Systems Medicine

MMG 835, SPRING 2016
Eukaryotic Molecular Genetics

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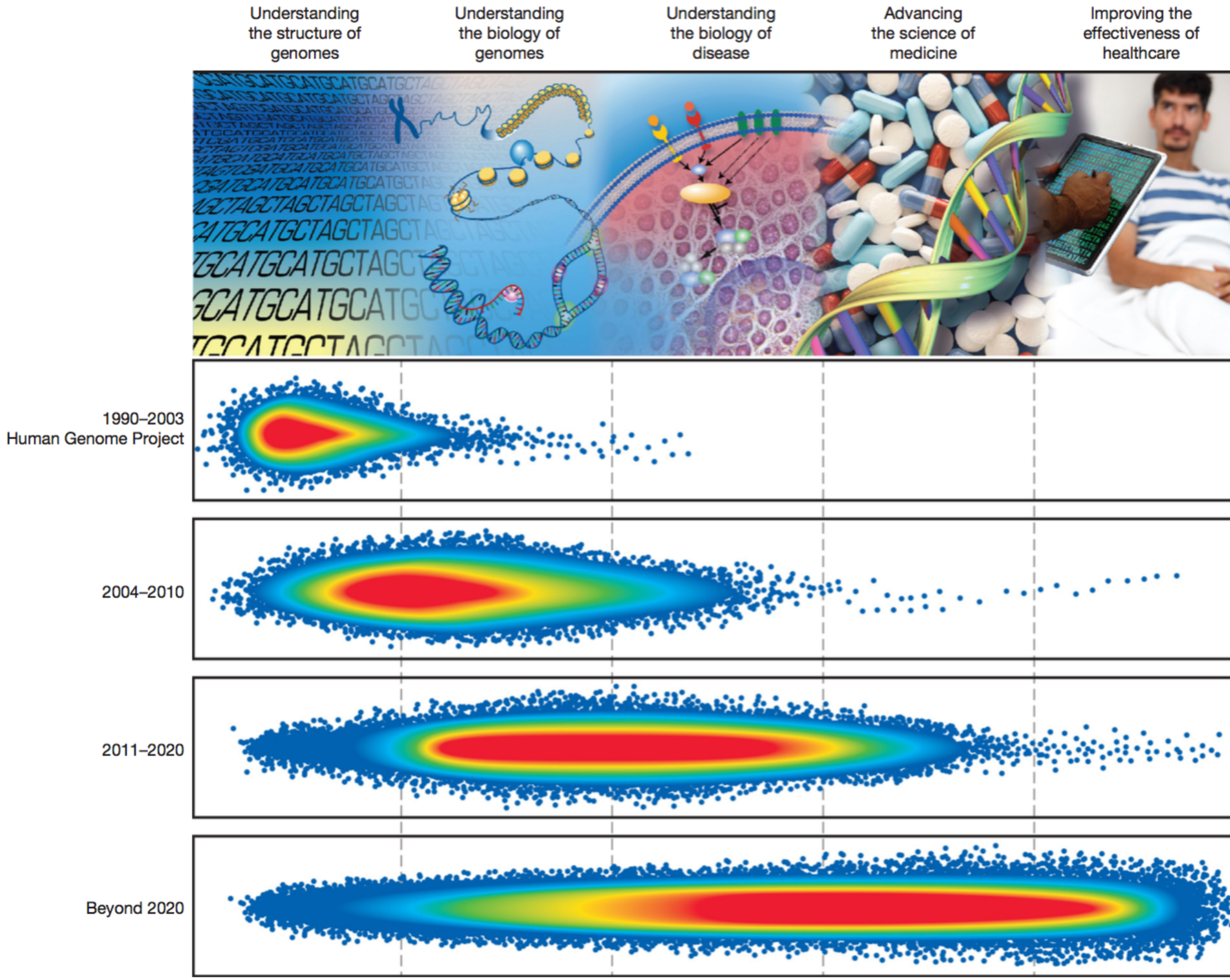
Future of Genomics



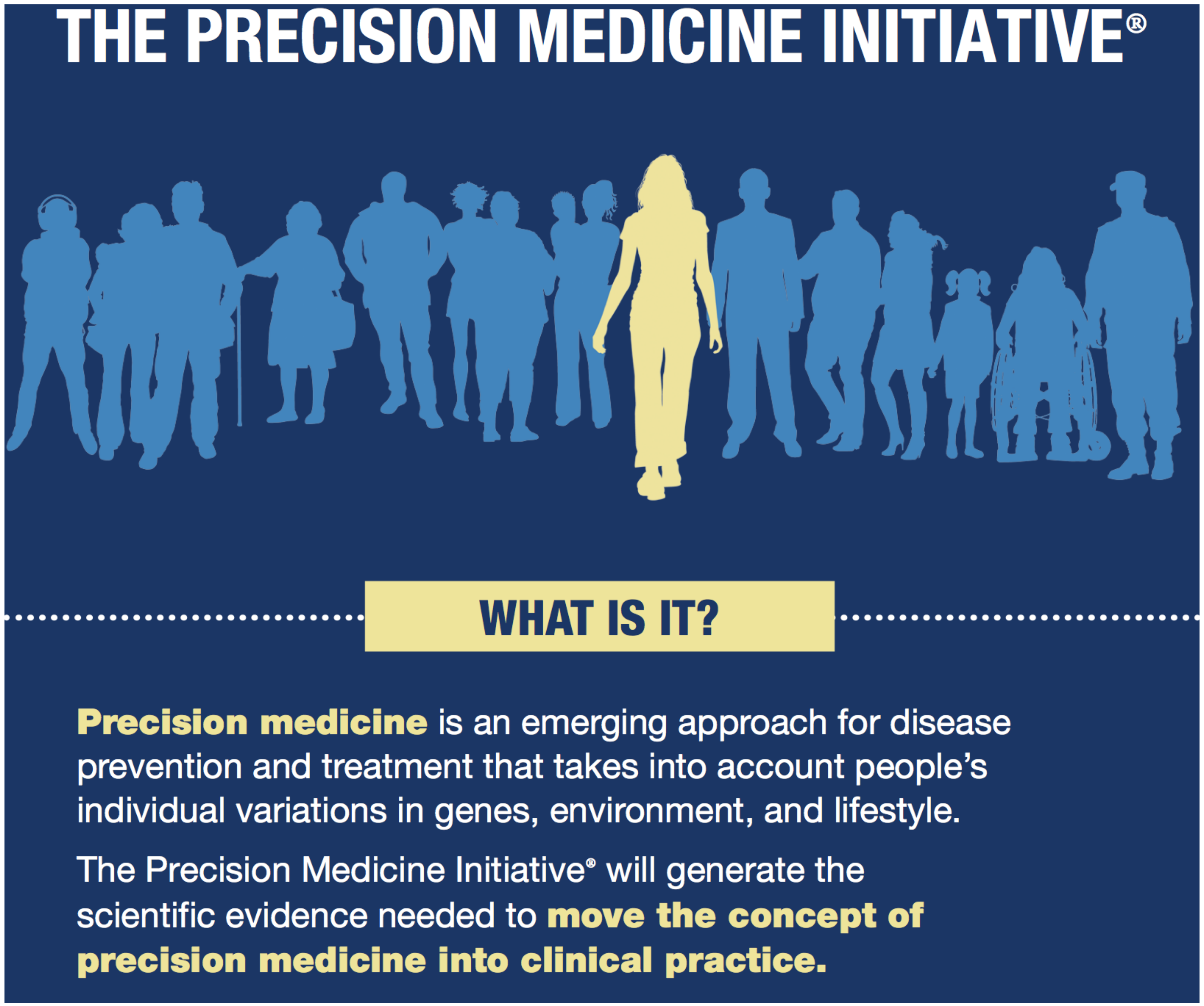
Green, Guyer & NHGRI, Nature 470, 204–213 (2011)

2015: Precision Medicine Initiative

- "I want the country that eliminated polio and mapped the human genome to lead a new era of medicine — one that delivers the right treatment at the right time. In some patients with cystic fibrosis, this approach has reversed a disease once thought unstoppable. Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier." ***President Barak Obama, State of the Union, 2015***

Precision Medicine Initiative

1 million participant research



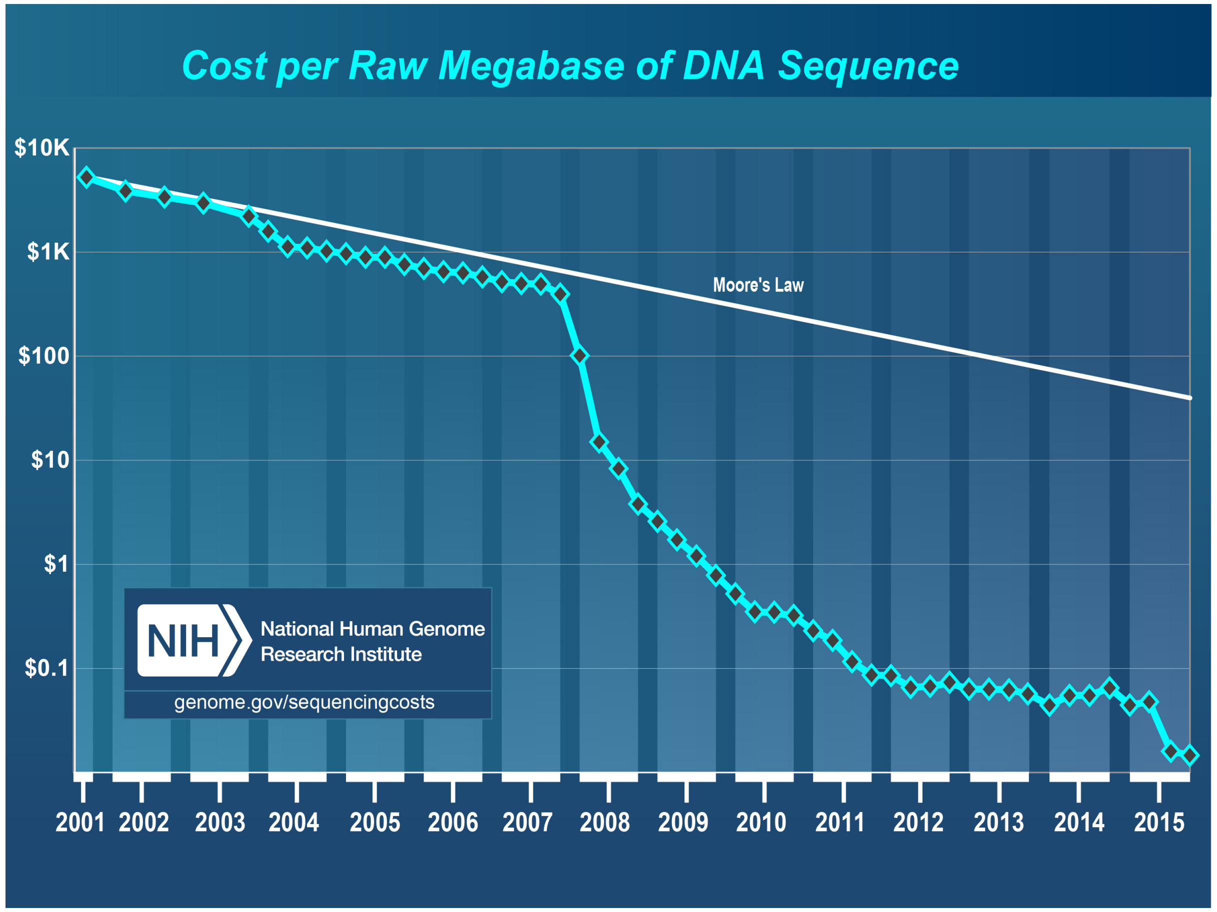
http://www.nih.gov/news-events/multimedia-nih-framework-points-way-forward-building-national-large-scale-research-cohort Credit: NIH

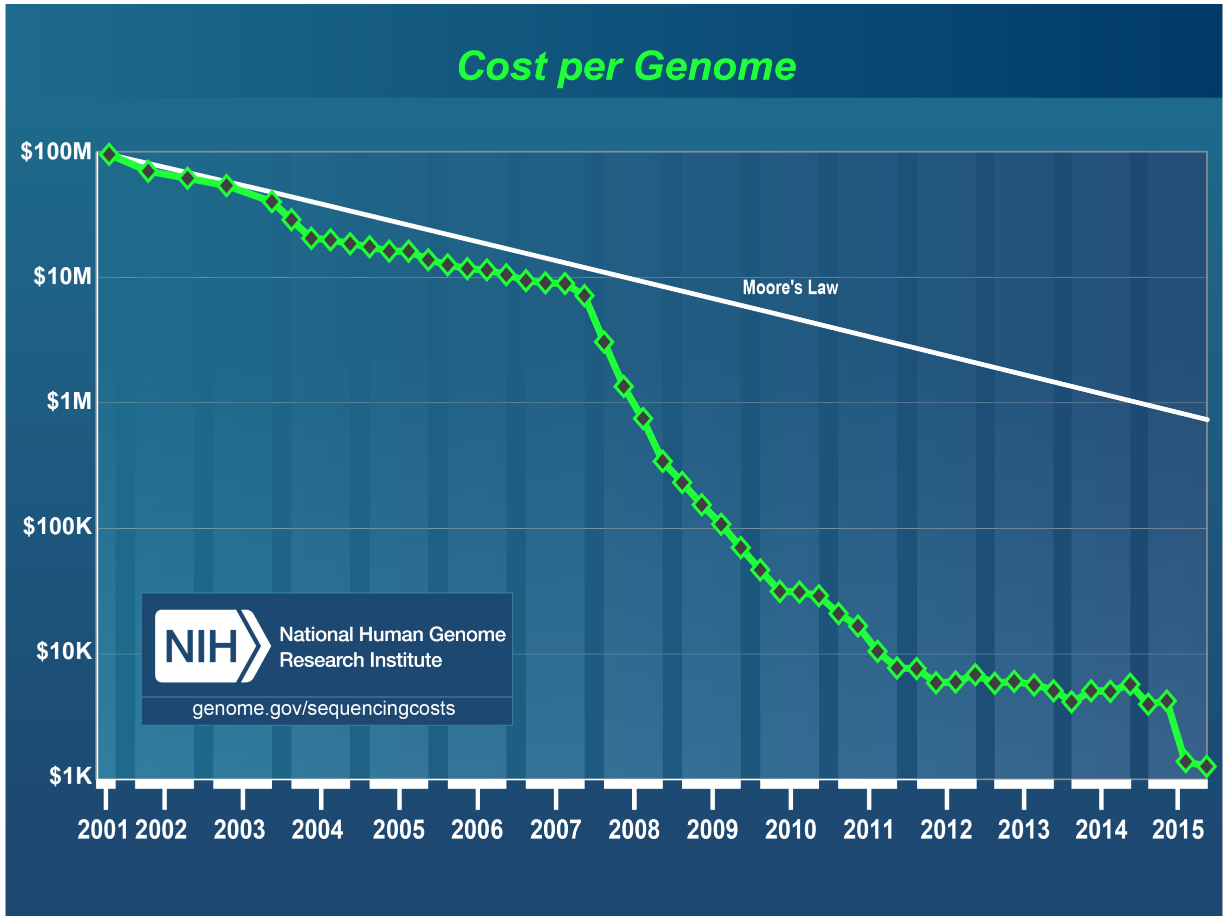
Precision Medicine Initiative

- Develop ways to measure risk for a range of diseases based on environmental exposures, genetic factors and interactions between the two;
- Identify the causes of individual differences in response to commonly used drugs (commonly referred to as pharmacogenomics);
- Discover biological markers that signal increased or decreased risk of developing common diseases;
- Use mobile health (mHealth) technologies to correlate activity, physiological measures and environmental exposures with health outcomes;
- Develop new disease classifications and relationships;
- **Empower study participants** with data and information to improve their own health; and
- Create a platform to enable trials of targeted therapies.

https://www.nih.gov/precision-medicine-initiative-cohort-program/scale-scope

Cost of Sequencing

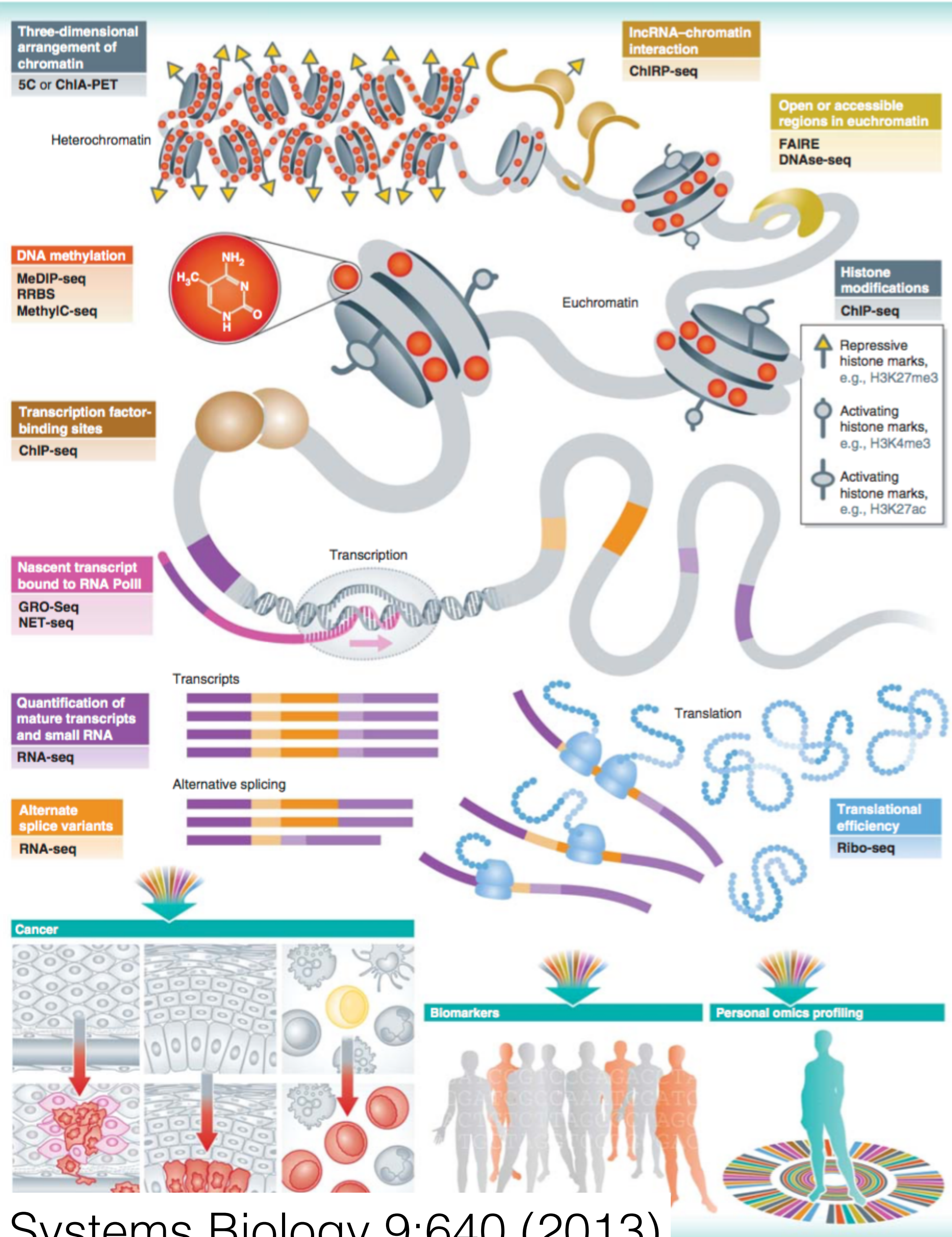




Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP) Available at: www.genome.gov/sequencingcosts. Accessed 3/25/16.

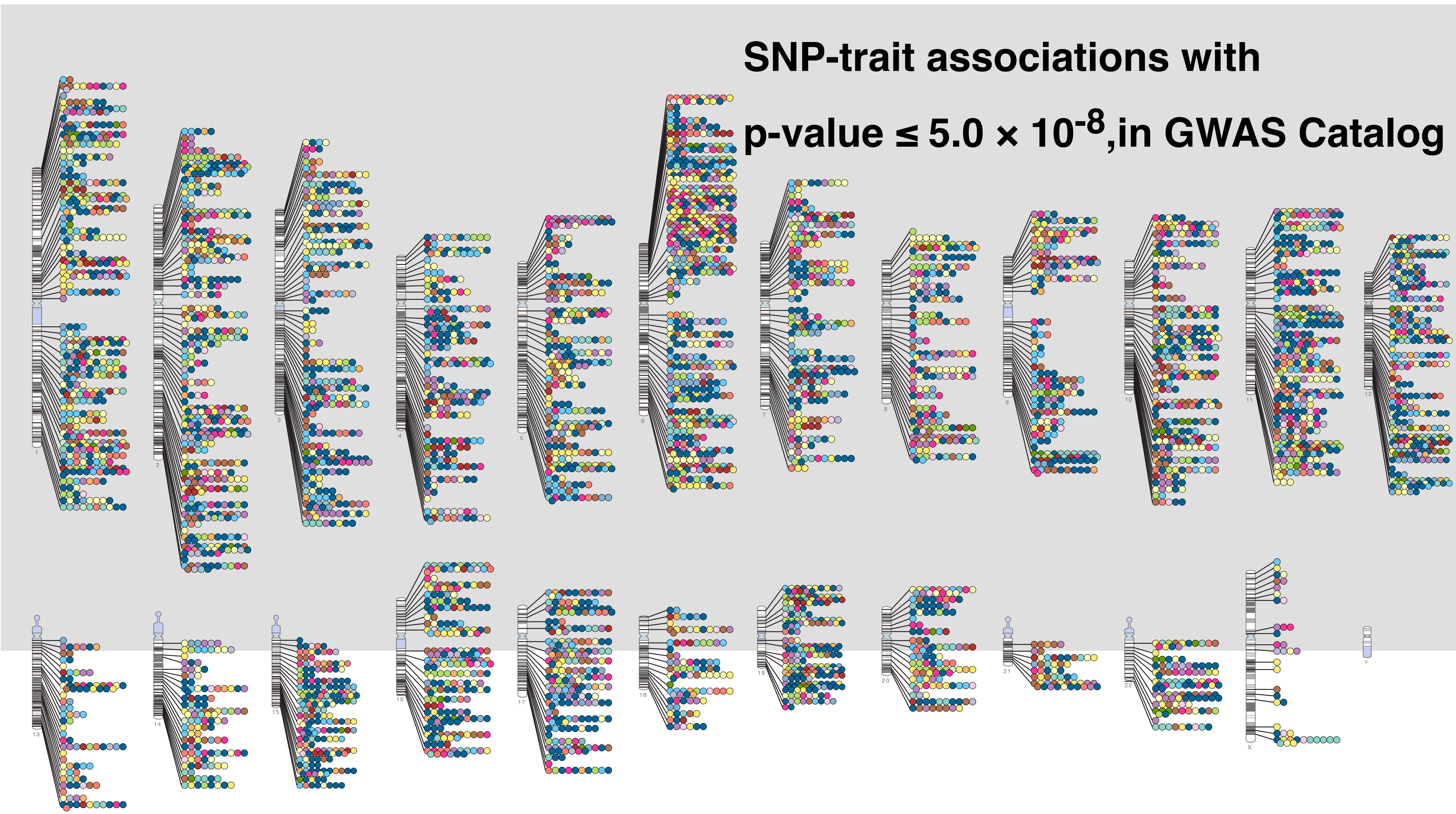
http://www.ncbi.nlm.nih.gov/genome/browse/ (3/26/2016)

Complete Genome Information



Song & Snyder, Molecular Systems Biology 9:640 (2013)

GWAS



]http://www.ebi.ac.uk/gwas/diagram (4/2016)

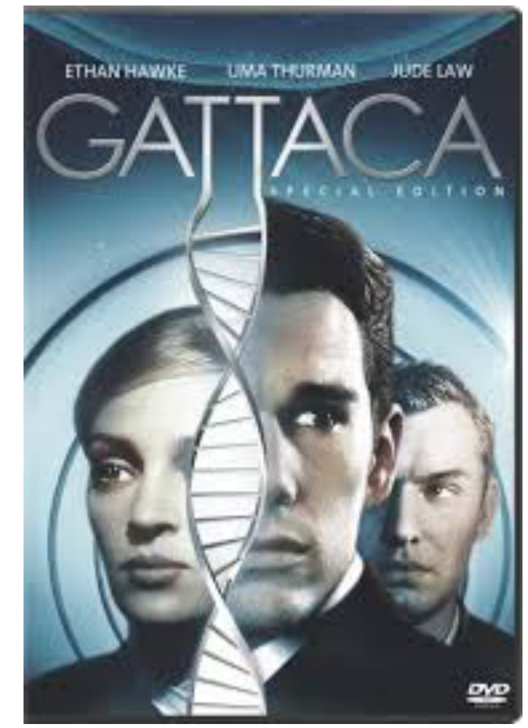
GWAS

Digestive system disease	422
Cardiovascular disease	170
Metabolic disease	142
Immune system disease	454
Nervous system disease	423
Liver enzyme measurement	65
Lipid or lipoprotein measurement	303
Inflammatory marker measurement	35
Hematological measurement	302
Body weights and measures	388
Cardiovascular measurement	217
Other measurement	1486
Response to drug	113
Biological process	111
Cancer	402
Other disease	315
Other trait	208

http://www.ebi.ac.uk/gwas/diagram (4/2016)

Genetic Screening

- **When?**
- Pre-conception
- Pre-natal testing
- Newborns
- Predictive Diagnostic screening (before symptoms?)
- Predisposition Screening

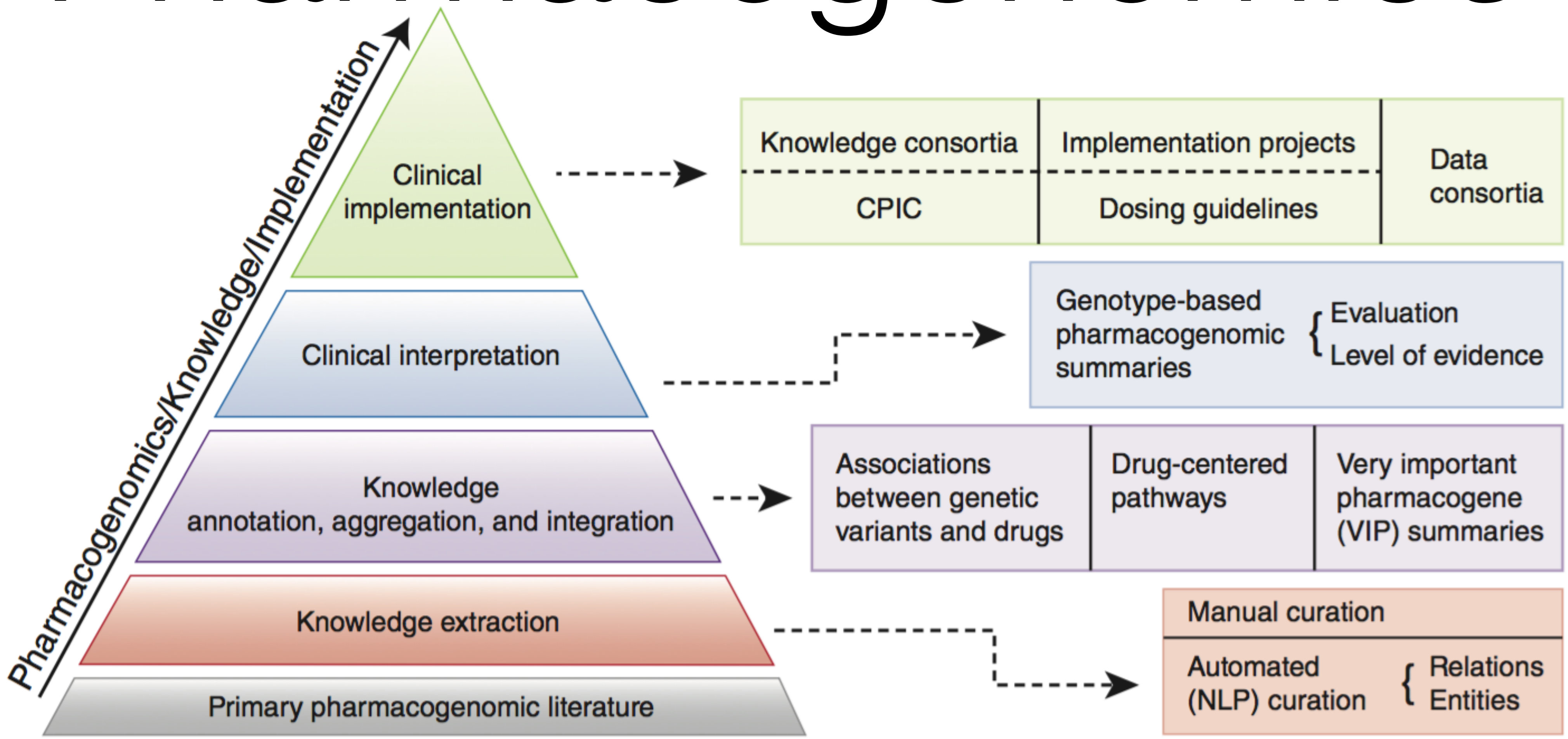


- **What for?**
- Disease risk
- Carriers
- Diagnosis
- Treatment
- Pharmacogenomics

- **Patient rights to know**
- Genetic Counseling
- Family Considerations
- Confusion
- Changing Information
- What is actionable?
- Who owns the data?

- **Protection of Subjects**
- Discrimination
- Genetic Information Non-discrimination Act (GINA, 2009)
- Personal Information
- Who owns the data?

Pharmacogenomics



- Pharmacogene = a gene involved in the response to a drug
- Pharmacogenetics = the study of genetic influence on drug response, typically one or only a few genes involved
- Pharmacogenomics = the study of how genomic variation influences drug response, looking at variation across the genome

https://www.pharmgkb.org/page/overview
Whirl-Carrillo et al. Clinical Pharmacology & Therapeutics 92(4): 414-417 (2012)

Pharmacogenomics

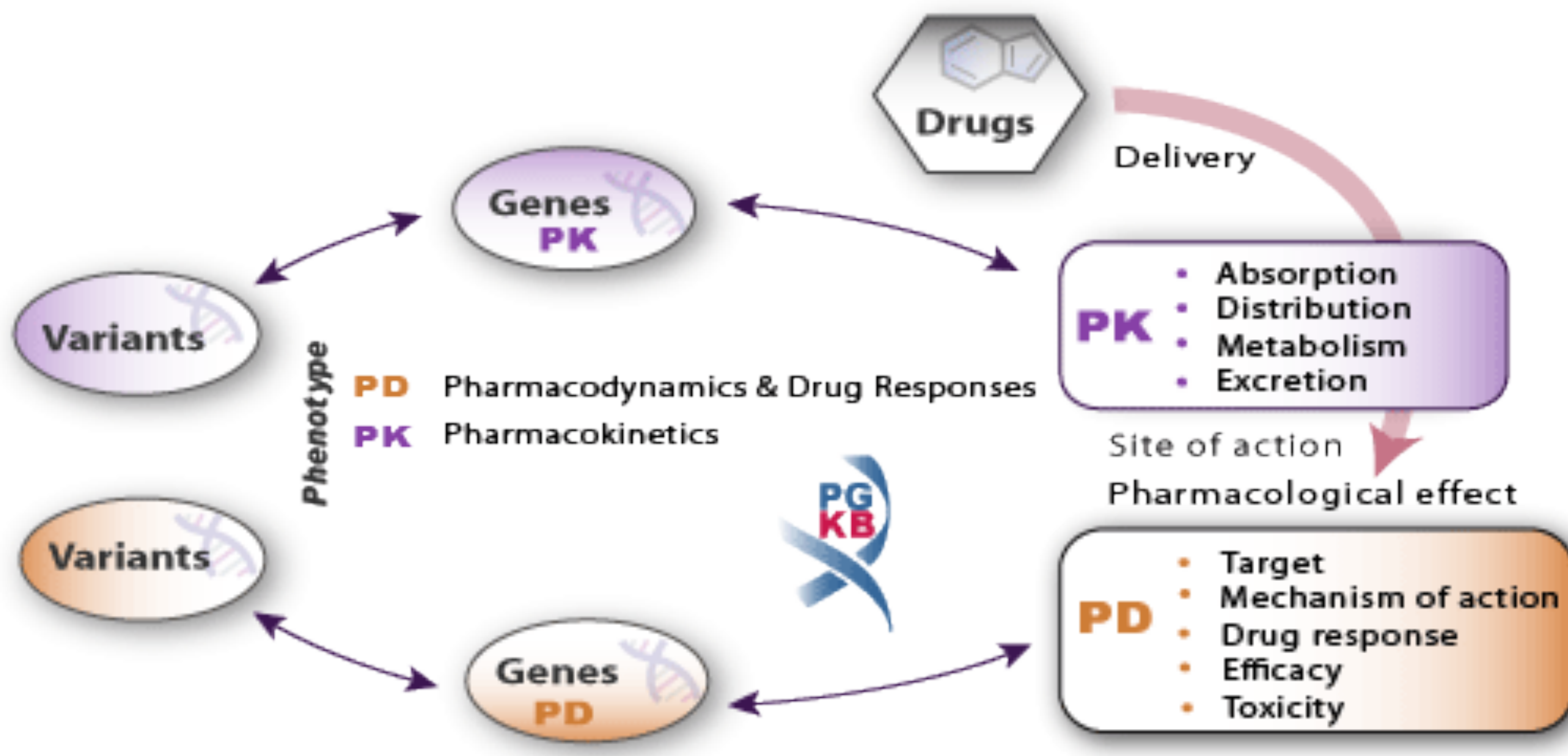
PharmGKB offers different information

- VA Variant Annotations (Research-level annotations of individual publications describing the relationship between genetic variants and drugs; these are created on a paper-by-paper basis)
- PW Drug-Centered Pathway
- VIP Very Important Pharmacogene Summaries
- CA Clinical Annotations (Genotype-based pharmacogenomic relationships summarizing all variant annotations regarding the same genetic variant-drug association)
- DG Pharmacogenomics-Based Drug-Dosing Guidelines
- DL Drug Labels with Pharmacogenomic Information

https://www.pharmgkb.org/page/overview

Pharmacogenomics

- pharmacokinetic (PK) pathways
  - what the body does to the drug
    - absorption
    - distribution
    - metabolism
    - elimination
- pharmacodynamic (PD) pathways
  - what the drug does to the body

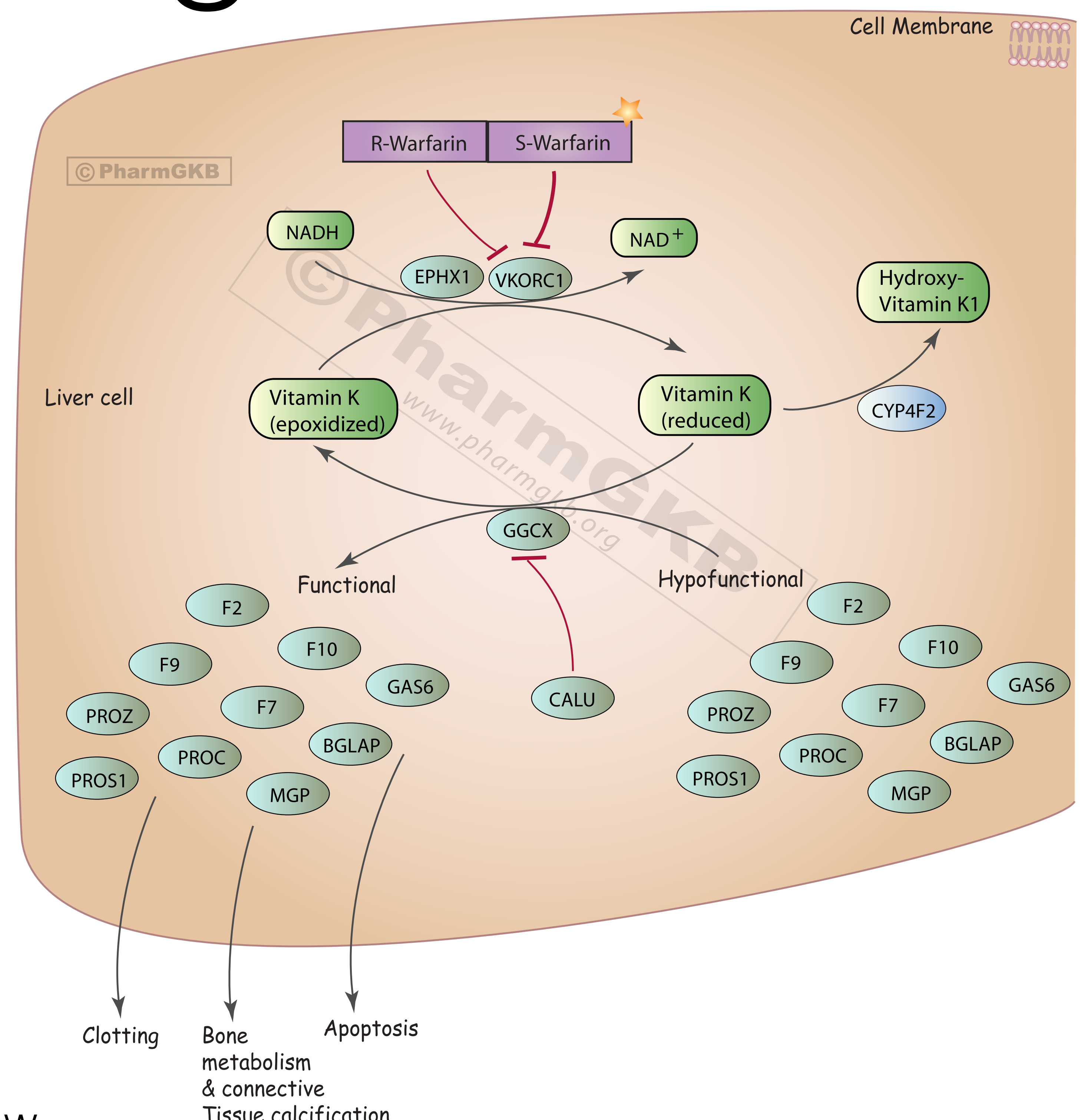


https://www.pharmgkb.org/page/overview

Pharmacogenomics

Warfarin Pharmacodynamics

- Widely used anticoagulant drug
- Highly effective at antagonising the vitamin K dependent clotting pathway
- Used for a wide range of diseases and conditions
  - Atrial fibrillation
  - Heart valve replacement.



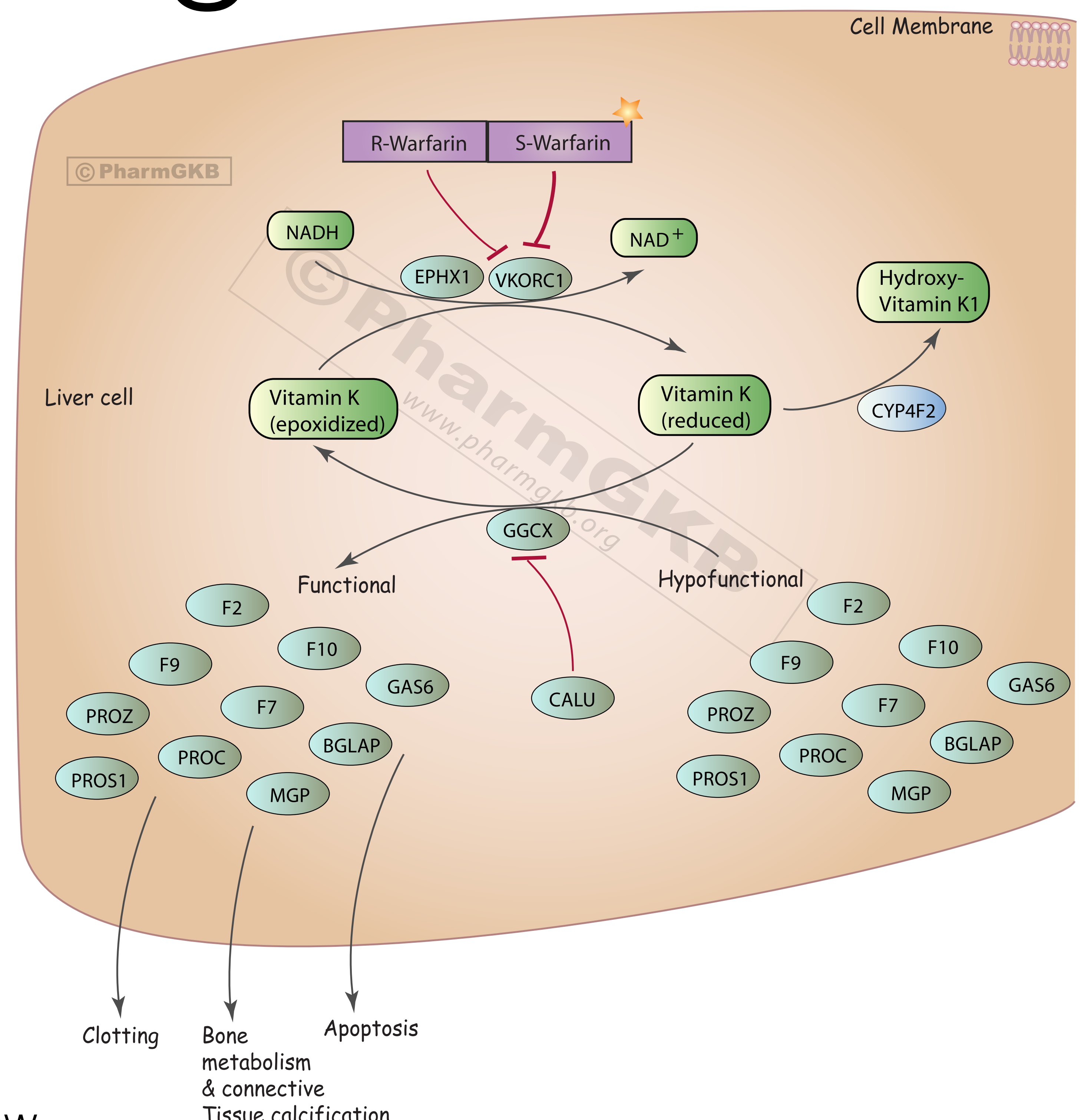
https://www.pharmgkb.org/page/overview

Whirl-Carrillo et al. Clinical Pharmacology & Therapeutics 92(4): 414-417 (2012)

Pharmacogenomics

Warfarin Pharmacodynamics

- Narrow therapeutic window and
- Wide inter-individual variability
- Under-anticoagulation can result in thrombosis
- Over-anticoagulation can result in dangerous bleeding episodes.
- Dosing
  - determined empirically
  - often based on age
  - underlying condition
  - genetics



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Pharmacogenomics

PATHWAY

Warfarin Pathway, Pharmacodynamics

Overview | Components | Related Pathways | Related Publications | Downloads

Entities in the Pathway

Genes (15)

BGLAP, CALU, CYP4F2, EPHX1, F10, F2, F7, F9, GAS6, GGCX, MGP, PROC, PROS1, PROZ, VKORC1

Relationships in the Pathway

Arrow From	Arrow To	Controllers	PMID
BGLAP, MGP	BGLAP, MGP	GGCX	16270630, 16493479
GAS6	GAS6	GGCX	16270630, 16493479
GGCX	GGCX	CALU	15075329, 16493479
NADH	NAD+	EPHX1, VKORC1	
Vitamin K (epoxidized)	Vitamin K (reduced)	EPHX1, VKORC1	14765194, 15358623, 15900282, 16270630, 16493479
Vitamin K (reduced)	Hydroxy-Vitamin K1	CYP4F2	17341693, 18250228, 19297519
Vitamin K (reduced)	Vitamin K (epoxidized)	GGCX	15900282, 16270630, 16493479
VKORC1	VKORC1	warfarin	15358623, 16270630, 16493479
F10, F2, F7, F9, PROC, PROS1, PROZ	F10, F2, F7, F9, PROC, PROS1, PROZ	GGCX	16270630, 16493479

Download data in TSV format. Other formats are available on the Downloads/LinkOuts tab.

https://www.pharmgkb.org/page/overview

Whirl-Carrillo et al. Clinical Pharmacology & Therapeutics 92(4): 414-417 (2012)

Pharmacogenomics

PATHWAY

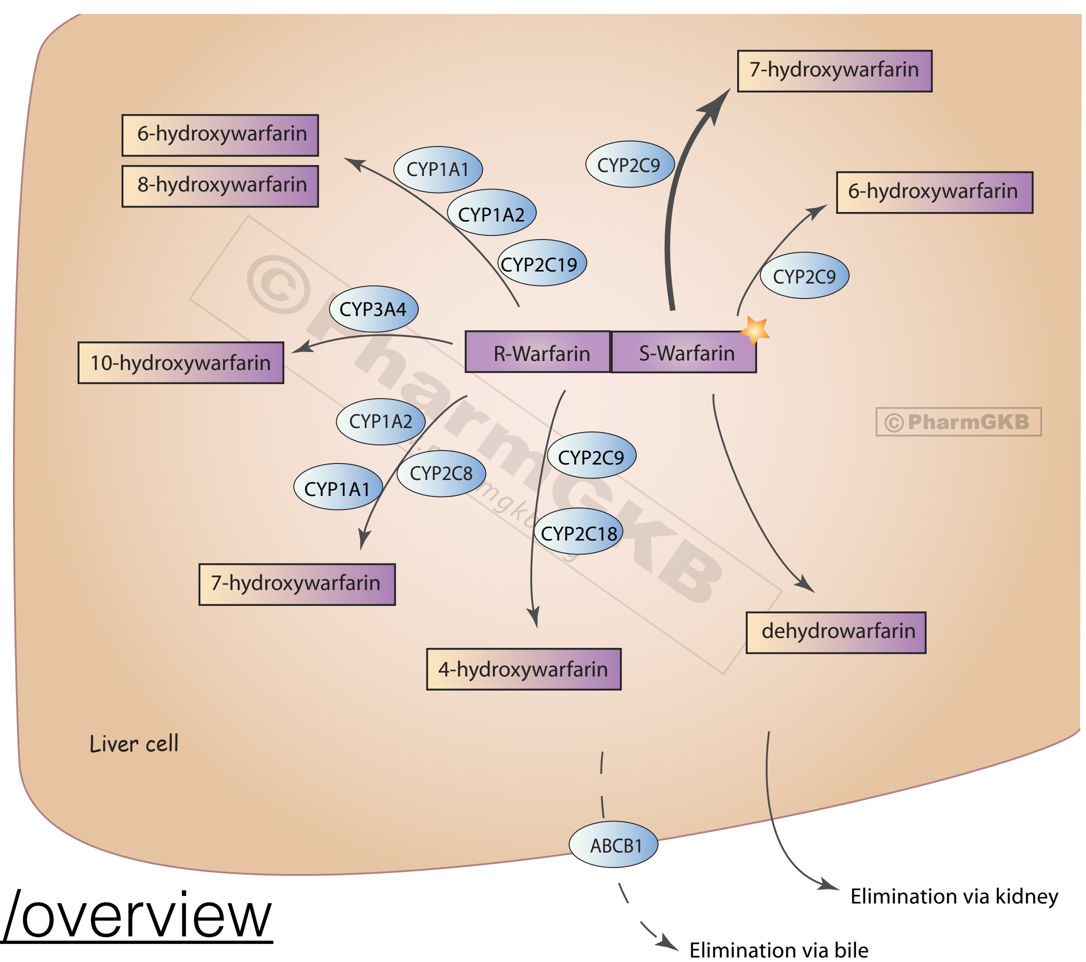
active farin Pathway, Pharmacodynamics

Overview | Components | Related Pathways | Related Publications | Downloads

Alternative Views

- Warfarin Pathway, Pharmacokinetics

Feedback | Citing PharmGKB | Acknowledgements



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Pharmacogenomics

PATHWAY

Warfarin Pathway, Pharmacodynamics

Overview | Components | Related Pathways | Related Publications | Downloads

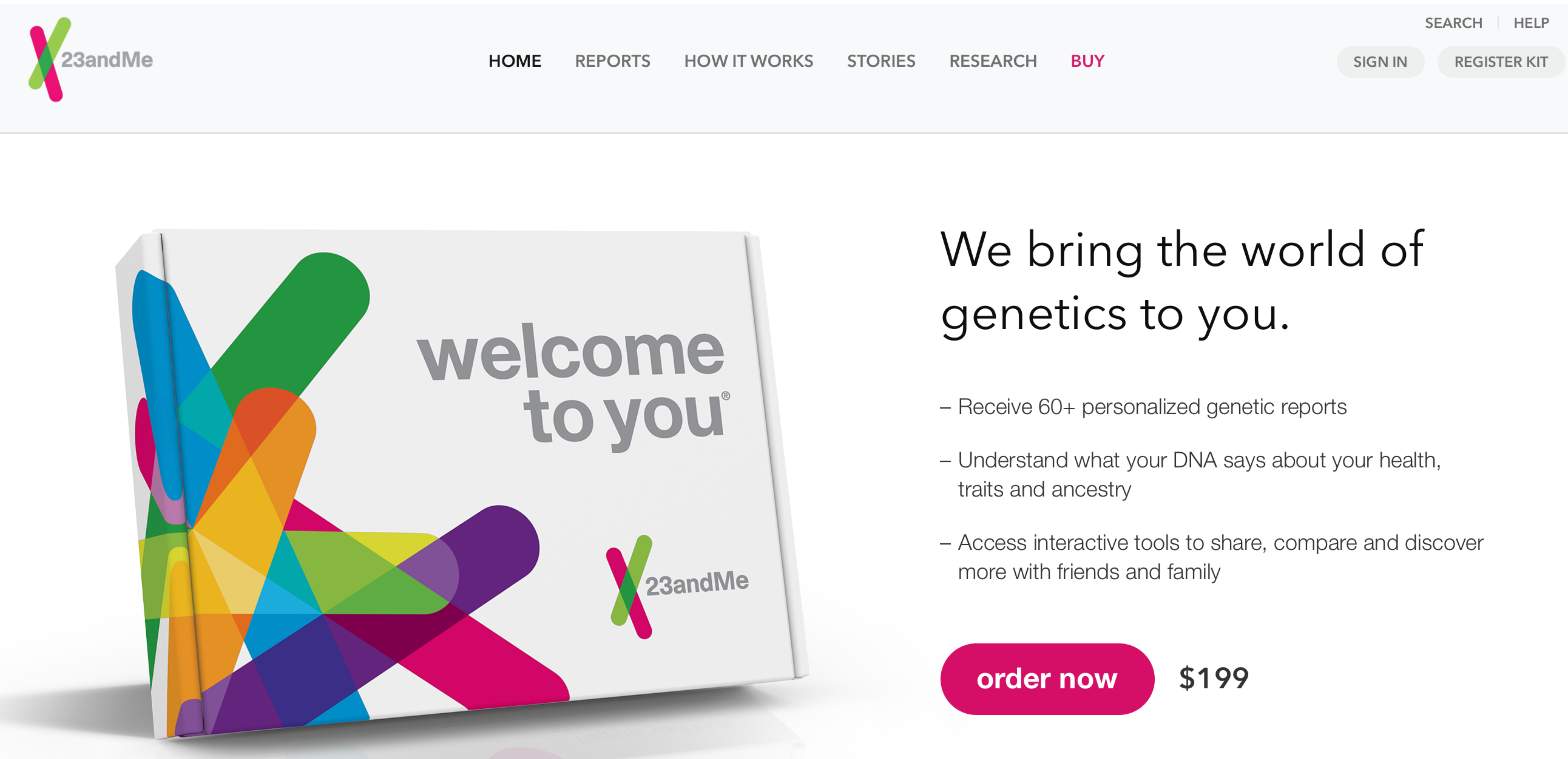
Related Publications

Reference
Pathway analysis of genome-wide data improves warfarin dose prediction. *BMC genomics.* 2013. Daneshjou Roxana, Tatonetti Nicholas P, Karczewski Konrad J, Sagreiya Hersh, Bourgeois Stephane, Drozda Katarzyna, Burmester James K, Tsunoda Tatsuhiko, Nakamura Yusuke, Kubo Michiaki, Tector Matthew, Limdi Nita A, Cavallari Larisa H, Perera Minoli, Johnson Julie A, Klein Teri E, Altman Russ B. PubMed
Development of a pharmacogenetic-guided warfarin dosing algorithm for Puerto Rican patients. *Pharmacogenomics.* 2012. Ramos Alga S, Seip Richard L, Rivera-Miranda Giselle, Felici-Giovanini Marcos E, Garcia-Berdecia Rafael, Alejandro-Cowan Yirelia, Kocherla Mohan, Cruz Iadelisse, Feliu Juan F, Cadilla Carmen L, Renta Jessica Y, Gorowski Krystyna, Vergara Cunegundo, Ruaño Gualberto, Duconge Jorge. PubMed

https://www.pharmgkb.org/page/overview

Whirl-Carrillo et al. Clinical Pharmacology & Therapeutics 92(4): 414-417 (2012)

Direct to Consumer Personalized Genomics



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Genetic reports.
Backed by science.

Our rigorous quality standards:

- ✓ Our Carrier Status Tests meet FDA criteria for being scientifically and clinically valid
- ✓ All saliva samples are processed in CLIA-certified and CAP-accredited labs
- ✓ Genotyping is a well-established and reliable platform for analyzing DNA
- ✓ Our scientists and medical experts use a rigorous process to develop the reports
- ✓ Your personalized reports are based on well-established scientific and medical research

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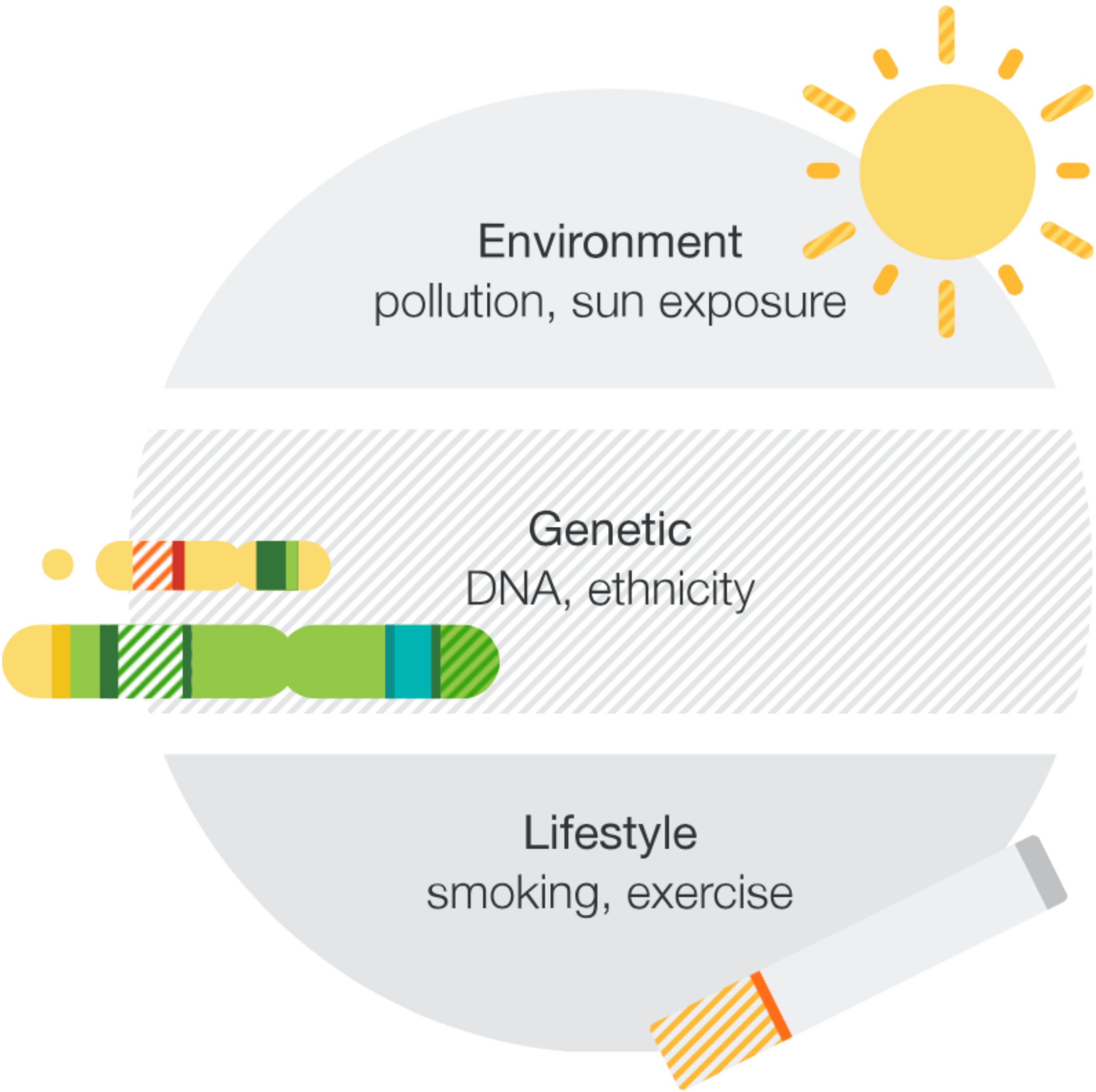

Why genetics is only part of the story.

When it comes to your health and traits, DNA is only part of the story. Other variables come into play, including non-genetic factors, such as your environment and lifestyle.

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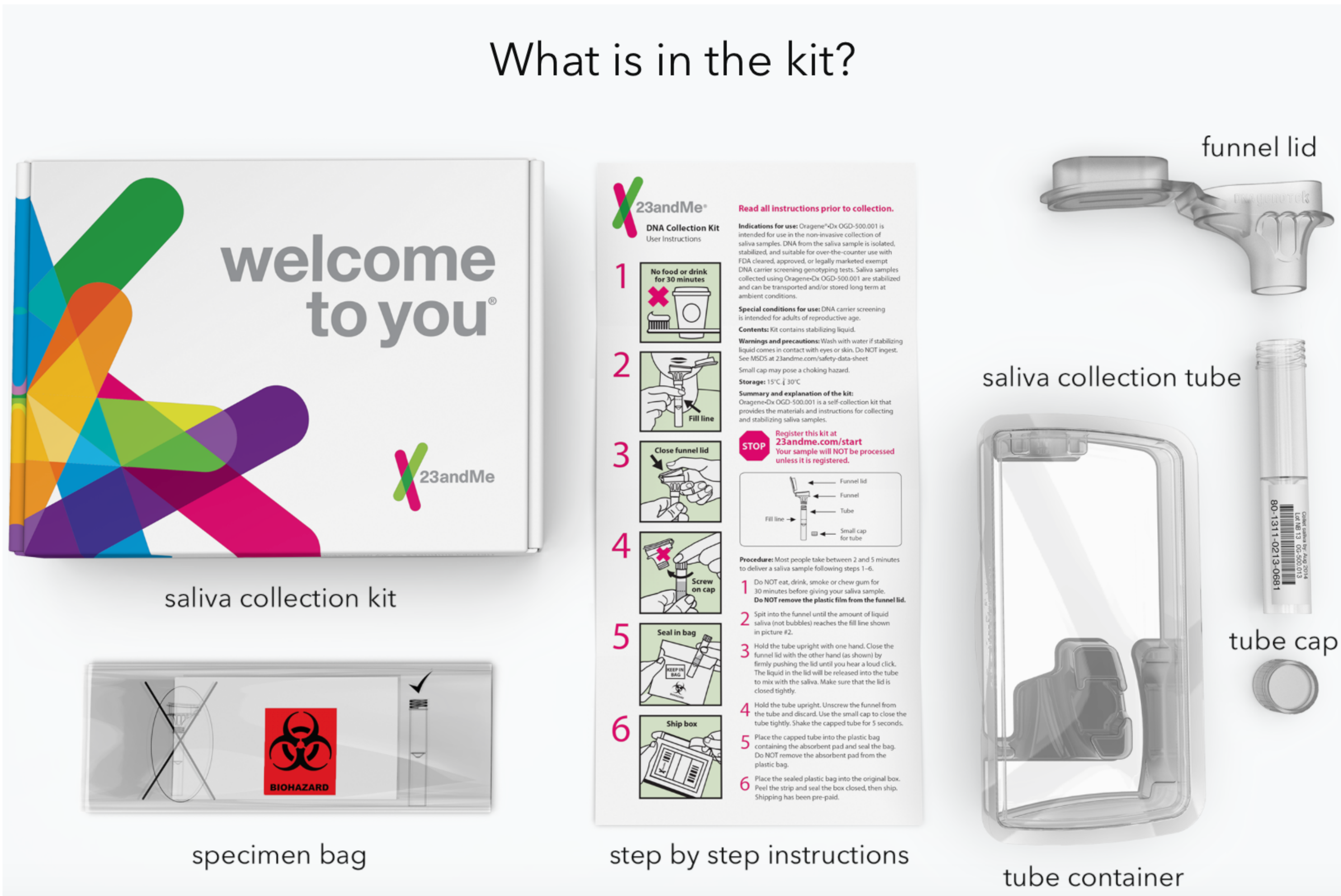

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SHOW RESULTS FOR George Mias

SEE NEW AND RECENTLY UPDATED REPORTS »

Health Risks (122)

ELEVATED RISKS	YOUR RISK	AVERAGE RISK
Psoriasis	16.8%	11.4%
Parkinson's Disease	2.2%	1.6%
Scleroderma (Limited Cutaneous Type)	0.08%	0.07%

more »

DECREASED RISKS	YOUR RISK	AVERAGE RISK
Gout	17.1%	22.8%
Alzheimer's Disease	4.3%	7.2%

more »

See all 122 risk reports...

Inherited Conditions (53)

REPORT	RESULT
Cystic Fibrosis	Variant Present
Hemochromatosis (HFE-related)	Variant Present
ARSACS	Variant Absent
Agenesis of the Corpus Callosum with Peripheral Neuropathy (ACCPN)	Variant Absent
Alpha-1 Antitrypsin Deficiency	Variant Absent

See all 53 carrier status...

Traits (63)

REPORT	RESULT
Alcohol Flush Reaction	Does Not Flush
Bitter Taste Perception	Unlikely to Taste
Blond Hair	<1% Chance
Earwax Type	Wet
Eye Color	Likely Brown

See all 63 traits...

Drug Response (25)

REPORT	RESULT
Proton Pump Inhibitor (PPI) Metabolism (CYP2C19-related)	Rapid
Warfarin (Coumadin®) Sensitivity	Increased
Phenytoin Sensitivity (Epilepsy Drug)	Increased
Sulfonylurea Metabolism	Greatly reduced
Abacavir Hypersensitivity	Typical

See all 25 drug response...

23andme.com (Older style reports pre FDA)

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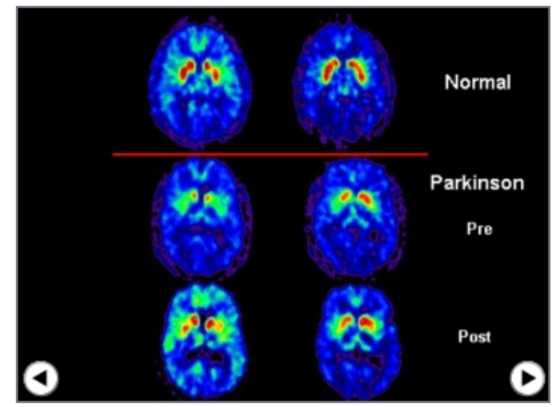
Parkinson's Disease

Printable Version

Parkinson's disease is a disorder of the brain's motor system caused by a loss of dopamine-producing brain cells. Approximately one and a half million Americans have the disease, and about 50,000 new patients are diagnosed each year. The main symptoms are trembling in the hands, arms, legs, jaw, and face; stiffness of the limbs and trunk; slowed movement; and impaired balance and coordination. Symptoms of Parkinson's disease usually come on gradually and affect people over the age of 50, although there are rare forms that progress more quickly and strike at a younger age. Though very little is known about the genetics of Parkinson's, mutations in a gene known as LRRK2 have been found to greatly increase a person's likelihood of developing the condition.

The following results are based on ★★★★ **Established Research** for 10 reported markers, updated April 26th, 2012.



1 of 2. Decreased dopamine activity in the brains of people with Parkinson's disease can be seen on a PET scan.

Your Results

Show information for George Mias assuming European ethnicity and an age range of 30-79

George Mias
2.2 out of 100
men of European ethnicity who share George Mias's genotype will develop Parkinson's Disease between the ages of 30 and 79.

Average
1.6 out of 100
men of European ethnicity will develop Parkinson's Disease between the ages of 30 and 79.

What does the Odds Calculator show me?

Use the ethnicity and age range selectors above to see the estimated incidence of Parkinson's Disease due to genetics for men with **George Mias**'s genotype. The 23andMe Odds Calculator assumes that a person is free of the condition at the lower age in the range. You can use the name selector above to see the estimated incidence of Parkinson's Disease for the genotypes of other people in your account.

The 23andMe Odds Calculator only takes into account effects of markers with known associations that are also on our genotyping chip. Keep in mind that aside from genetics, environment and lifestyle may also contribute to one's risk for Parkinson's Disease.

27 %
Attributable to Genetics

Understanding Your Results

The heritability of Parkinson's is relatively low but a recent study estimated it to be about 27% in European populations. This means that environment generally plays a larger role than genetics in determining a person's risk for the disease. However, a small fraction of Parkinson's cases are attributed to rare mutations in a small number of genes, including the G2019S mutation in LRRK2, which is included in this report. People with the LRRK2 G2019S mutation have a much higher than average risk of developing Parkinson's disease during their lifetimes. This report also discusses other genetic factors that are associated with higher risk for PD in European and Asian populations. (sources)

23andme.com (Older style reports pre FDA)

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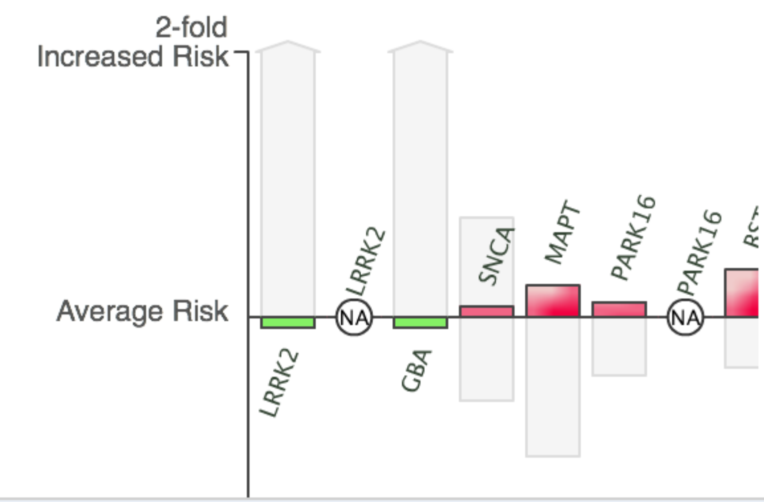
Marker Effects



What does this chart show?

The chart shows the approximate effects of the selected person's genotype at the 10 reported markers. Higher, red bars indicate increased risk from the average, while lower, green bars indicate decreased risk from the average. The light gray bars show the maximum possible effects for the possible genotypes at the marker.

Mouse over individual bars to view additional information about each marker. Click on a bar to view detailed information about that marker below. You can read more about all markers in the technical report.

LRRK2 **Marker:** rs34637584

Mutations in the LRRK2 gene are one of the most common known genetic causes of Parkinson's disease (PD).

More than 50 variants are known in the LRRK2 gene. Several of these have been associated with PD. This variant reported by 23andMe, rs34637584, also known as the G2019S mutation, is the best-studied LRRK2 SNP related to Parkinson's in individuals with European ancestry.

Parkinson's is a fairly rare disease. The average person has a 1-2% chance of developing the disease during his or her lifetime. The chance that a person with the G2019S mutation will develop Parkinson's is much higher than average and increases with age. One recent study found that people with the G2019S mutation have a 28% chance of developing Parkinson's by the age of 59, 51% by the age of 69 and 74% by the age of 79. However, estimates of PD risk due to the G2019S mutation vary greatly. While it is well established that the mutation's effect is very strong, there is no consensus about its exact magnitude.

Of all people with Parkinson's, few have the G2019S mutation, but it is present at high levels in patients from some ethnic groups. Up to 40% of people with PD who are of Arab-Berber ancestry and 20% of Ashkenazi Jewish people with PD have this mutation.

Scientists do not know why only some people with the G2019S mutation get PD. There may be unknown effects due to other genes or environmental factors.

Citations

Schapira (2006) . "The importance of LRRK2 mutations in Parkinson disease." *Arch Neurol* 63(9):1225-8.

Klein et al. (2007) . "Deciphering the role of heterozygous mutations in genes associated with parkinsonism." *Lancet Neurol* 6(7):652-62.

Healy et al. (2008) . "Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study." *Lancet Neurol* 7(7):583-90.

23andme.com (Older style reports pre FDA)

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Gene or Region	SNP	Genotype	Adjusted Odds Ratio
LRRK2	rs34637584	GG	0.98
LRRK2	rs34778348	GG	NA (not applicable)
GBA	i4000415	TT	0.99
SNCA	rs356220	CT	1.02
MAPT	rs393152	AA	1.09
PARK16	rs947211	GG	1.04
PARK16	rs823156	AA	NA (not applicable)
BST1	rs4698412	AA	1.13
DGKQ	rs11248060	CC	0.94
STK39	rs2390669	AC	1.15

23andme.com (Older style reports pre FDA)

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Detected the following variants: 2789+5G>A

23andMe Name	Other Name(s)	DNA Change	Genotype	Result
i3000001	DeltaF508	CTT to –	CTT,CTT	Has one mutation in the CFTR gene linked to cystic fibrosis. A person with one of these mutations typically does not have cystic fibrosis, but may pass the mutation to offspring. May still have other mutations in the CFTR gene (not reported here). Variants detected: 2789+5G>A
i4000292	DeltaI507	ATC to –	ATC,ATC	
i4000294	G85E	G to A	GG	
i4000296	R334W	C to T	CC	
i4000297	R347P/H	G to C,A	GG	
i4000291	A455E	C to A	CC	
i4000299	V520F	G to T	GG	
i4000300	G542X	G to T	GG	
i4000301	S549N	G to A	GG	
i4000305	G551D	G to A	GG	
i4000306	R553X	C to T	CC	
i4000307	R560T	G to C	GG	
i4000308	R1162X	C to T	CC	
i4000309	W1282X	G to A	GG	
i4000311	N1303K	C to G	CC	
i4000313	394delTT	TT to –	TT,TT	
i4000314	621+1G>T	G to T	GG	
i4000315	711+1G>T	G to T	GG	
i4000316	1078delT	T to –	T,T	
i4000317	1717-1G>A	G to A	GG	
i4000318	1898+1G>A	G to A	GG	
i4000320	**2789+5G>A**	**G to A**	**AG**	
i4000321	3120+1G>A	G to A	GG	
i4000322	3659delC	C to –	C,C	
i4000324	3905insT	– to T	–,–	
i4000325	3849+10kbC>T	C to T	CC	

Cystic Fibrosis

Cystic fibrosis (CF) is caused by mutations in a gene called CFTR. This gene codes for a protein that helps move salt and water through cells. Mutations in CFTR result in the build-up of thickened mucus and other secretions that can damage the lungs, pancreas, and other organs. The disease is inherited in a recessive manner, meaning that a person must inherit a mutated copy of the CFTR gene from both parents in order to develop the disease. Cystic fibrosis is most common in populations with European or Jewish ancestry, where about one out of every 25 to 30 people carries a CFTR mutation.

The following results are based on ★★★★ **Established Research** for 26 reported markers, updated May 29th, 2014.

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Warfarin (Coumadin®) Sensitivity

Warfarin is an anticoagulant (also known as a blood thinner). It is used to treat and prevent blood clots. Blood clots can block blood flow and cause a heart attack or stroke.

SNP	Genotype	Combination	Result
rs1799853	CT	CYP2C9*2/*3, VKORC1 -1673/3673 AG	Likely to be more sensitive to warfarin based on genetics. Genetic information may only be useful when determining an initial dose of warfarin. Many other factors also influence warfarin sensitivity. If you are taking warfarin, keep taking it as directed by your doctor.
rs1057910	AC		
rs9923231	CT		

Sulfonylurea Metabolism

Sulfonylurea drugs are commonly used to treat type 2 diabetes, a disease that affects about 350 million people worldwide. Genetic as well as non-genetic factors can influence how a person responds to these drugs. This report covers two genetic variants associated with the ability to clear to sulfonylurea drugs from the body. Decreased drug clearance can result in better chances for successful treatment but may also increase the risk of side effects.

The following results are based on ★★★★ **Established Research** for 2 reported markers.

SNP	Genotype	Combination	Result
rs1799853	CT	CYP2C9 *2/*3	Greatly reduced ability to clear sulfonylurea drugs from the body. Clearance may affect treatment effectiveness, likelihood of side effects, and optimal dose.
rs1057910	AC		

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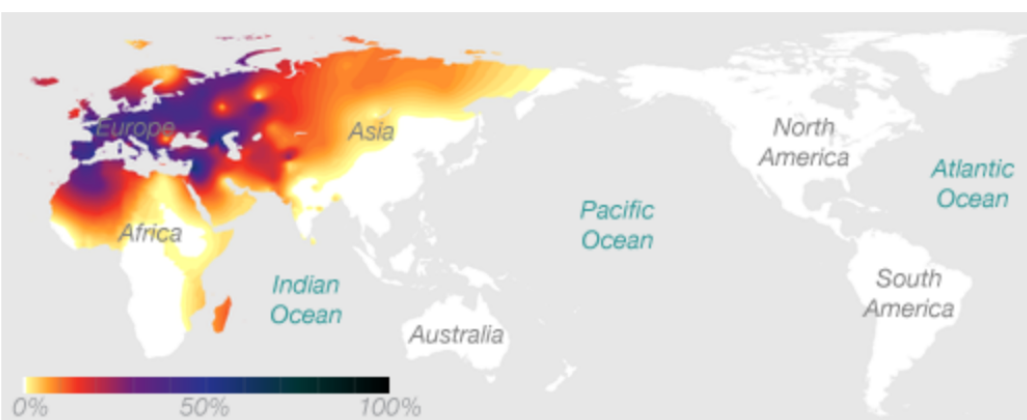
MATERNAL LINE: H

Overview | History | Haplogroup Tree | Community

Locations of haplogroup H before the widespread migrations of the past few hundred years.



H originated in the Near East and then expanded after the peak of the Ice Age into Europe, where it is the most prevalent haplogroup today. It is present in about half of the Scandinavian population and is also common along the continent's Atlantic coast.

PATERNAL LINE: E1B1B1A2*

Overview | History | Haplogroup Tree | Community

E1b1b1a2* is a subgroup of E1b1b1a

Locations of haplogroup E1b1b1a before the widespread migrations of the past few hundred years.

E1b1b1a is most common in northern Africa and southern Europe. It arose about 23,000 years ago in eastern Africa and spread into the Mediterranean region after the Ice Age. E1b1b1a, a subgroup of E1b1b, expanded out of the Near East 8,000 years ago into northern Africa and southern Europe. Today it is one of the most common haplogroups in those regions.

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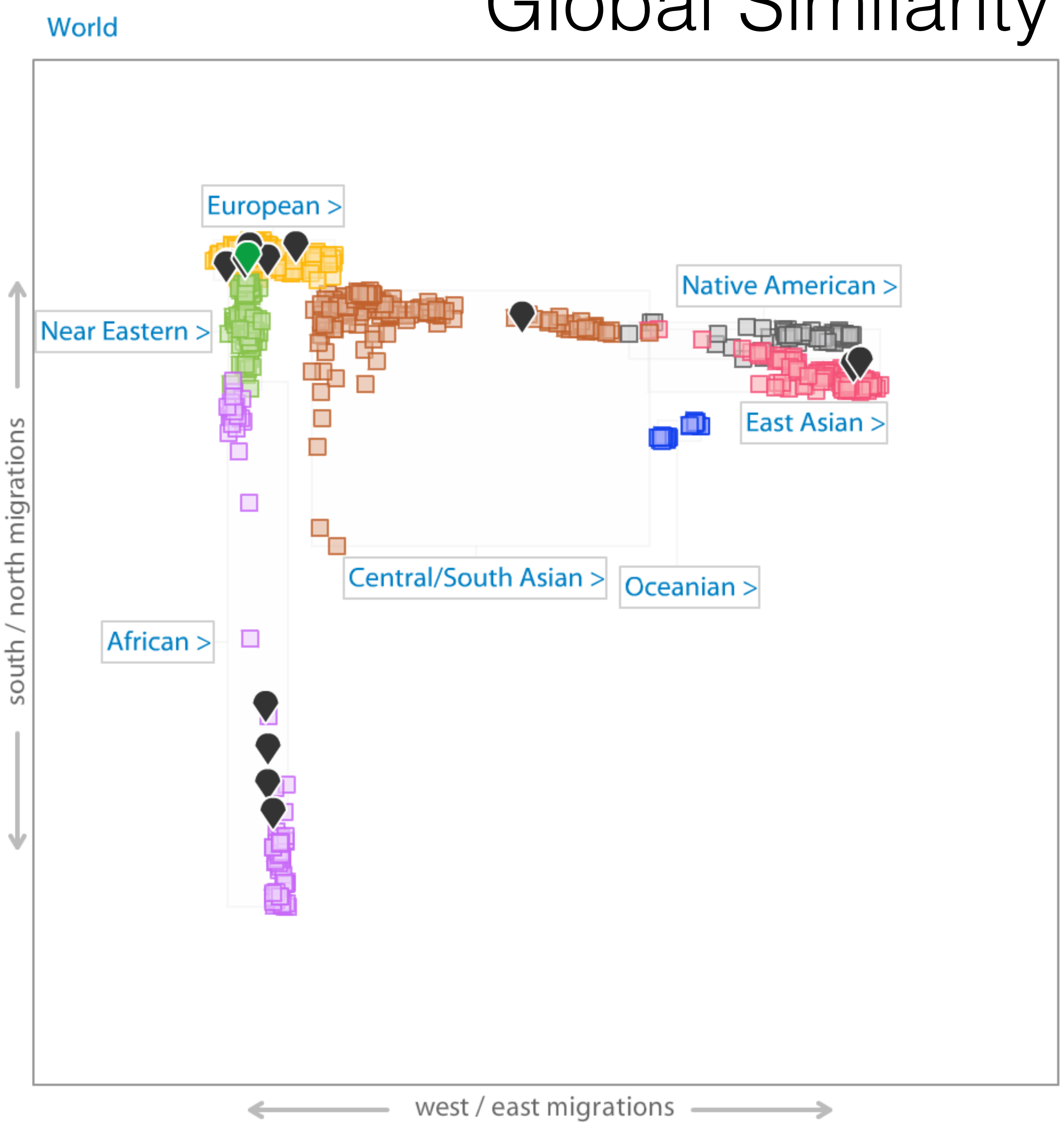
Global Similarity



DNA Relatives

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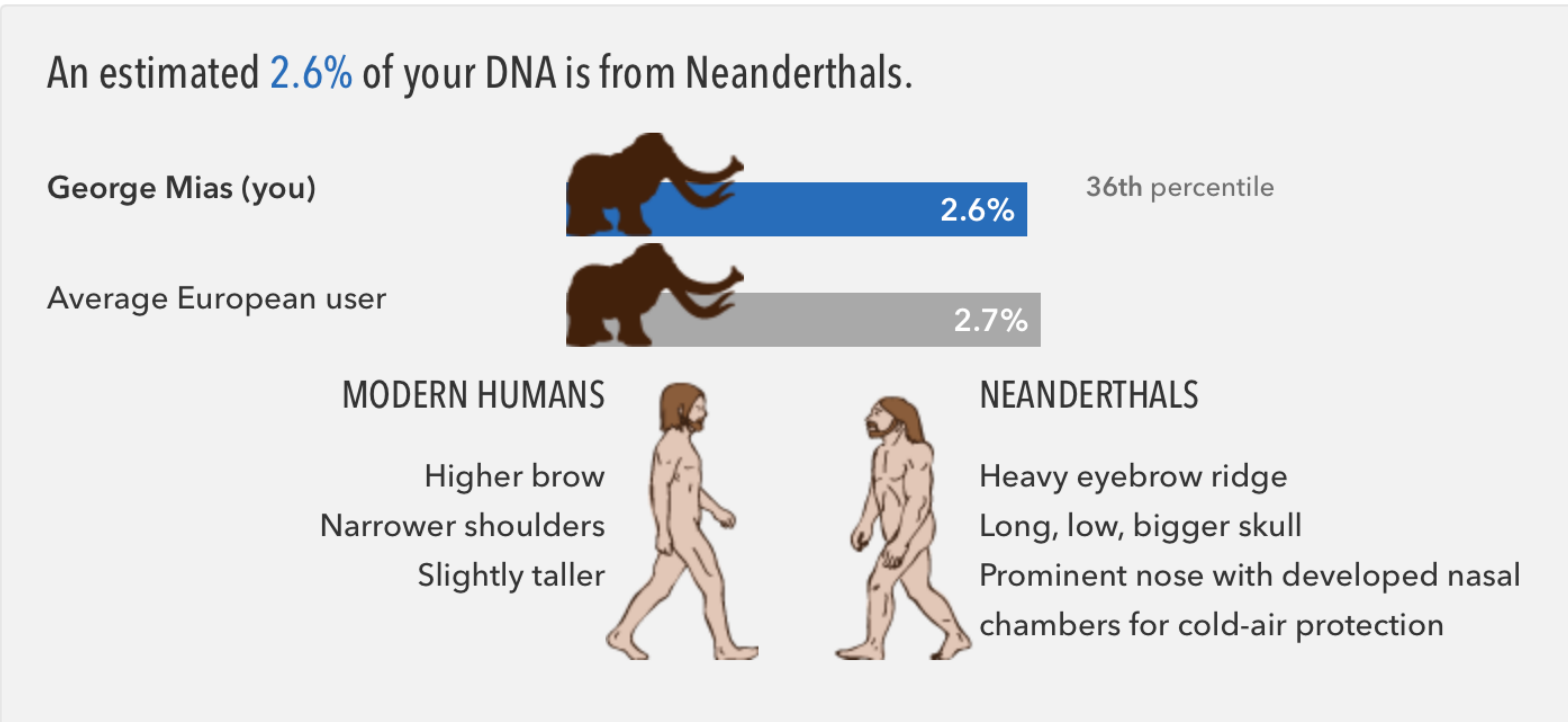
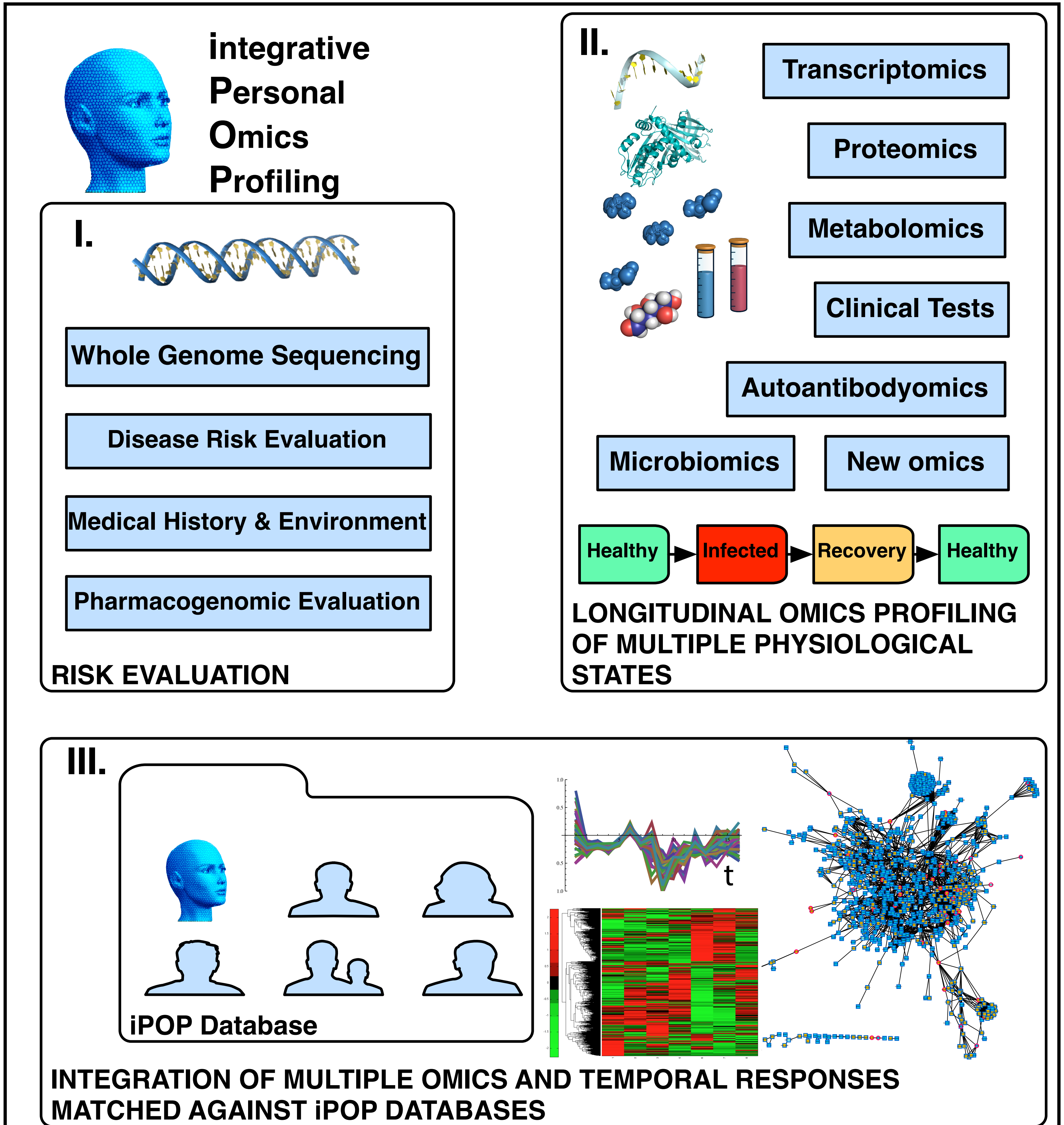
Got Neanderthal DNA?



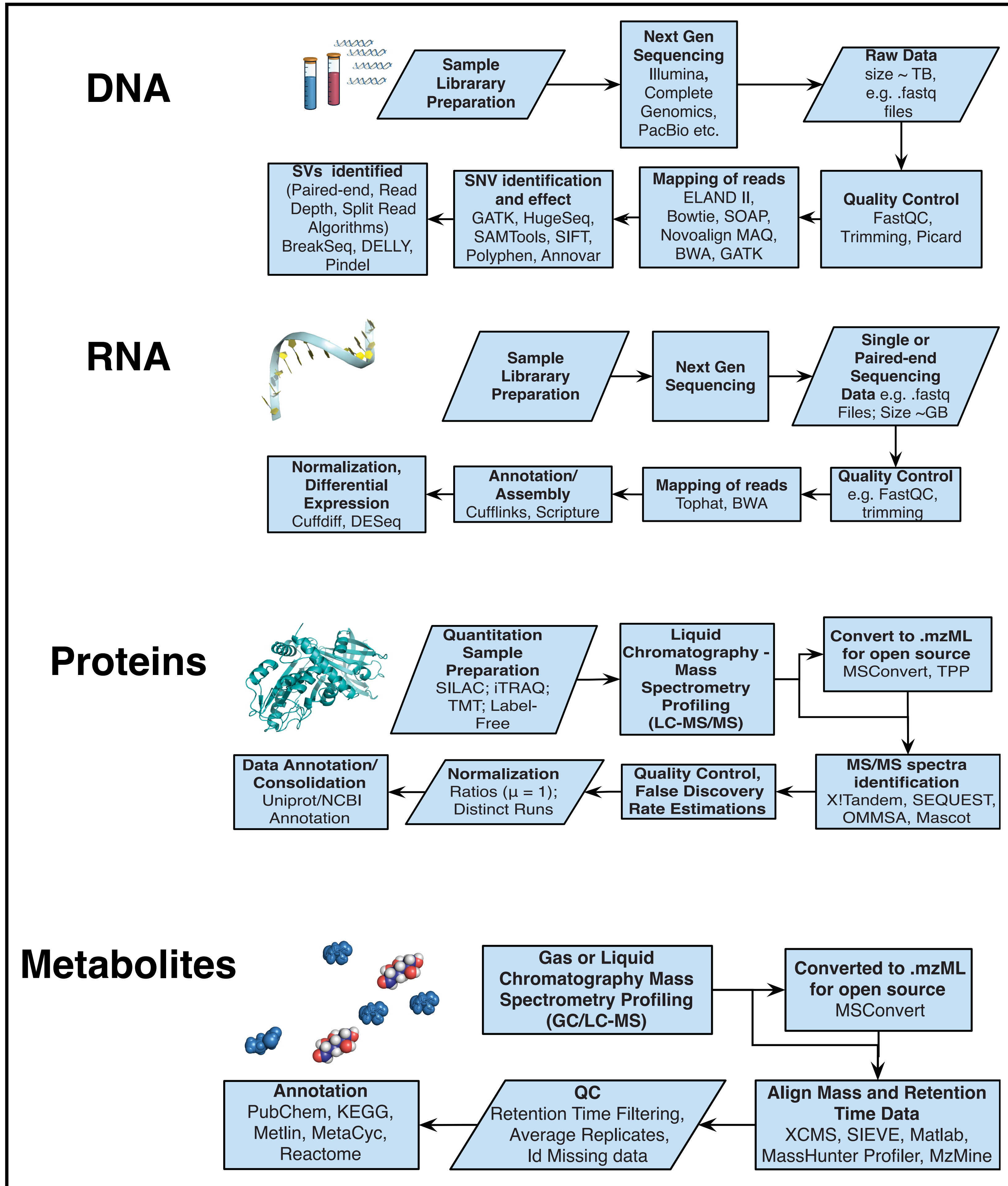
23andme.com (Older style reports pre FDA)



Mias & Snyder, Quantitative Biology (1)1 p72 (2013) http://goo.gl/iamZth

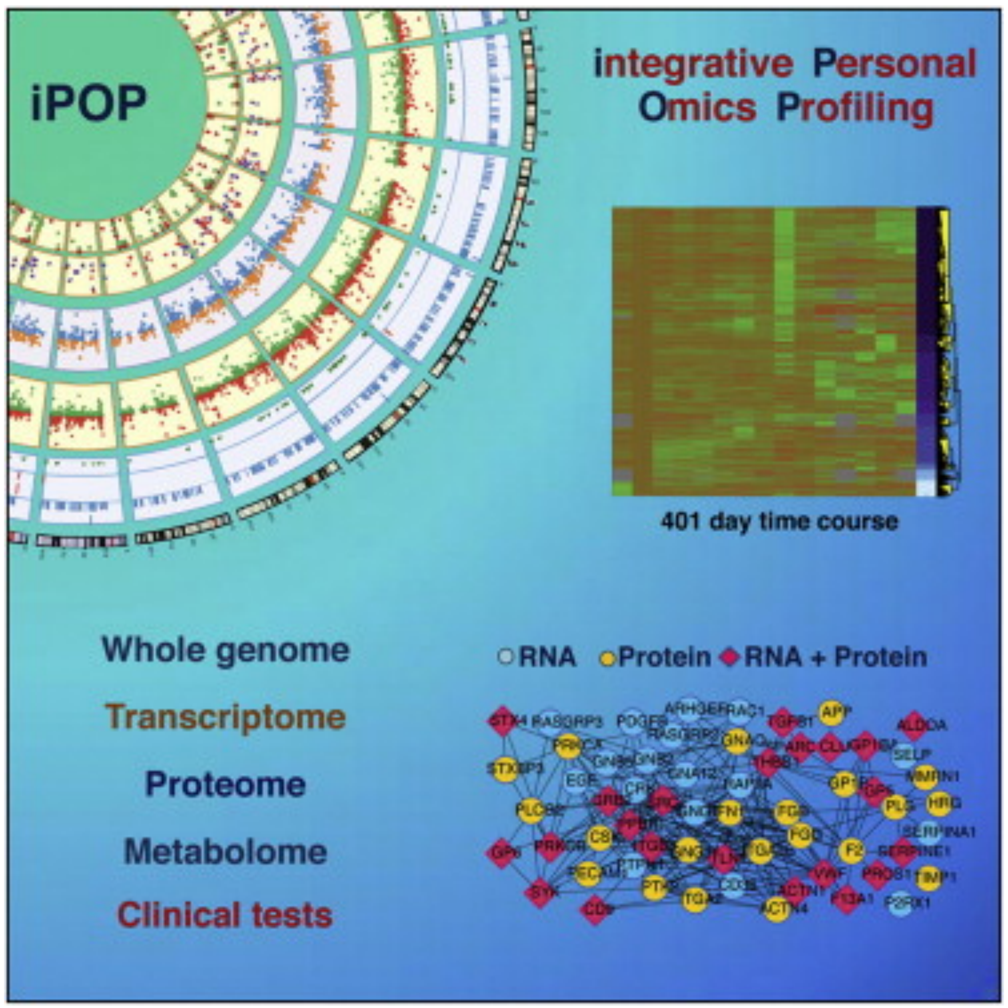
Personalized Medicine

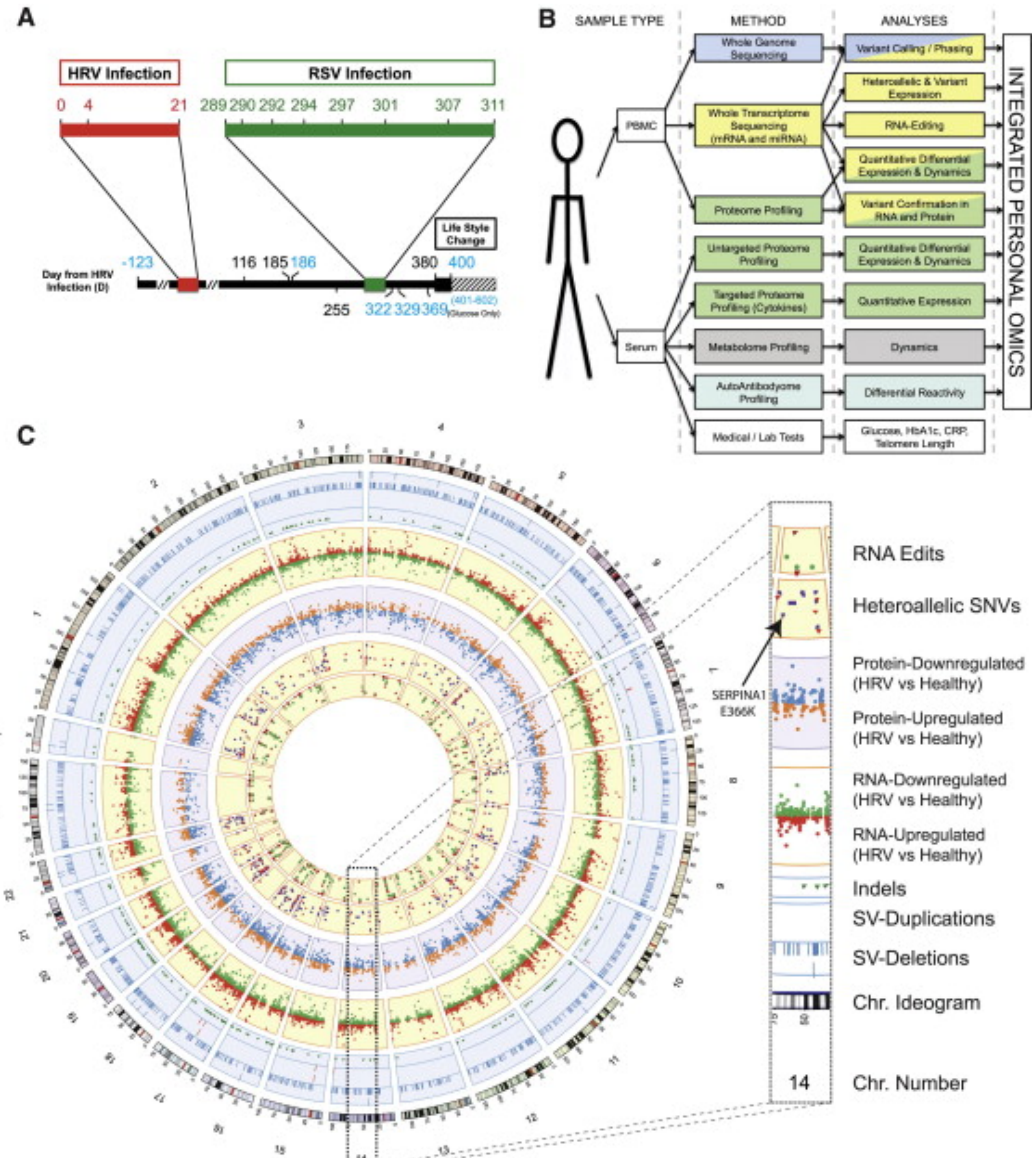
- Personalized
  - Determine risks
  - Monitor
  - Integrate



Mias and Snyder, Quantitative Biology 1(1) p. 71 (2013).

Integrative Personal Omics Profiling (iPOP)





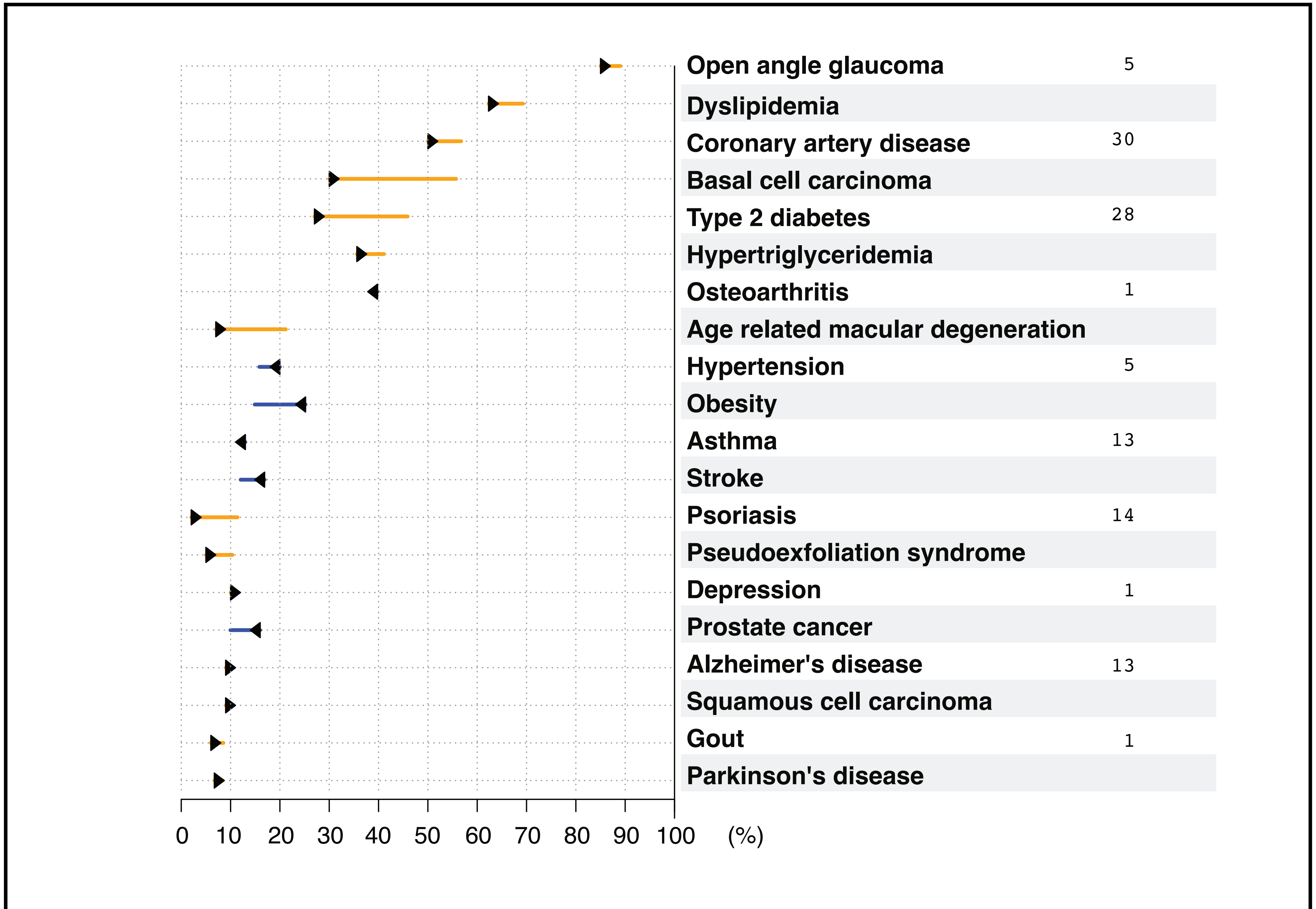
Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

I. Genome Sequencing

- Whole Genome Sequencing
  - Illumina (120-fold coverage)
  - Complete Genomics (150-fold coverage)
  - Exome Sequencing (Nimblegen, Agilent and Illumina) (80-100-fold coverage)
- Variants identified
  - ~ 3.3×10^6 Single Nucleotide Variants (SNVs)
  - ~ 2×10^5 Small insertions and deletions (InDels)
  - Structural variants (SVs > 1Kb changes)

Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

I. Genome Sequencing

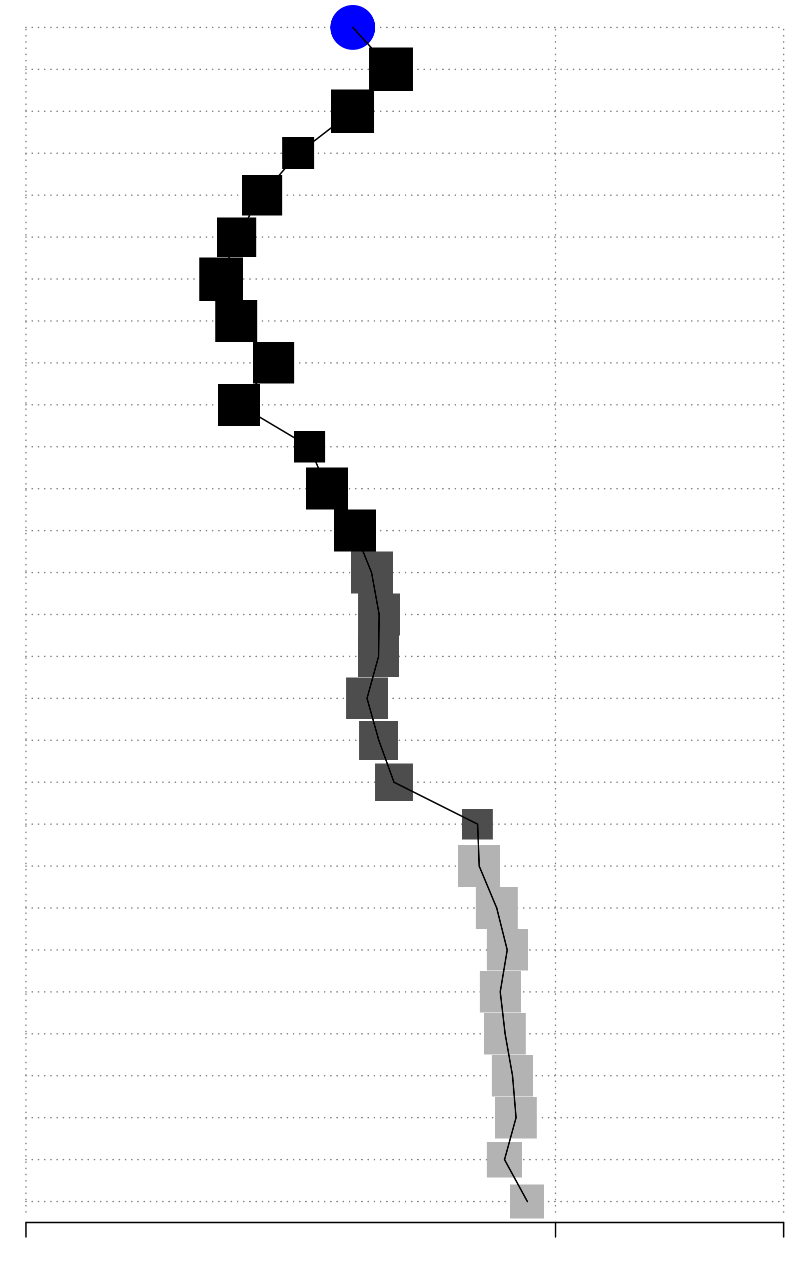


Rong Chen, Atul Butte

Ashley et al. Lancet 375, 1525-1535 (2010)

I. Genome Sequencing

Type 2 diabetes



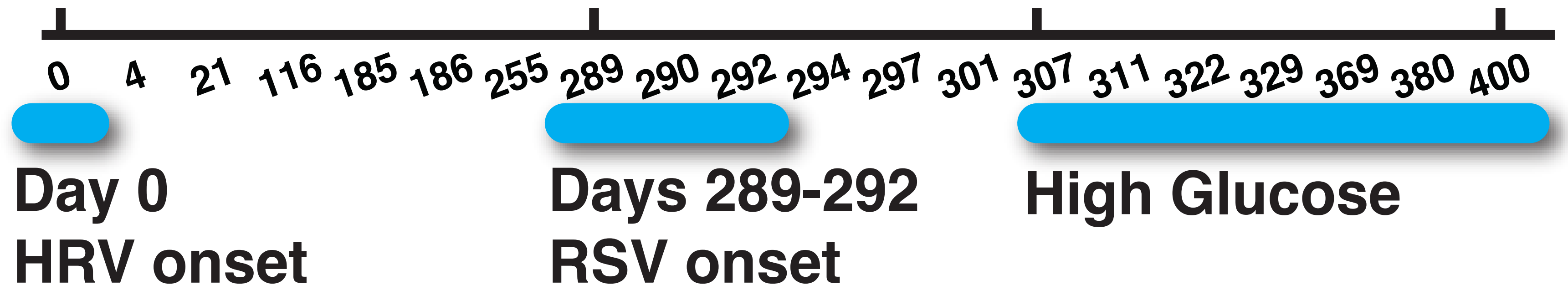
Genotype Test	LR	Studies	Samples	Probability
Prevalence				27%
TCF7L2 rs7903146 CT	1.18	49	140717	30%
rs10811661 TC	0.85	18	154141	27%
KCNQ1 rs2237892 CT	0.80	13	6570	23%
FTO rs8050136 CC	0.87	10	63470	20%
CDKAL1 rs7754840 GG	0.91	10	51327	19%
SLC30A8 rs13266634 CT	0.94	9	145718	18%
IGF2BP2 rs4402960 GT	1.06	8	104401	19%
KCNJ11 rs5219 TT	1.15	7	87066	21%
rs1111875 TT	0.88	6	93188	19%
PPARGC1A rs2970847 TC	1.31	4	5558	24%
rs7578326 AA	1.07	3	94337	25%
rs4457053 GG	1.12	3	94337	27%
KCNQ1 rs231362 GG	1.07	2	94337	29%
ARAP1 rs1552224 AA	1.03	2	94337	29%
JAZF1 rs864745 TC	1.00	2	89920	29%
RBMS1 rs1020731 GA	0.95	2	84605	28%
rs9300039 CC	1.05	2	42170	29%
WFS1 rs10010131 GG	1.07	2	30248	31%
EPO rs1617640 AA	1.48	2	4011	39%
TP53INP1 rs896854 TC	1.01	1	94337	40%
rs5945326 AA	1.09	1	94337	42%
rs12779790 AG	1.06	1	89920	43%
rs1153188 TA	0.96	1	89920	42%
THADA rs7578597 TT	1.03	1	89920	43%
rs4607103 CC	1.04	1	89920	44%
rs17036101 GG	1.02	1	89920	44%
MTNR1B rs10830963 CC	0.94	1	16061	43%
HNF1B rs4430796 GG	1.13	1	11320	46%

Sum over likelihood ratios for disease risk - probabilistic
VariMed curated database

Rong Chen, Atul Butte

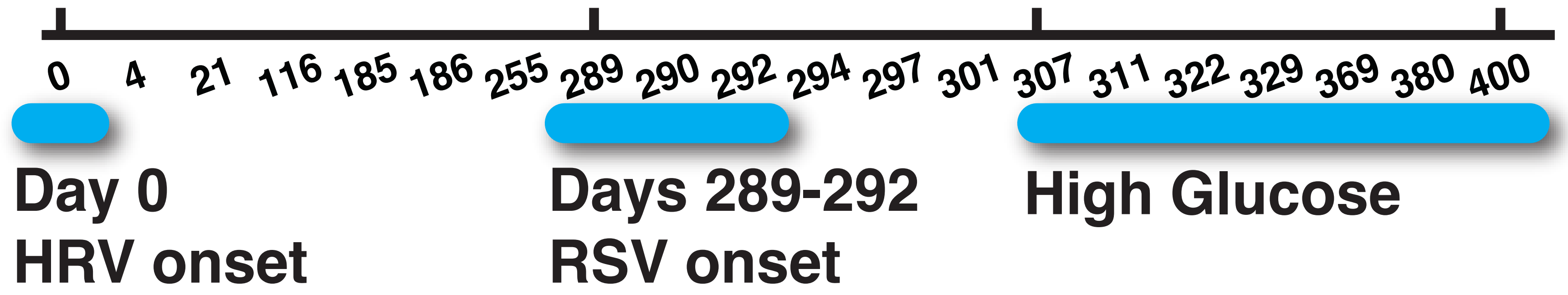
Ashley et al. Lancet 375, 1525-1535 (2010)

Data Timeline:



Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

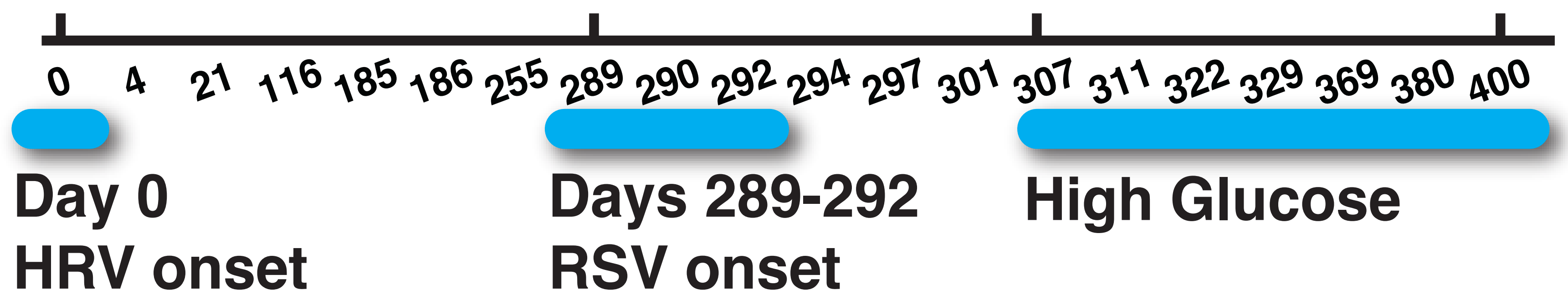
Data Timeline:

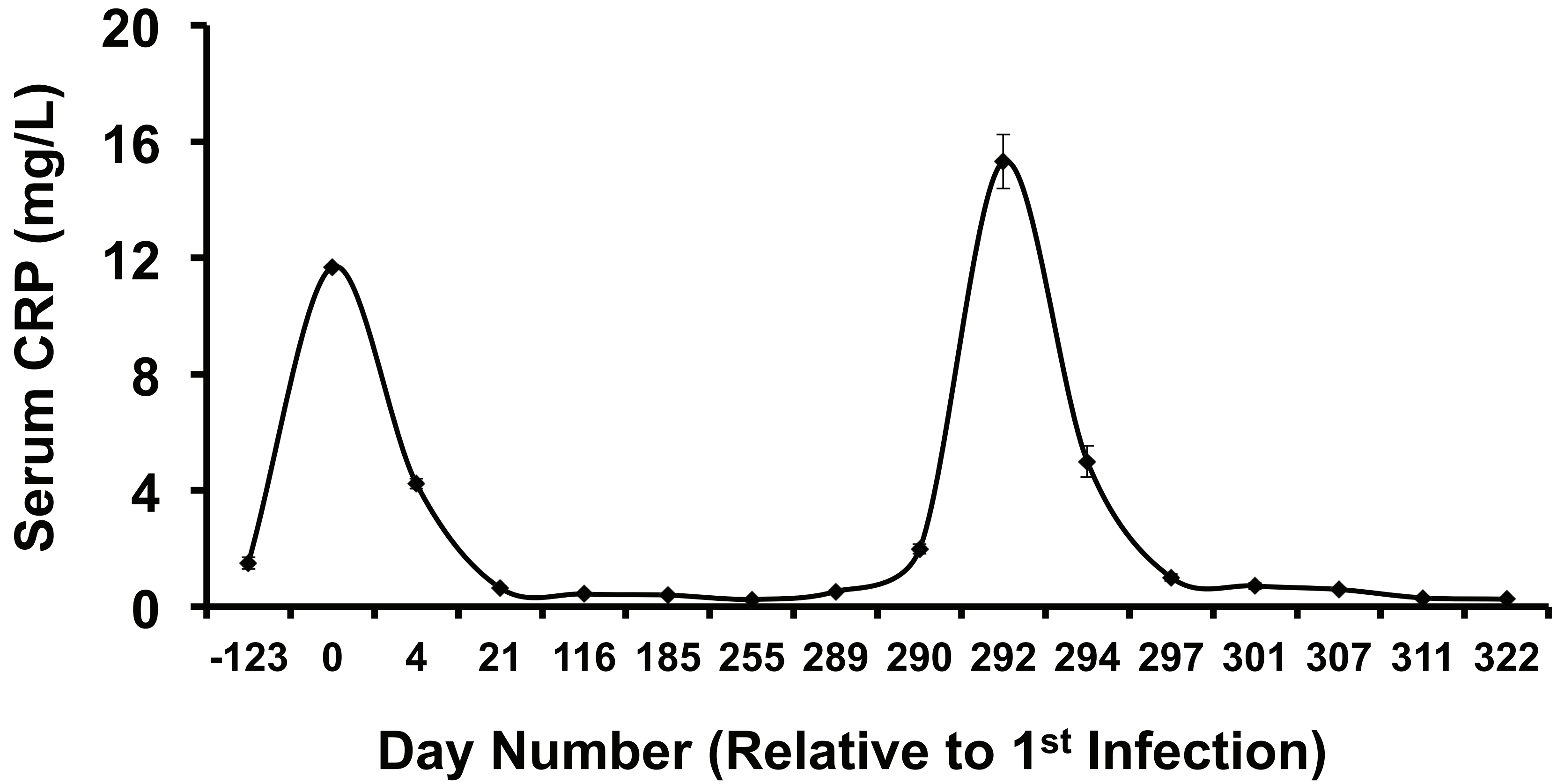


- Timeline Events
  - Human Rhinovirus (HRV)
  - Respiratory Syncytial Virus (RSV)
  - High Glucose (Type II Diabetes - as per physician)

Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

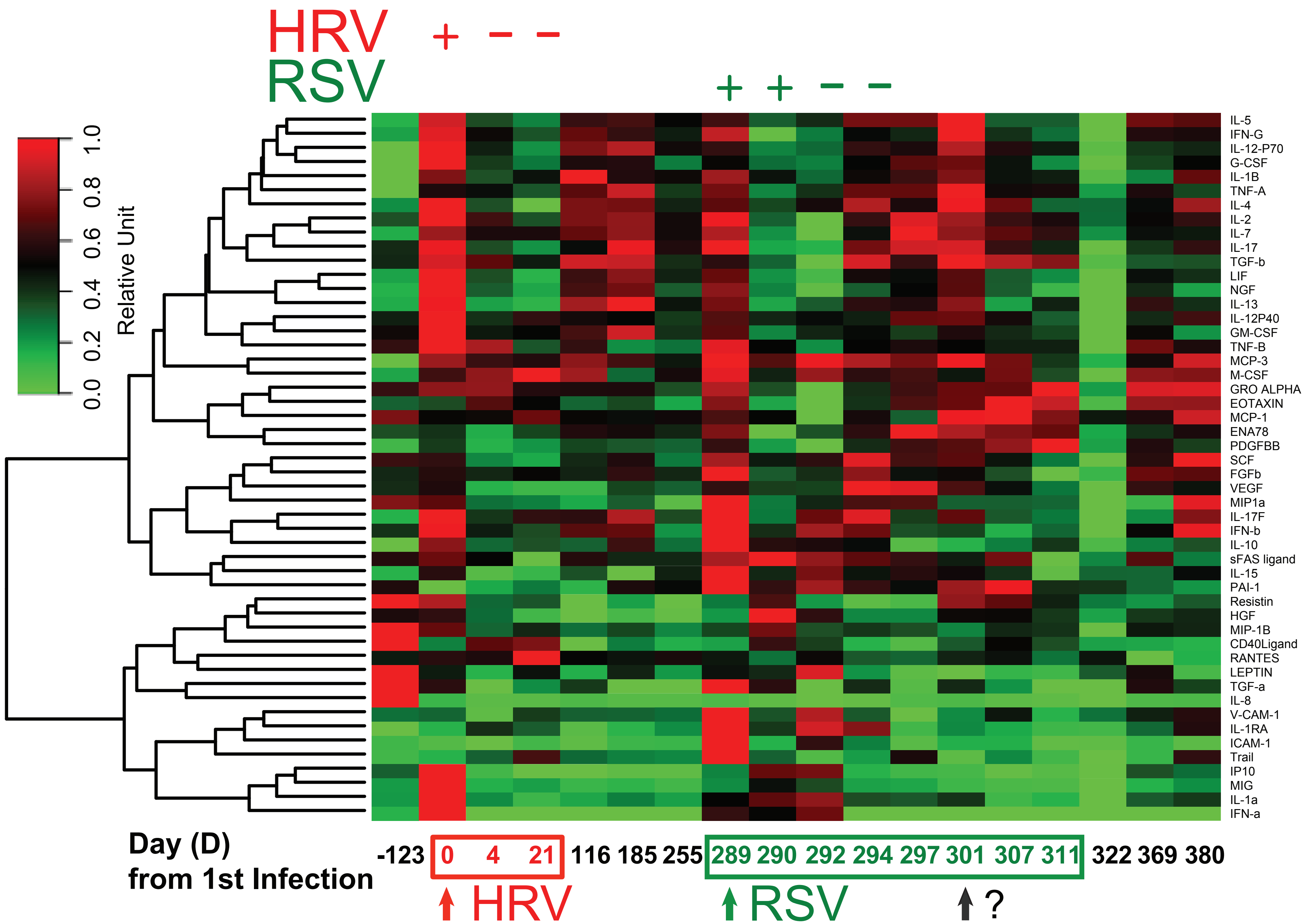
Data Timeline: Infections





Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

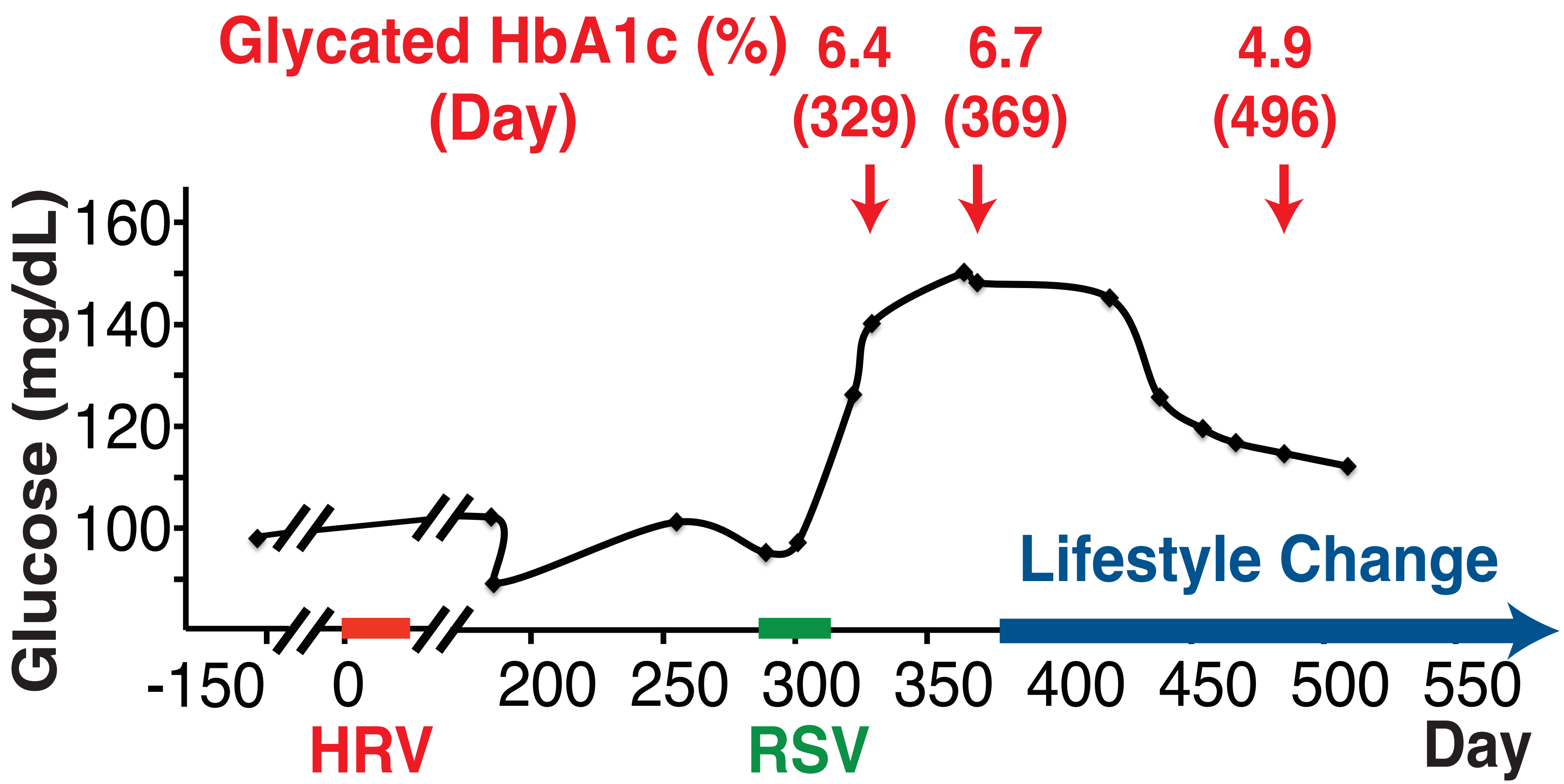
Data Timeline: Cytokines



Stanford Human Immune Monitoring Center

Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

Data Timeline: Glucose Levels

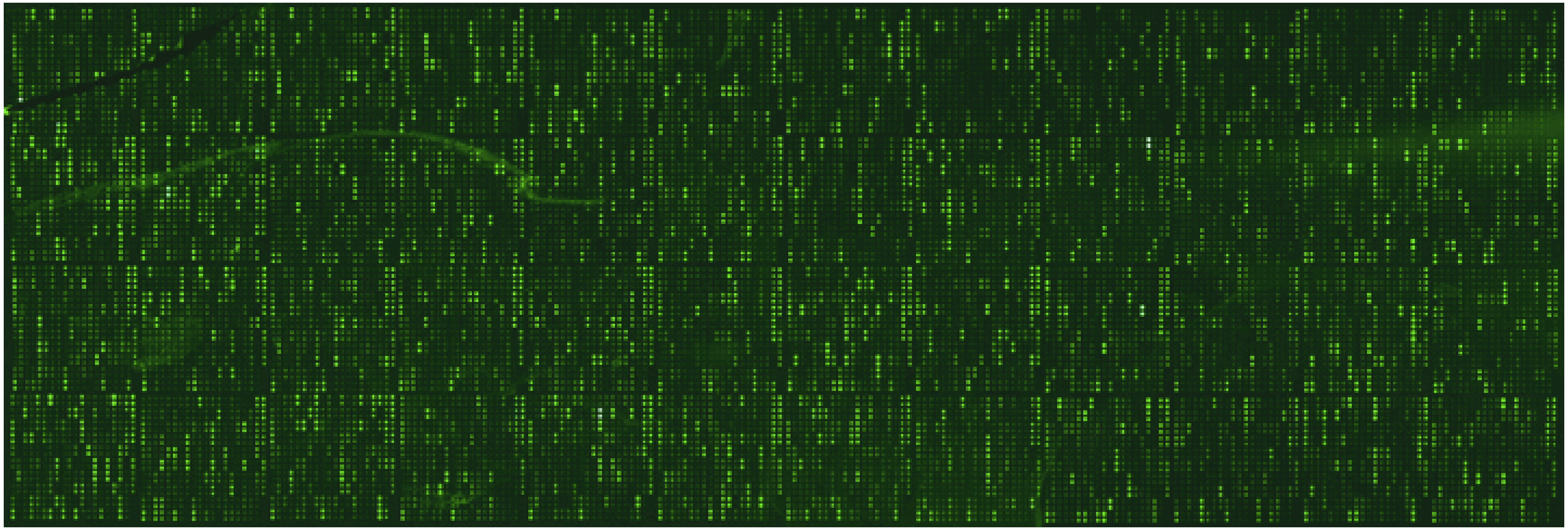


Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

Data Timeline: Autoantibody-ome

- ProtoArrays (Invitrogen)

532 nm channel example



Data Timeline: Autoantibody-ome

Higher in Test Subject Vs.
Healthy Group (40pts)

- **ARRDC3** arrestin domain containing 3
- **EIF3E** eukaryotic translation initiation factor 3
- **PAQR4** progestin and adipoQ receptor family member I
- **DOK6** docking protein 6 (insulin receptor docking)
- **GOSR1** golgi SNAP receptor complex member 1
- **BTK** Bruton agammaglobulinemia tyrosine kinase
- **ASPA** aspartoacylase

Blue intersect with RNA expression

Yellow insulin related

Red observed in insulin-resistant groups,
Winer et al. Nat Med. 17 p610 (2011).

Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).
Mias & Snyder, Quantitative Biology 1(1) p. 71 (2013).

II. Dynamics:Data Analysis Framework

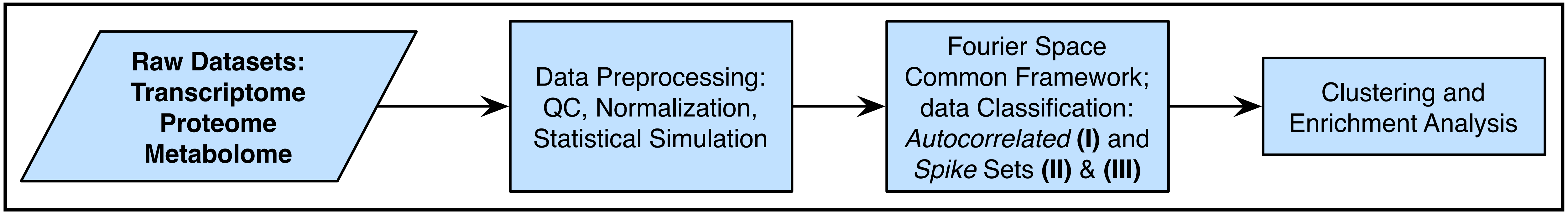
❖ Integration of Dynamic Omics

Transcriptome	Proteome	Metabolome

1. Preprocessing
2. Common Classification Scheme
   i. Overall trends (autocorrelation)
   ii. Spikes at specific timepoints
3. Clustering and Enrichment Analysis

Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

II. Dynamics:Data Analysis Framework

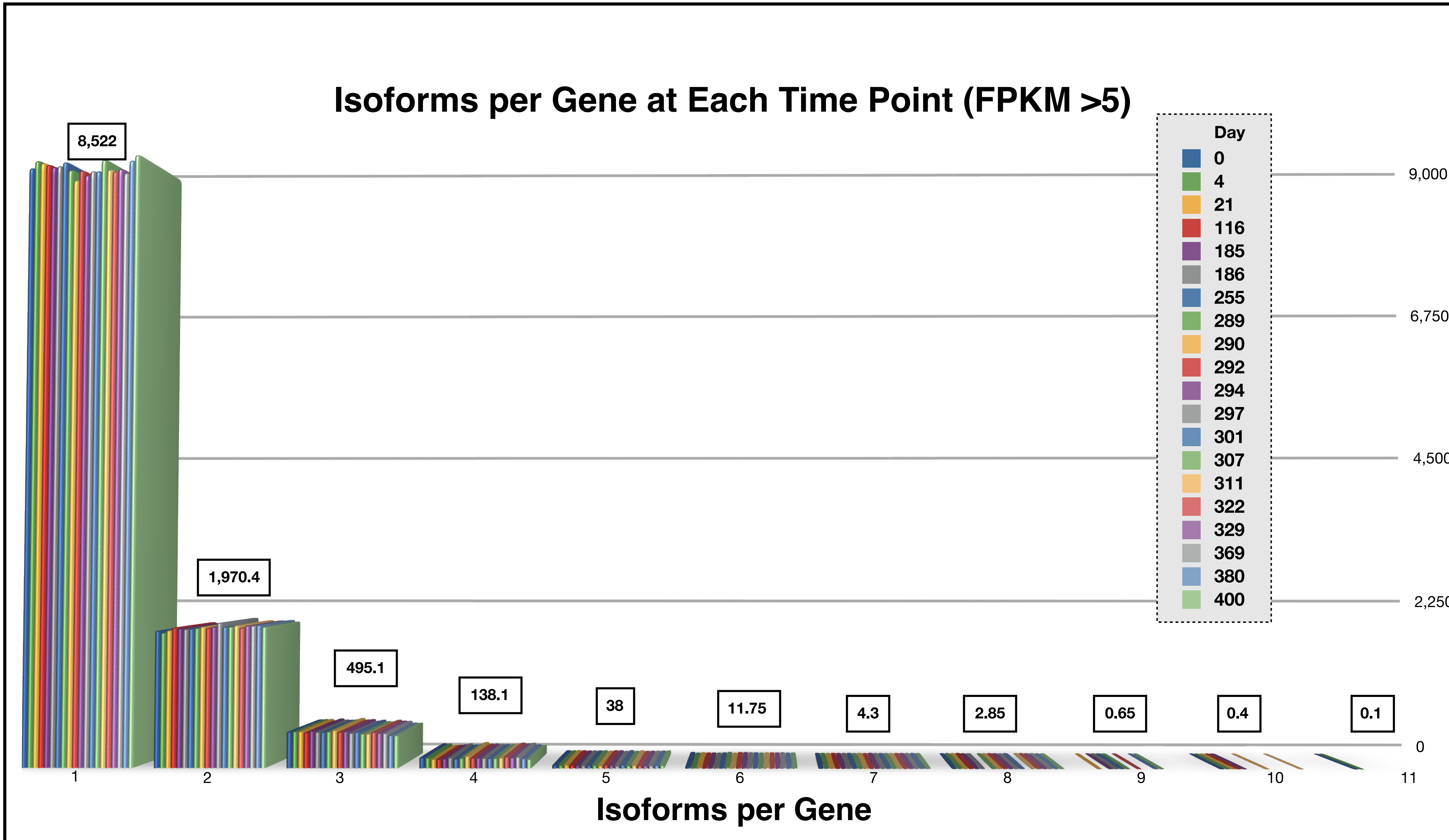


1. Preprocessing
2. Common Classification Scheme
    i. Overall trends (autocorrelation)
    ii. Spikes (maxima) at specific timepoints
    iii. Spikes (minima)
3. Clustering and Enrichment Analysis

Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

II. Dynamics:Data Analysis Framework

- (1) Data Preprocessing: Transcriptome

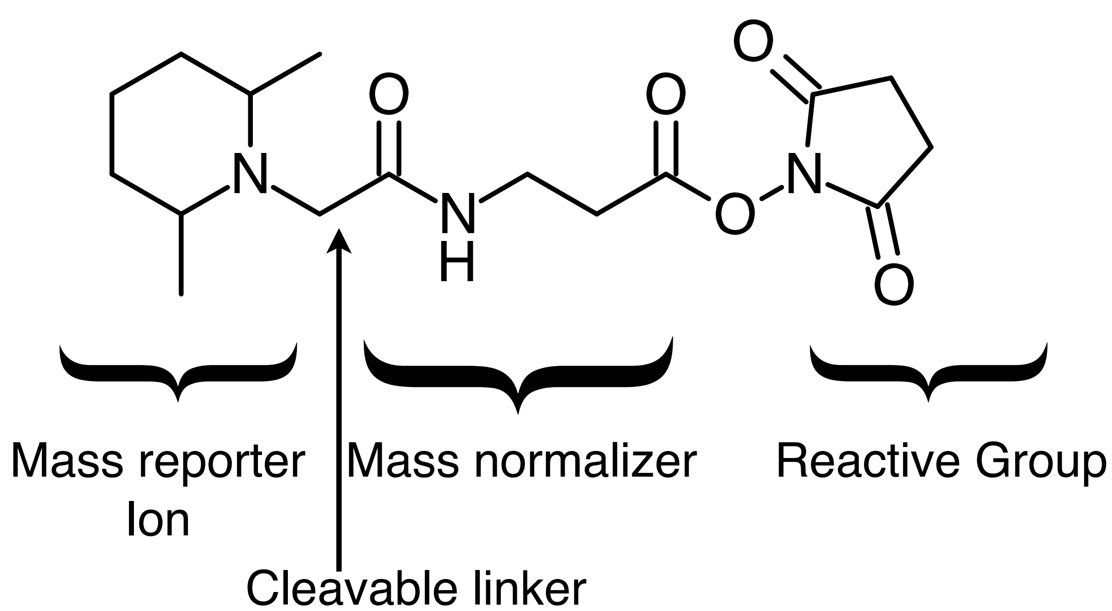


Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

II. Dynamics:Data Analysis Framework

- (1) Data Preprocessing: Proteome

Tracking Different Timepoints with Chemical Labeling (TMT 6plex)

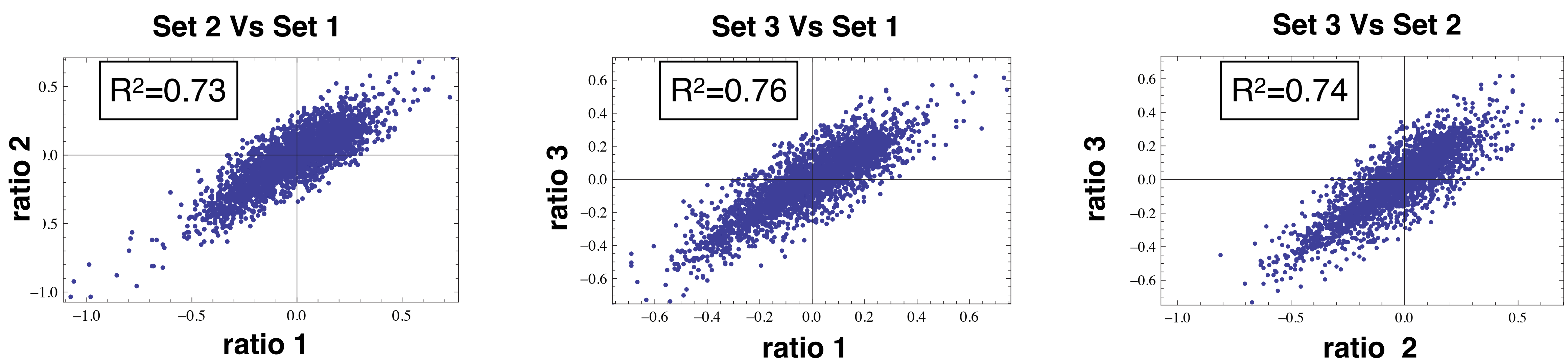


http://www.thermo.com

II. Dynamics:Data Analysis Framework

- (1) Data Preprocessing: Proteome

Tracking Different Timepoints with Chemical Labeling (TMT 6plex)

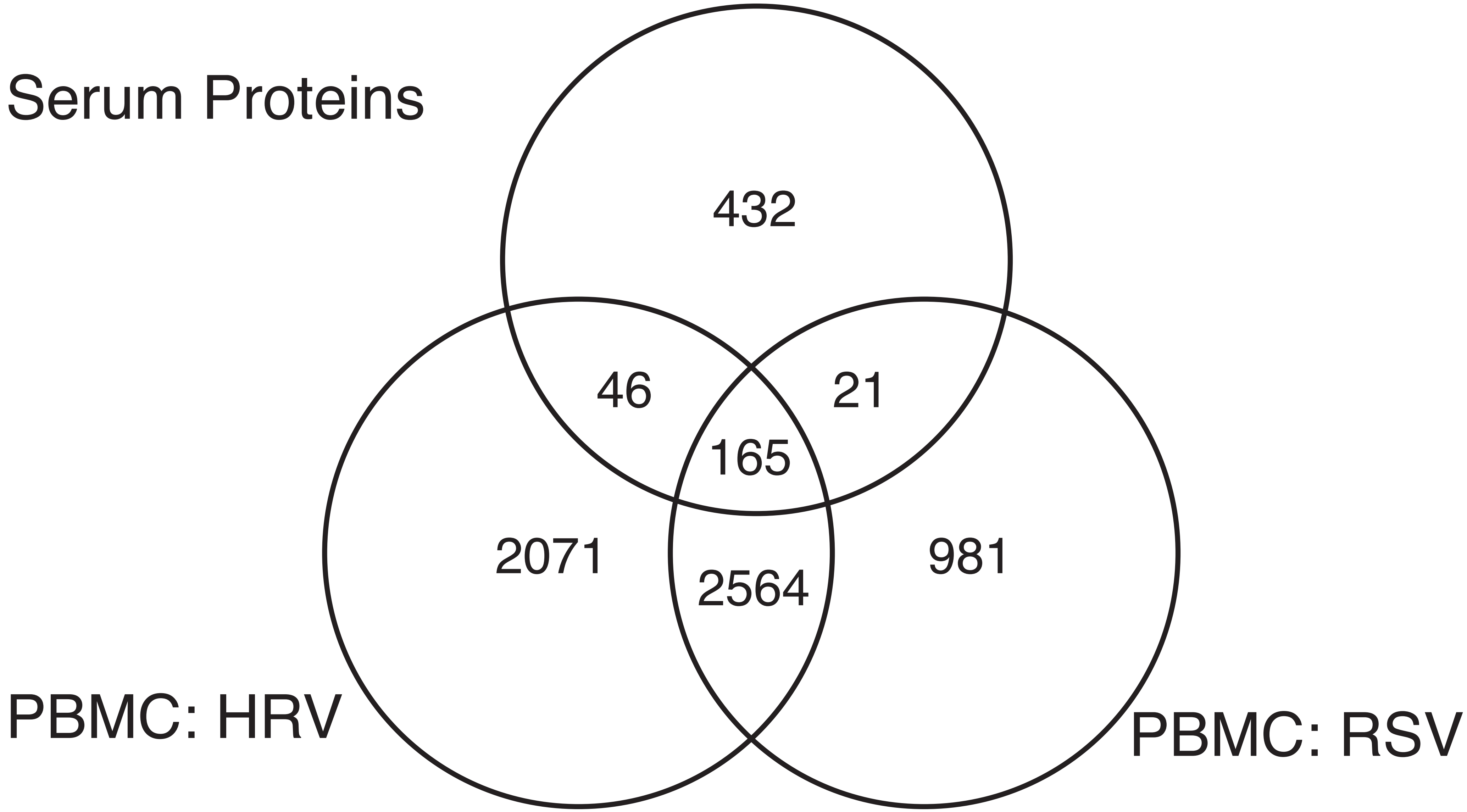


- Common reference ratio
  - Reproducible
  - Sets can be combined: 3,731 proteins followed over 14 timepoints

Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

II. Dynamics:Data Analysis Framework

- (1) Data Preprocessing: Proteome



Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

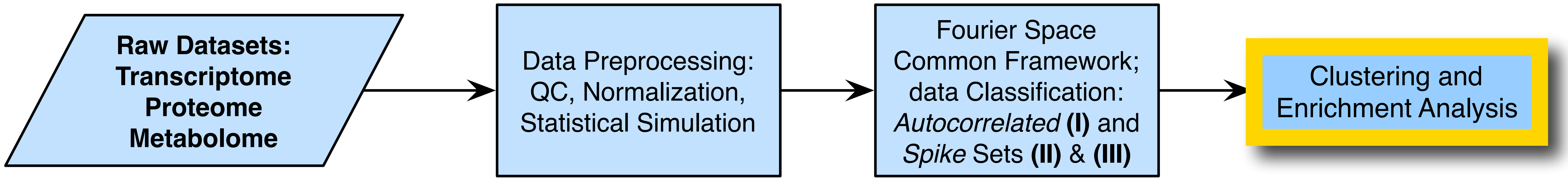
II. Dynamics:Data Analysis Framework

- (2) Common Framework Data Classification

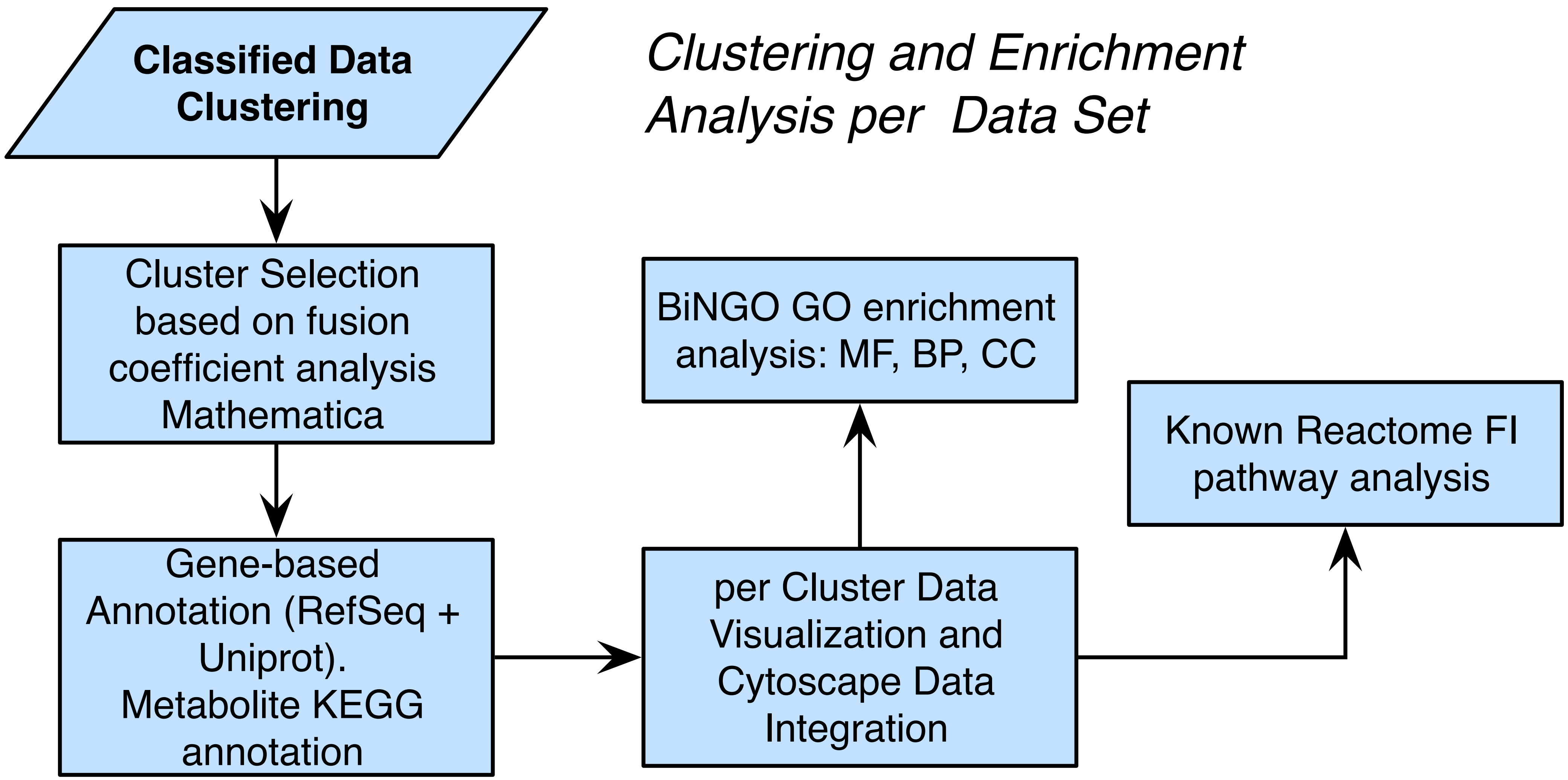
	Transcriptome (HRV+RSV)	Proteome (RSV)	Metabolome (RSV)
Total	19714	3731	4228
Autocorr	4922	257	475
Spike Max	3718	1240	577
Spike Min	7891	1194	884

Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

II. Dynamics:Data Analysis Framework



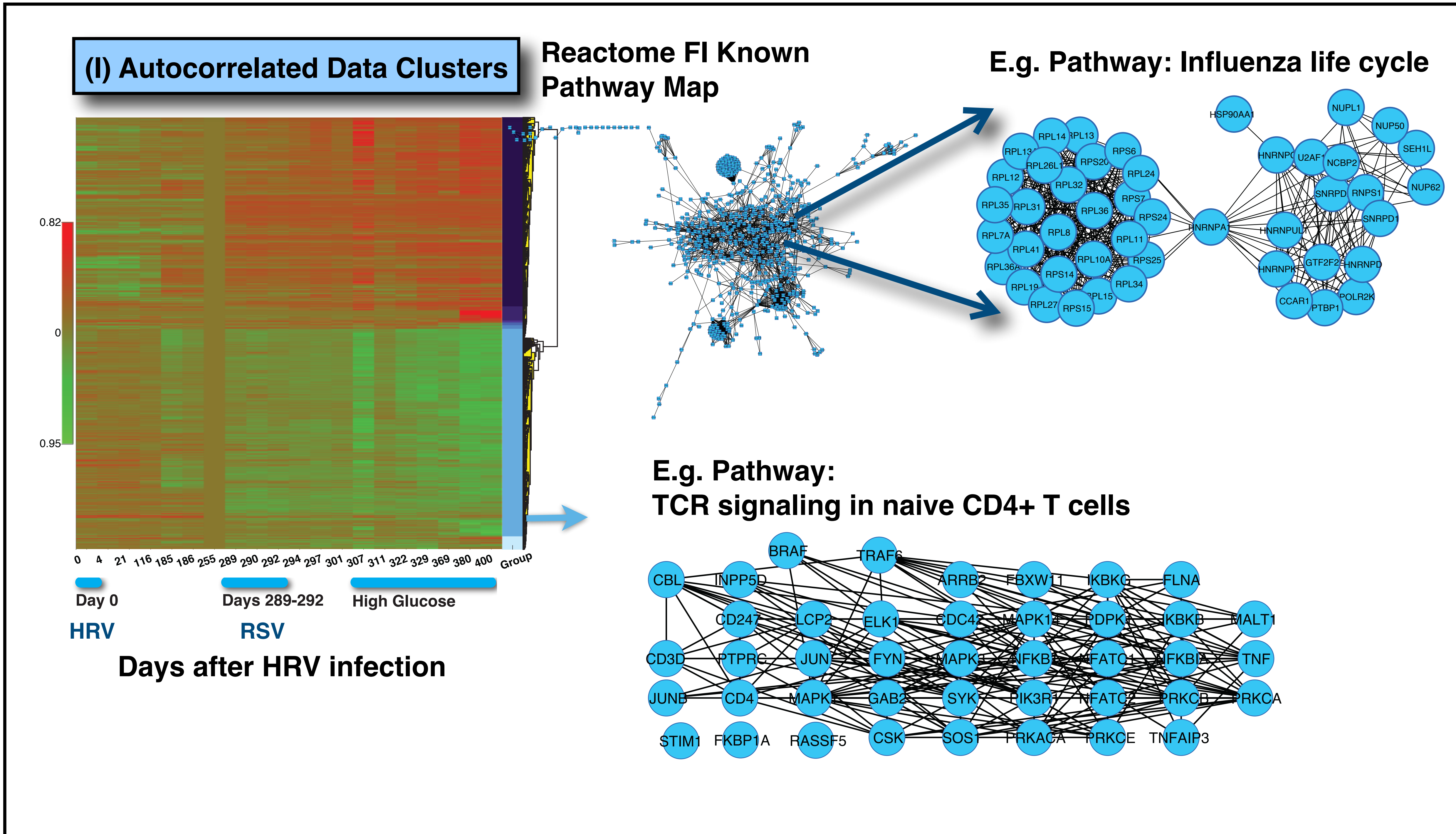
Clustering and Enrichment Analysis per Data Set



Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

III. Dynamics:Transcriptome

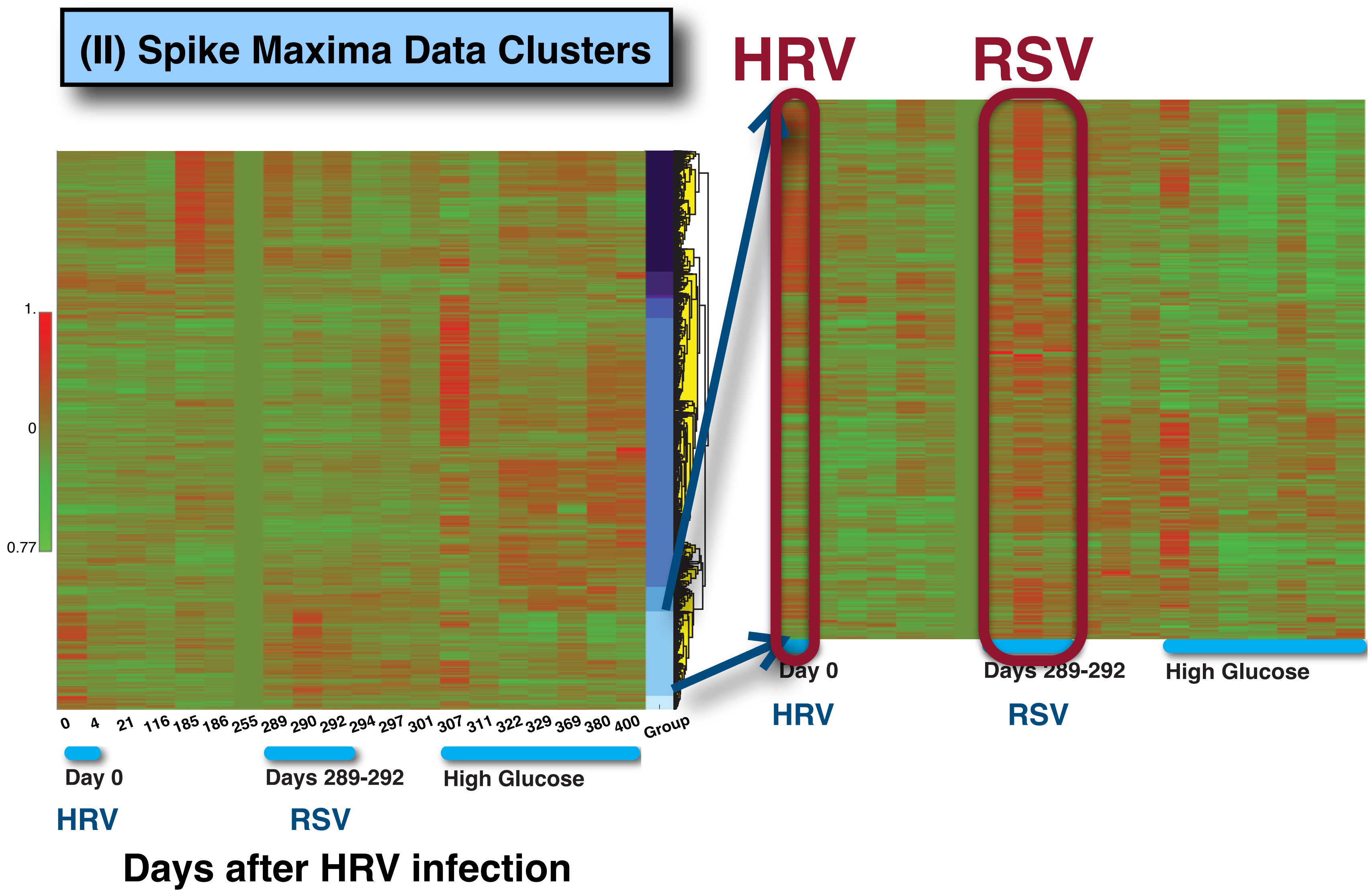
- (3) Clustering and Enrichment Analysis



Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

III. Dynamics:Transcriptome

- (3) Clustering and Enrichment Analysis



Gene Ontology analysis, $7x10^{-3} > p > 5x10^{-12}$

antigen processing and presentation
immune system process
immune response
antigen processing & presentation of peptide or polysaccharide antigen via MHC class II defense response
inflammatory response

E.g. Pathway analysis, FDR < $1x10^{-3}$

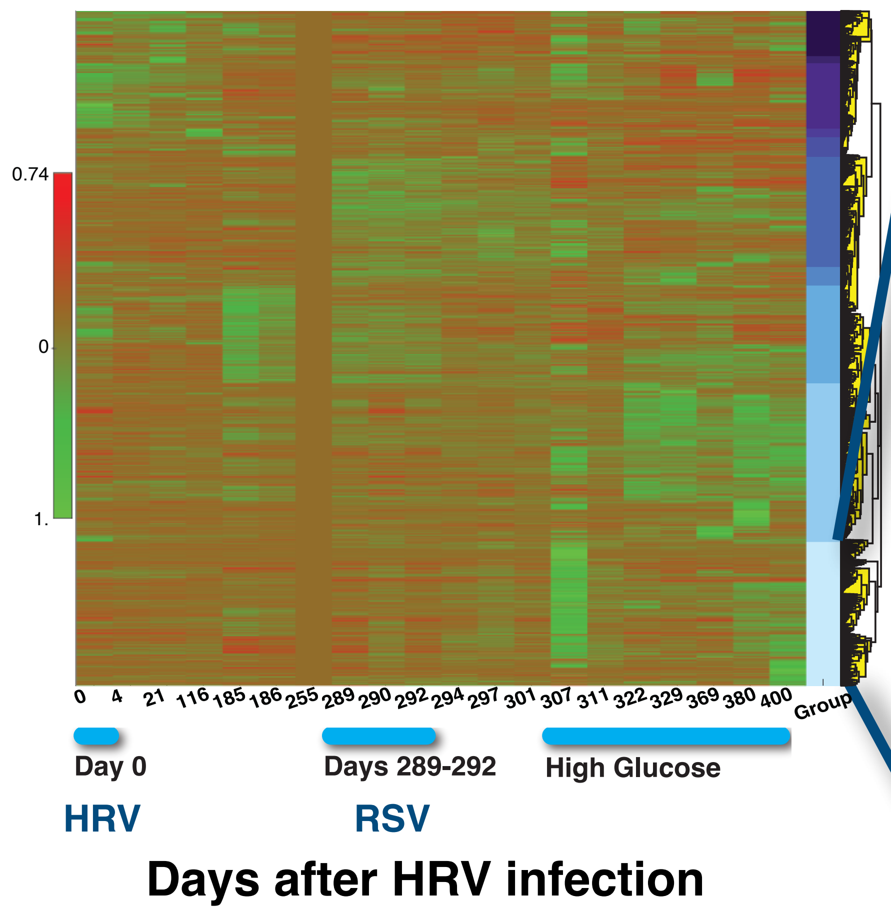
Allograft rejection(K)
Intestinal immune network for IgA production(K) Graft-versus-host disease(K)
Type I diabetes mellitus(K)
Phagosome(K)
Asthma(K)
Autoimmune thyroid disease(K)
Viral myocarditis(K)
Endocytosis(K)
Fc gamma R-mediated phagocytosis(K)

Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

III. Dynamics:Transcriptome

- (3) Clustering and Enrichment Analysis

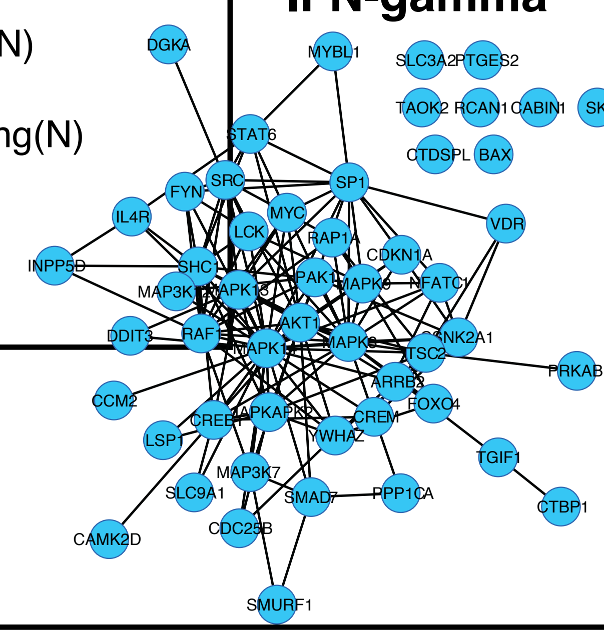
(III) Spike Minima Data Clusters



E.g. Pathway analysis, FDR < $1x10^{-3}$

TCR signaling in naive CD4+ T cells(N)
Signalling by NGF(R)
TRAIL signaling pathway(N)
p75(NTR)-mediated signaling(N)
TNF receptor signaling pathway(N)
Glypican pathway(N)
Neurotrophin signaling pathway(K)
IL1-mediated signaling events(N)
T cell receptor signaling pathway(K)
TCR signaling in naive CD8+ T cells(N)
Plasma membrane estrogen receptor signaling(N)
Proteogylcan syndecan-mediated signaling events(N)
EphrinB-EPHB pathwayN)
Trk receptor signaling mediated by PI3K and PLC-gamma(N)
BMP receptor signaling(N)
Regulation of cytoplasmic and nuclear SMAD2/3(N)
TGF-beta receptor signaling(N)
Neurotrophic factor-mediated Trk receptor signaling(N)
Insulin signaling pathway(K)
IFN-gamma pathway(N)
p38 signaling mediated by MAPKAP kinases(N)
BCR signaling pathway(N)

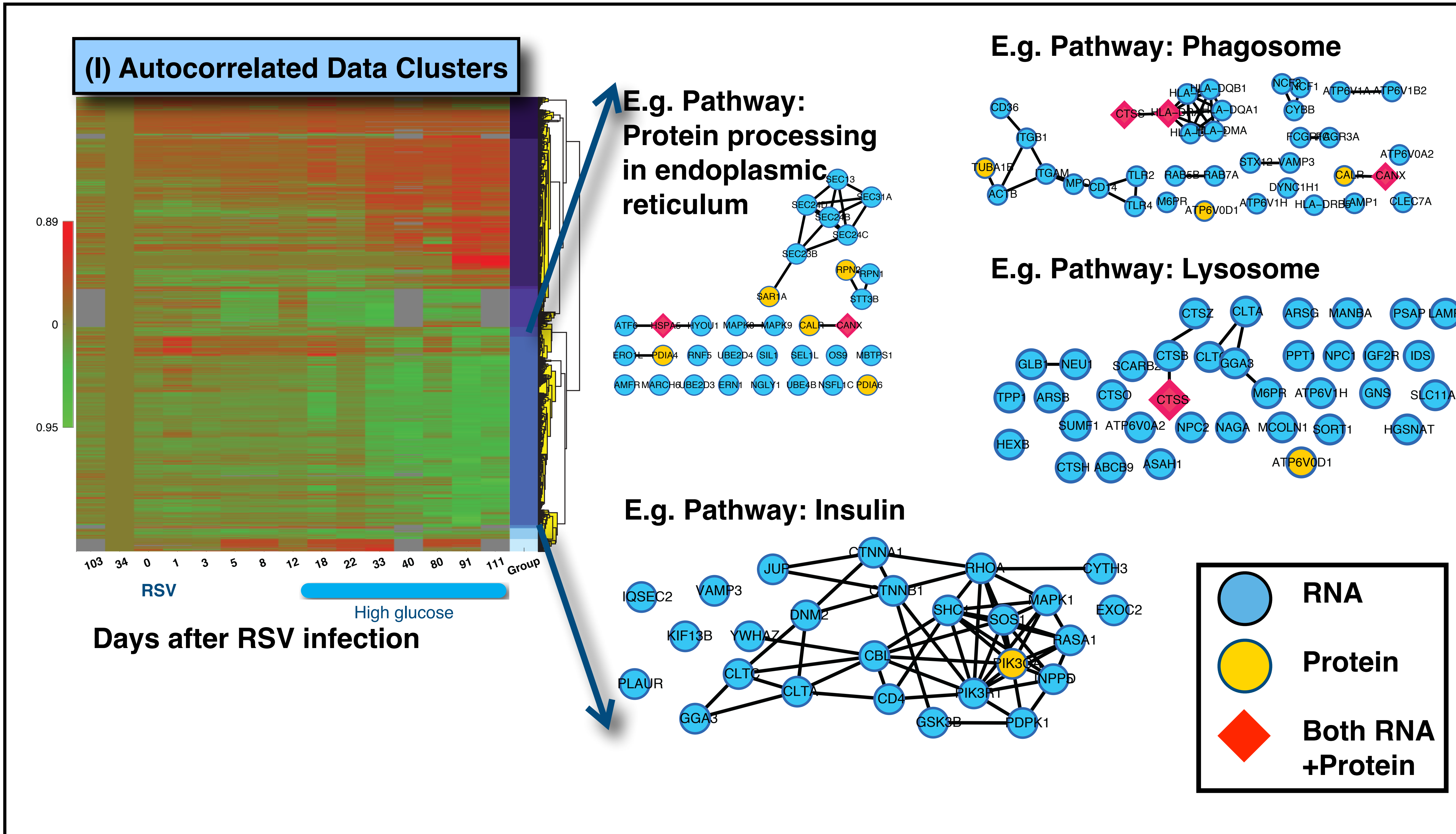
E.g. Pathway: IFN-gamma



Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

III. Dynamics:Integrated Omics

- (3) Clustering and Enrichment Analysis

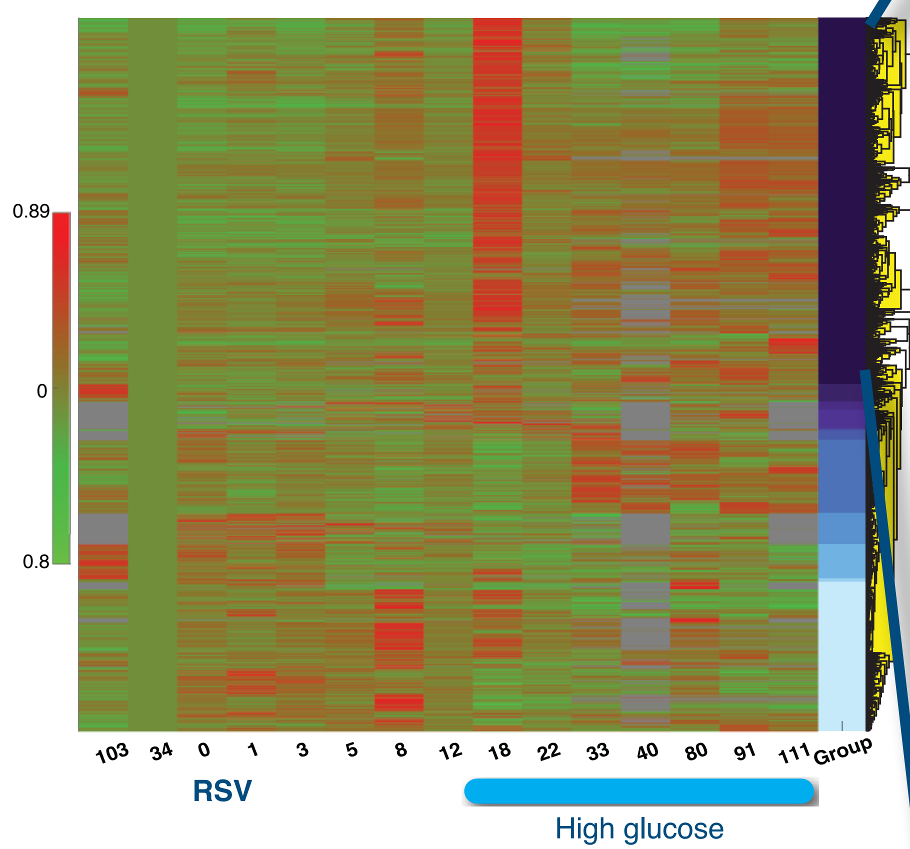


Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

III. Dynamics:Integrated Omics

- (3) Clustering and Enrichment Analysis

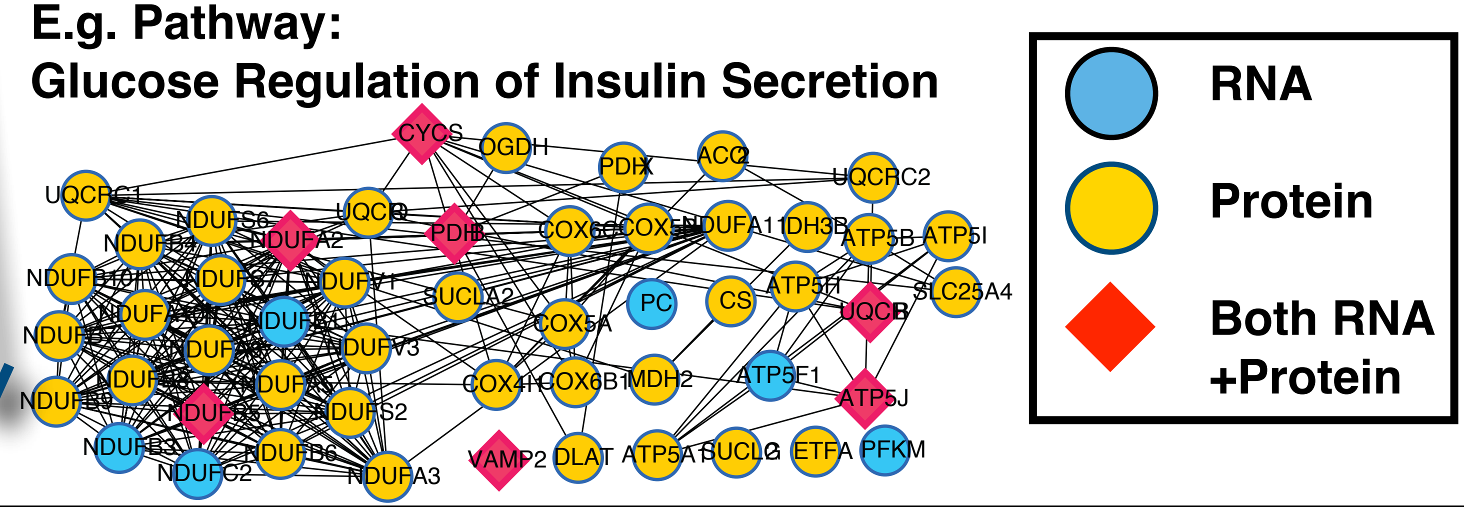
(II) Spike Maxima Data Clusters



Days after RSV infection

E.g. Pathway Analyses, FDR <5x10^{-2}	E.g. Metabolites in Cluster
Spliceosome(K) Glucose Regulation of Insulin Secretion(R) Formation and Maturation of mRNA Transcript(R) Oxidative phosphorylation(K) Electron Transport Chain(R) Parkinson's disease(K) Huntington's disease(K) Influenza Life Cycle(R) Metabolism of non-coding RNA(R) Transport of Mature Transcript to Cytoplasm(R) Protein export(K) Pyruvate metabolism and TCA cycle(R)	3R-hydroxy-5Z-dodecenoic acid 5,6-DiHETrE-EA 7-Ethoxycoumarin **Lauric acid** 1-O-(1Z-tetradecenyl)-2-(9Z-octadecenoyl)-sn-glycerol 1alpha-hydroxy-26,27-dinorvitamin D3 25-carboxylic acid / 1alpha-hydroxy-26,27-dinorcholecalciferol 12-oxo-9-octadecynoic acid GPCho(O-16:0/O-4:0[U]) 19-hydroxy-17-oxoandrost-5-en-3-beta-yl sulfate - 11.538899

E.g. Pathway:
Glucose Regulation of Insulin Secretion

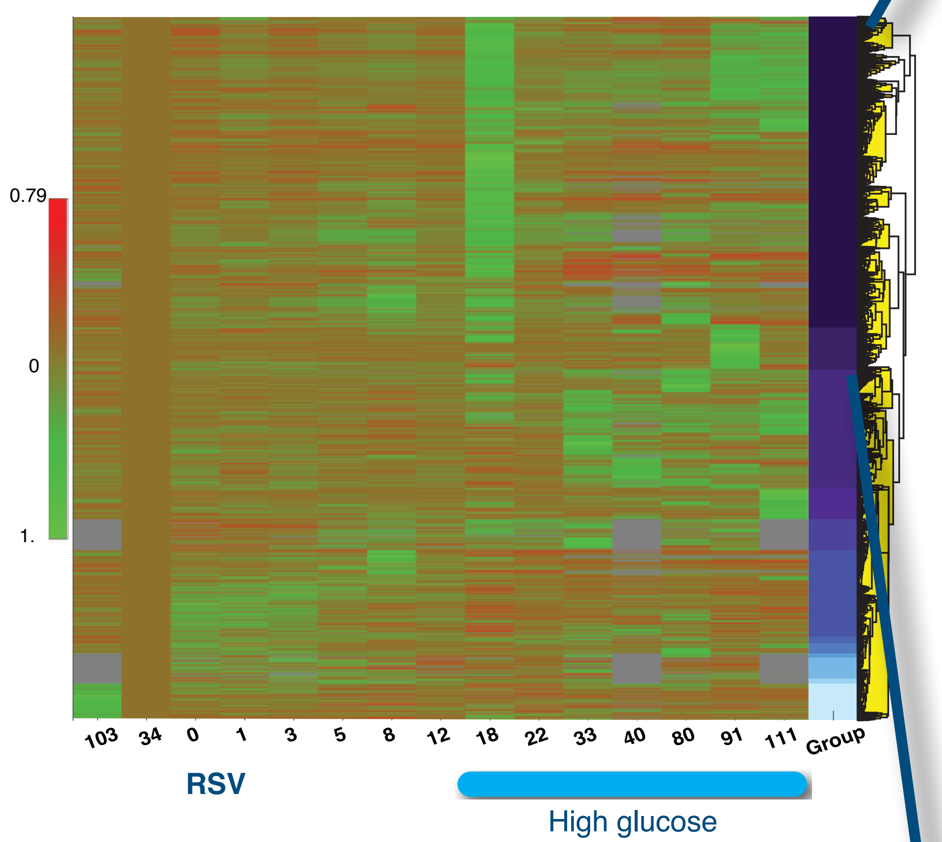


Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

III. Dynamics:Integrated Omics

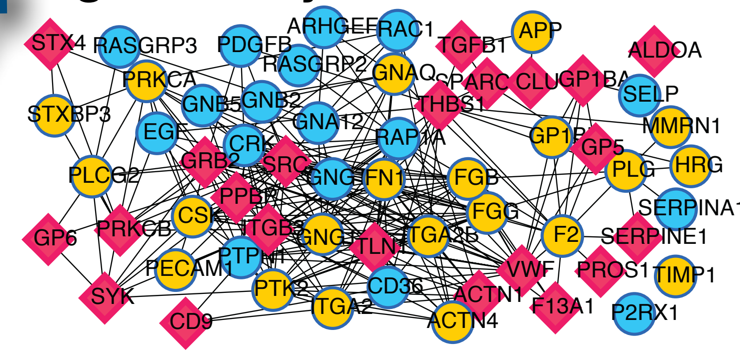
- (3) Clustering and Enrichment Analysis

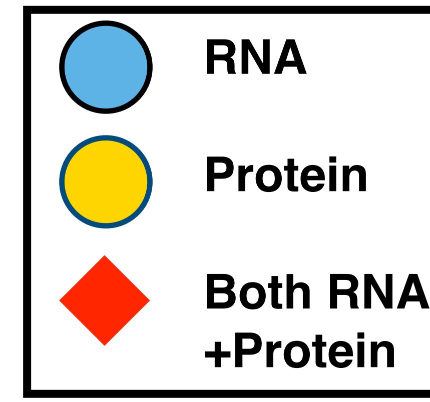
(III) Spike Minima Data Clusters



Days after RSV infection

E.g. Pathway: Formation of Platelet Plug





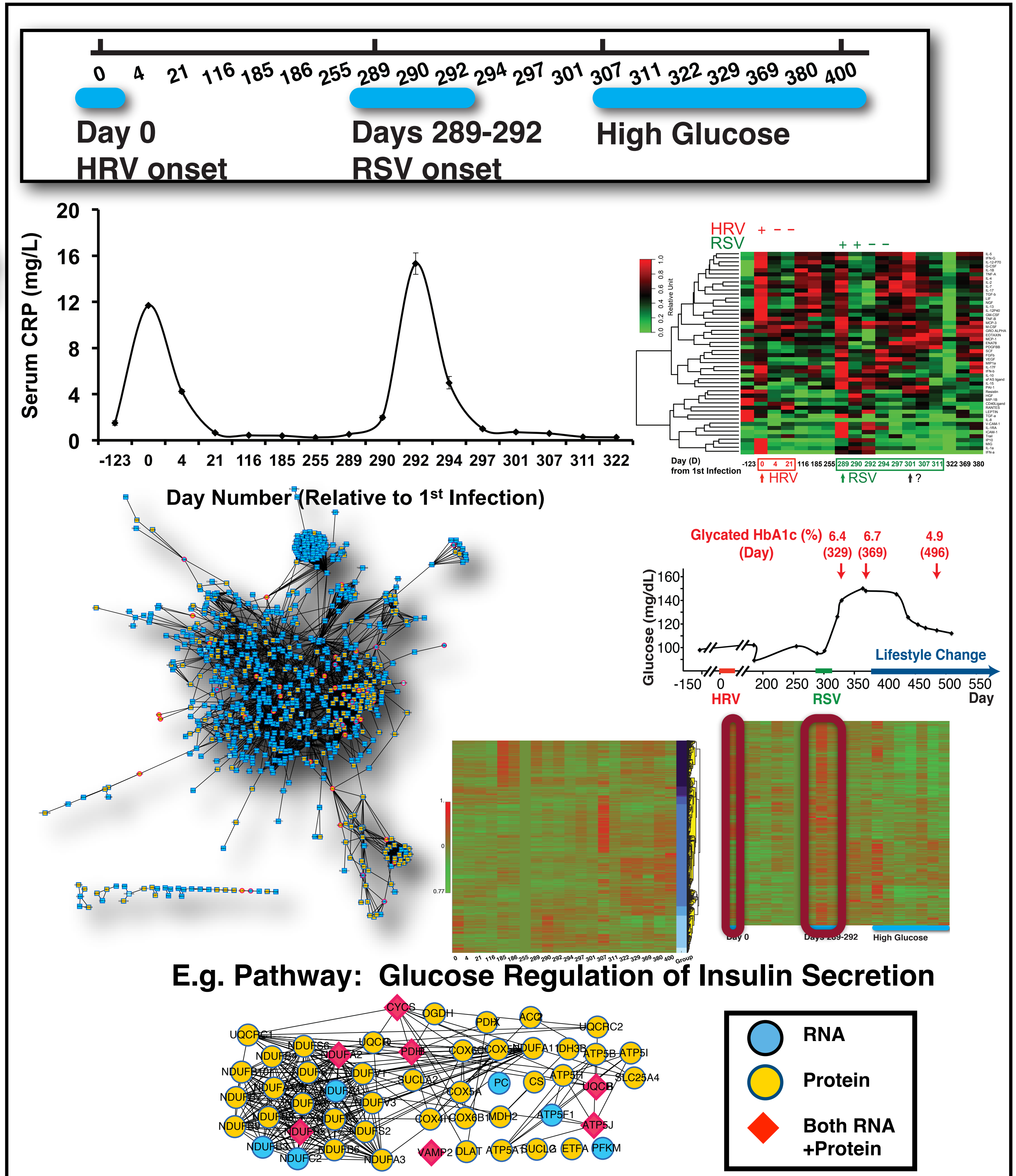
E.g. Pathway Analyses, FDR <5x10^{-2}	E.g. Metabolites in Cluster
TRAIL signaling pathway(N)	4,8,12,15,19,21-tetracosahexaenoic
Class I PI3K signaling events(N)	acid
Formation of Platelet plug(R)	Idebenone Metabolite
Glypican pathway(N)	p-Cymene
TNF receptor signaling pathway(N)	Cer(d18:0/24:0)
Signaling by NGF(R)	Normetanephrine sulfate
p75(NTR)-mediated signaling(N)	gamma-Hydroxyphenylbutazone
TCR signaling in naive CD4+ T cells(N)	glucuronide
Apoptosis(R)	Methoxyhydroxymethylhydrocinnamic acid
IGF1 pathway(N)	5,8-Dihydroxy-3,4-dihydrocarbostyril
Arf6 signaling events(N)	3-Methylsuberic acid - 7.6812496
Insulin Pathway(N)	5-Methyltetrahydropteroyltri-Lglutamate
IFN-gamma pathway(N)	3-keto palmitic acid - 12.719786
Signaling by Wnt(R)	Cholylglycine
Neurotrophin signaling pathway(K)	Protoporphyrin + 12.516361
IL2- & IL1 mediated signaling events(N)	Desmethyldehydroamlodipine
Fc gamma R-mediated phagocytosis(K)	Chenodeoxycholyltaurine

Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).

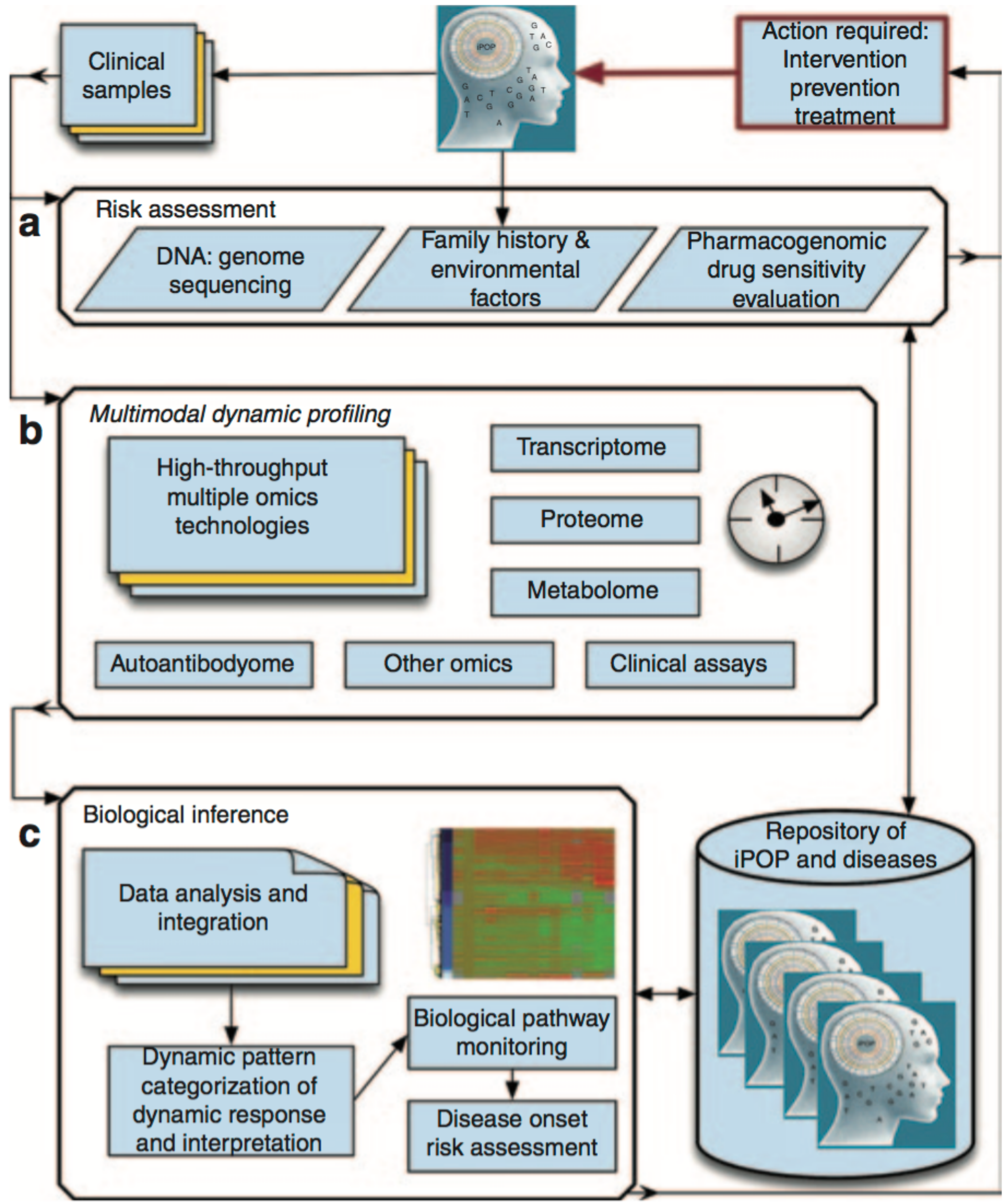
Precision Medicine

- Personalized
  - Determine risks
  - Monitor
  - Integrate

Mias and Snyder, Quantitative Biology 1(1) p. 71 (2013). Chen*, Mias*, Li-Pook-Than*, Jiang* et al Cell 148,1293 (2012).



A Framework for Personalized & Precision Medicine



Mias & Snyder, Clinical Pharmacology and Therapeutics 93, p29 (2013)