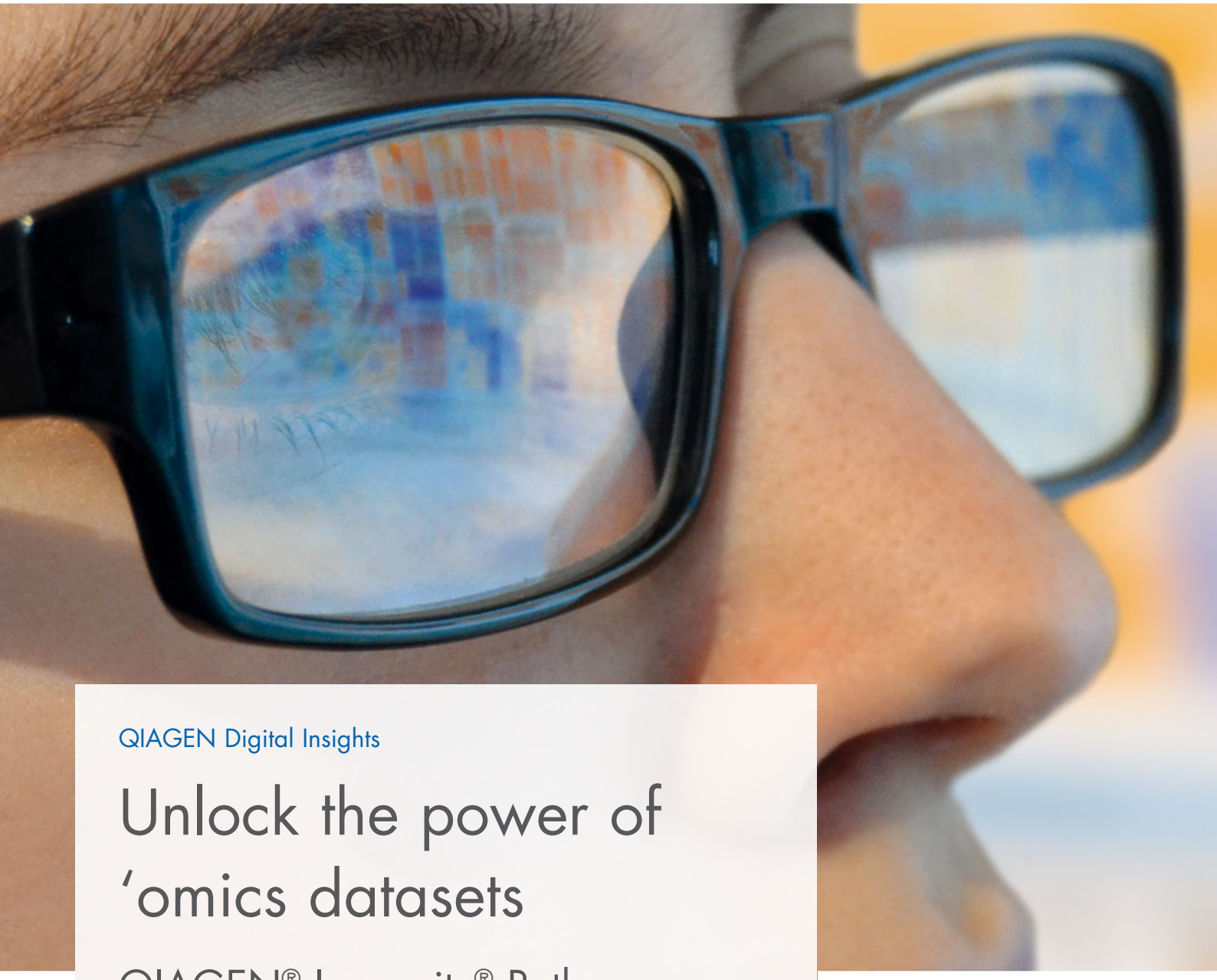
QIAGEN



QIAGEN Digital Insights

Unlock the power of ‘omics datasets

QIAGEN® Ingenuity® Pathway Analysis (IPA®) with Analysis Match

Sample to Insight

The power of analyzing and integrating thousands of 'omics datasets

Finding biological meaning through QIAGEN Ingenuity Pathway Analysis (IPA) with Analysis Match

Mammalian genomes are fascinatingly complex and regulated at multiple levels, which must be studied using a multitude of genomic assays and under a variety of conditions. Biological studies that are focused on single 'omics datasets provide limited information. To overcome this, significant efforts are made to compare multiple 'omics datasets from many mammalian samples, even those measured by different technology platforms.

Dataset integration approaches have evolved dramatically in basic biomedical research, due to the availability of new 'omics technologies and the rate and volume of data obtained.

Still, there remain critical challenges to understanding and integrating multiple 'omics datasets from thousands of studies to draw meaningful and insightful conclusions about the underlying molecular mechanisms in the sampled biological systems. It's difficult and complicated to explore available resources and use software to comprehend one's own data to tease out interpretable feature sets explaining phenotypic variation or to discern important mechanisms or targets, let alone to synthesize findings from multiple datasets across different sample types and 'omics experiments.

That's because there aren't many easy-to-use platforms for non-bioinformaticians to compare their data against the thousands of existing 'omics datasets. Many tools are available, and it's not always clear which one to use. There's no easy consensus on which method for analyzing and integrating the data is the 'right' one. For that reason, most tools are still in the development phase, and using them requires specific bioinformatics skills that most biologists lack.

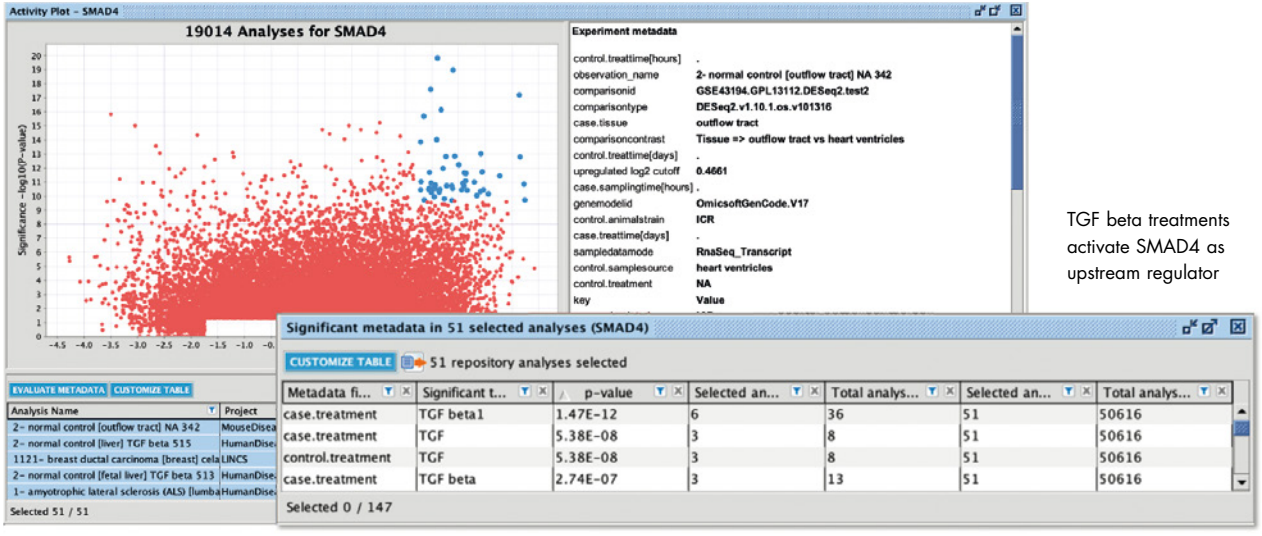
When combining and analyzing different 'omics datasets to discover underlying biological signatures, it becomes challenging to incorporate different layers of biological information to predict phenotypic outcomes. Efficient computational frameworks that can both uncover underlying mechanisms in biological samples, as well as integrate datasets to provide biological insights, become increasingly important.

A good match

QIAGEN Ingenuity Pathway Analysis (IPA) with Analysis Match automatically aligns analyses against tens of thousands of curated publicly available datasets. It allows you to compare results, validate interpretation and better understand causal connections between and among diseases, genes and networks of upstream regulators (Figure 1). Analysis Match enables strengthening of hypotheses and discovery of new biological insights by combining an enormous compilation of knowledge from the literature with a massive collection of gene expression measurements. Analysis Match is best suited for expression data, but is agnostic to whether the data was generated using RNA-seq, microarray or another technology. It also works across species, with its comparator compendium deriving from human, mouse and rat experimental datasets.

Want to try your own data in QIAGEN IPA with Analysis Match?

Start your free trial by visiting **digitalinsights.qiagen.com/IPA**



TGF beta treatments activate SMAD4 as upstream regulator

Figure 1. Visualize the conditions which activate or inhibit an upstream regulator. Here is an example of the datasets that impact the activation of the signal transduction protein SMAD4.

QIAGEN IPA with Analysis Match has been integral in the identification of oncology pathways, which is a fundamental challenge because the acquisition of cancer hallmarks requires molecular alterations at multiple levels. Researchers can use this tool to derive deeper biological insights by accessing the breadth and depth of information across thousands of curated datasets to find underlying biological patterns.

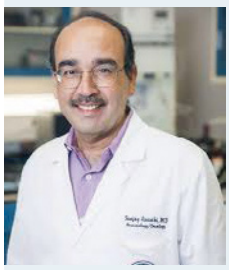
QIAGEN IPA with Analysis Match has also been used by biologists to integrate chromatin and lipidomics datasets, as well as single-cell expression datasets with spatial information, such as spatial transcriptomics to detect cell types, states and localization simultaneously in the various models.

The range of applications for QIAGEN IPA with Analysis Match is broad.

Professor Sanjay Awasthi, M.D., from Texas Tech University Health Sciences Center, says that while approaches based on individual experiments have contributed to the identification of cancer-specific mutations, epigenetic alterations and molecular subtyping of tumors, they lack the resolution to establish the relationship between molecular alterations and the phenotypic manifestation of cancer hallmarks. Since cancer studies that focus on isolated experiments have provided limited information regarding the etiology of onco-genesis and tumor progression, comparing individual 'omics experiments to thousands of other experiments can help identify biological patterns and underlying mechanisms that otherwise would not have been apparent. Along these lines, Dr. Awasthi's group has made great efforts to compare multi-platform-based genomics data from biospecimens.

To perform cancer research experiments, such as those to detect a single genetic mutation and to sequence the transcriptome, Dr. Awasthi relies on QIAGEN IPA with Analysis Match to compare his experiments to thousands of other curated datasets. "These experiments are much more difficult to interpret because they have two components: One is the mutation, and the second is the amount of RNA," Awasthi explains. "The mutations are difficult to interpret in those studies because you may have mutations in several genes, which may be passenger mutations or drivers, in which case the mutation is either a cause of the cancer, or it's causing the cancer to grow."

These studies can aid in identifying novel treatments, as the scientific community already has over 100 drugs targeted against proteins that harbor specific mutations or sequence alterations. Yet Dr. Awasthi doesn't think it's so straightforward.



"If you look at only the genes that we know, then very often these tests are not informative,"…
"… if you look at the entire set of mutations, then you can go to the next step where you start using programs like IPA, where you can actually enter the entire transcriptome data and the mutation data."

Professor Sanjay Awasthi, M.D., Texas Tech University Health Sciences Center

"If you look at only the genes that we know, then very often these tests are not informative," he says. "On the other hand, if you look at the entire set of mutations, then you can go to the next step where you start using programs like IPA, where you can actually enter the entire transcriptome data and the mutation data." So, Dr. Awasthi uses QIAGEN IPA with Analysis Match to compare his work to other datasets to discover the effect of the mutations on the pathway or gene function and determine similar or dissimilar phenomena across these datasets. In this way, IPA with Analysis Match helps him gain deeper insights into his own data.

QIAGEN IPA with Analysis Match provides researchers with a huge annotated database that offers information about related genetic networks, canonical pathways or upstream regulation that inform whether a driver mutation or changes in gene expression activate a specific pathway. In addition, Awasthi says that he uses this process to find inhibitors of particular pathways. "In fact, in IPA, there is a tool in which you can overlay something like 200 drugs."

Making sense of the myriad of data

To make sense of large amounts of data and the potential hits that emerge without bias requires several post-analysis approaches. QIAGEN IPA with Analysis Match provides a tremendous amount of curated information. It enables comparison of data to thousands of other analyses for validation and narrowing down potential hits to explain the underlying biology in an experimental system. This allows scientists to correlate and link the data obtained with other observations from similar and anti-similar datasets to draw new conclusions and potentially make a previously unknown connection of two conditions.

Therefore, it's essential to visualize biological pathway data directly and comprehensively. QIAGEN IPA provides visualization options that you can use to easily spot similarities and differences, as well as cycle through using filters based on several parameters such as disease, cell type and more. An example of such a visualization is shown in Figure 2 (next page), where selected analyses are displayed as a heat map. This view allows you to drill down to explore the underlying drivers of the similarity or dissimilarity to your analysis.

> "IPA with Analysis Match provides a tremendous amount of curated information. You can compare your data to thousands of other analyses that help you validate and narrow down potential hits to explain the underlying biology in your experimental system."

Learn how to strengthen your hypotheses and discover new biological insights.

Download our QIAGEN IPA Analysis Match White Paper. **https://go.qiagen.com/IPA-AM-WP**

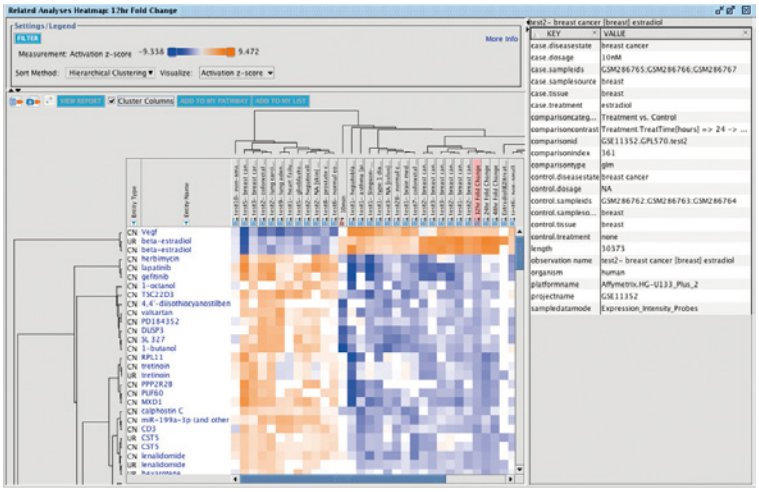


Figure 2. Explore the drivers of similarity from your analysis to those of interest drawn from >60,000 analyses. The analyses included in Analysis Match were created in QIAGEN IPA from more than 60,000 highly curated and quality-controlled human and mouse disease and oncology datasets re-processed from SRA, GEO, Array Express, LINCS and TCGA. These datasets were generated by QIAGEN OmicSoft and are the 'comparisons' found in DiseaseLand and OncoLand, representing various contrasts between disease versus normal, treatment versus non-treatment and much more. Here, selected analyses are displayed as a heat map. This view allows deeper exploration of the underlying drivers of the similarity or dissimilarity to your analysis.

Awasthi's research team compares micro-dissected samples of normal cells and cancer cells and uses QIAGEN IPA to analyze the transcriptome to home in on the pathways which are specifically abnormal. "IPA performs the analysis and tells us, 'these are the networks that may be activated'," Awasthi says.

Awasthi's lab performed concomitant transcriptomic and epigenomic analyses working with the lab of Arthur Riggs, who worked with Genentech® to express the first artificial gene in bacteria.

"We got excellent data, and we analyzed it using the KEGG database, which gave us a direction," says Awasthi. "However, I used a variety of techniques and sort of developed my own techniques to process the data I put into IPA." This allowed Awasthi to generate a unique gene set that is considered essential in cancer pathways. "Many of them are not previously known, so they are good targets. IPA was key in the analysis."

From their analysis with QIAGEN IPA, Awasthi's team found a chemical in oranges that turned out to have unique properties. This is used as the chemical basis for designing new cancer drugs that have been confirmed externally. "We're designing different types of treatment modalities. IPA has been and is going to be a big part of making this happen."

Awasthi's group uses bioinformatics tools in addition to QIAGEN IPA and Analysis Match, and his graduate students write programs with languages such as Python that can do some of these analyses. Still, the Awasthi lab relies on annotated databases like QIAGEN IPA with Analysis Match to interpret the findings. "You can either go to publicly available databases like KEGG, or you can go to newer programs

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that use annotations to give a variety of different visual representations that help you decide what genes are important, such as genes that could be used to make a targeted medicine. That helps you judge how likely a drug will work."

Shaping the future

As we mark the 20th anniversary of the first draft of the human genome and look beyond, integrating findings from multiple datasets will continue to accelerate the identification of patterns and relevant underlying mechanisms, which would otherwise not be apparent. This offers the opportunity to understand the flow of information that underlies basic biology and disease. The future of genetic medicine, Awasthi suggests, will hinge on identifying gene mutations, relative gene expression and "what may be more important, epigenomic data, and perhaps in the future, even proteomic data."

The development and use of programs such as QIAGEN IPA, which provide a rapid means to compare biological aspects from an investigator's own analyses to thousands of other analyses from the literature and make a vast amount of publicly-available data immediately accessible and easily interpretable, is crucial for this future and development of genetic medicine. By using these bioinformatics programs, researchers can identify key regulators and molecular activity to explain expression patterns, identify biomarkers and predict downstream effects on biological and disease processes. They can collect a vast amount of targeted data on genes, proteins, chemicals and drugs, as well as build interactive models of experimental systems.

With tools like QIAGEN IPA with Analysis Match, scientists are carving the path to the future of biological research.

QIAGEN Ingenuity Pathway Analysis (QIAGEN IPA) is intended for molecular biology applications. This product is not intended for the diagnosis, prevention or treatment of a disease. For up-to-date licensing information and product-specific disclaimers, see the respective Ingenuity product site. Further information can be requested from **ts-bioinformatics.qiagen.com** or by contacting your local account manager.

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Download our White Paper to learn how QIAGEN IPA with Analysis Match helps you discover new biological mechanisms in your data. Visit **https://go.qiagen.com/IPA-AM-WP**

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