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Nutritional metabolomics: Recent developments and future needs

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Abstract

Metabolomics has rapidly been adopted as one of the key methods in nutrition research. This review focuses on the recent developments and updates in the field, including the analytical methodologies that encompass improved instrument sensitivity, sampling techniques and data integration (multiomics). Metabolomics has advanced the discovery and validation of dietary biomarkers and their implementation in health research. Metabolomics has come to play an important role in the understanding of the role of small molecules resulting from the diet–microbiota interactions when gut microbiota research has shifted towards improving the understanding of the activity and functionality of gut microbiota rather than composition alone. Currently, metabolomics plays an emerging role in precision nutrition and the recent developments therein are discussed.

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Metabolomics, Nutrition, Biomarker, Dietary pattern, Endogenous metabolite, Gut microbiota, Precision prevention.

Introduction

Metabolomics has become a key methodological approach in nutrition research. It allows the characterization of the molecular phenotypes of individuals, their metabolic responsiveness to various foods and diets, and comprehensive assessment of their mechanistic and predictive role in health. Ultimately, this may pave the way for the development of novel precision prevention approaches [1]. The use of metabolomics in nutritional research also helps to gain a mechanistic understanding of the role of dietary compounds in nutritional status and metabolism, provides a read-out from gut microbiota composition and function, and may reflect other external exposures and their interactions with the host with implications for human health. Metabolomics may also provide novel, objective biomarkers that reflect specific dietary and lifestyle exposures. Single metabolites or metabolite profiles reflecting specific exposures could be used to assess individual responses to dietary interventions eventually enabling improved disease risk prediction. In precision nutrition, metabolomics is emerging as an important technique to assess the impact of foods and diets on an individual level [1] and to determine metabotypes, *i.e.*, subgroups of individuals with a similar metabolic response to diet [2]. Self-sampling and the use of non-invasive sample materials are emerging and could further enhance practical applications for precision nutrition and precision medicine, where frequent sampling is warranted, but comprehensive metabolomics techniques integrated and validated with the self-sampling techniques are yet lacking [3]. Advances in instrumentation, spectral databases, and computational tools have promoted the understanding of the complexity related to nutrition due to the wealth of biochemicals derived from foods, especially those produced from whole plants, although this "dark matter" of food remains mostly unresolved and poorly acknowledged [4*,5]. In this review, we highlight the most recent developments and challenges in nutritional metabolomics including methodological aspects and their application in nutrition research to reflect dietary and life-style exposures, molecular responses, diet–microbiota interactions, eventually offering possibilities for tailored precision nutrition.

Methodological advancements and challenges

The primary analytical techniques used in nutritional metabolomics are MS- and NMR-based methods.

Coupled with UHPLC, and more recently with ion mobility, the MS techniques provide broad metabolite coverage and high sensitivity [6,7]. Although ion mobility greatly enhances the separation and identification of metabolite and lipid isomers by providing an additional dimension to the measurements, its utilization in nutritional research has thus far been limited [8]. In NMR-based metabolomics, increased sensitivity of probes, optimized NMR excitation pulse schemes, hybrid NMR approaches and faster spectra preprocessing are important recent developments [9].

The main methodological advantages during the past few years have come from merging the metabolomics data with other omics, clinical, and dietary data alongside with developments of tools and pipelines for the purpose [10–13*,14**,15–21]. Since the plasma metabolome represents a snap-shot read-out modified by the host genetics, gut microbiota, diet and the exposome, recent research is increasingly focused on elucidating their interactions [11,22]. The most widely used multiomics approaches in current nutritional studies include combining metabolomics data and metagenomics data on gut microbial composition with a variety of available computational methods, such as metabolic networks, Spearman's correlation networks, and Sparse Generalized Canonical Correlation Analysis (SGCCA) [10–12,16,18–20]. Eventually, multiomics and data integration will help to unravel interactions between diet, gut microbiota and health [14**]. To promote this, novel multiomics databases are being introduced [14**,23]. Furthermore, the use of new sampling techniques, such as dried blood spot by finger-prick lancet [24], allowing for the first time quantitative measurement of metabolites in small volume samples [25], as well as alternative biofluids, including saliva [26], sweat [27], and breast milk [12], broaden the possibilities of metabolomics in human nutritional studies because of their non-invasive and less labor-intensive nature, allowing the samples to be collected at home. So far, these applications have been only used to a limited extent in nutritional studies. The variation of the reported metabolites in different biological matrices and the question of their representativeness of the food intake are challenging the field.

One of the biggest challenges in metabolomics is also to comprehensively characterize and annotate the vast number of compounds measured. This is particularly challenging in the case of nutritional metabolomics, as the immense pool of compounds gained from foods adds a level of complexity that needs to be addressed [4*,28]. In the case of lipidomics, essential improvements within the analytical methods as well as identification of lipids have been accomplished recently [29,30]. Besides the advancements in analytical technology, both open-access and commercial spectral databases are continuously expanding, and software utilizing machine learning and molecular networking have emerged to assist with the laborious process of metabolite identification [14**,15,17,31]. To fully understand the nutritional and eventually health properties of foods and diets, remarkable advancements are still required in our capacity to identify the individual metabolites to track down their metabolism and effects in the body. Randomized controlled trials represent the gold standard for establishing a causal relationship between food/diets and the metabolome of the collected sample material. Considering the inter- and intra-individual variability is vital and identifying responders and non-responders and their underlying determinants (*i.e.*, metabotypes) will provide new possibilities to tailored diets to improve the efficacy of interventions [1,32*].

Biomarkers of food intake and dietary patterns

Dietary biomarkers are metabolites objectively depicting the intake of certain foods or dietary patterns. Biomarkers can be classified based on the level of evidence [33**]. Recently, biomarker development and validation frameworks have been advanced [34] and the most promising biomarkers across important foods categories have been recently comprehensively reviewed [35**]. There are currently few validated food intake biomarkers, such as alkylresorcinols for whole grain wheat and rye intake, proline betaine for citrus fruits, and 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) for fish [33**,34,36*]. The search of novel biomarkers brings constantly emerging candidates for various food categories as summarized for the past 2–3 years in Table 1. For example, a study conducted by following the protocols of the Food Biomarker Alliance (FoodBAll) project aiming for the systematic coverage and validation of food biomarkers, shows promise for novel volatile biomarkers for dairy, cheese and soy-based drink intake [37]. Sex-specific differences in metabolic outcomes portray as one important aspect of biomarker discovery. Langenau et al. [38], for example, have reported differential biomarkers between men and women for coffee and fish.

In addition to individual foods, various studies have suggested biomarker candidates also for dietary patterns, as summarized for the past 2–3 years in Table 2. Mediterranean and Nordic diets are frequently referred as healthy dietary patterns with *e.g.* fish and whole-grain consumption as common elements. For example, Gürdeniz et al. [36*] reported urinary DHBA-glycine, CMPF and CMPF-glucuronide being significant metabolites associated with Healthy Nordic Diet. To accommodate both human and planetary health, plant-rich diets are increasingly important, which also shows in the recent research (Table 2).

Table 1

Most recently suggested biomarkers of food intake (reported in 2020–2023).

Food	Biomarker	HMDB ID	Sample; method	Reference
Almond	*alpha*-Tocopherol	HMDB0001893	Feces; GC–MS	[39]
	5-Hydroxyindoleacetic acid (5-HIAA)	HMDB0000763		
Beer	L-Cysteine	HMDB0000574	Plasma; GC–MS	[40]
	D-Lactose	HMDB0041627	Urine; GC–MS	
	D-Psicose	HMDB0250793		
Bell pepper	Six capsanthin- and capsorubin-derived glucuronides (see ref. for exact structures)	n/a	Urine; LC-MS, structural elucidation with NMR	[41]
Butter	Undecylenic acid (11:1*n*–1)	HMDB0033724	Serum; LC-MS/MS	[38]
Cheese	2-Heptanone	HMDB0003671	Plasma; GC–MS	[37]
	2-Undecanone	HMDB0033713		
Coffee	Glutamic acid	HMDB0000148	Plasma; GC–MS	[38,40]
	Quinic acid	HMDB0003072	Serum; LC-MS/MS	
	Paraxanthine (in men)	HMDB0001860	Urine; GC–MS	
	Catechol	HMDB0000957		
	Dimethyluric acid	HMDB0001857		
	Methyluric acid	HMDB0003099		
	Niacin	HMDB0001488		
	D-Psicose	HMDB0250793		
Dairy	3,5-Dimethyloctan-2-one	n/a	Plasma; GC–MS	[37]
Fish	EPA (20:5*n*–3) (in men)	HMDB0001999	Serum; LC-MS/MS	[38]
Milk	3-Ethylphenol	HMDB0059873	Urine; GC–MS	[37]
Poultry	3-Methylhistidine	HMDB0000479	Serum; LC-MS/MS	[38]
Spinach	Des-aminoarginine pentenol ester*	n/a	Urine; LC-MS	[42]
	D/L-Malic acid-*p*-coumarate	HMDB0303755		
Walnut	5-HIAA	HMDB0000763	Feces; GC–MS	[39]
	Uric acid	HMDB0000289		
White bread	Dodecanoic acid	HMDB0000638	Plasma; GC–MS	[40]
Whole-grain (wheat/rye)	5-Aminovaleric acid betaine (5-AVAB)	HMDB0240732	Serum; LC-MS	[43,44**]
	Pipecolic acid betaine	HMDB0304559		
	Tetradecanedioic acid	HMDB0000872		
Wine	Erythritol	HMDB0002994	Plasma; GC–MS	[40]
	Xylitol	HMDB0242149	Urine; GC–MS	
	Cinnamoylglycine	HMDB0011621		
	Citramalate	HMDB0000426		
	Erythritol	HMDB0002994		
	D-Gluconic acid	HMDB0000625		
	Tartaric acid	HMDB0000956		

* Tentative identification, novel structure not verified

Table 2

Examples of biomarker candidates of dietary patterns (reported in 2021–2022). Most of the biomarkers remain to be validated.

Food intake pattern	Associated foods	Associated metabolites	HMDB ID	Reference
Dietary approaches to stop hypertension (DASH)	Rich in fruits, vegetables, low-fat dairy products; moderate in meat, fish, poultry, nuts, and beans; low in sugar and red meat	2-Methylserine	n/a	[45–47]
		4-Allylphenol sulfate	HMDB0170765	
		beta-Cryptoxanthine	HMDB0033844	
		CAR 3:0	HMDB0000824	
		DG 18:2/18:3	HMDB0007249	
		DG 18:2/22:6	HMDB0007266	
		N-Methylproline	HMDB0094696	
		Ornithine	HMDB0000214	
		Panthotenate	HMDB0000210	
		Proline betaine	HMDB0004827	
		S-Allylcysteine	HMDB0034323	
		Threonate	HMDB0245425	
Healthy Nordic diet	Berries, fish, fruits, low/non-fat dairy, vegetables, whole-grain	3,5-Dihydroxybenzoic acid (3,5-DHBA)	HMDB0013677	[36*,48]
		3,5-DHBA-glycine	n/a	
		CEHC	n/a	
		3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid (CMPF)	HMDB0061112	
		CMPF-glucuronide	n/a	
		CAR 8:1	n/a	
		CAR 10:3	n/a	
		(Glycine) betaine	HMDB0000043	
		Hippuric acid	HMDB0000714	
		Indole-3-propionic acid	HMDB0002302	
		Linoleamide	HMDB0062656	
		Loliolide	HMDB0302428	
		Methylimidazoleacetic acid	HMDB0002820	
		Phenylalanine	HMDB0000159	
		Proline betaine	HMDB0004827	
Healthy plant-based diet (hPDI)	Coffee, fruits, legumes, nuts, plant protein, tea, vegetables, whole-grain	1-Methylnicotinamide	HMDB0000699	[49,50]
		1-Methyluric acid	HMDB0003099	
		3-Hydroxypyridine sulfate	HMDB0240652	
		4-Pyridoxic acid	HMDB0000017	
		4-Vinylphenol sulfate	HMDB0062775	
		Glyceric acid	HMDB0000139	
		Hippuric acid	HMDB0000714	
		Hydrocinnamic acid (3-phenylpropionic acid)	HMDB0000764	
		Indole-3-propionic acid	HMDB0002302	
		Lenticin (tryptophan betaine)	HMDB0061115	
		myo-Inositol	HMDB0000211	
		*N*1-methyl-2-pyridone-5-carboxamide	HMDB0004193	
		N-Acetylornithine	n/a	
		O-methoxycatechol-*O*-sulfate	HMDB0060013	
		Pantothenic acid	HMDB0000210	
		Pipecolic acid	HMDB0000070	
		Pyrocatechol sulfate	HMDB0059724	
		Quinic acid	HMDB0003072	
		Threitol	HMDB0004136	

		Threonic acid	HMDB0000943	
		Trigonelline	HMDB0000875	
Mediterranean diet	Fruits, legumes, olive oil, red wine, seafood, vegetables, whole-grain	5-Hydroxyindole	HMDB0059805	[10,51,52]
		Deoxycholic acid glucuronide	HMDB0002596	
		Hydroxyperoxyeicosapentaenoic acid	n/a	
		L-Aspartylphenylalanine	HMDB0000706	
		PC 35:1	n/a	
		PC 40:6	n/a	
		Succinic acid	HMDB0000254	
		TMA	HMDB0000906	
Plant-based diet (overall PDI)	Plant foods in general	4-Vinylphenol sulfate	HMDB0062775	[49,50]
		gamma-CEHC	HMDB0001931	
		gamma-Glutamyl peptides	n/a	
		(Glycine) betaine	HMDB0000043	
		Cinnamoylglycine	HMDB0011621	
		Glutamine	HMDB0000641	
		Glycerate	HMDB0000139	
		Glycine	HMDB0000123	
		Hippuric acid	HMDB0000714	
		Indole-3-propionic acid	HMDB0002302	
		Lenticin	HMDB0061115	
		myo-Inositol	HMDB0000211	
		N-Acetylornithine	n/a	
		N-Methylproline	HMDB0094696	
		O-methoxycatechol-*O*-sulfate	HMDB0060013	
		Paraxanthine	HMDB0001860	
		Pipecolic acid	HMDB0000070	
		Proline betaine	HMDB0004827	
		Pyrocatechol sulfate	HMDB0059724	
		scyllo-Inositol	HMDB0006088	
		Threonic acid	HMDB0000943	
		Trigonelline	HMDB0000875	
Sugar-rich diet	E.g. sugar-sweetened beverages	Chenodeoxycholic acid	HMDB0000518	[53]
		Glycocholic acid	HMDB0000138	
		Glutamic acid	HMDB0000148	
		Lithocholic acid	HMDB0000761	
		Phenylglycine	HMDB0002210	
		Tyrosine	HMDB0000158	
Unhealthy plant-based diet (uPDI)	Desserts, fruit juices, potatoes, refined grains, sugar-sweetened and artificially sweetened beverages, sweets	1,5-Anhydrosorbitol (1,5-anhydroglucitol)	HMDB0002712	[49]
		3-Methyl-2-oxovaleric acid	HMDB0000491	
		gamma-CEHC	HMDB0001931	
		Bilirubin (*Z*,*Z*)	HMDB0000054	
		Bradykinin	HMDB0004246	
		Hydroxyphenyllactic acid	HMDB0000755	
		*N*2,*N*2-Dimethylguanosine	HMDB0004824	
		Proline	HMDB0000162	
		S–*N*-Methylcysteine	HMDB0302211	
Ultra-processed foods	Industrially processed meat-containing products, instant noodles,	3-Methyl-2-oxovaleric acid	HMDB0000491	[54,55]
		4-Methylsyringol sulfate	n/a	
		Bradykinin	HMDB0004246	
		Elaidic acid	HMDB0000573	

(*continued on next page*)

Table 2. (*continued*)

Food intake pattern	Associated foods	Associated metabolites	HMDB ID	Reference
	confectionery, margarine	*N*2,*N*2-Dimethylguanosine	HMDB0004824	
		Saccharin	HMDB0029723	
Vegan diet	Fruits, legumes, vegetables, whole-grain	4-Acetylphenyl sulfate	n/a	[56,57]
		4-Allylpyrocatechol sulfate	HMDB0304934	
		4-Ethylphenyl sulfate	HMDB0062551	
		beta-Cryptoxanthin	HMDB0033844	
		alpha-Linolenic acid	HMDB0001388	
		Butyric acid	HMDB0000039	
		Folic acid	HMDB0000121	
		Glycohyocholic acid	HMDB0240607	
		Indole-3-propionic acid	HMDB0002302	
		N-Methylproline	HMDB0094696	
		Proline betaine	HMDB0004827	
		S-Methylmethionine	HMDB0038670	

Abbreviations: CAR, acylcarnitine; CEHC, carboxyethyl hydroxychroman; TMA, trimethylamine; PC, phosphatidylcholine.

Host and gut metabolites reflecting diet

Gut microbiota is an essential modulator of the metabolic response to diet and resulting health effects [10,53,58**,59,60]. Indeed, gut microbiota has been shown to contribute to approx. 13% of the total variation in plasma metabolites [58**]. The importance of microbiota is evidenced by the recent cataloguing of the metabolites related to diet–microbiota interactions [14**,59]. Indolepropionic acid is a microbial conversion product from dietary tryptophan linked with better insulin as well as lower risk of type 2 diabetes (T2D) and metabolic syndrome [61*], while indolelactic acid is associated with obesity, insulin resistance, and higher T2D risk [62]. Indolepropionic acid levels in blood were associated with a lower intake of animal-based food and a higher intake of fiber-rich plant-based foods [62], and partially explained by indolepropionic acid-associated gut bacteria, such as *Firmicutes* and *Bifidobacterium*. The interaction between diet, gut microbiota, and metabolite profiles was particularly shown by the association between higher milk intake, higher levels of bifidobacteria and serum indolepropionic acid (detected only among lactase non-persistent individuals) [62].

Among the most recently emerged compounds related to diet, gut microbiota and health is 5-aminovaleric acid betaine (5-AVAB) [44**,63,64]. It can be directly absorbed from its dietary sources, such as whole-grain cereals (Table 1), or conversion of other compounds with trimethyl groups potentially mediated by gut microbiota. Despite its anti-inflammatory, anticancer, and antioxidant properties, associations with fatty liver disease and cognitive decline have been reported, calling for further studies to disentangle if the association between 5-AVAB and health outcomes is depending on certain constraints or individual factors [44**].

Another controversial metabolite in terms of health relevance is trimethylamine *N*-oxide (TMAO), that has been linked with a higher risk of cardiovascular disease [65–67]. TMAO can enter circulation either directly from dietary sources such as fish, or *via* the activity of gut bacteria and liver metabolism from dietary precursors such as carnitine and choline rich in for example red meat [66,68,69]. Interestingly, females seem to have a higher abundance of bacteria producing trimethylamine, despite generally higher consumption of meat in males [68]. Even when TMAO levels can be associated with foods such as fish, whole-grains, poultry and eggs, these dietary items *per se* are not linked with adverse health outcomes, but merely the opposite, which highlights the fact that we have not yet fully understood the metabolic role of TMAO [66,67,70].

Short-chain fatty acids (SCFAs; formate, acetate, propionate, and butyrate) have been shown to benefit gut health *e.g.* by protecting epithelial integrity and

suppressing pro-inflammatory pathways [71]. SCFAs have also been shown to play roles in the regulation of intestinal hormones, appetite, and blood pressure, as well as glucose and lipid homeostasis [52]. Consumption of fiber-rich foods has been shown to increase SCFA levels, *e.g.* in vegan and Mediterranean diets [10,16]. Other determinants of SCFAs are intestinal gases, iron abundance, and colonic pH, all connected to both diet and gut microbial composition and activity [72]. Recent studies have suggested that plasma SCFA concentrations are of greater importance than fecal SCFA concerning metabolic risk factors and diseases [73–75].

Glycerophospholipids have been suggested to provide a pool of early biomarker candidates for metabolic syndrome, cardiometabolic diseases [13*,76,77*,78] and adherence to healthy eating patterns [36*]. Lysophosphatidylcholine (LPC) species may be the most interesting group of glycerophospholipids regarding the discovery of dietary biomarkers for metabolic health. For example, decreased LPC 18:2 levels have been suggested to indicate metabolic syndrome risk [13*,76] whereas a positive association has been found between LPC 18:1 and LPC 18:2 and adherence to dietary recommendations of The World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) [79]. As LPC 18:2 may play a role as a robust biomarker for healthy dietary patterns and metabolic health, acylcarnitine (CAR) with an 18:2 fatty acid tail has been found to correlate positively with the intake of linoleic acid (18:2), as well as with circulating ornithine and male sex [80]. In general, circulating acylcarnitines are often suggested as markers of impaired lipid and/or glucose metabolism [80].

Besides phospholipids, two other interesting categories to mention are bile acids and ceramides. Sex-based differences in fecal levels of bile acids have been observed [81]. Adherence to certain dietary patterns, such as vegan, Mediterranean or sugar-rich diet, has been shown to modulate such bile acids profiles and metabolic risk markers [10,16,52,53]. Fecal chenodeoxycholic acid, glycocholic acid, cholic acid, and hyodeoxycholic acid have been shown to be associated with higher circulating glucose, insulin, triglycerides, and LDL, especially in individuals with metabolic syndrome [13*]. Ceramides (Cer) seem to associate with either a higher or lower risk of T2D depending on the acyl chain length. For example, Cer 16:0, Cer 18:0 and dihydroceramide dhCer 20:0 were associated with higher risk, whereas Cer 20:0, dhCer 22:2 and dhCer 26:1 were associated with lower T2D risk [82]. These ceramides were also suggested to partly mediate the previously reported adverse effect of high red meat consumption on T2D risk. Similarly, Cer 22:2 was suggested to mediate the positive effect of coffee consumption on T2D risk. Ceramides may exemplify how metabolites may mediate the interaction between diet and cardiometabolic health [82].

Towards precision nutrition and prevention with metabolomics

It is well established that people vary in response to diet [83], which makes it important to find metabolites indicating or responsible for such variations in metabolic phenotypes (metabotypes) [84]. Thus, profiling such metabolites is promising in predicting dietary responses and stratifying the individuals based on their predicted responses. Once the metabolites are well characterized, further attempts can be made to trace the dietary sources or other factors responsible for such metabolites. This knowledge will aid in precision prevention, either using specific dietary components or lifestyle intervention to target the alteration of such metabolites to achieve the desired metabolite profiles. On the other hand, a precision intervention strategy specifically targeted to responders [47] will help improve the efficacy rate of the intervention [85]. For example, giving dietary intervention according to tissue-specific metabotypes has been shown to enhance improvement in cardiometabolic health markers in targeted participants [86]. The PERSonalized Glucose Optimization Through Nutritional Intervention (PERSON) study was one of the first randomized clinical trials to test effects of a personalized dietary intervention based on metabolism related phenotypes [87*]. Also in the PREVENTOMICS platform individuals are classified into clusters for personalized dietary plans [32*]. Although a personalized diet plan did not show significant improvement in the endpoint markers compared to a generic healthy diet, the PREVENTOMICS study may work as a pioneer study to further investigate the use of metabolomics together with other omics in biomarker-guided dietary interventions [32*].

Concluding remarks

Metabolomics holds the potential for wider utilization in all aspects related to nutrition as discussed in this review, as long as the computational methods to process, mine, and visualize the complex metabolomics data, including the identification of the metabolites, continue to be developed to provide reliable results and informative interpretations of the data. This is also the prerequisite in order to fully exploit the latest technological advancements and to have them more widely adopted. Metabolomics-based frameworks keep accelerating the discovery and validation of dietary biomarkers. Examples mentioned here raise the importance of the examination of metabolome profiles in investigating the links between diet, gut microbiota and metabolic health outcomes. Metabolomics has a key role in defining more detailed and personalized nutritional recommendations and dividing foods into more health-relevant categories.

Author contributions

Conceptualization: KH, RL; Writing – Original Draft: MK, SN, AK, JR, TM, VK; Writing – Review & Editing: RL, KH, MK, SN, VK, AK, TM, JR.

Declaration of competing interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: Kati Hanhineva reports a relationship with Afekta Technologies that includes: board membership, employment, and equity or stocks. Ville Koistinen reports a relationship with Afekta Technologies that includes: board membership, employment, and equity or stocks. Topi Meuronen reports a relationship with Afekta Technologies that includes: consulting or advisory and paid expert testimony.

Data availability

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** of outstanding interest

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