OPUS23 PRO

People. Nature. Technology.

Clinician User Guide

User Manual

Version 1.2

Programmed by Peter D'Adamo

Limitations and Warnings

The etiology of many diseases is multifactorial, that is, disease can occur as a result of various factors, including both inherited and acquired genetic variants, diet, lifestyle choices and age. The interpretations given by Opus23 Pro evaluates inherited genetic variants in data uploaded to our server, and interpretations are only as accurate as the data received from the genomic test. It is possible that inaccuracies in the genomic test results could lead to false interpretations. It is also possible that variants in genes and genetic regions not tested in the DNA sequencing test may contribute to an individual's risk for disease. Therefore, a negative result in a gene where no pathogenic variants are detected does not eliminate the individual's disease risk. Further, a positive test result does not guarantee an occurrence of disease since the variants in most genes are not 100% penetrant. Rather, pathogenic variants may predispose a person to a higher or lower risk of disease. The results of the test must be interpreted in the context of the individual's clinical background. Genetic counseling is recommended for the individual and for other at-risk family members.

Opus23 Pro strives to provide the most accurate possible data interpretation. As part of this mission, we constantly monitor and refine our data analysis algorithms. When an improvement is identified, the new algorithm becomes available immediately on creation. In that event, a corrected report will be available by re-indexing the patient's dataset and re-running the report. Such re-analysis of patient data may lead to reclassification of patient results. Opus23 Pro and Datapunk Bioinformatics, LLC, take no responsibility for any harm arising from incorrect data being uploaded to our server or incorrect data interpretation, errors, or omissions by the software or by the curating staff.

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Introduction

Welcome

Welcome to Opus23 Pro, a program written by Dr. Peter D'Adamo for use at the Center of Excellence in Generative Medicine (COEGM) to analyze and interpret raw genomic data for use with patients at the University of Bridgeport, CT. It is curated by various editors and students at the COEGM. Opus23 Pro is now available to physicians for use with their own patients after purchasing a user license.

Opus23 Pro is a suite of apps that provide a development environment for precision medicine. It allows the clinician to import raw genomic data (such as provided by 23andMe and other services) and perform a series of extraordinarily sophisticated analytics upon it, culminating in a fully annotated client report. Opus23 Pro features:

- **Complex multi-SNP algorithms**: Very few single SNPs have actionable consequences. The Opus23 Pro app LUMEN runs over 300 algorithms on multi-SNP clusters, identifying significant haplotypes and epistatic relationships.

- **Smart Interactive Network Maps:** We've all studied pathway maps. However, the Opus23 Pro app MAPPER can populate network maps with the actual genotype data from your client. It can even try to approximate gene function based on SNP outcomes and overall network efficiency.

- **Mega-Data Mashups:** Opus23 Pro synthesizes its results from a wide variety of data, including GWAS (genome wide association study) data, dbSNP, Interactome, Etiome, PubMed, HapMap, and many others. SUPERMOGADON takes GWAS data and displays it as interactive Manhattan plots.

- **Causes and Effects**: Opus23 Pro uses advanced data analysis tools to surf various networks and identify high value targets. ACCELERANT identifies complicating etiologic factors for the client by combining searches of the Diseasome and Etiome.

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- **Intelligent Prescriptives:** Opus23 Pro features a unique curated database of natural products known to regulate gene expression. The PSYCHIC app surfs the Interactome and identifies upstream and downstream targets, then identifies high value agents to consider.

- **Complex Syndrome Modeling**: Most complex syndromes are the result of genes acting in 'subgraphs' specific neighborhoods in the network. MOBOCASTER supplies you with this data.

- **Fully Interactive Learning Tool:** It's inevitable that you'll encounter genes or SNPs you've never heard of. Click on a gene or SNP and up pops an information screen. Click on an agent and up comes the PubMed citation.

- **Pharmacogenomics simplified:** Adverse drug reactions are a potential threat to patient health. The DRUGGIE app will report over 300 potential adverse reactions based on your client's genotype.

- **Safe and Secure:** Opus23 Pro uses SSL (https) to protect sensitive data during transmission. In addition all data on the Opus23 Pro server is protected with AEM (Authenticated Encryption Methodologies) encryption that actually exceeds HIPAA standards.

- **And Much More:** The Opus23 Pro app RARIFY checks for rare alleles. The FANTASMATRON app allows you to make dietary suggestions based on client genotype. The AGENCY app provides you with an interactome of genes and agents.

And there's even more...

This User Guide will take you through all these aspects of Opus23 Pro.

Tips/helpful suggestion boxes

In this manual, special tips or helpful suggestions or insights appear inside a green box:

This is a help/tip box.
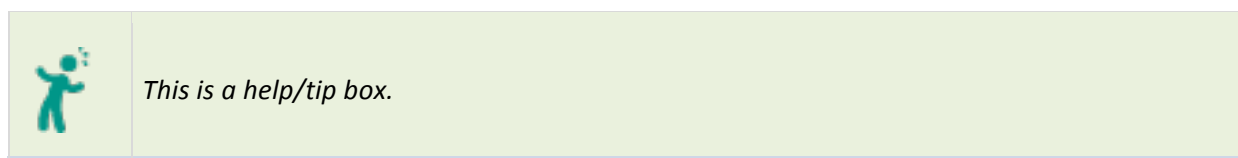
Getting Started

Opus23 Pro is available for use by licensed health professionals. To begin using Opus23 Pro you must first have the necessary tools and abilities. The next step is to create a professional account for yourself. See the details below.

Basic requirements

- **Technical requirements:** Opus23 Pro is completely web-based and runs on all modern Internet browsers. It utilizes many features that require that you have JavaScript enabled on your browser. This is usually the default setting, so you probably need not worry. However, if you've turned JavaScript off, you'll need to turn it back on. Opus23 Pro also uses cookies to maintain your connection to your data. Again, this is usually the default setting, but if you've turned cookies off, you'll need to turn them back on. We recommend the Google Chrome browser but Opus23 Pro will work well on Firefox and later versions of Internet Explorer.

- Mobile devices: Opus23 Pro is designed to be 'responsive,' i.e. it will conform visually to whatever device you are viewing it on. It works well with most tablet devices, such as the iPad. However, we do not recommend using devices with very small viewports, such as smartphones.

Creating an Opus23 Pro account

To begin using Opus23 Pro you must have an account. Creating an account is a simple two-step process and is free of charge. Here's how to do it:

- **Point Your Browser to www.opus23.com.** Navigate to the bottom of the page and complete the simple "I'm interested" form at the bottom, by providing a name, email and a summary of your professional qualifications. You will soon receive a response email that directs you to a link where you can create your account. Click on the link in the email to navigate to the *Create An Account* page.

- **Secure Environment:** As with the entire Opus23 Pro web environment, this page is protected by SSL (https) and full data encryption.

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- **Complete the Form.** The account form is straightforward. Many fields are required and you will be advised if upon submission your form is incomplete.
- **Professional Details:** Opus23 Pro is restricted solely for use by licensed health professionals, and we reserve the right to authenticate any professional information you supply. We reserve the right to terminate the account of anyone supplying false information.

Creating New Account Form

Licensing

After you create your Opus23 Pro Account you will have the option of moving onto the next screen and purchasing a multi-use license, or using Opus23 Pro in Tourist Mode, in which case you will be assigned a sample client and permitted to tour and experience Opus23 Pro. Tourist Mode has full functionality, although some 'save' functions are disabled.

A 5-user license is available directly online for $325 USD. This will allow you to upload raw data from 5 different clients. If you are a current member of the Institute for Naturopathic Generative Medicine (INGM) or the International College of Generative Medicine (ICGM) you qualify for a discounted license fee of $250 USD.

Getting Around

Log into Opus23 Pro

To log into Opus23 Pro, either:

- Go to the main page (https://www.opus23.com), scroll down to the bottom of the screen, then click the *Log In* link

- Or point your browser directly to the login page:

- https://www.datapunk.net/opus23/log_in_screen.pl

- Supply your email address and password to successfully log in

- After a successful log in, you will see the Opus23 Pro Welcome Screen:
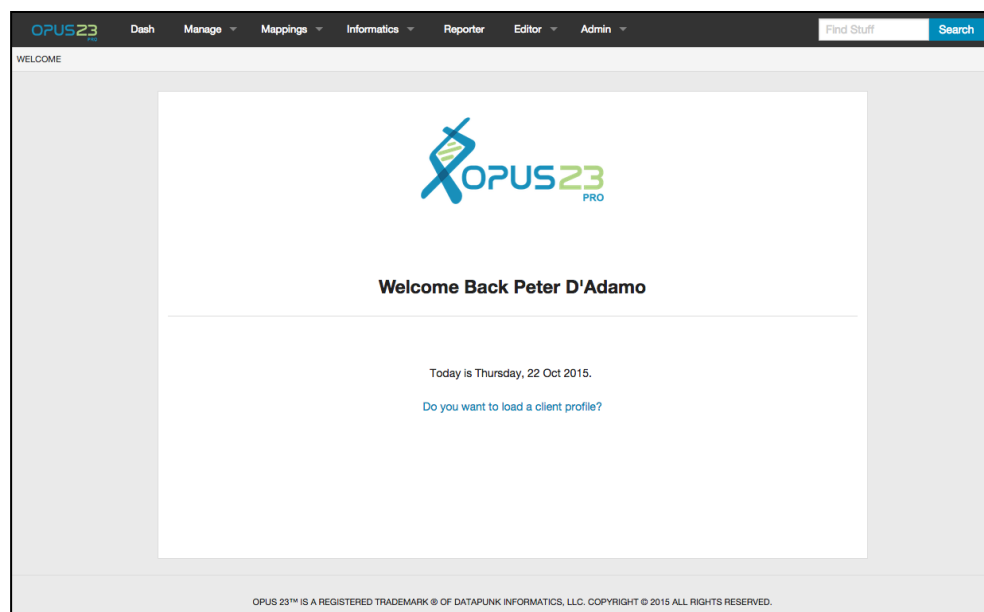
Opus23 Pro Welcome Screen

The Opus23 Pro Welcome Screen will prompt you to load a client. It is important to note that virtually no part of Opus23 Pro will work without first loading a client. Dealing with client data, uploading client raw genetic data files and other aspects of managing your account are discussed later in this manual.

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The Interface

Opus23 Pro has an intuitive interface that is consistent throughout the program. At the top of the screen is the menu bar. You can get to any part of Opus23 Pro by clicking the appropriate section heading. Each area is discussed in depth later on in this manual.

- **Manage**: Clicking this link will activate a drop-down menu with various options relating to your account, including access to the Dashboard

- **Mappings:** Clicking this link will activate a drop-down menu displaying various categories of molecular maps that are available for inspection, showing data for your client

- **Informatics**: Clicking this link will activate a drop-down menu displaying various categories of apps that are used to analyze client genomic data

- **Curation**: Clicking this link will take you to the curation menu and allow you to edit the reporting datasets and begin designing the client report

- **Help:** Clicking this link will allow you to download the complete PDF file of the User Manual (this document) or access the online help docs

- **Search Bar**: Entering any search term here will trigger the WANDERER app to return cross-app search returns

Pop-ups

Pop-up windows are shown by clicking on genes links in maps, or where SNP rs ID numbers are displayed with a link. Depending on the situation, pop-ups are also used to bring up context data such as PubMed, abstracts and other backup information. An important use of pop-ups is the ability to notate elements in Opus23 Pro. Elements notated in Opus23 Pro will appear in the Client Report and the Notes tool. The use of notations is discussed under its own section. Clicking on the 'X' in the upper right hand corner of the pop-up, or anywhere outside the pop-up window, closes the pop-up window.

SNP Pop-ups

Clicking on the link on any SNP rs ID number triggers a pop-up with the following information, if available:

- **Evidence basis:** higher values on a scale of 0-10 are assigned by Opus23 Pro editors to the evidence basis for a SNP where it is a key polymorphism in published research articles with large numbers of subjects and high statistical significance.

- **Power factor:** the value for power factor on a 0-10 scale is determined by Opus23 Pro editors according to the amount a polymorphism in this SNP is known to affect the overall gene function or have an effect on disease risk.

- **Curation level:** the number of times Opus23 Pro editors have manually added information to the SNP data.

- **Gene:** the HGNC symbol of the gene in which the SNP is located. Some SNPs might not be in a coding region of the chromosome, and instead will display location information, including chromosome number and locus number (position).

- **GMAF:** Global Minor Allele Frequency is a number indicating the minor allele frequency reported by dbSNP for the rs ID in a default global population.

- **Chromosome:** The chromosome on which the SNP is located.

- **Position:** The position on the chromosome where the SNP is located using the human GRCh38 reference assembly. N.B. 23andMe currently report position data based on GRCh37.

- **Risk Allele:** Shows which allele has been designated the risk by Opus23 Pro editors. This is usually the minor allele, that is, the nucleotide least frequently found in the general population. Sometimes the risk allele may be the dbSNP ancestral allele, as this has been assessed as being associated with a higher level of disease risk than the minor allele. The currently loaded client's genotype is listed with red/yellow/green color-coding for homozygous positive / heterozygous / homozygous negative.

- **Frequency:** if frequency data exists for the SNP it will show as a color-coded graph for various populations.

- **HapMap Revision:** shows the International HapMap Project revision number used for assessing the SNP data. The current release is #28.

- **dbSNP Orientation:** The direction in which the chromosomal strand is read according to dbSNP. This will be listed as 'PLUS', read in the forward direction, or 'MINUS (converted)', read in the reverse direction, and showing that Opus23 Pro has converted the nucleotides to correspond with dbSNP.

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- **Naturopathic Agents Known to Influence Expression:** These are hand-curated links from published studies showing how a natural agent has an agonist or antagonist effect on gene expression. Sometimes this may be 'unidentified' - this is where the agent is known to influence expression but a curator has not yet associated it as an agonist or antagonist.

- **Algorithms:** If any Opus23 Pro algorithms use this SNP they will be linked here.

- **Consequences:** These are hand-curated notes from editors who have added information about the SNP that may be useful.

- **Additional data:** If the SNP contains additional data that Opus23 Pro can retrieve from any of the public sources, it will display here. This typically includes clinical consequences and relevant PubMed references.
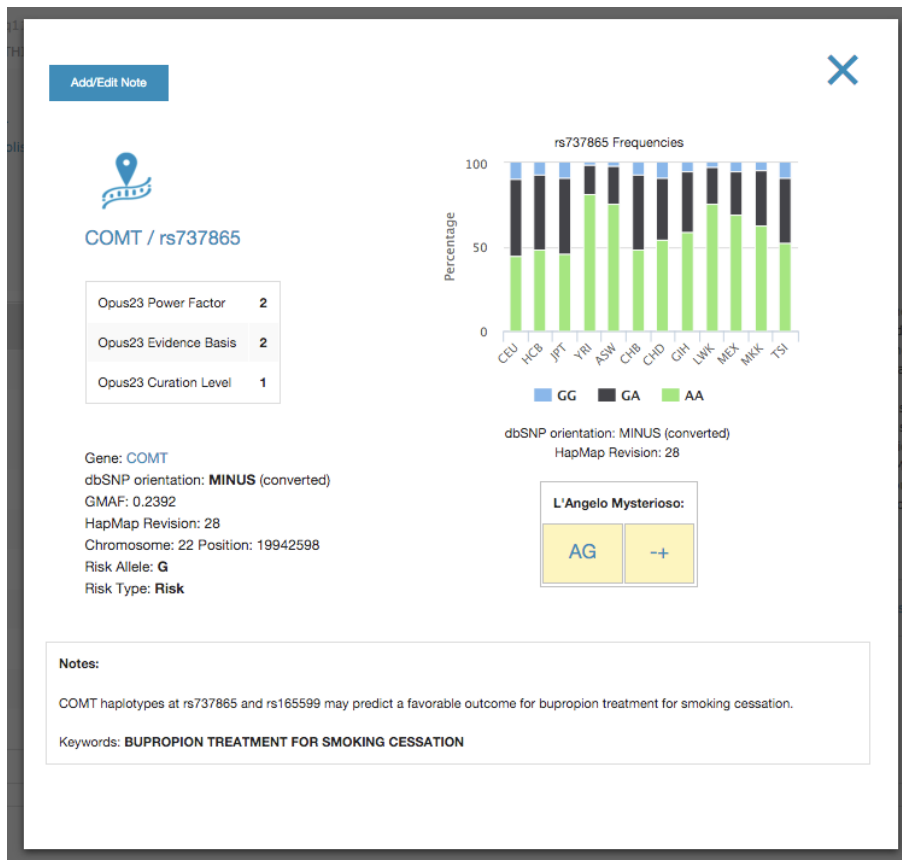
A typical SNP pop-up

Gene Pop-ups

Clicking on the link on a gene symbol shows a pop-up with the following information, if available:

- **Symbol for the gene**: Opus23 Pro always uses the approved gene symbol for every gene.

- **Full name of the gene:** The officially approved full name of the gene.

- **Gene Description**: A description of the gene. This text is typically retrieved from genome.gov.

- **PPI interactome connectivity:** A number representing the importance of the location of the gene in the Protein-Protein Interactome, generated from an estimation of the betweenness centrality and clustering coefficient. This is followed by a description of the significance (minimal, important, crucial, etc.).

- **Algorithms:** If any Opus23 Pro algorithms include this gene they will be linked here

- **Naturopathic Agents Known to Influence Expression:** These are hand-curated links from published studies showing how a natural agent has an agonist or antagonist effect on gene expression. Sometimes this may be 'unidentified'   this is where the agent is known to influence expression, but a curator has not yet associated it as an agonist or antagonist.

- **Agent Expression Fingerprint with drill-down:** If there are several agents known to influence a gene, a chart is displayed in the pop-up showing the agents and the occurrence of each agent as agonist (green) or antagonist (orange) to the gene. Clicking on any agent opens a pop-up of that agent's genomic fingerprint, showing all the known genes influenced by that agent, with an estimate of the strength of evidence and links to the relevant PubMed references.

- **SNP results for the client:** A list of SNPs linked to this gene that are in the Opus23 Pro database. Click on any SNP to bring up its information screen. SNP results are displayed according to a consistent color scheme: Orange-colored boxes indicate SNPs for which the client genotype is homozygous for the risk allele; yellow boxes indicate that the client is heterozygous for the risk allele; grey boxes indicate that the client is homozygous for the non-risk allele; green boxes indicate that the client is homozygous for a SNP associated with some positive benefit.

- **Genetic Diseases linked with the gene:** If any genetic diseases are linked with the gene, links to the relevant PubMed references are shown here.

- **Frequency pie chart with drill-down**: If Opus23 Pro can locate HapMap data for the SNPs in the gene it will display their frequencies as a pie chart with drill-down. The SNPs are displayed in the interior circle and its genotypes with their frequencies of occurrence in the outer circle.

- The gene pop-up also displays buttons for Add/Edit Note, Add Gene to Dataset and Add Protocol. These functions are described later under reporting.

It's elemental: In Opus23 Pro, anything that you can interact with is referred to as an 'element'. An element could be a SNP, gene, drug, herb, algorithm, etc. Generally, when the User Manual refers an element, it means that whatever it is describing applies to any of these things.

Typical gene pop-up

The Dashboard

Opus23 Pro dashboard is your control center, accessed from the Dash button under the Manage button in the toolbar. Here you will see your account status and a list of your uploaded client profiles. Clicking on the name of the client makes that client active in Opus23 Pro. Clicking on the pencil icon next to a client's name opens a pop-up box where you can edit the client's details and add data such as blood type, secretor status, GenoType and pathologies.

Other functions accessible from the Dashboard in scrollable boxes:

- **Editor PubMed Feed:** Showing the most recent high-impact PubMed articles added by editors. Clicking on a title opens a pop-up box showing the article abstract (if available), the average rating by Opus23 Pro editors and any agonist or antagonist action of genes by natural products defined in the article.

- **New SNPs:** Showing recently added SNPs by rs ID number, gene symbol and the power factor assigned by Opus23 Pro editors. Clicking on the rs ID opens a pop-up with details of the SNP. Clicking on the gene symbol opens a pop-up with information about the gene and all SNPs of that gene currently listed in the Opus23 Pro database.

- **New Maps:** This shows new maps that have been added to the Opus23 Pro database. Clicking on the map name will open it showing the currently loaded client's SNPs.

- **New Algorithms:** Showing recent additions of official Opus23 Pro algorithms that have been added to the database. Each link triggers a pop-up or action (i.e. clicking on a new algorithm will run that algorithm for the active client).

- **New Agent/Gene Links:** Showing natural agents, associated genes, the type of study, and whether agonist or antagonist. Clicking on the gene name will open a pop-up box showing a graph of all natural product associations with that gene listed in the Opus23 Pro database. The number of associations with antagonistic effects for each agent is shown as a negative number to the left of zero, and agonistic effects as a positive number to the right of zero.

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Managing Your Account

Account management is accessed from the Manage button on the toolbar. There are two basic aspects to account management in Opus23 Pro; Managing your account information, and managing your clients. The pull-down menu has the following options:

- **Your Account:** Clicking this option allows you to edit your details such as name, email, password, clinic address and contact details. This page also shows how many clients are currently loaded on your account and how many available client slots remain under your current license.

- **Your Profiles:** Hovering over this option exposes additional options, all of which are related to managing your client profiles. These include:

  - **Load/List Clients:** Selecting this option will present you with a list of your current clients. Click on any name to load their data. You can always check to see what client is currently loaded by looking at the line below the top menu bar.

  - **Import Raw Data:** Selecting this option will present you with a form that allows you to import 23andMe raw data. In order to upload client data you must have at least one open upload slot available on your current Opus23 Pro license. Enter the required fields (Name, Gender, Year of Birth, Ethnicity) and click on the Choose File button. This opens an Explorer window (PC) or Finder window (Mac). Navigate to the Downloads folder of your computer (or to wherever you have saved the zipped raw data file) and select the file. The file will take some time to upload, and most browsers will show a progress bar. Once uploaded, the client's profile will appear in the Load/List Profiles section of Opus23 Pro alongside the sample client. Click on your client's last name to load their data into Opus23 Pro. Their name will now appear in the top left corner of Opus23 Pro to show which client is currently loaded. You are now ready to explore that client's genome using the applications in the program and produce reports based on their data. For more information, see 'Working with Data' in the next section.

  - **Edit Current Profile:** Selecting this option will allow you to add further details about the current client or edit existing details.

  - **Re-Index Current Client:** If new SNP data has been added to Opus23 Pro, re-indexing will load the new SNPs from the client's 23andMe data and use that information in any mappings, algorithms, reports, etc.

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- **Log Out**: Clicking this option logs you out of Opus23 Pro and removes any tracking data (cookies) from your computer.
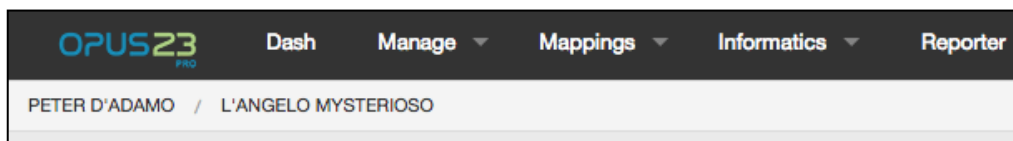
Status line showing account name and current loaded client

Working with Data

Before using Opus23 Pro, you will need some raw data from a genetic test. Opus23 Pro has been optimized for use with data from 23andMe, please contact us with regard to using data from other genome analysis services. Raw data is provided by 23andMe in the form of a compressed ZIP file.

There are different methods to getting client 23andMe raw data for use in Opus23 Pro. Some practitioners have accounts with 23andMe and offer the test kits through their clinic. In this situation, and where you have registered the client's kit using your own 23andMe account, you can access the client's data directly from the 23andMe website. Others simply advise their clients to purchase the kit directly from 23andMe and either email the ZIP file to their clinic or have the client provide the file on a USB thumb drive or CD-ROM. No matter the method, you will need to secure the 23andMe raw data ZIP file for the client.

If you are requesting that the client secure the data file directly from 23andMe, advise them that after 4-5 weeks from submission date (quicker if they are using a physician priority handling kit) they should log in to 23andMe. The location of the raw data depends on the date of processing of the kit.

- For more recently processed results, after logging in click on 'TOOLS' at the top of the page, then 'Raw Data', then click on the download link in the text (the direct link when logged in is https://you.23andme.com/tools/data/download/). Select 'All DNA' and enter the 23andMe password, and the zip file will download.

- For older results, in the top right corner is a box showing the client's name. They then click on the box and select 'Browse Raw Data'. On the next page in the top right hand corner under their name is a link to download the data. They will need to enter their password and the secret answer they set

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up when creating their account, select 'All DNA' as the dataset, and the file will download to their computer (usually to the Downloads folder). Ancestry results are not currently used by Opus23 Pro.

Import Raw Data screen

Uploading Raw Data

Opus23 Pro uses a text file from 23andMe.

When you download your raw data from 23andMe, it will be in a .zip file format (compressed to reduce the size). Some computers will automatically unzip these files after downloading. If this happens, you will need to zip the file again before uploading to Opus23 Pro:

- **On a PC in Windows Explorer**: Right click the file, point to 'Send to' and select 'Compressed (zipped) folder'. To rename the file, right click and type in the new name.
- **On a Mac**: Select the file in the Finder and right click or Control click, then select 'Compress'. To rename the file, right-click and type in the new name.

Tips/helpful suggestion boxes

In this manual, special tips or helpful suggestions or insights appear inside a green box:

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> *Virtually every aspect of Opus23 Pro requires that you have loaded an active client's genotype. If you try to run an app without having first loaded a client genotype, Opus23 Pro will alert you and gently suggest that you do so.*

Getting Help

Clicking the Help link on the main menu bar will present you with two choices from the pull-down menu:

- **Online Help Docs**: this will access the online help files. Most of the time, you will be directed to the appropriate help doc for whatever app you are working with. For example, if you are working in LUMEN, click this link will bring up the online help doc that specifically supports LUMEN.

- **User Manual (PDF):** This will open up a PDF version of the User Manual (this document) in a new window. You can then save the PDF file from your browser, using the 'Save Page' option from the browser's 'File' menu.

Working in Opus23 Pro

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The Opus23 Pro Work Environment

Unlike most conventional genomic reporting software, which more or less provides basic interpretation of raw genomic data typically displayed as some form of a table, Opus23 Pro was designed from the beginning for function as an *Interactive Development Environment,* or IDE. The IDE concept is common in software development, and simply signifies that in addition to its simple display, data can be additionally processed, interpreted and enriched by further human-computer interaction. The goal of Opus23 Pro is to display data contextually and imaginatively so that you can draw the necessary conclusions. The result is a powerful synthesis of precision medicine, clinical experience and bioinformatics heretofore unseen in nutritional genomics.

Opus23 Pro analytics are divided into two broad categories: *Mapping*s and *Informatics.* We'll discuss both in detail in this section of the manual, but first we'll introduce a powerful concept that ties everything together: Curation.

Curation with the NOTEPAD

Much like a museum's contents are codified, inventoried and displayed based on the skills and experience of the museum curator, Opus23 Pro allows the clinician considerable flexibility with regards to how, why, and if its data is displayed. Curation allows you to enrich virtually any aspect of Opus23 Pro with your recommendations, observations and cautions. This is typically accomplished by the use of a special pop-up window called the NOTEPAD. Any element (genes, SNPs, etc.) in Opus23 Pro with an attached note will be added to the notepad curator screen, and can be printed later; thus the notepad can be used either for 'personalizing' the information that is conveyed to the client, or for the therapist to make personal notes for reference during the consultation and to keep in the chart. There are two basic ways to create a Note in Opus23 Pro:

Leaving a Note via a Pop-up Window:

As we've seen, virtually any gene or SNP in Opus23 Pro is hyperlinked to a pop-up window. Clicking on its respective link brings up the information pop-up on that element. In the pop-up window, towards the

upper left hand corner, you will typically find a button labeled 'Add/Edit Note'. Clicking this button will launch the Opus23 Pro NOTEPAD in another pop-up window.
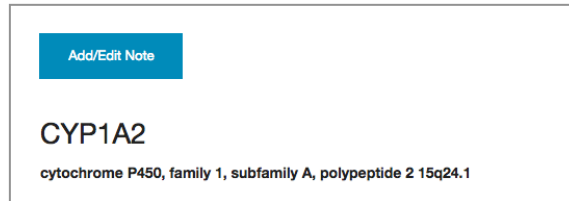
Add/Edit Note button in pop-up window

Clicking the NOTEPAD Icon:

Another way of notating an element in Opus23 Pro is to click on the NOTEPAD icon that is displayed in the various charts. If the element is 'active' and already has a note attached to it, the icon will be colored light blue. If not, the icon will be grayed out. Clicking on an active NOTEPAD link will bring it up for editing.

NOTEPAD icons in table. Note the 'active' icon for MTHFR**.**

The NOTEPAD Window:

Here you can make notations about the element you clicked on; in this case, we would be leaving a note about the CASP8 gene. NOTEPAD has the ability to modify text with styling, such as italics, bold, etc. Click the 'Save Note' button to store your note.

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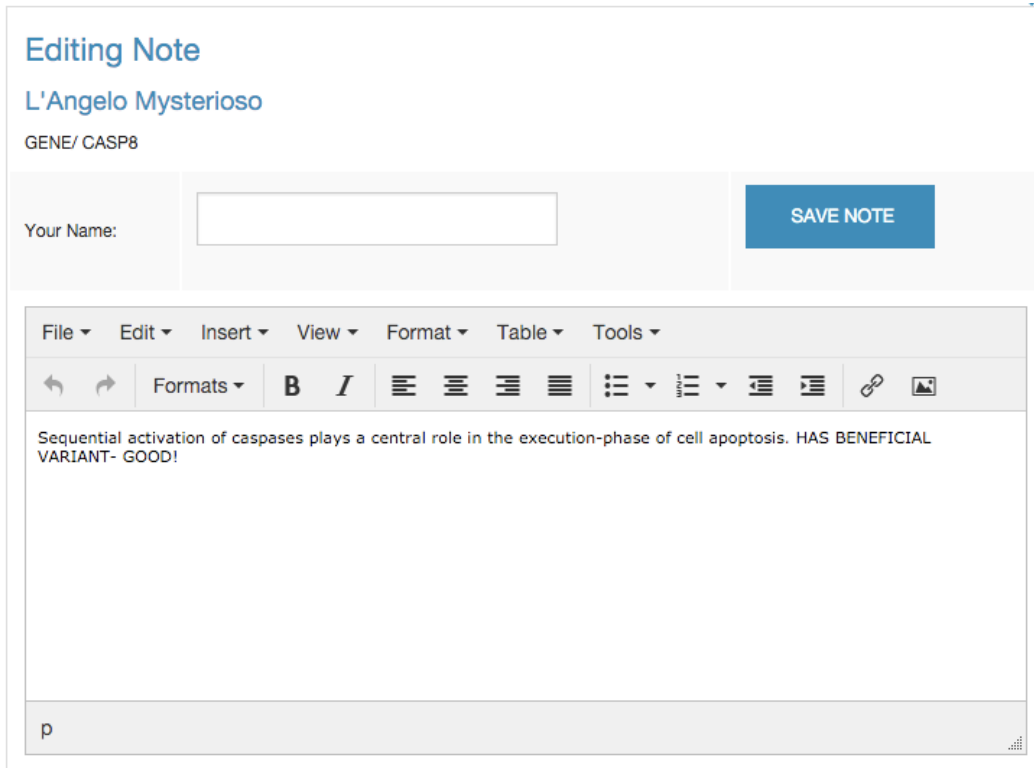
NOTEPAD Pop-up Window

You can add your name or other identifying data in the 'Your Name' box, or this can be left blank. Entries in the 'Your Name' box will appear in the 'Author' column of the printed version.

Notepad Curator

Add General Note | Printable Version

Note	Category	Element	Time	Notes	Author
	SNP	rs1042522	2015/ 11 /09 [13:11:51]	Low Prevalence of TP53 Mutations and MDM2 Amplifications in Pediatric RhabdomyosarcomaTwo SNPs in the TP53 pathway, associated with accelerated tumor onset in germline TP53 mutation carriers, (TP53 SNP72 (rs no. 1042522) and MDM2 SNP309 (rs no. 2279744)), were not found to confer earlier tumor onset.	
	Gene/ Molecule	CASP8	2015/ 11 /09 [05:12:29]	Sequential activation of caspases plays a central role in the execution-phase of cell apoptosis. HAS BENEFICIAL VARIANT- GOOD!	
	SNP	rs2229765	2015/ 11 /09 [05:10:17]	IGFIR is highly overexpressed in most malignant tissues where it functions as an anti-apoptotic agent by enhancing cell survival.	
	Gene/ Molecule	PTEN	2015/ 11 /09 [05:07:25]	This gene was identified as a tumor suppressor that is mutated in a large number of cancers at high frequency. NO MUTATION HERE/ GOOD	
	SNP	rs6740660	2015/ 11 /09 [05:06:42]	Adverse response to chemotherapy (neutropenia/leucopenia) (5-fluorouracil)	
	SNP	rs234709	2015/ 11 /09 [05:04:50]	CBS domain as such has no defined function(s) but plays a regulatory role for many enzymes and thus helps in maintaining the intracellular redox balance.	
	SNP	rs5030868	2015/ 11 /09 [05:03:17]	Should avoid high-dose vitamin C	

NOTEPAD Curator Window

Access to all notes is found in the Notepad Curator available from the Curation button. Add a general note by clicking on the 'Add General Note' button. Any text added in the 'Title' field will appear in the 'Element' column. Print all notes by clicking on the 'Printable Version' link. The number of notes visible can be adjusted by using the drop down 'Show' box, and a search box is available for searching the text of all existing notes.

N.B. Notes can be edited but not deleted.

Notes can be used to remind the practitioner of certain aspects about the client, or can be designed to be given to the client for use alongside the Client Report for a more personalized experience.

Apps and Analysis

Opus23 Pro features many methods to parse, skew, slice and dice your client's genomic data. These are referred to as 'apps' (short for applications.) Most apps run independently and perform some unique function on the data, much of which will eventually find its way to the Chart Report and perhaps eventually to the client. Apps also help organize and visualize data in ways that are not easily accomplished otherwise, and the ability to depict the same data in different reference frames is one way of insuring that a potentially actionable element is identified.

MAPPER: Dynamic network/pathway mapping

The MAPPER app allows you to visualize your client's genomic data directly in a number of hand-curated pathway maps. In addition to allowing for quick pattern recognition, MAPPER uses combinatorics and graph theory to ascertain certain functional characteristics of genes in the network, based on their position in a web of interconnections.

Working with MAPPER

From the main menu bar at the top of the screen, hover over the link labeled 'Mappings'. This will trigger a pull-down menu showing the current categories of maps available (Detoxification Networks, Inflammatory Networks, etc.) Select your area of interest or click on 'Show All Maps'. You will then be presented with thumbnails of the various maps under that category. Select a map by clicking on the image or the link below each thumbnail.
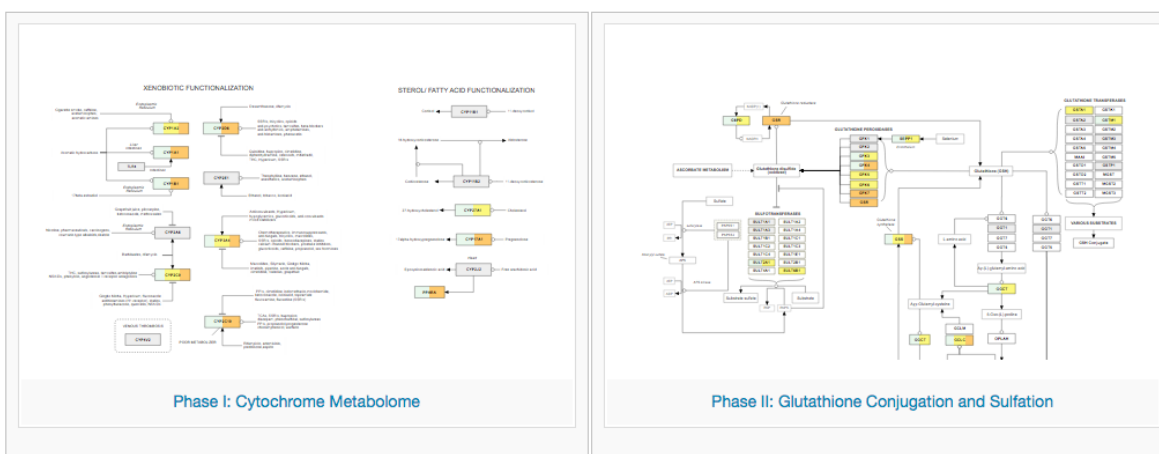
MAPPER thumbnails of the Detoxification category

This will load the map into the full window. Now we can begin to explore MAPPER.

We've selected the 'Phase I: Cytochrome Metabolome' map.
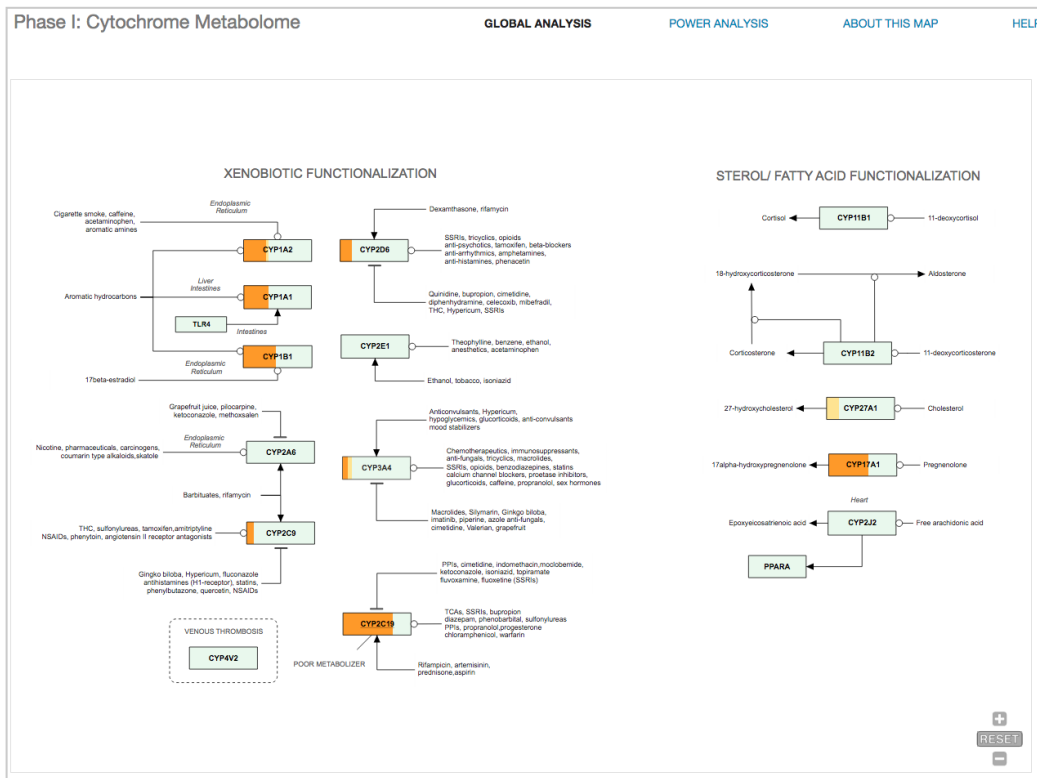
Phase I: Cytochrome Metabolome map in MAPPER.

Here we are presented with the various genes associated with cytochrome activity. When you first load a map into MAPPER, you are in 'Global Analysis' mode. As you can see the color fill of the box surrounding the gene symbol can differ from gene to gene. That's because MAPPER is telling us visually what is going on behind the scenes with the SNPs that are part of that gene. Hover over any gene for a second or two and MAPPER will tell you have many SNPs it currently tracks for that gene. Click on the gene symbol to bring up the information pop-up on that gene. You can zoom in or zoom out of the map by clicking the + or - buttons at the bottom right of the map. Clicking reset puts the map back to the default resolution. When the map is zoomed-in, you can move the map around inside its canvas by click-dragging it. To read a synopsis of the network map, click on 'About This Map.'

Interpreting MAPPER gene data

It's perhaps easiest to think a gene box in MAPPER as the equivalent of the battery icon on a smart phone. If there are bars all across the battery icon it's probably at full charge; however as the battery loses power, the bars get shorter from right to left. MAPPER uses the same iconography to tell you about the status of the genes in its network.

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Let's put them in a table to make things clear:
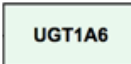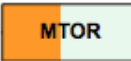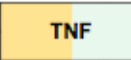
TRAF2	Genes that are in the map but are not represented by SNPs in Opus23 Pro are colored gray
UGT1A6	Genes that contain solely SNPs for which the client genotype does not contain risk alleles are entirely colored green
LEP	Genes that contain solely SNPs for which the client genotype is homozygous for risk alleles are entirely colored orange
MTOR	Genes that contain SNPs that are a mixture of different outcomes will display the outcomes as percentages of the SNP power factor
TNF	A gene with a mix of heterozygous and non-reactive SNPs of about equal significance
GCLC	A gene that has all three classes of outcomes represented

Table showing significance of color-coding in MAPPER when in Global Analysis mode

Layout

The MAPPER uses standard network pathway symbols. Genes are in boxes with bold outlines, gene products, substrates and inhibitors are in boxes with grey outlines.

A line ending with a circle at a gene signifies that the molecule is metabolized by the gene or genes. Cofactors along the pathway that they assist are colored grey:
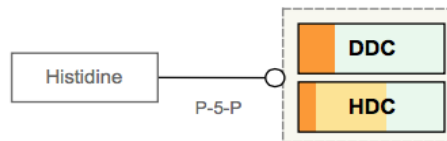
A line ending with an arrow signifies the direction of metabolism:

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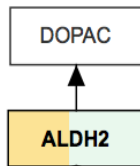
A line ending with a transverse line signifies inhibition:

Power analysis mode

When you first load a map into MAPPER, you start in 'Global Analysis' mode, where the map displays gene data as elements of the current client's genotype. Clicking the 'Power Analysis' link at the top of the map changes the display to instead reflect a semi-quantification of how much 'function' one might expect from the gene, given the status of its SNPs, and upstream substrates.

As with Global Analysis, genes without SNP representation in Opus23 Pro are colored gray. Active genes with Opus23 Pro data are shaded blue, the depth of the blue color indicating the total number of SNPs in the gene for which Opus23 Pro has data. Again, using the battery status analogy, gene function is represented by how much of a 'charge' is in the gene, from left to right. Hovering over the gene will tell you the number of SNPs and a quantitative estimate of gene functionality.

> *MAPPER gene functionality numbers are 'guesstimates' at best, since it is impossible to account for all factors contribution to the activity level of a gene. However, these numbers can be helpful in a broad sense.*

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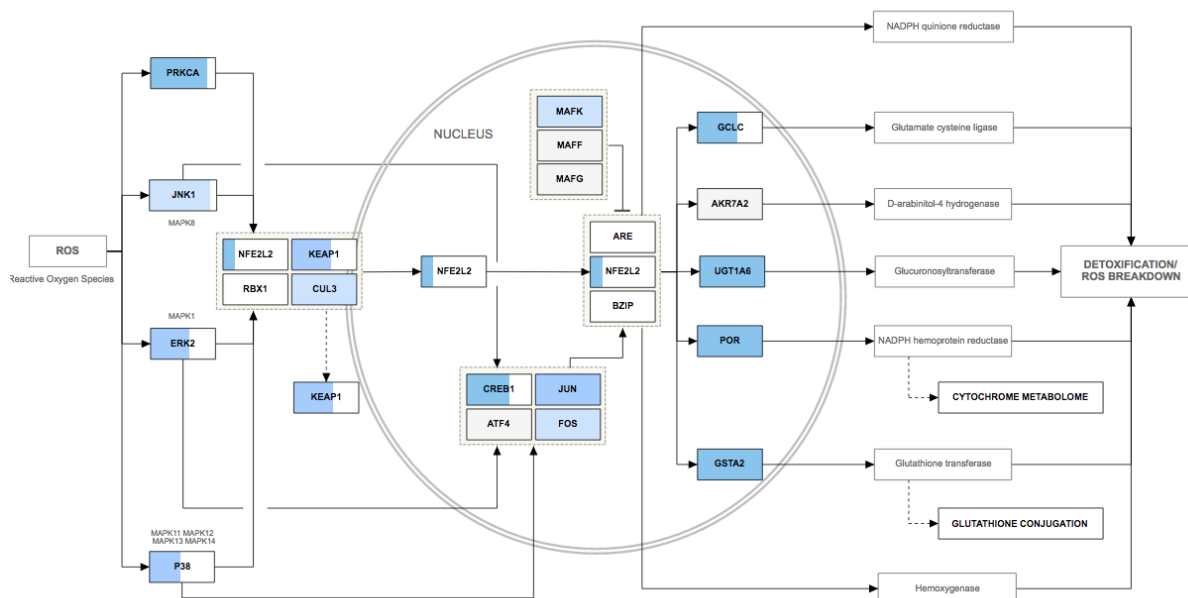
MAPPER network in Power Analysis mode.

> *MAPPER gene results will display in the Client Report when a gene is curated, or added to the genomic curation dataset from the gene pop-up*

Now that we've explored MAPPER, let's move on to the analytical and algorithm apps. These are accessed via the 'Informatics' link in the main menu bar. We'll introduce them in the order that we think makes for the best workflow.

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ARGONAUT: Flexible control over your data

ARGONAUT is a highly flexible search and sort tool that allows you to easily navigate through the client's genotype results from the Opus23 Pro database. ARGONAUT allows you filter your search results and sort the filtered results. In many ways ARGONAUT is the 'mission control' for notating SNPs or genes in Opus23 Pro and as such, it is probably the best place to start your curation workflow.

Getting around ARGONAUT

From the 'Informatics' link on the main menu, hover over 'Queries' into a second menu list appears, then select ARGONAUT. You will then be presented with the default table, which shows 'everything' and is sorted by SNP 'power factor' or magnitude.

Argonaut

ARGONAUT is a highly flexible search and sort tool that allows you to easily navigate through the client's genotype results from the Opus 23 database. Just enter any term in the search box and ARGONAUT will return with the filtered results for that search term. Click on any gene or SNP to trigger its infomation popup. Click on any column title to sort by that column.
Argonaut Quick Editor

Show
15

entries

Search:

Note	Gene	SNP	Specifics	Risk	Client	Outcome	Power Factor	Keywords
	F5	rs6025		T	CC	--	■■■■■■■■■	
	FUT2	rs601338	G428A, W143X	A	AG	+-	■■■■■■■■	SECRETOR STATUS
	BCMO1	rs11645428		G	AG	+-	■■■■■■■■	AMD BETA-CAROTENE 15 15-MONOOXYGENASE 1
	BCMO1	rs6420424		A	AG	+-	■■■■■■■■	AMD BETA CAROTENE CONVERSION
	MTHFR	rs1801133	C677T	A	AG	+-	■■■■■■■■	CANCER MIGRAINE HEADACHE HOMOCYSTEINE
	SHBG	rs1799941		A	GG	--	■■■■■■■■	SEX HORMONES
	TMPRSS6	rs855791		A	GG	--	■■■■■■■■	BLOOD IRON HEMOGLOBIN ERYTHROCYTE
	IL6	rs1800795		C	CG	+-	■■■■■■■■	DIABETES CANCER HYPERTENSION ALZHEIMERS PERIODONTITIS
	LOC100506236	rs1055144		T	CC	--	■■■■■■■■	WAIST-HIP RATIO

ARGONAUT data screen.

At the bottom of the window is a jump table that allows you to move from one screen to the next. You can control how many rows to display by selecting an option from the 'Show' pull down menu. The default is 15.

Filtering and sorting results

As you can see, there are over 100+ pages of SNP data in ARGONAUT, which would make grinding through the data rather impractical. To deal with large amounts of data, ARGONAUT features a 'filterable' display. Type full or partial search terms into the search box at the upper left hand corner and ARGONAUT immediately displays only those results.

The ARGONAUT table displays the following data by column: Gene Symbol, SNP, Specifics (extra SNP identifiers, i.e. 'C677T'), Risk Allele, Client Genotype, Outcome, Power Factor and Keywords. Data from all columns will be included in the search. Click on any gene or SNP to trigger its information pop-up. Click on the Notepad icon to add or edit a note for that SNP. If you want to create a note for the gene, click on it to open up its information pop-up, and then press the 'Add/Edit' button.

ARGONAUT columns are sortable. Click on any column title to sort by that column. Click that column again to reverse the sort order. Here's an example that returns all SNPs homozygous for the risk allele of COMT, with the results sorted by Power Factor.

Note	Gene	SNP	Specifics	Risk	Client	Outcome	Power Factor	Keywords
✎	COMT	rs4633	H62H	T	TT	++	▪▪▪▪▪▪	PAIN SENSITIVITY PARANOID SCHIZOPHRENIA HOMOCYSTEINE HYPERACTIVITY CHRONIC FATIGUE SYNDROME
✎	COMT	rs4646312		T	TT	++	▪▪▪▪▪▪	ESTROGEN ANDROGEN METABOLIZING
✎	COMT	rs4680	V158M	A	AA	++	▪▪▪▪▪▪	COMT ENZYME DOPAMINE STRESS BLOOD METABOLITES BREAST CANCER PAIN MEMORY ATTENTION
✎	COMT	rs165722	1187C>T	T	TT	++	▪▪	CANCER TREATMENT OPIOIDS MONOAMINE CANCER

Showing 1 to 4 of 4 entries (filtered from 1,490 total entries)   Previous **1** Next

ARGONAUT table filtered by search term 'COMT' and '++' and sorted by Power Factor
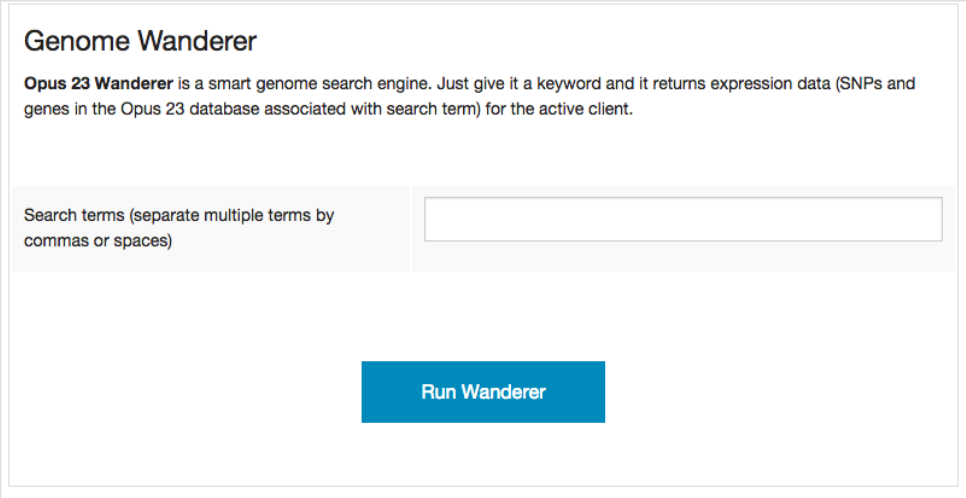
The right hand side has two columns headed 'More' and 'Extra'. The 'More' column shows a speech bubble if the entry in the Keywords column has too many words to display: hover over the speech bubble and the whole keywords entry will be displayed as a tooltip. The 'Extra' column may show two symbols, ⊕ indicates that extra searchable data will be included for that SNP (click on SNP popup to view it.) ♦ indicates that GWAS data is being included in the search data, in addition to any SNP data curated by Opus23 Pro editors.

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WANDERER: Multi-app search engine

WANDERER is a smart Opus 23 Pro search engine. Just give it a keyword and it returns a wide variety of expression data for the active client from several of the major Opus 23 Pro databases.

Getting around WANDERER

From the 'Informatics' link on the main menu, hover over 'Queries' until a second menu list appears, then select WANDERER. You will be presented with the WANDERER input screen. You can also access WANDERER from the search field at the top-right of the menu bar or from the search field in the WANDERER search return screen.

WANDERER search input screen

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Using WANDERER

WANDERER will accept up to four search terms, defined as any phrase separated by space characters or commas. The WANDERER search algorithm is 'greedy', meaning that entering 'COMT' and 'MTHFR' will return results with either search term. WANDERER will search:

- Opus 23 Pro's internal SNP database
- Opus 23 Pro's algorithms
- Opus 23 Pro's pharmacogenomic database
- Genome Wide Association Study (GWAS) databases
- Opus 23 Pro's natural products database

And return search results in the standard Opus 23 Pro sortable, filterable table format. Most table results contain links to pop-up information screens.

When possible, search results will be parsed with the client's genotype data.

WANDERER results screen

WANDERER returns each class of search results in the standard Opus 23 Pro sortable, filterable table format. Most table results contain links to pop-up information screens.

> *Searching WANDERER is a great way to get a 'feel' for how specific SNPs and genes function across a variety of analytical frameworks. With WANDERER you can search and cross-reference significant SNPs and genes with Opus 23 Pro SNP data, GWAS data, algorithm results, pharmacogenomic interactions and natural product data.*

MOBOCASTER: Scenario specifics

MOBOCASTER is an AI module/app that performs scenario-specific genomic analysis, since as clinicians, that's pretty much how we think about genomics.

MOBOCASTER entry screen

The entry screen in MOBOCASTER lists an overview of several genomic scenarios, such as the HPA Axis, displaying colored boxes representing potentially problematic genes for the current client in this scenario. The size and color of the box indicates the significance of the gene in relation to others in this scenario: The larger and darker the box, the more problematic a gene may be for this client. The genes with curated SNPs with the highest power factor assigned by Opus23 Pro editors will show up in a darker orange color and have a larger sized box. A bar below each scenario gives a key to the relative value assigned to each color. Hovering your mouse over a box will move the arrow along color key to indicate the aggregated power factor of that gene, as well as the number of SNPs used to calculate this value. Clicking on any box will open a pop-up with information about the gene and the SNP status for the active client. If your client has all homozygous negative SNPs for a gene in a MOBOCASTER scenario, that gene will not appear in the MOBOCASTER overview.

MOBOCASTER Entry Screen

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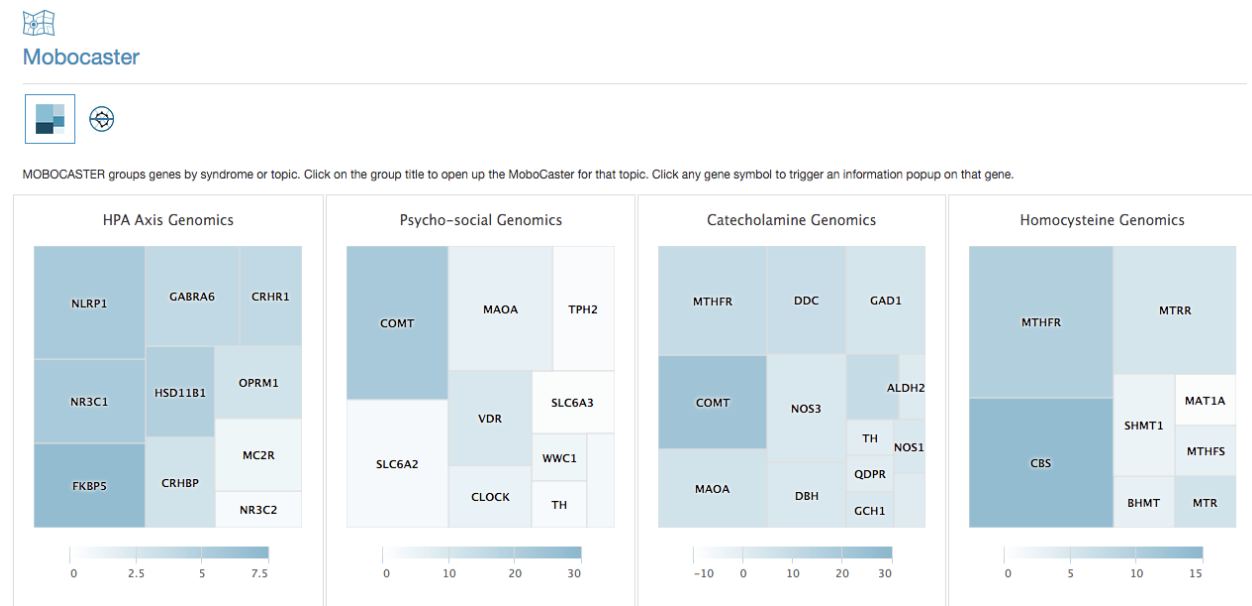
MOBOCASTER Scenario Screen

To find out more about the scenario, clicking on the scenario name links to a page with a description of the scenario and details of all the SNPs and their values in this scenario, listed in alphabetical order of the gene symbols. Clicking on a gene symbol from the list at the top of the page will take you directly to that gene and its description.

Under the list of genes in the scenario is a gene power factor chart. This is a color-coded bar graph showing all the client's SNPs for each gene in this scenario, grey for homozygous negative, yellow for heterozygous and orange for homozygous positive, green for having beneficial SNPs.

If a gene in the scenario is also listed in any maps or other MOBOCASTER scenarios, or has associated natural products, these will be listed under the gene with a hyperlink. The description of the gene may be curated to be specific to this scenario: to find out general information about the gene, click on the gene symbol link to open the gene pop-up. Clicking on the SNP rs ID link will open a SNP pop-up.

MOBOCASTER Scenario screen.

Some scenarios may examine only specific SNPs in a gene, for example, in the Phase I Detoxification scenario CYP1A2 lists only rs762551, as this SNP is known to be a high-inducibility variant. In this situation, clicking on the link to CYP1A2 will open a pop-up giving you information about the other CYP1A2 SNPs for the current client.

MOBOCASTER results will display in the Client Report when a gene is curated, or added to the genomic curation dataset from the gene pop-up

STROBE: Tissue distributions

Opus 23 provides many unique opportunities for data integration and visualization. STROBE is an Opus 23 analytic app that allows you drill-down client genomic data by organ, tissue or cell distribution. To do this Opus mashes up its own internal SNP data with gene tissue expression data derived from a variety of public databases. Opus 23 then sub-organizes the tissue expression data by system (immune, cardiovascular, etc) so that you can filter by clinical relevance.
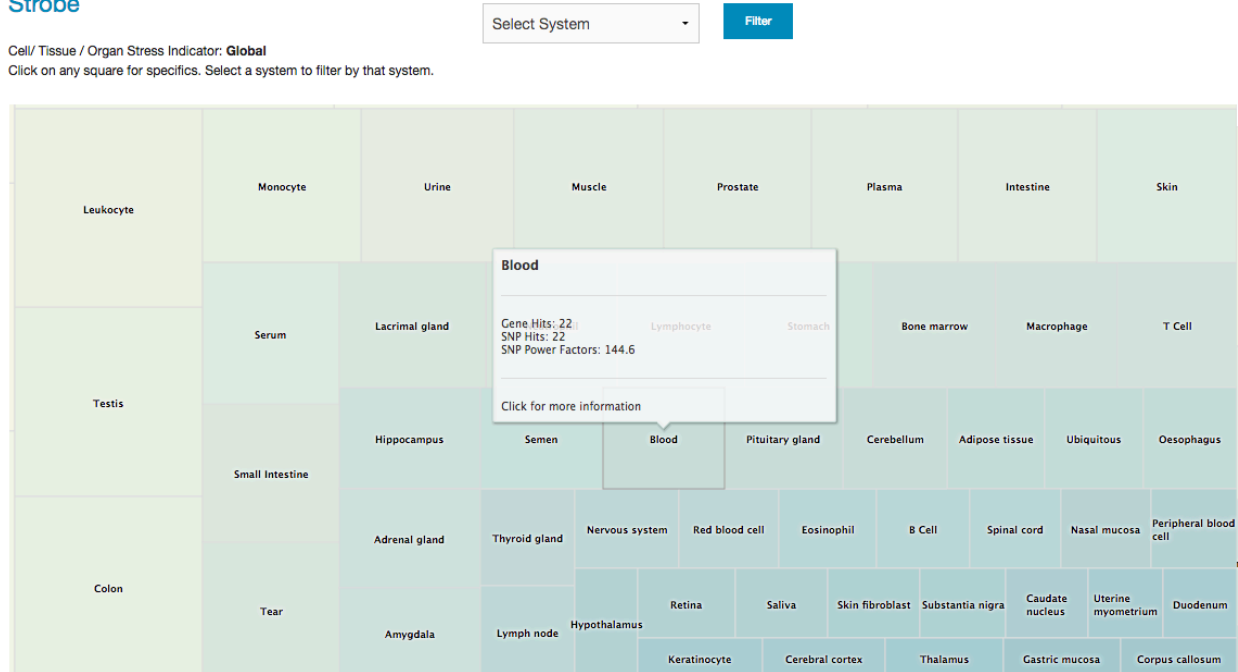
STROBE main Heat-map screen.

Getting around in STROBE

Once STROBE is fired up you're presented with the screen depicted above. It is a typical squarified heat-map. Values are assigned by virtue of the aggregate power factors of client SNP mutations number of genes associated with that tissue. Clicking on any tissue brings up a modal popup with a Manhattan-type gene distribution display.
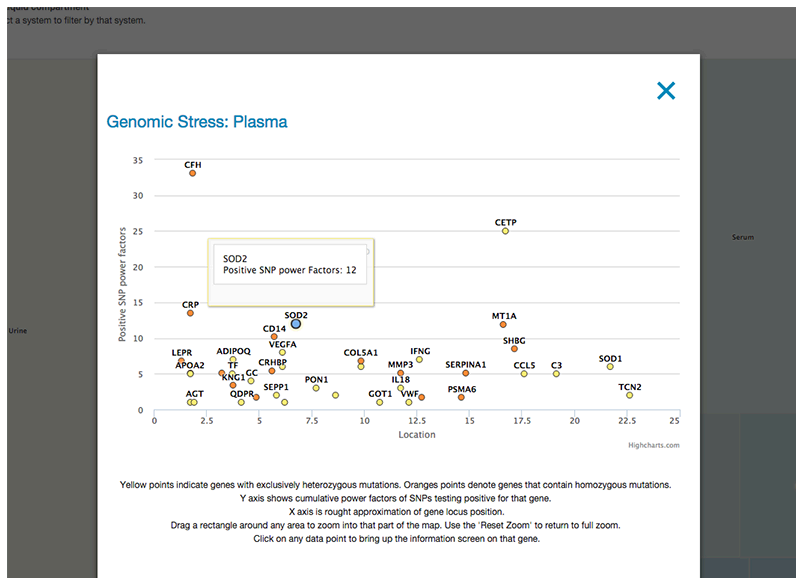
STROBE tissue information pop-up.

The Y axis shows cumulative power factors of SNPs testing positive for that gene. The X axis is rough approximation of gene locus position. Yellow points indicate genes with exclusively heterozygous mutations. Orange points denote genes that contain homozygous mutations.

Drag a rectangle around any area to zoom into that part of the map. Use the 'Reset Zoom' to return to full zoom. Clicking on any data point to bring up the information screen on that gene. Here you can notate, or even move on to examining SNPS, agents and algorithms associated with the gene.

From the main screen you can use the select pull-down menu to limit tissues to specific systems.

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LUMEN: Power over complexity

LUMEN is one of the most powerful apps in the Opus23 Pro toolbox. This app allows you to examine the effects of multi-SNP, multi-gene consequences. Very few single SNPs exert their effects independently; they more typically interact through epistatic relationships (where the phenotypic expression of one gene influences the genotypic expression of another) or as a haplotype: a set of several SNPs, on a single chromatid of a chromosome pair that are associated statistically.

LUMEN does this by using *algorithms*, small step-by-step programs that run inside of LUMEN and that look at the logical result of multi-SNP combinations. This type of logic is essentially 'Boolean' in that its queries yield a yes or no answer. The combination of both allows LUMEN to provide you with insight into complex SNP arrangements and relationships that might otherwise escape detection.

Getting around LUMEN

To start LUMEN, from the main menu bar at the top of the screen, hover over the *Informatics* link, and then scroll down to *Algorithms*. Click *Lumen.* You will be presented with the Lumen index page:
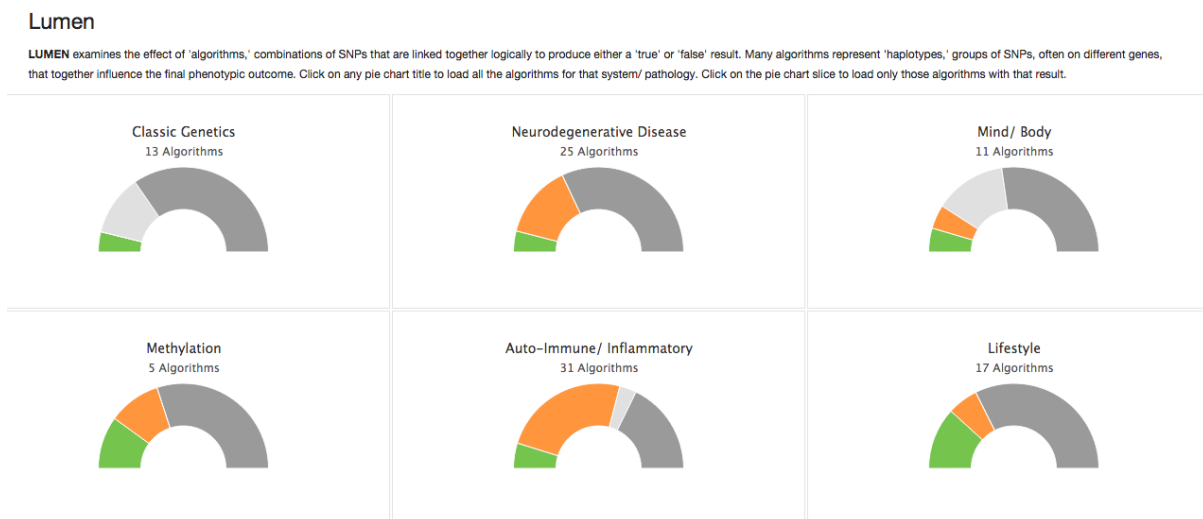
LUMEN Index Page

Here you will find all the LUMEN algorithms grouped by general category. Each category is displayed as a half-pie chart depicting the distributions of the various algorithms in that category.

The half-pie chart is color-coded and interactive. Let's take a look:

LUMEN Category
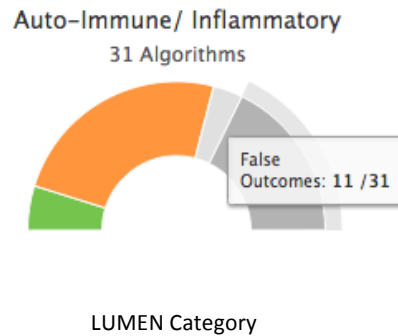
The chart displays four types of algorithms: three that indicate algorithms returning a true value (green, orange and light gray) and one indicating algorithms that return a false value (dark gray).

- The green-colored slice indicates algorithms that convey benefit (good repute) for which the client returned a true value
- The orange-colored slice indicates algorithms that convey risk (bad repute) for which the client returned a true value
- The light gray-colored slice indicates algorithms that have a neutral repute (i.e. they are not good or bad, such as one's blood type) for which the client returned a true value
- The dark gray-colored slice indicates algorithms for which the client returned a false value

If you hover over any section of the pie slice, a tooltip will describe the type of result for the category and the number of outcomes. In the example above, out of 31 algorithms classed as 'Autoimmune/Inflammatory' eleven out of thirty-one algorithms returned a false value for that client (i.e. the algorithm did not apply to them).

Clicking on any pie slice will display the algorithms in that category. Clicking on the category name will display all the algorithms in that category, including those with a false result.

Let's click on the title (Autoimmune/Inflammatory) and see what LUMEN can do.

Using LUMEN

Algorithms are displayed as individual boxes, one below the other. Let's examine one in detail:

AG004 OUTCOME: Increased risk of allergic asthma	
Repute: BAD **Power Factor:** 2.5 **Gene(s):** ADRB2, IL4, ADAM33	**INTERPRETATION:** This client has an increased risk of allergic asthma. Genetic polymorphism in the IL-4 promoter, ADRβ2, and ADAM33 is associated with asthma. Furthermore, ADAM33 genetic polymorphism modifies the phenotype of asthma in atopy and hyperresponsiveness. The T allele for the IL-4 C-589T IL-4 promoter (rs2243250), the C allele frequency for ADRβ2 Gln27Glu locus (rs1042714), and the A allele for the ADAM33 gene (rs2280091, T1) were higher in asthma patients than in normal individuals. In asthmatic patients, the A allele of ADAM33 (rs2280091) was associated with higher eosinophil count and increased hyperresponsiveness compared to the C allele. Combination of the three risk genes SNP had an additive effect on the risk of asthma (OR: 3.46; CI: 1.51-7.93) [PMID 23245479]

Typical LUMEN algorithm

This algorithm (AG004) looks at three SNPs on three different genes to determine if the client's genotype may indicate an increased risk of allergic asthma. Starting from the top left, we see the now familiar NOTEPAD icon that would allow us to add a note about this algorithm. Next follows the algorithm id and the conclusion summary.

> *Many of these summaries are dynamic: for example, depending on this algorithm's outcome, it might have 'Risk of..' or 'Increased risk of..' or 'Significantly increased risk of..'*

Next, we have a box with several details: If the selected algorithm has a bad repute it will be colored orange, if the algorithm results in some benefit, it will be colored green, and if the algorithm is neutral it will be colored gray. The *Power Factor* or magnitude is a number (1-10) added by the Opus23 Pro curators. It reflects a combination of pathology severity, evidence basis and p-values and odds ratios

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when available. Next row shows the genes included in the algorithm, and like most gene symbols in Opus23 Pro, clicking on this will trigger an information pop-up.

If HapMap data on gene/SNP frequencies are available they will be shown in a separate box directly underneath.

To the right is the interpretation abstract. This is usually a paragraph or two describing the algorithm and what are its criteria. When possible, a PubMed ID number is provided. Underneath the abstract will be a table showing the client's genotype for the SNPs involved, and like most rs ID numbers in Opus23 Pro, clicking on this will trigger an information pop-up.

Variations in algorithm output

Depending on the type of criteria, LUMEN will sometimes present data in a table format. This is typically done in situations where an algorithm's SNPs outcome might convey benefit in one pathology but risk in another. Depending on if the genes are SNPs, you might be alerted to the presence of other data available. For example, if there are natural products associated with any of the genes or SNPs in the algorithm you will see the following:

Clicking on this link will trigger a pop-up and display any relevant information. In addition, if any genes in the algorithm are included in MAPPER you will be alerted.

Algorithm returning positive for a trait considered 'good'

If you wish, LUMEN can return algorithms for which the client returned a false result. To distinguish these from true algorithms the algorithm box border is colored orange and the following warning is displayed:

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SUPERMOGADON: GWAS in words and pictures

SUPERMOGADON is a highly flexible search and sort tool that allows you to easily compare through the client's genotype with results from Genome Wide Association Studies (GWAS) the Opus23 Pro database. Just enter any term in the search box and SUPERMOGADON will return with the filtered results for that search term. Click on the graph icon to display SNP distribution for that pathology or trait as a Manhattan Plot. Click on any column title to sort by that column.

Getting around SUPERMOGADON

As you can see, there are over 50+ pages of GWAS data in SUPERMOGADON, which would make grinding through the data rather impractical. To deal with large amounts of data, SUPERMOGADON features a 'filterable' display. Type full or partial search terms into the search box at the upper left hand corner and SUPERMOGADON immediately displays only those results.

The SUPERMOGADON table displays the following data by column:

- Pathology/Trait

- Specifics (metabolites, etc.)

- Total SNP hits in the GWAS database for the disease/trait

- Total heterozygous results for client

- Total homozygous results for client

- A synthesis of the aggregate log p value for the combination of heterozygous and homozygous; SNPs in the client's genome

- Link to infographic depiction of SNPs for that trait

Click on the NOTEPAD icon to add or edit a note for that disease/trait.

SUPERMOGADON columns are sortable. Click on any column title to sort by that column. Click that column again to reverse the sort order.

Supermogadon

SUPERMOGADON is a highly flexible search and sort tool that allows you to easily compare through the client's genotype with results from Genome Wide Association Studies (GWAS) the Opus 23 database. Just enter any term in the search box and Supermogadon will return with the filtered results for that search term. Click on the graph icon to display SNP distribution for that pathology or trait as a Manhattan Plot. Click on any column title to sort by that column.

Show
15
entries

Search:

Note	Pathology/ Trait	Specifics	Total SNP Hits	Heterozygous Risk SNPs	Homozygous Risk SNPs	Synthetic Aggregate Log p value	Show Plot
	Height		436	94	59	939.83	
	Blood metabolite ratios	(N-acetylornithine/myo-inositol)	1		1	723.42	
	Blood metabolite ratios	(isoleucine/X-11529)	1		1	723.42	
	Inflammatory bowel disease		112	25	22	667.51	
	Crohns disease		167	44	28	574.31	
	HDL cholesterol		129	32	9	573.75	
	Rheumatoid arthritis		144	33	16	546.58	
	Triglycerides		92	25	6	434.15	
	Body mass index		129	26	23	431.45	
	Type 2 diabetes		150	44	31	391.70	
	Breast cancer		97	32	17	363.25	
	Fasting glucose-related traits	(FPG)	16	6	6	326.72	
	End-stage coagulation	(FXIII activity)	2		2	326.62	
	Menarche (age at onset)		159	28	17	324.08	
	Blood metabolite levels	(isoleucine/X-11529)	1		1	314.22	

Showing 1 to 15 of 775 entries   Previous **1** 2 3 4 5 … 52 Next

SUPERMOGADON index page

Manhattan plots in SUPERMOGADON

Clicking on the blue graph icon in the 'Show Plot' column will launch the SUPERMOGADON Manhattan plotter for that disease/trait. We'll click the graph for 'Inflammatory Bowel Disease':

Inflammatory bowel disease
GWAS Analysis (Central Release, March 2015)

Significance (-log p Value)

Chromosome

Highcharts.com
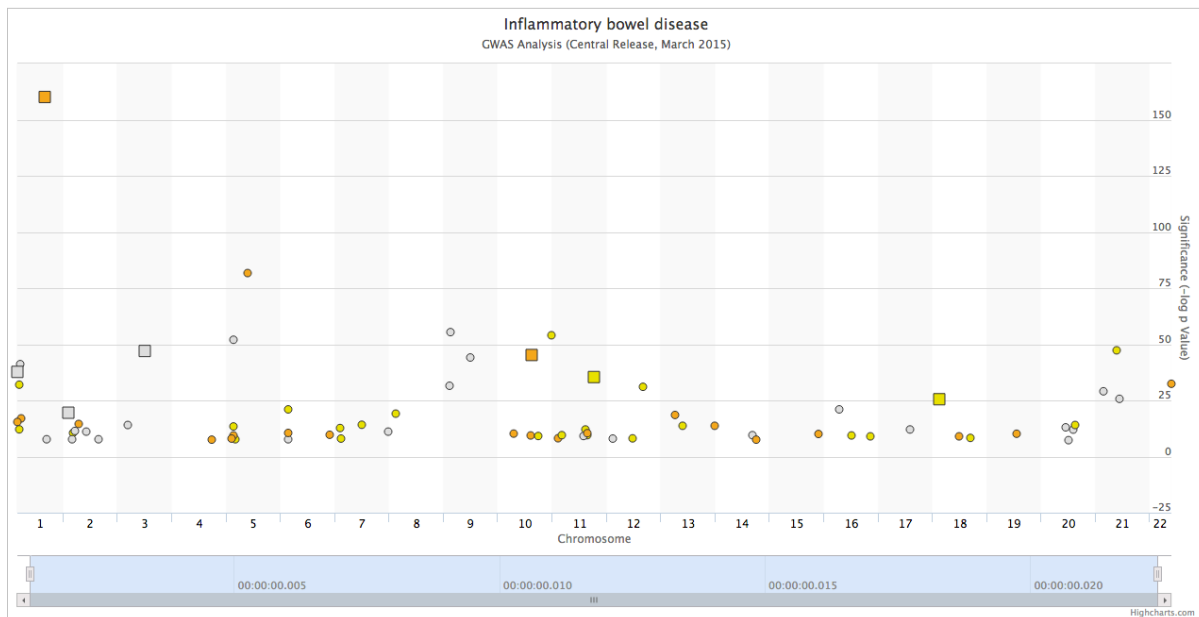
GWAS Manhattan plot of 'Inflammatory Bowel Disease' in SUPERMOGADON

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The SUPERMOGADON Viewer is a GWAS Manhattan plotter, a type of scatter chart used to display data with a large number of data-points. Genomic SNP coordinates are displayed along the X-axis, with the negative logarithm of association P-value for the disease or pathology displayed on the Y-axis. Because the strongest associations have the smallest P-values (e.g., 10^{-15}), their negative logarithms will be the greatest (e.g., 15).

Client SNP genotypes results are shape and color-coded:

- Gray-colored points denote client SNPs that do not contain the risk allele

- Orange-colored points denote that the client is homozygous for the risk allele

- Yellow-colored points denote that the client is heterozygous for the risk allele

- Square-shaped points signify that the SNP is in the GWAS and Opus23 Pro databases and when clicked will trigger an information pop-up

- Circle-shaped points signify that the SNP is not in the Opus23 Pro database but is in the GWAS database and is reported by 23andMe. When clicked these SNPs will bring up its GWAS PubMed reference article

Drag-select to zoom section or use the scroller at the bottom. Hover over any point to learn more.

Like any other element in Opus23 Pro, you can notate the SNP in SUPERMOGADON Viewer by clicking on the link to bring up the information pop-up, then clicking the 'Add/Edit Note' button at the top of the pop-up screen.

DRUGGIE: Pharmacogenomics and adverse reactions

The DRUGGIE app provides information on SNP-mediated pharmacogenomic interactions and potential adverse reactions.

Getting around DRUGGIE

From the 'Informatics' link on the main menu, hover over 'Prescriptives' until a second menu list appears, then select DRUGGIE. You will then be presented with the default table, which shows 'everything' and is sorted by the 'Alert' column. Like most data-driven apps in Opus23 Pro, DRUGGIE uses a filterable/sortable table to display its data:

Note	Drug	SNP	Gene	Defining Allele(s)	Client	Alert	Adverse Reactions/ Pharmacological Effects
	Acitretin	rs429358	APOE	C	CT	⚠	Psoriasis
	Acitretin	rs7412	APOE	C	CC	⚠	Psoriasis
	Amitriptyline	rs1045642	ABCB1	AA	AA	⚠	Postural hypotension
	Amitriptyline	rs4244285	CYP2C19	A	AG	⚠	Those with the AA or AG genotype are poor metabolizers of amitriptyline
	Azathioprine	rs1142345	TPMT	C	CT	⚠	Hepatotoxicity
	Azathioprine	rs1142345	TPMT	C	CT	⚠	Patients with CC or CT genotype have decreased inactivation of thiopurines and increased risk of toxicity
	Caffeine	rs762551	CYP1A2	C	AC	⚠	Myocardial infarction
	Carbamazepine	rs2227956	HSPA1L	A	AA	⚠	Hypersensitivity reaction, mild erythematous skin rashes, macropapular eruption, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis
	Carbamazepine	rs3909184	FLOT1	G	CG	⚠	Patients with the CG or GG genotype (in Asian patients) were at a higher risk of Steven-Johnson Syndrome compared to those with the CC genotype (non-carriers of HLA-b*1502)
	Carbamazepine	rs2844682	MUC21	G	AG	⚠	Patients with the AG or GG genotype (in Asian patients) were at a higher risk of Steven-Johnson Syndrome compared to those with the AA genotype
	Cisplatin	rs1695	GSTP1	A	AG	⚠	Tinnitus, hearing impairment, Raynaud syndrome
	Citalopram	rs4675690	CREB1	T	TT	⚠	Elevated suicide risk

DRUGGIE app data screen.

At the bottom of the window is a jump table that allows you to move from one screen to the next. You can control how many rows to display by selecting an option from the 'Show' pull down menu. The default is 15.

Filtering and sorting results

As you can see there are over 16+ pages of drug data in DRUGGIE that would make grinding through the data impractical. To deal with large amounts of data, DRUGGIE features a 'filterable' display. Type full or partial search terms into the search box at the upper left hand corner and DRUGGIE immediately

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displays only those results. Click on any column title to sort by that column. Click that column again to reverse the sort order. Click on the NOTEPAD icon to add or edit a note for that drug. If you want to create a note for the gene or SNP, click on it to open up its information pop-up, and then press the Add/Edit button. Clicking on the drug name will bring up information pop-up with the relevant PubMed abstract.

The DRUGGIE table displays the following data by column: Drug, Implicated SNP, Gene, Defining (risk) allele, Client Genotype, Alert, and a description of the potential adverse reaction. Table rows that display the alert icon indicate that the client's genotype for that SNP is positive for a potential drug reaction.

DRUGGIE alert icon

DRUGGIE data can be added to the Client Report in the Client Report Routing section.

DRUGGIE only examines single-SNP pharmacogenomic associations. To examine multi-SNP pharmacogenomic outcomes, click on the 'Pharmacogenomics' category in the LUMEN app.

ACCELERANT: Etiome and diseaseome causation

THE ACCELERANT app interprets client genome data against two databases: one tracking etiology (the Etiome) and another cross-referencing etiology with disease (Diseasesome).

Both genetic and environmental factors contribute to human diseases. Most common diseases are influenced by a large number of genetic and environmental factors, most of which individually have only a modest effect on the disease. Etiologies of human diseases include factors which are both genetic and non-genetic (here considered as 'environmental' in the broadest sense), such as behaviors and chemical exposures. ACCELERANT defines 'disease' broadly, including syndromes, accidents, and conditions. It displays potentially causative or contributory factors that might compromise or otherwise interact with other therapies or strategies. One could even speculate that these results constitute a type of 'therapeutic order,' highlighting factors that might need to be addressed even prior to addressing viable pathology.

Getting around ACCELERANT

From the 'Informatics' link on the main menu, hover over 'Analytics' until a second menu list appears, then select ACCELERANT. You will then be presented with the default table, which shows 'everything' and is sorted by the 'Magnitude' column. Like most data-driven apps in Opus23 Pro, ACCELERANT uses a filterable/sortable table to display its data. At the bottom of the window is a jump table that allows you to move from one screen to the next. You can control how many rows to display by selecting an option from the 'Show' pull down menu. The default is 15.

Filtering and sorting results
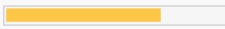
As you can see there are over 160+ pages of etiology data in ACCELERANT, making grinding through the data impractical. To deal with large amounts of data, ACCELERANT features a 'filterable' display. Type full or partial search terms into the search box at the upper left hand corner and ACCELERANT immediately displays only those results. Click on any column title to sort by that column. Click that

column again to reverse the sort order. Click on the NOTEPAD icon to add or edit a note for that etiologic factor.

Besides the tag and notation fields, each row displays the following data on etiologic factors; the ACCELERANT table displays the following data by column:

- **Etiologic factor:** A causative or potentially contributive factor
- **Magnitude:** The significance of the etiologic factor. These are indexed relative to the highest-ranking result, which is assigned an impact of 100, all subsequent impact factors being scaled to that.
- **Aggregate Magnitude**: The total magnitude value
- **Causal Genes:** The implicated genes

Clicking on the gene symbol will bring up the information pop-up for that gene. If you want to create a note for the gene, click on it to open up its information pop-up, and then press the 'Add/Edit' button.

Note	Factor	Magnitude	Aggregate Magnitude	Causal Genes
	Environmental Exposure		8641.28	ACE | ABO | HFE
	Contraceptives, Oral		8306.35	ACE | ABO | HFE
	Hormone Replacement Therapy		7368.53	ACE | ABO | HFE
	Anti-Inflammatory Agents, Non-Steroidal		7100.59	ACE | ABO | HFE
	Anti-HIV Agents		6028.80	ACE | ABO | HFE
	Air Pollutants		5415.60	VKORC1
	Solvents		4874.04	VKORC1
	Estrogens		4421.12	ACE | ABO | HFE

The ACCELERANT data screen

GWASFED: Genome Wide Association Study data in detail

The GWASFED app allows you to perform a traditional search of PubMed. Depending on the article, it may supply you with additional information from the Opus23 Pro databases.

Getting around GWASFED

From the 'Informatics' link on the main menu, hover over 'Analytics' until a second menu list appears, then select GWASFED.

Disease	Avg Log P	Wow factor	Disease SNPs	Client + SNPs	Rare — Sml	Rare — Mod	Rare — Lrg	Low Frequency — Sml	Low Frequency — Mod	Low Frequency — Lrg	Common — Smll	Common — Mod	Common — Lrg
Blood metabolite ratios (acetylcarnitine/hexanoylcarnitine)	85.85	86	1	0 1							1		
Blood metabolite ratios (glucose/mannose)	73.76	74	1	0 1							1		
End-stage coagulation (FXIII activity)	70.55	71	2	1 0							1		
Blood metabolite levels (X-13431--nonanoylcarnitine)	67.00	67	2	1 0							1		
Blood metabolite levels (X-11441)	64.28	321	9	5 0							5		
Blood metabolite levels (X-11787)	62.55	125	2	1 1							2		
Metabolite levels (C9/C10:2)	59.52	476	1	1 0						1			
Blood metabolite ratios (myristate (14:0)/myristoleate (14:1n5))	57.50	115	1	0 1				1					
Blood metabolite levels (4-acetamidobutanoate)	57.40	57	1	1 0							1		
Metabolite levels (C3/C4)	47.65	381	1	0 1						1			
Protein biomarker (Galectin-3)	46.92	47	2	0 1							1		
Iron levels (transferrin)	46.52	372	1	1 0						1			

GWASFED data screen

Like most data-driven apps in Opus23 Pro, GWASFED uses a filterable/sortable table to display its data. At the bottom of the window is a jump table that allows you to move from one screen to the next. You can control how many rows to display by selecting an option from the 'Show' pull down menu. The default is 15.

Filtering and sorting results

As you can see, there are over 100+ pages of etiology data in GWASFED, making grinding through the data impractical. To deal with large amounts of data, GWASFED features a 'filterable' display. Type full or partial search terms into the search box at the upper left hand corner and GWASFED immediately

displays only those results. Click on any column title to sort by that column. Click that column again to reverse the sort order. Click on the NOTEPAD icon to add or edit a note for that disease/trait.

The default sort in GWASFED is by 'Wow Factor' a semi-synthetic number that is calculated by the aggregate log p-value and the distribution and effects of the related SNPs and their power factor. Click on the disease/trait to bring up a pop-up window with the PubMed citation.

Each row in GWASFED depicts the following:

- Disease/trait
- Aggregate log p value
- Wow Factor
- Number of disease SNPs
- Client SNPs and Heterozygous and Homozygous count
- Risk Allele Frequency and Effects

The 'Risk Allele Frequency and Effects' affords considerable insight into the nature of the client's relationship with the disease/trait. Rare or low frequency SNPs with large effects will probably be more noteworthy than small effect SNPs with large frequencies.

FANTASMATRON: Nutrient data and analysis

FANTASMATRON uses a unique Opus23 Pro database that contains micro and macronutrient data on over 700 common foods in the diet. It uses its AI to determine the appropriateness of these foods based on indications such as SNP genotypes and levels of gene function.

Getting around FANTASMATRON

From the 'Informatics' link on the main menu, hover over 'Prescriptives' until a second menu list appears, then select FANTASMATRON. You will be presented with the FANTASMATRON screen:

FANTASMATRON input screen

At the top of the screen, you will see 4 radio buttons. These select the base value set for FANTASMATRON's calculations

- **ABO/FUT2**: Selecting this will use the advanced blood type diet value set
- **Paleolithic:** Selecting this will use a pseudo-Paleolithic diet value set
- **FODMAP:** Selecting this will use a pseudo-FODMAP diet value set
- **Vegan:** Selecting this will use a pseudo-Vegan diet value set

In the center is a box to enter the client's SWAMI GenoType Pro client ID if known. This is the string of numbers that appears on the SWAMI report for use as a login to the SWAMI mobile food list. Entering the client ID here will load the values in the client's SWAMI matrix.

To the right are several action buttons:

- **Save:** Pressing this saves the selections
- **Clear:** Pressing this erases all the current selections
- **Re-run:** Pressing this returns FANTASMATRON to the initial AI recommendations
- **Re-load:** Pressing this loads the saved selections

Underneath is a jump table to various categories of micronutrients. The FANTASMATRON window is scrollable. This simply provides a quick way to get around.

Underneath are the FANTASMATRON switches, organized by category. There are three types of switch for each nutrient. They control how the nutrient is valued:

- The left-most switch removes the nutrient from analysis
- The center switch tags the nutrient as 'desirable.' Foods that have this nutrient will be emphasized. This is identified by its green color when active.
- The right-most switch tags the nutrient as 'undesirable.' Foods that have this nutrient will be de-emphasized. This is identified by its orange color when active.

Some nutrients may have a de-emphasis or emphasis switch inactivated. This option is not available for that nutrient.

> If you want FANTASMATRON results to appear in the Client Report you will first need to run and save FANTASMATRON, then select the 'Rout to Report' check box in the Report Routing screen and save the report routing settings

Accessory Apps and Tools

In addition to its core app, Opus23 Pro also contains several apps with a more limited scope of action. However, these apps can be very helpful under specific circumstances. We've also included a few extra tools' to make your job a bit easier.

PSYCHIC: Interactome-based prescriptives

PSYCHIC allows you to search for natural products known to control gene expression. However, unlike a simple search engine, PSYCHIC is able to crawl up and down the molecular 'interactome' to determine the upstream and downstream genes that interact with the gene you've searched for. In addition, PSYCHIC allows you to choose which type of natural products (agonists/antagonists) to include in the upstream and downstream results.

Getting around PSYCHIC

From the 'Informatics' link on the main menu, hover over 'Prescriptives' until a second menu list appears, then select PSYCHIC. When the PSYCHIC screen loads you will be presented with the results of the default search term, the MTOR gene:
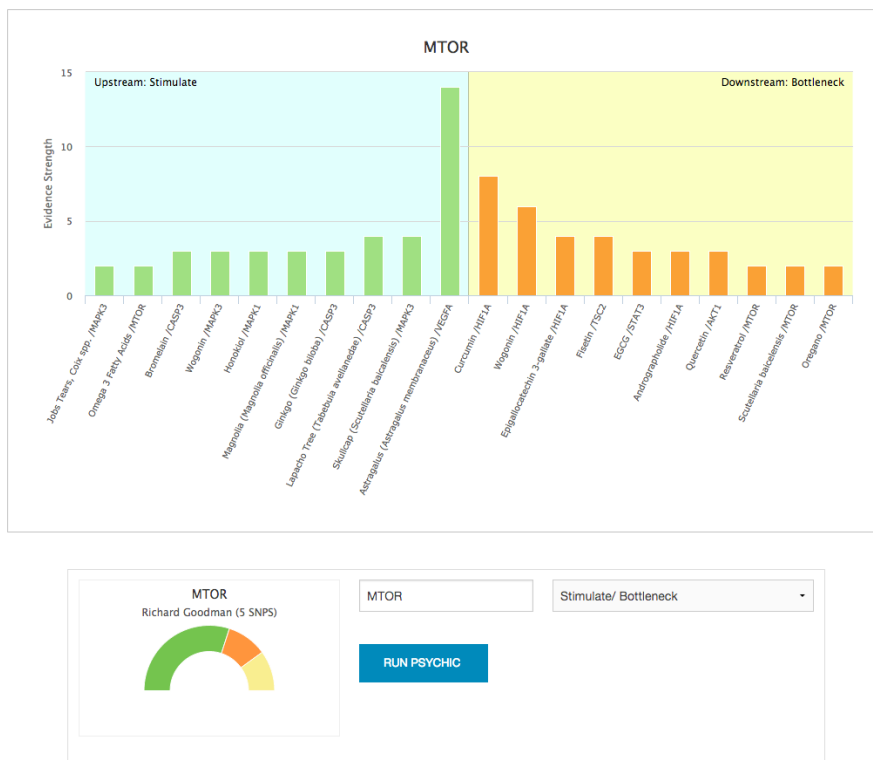
PSYCHIC default screen

As seen here the main infographic is comprised of a bar graph divided into two halves. The left half displays the upstream results, while the right half displays the downstream results, based on MTOR's position in the Interactome. The labels along the x-axis display the various natural products and their gene targets PSYCHIC has found that meet the search criteria. The y-axis value of each bar in the graph is determined by the evidence basis and strength of the position in the network for the gene depicted.

You can set filters on each half of the graph to limit results to a specific type (agonism or antagonism) by selecting an option from the pull down menu below. There are four options:

- **Inhibit/Drain:** This will tell PSYCHIC to return all upstream *antagonists* and downstream *agonists*
- **Inhibit/Bottleneck:** This will tell PSYCHIC to return all upstream *antagonists* and downstream *antagonists*
- **Stimulate/Drain:** This will tell PSYCHIC to return all upstream *agonists* and downstream *agonists*
- **Stimulate/Bottleneck:** This will tell to PSYCHIC return all upstream *agonists* and downstream *antagonists*

A small half-pie chart depicts the SNPs for that gene contained in the Opus23 Pro database.

To select a gene to run in PSYCHIC, simply begin typing in its gene symbol in the text input field; PSYCHIC will auto-complete the entry with any genes for which it has data. If multiple options are displayed, simply select the gene you wish to analyze.

When you're ready, press the 'Run Psychic' button to have PSYCHIC run results.

RARIFY: Rare allele analysis

RARIFY cross-references the client's genotype against a 62K SNP dataset from the human genome project which contains all alternative alleles that occur less than 1% of the time. If the client is either heterozygous or homozygous for the minor allele, RARIFY will display the results.

GETTING AROUND RARIFY

From the 'Informatics' link on the main menu, hover over 'Queries' until a second menu list appears, then select RARIFY. You will be presented with the RARIFY screen, a simple scrollable window:

CHROMOSOME	SNP	RARE ALLELE	STATUS	CLIENT GENOTYPE	GWAS PATHOLOGY
01	rs12756745	C	HETERO	CT	NO GWAS DATA
01	rs17365584	T	HETERO	CT	NO GWAS DATA
01	rs17394875	T	HETERO	CT	NO GWAS DATA
01	rs41264271	A	HETERO	AT	NO GWAS DATA
01	rs4656345	A	HETERO	AG	NO GWAS DATA
01	rs964201	A	HETERO	AG	NO GWAS DATA
02	rs10865486	C	HETERO	CT	NO GWAS DATA
02	rs13027534	G	HETERO	AG	NO GWAS DATA
02	rs17354256	A	HETERO	AG	NO GWAS DATA

RARIFY data screen

RARIFY displays the following row data:

• Chromosome location

• SNP ID

• Rare Allele

• Client Genotype Status

• Client Genotype

• GWAS Pathology Data (if available)
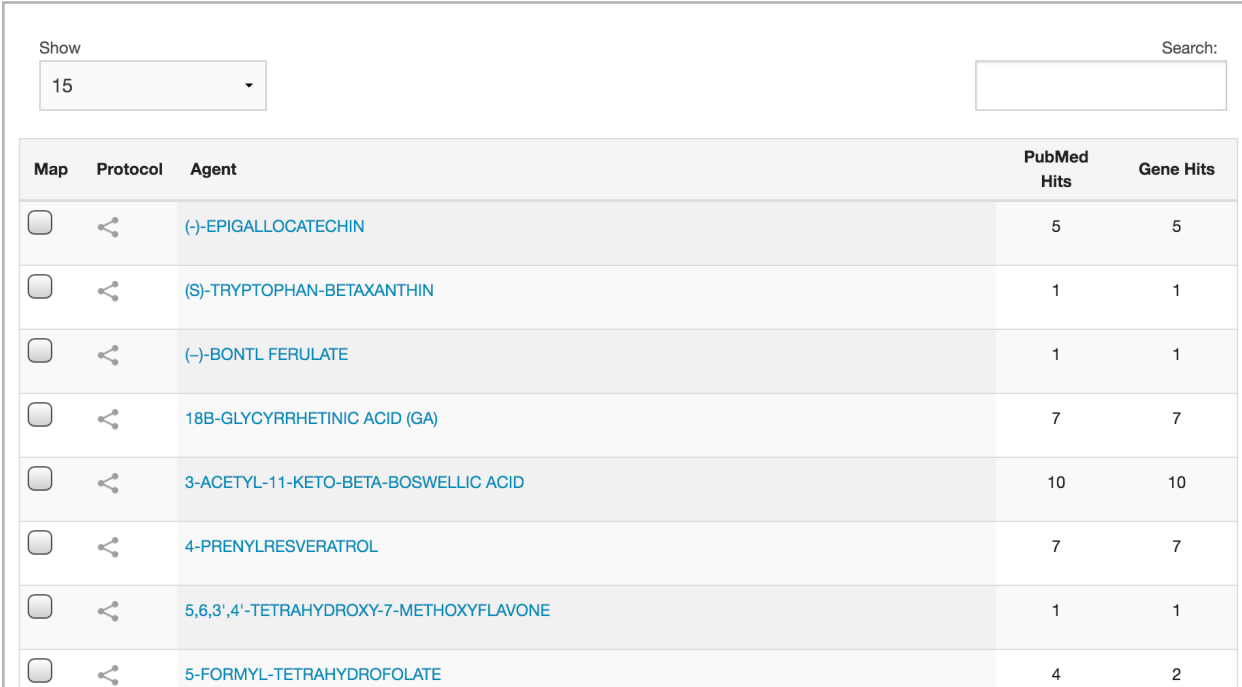
Most of the time these results will not be significant (these alleles are rare after all) but any SNP genotyped homozygous for a rare risk allele (especially if it is a SNP that may indicate a mitochondrial defect should be investigated). Many of these SNPs have not been thoroughly studied. Click on the rs ID number to trigger an information pop-up on that SNP. If Opus23 Pro has information on the SNP it will be displayed. If not, it will attempt to aggregate information from a variety of sources.

AGENCY: Agent visualization

AGENCY is the portal to the Opus23 Pro gene-agent visualizer network map. This tool may be useful when selecting appropriate agents for modifying the expression of the client's target genes or related genetic pathways, as well as for identifying the effects of neighboring agents. If the gene of interest is associated with agents in the database, AGENCY will show you which other genes are influenced by the selected agent and which other agents interact with the target gene.

Getting around AGENCY

From the 'Informatics' link on the main menu, hover over 'Prescriptives' until a second menu list appears, then select AGENCY. You will be presented with the AGENCY screen:

Map	Protocol	Agent	PubMed Hits	Gene Hits
		(-)-EPIGALLOCATECHIN	5	5
		(S)-TRYPTOPHAN-BETAXANTHIN	1	1
		(–)-BONTL FERULATE	1	1
		18B-GLYCYRRHETINIC ACID (GA)	7	7
		3-ACETYL-11-KETO-BETA-BOSWELLIC ACID	10	10
		4-PRENYLRESVERATROL	7	7
		5,6,3',4'-TETRAHYDROXY-7-METHOXYFLAVONE	1	1
		5-FORMYL-TETRAHYDROFOLATE	4	2

AGENCY data screen

The AGENCY screen can be sorted by the Agent column, the PubMed Hits column or the Gene Hits column, just click on the column heading to sort, and click on the same column heading again to reverse

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the sort order. The default view sorts the columns by agent. Change the number of rows visible in AGENCY by clicking on the drop-down 'Show' menu and selecting the number of rows to display. Search for any text in the Agent column by typing in the search box.

Some agents may have an effect on multiple genes, and some agents have entries in multiple PubMed articles, the number of article and gene hits for each agent can be seen in the relevant column. Clicking on an agent opens a pop-up for that agent.

Using the AGENCY visualizer
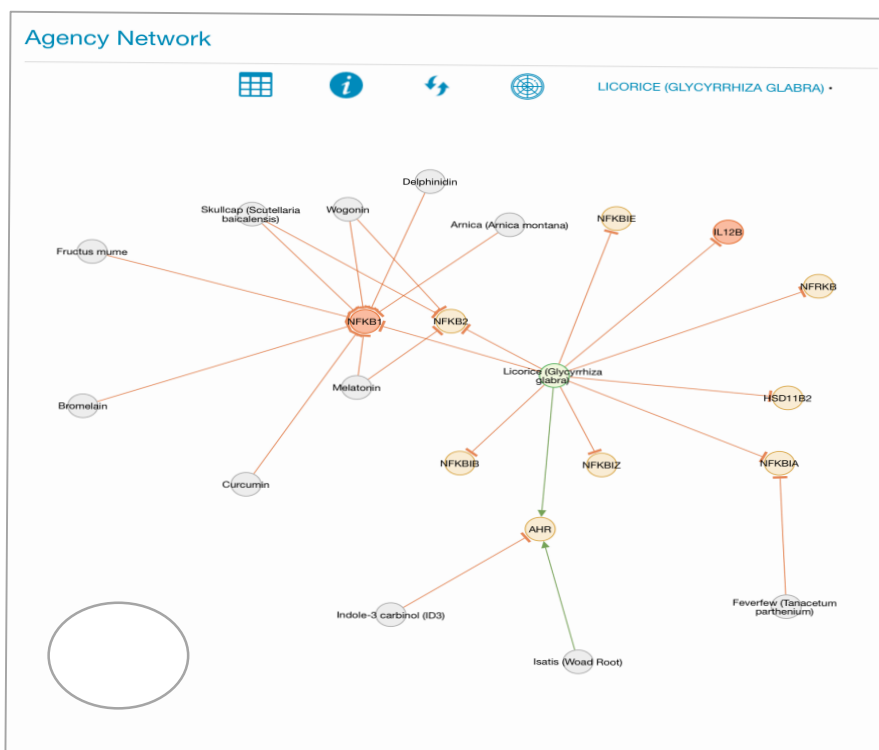
AGENCY visualizer showing the network map for licorice

The visualizer in AGENCY is a powerful graphic representation of the potential interaction between multiple agents and genes. AGENCY can be used to display the network map of a single agent with its gene connections, or the interaction between multiple agents. Select one or more agents by ticking the Map checkbox and then press 'Map selections'. A network map will open displaying the interactome for the selected agents. The elements are color-coded as follows:

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- Agents selected in the AGENCY data screen are in a green circle.

- Gene symbols affected by agents are in a light orange circle.

- Gene symbols that are particularly stressed are in a dark orange circle.

- Secondary agents that also influence the genes in the map and which have two or more associations to the agent, are colored gray.

- A green arrow coming from the selected agent to a gene symbol, or from another agent known to influence expression of that gene product, signifies an agonist (stimulating or enhancing) effect on expression of the gene.

- An orange line with a T-bar across the end indicates an antagonist (inhibiting or reducing) effect of the agent.

Use the mouse scroller to zoom. Grab and hold the canvas to move it, and grab any individual node to move it around the canvas. Click on any node to trigger an information pop-up.
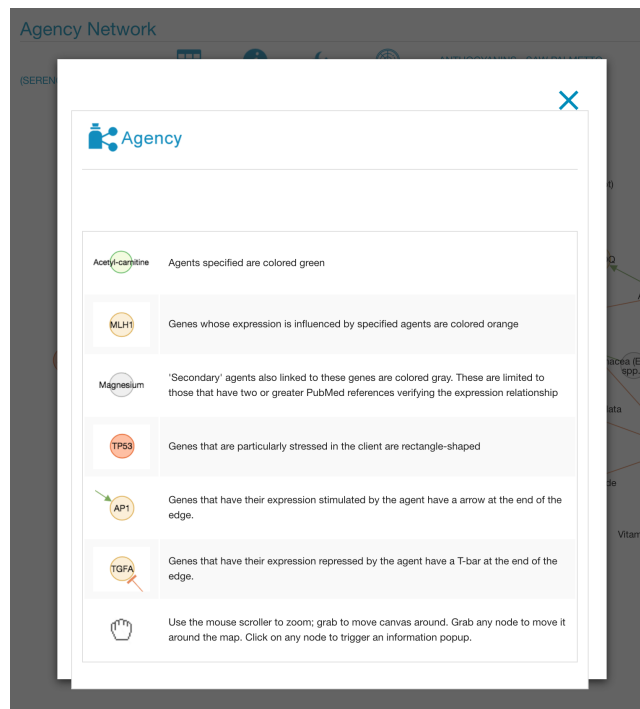
Pressing the 'i' button brings up a pop-up window with a key to the color codes on the map.

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Agents can be added to the current client protocol dataset by clicking on the protocol icon in the AGENCY data screen, or from the agent pop-up. The selected agents can be viewed and further edited in the Protocol Dataset, accessible from the Client Report Routing screen under the Curation menu.
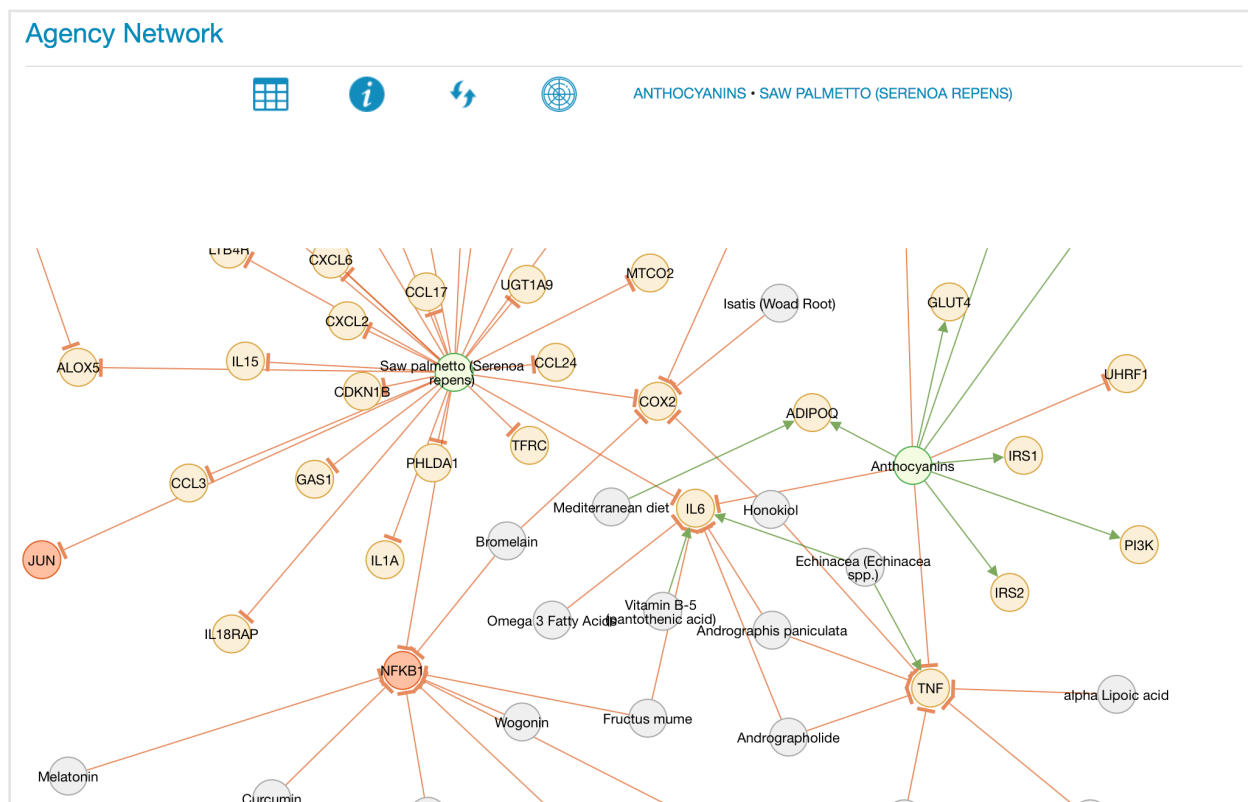
AGENCY visualizer showing the interactome network map for two agents

In the example above, the network map shows how anthocyanins and saw palmetto are both an antagonist for IL-6. Anthocyanins are also an antagonist of TNF-α. If this is the intended outcome, you may also want to advise the client to avoid echinacea, which has an agonistic effect on both IL6 and TNF. You could also be considering an alternative or complementary agent to anthocyanins by using andrographis, which is also an antagonist of IL6 and TNF. In this case you may want to return to the AGENCY data screen and select saw palmetto and andrographis to review their combined visualizer interactome.

Clicking on the name of each agent switches from the network map to a genomic expression fingerprint of the selected agent, and the circle icon displays a single combined genomic expression map for all

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agents selected. Clicking on the circular arrows icon reloads the network map. The grid icon returns to the AGENCY data screen.

POWERSPOT: Gene Insights

PowerSpot is a flexible sort and search tool that allows you to visualize the aggregated power factors of SNPs for any gene in the Opus 23 Pro database. Power factors have been estimated by Opus23 Pro editors on a scale of 1-10 based on research on each SNP and it's potential influence on the function of the gene and the client's health.

GETTING AROUND POWERSPOT

From the 'Informatics' link on the main menu, hover over 'Analytics' until a second menu list appears, then select PowerSpot. You will be presented with the PowerSpot entry screen:
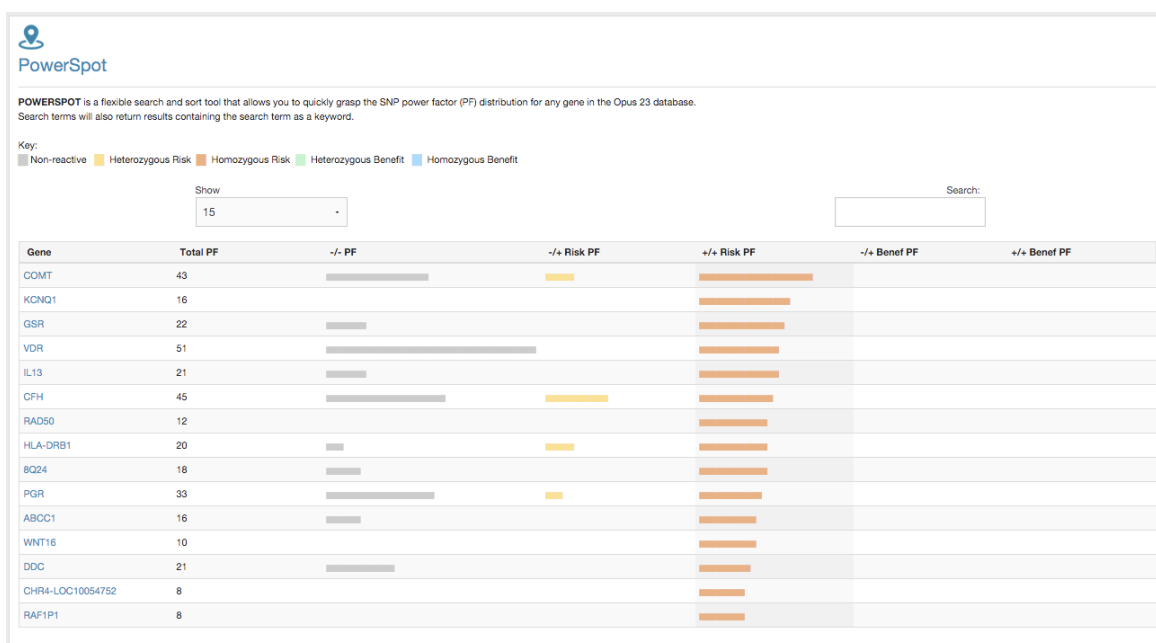
PowerSpot data screen

The following columns are available in PowerSpot:

- Gene, a clickable link to a gene pop-up, where the gene can be added to the Notes tool and the genomic and protocol curation areas.
- Total PF, giving the sum of the power factors for all SNPs for each gene in the Opus23 Pro database.
- -/- PF is the total power factor of all the homozygous negative SNPs for that gene
- -/+ Risk PF is the total power factor of all the heterozygous risk SNPs for that gene
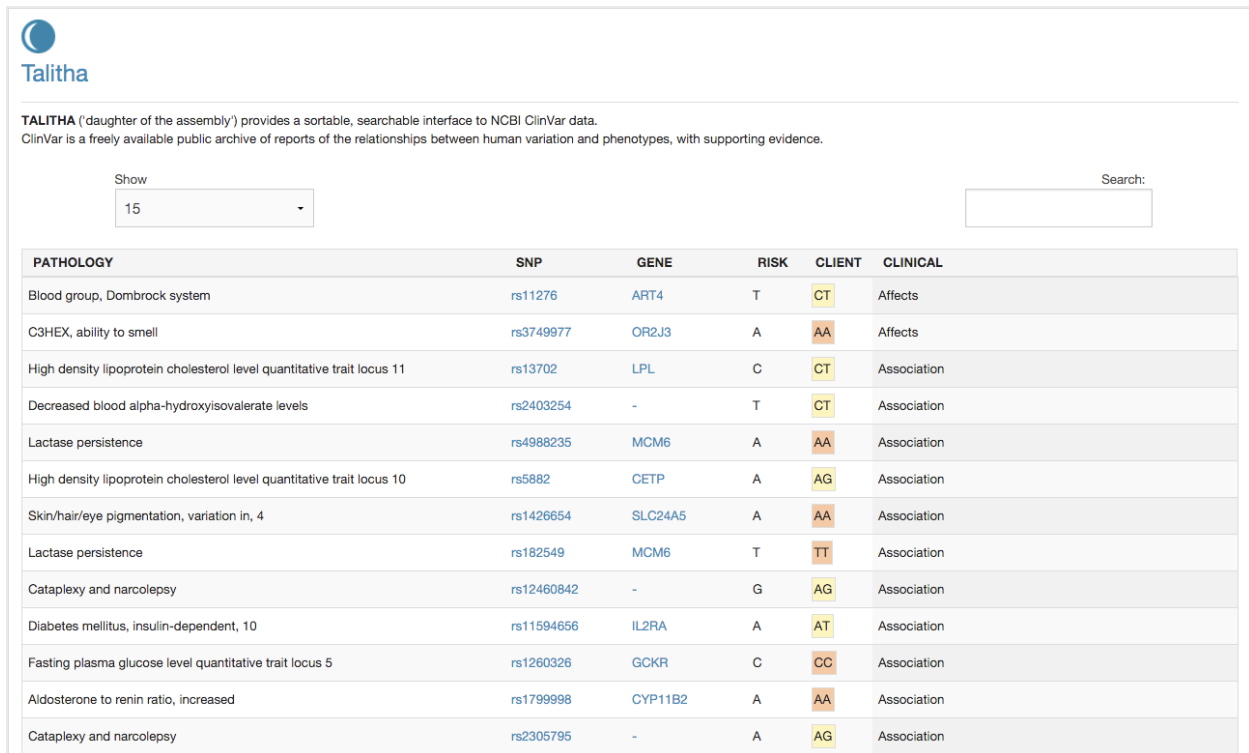
- +/+ Risk PF is the total power factor of all the homozygous positive risk SNPs for that gene

- -/+ Benef PF is the total power factor of all the heterozygous SNPs for that gene which are viewed as conferring a benefit to the client

- +/+ Benef PF is the total power factor of all the homozygous SNPs for that gene which are viewed as conferring a benefit to the client

By default PowerSpot will be sorted by +/+ Risk PF. To sort by another column click on the column header. To search enter a search term in the search box. To change the number of rows displayed use the drop-down 'Show' box.

TALITHA: ClinVar Data

TALITHA provides a sortable, searchable interface to NCBI ClinVar data. ClinVar is a freely available public archive of records of the relationships between human variation and phenotypes, with supporting evidence. The database is maintained by the NCBI, and aggregates information about genomic variation and its relationship to human health.

Currently as there is little consensus about how to describe the clinical condition that results from variation, there are often multiple Reference ClinVar Record accessions assigned to the same variant. It is anticipated that these will be merged by ClinVar staff over time as expert panels review the data and decide how to describe the phenotype. Meanwhile TALITHA has merged multiple ClinVar records for the same SNP for ease of use.

Talitha

TALITHA ('daughter of the assembly') provides a sortable, searchable interface to NCBI ClinVar data.
ClinVar is a freely available public archive of reports of the relationships between human variation and phenotypes, with supporting evidence.

Show
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Search:

PATHOLOGY	SNP	GENE	RISK	CLIENT	CLINICAL
Blood group, Dombrock system	rs11276	ART4	T	CT	Affects
C3HEX, ability to smell	rs3749977	OR2J3	A	AA	Affects
High density lipoprotein cholesterol level quantitative trait locus 11	rs13702	LPL	C	CT	Association
Decreased blood alpha-hydroxyisovalerate levels	rs2403254	-	T	CT	Association
Lactase persistence	rs4988235	MCM6	A	AA	Association
High density lipoprotein cholesterol level quantitative trait locus 10	rs5882	CETP	A	AG	Association
Skin/hair/eye pigmentation, variation in, 4	rs1426654	SLC24A5	A	AA	Association
Lactase persistence	rs182549	MCM6	T	TT	Association
Cataplexy and narcolepsy	rs12460842	-	G	AG	Association
Diabetes mellitus, insulin-dependent, 10	rs11594656	IL2RA	A	AT	Association
Fasting plasma glucose level quantitative trait locus 5	rs1260326	GCKR	C	CC	Association
Aldosterone to renin ratio, increased	rs1799998	CYP11B2	A	AA	Association
Cataplexy and narcolepsy	rs2305795	-	A	AG	Association

Getting around TALITHA

From the 'Informatics' link on the main menu, hover over 'Queries' until a second menu list appears, then select TALITHA. You will then be presented with the default table, which shows 'everything' and is sorted by the 'Client' column. Like most data-driven apps in Opus 23 Pro, TALITHA uses a filterable/sortable table to display its data. At the bottom of the window is a jump table that allows you to move from one screen to the next. You can control how many rows to display by selecting an option from the 'Show' pull down menu. The default is 15.

Filtering and sorting results

The table will show results for the client's genotypes that have a positive match or 'no call' for ClinVar entries. Each of the six columns can be sorted in ascending or descending order by clicking on the column heading, and can be filtered by typing a search term in the search box. This can be a pathology or clinical condition, such as "Parkinson", "Cancer" or "Acetylator", an outcome such as "Risk factor" or "Protective", a SNP rs number, a gene, a genotype such as "TT", "AG", or any other text that appears in the table.

The columns represent the following aspects of the ClinVar record:

PATHOLOGY

This column shows the possible outcome of the client having this SNP, but must be read in conjunction with the other columns. In autosomal recessive conditions the outcome may only manifest when the client has both risk alleles and if the clinical picture is pathogenic or risk factor. It is recommended to review these carefully and in light of the client's other known risk factors, lifestyle and environment. It may be important to be aware of the client's "carrier" status if they are heterozygous and may become a parent in the future, or that they may have passed a recessive SNP on to their offspring.

Some entries in this field are "Not specified": some submissions to ClinVar are intended to report that a variant is benign with respect to a specific condition, which leaves the possibility that it is clinically relevant for a different condition. Other submissions want to report that the variant is generally benign, in that it does not appear to cause any genetic disorder that should be observable because it is highly

penetrant. ClinVar has suggested that "not specified" is provided as the condition in submissions which are designed to indicate that they are not specifying any single condition, but rather that the variant is generally benign. Refer to ClinVar for more information.

SNP

The SNPs displayed in TALITHA may be rare, and as such may not necessarily be in the Opus 23 SNP database, but are collated from a comparison of the client's uploaded raw data and the ClinVar database. SNPs which do not have any data curated by Opus 23 editors have a pop-up which will display an aggregation of data from various sources.

GENE

Some of the ClinVar SNPs do not have genes associated with them: these may be intergenic, or the gene may not have been associated with the SNP at the time of the ClinVar submission. We recommend looking up the gene in 23andMe and/or dbSNP if necessary. Sometimes genomic locations may cover multiple overlapping genes, including those with shared exons, and so different sources may show a relationship with a different gene or genes.

RISK

This is the ClinVar risk allele for the specified pathology, or the protective allele where a mutation confers protection against a condition or disease.

CLIENT

This is the client's genotype as specified by the uploaded raw data. In some cases this may be "--", which designates a 'No call' in the client's raw data. In 23andMe this means a client's data may not allow determination of his or her genotype confidently at a particular SNP. The color of the box in this column is for ease of interpretation: red designates homozygous positive (or no call) for the 'risk' allele as listed by ClinVar, yellow designates heterozygous.

CLINICAL

This column represents the ClinVar interpretation of the effect of the risk genotype on the pathology. In some cases this is blank, in others it may contain an aggregation of several ClinVar entries. Refer to ClinVar for more information.
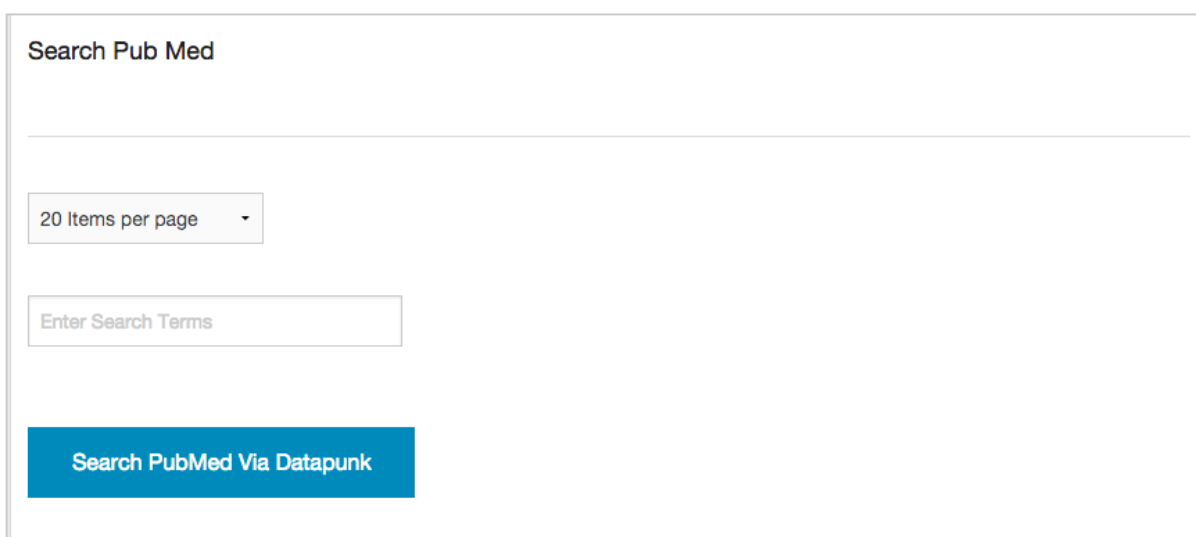
PUBMED CRAWLER

PUBMED CRAWLER allows you to perform a traditional search of PubMed. Depending on the article, it may supply you with additional information from the Opus23 Pro databases.

Getting around PUBMED CRAWLER

From the 'Informatics' link on the main menu, hover over 'Tools Extra' until a second menu list appears, then select PUBMED CRAWLER.

Use the search facility to find articles on PubMed in order of publication date. The maximum number of articles displayed per page can be changed by toggling the drop down menu in the top right of the search results page. On loading an article abstract, a link to the article page if available will be displayed, along with related articles, and Medical Subject Headings (MeSH) terms if available.

If an Opus23 Pro editor has rated the article or added gene-agent associations, these will be displayed on loading the article.

PUBMED CRAWLER search screen

TOXINFORM: In-depth exposome data

TOXINFORM is a toxin/target tissue database search engine.

The exposome is defined as the totality of all human environmental exposures from conception to death. It is often regarded as the complement to the genome, with the interaction between the exposome and the genome ultimately determining one's phenotype. The 'toxic exposome' is the complete collection of chronically or acutely toxic compounds to which humans can be exposed.

Getting around TOXINFORM

From the 'Informatics' link on the main menu, hover over 'Tools/Extras' until a second menu list appears, then select TOXINFORM. You will be presented with the TOXINFORM search box. Type any search term and press the 'Run Toxinform' button.

TOXINFORM will return any data that includes the search term. This will include:

- Description
- Toxin type
- Synonyms
- Exposure Routes
- Mechanism of Toxicity
- Metabolism
- Cellular Locations
- Lethal Dose
- Carcinogenicity
- Symptoms
- Treatment

TOXINFORM entry screen

See: Wishart D, et. al: T3DB: the toxic exposome database. *Nucleic Acids Res*. 2015 Jan;43 (Database issue):D928-34. PMID 25378312

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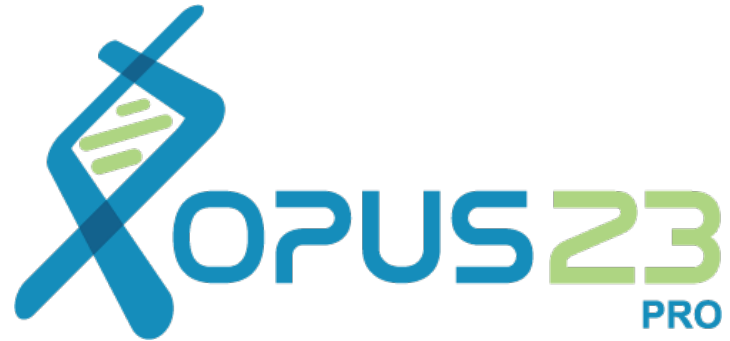
Reporting in Opus23 Pro

Report Generation

'Sixty percent of the value of any dance is its ending.' --Martha Graham

Opus23 Pro generates two types of reports: A Client Report and the Clinician Notepad output. The Client Report is created by a combination of artificial intelligence (AI) and human curation, and contains the main report section and a protocol section. Opus23 Pro has an innovative report structure, the final product of which (the Client Report) is actually generated by choices and selections that you make during the curation process.

Adding elements to the Client Report

Navigating the apps in Opus 23 Pro allows you to add elements to the Client Report and Protocol at any point when you see the following icons:

- Clicking the ADD UNCURATED button will add that element to the dataset and Client Report section based on where you are currently navigating the app.
- Clicking the ADD PROTOCOL button will add the element to the Client Protocol.

Working with Datasets

Opus23 Pro allows you to add elements to different datasets and select which dataset to add to the Client Report. This can be used for different client visits, dealing with the main or simplest aspects on the first visit and more complex issues later; or a particular dataset can be reserved for specific issues to discuss with the client in a separate report. Opus23 Pro has separate datasets for the following sections:

- Genomic Curation Dataset, containing elements added from Mobocaster scenarios, Mapper maps and other apps

- Algorithm Curation Dataset, containing elements added from Lumen algorithms

- Protocol Curation Dataset, to build visit-specific protocols

- Agent Curator Dataset, a Run-Time Curation for adding agents to the Protocol Dataset

- Food Curator Dataset, a Run-Time Curation for adding foods to the Protocol Dataset

- Pharmacogenomic Dataset is automatically generated from DRUGGIE data, and cannot be edited

- Etiome/Diseasome Dataset is automatically generated from ACCELERANT data, and cannot be edited

Client Report Routing screen

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The above Client Report Routing screen is for a newly-uploaded client who has no elements, agents or foods added to the datasets. The lines for Dataset-Based Curations and Run-Time Curations are colored red. After the dataset has elements added, the dataset line turns green and a checkbox appears in the 'Rout to Report' column. Selecting the checkbox will include all elements in the currently selected dataset to the Client Report.

Checking the 'Print Abbreviated Report Header' reduces the amount of introductory text at the beginning of the Client Report.

Changing Dataset

The Client Report is built using the currently loaded dataset. New Datasets can be added and Dataset names can be edited for the dataset-based curations (Genomic and Algorithm datasets), and for the Run-Time Curations (Agent and Food datasets). From the Client Report Routing screen under the Curation button in the Toolbar, select the type of dataset listed under the Curation column. This links to a new page where the dataset name can be edited and a new dataset can be created. The checkmark under the Report column shows which dataset is currently the default, and can be routed to the Client Report.

Dataset editing screen for the Algorithm Curator Dataset showing two datasets

If a new dataset is created and made default, any elements added to that section will be added to the new dataset. To change the default dataset or the name of a dataset click on the Edit link from the dataset curator screen, and change the name or select 'Default' and save the edit.

Working with the Client Protocol

To view the current Client Protocol press the 'Generate Protocol Report' under the 'Curation' button. To edit the protocol select the Protocol Curator button in the Curation / Client Curation menu. Click on the link for a protocol dataset. This opens the Protocol Mapper screen 'Proto', where the protocol can be modified. The name of the protocol being edited shows at the top.
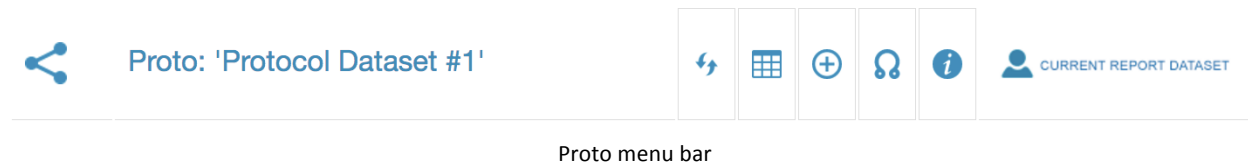
Proto menu bar

There are a row of boxes along the top of Proto with the following functions:

- Refresh the page and graph layout

- Back to the protocol dataset list

- Add new node (plus sign)

- Add new edge (two connected nodes)

- Information pop-up with details of how to use Proto

Elements that have been added to the current client protocol will appear on this screen as Nodes. Proto can be used to edit, arrange and link nodes in an order that makes sense to the client. To edit or link a node in Proto, select it and a pop-up window opens. This shows the current node label, which can be edited, and the current node class as a radio button.
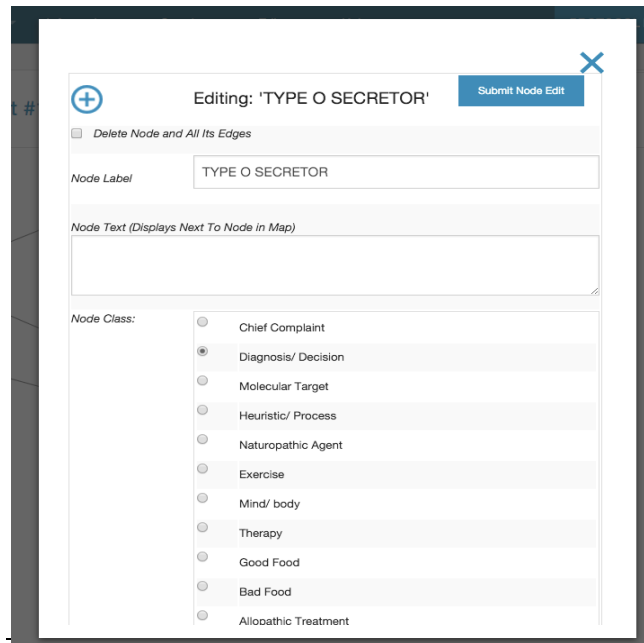
Editing a node in Proto

To make changes to the node or to add additional text enter the changes and press 'Submit Node Edit'. The Proto screen automatically refreshes to display the changes.
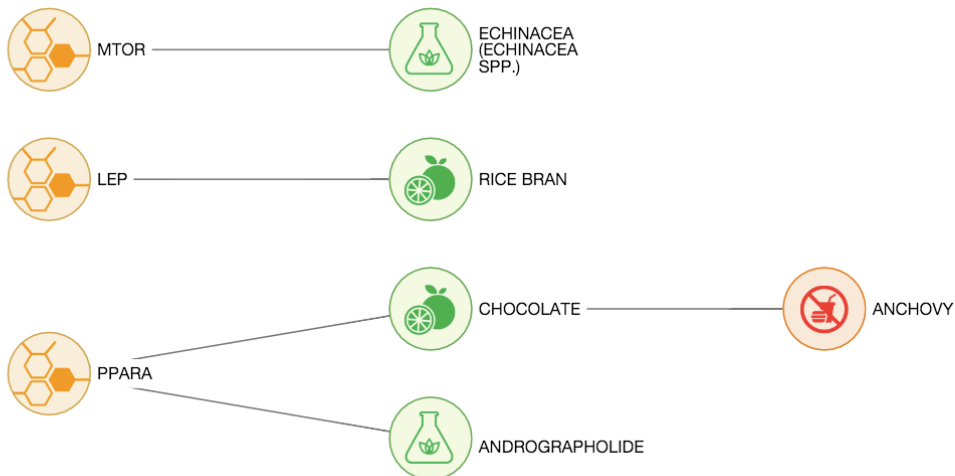
An example protocol

OPUS23™ PRO/ USER MANUAL

Add edges to put nodes into a logical sequence. Nodes can be dragged around the screen, however when printed, the protocol will revert to the default layout.

Adding/Editing Notes

As with the rest of Opus23 Pro, you can add notes via the NOTEPAD pop-up for almost every element in the report. Clicking on the NOTEPAD icon will launch the NOTEPAD pop-up directly, or an information pop-up that contains the 'Add/Edit Note' button. As with the rest of Opus23 Pro, elements with an existing note have an icon that is colored blue, while elements without an existing note have a grayed-out icon. Clicking a grayed out notepad icon adds the note, while clicking the blue colored note brings up the note for further editing.

The Client Report

The Client Report is tailored to the communication of information to the layperson. Gene and algorithm descriptions have an alternate text for the layperson which is displayed only on the Client Report.

Although designed for easy reading on a computer screen or tablet, the Client Report is optimized for printing; either via traditional paper printing or conversion to a PDF file. Depending on how much information you've notated in the program or tagged in the Chart Report the Client Report can run anywhere from 25-45 pages.

An effective way to share information with the client is to print the Client Report, protocol and Notes as PDF files (sometimes this option is labeled 'Save as PDF' from the browser Print Menu) and then provide the client with the reports on a thumb drive, CD-ROM or via email.
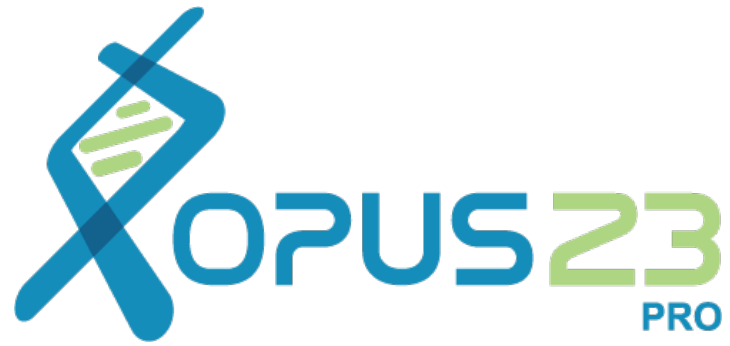
Workflow

Workflow in Opus23 Pro

There is no specific right or wrong way to structure your workflow in Opus23 Pro. We've put this outline together as one way to do it that works for us:

Preliminaries

- Upload data
- Load client

Data Gathering Period

- Run through the MAPPER maps
  - Look for particularly stressed/low functioning genes to add to the Genomic dataset. Make a note on significant genes.

- Launch ARGONAUT app
  - Sort and filter by outcome and power factor identifying SNPS of interest, add to the Genomic dataset. Make a note on significant SNPs.

- Launch LUMEN app
  - Run through the LUMEN algorithms and add significant ones to the Algorithm dataset. Make a note on significant algorithms .

- Launch WANDERER app
  - Search and cross-reference significant SNPs and genes with Opus 23 Pro SNP data, GWAS data, algorithm results, pharmacogenomic interactions and natural product data. Add to add to the Genomic dataset as appropriate.

- Launch POWERSPOT appp
  - Find relevant high-power genes for the client and ensure they are curated in the Genomic dataset. Make notes as required.

- Launch MOBOCASTER app
  - Run through the MOBOCASTER scenarios to add to the Genomic dataset. Make a note on significant genes or SNPs.

- Launch DRUGGIE app

- o   Sort and filter by outcome and power factor identifying drugs of interest. to add to the Genomic dataset. Make a note on significant genes or SNPs relating to relevant drugs.

- Launch SUPERMOGADON app
  - o   Sort and filter by outcome and power factor identifying pathology/traits of interest. Note/tag significant genes relating to pathology/traits and to add to the Genomic dataset.

- Launch GWASFED app
  - o   Sort and filter by outcome and power factor identifying pathology/traits of interest. Make a note on genes with significant pathology/traits (in particular disease/traits with large effects and smaller frequencies).

- Launch FANTASMATRON app
  - o   Adjust FANTASMATRON settings incorporating AI suggestions and adding other foods from the Food Curator if warranted. Link to SWAMI Pro data if available.

- Launch RARIFY app
  - o   Check to see if any rare SNPs are homozygous for the rare alleles. Make a note as necessary.

- Optional:

  - o   Launch TALITHA app and search for any relevant issues, make a note on genes with significant pathology/traits.
  - o   Launch ACCELERANT app and search for any relevant etiological factors, make a note on genes relating to significant issues.
  - o   Launch PSYCHIC app to identify additional natural products to consider utilizing.
  - o   Launch AGENCY to review the interactions of your natural products selections and ensure they are suitable. Adjust agents sent to the protocol section of the client report if necessary.

Curation Period

- Review each section of the Client Curation

- o Genomic Curation: ensure an appropriate number of elements are included in the Genomic Dataset. Select or deselect as appropriate and save the dataset.
- o Algorithm Curation: ensure an appropriate number of algorithms are included in the Algorithm Dataset. Select or deselect as appropriate and save the dataset.
- o Agent Curation: ensure an appropriate number of agents are included in the Agent Dataset. Select or deselect to the curator or the protocol as appropriate and save the dataset.
- o Food Curation: ensure an appropriate number of foods are included in the Agent Dataset. Select or deselect to the curator or the protocol as appropriate and save the dataset.
- o Protocol Curation: complete the network map for the client protocol.

Reporting Period

- • Generate Client Report:
  - o From the Report Routing screen under the Curation button, select the checkboxes for the datasets that you want to be included in the Client Report and Save Settings.
  - o Generate the Client Report by pressing the Generate Client Report button under the Curation button. This will open in a new window.
  - o Print the report or save to PDF for the client.
- • Generate Protocol Report:
  - o Generate the Protocol Report by pressing the Generate Client Report button under the Curation button. This will open in a new window.
  - o Print the report or save to PDF for the client.
- • Generate Notepad Report:
  - o From the Notepad Curator screen review the notes and add any general notes.
  - o Click on 'Printable Version to view printable output on screen. Print or save to PDF for the client or for your chart report, depending on content.

Once you've gotten the hang of using Opus23 Pro, data gathering, curation and reporting can be done can be in less than 30 minutes.

Notes on Consultations

We typically set aside 60 minutes for the genomic consult. We have discovered that working with the client from the computer screen is more effective than working with a printed report, although either is fine. In our clinic, we've created a setup that has a small laptop that is used by the clinician and is plugged into a larger monitor that is viewed by the client.

Either way, work from the client report. Start at the top by discussing the most important elements you've notated. Then move onto the algorithms, syndromes and networks (if selected in the report options), GWAS data, pharmacogenomics, agents and foods. We've found that ending with a discussion of the selected maps is effective at reinforcing what has been previously discussed.

One advantage of working from a computer is that you can easily switch back and forth between windows. One approach that we think is effective is to have the Client Report in one browser tab and the regular Opus23 Interface in another. Besides being able to bring up the information pop-ups, this allows you to provide additional context, such as:

- When discussing a client's risk alleles for BCO1 (beta-carotene oxygenase) you can bring up the SUPERMOGADON Manhattan plot for macular degeneration.
- When discussing a client's CYP3A4 issues you can bring up the MOBOCASTER scenario for Phase I detoxification or the interactive MAPPER pathway map.

Some final thoughts

Remember that any information you give to the client should be done in the context of genetic counseling, and appropriate support should be available to ensure they fully understand the implications of disease risk and potential benefit of interventions.

Make sure the client understands the basics of the probability. It will be distressing to the client to hear that they have double the risk of a certain disease if they are not also told that the disease itself has a low rate of occurrence. We like to remind the client that it can be unsettling to hear that they have double the risk of getting struck by lightning, unless they are also reminded that the base odds of getting hit by lightning are extremely low.
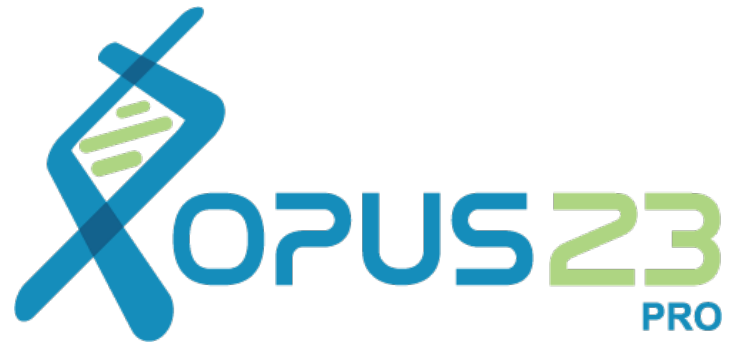
Appendix

Opus23 Pro: Data integration and curation
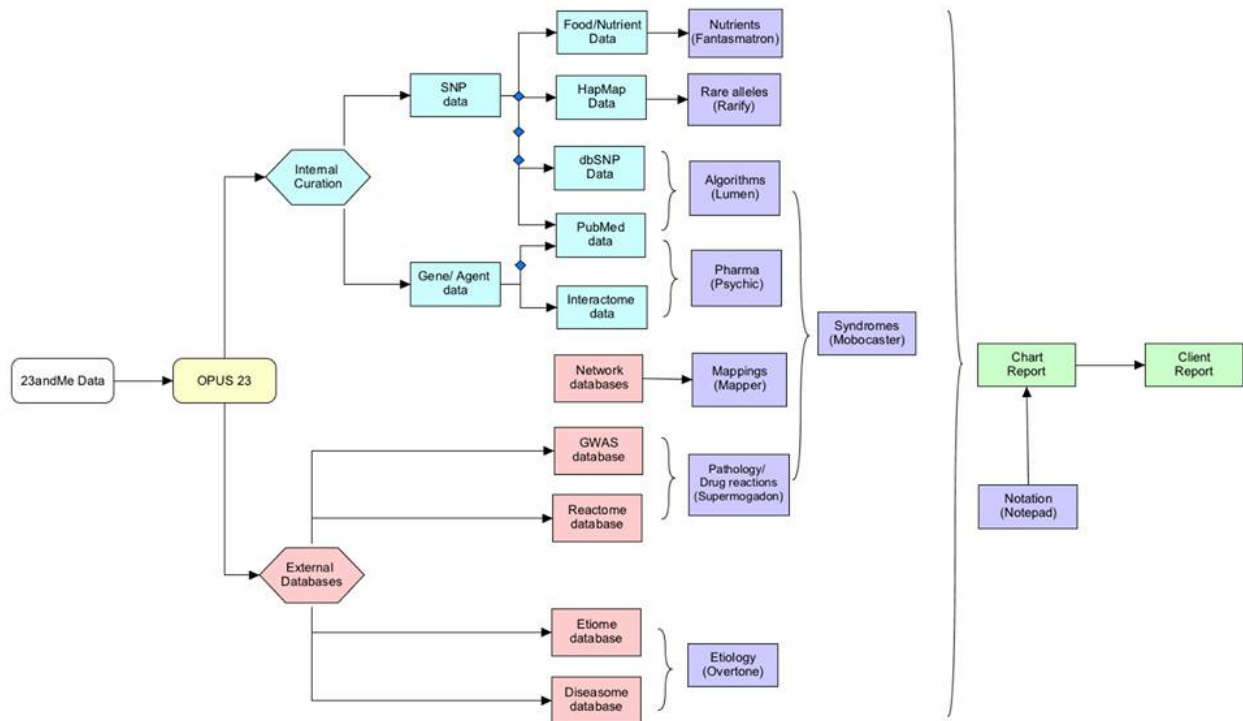
This chart lists the various internal and external databases used in Opus23 Pro

GLOSSARY

- dbSNP: the database of single nucleotide polymorphisms (SNPs) hosted by the National Center for Biotechnology Information (NCBI)
- Diseasome: all the disorders, diseases and genetic risks of a person, viewed as a whole
- Etiome: all the causes of disease of a person, viewed as a whole
- GRCh37/ 38: the version number of the Genome Reference Consortium reference assembly for the human genome. Any raw data file downloaded from 23andMe since 1st August 2012 uses the GRCH37 location reference

- HapMap: haplotype map from the International HapMap Project, a catalog of common genetic variants occurring in humans

- PubMed: the NCBI National Institutes for Health (NIH) repository for peer-reviewed primary research reports in the life sciences

- PMID: the report identifier for an entry in PubMed

- Reactome: the data model for a network of interactions between entities (nucleic acids, proteins, complexes and small molecules)

- rsID: reference SNP cluster ID, a number assigned by dbSNP to a specific SNP