Pharmacometabonomics: The Prediction of Drug Effects Using Metabolic Profiling

Jeremy R. Everett

Contents

Abstract

Metabonomics, also known as metabolomics, is concerned with the study of metabolite profiles in humans, animals, plants and other systems in order to assess their health or other status and their responses to experimental interventions. Metabonomics is thus widely used in disease diagnosis and in understanding responses to therapies such as drug administration. Pharmacometabonomics, also known as pharmacometabolomics, is a related methodology but with a prognostic as opposed to diagnostic thrust. Pharmacometabonomics aims to predict drug effects including efficacy, safety, metabolism and pharmacokinetics, prior to drug administration, via an analysis of pre-dose metabolite profiles. This article will review the development of pharmacometabonomics as a new field of science that

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has much promise in helping to deliver more effective personalised medicine, a major goal of twenty-first century healthcare.

Keywords
Metabolic phenotyping · Metabolomics · Metabonomics · Metabotypes · NMR spectroscopy · Personalised medicine · Pharmacometabolomics · Pharmacometabonomics · Precision medicine · Systems medicine

1 Introduction

Metabolic profiling of biological fluids has a long history going back hundreds, if not thousands, of years, to simple methods for detecting sweet-tasting urine as a biomarker for diabetes (Burt and Nandal 2016; Lindon and Wilson 2016). The science of metabolic profiling developed rapidly in the 1980s as huge advances were made in the power and sensitivity of the nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) detection technologies used in most metabolic profiling studies. Then in the late 1990s the sciences of metabonomics and metabolomics were named and defined. Metabonomics was defined in an interventional, i.e. experimental paradigm by the groups of Jeremy Nicholson and Jeremy Everett at Birkbeck College/Imperial College and Pfizer respectively as "the quantitative measurement of the multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification" (Lindon et al. 2000). The alternative term metabolomics was defined in an observational fashion a few years later by Fiehn as "a comprehensive analysis in which all the metabolites of a biological system are identified and quantified" (Fiehn 2002). The two terms are now used inter-operatively in spite of the stark differences between the definitions. The blanket term metabolic profiling is also used interchangeably with both terms (Lindon et al. 2007, 2019).

Metabonomics has many uses in the clinical arena including studies of disease mechanisms and biomarkers, disease diagnosis, detection of inborn errors of metabolism, the effects of therapeutic interventions on patients, drug metabolism, drug efficacy and drug safety (Lindon et al. 2007, 2019). The experiments are typically performed using NMR and MS technologies to detect and identify large numbers of metabolites in biological fluids such as urine, blood plasma, sweat, cerebrospinal fluid, tears, etc., but occasionally in body tissues as well. The metabolites detected in these metabonomics experiments are derived from a variety of sources including human endogenous, non-human endogenous (mainly the microbiome) and exogenous (external) sources including food, drink, drugs and the exposome. The phenotype of an organism is dictated by both the metabolites and the proteins that it contains and these may derive from many sources (Fig. 1).

Metabonomics experiments are typically conducted in an interventional or a diagnostic paradigm. Differences in metabolite profiles following an experimental intervention such as drug treatment are used to interpret the biological and biochemical effects of that treatment. In some cases, the intervention will produce a simple

metabolites			proteins: functional and structural		
human endogenous	non-human endogenous	environmental exogenous	human endogenous	non-human endogenous	environmental exogenous
metabonome					
proteome	bacteriome		post-translational modification		
transcriptome	mycome	food	transcriptome		food
epigenome	virome	drugs	epigenome	microbiome	drugs
genome	parasitome	exposome	genome	parasitome	

Fig. 1 The metabolites and proteins found in the human body may originate from inside the body (endogenous) or from various sources outside (exogenous). The pathway from gene to product is shown for the human endogenous metabolites and proteins, and the origins of non-human endogenous and exogenous metabolites and proteins are given

change, such as the reduction or increase in the concentration of one or a small number of key metabolites. In other cases, the intervention may produce widespread changes in the concentrations of a large number of metabolites and multivariate statistical analysis methods such as principal components analysis (PCA) can be used to simplify the data analysis and visualise the changes in metabolite space (Fig. 2a). In this "event interpretation" mode of metabonomics, the changes from pre-intervention (open circles) to post-intervention metabolic state (black squares) are interpreted in relation to the nature of the intervention applied. Another typical use of metabonomics is to distinguish between different groups of subjects, such as patients with a disease, such as liver failure (orange squares), compared to age- and gender-matched healthy human controls (green circles, Fig. 2b). In fact, the diagnostic paradigm of metabonomics is equivalent to the interventional paradigm if one considers that the intervention could be, for example, the presence or absence of a disease.

The technologies with which metabonomics experiments are conducted are important. There are two main technologies in use for metabolite detection and identification in biological fluids and tissues/tissue extracts today: mass spectrometry (MS), usually hyphenated together with a separation technology such as HPLC, UPLC, GC or CE, and NMR spectroscopy (Lindon et al. 2007, 2019; Markley et al. 2017; Nicholson et al. 2016; Wehrens and Salek 2019; Wilson 2015). Good protocols and guides for conducting the experiments by MS (Chen et al. 2016; Scalbert et al. 2009) or NMR (Beckonert et al. 2007; Gowda and Raftery 2017) and good methodologies for identifying the metabolites by MS (Kind and Fiehn 2010; Watson 2013) or NMR (Dona et al. 2016; Markley et al. 2017) are available.

Metabonomics experiments typically analyse the concentrations of metabolites before and after an intervention (Fig. 2a). Modern NMR spectrometers are capable

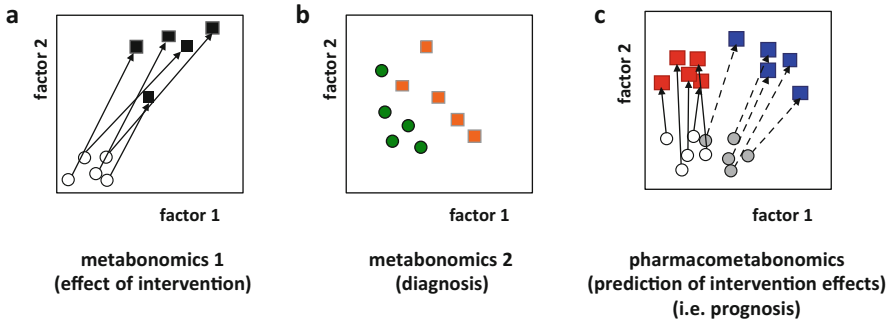


Fig. 2 Schematic representations of the outcomes from the two key experimental approaches to metabolic phenotyping, based on multivariate analysis, e.g. principal components scores, of the metabolic profiles of a number of individuals and showing the first two components (factor 1 and factor 2). Each square or circle represents an individual subject in the study. (**a**) Metabonomics approach 1 (effect of intervention), where open circles represent pre-intervention biofluid metabolic spectral profiles, and black squares represent post-intervention metabolic profiles in the same individuals, where some metabolic perturbation has occurred. The arrows indicate the metabolic trajectory that each individual underwent across metabolic hyperspace as a consequence of the intervention; (**b**) metabonomics approach 2: diagnosis. The metabolite profiles of patients with a disease (orange squares) are distinct from those of healthy controls (green circles) and thus a diagnosis can be made; (**c**) the predictive or prognostic approach. The difference in the *pre-intervention* metabolic profiles of two sub-groups of subjects (white circles v grey circles) allows *prediction* of different post-intervention states for these sub-groups (red and blue squares, respectively). For pharmacometabonomics, the intervention will be drug treatment and the prediction will be of drug PK, metabolism, efficacy or toxicity

of accurately quantifying the biofluid concentrations of dozens to hundreds of metabolites in a few minutes (Fig. 3).

A comparison of the attributes of MS and NMR for conducting metabonomics experiments is given in Table 1. Although far more studies are reported using MS-based detection (see Table 2 below), there is currently a trend to the increasing use of NMR due to its greater stability, ease of automation and reliability, which are important when dealing with large sample number studies, often the case in a clinical setting.

Metabonomics experiments can however be conducted not just by measuring metabolite levels. Metabolite concentration trajectories through time, metabolite entropies and metabolite correlations or networks can also be measured (Fig. 4) and these can often give additional information relative to that obtained from simple concentration measurements before and after an intervention (Everett et al. 2019).

Metabonomics experiments are sometimes categorised as to whether they are targeted or untargeted (Wishart 2016). In the targeted experiments, a selected group of metabolites is analysed, often quantifying the metabolite concentrations relative to an authentic reference standard. In the untargeted experiments, an unbiased approach is used and all the metabolites detected above the sensitivity threshold of the technology employed are analysed. Given the current lack of knowledge of mammalian biology and the complexities of genome – microbiome interactions, adopting

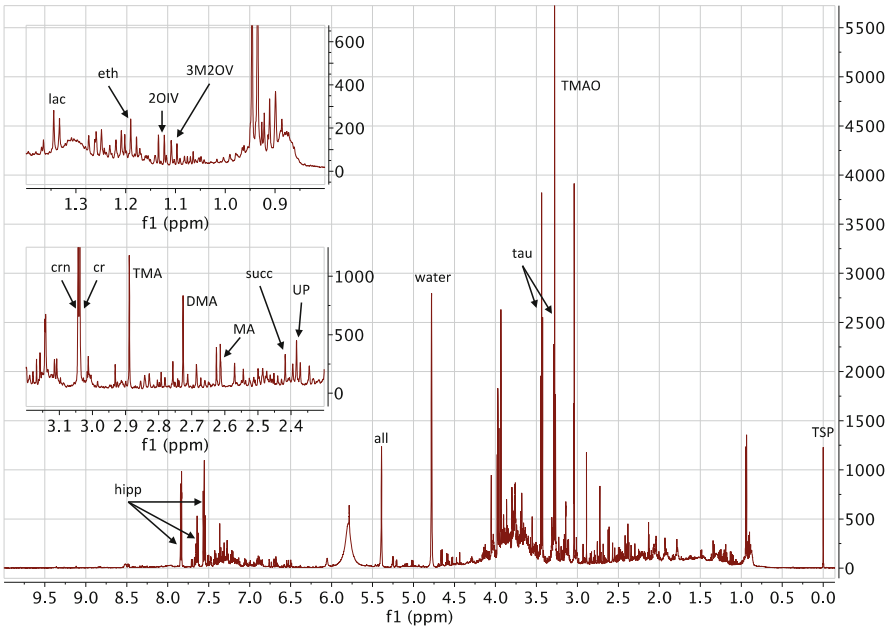


Fig. 3 The 600 MHz ^{1}H NMR spectrum of the urine of a control, male C57BL/6 mouse together with expansions of two low frequency regions, demonstrating the large number of metabolites that can be detected. The identities of some key metabolites are given: *2OIV* 2-oxoisovalerate, *3M2OV* 3-methyl-2-oxovalerate, *all* allantoin, *cr* creatine, *crn* creatinine, *eth* ethanol, *lac* lactate, *DMA* dimethylamine, *hipp* hippurate, *MA* methylamine, *succ* succinate, *TMA* trimethylamine, *TSP* trimethylsilylpropionate-d4 (the chemical shift and quantification reference), *UP* ureidopropionate, *water* the residual signal after water suppression

a targeted approach to metabonomics is only recommended when there is a well-understood biological hypothesis regarding the subjects and the intervention of the experiment. Many surprising and important discoveries are to be made by untargeted methods particularly because our understanding of mammalian biology is so primitive.

Metabonomics experiments can be conducted on a wide variety of sample types including biological fluids such as urine, blood plasma, cerebrospinal fluid, breath condensate, joint fluids, etc. (Lindon et al. 2007). The choice of sample will influence the sort of information that the experiments can provide. Analysis of breath condensates will provide information on the large number of volatile, low molecular weight compounds in exchange with lung tissue, whereas the analysis of blood plasma will provide information on low molecular weight metabolites including sugars, organic acids and amino acids, together with macromolecular compounds such as proteins, glycoproteins and lipoproteins. The analysis of urine (Emwas et al. 2015) can be advantageous: it contains a wide variety of metabolites including amines, organic acids, amino acids and sugars and in mammals, reports on both endogenous mammalian and endogenous microbial metabolites, as well as

Table 1 The attributes and capabilities of mass spectrometry and NMR spectroscopy in metabonomics experiments

NMR spectroscopy	Mass spectrometry
Powerful structure elucidation capability for small molecules in solution giving information on molecular structure, isomerism, conformations and dynamics	Powerful structure analysis capability to generate metabolite mass and molecular fragment information together with molecular formulae at high resolution
Relatively insensitive, but sensitivity improved recently with digital spectrometers, cryoprobes and low volume probes	Highly sensitive
Instrumentation expensive but per sample cost relatively low	Instrumentation relatively inexpensive but running costs high and isotopically-labelled reference standards for quantitation can be expensive
Absolute quantitative measurements and no reference standard required when used with ERETIC technology(Bharti and Roy 2012)	Not absolutely quantitative in absence of specific reference standards, but has relative quantification capability
Highly stable as no contact between sample and spectrometer Little effect of history on data Suitable for large-scale experiments on hundreds to thousands of samples in full automation	Relatively unstable, and may have detector gain changes with large sample numbers Column and spectrometer performance can be affected by history Large sample number runs are difficult due to challenges of maintaining instrument stability
Minimal sample preparation and direct analysis of biological samples	Generally requires a chromatographic separation step prior to MS analysis Gas chromatographic (GC) analysis requires metabolite derivatisation in order to obtain metabolite volatilisation
One set of unique signals for each isomer of each metabolite	Soft ionisation mass spectra may be complicated by multiple adduct formation with multiple spectra for different metal ion and solvent adducts observed for each metabolite GC-MS analyses may be complicated by formation of multiple derivatives
Completely non-destructive technique: Samples can be stored and re-analysed	Sample destroyed in analysis

mammalian – microbial co-metabolites. When the metabolism of a mammal such as a human is perturbed by disease or perhaps the effects of another intervention, such as drug treatment, the metabolic control systems will try to re-establish homeostasis. This will frequently occur by the elimination of unwanted metabolites via the urine, leaving the plasma less affected, thus giving the opportunity to identify the nature of the metabolic perturbation. Frequently, changes to the status of the gut microbiome can be detected by the observation of metabolic perturbations in urine samples.

Although most metabonomics experiments are diagnostic or interventional in mode, some experiments can be prognostic; that is, the metabolite patterns observed can be used to predict future events. The rest of this chapter will be devoted to prognostic metabonomics.

Table 2 A list of pharmacometabonomics studies from 2006 to 2019, sorted by study type and date order

#	Study and reference	Species	Metabolite profiling technology
Prediction of pharmacokinetics (PK)			
1	Prediction of tacrolimus PK in healthy volunteers (Phapale et al. 2010)	Human	LC-MS
2	Prediction of pharmacokinetics of triptolide (Liu et al. 2012)	Rat	GC-MS
3	Prediction of atorvastatin pharmacokinetics in healthy volunteers (Huang et al. 2015)	Human	GC-MS
4	Prediction of methotrexate clearance in patients with lymphoid malignancies (Kienana et al. 2016)	Human	GC-MS
5	Prediction of midazolam clearance in female volunteers (Shin et al. 2016)	Human	GC-MS
6	Pharmacometabonomic prediction of busulphan clearance in haematopoietic stem cell transplant recipients (Navarro et al. 2016)	Human	LC-MS
7	Prediction of intravenous busulphan clearance by endogenous plasma biomarkers using global pharmacometabolomics (Lin et al. 2016)	Human	LC-MS
8	Prediction of busulphan AUC in haematopoietic stem cell transplantation patients (Kim et al. 2017)	Human	LC-MS
9	Prediction of d4-cholic acid pharmacokinetics (Zhang et al. 2017b)	Rat	LC-MS
10	Integrated use of pharmacometabonomics and pharmacogenomics to predict the pharmacokinetics of a novel transient receptor potential vanilloid type 1 (TRPV1) antagonist (Oh et al. 2018)	Human	LC-MS
11	Prediction of zonisamide pharmacokinetics parameters in volunteers (Martinez-Avila et al. 2018a, b)	Human	LC-MS
12	Prediction of methylphenidate PK in healthy volunteers (Kaddurah-Daouk et al. 2018)	Human	LC-MS
13	Prediction of midazolam clearance in *male* volunteers (Lee et al. 2019)	Human	GC-MS
Prediction of drug metabolism			
1	Prediction of paracetamol/acetaminophen metabolism (Clayton et al. 2006) ** *First demonstration of pharmacometabonomics*	Rat	NMR
2	Prediction of metabolism of paracetamol/acetaminophen in human volunteers (Clayton et al. 2009) ** *First demonstration of pharmacometabonomics in humans*	Human	NMR

(continued)

Table 2 (continued)

#	Study and reference	Species	Metabolite profiling technology
3	Prediction of CYP3A4 induction in volunteer twins (Rahmioglu et al. 2011)	Human	NMR
4	Prediction of CYP3A activity in healthy volunteers (Shin et al. 2013)	Human	GC-MS
5	Prediction of losartan metabolism in healthy volunteers (He et al. 2018)	Human	NMR and LC-MS
6	Prediction of methylphenidate (Ritalin [for ADHD]) metabolism in healthy genotyped volunteers (Kaddurah-Daouk et al. 2018)	Human	LC-MS
Prediction of drug efficacy			
1	Prediction of simvastatin efficacy in patients on the cholesterol and pharmacogenomics study (Kaddurah-Daouk et al. 2010; Trupp et al. 2012)	Human	TLC plus GC and GC-MS
2	Prediction of chemotherapy efficacy in breast cancer patients (Stebbing et al. 2012)	Human	NMR
3	Prediction of citalopram/escitalopram response in patients with major depressive disorder (MDD) (Ji et al. 2011) ** *First demonstration of pharmacometabonomics-informed pharmacogenomics approach to personalised medicine* See also Abo et al. (2012) and Gupta et al. (2016)	Human	GC-MS and LC-ECA (LC-electrochemical coulometric array detection)
4	Prediction of sertraline and placebo responses in patients with MDD (Kaddurah-Daouk et al. 2011, 2013; Zhu et al. 2013)	Human	LC-ECA and GC-MS
5	Prediction of efficacy of anti-psychotics in schizophrenia patients (Condray et al. 2011)	Human	LC-ECA
6	Prediction of response to aspirin in healthy volunteers (Ellero-Simatos et al. 2014; Lewis et al. 2013; Yerges-Armstrong et al. 2013)	Human	LC-MS and GC-MS
7	Prediction of efficacy with anti-TNF therapies in rheumatoid arthritis (Kapoor et al. 2013)	Human	NMR
8	Prediction of thiopurine-*S*-methyltransferase phenotype in Estonian volunteers (Karas-Kuzelicki et al. 2014)	Human	HPLC
9	Prediction of efficacy of L-carnitine therapy for patients with septic shock (Evans et al. 2019; Puskarich et al. 2015, 2018)	Human	NMR and LC-MS
10	Prediction of acamprosate treatment outcomes in alcohol-dependent patients (Nam et al. 2015)	Human	LC-MS

(continued)

Table 2 (continued)

#	Study and reference	Species	Metabolite profiling technology
11	Prediction of blood pressure lowering in hypertensive patients treated with atenolol and hydrochlorothiazide (Rotroff et al. 2015)	Human	GC-MS
12	Prediction of response in lung cancer patients (Hao et al. 2016a)	Human	NMR and GC-MS
13	Prediction of patient response to trastuzumab-paclitaxel neoadjuvant therapy in HER-2 positive breast cancer (Miolo et al. 2016)	Human	LC-MS
14	Prediction of patient response in SSRI treatment of major depressive disorder (Gupta et al. 2016)	Human	LC-ECA
15	Prediction of clopidogrel high on treatment platelet reactivity (HTPR) in CAD patients [NMR] (Amin et al. 2017)	Human	NMR
16	Prediction of chemosensitivity of treatment of AML patients with cytarabine and anthracycline (Tan et al. 2017)	Human	LC-MS
17	Prediction of efficacy in pancreatic ductal adenocarcinoma patients receiving gemcitabine (Phua et al. 2017)	Human	GC-TOFMS
18	Prediction of blood pressure lowering by hydrochlorothiazide [lipidomics and pharmacogenomics] (Shahin et al. 2017)	Human	
19	Prediction of efficacy of gemcitabine and carboplatin treatment of metastatic breast cancer patients (Jiang et al. 2018)	Human	NMR
20	Prediction of gemcitabine efficacy in pancreatic ductal adenocarcinoma patients (Phua et al. 2018)	Human	GC-MS
21	Prediction of response to metformin treatment in early T2DM patients (Park et al. 2018)	Human	GC-MS
22	Prediction of efficacy of propranolol in reducing hepatic venous pressure gradient (HPVG) in patients with liver cirrhosis (Reverter et al. 2019)	Human	LC-MS
23	Prediction of efficacy of meglumine antimonite efficacy if patients with cutaneous leishmaniasis (Alejandro Vargas et al. 2019)	Human	LC-MS
24	QUASI-prediction of dexamethasone steroid treatment efficacy in pre-term infants with respiratory syndrome (Cao et al. 2019)	Human	GC-TOF-MS

(continued)

Table 2 (continued)

#	Study and reference	Species	Metabolite profiling technology
25	Prediction of warfarin efficacy in atrial fibrillation patients (Bawadikji et al. 2019)	Human	NMR
Prediction of adverse events			
1	Prediction of toxicity from paracetamol/acetaminophen dosing (Clayton et al. 2006) ** *First demonstration of pharmacometabonomics*	Rat	NMR
2	Prediction of weight gain in breast cancer patients undergoing chemotherapy (Keun et al. 2009) ** *First demonstration of pharmacometabonomics in patients*	Human	NMR
3	Prediction of onset of diabetes in rats administered with streptozotocin (Li et al. 2007)	Rat	GC-MS
4	Prediction of liver injury markers in patients treated with ximelagatran (Andersson et al. 2009)	Human	NMR, GC-MS and LC-MS
5	Prediction of toxicity of paracetamol/acetaminophen ("early-onset pharmacometabonomics") (Winnike et al. 2010)	Human	NMR
6	Prediction of nephrotoxicity of cisplatin (Kwon et al. 2011)	Rat	NMR
7	Prediction of toxicity in patients with inoperable colorectal cancer treated with capecitabine (Backshall et al. 2011)	Human	NMR
8	Prediction of toxicity of isoniazid in rats (Cunningham et al. 2012)	Rat	NMR
9	Prediction of hyperglycaemia in Caucasian hypertensive patients on the PEAR study with atenolol (Weng et al. 2016)	Human	LC-MS
10	Prediction of variability in response to galactosamine treatment (Coen et al. 2012)	Rat	NMR
11	Prediction of hyperglycaemia in Caucasian hypertensive patients on the PEAR study with atenolol (de Oliveira et al. 2016)	Human	GC-TOF-MS and genomics
12	Prediction of toxicity from lipopolysaccharide treatment in rats (Dai et al. 2016)	Rat	LC-MS and GC-MS
13	Prediction of 'high on treatment platelet reactivity (HTPR)' in patients on clopidogrel anti-platelet therapy to prevent stent thrombosis in urine (Amin et al. 2017)	Human	NMR
14	Prediction of nephrotoxicity of cisplatin in rats (Zhang et al. 2017a)	Rat	GC-MS and LC-MS

(continued)

Table 2 (continued)

#	Study and reference	Species	Metabolite profiling technology
15	prediction of "high on treatment platelet reactivity (HTPR)" in patients on clopidogrel anti-platelet therapy to prevent stent thrombosis in plasma (Amin et al. 2018)	Human	NMR
16	Prediction of peripheral neuropathy in breast cancer patients treated with Paclitaxel (Sun et al. 2018)	Human	NMR
17	Prediction of irinotecan gastrointestinal toxicity (Gao et al. 2019)	Rat	GC-MS and LC-MS
Predictive metabonomics			
1	Prediction of developing diabetes (Wang et al. 2011) ** *First predictive metabonomics study*	Human	LC-MS
2	Prediction of pre-diabetes (Wang-Sattler et al. 2012)	Human	LC-MS and flow-injection analysis-MS
3	Prediction of renal function recovery after relief of obstructive uropathy (Dong et al. 2013)	Human	NMR
4	Prediction of all-cause death (Fischer et al. 2014)	Human	NMR
5	Prediction of stroke recurrence after transient ischemic attack (Jove et al. 2015)	Human	LC-MS
6	Prediction of breast cancer risk (Bro et al. 2015)	Human	NMR
7	Prediction of preeclampsia and gestational hypertension (Austdal et al. 2015)	Human	NMR
8	Prediction of development of obesity (Ni et al. 2015)	Human	LC-MS
9	Prediction of 1-year outcome in subarachnoid haemorrhage (Sjoberg et al. 2015)	Human	GC-MS
10	Prediction of survival of lung cancer patients undergoing treatment (Hao et al. 2016a, b)	Human	GC-MS and NMR
11	A predictive metabolic signature for the transition from gestational diabetes to type 2 diabetes (Allalou et al. 2016)	Human	GC-MS and LC-MS
12	Prediction of survival of patients with decompensated cirrhosis s 2016 (McPhail et al. 2016)	Human	NMR and LC-MS
13	Prediction of postoperative hypoxaemia (Maltesen et al. 2016)	Human	NMR
14	Prediction of ALS clinical progression (Blasco et al. 2018)	Human	LC-MS
15	Prediction of all-cause death (Deelan et al. 2019)	Human	NMR

Significant studies are highlighted with *double asterisks in italic* **
Some studies have several publications associated with them
The table is unlikely to be exhaustive due to the different keywords used for some studies

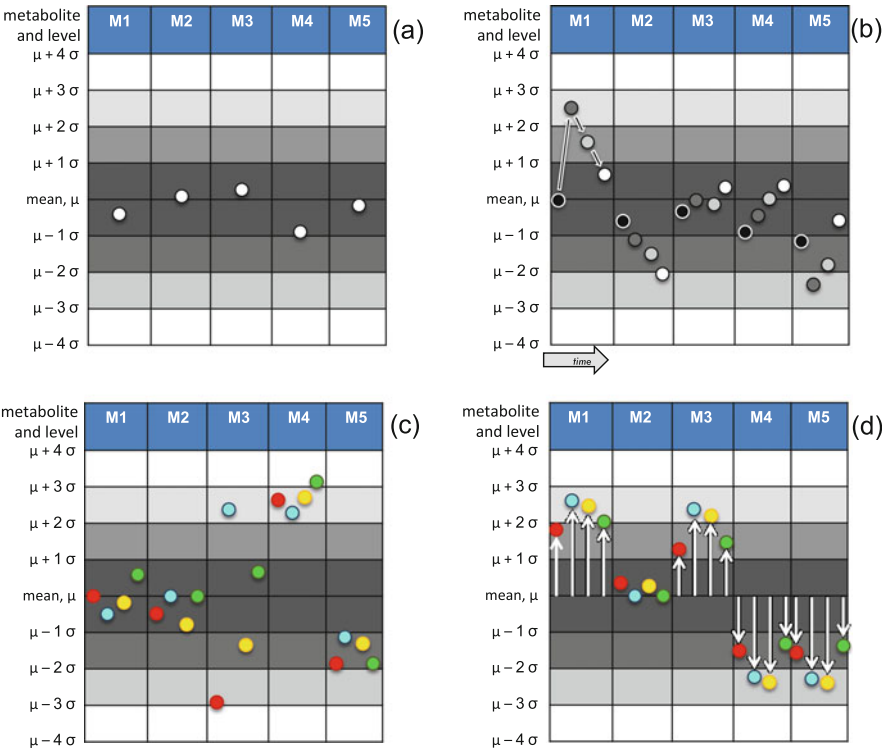


Fig. 4 A *schematic* representation of the four principal approaches to the measurement of metabonomic data: via (**a**) metabolite levels, (**b**) trajectories, (**c**) entropies or (**d**) correlations/dependencies. In Box (**a**), the *levels* of five different metabolites M1–M5 in one normal individual (white circles) are superimposed on a chart that represents the normal population distribution of metabolite levels. Symbols μ and σ are the mean and standard deviations of the levels of the metabolites for that population and with normal distribution. In Box (**b**), we see the *trajectories* over time for the same five metabolites M1–M5 in one individual subjected to an intervention of some kind. The time course of the metabolic trajectory moves from left to right in each metabolite column and is represented by circles, whose shading gets lighter over time. Arrows connect the time points for metabolite M1 but others are omitted for clarity. It can be seen that as a result of the challenge, the levels of some metabolites (M1, M2 and M5) undergo positive and negative excursions from the normal population values, whereas other metabolites are less affected. In Box (**c**), the metabolic *entropies* of a cohort of four individuals that have been subjected to a challenge are represented. The metabolite level for each individual is coloured differentially (red, blue, yellow and green circles represent individuals 1, 2, 3 and 4, respectively). It can be seen that in this cohort there is high metabolic entropy for metabolite M3 (metabolite levels are distributed across a very wide range of values/configurational states following the intervention) and significant disturbances in the metabolite *levels* for M4 and M5, but much lower metabolic *entropy* for metabolites, M1, M2, M4 and M5. In Box (**d**), the metabolite correlations seen for five metabolites (M1–M5) in four human subjects (red, blue, yellow and green circles represent individuals 1, 2, 3 and 4, respectively) are shown following an intervention. The intervention causes a significant increase in the concentrations of metabolite M1 for all four subjects (white vertical arrows), although to differing degrees. The same pattern of disturbance is seen for metabolite M3 in all four subjects. It is clear that the concentrations of metabolites M1 and M3 are correlated, with the excursions from the mean

2 Discovery of Pharmacometabonomics

A high degree of "biological variation", i.e. widely varying results, was often observed in early drug metabolism and drug safety studies in Beecham Pharmaceuticals and Pfizer R & D in the 1980s and 1990s. The causes of this variance were unknown but could lead to widely disparate results, sometimes to the extent that doubts were raised as to whether the drug in question had been dosed properly. Pfizer and Imperial College had established a panomics study of early drug safety signals in the 1990s. At a collaboration meeting in Amboise, France on 18th October 2000, the topic of widely varying safety data on galactosamine and isoniazid was discussed. The notion emerged from the meeting that the metabolic phenotype of the animals *prior to dosing* was influencing differential responses to the drug *post-dose*. A series of experiments was designed to test this notion, and the concept of pharmacometabonomics was born.

The first key experiment was to test the hypothesis that pre-dose rat metabolite profiles could predict post-dose drug metabolism and safety for the common analgesic paracetamol, also known as acetaminophen (Clayton et al. 2006). A dose of 600 mg/kg was administered to 65 Sprague-Dawley rats, and urine samples were collected both pre- and post-dosing and then analysed by 600 MHz ^{1}H NMR spectroscopy. A validated projection to latent structure (PLS) model showed a statistically significant correlation between pre-dose urine metabolite concentrations and the post-dose ratio of the metabolite paracetamol glucuronide (G) to the parent drug paracetamol (P, Fig. 5).

In addition, unbiased principal components analysis (PCA) of the pre-dose urine ^{1}H NMR spectra showed a partial correlation between the mean liver histopathology score (MHS) and principal component 2 (PC2) of the data (Fig. 6). A Mann–Whitney *U* test showed the statistical significance of the separation of the *pre-dose* NMR data for rats in class 1 (minimal/no liver pathology) and class 3 (significant liver pathology) with $p = 0.002$. The pre-dose levels of taurine were negatively correlated with the post-dose degree of liver pathology, consistent with taurine's known role in protecting against paracetamol toxicity (Waters et al. 2001). The taurine levels may have reflected the availability of inorganic sulphate to individual rats. Inorganic sulphate is needed for the biosynthesis of both taurine and for the paracetamol-sulphating agent phosphoadenosine phosphosulphate (PAPS). Consistent with this, rats with a high degree of liver necrosis showed a low degree of paracetamol sulphation (Clayton et al. 2006).

Thus it was clearly demonstrated that pre-dose metabolite profiles could enable the prediction of post-dose effects including drug metabolism and toxicity. This is pharmacometabonomics, which was defined as "the prediction of the outcome (for

Fig. 4 (continued) greatest for the yellow and blue subjects. By contrast the concentrations of metabolites M4 and M5 are anti-correlated with those of M1 and M3. It could be inferred from the correlations of the concentrations of these metabolites that they may be in the same or a related biochemical pathway. The levels of metabolite M2 are relatively undisturbed

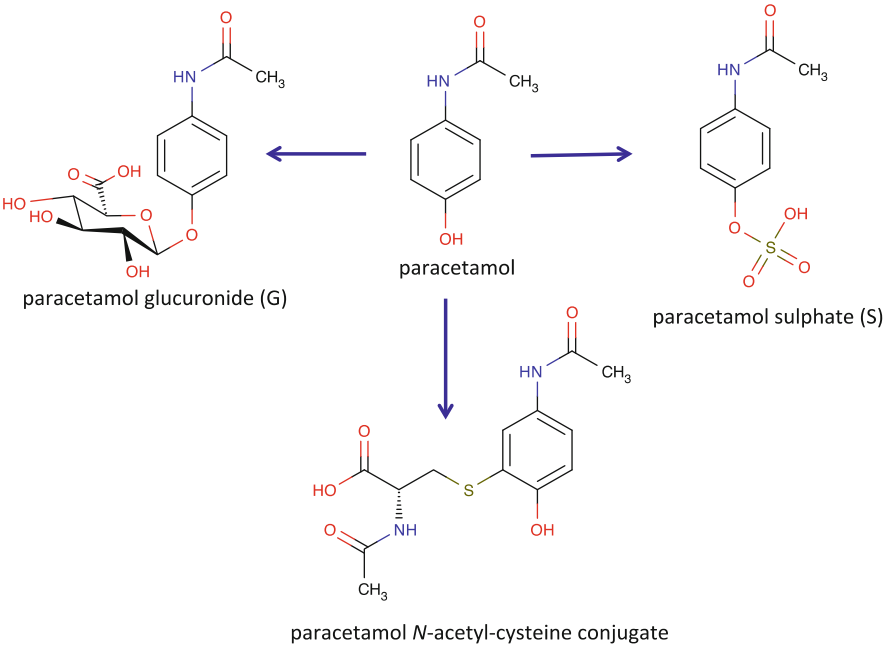


Fig. 5 The molecular structures of paracetamol (P) and its major metabolites

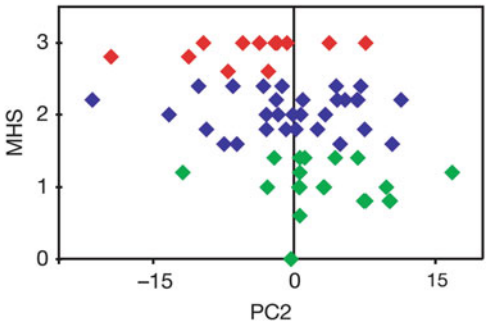


Fig. 6 A plot of paracetamol liver toxicity as measured by the mean liver histopathology score (MHS) against principal component 2 (PC2) of the *pre-dose* urine NMR spectral data. A partial class separation is observed. Each point represents a single rat and is colour-coded by its histology class with increasing degree of liver pathology: class 1 is green (minimal/no pathology), class 2 is blue (intermediate pathology), class 3 is red (significant pathology). Figure reproduced from Nature Publishing Group (Clayton et al. 2006)

example, efficacy or toxicity) of a drug or xenobiotic intervention in an individual based on a mathematical model of pre-intervention metabolite signatures" (Clayton et al. 2006). Pharmacometabonomics is a prognostic or predictive methodology, in contrast to the diagnostic mode of metabonomics and it is the metabolic equivalent

of pharmacogenomics, which is the use of genetic information to predict drug effects in advance of dosing (Salari et al. 2012).

The initial success of pharmacometabonomics experiments in animals prompted the question of whether the method would work in humans. A Pfizer/Imperial College research team therefore set up an experiment to test the hypothesis that pre-dose urine metabolite profiles could predict post-dose drug metabolism, again in the analgesic paracetamol. A normal clinical dose of paracetamol (two 500 mg tablets with water) was administered to 100, normal, male volunteers in March and April 2003. Urine samples were collected both pre-dose and 0–3 and 3–6 h post-dose and these were analysed by both 600 MHz ^{1}H NMR spectroscopy (Fig. 7) and UPLC-MS (Clayton et al. 2009).

The pre-dose ^{1}H NMR spectrum of volunteer 1 (Fig. 7a) showed signals from microbial metabolites such as hippurate (2) and human metabolites such as citrate (5) in addition to an unknown metabolite (4) with a singlet methyl signal at ca 2.35 ppm and second-order aromatic doublet signals between ca 7.2 and 7.3 ppm. This volunteer excreted more paracetamol glucuronide metabolite (8) than paracetamol sulphate (7) as is clear in the ^{1}H NMR spectrum of the 0–3 h post-dose urine (Fig. 7b) where both methyl group singlet and second-order aromatic doublet signals for these metabolites are clearly visible. By contrast, volunteer 2 excreted no visible quantity of unknown metabolite 4 pre-dose but excreted a much higher ratio of paracetamol sulphate (7) to glucuronide (8) post-dose (Fig. 7c, d).

Analysis of the remaining urinary ^{1}H NMR data showed that this pattern was present across all of the volunteers (Fig. 8).

It is clear from Fig. 8 that when the pre-dose ratio of metabolite 4 normalised to creatinine is greater than 0.06, then the post-dose paracetamol sulphate (S) to paracetamol glucuronide (G) ratio is always less than 0.8. The same pattern was found when the 3–6 h post-dose urines were analysed. Mann–Whitney U tests in conjunction with a Bonferroni correction to counter the effects of multiple hypothesis testing showed that the association of high metabolite 4 to creatinine ratios with low S/G ratios was statistically significant for both the 0–3 h ($p = 0.0001$) and 3–6 h ($p = 0.00012$) post-dose urines. With a Bonferroni correction of 100, the p value for statistical significance is 0.0005 instead of 0.05 (Broadhurst and Kell 2006).

Thus, it was clear that there was a statistically significant correlation, between the presence of metabolite 4 at high levels pre-dose and diminished paracetamol sulphate (S) to paracetamol glucuronide (G) ratios post-dose. It therefore became important to identify unknown metabolite 4.

Metabolite 4 possesses a singlet, three proton signal at ca 2.35 ppm indicating the presence of a methyl group attached to an sp^2 carbon on the basis of its chemical shift. The metabolite also possessed two, second-order aromatic doublet signals of two hydrogens each, indicating that metabolite 4 had a methyl group attached to a benzene ring with a substituent para to the methyl group. Metabolite 4 was identified as 4-cresolsulphate (HMDB11635) (Wishart et al. 2018) by both unambiguous chemical synthesis and spiking and by enzymatic desulphation to 4-cresol in situ (Fig. 9) (Clayton et al. 2009).

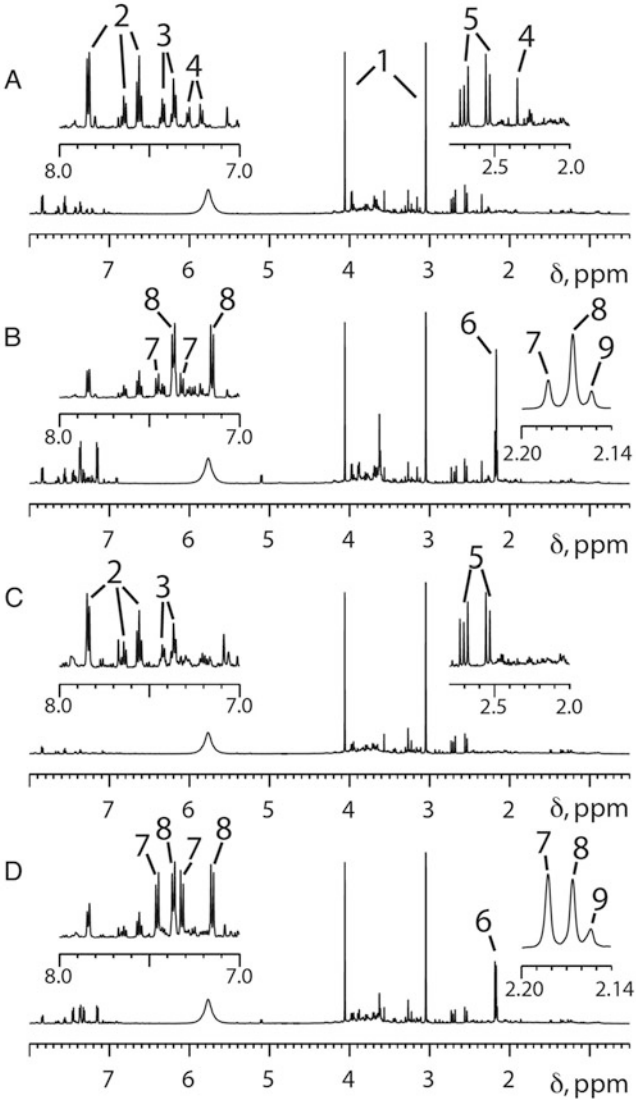


Fig. 7 600 MHz ^{1}H NMR spectra of the urines of volunteers taking a 1 g oral dose of paracetamol. (**a**) Spectrum of pre-dose urine of volunteer 1 together with expansions of the aromatic and lower frequency regions. (**b**) 0–3 h post-dose urine spectrum of volunteer 1. (**c** and **d**) The corresponding pre-dose and post-dose urine spectra of volunteer 2, respectively. Key to NMR signal numbers: 1, creatinine; 2, hippurate; 3, phenylacetylglutamine; 4, unknown metabolite; 5, citrate; 6, cluster of signals from N-acetyl groups from paracetamol-related compounds that resolves into 7, 8 and 9 on expansion; 7, paracetamol sulphate; 8, paracetamol glucuronide; 9, other paracetamol-related compounds. Reproduced with permission from PNAS (Clayton et al. 2009)

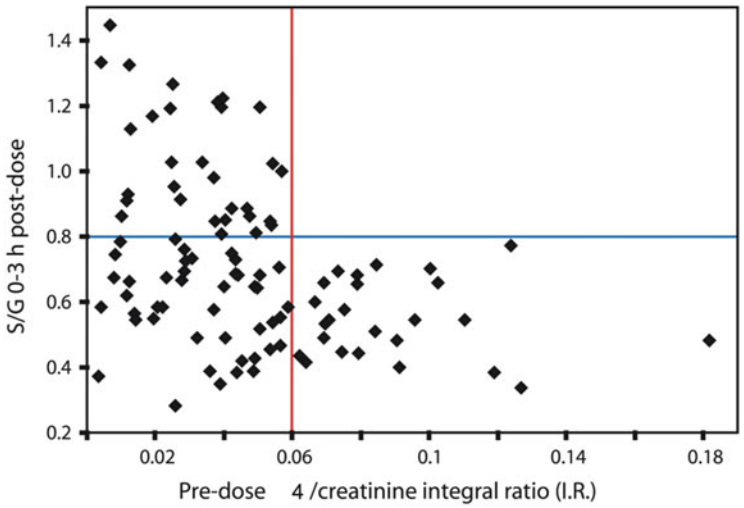


Fig. 8 The urinary ratio of paracetamol sulphate (S) to paracetamol glucuronide (G) excreted 0–3 h post-dose plotted against the pre-dose ratio of metabolite 4 normalised to creatinine. Reproduced with permission from PNAS (Clayton et al. 2009)

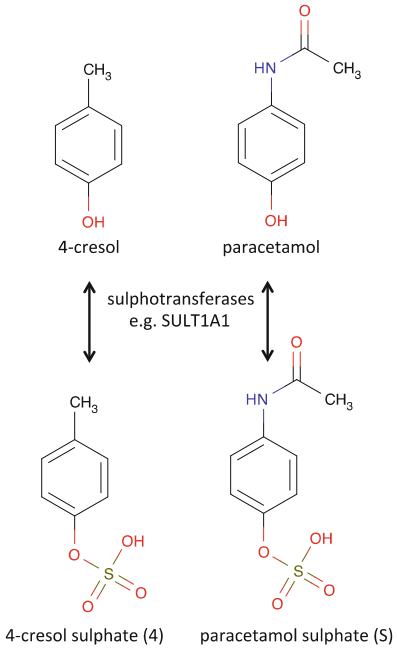


Fig. 9 The molecular structures of 4-cresol and paracetamol and their corresponding sulphate metabolites

The revelation that 4-cresolsulphate was a biomarker that, at least in part, could enable the prediction of the metabolic fate of paracetamol in humans was a surprise. 4-Cresolsulphate is made in humans by the sulphation of 4-cresol, itself a product of gut bacteria, particularly *Clostridia* species. Thus the human metabolism of the widely used analgesic paracetamol (acetaminophen) is at least in part under the control of gut bacterial metabolites. The influence of the gut microbiome on drug properties was not widely recognised at this time and this paper helped to highlight these important effects (Wilson 2009).

The reason for the relationship between 4-cresol and paracetamol metabolism is evident from an inspection of Fig. 9. The molecular structures of 4-cresol and paracetamol are quite similar and both are sulphated by the same sulphotransferases, particularly SULT1A1. In humans, as opposed to rodents, 4-cresol is metabolised almost exclusively by sulphation with no significant glucuronidation. However, this sulphation requires the sulphate donor cofactor 3-phosphoadenosine 5-phosphosulfate (PAPS) and its supply is limited in humans (Gamage et al. 2006). Therefore in a human with a high 4-cresol burden due to their gut microbiome, a significant amount of PAPS is used in 4-cresol sulphation and a challenge to the body of that person of a large dose of a drug requiring sulphation, results in the body turning to the alternative elimination pathway of glucuronidation and the consequent decreased S/G metabolite ratios. Note that these findings have implications for all drugs metabolised by sulphation and implications also for endogenous metabolism involving sulphation (Clayton et al. 2009). Finally, it is worth noting that a number of diseases including childhood autism, childhood hyperactivity and Parkinson's disease are associated with increased 4-cresolsulphate levels or altered S/G ratios after paracetamol administration and it is therefore likely that there is a microbiome influence on these disease states (Clayton et al. 2009).

3 Recent Developments in Pharmacometabonomics and the Delivery of Personalised Medicine

The prediction of paracetamol metabolism and safety described above represented the first definitive demonstration of pharmacometabonomics. Since that study was published (Clayton et al. 2006) numerous other studies have emerged demonstrating the ability of pharmacometabonomics methodologies to predict drug pharmacokinetics, metabolism, efficacy and safety in animals and humans (Burt and Nandal 2016; Everett 2016; Everett et al. 2013, 2016). These studies are important because they promise a new way to help deliver personalised medicine, which is a key objective of twenty-first century healthcare (Nicholson et al. 2011, 2016). The aim of personalised medicine is to select treatments that provide optimal efficacy with minimal toxicity or side effects for a given patient group, rather than giving the same standard treatment to all patients regardless of outcomes. It is a shocking fact that many drugs are ineffective or even unsafe in a high percentage of patients. It has been estimated that in the USA in 1994, over two million patients had serious

adverse drug reactions (ADRs), resulting in hospitalisation, disability or, in 106,000 cases, death (Lazarou et al. 1998). A more recent study put the cost of ADRs to the US economy in the range $30 billion to $100 billion per year. Thus the need to be able to prescribe medicines that are both effective and also safe for patients is clear.

Pharmacogenomics, i.e. the use of patient genetic information to predict drug effects has been important in enabling the development of personalised medicine in some areas especially in the prediction of the effects of "drug metabolising" enzymes such as cytochrome P450s on drug efficacy and safety (Lee et al. 2014). However, in many complex, multi-factorial diseases, the use of pharmacogenomics information has had more limited success (Pirmohamed 2014). Given the impact of environmental factors on drug effects, such as the status of the gut microbiome (Clayton et al. 2009), and the impact of drug-drug interactions, especially in phenoconversion (Shah and Smith 2015), it is not surprising that human pharmacogenomics studies have encountered challenges in progressing from success in the laboratory to success in clinical practice (Pirmohamed 2014). It is therefore encouraging that metabolic studies in the form of pharmacometabonomics can assist in the prediction of drug effects and with the implementation of personalised medicine. We will review progress in this area in the remainder of this chapter.

Table 2 provides an overview of the key pharmacometabonomics and predictive metabonomics studies that we are aware of, using the keywords pharmacometabonomics and pharmacometabolomics in PubMed. However, the list is unlikely to be exhaustive as some authors do not put these terms in either the title or keyword list. In addition, there are a minority of authors who are using the term pharmacometabonomics or pharmacometabonomics to describe diagnostic experiments with no prognostic elements.

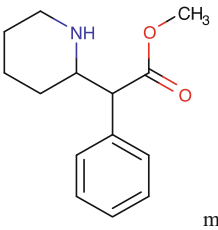
It can be seen from Table 2 that there are 13 studies dealing with the prediction of drug pharmacokinetics, 6 on prediction of drug metabolism, 25 on prediction of drug efficacy, 17 on prediction of adverse events and a further 15 predictive metabonomics studies where the prediction is based on an intervention other than drug administration. Thus we have at least 61 pharmacometabonomics studies in the literature to date. Of these 61 pharmacometabonomics and 15 predictive metabonomics studies, 65 were conducted in humans and 11 in the rat.

The development of pharmacometabonomics has been significant over the past 10 years especially. Several reviews of the field have already appeared (Burt and Nandal 2016; Everett 2016), so in the remainder of this chapter, we will focus on recent developments in the four key areas of prediction of drug pharmacokinetics, metabolism efficacy and safety.

3.1 Prediction of Drug Pharmacokinetics (PK)

The prediction of drug PK is especially important in situations where the therapeutic index (TI) of a drug is relatively low and also variable. Inappropriately high drug doses may lead to adverse effects in individual patients. The group of Rima Kaddurah-Daouk et al. used LC-MS methodologies to measure correlations between

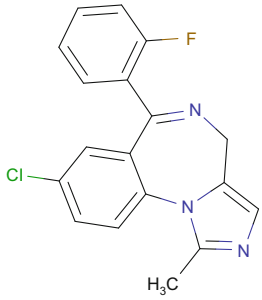
baseline plasma lipids of healthy volunteers and the PK of methylphenidate, trade name Ritalin (Kaddurah-Daouk et al. 2018).



methylphenidate, Ritalin

The phosphatidylcholine PC(38:5) was negatively correlated with the drug AUC and the blood plasma C_{max} values and the ceramide Cer(d18:1/24:1) was positively correlated with the plasma half-life of the drug metabolite ritalinic acid. Carboxylesterase 1(CES1) metabolises methylphenidate and other drugs such as cocaine and heroin via amide and ester bond hydrolysis. It was suggested that CES1 has a role in lipid metabolism and that the findings could be used for the prediction of the PK not only of methylphenidate, but other drugs metabolised by CES1 (Kaddurah-Daouk et al. 2018).

Differences in cytochrome P450 3A activities are a major source of variability in patient drug responses. Lee et al. (2019) developed a model for the prediction of CYP3A activity in the presence of inhibitors and inducers that was able to predict the clearance of midazolam with $r^2 = 0.75$. GC and GC-MS methodology was used in a targeted fashion to measure the concentrations of a small number of endogenous steroids in human volunteer urine and plasma samples.

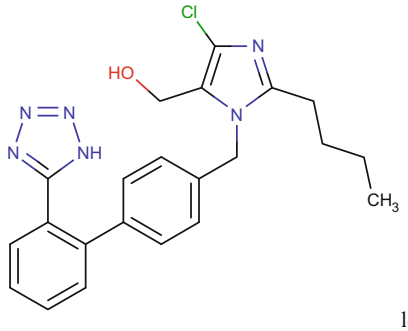


midazolam

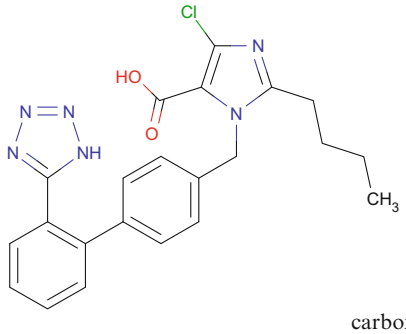
These data were amalgamated together with CYP3A5 genotype information to develop a model for the prediction of midazolam clearance. It was concluded that use of the model could be valuable for predicting CYP3A activities generally in drug development but that further validation was required.

3.2 Prediction of Drug Metabolism

He et al. have shown that pre-dose profiling by NMR spectroscopy of volunteer blood plasma could allow prediction of some metabolic and PK characteristics of losartan and its metabolite EXP3174 (He et al. 2018).



losartan



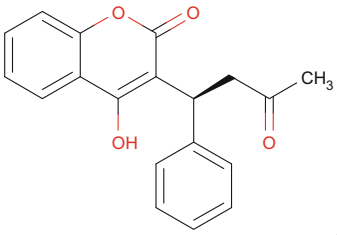
carboxylosartan, E3174

Losartan and its bioactive metabolite EXP3174 show a large degree of inter-individual differences in blood plasma concentrations that impact upon efficacy and safety. He et al. showed that pre-dose LDL/VLDL, lactate, citrate, creatine and glucose concentrations were positively correlated with, and HDL, creatinine, choline, glycine and phosphorylcholine concentrations were negatively correlated with the ratio of AUCs of EXP3174 and losartan. Pre-dose LDL/VLDL, lactate and glucose concentrations were positively correlated with, and choline, citrate concentrations were negatively correlated with the ratio of C_{max} values of EXP3174 and losartan. The switch of citrate from positively correlating with the ratio of AUCs to negatively correlating with the ratio of C_{max} values of EXP3174 and losartan was not commented upon. However, as Table 2 in the paper shows that the FDR value for citrate in the pathway analysis was 0.64, i.e. a >60% chance of a false discovery, then perhaps that switch is not surprising. Simple formulae

involving creatinine and lactate and also choline and glucose were derived for calculating the ratios of the AUCs and the C_{max} values of EXP3174 and losartan, respectively (He et al. 2018).

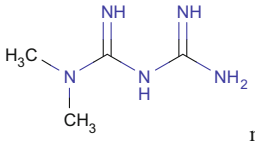
3.3 Prediction of Drug Efficacy

NMR spectroscopy of blood plasma was used to show a discrimination between atrial fibrillation patients on warfarin treatment that had stable versus unstable blood thickness. However, the study was not able to demonstrate any such discrimination for patients who were newly treated with warfarin and it was concluded that further studies were required (Bawadikji et al. 2019).



warfarin

Park and co-workers used GC-MS analysis of urine metabolites in early-phase type 2 diabetes mellitus (T2DM) patients to show that baseline levels of citrate and hippurate were significantly different for responders and non-responders to metformin treatment (Park et al. 2018).

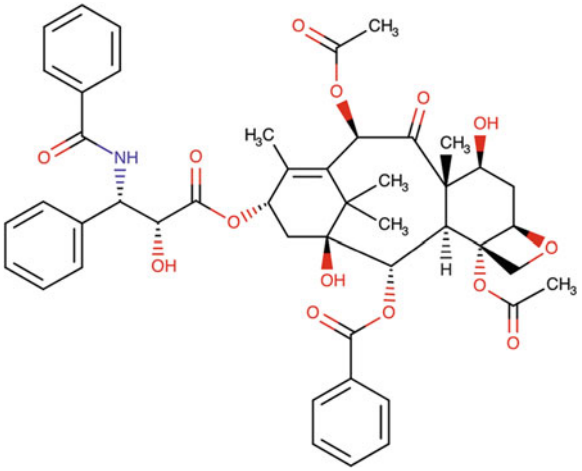


metformin

The response to treatment was assessed on the basis of changes in glycated haemoglobin A1c (HbA1c) levels from baseline. Pre-dose levels of myo-inositol were also marginally significantly different between these groups. This study was seen to be important in the context of developing personalised medicine, given the significant global burden of T2DM and the variability of patient response to treatment with metformin, a key medicine for treatment of the disease.

3.4 Prediction of Drug Safety

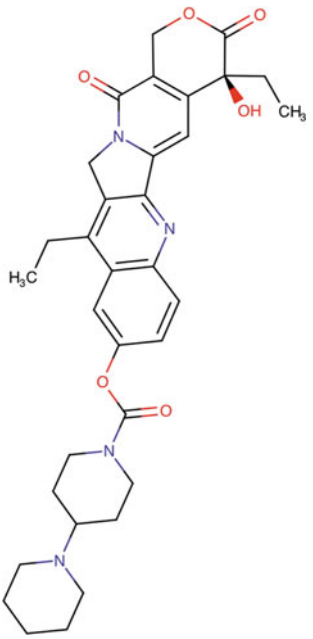
Paclitaxel (brand name Taxol) is a natural product widely used in the treatment of breast cancer. However, its usage is limited by many side effects including the development of peripheral neuropathy, which causes treatment delays or discontinuation in about one quarter of the patients (Sun et al. 2018).



paclitaxel, HMDB0015360, (Wishart et al. 2018)

The group of Sun et al. used an NMR spectroscopic approach to show that pre-treatment levels of blood histidine, phenylalanine and threonine were inversely associated with maximal change in the peripheral neuropathy index CIPN8 (Sun et al. 2018). This work promises to inform personalised medicine approaches to the selection of patients for treatment who will not suffer peripheral pain side effects.

Colorectal cancer is commonly treated with the topoisomerase I inhibitor, irinotecan.



irinotecan (HMDB14900, (Wishart et al. 2018)

However, several adverse effects are associated with its use, including gastrointestinal toxicity (delayed onset diarrhoea) and myelosuppression. Gao et al. used untargeted GC-MS and LC-MS as well as other targeted metabonomics methods to analyse biofluids from rats treated with the drug (Gao et al. 2019). OPLS-DA analysis of pre-dose serum metabolites showed a significant discrimination between sensitive rats displaying adverse drug side effects and non-sensitive rats. The bile acids cholic acid, deoxycholic acid and glycocholic acid together with phenylalanine were predictors for late-onset diarrhoea. The ketogenic amino acids phenylalanine, lysine and tryptophan were predictive of myelosuppression (Gao et al. 2019).

3.5 Not Pharmacometabonomics!

One issue that readers should be aware of is that many studies purporting to be pharmacometabonomics studies are merely metabonomics studies of the effects of drugs and nothing to do with predicting the effects of drug treatment. This growing confusion in the literature is to be regretted and resisted (Balashova et al. 2018; Kaddurah-Daouk et al. 2015).

3.6 Prediction of Interventions Other Than Drug Treatment: Predictive Metabonomics

In the original discovery of pharmacometabonomics, it was envisaged that the methodology would work for interventions other than drug treatment, such as diet changes, physical exercise or even just the passage of time (Clayton et al. 2006). This type of experiment is termed predictive metabonomics rather than pharmacometabonomics. Indeed, pharmacometabonomics is one member of the broader class of predictive metabonomics experiments, where the intervention is drug treatment. Predictive metabonomics has been defined as "the prediction of the outcome of an intervention in an individual based on a mathematical model of pre-intervention metabolite signatures" (Everett 2015). We will now illustrate the application of this prognostic methodology with some recent examples (see Table 2 for a fuller listing).

Pulmonary dysfunction resulting in hypoxaemia is a common complication following cardiac surgery. No predictive biomarkers are available to help identify patients that might suffer from this disease, which is characterised by low partial pressure of oxygen in arterial blood (PaO_2). Maltesen et al. used ^{1}H NMR spectroscopy to study blood serum taken from the pulmonary artery and left atrium of 47 coronary artery bypass graft patients, 16 h after weaning off their cardiopulmonary bypass (Maltesen et al. 2016). At day 3 post-operation, 32 patients had developed hypoxaemia. It was found that levels of carnitine, arachidonic and eicosapentaenoic acid, glycoprotein, citrate, phenylalanine, glycine, plasmalogen, and lysophosphocholine (Lyso-PC) were the most significant in the prediction of day 3 hypoxaemia from day 1 serum analysis. The concentrations of several of these metabolites were found to be individually correlated to day 3, PaO_2 levels. Thus predictive metabonomics methods are capable of prognosing later adverse effects of surgery well before any clinical sign. The results are promising in terms of targeting further treatments to affected patients and also directing research for new drugs to treat this disease on the basis of the perturbed metabolic pathways discovered.

Estimating mortality risk in ageing patients is important for decisions on treatment options. Current methods of mortality prediction are limited and some of the parameters, including systolic blood pressure and total cholesterol show opposite trends in the elderly compared with middle-aged people (Deelan et al. 2019). A predictive method based on metabolite profiles would find great clinical utility. Fischer and co-workers used ^{1}H NMR spectroscopy of the plasma of 9,842 individuals (randomly sampled from the Estonian Biobank) to elucidate that albumin, glycoprotein acetyls, citrate and the mean diameter of VLDL particles are associated with all-cause and cause-specific (cardiovascular and cancer) mortality (Fischer et al. 2014). The group of Deelan et al. recently published the results of a much larger study of 44,168 individuals, 5,512 of who died during follow-up, using ^{1}H NMR spectroscopy of EDTA plasma and serum (Deelan et al. 2019). A set of 14 metabolic biomarkers was found to independently associate with all-cause mortality. A mortality score based on gender and these 14 biomarkers led to an improved risk prediction compared to the conventional risk score. The biomarkers

included albumin, glycoprotein acetyls and mean diameter of VLDL particles, as found by Fischer, but also included acetoacetate, glucose and a number of amino acids. It was concluded that predictive metabonomics methods could be used in the future to guide patient care, if further validated in other clinical settings (Deelan et al. 2019).

4 Conclusions

Metabonomics and predictive metabonomics, including pharmacometabonomics, are starting to have an impact on biomedical and medical research, and in the future it is expected that these technologies will be widely used for both diagnostic and prognostic applications in real clinical settings. Metabolic profiling will be used synergistically with genomic analyses to assist in the delivery of personalised medicine. The approach of metabolite profiling, as opposed to genetic analysis, benefits hugely from the fact that it is a systems biology approach that integrates both genetic and environmental information and gives insights into the real-time status of a subject, as opposed to information on genetic risk factors that may not develop into a disease phenotype. In this context it is encouraging to see the work done by the groups of Kaddurah-Daouk and Weinshilboum on the development of pharmacometabonomics-led pharmacogenomics (Ji et al. 2011; Neavin et al. 2016).

The advent of large biobanks and the development of phenome centres such as those in London, Singapore and Birmingham, amongst others, gives the opportunity for very large-scale clinical studies that will undoubtedly lead to new insights into patient treatments in many disease areas. The great stability and automation capabilities of NMR spectroscopy as a metabolite detection technology are well matched to the task of analysing these huge numbers of samples, as was seen above in the work of Deelan and co-workers on all-cause mortality prediction (Deelan et al. 2019).

One major area that still needs much attention is metabolite identification. This is a significant challenge for both NMR- and MS-based technologies and in spite of the many advances in both areas in recent years, it is still the fact that most metabolites detected in most untargeted metabonomics experiments are unidentified. Progress on this issue promises to enable much more comprehensive biochemical insights into complex organisms including humans and their diseases.

The future for the use of metabolic profiling in clinical pharmacology and medicine in general is very bright.

Acknowledgements I would like to acknowledge productive and enjoyable collaborations with Professor Jeremy Nicholson, Professor John Lindon, Professor Ian Wilson, Professor Elaine Holmes and Professor Elizabeth Shephard over the past 35 years or more. I have gained very much from these stimulating interactions.

Glossary

Area under the curve (AUC) The integral over time of the concentration of a drug in blood plasma: a measure of the exposure of a patient to the drug.

Capillary electrophoresis (CE) An electrophoretic separation methodology based on molecular charge and mobility that can be hyphenated to mass spectrometry.

C_{max} The maximal blood plasma concentration achieved by a drug.

Diagnosis The characterisation of an organism, disease state, phenotype or response to an intervention.

GC Gas chromatography: a powerful method for the separation of volatile compounds. For use in metabonomics, pre-derivatisation of metabolites is required in order to achieve volatility.

HDL High density lipoprotein.

HPLC High performance liquid chromatography: a powerful analytical separation technology often hyphenated with mass spectrometry.

LDL Low density lipoprotein.

Metabolic entropy The degree of disorder of metabolite concentrations in an individual or in a group of subjects.

Metabolic phenotype Multicomponent metabolic characteristics that result from the cumulative interactions of genetic variation, gene products and environmental exposures and that can be related directly to disease risks and therapeutic responses: also known as the metabotype.

Metabolic trajectory The changes in metabolite concentrations over time in response to an intervention.

Metabolite A compound in a biological matrix of an organism that is produced in that organism by an enzymatic pathway.

Metabolome The full set of metabolites within, or that can be secreted from, a biological system such as a cell type or tissue.

Metabolomics Metabolic profiling defined in an observational fashion as "a comprehensive analysis in which all the metabolites of a biological system are identified and quantified".

Metabonome The full set of metabolites contained within an organism, i.e. the sum of all the metabolomes.

Metabonomics Metabolic profiling defined in an experimental fashion as "the quantitative measurement of the multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification".

Metabotype A probabilistic, multiparametric description of an organism in a given physiological state based on analysis of its cell types, biofluids and tissues: see metabolic phenotype.

Microbiome The collection of microorganisms present both in and on an organism, in a variety of environmental niches.

MS Mass spectrometry: a sensitive analytical methodology for the detection and characterisation of metabolites in biological matrices.

Multivariate analysis: MVA Multivariate (statistical) analysis: a method for the analysis of multiple variables in an experiment or observation at a time and the

simplification of the analysis problem by reduction of the large number of initial variables to a small number of key factors.

NMR spectroscopy Nuclear magnetic resonance spectroscopy: the most powerful method for molecular structure identification in solution, including metabolites in biological fluids.

OPLS-DA Orthogonal projection to latent structures with discriminant analysis: a supervised (and therefore potentially biased) approach to multivariate data analysis with the aim of finding metabolites that are statistically significantly discriminating between two groups, e.g. responders and non-responders, and which also discards metabolite variations that are orthogonal to the group discrimination.

Personalised medicine The use of genomic, molecular and clinical information to select treatments or medicines that are more likely to be both effective and safe for that patient: also known as precision medicine or stratified medicine.

Pharmacogenomics The prediction of the effects of a drug on the basis of individual genetic profiles.

Pharmacokinetics (PK) The measurement of the time course of the absorption, distribution, metabolism and excretion of a drug.

Pharmacometabolomics This term is used synonymously with pharmacometabonomics (see below), but is sometimes erroneously used to describe the investigation of the effects of a drug on an organism: this is just diagnostic metabonomics.

Pharmacometabonomics The prediction of the effects of a drug on the basis of a mathematical model of pre-dose metabolite profiles.

Phenotype The quantitative or qualitative measurement of specific parameters or traits that characterise individual functional biological classes or groups.

Predictive metabolic phenotyping or predictive metabonomics The prediction of the outcome of an intervention in an individual based on a mathematical model of pre-intervention metabolite profiles. The intervention could be a change in diet, exercise, the passage of time, surgical treatment, etc. Pharmacometabonomics is one case of predictive metabonomics, which covers the prognosis of any intervention.

Principal components analysis (PCA) An unsupervised (and therefore unbiased) multivariate statistical method for analysing high dimensional data, such as spectral data from metabonomics experiments. The PCA effects a drastic dimensionality reduction and transformation so that new principal components readily display the variance present in the dataset and therefore patterns in the data like clusters or groupings can be readily discerned and outliers identified.

Prognosis The prediction of disease onset, disease outcome or the outcome of an intervention such as drug treatment.

T2DM Type 2 diabetes mellitus.

Therapeutic index (TI) The TI measures the ratio of the effective dose of a drug for 50% of patients (expressed as ED50) to the toxic dose expressed as the TD50.

Usually a minimal TI of 10 is required in drug development: some companies will aim for a more conservative TI of 30.

UPLC Ultra-performance liquid chromatography: a more efficient and effective form of HPLC using smaller column packings and higher pressures.

VLDL Very low density lipoprotein.

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