

KEY PATHWAY ADVISOR (KPA)

KEY PATHWAY ADVISOR DELIVERS THE BIOLOGICAL INSIGHT YOU NEED – NO BIOINFORMATICS EXPERIENCE REQUIRED



KPA HIGHLIGHTS

- Find the biological meaning of your data with a drag-and-drop wizard
- Predict key molecules in your data that may be causative for the changes observed (causal reasoning network analysis)
- Align your data with current drug target and biomarker knowledge
- Download results in several formats for further analysis or sharing

WHO CAN BENEFIT

- Discovery biologists, including those without bioinformatics experience
- Bioinformaticians
- Preclinical scientists
- Translational researchers

COMPREHENSIVE PATHWAY ANALYSIS

High throughput analysis workflows (such as gene expression) are generally focused on identification of entities whose concentration differs between two conditions (case/control studies) and the biological pathways affected as a result. However, the observed molecular changes themselves may be a symptom/effect rather than the root cause of the condition under investigation. For example, gene expression changes could be caused by environmental factors or gene variants with protein function impact further upstream in the signaling cascade.

Key Pathway Advisor (KPA) uses causal reasoning network analysis with your gene expression data to predict key hubs that may be transcriptional factors responsible for the observed expression changes. KPA leverages more than 100,000 manually annotated high-quality protein/RNA/compound interactions (including more than 34,000 transcriptional regulation interactions) stored in Thomson Reuters MetaBase® to perform this analysis.

KPA also uses synergy pathway analysis to automatically define processes and pathway maps enriched with experimentally defined and predicted key hubs to highlight potentially biologically relevant results.

INTEGRATED OMICS DATA ANALYSIS COMBINED WITH PRIOR KNOWLEDGE

KPA enables faster, more intuitive analysis of gene expression and associated gene variant data. Like a biological version of the GPS in your car, KPA doesn't just visualize all possible pathways, it uses causal reasoning to point you to the most promising "routes," analyzing the key pathways activated in your data and showing the key genes or proteins driving the distribution of your data.

KPA will annotate your experimentally defined gene variant list and narrow it down to as few as 150 of the most promising protein function impact variants. Viewing these alongside your predicted key hubs and on biological pathway results allows you to see the true multilayered biological meaning.

KPA also allows you to align your molecular changes with current knowledge on drug targets and putative biomarkers from Thomson Reuters MetaBase and Integrity – all in the same report as your analytical results. Combining these results allows you to see whether your observed changes have been seen before in your chosen condition or what clinical stage drugs targeting them in that condition have reached. KPA's guided workflows make it easy to gain insight into your results in a straightforward, highly reproducible workflow.

SIMPLE, INTUITIVE INTERFACE

Import your data, apply default analytical parameters, and KPA automatically calculates a comprehensive workflow and delivers your results in structured reports:

- Online interactive report – browse enrichment distributions, pathway maps, and significant molecular components
- PDF report – contains lists of enrichment distributions and top 10 pathway map pictures overlaid with significant molecular components; ideal for showing pathway snapshots and distributions to your colleagues
- XLS report – contains expanded lists of molecular components and cross-references between them; allows you to sort/filter all molecules on the basis of various molecular characteristics, narrowing down your data and making them appropriate for use in the other system biology tools and workflows

No bioinformatics experience required. In just a few clicks, KPA delivers the biological insight you need.

QUICK AND INTUITIVE OMICS RESEARCH WITH KPA

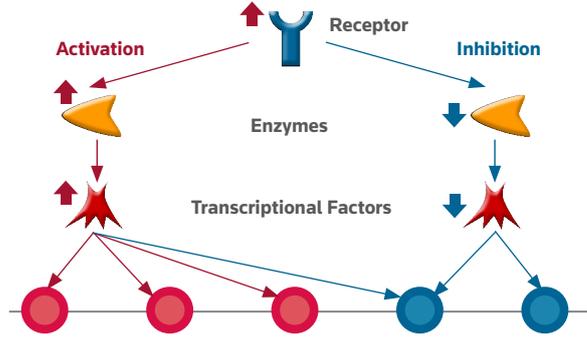
Key Pathway Advisor (KPA) is a Web application that allows you to submit gene expression data and apply a comprehensive workflow that analyzes data in both upstream and downstream directions. Like a biological version of the GPS in your car, KPA doesn't just visualize all possible pathways, it uses causal reasoning to point you to the most promising "routes," analyzing the key pathways activated in your data and showing the key genes or proteins driving the distribution of your data.



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KPA ANALYSIS APPROACH

Predict key hubs and their activity using molecular interaction networks, which drive differential expression changes



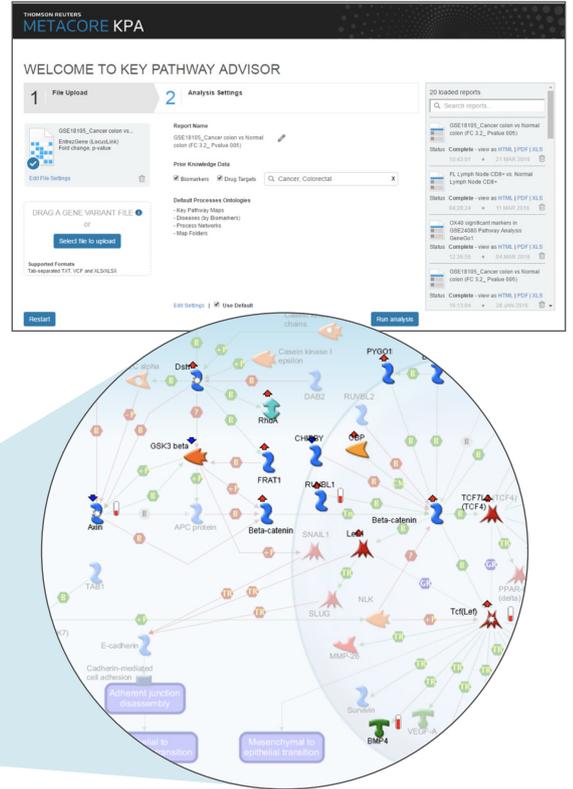
Differentially expressed genes

Identify key pathways affected by differential expression and deregulated key hubs

#	Name	Input Objects p-value	Key Hubs p-value	Union Objects p-value	stacked	grouped
1	Cell cycle_Role of APC in cell cycle regulation	2.763E-8	6.944E-4	5.605E-10	<input type="checkbox"/>	<input type="checkbox"/>
2	Development_WNT signaling pathway. Part 2	1.41E-3	1.697E-8	7.332E-10	<input type="checkbox"/>	<input type="checkbox"/>
3	IGF family signaling in colorectal cancer	3.648E-8	5.43E-4	1.169E-8	<input type="checkbox"/>	<input type="checkbox"/>
4	Cytoskeleton remodeling_TGF, WNT and cytoskeletal remodeling	8.263E-7	8.075E-5	2.453E-8	<input type="checkbox"/>	<input type="checkbox"/>
5	Development_Regulation of epithelial-to-mesenchymal transition (EMT)	1.849E-5	9.178E-4	4.571E-8	<input type="checkbox"/>	<input type="checkbox"/>
6	Some pathways of EMT in cancer cells	4.524E-5	2.473E-5	8.67E-8	<input type="checkbox"/>	<input type="checkbox"/>

UPSTREAM ANALYSIS

DOWNSTREAM ANALYSIS



KPA enables researchers to easily perform upstream and downstream analysis of gene expression – even with little to no bioinformatics experience.

KPA SUPPORTS A RANGE OF RESEARCHERS FOR DISEASE UNDERSTANDING AND DISCOVERY

DISCOVERY BIOLOGISTS:

- Submit your data and generate an automatic comprehensive analysis, even with no bioinformatics experience
- Combine gene expression and gene variant data
- Get a better understanding of aberrant signal transduction visually, using detailed pathway maps with differentially expressed genes and key hubs highlighted
- Use biomarker and drug target knowledge alignment to learn the biology of the disease you are working on

TRANSLATIONAL RESEARCHERS:

- Connect experimental research and clinical studies for insights
- Study detailed candidate disease drivers, biomarkers, and target relations and their effect on signal transduction pathways

BIOINFORMATICIANS:

- Provide advanced causal reasoning and synergy pathway analyses to identify possible disease-driving molecules and aberrant signal transduction pathways
- Analyze connections between expression, gene variant, and predicted key hubs using a detailed XLS report
- Share analysis results with biologist colleagues using a PDF report with pathway images and descriptions

PRECLINICAL SCIENTISTS:

- Find novel biomarker and drug target candidates by comparing your data with current knowledge – automatically
- Identify drug response molecular changes and their signal transduction effect

KEY PATHWAY ADVISOR: A SMALL INVESTMENT WITH A POTENTIALLY BIG RETURN

Understanding the science behind your research has multiple commercial benefits. With Thomson Reuters systems biology solutions, you maximize your chances for success and reduce your risk by using the best quality information available. Additionally, Thomson Reuters systems biology solutions can provide an increase in scientific understanding and result in increased productivity, cost savings, and risk reduction.

SAVE TIME WITH MORE POWERFUL ANALYTICS

“Something that I do with MetaCore in one afternoon now would have taken a week before.”

– **Dr. Charles Lecellier,**
Principal Investigator, IGMM

“Within a couple of hours, we can now identify targets that we previously hadn’t considered.”

– **A computational drug development team**
in a top five pharma company

“It would have taken up to a year previously to make a decision, but we have been able to make decisions now in a matter of months.”

– **A research scientist in a leading medical**
technology company

According to Payscale.com, a research scientist earns an average salary of \$76,601 per year. If that scientist takes one afternoon rather than a week to integrate and understand their data, and if this task is done weekly, this could provide a potential annual savings of up to the equivalent salaries for 10 research scientists (\$766,010).

MAKE THE RIGHT DECISIONS WITH HIGH-QUALITY DATA

Making fast decisions is not enough – they must also be the right decisions. The average drug takes up to 14 years to reach full market approval,¹ and there is increasing pressure on researchers to publish research early to secure further rounds of funding. If decisions are made on faulty data, a significant amount of wasted time, effort, and money can result.

Content in Thomson Reuters systems biology solutions is manually curated by scientists (PhD and MD-level). Independent studies have shown that the quality and completeness of the content in our solutions is significantly higher than any other solution studied – both commercial and public. In a 2011 study by Shmelkov et al. from the New York School of Medicine, MetaCore was found to have significantly higher levels of correct prediction of gold standard transcription factor targets when compared to other commercial and public databases (MetaCore 84% vs. second place 36%).²

INCREASE YOUR CHANCES FOR CLINICAL SUCCESS

An increased knowledge of the biology of your target and disease has a significant positive effect on clinical success. Recently, AstraZeneca introduced their “five Rs” for success.³ As part of the analysis, they found that 40% of clinical failures due to efficacy had no target disease linkage established and that 82% of projects with efficacy biomarkers succeeded.

Their in-depth analysis of their pipeline successes and failures showed a clear correlation between an understanding of basic target and disease biology on project success: “Projects that showed greater confidence in target validation, genetic target linkage to disease, or a stronger understanding of the role of the target in the disease etiology were less likely to fail owing to lack of efficacy.”

Pfizer also found that 43% of their failures due to efficacy had not had their mechanisms sufficiently tested. Understanding the mechanisms and biology behind your research is a key indicator for success.⁴ Good understanding appears to correlate with good chances of success.

Thomson Reuters systems biology solutions allow an increase in scientific understanding and facilitate a significant opportunity to increase productivity, save money, and reduce risk.

References

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- Nelson, Matthew R.; Johnson, Toby; Warren, Liling; Hughes, Arelene R.; Chisoe, Stephanie L.; Xu, Chun-Fang; and Waterworth, Dawn M. The genetics of drug efficacy: Opportunities and challenges. *Nature Reviews: Genetics* 17: 197–206.

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IP & SCIENCE REGIONAL OFFICES

North America

Philadelphia +1 800 336 4474
+1 215 386 0100
San Diego +1 858 273 8616

Latin America

Brazil +55 11 8370 9845
Other Countries +1 215 823 5674

Europe, Middle East and Africa

Barcelona +34 93 459 2220
London +44 20 7433 4000

Asia Pacific

Singapore +65 6775 5088
Tokyo +81 3 5218 6500

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