

# Precision medicine approaches in metabolic disorders and target organ damage: where are we now, and where are we going?

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## Summary

In this review, we discuss selected topics, which are relevant to implementing precision medicine in metabolic disorders.

Personalization of diet and exercise may help in preventing obesity and type 2 diabetes (T2D). Weight loss should be personalized based on age, sex, ethnicity and coexisting comorbidities. Advances in our understanding of pathophysiology, genetics and epigenetics of obesity promise to offer tailored management options. Careful risk assessment is necessary prior to intervention. Risk may be underestimated, e.g., in women, in different ethnic groups and in people with T2D. More personalized approaches could be useful among persons who failed to respond to traditional risk factor management, such as pharmacological treatment for dyslipidemia and arterial hypertension.

Nonalcoholic fatty liver disease/metabolic-associated fatty liver disease (NAFLD/MAFLD) is both a cause and an effect of altered glucose and lipid metabolism. Personalized medicine approaches could be key to identifying more effective pharmacological strategies also to reverse this common and burdensome metabolic liver disease.

Finally, metabolomics could be used to identify relevant biomarkers for cancer diagnosis, staging and prognostication. Cancers of colon and rectum, breast, prostate, thyroid and ovaries illustrate the notion that cancer cell metabolic derangements may be utilized in clinical practice. A true personalization of pharmacotherapies should be pursued especially in obese patients with cancer.

EWC 208

**Key words:** arterial hypertension; biomarkers; breast; cancer; cardiovascular risk; epigenetics; genetics; gut microbiota; MAFLD; management; metabolic syndrome; metabolomics; NAFLD; pathophysiology; personalized medicine; precision medicine; prevention; prostate; research; thyroid; type 2 diabetes.

## List of abbreviations used

ACE-2 - angiotensin-converting enzyme 2  
AMD - Italian Association of Diabetologists  
BMI - body mass index  
CAD - coronary artery disease  
CVD - cardiovascular disease  
CRC - colorectal cancer  
FNAB - fine needle aspiration biopsy  
GLP-1 RAs - glucagon-like peptide-1 receptor agonists  
HTN - arterial hypertension  
IGB- intra-gastric fluid-filled balloon  
MAFLD - metabolic-associated fatty liver disease  
MetS – metabolic syndrome  
NAFLD - nonalcoholic fatty liver disease  
NMR - nuclear magnetic resonance  
PSA - prostate-specific antigen  
SCFA - short-chain fatty acids  
SOT - solid organ transplant  
T2D – type 2 diabetes

# 1. Background

## 1.1 Definitions

Metabolic disorders comprise a pathogenically and clinically heterogeneous set of conditions, which affect all age groups and exact a heavy clinical and financial burden [1]. Among the most prevalent metabolic disorders, obesity and type 2 diabetes (T2D) affect hundreds of millions of individuals globally, and are projected to increase during the next decade [2].

Precision medicine focuses on tailoring medical treatment to the individual characteristics of each patient and is aimed at improving clinical outcomes in a patient, thereby minimizing adverse events, while maximizing the therapeutic gains of any given treatment [3]. In precision medicine, the focus is on identifying which medical approaches will be effective for which patients based on genetic, environmental and lifestyle factors. [4]. There is a substantial overlap between the terms "precision medicine" and "personalized medicine". According to the National Research Council, the word "personalized" should not be used to imply that treatments and preventions are developed uniquely for each individual [4]. That said, the two terms will be used synonymously and interchangeably in this article.

## 1.2. Purpose

Here, we try to identify some of the lines of research that promise to become relevant in the near future to implementing precision medicine in metabolic disorders. Rather than delivering a systematic overview for all metabolic diseases, we propose to focus on the metabolic syndrome (MetS) and its hepatic correlate, i.e., nonalcoholic fatty liver disease/metabolic-associated fatty liver disease (NAFLD/MAFLD). Additionally, we will also address some cancer types that are strongly associated with MetS and its individual features. Finally, we also discuss the areas of potential development in this field

## 1.3. Methods

We searched PubMed database using the following key words: "personalized medicine"; "precision medicine"; "metabolic syndrome"; "MAFLD"; "NAFLD"; "nonalcoholic steatohepatitis" (or "NASH"); "diagnosis and management"; and "cancer". Although this is a narrative rather than a systematic literature review, we have done our best to identify all pertinent articles published as of the date of our writing. Only those papers that were felt to be relevant based on the Authors' agreement were retained.

# 2. Metabolic Syndrome

Prevention of obesity and T2D remains an unmet clinical and public health issue, and personalization of diet and exercise regimes is an important goal to help in achieving this aim. Pioneering observations between 1960 and 1989 from several researchers, including Denis Burkitt, eventually led to the so called "fiber hypothesis" [5]. The dietary fibre hypothesis suggested that the risk of obesity, T2D or heart attack increased as a result of fibers being

removed during the refinement process of grains, rather than being due to a too high consumption of refined sugar. This had become commonplace in developed countries since 1760, when the first industrial revolution took place in the UK [6]. Fibers reduce appetite, improve gut transit and microbiome composition, and via microbial fermentation in the large bowel, increase the production of short-chain fatty acids (SCFA). SCFA, in turn, may induce epigenomic changes via metabolic regulatory receptors in distant organs, thereby promoting metabolic health through reducing the development of obesity, T2D, atherosclerosis, and certain cancer types [7]. How fibers are defined and what are the optimum amounts of daily fibers, which are necessary for maintaining and promoting metabolic health, is still poorly defined. However, it seems appropriate to define fiber as a complex mixture of dietary residues that convey health benefits, e.g., carbohydrate polymers (with three or more monomeric units); non-starch polysaccharides (from fruits and vegetables; cell wall components linked to polysaccharides); non-digestible oligosaccharides; resistant starch, associated with non-carbohydrate substances (such as lignin) that are neither digested nor absorbed by the human small intestine, but are metabolized by gut microbiota. [7,8].

Evidence suggests that an increased dietary fiber intake up to 50 g/day is associated with increased life expectancy, as well as improved quality of life added years (QALYs), and reduced health-care expenditures [7]. Given the strong interactions of the intestinal microbiome with normal and diseased metabolism, the evaluation of inter-individual differences in microbiome composition and function promise to pave the way towards personalized microbiome-based medicine in treating common metabolic disorders belonging to the MetS spectrum [9].

## **2.1 Type 2 diabetes (T2D)**

### **2.1.1 Awareness**

Awareness of T2D risk among individuals with a positive family history for T2D may potentially improve risk-reducing behaviors. However, a recent study found that roughly one in four individuals were concordant between their perceived and clinical risk for T2D [10]. This study suggested that personalized interventions should be carried out to specifically engage in early risk reduction strategies those patients who tend to downplay and underestimate their overall T2D risk. Conceptually, similar findings have been identified for cardiovascular risk factors. Kim *et al.* conducted a cross-sectional survey among 1584 patients using a bi-lingual (English and Spanish) 32-item questionnaire, aimed at assessing understanding of cardiovascular risk factors [11]. Data from this study showed that, compared to White participants, Afro-Americans and Hispanics had a significantly higher misperception about their personal risk of T2D (OR 2.22; 95% CI, 1.08-5.57; and OR 3.50; 95% CI, 1.49-8.20, respectively) and Hispanics also for dyslipidemia (OR 2.21; 95% CI, 1.19-4.10). This study strongly supports the notion that different ethnic groups have gaps between awareness and personalization of risk in major modifiable cardiovascular risk factors.

### 2.1.2. Classification of diabetes subtypes

Although invariably defined by chronic hyperglycemia, diabetes is characterized by a high level of clinical heterogeneity. Therefore, the identification of disease subtypes with different determinants at diagnosis and variable risk profiles remains a major aim of personalized medicine in diabetes arena [12]. This could pave avenues for allocating resources especially to those patients, who are at highest risk of developing chronic diabetic complications, as well as for enhancing power in experimental, genetic, and clinical studies by identifying more homogeneous patient populations [12]. With this backdrop, a consistent line of research has recently shown that a first step towards precision medicine in diabetes practice and research may be the stratification into homogenous subsets of patients. Recently, Ahlqvist et al. [13] conducted a data-driven cluster of data in 8980 patients with newly-diagnosed diabetes from the Swedish All New Diabetics in Scania cohort. Three large independent cohorts [the Scania Diabetes Registry (n=1466), All New Diabetics in Uppsala (n=844), and Diabetes Registry Vaasa (n=3485)] were used for replication purposes and clusters were based on six variables: glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA1c, and homeostatic model assessment (HOMA) estimates of  $\beta$ -cell function and insulin resistance. Data have shown that five replicable clusters of patients with diabetes could be identified. Of these 5 different patient clusters, those in cluster 3, which had more severe insulin resistance, were at highest risk of diabetic kidney disease compared to those included in clusters 4 and 5. However, treatment administered was similar across clusters 3 to 5. Patients in cluster 2 were more insulin deficient and had the highest risk of diabetic retinopathy [13]. Further evidence that distinct diabetes clusters may exhibit specific risk patterns of diabetes-related complications comes from the study by Zaharia *et al.* [14]. These authors performed a 5-year follow-up study of a cohort of 1105 well-phenotyped patients with newly diagnosed type 1 or type 2 diabetes enrolled in the German Diabetes Study. At baseline, 35% were classified as mild age-related diabetes (MARD), 29% to mild obesity-related diabetes (MOD), 22% to severe autoimmune diabetes (SAID), 11% to severe insulin-resistant diabetes (SIRD), and 3% to severe insulin-deficient diabetes (SIDD). At 5-year follow-up, 367 of these patients were re-assessed; 35% of them had MARD, 29% had MOD, 24% had SAID, 10% had SIRD, and 3% had SIDD. In patients with newly diagnosed diabetes, intrahepatic fat content was highest at baseline in patients assigned to the SIRD cluster compared to all other clusters, irrespective of baseline glucose-lowering medications. Consistently, hepatic fibrosis at 5-year follow-up was more pronounced in patients with SIRD than in those with SAID, MARD, MOD or SIDD. Confirmed diabetic sensorimotor polyneuropathy was also more prevalent at baseline in patients with SIDD than in those with SAID, MARD, MOD and SIRD. Collectively, these findings suggest the conclusion that specific diabetes clusters have variably different risks of chronic diabetes complications.

### 2.1.3. Management

Achieving cardio-metabolic control is a largely unmet clinical goal that can best be obtained through personalization of drug treatment, in people with T2D. Conflicting with this practice gap, treatment trials are rarely designed to specifically address individual subsets of T2D

patients (typically elderly patients or those with chronic kidney injury) [15–17]. Therefore, additional studies should be aimed at suggesting optimized therapeutic strategies. A choice of drugs and dosages should be used to promote maximal benefit while keeping side effects to a minimum [15]. As we are going to discuss later in this article, one approach useful to reaching this goal could be to move further to clinical phenotypes by using an omics-based approach. Initiatives from scientific societies are also expected to contribute to further promoting research in this area. For example, the Italian Association of Diabetologists (AMD) conducted an international survey to ascertain the opinions of physicians regarding those tailored therapeutic algorithms that have been developed by AMD [16]. Despite the inherent heterogeneity of T2D, the 452 participating physicians (the majority of whom were men and were Diabetologists) widely agreed that there is a need for a personalized therapeutic approach that is accessible and easy to use [16].

Weight loss achievement and maintenance is a mainstay in T2D prevention and management. However, a recent study suggests that timing, extent, and body mass index (BMI) affect clinically relevant outcomes for weight loss maintenance, after a diagnosis of T2D. Strelitz *et al.* [17] conducted an observational analysis on 2730 European individuals with screen-detected T2D. These authors reported that compared to maintaining body weight, both weight loss and weight gain after screen-detected diagnosis of T2D were significantly associated with a higher risk of mortality, but not adverse cardiovascular events, particularly among non-obese individuals. This pioneering study suggests the importance of exploring avenues of personalization of weight loss advice. Additional parameters that predictably affected personalization of care in T2D were age, sex, and ethnicity. Eiland *et al.* [18], by reviewing the current state of diabetes technology adoption, found that “diabetes technology” (i.e., insulin delivery and glucose monitoring devices, as well as mobile medical applications, and telemedicine) had modest effects in improving those disparities that result from age, sex and ethnicity, despite the fact that this technology has great potential to improve disease complications and quality of life of people with T2D. However, the access to and use of technology is still very patchy. Additional research is needed to identify the specific grounds underlying disparities of access and use and how lacunas in health equity can be improved through targeted educational interventions while providing the ‘right’ patient with the ‘right’ technological tool.

In the last years, accumulating evidence also supports the use a person-centered approach for treatment of type 2 diabetes, which is based on the individual risk of chronic vascular complications (i.e., CVD, CKD or heart failure). Nowadays, the approach to diabetes therapy is very personalized and includes several combinations of antidiabetic agents with important favorable effects on CV risk, renal outcomes and -of course- glucose management. In 2019 the new version of the ESC-EASD guidelines on “Diabetes, prediabetes and cardiovascular diseases” included the novel evidence generated over the last 6 years in large cardiovascular outcome trials with novel glucose-lowering drugs. The recommendations of these guidelines led to a completely novel positioning of medications for lowering blood glucose levels in the reduction of adverse cardiovascular and renal outcomes for patients with T2D [19].

## 2.2 Obesity

Obesity is a globally growing concern both in the general population and in specific patient groups. Given that various therapeutic approaches are now available ranging from lifestyle changes to drug options and endoscopic or surgical techniques, precision medicine is needed in this specific field of research to identify the best candidates and the best therapeutic approaches. For example, progresses in genetics and epigenetics of obesity might help in understanding the variable responses to treatments [20].

Currently, dietary regimens remain a mainstay of treatment for the metabolic syndrome and its individual components and personalization of diet is also a rational expectation for weight management and associated cardiovascular risk reduction. Recently, Ge *et al.* undertook a network meta-analysis of randomized trials to estimate the relative effectiveness of various types of diets, such as low carbohydrate (e.g., Atkins, Zone), low fat (e.g., Ornish), and moderate macronutrient (e.g., DASH, Mediterranean) diets, for weight and cardiovascular risk factor reduction in adults [21]. Based on this meta-analysis of 121 randomized trials (21,942 participants), the authors showed that small to trivial differences exist among different dietary programs for weight and cardiovascular risk factor reduction, and these are often based on low certainty evidence. Of concern, weight reduction after 12 months of follow-up diminished in most of these randomized trials, and aside from the Mediterranean diet for plasma LDL-C reduction, improvements in cardiovascular risk factors also largely disappeared. While the results of this meta-analysis could suggest to prescribe a Mediterranean diet to specifically reduce hypercholesterolemia especially in obese individuals, further studies are necessary to better ascertain whether or not certain types of diets are more effective among specific obesity phenotypes.

Endoscopic placement of an intra-gastric fluid-filled balloon (IGB) is also a commonly used technique aimed at inducing weight loss but this device is not devoid of side effects and requires removal in some patients. A pilot study conducted in 32 patients utilized a gastric emptying study, before and 2-3 months after placement of an IGB, to investigate intolerance and response to the single fluid-filled IGB [22]. These results showed that utilization of baseline gastric emptying data could have prevented removal in 75% of cases. Moreover, decreased gastric emptying three months following IGB placement was associated with weight loss at 6 and 12 months. Although this study needs confirmation in a prospective validation cohort, it nicely proves the concept that the era of personalized endoscopic bariatric therapies has begun to help maximize the patients' tolerance, the cost-effectiveness ratio, and efficacy of intervention [22].

Polygenic obesity in solid organ transplant (SOT) populations is deemed to be a risk factor for graft survival, owing to the development of metabolic disorders. However, little is known about the genetics of weight gain in SOT recipients. One study by Saigi-Morgui *et al.* evaluated the association between weighted genetic risk scores and BMI, as well as the influence of clinical and genetic factors on 10% of weight gain, 1-year after transplantation



[23]. This study highlighted the importance of integrating genetics of obesity in SOT recipients that may contribute to treatment personalization and prediction of weight gain following SOT.

### **2.3 Preventing cardiovascular disease in women**

Despite the fact that more women than men have died of cardiovascular disease (CVD) every year since 1984 [24], preventive recommendations have not been optimally applied to women [25]. In her article, Hayes highlighted that emphasis of prevention has shifted toward assessment of a woman's "global" CVD risk as opposed to treatment of individual CVD risk factors [25]. Interestingly, consolidated tools, such as the Framingham risk score, do take age, sex, smoking history, plasma lipids and blood pressure into account [26], and may, therefore, be considered pioneering attempts to conduct a personalized medicine approach. Estimates of the overall CVD risk will dictate, in turn, tailored intervention intensity, with persons exposed to the most elevated CVD risk being the recipients of the most aggressive risk-lowering pharmacological strategies. This implies that, in the absence of any specific contraindications, women at a high CVD risk should be offered treatment with aspirin, beta-blockers, statins and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers whenever indicated. Furthermore, maintenance or even improvement of their healthy lifestyle practices should be encouraged for women who have already achieved a low CVD risk. Diligent application of preventive strategies is expected to effectively decrease CVD mortality and morbidity [26].

### **2.4. Hypertension**

In countries such as the United States, arterial hypertension (HTN) affects up to one third of adults. Current guidelines for the diagnosis and treatment of hypertension, offer convenient heuristics algorithms for clinicians. However, they are limited by their involving little diagnostic testing and therefore are not highly personalized to the pathophysiology of individual patients, while more personalized treatment approaches might be useful [27]. Additionally, while a standardized treatment strategy for HTN will prove effective in most cases, a more personalized approach could be useful in selected patients, such as those who fail to respond to treatment [28]. The rationale for personalized therapy of HTN, obstacles to its implementation, together with examples of personalization measures, are discussed elsewhere [27]. A framework for the personalized treatment of HTN based, on the one hand, on a trade-off between simplicity and personalization and, on the other hand, on a classification of treatment approaches into low, medium, or high information burden approaches have also been proposed [28].

## **3. Target organ damage**

### **3.3 NAFLD/MAFLD**

NAFLD, which may be renamed and re-classified to MAFLD [29], is a major challenge for contemporary Hepatology, Diabetology and Internal medicine. This condition is the prototypic manifestation of a target organ (the liver) being associated, in a closed loop, with

metabolic derangements of which NAFLD is both a cause and an effect [30,31]. Confronted with the pathophysiological complexity and high clinical heterogeneity of this metabolic liver disease, attempts to conduct innovative treatment strategies have failed so far [32]. Although many explanations may account for such failures, it seems logical to postulate that personalization of cure could be key to identifying more effective therapeutic approaches. Analysis of published papers on personalized medicine as applied to the NAFLD/NASH shows that many experts agree on identifying certain common grounds of interest in these areas: genetics/epigenetics; gut microbiota and lysophospholipids/bile acids [33-37].

The analytic discussion of all innumerable modifiers of pathogenic and clinical variables is beyond the scope of this article. Suffice here to say that, in recent years, two main concepts have gained major interest: genetic (as opposed to metabolic) NAFLD; and sexual differences in NAFLD arena.

In their seminal paper, Luukkonen et al. profiled liver lipidome in 125 subjects with biopsy-proven NAFLD, who were classified into four groups based on their median HOMA-IR ('High and Low HOMA-IR', n=62 and n=63) and PNPLA3 genotype (PNPLA3(148MM/MI), n=61 vs. PNPLA3(148II), n=64). Data have shown that similar increases in steatosis extent and NASH prevalence were associated with a metabolically harmful saturated, ceramide-enriched liver lipidome in 'metabolic NAFLD', but not in 'genetic NAFLD' and this difference may account for why metabolic NAFLD (rather than genetic NAFLD owing to PNPLA3 polymorphism) increases cardiometabolic risk profile of these patients [38]. Together with other lines of evidence going in the same direction [reviewed in 39,40], this study has conceptually paved the way towards renaming "metabolic NAFLD" to MAFLD.

Sex differences are a major modifier of health, diseases, medical practice and research in many areas [41]. As regards NAFLD, a recent large meta-analysis of 54 observational studies (including a total of 62,239 individuals) showed that women had a ~20% lower risk of NAFLD than men and, despite having a similar risk of NASH, they also had a higher risk of advanced fibrosis, especially after age 50 years [42]. These epidemiological data, together with the complex biological variations underlying sexual dimorphism in NAFLD [43], strongly supports the necessity to implement gender medicine for a personalized management of NAFLD.

In an attempt to dissect systematically, in the individual patient, the relative weight of this the large gamut of NAFLD risk factors and clinical variables, Lonardo *et al.* have recently proposed adoption of the so-called "LDE system". This includes a set of modifiers spanning from histologically/non-invasively defined liver histology (L) to determinants (D), such sex/reproductive status; genetics; endocrine disorders and (E) extra-hepatic manifestations of NAFLD (cardio-metabolic diseases and some cancers) that may address the unmet aim of achieving a personalized diagnosis [3,44,45]. The LDE system or similar, logically structured, descriptors of the pathobiological complexity, promise to identify more homogenous subsets of NAFLD/MAFLD patients with comparable courses of disease and identifiable treatment responses.

### 3.4 Cancer

Cancer is a major global health problem issue, which exacts a heavy toll on health care systems [46]. Metabolomics defines a post-genomic research field, embracing small molecule analysis applied to utilizing biomarkers for cancer detection, monitoring, and prognostication [47]. Emerging discoveries of metabolomics promise to provide a suitable alternative for the current cancer diagnostic methods, notably including standard histopathological analysis [47]. Interestingly, formalin-fixed paraffin-embedded tissue specimens, which are commonly obtained for histopathological evaluation, are a valuable source for metabolomics investigations and can provide additional informative data for assessing disease stage and individual treatment responses. However, there remain some limitations to be addressed to optimize their utilization for metabolomics analysis [47].

Precision oncology aims at selecting the best therapy for the 'right' patient by considering variables related to both specific features of each individual's unique disease, as well as the patient's health status [48]. One of the biological phenomena underlying precision oncology is the fact that, in cancer, cells reprogram their metabolism to support all phases of disease from tumor initiation, progression, metastasis and also drug resistance [49].

Precision oncology can ideally be applied to patients with cancers of the colon and rectum, breast, prostate, thyroid and ovaries, which are suitable paradigms for illustrating the notion that metabolic derangements of cancer cell may be targeted for therapeutic gain. **Table 1** illustrates the concept of a personalized approach based on metabolic analysis in some common types of cancer.

**Table 1** A personalized approach based on metabolic analysis in some common types of cancer [48,50-53].

Cancer types	Main Findings	[Ref.]
Colo-rectal (CRC)	The following pathways are involved during CRC progression: redox status, energy metabolism, as well as intermediates of amino acids, choline and nucleotide metabolism.	[50]
Breast	Nuclear Magnetic Resonance metabolomics may be used for phenotyping of breast cancer patients, using different bio-specimens, such as tissues, blood serum/plasma, and urine.	[48]
Prostate	Some urine metabolomics studies identified consistency in the dysregulation of 15 metabolites while 18 metabolites were found consistently altered in the	[51]

	<p>prostate tissue, including alanine, arginine, uracil, glutamate, fumarate, and citrate.</p> <p>Of great interest are reports of altered valine, taurine, leucine and citrate as the common denominators in both urine and tissue studies, thereby emphasizing the human metabolome as a promising target for identifying novel biomarkers for prostate cancer diagnosis.</p>	
Ovaries	<p>Down-regulation of both phospholipids and histidine, citrulline, alanine, and methionine were the most often observed biochemical changes. Compared to a single metabolite, the combination of multiple metabolites as a panel, achieved a better diagnostic accuracy.</p>	[52]
Thyroid	<p>Identification of novel molecular markers of thyroid cancer promises to help identify distinct disease metabolic phenotypes, which may lead to a more personalized therapy while assisting both in the diagnosis and prediction of disease behavior.</p>	[53]

### 3.4.1 Colo-rectal Cancer

Globally, colorectal cancer (CRC) ranks among the principal causes of cancer-related mortality and is associated with MetS [54,55]. The prognosis of CRC patients largely depends on prompt diagnosis and accurate staging of the disease. The latter can be achieved with novel non-invasive molecular tools, which characterize metabolite profiles associated with different cancer stages [50]. However, additional research is needed to reconcile the differences found among different studies in the levels of individual metabolites, which may probably result from different study populations, sampling techniques and data processing.

### 3.4.2. Breast Cancer

Breast cancer is strongly associated with the MetS [56]. Given that breast cancer is an extremely heterogeneous disease, it is necessary to carefully stratify patients to maximize their survival rates while optimizing their quality of life. For example, the risk of recurrence and the potential benefits from adjuvant chemotherapies may be estimated with gene-expression tools [48–38]. However, additional research is needed to further reduce the proportion of breast cancer patients who are potentially exposed to unnecessary chemotherapy, additional prognostic and stratification tools are eagerly awaited

### 3.4.3 Prostate cancer

Globally, prostate cancer is the second most often diagnosed cancer in men and considerable body of evidence now suggests that abdominal obesity and chronic hyperinsulinemia are associated with a higher risk of this disease [57,58]. One of the main limitations of using prostate-specific antigen (PSA) serum levels is that it cannot invariably differentiate benign prostate hypertrophy from cancer, while identifying persons with indolent from those with aggressive prostate cancer [51,59]. Recent progresses in metabolomics, genomics, and proteomics could reveal new potential biomarkers [51]. In this connection, researches on metabolomics application for prostate cancer have focused on improved techniques to better analyze exosomes. These are extracellular vesicles which, being secreted from mammalian cells and virtually detected in all bio-fluids, are amenable to be used as tumor biomarkers [51]. Although data from pioneering clinical studies on potential prostate cancer biomarkers are still inconclusive [51], this line of research will be better developed in the near future. In addition, metabolomics assessment in urine and prostate tissues ideal approaches for disclosing specific changes that may occur with prostate cancer development [59].

#### **3.4.4 Ovarian Cancer**

Multi-faceted and incompletely understood pathomechanisms explain the associations of obesity, T2D or other metabolic derangements and increased risk of mortality due to ovary cancer. These include dysregulated adipokine and cytokine profiles in subjects with excess adipose tissue; the ensuing altered immune responses and altered endocrine functions that can promote pro-tumorigenic signal transduction pathways [60]. Ovarian cancer is deemed to be "*a silent killer* ", owing to the risk of late diagnosis resulting from non-specific clinical presentation and lack of any effective diagnostic techniques [61]. In this setting, in as much as they faithfully mirror tumor-host interactions, metabolomics profiles promise to be useful to improving ovarian cancer diagnosis, as well as identifying different metabolic signatures associated with different clinical phenotypes [61]. A recent systematic review evaluated metabolomics of biofluids and tumor tissue as potential biomarkers for the diagnosis, prognostication and management response of ovarian cancer. [62]. Although findings addressing prognosis, treatment, and recurrence rates were more variable across various studies, lower levels of lysine mirrored either increased cell or glutamine dependency of rapidly proliferating cancer cells, suggesting that metabolic changes mirror cell proliferation and invasion associated with poor prognosis and higher recurrence rates [62]. To overcome those issues that limit their utility, further validation studies are awaited, aimed at introducing metabolites and biochemical pathways as significant aids in routine clinical practice.

#### **3.4.5 Thyroid Cancer**

In general population studies, MetS is associated with an increased risk of incident thyroid cancer [63]. Thyroid cancer is the most common endocrine malignancy and its diagnostic is fine needle aspiration biopsy (FNAB) [64]. However, FNAB is not exempt from indeterminate results and is often unable to differentiate different thyroid cancer types, thereby necessitating additional tissue sampling to achieve a definite diagnosis [65].

Within this scenario, metabolomics studies have gained increasing popularity over the last decade (**Table1**)

### 3.4.6 Cancer in obese people

Obesity is also a recognized risk factor for the development of various types of cancer [66]. Additionally, obesity is associated with lower survival rates for many cancer types [67]. This close link between obesity and cancer development may be accounted for by different pathophysiological mechanisms which can promote the initiation and progression of tumors including chronic hyperinsulinemia, increased Insulin-like Growth Factors, as well as expanded and dysfunctional adipose tissue producing sex hormones, pro-inflammatory cytokines and hypoxia [67].

Although concerns of chemotherapy-related toxicity have been raised regarding obese cancer patients, some recent studies have shown that obese cancer patients do not experience more chemotherapy-related toxicity compared with their non-obese counterparts. This implies that what should be aimed at is a true personalization of therapy in obese patients with cancer rather than simple chemotherapy "depotentialization" [67]. In this connection, we know that achieving weight loss reduces overall cancer risk and improves compliance to therapy. This notion supports the implementation of social policies as well as medical/endoscopic/surgical therapies for obesity aimed at reducing cancer risk development, improving treatment outcomes and survival rates of people with obesity [67].

### 3.5 SARS-CoV-2 Infection

Starting from early 2020, the SARS-CoV-2 pandemic has exacted a major toll on global health exerting a strong 'stress test' on healthcare systems globally and enormously affecting world economics [68,69]. On these grounds, it comes as no surprise that research into this novel viral disease has revolutionized priorities in the research agenda [44]. Notably, a consistent line of research has identified a dangerous interaction of SARS-CoV-2 infection with the host's metabolic health (as summarized in **Table 2**).

**Table 2. Evidence supporting a strong interaction between COVID-19 and metabolic disorders [70-73]**

Author, year [Ref.]	Method	Findings	Conclusion
Targher, 2020 [70]	Retrospective study of 339 individuals consecutively hospitalized at four sites in China between January and February 2020.  COVID-19 was diagnosed with analysis of oropharyngeal swab specimens.	At binary logistic regression analysis, the presence of T2D was associated with an approximate 4-fold increased risk of severe COVID-19 illness (odds ratio [OR] 3.83, 95% CI 2.06– 7.13, P<0.0001)	Having diabetes at hospital admission was associated with an increased risk of severe COVID-19 which was unaffected by

	COVID-19 severity was classified as mild, moderate, severe or critical.	even after adjustment for confounding factors. Other strong predictors of severity of COVID-19 were older age, male sex and obesity.	adjustment for confounders.
Mantovani, 2020 [71]	Meta-analysis of 83 studies involving 78,874 hospitalized patients with laboratory-proven COVID-19.	Pre-existent T2D was associated with an approximate twofold higher risk of having severe/critical COVID-19 illness (random-effects odds ratio 2.10, 95% CI 1.71-2.57; I <sup>2</sup> = 41.5%) and ~threefold increased risk of in-hospital mortality (random-effects odds ratio 2.68, 95% CI 2.09-3.44; I <sup>2</sup> = 46.7%). Funnel plots and Egger's tests did not reveal any significant publication bias.	Pre-existent diabetes, often type 2 diabetes, is associated with a 2-to-3 times increased risk of severe/critical illness and in-hospital mortality owing to COVID-19.
Targher, 2020 [72]	<p>310 consecutive patients with laboratory-proven COVID-19 who had been hospitalized at four sites in China, between January and February 2020.</p> <p>Hepatic steatosis was assessed with CT scanning.</p> <p>The (low, intermediate or high) risk of liver fibrosis was assessed with FIB-4 and NFS.</p> <p>COVID-19 was classified as severe and non-severe</p>	<p>The severity of COVID-19 markedly increased among MAFLD patients who had either intermediate or high FIB-4 scores, and this association remained significant after adjusting for sex, obesity and T2D.</p> <p>Similarly, the intermediate/high NFS (unadjusted-OR 5.21, 95% CI 2.39 to 11.3) was associated with a higher risk of severe COVID-19 illness. This significant association persisted after adjustments for sex, obesity and T2D.</p>	Patients with MAFLD with increased FIB-4 or NFS scores are at higher risk of severe COVID-19, irrespective of metabolic comorbidities.
Gao, 2020 [73]	<p>A cohort of 150 adults with COVID-19 from three hospitals in China was enrolled.</p> <p>Seventy-five obese case subjects were randomly</p>	Obesity was associated with an approximately three-fold increased risk of having severe COVID-19 and a 12% increase in the risk of severe COVID-19 was	Health care providers should be aware that obese patients have an increased

	matched with as many nonobese control subjects paired by age and sex.	observed per each 1-unit increase in BMI.  These associations remained significant even after adjusting for confounding factors.	risk of severe COVID-19.
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**List of abbreviations:** BMI – body mass index; COVID-19 – Corona Virus 19 disease; CI – Confidence Interval; CT – computed tomography; FIB-4 Fibrosis 4; MAFLD – metabolic-associated fatty liver disease; NFS- NAFLD Fibrosis Score; OR – Odds Ratio

Data summarized in **Table 2** have suggested that perturbed metabolic homeostasis, such as occurring in people with obesity, T2D or fibrosing MAFLD, may carry a greater risk of severe disease owing to SARS-CoV-2 infection. The mechanisms underlying such dangerous associations may be variably explained based on specific metabolic phenotypes. For example, not only do those individuals with T2D have a low-grade inflammatory state but also they may suffer from impaired leukocyte phagocytosis, neutrophil chemotaxis, bactericidal activity, and innate cell-mediated immunity. Collectively, these features predispose individuals with T2D to more infectious disorders in general [70]. As specifically regards SARS-CoV-2 infection, people with T2D may be prone to an increased risk of severe infection owing to an enhanced expression of the angiotensin-converting enzyme 2 (ACE-2), which facilitates viral entry into cells. T2D might also facilitate the emergence of more pathogenic SARS-CoV-2 strains capable of causing greater severity of COVID-19 [70].

As far as obesity is concerned, these individuals are also exposed to uncoordinated innate and adaptive immune responses, insufficient antibody response, and risk of SARS-CoV-2 infection-related cytokine ‘storm’, i.e., a pro-inflammatory and pro-thrombotic state sustained by adipose tissue secreting cytokines and adipokines. Of concern, obesity could specifically worsen the severity of symptoms owing to COVID-19 among younger individuals [74].

Finally, MAFLD/NAFLD with significant/advanced fibrosis may exacerbate the cytokine ‘storm’ induced by SARS-CoV-2 infection, probably via the release of multiple proinflammatory hepatokines, thereby mechanistically contributing, in its turn, to the development of more severe illness owing to SARS-CoV-2 infection [72].

#### 4. Conclusions and research agenda

In this narrative review, we have briefly discussed some key concepts that may be useful to implementing future research regarding personalized/precision medicine in the field pertaining to the MetS; NAFLD/MAFLD; and cancer development. We have analyzed the evidence that prevention of obesity and T2D may be achieved with personalization of diet and exercise and other available management options. Women and all persons who are at the highest CVD risk should be offered the most complete and aggressive treatment options. NAFLD/MAFLD is mutually and bi-directionally associated with T2D and other metabolic disorders. Personalization of cure could be key to identifying more effective management approaches. Metabolomics could be effectively applied to utilizing biomarkers for cancer



detection, monitoring, staging and prognostication. Cancers of colon-rectum, breast, prostate, thyroid and ovaries excellently illustrate the notion that (measurable) markers/biomarkers of cancer cell metabolic derangements can fruitfully be manipulated for clinical benefit. A true personalization of chemotherapy should be pursued in obese cancer patients. Weight loss reduces cancer risk and improves compliance to therapy. Very recent data suggests that dysregulated metabolic homeostasis, such as occurs in individuals with obesity, T2D or fibrosing MAFLD, also increases the risk of severe disease owing to SARS-CoV-2 infection.

In this review, we have presented a view of research gaps in the field. Additional areas that, in our opinion, are worthy of future research include valuation of the impact of circadian clocks on normal metabolism and cardiometabolic disorders [75]; Characterization of the hormonal profile, notably including thyroid profile, among persons with the MetS [76]; and Diagnosis and management of cardiovascular risk among persons with autoimmune or auto-inflammatory disorders [77-79].

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