Metabolomoics: Challenges and Opportunities

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PRESENTATION OUTLINE

- Introduction to Metabolomics
- Opportunities and challenges
- Imposing Rigor in Biomarkers Verification (The business of Failing)

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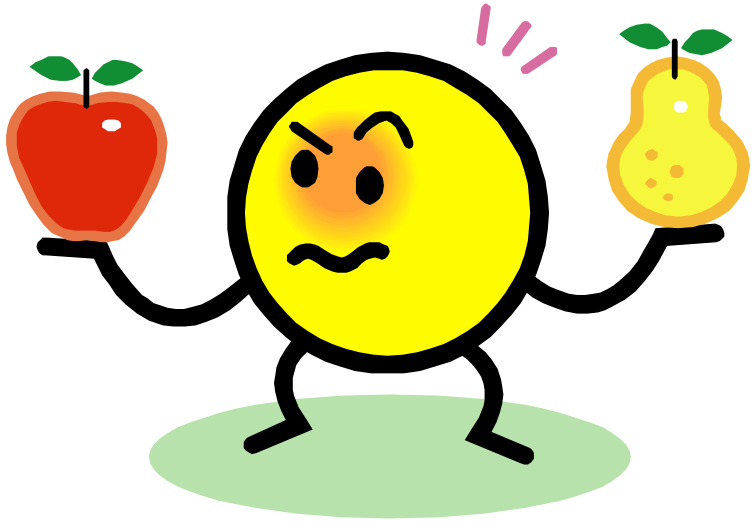
Metabolomics is Concerned with the Simultaneous, Comprehensive Measurements of Small Molecules

Metabolomics is the comparative analysis of endogenous metabolites found in biological samples:

- ***Compare*** two or more biological groups
- Find and identify potential biomarkers
- Look for biomarkers of toxicology
- Understand biological pathways
- Discover new metabolites

Metabolites are the by-products of metabolism

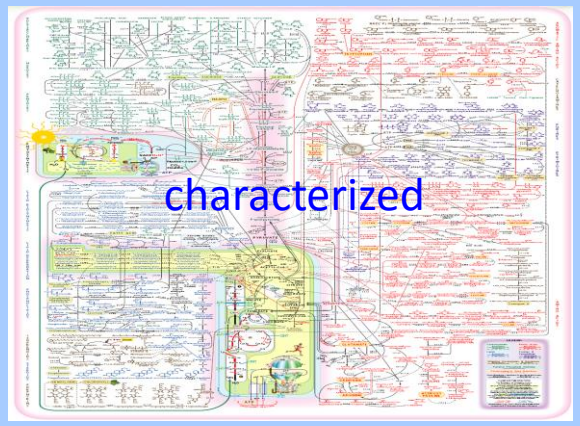
- Range of physico-chemical properties
- Classes: Amino acids, Sugars, organic acids, fatty acids, lipids…



What are the chemical differences that result in the observable difference

Scope of the Metabolome

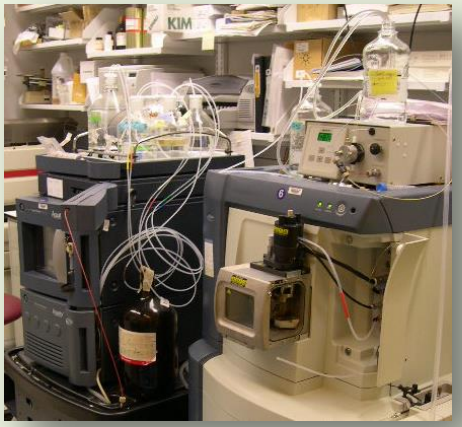
uncharacterized



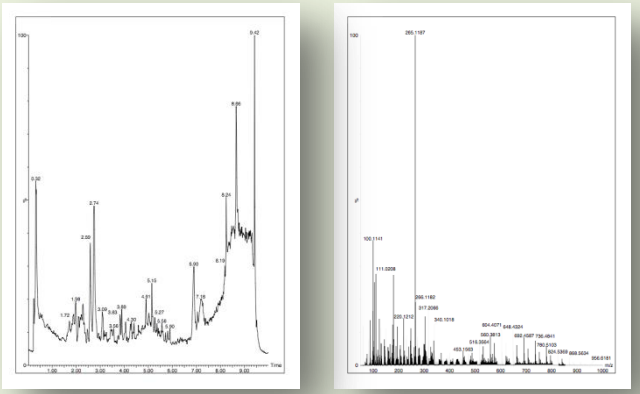
uncharacterized

Metabolomics Workflow

Urine

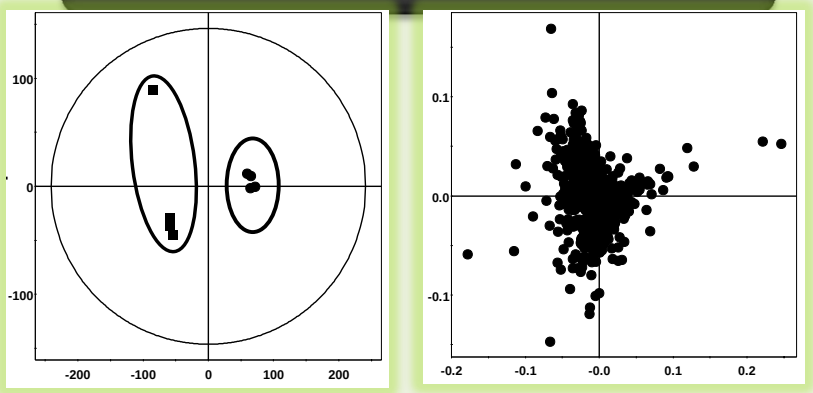


UPLC/QTOFMS



Superior resolution - UPLC
High mass accuracy - QTOFMS

DATA ANALYSIS



PCA, OPLS

Database search

BIOMARKERS

Biomarker Development Using a Metabolomic Approach

Designing a study

1. Delineate samples to achieve the goal of the study

2. Statistical justification of sample size

3. Evaluating pre-analytic variables – sample collection, storage etc.

4. Choice of the analytical platform – instrumentation, extraction procedures, gradients etc.

Analysis of LC-MS Data

1. Data Pre-processing – log transformation, normalization..

2. Feature Selection – ANOVA, LASSO..

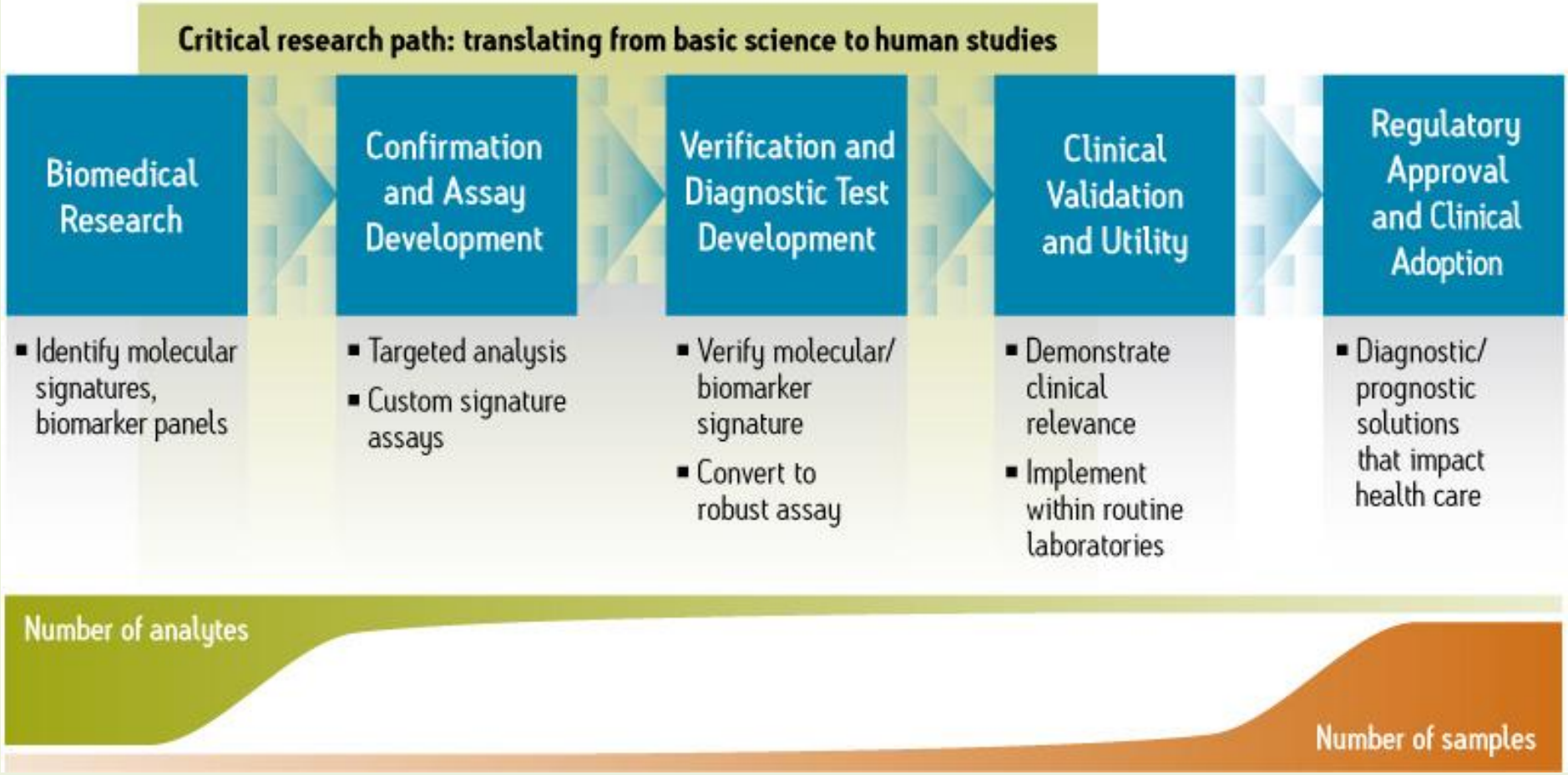
3. Biomarker Performance Evaluation – ROC Curves

4. Development of an Index

The omics “principle”

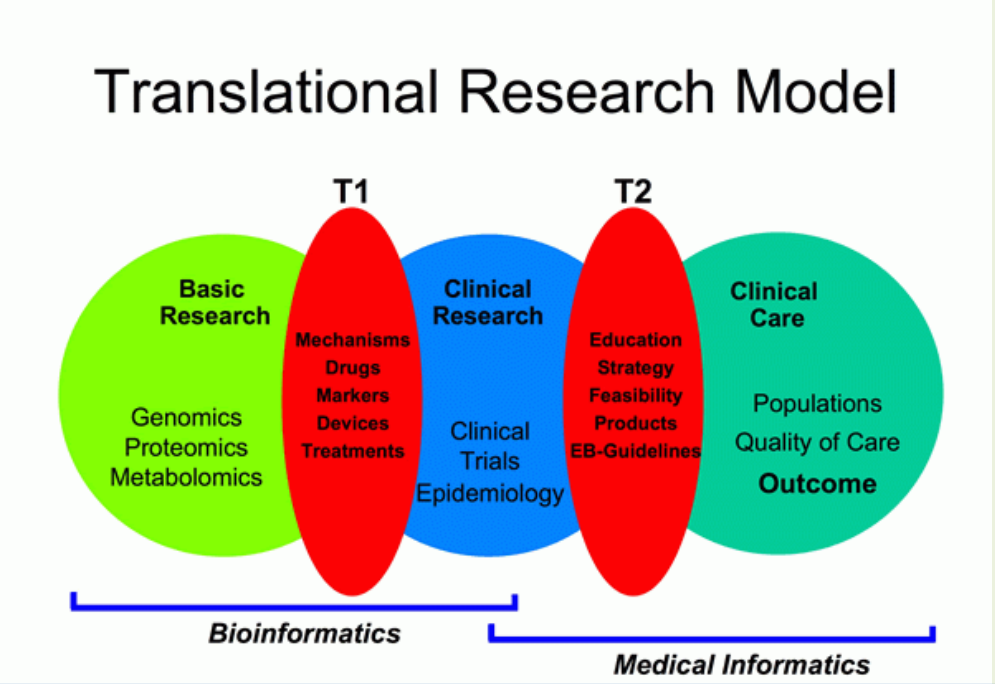
- Assume you know nothing
- Try to measure everything
- Is this a hypothesis-driven approach to science?
- Advantages – new discovery
- Disadvantages – false positives, cost

Health Sciences Continuum: Translating Discoveries to Diagnostics



Increased Focus on Translational Research

Translational research is scientific research that helps to make findings from basic science useful for practical applications that enhance human health and well-being.

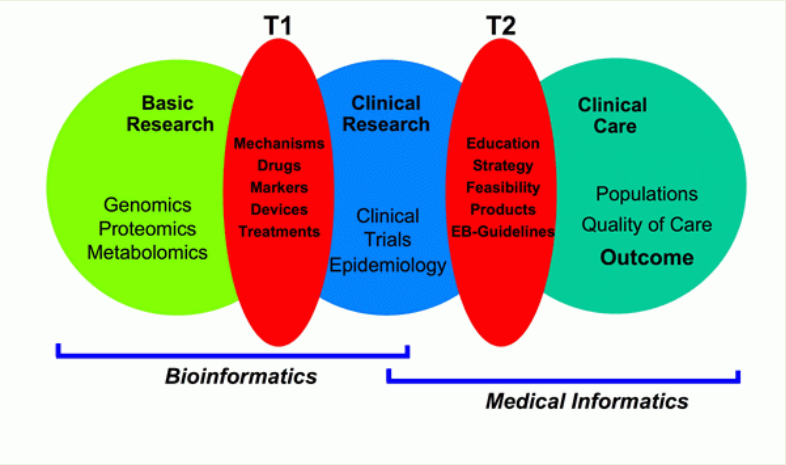


1. A candidate test may not be designed adequately for answering the relevant clinical question
2. Omics based discovery studies may not be conducted with adequate statistical or bioinformatics rigor, making it impossible that the candidate test will prove useful.

Michael *et. al.* (2012) The National Academy Press

Translation

- Translate discovery findings to clinical test
  - "Bench to Bedside"
  - Translational Research
  - Translational Effectiveness



- Two major roadblocks
  - Translational block (T1) prevents basic research findings from being tested in a clinical setting
  - Translational block (T2) prevents proven interventions from becoming standard practice

Assessment of risk of bias in translational science
*Barkhordarian et al. Journal of Translational Medicine 2013, **11**:184*

T1 Roadblocks in Translational Science

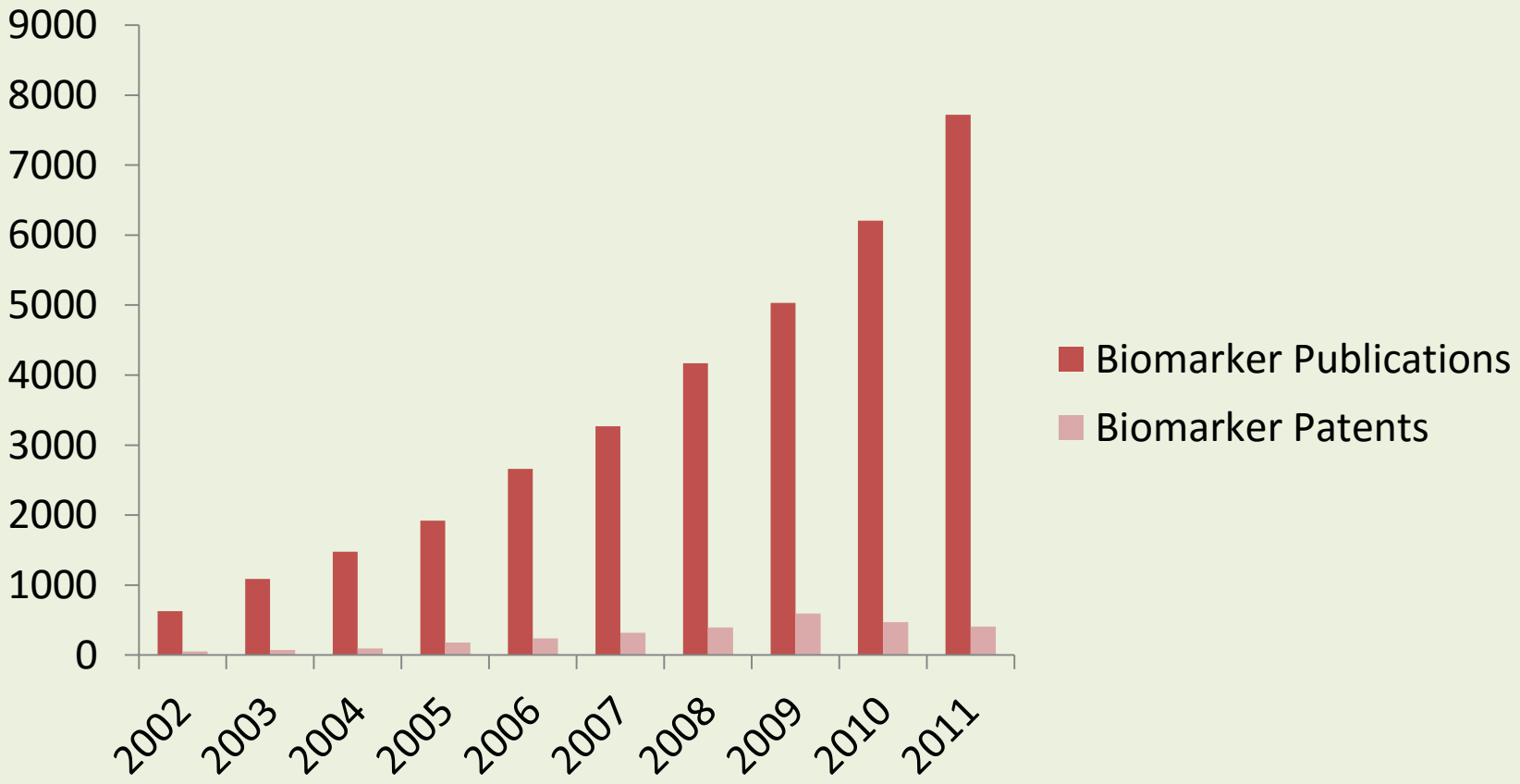
- Small number of samples that are analyzed
- Lack of information on the history of the samples
- Case and control specimens which are not matched with age and sex
- Limited metabolic and proteomic coverage
- The need to follow clear standard operating procedures for sample selection, collection, storage, handling, analysis and data interpretation

Pitfalls and limitations in translation from biomarker discovery to clinical utility in predictive and personalised medicine
*Druker and Krapfenbauer The EPMA Journal 2013, **4**:7*

Challenges to the use of biomarker approaches to Clinical Drug Development and PM – the T2 Roadblock

1. We don't know as much as we think we do!
2. Failure to distinguish between predictive and prognostic markers.
3. Data over-fitting and reliance on retrospective analyses.
4. Lack of incentives. Even successful drugs work only in a subset of patients who receive them. Better defining that subset post-marketing (where the N is large enough) may lead to better efficacy in that now-smaller population -- and a label restriction
5. Making binary decisions ("treat" / "don't treat") on continuous data.
6. Lack of cross platform; inter-institutional biomarker verification studies
7. Regulatory Constraints

Publications vs Patents



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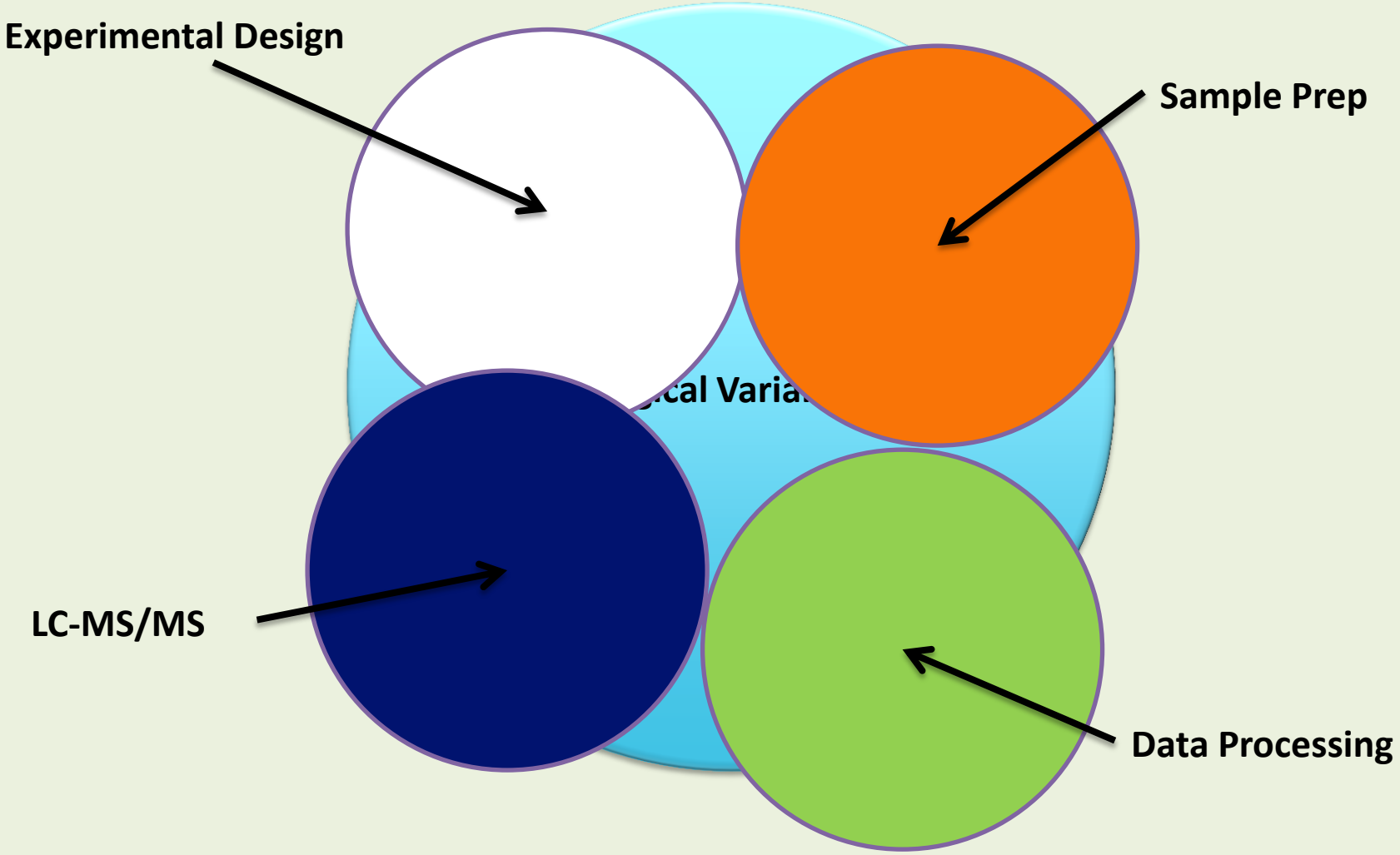
Controlling Variance



Experimental Considerations

- Understand as much as you can about the samples
  - Where did they come from?
  - How were they collected?
  - What were they collected for?
  - What happened to them since?

- Carefully consider the question you are asking
  - Is this sample set able to answer my question?
  - Are there enough samples available to answer my question?

- Anticipate confounding variations
  - Age, Strain/Ethnicity, Gender, Diet, Stress, Xenobiotics

Hope (or hype) of Personalized Medicine

- Understanding the molecular basis of disease: Which therapy or combination of therapies to use
- Defining molecular changes or markers associated with disease progression, response to treatment and relapse: When to treat with a particular regime.
- Identifying markers associated with safety & toleration: Choosing the safest therapies and correct dose.
- Identifying the right population for clinical trials
  - efficacy may only be evident in a subset of patients, rather than being uniform across the whole population
- Rescue a “failed” drug
  - Better understand the molecular characteristics of responsive vs. non-responsive patients

Acknowledgements:

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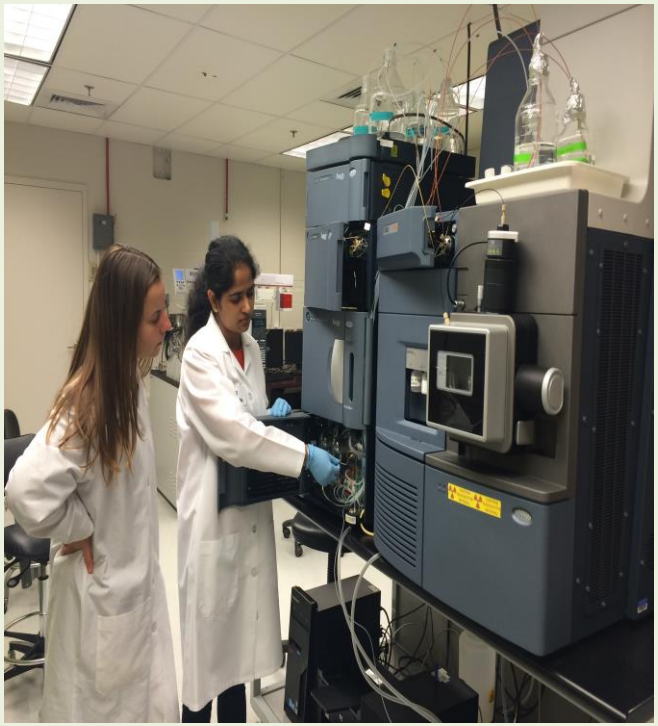

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