



博淼生物  
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# 质谱代谢组学测量技术赋能精准医学研究

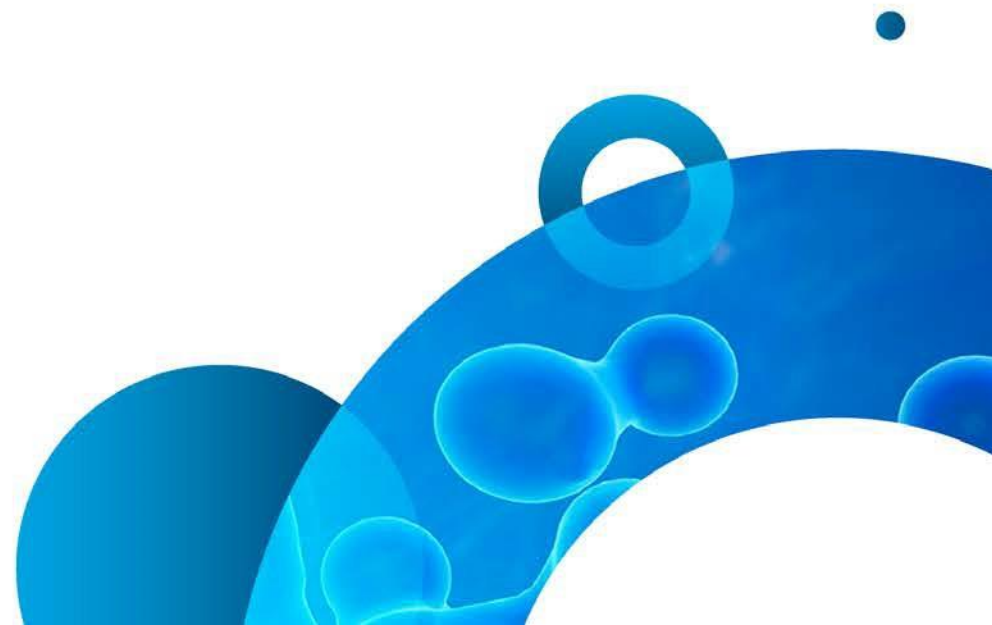
## Metabolomics Technologies Enable Precision Medicine Research

全国统一服务电话：400-6506-908

网址：[www.biomiao.com](http://www.biomiao.com)

邮箱：[marketing@biomiao.com](mailto:marketing@biomiao.com)

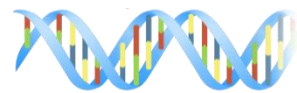
地址：北京市丰台区丰管路优橙创新中心3012-3015



- 代谢组学研究什么?
- 代谢组学怎么做?
- 代谢组学能解决什么问题?
- 我们的代谢组学科研服务的解决方案
- 代谢组学落地临床科研的场景与案例

# 代谢组学是系统生物学的重要组成部分，是精准医学研究的重要方法手段

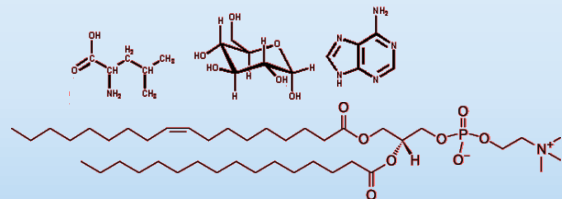
**Genotype**  
遗传因素，生命蓝图



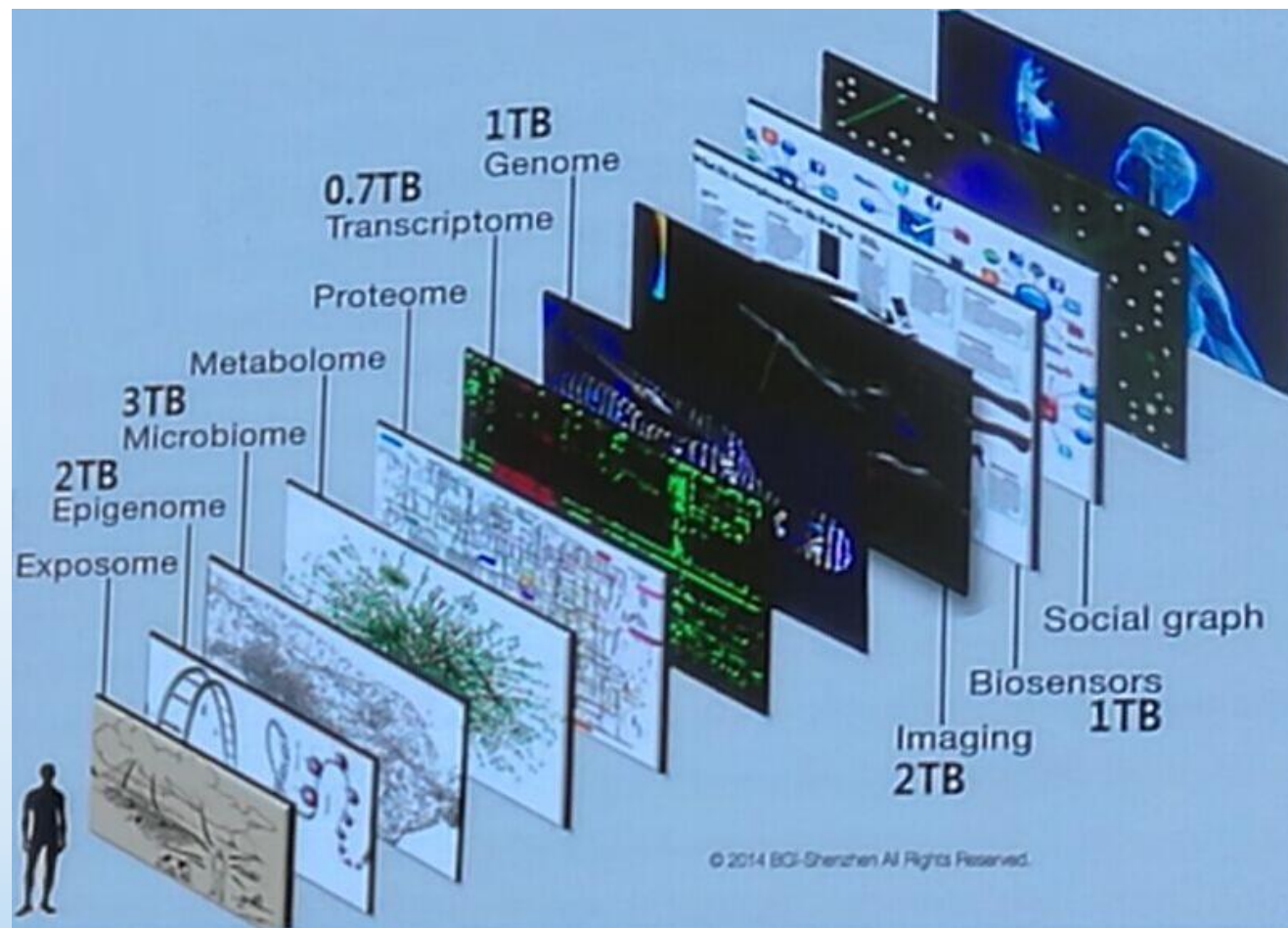
**蛋白质组**  
1M 蛋白质



**代谢组**  
3K 内源性小分子



## 测序与质谱 **Gene Sequencing + Mass Spectrometry**

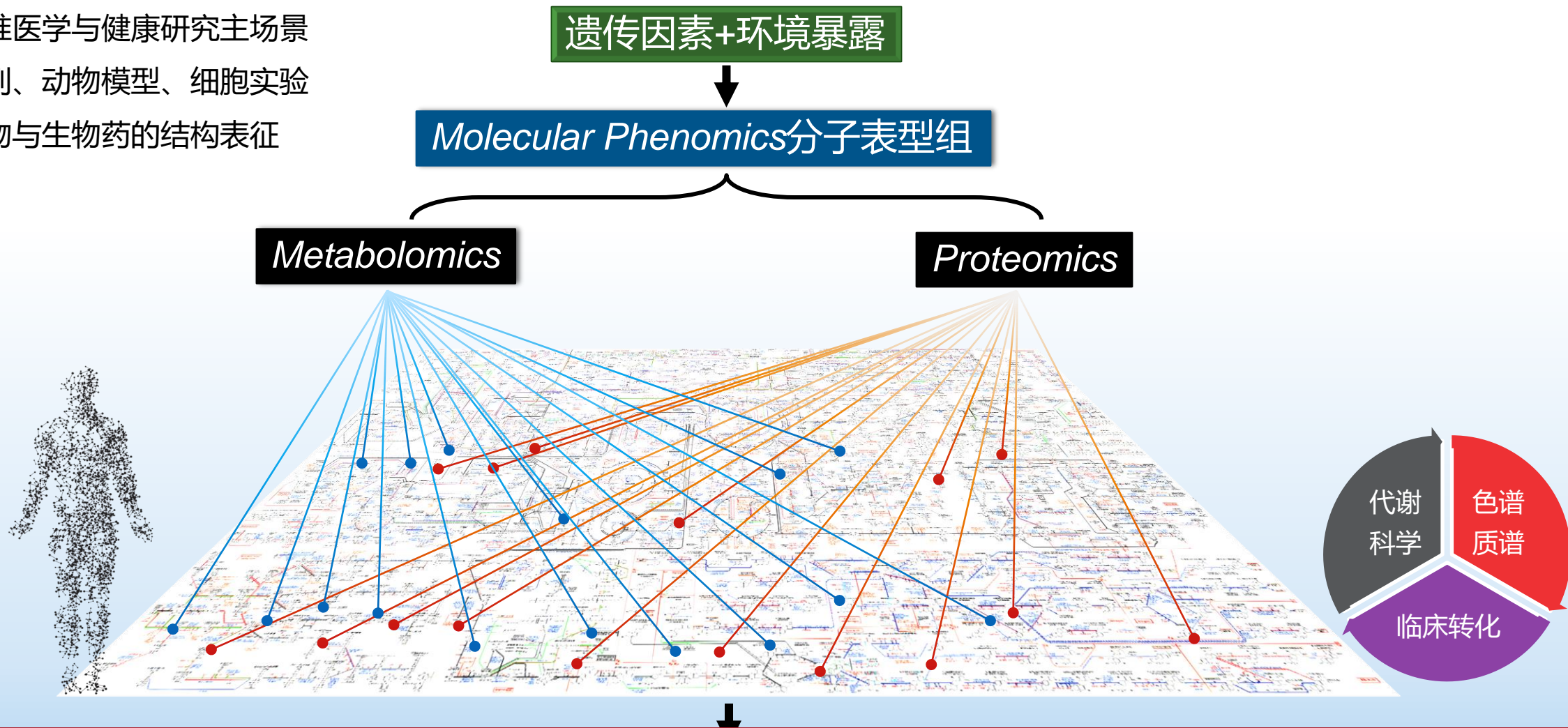


**Phenotype**  
分子表型，动态演变

**Guilt-by-Association 关联推定的哲学:** Biological changes observed in one molecular level often imply changes in another level of cellular control. Molecular phenotyping can actively measure disease-related changes.

# 我们致力于深度代谢组×蛋白质组测量技术研发与科技服务

- 聚焦精准医学与健康研究主场景
- 人群队列、动物模型、细胞实验
- 天然产物与生物药的结构表征



高覆盖、高解析、高准确、定量化的质谱多组学技术平台  
赋能代谢物与蛋白质相关的精准医学与生命科学研究，临床检测转化



# 代谢组：链接分子表型与人体健康的分子层 Linking molecular phenotype with health status

**SYSTEMS BIOLOGY**  
**Metabonomics**  
 Jeremy K. Nicholson and John C. Lindon

Organisms often respond in complex and unpredictable ways to stimuli that cause disease or injury. By measuring and mathematically modeling changes in the levels of products of metabolism found in biological fluids and tissues, metabonomics offers fresh insight into the effects of diet, drugs and disease.

**What are the origins of the field?**  
 The idea that changes in tissue and biological fluids are indicators of disease goes back as far as ancient Greece. Diagnostic urine charts were widely used from the Middle Ages onwards (Fig. 1). These charts linked the colors, smells and tastes of urine to various medical conditions. Such features are, of course, metabolic in origin. Metabonomics, and the related field of metabolomics, uses modern techniques to analyse samples, but the basic principle of relating chemical patterns to health is the same.

**How does this approach fit in with systems biology?**  
 Metabonomics dovetails beautifully with the philosophy of systems biology, because it provides a top-down, integrated view of biochemistry in complex organisms, as opposed to the traditional 'bottom-up' approach that investigates the network of interactions between genes, proteins and metabolites in individual cell types. It provides with systems biology in that each level of biological organization and control — genetics, gene expression, protein expression and metabolism — operates on a markedly different timescale from the others, making it difficult to find causal linkages. Moreover, environmental and lifestyle factors greatly influence metabolism, making it difficult to discern their effects from gene-related outcomes. Environmental influences on gene expression also make it hard to interpret genomic data, for example to predict an individual's susceptibility to disease. Metabonomics cuts through these problems by monitoring the global outcome of all the following factors, without making assumptions about the effect of any single contributor to that outcome. To us, it is linking the individual contributions to be treated out.

**Figure 1 Metabolism of urine.** This urine chart was published in 1706 by Charles Boerhaave in his book *Apparatus Medicorum*. It describes the possible colors, smells and taste of urine, and uses them to diagnose disease.

Introduction to science community in 2008

**Cell Metabolism**

HIF-1 suppresses mitochondrial function

Cell started Cell Metabolism in 2005

**SPECIAL SECTION**  
**Metabolism Is Not Boring**

**INTRODUCTION**

DO INVESTIGATORS EVEN MENTION METABOLISM? HAS ANYBODY LEFT BEHIND after a presentation at a conference (on metabolism and cancer, no less). It may have been "too boring" for them, but what had been in their mind such a "boring" topic? It seems that for a generation of biological scientists, metabolism was an area of background to be mentioned and then put aside. Metabolism was always there in the background, providing the cell with the energy and resources to do what was required, but rarely recognized for its biological influence, and the influence by the physiological state of the cell.

The special issue of Science celebrates a resurgence of interest in metabolism and an appreciation of its central role in disparate areas of cell biology, physiology, medicine, and synthetic biology. It was a resurgence of interest that was encouraged by the interdisciplinary McKnight Perspectives (p. 1335) that took a broad look at the field and justified its excitement that recognizing the reciprocal regulation of metabolism and other cellular processes promises to advance our understanding of complex physiology.

There is renewed interest in the mechanism of cancer cells and its potential as a therapeutic target. Levine and Purohit-Kumar (p. 1340) review metabolic changes in cancer cells, as well as the recent suggestion that alterations in a metabolic enzyme can lead to the production of an "oncometabolite" that supports cancer cell growth. When energy reserves are limited, cells use a glyoxylate shunt as a pathway for breaking down cellular components to provide substrates for metabolism. Falmagne and White (p. 1342) discuss roles of shunting in metabolism, its regulation, and its implications for cancer and degenerative diseases.

Of course, not all fields have neglected metabolism over the years, and an extensive literature describes the role of waste and related biomass in controlling cellular metabolism. In a focus issue of Science Signaling, a Research Article and Perspectives describe an unexpected signal from the insulin receptor that confers sensitivity to cell death when insulin is not present. Also highlighted was a role for lipids as cellular sensors of glucose metabolism and a mechanism by which cells can sense oxidative stress by altering the activity of their protein degradation complex, the proteasome.

In Science Translational Medicine, Vallbo and Hatanpää review how a strategy to control obesity and insulin resistance, a therapeutic inhibitor of cell signaling pathways, may have unintended actions in multiple cell types. Back to Science, Hsu and Tallant (p. 1349) review new insights into the interaction of metabolism with insulin signaling. Deposition of amyloid and amyloid precursor protein from the normal light-dark cycle, as experienced in jet lag or shift work, have implications for metabolic disease. Deposition of amyloid and amyloid precursor protein in cellular senescence, particularly in yeast or bacteria, can be regulated by synthetic compounds that are difficult or expensive to produce by other means. Kaur and colleagues (p. 1351) review advances in metabolic engineering and discuss how to a future in which customized microbes may be computer-aided design can efficiently produce desired chemicals, ranging from fuels to pharmaceuticals.

— L. BREWER

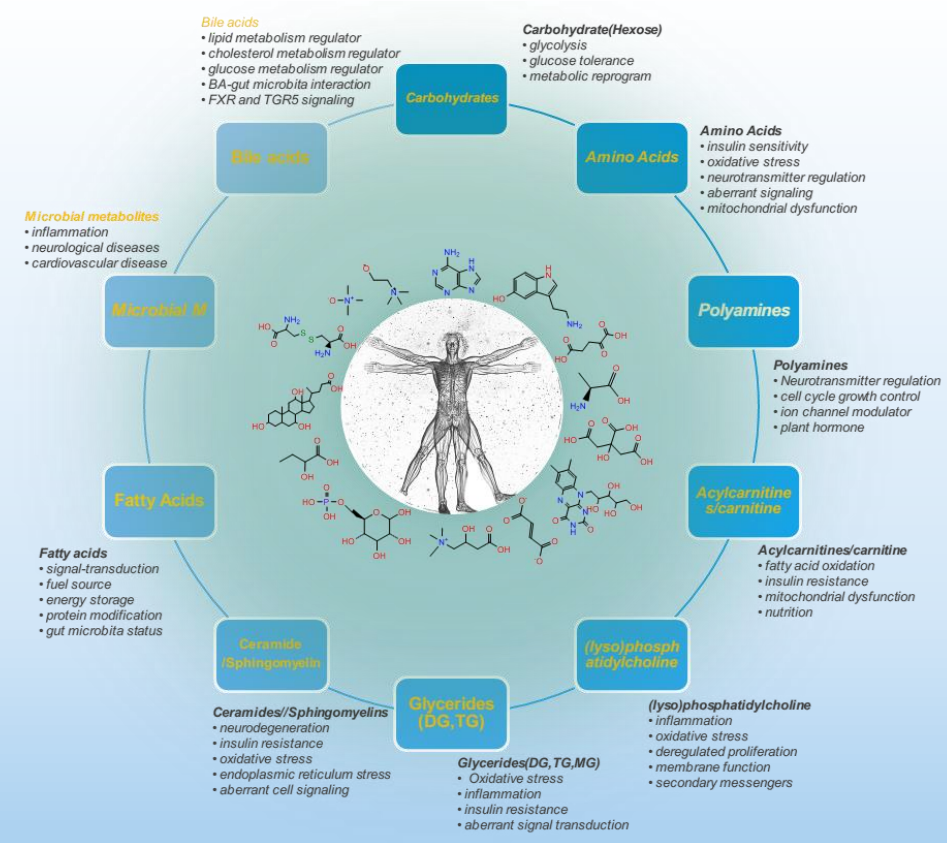
Science released special metabolism in 2010

**nature metabolism**

Metabonomic insight into bacterial cell division

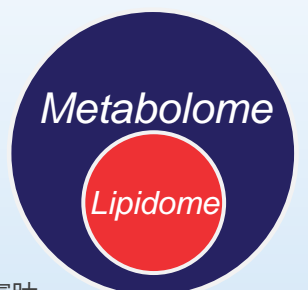
Nature started Nature Metabolism in 2017

- **Metabolism is NOT boring!** 深远广泛的生物学功能与广阔临床转化前景
- This special issue celebrates a **resurgence of interest in metabolism and an appreciation of its central role in disparate areas of cell biology, physiology, medicine and synthetic biology.**
- What we measure for metabolomics?
- **small molecular endogenous metabolites in bio-fluids blood, urine, feces, and tissues et al (Molecular Weight < 2000 Da)**



## Hydrophobic脂溶性 (脂质)

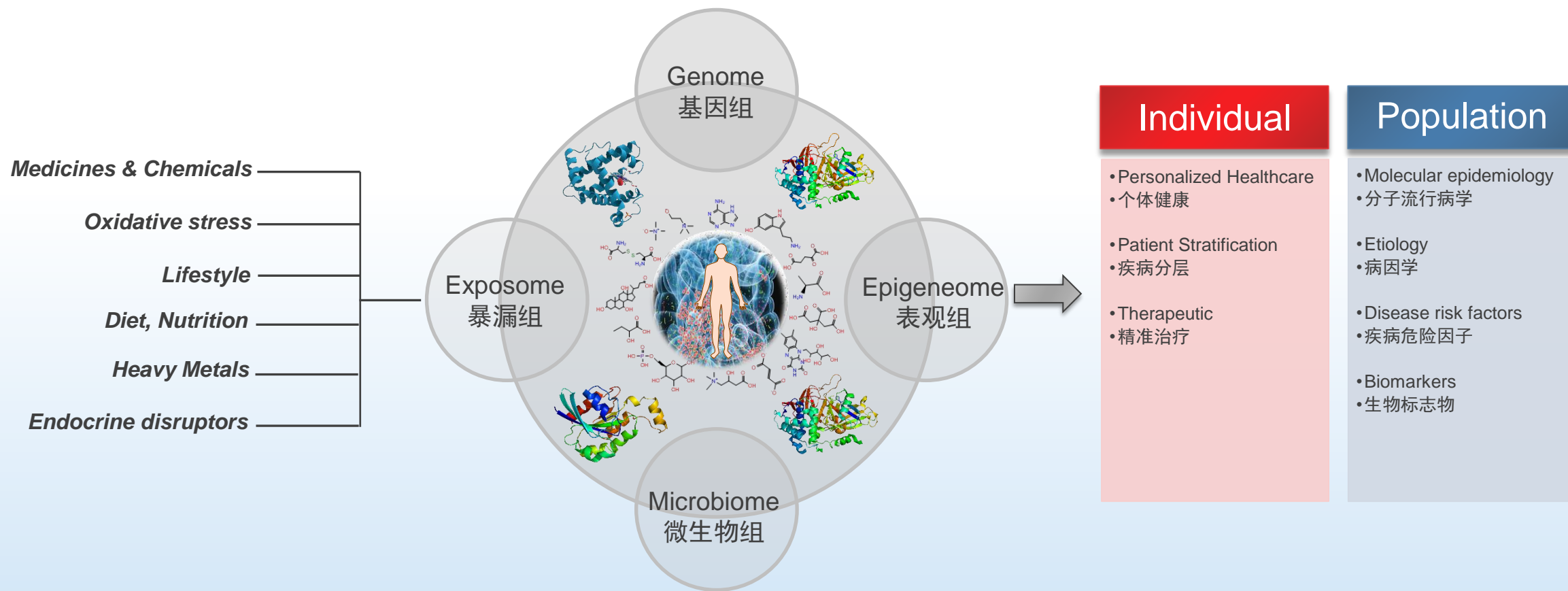
- 胆固醇酯、甘油酯
- 磷脂、鞘酯
- 脂溶性维生素
- 甾体激素
- 长链脂肪酸/肉碱
- 胆汁酸
- .....
- 水溶性维生素
- 氨基酸、二肽、寡肽
- 核苷酸、有机酸
- 糖、糖醇、磷酸戊糖
- 季铵盐
- 磷酸、硫酸、尿素



## Hydrophilic水溶性 (代谢物)

# 代谢组学：遗传因素、环境暴露、肠道菌群共同构建的分子表型

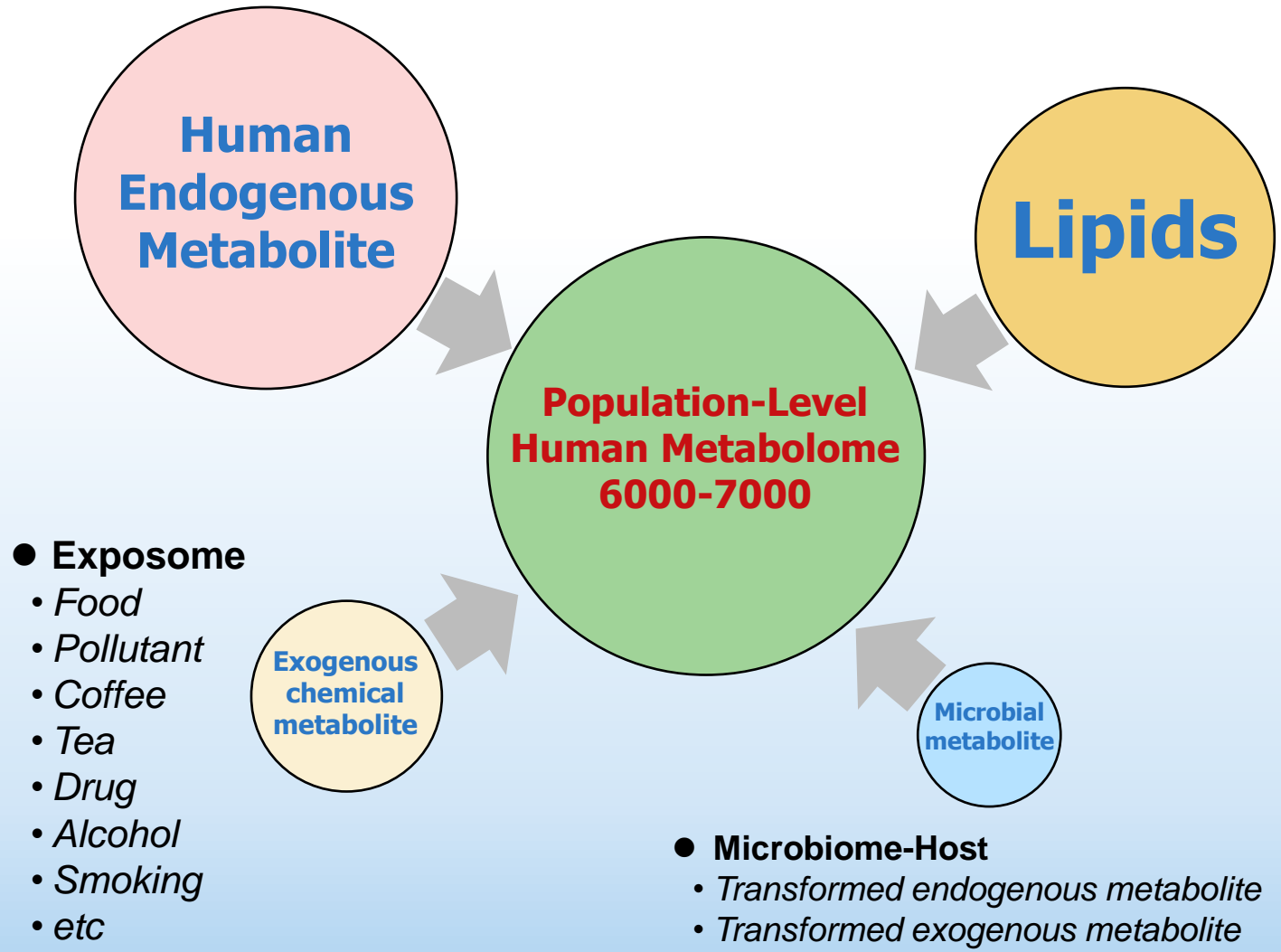
人体代谢组与蛋白质组的分子表型测量反映健康状态 *Molecular Phenotyping Technologies: Proteotype + Metabotype (Functional readout)*



- Metabolomics is an essential component of systems biology, and studies of metabolism abound in fields ranging from agriculture to the study of human disease. —Nature Methods 2017
- metabolomics studies have been revealing that metabolites (both exogenous and endogenous) have a far more central role in disease development, cellular signaling and physiological control than previously thought. —David S. Wishart, 系统生物学家



# Composition of Human Metabolome



**50 YEARS OF NEWBORN SCREENING** baby's first test

*Did you know...* Children should be **SCREENED SHORTLY AFTER 24 HOURS** of being born

MOST STATES SCREEN FOR **29** out of **31** RECOMMENDED HEALTH CONDITIONS

More than **1 IN 300 NEWBORNS** have a condition detectable through Newborn Screening

In **1963** Newborn Screening begins with a **HEEL STICK**

In **1999** **HEARING SCREENING** is recommended for newborns

In **2012** the **PULSE OXIMETRY** test becomes a part of Newborn Screening

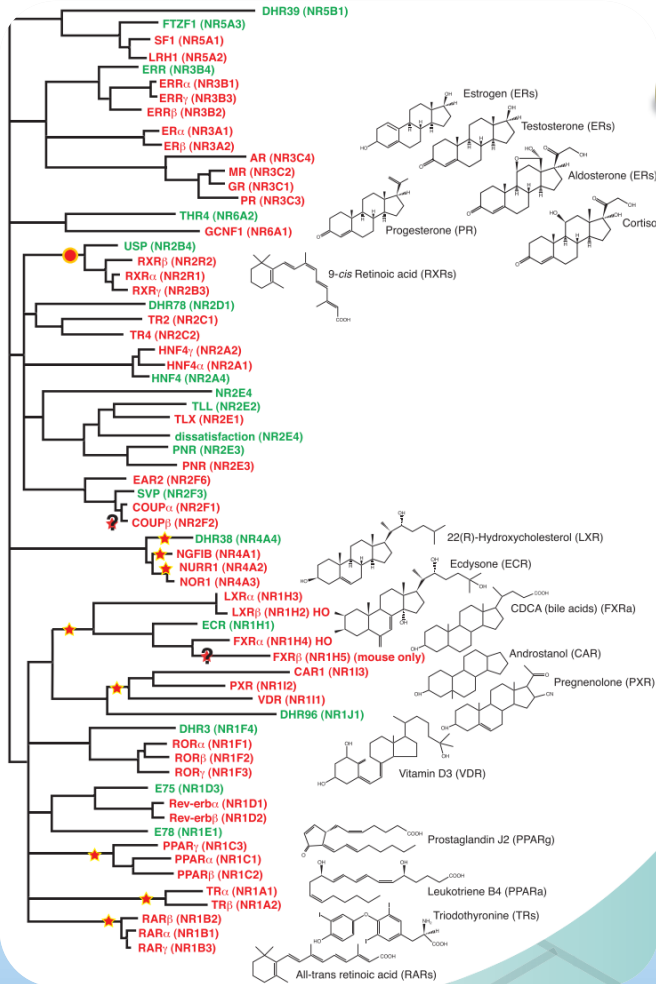
In **2013** Newborn Screening celebrates its **50TH Anniversary**

Most babies with serious but treatable conditions caught by Newborn Screening **GROW UP HEALTHY** with expected development

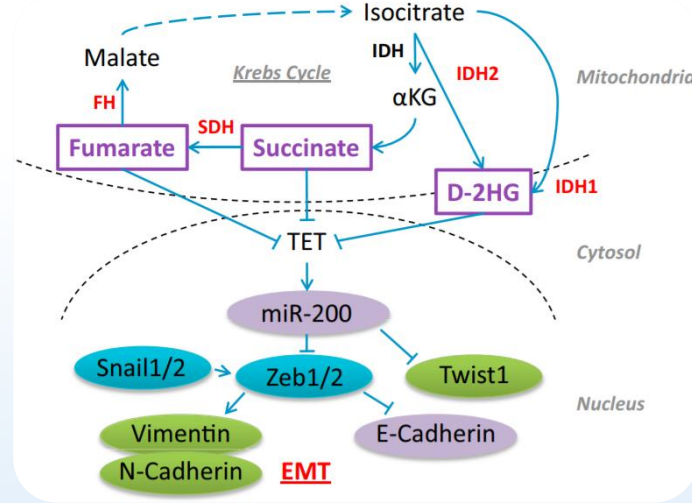
Source: [BabysFirstTest.org](http://BabysFirstTest.org)

# 代谢物具有丰富的生物功能: 转录应答, 表观遗传, 细胞信号

核受体为代表的  
转录应答 → 代谢物信号分子  
甾体、胆汁酸等



代谢物 → 表观遗传



## L-2-Hydroxyglutarate: An Epigenetic Modifier and Putative Oncometabolite in Renal Cancer

*Cancer Discovery 2014*

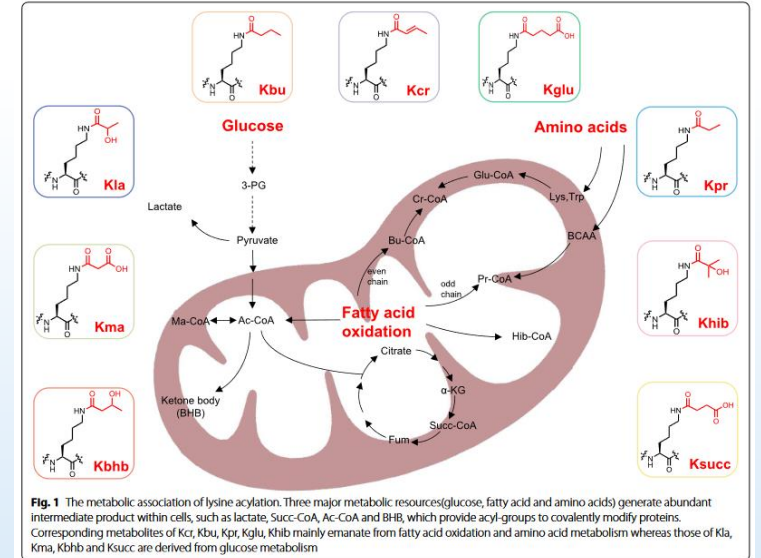
## Fumarate is an epigenetic modifier that elicits epithelial-to-mesenchymal transition

*Nature 2016*

## Alcohol metabolism contributes to brain histone acetylation

*Nature 2019*

代谢物 → 蛋白PTMs



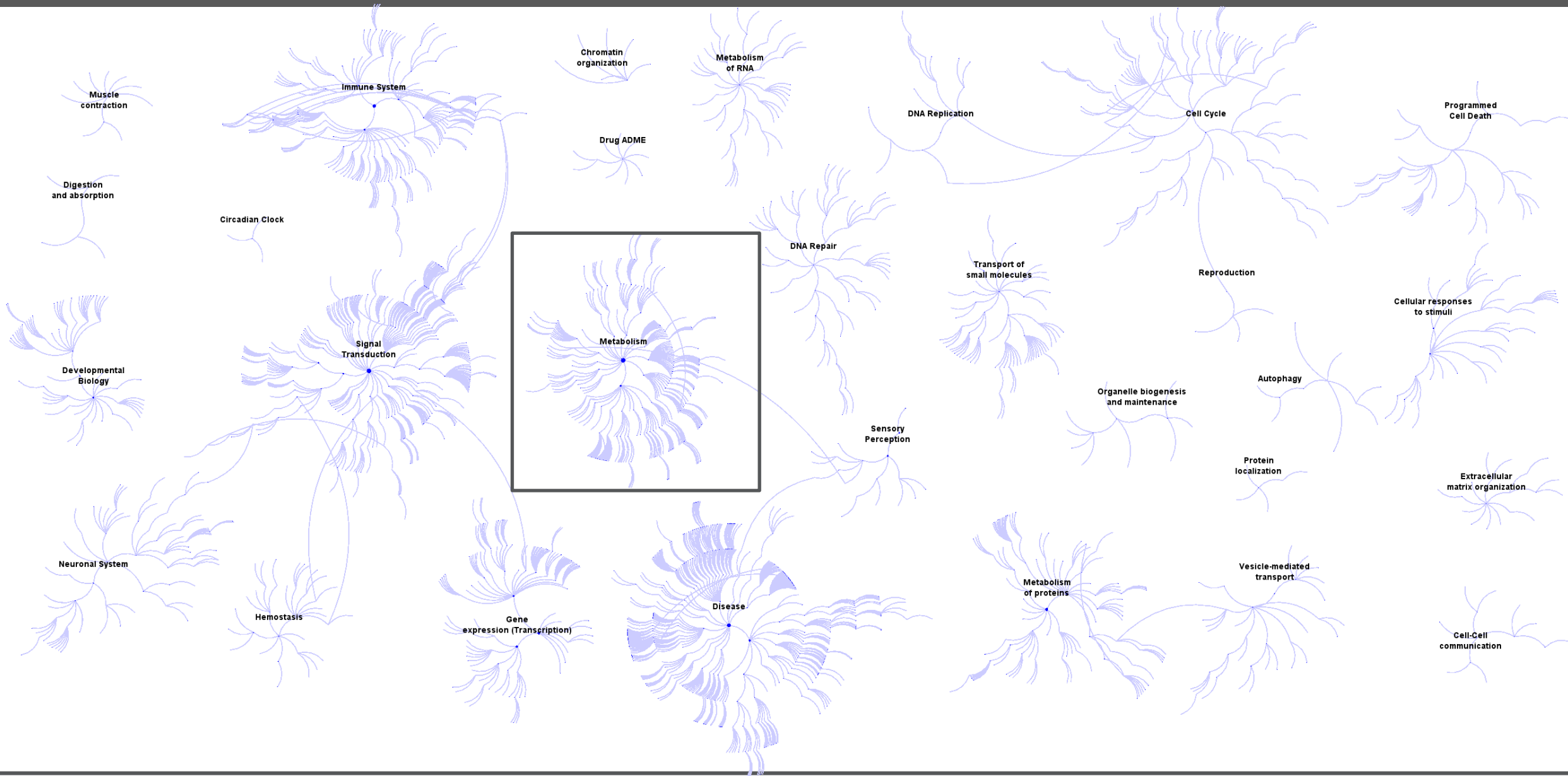
**Fig. 1** The metabolic association of lysine acylation. Three major metabolic resources (glucose, fatty acid and amino acids) generate abundant intermediate product within cells, such as lactate, Succ-CoA, Ac-CoA and BHB, which provide acyl-groups to covalently modify proteins. Corresponding metabolites of Kcr, Kbu, Kpr, Kglu, Khib mainly emanate from fatty acid oxidation and amino acid metabolism whereas those of Kla, Kma, Khib and Ksucc are derived from glucose metabolism.

Oncometabolites drive tumorigenesis by enhancing protein acylation: from chromosomal remodelling to nonhistone modification

*J Exp Clin Cancer Res 2022*



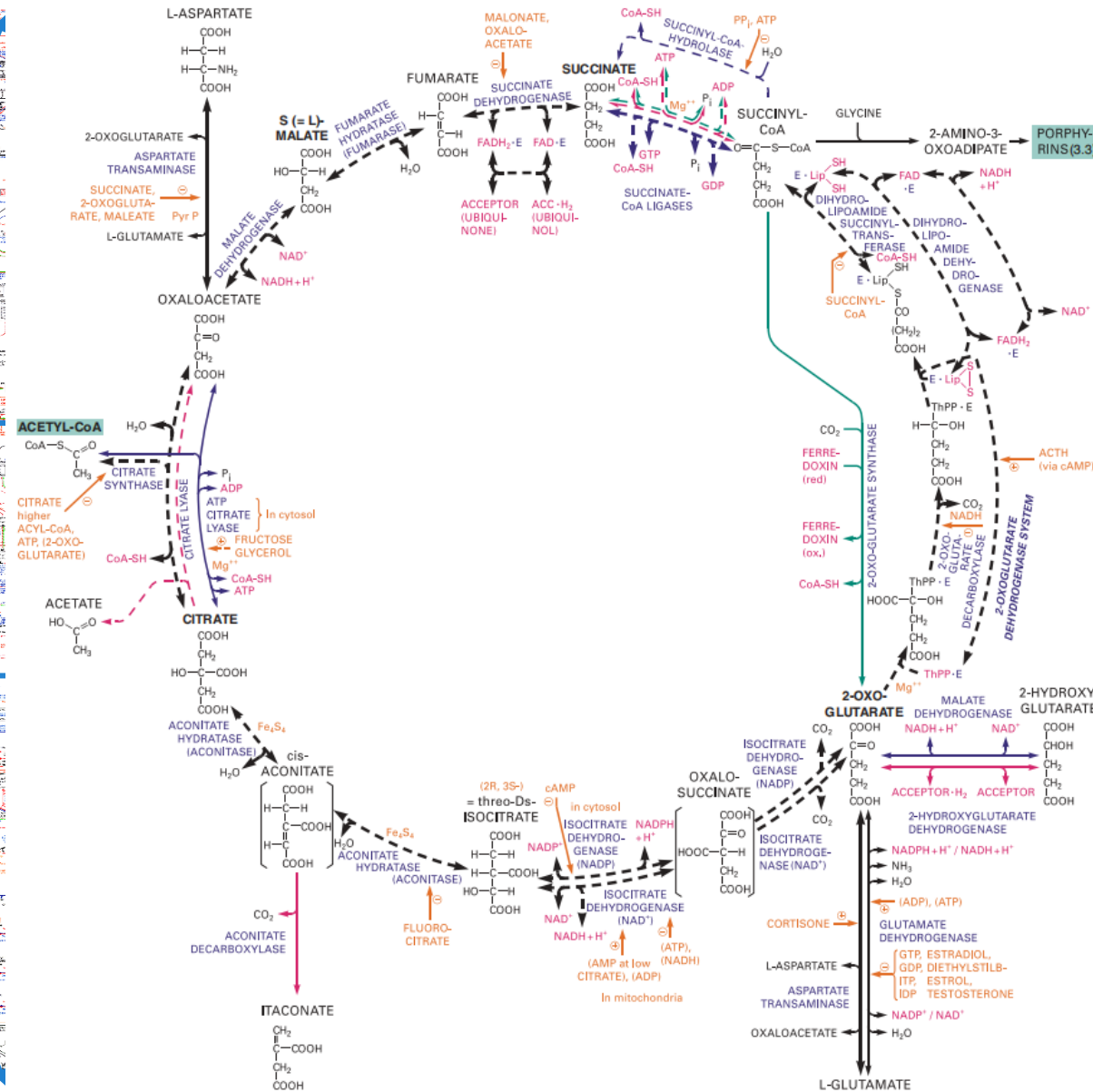
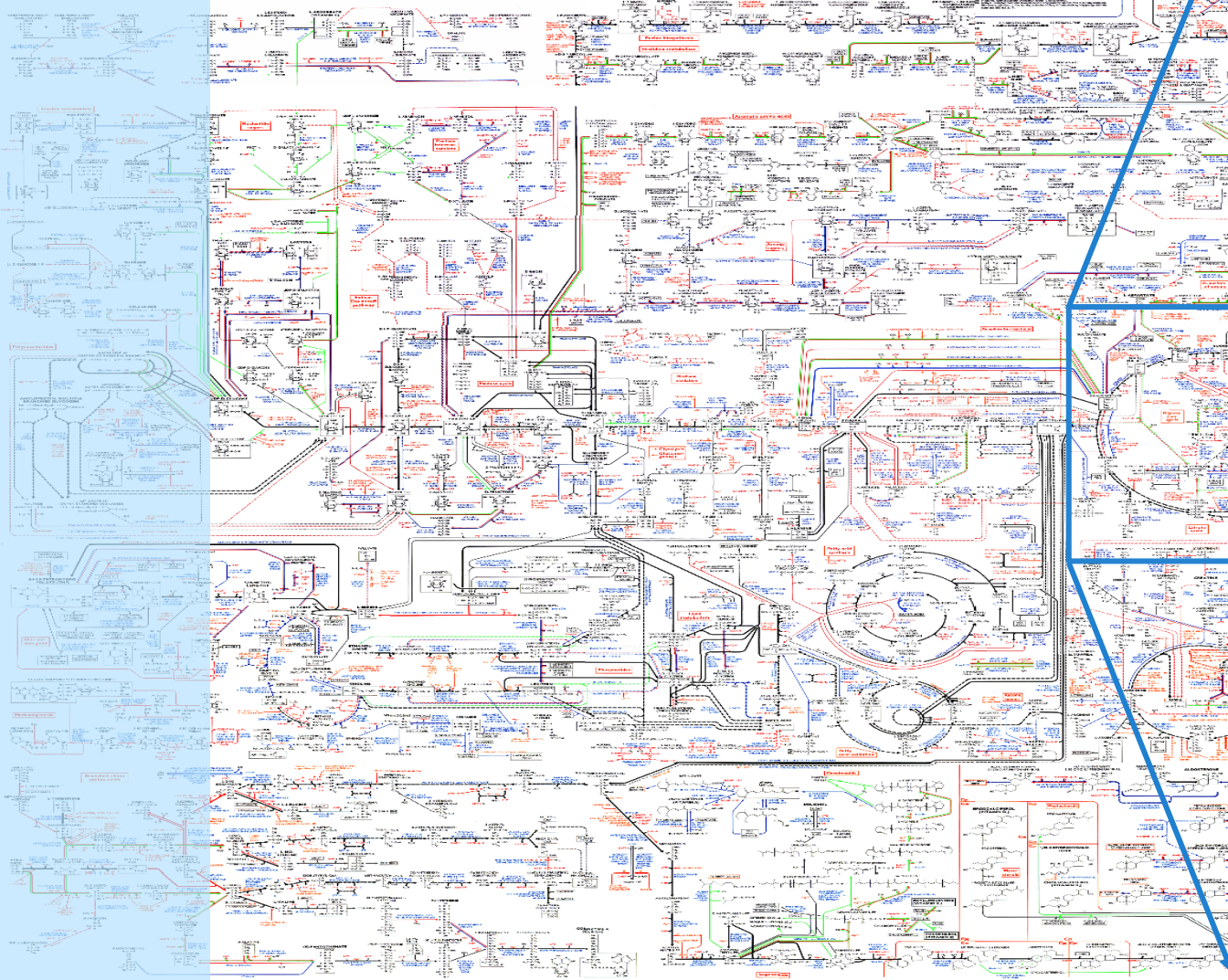
# Metabolism 新陈代谢在已知生物化学与分子生物学知识图谱的位置



# 代谢组学测试的技术本质：准确**定性**、精确**定量**代谢物

## Roche biochemical pathway

-by Dr. Gerhard Michal



# 代谢组的化学分析技术：质谱是最主要的代谢组学测量技术

## Mass Spectrometry

## NMR

UPLC-HRMS

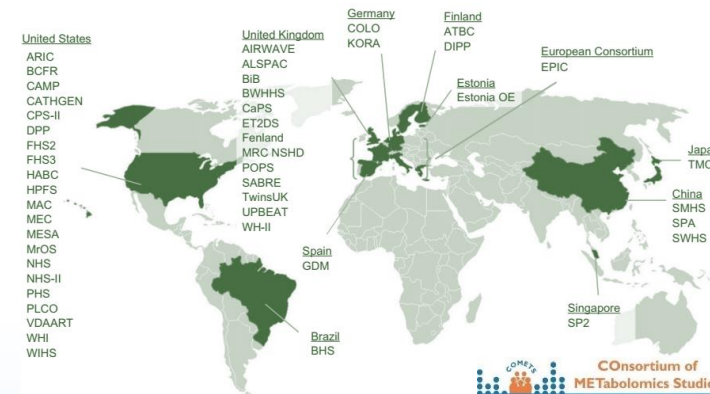


UPLC-MS/MS

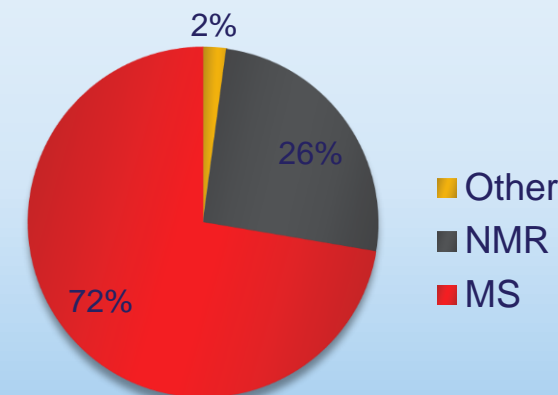


技术	LC-MS液相色谱-质谱	NMR 核磁共振
优势	<ul style="list-style-type: none"> <li>High sensitivity to <math>ag\sim fg</math> LOD</li> <li>High flexibility</li> <li>High metabolome coverage</li> <li>High throughput to</li> <li>Less sample amount needed</li> </ul>	<ul style="list-style-type: none"> <li>non-destructive</li> <li>non-biased</li> <li>identification of unknown</li> <li><b>easily quantifiable</b></li> <li><b>Very robust for large cohort</b></li> </ul>
弱点	<ul style="list-style-type: none"> <li>Sample cleanup needed</li> <li>Sophisticated experienced need for <i>de novo</i> Met ID</li> </ul>	<ul style="list-style-type: none"> <li>not very sensitive <math>\sim 5 \mu M</math></li> <li>Narrow coverage <math>\sim 50\text{-}150</math> metabolites</li> <li>Limited dynamic range</li> </ul>

- 化学衍生+GC-MS气相色谱-质谱



- The **Largest consortium** of metabolomics cohort studies
  - 47 prospective cohorts, 13,8670 participants (up to 2018 April)
  - Blood metabolomics (Serum, EDTA-plasma)
  - Follow-up outcomes (Cancer, diabetes, CAD, et al)
  - 多组学68% participants with Genome-wide SNP information
- Convened by USA **National Cancer Institute** from 2014





# 质谱技术：具有广泛普适性的分析工具

## • 质谱是什么？

- “特殊的天平”，电场或磁场下称量气相离子的质量（质荷比 $m/z$ ）

## • 质谱的原理

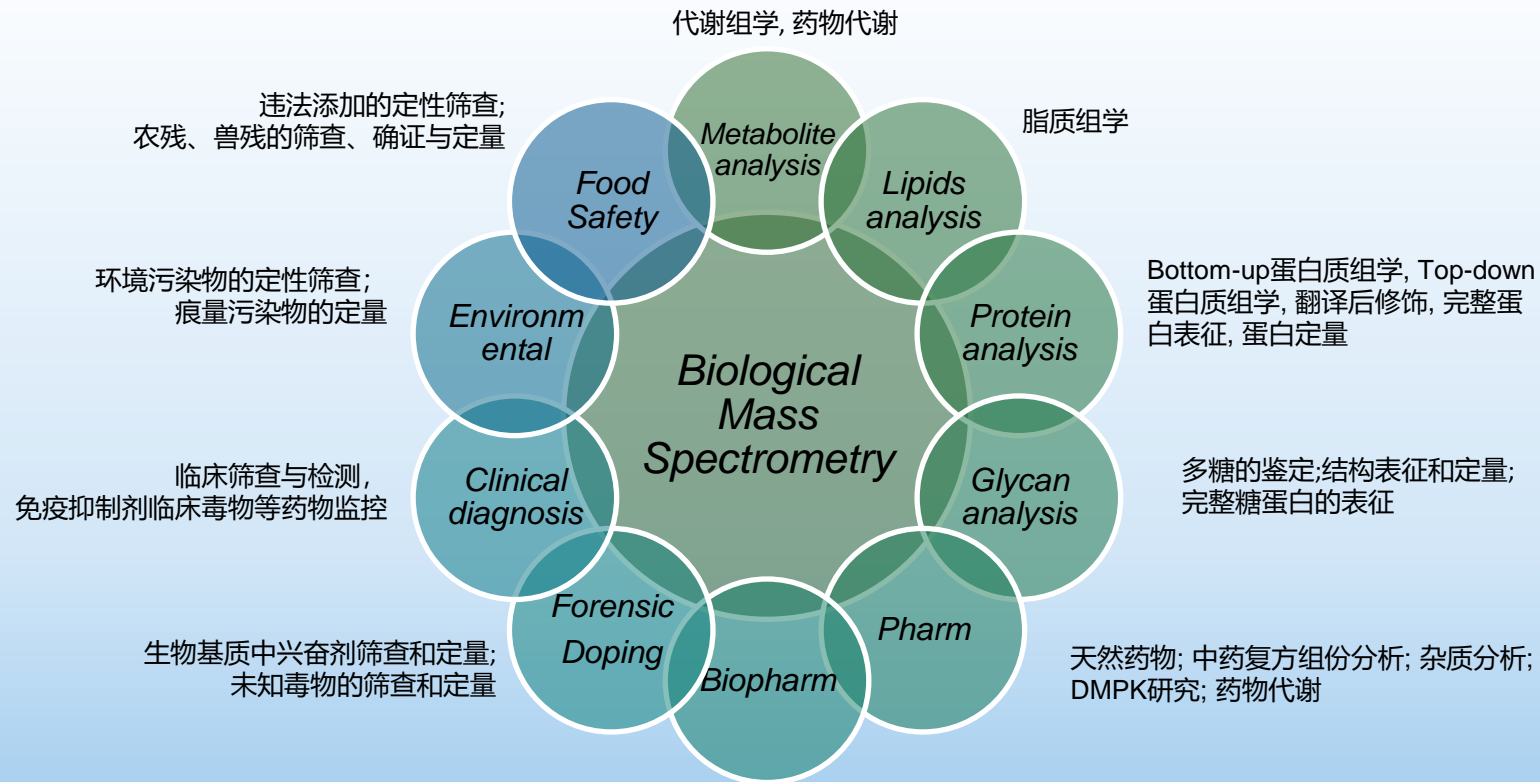
- 使化合物形成离子，在质量分析器中按其 $m/z$ 进行分离和检测

## • 质谱能干什么？

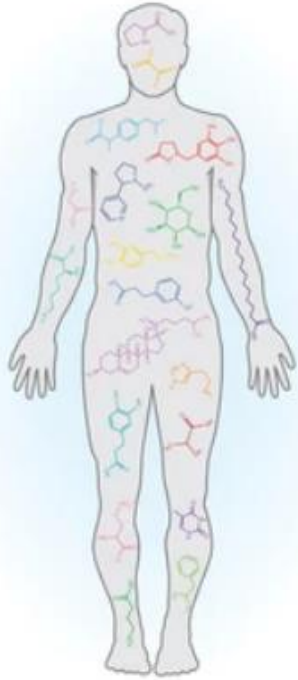
- 核心：①定性—结构推测与发现；②定量—含量测定；③成像

## • 行业评述

- 区别于测序市场，质谱作为一种通用型的检测技术，行业中最上游的6家进口设备厂商并不提供拿来即用的解决方案。
- 中下游的代谢组学技术服务商需要**专业团队、持续投入、专门开发**自己的代谢组学测量技术平台=Core facility。
- 特点：行业入门的门槛低，做好的门槛很高。







Metabolites play crucial biological roles; methods are needed for their study.

External users can access EMBL experimental services in the fields of structural biology, imaging, genomics, proteomics, metabolomics, in vivo gene editing, and chemical biology.

**Proteomics and metabolomics may lag behind genomics.**

— *Director of The European Molecular Biology Laboratory, EMBL*

The ability to measure the metabolome on a global scale lags behind other omics techniques. Given the diverse chemistries of metabolites, **no single analysis method offers a 'one-size-fits-all' solution.**

— *Nature Methods* **14**, 32 (2017)

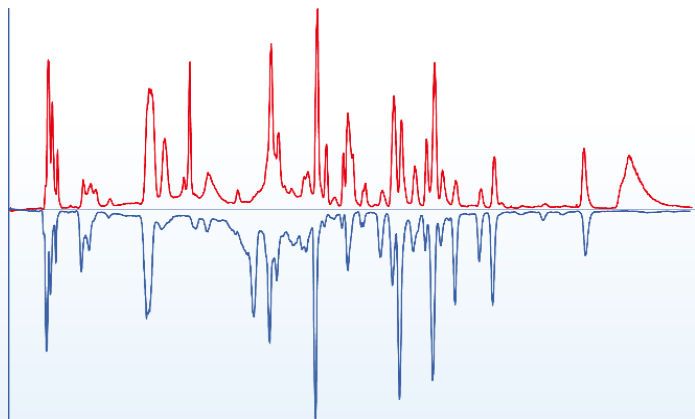
Metabolome代谢组所固有的化学结构高度多样性、理化性质极端异质性、浓度分布差异悬殊等等天然属性，决定了代谢组学的测量策略和技术路线

# 质谱代谢组学研究的两种策略：非靶向代谢组学、靶向代谢组学

- **Untargeted Metabolomics 非靶向策略: Global Profiling Survey**

**WITHOUT** a predefined compound detection list, **Semi-quantitative** Omics-level data

- 实现形式: UPLC-HRMS 超高效液相色谱-高分辨质谱

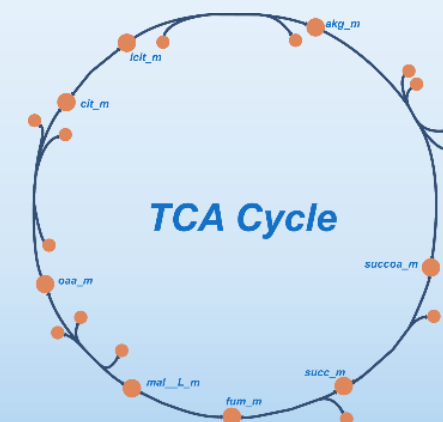
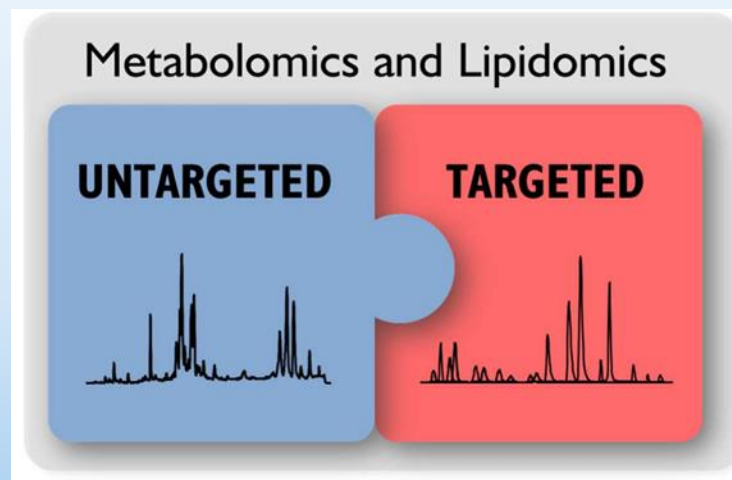
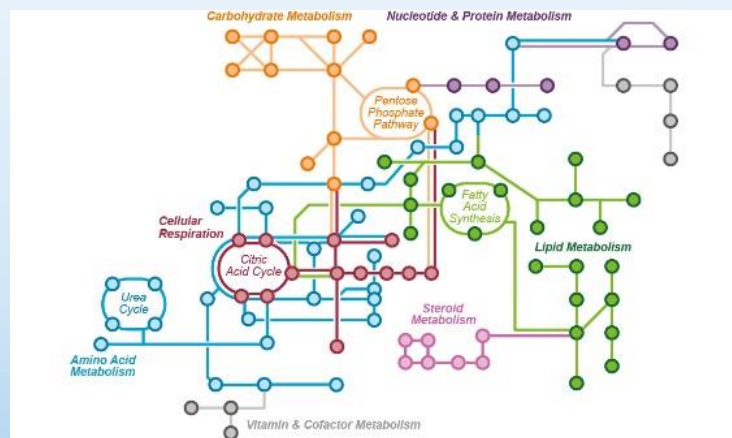
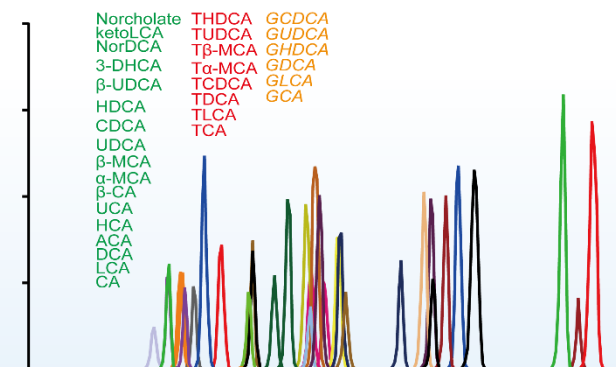


非靶向与靶向是代谢组学研究的两种策略，两者都能提供生物样本代谢组测量的定性与定量信息，两者间不存在非此即彼、“彼可取而代之”、孰优孰劣的竞争性关系。两者是互补的，技术的选择与课题目标以及研究者偏好、预算、技术可及性等因素有关。

- **Targeted Metabolomics 靶向策略: Targeted Survey**

**WITH** a predefined compound detection list, **Quantitative** data

- 实现形式: UPLC-MS/MS 超高效液相色谱-串联三重四极杆质谱



# 质谱代谢组学研究的两种策略：与OpenAI ChatGPT的对话

ZE

Hi ChatGPT, What is untargeted metabolomics?



Untargeted metabolomics is a comprehensive approach to the study of metabolites in biological systems, where all metabolites in a sample are detected and identified without prior knowledge or targeting of specific metabolites. This method allows for the unbiased discovery of metabolites and metabolic pathways, providing a broad view of the metabolic state of a system.



ZE

So, what's targeted metabolomics?



Targeted metabolomics is a quantitative and selective approach to the study of metabolites in biological systems, where specific metabolites or a predefined set of metabolites are measured and analyzed. This method is used when the researcher is interested in quantifying and characterizing known metabolites or metabolic pathways. Targeted metabolomics allows for higher sensitivity and specificity compared to untargeted metabolomics, as it focuses on a specific subset of metabolites.



ZE

Well, will targeted metabolomics replace untargeted metabolomics, or vice versa?



Neither targeted nor untargeted metabolomics can replace the other, as they both have unique strengths and limitations. Targeted metabolomics is ideal when the researcher is interested in a specific set of metabolites or metabolic pathways and requires high sensitivity and specificity. On the other hand, untargeted metabolomics is suitable for identifying unknown metabolites and global metabolic profiling, providing a broad view of the metabolic state of a system. Therefore, the choice of which method to use depends on the research question, the available resources, and the analytical goals. In some cases, both targeted and untargeted metabolomics can be used in combination to obtain a comprehensive understanding of the metabolic system under investigation.



ZE

I am shocked for your such professional comment! Is this your personal thinking, where do you get such comment?



As an AI language model, I don't have personal opinions or beliefs. The answer I provided is based on the current scientific consensus in the field of metabolomics, as well as the definitions and applications of targeted and untargeted metabolomics as described in peer-reviewed literature. My training data consists of a large corpus of text, including scientific papers, books, and articles, which allows me to provide accurate and informative responses to a wide range of questions.



# 质谱代谢组学技术体系：非靶向与靶向，坚定地两手抓！

- *Untargeted Global Profiling*非靶向策略：Omics-level数据，高覆盖（测得到）与高解析（定性出），最大化发挥高分辨质谱提供的卓越定性/定量效能
- 解决方案：领先的非靶向代谢组学技术平台 **Meta-Phenotyper™** 高解析代谢全谱技术

## 非靶向代谢组学的研究目标：

1. 刻画代谢表型全貌：获悉生物洞见 From biochemical landscape to biological insights
2. 筛查与发现：驱动科学假设 Trough screening to drive hypothesis

- *Targeted quantitative*靶向策略：因物制宜，分门别类，追求极致，充分验证，最大化发挥串接质谱具备的定量效能
- 解决方案：靶向代谢分析技术平台 **AccuQuanter™** 代谢物定量方法集群与试剂盒；**AQ1800**：1800种人体内源性代谢物与脂质的绝对定量



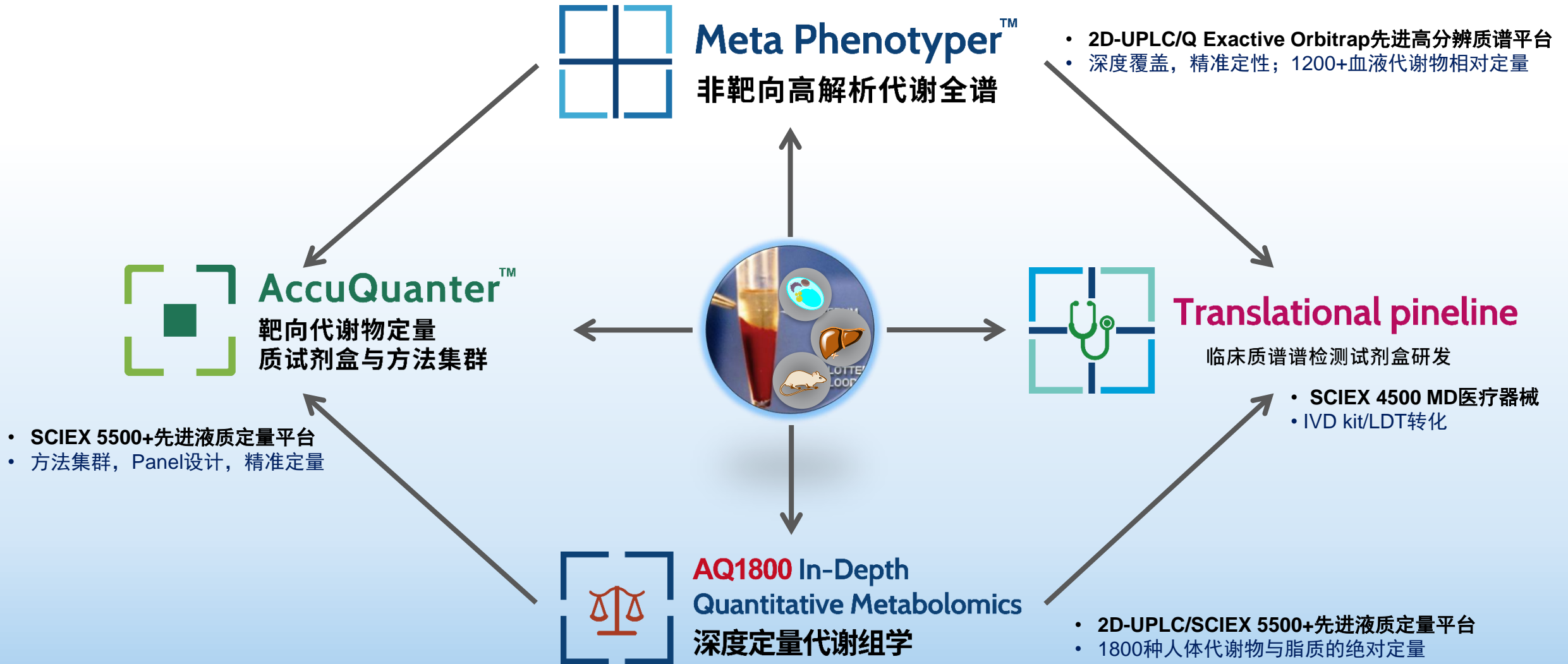
## 靶向代谢组学的研究目标：

1. 生物功能导向：Metabolites panel of biological relevance
2. 痕量检测：Trace level metabolites can not be covered with Untargeted profiling



# 我们的代谢组学技术与产品矩阵

愿景：聚焦代谢物与蛋白质的质谱检测，不断研发迭代更精准的代谢组学和定量蛋白质组学高通量、高内涵表征技术，打造高效的工业级大数据生产能力体系，赋能临床科研、转化，开发精准医学诊断产品。





**Meta Phenotyper™**  
非靶向高解析代谢全谱

自主知识产权，全流程可控  
核心技术攻关：**方法、定性与质控**

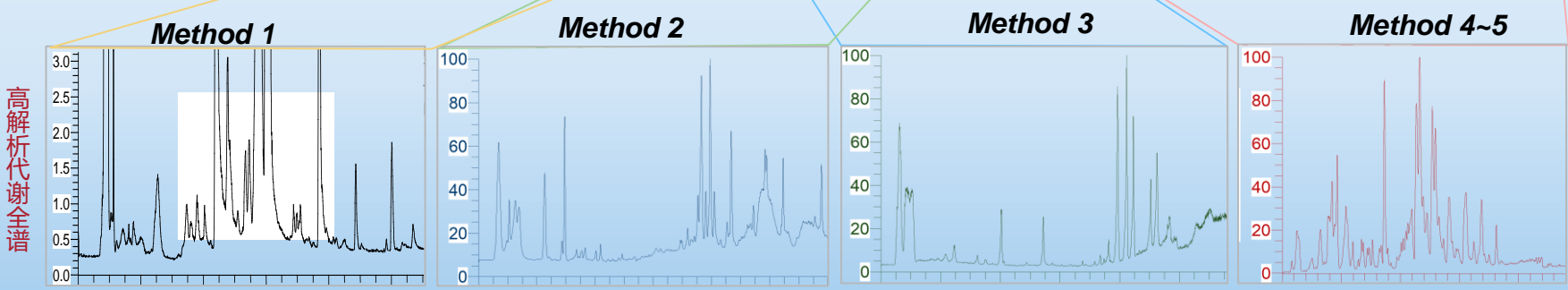
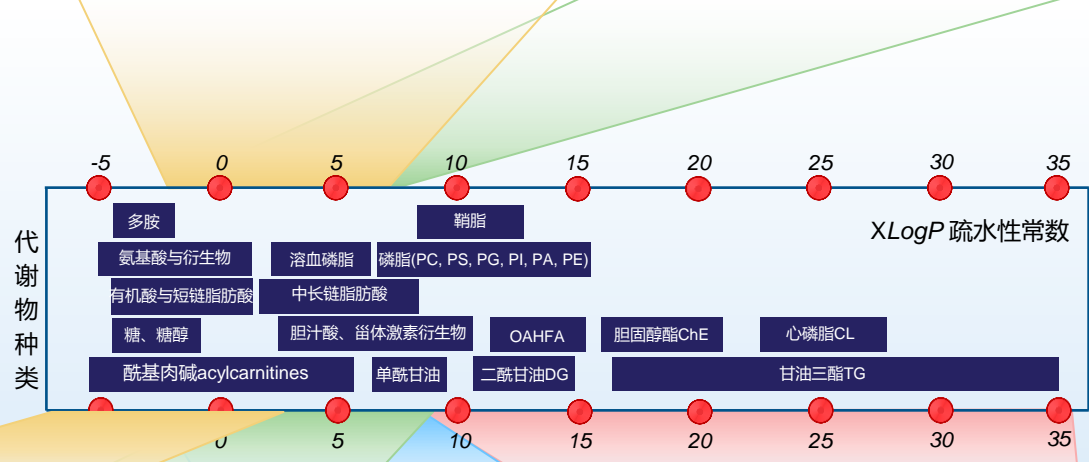
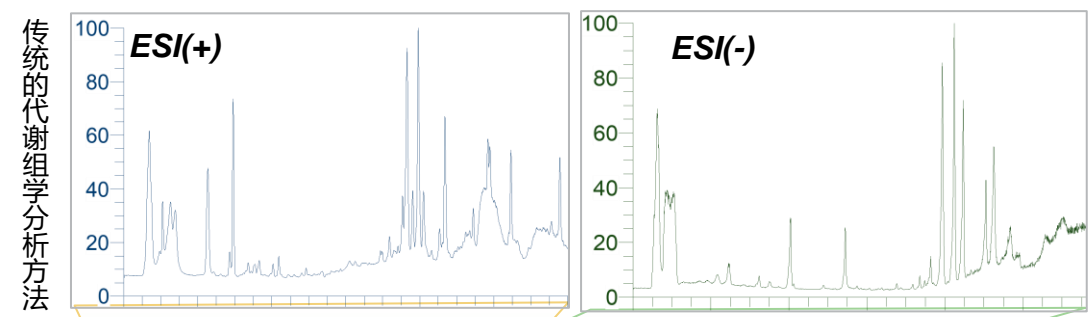
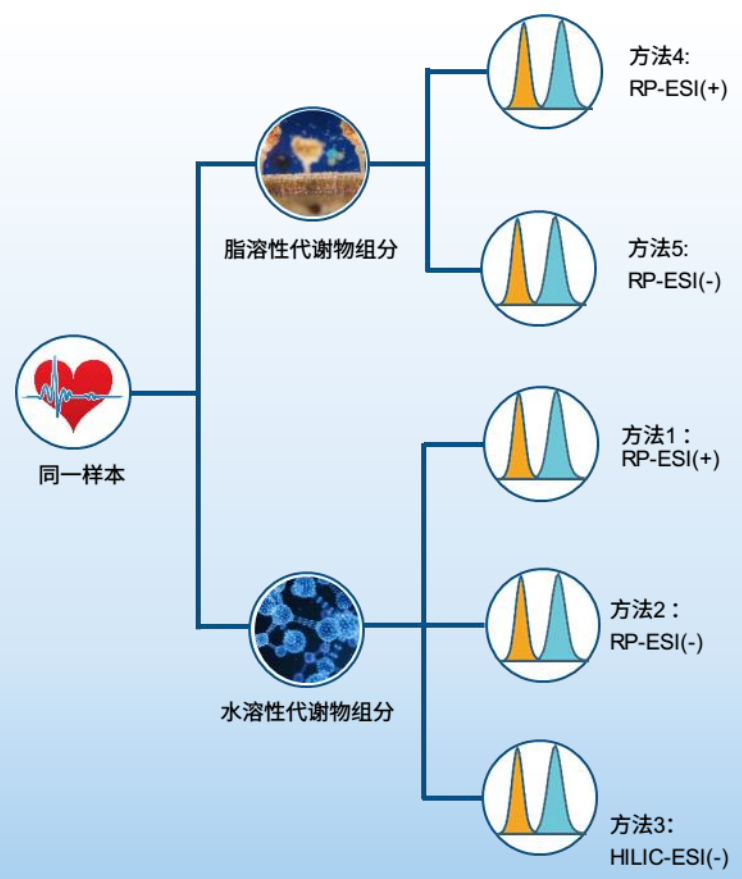


## ■ 国际领先的非靶向代谢组学技术平台

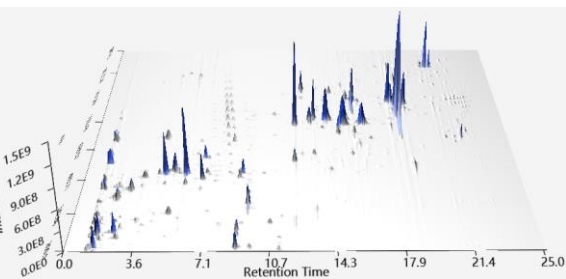
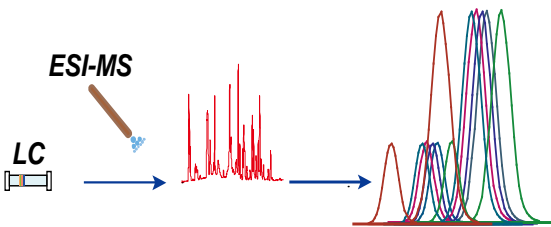
- 与国际顶级实验室同步的先进测量技术，同一样本采用2~4种独立的LC-MS方法检测
- 自主开发SMOL谱图库，已收录~8000个化合物和33980张谱图，并持续扩容
- Metabolomics QCMaster质控大师软件实时多维监控 + SQ500中国自然人群参比血清，全流程质控
- Metabolome FastPep专利提取试剂盒，极致提取，水溶性与脂溶性组分同时兼得

# Meta-Phenotyper™ 高解析代谢全谱 关键技术1：国际先进水平的测量方法

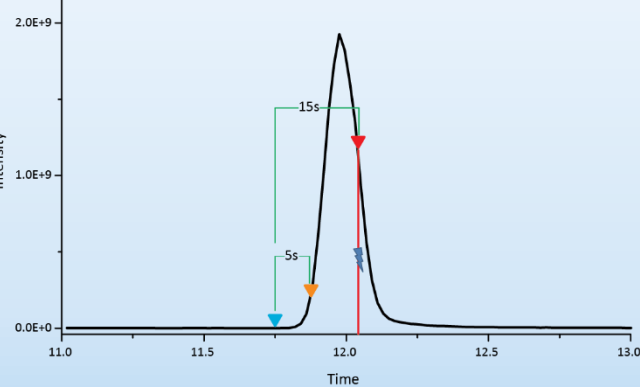
- 实现更丰富、更精准的代谢物定性与定量测量
  - 1份样本2次制备，极性组分(一般意义上的代谢组) & 弱极性组分(脂质组)
  - 2~4个独立分析方法整合互补
  - 色谱分离与质谱检测耦合，覆盖最大化
  - 模块化：套餐模块化，按需组合 (预算、测试深度需求)



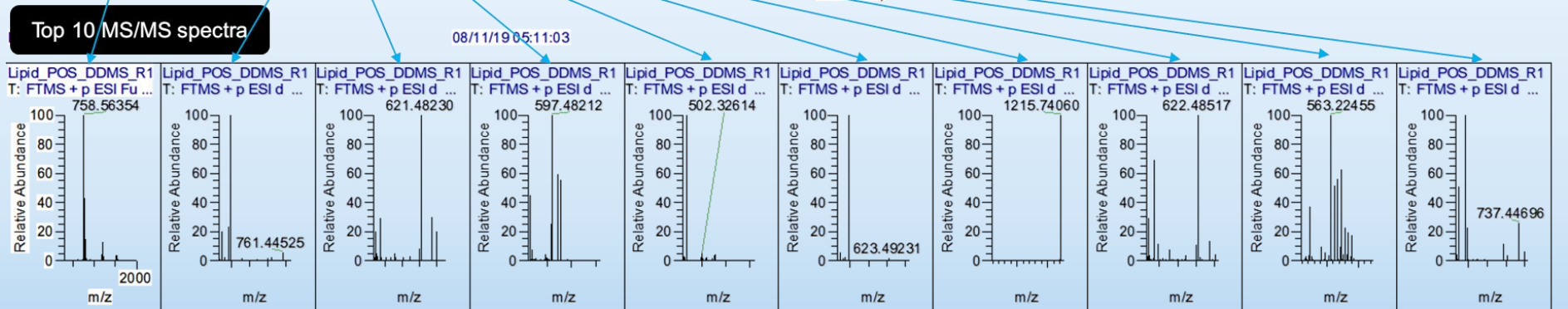
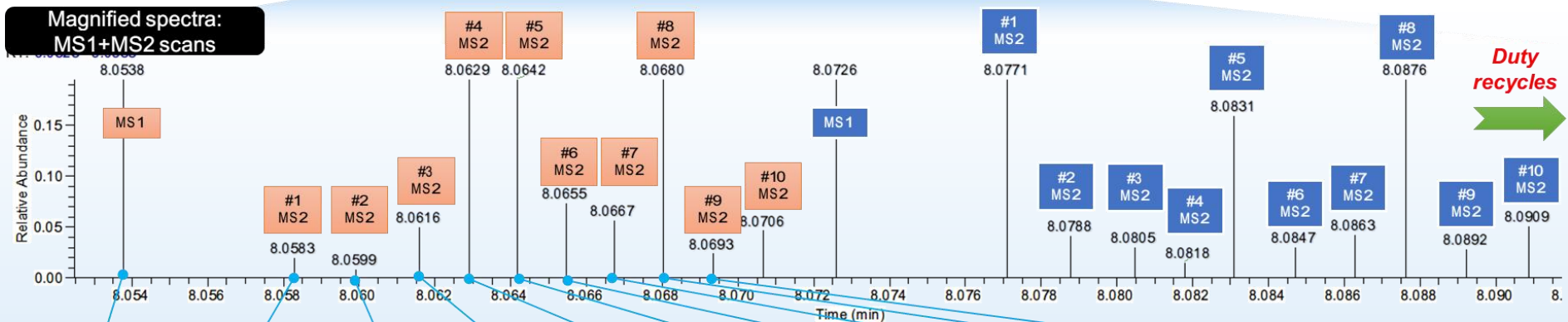
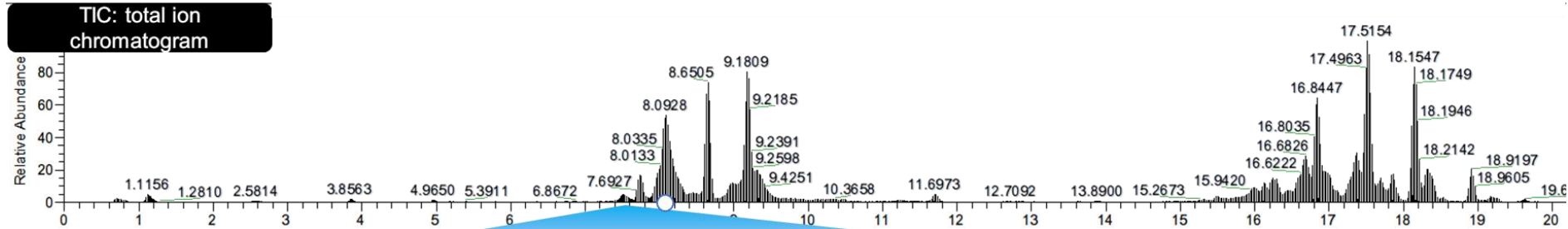
# 非靶向代谢组学数据采集： 色谱保留时间, 一级质谱, 二级质谱



原始数据结构: 色谱×质谱, Rt×m/z×Intensity



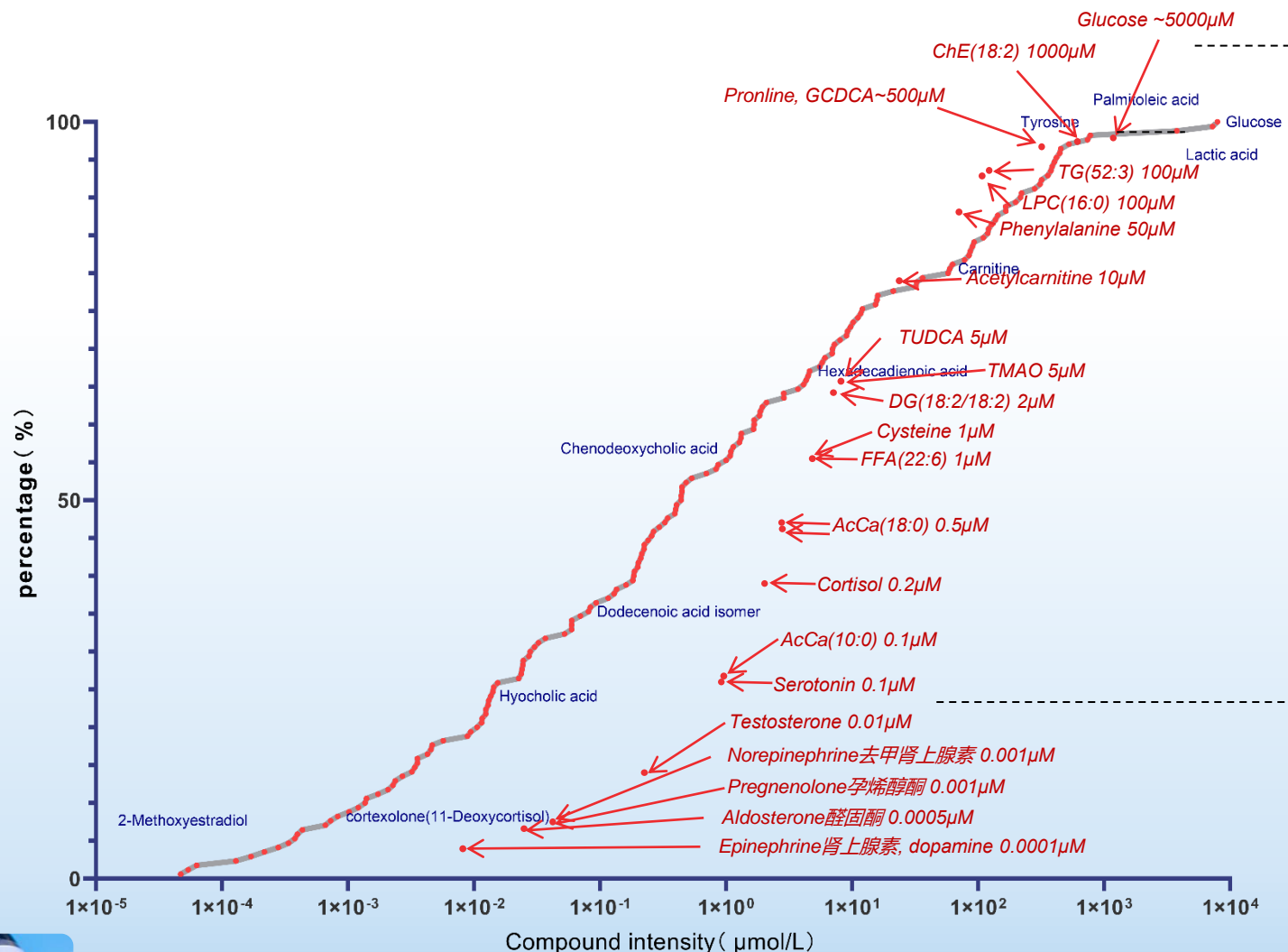
MS/MS spectra were repeatedly acquired



- Untargeted metabolomics: 小分子代谢物无标记的相对定量 Label-free relative quantitation MS1=定量, LC+MS2 + MS1=定性



# 多种LC-MS方法整合的必要性：认清矛盾才能解决问题——悬殊的浓度分布



Detectable with cutting-edge  
**Untargeted Metabolomics**

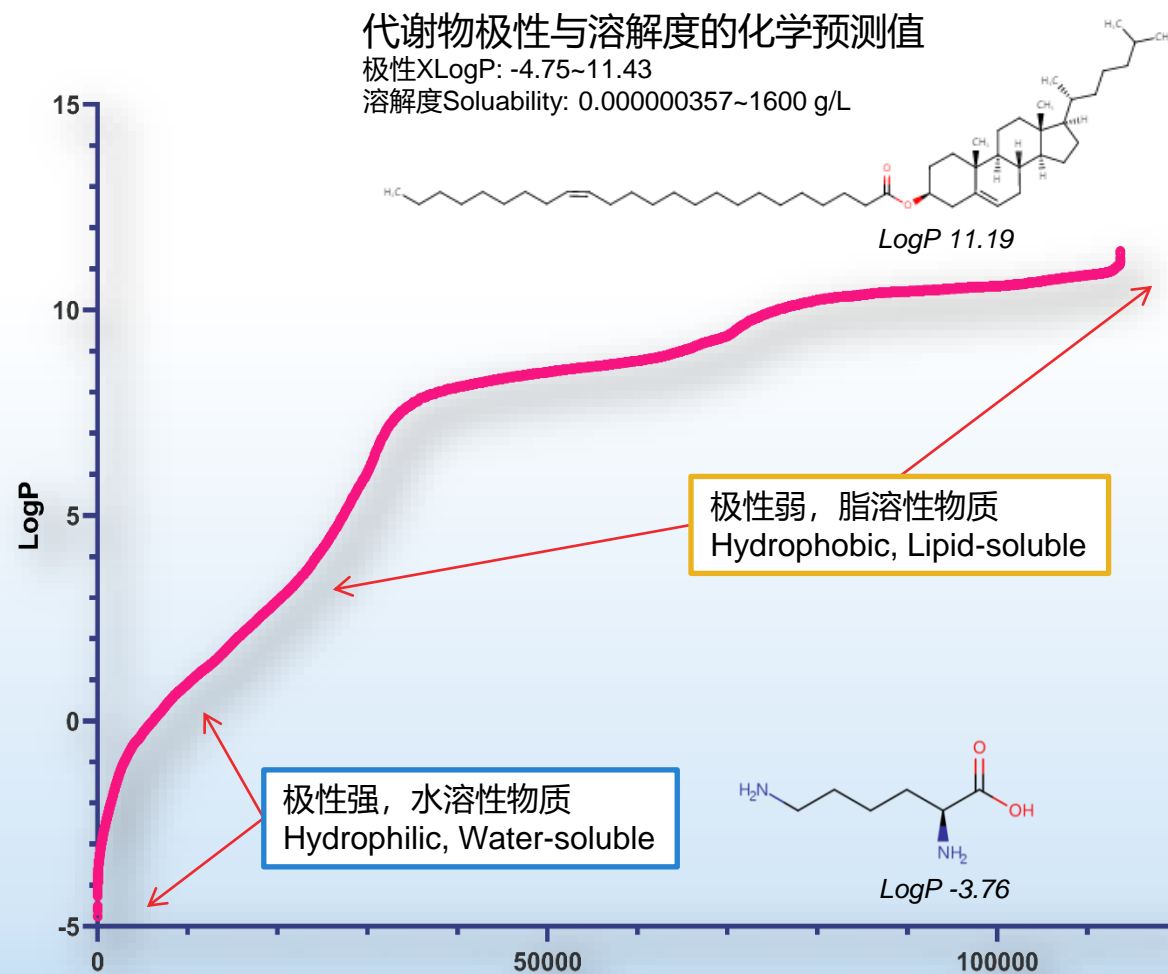
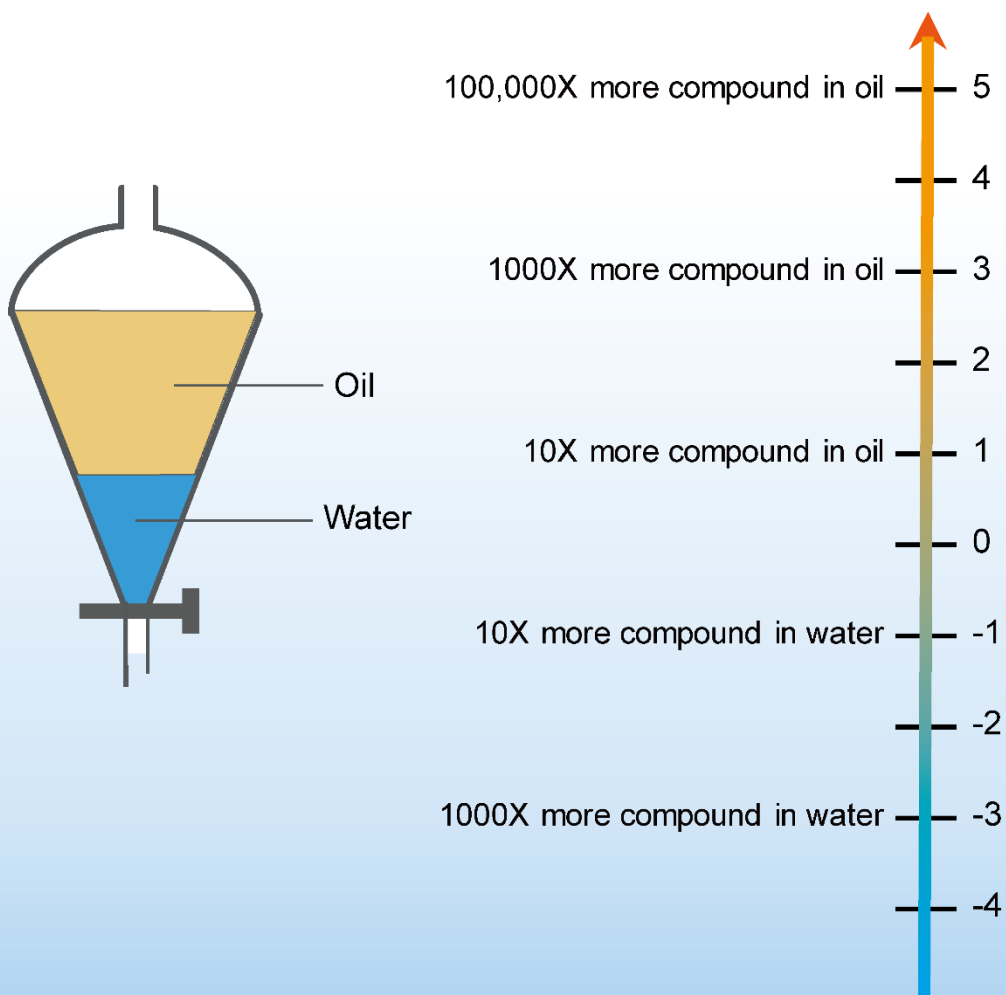
**Arena of Targeted Metabolomics**



- 体内浓度6~7个数量级的跨度，远远超越任何仪器的线性范围极限
- 痕量代谢物检测大都同时需要有针对性的富集前处理与优化的质谱检测方法

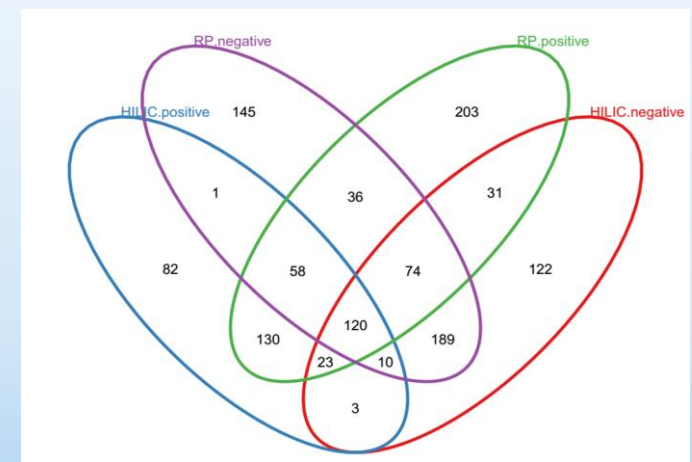
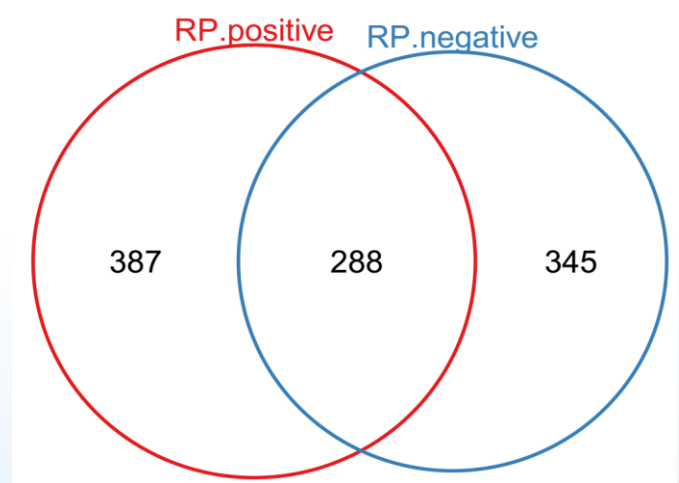
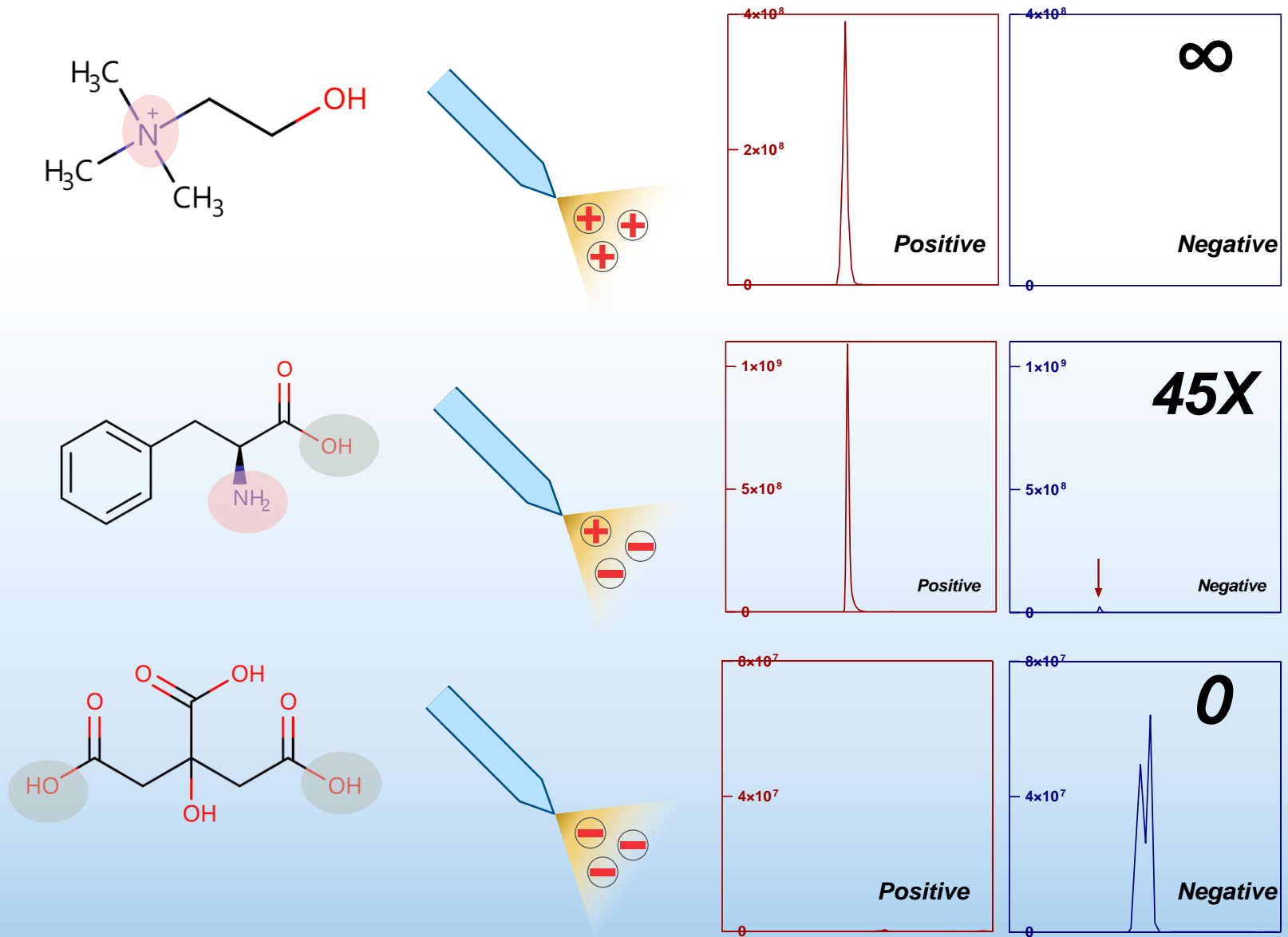
# 多种LC-MS方法整合的必要性：认清矛盾才能解决问题—悬殊的理化性质

$$\log P_{oct/wat} = \log \left( \frac{[solute]_{octanol}}{[solute]_{un-ionized}^{water}} \right)$$



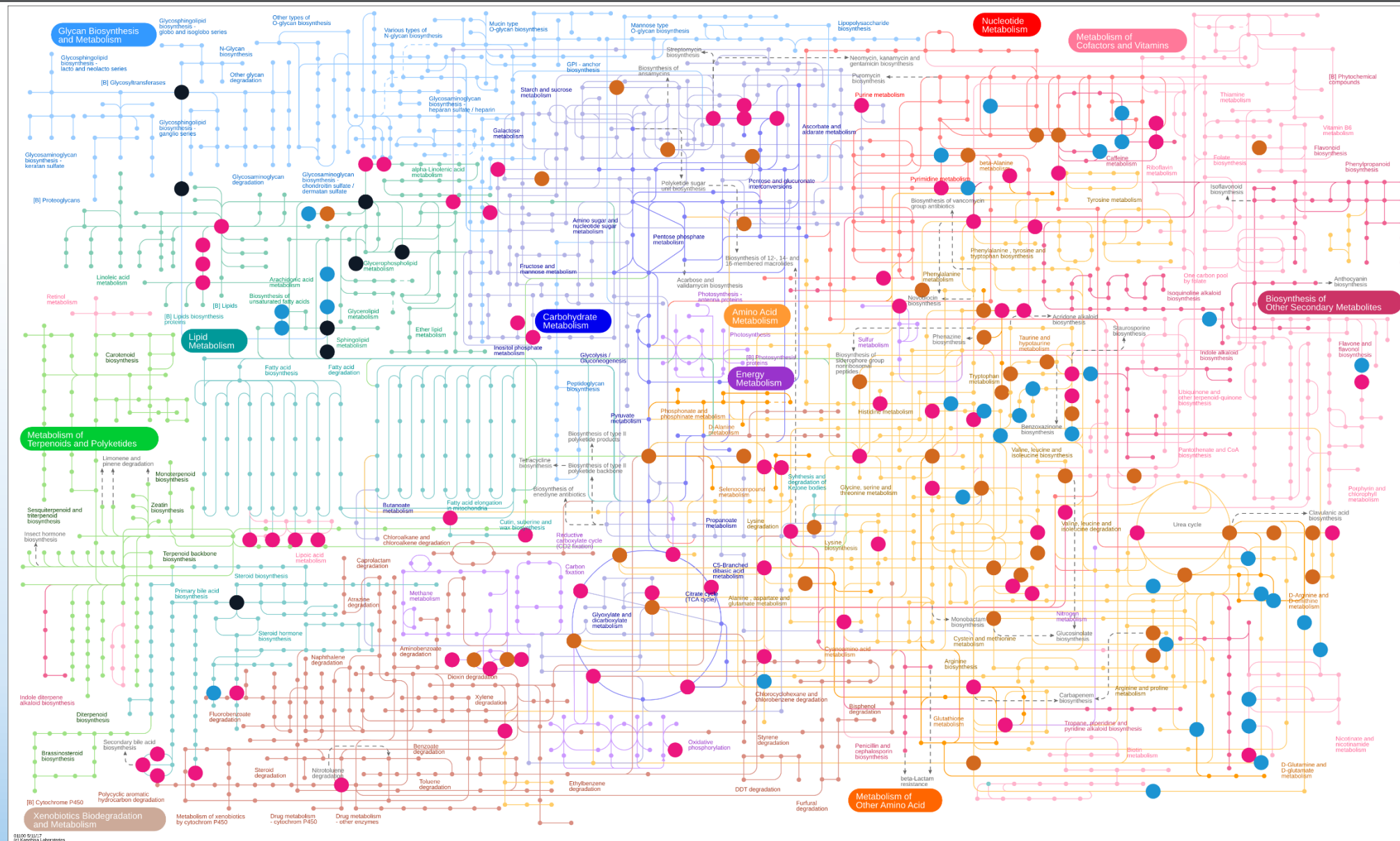
- 代谢物的极性、溶解度等理化性质差异悬殊
- 以溶解度为例，糖与甘油酯的水溶解度相差9个数量级

# 不同检测方法的有效整合有助于提高对代谢组的覆盖度





# 不同检测方法的有效整合有助于提高对代谢组的覆盖度



- Method 1
- Method 2
- Method 3
- Method 4, 5

Only metabolites with KEGG identifier are mapped in the diagram

Only 31% annotated metabolites have KEGG identifier

## Blood metabolome predicts gut microbiome $\alpha$ -diversity in humans

Tomasz Wilmanski<sup>1,6</sup>, Noa Rappaport<sup>1,6</sup>, John C. Earls<sup>1</sup>, Andrew T. Magis<sup>2,5</sup>, Ohad Manor<sup>2</sup>, Jennifer Lovejoy<sup>1,2</sup>, Gilbert S. Omenn<sup>3</sup>, Leroy Hood <sup>1\*</sup>, Sean M. Gibbons <sup>1,4\*</sup> and Nathan D. Price <sup>1\*</sup>

maximum recovery of small molecules. The resulting extract was divided into **five fractions**, one for each of the **4 methods** and a **fifth as a backup**. Samples were placed briefly on a

be the minimum observed value for that metabolite. These preprocessing resulted in **619 metabolites** from 648 samples kept for further analysis.

Nature biotechnology 2019

## ARTICLE

OPEN

<https://doi.org/10.1038/s41586-019-1237-9>

## Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases

*LC-MS analyses.* A combination of **four LC-MS methods** were used to profile metabolites in the faecal homogenates, as previously published<sup>58</sup>; two methods that measure polar metabolites, a method that measures metabolites of intermediate

biochemically related metabolites further suggest that the differences seen during dysbiosis do not stem simply from the wholesale dilution of stool. Numerous other metabolites were also significantly altered in individuals with dysbiotic IBD (117 of **548 tested known metabolites** with FDR  $P < 0.05$ ; Extended Data Fig. 4d, Supplementary Table 16), showing large-scale dysregulation of metabolite pools in tandem with host- and microbiome-specific taxonomic and molecular features

Nature 2019

# 我们的技术能力同步或局部领先于国际同行的最新水平

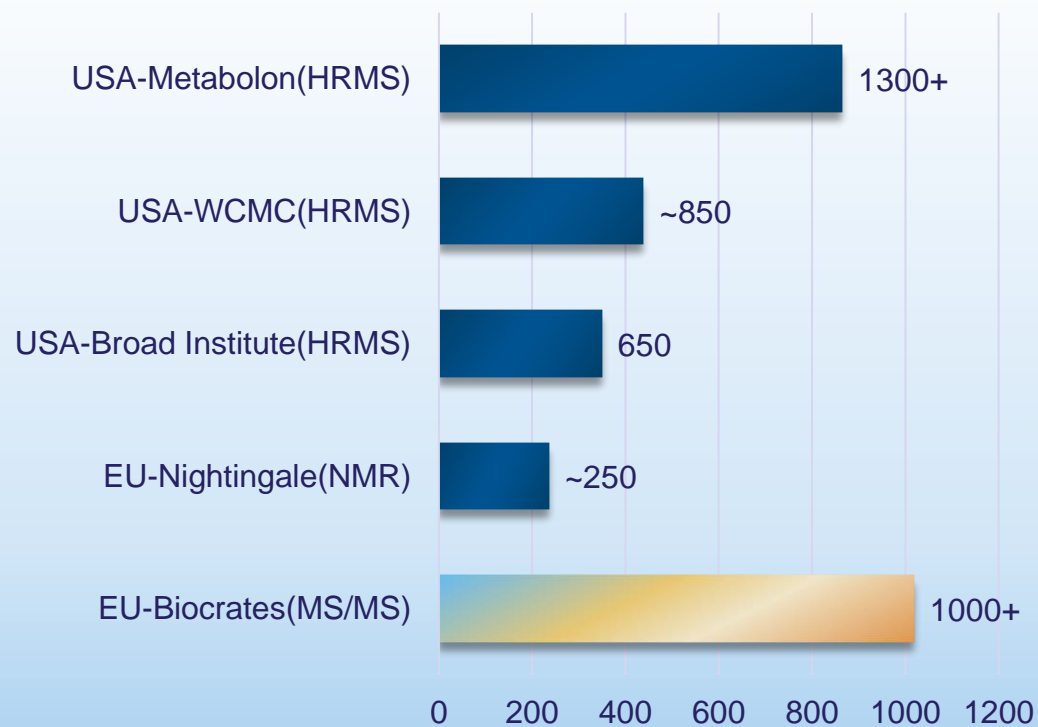
## State-of-the-art metabolomics technology 国际水平与技术路线

- 3~4种LC-MS方法集成
- 或, 靶向定量试剂盒

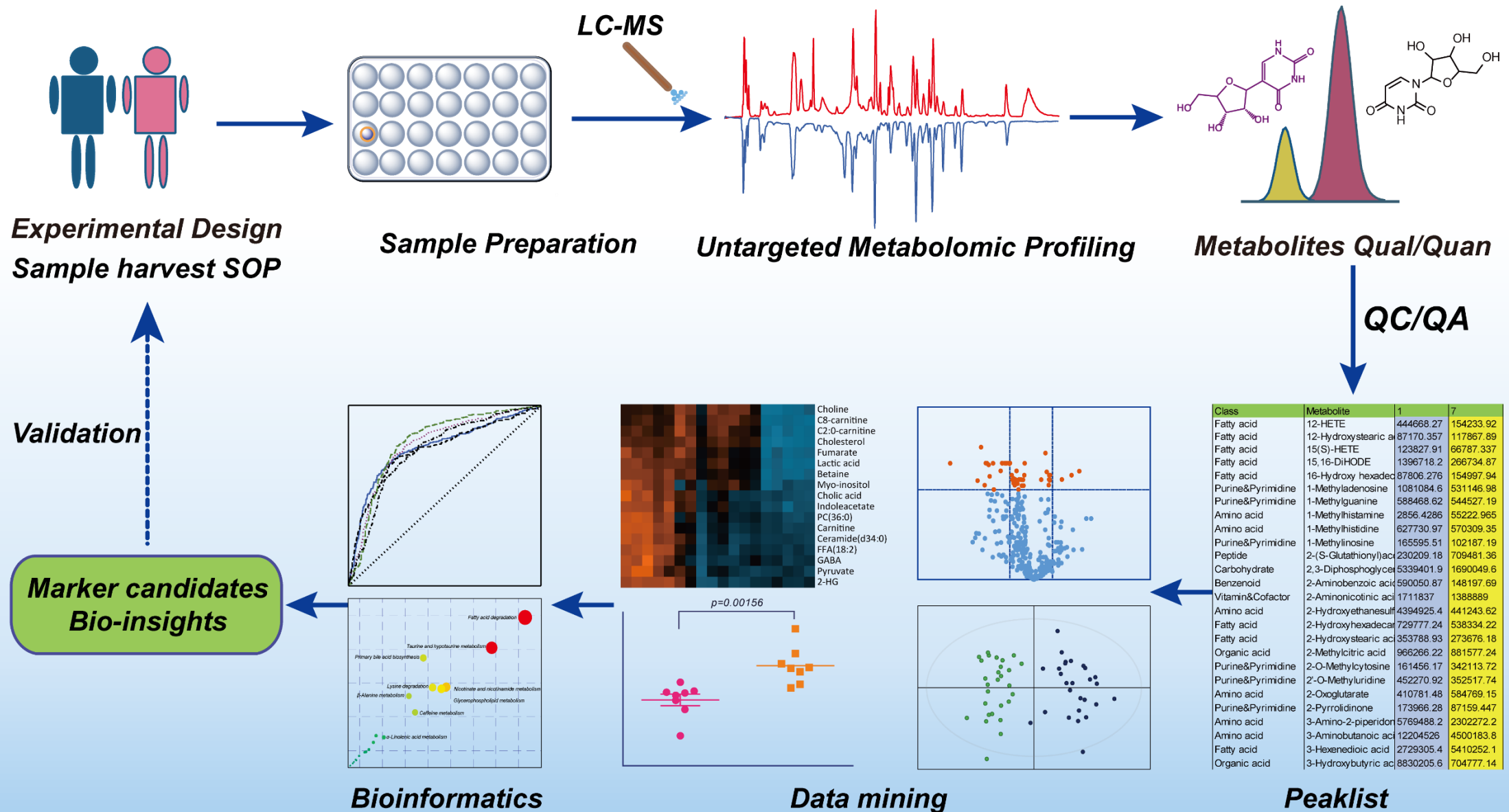
## 我们Meta-Phenotyper™ 非靶向代谢组学技术平台的能力

- 2~4种LC-MS方法集成
- 人血中结构鉴定1200~1400种代谢物

### Identified Metabolites by Top Labs



# 实验流程：代谢物的准确可靠定性是非靶向代谢组学研究的核心与关键





## 完整的代谢物结构注释技术步骤

### • 分子式确定 Elemental composition prediction

1. Charge state 电荷数
2. Exact mass 精确质量数 **<3~5 ppm**
3. 同位素丰度比、精细同位素轮廓
4. MS/MS filter
5. Heuristic rule (seven-golden rules)

### • 一级质谱数据检索 Database Search

- ❑ KEGG
- ❑ Human Metabolome Database
- ❑ METLIN
- ❑ ChemSpider
- ❑ LipidMAPS, etc

### • 二级质谱谱图比对 MS/MS Library search

- METLIN
- HMDB
- MassBank
- mzCloud

### • Identification, annotation 代谢物结构鉴定、注释



## Metabolomics Standards Initiative(MSI)公认的代谢物鉴定四个层次

### Unambiguously identified 确信的鉴定

独立或正交的条件下使用标样验证LC-MS分析时保留时间、精确质量数、同位素峰丰度比和串联质谱图均与标样一致

### putatively annotated 推定性注释

代谢物未经标样验证，但其质谱图与文献报道或数据库中的参考谱图一致

### Putatively characterized 推定性表征

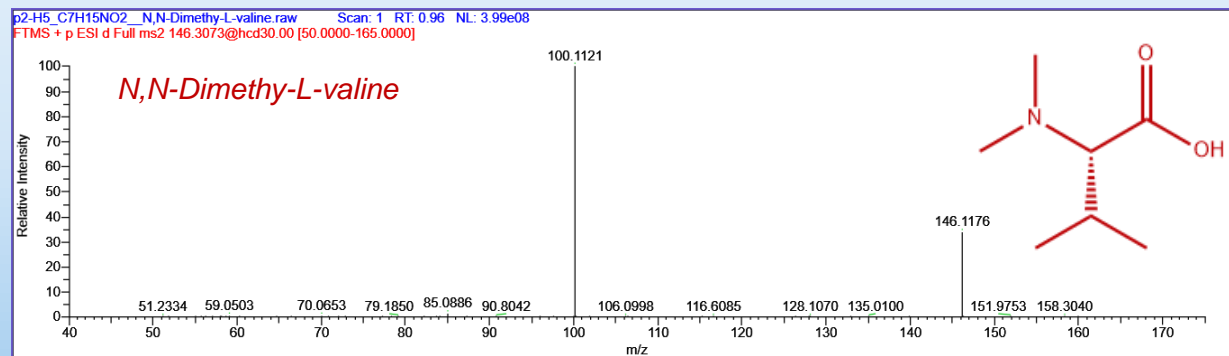
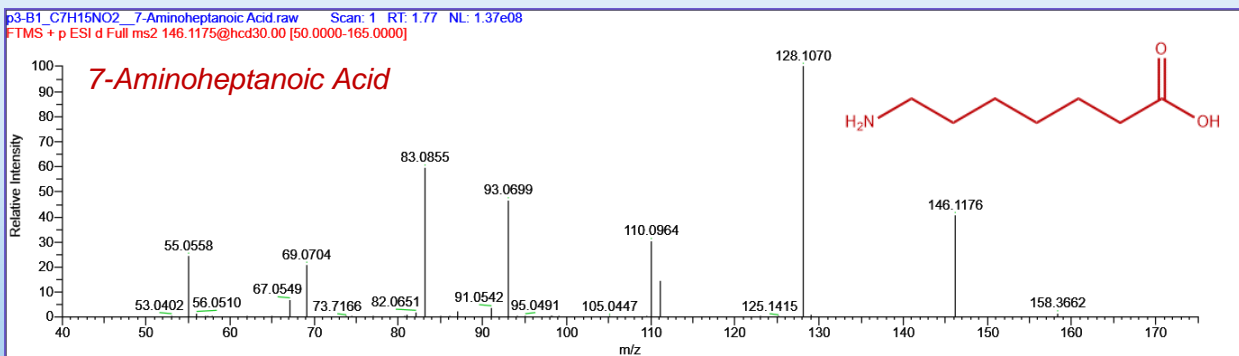
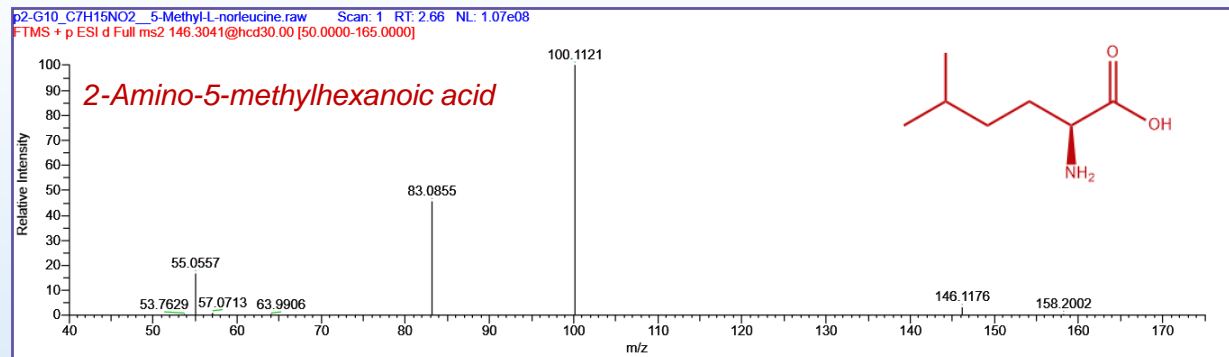
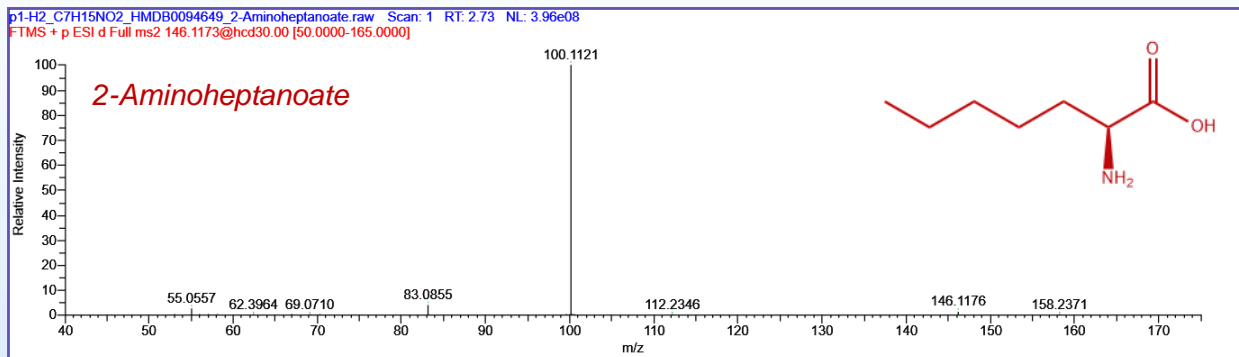
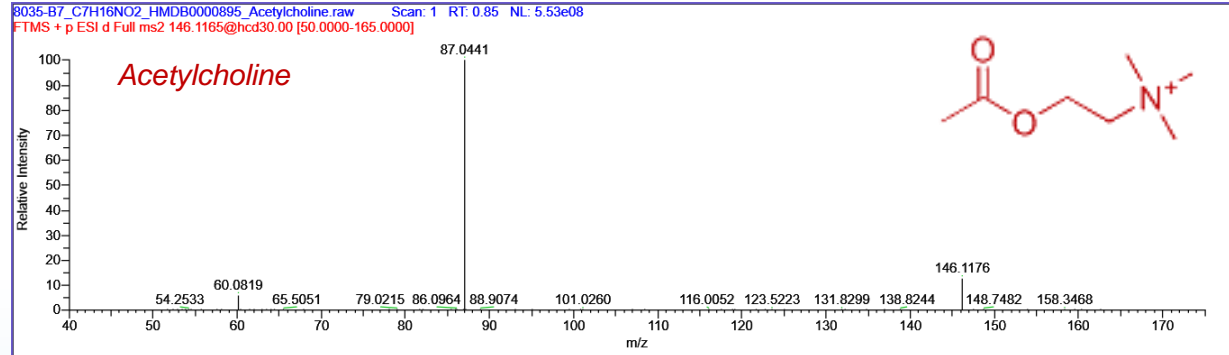
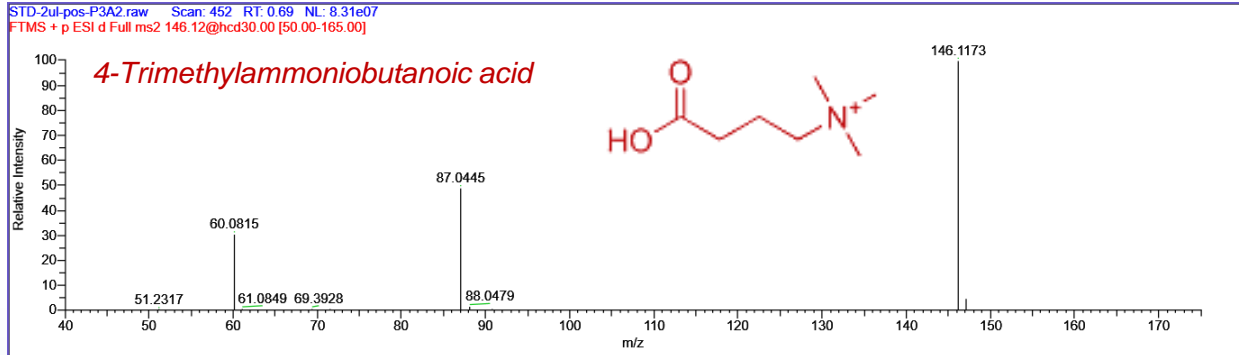
与2类似，代谢物未经标样验证，其质谱图与已知同类物质的质谱图类似

Unknown X  
未知形式

# 我们团队15年代谢组学从业心得：自建二级谱图库是科技服务转化的必由之路

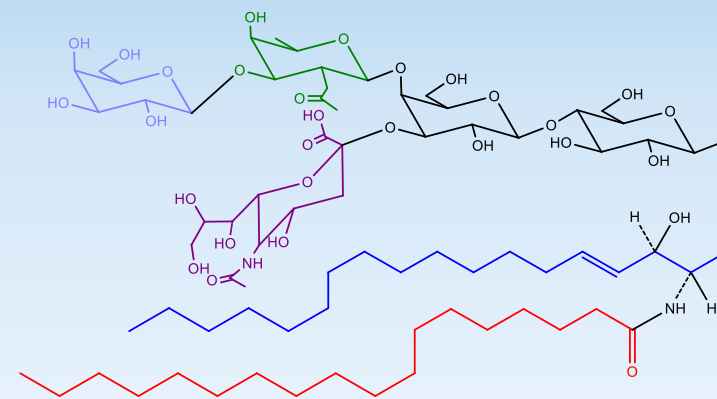
二级质谱谱图是代谢物结构鉴定的必需条件!

举例:  $C_7H_{15}NO_2$ ,  $m/z$  146.11756

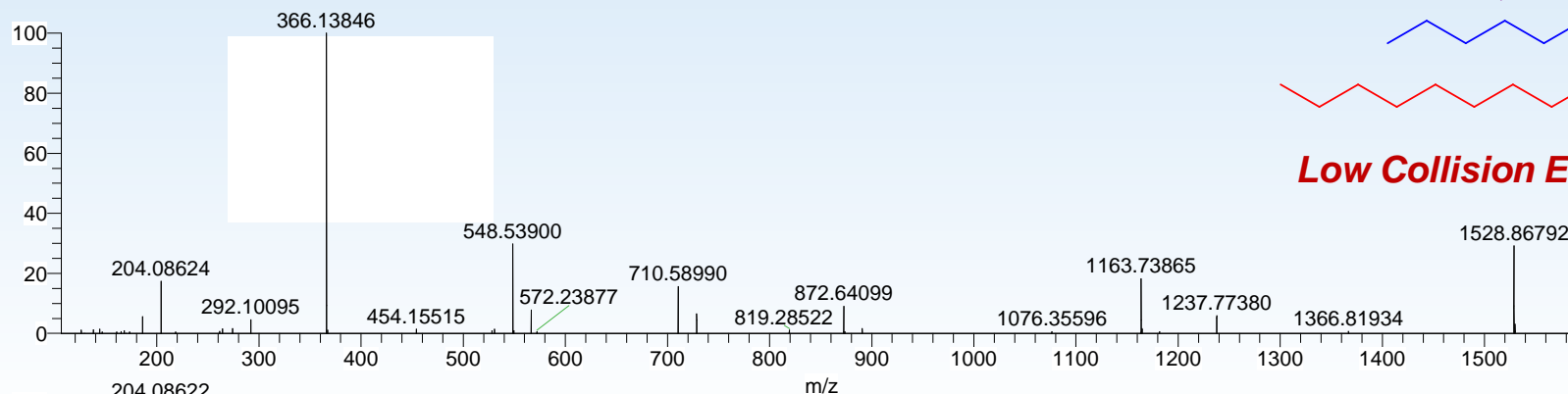


# 为什么要开发自主知识产权的本地化质谱谱图库？为之，则难者亦易矣

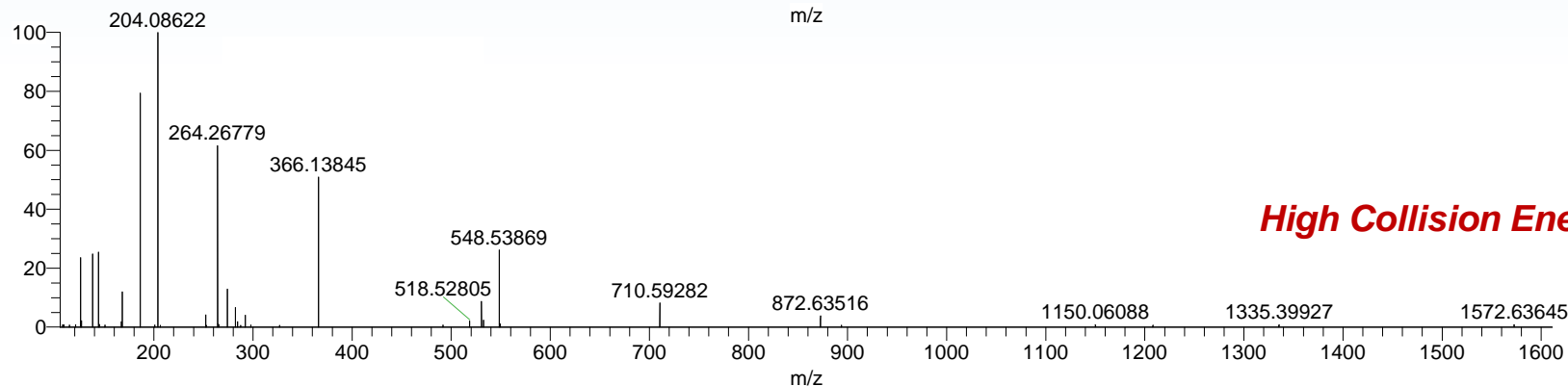
- 每家的质谱设计生产都不一样，市面上存在几十种产品形式，这一复杂混乱的行业现状导致LC-MS的二级谱图库难以统一。
- 同一物质在不同的质谱平台上采集到的谱图可能相近，也可能迥然有别。
- Garbage in, Garbage out
- 实践证明：使用在**同一种质谱平台**上采集的谱图做谱库检索，鉴定的准确性更高，检索效率更高
- **硬核创新：核心技术既不会从天而降，也买不来，需要独立自主建库！**



**Low Collision Energy**



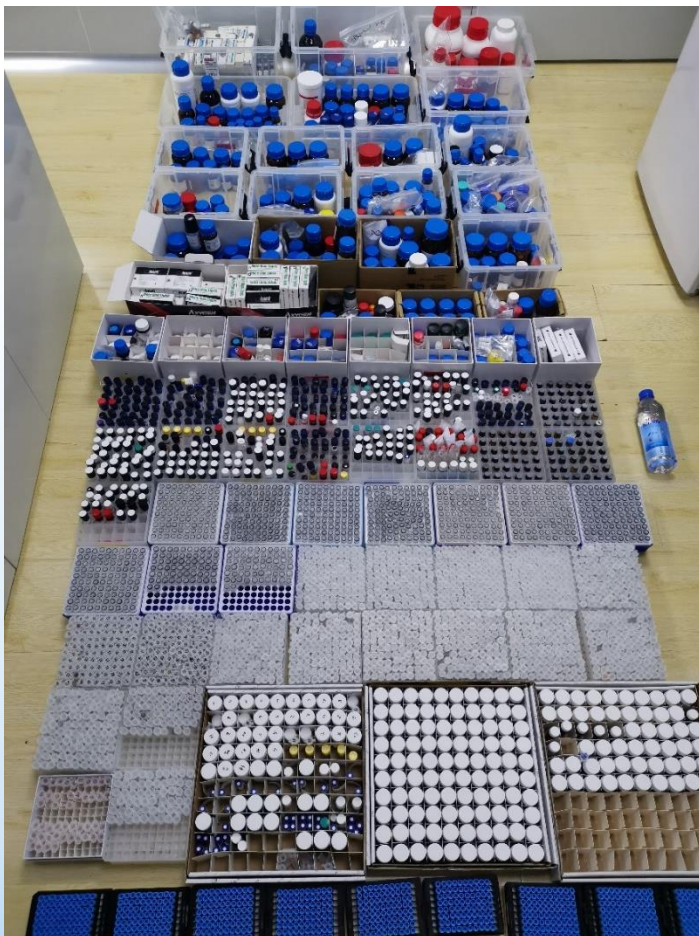
**High Collision Energy**



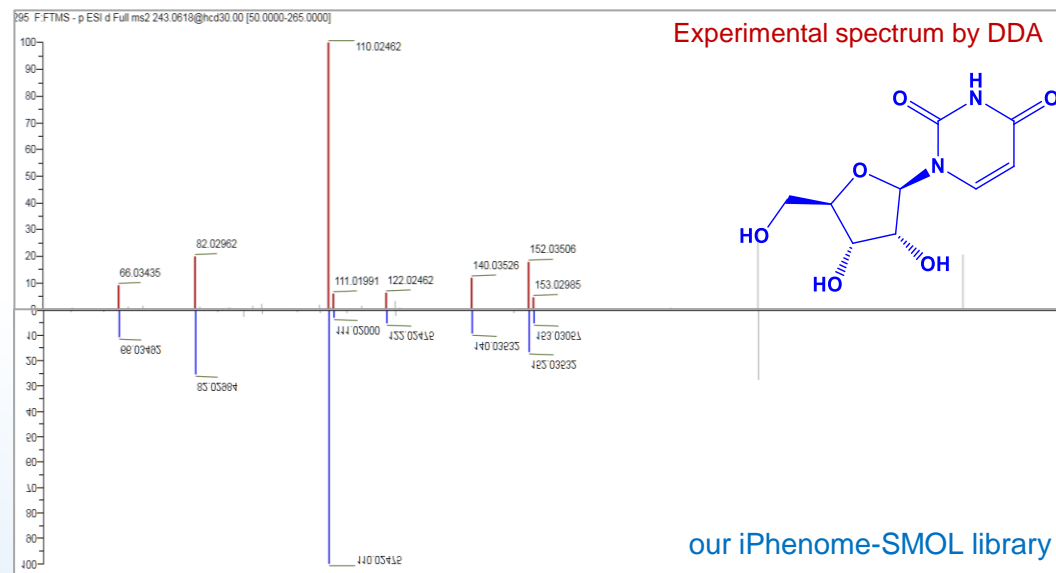
# Meta-Phenotyper™ 高解析代谢全谱 关键技术2: 自主知识产权的SMOL谱图库

## SMOL: Small Molecules Orbitrap-based Spectrum Library

### 自建实测谱图库

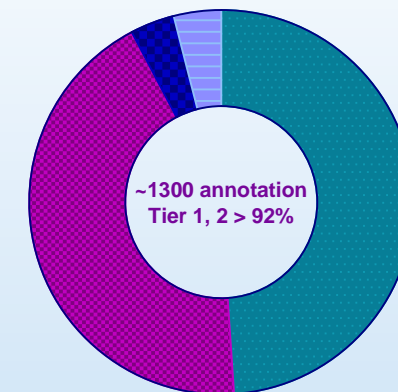


- 实验室现存标准品4500+种, 同位素内标300+种
- 部分标准品照片, 摄于2021年初



## iPhenome SMOL Spectrum Library

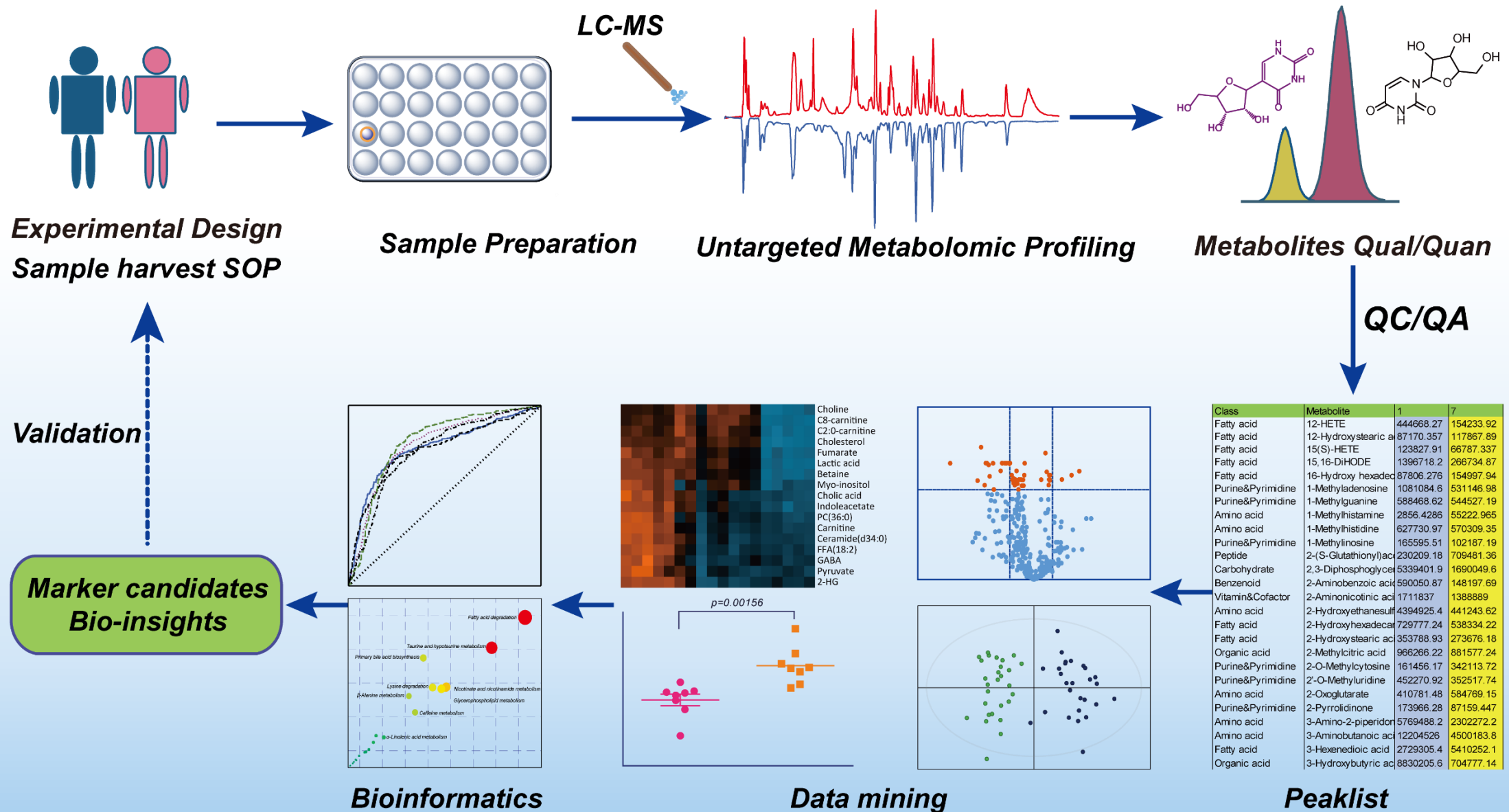
- 48.9% Tier Level 1
- 43.3% Tier Level 2
- 3.73% Tier Level 3
- 3.99% Tier Level 4



指导原则	遵循Metabolomics Standards Initiative行业指南规范, 坚持自律
鉴定策略	MS1 + MS2 + Accurate retention time database
SMOL库	~8000种内源性代谢物/暴漏组化合物/药物等, 34000+张高质量谱图逐一人工核实、校正和复核
目前能力	~1300个结构注释的血清代谢物中, >92%的结构鉴定层级为1和2。
开源谱图库	参考使用mzCloud、NIST Tandem、MassBank/MoNA、Fiehn Lab's Libraries、LipidBlast等开源谱图库

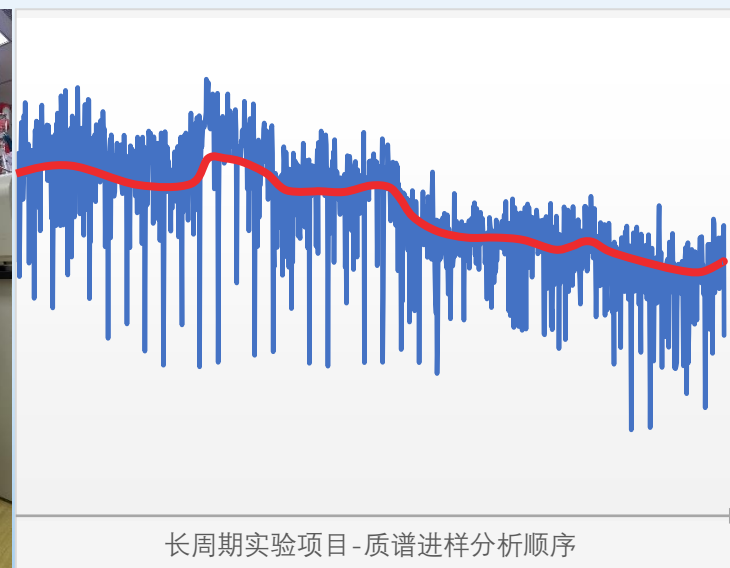
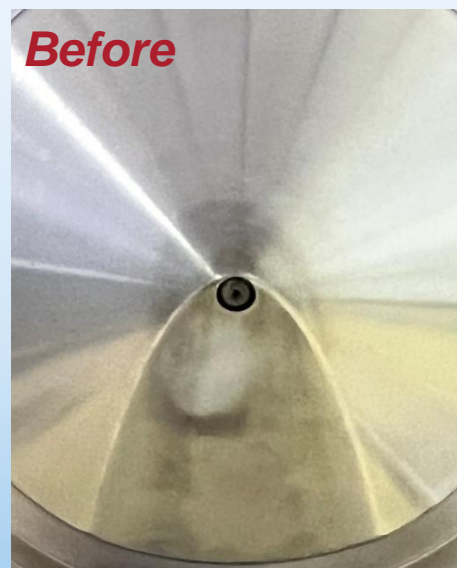
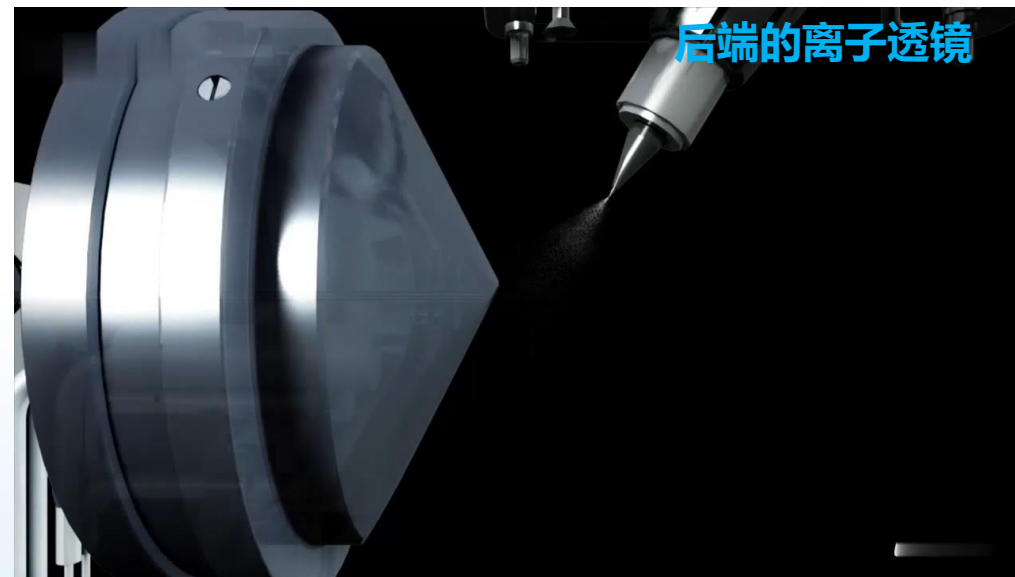
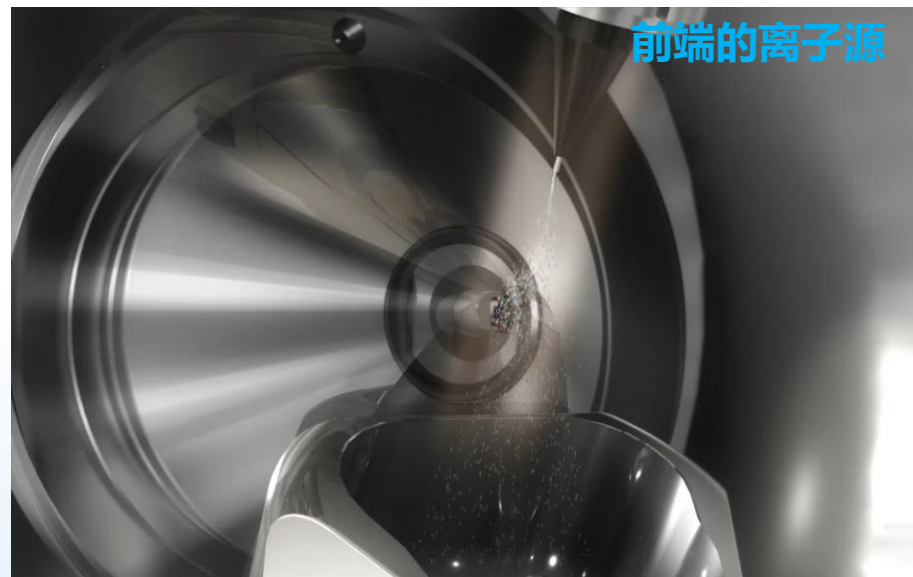


# 实验流程：分析质量控制是非靶向代谢组学测试的重要环节



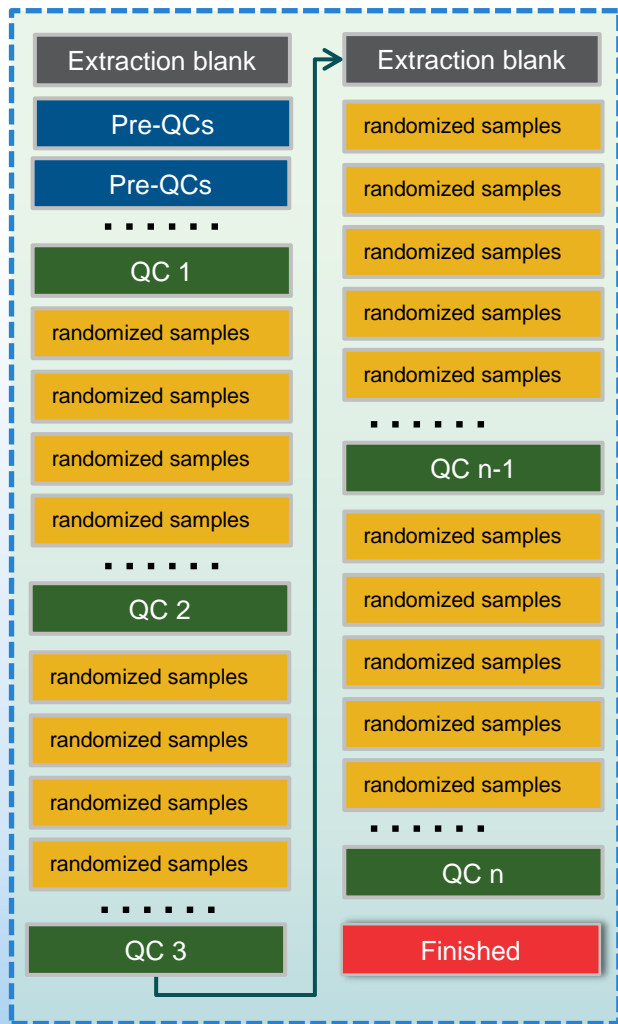
# 质控对于质谱代谢组学研究实践尤为重要

天然上，质谱不是无接触型的检测器，而是随时受到测试样本的污染，只能有限稳定。因此，合格的数据质量是需要用心与经验、完善的流程管理体系才能生产出来的。



# 体系的鲁棒性、大队列分析数据质量

## Analytical Batch Arrange 样本分析序列的设置

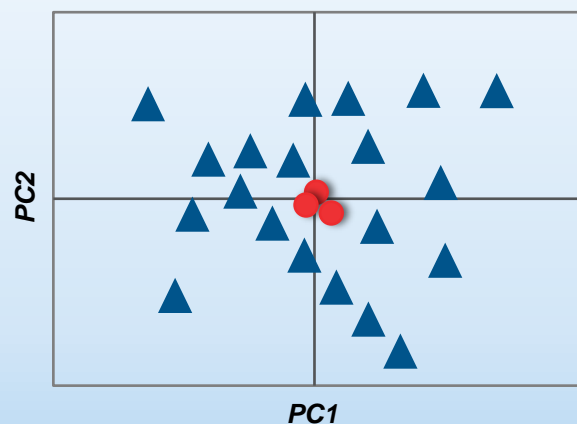


1. 混合质控策略 (Pooled Quality Control) : 主要目的是评价、监控质谱设备在做样过程中的性能变化
2. 同位素标记内标 Isotope labelled internal standards: 评估样本前处理的平行性

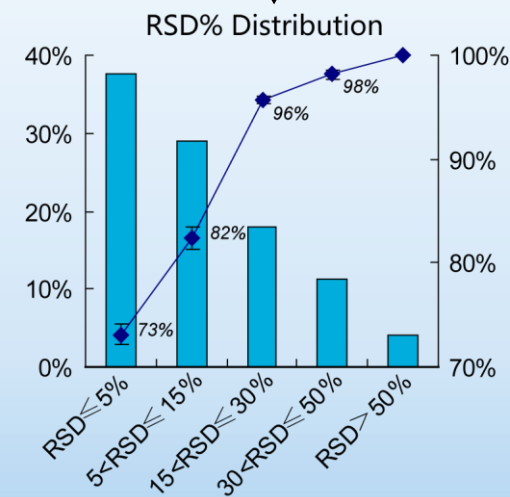


Pooled all the samples evenly together  
or, reference samples, NIST SRM1950

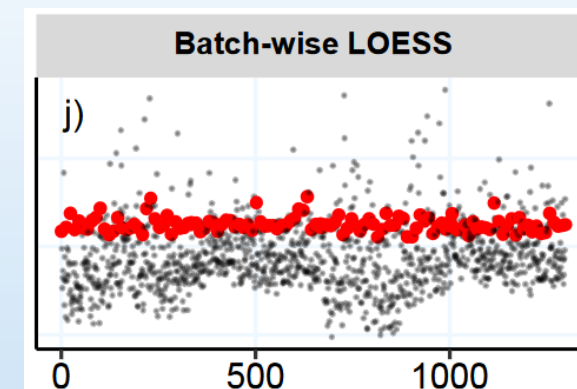
QC sampled analyzed repeatedly  
during analytical batch!



1. 评价分析性能, 判断数据质量



2. 选取阈值cutoff, CV < 30%



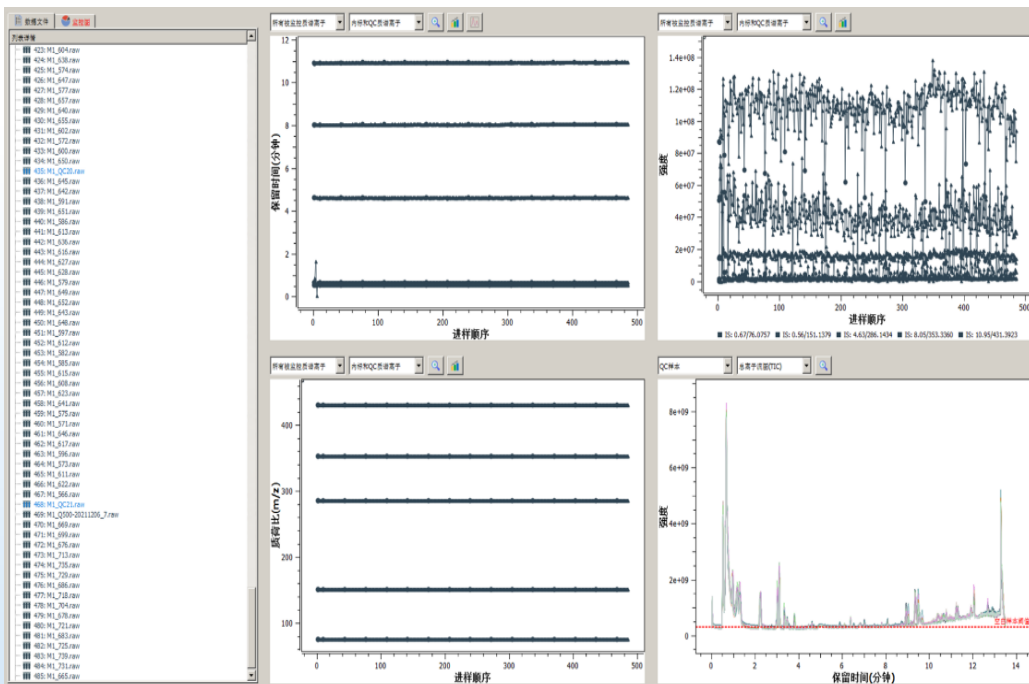
3. 大队列, 不同批次间的数据校正与整合

# Meta-Phenotyper™ 高解析代谢全谱 关键技术3: 干实验+湿实验并重的全流程质控体系

- 我们秉承的质控方法论：优秀的质谱代谢组学数据质量是用心与经验、用良好的流程管理生产出来的。



- 15年质谱代谢组学实践，自主设计开发质控大师软件
- 实时多维度的即时诊断：上工治未病，善战者无赫赫之功



- Wet Lab Work 实验科学:**
  - 规范的质量管理体系与落实执行、丰富的项目经验加持
- 严格的前处理规范:**
  - 液体机器人与专家半自动相结合的样本制备
- Dry Lab work 人工复核:**
  - 训练有素的质谱工程师对所有定量数据逐一进行人工核实



- sQ500参比血清:** 用于实验室内部的分析质量控制、设备长周期性能监控、数据校正与批次数据整合等
- 非靶向质谱试剂盒+质控大师软件:** iPhenome® Metabolome FastPep 试剂盒, QC Master™软件
- 双重质控:** 大项目Pooled QC + sQ500实验室内控标准参比血清





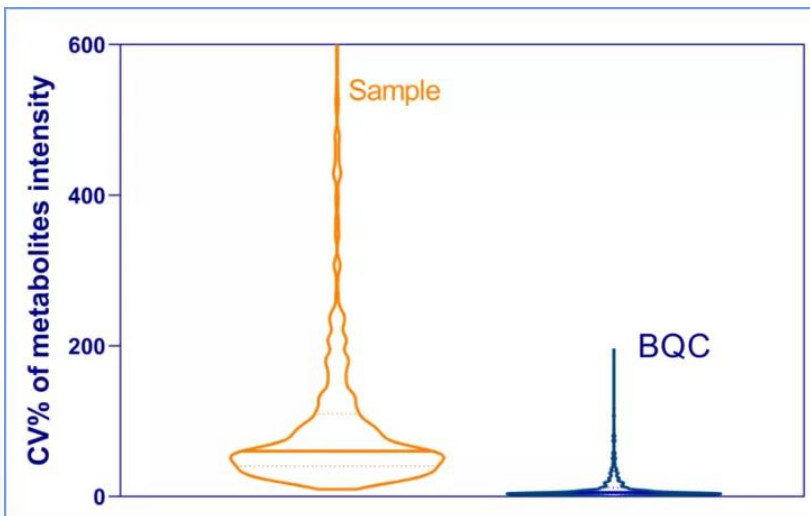
# 已结题案例：非靶向代谢组学数据质量

覆盖广

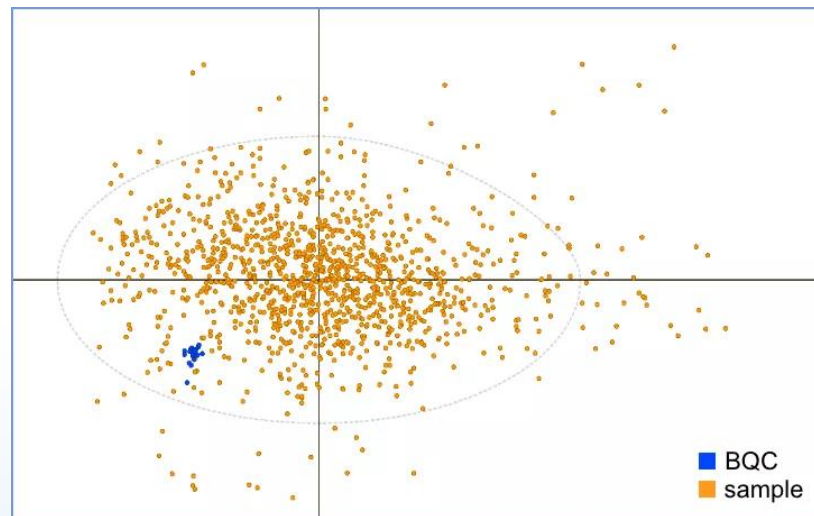
测量深

定性准

质控稳

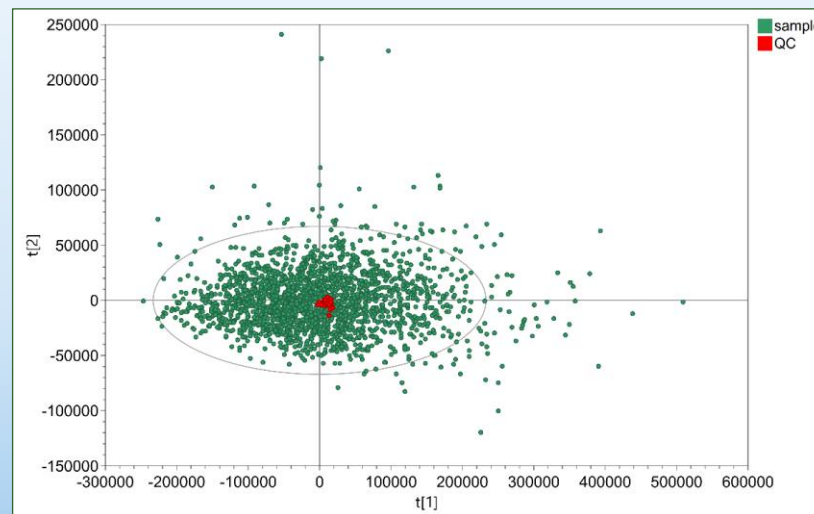
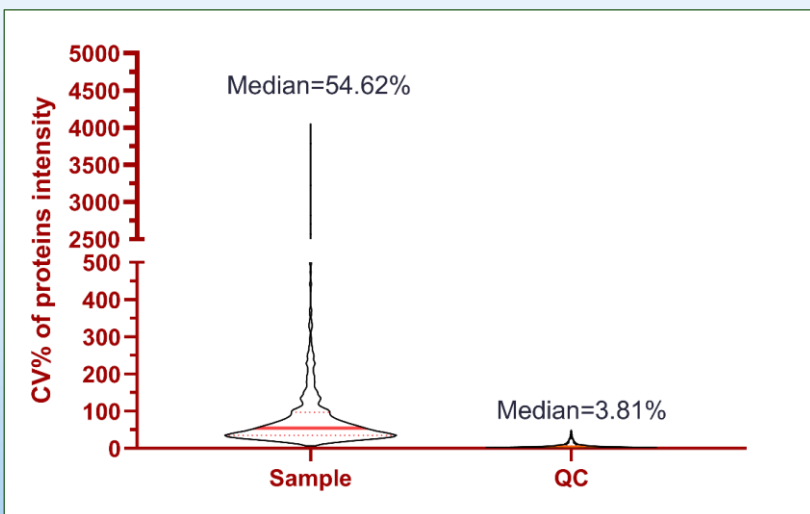


单一项目1210个血浆样本，QC中91%以上的代谢物定量值CV<30%，CV中位数5.46%



1210个血浆样本非靶向代谢组学项目  
质控结果PCA图

2021年：  
1200+例人血浆  
非靶向代谢组学检测  
CV=5.46%



2022年：  
2000+例人血浆  
非靶向代谢组学检测  
CV=3.81%

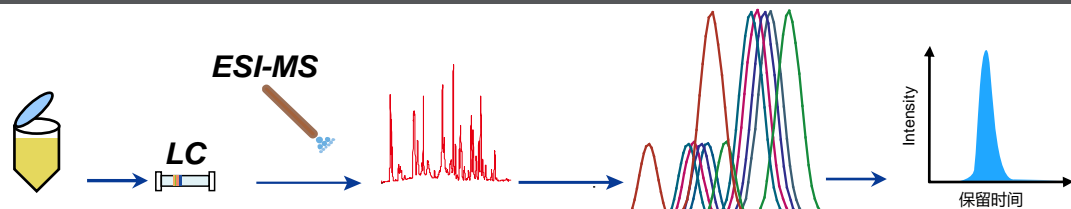
# 非靶向代谢组学测试 **meta-Phenotyper™**: 模块化组合套餐

- 目标: 定性可靠, 定量精准
- 质控体系: 秉承“好的质量是生产出来的”的数据质量观, 关口前移, 测试全流程质控
- 模块化: 五种标准化方法, 按需组合 (预算、测试深度需求), 推荐三种最常见检测套餐

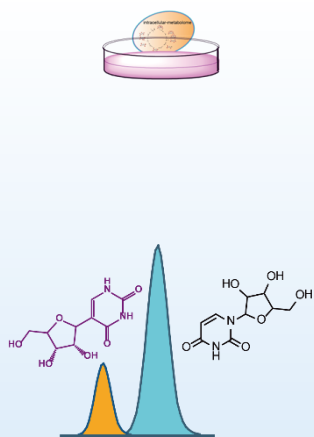


提示: 代谢物的最终鉴定数目与样本类型、质量有关。

# 基础知识：质谱是如何定量？



## 1. 非靶向-相对定量

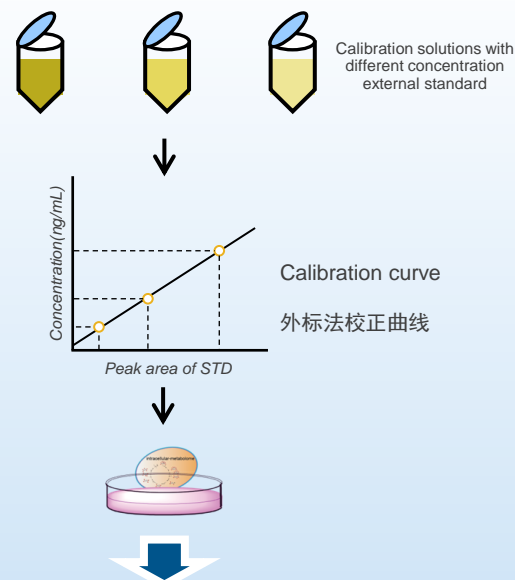


- 峰面积Peak area(无量纲)
- No Calibration curve

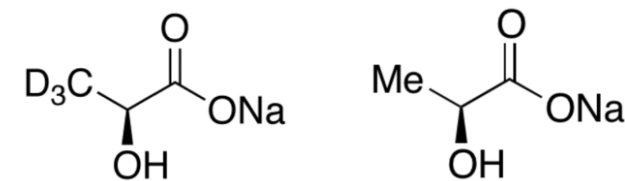
1. 操作简便
2. 与非靶向代谢组学分析无缝衔接
3. 相对定量结果（峰面积值）
4. 适于面积归一化法等其他定量计算

## 2. 外标法绝对定量

- 未经同位素标记的外标物

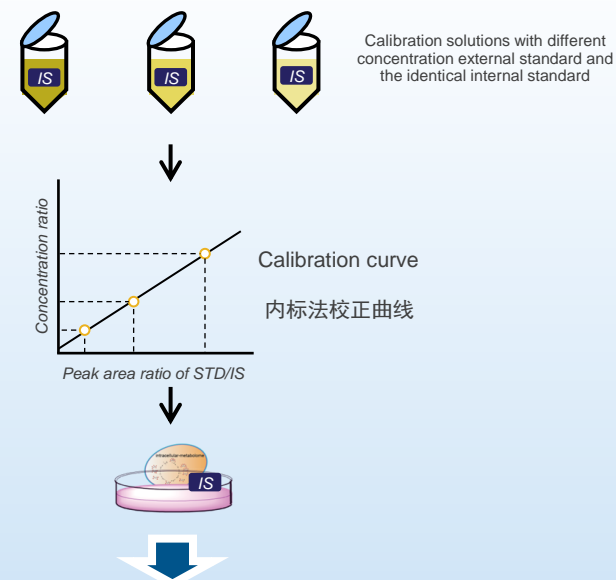


1. 最常用定量方法，结果较为准确
2. 进样量必须准确
3. 仪器稳定性要求高
4. 对样品前处理过程中被测组分的变化无法进行补偿



## 3. 内标法绝对定量

- 未标记的外标物 & 同位素标记的内标物 & 基质匹配空白样



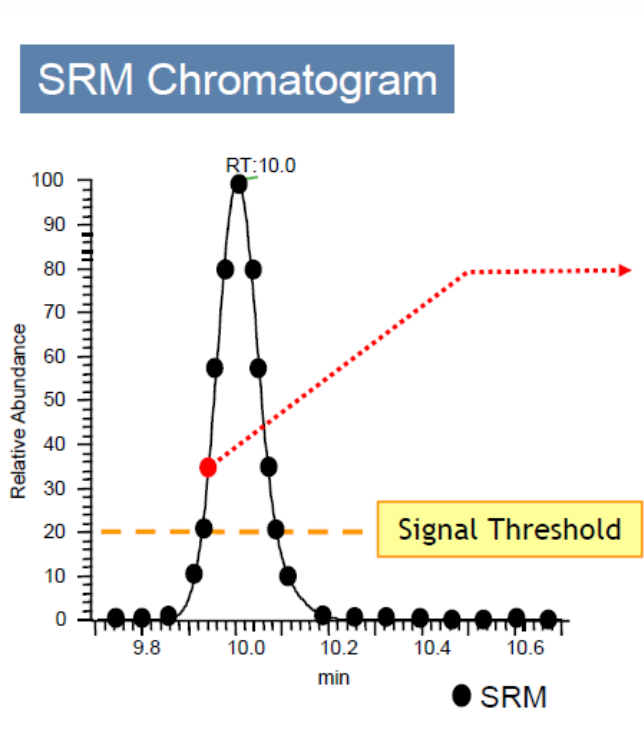
1. 检测内源性化合物金标准
2. 对分析方法细微变化较耐受
3. 可部分补偿被测组分样品前处理过程的损失
4. 操作相对繁琐，成本高
5. 受限于同位素标记标准品

# 靶向代谢组学数据采集：色谱保留时间，SRM离子对

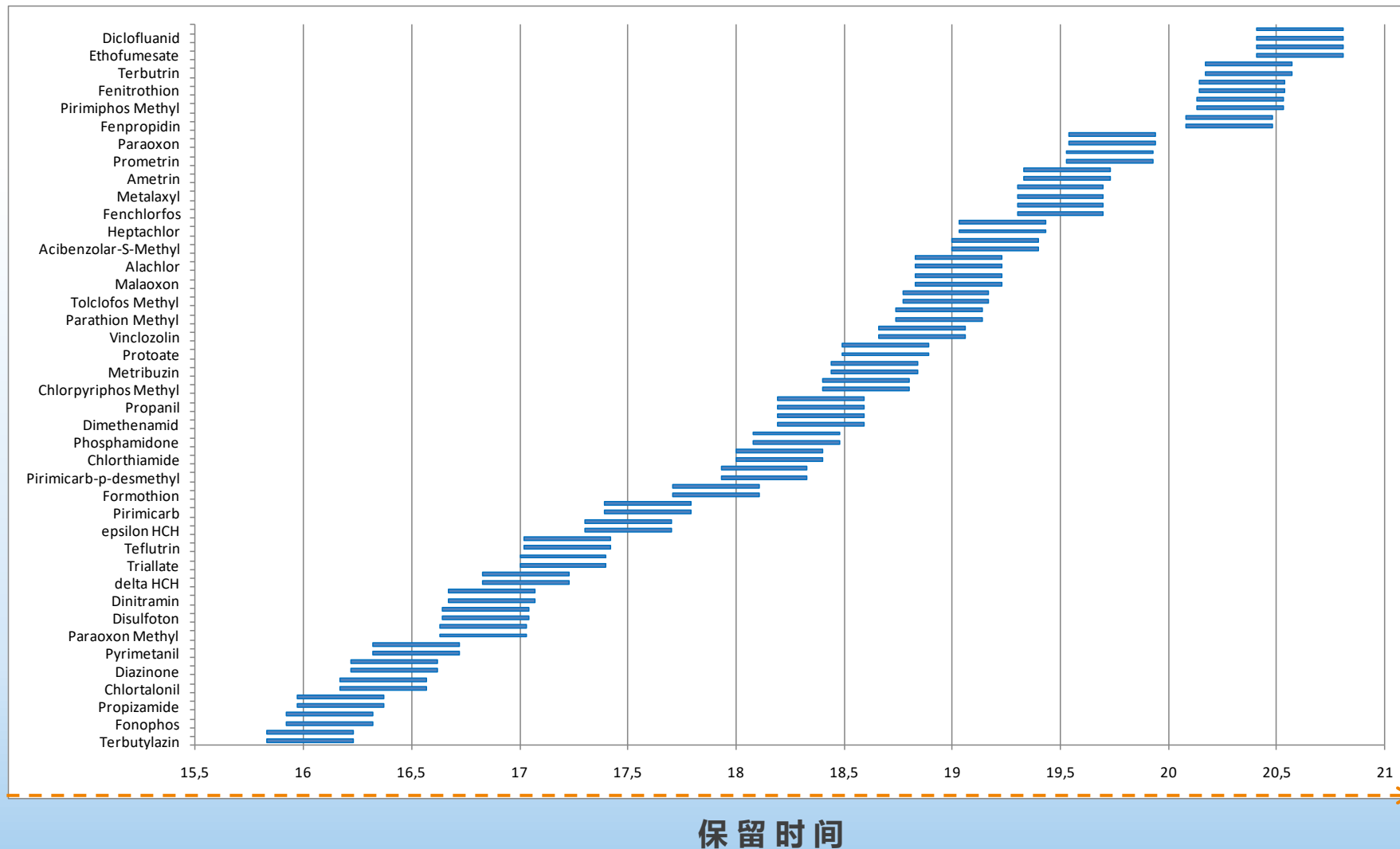
## SRM选择反应监测模式 Selected Reaction Monitoring

SRM离子对 Transition:

母离子88.1  $\xrightarrow{\text{CID 碎裂}}$  子离子66.1



- 动态SRM扫描色谱保留时间信息，自动分配、合理安排每个SRM离子对的扫描时间，完成数据采集
- 但精确地描绘一个色谱峰，至少需要10~15个质谱扫描点以确保定量效果。因此，SRM扫描离子对是有规模上限的。







## • 先进的质谱测试平台

- SCIEX Triple Quad 5500+ 二维超高效液相色谱-串联三重四极杆质谱
- SCIEX QTRAP 4500 MD 医疗器械许可的临床质谱
- Eppendorf 全自动样本前处理机器人



## • 专业严谨的靶向定量开发理念

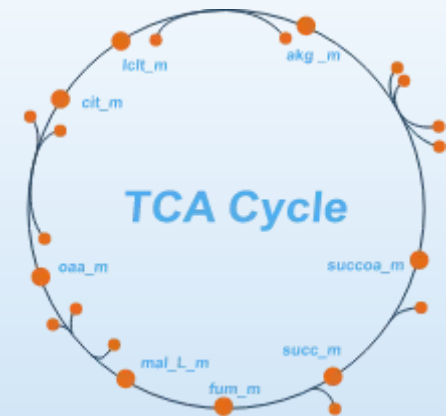
- 因物制宜、分门别类、追求极致、充分验证、灵活组合
- 参考欧盟EMA、美国FDA行业指南，充分的分析化学方法学验证
- 严格的批次QC与内部参比样SQ500双重质控



## • 丰富的方法集群和化学配套

- AccuQuanter-1800, 靶向定量600种代谢物与1200种脂质
- 现货储备300+同位素内标, 1500+质谱级外标标准品
- 个性化定量Panel设计与实施

### Metabolomics and Lipidomics



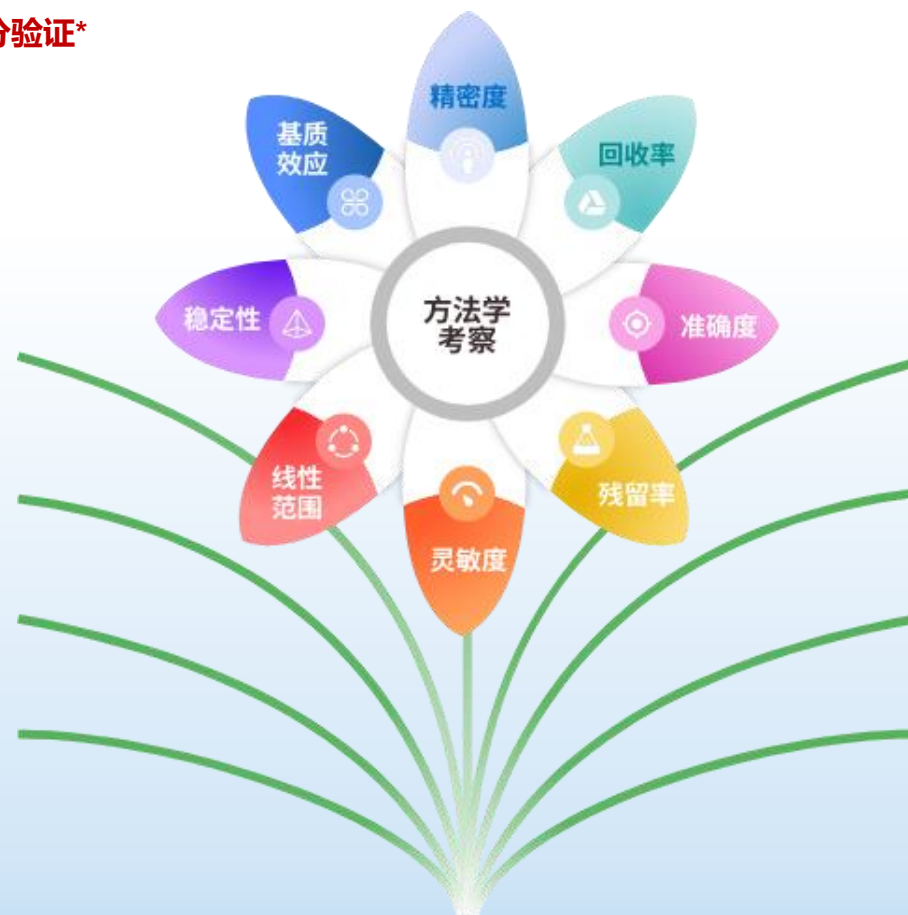
瞄准临床检验与诊断应用的技术转化来布局代谢物靶向定量方法开发和技术迭代

“乐高式” 组合=大规模靶向定量


# 靶向代谢物定量AccuQuanter™测试方法集群：聚是一团火，散是满天星

- 测试平台：行业领先的 SCIEX QTRAP 5500+ 二维超高效液相色谱-串联三重四极杆质谱；SCIEX QTRAP 4500 MD医疗诊断设备
- 标样库：常备300+种同位素标记内标，~1500种非标记外标标准品
- 开发原则：**因物制宜，分门别类，追求极致，充分验证\***

- ◆ AccuQuanter™-Bile acids **胆汁酸**
  - ◆ **70种**胆汁酸
  - ◆ 同位素内标法定量
- ◆ AccuQuanter™-SMCFAs **短中链脂肪酸**
  - ◆ **15种**短链+中链脂肪酸
  - ◆ 同位素内标法定量
- ◆ AccuQuanter™-Carnitines **酰基肉碱**
  - ◆ **63种**中长链脂肪酸
  - ◆ 同位素内标法定量
- ◆ AccuQuanter™-Steroid hormones **甾体激素**
  - ◆ **32种**甾体激素
  - ◆ 同位素内标法定量



- ◆ AccuQuanter™-**有机酸与糖类**
- ◆ **86种**能量代谢、有机酸类代谢物
- ◆ 同位素内标法定量
- ◆ AccuQuanter™-**氨基酸核苷酸**
- ◆ **132种**氨基酸、核苷酸及其主要降解代谢物
- ◆ 同位素内标法定量
- ◆ AccuQuanter™-**肠道菌群特异性代谢物**
- ◆ **82种**肠道菌群特异性代谢物，文献荟萃验证
- ◆ 同位素内标法定量
- ◆ AccuQuanter™-**溶血型磷脂**
- ◆ **105种**LysoPC, LysoPI, LysoPE等
- ◆ 同位素内标单点法定量
- ◆ Lipid-Quan**定量脂质组学**
- ◆ **1200种**脂质
- ◆ 同位素内标单点法定量

 **AccuQuanter™**  
靶向代谢物定量  
质试剂盒与方法集群

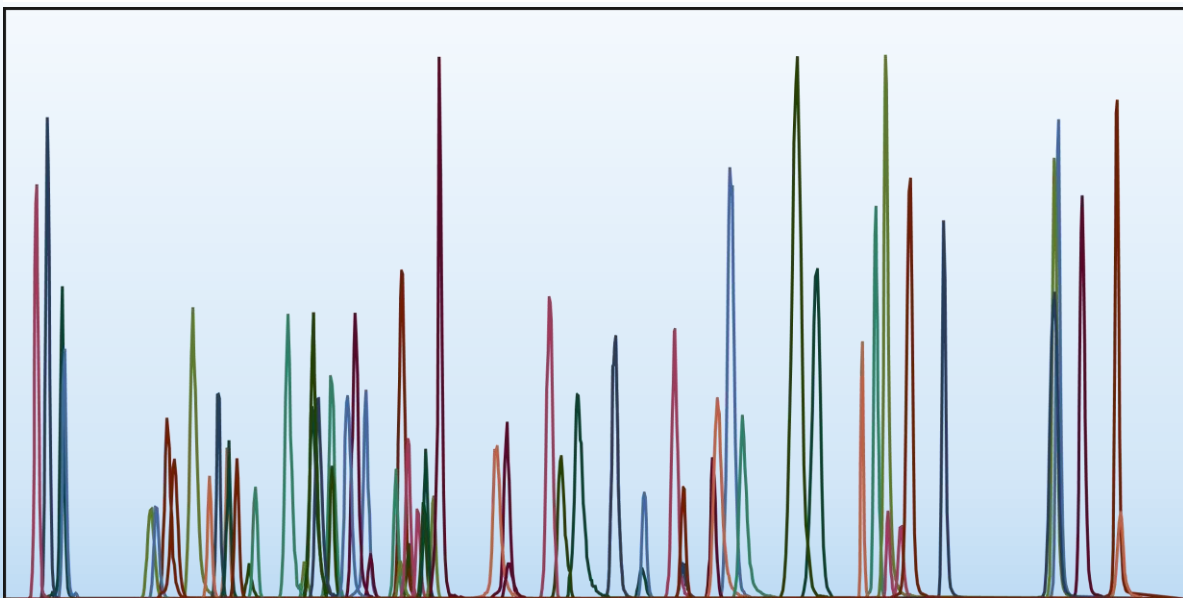
\*: 参考美国FDA，欧盟EMA以及中国药典对生物样品分析方法验证的指导原则

# 靶向代谢物定量AccuQuanter™测试方法集群： 举例

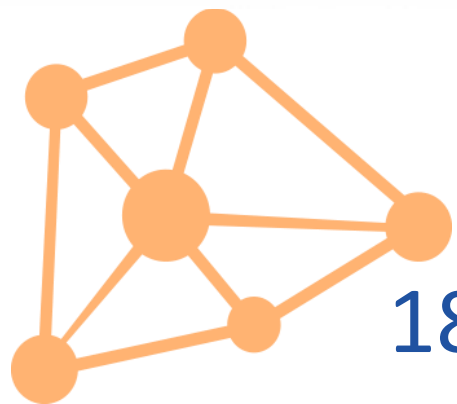
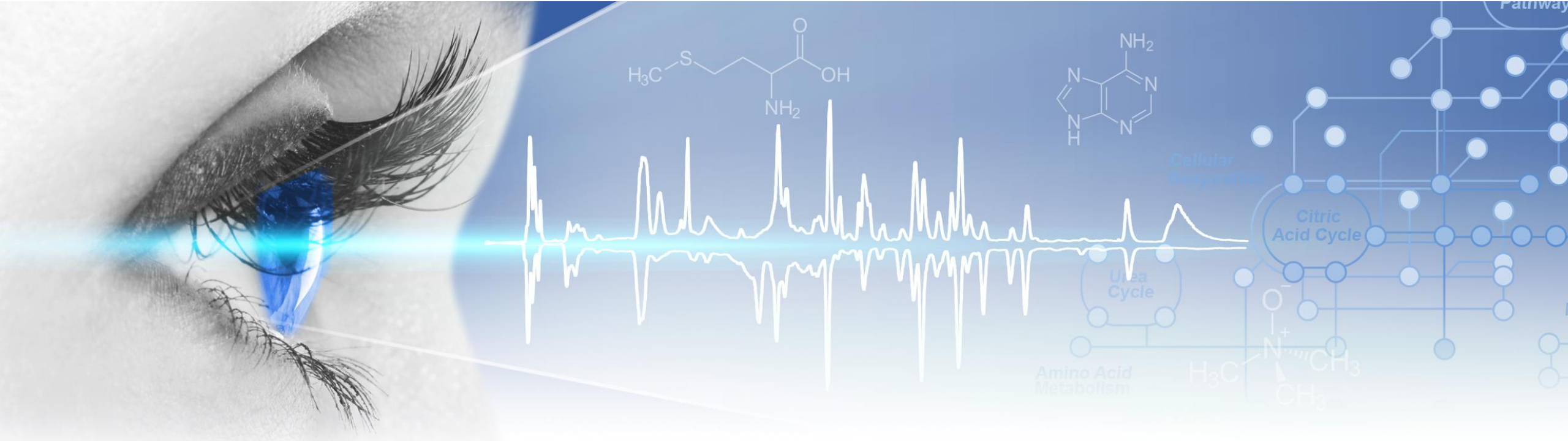
- 测试平台：行业领先的 SCIEX QTRAP 5500+ 二维超高效液相色谱-串联三重四极杆质谱；SCIEX QTRAP 4500 MD医疗诊断设备
- 标样库：常备300+种同位素标记内标，~1500种非标记外标标准品
- 开发原则：**因物制宜，分门别类，追求极致，充分验证\***



## AccuQuanter-Bile Acids 70种胆汁酸定量套餐



方法学参数	范围
精密度	0.29%~12.89%
回收率	83.23%~122.73%
准确度	81.17%~127.98%
残留率	0~18.30%
检测限	0.227 ng/mL~0.908 ng/mL
定量限	0.227 ng/mL~3.633 ng/mL



In-Depth Quantitative Metabolomics 深度定量  
AccuQuanter-1800 (AQ1800)  
1800种人类内源性代谢物与脂质的绝对定量服务



# 深度定量代谢组学：AQ1800—从非靶向出发，定量广泛地真实存在于人体内的内源性代谢物

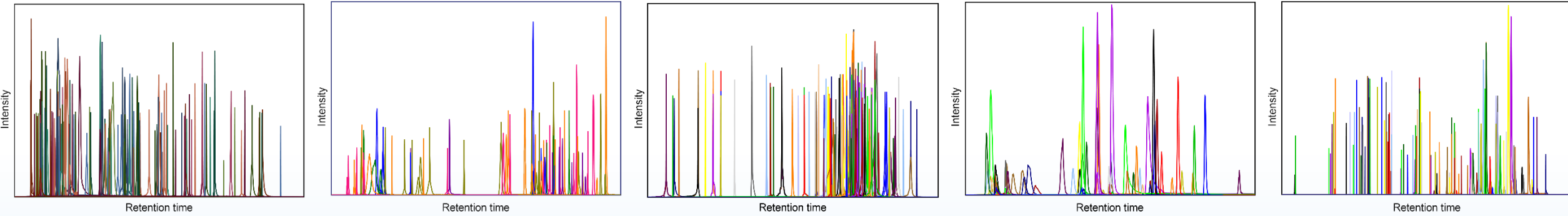
AQ1800：600多种极性代谢物+1200多种脂质；行业内覆盖最广的人体代谢组定量化测量

极性代谢物种类	检测数目	举例 (3个)
氨基酸及其衍生物 二肽 短肽	94	甲状腺素 眼酸 麦角硫因
核苷酸代谢 B族维生素 胆碱类	38	5'-甲硫基腺苷 1-甲基-6-氧代吡啶-3-甲酰胺 假尿苷
中长链脂肪酸 脂肪酸类衍生物	63	二十碳五烯酸 3-羟基癸酸 12-HETE
胆汁酸	57	甘氨酸猪胆酸 3-硫酸石胆酸 7-酮石胆酸
碳水化合物 氨基酸与能量代谢下游的有机酸 短链脂肪酸	83	异丁酸 3-羟基戊二酸 果糖
特异性肠道菌群代谢物 其他类	105	吲哚-3-丙酸 4-硫酸雌马酚 肠内酯
溶血型磷脂	105	LysoPC(16:0e/0:0) LysoPE(16:0p/0:0) LysoPI(0:0/20:4)
酰基肉碱	66	异戊酰肉碱 十四二烯酰肉碱 二十烯酰肉碱

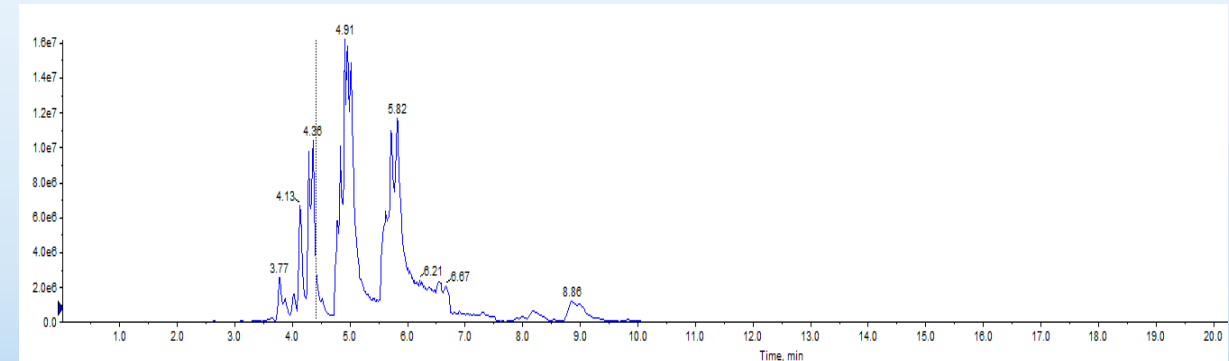
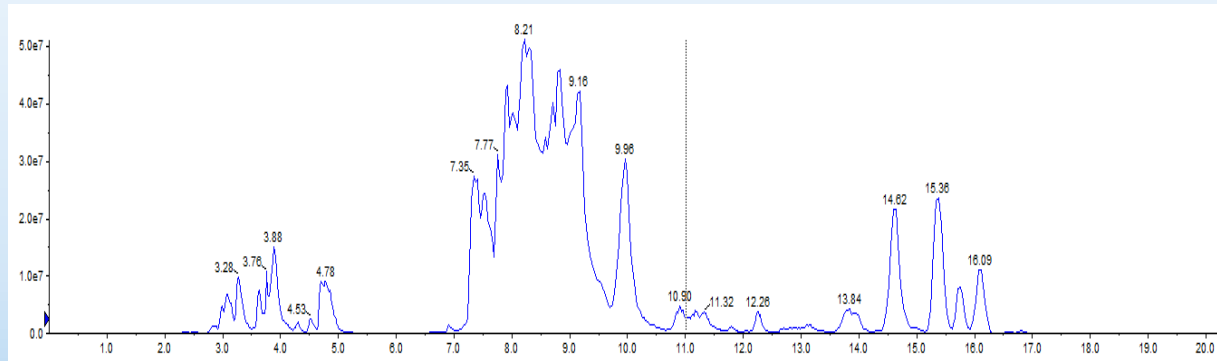
脂质种类	检测数目	脂质种类	检测数目
PC磷脂酰胆碱	95	Cho胆固醇	7
PE磷脂酰乙醇胺	127	PG磷脂酰甘油	28
LysoPC	37	PI磷脂酰肌醇	22
LysoPE	27	PS磷脂酰丝氨酸	12
SM鞘磷脂	55	PA磷脂酸	6
TAG甘油三酯	466	LysoPI	12
ChE胆固醇酯	26	FFA脂肪酸	33
DAG甘油二酯	60	Steroid甾体类	8
CER神经酰胺	28	AcCa	40
DCER二氢神经酰胺	12	Sulfatide硫苷酯	16
LCER乳糖神经酰胺	12	CL心磷脂	84
GluCER己糖神经酰胺	7	Sphingosine base	6
HCER羟基神经酰胺	12	氘代同位素内标	15

# AQ1800深度定量代谢组学：整合多种靶向定量方法实现极致的定量可靠性

- 600多种极性代谢物：标准品提取离子色谱图



- 1200多种脂质：Hyperlipidemia血清检测总离子流谱图



# AQ1800深度定量代谢组学：稳定地定量出1000个以上的人血代谢物浓度值

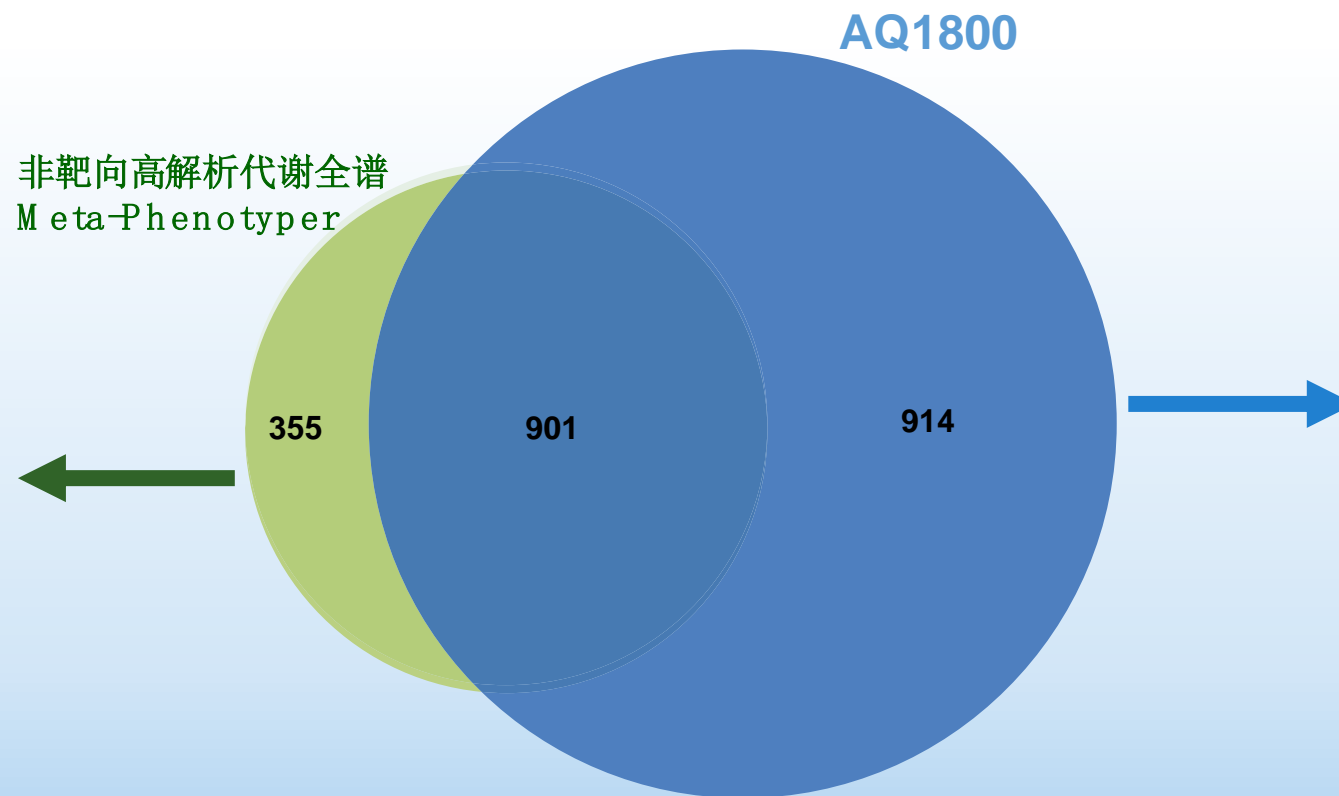
辨析：Intend to detect **VS.** Have been detected successfully

AQ1800：方法**可定量**检测1800种人体内源性代谢物与脂质

AQ1800：人血清中**能够定量到**1100±100种内源性代谢物与脂质

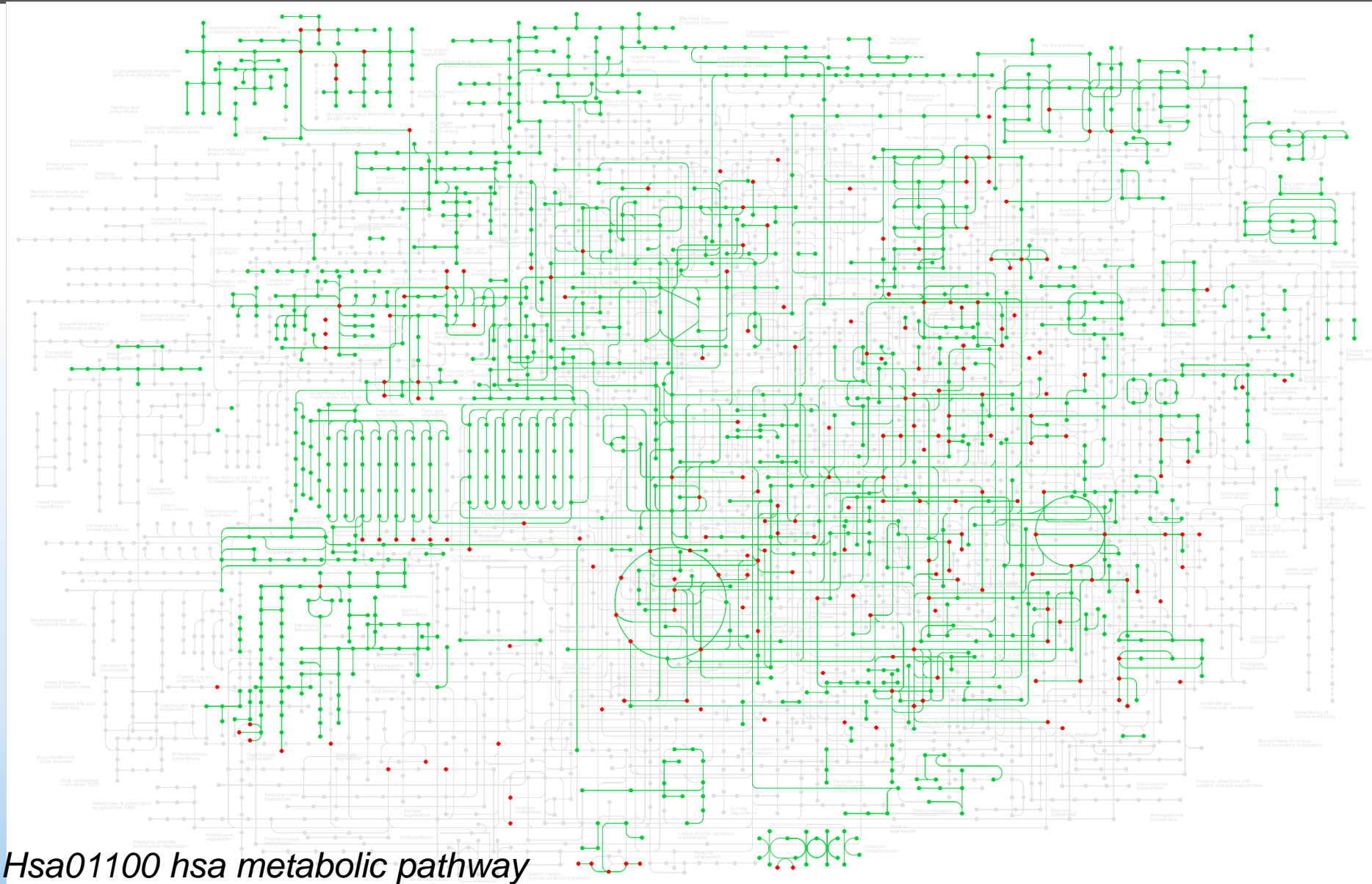
Asn-Val
Asp-Ile
Asp-Leu
Cys-Cys
Glu-Ile
Glu-Leu
Glu-Trp
Perfluorooctanesulfonic acid(PFOS)
Perfluorooctanoic acid(PFOA)
2,3-Dihydroxy-5-methylthio-4-pentenoic acid
Human Fibrinopeptide B residual [1-12, XGVNDNEEGFFS]
Human Fibrinopeptide B residual [1-13, XGVNDNEEGFFSA]
Human Fibrinopeptide B residual [1-11, XGVNDNEEGFF]
Human Fibrinopeptide A residual [2-16, DSGEGDFLAEGGGVR]
Human Fibrinopeptide A residual [3-16, SGE GDFLAEGGGVR]
Human Fibrinopeptide A residual [2-15, DSGEGDFLAEGGGV]
Human Fibrinopeptide A residual [3-15, SGE GDFLAEGGGV]
Androsterone sulfate (2)
Androsterone sulfate (3)
Androsterone sulfate (4)
Androsterone sulfate (5)
M1X-RT61MZ86
M1X-RT68MZ86
M1X-RT84MZ86
M1X-RT266MZ120
M1X-RT214MZ130
M1X-RT188MZ132
M1X-RT186MZ158

非靶向高解析代谢全谱  
Meta-Phenotyper



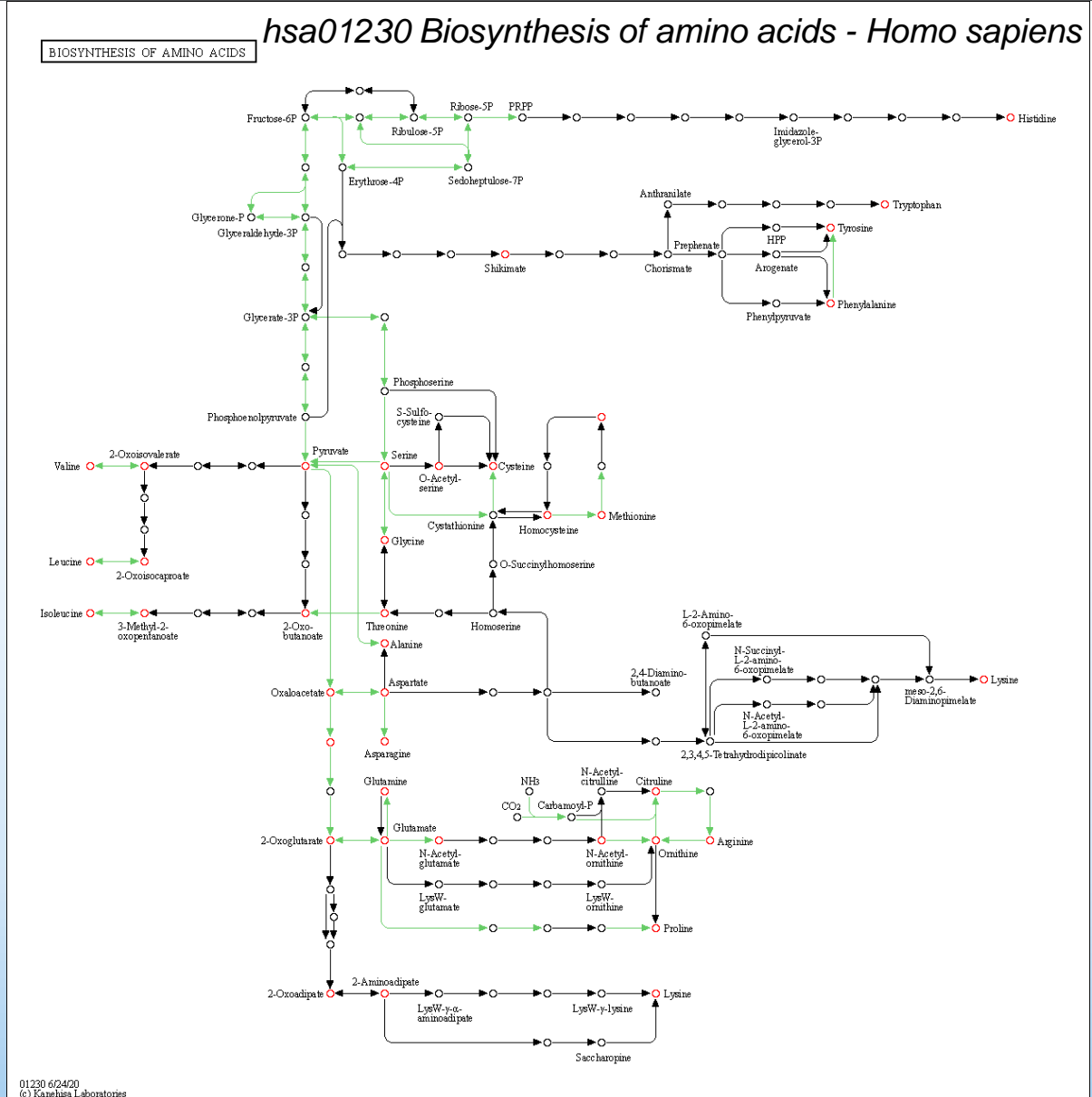
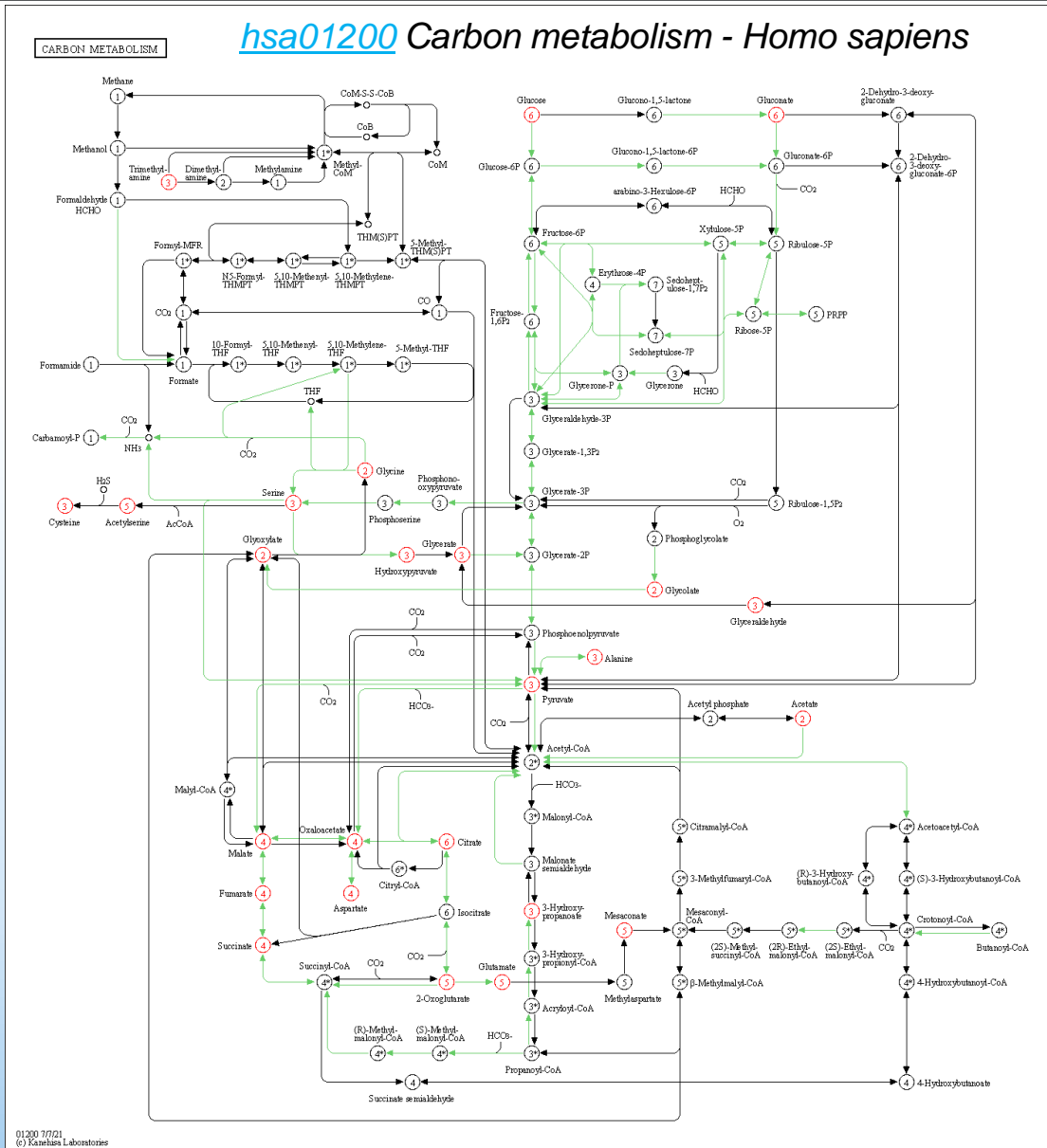
Butyric acid
Acetic acid
Beta-Alanine
Acetoacetic acid
Dopamine
N,N-Dimethylglycine
Glycolic acid
Homovanillic acid
Glutathione
D-Galactose
Ethanolamine
Dopa
Methylmalonic acid
Phenylacetic acid
Oxalacetic acid
Oxoadipic acid
Orotic acid
Phenol
Propionic acid
Tyramine
Taurolithocholic acid
3-Hydroxy-kynurenine
Indoleacrylic acid
Indole
Homocysteine
Mesaconic acid
Lithocholic acid
Nonadecanoic acid
5-Methoxyindole-3-acetate
Dopamine-4-sulfate
Acetyl-N-formyl-5-methoxykynurenamine
(+/-)-Enterodiol
Ophthalmic acid
Enterolactone
Hydroxy-tetradecenoylcarnitine
Hydroxy-tetradecadienylcarnitine
Hydroxy-hexadecenoylcarnitine
Hydroxy-hexadecadienylcarnitine
Hydroxyhexadecanoylcarnitine
Hydroxy-octadecenoylcarnitine

# AQ1800深度定量代谢组学：覆盖了丰富多样的代谢通路，举例1



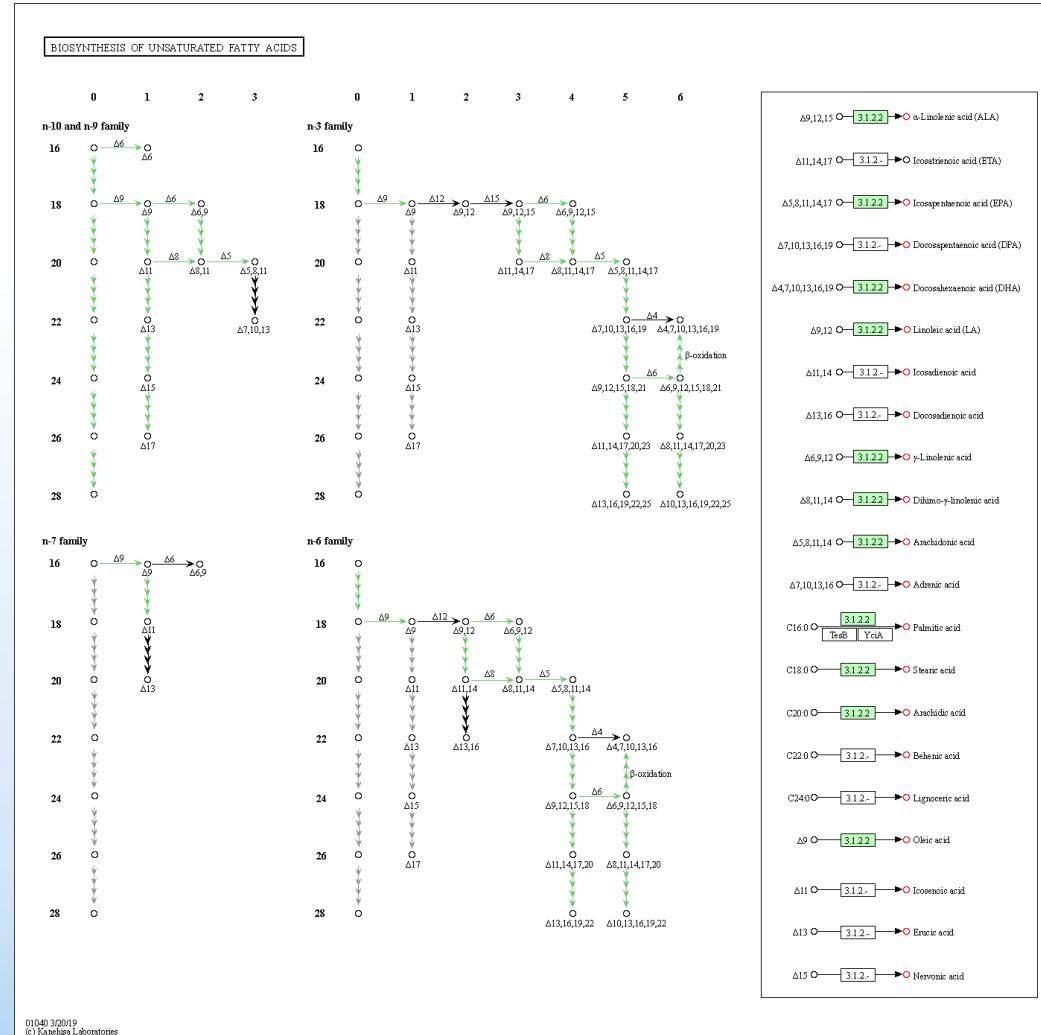


# AQ1800深度定量代谢组学：覆盖了丰富多样的代谢通路，举例2

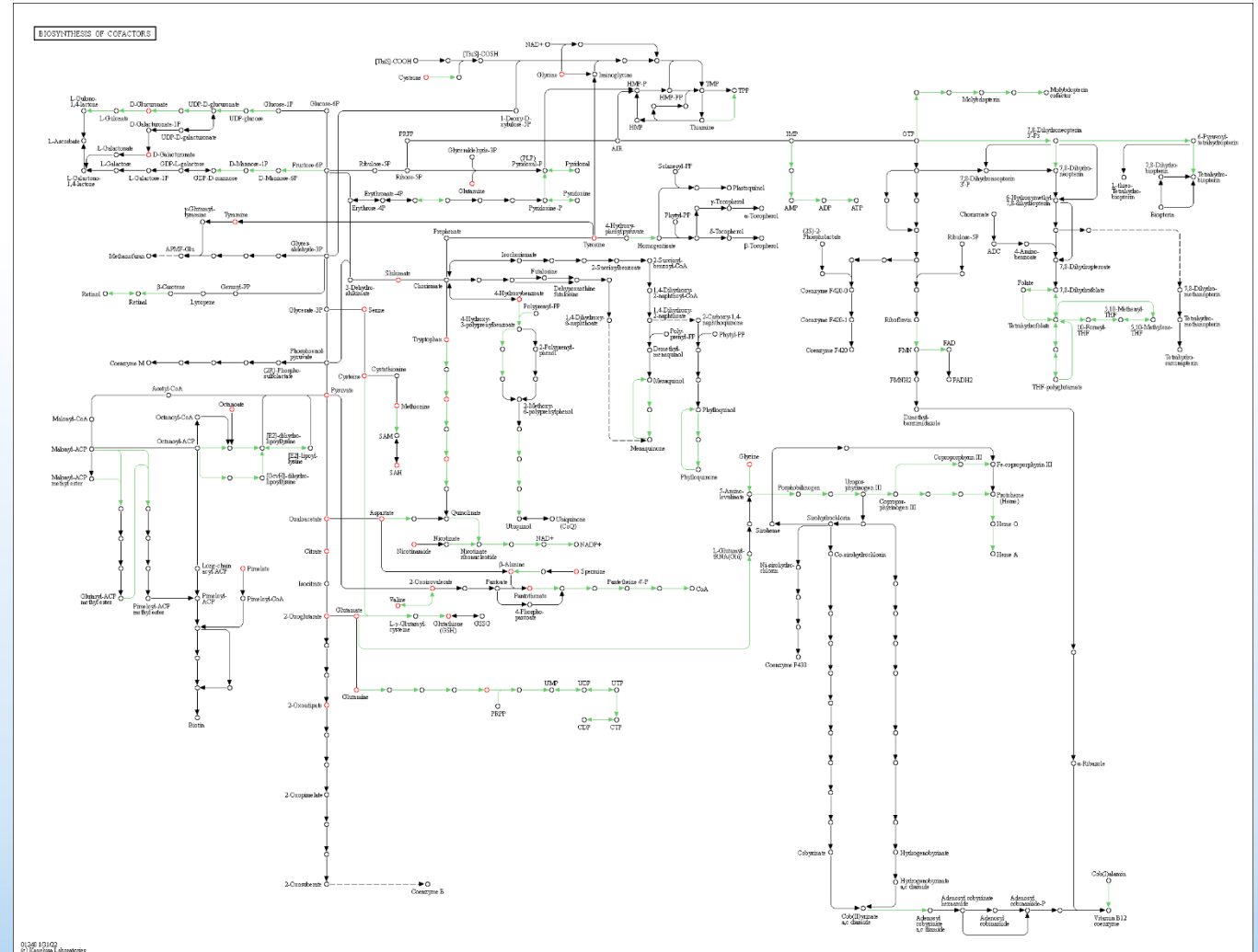


# AQ1800深度定量代谢组学：覆盖了丰富多样的代谢通路，举例3

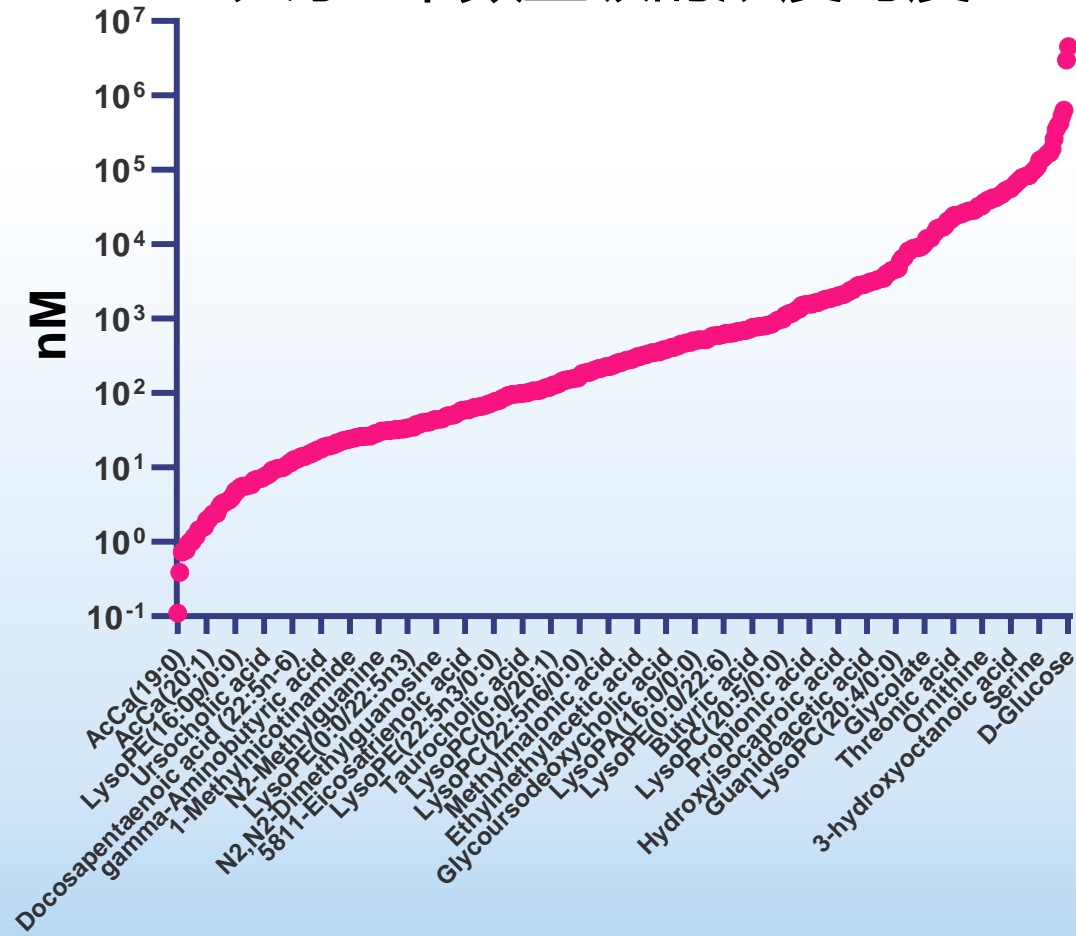
[hsa01040](#) Biosynthesis of unsaturated fatty acids - Homo sapiens



[hsa01240](#) Biosynthesis of cofactors - Homo sapiens

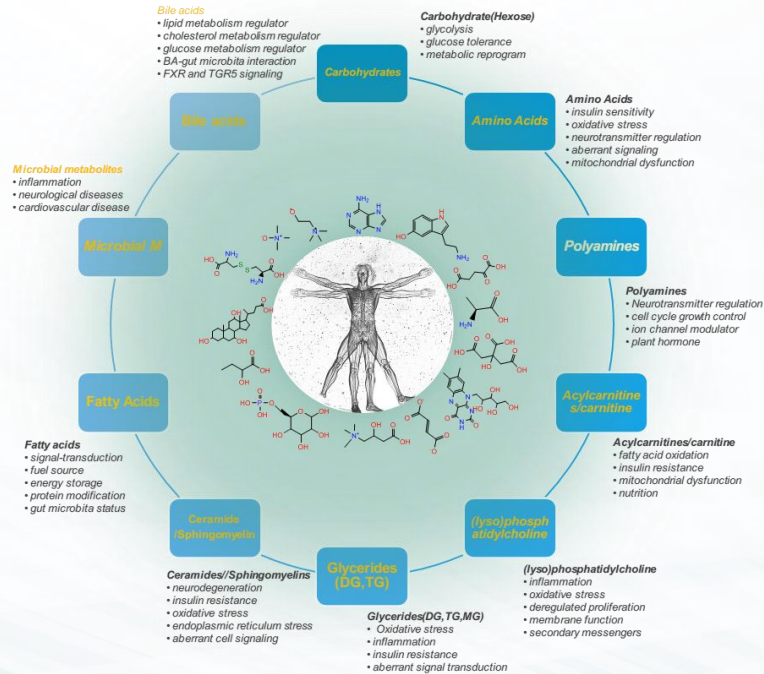


### 大于6个数量级的浓度跨度



# 代谢组学技术赋能精准医学研究：发现鉴定疾病相关的代谢性因素 metabolic factor

- 质谱多组学（代谢组学×蛋白质组学）是精准医学创新研究的新赛道与蓝海
- Proteomics and Metabolomics Enables Precision Medicine through:



## Small molecule Biomarkers 生物标志物

provide predictive, prognostic, diagnostic, and surrogate markers of diverse disease states

## Deep insight of disease molecular mechanism 疾病机制

inform on underlying molecular mechanisms of diseases

## Stratification, sub-classification 亚类分型与病人分类

Allow for sub-classification of diseases, and stratification of patients based on metabolic pathways impacted

## Pharmaco-metabolomics 药物治疗反应预测

Reveal biomarkers for drug response phenotypes, providing an effective means to predict variation

## Correlating genotype-phenotype 基因型-表型关联

Define a metabotype for each specific genotype, offering a functional read-out for genetic variants

应用场景

Metabolomics (2016) 12:149  
DOI 10.1007/s11306-016-1094-6



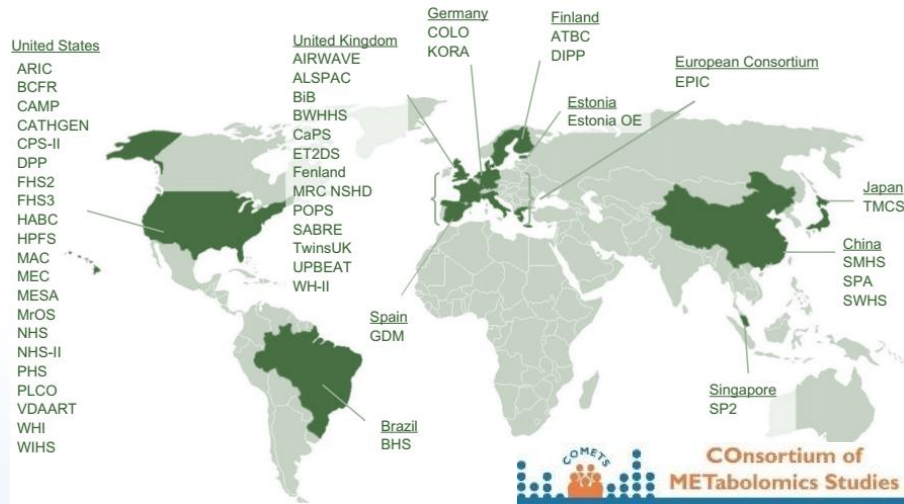
ORIGINAL ARTICLE

## Metabolomics enables precision medicine: “A White Paper, Community Perspective”

Richard D. Beger<sup>1</sup>, Warwick Dunn<sup>2</sup>, Michael A. Schmidt<sup>3</sup>, Steven S. Gross<sup>4</sup>, Jennifer A. Kirwan<sup>5</sup>, Marta Cascante<sup>6,7</sup>, Lorraine Brennan<sup>8</sup>, David S. Wishart<sup>9</sup>, Matej Oresic<sup>10</sup>, Thomas Hankemeier<sup>11</sup>, David I. Broadhurst<sup>12</sup>, Andrew N. Lane<sup>13</sup>, Karsten Suhre<sup>14</sup>, Gabi Kastenmüller<sup>15</sup>, Susan J. Sumner<sup>16</sup>, Ines Thiele<sup>17</sup>, Oliver Fiehn<sup>18,19</sup>, Rima Kaddurah-Daouk<sup>20</sup>, for “Precision Medicine and Pharmacometabolomics Task Group”-Metabolomics Society Initiative

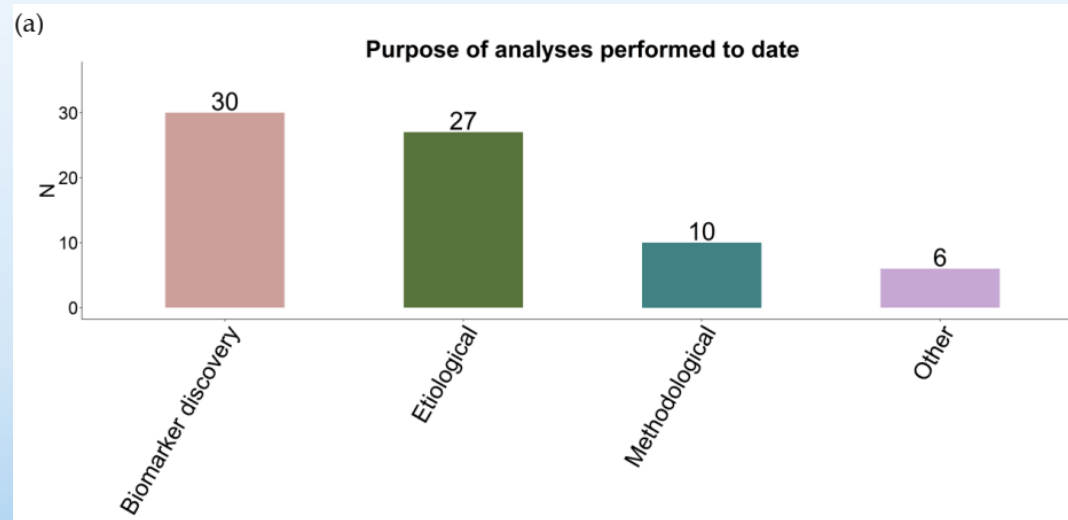
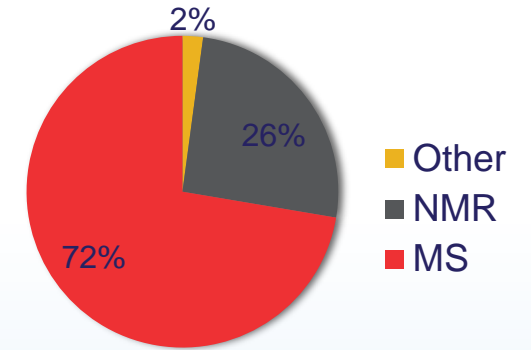


# 实验设计: Study Design of Human Metabolomics Studies (服务临床科研创新)

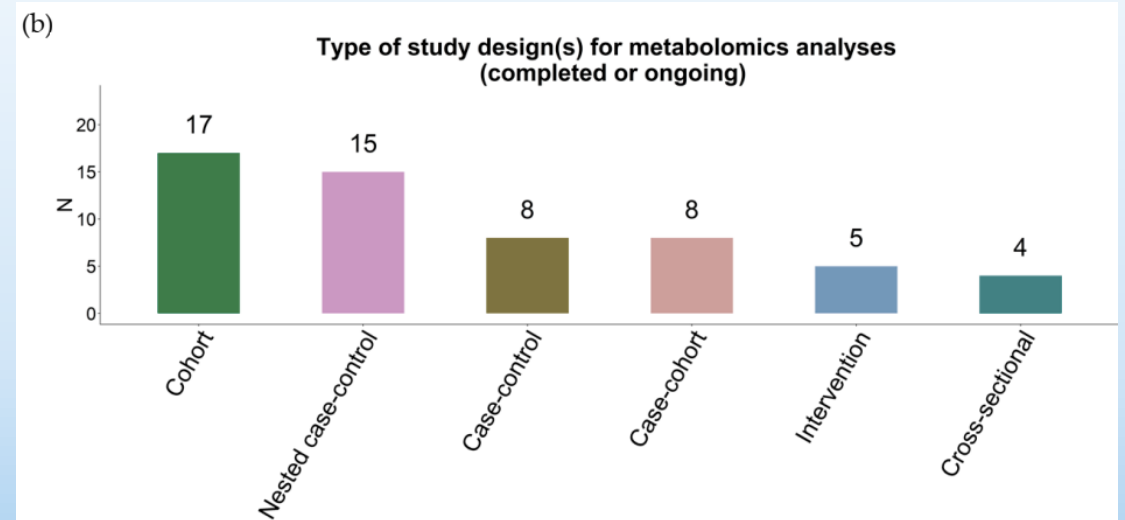


- Consortium of Metabolomics Studies 国际代谢组学研究联盟
- The **Largest consortium** of metabolomics cohort studies
  - 47 prospective cohorts, 13,8670 participants(up to 2018 April)
  - Blood metabolomics (Serum, EDTA-plasma)
  - Follow-up outcomes (Cancer, diabetes, CAD, et al)
  - 多组学68% participants with Genome-wide SNP information
- Convened by USA **National Cancer Institute** from 2014

## Technology used in COMETS

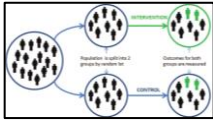
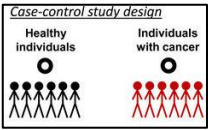
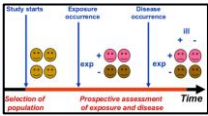
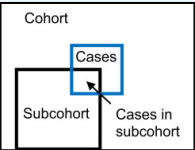
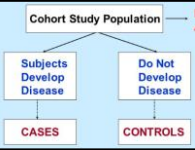




研究目的: Beyond metabolite markers, Towards Mechanism



实验设计: 研究目的, 学科特点, 疾病病种

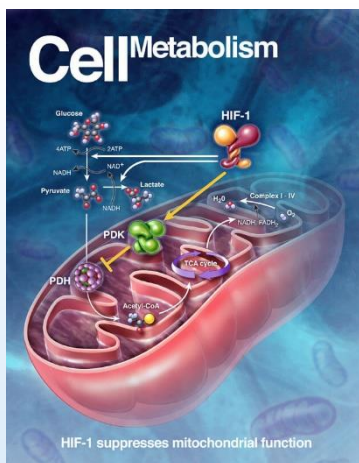
# 实验设计：不要拘泥于组学的陈规，从临床问题出发，代谢组学就是一种分子表型的观测，技术服务科学

<p><b>FODMAPs alter symptoms and the metabolome of patients with IBS: a randomised controlled trial</b></p> <p><i>Gut 2017</i></p>	 <p>Randomized Controlled Trial 随机对照试验</p>	<p>设计：20低剂量 vs. 20高剂量 实验时间：3周 数据规模：16S rRNA, 200 尿液代谢物</p>
<p><b>Metabolomics analysis identifies different metabolypes of asthma severity</b></p> <p><i>Eur Respir J 2017</i></p>	 <p>Case-Control study 病例对照试验</p>	<p>设计：54 cases vs. 22 NCs) 技术：Serum metabolomic 数据规模：66 metabolites</p>
<p>Metabolite changes in blood predict the onset of tuberculosis</p> <p><i>Nature Communications 2018</i></p>	 <p>Prospective Cohort Study 前瞻性队列研究</p>	<p>设计：发现集 (66 vs. 211 NCs) 测试集：38 vs. 116 NCs 数据规模：1000+ metabolites</p>
<p>Plasma Lipidomic Profiling and Risk of Type 2 Diabetes in the PREDIMED Trial</p> <p><i>Diabetes Care 2018</i></p>	 <p>Case-Cohort study 病例-队列研究 病例参比式研究</p>	<p>设计：250 cases vs. 636 non, 53 overlap 技术：Plasma Lipidomics 数据规模：207 plasma lipids</p>
<p><b>A Metabolomics Analysis of Body Mass Index and Postmenopausal Breast Cancer Risk</b></p> <p><i>J Natl Cancer Inst, 2018</i></p>	 <p>Nested Case-Control study 巢式病例对照研究 队列内病例对照研究</p>	<p>设计：621 cases vs. 621 controls 技术：serum metabolomics 数据规模：617 metabolites</p>
<p>Serum metabolites detect the presence of advanced fibrosis in derivation and validation cohorts of patients with non-alcoholic fatty liver disease</p> <p><i>Gut 2019</i></p>	 <p>Cross-Sectional study 横断面研究</p>	<p>设计：156 derivation cohort, 201 validation 技术：serum metabolomics 数据规模：652 metabolites</p>
<p><b>Longitudinal plasma metabolomics of aging and sex</b></p> <p>Burcu F. Darst<sup>1</sup>, Rebecca L. Kosciak<sup>2</sup>, Kirk J. Hogan<sup>2,3</sup>, Sterling C. Johnson<sup>2,4,5</sup>, Corinne D. Engelman<sup>1,2,5</sup></p> <p><i>Aging 2019</i></p>	 <p>Longitudinal study 纵贯研究，纵向研究</p>	<p>设计：2344 fasting plasma 技术：untargeted metabolomics 数据规模：750 metabolites</p>

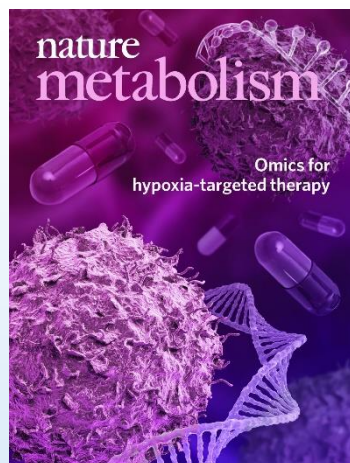
Over the past decade, the field of metabolism has witnessed remarkable scientific discoveries that reshaped the understanding of metabolic physiology and disease. As we launch Nature Metabolism, we look at what the future holds for metabolic research

## The next decade of metabolism

2005~



2017~



- Microbiome research 微生物组
- Non-alcoholic fatty liver disease (NAFLD)
- Cancer and stem cell metabolism 肿瘤与干细胞
- Adipose tissue biology and obesity
- Ageing, Diabetes, Nutrient sensing and signaling
- Immunometabolism 免疫-代谢
- Omics technologies in metabolism





Thank you.