

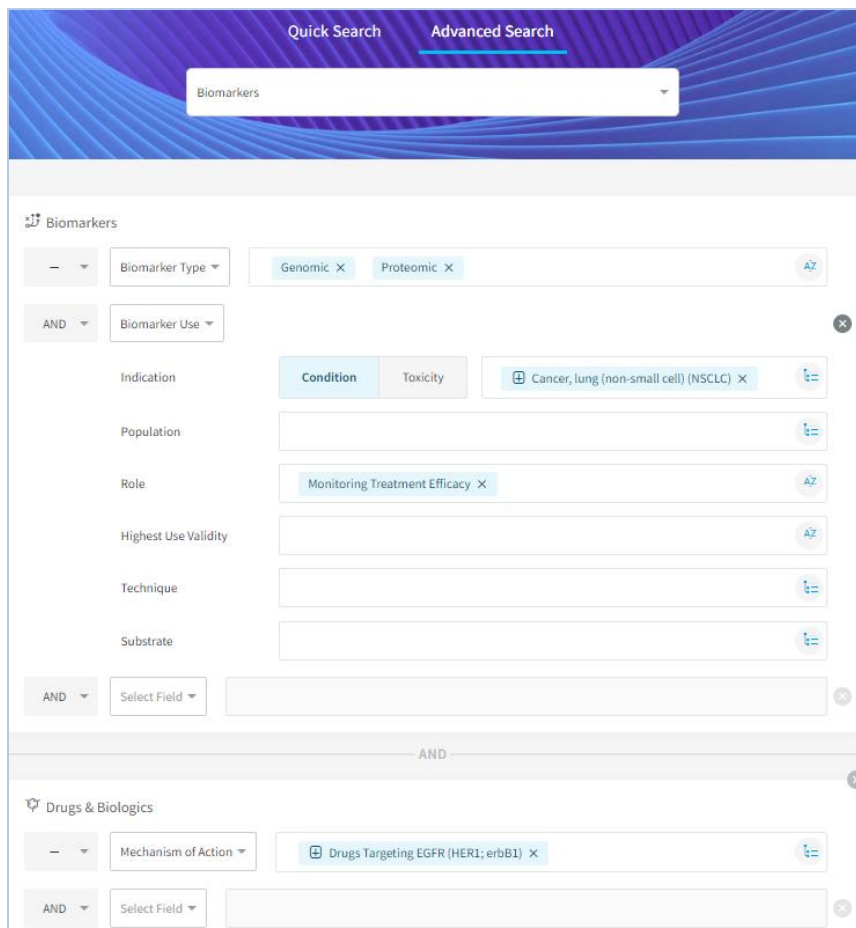
Selecting biomarkers by mechanistic rationale

Cortellis Drug Discovery Intelligence & MetaCore

If you have a long list of biomarkers from the **Cortellis Drug Discovery Intelligence Biomarkers Module**, you can reduce the list using **MetaCore's** enrichment analysis (separate subscription required) to identify those biomarkers that are related to a common signaling pathway or process.

Use Advanced Search in Cortellis Drug Discovery Intelligence to find your biomarkers of interest

In this example, we are searching for genomic/proteomic biomarkers to monitor the efficacy of drugs that target Epidermal Growth Factor Receptors in the context of non-small cell lung cancer:



The screenshot displays the 'Advanced Search' interface in the Cortellis Drug Discovery Intelligence platform. The search is configured as follows:

- Search Type:** Biomarkers
- Biomarkers Section:**
 - Biomarker Type:** Genomic, Proteomic
 - AND** **Biomarker Use:**
 - Indication:** Condition, Toxicity (Selected: Cancer, lung (non-small cell) (NSCLC))
 - Population:** (Empty)
 - Role:** Monitoring Treatment Efficacy
 - Highest Use Validity:** (Empty)
 - Technique:** (Empty)
 - Substrate:** (Empty)
 - AND** **Select Field:** (Empty)

AND

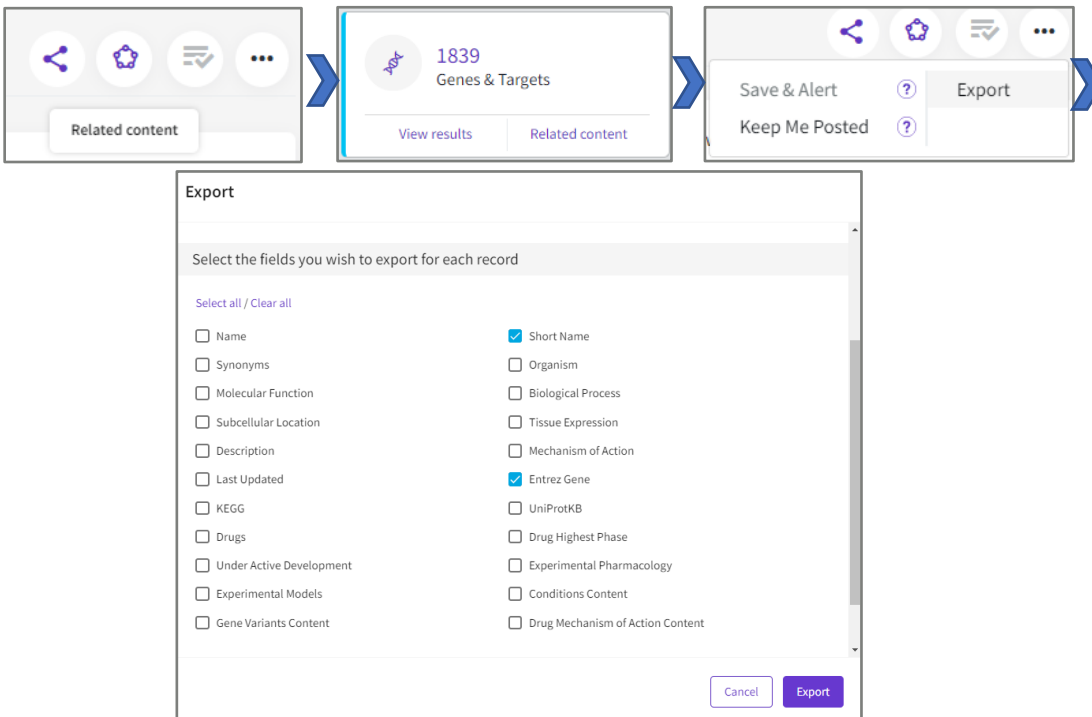
- Drugs & Biologics Section:**
- Mechanism of Action:** Drugs Targeting EGFR (HER1; erbB1)
- AND** **Select Field:** (Empty)

Despite applying multiple search parameters, we still have a long list of potential biomarkers, almost 1,800 in this example.

Showing **1-50** of **1769** Biomarkers records for Biomarker Type: **Genomic OR Proteomic** AND (Biomarker Use Condition: **Cancer, lung (non-small cell) (NSCLC)** AND Biomarker Use Role: **Monitoring Treatment Efficacy**) AND Mechanism of Action: **Drugs Targeting EGFR (HER1; erbB1)**

Export the list to MetaCore for analysis

- From the Biomarker results page, click the *Related content* button > select Genes & Targets > Options, Export > Then select the Short name and Entrez gene ID to export to excel



The first screenshot shows a toolbar with icons for sharing, favorites, and a 'Related content' button. The second screenshot shows the '1839 Genes & Targets' page with 'View results' and 'Related content' buttons. The third screenshot shows the 'Export' dialog box with the following fields selected for export:

- ☒ Name
- ☒ Short Name
- ☐ Synonyms
- ☐ Organism
- ☐ Molecular Function
- ☐ Biological Process
- ☐ Subcellular Location
- ☐ Tissue Expression
- ☐ Description
- ☐ Mechanism of Action
- ☐ Last Updated
- ☒ Entrez Gene
- ☐ KEGG
- ☐ UniProtKB
- ☐ Drugs
- ☐ Drug Highest Phase
- ☐ Under Active Development
- ☐ Experimental Pharmacology
- ☐ Experimental Models
- ☐ Conditions Content
- ☐ Gene Variants Content
- ☐ Drug Mechanism of Action Content

Buttons at the bottom: Cancel, Export

- Re-format the list ready for uploading to MetaCore
 - Open the downloaded Excel > Enable editing > Delete the sheet "Export Information"
 - File > Save as > Save as Type = Text (Tab delimited)
- From the **MetaCore** home page > Upload > Upload Experiments with Gene or Protein IDs and follow the workflow steps > Once the upload is complete, click the Experiment name to activate your list





Experiment name
EGFR MTE BMK

Use MetaCore's enrichment analysis to identify processes and pathways that are over-represented in your biomarker list

MetaCore's home page > Workflows & Reports > Biomarker Assessment > Follow the guided setup. In this example, because I am interested in biomarkers of EGFR inhibition, I will select target = EGFR (optional step); and disease group = Cancer. The final step is to allow you to select thresholds and P-values, but this does not apply as we just have a gene list without any experimental data > Apply. The calculation can take some time.

▼ Diseases (selected group of diseases)

Export Export to image Total results: 10





	#	Cancer Diseases	0	50	100	150	200	250	300	350	400	-log(pValue)	pValue	FDR	Ratio
<input type="checkbox"/>	1	Digestive System Neoplasms											0.000e+0	0.000e+0	2407/15561
<input type="checkbox"/>	2	Endocrine Gland Neoplasms											0.000e+0	0.000e+0	1871/6741
<input type="checkbox"/>	3	Carcinoma, Non-Small-Cell Lung											0.000e+0	0.000e+0	1432/3628
<input type="checkbox"/>	4	Carcinoma, Hepatocellular											0.000e+0	0.000e+0	1487/4879

- When the cancer disease name is green, this indicates that EGFR (the target we selected in the biomarker assessment setup) is one of the biomarkers for this disease.
- Ratio: the red number is the total number of biomarkers in MetaCore associated with that disease, and the green number is the number of biomarkers in our list for that disease
- The top 10 results are displayed. Pick from the drop-down menu to see more
- Note, although we selected this list for NSCLC, there is a very strong enrichment for other cancers, implying common mechanisms for all these cancers

Pathway Maps and Process Networks are a good mechanism to filter your biomarker list based on co-occurrence in the same causal pathway.

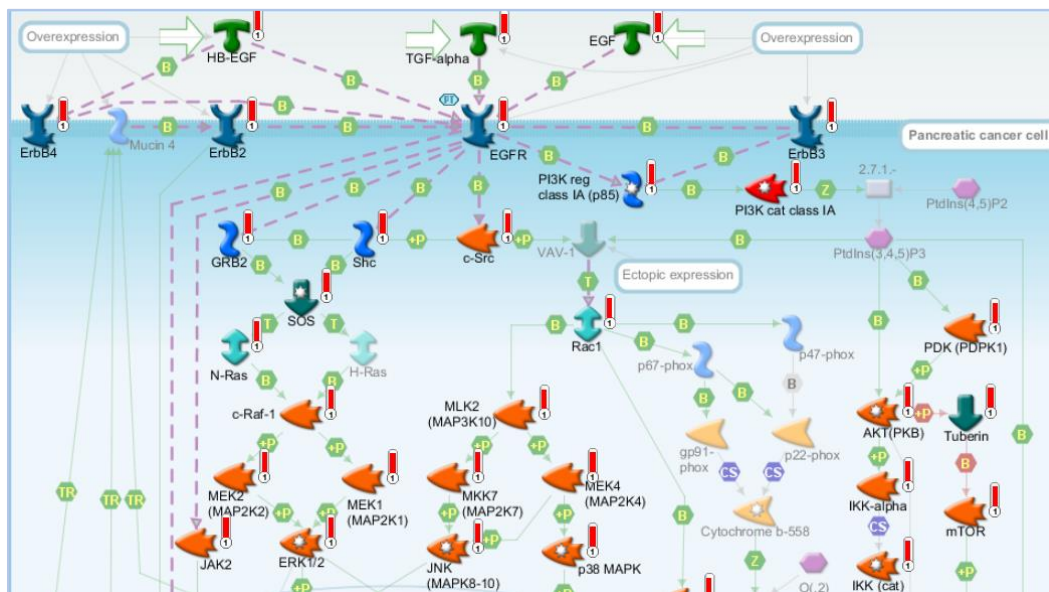
▼ Pathway Maps (for selected group of diseases)

Export Export to image Total results: 10

	#	Cancer Maps	0	3	6	9	12	15	18	21	24	-log(pValue)	pValue	FDR	Ratio
<input type="checkbox"/>	1	Development EGFR signaling pathway											2.446e-30	1.565e-27	60/71
<input type="checkbox"/>	2	EGFR family signaling in pancreatic cancer											8.882e-28	2.842e-25	60/75
<input type="checkbox"/>	3	TGF-beta signaling via kinase cascades in breast cancer											2.765e-26	5.898e-24	50/58
<input type="checkbox"/>	4	Transcription HIF-1 targets											2.618e-24	4.056e-22	66/95

- Click on the map title to view the map and see how biomarkers from your list are related in a mechanistic pathway

- Click the green number under *Ratio* to export the shortlist of biomarkers, or to save it for further analysis.



Using this approach, we have quickly reduced a list of almost 1800 biomarkers to around 50 or 60 mechanistically related pharmacodynamic markers of response to EGFR inhibitors.

For more information contact Customer Service at **LS Product Support**.