



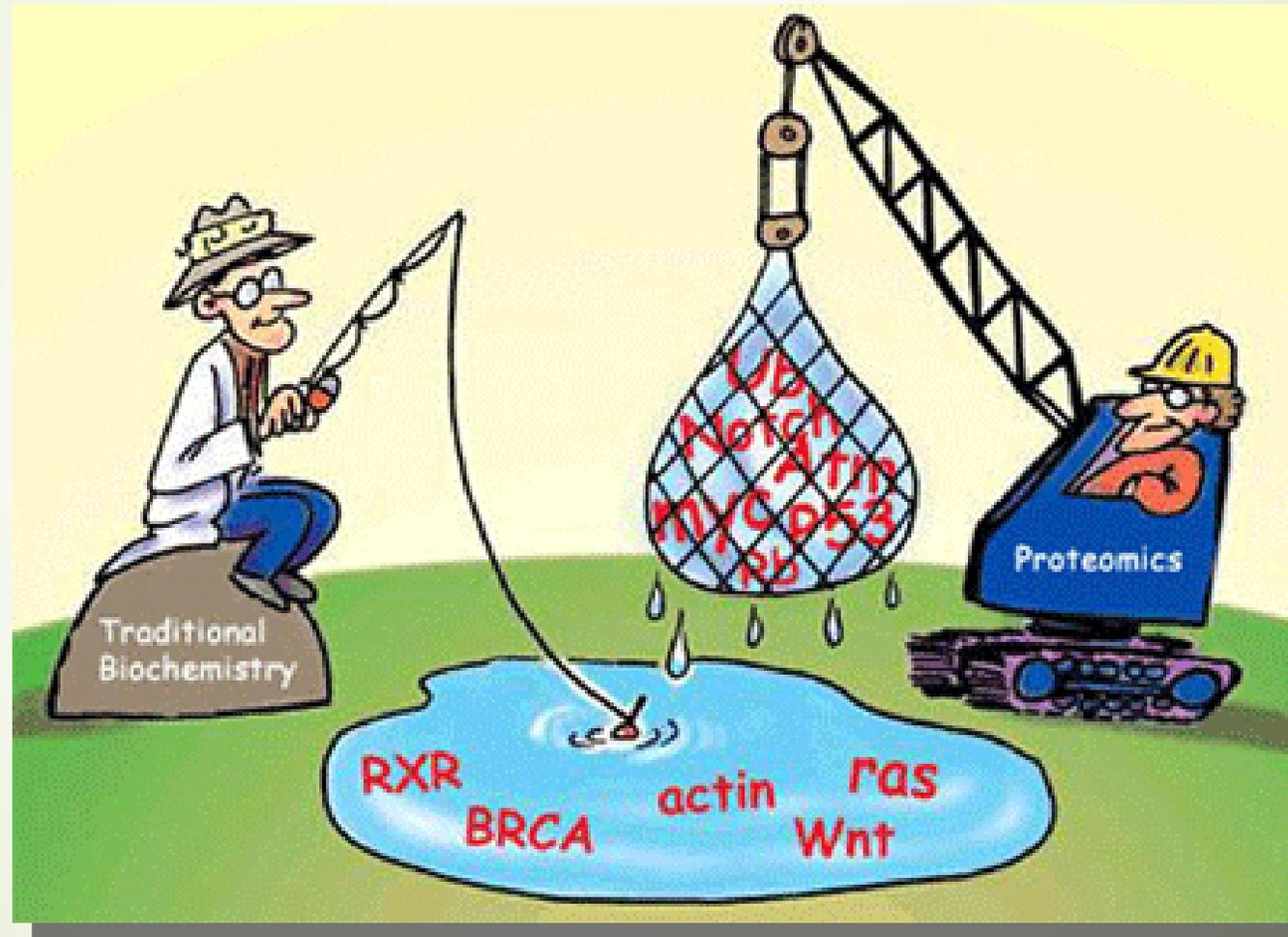
Infertile men and metabolomics: from bench to clinic

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Omic?



What is this “new” omics?

▶ Metabolome

BIOCHEMISTRY

Noun: **metabolome**; plural noun: **metabolomes**

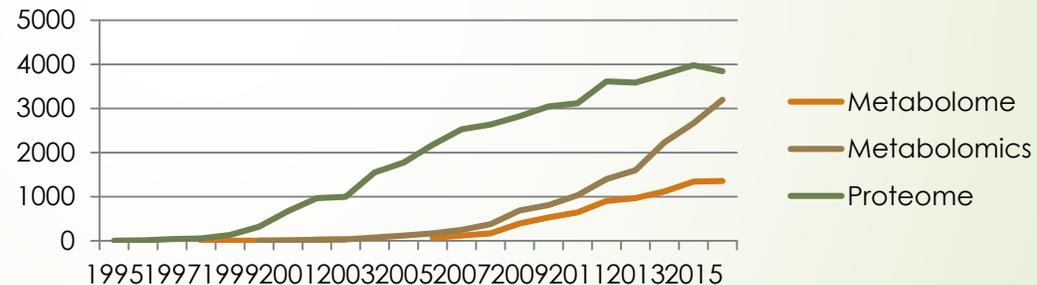
- ▶ the total number of metabolites present within an organism, cell, or tissue.

▶ Metabolomics

BIOCHEMISTRY

noun: **metabolomics**

the scientific study of the set of metabolites present within an organism, cell, or tissue, often by measuring simultaneously (100s -10000s), many of which are not identified (features or analyst,)



Metabolome age?

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REVIEW ARTICLE

The metabolome 18 years on: a concept comes of age

Douglas B. Kell^{1,2,3} · Stephen G. Oliver^{4,5}

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Abstract

Background The term ‘metabolome’ was introduced to the scientific literature in September 1998.

Aim and key scientific concepts of the review To mark its 18-year-old ‘coming of age’, two of the co-authors of that paper review the genesis of metabolomics, whence it has come and where it may be going.

Keywords Metabolome · Functional genomics · Systems biology · Precision medicine

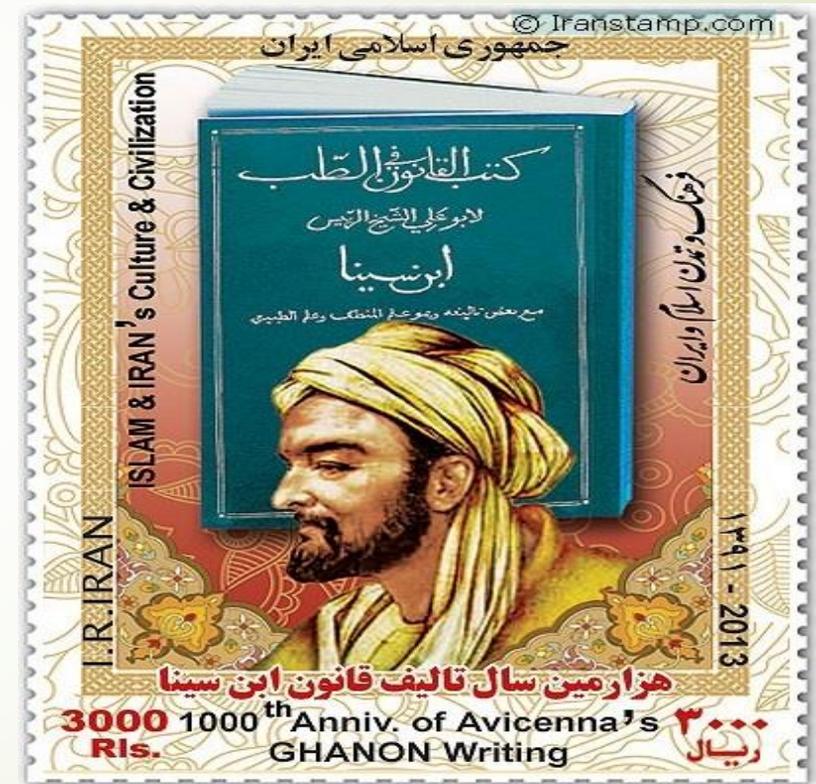
1 Introduction

The great advances in biology leading up to the discovery of the structure of DNA and the definition of the genetic code

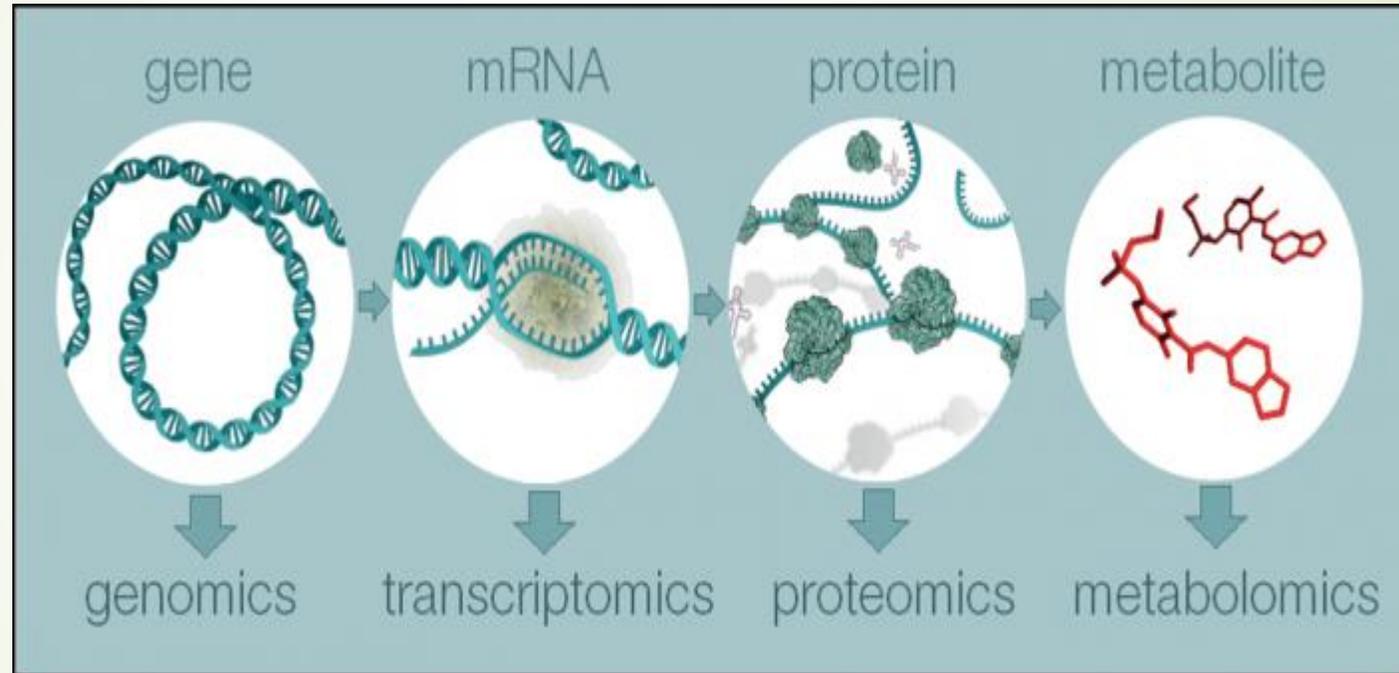
since then, have been mainly pioneered by molecular genetic studies on model organisms such as *Escherichia coli* and yeasts (*Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*) (Castrillo and Oliver 2004). The genius of molecular genetics lay in the design of experiments whereby fundamental theories of the workings of living cells at the molecular level could be rigorously tested by performing experiments that had a qualitative read-out (either the cells grew or they did not; either colonies were blue or they were not). This was set to change when the first chromosome sequence to be completed (that of *S. cerevisiae* chromosome III; Oliver et al. 1992) revealed that only about 20 % of the protein-encoding genes had previously been discovered by classical genetics augmented by recombinant DNA technology. It was immediately evident that the normal course of genetic research, which proceeds from mutant phenotypes to

Metabolomics has a long road behind

- Approximately 1,000 years ago, the Persian physician Avicenna observed that an individual's urine changes during illness. In modern times, changes in the smell or color of urine are known to be related to changes in the concentration of chemical components and dysregulation of biochemical pathways that indicate certain metabolic diseases.



Central biological dogma



Definitions and Background

Material

The ultimate potential of a cell
DNA (Genome) What is possible

The current direction of a cell
RNA (Transcriptome) What appears to be happening

The functional capabilities of a cell
Proteins (Proteome) What makes it happens

The limiting currency of a cell
Metabolites (Metabolome) What is happening

Information

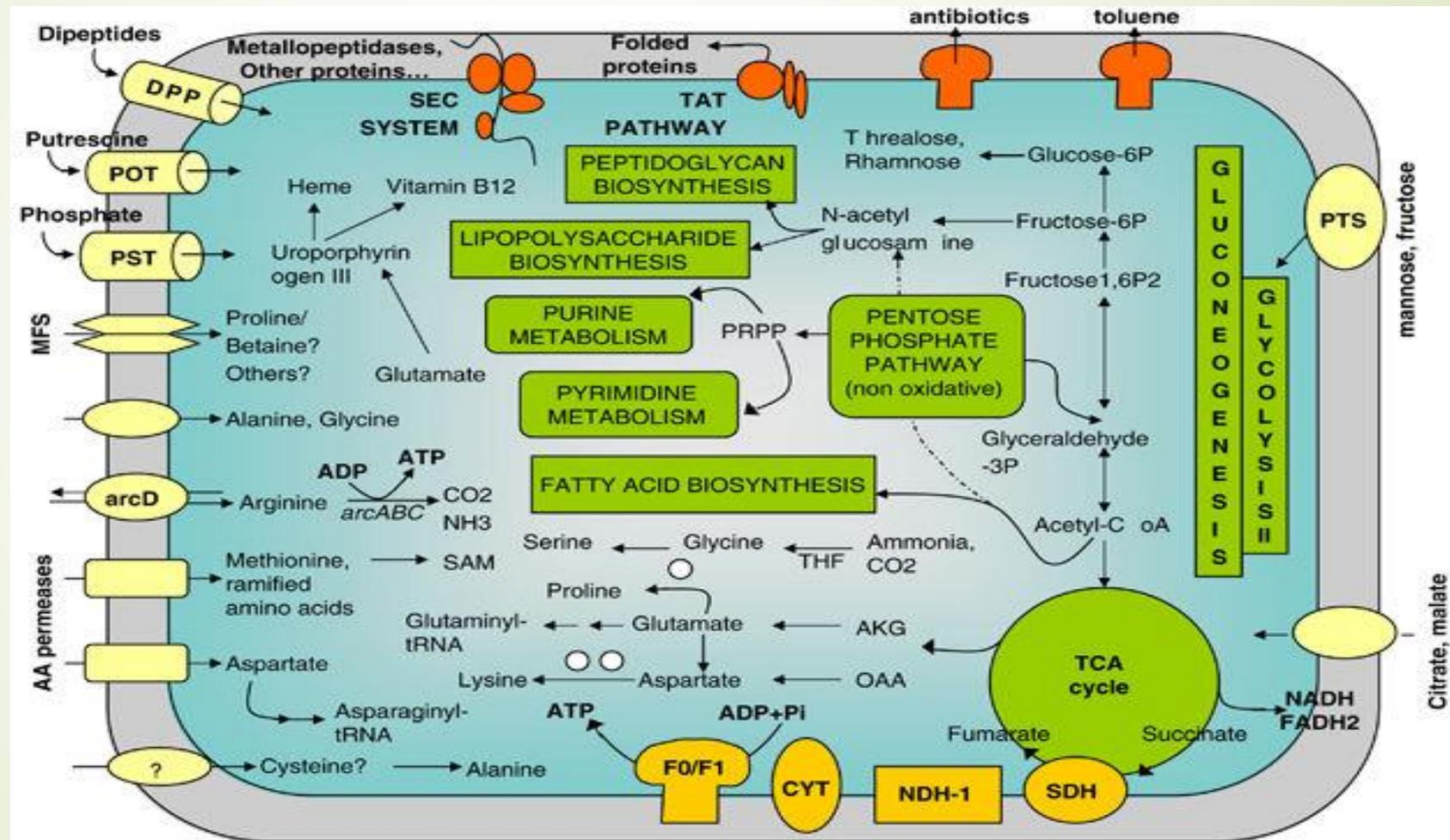
Omics by Number

"Omics"	Results	Number
Genomics	DNA sequence	25-30,000
Transcriptomics	Gene expression	100,000
Proteomics	Protein expression	2,000,000?
Metabolomics	Compounds/ Metabolites	114,215 (HMDB) Anno 2020*

*It is estimated that all plant species contain 90,000 - 200,000 compounds. Each individual plant species contains about 5,000 – 30,000 compounds

- Metabolites have a vast range of chemical structures and properties. Their molecular weights span two orders of magnitude
- No single extraction or analysis method works for all metabolites
- Many metabolite levels change with half times of minutes or seconds – far faster than nucleic acids or proteins

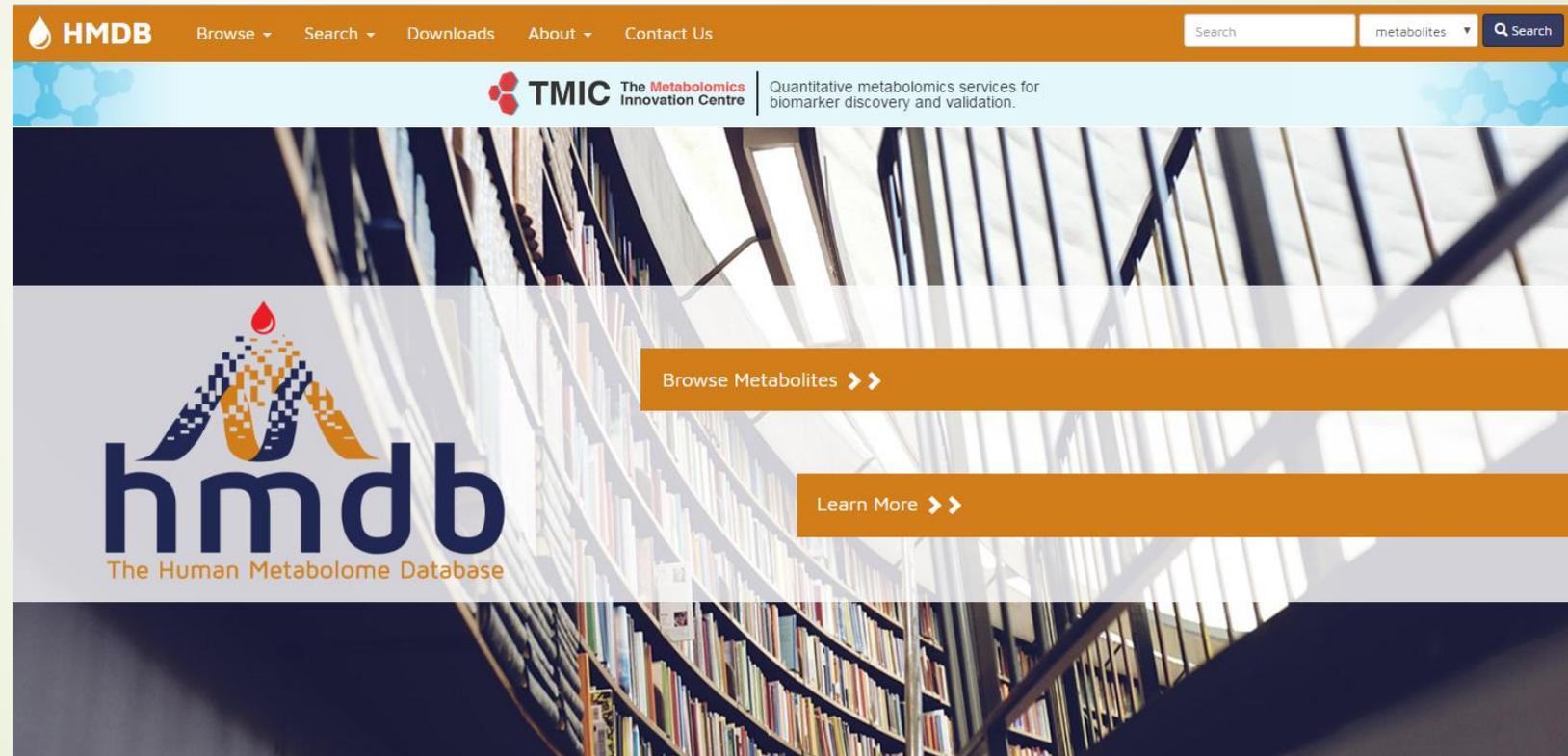
Metabolite < 2000 Da



Classification of metabolomics

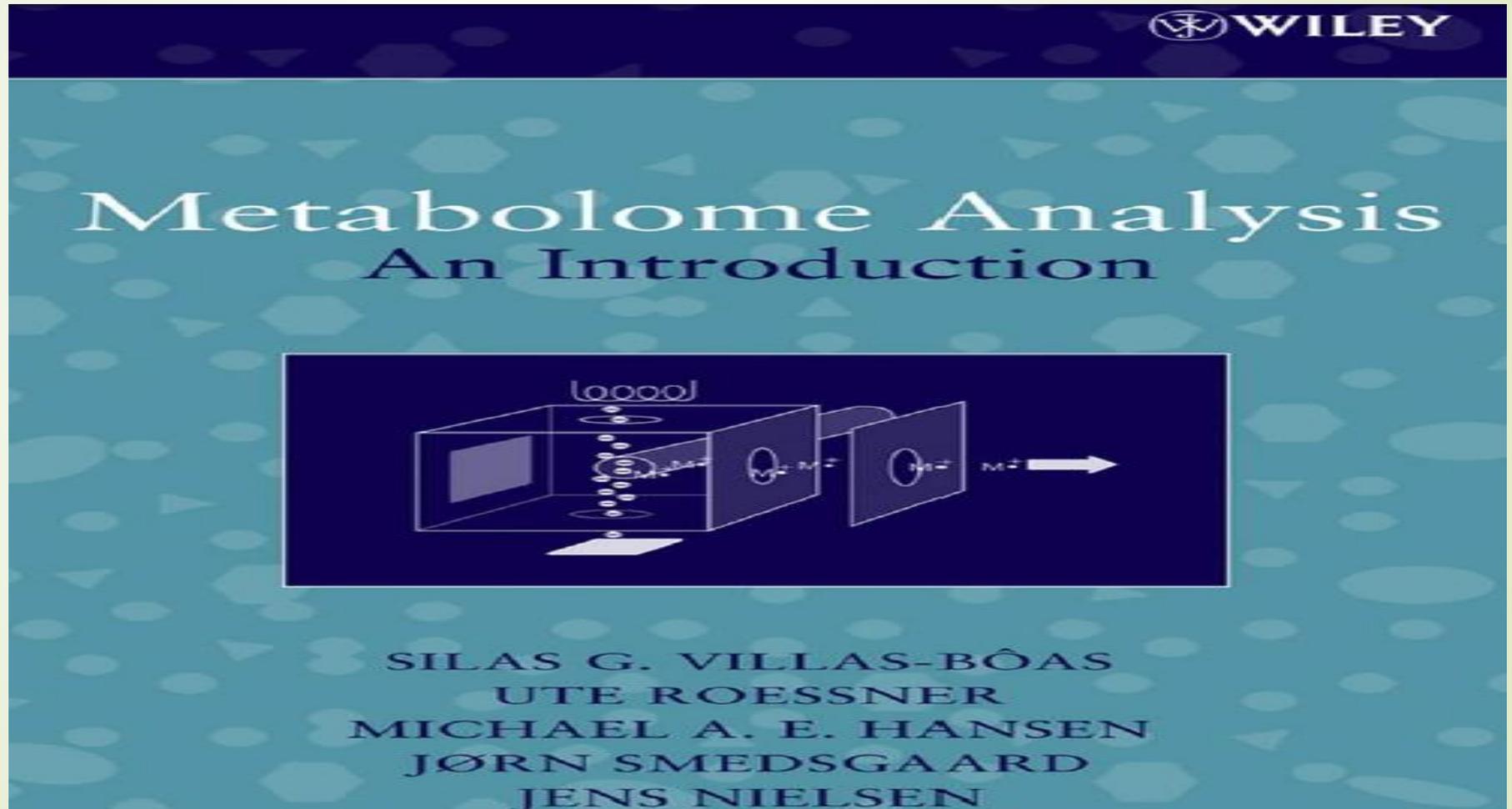
Term	Definition
Metabolome	The complete set of all low-molecular-weight metabolites to be found in a biological sample, which are the end products of gene expression.
Metabolome mapping	The comprehensive metabolite identifications.
Metabolomics	Nonbiased identification and quantification of <i>all</i> metabolites in a biological system.
Metabolic profiling	Identification and quantification of a selective number of predefined metabolites, which are generally related to a specific metabolic pathway.
Metabolic/Metabolomics fingerprinting	Global, rapid and high-throughput analysis of crude samples or sample extracts for sample classification or screening of samples. Identification and quantification is not performed.
Metabolic footprinting	Analysis of the extracellular metabolome of an organism, composed of metabolites not consumed from the organism's environment and those metabolites secreted from the intracellular volume. In the example of microbial systems, the organism's environment is the growth medium.
Metabolic/Metabolite target analysis	Qualitative and quantitative analysis of one or several metabolites related metabolic reaction.
Untargeted metabolic profiling	The untargeted metabolic profiling is typically carried out as comparative analysis between control and treatment groups.
Metabonomics	The quantitative measurement of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification.

Human Metabolome Database (HMDB) >114,000 metabolites



The image shows the homepage of the Human Metabolome Database (HMDB). The website features a navigation bar with the HMDB logo and links for Browse, Search, Downloads, About, and Contact Us. A search bar is located in the top right corner, with the text "metabolites" entered and a "Search" button. Below the navigation bar is a banner for TMIC (The Metabolomics Innovation Centre), which provides quantitative metabolomics services for biomarker discovery and validation. The main content area is a large image of a library with bookshelves. On the left side of this image is the HMDB logo, which consists of a stylized 'M' made of blue and orange dots, with a red drop above it, and the text "hmdb" in blue and "The Human Metabolome Database" in orange below it. On the right side of the image are two orange buttons: "Browse Metabolites >>" and "Learn More >>".

Recommended book





Male infertility?

Is this modern disease?

LOVE: what does have to do with
Metabolomics?



Infertile Couples?

- **WHO: 1 year -> 3 years!** intercourse **NO** baby ☹
- 15-20% couples are infertile
- It is distribute equally on couples:
 - 10% women
 - 10 % men



Semen analysis

- ▶ Classical parameter for analysis of semen:
 - ▶ Parameter for **Sperm**:
 - ▶ Motility
 - ▶ Morphology
 - ▶ Concentration/Count
 - ▶ Non classic parameter:
 - ▶ pH, Volume, Viscosity, Liquefaction
 - ▶ Parameter for **Seminal Plasma**: **NON !!!**



Seminal Plasma Content

- Genome
- Transcriptome
- Proteome
- **Metabolome**



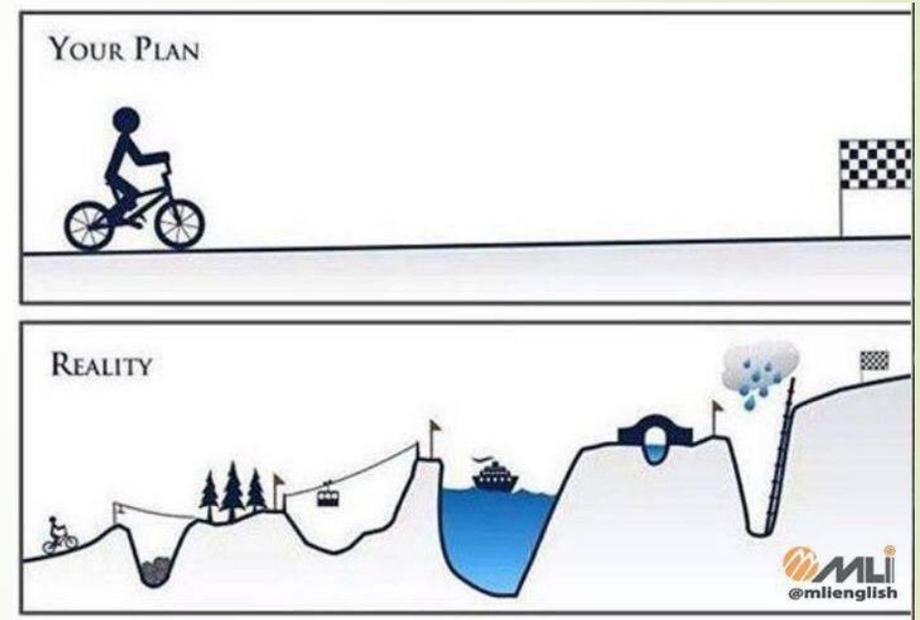


Strategy of Metabolomics Research

Can I walk alone with metabolomics?

Metabolomics is a Team Work!

- Sample preparation
- Instrumentation
- Data Analysis
- Interpretation

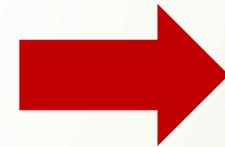


Sample preparation is the key to success

KISS!

➔ **(Keep It Simple S.....)**

**Extract
the metabolome!!!**



Instrumentations for metabolomics studies



Data Analysis and Interpretation:
Takes more time than you think!





Examples of Application of Metabolomics in Male Infertility

How far can we go?

Asthenozoospermia?

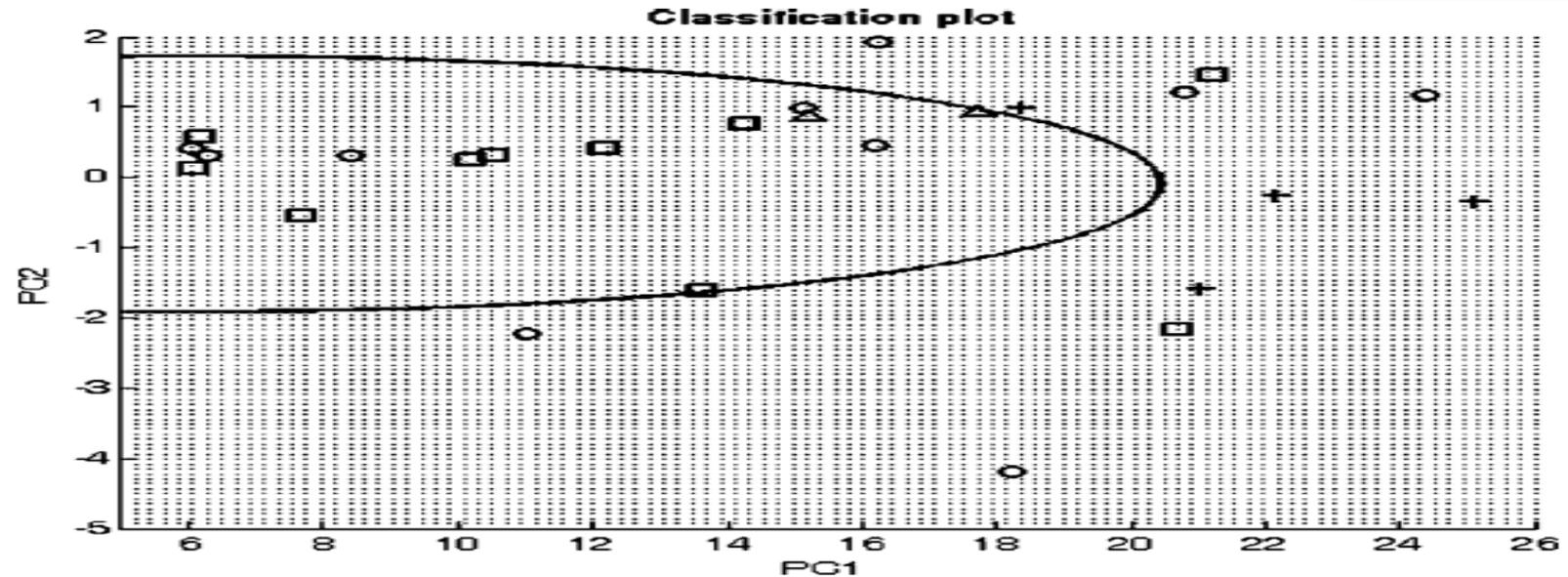
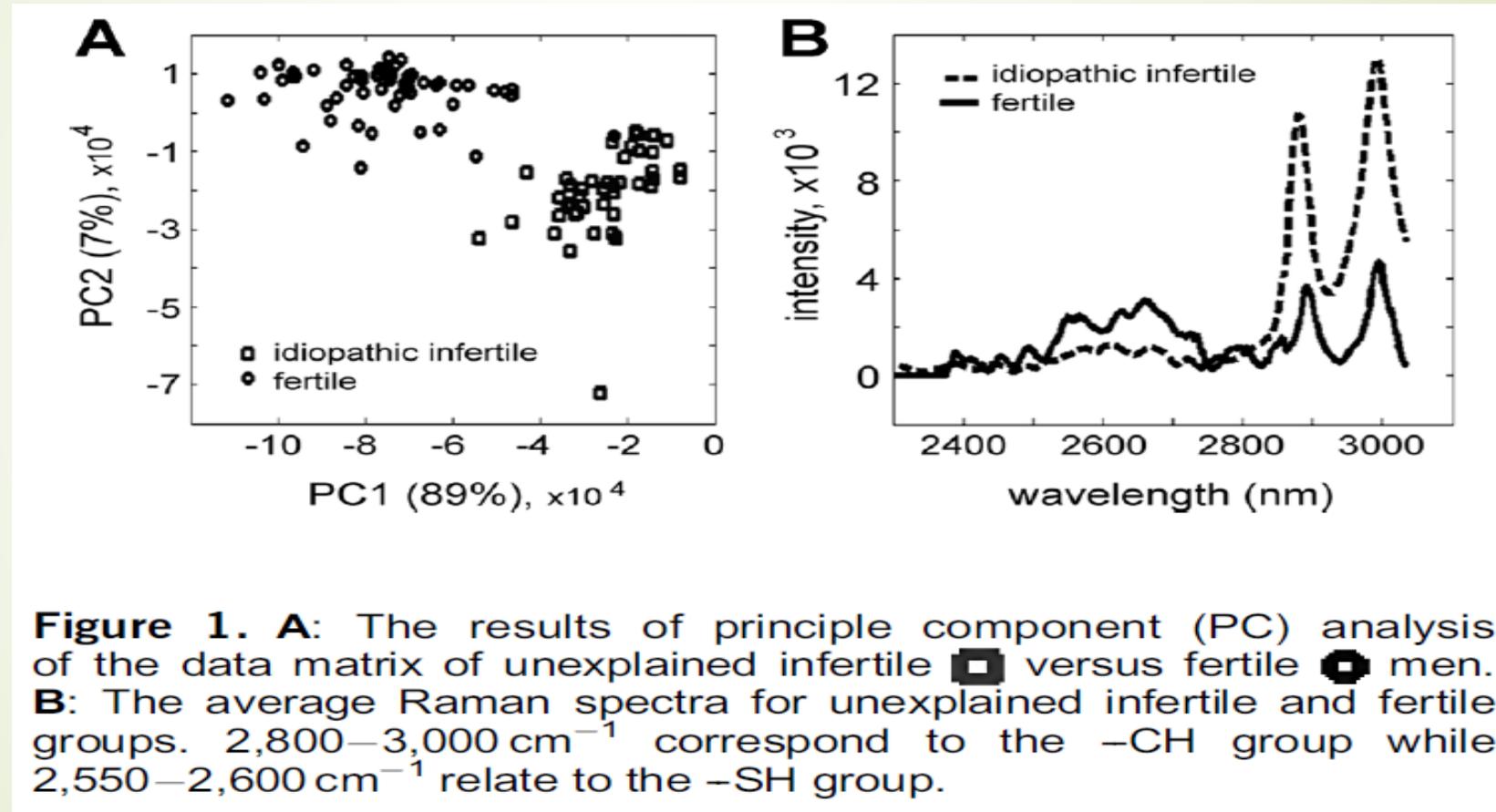
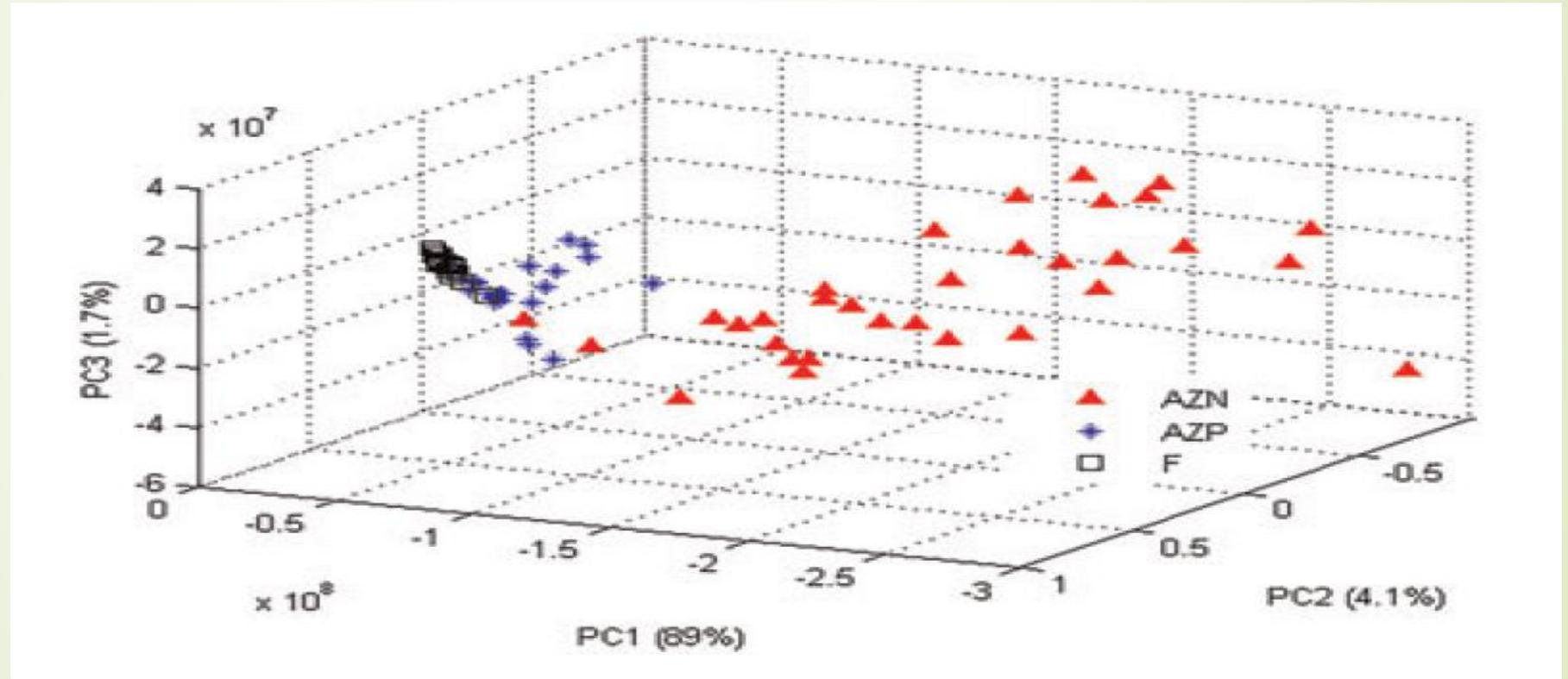


Figure 1. Chemometrics classification model applied on the Raman spectra of 10 normozoospermic and 10 asthenospermic men used as a training set. The curved line encompasses the region of mostly asthenozoospermic men. \square Asthenozoospermic man, training set. \times Normozoospermic man, training set. $+$ Predicted normozoospermic man, validation set. Δ Predicted asthenozoospermic man, validation set. The (+) closest to the curvature line is an asthenozoospermic man that the classification model predicted incorrectly.

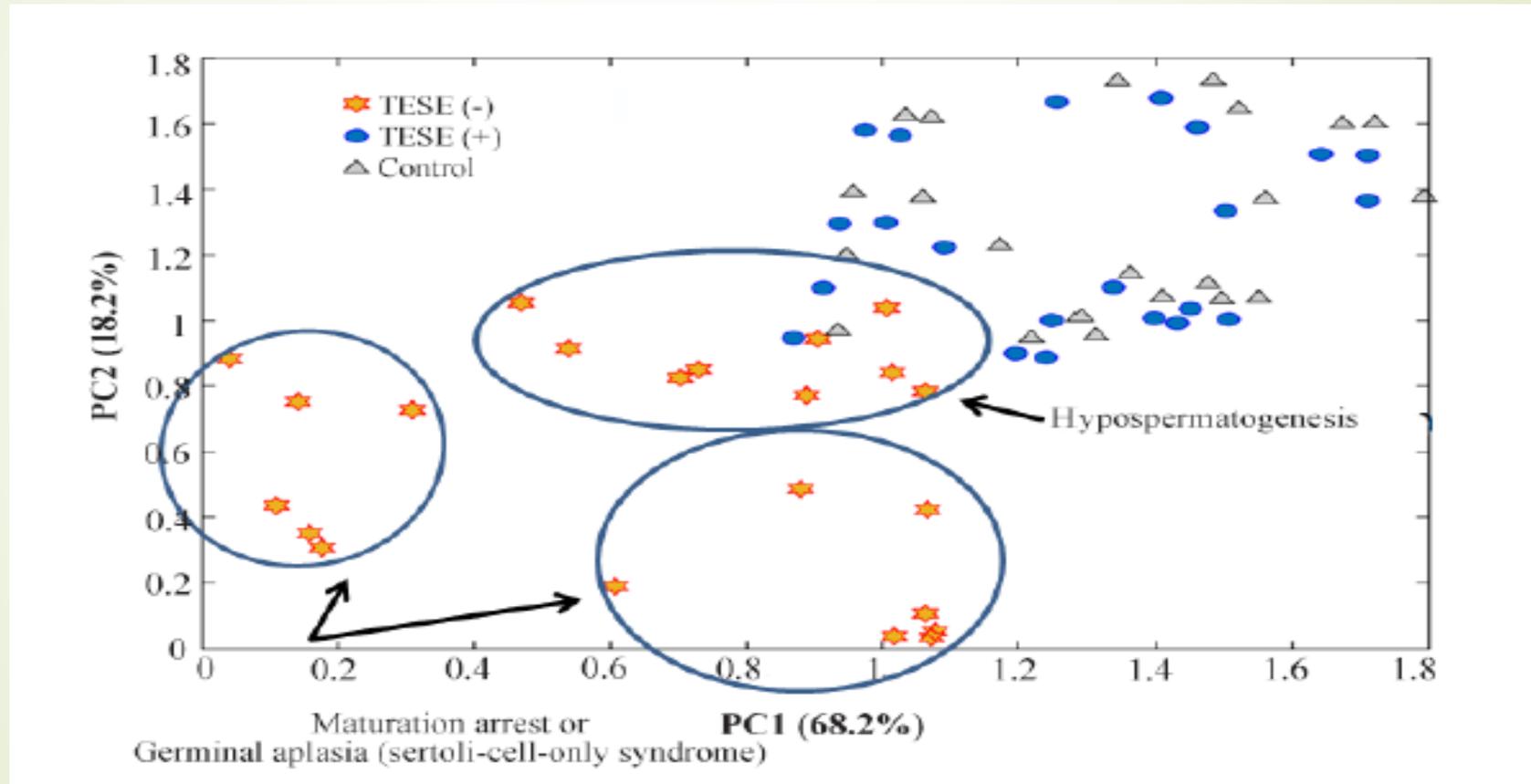
Unexplained Infertile Men?



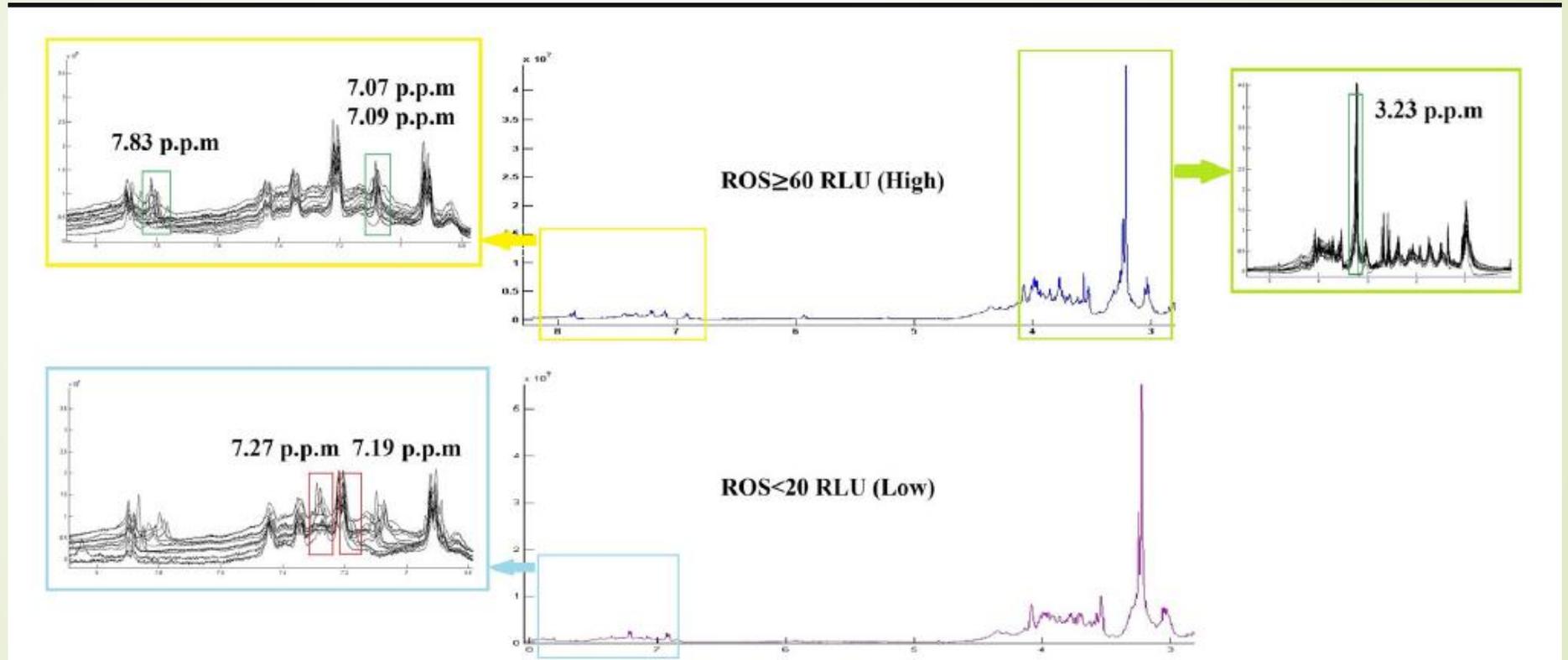
Non-obstructive Azoospermia (GCMS)?



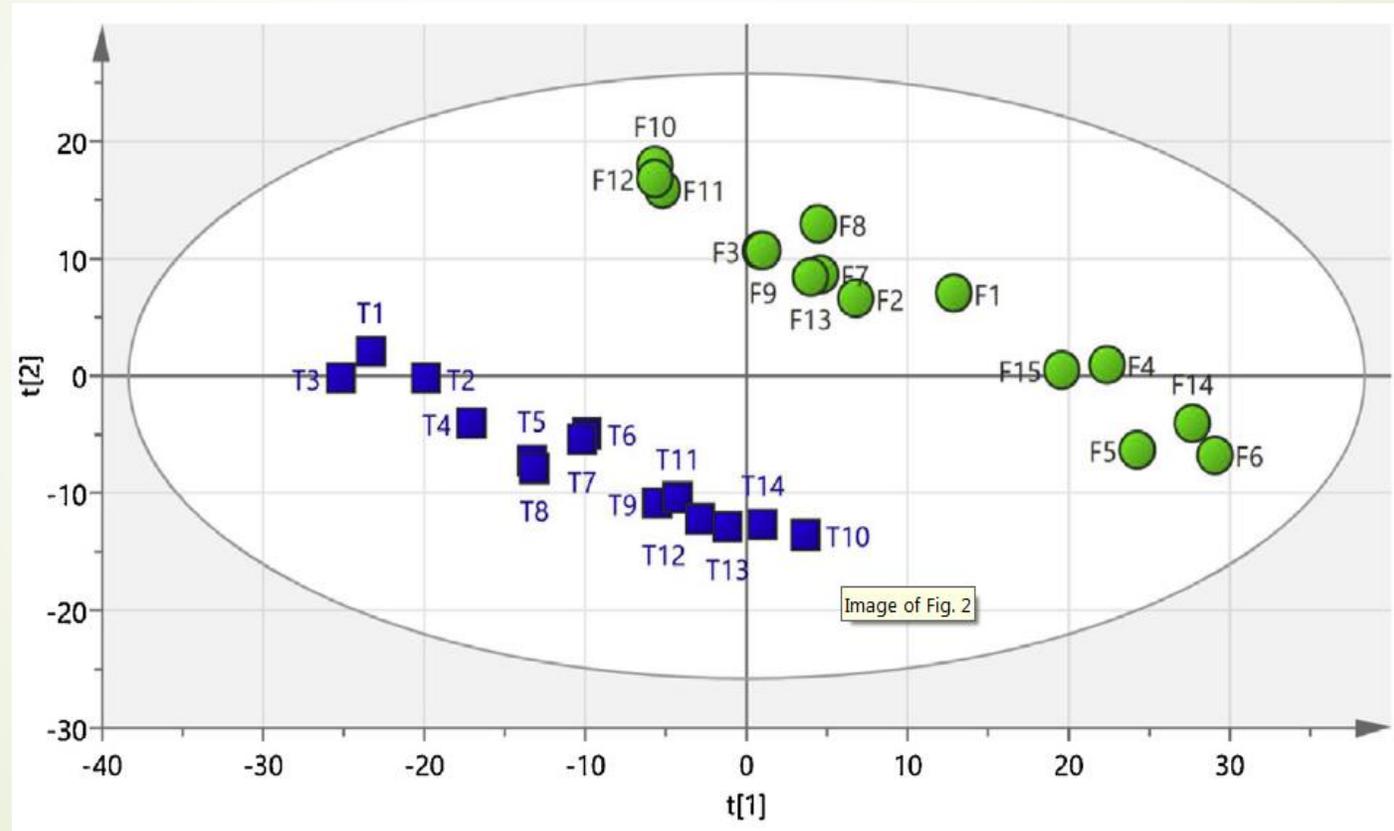
Non-obstructive azoospermia (Raman)?



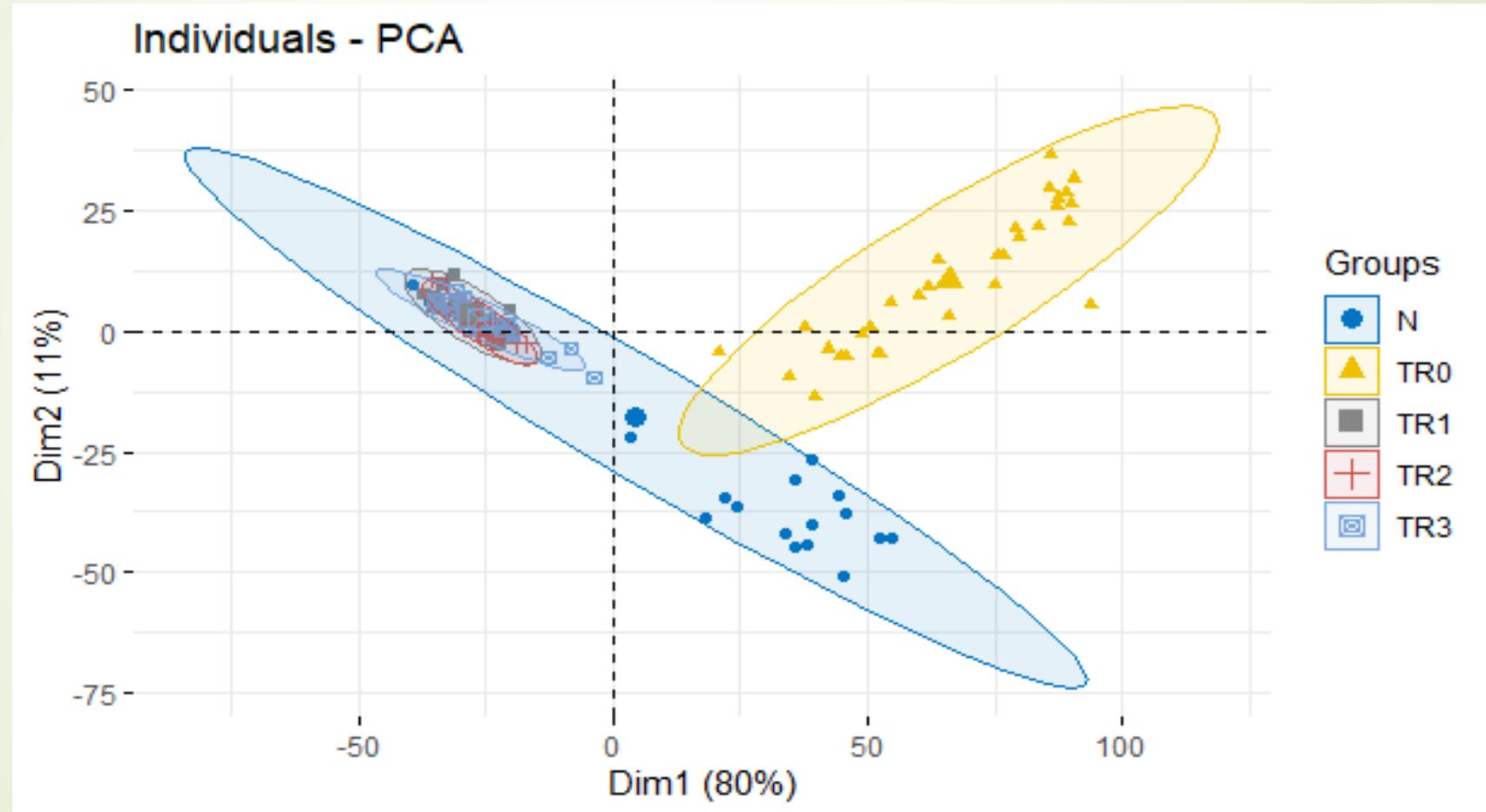
Men with High ROS level (NMR)?



Teratozoospermia (NMR)?



Teratozoospermia (Raman)?



TNX...

Any questions?

