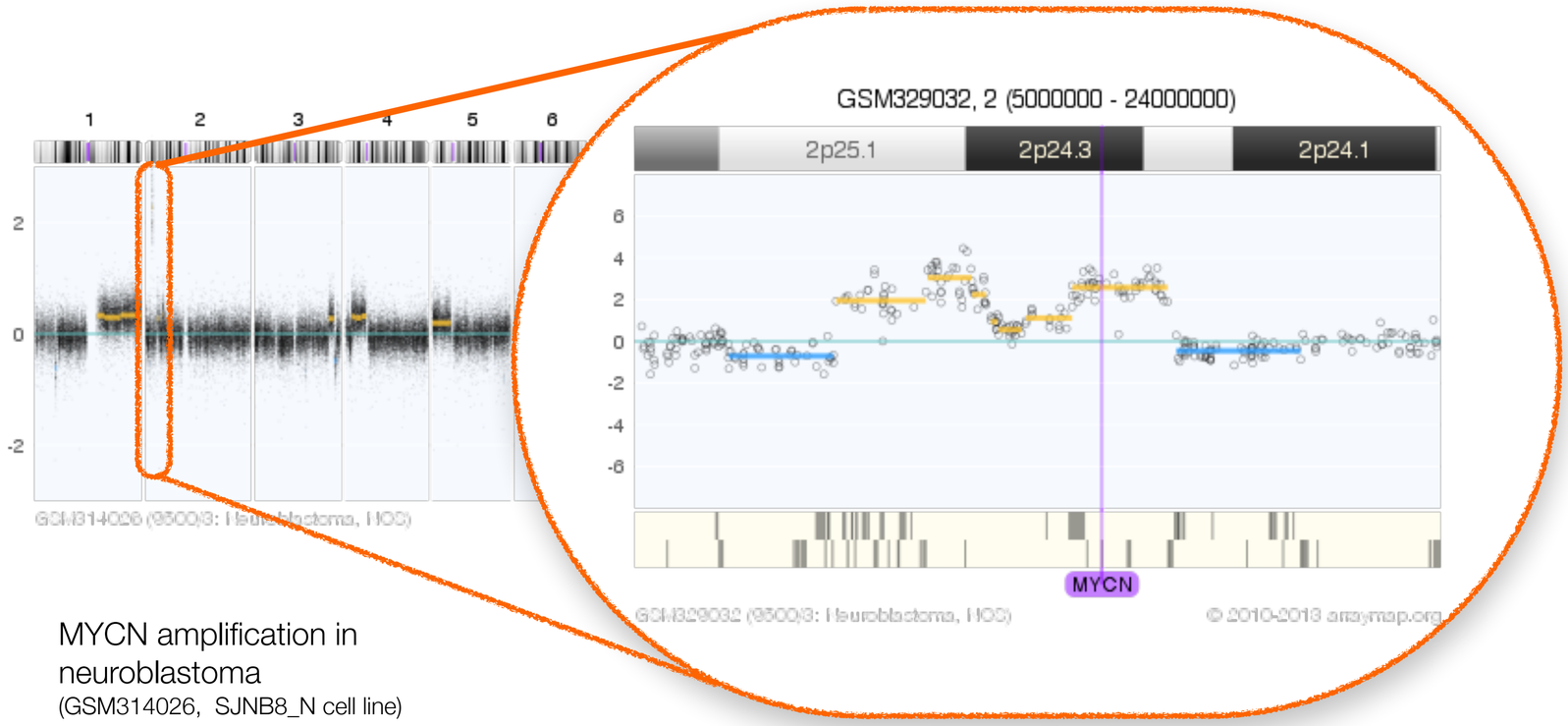
Somatic Copy Number Variations



Gain of chromosome arm 13q in colorectal carcinoma



2-event, homozygous deletion in a Glioblastoma

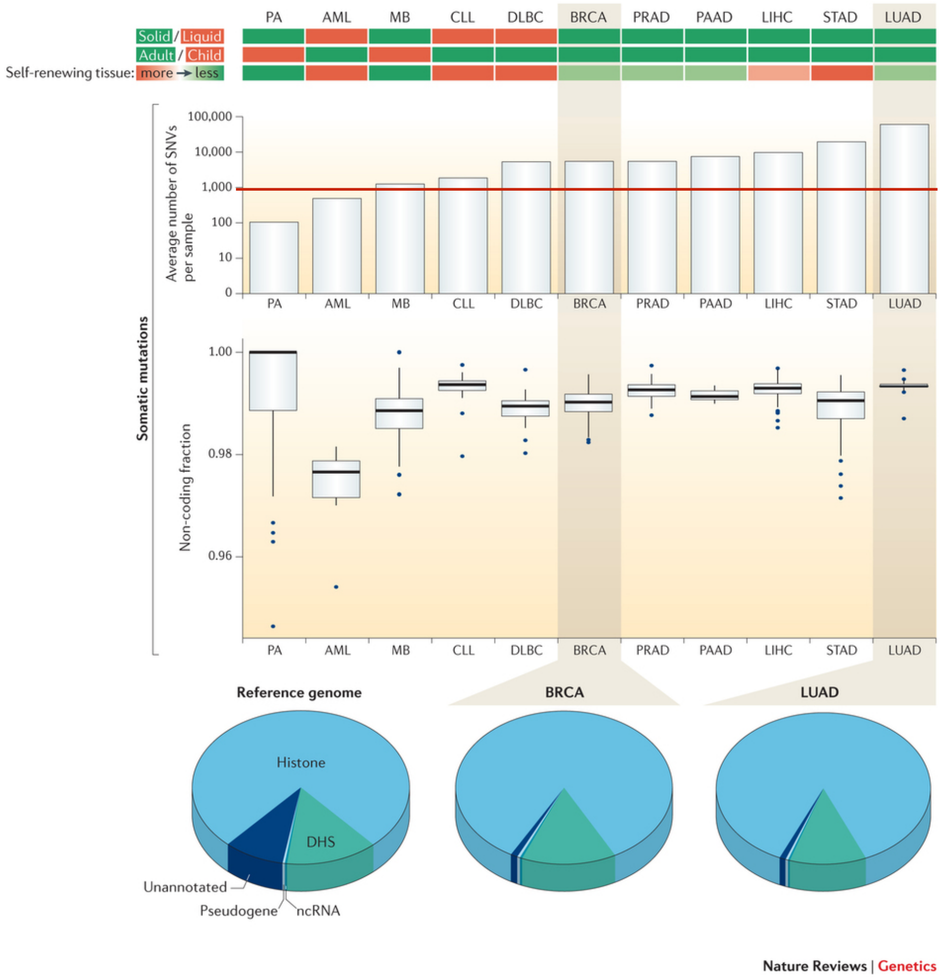


MYCN amplification in neuroblastoma
(GSM314026, SJNB8_N cell line)

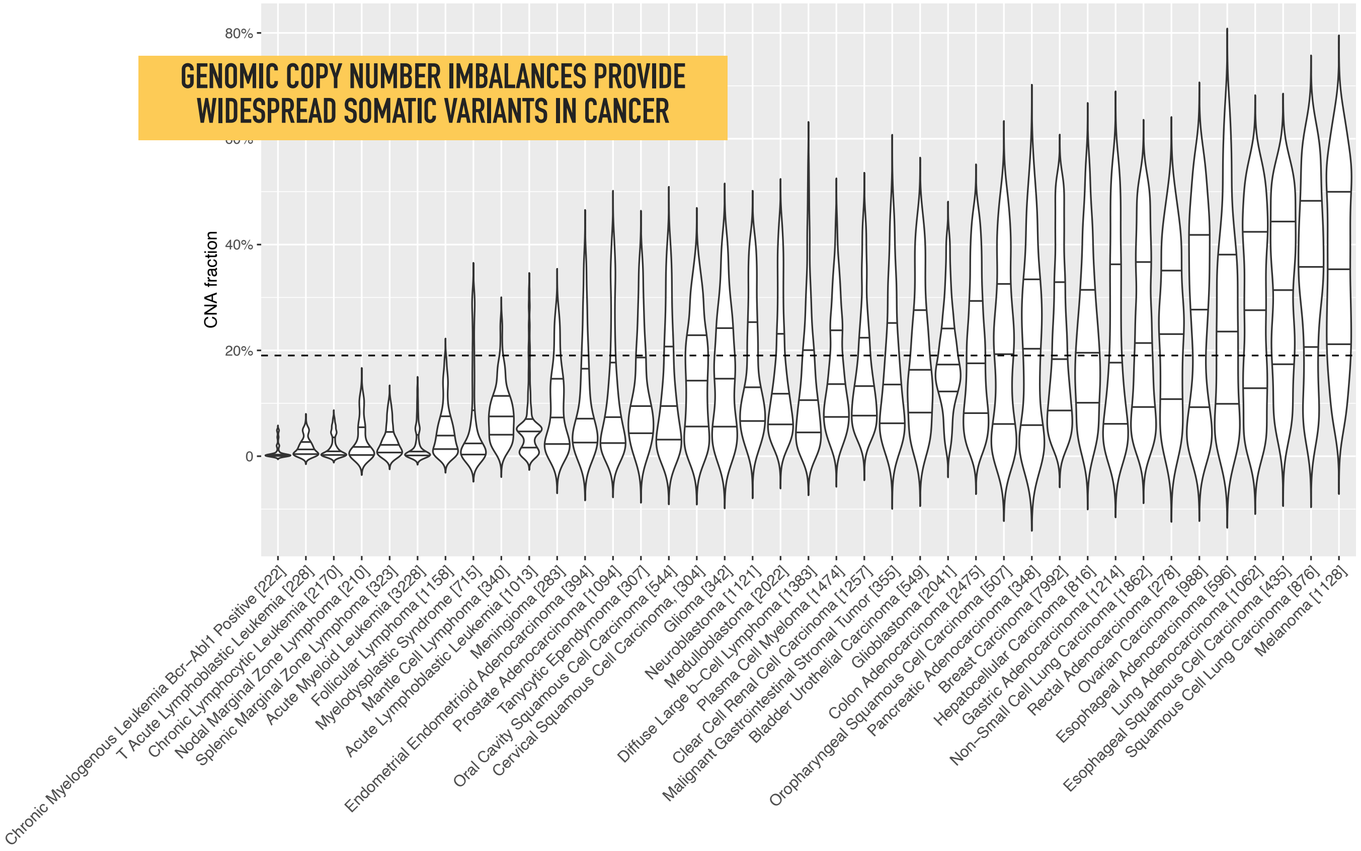
low level/**high level** copy number alterations (CNAs)

arrayMap

Quantifying Somatic Mutations In Cancer



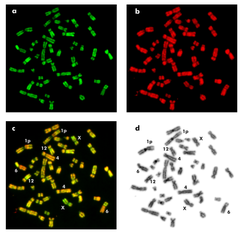
CANCERS SHOW THOUSANDS OF SINGLE NUCLEOTIDE VARIANTS PER SAMPLE, MOSTLY IN NON-CODING REGIONS



Pan-Cancer Analysis of Whole Genomes (PCAWG) data show widespread mutations in non-coding regions of cancer genomes (Khurana et al., Nat. Rev. Genet. (2016)

On average ~19% of a cancer genome are in an imbalanced state (more/less than 2 alleles); Original data based on 43654 cancer genomes from progenetix.org

Comparative Genomic Hybridization



Molecular-Cytogenetic Technology for Genomic Imbalance Screening

- Molecular-cytogenetic technique to identify regional genomic copy number variations (CNV/CNA)
- based on ***in situ*** suppression **hybridization** of labeled **genomic** tumor and reference DNA against a karyotypically normal metaphase chromosomes
- analysis of relative fluorescence ratio allows **semi-quantitative copy number** read-out
- **indirect** attribution of involved target genes through cytogenetic bands (megabase resolution)

- Kallioniemi A, Kallioniemi OP, Sudar D, Rutovitz D, Gray JW, Waldman F, Pinkel D. Comparative genomic hybridization for molecular cytogenetic analysis of solid tumors. Science. 1992;5083:818-821.
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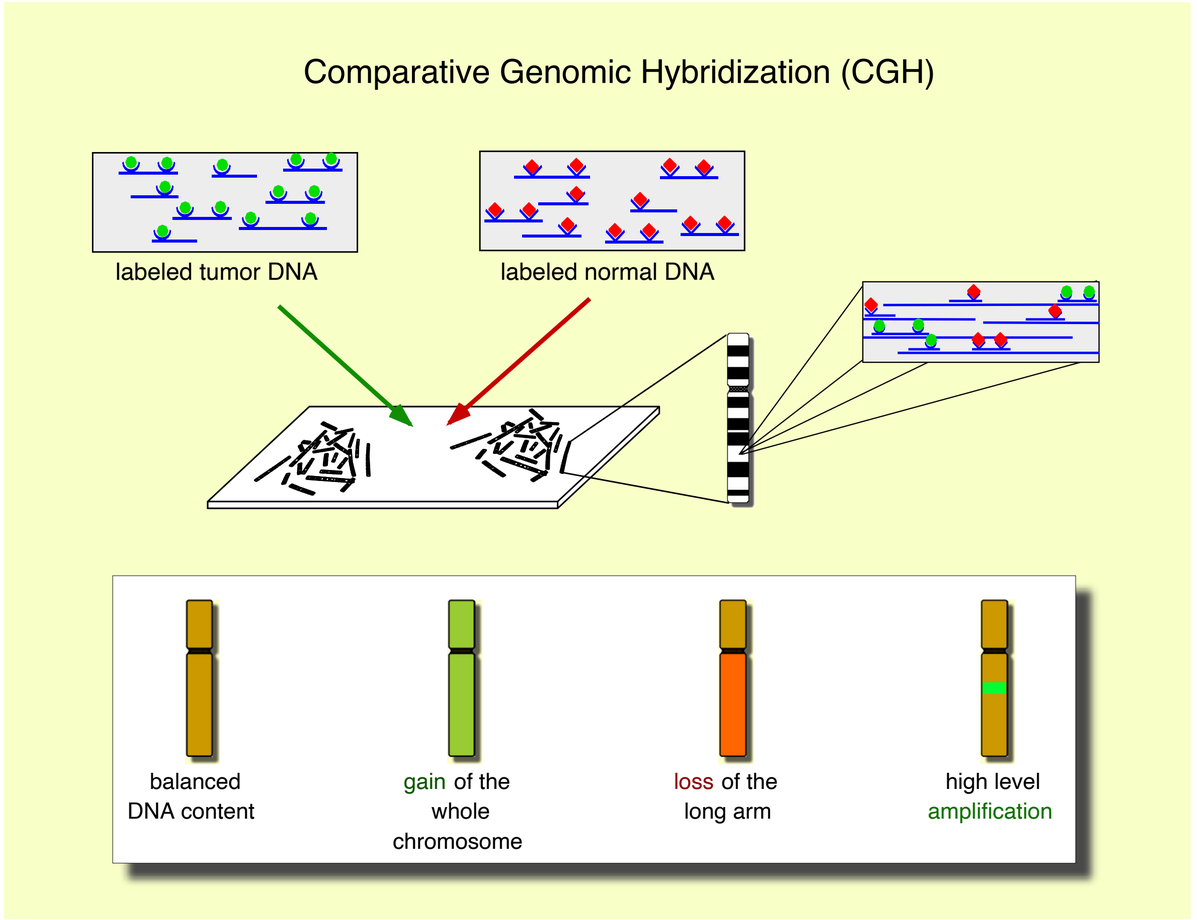

Chromosomal CGH: Normal metaphase spreads (cultured lymphocytes from healthy donors) on microscopy slides serve as the hybridization matrix for whole-genome DNA from tumor and reference tissue, labeled with different fluorophores. The regional ratio between the two colors points to (relative) changes in the copy number in the tumor DNA. Michael Baudis, 1998

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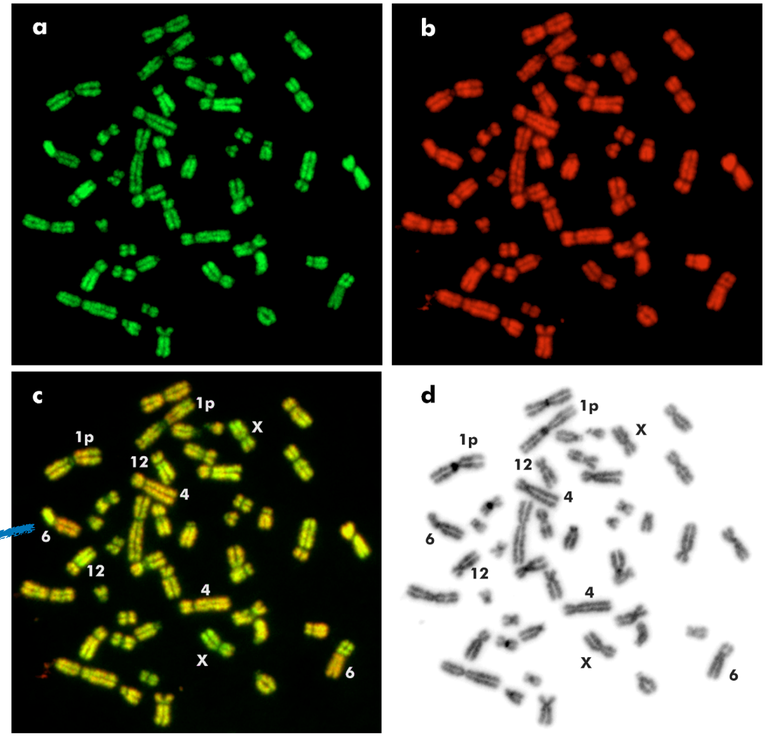
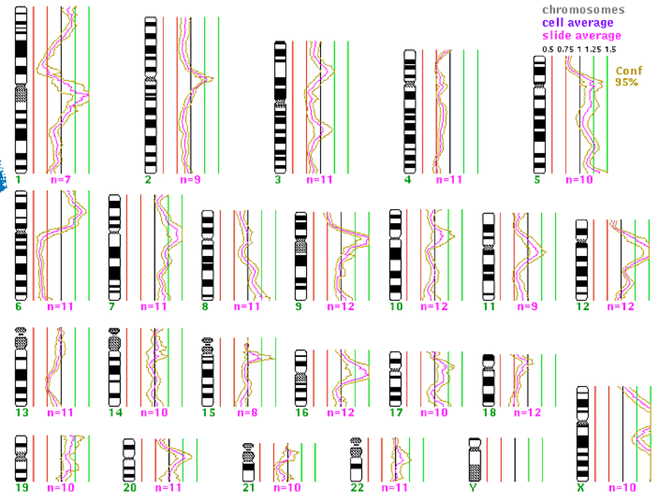


CGH-Experiment: **a** Hybridisierung mit Tumor-DNA; **b** Hybridisierung mit normaler menschlicher DNA als Kontrolle; **c** Überlagerung der Signale; **d** Bänderungsfärbung zur Identifizierung der Chromosomen



Auswertung: Summationsprofil der computergestützten Analyse mehrerer Metaphasen des dargestellten Falles; die Profilausschläge stehen für Zugewinne bzw. Verluste von chromosomalen Anteilen im Tumorgenom

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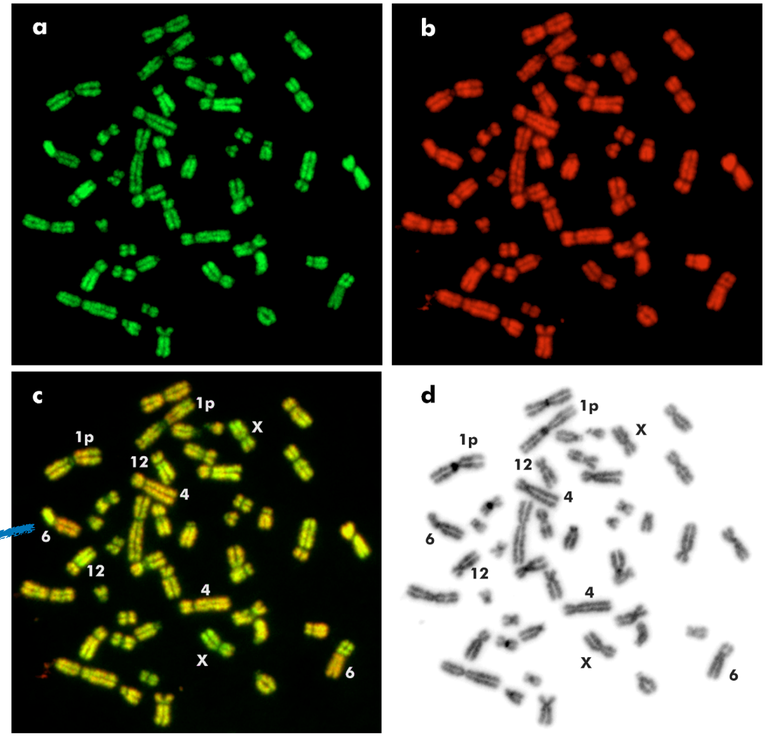

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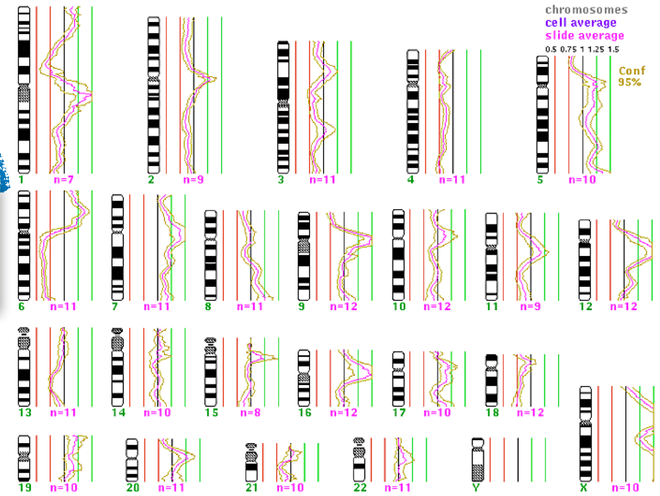
+6p, -6q...



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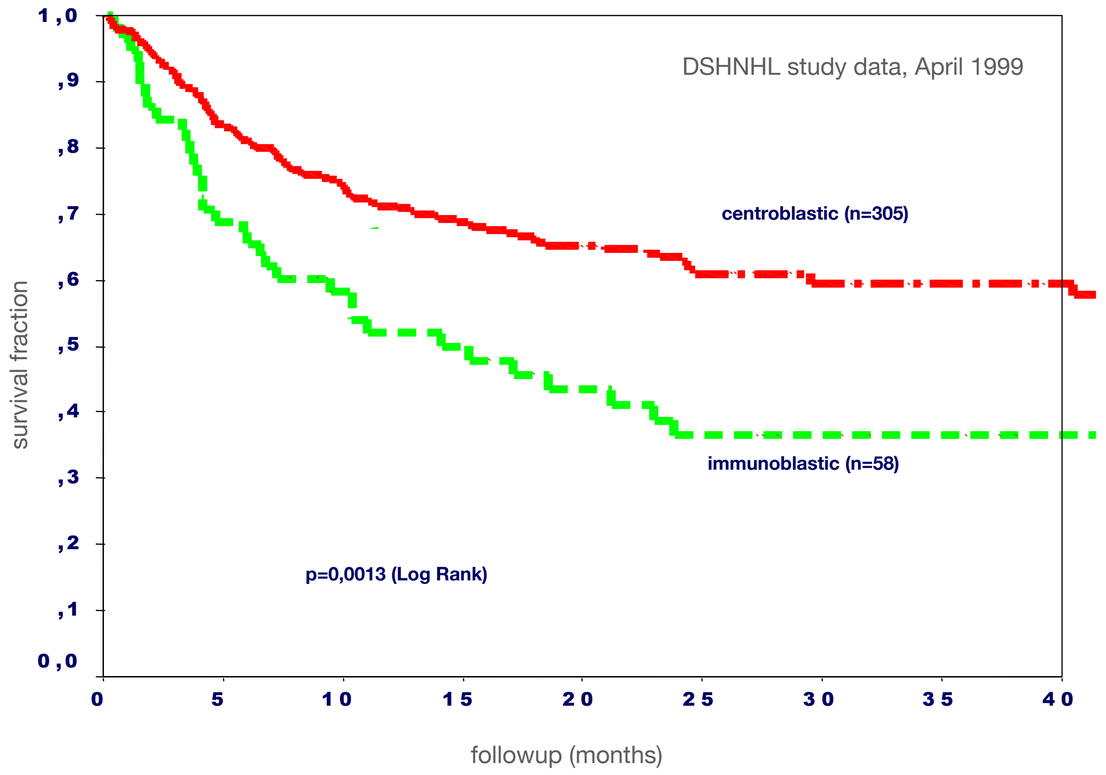
Cancer CNVs | Diagnostics | Prognosis

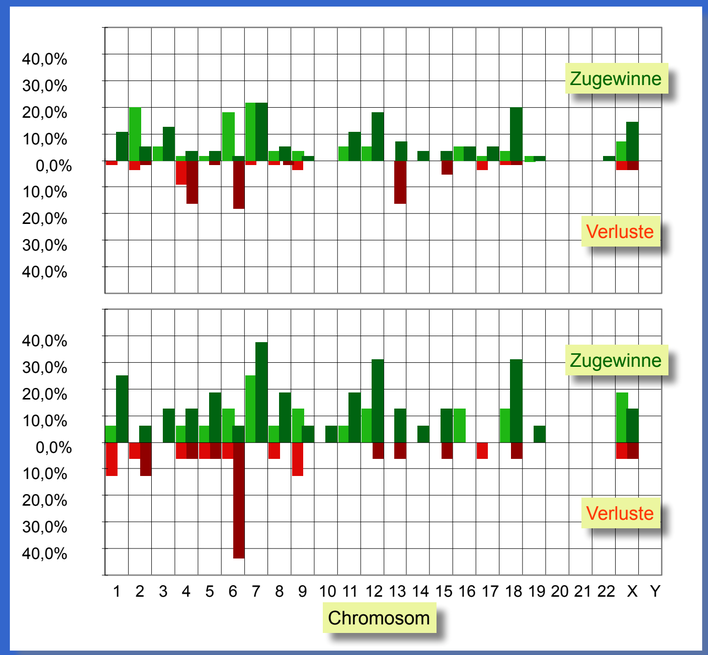
Single-study CNV frequencies correspond to diagnostic subsets



55 cb NHL

Chromosomale Imbalancen

16 ib NHL



dilbert.com | Tuesday February 27, 1996

Let's build a database!

... using archaic tools

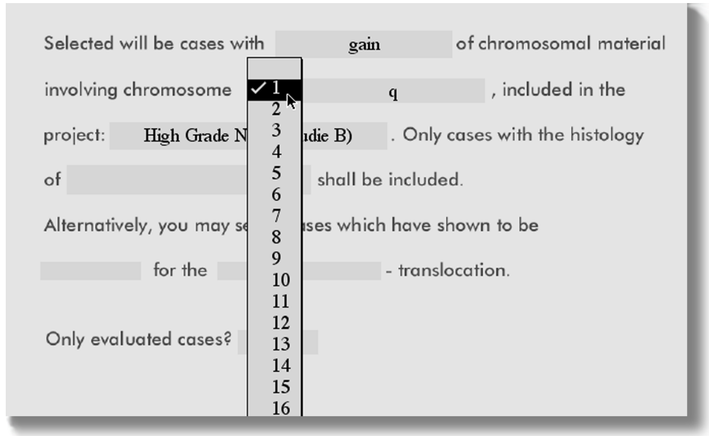
dilbert.com | Tuesday September 08, 1992

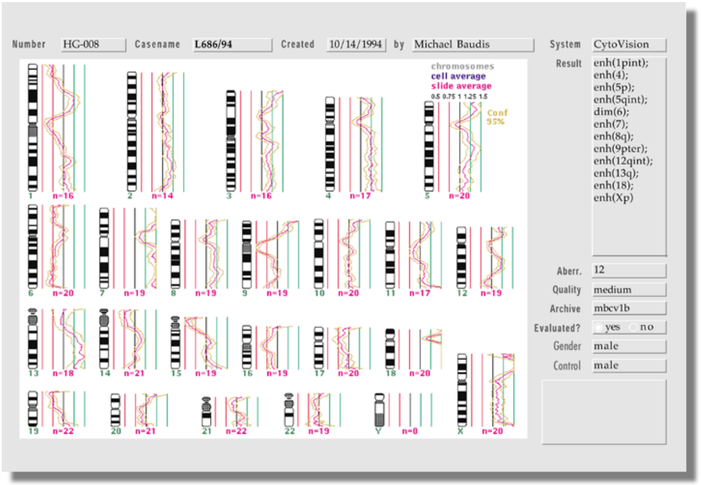
Progenetix CGH Database and Website

HEIDELBERG UNIVERSITY HOSPITAL

dkfz.

- originally an internal FileMaker Pro database, to store CGH profiles and annotations for the "Organization of Complex Genomes" group (head: Peter Lichter) at the German Cancer Research Center (DKFZ), starting in 1998
- expansion to include literature derived data, with a focus on malignant non-Hodgkin's lymphomas
- in 2000 online version



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Registry Domain ID: 45628826_DOMAIN_NET-VRSN
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Registrar URL: http://www.epag.de
Updated Date: 2019-06-01T04:20:49Z
Creation Date: 2000-11-29T18:17:38Z
```

- Dec 6, 2000
  - first time online
- Nov 30, 2000
  - addition of graphical representation and gene table
- Nov 17, 2000
  - generation of website layout and database automatisation

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

michael baudis, md

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

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

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

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

Data selection

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

Transformation of input data

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

Data storage

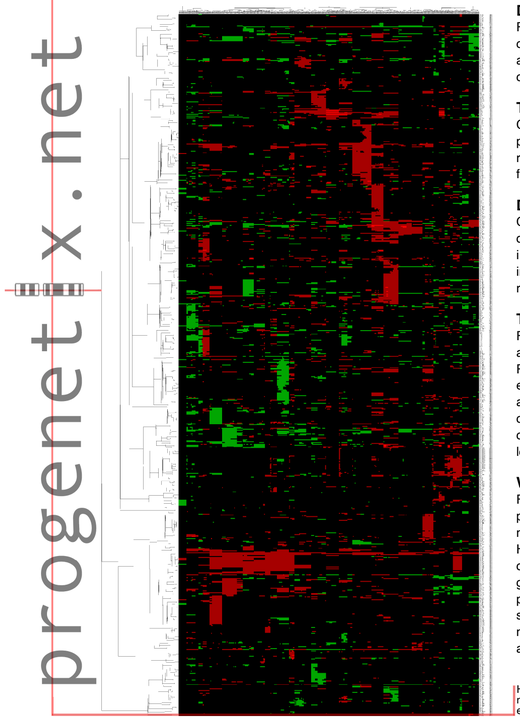
Currently, the primary data is stored in a dedicated “off-line” database. Besides case identifier and ISCN adapted chromosomal imbalance data, tumor classification and source information including the PubMed identifier is recorded. Disease entities are reclassified to ICD-O-3 codes.

Text parsing and generation of aberration matrix

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

Website generation

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



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

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

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

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ABSTRACT

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

Availability: http://www.progenetix.net

Contact: mbaudis@stanford.edu

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

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

In addition to metaphase analysis of short-term cultivated tumor cells or tumor cell lines, molecular cytogenetic techniques have recently been applied to the analysis of chromosomal abnormalities in primary tumor tissues. One of the more widely used screening techniques is Comparative Genomic Hybridization (CGH; Kallioniemi *et al.*, 1992; du Manoir *et al.*, 1993). Briefly, this method is based on the competitive *in-situ* hybridization of differentially labeled tumor versus normal genomic DNA to normal human metaphase spreads. The calculation of the intensity ratios of the two fluorochromes gives an overview about relative gains and losses of DNA in the tumor genome with mapping to the respective chromosomal bands. The identification of frequently imbalanced regions in tumor entities may point towards tumor suppressor gene or proto-oncogenes mapping to the respective chromosomal bands. Usually, the result of those experiments is communicated either in text format according to the International System for Cytogenetic Nomenclature (Mitelman, 1995) or graphically, with aberration bars next to chromosomal ideograms for the representation of chromosomal gains and losses.

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

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

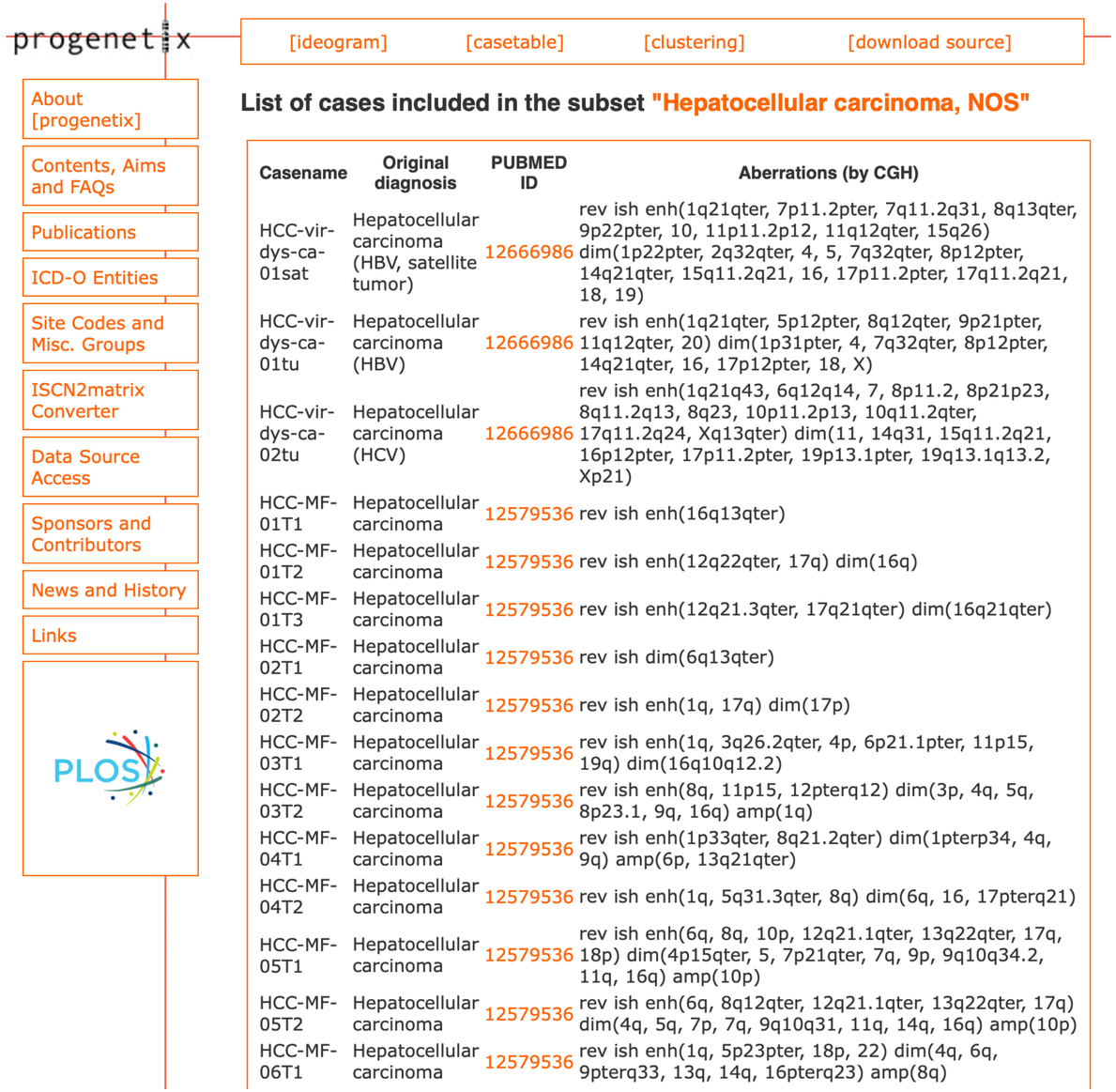
Due to format variations of the published data, step 1 consists of the manual conversion of the text data or evaluation and conversion of the graphical representations, respectively. Due to the (in computational terms) odd

*To whom correspondence should be addressed.

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

Progenetix Database in 2003
Text conversion for CNVs

- based on listed CGH results from publications
  - literature detection using optimized PubMed queries
  - extraction (copy/paste, typing) of rev ish ISCN karyotypes from articles and supplementary material
  - annotation cleanup using scripting with regular expressions (Perl)
  - custom script to convert cleaned ISCN annotations to cytoband status maps
  - custom graphics libraries to create graphical representations of CNV frequencies



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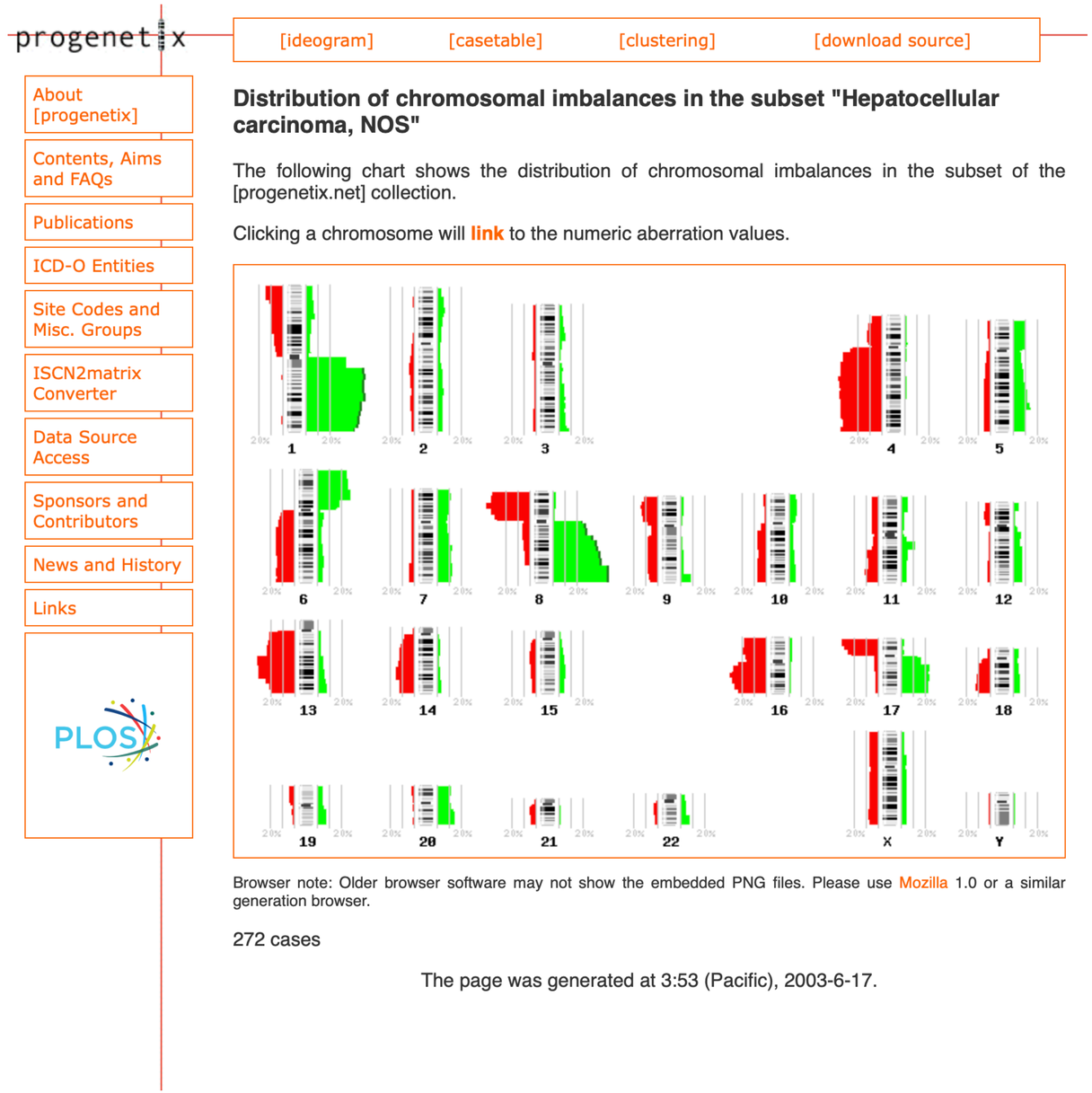


Progenetix Database in 2003
Text conversion for CNVs

- articles and supplements with **cytoband-based** *rev ish* CGH results
- sometimes rich, but **unstructured** associated information
- **PDFs** readable, but **not well suited for data** extraction (character entities, text flow)

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)

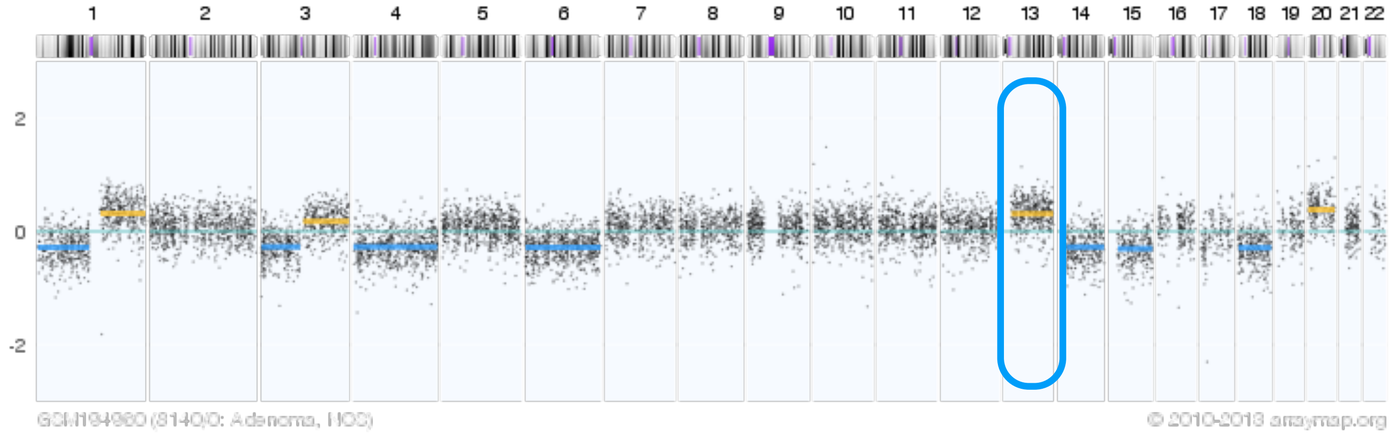
Chromosome Arm 20q Gains and Other Genomic Alterations in Colorectal Cancer Metastatic to Liver, as Analyzed by Comparative Genomic Hybridization and Fluorescence In Situ Hybridization

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]

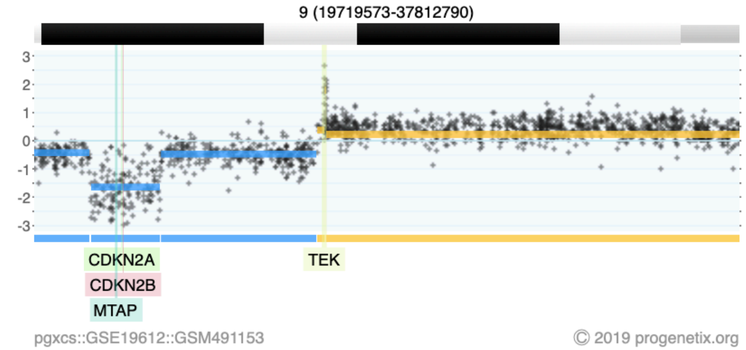
https://progenetix.org/2003-06-17/

progenetix

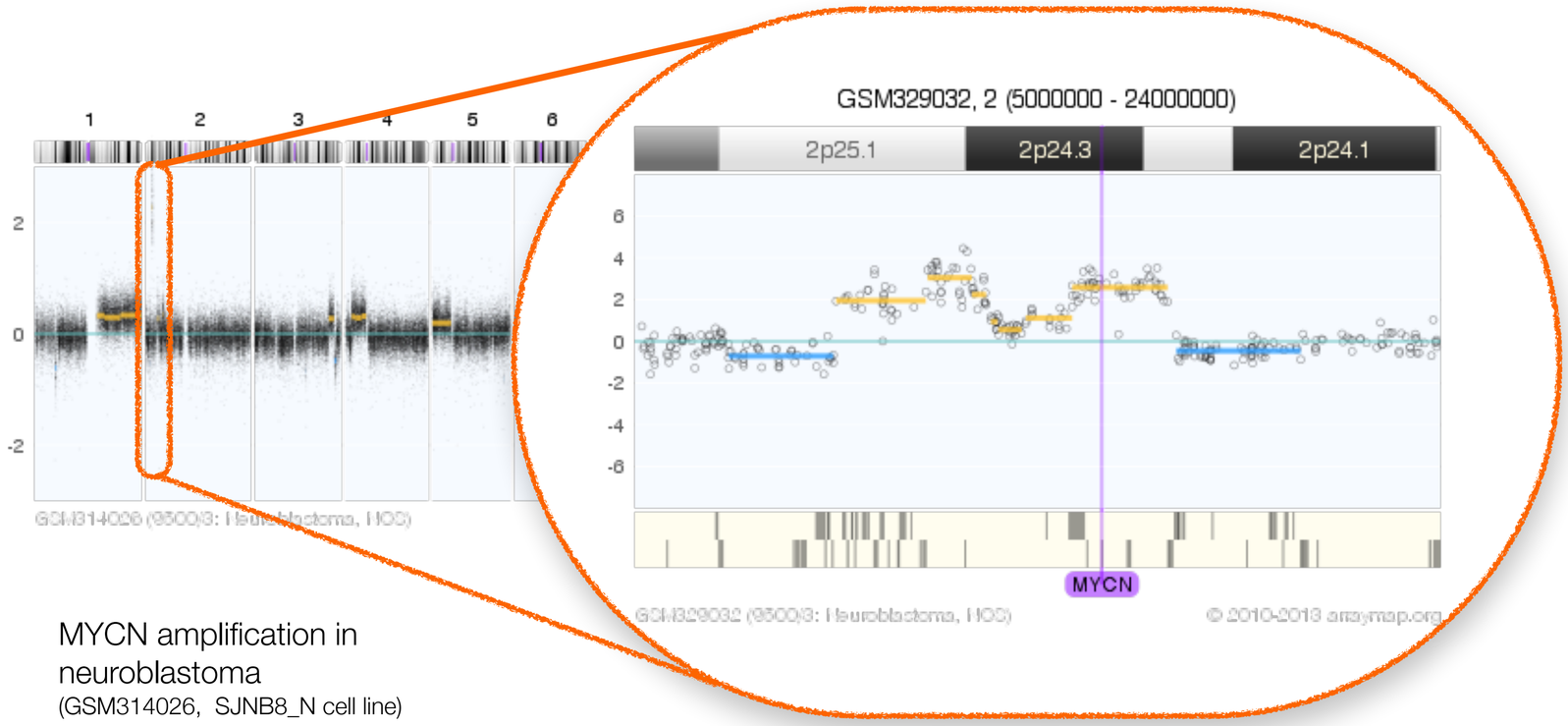
Array-based Detection of Copy Number Variations



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

arrayMap (2012 - 2020)

Probe-Level Genomic Array Data in Cancer

arrayMap

- Search Samples
- Search Publications
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University of Zurich[UZH]

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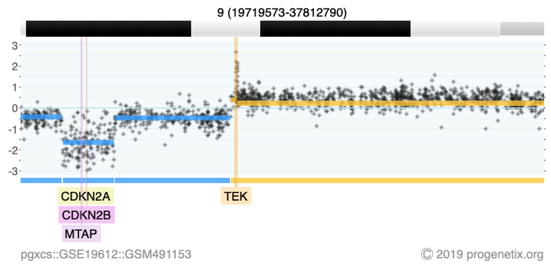
visualizing cancer genome array data @ arraymap.org

arrayMap is a curated reference database and bioinformatics resource targeting copy number profiling data in human cancer. The arrayMap database provides an entry point for meta-analysis and systems level data integration of high-resolution oncogenomic CNA data.

The current data reflects:

- 72724 genomic array profiles
- 898 experimental series
- 257 array platforms
- ICD-O 341 ICD-O cancer entities
- 795 publications (Pubmed entries)



Genomic copy number imbalances on chromosome 9 in a case of Glioblastoma (**GSM491153**), indcating, among others, a homozygous deletion involving CDKN2A/B.

For the majority of the samples, probe level visualization as well as customized data representation facilitate gene level and genome wide data review. Results from multi-case selections can be connected to downstream data analysis and visualization tools, as we provide through our Progenetix project.

arrayMap is developed by the group "Theoretical Cytogenetics and Oncogenomics" at the Institute of Molecular Life Sciences of the University of Zurich.

RELATED PUBLICATIONS

Cai H, Gupta S, Rath P, Ai N, Baudis M. arrayMap 2014: an updated cancer genome resource. Nucleic Acids Res. 2015 Jan;43(Database issue). Epub 2014 Nov 26.

Cai, H., Kumar, N., & Baudis, M. 2012. arrayMap: A Reference Resource for Genomic Copy Number Imbalances in Human Malignancies. *PLoS One* 7(5), e36944.

Baudis, M. 2007. Genomic imbalances in 5918 malignant epithelial tumors: An explorative meta-analysis of chromosomal CGH data. *BMC Cancer* 7:226.

Baudis, M. 2006. Online database and bioinformatics toolbox to support data mining in cancer cytogenetics. *Biotechniques* 40, no. 3: 296-272.

Baudis, M, and ML Cleary. 2001. Progenetix.net: an online repository for molecular cytogenetic aberration data. *Bioinformatics* 12, no. 17: 1228-1229.

Feel free to use the data and tools for academic research projects and other applications. If more support and/or custom analysis is needed, please contact Michael Baudis regarding a collaborative project.

UID	SERIESID	PMID	ICDMORPHOLOGYCODE	ICDTOPOGRAPHYCODE
GSM1000061	GSE36942	23457519	8070/3	C10
GSM1000062	GSE36942	23457519	8070/3	C10
GSM1001316	GSE40777	23571474	8070/3	C53
GSM1001317	GSE40777	23571474	8010/3	C34
GSM1001318	GSE40777	23571474	8070/3	C09
GSM1001319	GSE40777	23571474	8010/3	C34
GSM1002668	GSE40834	24047479	9823/3	C42
GSM1002669	GSE40834	24047479	9823/3	C42
GSM1002670	GSE40834	24047479	9823/3	C42
GSM1002671	GSE40834	24047479	9823/3	C42
GSM1002672	GSE40834	24047479	9823/3	C42
GSM1002673	GSE40834	24047479	9823/3	C42
GSM1002674	GSE40834	24047479	9823/3	C42
GSM1002675	GSE40834	24047479	9823/3	C42
GSM1002676	GSE40834	24047479	9823/3	C42
GSM1002677	GSE40834	24047479	9823/3	C42
GSM1002678	GSE40834	24047479	9823/3	C42
GSM1002679	GSE40834	24047479	9823/3	C42
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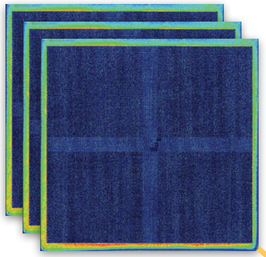
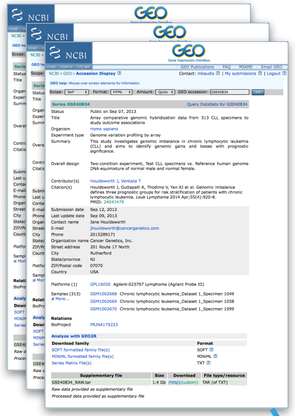
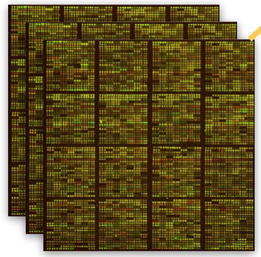
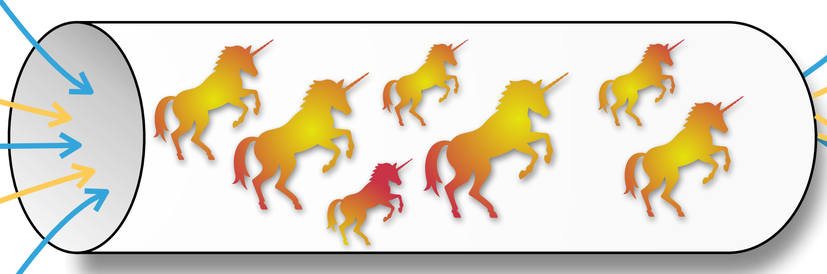
arrayMap

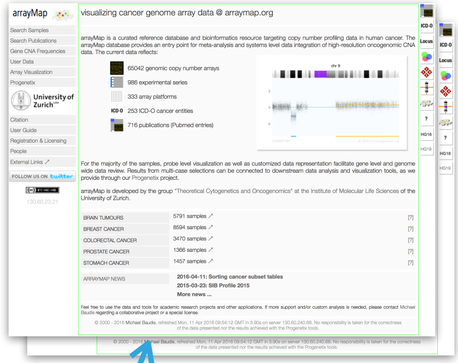
DATA PIPELINE

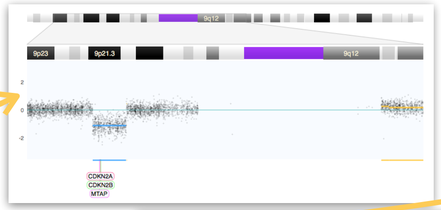


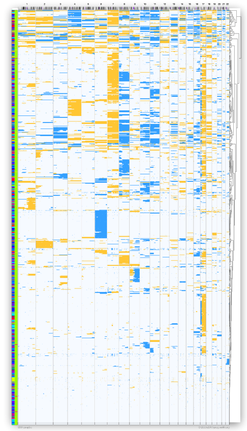


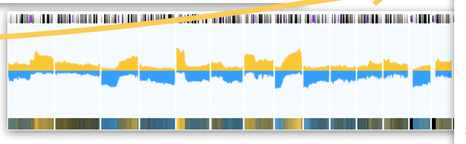


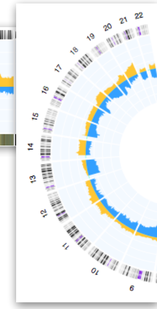


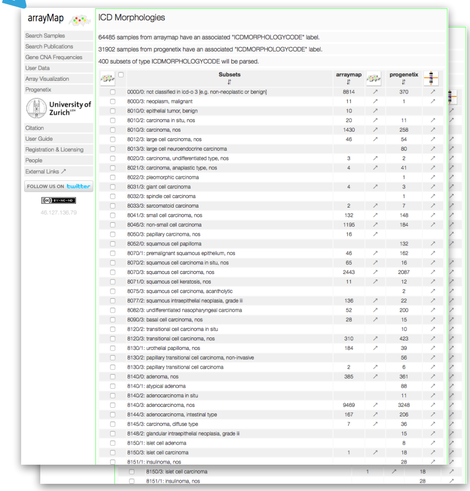












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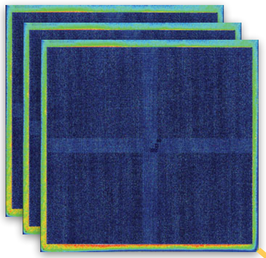
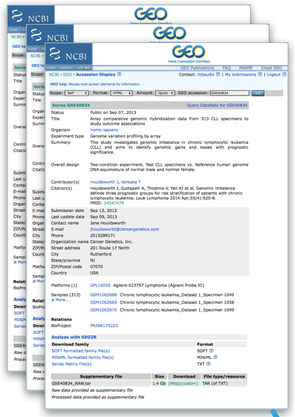
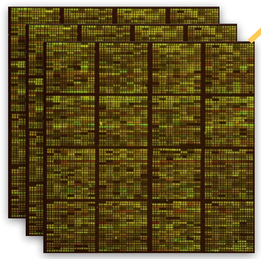
DATA PIPELINE

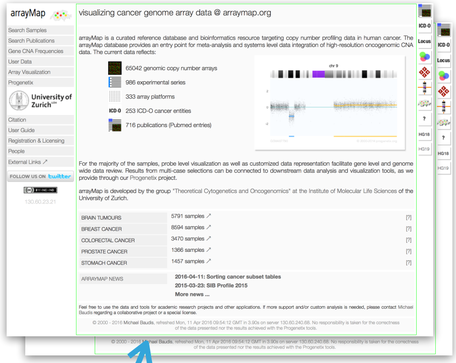
BIOCURATION

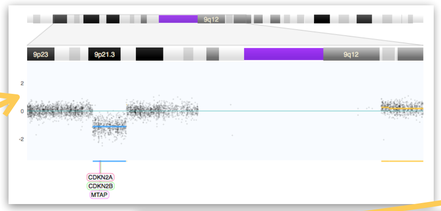
BIOINFORMATICS

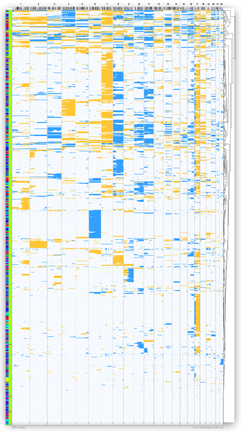


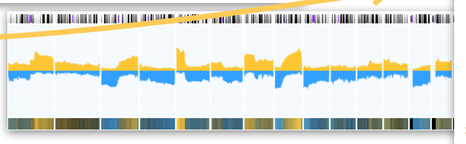


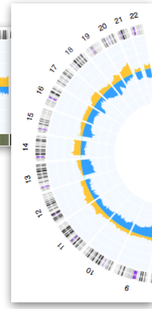


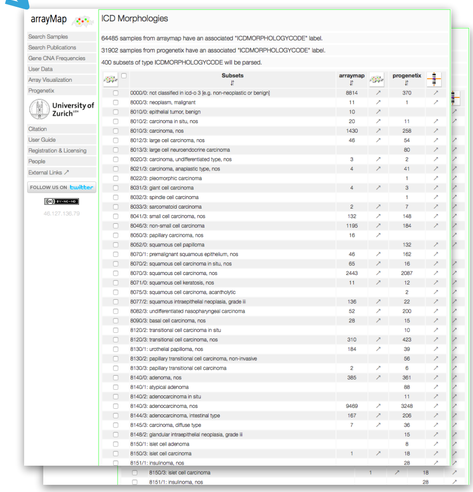












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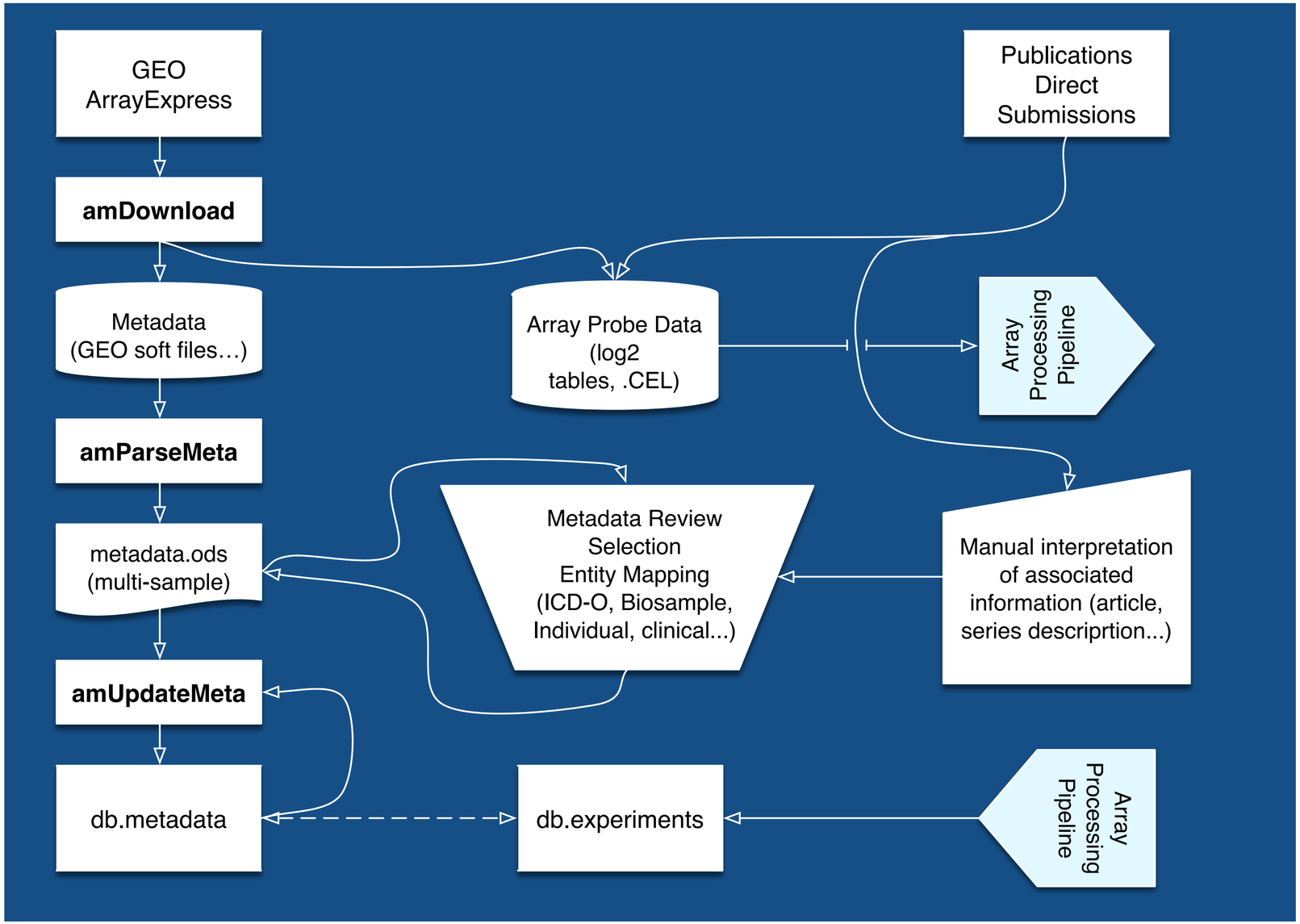
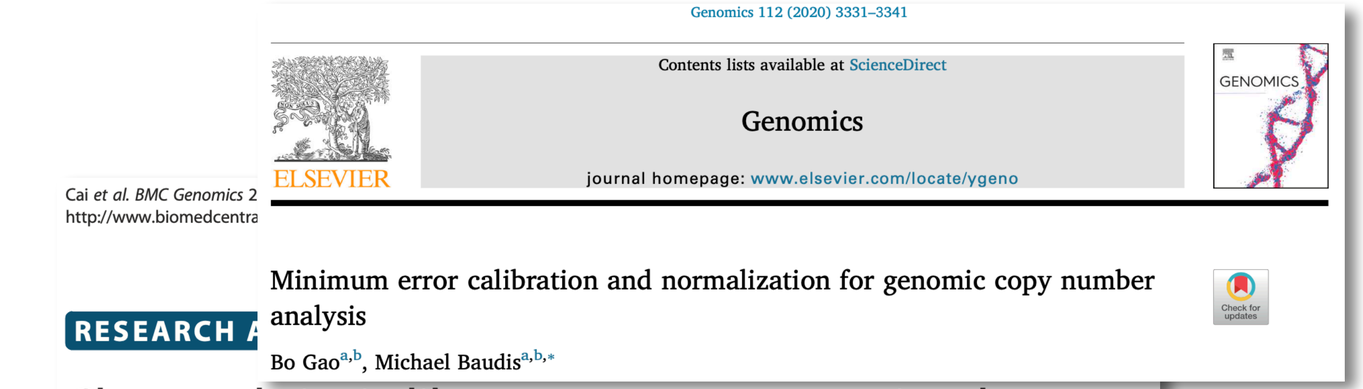
Bioinformatics & Data Curation - arrayMap data “Pipeline”



Recent Publications

CNV Data Analysis & Methods

- collaborative projects utilizing the Progenetix data for multi-omics analyses
- data and bioinformatics analysis support for e.g. translational studies w/o "omics" focus



Progenetix & arrayMap: Data Scopes

Biomedical and procedural "Meta"data types

- Diagnostic classification
  - mapping text-based cancer diagnoses to standard classification systems
- Provenance data
  - store identifier-based pointers
  - geographic attribution (individual, biosample, experiment)
- Clinical information
  - **core set** of typical cancer study values:

    ➡ stage, grade, followup time, survival status, genomic sex, age at diagnosis
  - balance between annotation effort and expected usability

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Data sets in tutorials

Data sets in the wild

Cancer Classifications need an Einstein to sort them out

University of Zurich[UZH]

ARRAYID	NCIT:CODE	NCIT:TERMID	MORPHOLOGYCODE	ICDTOPOGRAPHYCODE
GSM393758	C2773	Acute Myeloid Leukemia Not Otherwise Specified	9861/3	C42
GSM302275	C2852	Adenocarcinoma	8140/3	C34
GSM918983	C3222	Medulloblastoma	9470/3	C7169
GSM551398	C4017	Ductal Breast Carcinoma	8500/3	C50
GSM412374	C3163	Chronic Lymphocytic Leukemia	9823/3	C42
GSM121826	C4017	Ductal Breast Carcinoma	8500/3	C50
GSM714412	C2852	Adenocarcinoma	8140/3	C569
GSM110923	C9306	Soft Tissue Sarcoma	8800/3	C499
GSM711848	C2852	Adenocarcinoma	8140/3	C25
GSM746794	C89476		8077/2	C53
GSM198528	C4017	Ductal Breast Carcinoma	8500/3	C50
GSM271399	C7949		8500/2	C50
GSM533469	C9349	Plasmacytoma	9731/3	C42

Data Curation - Happy RegExing!

Extracting clinical and technical metadata from GEO SOFT file

```
^SAMPLE = GSM174832
!Sample_title = 9194
!Sample_geo_accession = GSM174832
!Sample_status = Public on May 01 2007
!Sample_submission_date = Mar 13 2007
!Sample_last_update_date = Mar 13 2007
!Sample_type = genomic
!Sample_channel_count = 1
!Sample_source_name_ch1 = Bone marrow with 96% blasts
!Sample_organism_ch1 = Homo sapiens
!Sample_taxid_ch1 = 9606
!Sample_characteristics_ch1 = Immunotype: common ALL; Age: 9.2 yrs; Gender: F
!Sample_molecule_ch1 = genomic DNA
!Sample_extract_protocol_ch1 = QiaAmp purification kit (Qiagen)
!Sample_label_ch1 = biotin
!Sample_label_protocol_ch1 = Biotinylated DNA was prepared according to the standard Affymetrix protocol from 250 ng genomic DNA (Genechip Mapping 500k assay
manual 701930 Rev.3 or 100k assay manual 701684 Rev.3, Affymetrix).
!Sample_hyb_protocol = Hybridizations were performed according to the standard Affymetrix protocol from 250 ng genomic DNA (Genechip Mapping 500k assay manual
701930 Rev.3 or 100k assay manual 701684 Rev.3, Affymetrix) using an Affymetrix hybridisation oven 640 and an Affymetrix Fluidic station 450.
!Sample_scan_protocol = Scanning performed according to the standard Affymetrix protocol from 250 ng genomic DNA (Genechip Mapping 500k assay manual 701930 Rev.3
or 100k assay manual 701684 Rev.3, Affymetrix) using an Affymetrix scanner 3000.
!Sample_description = primary ALL diagnosis sample
!Sample_data_processing = copy number detection using CNAG2.0 software (http://www.genome.umin.jp/)
!Sample_platform_id = GPL3718
!Sample_contact_name = Roland,P.,Kuiper
!Sample_contact_email = r.kuiper@antrg.umcn.nl, e.verwiel@antrg.umcn.nl
!Sample_contact_phone = +31243610868
!Sample_contact_fax = +31243668752
!Sample_contact_department = Human Genetics
!Sample_contact_institute = Radboud University Nijmegen Medical Centre
!Sample_contact_address = Geert Grooteplein 10
!Sample_contact_city = Nijmegen
!Sample_contact_zip/postal_code = 6525GA
!Sample_contact_country = Netherlands
!Sample_supplementary_file = ftp://ftp.ncbi.nlm.nih.gov/geo/samples/GSM174nnn/GSM174832/suppl/GSM174832.CEL.gz
```

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Data Curation - Happy RegExing!

Extracting clinical and technical metadata from GEO SOFT file

```
^SAMPLE = GSM174832
!Sample_title = 9194
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!Sample_label_ch1 = biotin
!Sample_label_protocol_ch1 = Biotinylated DNA was prepared according to the sta
manual 701930 Rev.3 or 100k assay manual 701684 Rev.3, Affymetrix).
!Sample_hyb_protocol = Hybridizations were performed according to the standard
701930 Rev.3 or 100k assay manual 701684 Rev.3, Affymetrix) using an Affymetrix
!Sample_scan_protocol = Scanning performed according to the standard Affymetrix
or 100k assay manual 701684 Rev.3, Affymetrix) using an Affymetrix scanner 3000
!Sample_description = primary ALL diagnosis sample
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!Sample_contact_email = r.kuiper@antrg.umcn.nl, e.verwiel@antrg.umcn.nl
!Sample_contact_phone = +31243610868
!Sample_contact_fax = +31243668752
!Sample_contact_department = Human Genetics
!Sample_contact_institute = Radboud University Nijmegen Medical Centre
!Sample_contact_address = Geert Grooteplein 10
!Sample_contact_city = Nijmegen
!Sample_contact_zip/postal_code = 6525GA
!Sample_contact_country = Netherlands
!Sample_supplementary_file = ftp://ftp.ncbi.nlm.nih.gov/geo/samples/GSM174nnn/GSM174832/suppl/GSM174832.CEL.gz
```

```perl
foreach (grep { ! /characteristics_ch\d/ } @in) {
    my ($key, $value) = split(' = ', $_);
    $key =~ s/[^\w]/_/g;
    if ($key =~ /submission_date/i) {
        $sample->{ YEAR } = $value;
        $sample->{ YEAR } =~ s/^.*?(\d\d\d\d)$/\1/;
    }
```

```perl
$mkey->{ samplekey } = 'AGE';
$mkey->{ matches } = [ qw( age )];

( $mkey->{ retv }, $mkey->{ retk } ) = _grepmeta( $mkey, $meta );

if ($mkey->{ retv } =~ /^(.+?)$/) {
    if ($mkey->{ retv } =~ /month/i) {
        $mkey->{ retk } .= '_months';
        $mkey->{ retv } =~ s/[^\d\.]//g;
    }

    $sample->{ $mkey->{ samplekey } } = _normNumber($mkey->{ retv });
    if ($mkey->{ retk } =~ /month/i) { $sample->{ $mkey->{ samplekey } } /= 12 }
    if ($sample->{ $mkey->{ samplekey } } == 0) { $sample->{ $mkey->{ samplekey } } = 'NA' }
    $sample->{ $mkey->{ samplekey } } = sprintf "%.2f", $sample->{ $mkey->{ samplekey } };
}
```

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Data Curation - Happy RegExing!

Extracting clinical and technical metadata from GEO SOFT file

```
^SAMPLE = GSM286922
!Sample_title = 481 - mAdbID:75320
!Sample_geo_accession = GSM286922
!Sample_status = Public on Sep 04 2008
!Sample_submission_date = May 06 2008
!Sample_last_update_date = Nov 26 2008
!Sample_type = genomic
!Sample_channel_count = 2
!Sample_source_name_ch1 = Normal Lymphocytes
!Sample_organism_ch1 = Homo sapiens
!Sample_taxid_ch1 = 9606
!Sample_characteristics_ch1 = Tissue: lymphocytes
!Sample_molecule_ch1 = genomic DNA
!Sample_extract_protocol_ch1 = Sample DNA Extraction Protocol
!Sample_extract_protocol_ch1 = Other: The DNA was isolated by Qiagen DNe
!Sample_label_ch1 = cy5
!Sample_label_protocol_ch1 = Nimblegen Cy5 Sample Labeling Protocol
!Sample_label_protocol_ch1 = Other: Proprietary protocol information available at http://www.nimblegen.com/technology/index.html
!Sample_source_name_ch2 = 481
!Sample_organism_ch2 = Homo sapiens
!Sample_taxid_ch2 = 9606
!Sample_characteristics_ch2 = Gender: male
!Sample_characteristics_ch2 = Age: 49
!Sample_characteristics_ch2 = Tissue: lymph node
!Sample_characteristics_ch2 = Disease state: Lymphoma
!Sample_characteristics_ch2 = Individual: 481
!Sample_characteristics_ch2 = Clinical info: Submitting diagnosis: DLBCL
!Sample_characteristics_ch2 = Clinical info: Final microarray diagnosis: ABC DLBCL
!Sample_characteristics_ch2 = Clinical info: Follow up status: ALIVE
!Sample_characteristics_ch2 = Clinical info: Follow up years: 10.75
!Sample_characteristics_ch2 = Clinical info: Chemotherapy: CHOP-Like Regimen
!Sample_characteristics_ch2 = Clinical info: ECOG performance status: 2
!Sample_characteristics_ch2 = Clinical info: Stage: 4
!Sample_characteristics_ch2 = Clinical info: LDH ratio: 0.82
!Sample_characteristics_ch2 = Clinical info: Number of extranodal sites: 1
```

Channel 1 is normal -> Cave value swap!

Gender or "chromosomal sex"?

context indicates years, but if it would be a medulloblastoma...

Not yet registered way to express "alive"!

```
$mkey->{ samplekey } = 'DEATH';
$mkey->{ matches } = [ (
    'death',
    'dead ',
    'vital_status',
    'dead_alive',
    'alive_dead',
) ];

( $mkey->{ retv }, $mkey->{ retk } ) = _grepmeta( $mkey, $meta );

if ($mkey->{ retv } =~ /^(.+?)$/) {
    $sample->{ $mkey->{ samplekey } } = _normDeath($mkey->{ retv }) }
```

Data Curation

Happy RegExing!

Source: https://xkcd.com/208/

```yaml
extraction_scopes:
  description: >-
    Detection and processing of clinical scopes goes through several stages:
    1. line cleanup - so far run for the input before processing the individual
    scopes
    2. line match using sme general pattern expected in all lines containing
    data for the current scope (`filter` pattern)
    3. finding and extracting the relevant data by looping over a list of
    specific patterns with memorized matches (`find`)
    4. post-processing using empirical cleanp replacements (`cleanup`)
    5. checking the correct structure (`final_check` - a global pattern can be
    used if other post-processing is performed)


  survival_status:
    filter: '(?i).*?(?:(?:dea(?:d|th))|alive|surviv|outcome|status)'
    preclean:
      - m: '(?i)days to death or last seen alive[^\w]+?\d+?(?:[^\w\.]|$)'
        s: ''
      - m: '[^\w]+?NA(?:[^\w\.]|$)'
        s: ' '
      - m: 'remission status past double induction .cr. complete remission. RD. refractory disease. ED. early death[^\w]+?ED'
        s: 'survival: dead'
      - m: 'remission status past double induction .cr. complete remission. RD. refractory disease. ED. early death[^\w]+?NA'
        s: ''
      - m: 'remission status past double induction .cr. complete remission. RD. refractory disease. ED. early death[^\w]+?CR'
        s: 'survival: alive'
      - m: 'remission status past double induction .cr. complete remission. RD. refractory disease. ED. early death[^\w]+?RD'
        s: '' # alive but not responding to therapy so removed?
      - m: 'Event Free Survival[^\w]+?no event'
        s: 'recurrence: no'
      - m: 'Event Free Survival.event'
        s: 'recurrence: yes'
      - m: 'Outcome[^\w]+?no event'
        s: 'survival: alive'
      - m: 'Outcome[^\w]+?event'
        s: 'survival: dead'
      - m: 'survival status[^\w]+?0'
        s: 'survival: dead'
      - m: 'survival status[^\w]+?1'
        s: 'survival: alive'
      - m: 'overall[^\w]+?survival[^\w]+?days[^\w]+?NA'
        s: ''
      - m: 'survival(?: time|from diagnosis)?[^\w]+?(days|months|years?)[^\w]+?(\d\d?\d?\d?\.?\d?\d?)'
        s: 'survival: \2\1'
```

Disease annotations in Progenetix

From some text, somewhere, to ontology classes

- **diagnostic categories** are the **most important** labels to associate with genomic observations
- original data almost *never* uses **modern**, **hierarchical** classification systems but provides circumstantial ("breast cancer in pre-menopausal...") or domain-specific ("CLL Binet B", "colorectal carcinoma Dukes C") information
- clinical classifications (ICD-10 ...) have very limited relation to tumor biology
- concepts change over time ...
- for cancer, the "International Classification of Diseases in Oncology" (**ICD-O 3**) by IARC / WHO traditionally has been a good compromise to map to - but with non-hierarchical structure and is used by international reference projects

NCIthesaurus

From Classification to Hierarchical Ontology: ICD-O -> NCIt

example_dx	ICDMORPHOLOGY	ICDOM	ICDTOPOGRAPHY	ICDOT	NCIT:CODE
malignant melanoma [metastatic cell line MaMel19]	Malignant melanoma NOS	8720/3	skin	C44	C3224
malignant melanoma [vagina]	Malignant melanoma NOS	8720/3	vagina and labia	C510	C3224
malignant melanoma [uvea metastasized]	Malignant melanoma NOS	8720/3	retina	C692	C3224
meningioma	Meningioma NOS	9530/0	meninges cerebral spinal	C700	C3230
mesothelioma	Mesothelioma NOS	9050/3	lung and bronchus	C34	C3234
pleural mesothelioma	Mesothelioma NOS	9050/3	pleura	C384	C3234
mesothelioma	Mesothelioma NOS	9050/3	connective and soft tissue NOS	C499	C3234
multiple myeloma	Plasma cell myeloma	9732/3	hematopoietic and reticuloendothelial syste	C42	C3242
Mycosis fungoides	Mycosis fungoides	9700/3	skin	C44	C3246
Myelodysplastic syndrome	Myelodysplastic syndrome NOS	9989/3	hematopoietic and reticuloendothelial syste	C42	C3247
Acute myeloblastic leukemia with maturation [FAB M2]	Acute myeloblastic leukemia with maturation [FAB M2]	9874/3	hematopoietic and reticuloendothelial syste	C42	C3250
neuroblastoma	Neuroblastoma NOS	9500/3	peripheral nervs incl. autonomous	C47	C3270
Cerebral neuroblastoma [cerebral region midline frontal lobe]	Neuroblastoma NOS	9500/3	cerebrum	C710	C3270
neuroblastoma [adrenal gland cell line]	Neuroblastoma NOS	9500/3	adrenal gland	C76	C3270
Cutaneous neurofibroma	Neurofibroma NOS	9540/0	skin	C44	C3272
Plexiform neurofibroma	Neurofibroma NOS	9540/0	Nervous system NOS	C729	C3272
Oligodendroglioma [Supratentorial Frontal Lobe]	Oligodendroglioma NOS	9450/3	cerebrum	C710	C3288
oilgodendroglioma	Oligodendroglioma NOS	9450/3	Brain NOS	C719	C3288
oligodendroglioma	Oligodendroglioma NOS	9450/3	brain nos	c719	C3288
Paraganglioma	Paraganglioma NOS	8680/1	Nervous system NOS	C729	C3308
paraganglioma	paraganglioma NOS	8680/1	adrenal cortex	C740	C3308

- since its beginning Progenetix samples have been classified using the 2 arms of the ICD-O system (morphology ~ histology/biology + topography ~ organ/tissue)
- over the last years we have established mappings between ICD-O code pairs and the NCIt "neoplasm" part of the NCI metathesaurus, thereby empowering hierarchical data structures for search and analysis

DX Ontologies

Hierarchical NCIt Neoplasm Core replaces heterogeneous primary annotations

- heterogeneous and inconsistent diagnostic annotations are common in clinical reports and research studies ("text", ICD-10, ICD-O 3, OncoTree, domain-specific classifications)
- highly **variable granularity** of annotations is a major road block for comparative analyses and large scale data integration
  - "Colorectal Cancer" or "Rectal Mucinous Adenoca."
- initiatives and services such as Phenopackets, MONDO, OXO ... rely on and/or provide mappings to hierarchical ontologies

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NCIt Neoplasm Core coded display (excerpt) for samples in the Progenetix cancer genome data resource allows sample selection on multiple hierarchy levels →

Collapse all | Expand | All

	Subsets	Samples
☐	NCIT:C3262: Neoplasm	88844
☐	NCIT:C3263: Neoplasm by Site	84747
☐	NCIT:C156482: Genitourinary System Neoplasm	11616
☐	NCIT:C156483: Benign Genitourinary System Neoplasm	219
☐	NCIT:C4893: Benign Urinary System Neoplasm	90
☐	NCIT:C4778: Benign Kidney Neoplasm	90
☐	NCIT:C159209: Kidney Leiomyoma	1
☐	NCIT:C4526: Kidney Oncocytoma	82
☐	NCIT:C8383: Kidney Adenoma	7
☐	NCIT:C7617: Benign Reproductive System Neoplasm	129
☐	NCIT:C4934: Benign Female Reproductive System Neoplasm	129
☐	NCIT:C2895: Benign Ovarian Neoplasm	58
☐	NCIT:C4510: Benign Ovarian Epithelial Tumor	58
☐	NCIT:C40039: Benign Ovarian Mucinous Tumor	58
☐	NCIT:C4512: Ovarian Mucinous Cystadenoma	58
☐	NCIT:C4060: Ovarian Cystadenoma	58
☐	NCIT:C4512: Ovarian Mucinous Cystadenoma	58
☐	NCIT:C3609: Benign Uterine Neoplasm	71
☐	NCIT:C3608: Benign Uterine Corpus Neoplasm	71
☐	NCIT:C3434: Uterine Corpus Leiomyoma	71
☐	NCIT:C156484: Malignant Genitourinary System Neoplasm	11171
☐	NCIT:C157774: Metastatic Malignant Genitourinary System Neoplasm	2
☐	NCIT:C146893: Metastatic Genitourinary System Carcinoma	2
☐	NCIT:C8946: Metastatic Prostate Carcinoma	2
☐	NCIT:C164141: Genitourinary System Carcinoma	10561
☐	NCIT:C146893: Metastatic Genitourinary System Carcinoma	2
☐	NCIT:C8946: Metastatic Prostate Carcinoma	2
☐	NCIT:C3867: Fallopian Tube Carcinoma	19

Standardized Data

Data re-use depends on standardized, machine-readable metadata

- Multiple international initiatives (ELIXIR, GA4GH, MONARCH...) and resource providers (EBI, NCBI ...) work on the generation and implementation of data annotation standards
- emerging / established principles are the use of hierarchical coding systems where individual codes are represented as CURIEs
- other formats for non-categorical annotations 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 (e.g. Phenopackets ...)

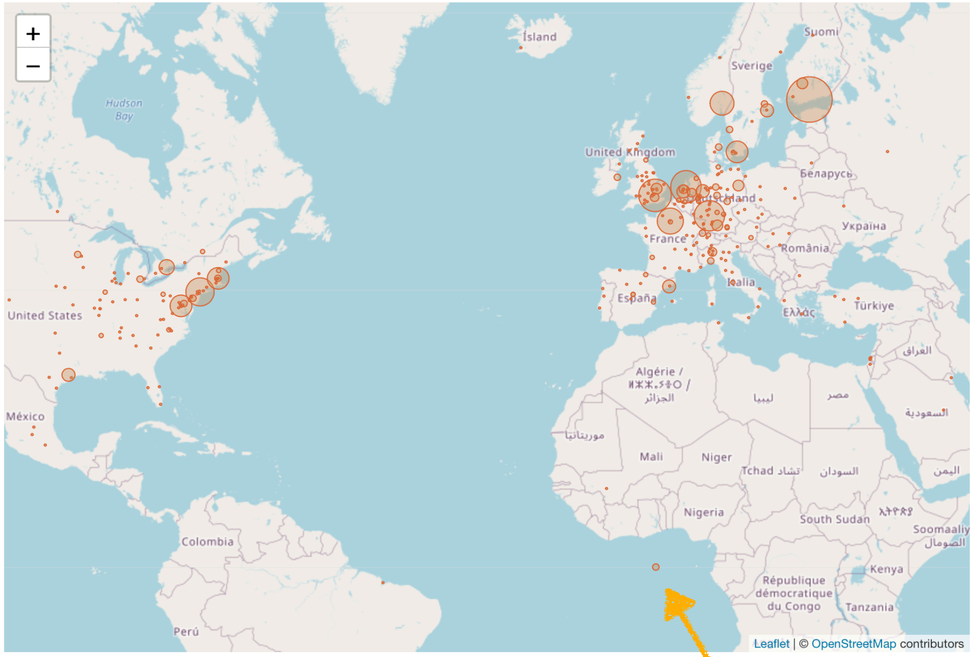

```
    "label" : "no restriction",
    "id" : "DUO:0000004"
  },

  "provenance" : {
    "material" : {
      "type" : {
        "id" : "EFO:0009656",
        "label" : "neoplastic sample"
      }
    },
    "geo" : {
      "label" : "Zurich, Switzerland",
      "precision" : "city",
      "city" : "Zurich",
      "country" : "Switzerland",
      "latitude" : 47.37,
      "longitude" : 8.55,
      "geojson" : {
        "type" : "Point",
        "coordinates" : [
          8.55,
          47.37
        ]
      },
      "ISO-3166-alpha3" : "CHE"
    }
  },
  {
    "age": "P25Y3M2D"
```

Data Curation

Provide "clean and correct data" - but final verification of data from external resources lies with the user ...

- correct data is important for any type of scientific analysis
- errors in formats and values can occur during all steps between data acquisition and analysis (numerous "Excelgates"!)
- "meta"-resources and analyses are prone to erroneous data due to varying input formats and lack of source control

➡ always look for batch effects and outliers!



Geographic distribution (by corresponding author) of the **118554** genomic array, **36766** chromosomal CGH and **42105** whole genome/exome based cancer genome datasets from the **3306** listed publications. Area sizes correspond to the sample numbers reported from a given location.

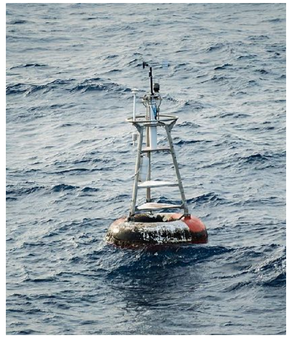
Progenetix publication collection
progenetix.org/publications/list
2020-11-28

25 / 3306 publications

Data Curation - Geolocations

Provide "clean and correct data" - but final verification of data from external resources lies with the user ...

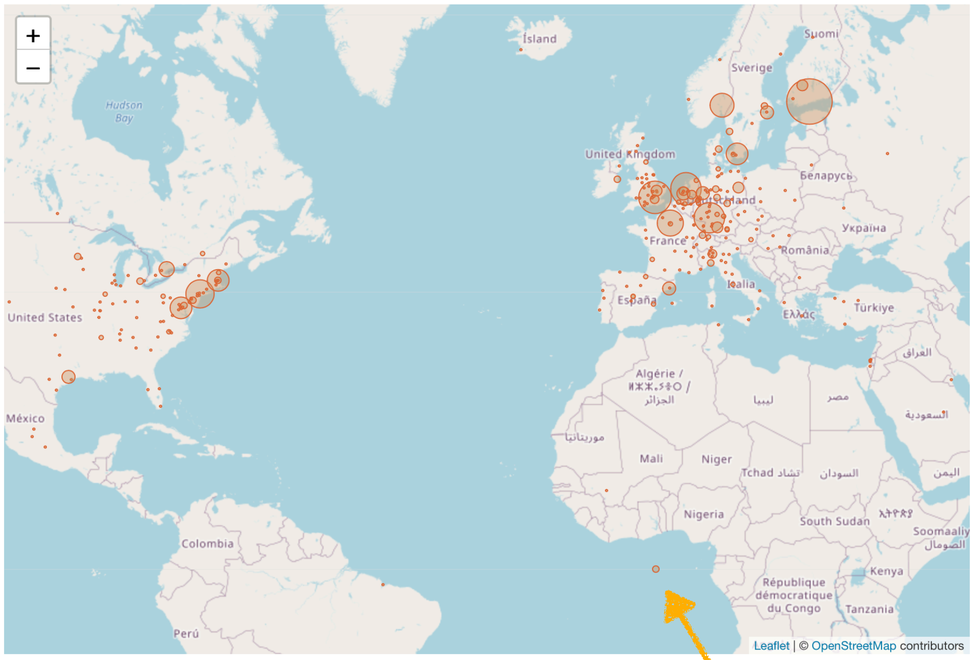
The most geo-tagged place on earth is Null Island



*A troubleshooting country has been added with an Indeterminate sovereignty class called **Null Island (1, 2)**. It is a fictional, 1 meter square island located off Africa where the equator and prime meridian cross. Being centered at 0,0 (zero latitude, zero longitude) it is useful for flagging geocode failures which are routed to 0,0 by most mapping services. Aside: "Null Islands" exist for all local coordinate reference systems besides WGS84 like State Plane (and global if not using modern Greenwich prime meridian). Null Island in Natural Earth is scaleRank 100, indicating it should never be shown in mapping. Side note: Rank 30 (zoom 29 in Google speak)*

https://en.wikipedia.org/wiki/Null_Island

Michael Szell: The Data Science Process 2
http://michael.szell.net/downloads/lecture26_datasciprocess2.pdf
2020-11-25



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Progenetix publication collection
progenetix.org/publications/list
2020-11-28

25 / 3306 publications

Progenetix in 2023

An oncogenomic reference resource

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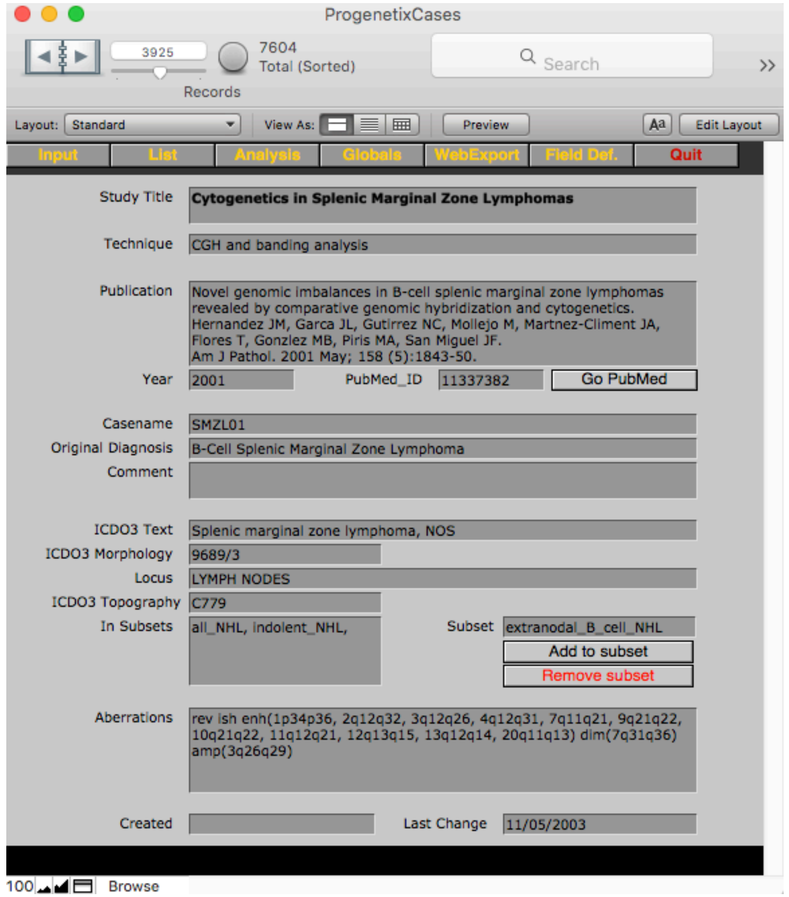
Database Structure

From flat database to hierarchical object storage



Archived version of 2003 "ProgenetixCases" FMP solution

2003

- custom FileMaker database
- text-based annotations
- export & generation of static webpages and data files

2023

- non-SQL document database (MongoDB)
- different object domains connected through identifiers
- data-driven website with JavaScript based frontend and data population through API calls


```
{
  "id" : "pgxind-kftx394x",
  "biocharacteristics" : [
    {
      "description" : "female",
      "type" : {
        "id" : "PATO:0020002",
        "label" : "female genotypic sex"
      }
    },
    {
      "description" : null,
      "type" : {
        "id" : "NCBITaxon:9606",
        "label" : "Homo sapiens"
      }
    }
  ],
  "data_use_conditions" : {
    "label" : "no restriction",
    "id" : "DUO:0000004"
  },
  "geo_provenance" : {
    "label" : "Salamanca, Spain",
    "precision" : "city",
    "city" : "Salamanca",
    "country" : "Spain",
    "latitude" : 40.43,
    "longitude" : -3.68
  },
  "info" : {
    "legacy_id" : "PGX_IND_SMZL01"
  },
  "updated" : ISODate("2018-09-26T09:51:39.775Z")
}

  _
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  {
    "type" : {
      "id" : "icdot-C42.2",
      "label" : "Spleen"
    }
  },
  {
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      "id" : "icdom-96893",
      "label" : "Splenic marginal zone B-cell lymphoma"
    }
  },
  {
    "type" : {
      "id" : "NCIT:C4663",
      "label" : "Splenic Marginal Zone Lymphoma"
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  }
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"individual_id" : "pgxind-kftx394x",
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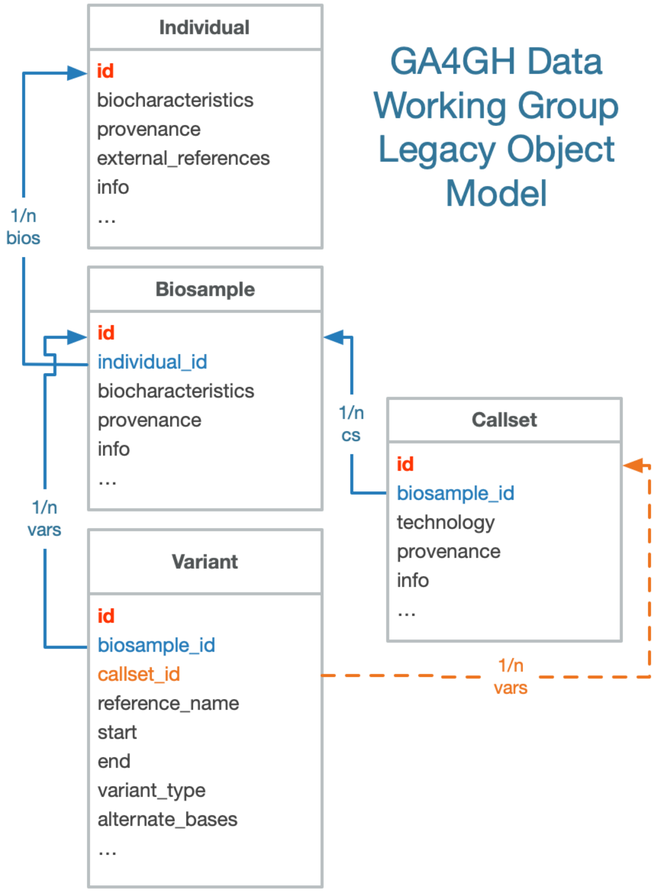
Database Structure

From flat database to hierarchical object storage



GA4GH Data Working Group Legacy Object Model

- collections in Progenetix MongoDB database reflect a consensus domain model for genomic data repositories
- flexible linking and object structure facilitates rapid change-overs
- BSON/JSON format in DB
  - equals data in JavaScript
  - "equals" objects in Python, Perl

➡ **rapid prototyping and implementation**

2023

- non-SQL document database (MongoDB)
- different object domains connected through identifiers
- data-driven website with JavaScript based frontend and data population through API calls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    },
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  _
  "assembly_id" : "GRCh38",
  "digest" : "7:107200000-158821424:DEL",
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  {
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      "id" : "PMID:11337382"
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  }
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  },
  "geo" : {
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    "precision" : "city",
    "city" : "Salamanca",
    "country" : "Spain",
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        40.43
      ]
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    "ISO-3166-alpha3" : "ESP"
  }
},
```

Progenetix in 2023

Cancer Genomics Reference Resource

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- focus on copy number variations (CNV)
- >116'000 cancer CNV profiles, from >800 NCIt codes
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- structured diagnostic encodings for NCIt, ICD-O 3, UBERON
- identifier mapping for PMID, GEO, Cellosaurus, TCGA, cBioPortal where appropriate
- core biosample and technical metadata annotations where accessible (TNM, genotypic sex, survival ...)
- publication database and code mapping services

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Cancer CNV Profiles
- ICD-O Morphologies
- ICD-O Organ Sites
- Cancer Cell Lines
- Clinical Categories

Search Samples

arrayMap
- TCGA Samples
- 1000 Genomes Reference Samples
- DIPG Samples
- cBioPortal Studies
- Gao & Baudis, 2021

Publication DB
- Genome Profiling
- Progenetix Use

Services
- NCIt Mappings
- UBERON Mappings

Upload & Plot

Beacon+

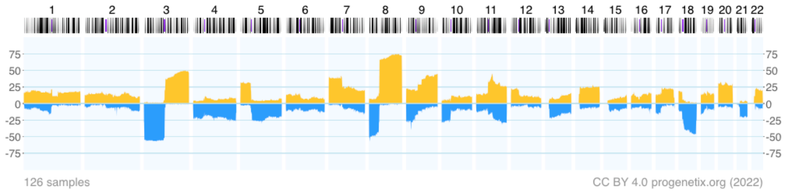
Documentation
- News
- Downloads & Use Cases
- Sevices & API

Baudisgroup @ UZH

Cancer genome data @ progenetix.org

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

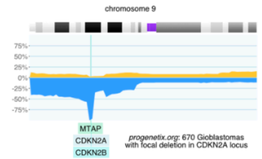
Floor of the Mouth Neoplasm (NCIT:C4401)



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 in 2023

Cancer Genomics Reference Resource

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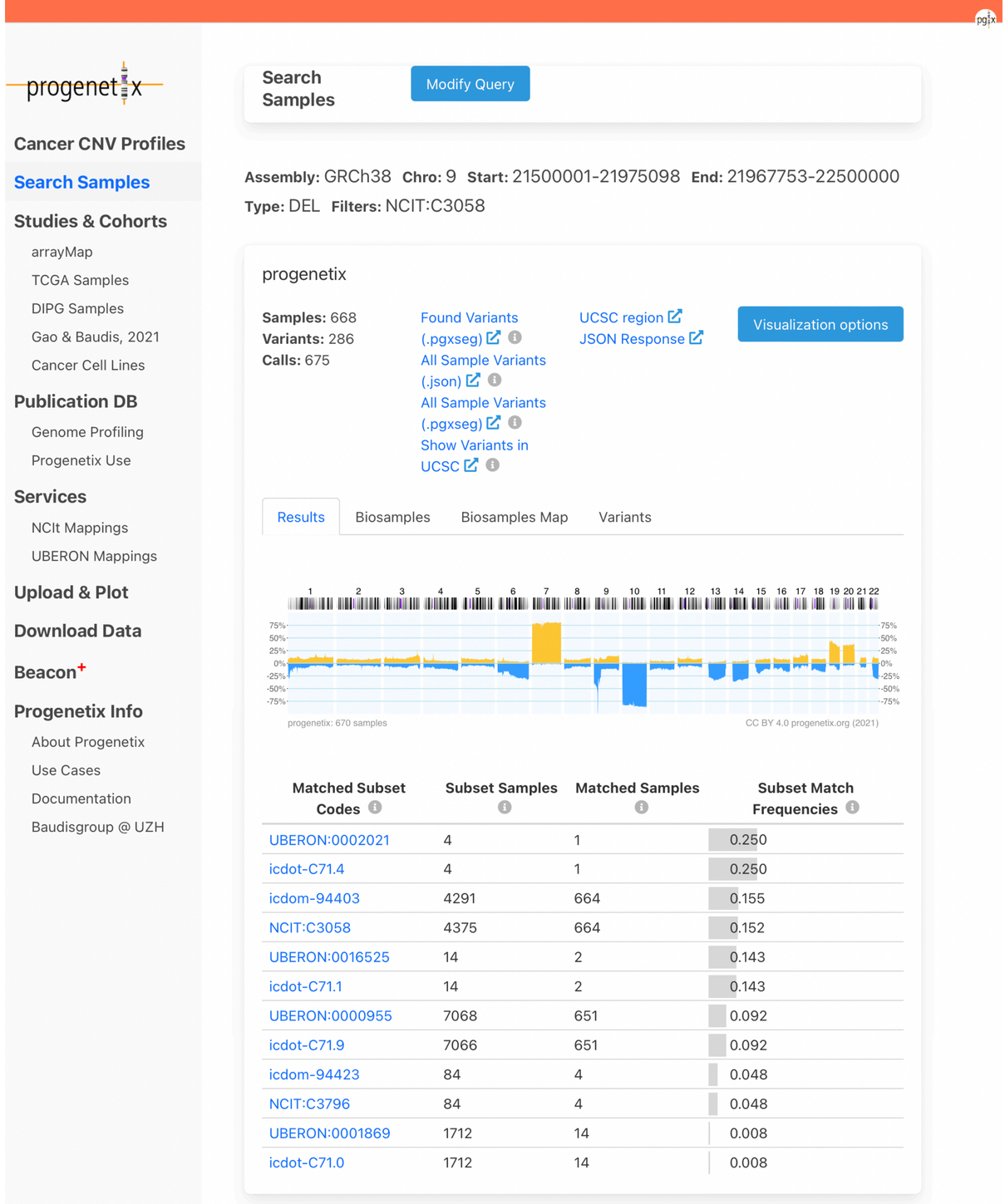
- core biosample and technical metadata annotations where accessible (TNM, genotypic sex, survival ...)
- publication database and code mapping services

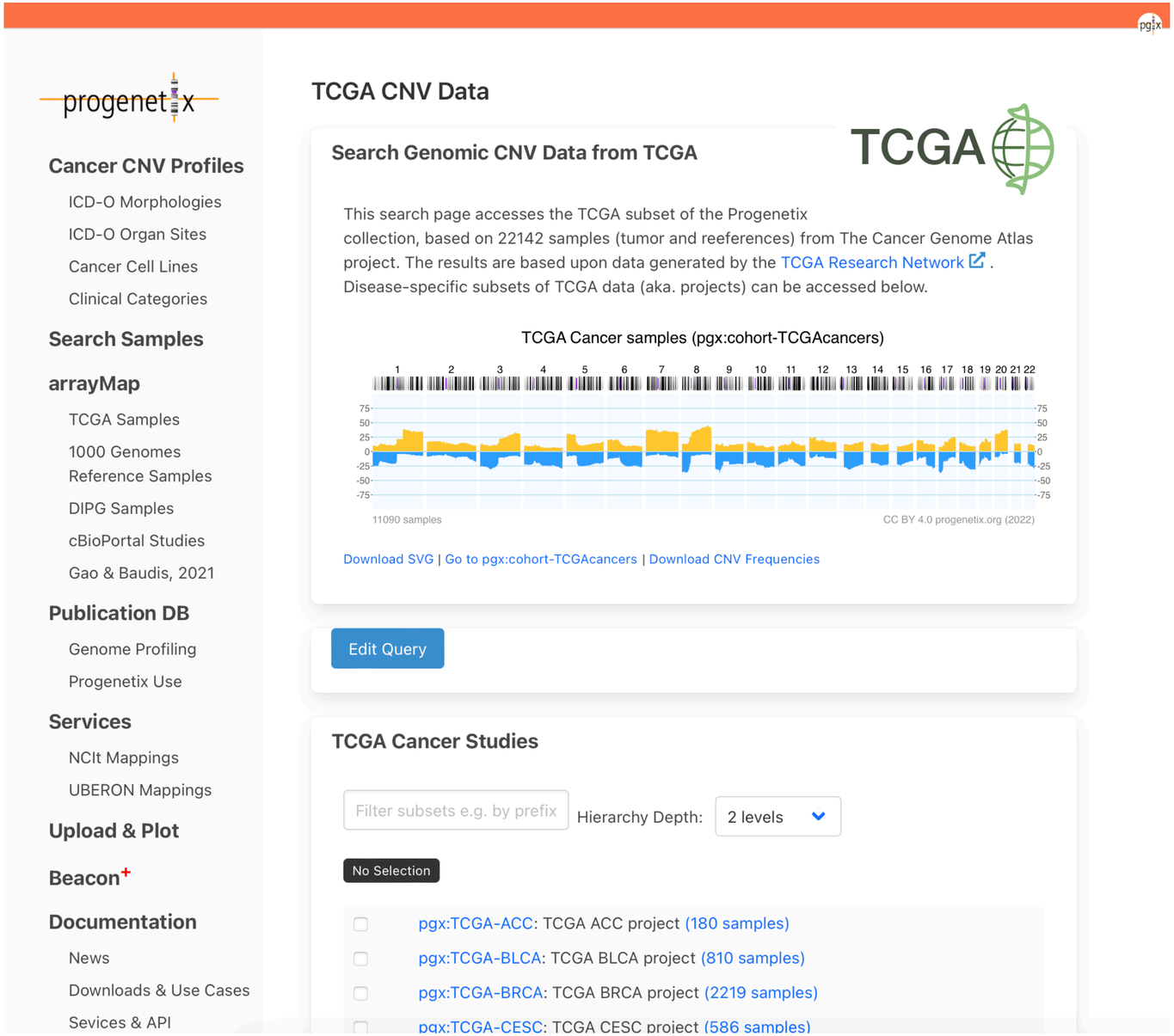
progenetix



Progenetix in 2023

Cancer Genomics Reference Resource

- contains special data subsets, identified using the "cohorts" concept
  - TCGA CNV data
  - 1000Genomes germline CNVs (WGS)
  - Cancer cell line CNVs with upcoming addition of annotated SNV ... data
  - cBioPortal studies
  - ...



progenetix

Progenetix in 2023

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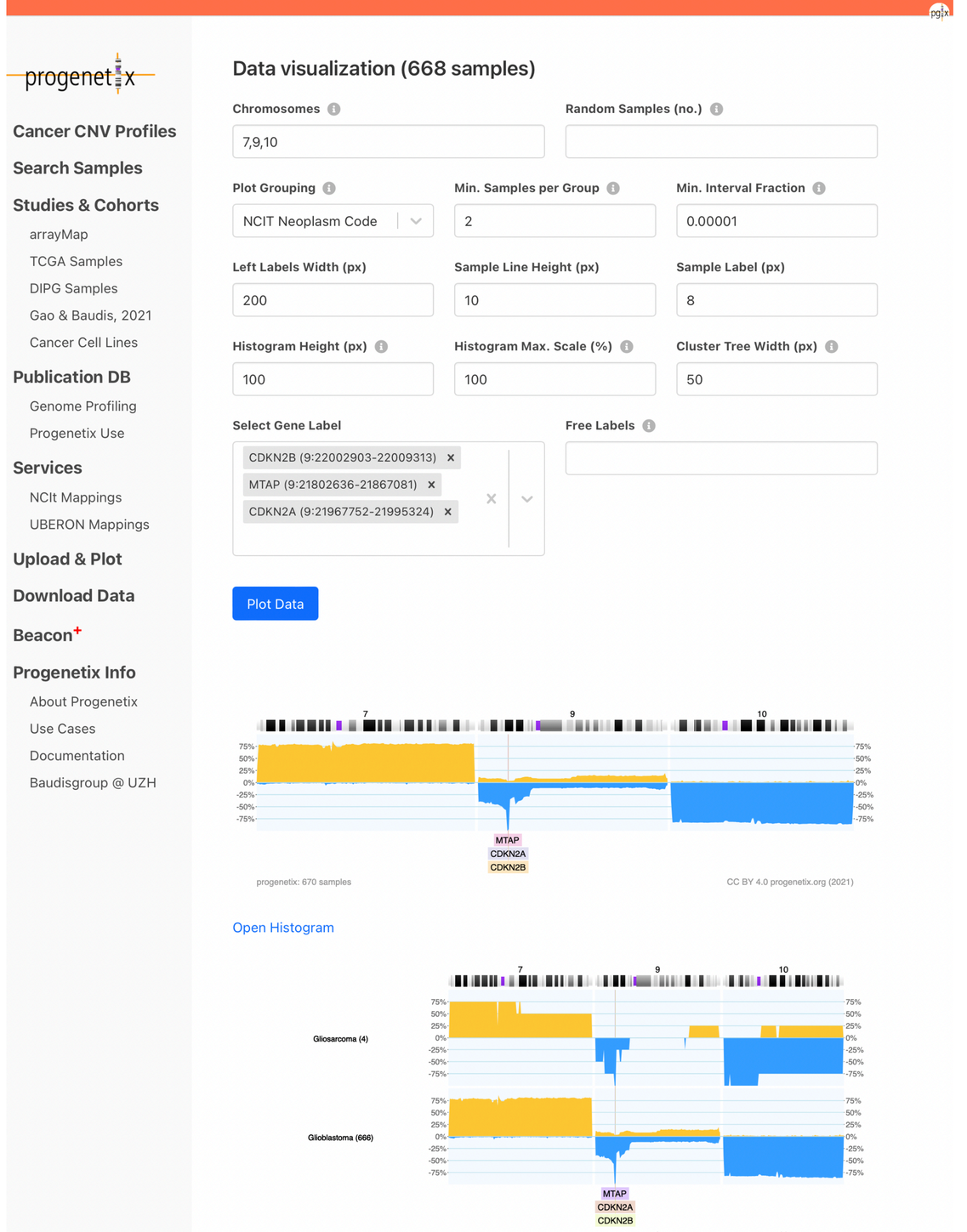
progenetix



Progenetix in 2023

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 ...)
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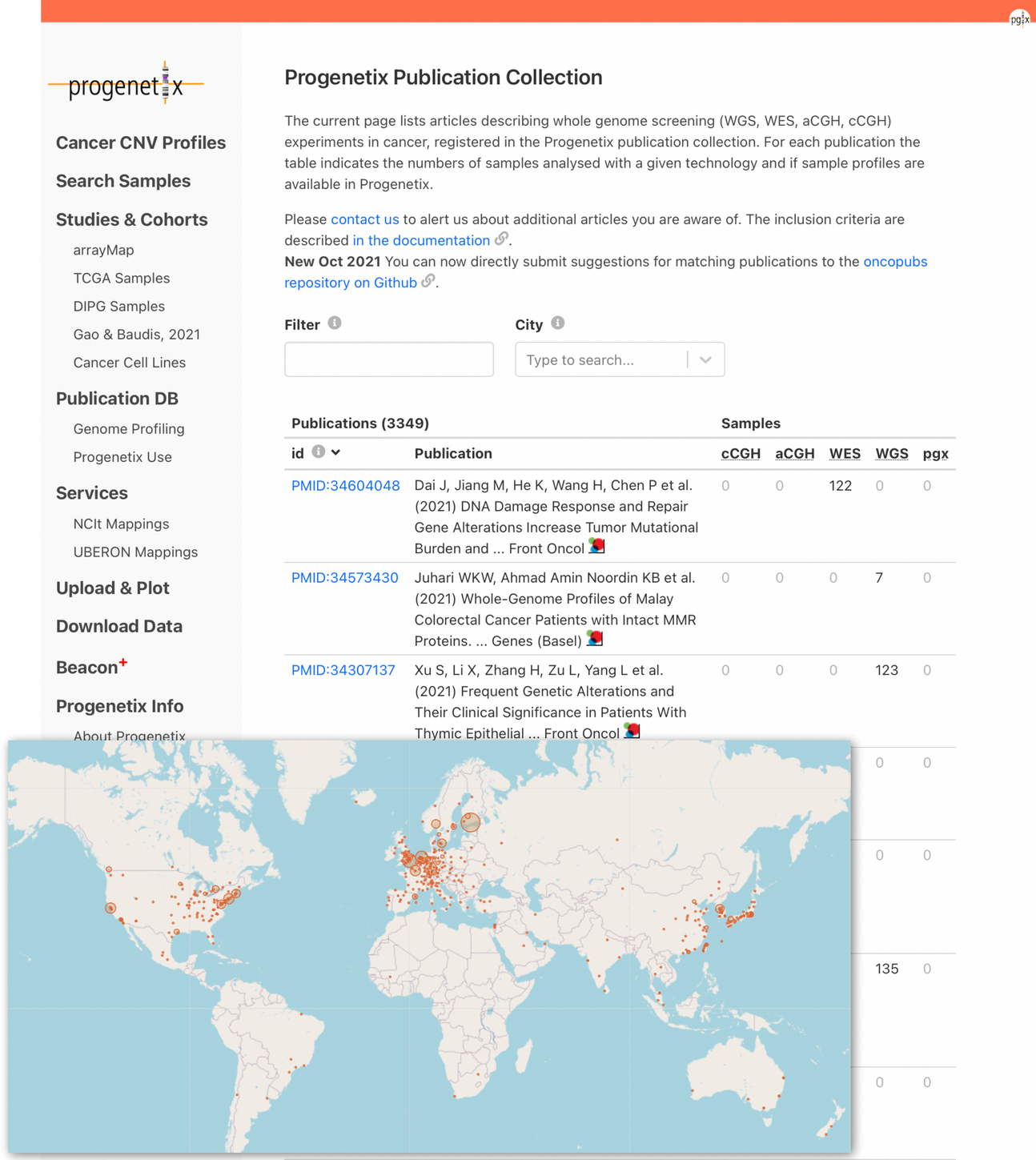
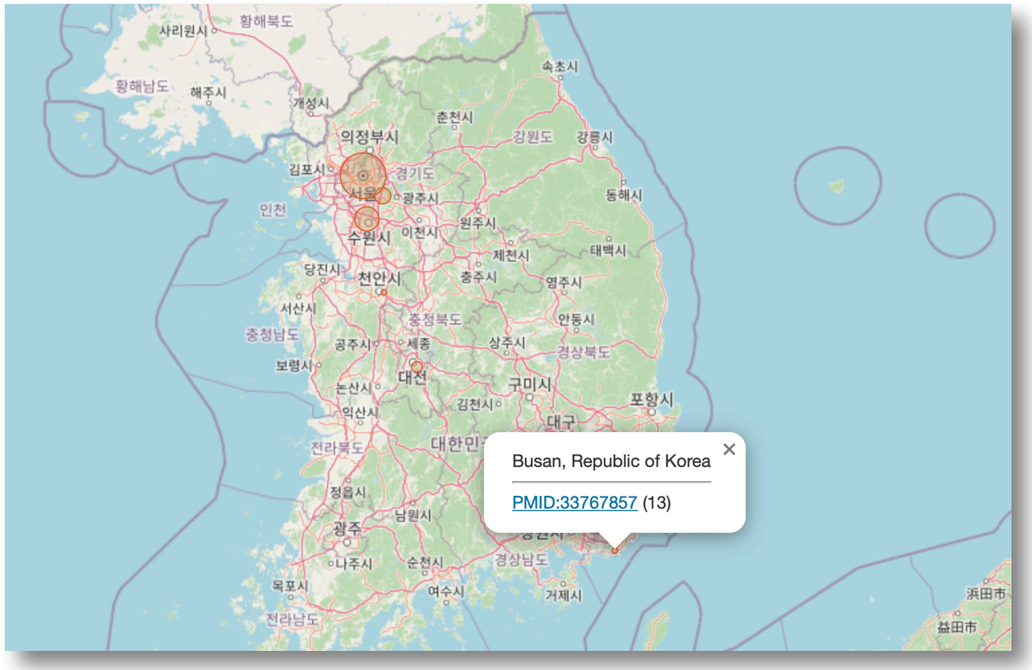
progenetix



Service: Publications

Location Mapping for Statistics and Discovery...

- all publications are tagged for "best fit" geographic origin in order
    1. specific sample origin
    2. processing laboratory
    3. corresponding author
- enables searches for e.g. "all publications or samples in HCC from 2000km around Taipeh"
- handy utility for discovering locally performed research, partners...



PMID:33767857

Methylation and molecular profiles of ependymoma: Influence of patient age and tumor anatomic location.

Cho HJ, Park HY, Kim K, Chae H, Paek SH, Kim SK, Park CK, Choi SH, Park SH.

Mol Clin Oncol PMID:33767857

http://progenetix.org/services/publications/?filters=genomes:>0&ISO3166alpha2=kr&output=map

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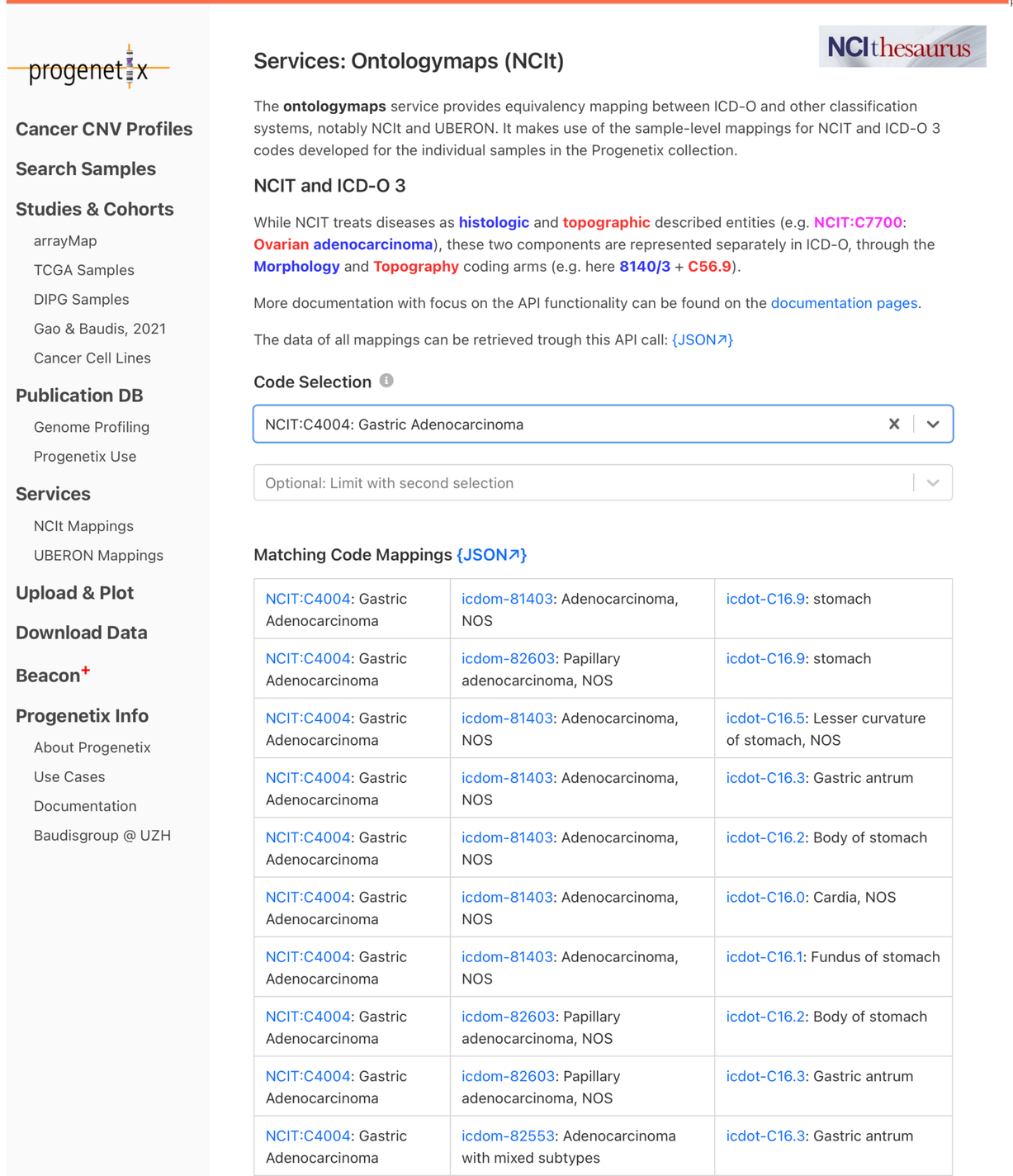
progenetix



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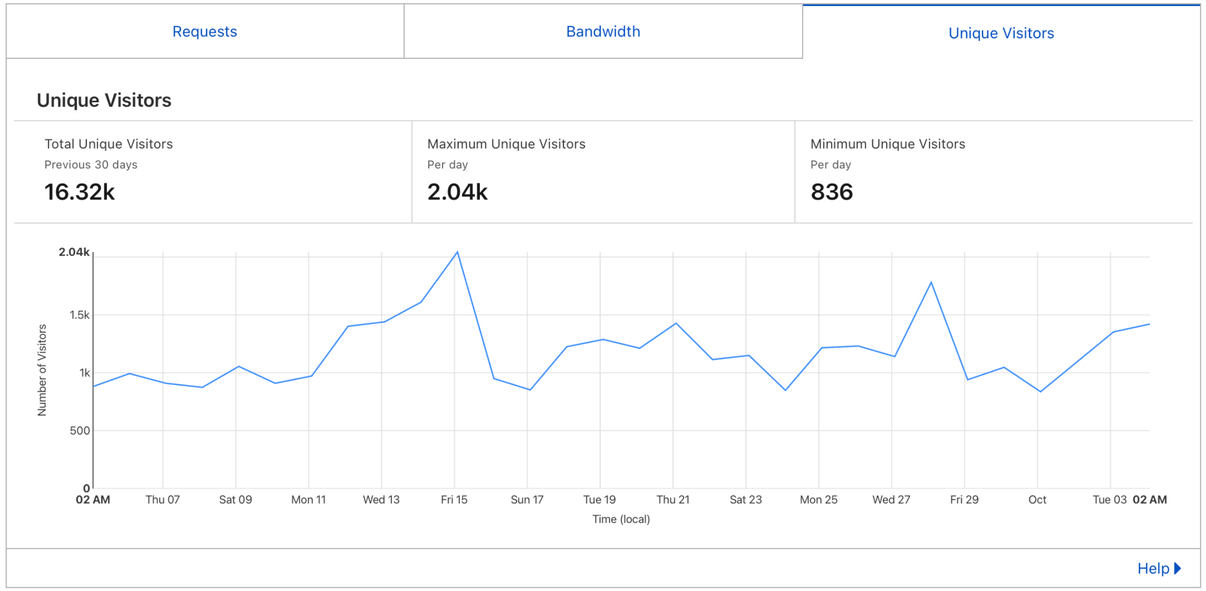
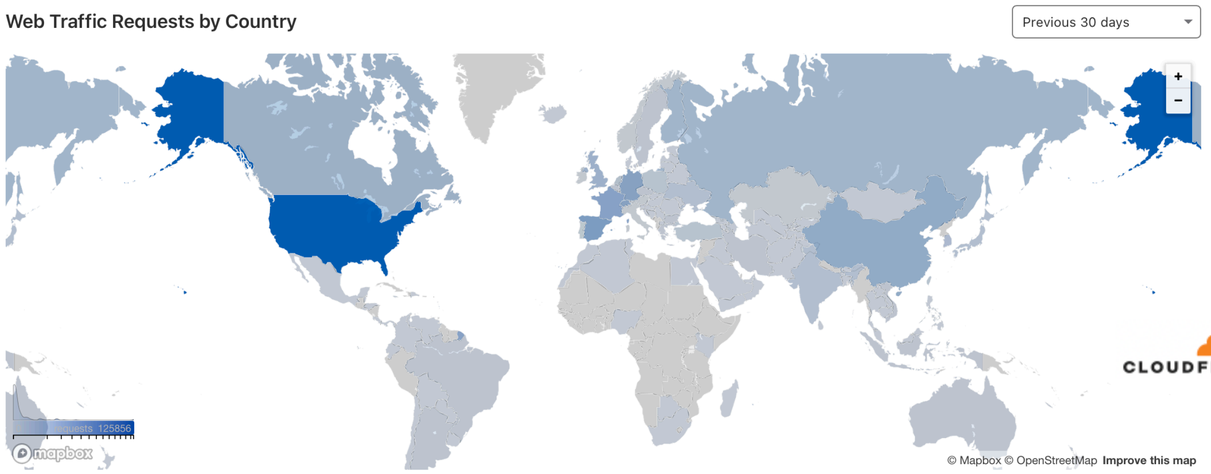
progenetix





Top Traffic Countries / Regions

Previous 30 days

Country / Region	Traffic
United States	125,856
Singapore	34,121
Spain	22,369
Switzerland	16,910
Germany	16,459

Help

Cloudflare | progenetix.org | October 2023

Database, 2021, **2021(0)**, 1–9
DOI: https://doi.org/10.1093/database/baab043
Database update

The Progenetix oncogenomic resource in 2021

Qingyao Huang[1,2], Paula Carrio-Cordo[1,2], Bo Gao[1,2], Rahel Paloots[1,2] and Michael Baudis[1,2,*]

[1]Department of Molecular Life Sciences, University of Zurich, Winterthurerstrasse 190, Zurich 8057, Switzerland
[2]Swiss Institute of Bioinformatics, Winterthurerstrasse 190, Zurich 8057, Switzerland

*Corresponding author: Tel: +41 44 635 34 86; Email: michael.baudis@mls.uzh.ch

Citation details: Huang, Q., Carrio-Cordo, P., Gao, B. *et al.* The Progenetix oncogenomic resource in 2021. *Database* (2021) Vol. 2021: article ID baab043; DOI: https://doi.org/10.1093/database/baab043

Abstract

In cancer, copy number aberrations (CNAs) represent a type of nearly ubiquitous and frequently extensive structural genome variations. To disentangle the molecular mechanisms underlying tumorigenesis as well as identify and characterize molecular subtypes, the comparative and meta-analysis of large genomic variant collections can be of immense importance. Over the last decades, cancer genomic profiling projects have resulted in a large amount of somatic genome variation profiles, however segregated in a multitude of individual studies and datasets. The Progenetix project, initiated in 2001, curates individual cancer CNA profiles and associated metadata from published oncogenomic studies and data repositories with the aim to empower integrative analyses spanning all different cancer biologies. During the last few years, the fields of genomics and cancer research have seen significant advancement in terms of molecular genetics technology, disease concepts, data standard harmonization as well as data availability, in an increasingly structured and systematic manner. For the Progenetix resource, continuous data integration, curation and maintenance have resulted in the most comprehensive representation of cancer genome CNA profiling data with 138 663 (including 115 357 tumor) copy number variation (CNV) profiles. In this article, we report a 4.5-fold increase in sample number since 2013, improvements in data quality, ontology representation with a CNV landscape summary over 51 distinctive National Cancer Institute Thesaurus cancer terms as well as updates in database schemas, and data access including new web front-end and programmatic data access.

Database URL: progenetix.org

Table 1. Statistics of samples from various data resources

Data source	GEO	ArrayExpress	cBioPortal	TCGA	Total
No. of studies	898	51	38	33	1939
No. of samples	63 568	4351	19 712	22 142	138 663
Tumor	52 090	3887	19 712	11 090	115 357
Normal	11 478	464	0	11 052	23 306
Classifications					
ICD-O (Topography)	100	54	88	157	209
ICD-O (Morphology)	246	908	265	140	491
NCIt	346	148	422	182	788
Collections					
Individuals	63 568	4351	19 712	10 995	127 549
Biosamples	63 568	4351	19 712	22 142	138 663
Callsets[a]	63 568	4351	19 712	22 376	138 930
Variants	5 514 126	118 4170	1 778 096	2 654 065	10 716 093

[a]set of variants from one genotyping experiment; ICD-O, International Classification of Diseases for Oncology; NCIt, National Cancer Institute Thesaurus.

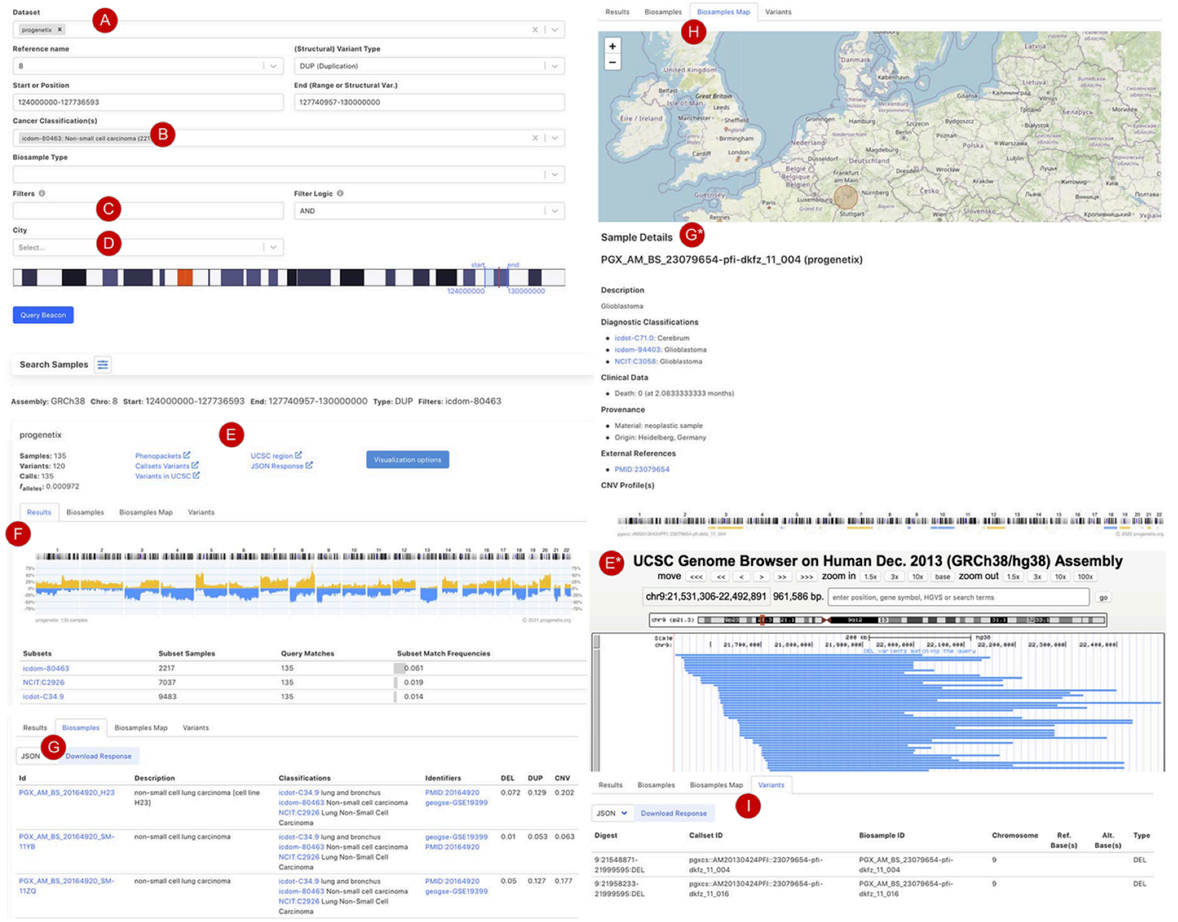
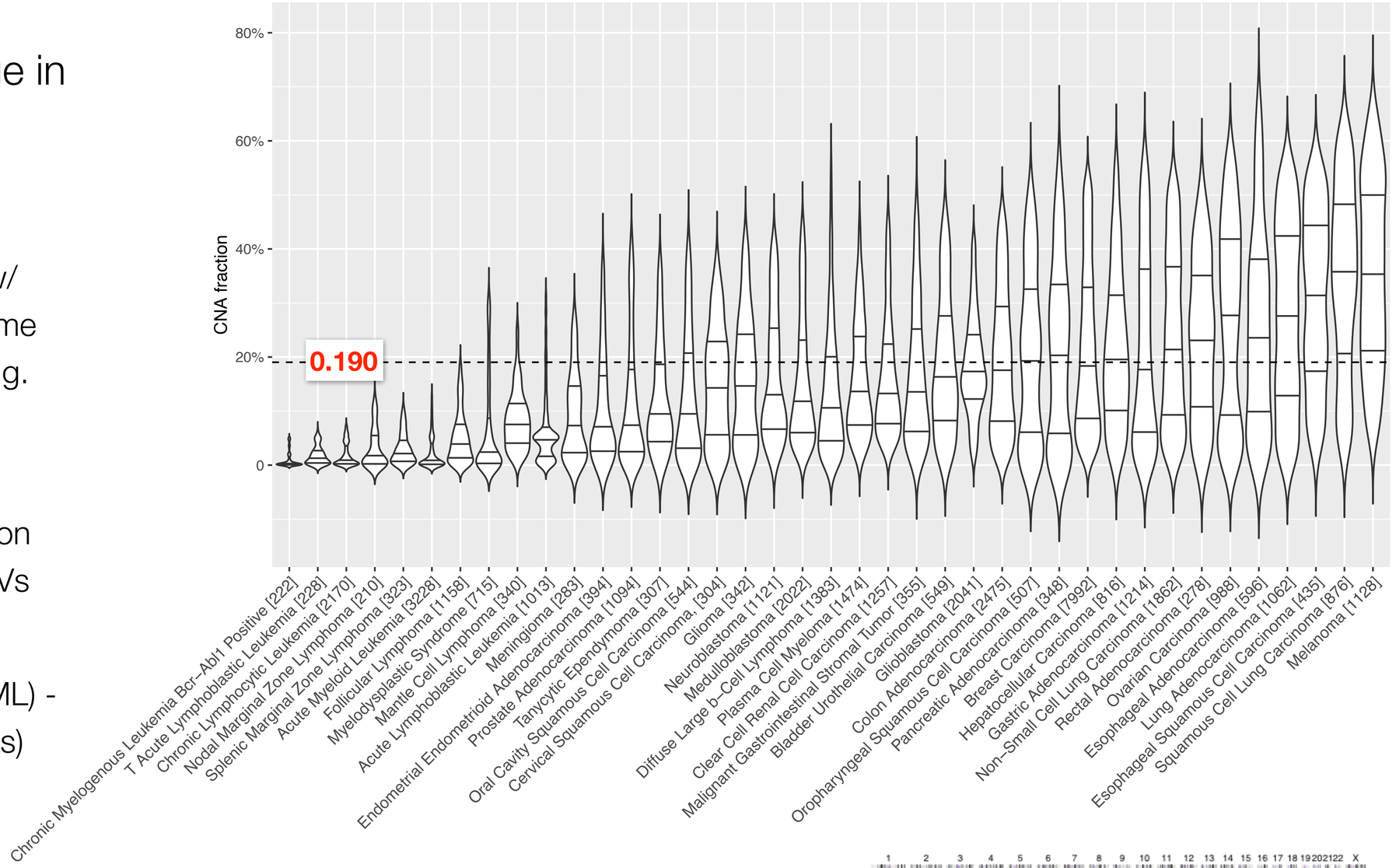


Figure 3. Beacon-style query using fuzzy ranges to identify biosamples with variants matching the CNA range This example queries for a continuous, focal duplication covering the complete MYC gene's coding region with < = 6 Mb in size. A: Filter for dataset; B: filter for cancer classification (NCIt and ICD-O-3 ontology terms available); C: additional filter, e.g. Cellosaurus; D: additional filter for geographic location; E: external link to UCSC browser to view the alignment of matched variants; F: cancer type classification sorted by frequency of the matched biosamples present in the subset; G: list of matched biosamples with description, statistics and reference. More detailed biosample information can be viewed through 'id' link to the sample detail page; H: matched variants with reference to biosamples can be downloaded in json or csv format.

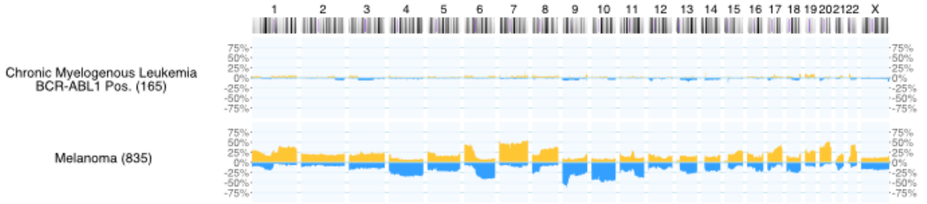
Data Use Cases

Genome CNV coverage in Cancer Classes

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



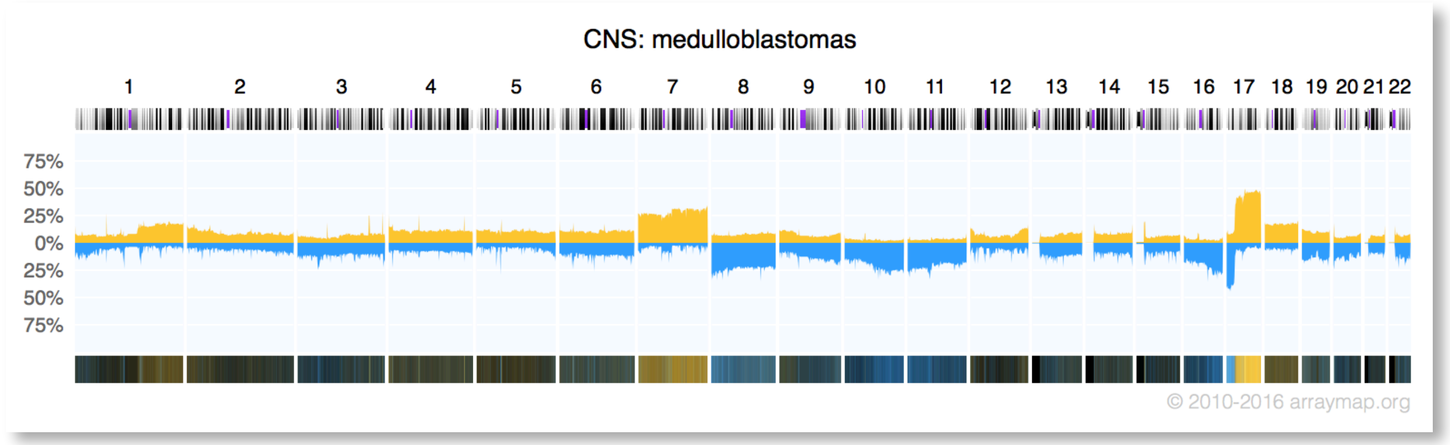
Lowest / Highest CNV fractions =>

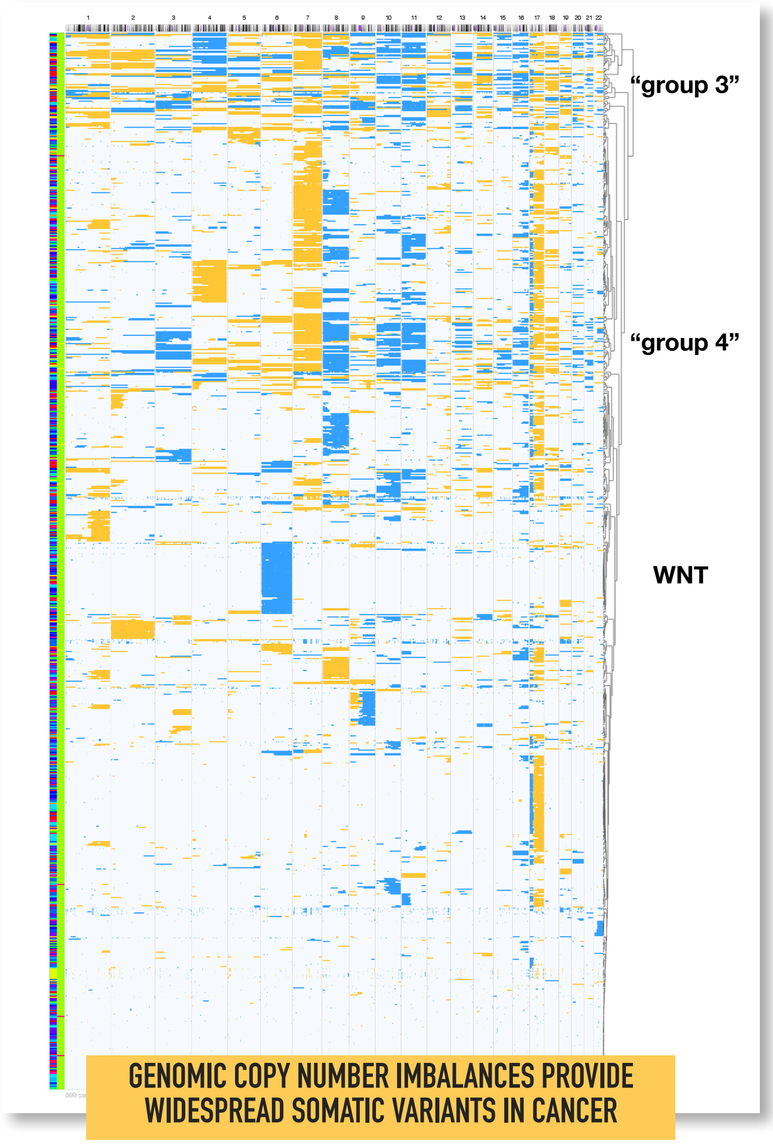


Somatic CNVs In Cancer

Recurrent mutation patterns

How can those patterns be used for classification and determination of biological mechanisms?





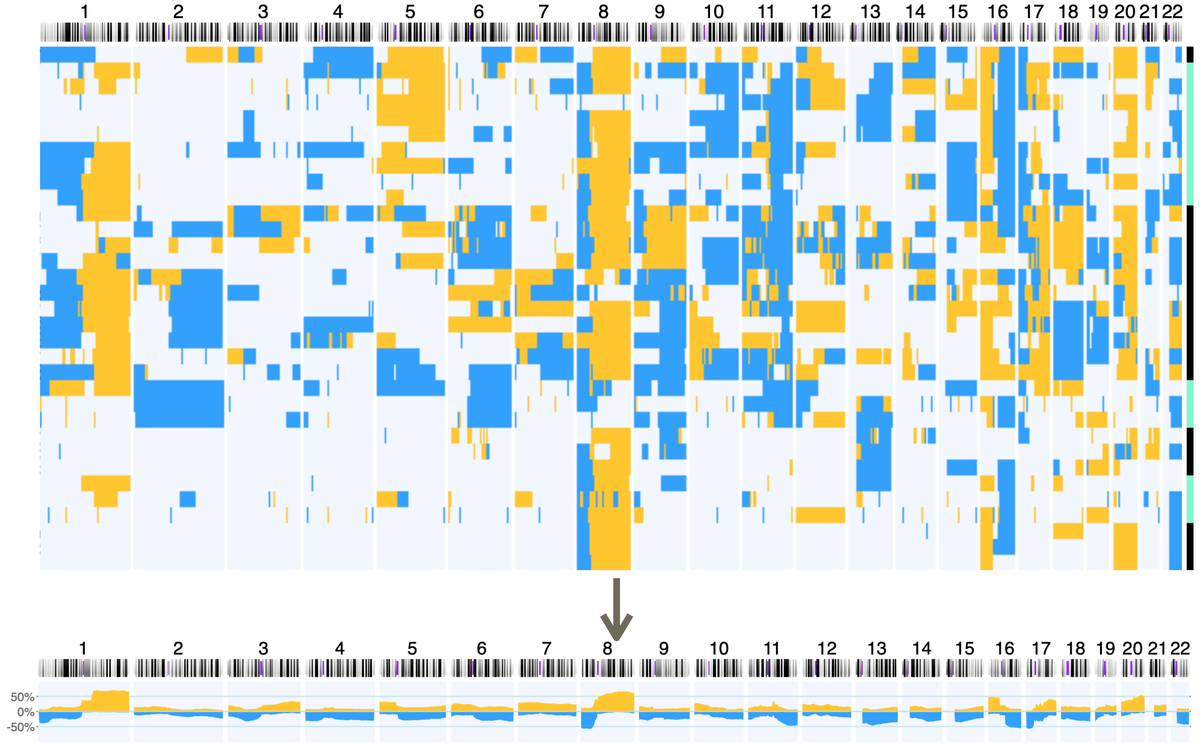
A genomic copy number histogram for malignant medulloblastomas, the most frequent type of pediatric brain tumors, displaying regions of genomic duplications and deletions. These can be decomposed into individual tumor profiles which segregate into several clusters of related mutation patterns with functional relevance and clinical correlation.

arrayMap

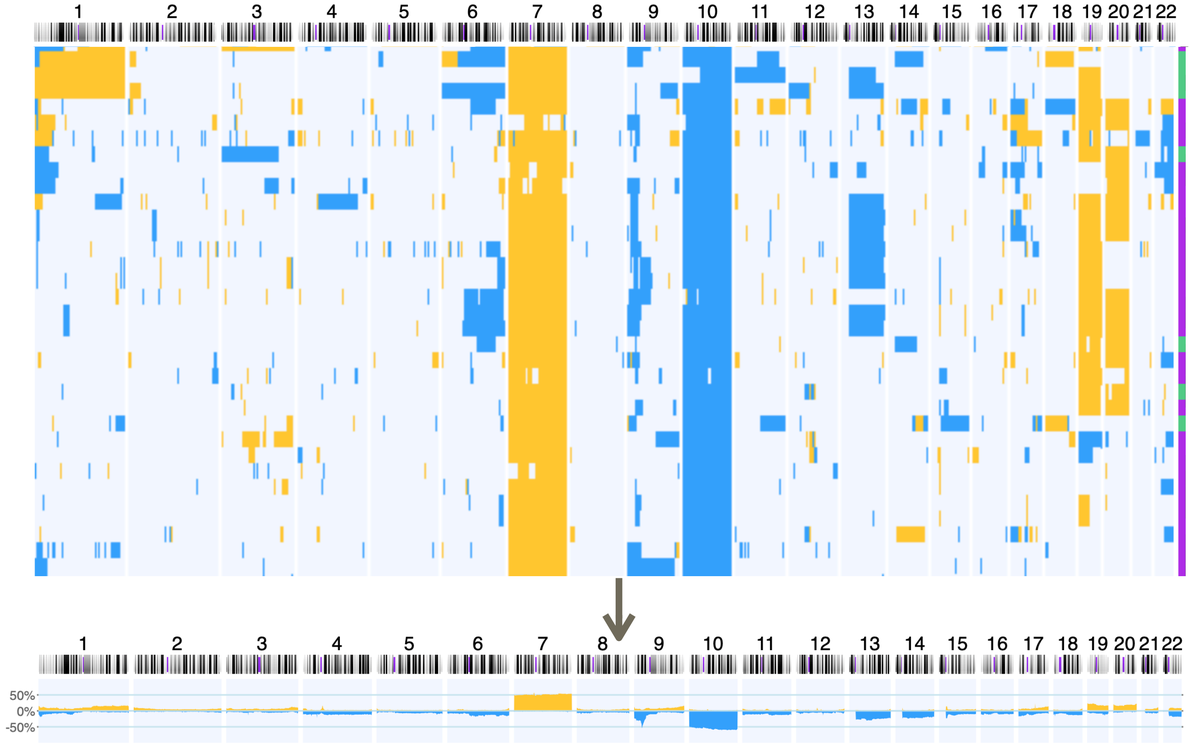
Drivers? Passengers? Markers?

Disentangling CNA Patterns

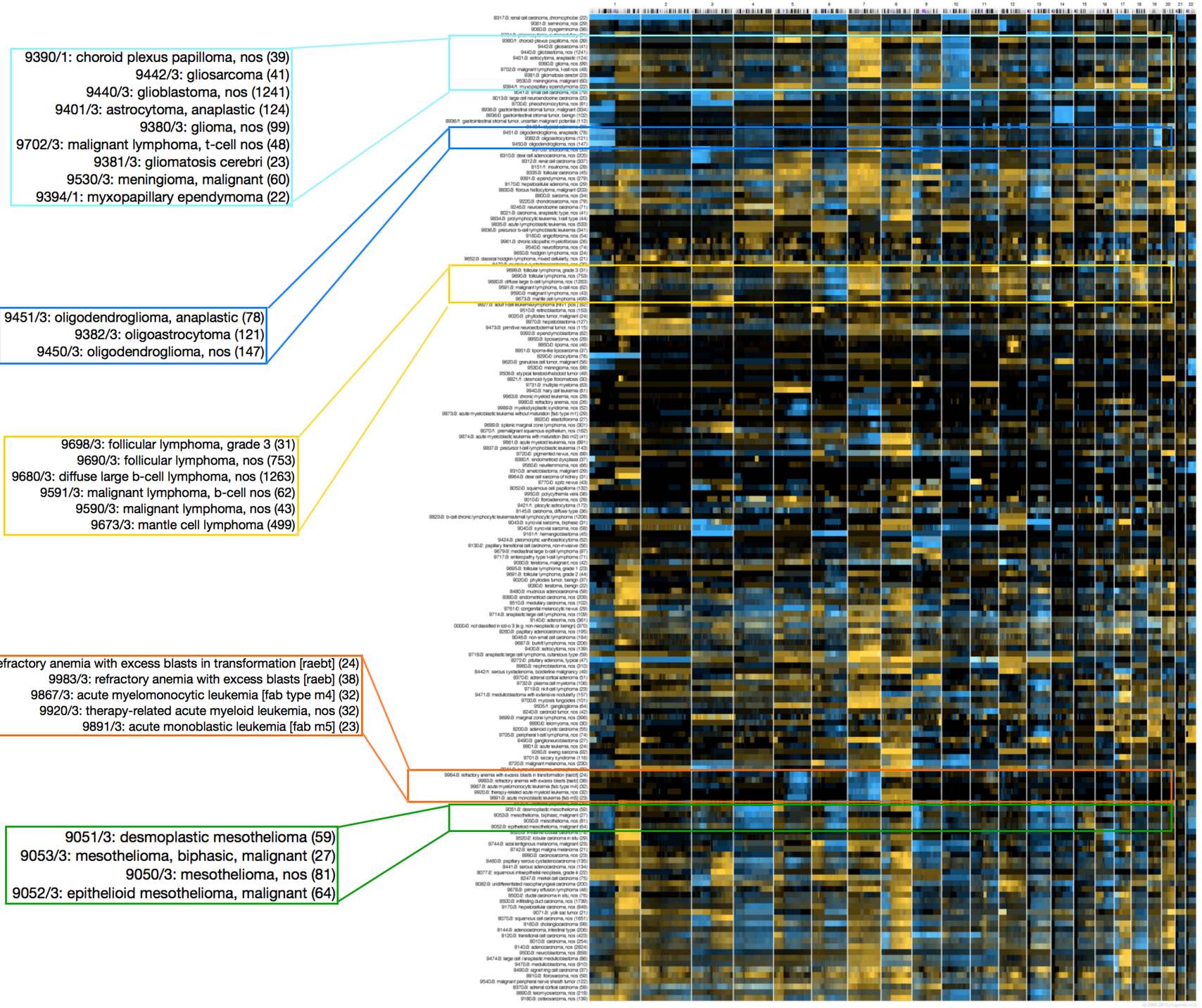
Ductal Breast Carcinoma



Glioblastoma



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



arrayMap

frontiers in Genetics

ORIGINAL RESEARCH
published: 13 May 2021
doi: 10.3389/fgene.2021.654887

Signatures of Discriminative Copy Number Aberrations in 31 Cancer Subtypes

Bo Gao [1,2] *and Michael Baudis* [1,2*]

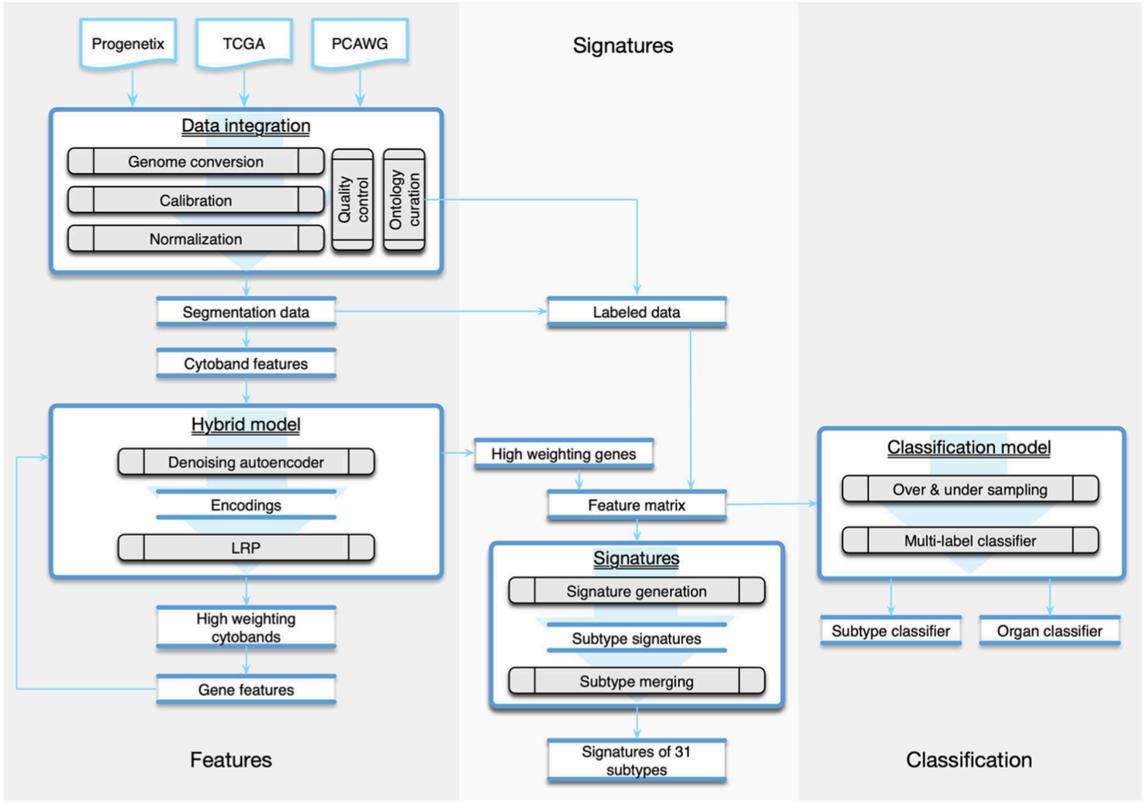


FIGURE 1 | The workflow of the study was composed of three parts. The *Features* part consisted of methods of data integration and feature generation. The *Signature* part focused on creating CNA signatures for cancer subtypes and the categorization of subtypes. The *Classification* part recruited machine learning techniques to predict the organ and the subtype from a given copy number profile.

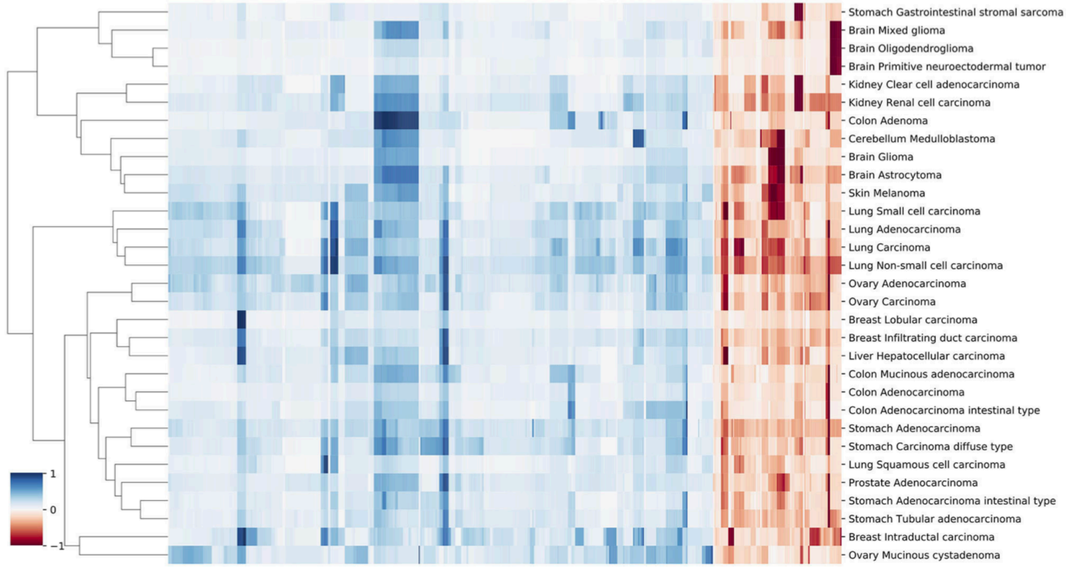


FIGURE 5 | A clustering heatmap of features in 31 signatures. Columns are normalized average CNV intensities of feature genes, where the blue colors are duplication features and red colors are deletion features. Duplication and deletion frequencies are normalized separately.

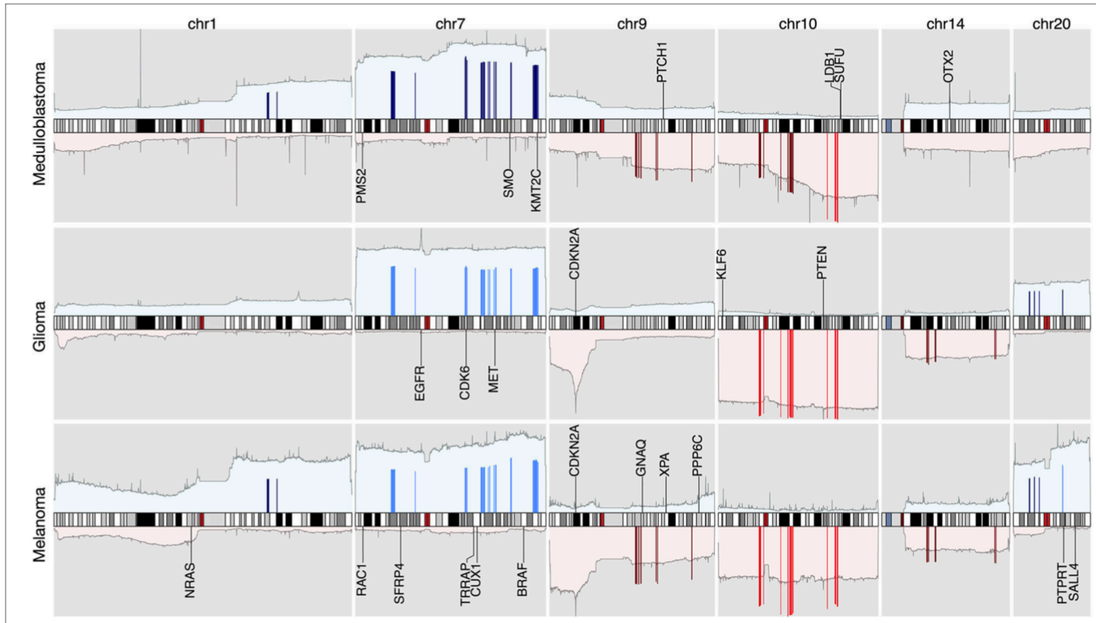
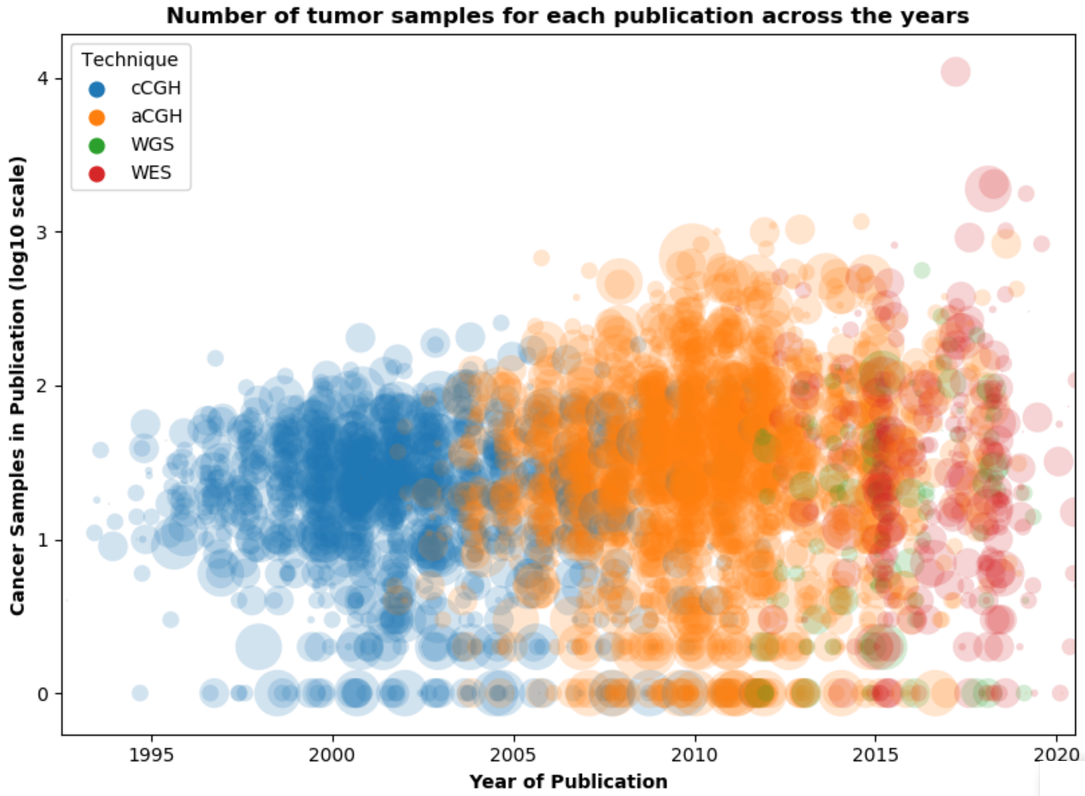


FIGURE 6 | The integrated view of the original data and the selected features, in the neural crest originating entities medulloblastoma, glioma, and melanoma. The shaded background area color illustrates the original data. Color bars illustrate the feature genes, where brighter colors indicate stronger signal intensity. The blue colors above the chromosome axis represent the average amplifications, and the red colors below the chromosome axis represent the average deletions. The amplitude of amplifications and deletions are normalized to [0,1] separately. The adjacent known driver genes are also included for each tumor type.



Map of the geographic distribution (by first author affiliation) of the 104'543 genomic array, 36'766 chromosomal CGH and 15'409 whole genome/exome based cancer genome datasets.

The numbers are derived from the 3'240 publications registered in the Progenetix database.

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- Cancer CNV Profiles
- Search Samples
- Studies & Cohorts
  - arrayMap
  - TCGA Samples
  - DIPG Samples
  - Gao & Baudis, 2021
  - Cancer Cell Lines
- Publication DB
- Services
  - NCIt Mappings
  - UBERON Mappings
- Upload & Plot
- Download Data

Progenetix Publication Collection

The current page lists articles describing whole genome screening (WGS, WES, aCGH, cCGH) experiments in cancer, registered in the Progenetix publication collection. For each publication the table indicates the numbers of samples analysed with a given technology and if sample profiles are available in Progenetix.

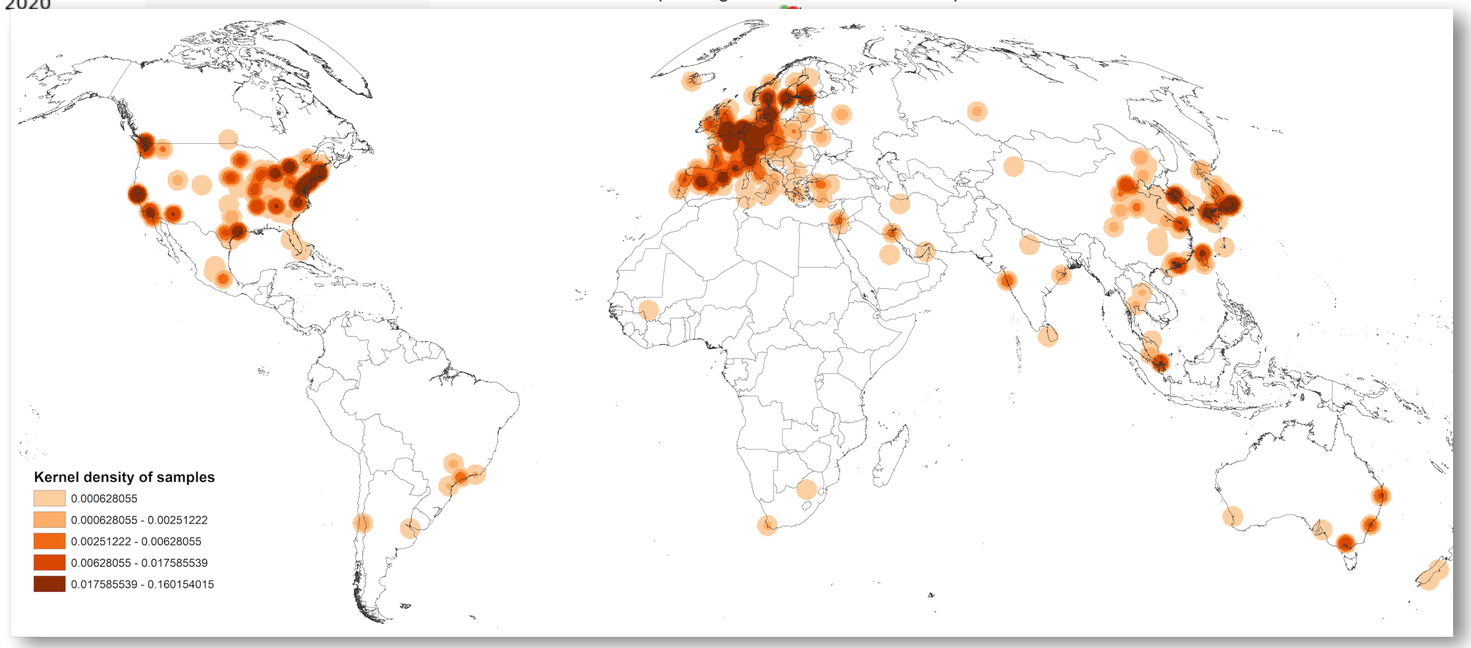
Please contact us to alert us about additional articles you are aware of. The inclusion criteria are described in the documentation.

Filter

City

Type to search...

Publications (3324)		Samples				
id	Publication	cCGH	aCGH	WES	WGS	pgx
PMID:34103027	Peng G, Chai H, Ji W, Lu Y, Wu S et al. (2021) Correlating genomic copy number alterations with clinicopathologic findings in 75 cases of ... BMC Med Genomics	0	79	0	0	0
PMID:34059130	Tsui DWY, Cheng ML, Shady M, Yang JL et al. (2021) Tumor fraction-guided cell-free DNA profiling in metastatic solid tumor patients. ...	0	0	5	113	0



Population stratification in cancer samples based on SNP array data

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

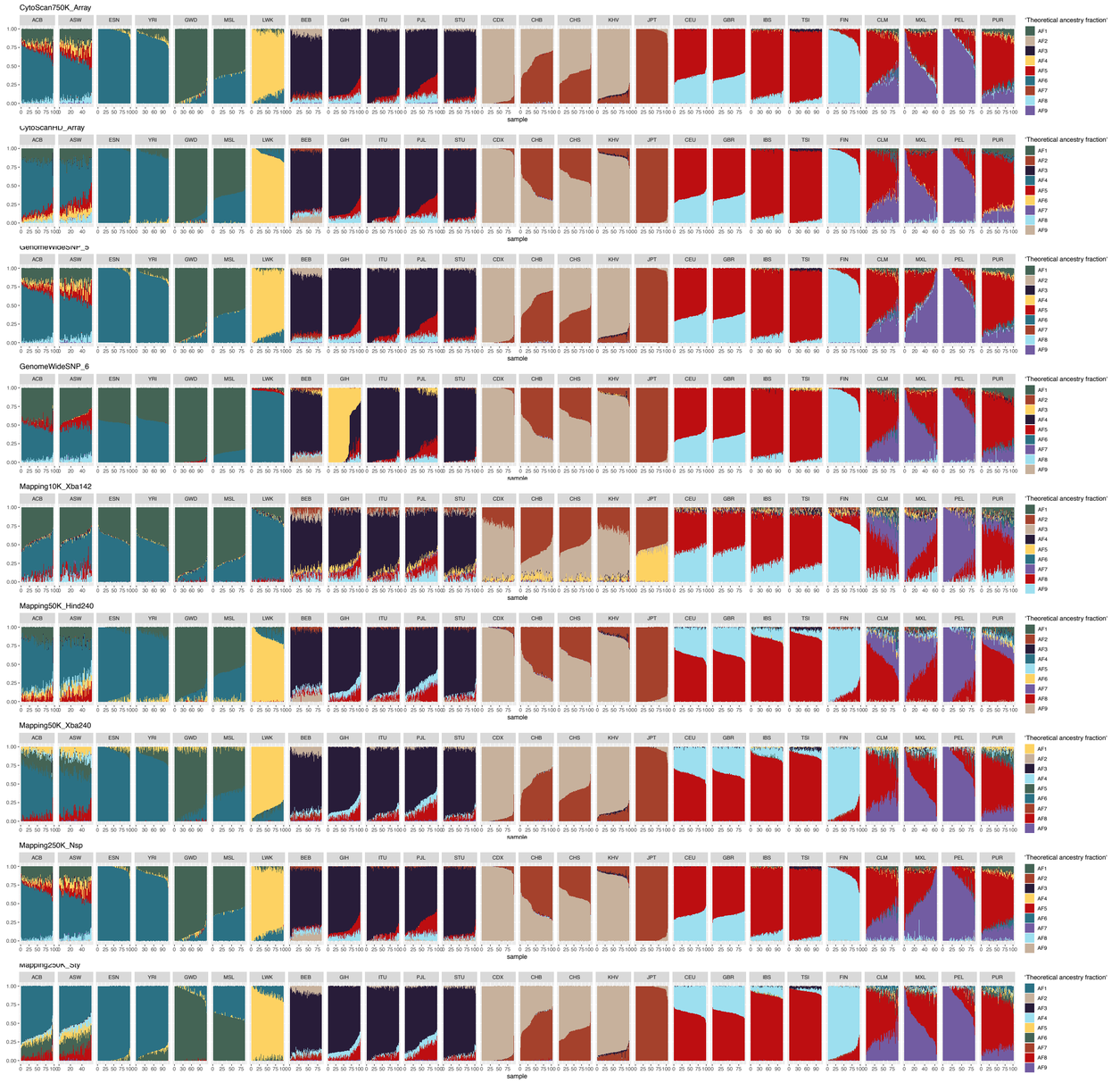


Figure S1 The fraction or contribution of theoretical ancestors (k=9) in reference individuals from 1000 Genomes Project with regard to nine SNP array platforms. The x-axis are individual samples, grouped by their respective population. Groups belonging to the same continent/superpopulation are placed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

arrayMap

Qingyao Huang

Progenetix and GA4GH Beacon

Implementation driven development of a GA4GH standard

progenetix

GENOMICS

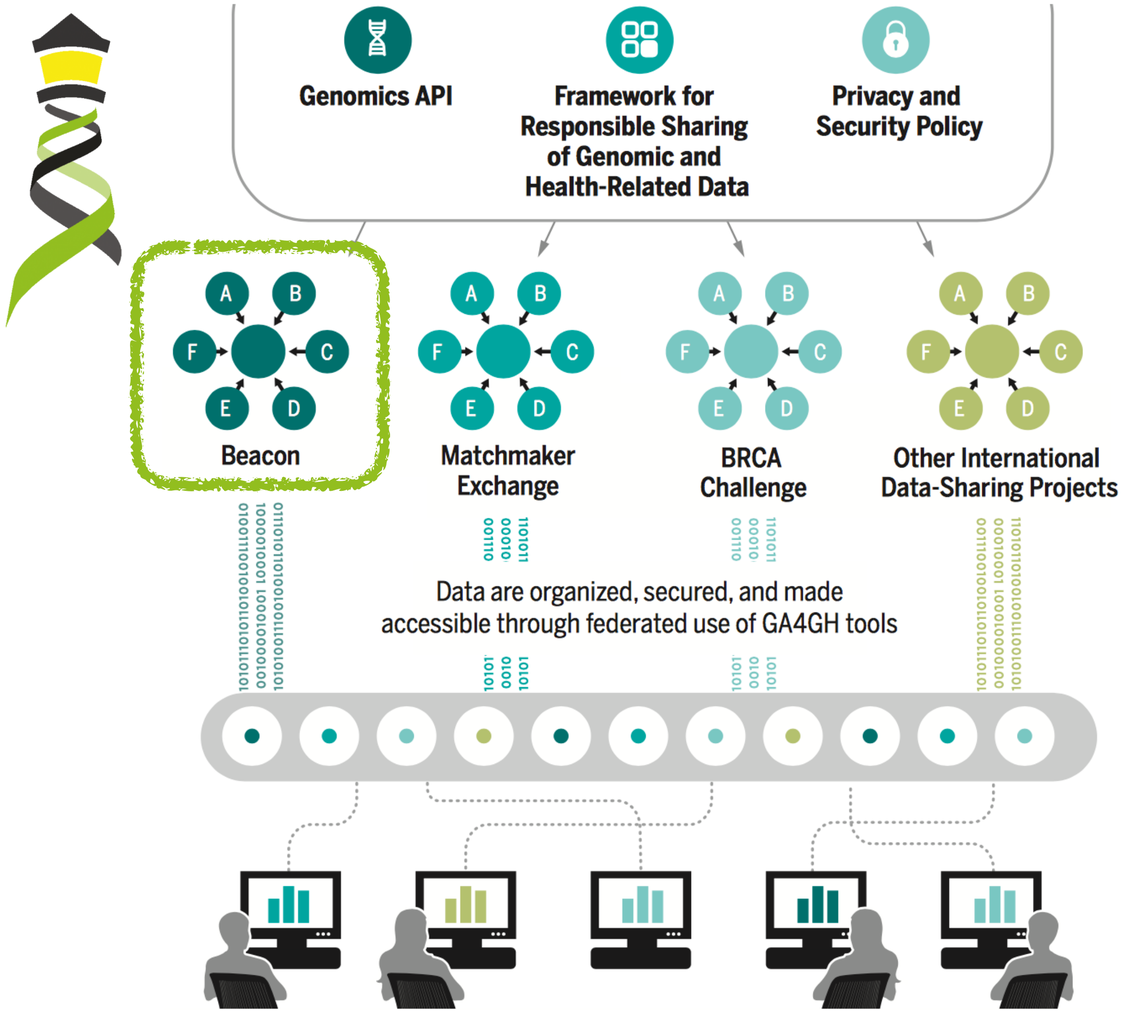
A federated ecosystem for sharing genomic, clinical data

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

The Global Alliance for Genomics and Health*

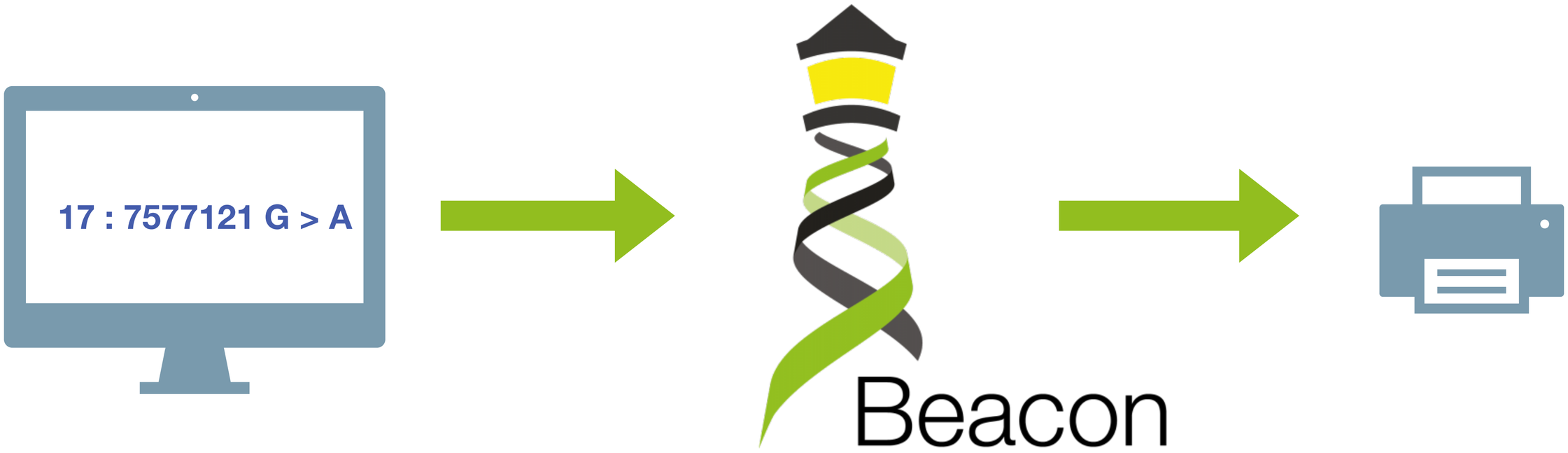
SCIENCE 10 JUNE 2016 • VOL 352 ISSUE 6291

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



DNASTACK

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.

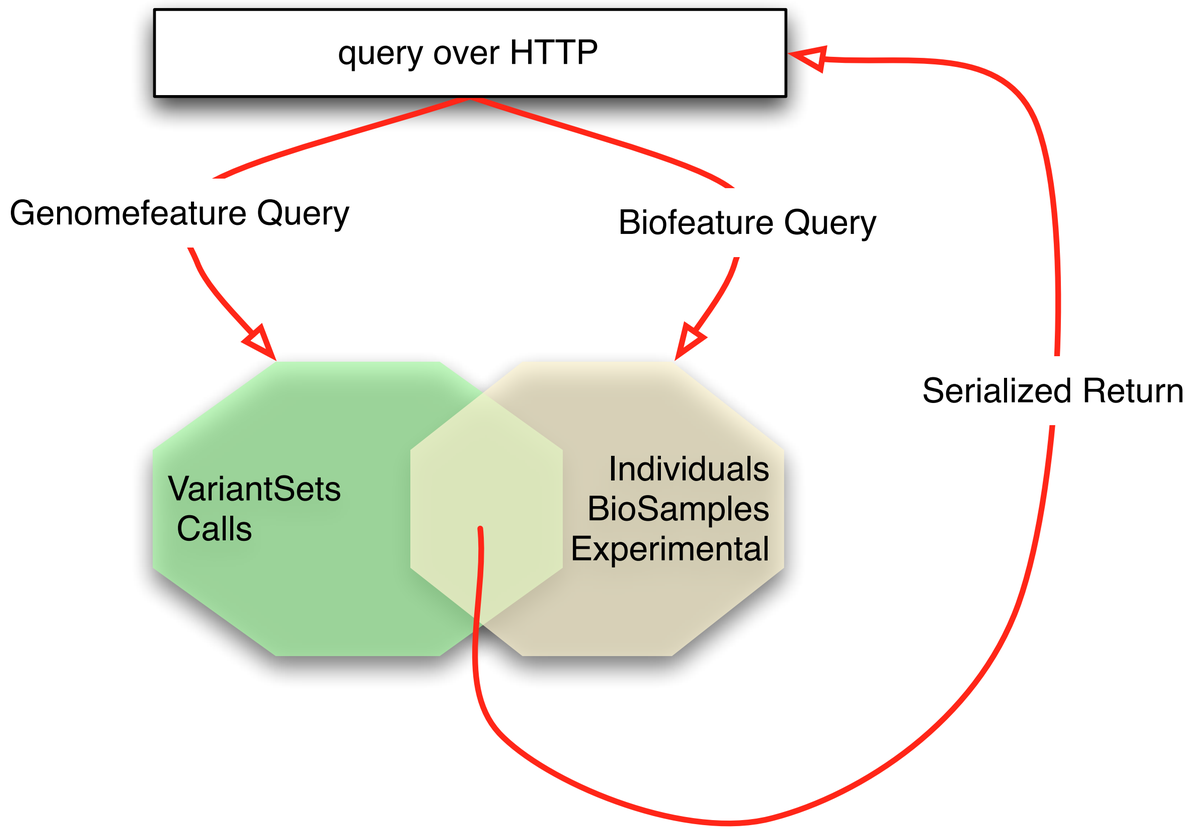
1. Provide *frequencies of all alleles* at that point
2. Ask for all alleles seen in a gene *region* (and more elaborate versions of this)
3. Other more complicated queries

"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* …

Minimal GA4GH query API structure



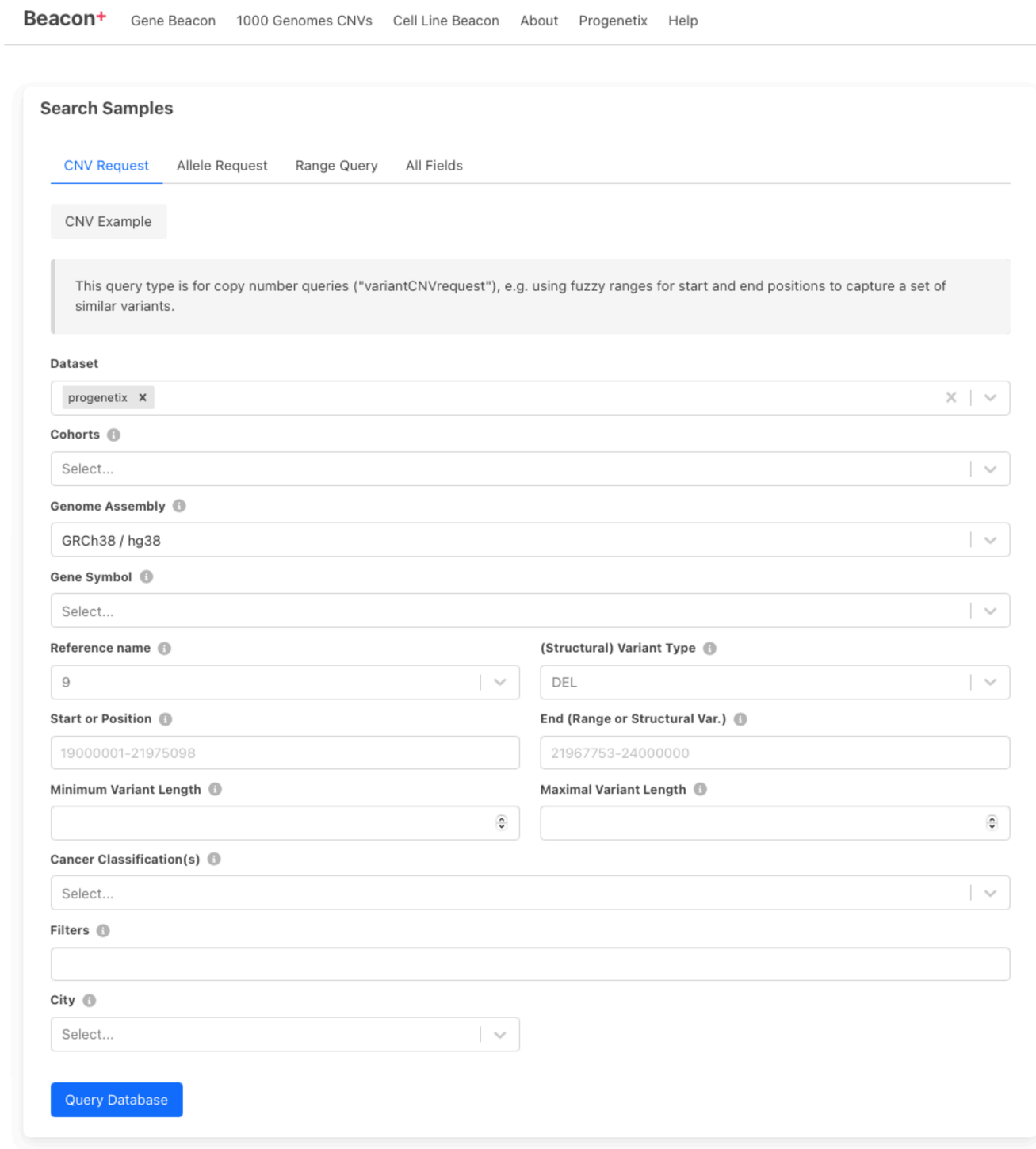
Beacon(+) “Metadata”

Beacon+ by Progenetix

From Beacon Query to Explorative Analyses of CNV Patterns

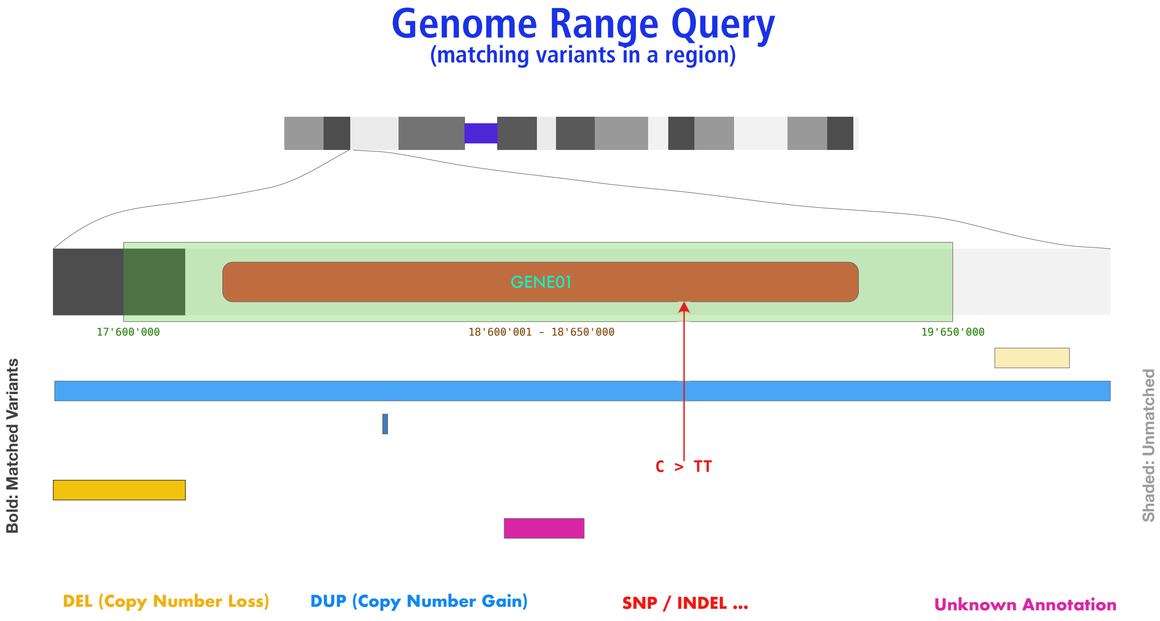
- Since 2016 the Progenetix resource has been used to model options for Beacon development
  - 138334 individual samples from 698 cancer types
- The consistent use of hierarchical diagnostic codes allows the use of Beacon "filters" for histopathological/clinically scoped queries
- Beacon's handover protocols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

progenetix

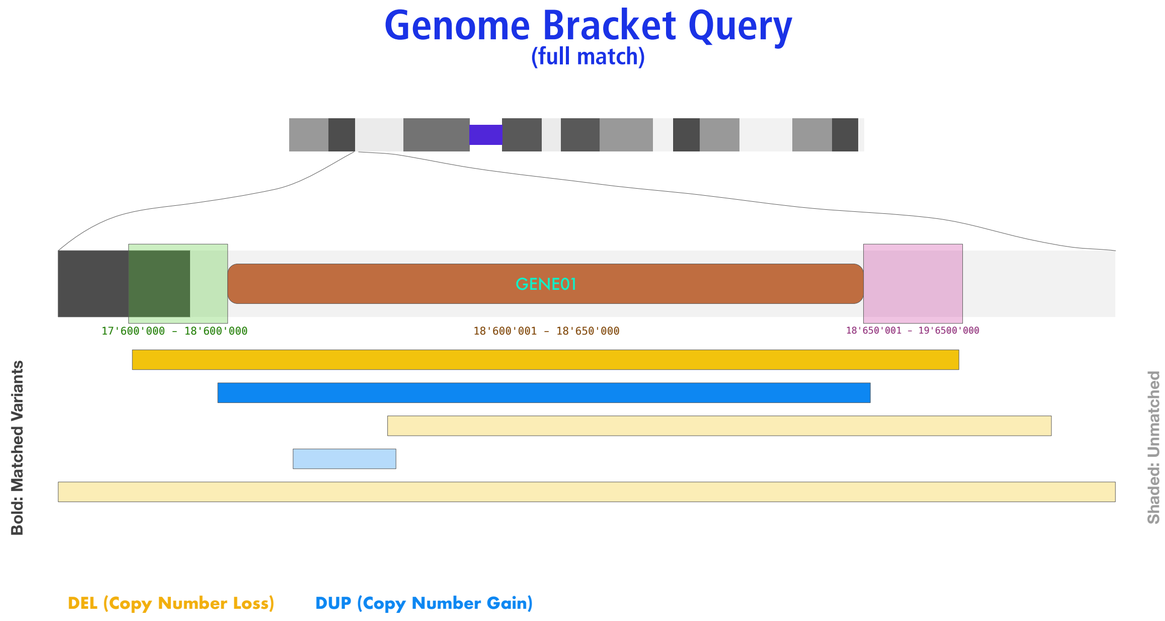


Beacon v2: Extended Variant Queries

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, regerence 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 v2 Filters

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

- Beacon v2 "filters" assumes inclusion of child terms when using hierarchical classifications

  ➡ implicit *OR* with otherwise assumed *AND*

- implementation of hierarchical annotations overcomes some limitatiions of "fuzzy" disease annotations

Beacon+ specific: Multiple term selection with OR logic

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

progenetix

Variants: 0
Calls: 0
Samples: 523

$f_{alleles}$: 0

Callsets Variants | Legacy Interface | UCSC region

Show JSON Response

Results | Biosamples

Id	Description	Classifications	Identifiers	DEL	DUP	CNV
PGX_AM_BS_MCC01	Merkel cell carcinoma	icdot-C44.9 Skin, NOS icdom-82473 Merkel cell carcinoma NCIT:C9231 Merkel Cell Carcinoma	PMID:9537255	0.116	0.104	0.22
PGX_AM_BS_MCC02	Merkel cell carcinoma	icdot-C44.9 Skin, NOS icdom-82473 Merkel cell carcinoma NCIT:C9231 Merkel Cell Carcinoma	PMID:9537255	0.154	0.056	0.21
PGX_AM_BS_MCC03	Merkel cell carcinoma	icdot-C44.9 Skin, NOS icdom-82473 Merkel cell carcinoma NCIT:C9231 Merkel Cell Carcinoma	PMID:9537255	0.137	0.21	0.347
PGX_AM_BS_MCC04	Merkel cell carcinoma	icdot-C44.9 Skin, NOS icdom-82473 Merkel cell carcinoma NCIT:C9231 Merkel Cell Carcinoma	PMID:9537255	0.158	0.056	0.214
PGX_AM_BS_MCC05	Merkel cell carcinoma	icdot-C44.9 Skin, NOS icdom-82473 Merkel cell carcinoma NCIT:C9231 Merkel Cell Carcinoma	PMID:9537255	0.107	0.327	0.434

Page **1 of 105**

Beacon v2 Requests

POSTing Queries

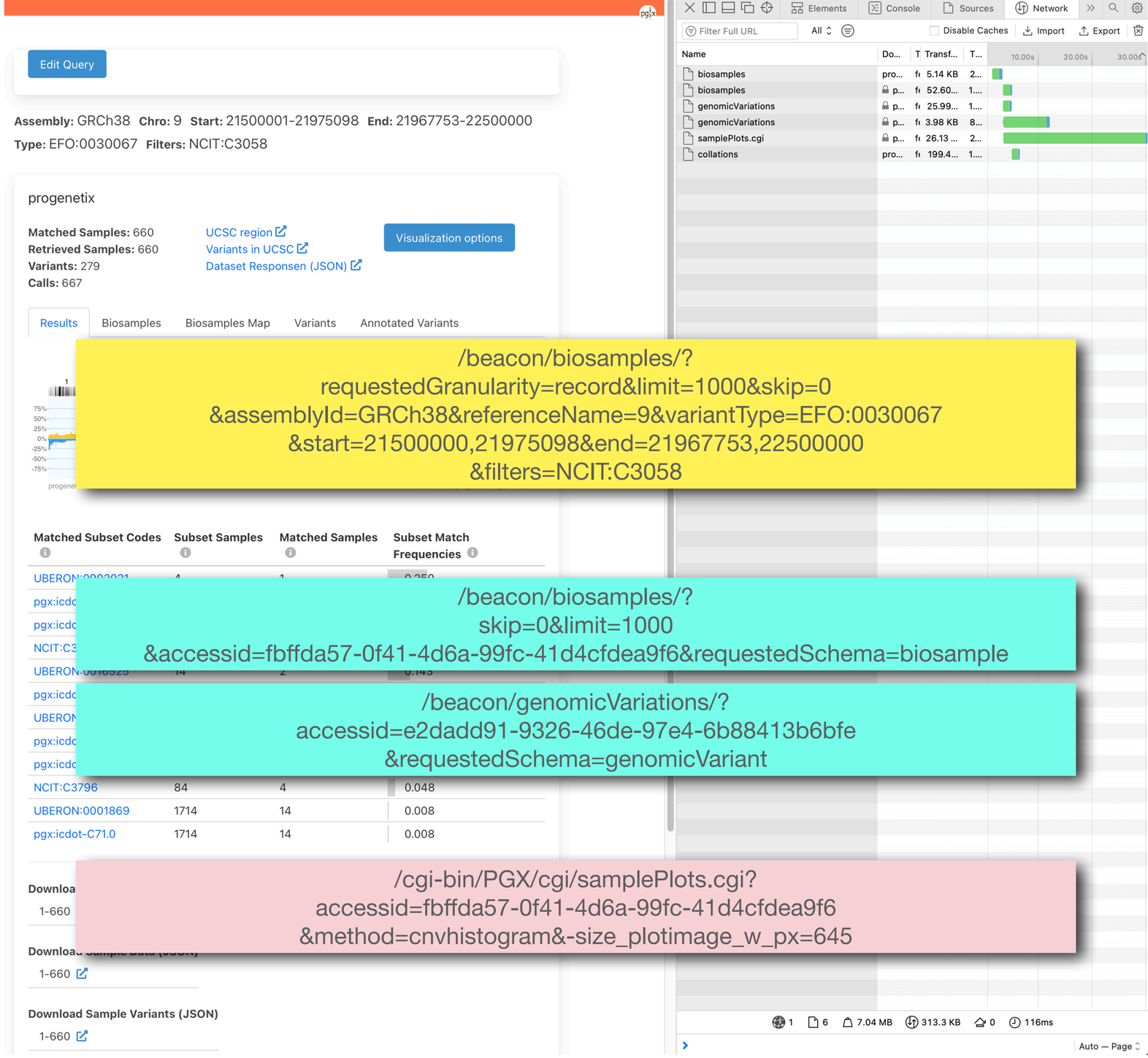
- Beacon v2 supports a mix of dedicated endpoints with REST paths
- POST requests using JSON query documents
- final syntax for core parameters still in testing stages

```
{
    "$schema":"beaconRequestBody.json",
    "meta": {
        "apiVersion": "2.0",
        "requestedSchemas": [
            {
                "entityType": "individual",
                "schema": "https://progenetix.org/services/schemas/Phenopacket/"
            }
        ]
    },
    "query": {
        "requestParameters": {
            "datasets": {
                "datasetIds": ["progenetix"]
            }
        },
        "filterLogic": "OR"
    },
    "pagination": {
        "skip": 0,
        "limit": 10
    },
    "filters": [
        { "id": "NCIT:C4536" },
        { "id": "NCIT:C95597" },
        { "id": "NCIT:C7712" }
    ]
}
```

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



Beacon v2 Paths

Progenetix utilizes Beacon v2 REST paths

- Beacon v2 paths are used in the Beacon specification to scope query and delivery
- Progenetix uses a default /biosamples/ + query path for its front end queries, and then collection specific methods for data retrieval (see next)
- current implementation addresses a core subset of all options, and evaluates some still moving targets
  - ➡ variants_interpretations
  - ➡ variant instances versus prototypes
  - ➡ ...

progenetix

Base `/biosamples`

`/biosamples/` + query

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

`/biosamples/{id}/`

- /biosamples/pgxbs-kftva5c9/
  - retrieval of a single biosample

`/biosamples/{id}/variants/` & `/biosamples/{id}/variants_in_sample/`

- /biosamples/pgxbs-kftva5c9/variants/
- /biosamples/pgxbs-kftva5c9/variants_in_sample/
  - retrieval of all variants from a single biosample
  - currently - and especially since for a mostly CNV containing resource - `variants` means "variant instances" (or as in the early v2 draft `variantsInSample`)

Base `/variants`

There is currently (April 2021) still some discussion about the implementation and naming of the different types of genomic variant endpoints. Since the Progenetix collections follow a "variant observations" principle all variant requests are directed against the local `variants` collection.

If using `g_variants` or `variants_in_sample`, those will be treated as aliases.

`/variants/` + query

- /variants/?assemblyId=GRCh38&referenceName=17&variantType=DEL&filterLogic=AND&start=7500000&start=7676592&end=7669607&end=7800000
  - This is an example for a Beacon "Bracket Query" which will return focal deletions in the TP53 locus (by position).

`/variants/{id}/` or `/variants_in_sample/{id}` or `/g_variants/{id}/`

- /variants/5f5a35586b8c1d6d377b77f6/
- /variants_in_sample/5f5a35586b8c1d6d377b77f6/

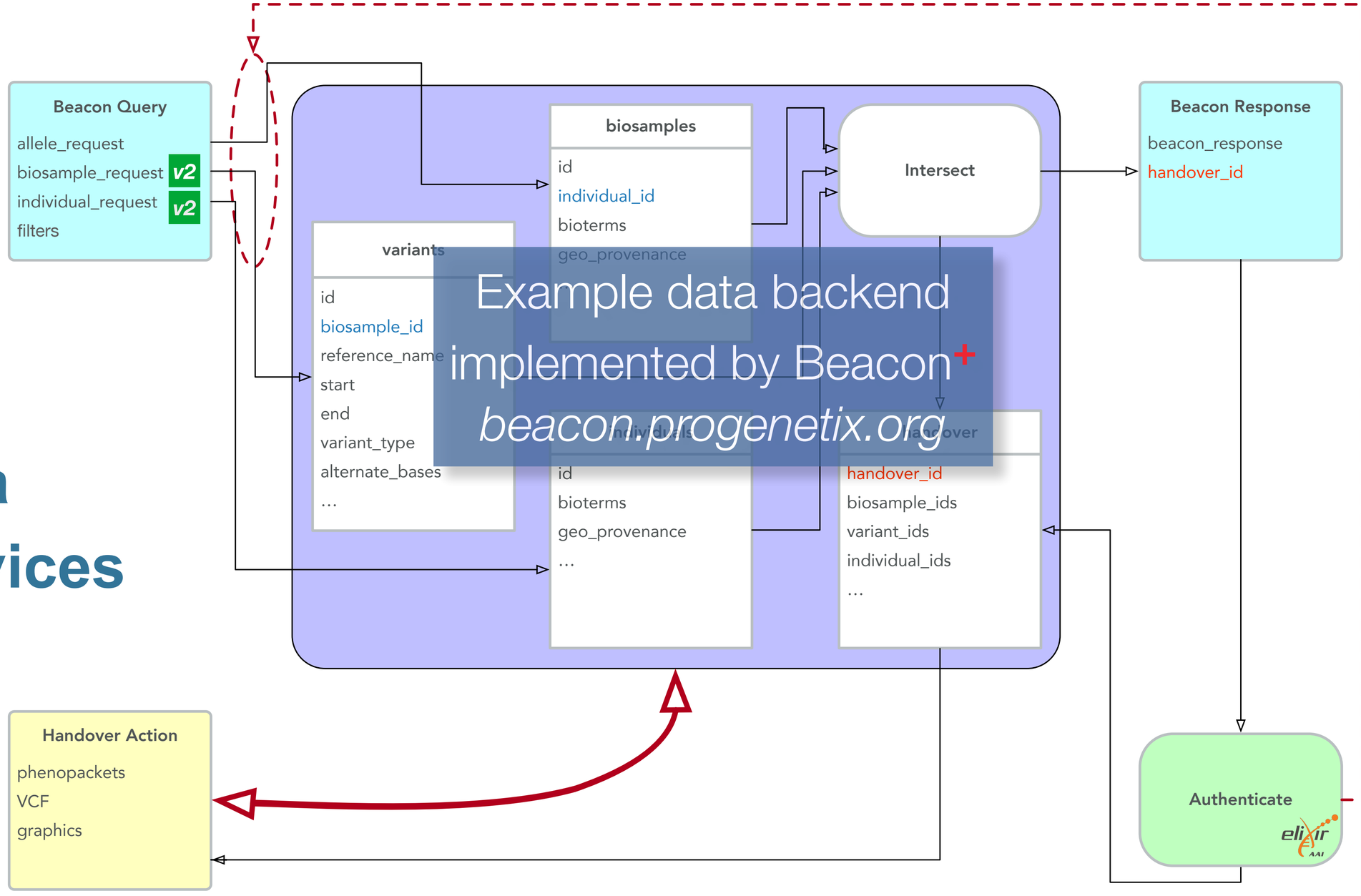
`/variants/{id}/biosamples/` & `variants_in_sample/{id}/biosamples/`

- /variants/5f5a35586b8c1d6d377b77f6/biosamples/
- /variants_in_sample/5f5a35586b8c1d6d377b77f6/biosamples/

https://github.com/ga4gh-beacon/implementations-v2/

Beacon & Handover

Beacons v1.1 supports **data delivery services**



Beacon I/O

Handover

Authentication

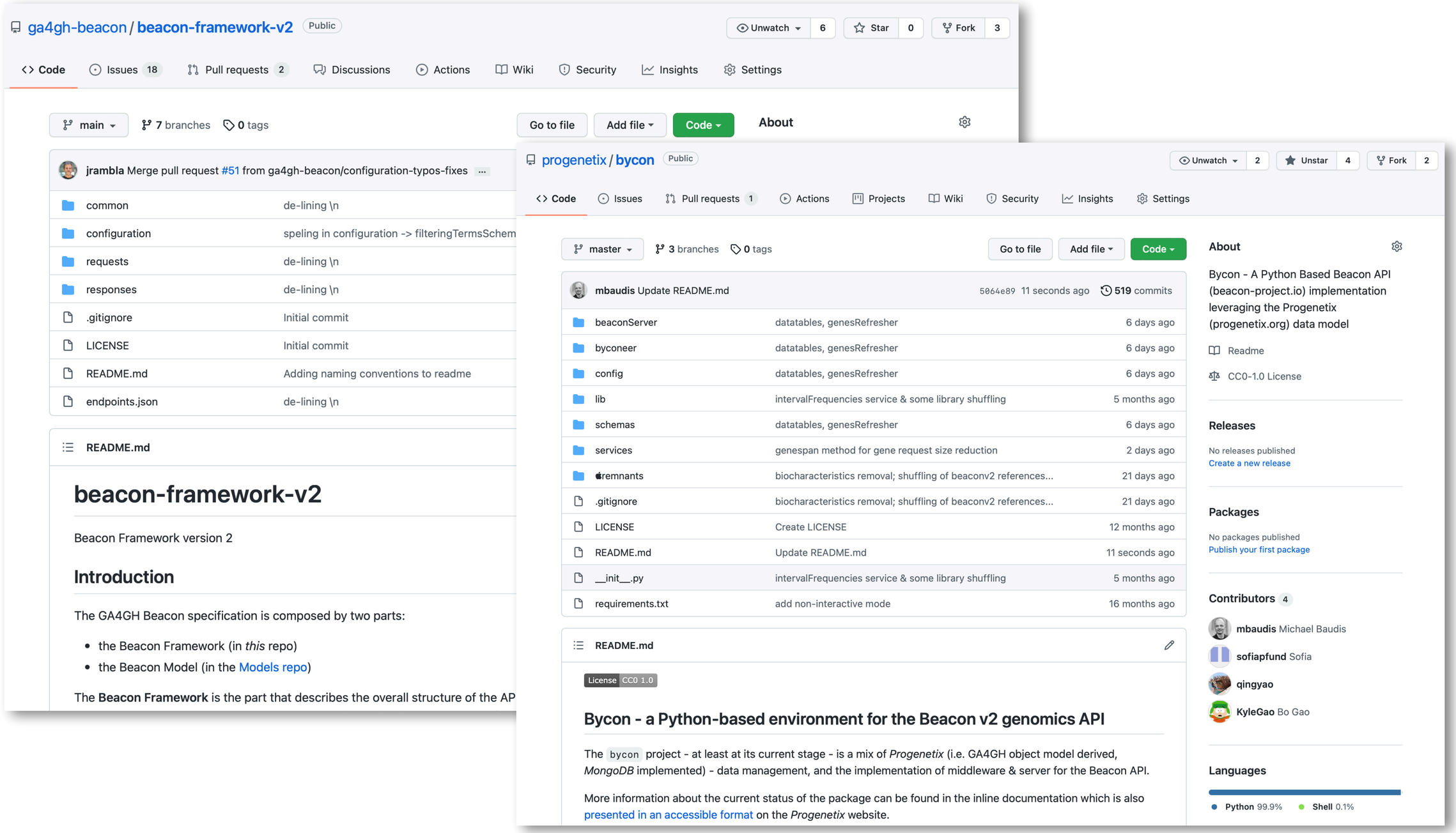
Michael Baudis

Global Alliance for Genomics & Health

SIB

University of Zurich UZH

elixir


ga4gh-beacon / beacon-framework-v2
Public
Unwatch 6
Star 0
Fork 3
Code
Issues 18
Pull requests 2
Discussions
Actions
Wiki
Security
Insights
Settings
main
7 branches
0 tags
Go to file
Add file
Code
About
jrambla Merge pull request #51 from ga4gh-beacon/configuration-typos-fixes
common de-lining \n
configuration speling in configuration -> filteringTermsSchem
requests de-lining \n
responses de-lining \n
.gitignore Initial commit
LICENSE Initial commit
README.md Adding naming conventions to readme
endpoints.json de-lining \n
README.md
beacon-framework-v2
Beacon Framework version 2
Introduction
The GA4GH Beacon specification is composed by two parts:
the Beacon Framework (in this repo)
the Beacon Model (in the Models repo)
The Beacon Framework is the part that describes the overall structure of the AP
progenetix / bycon
Public
Unwatch 2
Unstar 4
Fork 2
Code
Issues
Pull requests 1
Actions
Projects
Wiki
Security
Insights
Settings
master
3 branches
0 tags
Go to file
Add file
Code
mbaudis Update README.md
5064e89 11 seconds ago
519 commits
beaconServer datatables, genesRefresher 6 days ago
byconeer datatables, genesRefresher 6 days ago
config datatables, genesRefresher 6 days ago
lib intervalFrequencies service & some library shuffling 5 months ago
schemas datatables, genesRefresher 6 days ago
services genespan method for gene request size reduction 2 days ago
remnants biocharacteristics removal; shuffling of beaconv2 references... 21 days ago
.gitignore biocharacteristics removal; shuffling of beaconv2 references... 21 days ago
LICENSE Create LICENSE 12 months ago
README.md Update README.md 11 seconds ago
__init__.py intervalFrequencies service & some library shuffling 5 months ago
requirements.txt add non-interactive mode 16 months 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.
About
Bycon - A Python Based Beacon API (beacon-project.io) implementation leveraging the Progenetix (progenetix.org) data model
Readme
CC0-1.0 License
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 99.9%
Shell 0.1%

Onboarding

Demonstrating Compliance

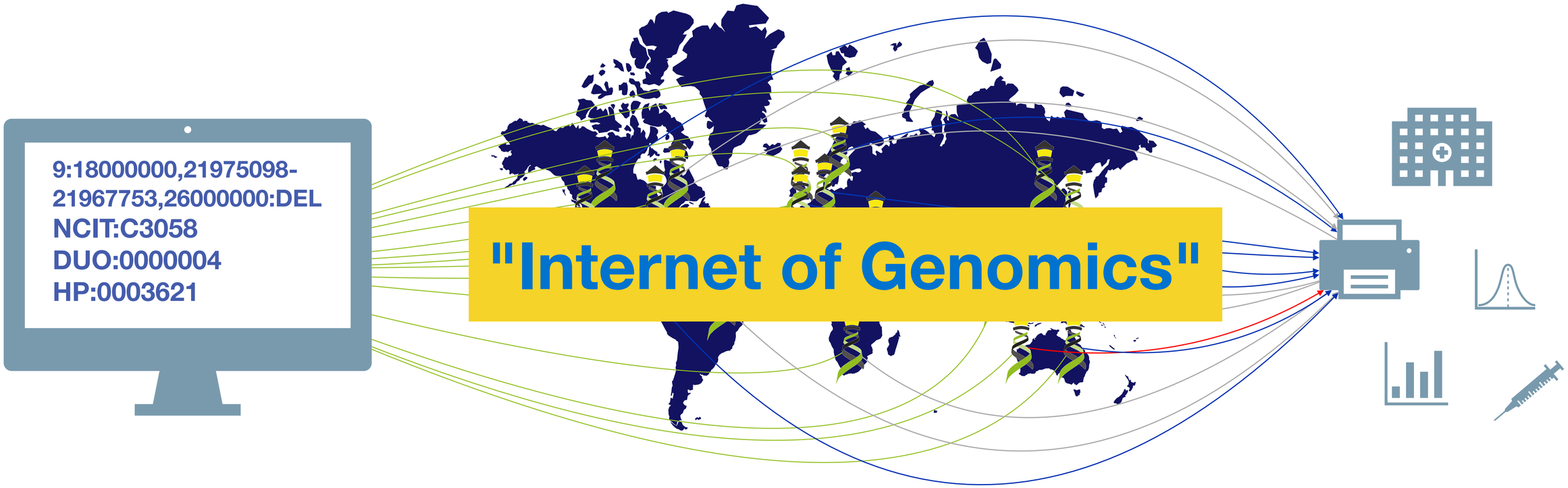
- Progenetix Beacon+ has served as implementation driver since 2016
- Beacon v2 as service with protocol-driven registries for federation
- GA4GH approved Beacon v2 in April 2022

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**".



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**".

Making use of Progenetix' Beacon API

Data analysis through integration with R

pgxRpi

An interface API for analyzing Progenetix CNV data in R using the Beacon+ API

	All users	R users
Interface	 	 
Variant query	https://progenetix.org/beacon/biosamples/pgxbs-kftvh94d/g_variants	variants <- pgxLoader(type="variant",biosample_id="pgxbs-kftvh94d")

Output


```
"results": [
    {
        "caseLevelData": [
            {
                "analysisId": "pgxcs-kftvu6cg",
                "biosampleId": "pgxbs-kftvh94d",
                "id": "pgxvar-5bab5837727983b2e0121e97"
            }
        ],
        "variantInternalId": "11:0-134452384:DEL",
        "variation": {
            "copyChange": "efo:0030067",
            "identifiers": {},
            "subject": {
                "interval": {
                    "end": {
                        "type": "Number",
                        "value": 134452384
                    },
                    "start": {
                        "type": "Number",
                        "value": 0
                    },
                    "type": "SequenceInterval"
                },
                "sequence_id": "refseq:NC_000011.10",
                "type": "SequenceLocation"
            },
            "variantAlternativeIds": []
        }
    },
    {
        "caseLevelData": [
            {
                "analysisId": "pgxcs-kftvu6cg",
                "biosampleId": "pgxbs-kftvh94d",
                "id": "pgxvar-5bab5837727983b2e0121e99"
            }
        ],
        "variantInternalId": "1:0-84699999:DEL",
        "variation": {
            "copyChange": "efo:0030067",
            "identifiers": {},
            "subject": {
                "interval": {
```


	variant_id	biosample_id	analysis_id	reference_genome	variant
1	pgxvar-5bab5837727983b2e0121e99	pgxbs-kftvh94d	pgxcs-kftvu6cg	refseq:NC_000001.11	1:0-84699999:DEL
2	pgxvar-5bab5837727983b2e0121e9a	pgxbs-kftvh94d	pgxcs-kftvu6cg	refseq:NC_000001.11	1:124300000-247249719:DEL
3	pgxvar-5bab5837727983b2e0121e9c	pgxbs-kftvh94d	pgxcs-kftvu6cg	refseq:NC_000002.12	2:12800000-61099999:DEL
4	pgxvar-5bab5837727983b2e0121e9d	pgxbs-kftvh94d	pgxcs-kftvu6cg	refseq:NC_000002.12	2:197100000-242951149:DEL
5	pgxvar-5bab5837727983b2e0121e94	pgxbs-kftvh94d	pgxcs-kftvu6cg	refseq:NC_000003.12	3:14700000-71799999:DEL
6	pgxvar-5bab5837727983b2e0121e8d	pgxbs-kftvh94d	pgxcs-kftvu6cg	refseq:NC_000004.12	4:35500000-191273063:DUP
7	pgxvar-5bab5837727983b2e0121e8e	pgxbs-kftvh94d	pgxcs-kftvu6cg	refseq:NC_000005.10	5:18500000-143099999:DUP
8	pgxvar-5bab5837727983b2e0121e91	pgxbs-kftvh94d	pgxcs-kftvu6cg	refseq:NC_000006.12	6:0-60499999:DEL
9	pgxvar-5bab5837727983b2e0121e92	pgxbs-kftvh94d	pgxcs-kftvu6cg	refseq:NC_000006.12	6:130400000-170899992:DEL

pgxRpi

An interface API for analyzing Progenetix CNV data in R using the Beacon+ API

Metadata query

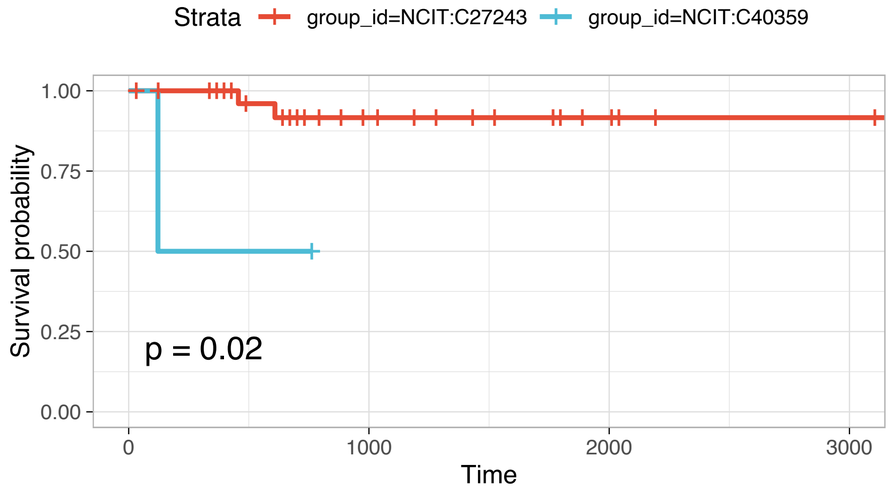
https://progenetix.org/beacon/individuals/?filters=NCIT:C3697

```
individuals <- pgxLoader(type='individual',filters='NCIT:C3697')
```

Output


```
{
    "description": null,
    "id": "pgxind-kftx359j",
    "indexDisease": {
        "clinicalTnmFinding": [],
        "diseaseCode": {
            "id": "NCIT:C3697",
            "label": "Myxopapillary Ependymoma"
        },
        "followupState": {
            "id": "EFO:0030041",
            "label": "alive (follow-up status)"
        },
        "followupTime": "P178M",
        "onset": {
            "age": "P16Y",
            "ageDays": 5843.88
        },
        "stage": {
            "id": "NCIT:C92207",
            "label": "Stage Unknown"
        }
    },
    "info": {
        "legacyIds": [
            "PGX_IND_Epend-car-01"
        ]
    },
    "provenance": {
        "geoLocation": {
            "geometry": {
                "coordinates": [
                    -1.4,
                    50.9
                ],
                "type": "Point"
            },
            "properties": {
                "city": "Southampton",
                "continent": null,
                "country": "United Kingdom",
                "latitude": 50.9,
                "longitude": -1.4,
                "precision": "city"
            },
            "type": "Feature"
        }
    },
    "sex": {
        "id": "PATO:0020001",
        "label": "male genotypic sex"
    },
    "updated": "2018-09-26 09:51:34.766000",
    "vitalStatus": {
        "status": "ALIVE",
        "survivalTimeInDays": 5384
    }
},
```


individual_id	sex_label	age_iso	histological_diagnosis_id	index_disease_followup_time	index_disease_followup_state_label
pgxind-kftx359j	male genotypic sex	P16Y	NCIT:C3697	P178M	alive (follow-up status)
pgxind-kftx35a0	male genotypic sex	P23Y	NCIT:C3697	P115M	alive (follow-up status)
pgxind-kftx35aa	male genotypic sex	P15Y	NCIT:C3697	P114M	alive (follow-up status)
pgxind-kftx35ac	male genotypic sex	P24Y	NCIT:C3697	P30M	alive (follow-up status)
pgxind-kftx35ai	female genotypic sex	P44Y	NCIT:C3697	P101M	alive (follow-up status)
pgxind-kftx35as	male genotypic sex	P50Y	NCIT:C3697	P331M	dead (follow-up status)
pgxind-kftx35bb	male genotypic sex	P28Y	NCIT:C3697	P48M	alive (follow-up status)



pgxRpi

An interface API for analyzing Progenetix CNV data in R using the Beacon+ API

GitHub: https://github.com/progenetix/pgxRpi

Bioconductor

README.md

pgxRpi

Welcome to our R wrapper package for Progenetix REST API that leverages the capabilities of Beacon v2 specification. Please note that a stable internet connection is required for the query functionality. This package is aimed to simplify the process of accessing oncogenomic data from Progenetix database.

You can install this package from GitHub using:

```
install.packages("devtools")
devtools::install_github("progenetix/pgxRpi")
```

For accessing metadata of biosamples/individuals, or learning more about filters, get started from the vignette Introduction_1_loadmetadata.

For accessing CNV variant data, get started from this vignette Introduction_2_loadvariants.

For accessing CNV frequency data, get started from this vignette Introduction_3_loadfrequency.

For processing local pgxseg files, get started from this vignette Introduction_4_process_pgxseg.

If you encounter problems, try to reinstall the latest version. If reinstallation doesn't help, please contact us.

pgxRpi

platforms all | rank 2218 / 2221 | support 0 / 0 | in Bioc devel only
build ok | updated < 1 month | dependencies 144

DOI: 10.18129/B9.bioc.pgxRpi
This is the **development** version of pgxRpi; to use it, please install the devel version of Bioconductor.

R wrapper for Progenetix

Bioconductor version: Development (3.19)

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

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

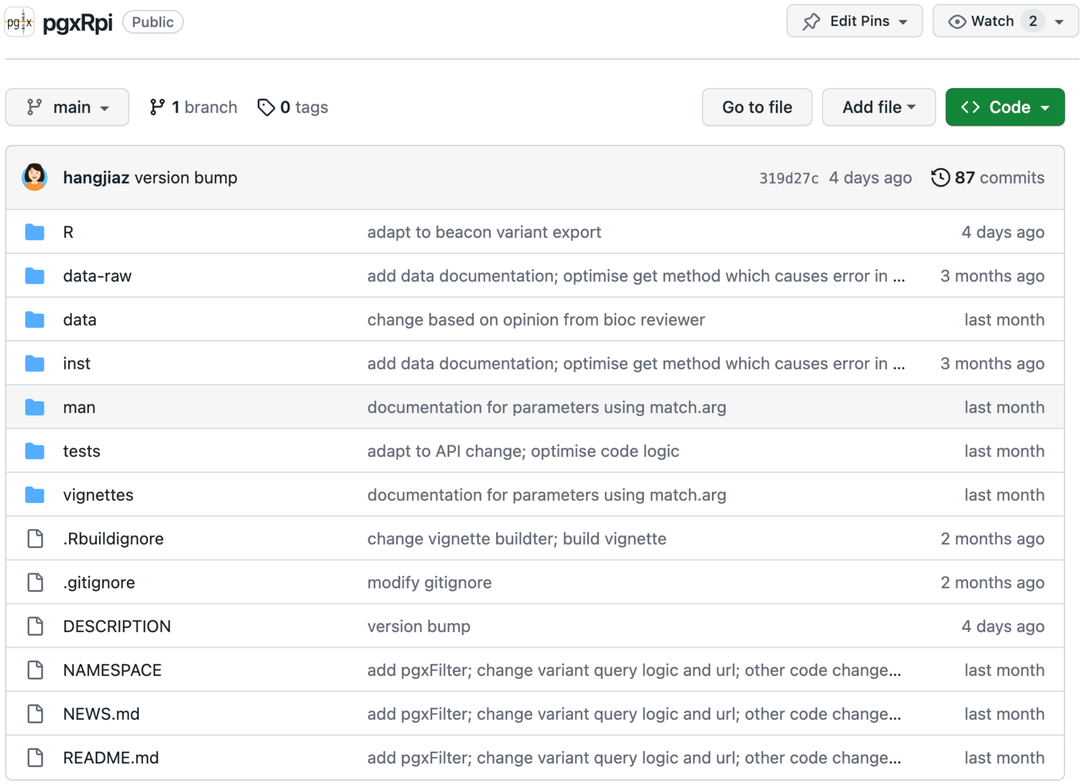
Maintainer: Hangjia Zhao <hangjia.zhao at uzh.ch>

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

Zhao H, Baudis M (2023). *pgxRpi: R wrapper for Progenetix*. doi:10.18129/B9.bioc.pgxRpi, R package version 0.99.9, https://bioconductor.org/packages/pgxRpi.

pgxRpi

An interface API for analyzing Progenetix CNV data in R using the Beacon+ API



pgxRpi Public

Edit Pins | Watch 2

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

hangjiaz version bump 319d27c 4 days ago 87 commits

R	adapt to beacon variant export	4 days ago
data-raw	add data documentation; optimise get method which causes error in ...	3 months ago
data	change based on opinion from bioc reviewer	last month
inst	add data documentation; optimise get method which causes error in ...	3 months ago
man	documentation for parameters using match.arg	last month
tests	adapt to API change; optimise code logic	last month
vignettes	documentation for parameters using match.arg	last month
.Rbuildignore	change vignette buildter; build vignette	2 months ago
.gitignore	modify gitignore	2 months ago
DESCRIPTION	version bump	4 days ago
NAMESPACE	add pgxFilter; change variant query logic and url; other code change...	last month
NEWS.md	add pgxFilter; change variant query logic and url; other code change...	last month
README.md	add pgxFilter; change variant query logic and url; other code change...	last month

2 Retrieve meatdata of samples

2.1 Relevant parameters

type, filters, filterLogic, individual_id, biosample_id, codematches, limit, skip

2.2 Search by filters

Filters are a significant enhancement to the Beacon query API, providing a mechanism for specifying rules to select records based on their field values. To learn more about how to utilize filters in Progenetix, please refer to the documentation.

The `pgxFilter` function helps access available filters used in Progenetix. Here is the example use:

```
# access all filters
all_filters <- pgxFilter()
# get all prefix
all_prefix <- pgxFilter(return_all_prefix = TRUE)
# access specific filters based on prefix
ncit_filters <- pgxFilter(prefix="NCIT")
head(ncit_filters)
#> [1] "NCIT:C28076" "NCIT:C18000" "NCIT:C14158" "NCIT:C14161" "NCIT:C28077"
#> [6] "NCIT:C28078"
```

The following query is designed to retrieve metadata in Progenetix related to all samples of lung adenocarcinoma, utilizing a specific type of filter based on an NCIt code as an ontology identifier.

```
biosamples <- pgxLoader(type="biosample", filters = "NCIT:C3512")
# data looks like this
biosamples[c(1700:1705),]
#>       biosample_id group_id group_label   individual_id    callset_ids
#> 1700 pgxbs-kftvjjhx       NA          NA pgxind-kftx5fyd pgxcs-kftwjevi
#> 1701 pgxbs-kftvjjhz       NA          NA pgxind-kftx5fyf pgxcs-kftwjew0
#> 1702 pgxbs-kftvjji1       NA          NA pgxind-kftx5fyh pgxcs-kftwjewi
#> 1703 pgxbs-kftvjjn2       NA          NA pgxind-kftx5g4r pgxcs-kftwjg5r
#> 1704 pgxbs-kftvjjn4       NA          NA pgxind-kftx5g4t pgxcs-kftwjg6q
#> 1705 pgxbs-kftvjjn5       NA          NA pgxind-kftx5g4v pgxcs-kftwjg78
```

Components of an Online Bioinformatics Resource

Going Full Stack?

Components of an Online Bioinformatics Resource

A Stack to work with/through

- dedicated server or cloud storage
- own domain | institutional sub-domain or fixed address | cloud service sub-domain
  - ➙ `progenetix.org | mls.uzh.ch/en/research/baudis | baudisgroup.github.io`
- database or flat file data management
  - ➡ SQL databases such as PostGres, MySQL
  - ➡ document databases such as MongoDB, CouchDB ...
  - ➡ hierarchical file system & index files
- webserver gateway for server-side generated, active content delivery
  - ➡ Perl CGI, Python, PHP ...
- active front-end (JavaScript environment)?

Progenetix Stack

progenetix

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

React

APACHE HTTP SERVER PROJECT

python™

mongoDB

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

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


variants


analyses


biosamples


individuals

Entity collections


collations


geolocs


genespans


publications


qBuffer

Utility collections

Last but NOT Least…

Documentation is, actually, rather important

Documentation Strategies

(Not so) Best Practices

```
f_d = f_d_s[c_t]
r = {}
for k in res_schema.keys():
    if k in f_d:
        r.update({k:f_d[k]})
```

- What is documentation? I'll remember this! ¯_(ツ)_/¯
- Just email me if help is needed, unexpectedly
- We had money for a chat bot.
- Clean code documents itself - Just use explicit variable/function names.
- Clean code documents itself - Never use explicit variable/function names.
- Perl POD it is. There is a command to show the notes in your terminal…
- I wrote a paper about the resource. In 2001.
- Haven't you found the GoogleGroups account?
- Documentation? StackOverflow, whelp!

mbaudis@netscape.net

```
normalize_variant_values_for_export(v, byc, drop_fields=None):
```

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

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

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

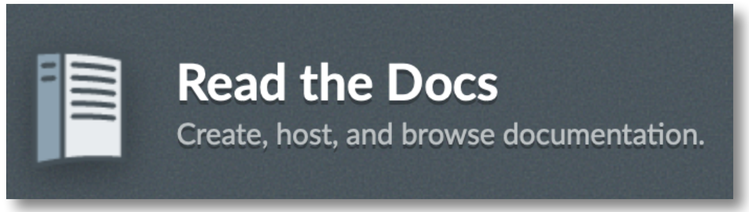
[1]Medizinische Klinik und Poliklinik V der Universität Heidelberg, Germany and [2]Department of Pathology, Stanford University Medical Center, Stanford, CA 94305, USA

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

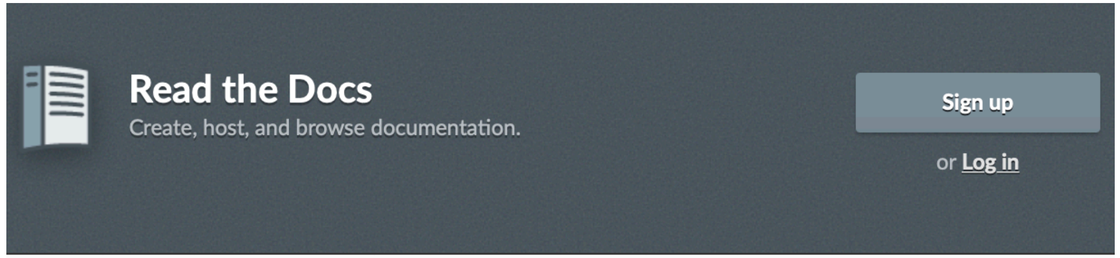
Documentation Strategies

Currently en Vogue

- Cloud-based documentation systems with online compilation
- written in simplified markup languages
  - ➡ Markdown (Yeah!)
  - ➡ Restructured Text (Meeh...)
- local and/or service based compilation and hosting
- build systems & output hosting
  - ➡ ReadTheDocs
    - direct building from .rst document tree or MkDocs based
  - ➡ Github Pages
    - direct using Jekyll or over MkDocs through GH actions



Documentation Strategies



Technical documentation lives here

Read the Docs simplifies software documentation by automating building, versioning, and hosting of your docs for you.

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Always up to date

Whenever you push code to your favorite version control service, whether that is GitHub, BitBucket, or GitLab, we will automatically build your docs so your code and documentation are never out of sync.

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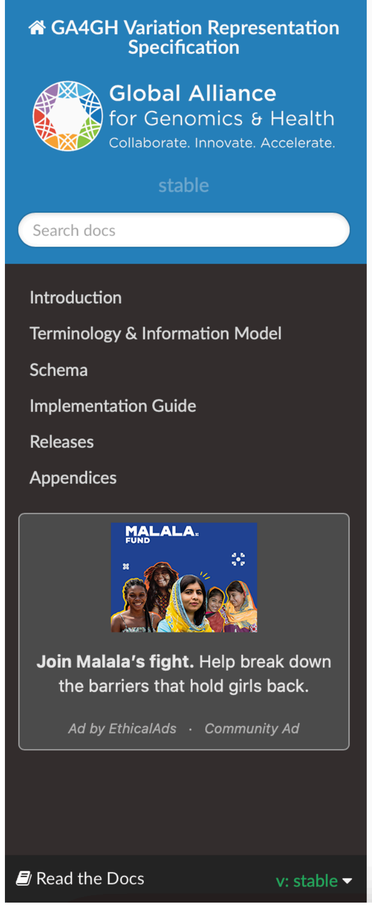
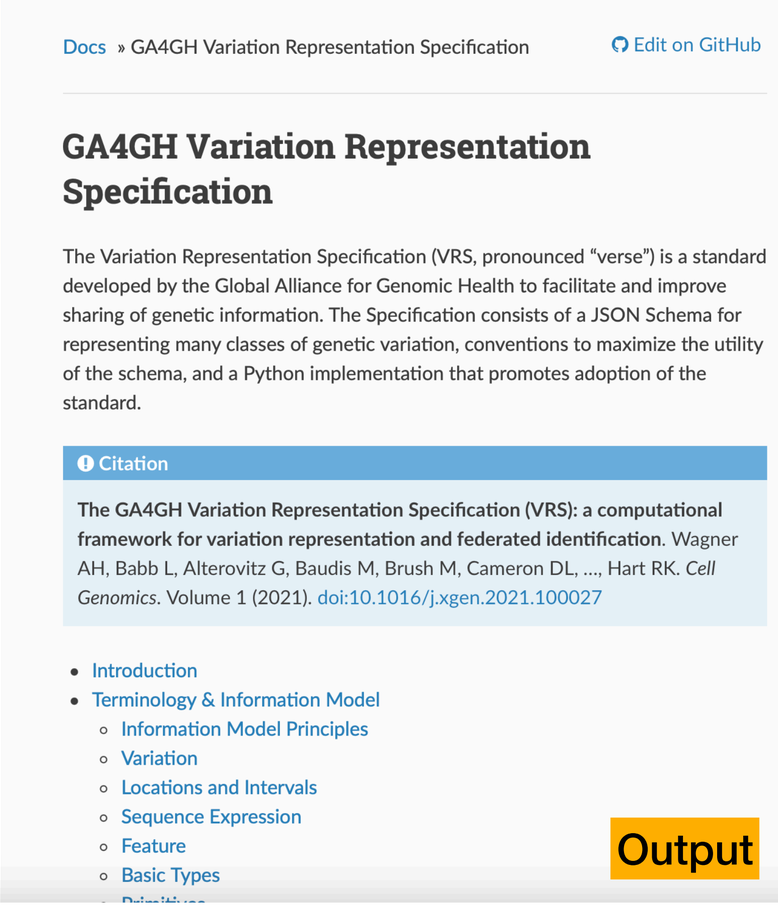
We build and host your docs for the web, but they are also viewable as PDFs, as single page HTML, and for eReaders. No additional configuration is required.

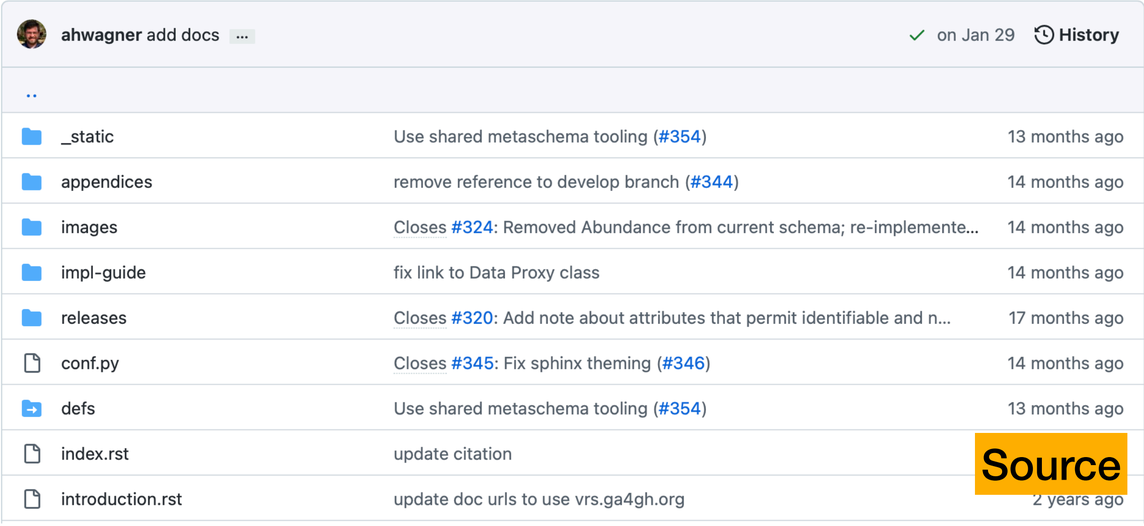
Multiple versions

We can host and build multiple versions of your docs so having a 1.0 version of your docs and a 2.0 version of your docs is as easy as having a separate branch or tag in your version control system.

Example: GA4GH Variation Representation Standard ->





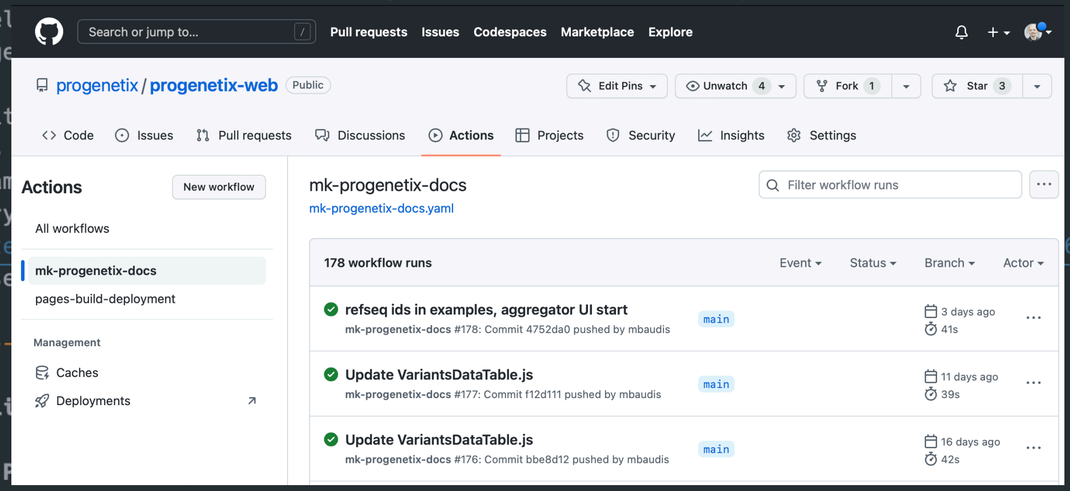


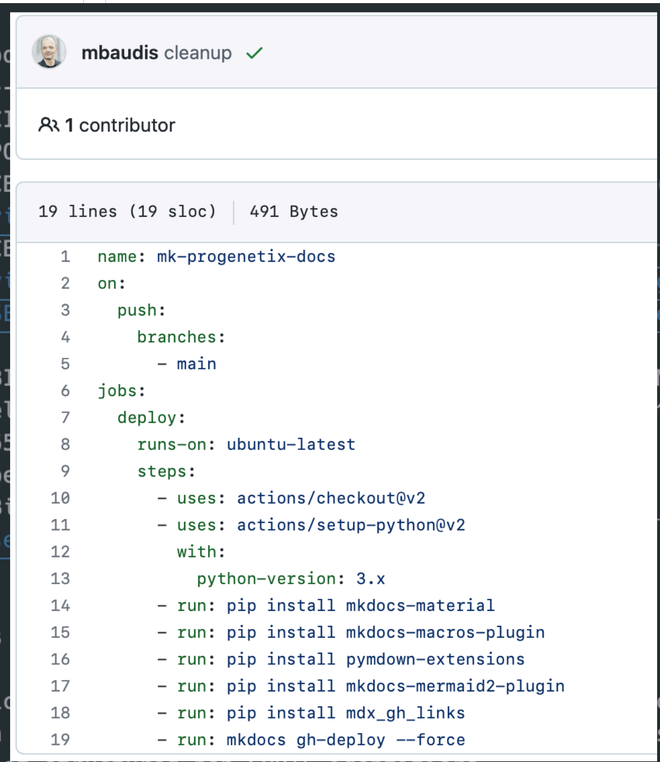

FOLDERS
progenetix-web
.github
.next
docs
css
img
javascripts
news
beaconplus.md
changelog.md
classifications-an
CNAME
index.md
progenetix-data-r
progenetix-websi
publication-collec
services.md
technical-notes.m
ui.md
use-cases.md
extra
node_modules
out
public
src
.babelrc
.env.development
.env.production
.eslintrc.json
.gitignore
.prettierrc
jest.config.js
mkdocs.yaml
next.config.js
package-lock.json
package.json
README.md
mkdocs.yaml
site_name: Progenetix Documentation
site_description: 'Documentation for the Progenetix oncogen
site_author: Michael Baudis
copyright: '© Copyright 2022, Michael Baudis and proge
repo_name: 'progenetix-web'
repo_url: https://github.com/progenetix/progenetix-web
nav:
- Documentation Home: index.md
- News & Changes: news
- Publication Collection: publication-collection
- Data Review: progenetix-data-review
- Technical Notes: technical-notes
- Progenetix Website Builds: progenetix-website-builds
- Progenetix Data ↗: http://progenetix.org
- Baudisgroup @ UZH ↗: http://info.baudisgroup.org
markdown_extensions:
- toc:
toc_depth: 2-3
permalink: true
- admonition
- attr_list
- footnotes
- md_in_html
- pymdownx.critic
- pymdownx.caret
- pymdownx.details
- pymdownx.keys
- pymdownx.magiclink:
hide_protocol: true
- pymdownx.mark
- pymdownx.tilde
- pymdownx.saneheaders
classifications-and-ontologies.md
Classifications, Ontologies and Standards
The Progenetix resource utilizes standardized diagnostic coding systems, with a move towards hierarchical ontologies. As part of the coding process we have developed and provide several code mapping resources through repositories, the Progenetix website and APIs.
Additionally to diagnostic and other clinical concepts, Progenetix increasingly uses hierarchical terms and concepts for the annotation and querying of technical parameters such as platform technologies. Overall, the Progenetix resource uses a query syntax based around the [Beacon v2 "filters"](https://beacon-project.io/v2/filters.html) concept with a [CURIE](https://www.w3.org/TR/2010/NOTE-curie-20101216/) -based syntax
MkDocs & Material for MkDocs & Github Actions
Public Ontologies with CURIE-based syntax
CURIE prefix	Code/Ontology	Examples
NCIT	NCIt Neoplasm[^1]	NCIT:C27676
HP	HPO[^2]	HP:0012209
PMID	NCBI Pubmed ID	[PMID:18810378](http://progenetix.org/services/ids/PMID:18810378)
geo	NCBI Gene Expression Omnibus[^3]	[geo:GPL6801](http://progenetix.org/services/ids/geo:GPL6801), [geo:GSE19399](http://progenetix.org/services/ids/geo:GSE19399), [geo:GSM491153](http://progenetix.org/services/ids/geo:GSM491153)
arrayexpress	EBI ArrayExpress[^4]	arrayexpress:E-MEXP-1008
cellosaurus	Cellosaurus - a knowledge resource on cell lines [^5]	cellosaurus:CVCL_1650
UBERON	Uberon Anatomical Ontology[^6]	UBERON:0000992
cbioportal	cBioPortal[^9]	[cbioportal:msk_impact_2017](http://progenetix.org/services/ids/cbioportal:msk_impact_2017)
Private filters
Since some classifications cannot directly be referenced, and in accordance with the upcoming Beacon v2 concept of "private filters", Progenetix uses additionally a set of structured non-CURIE identifiers.

Local Testing

```
→  progenetix-web git:(main) mkdocs serve
INFO     -  Building documentation...
INFO     -  [macros] - Macros arguments: {'module_name': 'main',
           'modules': [], 'include_dir': '', 'include_yaml': [],
           'j2_block_start_string': '', 'j2_block_end_string': '',
           'j2_variable_start_string': '', 'j2_variable_end_string': '',
           'on_undefined': 'keep', 'on_error_fail': False, 'verbose': False}
INFO     -  [macros] - Extra variables (config file):
           ['excerpt_separator', 'blog_list_length', 'social']
INFO     -  [macros] - Extra filters (module): ['pretty']
INFO     -  MERMAID2  - Initialization arguments: {}
INFO     -  MERMAID2  - Using javascript library (8.8.0):
              https://unpkg.com/mermaid@8.8.0/dist/mermaid.min.js
INFO     -  Cleaning site directory
INFO     -  The following pages exist in the docs directory, but are not
           included in the "nav" configuration:
             - beaconplus.md
             - changelog.md
             - classifications-and-ontologies.md
             - progenetix-data-review.md
             - progenetix-website-builds.md
             - publication-collection.md
INFO     -  MERMAID2  - Found superfences config: {'custom_fences': [{'name':
           'mermaid', 'class': 'mermaid', 'format': <function fence_mermaid at
           0x104075ab0>}]}
INFO     -  MERMAID2  - Page 'Technical Notes': found 2 diagrams, adding scripts
INFO     -  Documentation built in 0.83 seconds
INFO     -  [09:05:32] Watching paths for changes: 'docs', 'mkdocs.yaml'
INFO     -  [09:05:32] Serving on http://127.0.0.1:8000/
INFO     -  [09:05:33] Browser connected:
           http://127.0.0.1:8000/classifications-and-ontologies/
```

Web Deployment (Github)





Classifications, Ontologies and Standards

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Additionally to diagnostic and other clinical concepts, Progenetix increasingly uses hierarchical terms and concepts for the annotation and querying of technical parameters such as platform technologies. Overall, the Progenetix resource uses a query syntax based around the Beacon v2 "filters" concept with a CURIE based syntax.

List of filters recognized by different query endpoints

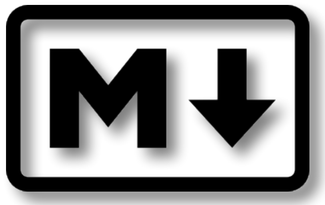
Public Ontologies with CURIE-based syntax

CURIE prefix	Code/Ontology	Examples
NCIT	NCIt Neoplasm[1]	NCIT:C27676

Documentation Strategies

Best Practices

- start early
- update often
- sometimes try to follow your own guide
- balance between inline documentation & doc system
- use Markdown
- plan for contingencies
  - ➡ cloud providers disappear | cancel services | change terms



https://en.wikipedia.org/wiki/List_of_defunct_social_networking_services

https://en.wikipedia.org/wiki/List_of_search_engines#Defunct_or_acquired_search_engines

Progenetix as Example Genomics Resource

Some trajectories ...

- from local database to **online resource**
- from flat database to **hierarchical object storage**
- from dedicated database to mix of **open software tools**
- from static pages to **data driven website**
- from copy, paste, clean to **automated download & process** - still edit & clean
- from registered access to raw data & commercial licensing to **CC BY 4.0** (CC0 for tools)
- from local software development to **open code on Github**
- from standalone resource to federated data, **APIs** and services

progenetix

(Bio)informatics Skill Set

What has been needed to develop & maintain progenetix.org?

- Scripting and application development using Python, Perl and JavaScript
- Data analysis and plotting in R, Python and Perl
- Regular expressions for data entry an (programmatic) identifier matching
- JSON, YAML, tab-delimited text as file formats; some binary source files (.CEL)
- non-SQL database (MongoDB) for flexibility and document structure
- web development with Perl, Python, JS, React and Apache server; Cloudflare
- No proprietary software involved (some OpenOffice Calc / Google Sheets spreadsheets for data cleanup)

progenetix

(Bio)informatics Skill Set

What has been needed to develop & maintain progenetix.org?

GitHub

Perl

regular expressions

```
s/knowledge/mastery/
```

text mining

React

mongoDB

M↓

APACHE HTTP SERVER PROJECT

R

MkDocs

Project documentation with Markdown.

python™

HTML CSS JS

array & sequencing pipelines

BIO390: Course Schedule

- 2023-09-19: Christian von Mering - Sequence Bioinformatics
- 2023-09-26: Michael Baudis - What is Bioinformatics? Introduction and Resources
- 2023-10-03: Mark Robinson - Statistical Bioinformatics
- 2023-10-10: Shinichi Sunagawa (ETHZ) - Metagenomics
- 2023-10-17: Izaskun Mallona - Regulatory Genomics and Epigenomics
- 2023-10-24: Valentina Boeva (ETHZ) - Machine Learning for Biological Use Cases
- 2023-10-31: Katja Baerenfaller (SIAF) - Proteomics
- 2023-11-07: Pouria Dasmeh - Biological Networks
- 2023-11-14: Patrick Ruch - Text mining & Search Tools
- 2023-11-21: Ahmad Aghaebrahimian (ZHAW) - Semantic Web
- 2023-11-28: Michael Baudis - Building a Genomics Resource
- **2023-12-05: Valérie Barbie (SIB) - Clinical Bioinformatics**
- 2023-12-12: Michael Baudis - Genome Data & Privacy | Feedback
- 2023-12-19: Exam (Multiple Choice)

Master Project in Data Wrangling? Ask!

BIO390 HS23

Exam planning

- On site exam!
- 2023-12-19
- time: 08:15-09:45
- multiple (single + multiple) choice w/ one or two open questions
- no material, phones etc.
- student ID for entrance