2nd International Electronic Conference on Metabolomics
20-27 November 2017
chaired by Dr. Peter Meikle
sponsored by metabolites

Clinical Metabolomics: An Integral Tool Driving Patient Phenotyping in Precision Medicine.

Vladimir Tolstikov, Ph.D. [1,*]

[1] Director of Metabolomics, BERG LLC, Framingham, MA 01701, U.S.A.

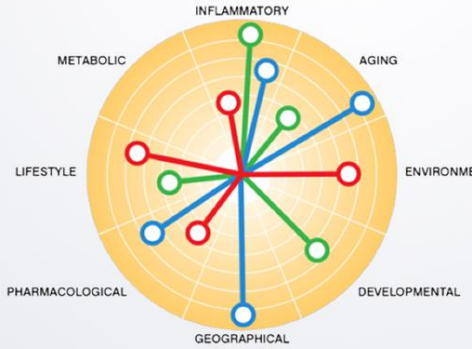
* Corresponding author: vladimir.tolstikov@berghealth.com

Clinical Metabolomics: An Integral Tool Driving Patient Phenotyping in Precision Medicine.

Deep Biological Assessment: Phenomics

Environmental Influence

Genome	Transcriptome	Proteome (Including PTM)	Metabolome/Lipidome
(~30,000 genes)	*(~10^5 RNA transcripts)*	*(10^5 proteins)*	*(1,000's Metabolites/Lipids)*
Phenome	Population Variation/Molecularly Signature of Co-Morbidities		Population Molecular Diversity



BERG

IECM
2nd International Electronic Conference on Metabolomics
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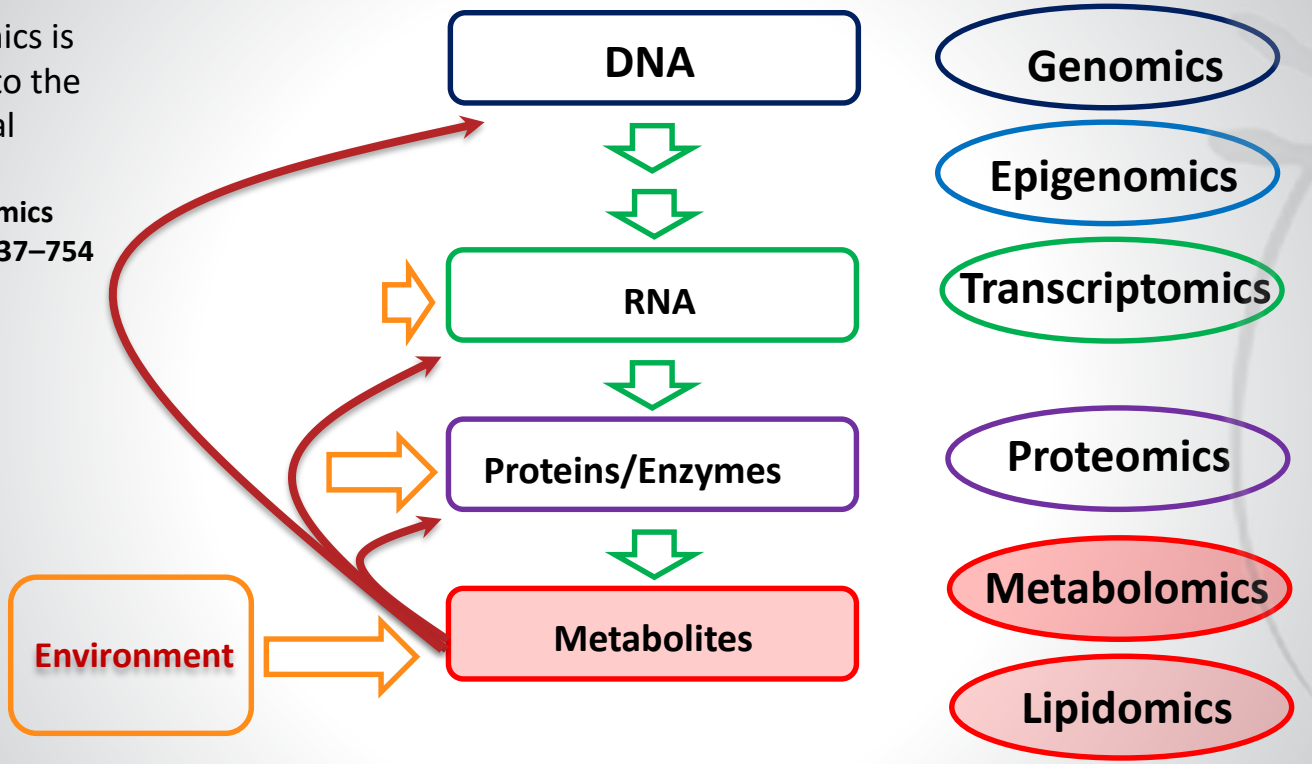
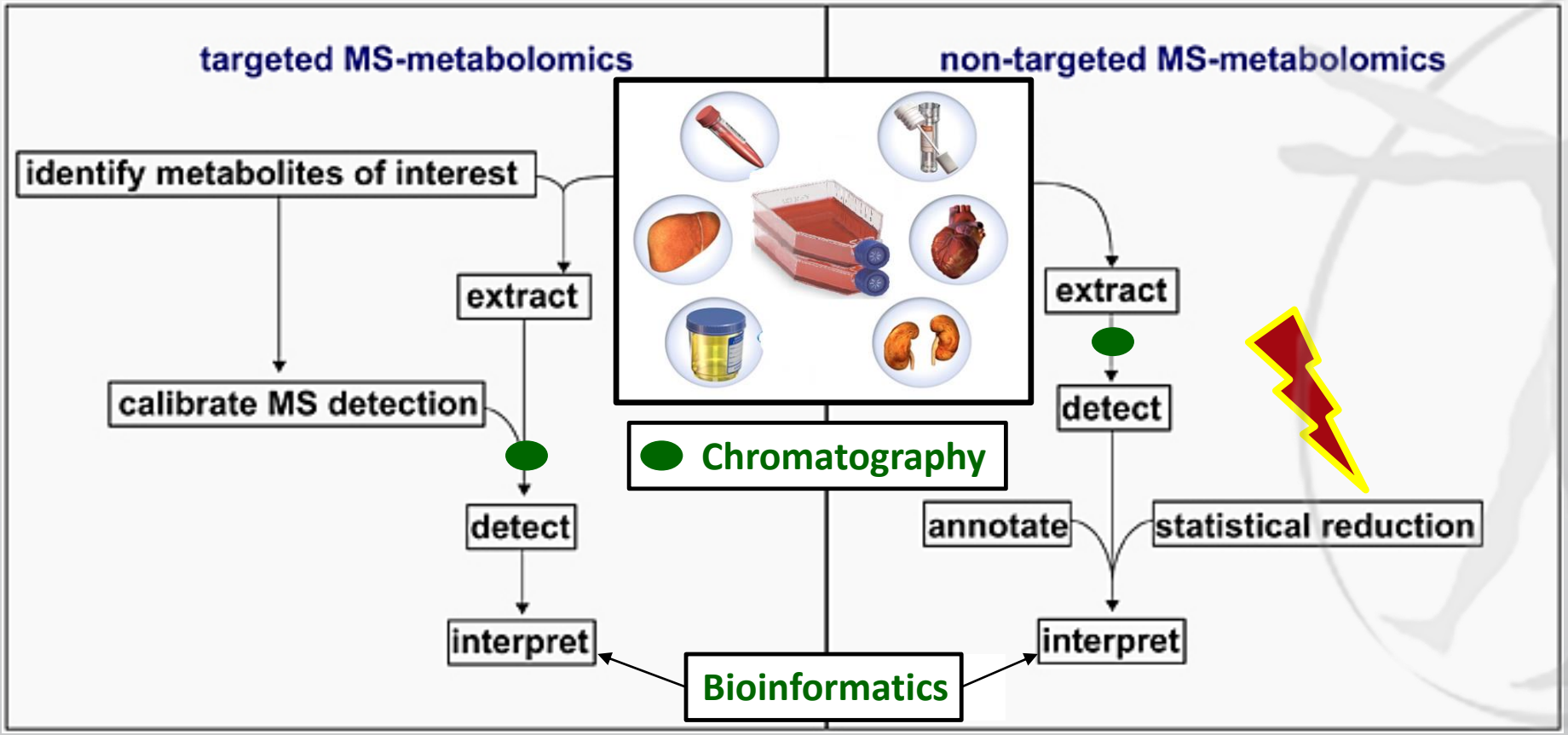
sponsors: MDPI metabolites

Abstract: Precision medicine is experiencing rapid growth and acceptance in the health-care landscape as a driving force for the future of medicine and is defined by the development of treatment strategies that are tailored to groups of patients based on specific biomarkers. Current precision medicine driven clinical trials assign patients to therapies based on the genetic alterations that are thought to be driving their diseases/cancers. BERG has validated the vision of Interrogative Biology® Platform to understand patients by “phenotype” rather than “genotype” by integrating molecular data directly from a patient with clinical and demographic information to develop artificial intelligence driven clinical trials. BERG is applying Bayesian causal inference to deconvolute unstructured clinical and molecular data and integrate this into models with cause and effect relationships that infers the health status of patients and outcome driven trials At BERG, we have implemented an industrial level high throughput metabolomics platform providing both high quality and depth of information allowing for reliable and broadest capture of the metabolome for the pre-clinical and clinical matrices analyzed. Highlights of the BERG’s in-depth patient stratification approach as well as a route of complementary biomarker discovery will be presented.
Keywords: biomarker; phenotype; omics; clinical; stratification.

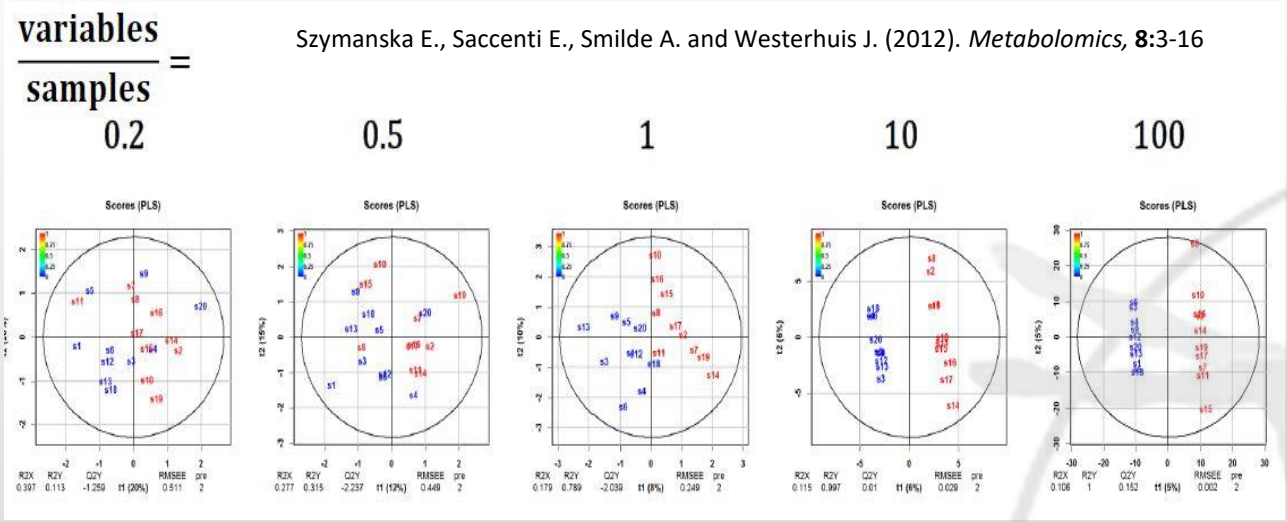
SYSTEMS BIOLOGY

…Pure genomics is almost blind to the environmental elements….
Pharmacogenomics (2015), 16(7), 737–754



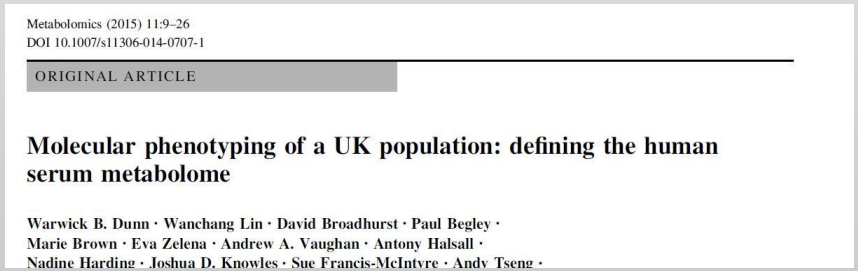


Systems-Level Annotation of a Metabolomics Data Set Reduces 25 000 Features to Fewer than 1000 Unique Metabolites
Nathaniel G. Mahieu and Gary J. Patti*
Department of Chemistry, Washington University, St. Louis, Missouri 63130, United States
Anal. Chem., Publication Date (Web): September 15, 2017. Copyright © 2017 American Chemical Society



Szymanska E., Saccenti E., Smilde A. and Westerhuis J. (2012). *Metabolomics,* **8**:3-16

…Ensemble methods like bagging and random forest are practical for mitigating both underfitting and overfitting, as we've seen with our regression and classification examples….
NATURE METHODS, Vol14, No.10, pp 933-934, October 2017



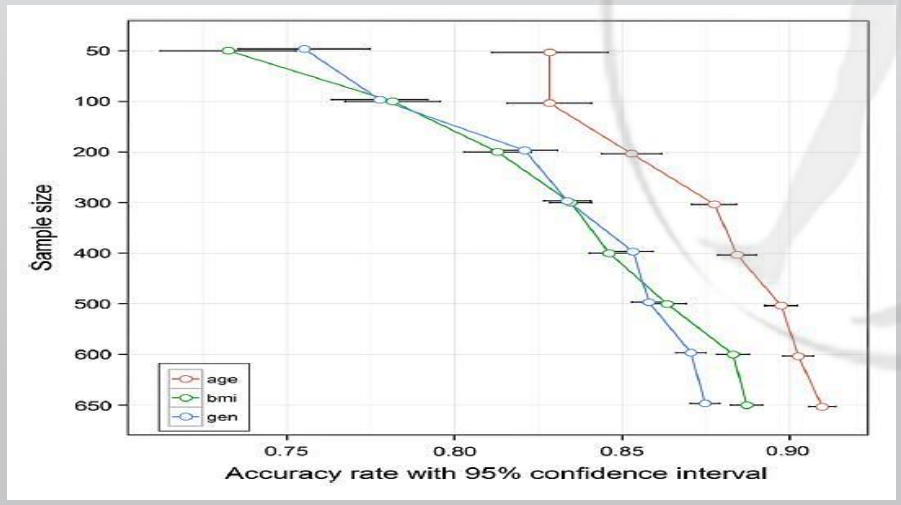
Metabolomics (2015) 11:9–26
DOI 10.1007/s11306-014-0707-1

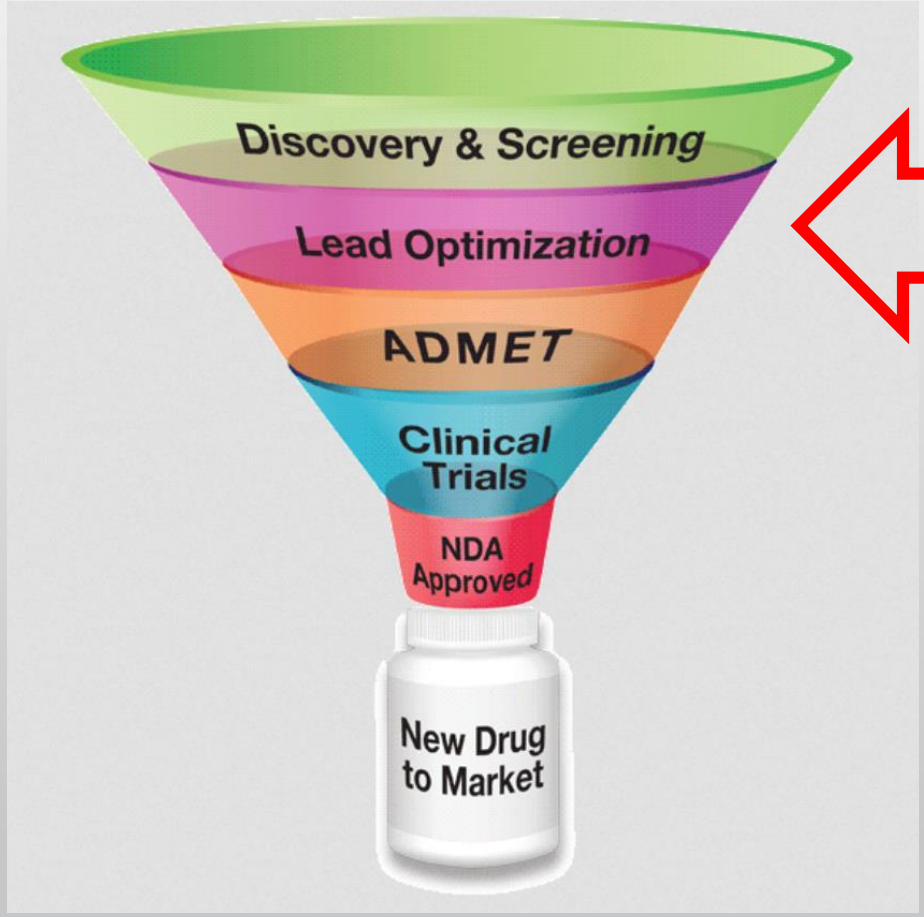
ORIGINAL ARTICLE

Molecular phenotyping of a UK population: defining the human serum metabolome

Warwick B. Dunn · Wanchang Lin · David Broadhurst · Paul Begley · Marie Brown · Eva Zelena · Andrew A. Vaughan · Antony Halsall · Nadine Harding · Joshua D. Knowles · Sue Francis-McIntyre · Andy Tseng ·

….. It is becoming increasingly evident that many biological studies are underpowered with regard to their ability to come to a robust and statistically significant and justifiable biological conclusion …..

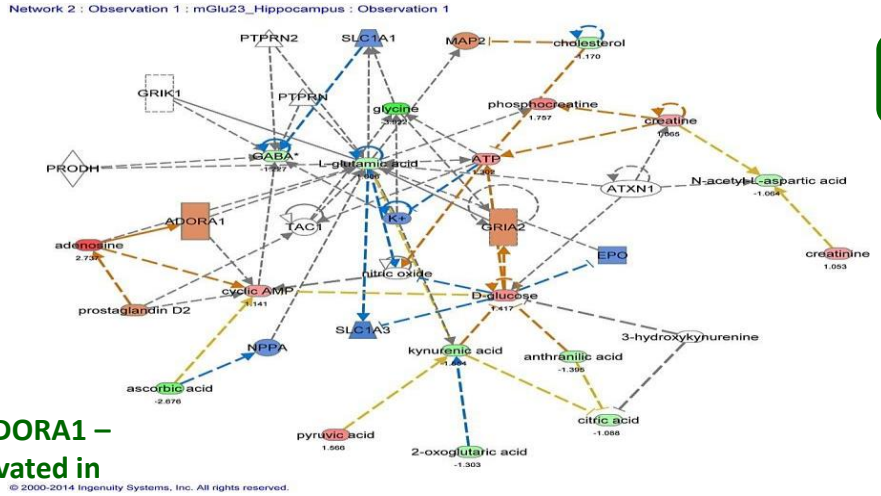




Metabolomics

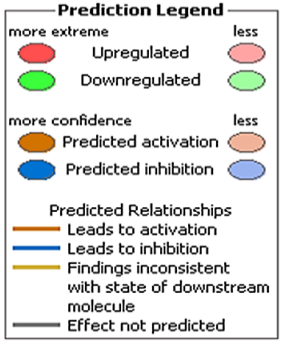
Metabolomics

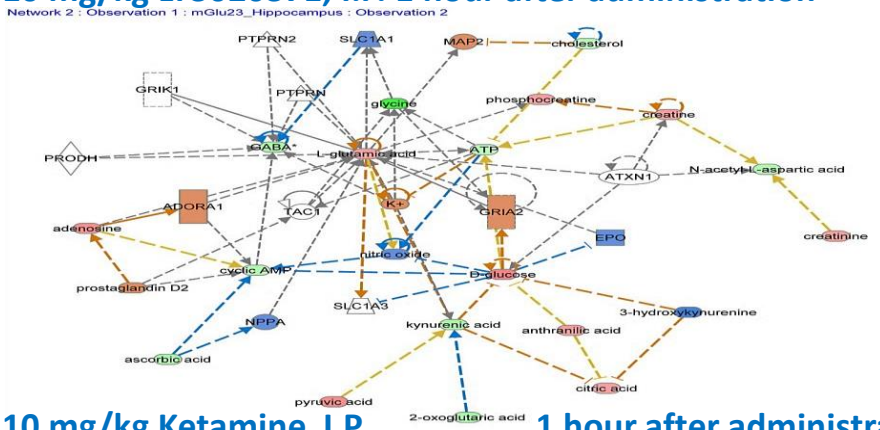
Metabolomics approaches to tackling MOA in preclinical animal study.



10 mg/kg LY3020371, I.P. 1 hour after administration

Common pathways - GRIA2(mGlu2/3) and ADORA1 – are predicted to be activated in Hippocampus.

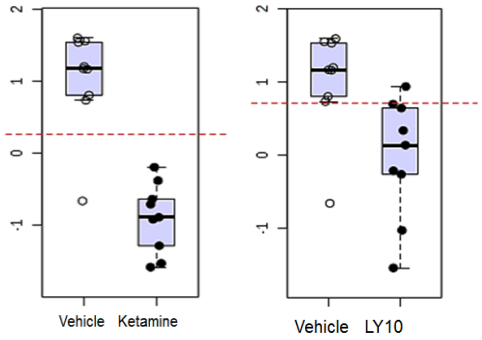




10 mg/kg Ketamine, I.P. 1 hour after administration

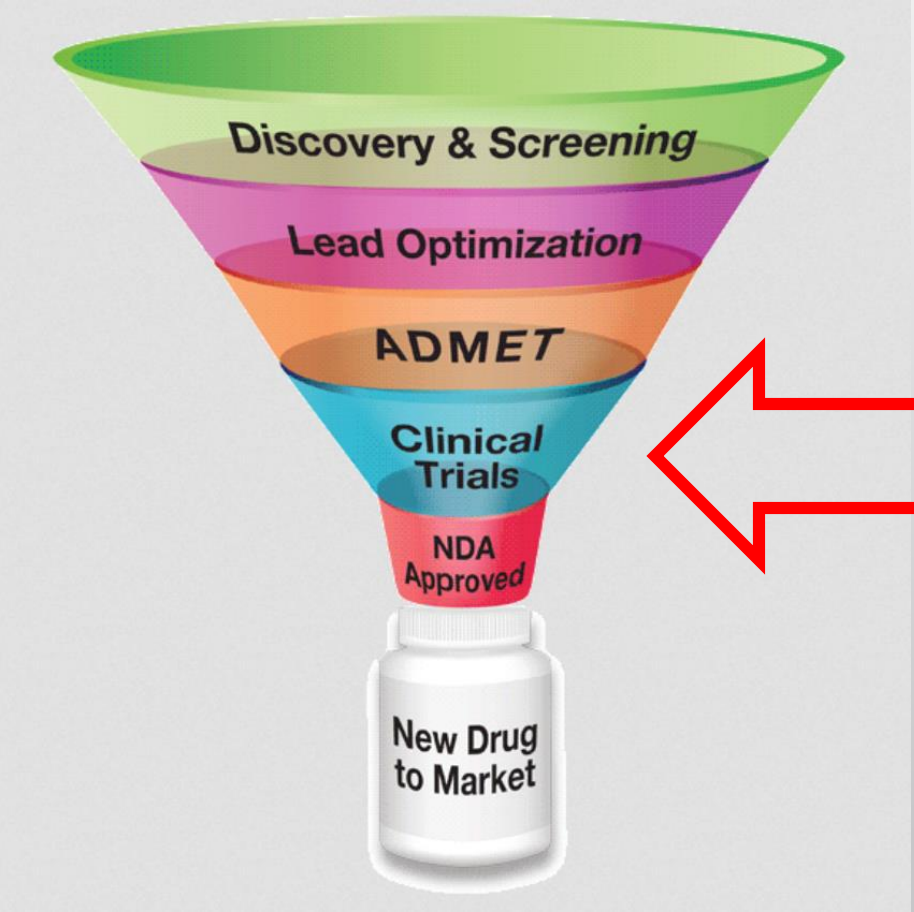
Common markers found in CSF

Hydroxyisocaproic acid/nicotinamide ratio in CSF 1 hour after administration



Comparative Effects of LY3020371, a Potent and Selective mGlu2/3 Receptor Antagonist, and Ketamine, a Non-Competitive NMDA Receptor Antagonist, in Rodents: Evidence Supporting Use for the Treatment of Depression.
Witkin JM, Mitchell S, Wafford K, et al.
***J Pharmacol Exp Ther*. 2017 Jan 30. doi: 10.1124/jpet.116.238121.**

Ketamine has been tested in treatment-resistant bipolar disorder, major depressive disorder, and people in a suicidal crisis in emergency rooms. *Wikipedia*



Multi-omics + AI

BERG has validated the vision of Interrogative Biology® Platform to understand patients by "phenotype" rather than "genotype" by integrating molecular data directly from a patient with clinical and demographic information to learn predictive patterns.

- **Use of adaptive multi-omics measurements (proteomics, lipidomics, and metabolomics protocols) in multiple bio-fluids to capture signatures of efficacy and adverse events during clinical trials.**
- **Development of integrated data analytics to merge clinical phenotypes with OMICs signatures.**
- **Engaging the structure of clinical trial phases to streamline development of companion diagnostics for multiple aspects of the clinical trial for a unique precision medicine approach.**

TECHNOLOGY: INTEGRATED PHENOME ASSESSMENT

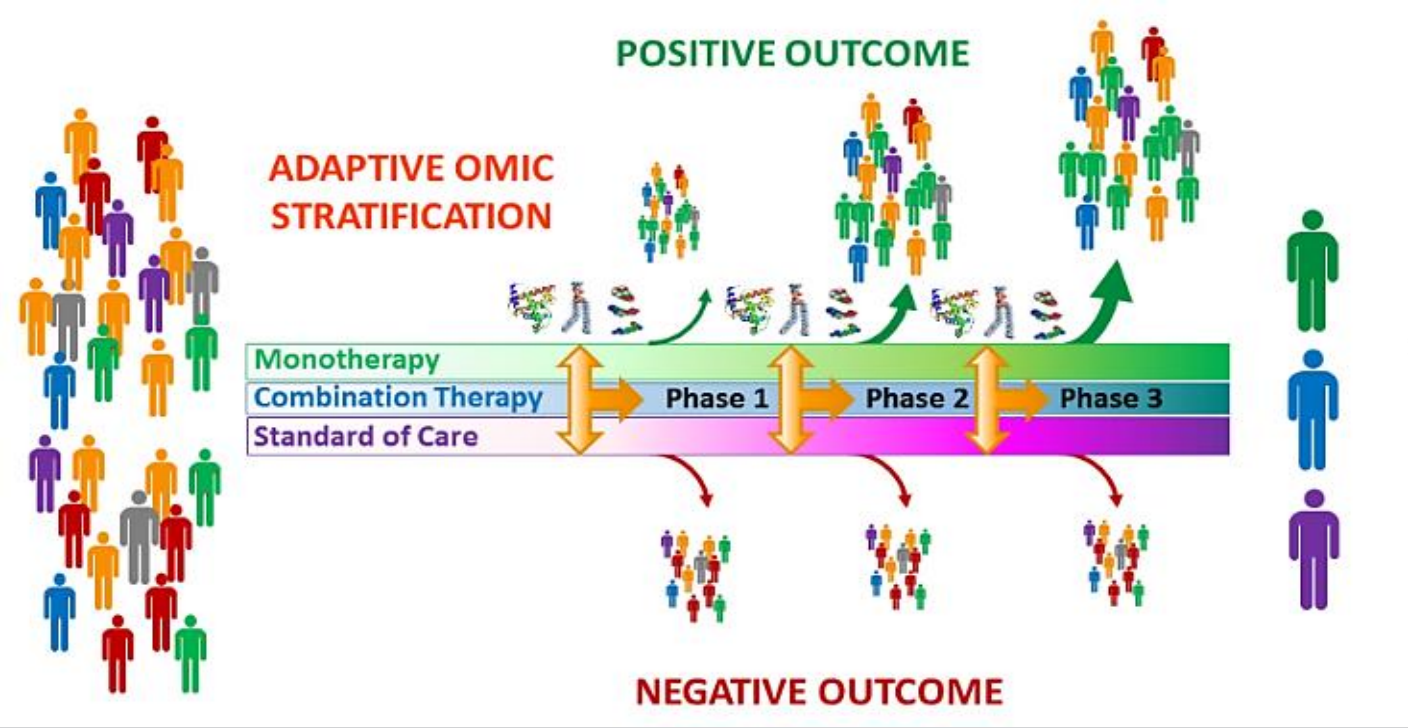
IN HOUSE MULTI-OMICS PROTOCOLS:

PROTEOMICS 400+ (BIO FLUIDS)
PTM 4000+ (TISSUE/CELLS)

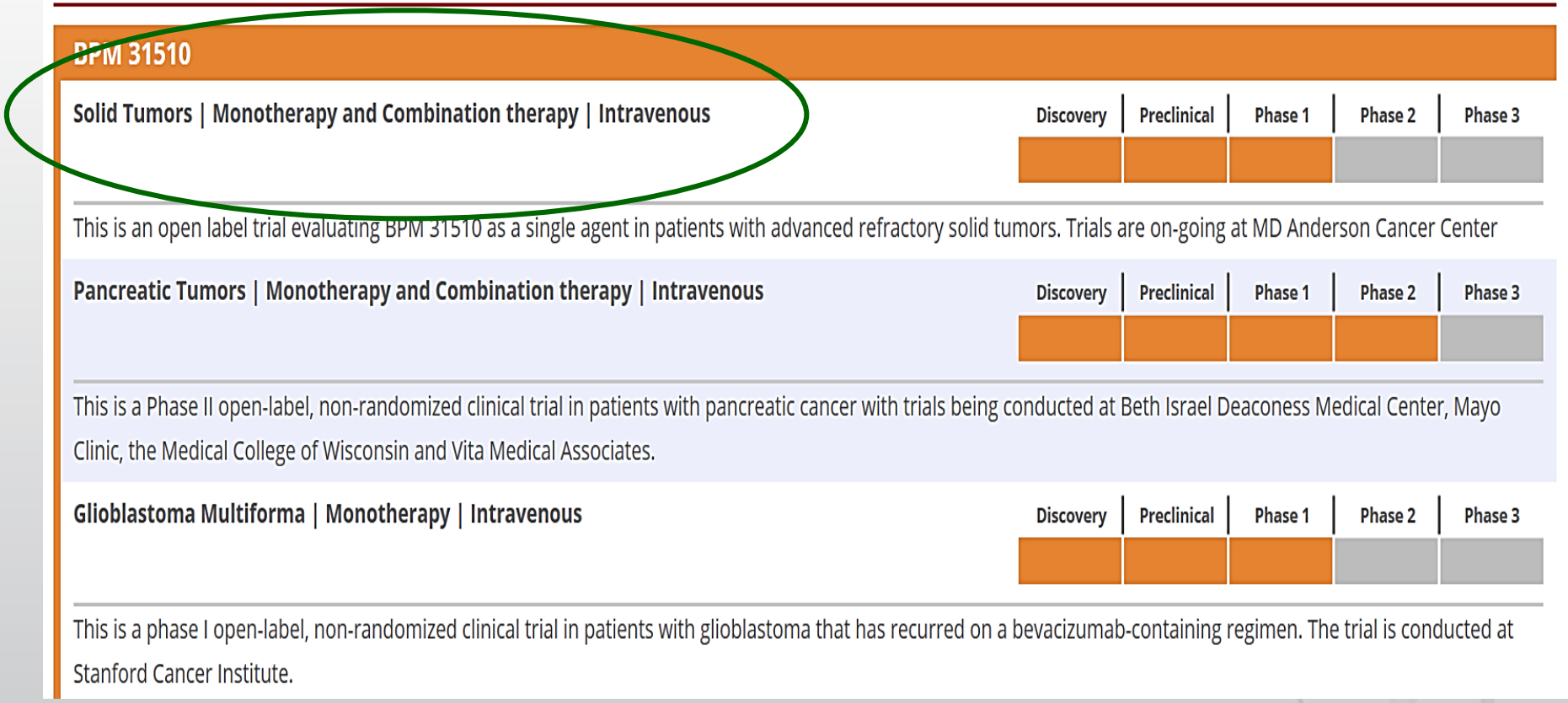
LIPIDOMICS 110+ OXIDIZED/MEDIATORS
1100+ STRUCTURAL

METABOLOMICS 600+ POLAR ENDOGENOUS METABOLITES

CAPABILITY ~ 6000 SAMPLES PER YEAR



Preclinical: Earlier biomarkers associated with MOA
Phase I: Biomarkers for Adverse Events
Phase II: Biomarkers for Efficacy
Phase III: Assessment of Utility of Biomarker Panel in Broader Population

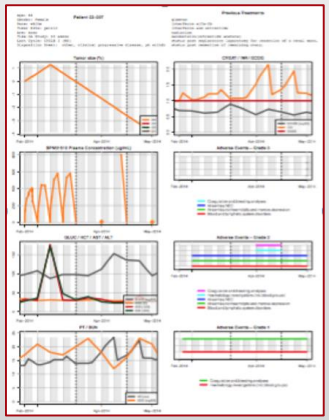


This is an open label trial evaluating BPM 31510 as a single agent in patients with advanced refractory solid tumors. This is a dose-finding trial currently on-going at the following clinical sites: Weill Cornell Medical College, MD Anderson Cancer Center, and Palo Alto Medical Center.

BERG AI CLINICAL INFORMATION SYSTEM

bAIcis™

Patient Dashboard



Longitudinal Molecular and Clinical Profile

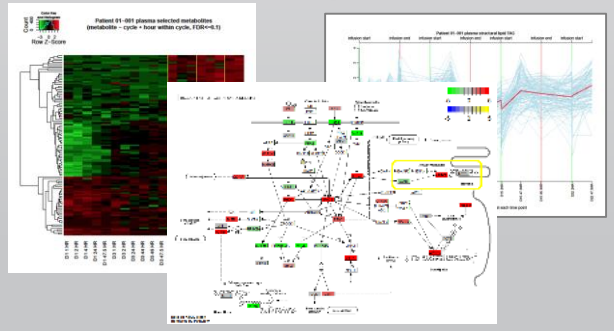
bAIcis™

Candidate CDx markers

Validation

Patient Stratification

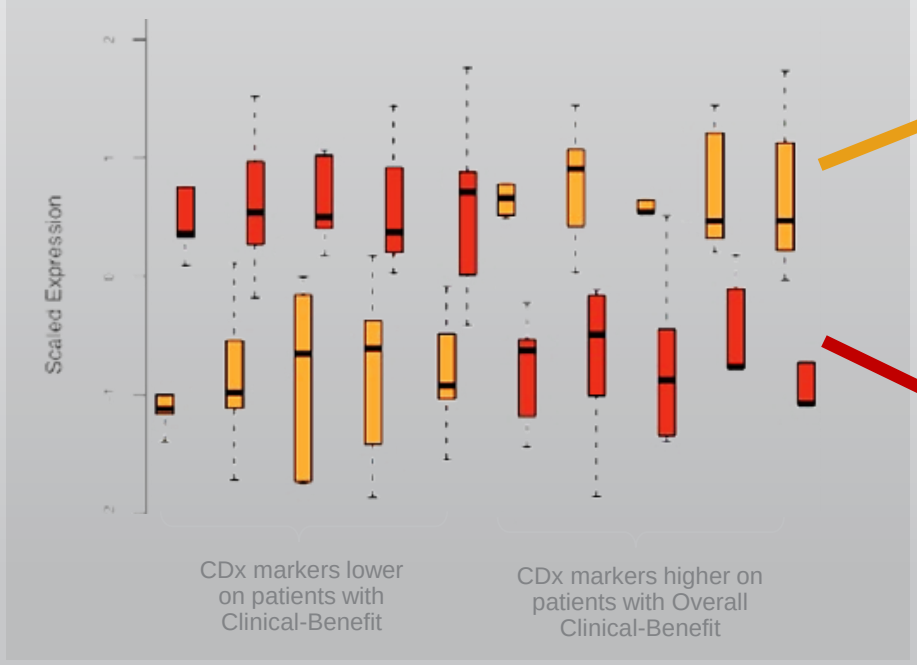
Statistical Analysis



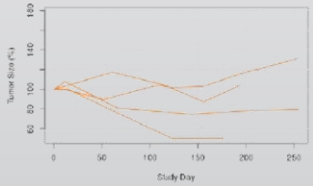
Cause-and-effect Networks

DECISION SUPPORT TOOLS TO HELP MANAGE PATIENT TREATMENT

Potential Top 10 Molecules In Blood Measured Before Initial Treatment That Potentially Predicts Benefit To BPM 31510 Treatment

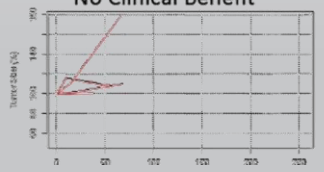


Overall Clinical Benefit



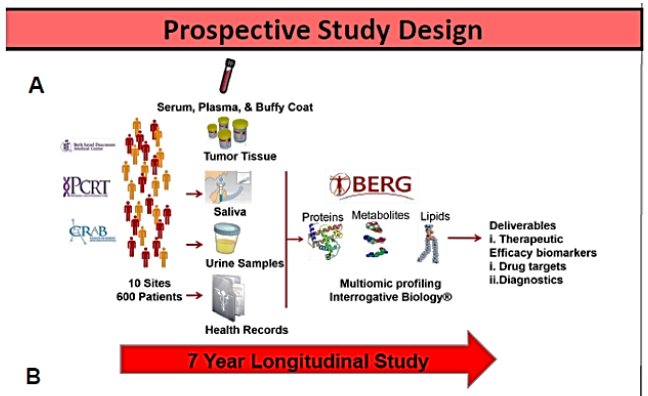
different tumor types

No Clinical Benefit



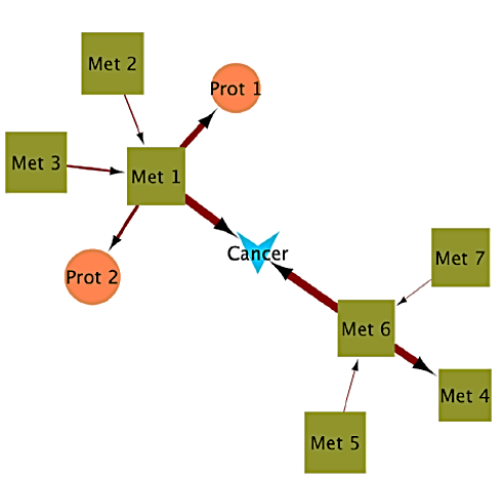
different tumor types

AACR 2017, #2769: Project Survival: Prospective Clinical Study Utilizing Multi-omics and Artificial Intelligence to Discover Novel Molecular Markers for Detection, Stratification, and Outcome in Pancreatic Cancer



Health Status/Tumor Type	Timepoints Collected per year	Enrollment Goal	Analyzed to Date
Healthy relative of Pancreatic cancer patient	1	50	30
Pancreatitis	2	50	14
Pancreatic cystic neoplasm	2	50	2
Suspected Pancreatic cancer but non Pancreatic	4	50	18
Early stage Pancreatic cancer	4	200	37
Borderline Pancreatic cancer or locally advanced	4		53
Metastatic Pancreatic cancer	6	200	10
	Total	600	164

Figure 1. Project Survival Workflow (A) and Study Design (B)



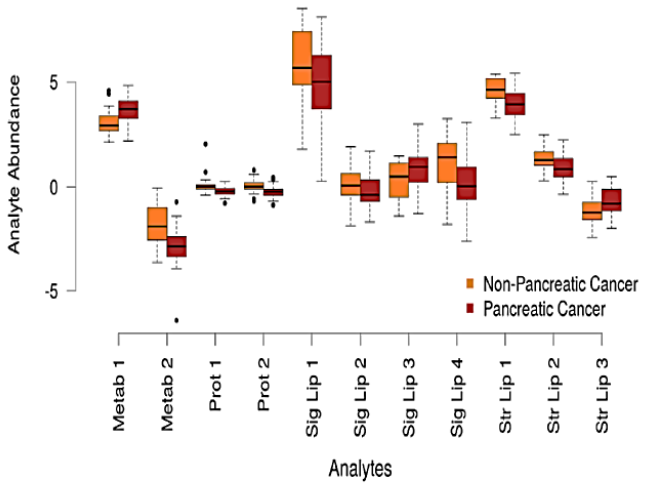


Figure 7. An Interim Cause-and-Effect Network Generated by bAIcis™ on the Current Dataset. Key molecular drivers of disease (Pancreatic Cancer) were identified from the bAIcis™ network. Network legend: Green Squares = Metabolite, Blue Vee= Outcome, Orange Circle = Protein.

Serum Biomarkers	AUC
Metab 1	0.782
Metab 2	0.759
Prot 1	0.77
Prot 2	0.766
Lipid 1	0.674
Lipid 2	0.592
Lipid 3	0.622
Lipid 4	0.632
Lipid 5	0.711
Lipid 6	0.748
Lipid 7	0.72

Utilizing the power of the Bayesian Network learner, bAIcisTM (BERG Artificial Intelligence Clinical Information System), multi-omics profiles were aligned to the longitudinal clinical information and subjected to the AI-algorithms that inferred probabilistic cause-and-effect relationships among molecular and clinical variables inferring markers of pancreatic cancer status and defining the interconnectivity of molecular features with clinical phenotype. Network features linking clinical endpoints and key network pressure points will be identified as molecular drivers.

Healthy Controls

The Problem:

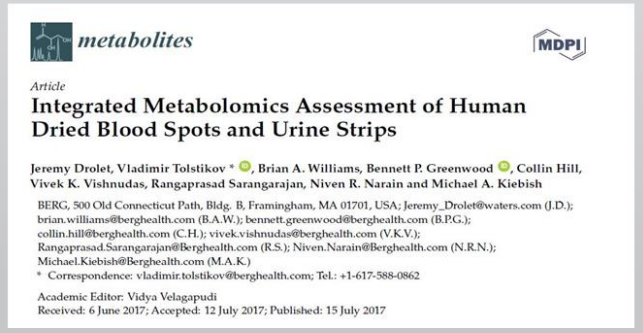
- Metabolic health assessment requires a visit to the clinic to measure ~20 different molecules that currently defines a patients metabolic health status
- There needs to be new approaches developed that 1) are cost effective, 2) allow patients to collect several samples at home when they feel sick, 3) are more stable than conventional blood collection, 4) collect ***100 times*** the information than traditional approaches

The Solution:

- Utilizing dried blood spots (DBS) [a technique used in newborn screening] and dried urine strips combined with metabolomics, shotgun lipidomics, and flux metabolomics analysis, we have demonstrated that these combined approaches can provide informative, stable, and economic solutions for population health assessment

Evidence:

- These studies have recently been published demonstrating the utility of these approaches for population health assessment


metabolites

MDPI

Article

Integrated Metabolomics Assessment of Human Dried Blood Spots and Urine Strips

Jeremy Drolet, Vladimir Tolstikov *, Brian A. Williams, Bennett P. Greenwood, Collin Hill, Vivek K. Vishnudas, Rangaprasad Sarangarajan, Niven R. Narain and Michael A. Kiebish

BERG, 500 Old Connecticut Path, Bldg. B, Framingham, MA 01701, USA; Jeremy_Drolet@waters.com (J.D.); brian.williams@berghealth.com (B.A.W.); bennett.greenwood@berghealth.com (B.P.G.); collin.hill@berghealth.com (C.H.); vivek.vishnudas@berghealth.com (V.K.V.); Rangaprasad.Sarangarajan@Berghealth.com (R.S.); Niven.Narain@Berghealth.com (N.R.N.); Michael.Kiebish@Berghealth.com (M.A.K.)

* Correspondence: vladimir.tolstikov@berghealth.com; Tel.: +1-617-588-0862

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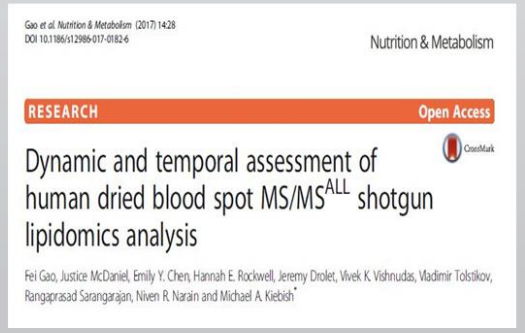

Gao et al. Nutrition & Metabolism (2017) 14:28

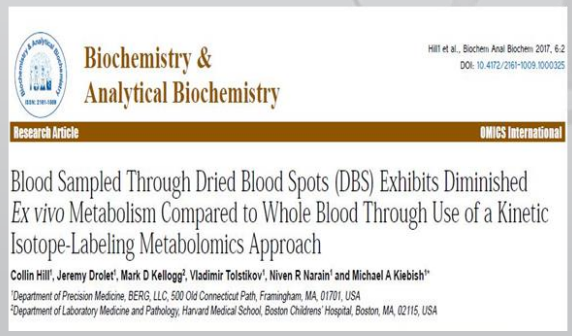
DOI 10.1186/s12986-017-0182-6

Nutrition & Metabolism

RESEARCH Open Access

Dynamic and temporal assessment of human dried blood spot MS/MS^{ALL} shotgun lipidomics analysis

Fei Gao, Justice McDaniel, Emily Y. Chen, Hannah E. Rockwell, Jeremy Drolet, Vivek K. Vishnudas, Vladimir Tolstikov, Rangaprasad Sarangarajan, Niven R. Narain and Michael A. Kiebish*


Biochemistry & Analytical Biochemistry

Hill et al., Biochem Anal Biochem 2017, 6:2

DOI: 10.4172/2161-1009.1000325

Research Article OMICS International

Blood Sampled Through Dried Blood Spots (DBS) Exhibits Diminished *Ex vivo* Metabolism Compared to Whole Blood Through Use of a Kinetic Isotope-Labeling Metabolomics Approach

Collin Hill[1], Jeremy Drolet[1], Mark D Kellogg[2], Vladimir Tolstikov[1], Niven R Narain[1] and Michael A Kiebish[1]*

[1]Department of Precision Medicine, BERG, LLC, 500 Old Connecticut Path, Framingham, MA, 01701, USA

[2]Department of Laboratory Medicine and Pathology, Harvard Medical School, Boston Childrens' Hospital, Boston, MA, 02115, USA

Conclusions

- **There are major challenges implementing and streamlining precision medicine in global healthcare and clinical trial development**

- **However, there are solutions that unravel the paradox of giving the right drug, to the right person, at the right time**

- **These solutions can be beneficial if engaged early on in clinical trial development using phenomic technologies**

Acknowledgments

- The patients and families participating in BERG clinical trials
- Investors: Carl Berg
- Senior Leadership:
- Niven Narain, Rangaprasad Sarangarajan, Slava Akmaev, Michael Kiebish
- Metabolomics Team:
- Brian Williams, Bennett Greenwood, Collin Hill, Jeremy Drolet, Alexander Kitayev .