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LIBRARY OF ARIZONA STATE UNIVERSITY, U.S.: Targeted  
BEL network representation and characterization of  
commonly mutated genes in Non-Small Cell Lung Carcinoma  
(NSCLC)**

Shradha Mukherjee

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1 **Title:** Targeted BEL network representation and characterization of commonly mutated genes in  
2 Non-Small Cell Lung Carcinoma (NSCLC)

3  
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8 **Source:** Arizona State University (ASU) MAS Health Informatics BMI\_593 Applied Project of  
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10  
11 **Summary Statement:** A computational pipeline for mobilization of scientific knowledge to  
12 inform drug selection based on patient genetic variation profile for precision medicine in Non-  
13 Small Cell Lung Carcinoma (NSCLC).

#### 14 15 **Abstract:**

16 Non-Small Cell Lung Carcinoma (NSCLC) is the most common form of lung cancer and the  
17 third most common cancer overall with respect to numbers, and deaths (American Cancer  
18 Society, Cancer Facts and Figures, Feb 2019). Previous studies have shown that targeting a  
19 commonly mutated NSCLC gene EGFR with Tyrosine kinase inhibitor (TKI) drugs is successful  
20 in patients who have EGFR mutations. It is now being recognized that overall NSCLC patient  
21 outcomes can be further improved by targeting other commonly mutated NSCLC genes in  
22 addition to the widely studies and targeted EGFR. However, DNA sequencing outputs show  
23 multiple mutations or variations in genes, which are too many to interpret, study and target with  
24 drugs. To overcome this limitation, the goal of the present study was to build a NSCLC specific  
25 knowledge base that can be used to prioritize mutated genes from a given patient genetic profile  
26 and drugs to target these genes. Commonly mutated NSCLC genes reported in NSCLC cases  
27 were used as a ‘bait’ to ‘capture’ and create a computable NSCLC knowledge base using BEL  
28 (Biological Expression Language) statements. This NSCLC specific knowledge base consisted  
29 of 33 pathogenic variants, 129 significant gene functional annotations (GO, gene ontology terms)  
30 and 568 drugs BEL knowledge statements. Overlaying 17 different NSCLC patient genetic  
31 profiles against our NSCLC specific knowledge base, successfully computed and prioritized  
32 distinct genes harboring mutations, and drugs to target these genes in patients. Here we  
33 developed this computational pipeline for NSCLC and this methodology can be adapted for other  
34 diseases with known common gene mutations. Taken together, we provide a paradigm to  
35 prioritize and select drugs based on patient’s genetic profile for precision medicine based clinical  
36 decision support.

#### 37 38 **Introduction:**

39 Treatment options for NSCLC include surgery, radiation, chemotherapy, immunotherapy  
40 and targeted treatment. The advantage of targeted therapy is that unlike the other forms of  
41 treatment targeted therapy is designed to specifically attack cancer by blocking molecular targets  
42 in the cancer. EGFR is one of the most common mutations found in 10-35% of NSCLC patients  
43 and tyrosine kinase inhibitors (TKIs) drugs that target EGFR pathway specifically are  
44 successfully used in these cases (1). In addition to EGFR, there are also other gene mutations  
45 found in NSCLC that could be targeted with drugs avoiding a “one-size-fits-all” approach, and  
46 offers potential to use a combination of drugs to target multiple mutations in NSCLC for

47 successful treatment (2). It still remains a challenge to find an optimal combination of drugs,  
48 which targets most of the disease related cellular changes caused by gene mutation without drug  
49 overuse. One drug development strategy is to pick a combination of drugs that each directly  
50 target different regulatory hub genes in the networks, which can then initiate a ‘domino effect’  
51 by modulating different cohorts of interacting genes connected to the hub gene. This strategy is  
52 the basis of the growing field of ‘network medicine’ (3).

53 Given the growing appreciation of the benefit of taking a global systems approach to  
54 target an ensemble of commonly mutated NSCLC gene with drugs, the development of suitable  
55 biomedical knowledge and big data driven informatics tools and workflows to identify key  
56 regulatory NSCLC mutations and inform clinical decision making for development of  
57 combinatorial targeted drug delivery has become increasingly important. ‘Omics’ or genomics  
58 data and biomedical literature text data are the two major sources for information about genes  
59 and gene interaction in the context of human health and disease. Both omics data and text data  
60 resources have been the basis of extensive research for development of gene networks and  
61 pathways to identify key regulators underlying disease phenotype and can serve as drug targets.  
62 Extensive research endeavors have led to the collection of RNA-sequencing (RNA-seq),  
63 chromatin immunoprecipitation sequencing (ChIP-seq), ES (Exome Sequencing), Whole Exome  
64 Sequencing (WES), high-throughput proteomics and other ‘omics’ data from patients (4). The  
65 Cancer Genome Atlas Research Network (TCGA <http://cancergenome.nih.gov/>), International  
66 Cancer Genome Consortium (ICGC <http://icgc.org/>), Alzheimer’s Disease Genetics Consortium  
67 (ADGC <http://www.adgenetics.org/>) are some of the examples of a few projects where the omics  
68 data is collected and stored from a wide sample of patients.

69 Though omics datasets are fast growing, most of the biomedical research knowledge on  
70 gene interaction, effects and context is present in the form open text in biomedical literature.  
71 Pubmed <https://www.ncbi.nlm.nih.gov/pubmed/> is the online site where a large volume of  
72 biomedical literature is housed and the vastness of this resource is demonstrated by the fact that a  
73 quick search with the term ‘non-small cell lung cancer’ shows 76958 results on Pubmed. The  
74 availability of omics data and text data has opened unprecedented opportunities to study gene-  
75 gene interaction networks, called ‘interactome’ and the effects of gene-gene interactions on  
76 phenotype in the context of human disease. For high throughput omics data, construction of  
77 disease specific networks relies on advanced computational and statistical methods that can  
78 handle the high complexity and high dimensionality of biological networks. Initial approaches  
79 for development of omics data based regulatory networks regulated by central hubs included  
80 Boolean networks, Bayesian networks and differential equation models, which due to limitation  
81 in scalability were later replaced by Poisson graphical models and negative binomial  
82 distributions (5, 6). For open text data on gene interactions, construction of disease specific  
83 networks relies on text-mining techniques and methods, where gene-gene interaction and context  
84 information extracted from a body of text called ‘corpus’ is used as a foundation, converted to a  
85 computable form and manually curated to build a regulatory network (7, 8). For text-mining  
86 biomedical literature and representing the biological relations, such as gene-gene interactions in  
87 a computable form, the well-established standards available are Systems Biology Markup  
88 Language (SBML), Biological Pathway Exchange Language (BPEL) and Biological Expression  
89 Language (BEL) (9).

90 Presently, a NSCLC specific knowledge base was built to prioritize genes to target with  
91 drugs from patient genetic variation profile. Drugs for a given patient genetic profile was  
92 suggested based on overlap with gene variant and/or gene ontology NSCLC specific knowledge

93 base. Testing this pipeline on publicly available genetic variation profile of NSCLC patients  
94 revealed 3 classes of patients based on if matches were found or not in one or both NSCLC  
95 knowledge base subsets, genetic variation and gene ontology. In future, this NSCLC pipeline can  
96 be used to support development drug-gene pair rules-based treatment plans for a given gene  
97 mutation profile of NSCLC patients.  
98  
99

## 100 **Methods:**

### 101 Code Availability

102 Computational code with html or pdf rendering showing input and output of code chunks is  
103 available as a git local repository at <https://icedrive.net/s/Ww9Y35fjuZu6akSkYa8xaChFQTG6>  
104 with all files and as a git remote repository at  
105 [https://gitlab.com/smukher2/nsclc\\_drugtargetsmutations\\_nov2019](https://gitlab.com/smukher2/nsclc_drugtargetsmutations_nov2019) with large files ignored or  
106 removed.  
107

### 108 Retrieval of commonly mutated NSCLC genes

109 Mycancergenome (<https://www.mycancergenome.org/>) is an online open source curated  
110 knowledge resource that has current information on cancer related mutations, clinical trials,  
111 drugs, pathways and biomarkers designed to facilitate development of precision medicine (10). A  
112 list of commonly mutated genes in NSCLC reported in this site  
113 (<https://www.mycancergenome.org/content/disease/non-small-cell-lung-carcinoma/>) were copied  
114 and stored in excel format. A total of 28 genes commonly mutated in NSCLC and the number of  
115 cases for each were retrieved in this manner.

### 116 Python as the language of choice

117 All computational codes in this work were written using python because of its human readable  
118 and intuitive syntax, fast performance and rich resource of libraries that enable accomplishment  
119 of complex tasks with only a few lines of code (11).  
120

### 121 NSCLC GO knowledgebase: GO annotation of commonly mutated NSCLC genes

122 Enrichr (<https://amp.pharm.mssm.edu/Enrichr/>) is an online web-tool, also available through  
123 API, which can perform statistical enrichment analysis on any list of genes by comparing the  
124 gene list to several biological functional annotation resources such as GO (12). The commonly  
125 mutated NSCLC genes, were searched using python search API to retrieve significant gene  
126 ontology terms characterized with GO terms significantly associated with NSCLC. Each GO  
127 term is associated with multiple genes so the results were parsed by gene name column to create  
128 a table of gene-GO term to build a population level NSCLC GO term knowledge base primed for  
129 comparison with patient genes. The results were exported and saved in .excel format.  
130

### 131 NSCLC pathogenic variants knowledgebase: Pathogenic variant annotation of commonly 132 mutated NSCLC genes

133 Simple ClinVar (<http://simple-clinvar.broadinstitute.org/>) is an online web-tool that curates  
134 reported variants associated with diseases as pathogenic, probable pathogenic, benign and  
135 unknown (13). Simple ClinVar was searched with search term “non-small cell lung cancer” to  
136 retrieve a table of NSCLC associated variants. The results were exported as excel file and used  
137 as input in the Python code to keep only the pathogenic NSCLC variants. The results from this

138 analysis comprised population level NSCLC pathogenic variants knowledge base primed for  
139 comparison with patient genes. The results were exported and saved in .excel format.

140

#### 141 NSCLC gene-drug pair knowledgebase: Drugs to target commonly mutated NSCLC genes

142 The DGIdb ([http://www.dgidb.org/search\\_interactions](http://www.dgidb.org/search_interactions)) is a drug gene interaction database built  
143 from over thirty sources, with each drug-gene interaction referenced to Pubmed (14). DGIdb is  
144 available as a web-tool and is also searchable through python search API. Python API search of  
145 DGIdb with commonly mutated NSCLC genes provided a list of drug-gene pairs and associated  
146 scores for number of citations associated with a given interaction. The resultant population level  
147 NSCLC gene-drug pair knowledge base was exported and saved in .excel format.

148

#### 149 Visualization of commonly mutated NSCLC network using BioDati Studio

150 BioDati Studio (<https://studio.demo.biodati.com/>) is powered by a well-defined and extensive  
151 collection of essential gene interaction evidence lines extracted from biomedical literature in  
152 Pubmed and coded into BEL statements by BEL coding experts. This extracted BEL statements  
153 can be utilized by users using BioDati Studio's user-friendly web interface for building gene  
154 networks. To build a network on BioDati Studio, the interactions in NSCLC pathogenic variants,  
155 NSCLC GO terms and NSCLC drug-gene pairs knowledgebases were converted to BEL  
156 statements. Next, the BEL statements annotated with citation urls and database urls, and other  
157 metadata were saved as nanopubs (small units of knowledge represented as BEL). The nanopubs  
158 were imported into BioDati Studio using the "import nanopubs" function and the network was  
159 visualized using "draft network" function. This network was then visualized by clicking  
160 'Visualizer' function on BioDati Studio and by using the "zoom" tool, it was possible to see the  
161 genes (nodes) and connections (edges) in the network.

162

#### 163 Retrieval of patient genetic profiles

164 Full patient genetic profiles are not readily available through open access due to HIPA  
165 restrictions. A truncated list of total ~3.5K validated NSCLC patient genetic variation or  
166 mutation profiles were obtained for a total of 12 patients from previously published work (15).

167

#### 168 Overlay of patient genetic profile on NSCLC knowledgebase

169 Validated patient genetic profiles for the 12 NSCLC patients were overlapped against the  
170 population level NSCLC knowledge base. The computational analysis resulted in  
171 recommendations of different potential drugs for each of the patients. Drug suggestions were  
172 computed based on overlap of patient's genetic profile with NSCLC pathogenic variant  
173 knowledgebase and NSCLC GO term knowledgebase. For visualization, patient genes that  
174 overlapped with the population level NSCLC knowledgebase were zoomed on and viewed on the  
175 population level NSCLC knowledgebase or nanopubs that had been built on BioDati studio.

176

177

#### 178 **Results:**

#### 179 Pathogenic variants and GO terms knowledgebases from commonly mutated genes in NSCLC 180 and knowledgebases

181 The distribution of frequency of cases with mutations or variants that commonly occur in  
182 NSCLC was highest for TP53 (4463 cases) followed by KRAS (2637cases) and EGFR (1969  
183 cases) (Fig. 2A). The frequency of cases with mutations or variants was comparable for the

184 remainder of the 28 genes commonly mutated in NSCLC (Fig. 2A). From ClinVar, 13 KRAS  
185 variants, 8 EGFR variants, 4 PIK3CA variants and 8 BRAF variants reported to be pathogenic in  
186 NSCLC were computationally retrieved (Fig. 2B). The report of only 4 out of 28 commonly  
187 mutated genes known to be pathogenic suggests that more research is required to gather more  
188 information on the pathogenicity of NSCLC genetic variation. From enrichr, a total of 130  
189 significant (p-value <0.05) GO terms were obtained for the 28 commonly mutated NSCLC  
190 genes, with EGFR, TP53, ERBB4, NTRK3 and KDR genes associated with >40 GO terms (Fig.  
191 2C). This suggests that either these 5 highly GO term enriched genes have a multitude of  
192 biological functions or have been studied more by researchers relative to the other 23 commonly  
193 mutated NSCLC genes. Search of the DGIdb database for drugs that can target the 28 commonly  
194 mutated NSCLC genes, retrieved 329 drugs for the NSCLC pathogenic variants knowledgebase  
195 genes and 569 drugs for the NSCLC GO terms knowledgebase genes.

#### 197 Visualization of NSCLC pathogenic variants and drug-gene interaction knowledge bases on 198 BioDati Studio

199 Visualization of the NSCLC pathogenic variants knowledge base nanopub and NSCLC drug-  
200 gene interaction knowledgebase nanopub revealed a complex network of interactions between  
201 the genes and drugs, with 1119 edges and 629 nodes (Fig. 3). The 4 NSCLC variant  
202 knowledgebase genes KRAS, EGFR, PIK3CA and BRAF genes, and the drugs they interact with  
203 accounted for ~50% of all nodes (sub-node count of 333), with the drugs targeting one or more  
204 of these 4 genes (Fig. 3).

#### 206 Visualization of NSCLC GO terms and drug-gene interaction knowledge bases on BioDati 207 Studio

208 Visualization of the NSCLC GO terms knowledge base nanopub and NSCLC drug-gene  
209 interaction knowledgebase nanopub revealed a complex network of interactions between the  
210 genes and drugs, with 1697 edges and 725 nodes (Fig. 4). The 28 NSCLC GO terms enriched  
211 genes and the drugs they interact with accounted for ~80% of all nodes (sub-node count of 597),  
212 with the drugs targeting one or more of these 4 genes (Fig. 4). The other 20% of the nodes were  
213 comprised of the GO terms themselves and with the most significant GO terms of the knowledge  
214 base also accounted for the highest number of connections. These highly connected and most  
215 significant GO terms all belonged to regulation of cell signaling, namely “negative regulation of  
216 cell communication” (GO:0010648, p-value = 9.98E-12),  
217 “negative regulation of response to stimulus” (GO:0048585, p-value = 5.54E-12),  
218 “negative regulation of signaling” (GO:0023057, p-value = 5.92E-12),  
219 “regulation of kinase activity” (GO:0043549, p-value = 2.72E-11), and  
220 “positive regulation of protein phosphorylation” (GO:0001934, p-value = 3.24E-10) (Fig. 4).

#### 222 ‘Best scenario’ patients with genetic profile overlap with NSCLC pathogenic variants and GO 223 terms knowledge bases

224 Comparison of patient genetic profile with the NSCLC knowledge bases computationally  
225 revealed three types of overlaps and formed the basis of classification of the patients. The first  
226 category of patients called ‘best scenario’ comprised of patients (Patient 1, 2, 6, 10 and 13)  
227 whose genetic profile found matches in both the NSCLC pathogenic variants and GO terms  
228 knowledge bases (Fig. 5A). Patients 1, 2 and 6 had only one overlapped gene, while patient 10  
229 and 13 had more than one overlapped gene. Though several drugs were suggested to target the

230 overlapped genes from the patients, a score based on number of citations was used to prioritize  
231 drug selection (Fig. 5A). As an illustration of the utility of the BioDati Studio for visualization of  
232 patient overlapped genes, a zoomed view of Patient 1's overlapped gene KRAS on the NSCLC  
233 pathogenic variants knowledge base nanopub and NSCLC drug-gene interaction knowledgebase  
234 nanopub is shown (Fig. 5B). Also shown is a zoomed view of Patient 1's overlapped gene KRAS  
235 on the NSCLC GO terms knowledge base nanopub and NSCLC drug-gene interaction  
236 knowledgebase nanopub is shown (Fig. 5C).

237

238 'Good scenario' patients with genetic profile overlap with NSCLC pathogenic variants and GO  
239 terms knowledge bases

240 The second category of patients called 'good scenario' comprised of patients (Patient 4, 8, 9, 11  
241 and 14) whose genetic profile found matches in only the NSCLC GO terms knowledge base (Fig.  
242 6A). Patients 4 and 11 had only one overlapped gene, while patient 8, 9 and 11 had more than  
243 one overlapped gene. Though several drugs were suggested to target the overlapped genes from  
244 the patients, a score based on number of citations was used to prioritize drug selection (Fig. 6A).  
245 As an illustration of the utility of the BioDati Studio for visualization of patient overlapped  
246 genes, a zoomed view of Patient 1's overlapped gene KRAS on the NSCLC GO terms  
247 knowledge base nanopub and NSCLC drug-gene interaction knowledgebase nanopub is shown  
248 (Fig. 6B).

249

250 'No Good scenario' patients with no genetic profile overlap with NSCLC pathogenic variants  
251 and GO terms knowledge bases

252 The third category of patients called 'no good scenario' comprised of patients (Patient 4 and 16)  
253 whose genetic profile found no matches in either the NSCLC pathogenic variants and GO terms  
254 knowledge bases (no data to show). These patients potentially house novel variants on genes not  
255 common in the population and require further investigative research.

256

257

258 **Discussion:**

259 There is increasing demand for global systems based unbiased approaches for  
260 identification of druggable targets for development of safer and effective combinatorial patient  
261 treatment. NSCLC is the most common form of lung cancer, accounting for 85% of lung cancers  
262 and the third most prevalent cause of cancer deaths (American Cancer Society, Cancer Facts and  
263 Figures, Feb 2019). Therefore, there is a great need to understand NSCLC mechanism and drug  
264 development. In the context of NSCLC, gefitinib that targets EGFR has become the most widely  
265 used drug, but development of drug resistance in NSCLC has made it critical to develop  
266 alternative approaches to treatment of NSCLC (2). In the present project, an informatics  
267 workflow for 'network medicine' using different existing web-tools is demonstrated.

268

269 The biochemical process by which cells communicate and coordinate activities in  
270 response to stimuli from their environment is called cell signaling. Here we found several cells  
271 signaling pathways, especially kinase activity and kinase activity regulation through  
272 phosphorylation as the major theme underlying the significant GO terms enriched in NSCLC.  
273 This is consistent with the presence of several protein kinases, 11 out of 28 genes, among the  
274 commonly mutated NSCLC genes, EGFR, STK11, ATM, BRAF, MET, ALK, EPHA3, ERBB4,  
275 EPHA5, NTRK3 and KDR. Phosphorylation of target proteins by kinases is one of the major  
276 mechanisms of on-off switch for regulation of signaling pathways. Several studies have

276 demonstrated the importance of maintenance of protein kinase activity in NSCLC or other  
277 cancers. NSCLC cells that depend on EGFR for survival, constitutively maintain activation of  
278 EGFR through its overexpression and overexpression its binding partners from the ERBB family  
279 such as ERBB4 (16). Overexpression, gene amplification and increases activation of MET has  
280 been reported to be associated with poor prognosis in NSCLC (17). BRAF mutations that occur  
281 in NSCLC either enhance its kinase activity, which increases activation of its target MAPK  
282 pathway and PI3K pathway, while other mutation in BRAF render it completely inactive (18).  
283 Thus, modulation of protein phosphorylation by kinases that makes them hyperactive or inactive  
284 can both be detrimental to the cell and promote NSCLC. Presently, we have developed a  
285 computational pipeline that can prioritize patient genetic variants in kinases that are commonly  
286 mutated in NSCLC and suggest drugs to target these kinases.

287 In this study, we built a NSCLC specific knowledge base to filter and prioritize patient  
288 genetic variation data aimed towards personalized medicine. The pipeline successfully suggested  
289 drugs that could be used for 10 out of 12 patients whose genetic profile overlapped with the  
290 NSCLC knowledge bases built for this work. However, two patients' genetic profiles showed no  
291 overlap with any of the genes present in the NSCLC knowledge bases built for this work. One  
292 possible solution is to expand the avenues of NSCLC knowledge bases to increase the  
293 probability of overlap with patients' genetic profiles. During the data mining for reported  
294 pathogenic variants of genes in NSCLC we retrieved reported pathogenic variants for only 4 out  
295 of the 28 genes commonly mutated in NSCLC, while other genes had unknown or benign  
296 reported variants. Thus, more research is required into pathogenicity of variants, which will help  
297 expand the NSCLC pathogenic variants knowledgebase. Modern high-throughput sequencing  
298 tools such as Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) have  
299 provided a plethora of data to analyze for identification of disease related variants (19).  
300 However, gene variant disease pathogenicity are challenging to study because any given gene-  
301 disease association may involve multiple genetic interactions and depend on context related  
302 variables (20). Recently big data analytics methodologies are being applied and developed, such  
303 as VarCoPP specifically to predict the causal role of combination of genetic variants and their  
304 combined pathogenicity in diseases (21).

305 This project provides a paradigm for utilization of BEL statements derived from  
306 biomedical literature to build networks and identify hubs/modules in diseases such as NSCLC.  
307 Furthermore, the workflow presented here shows the utility of online web-tools for  
308 characterization of the modules and identification of drugs that can target the hub genes. Taken  
309 together the power of a systems based global approach for network building, network  
310 characterization and identifying drug targets at network hubs is demonstrated.

311  
312

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372

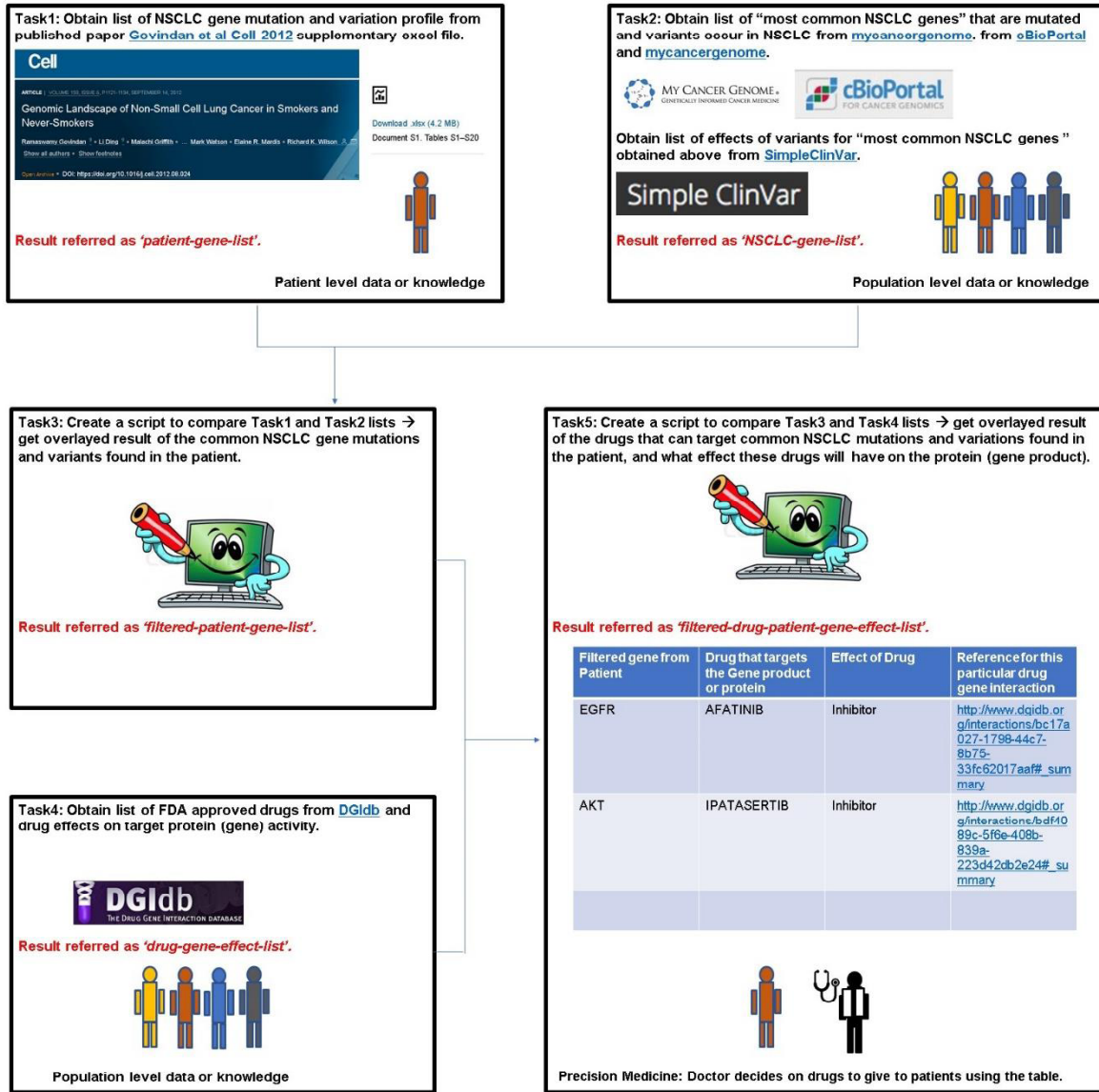
373 **Access to Codes:**

374 <https://icedrive.net/s/Ww9Y35fjuZu6akSkYa8xaChFQTG6> and

375 [https://gitlab.com/smukher2/nsclc\\_drugtargetsmutations\\_nov2019](https://gitlab.com/smukher2/nsclc_drugtargetsmutations_nov2019). Please cite this paper if you  
376 use these codes. Thank you.

377

**Figure 1: Workflow showing all steps of project**

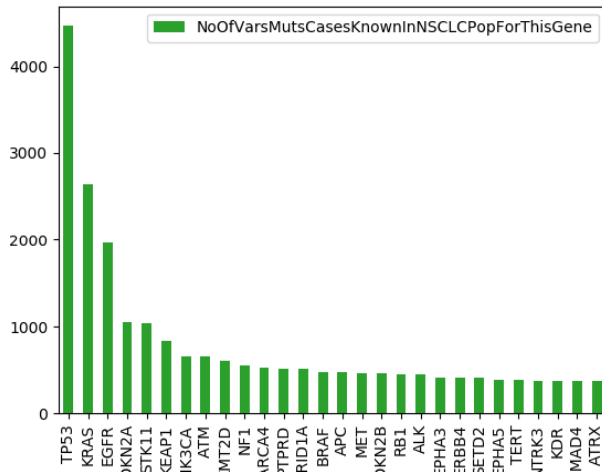


**Figure 2: A: Commonly mutated genes in NSCLC obtained from mycancergenome B:**

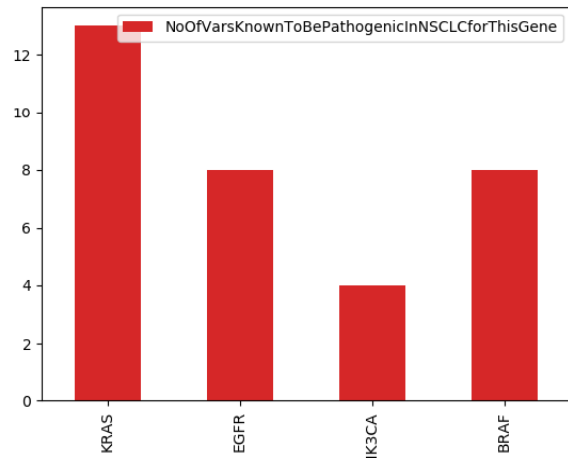
**Pathogenic variants reported in ClinVar for commonly mutated NSCLC genes C:**

**Significant Gene Ontology (GO) terms from enrichr for commonly mutated NSCLC genes**

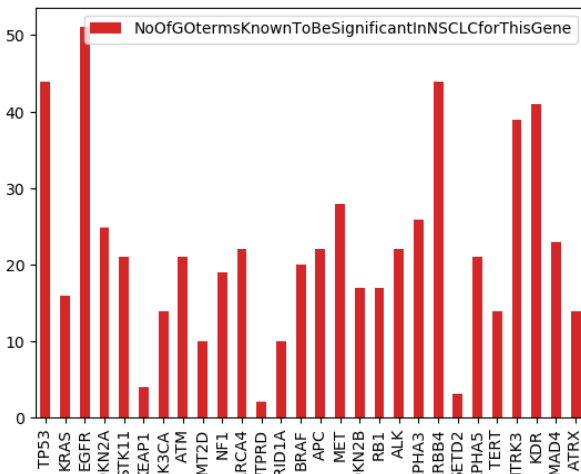
**A**



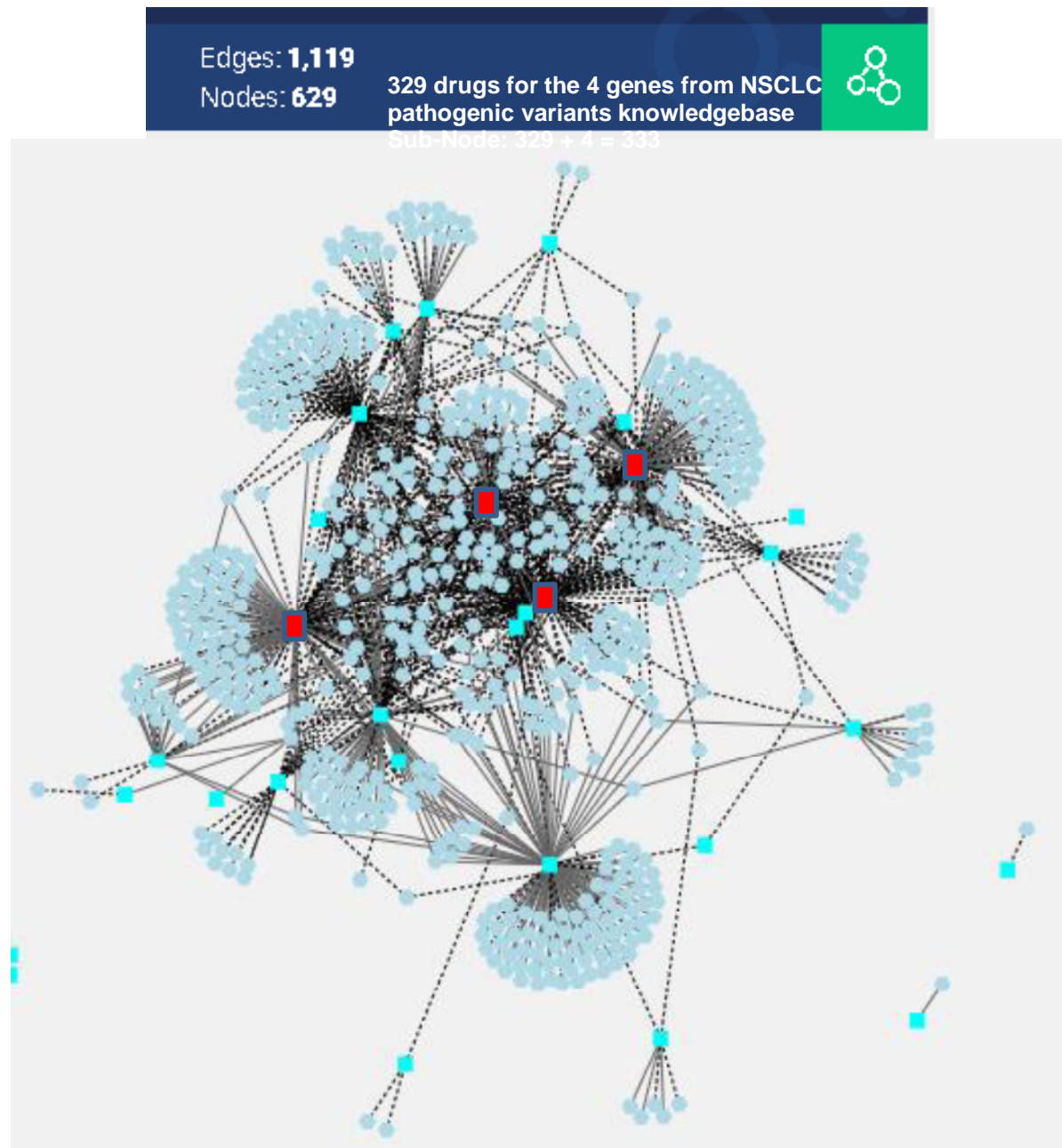
**B**



**C**

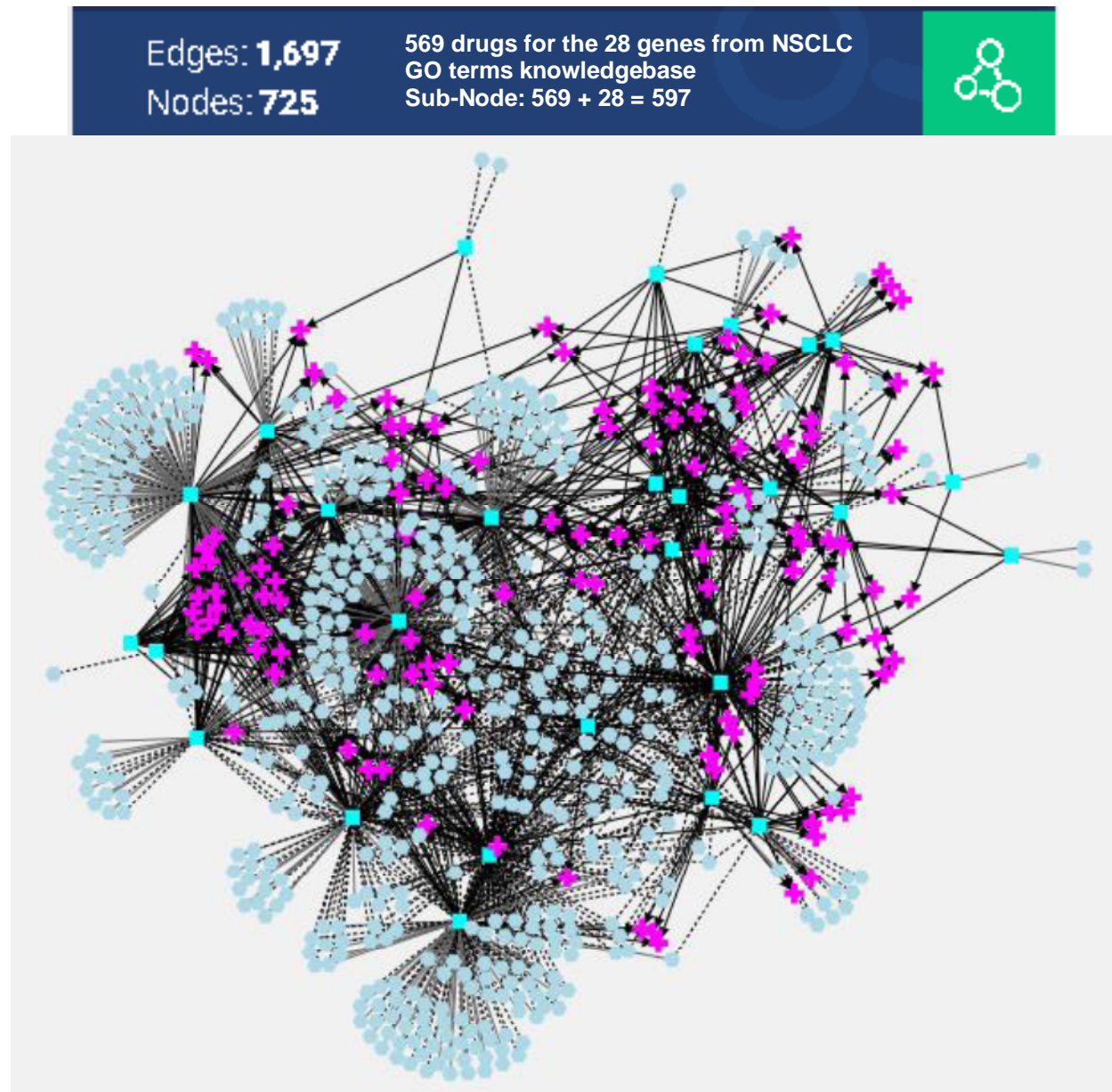


**Figure 3: BioDati Studio network for population level NSCLC drug-gene interaction knowledgebase (blue-green and red square) and NSCLC pathogenic variant knowledgebase genes (red square).**



**Legend:**  
Blue circles=drugs  
Blue-green squares=genes and their variants

**Figure 4: BioDati Studio network for population level NSCLC drug-gene interaction knowledgebase (blue-green squares) and NSCLC significant GO terms knowledgebase genes (blue-green squares).**



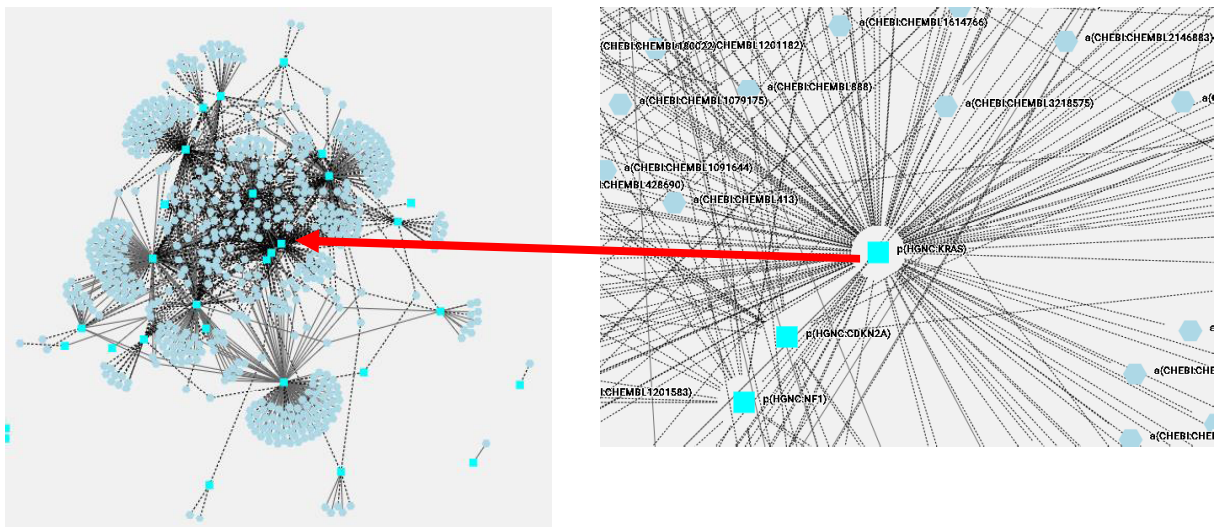
**Legend:**  
**Blue circles**=drugs  
**Blue-green squares**=genes  
**Pink+** = GO terms

**Figure 5: A: 2of2Match, Best scenario: Five patients' genetic profile found overlaps with population level NSCLC pathogenic variants, GO terms and drug-gene knowledgebases. B: BioDati Studio visualization showing Patient 1 overlapping gene in the population level NSCLC pathogenic variants and drug-gene knowledgebases. C: BioDati Studio visualization showing Patient 1 overlapping gene in the population level NSCLC GO terms and drug-gene knowledgebases.**

**A**

		<u>NoOfVars In This Patient For This Gene</u>	<u>NoOfVarsMuts Cases Known In NSCLC Pop For This Gene</u>	<u>NoOfVars Known To Be Pathogenic In NSCLC for This Gene</u>	<u>NoOfGOterms Known To Be Significant In NSCLC for This Gene</u>	<u>NoOfDrugs for This Gene</u>	Best inhibitor action drug selected by highest score
Patient1	KRAS	1	2637	13	16	148	CHEMBL1614701, SELUMETINIB, score 44
Patient2	BRAF	1	474	8	20	100	CHEMBL1229517, VEMURAFENIB, score 169
Patient6	EGFR	1	1969	8	51	146	CHEMBL1173655, AFATINIB, score 141
Patient10	KRAS	1	2637	13	16	148	CHEMBL1614701, SELUMETINIB, score 44
	ERBB4	1	407	0	44	24	CHEMBL2110732, DACOMITINIB, score 6
	ATM	1	656	0	21	25	CHEMBL1221601, (no common name), score 1
Patient13	KRAS	1	2637	13	16	148	CHEMBL1614701, SELUMETINIB, score 44
	EPHA3	1	412	0	26	2	CHEMBL24828, VANDETANIB, score 1

**B**





**Figure 6: A: 1of2Match, Good scenario: Five patients' genetic profile found overlaps with population level NSCLC GO terms and drug-gene knowledgebases, but not with NSCLC pathogenic variants knowledgebase. B: BioDati Studio visualization showing Patient 8 overlapping gene in the population level NSCLC GO terms and drug-gene knowledgebases.**

**A**

		NoOfVars In This Patient For This Gene	NoOfVarsMuts Cases Known In NSCLC Pop For This Gene	NoOfVars Known To Be Pathogenic In NSCLC For This Gene	NoOfGOterms Known To Be Significant In NSCLC for This Gene	NoOfDrugs for This Gene	Best inhibitor action drug selected by highest score
Patient4	APC	1	472	0	22	23	No known inhibitor
Patient8	TP53		4463	0	44	108	CHEMBL325041, BORTEZOMIB, score 1
	EPHA3		412	0	26	2	CHEMBL24828, VANDETANIB, score 1
Patient9	TP53	1	4463	0	44	108	CHEMBL325041, BORTEZOMIB, score 1
	MET	1	460	0	28	81	CHEMBL601719, CRIZOTINIB, score 52
	NF1	1	547	0	19	22	No known inhibitor
	TERT	1	379	0	14	7	CHEMBL129, ZIDOVUDINE, score 2
	EPHA3	2	412	0	26	2	CHEMBL24828, VANDETANIB, score 1
	SMARCA4		525	0	22	2	No known inhibitor
Patient11	SETD2	1	402	0	3	1	CHEMBL299763, (no common name), score 1
Patient14	ATM	1	656	0	21	25	CHEMBL1221601, (no common name), score
	ARID1A	1	505	0	10	3	No known inhibitor

**B**

