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Milk phenomics: leveraging biological bonds with blood and infrared technologies for evaluating animal nutritional and health status

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ABSTRACT

Over recent decades, there was a substantial evolution in the productive management of dairy animals worldwide with a consequent boost in individual milk yield. This evolution positioned the milk production as the central metabolic priority around which all other physiological functions are coordinated and partially minimised. This shift underscores the crucial role of effectively managing stressful phases in intensive dairy farming systems, also highlighting the resilience exhibited by the animals. Indeed, monitoring the nutritional and health status becomes paramount, aiming for an early detection of (sub)clinical health impairments. Given the mammary gland's centrality in high-yielding dairy breeds, it's unsurprising that the milk matrix provides insights about udder itself but also systemic metabolic function. The emerging field of milk phenomics explores links between milk components and animal health, holding great promise for studying dairy cow resilience. The use of infrared spectroscopy on milk to predict indicators and complex traits at the herd level is a promising approach. In the dairy sector, the available infrared instruments mainly implement the Fourier transform infrared (FTIR) spectroscopy. This method is widely employed in milk recording schemes worldwide for animal monitoring and breeding purposes. In addition, visible and near-infrared (NIR) spectroscopy is increasingly integrated into milking systems for daily on-farm monitoring of milk quality and animals' physiological status. This review examines the topic of milk phenomics together with potential and challenges of infrared spectroscopy to predict indicators and complex traits related to health and nutritional disorders exploiting the biological bonds that exist between milk and blood in dairy animals.

HIGHLIGHTS

- Milk is a valuable source of information for assessing nutritional and health proxies in dairy animals.
- Infrared spectroscopy is used within routine milk recording systems for the determination of major components, but other useful applications exist.
- This review summarises research on milk phenomics carried out by mean of infrared spectroscopy to predict complex traits related to animals' health and nutritional disorders.

Introduction

In the last decades, management and productive performance of livestock have transformed and developed dramatically, especially in the dairy cattle sector. In the past 40 years the milk yield per cow has more than doubled in specialised breeds like Holstein, now being approximately six times greater than 100 years

ago (Gross 2023). High-producing cows nowadays can easily deliver 12,000 kg of milk per year (Gross 2023). With this in mind, it is evident that in modern lactating animals milk production represents the metabolic priority around which all other physiological activities are coordinated and, in some respects, minimised (e.g. fertility). This phenomenon, known as homeorhesis, is

particularly evident in animals belonging to cosmopolitan and highly selected breeds, which suffer from negative energy balance on a regular basis in early lactation and often present major metabolic disorders like ketosis and hypocalcaemia (Bauman and Currie 1980). This is particularly the case of breeds or populations under strong selective pressure like Holstein and Brown Swiss cows, East Friesian ewes and Saanen goats (Brito et al. 2021; Li et al. 2022; Teissier et al. 2024) where the most crucial activity is the supply of the mammary gland with energetic nutrients taken from the bloodstream: circulating glucose, volatile fatty acids from the rumen (and to a lesser extent from the large intestine), medium-long chain fatty acids, sugars, minerals and vitamins from the digestion and absorption process in the small intestine, non-esterified fatty acids (NEFA) from adipose tissue, calcium from bones, and amino acids from muscle tissue.

In intensive farming systems, an efficient transition from a non-productive period (dry off) to lactation is crucial to limit the risk of diseases and increase the productive lifespan of dairy animals (Proudfoot 2023). Although most of farmers pay close attention to the diet/supplements administered to the parturient animals, unsuccessful and inadequate homeorhetic and homeostatic adaptations continue to occur at economically important rates in the field, negatively affecting animals' health and farmer's income. This issue is progressively emerging in certain dual-purpose breeds too.

The current high productivity level in dairy animals, particularly cattle, has been paralleled by a significant increase in nutritional, metabolic and fertility issues (Miglior et al. 2017), which have been overlooked for years by the main stakeholders, breeders included. As a matter of fact, pleiotropic and/or latent undesired effects have resulted in about one third of cows having at least one clinical disease (metabolic and/or infectious) during the career and more than half of dairy cows having at least one subclinical event within the first 90 days of lactation (Caixeta and Omontese 2021). In other dairy species, the situation is quite similar. According to Bertoni and Trevisi (2013), enhancing the animals' resilience and adaptation to metabolic stress is an effective strategy to boost profits by reducing indirect costs, such as those associated to poor animal health and scarce fertility.

Monitoring the nutritional and the health status of lactating animals is of particular interest in this context, with the main goal being prevention and early detection of metabolic issues and health events. Turned into practice, the availability of automated, non-invasive and cost-effective diagnostic tools at the herd scale is pivotal in the contemporary dairy sector. Coupled with that, different stakeholders of the milk supply chain can benefit from novel and easily interpretable proxies to identify health impairments that could span throughout the lactation period, monitoring side effects of metabolic changes (Giannuzzi et al. 2023).

During lactation, the mammary gland of mammals produce milk, which is a matrix available on a daily basis in dairy animals, easy to sample and manipulate, and in part a potential mirror of the animal's condition. Gross and detailed milk components, in fact, are recognised as a readily accessible source of information. For instance, changes in the milk concentration of some minerals or metabolites can reflect fluctuations in health, nutritional status (Overton et al. 2017), overall wellbeing and behaviour (Gengler et al. 2016). This occurs because the blood-milk barrier regulates the passage of molecules from the bloodstream to the alveolar lumen (milk) and vice versa (Bramley et al. 1992; Costa et al. 2019). Considering that the concentration of some specific molecules increases in blood in presence of a disease/disorder, it becomes evident how milk can be a highly informative medium available at a low cost with no need of invasive sampling procedures. Milk collection and sampling, in fact, are already integrated into standard milking routines in commercial farms and analyses are carried out regularly for milk quality monitoring. For the majority of traditional milk composition traits, the punctual determination is performed *via* infrared spectroscopy, a fast, non-polluting, and cost-effective technique that utilises infrared light to scan the matter and detect the vibration of specific chemical bonds, which produces an absorption profile with absorbance values for individual infrared light wavenumbers. Within the spectrum, there are known regions associated to specific milk components, e.g. for milk proteins, carbohydrates (sugars), or lipids (Soyeurt et al. 2011).

Even though review articles on infrared spectroscopy applications for predicting various traits in milk are numerous (McParland and Berry 2016; Bresolin and Dórea 2020, Evangelista et al. 2021), there is currently no comprehensive report on the infrared spectroscopy predictive ability for the animals' health and metabolic status. Therefore, the present review aims to i) explore the literature on the role of milk matrix as mirror of animal nutritional and health status in dairy animals, and ii) summarise the current state of the use of milk spectra for precise monitoring of dairy animals, while highlighting the challenges and perspectives in terms

of precision farming, tailored feeding, and selective breeding.

Popular types of spectroscopy in dairy

Fourier transform infrared spectroscopy

Traditionally, the Fourier Transform Infrared (FTIR) spectroscopy, which cover a wavelength range from 2,500 to 25,000 nm (Bittante and Cecchinato 2013), is worldwide used within the Dairy Herd Improvement (DHI) framework for routine milk analysis. Existing FTIR devices and models are able to provide information on major components of cow, buffalo, ewe, and goat milk (Barbano and Clark 1989) and there are universal standards available to keep the reproducibility similar among laboratories. Anyhow, it has been demonstrated by several authors how FTIR possesses a further significant potential beyond its basic application. It has been demonstrated, in fact, that FTIR can be successfully exploited for predicting fine milk components, milk properties, and animal- or farm-related complex traits (Barbano et al. 2016; Aernouts et al. 2020), e.g. milk coagulation properties (Cecchinato et al. 2009; Cellesi et al. 2019), fatty acids (Soyeurt et al. 2011), protein fractions (Mota et al. 2023a), trace minerals (Zaalberg et al. 2021), presence of adulterants (Ceniti et al. 2023), metabolites, and ketone bodies (Grelet et al. 2016). Moreover, by mean of the milk spectrum, blood biomarkers not detectable in milk can be indirectly predicted with a certain accuracy (Luke et al. 2019; van den Berg et al. 2021; Giannuzzi et al. 2023). The same applies to third characteristics like dry matter intake (DMI; Seymour et al. 2019; Ouweltjes et al. 2022; Shadpour et al. 2022b), daily milk productivity, milk somatic cell count (SCC), methane emission (Dehareng et al. 2012; Shadpour et al. 2022a; van Staaveren et al. 2024), acute and chronic clinical mastitis (Rienesl et al. 2022), body condition score (BCS; Frizzarin et al. 2023a,2023b), energy intake (McParland et al. 2014) or balance (Rovere et al. 2024), fertility (Ho et al. 2019), body weight (Zhang et al. 2021), lameness (Mineur et al. 2020), and hyperketonemia/ketosis (Benedet et al. 2019; Aernouts et al. 2020; Walleser et al. 2023).

While on one hand, most of these FTIR models exhibit moderate to low prediction accuracy, numerous studies nonetheless support the large-scale screening potential of FTIR-predicted metabolites (Pryce et al. 2016) and the important role of FTIR for genomic selection of dairy animals (Tiplady et al. 2020). So far, most of the work done and published in the literature has been focused on dairy cows, due to

the greater economic interest, numerosity, and international collaborations and projects. This means that, compared to other dairy species, there is a larger availability of accurate reference phenotypes for cows' models development. However, with FTIR analysis becoming easily available and somehow cheaper worldwide, there are concrete attempts to produce prediction models for complex traits in other dairy species.

Considering the impact of metabolic diseases for farmers and the importance of health events early detection, being able to identify animal at risk through the predicted concentration of blood biomarkers is an outstanding opportunity. The milk spectrum becomes therefore informative for both farmers and breeders for decision-making and selection purpose, respectively. Noteworthy, assuming that individual milk spectra are archived, it's possible to predict new milk traits retroactively by applying updated calibration equations to the spectra stored. A systematic collection of milk spectra, along with registration of the animal-related information and, even more important, the availability of high-quality (reference) phenotypes, offer an opportunity to explore and predict traits that are typically not measurable on a large scale.

Thanks to specific interferometers automatically performing the Fourier transformation of signals, milk analyses rely entirely on FTIR – usually adopted to explore chemical composition of matter and disclose molecular structures. While bulk milk analysis represents the basis for the milk payment within the supply chain, individual characteristics of milk are interesting for the other purposes described above, i.e. animals monitoring and breeding within the DHI framework (Barbano and Clark 1989). Laboratories in charge of the official milk analyses adopt the FTIR machineries and are subjected to inspections and ring tests of the International Committee for Animal Recording (ICAR). Specific guidelines must be followed to produce high-quality standardised phenotypes and most of the official laboratories are under control of public bodies. In Italy, for example, official milk laboratories are in the hand of the Italian Breeders Association (AIA, Rome, Italy), which, in turn, is an ICAR member. Ring tests are regularly performed on a national and international dimension to ensure comparability, reproducibility, and repeatability of FTIR predictions. What is more, spectra obtained from machineries of different brands working in the mid-infrared region can be harmonised through standardisation procedures (Bonfatti et al. 2017). A limited number of manufacturers detain the market of FTIR devices globally (e.g.

Table 1), namely Foss Electric A/S (Hillerød, Denmark), Bentley Instruments (Chaska, MN, US), and Perten – formerly Delta - Instruments (Drachten, the Netherlands).

According to the manufacturers' application notes and ICAR periodic reports, the FTIR-based machineries are powerful and the installed models for fat and protein content outperforming. As a matter of fact, prediction accuracies up to 1 are declared for cow, goat, ewe, and buffalo milk major components (Foss Application Note 5373 Rev. 3 MilkoScan^{TM} 7 RM/FT+; International Committee for Animal Recording (ICAR), 2020; Zaalberg et al. 2021). The models developed for third traits like health status are instead characterised by lower – but still exploitable - prediction accuracy and precision. A list of pioneering studies attempting to use FTIR for predicting indicators of clinical and subclinical diseases are given in Table 1 and Table 2. Some models for disease detection work in regression (indicator traits prediction), some others in classification mode (at risk vs healthy). In general, despite promising, the FTIR equations reported in literature for health indicators are far from being considered as efficient as for fat and protein content prediction and most of them result in too high amount of false positives and/or false negatives. When dealing with health data, model robustness is affected by the information available, i.e. the reference data used for model development. As a general rule, in fact, machine learning approaches require a substantial and representative number of pathological animals to be present in the training dataset to boost variability, avoid overfitting, and improve classification accuracy.

On the flip side, FTIR spectroscopy is currently available for benchtop instruments exclusively. This means that none of the portable systems commercially available operate in the working range of the mid-infrared region, limiting the use of already developed FTIR models for early prediction and detection on farm. At the moment, in fact, only the near-infrared spectroscopy (NIR) provides targeted alerts to farmers on a daily basis, because the DHI FTIR-based milk tests are carried out on individuals every 4-5 weeks, with no possibility to monitor specific animals such as transition cows more frequently, e.g. every day. Although rather less sensitive compared to FTIR, NIR is popular in both agricultural and dairy sector and mostly intended to in field and real-time analyses.

In summary, limitations of FTIR include the high initial price of the device, mainly due to the price of optical components (e.g. photodetectors) and the non-negligible maintenance costs, i.e. for renewal of

optics such as cuvettes and/or salts (Hindle 2008). Finally, FTIR-based devices of milk laboratories are designed for the analysis of liquid samples. In other words, cannulas and pumps of these machineries are not capable to deal with semi-solids and solid matrix such as colostrum (Goi et al. 2023).

Near infrared spectroscopy

Apart from FTIR, the dairy sector is also familiar with the visible spectroscopy (400 to 800 nm; VIS) and the NIR (800 to 2,500 nm) spectroscopy. Melfsen et al. (2012) explained how these regions are used for prediction of milk components and suggested that NIR is a promising technique for real-time monitoring of major milk solids (Diaz-Olivares et al. 2020). As for FTIR, NIR-based devices offer fast results at a reasonable cost. In addition, these devices are designed to be resistant and are equipped with robust and long-lasting detectors.

Even though the milk analysis requires some sample pre-treatments, NIR devices can be integrated either in-line or, if portable, used at-line, i.e. on a representative sample separately from the milking machinery itself (Guerra et al. 2024).

With NIR implemented, a continuous on-farm monitoring is feasible and could be exceptionally advantageous and straightforward compared to analyses obtained once per month with FTIR benchtop instruments (Evangelista et al. 2021). Another advantage of NIR technology is the potential to produce accurate phenotypes every day in each single animal with milk spectra available. Also, the integration of NIR spectrum wavelengths with additional animal-specific information (e.g. season, breed, daily milk yield, days in milk, and parity) has been shown to enhance the accuracy and robustness of milk prediction models (Giannuzzi et al. 2022).

VIS and NIR devices available in the market are several, but the smallest and the portable ones are the most interesting for producers for the quality/price ratio, resistance and ease of use. They primarily work in the VIS and short-wave NIR wavelength range (400 to 1,000 nm), but few operate in the long-wave NIR (1,000 to 1,700 nm) (Bittante and Cecchinato 2013). Although the long-wave NIR region usually demonstrates greater performance in predicting milk-related traits compared to the others, it presents greater challenges for the in-line implementation (Tsenkova et al. 2000; Kawasaki et al. 2006). As it does for FTIR, NIR spectra have been exploited in recent years to predict phenotypes different from major milk solids such as

Table 1. Technical features of milk FTIR for predicting biomarkers for the animal's health status.

Reference[1]	n. animals	Matrix of the reference sample	Investigated metabolite/ disease	Type of response variable	Manufacturer name spectrometer	Method[2]	Software
de Roos et al. 2007	1,080 (2,165 spectra)	Milk	acetone, BHB and acetoacetate and SCK	Continuous and categorical	MilkoScan FT6000 (Foss Electric A/S, Hillerød, Denmark)	Foss-developed algorithms	Matlab
Grelet et al. 2016	566	Milk	BHB, acetone, citrate	Continuous	FT6000, FT+ (Foss Electric, Hillerød, Denmark) and FTS (Bentley Instruments, Chaska, MN)	PLS	Matlab PLS toolbox
Belay et al. 2017	826	Blood	BHB	Continuous	Milkoscan Combifoss 6500 (Foss Electric, Hillerød, Denmark)	PLS	WOMBAT software, DMU package
Pralle et al. 2018	1,013 (3,629 spectra)	Blood	BHB and HYK	Continuous and categorical	MilkoScan FT+ (Foss Analytical, Hillerød, Denmark)	MLR, PLS, ANN	JMP Pro 12 software
Bonfatti et al. 2019	542	Blood	BHB and HYK	Continuous and categorical	MilkoScan FT1 (Foss Electric A/S, Hillerød, Denmark)	PLS-DA	R package mixOmics
Luke et al. 2019	773	Blood	NEFA, BHB, BUN, Ca, Mg, albumin, globulins	Continuous	NexGen Series FTS Combi (Bentley Instruments, Chaska, MN)	PLS-DA	Matlab PLS Toolbox
Benedet et al. 2019	194	Blood	Glucose, NEFA, BHB, cholesterol, BUN, TG, AST, GPT	Continuous	MilkoScan FT7 (Foss, Hillerød, Denmark)	PLS	SAS PLS procedure
Grelet et al. 2019	241	Blood	Glucose, NEFA, BHB, IGF-I and metabolic status	Continuous and categorical	FT2 and FT6000 spectrometers (Foss, Hillerød, Denmark)	PLS, PLS-DA	Winisi software, Matlab PLS Toolbox
De Koster et al. 2019	107	Milk	metabolic clusters (glucose, IGF-I, NEFA, BHB) using milk 9 IgG N-glycans and 8 milk metabolites	Categorical	FT2 and FT6000 spectrometers (Foss, Hillerød, Denmark)	RF	R package randomForest
Caldeira et al. 2020	420	Blood	BHB, SCK and CK	Continuous and categorical	MilkoScan FT6000 analyser (FOSS, Hilleroed, Denmark)	Foss-developed algorithms	SAS, Sigmaplot software
Bonfatti et al. 2020	3,771	Other	Lameness	Categorical	NexGen Series FTS Combi (Bentley Instruments, Chaska, MN)	PLS-DA	R package mixOmics
Foldager et al. 2020	234	Milk	body energy balance (EBAL), index for physiological imbalance (PI-index) and metabolic clusters (glucose, IGF-I, NEFA, BHB) using 9 IgG N-glycans and 8 milk metabolites	Categorical	FT2 and FT6000 spectrometers (Foss, Hillerød, Denmark)	RF	R package randomForest
Ho et al. 2021	3,027	Blood	NEFA, BHB, BUN	Continuous	NexGen Series FTS Combi (Bentley Instruments, Chaska, MN)	PLS	R package pls
Mensching et al. 2021	100	Milk (coupled with wearable sensors)	Subacute ruminal acidosis risk score (SRS) derived from measurements of pH and temperature in the reticulum, chewing behaviour, and milk yield	Categorical	MilkoScan FT+ (Foss, Hillerød, Denmark)	PLS	R package pls

Table 1. Continued.

Reference[1]	n. animals	Matrix of the reference sample	Investigated metabolite/ disease	Type of response variable	Manufacturer name spectrometer	Method[2]	Software
Rienesl et al. 2022	59,002 (1,183,282 spectra)	Other	Clinical mastitis	Categorical	FOSS Instruments, Hillerød, Denmark	PLS-DA	R package *caret*
Giannuzzi et al. 2023	1,204 and 2,711 (BHB)	Blood	Glucose, cholesterol, BUN, Ca, Mg, P, K, Na, Cl, Zn, NEFA, BILt, CuCp, MPO, PON, AST, GGT, ALP, haptoglobin, creatinine, ROMt, SHp, AOPP, FRAP, PROTt, albumin, globulins	Continuous	MilkoScan FT6000 (Foss Electric A/S, Hillerød, Denmark)	ANN, EN, GBM, Stacking ensemble, GLM, RF	R package *h2o*
Mota et al. 2023b	1,150	Blood	Glucose, BHB, BUN, Ca, K, Zn, CuCp, PROTt, globulins, AST, GGT, PON, AOPP, FRAP, ROMt	Continuous	MilkoScan FT6000 (Foss Electric A/S, Hillerød, Denmark)	BayesB, GBM	R package *BGLR* and *h2o*
Walleser et al. 2023	5,747 (20,060 spectra)	Blood	HYK	Categorical	MilkoScan™ 7 RM (FOSS GmbH, Hamburg, Germany)	LDA, EN, ANN, GBM, DNN,1DCNN, 2DCNN	Scikit-learn, TensorFlow
Gruber et al. 2023	9,958 (mastitis) 1,391 (CK)	Other	Clinical mastitis and CK	Categorical	Foss, Hillerød, Denmark	PLS, SVM, LASSO, RF	R package *e1071, glmnet, caret, randomForest*

[1]Studies were selected according to the ability of providing enough information on the characteristics of the spectrometers and the software used for calibration.

[2]1DCNN = one-dimensional convolutional neural network, 2DCNN = two-dimensional convolutional neural network, ANN = artificial neural network, AST = aspartate aminotransferase, AOPP = advanced oxidation protein products, BILt = total bilirubin, BHB = β-hydroxybutyrate, BUN = blood urea nitrogen, CK = clinical ketosis, CuCp = ceruloplasmin, DNN = dense multiple-layer deep neural network, EN = elastic net, FRAP = ferric reducing antioxidant power, GBM = gradient boosting machine, GGT = γ-glutamyl transferase, GLM = generalised linear models, GPT = glutamate-pyruvate transaminase, HYK = hyperketonemia, IGF-I = insulin-like growth factor 1, IgG = immunoglobulin G, LDA = linear discriminant analysis, NEFA = non-esterified fatty acids, PLS = partial least square regression, PLS-DA = partial least square regression discriminant analysis, PON = paraoxonase, PROTt = total proteins, RF = random forest, ROMt = total reactive oxygen metabolites, SCK = subclinical ketosis, SHp = total thiols group, SVM = supporting vector machine, TG = triglycerides.

Table 2. Technical features of milk FTIR for predicting biomarkers for the animal's nutritional status.

Reference[1]	n. animals	Matrix of the reference sample	Investigated metabolite/ disease	Type of response variable	Manufacturer name spectrometer	Method	Software
Soyeurt et al. 2006	275 (600 spectra)	Milk	Milk FA profile	Continuous	MilkoScan FT6000 (Foss Electric A/S, Hillerød, Denmark)	PLS	Winisi software
Soyeurt et al. 2011	517	Milk	Milk FA profile	Continuous	MilkoScan FT6000 (Foss Electric A/S, Hillerød, Denmark)	PLS	Winisi software
McParland et al. 2011	268 (1,731–1,883 spectra)[2]	Milk and others	EB, energy content, BCS, EEI (daily MY, fat percent, protein percent, DMI, BCS, and BW)	Continuous	MilkoScan FT6000 (Foss Electric A/S, Hillerød, Denmark)	PLS	SAS PLS procedure
McParland et al. 2012	581 (3,836 spectra)	Milk and others	EB, energy content, EEI (daily MY, fat percent, protein percent, DMI, BCS, and BW)	Continuous	MilkoScan FT6000 (Foss Electric A/S, Hillerød, Denmark)	PLS	SAS PLS procedure
McParland et al. 2014	378 (1,535 spectra)	Milk and others	EB, EEI, RFI (milk fat, protein, lactose, MY, BCS, BW, ΔBW, and ΔBCS)	Continuous	MilkoScan FT6000 (Foss Electric A/S, Hillerød, Denmark)	PLS	SAS PLS procedure
McParland et al. 2015	1,102–2,441 (1,270–51,511 spectra)[2]	Milk and others	EI, EB, ΔBW, and ΔBCS	Continuous	MilkoScan FT6000 (Foss Electric A/S, Hillerød, Denmark)	PLS	SAS PLS procedure
Fleming et al. 2017	373 (1,911 spectra)	Milk	Milk FA profile	Continuous	MilkoScan FT6000 (Foss Electric A/S, Hillerød, Denmark)	PLS	SAS PLS procedure
Shetty et al. 2017	140 (4,089 spectra)	Milk and others	DMI and RFI (using BW, milk fat, protein and lactose, MY, BCS)	Continuous	MilkoScan FT+ (Foss, Hillerød, Denmark)	PLS	Matlab PLS toolbox
Wallén et al. 2018	160 (857 spectra)	Milk and others	DMI and net energy intake (using milk fat, protein and lactose, MY, and BW)	Continuous	MilkoScan FT6000 (Foss Electric A/S, Hillerød, Denmark)	Linear regression, PLS, and BLUP	Unscrambler X program, SAS PLS procedure, and Matlab (BLUP)
Rachah et al. 2020	63 (2,371 spectra)	Milk and others	EB, EEI, and DMI	Continuous	Tensor 27 spectrometer (both Bruker Optik GmbH, Germany)	PLS	Matlab in-house algorithms
Maurice-van Eijndhoven et al. 2013	190 (1,236 spectra)	Milk	Milk FA profile	Continuous	MilkoScan FT6000 (Foss Electric A/S, Hillerød, Denmark)	PLS	Winisi software
Zhang et al. 2021	363 (1,708 spectra)	Milk and others	BW (using days in milk, parity, MY and spectra wavelengths)	Continuous	MilkoScan FT + or FT6000 (Foss, Hillerød, Denmark) Standard/Lactoscope FT-MIR automatic (PerkinElmer, Waltham, United States)	PLS and EN	R packages *pls*, *caret*, and *plsVarSel*
Mota et al. 2021	471	Blood and others	BCS	Continuous	MilkoScan FT6000 (Foss Electric A/S, Hillerød, Denmark)	LASSO, RR, EN, PLS, RF, GBM	R package *pls* and *h2o*
Ouweltjes et al. 2022	391 (27,214 spectra)	Milk and others	DMI and residual DMI (using BW, MY)	Continuous	MilkoScan FT6000 (Foss Electric A/S, Hillerød, Denmark)	PLS	R package *pls*
Shadpour et al. 2022a	509 (7,398 spectra)	Milk and others	DMI	Continuous	MilkoScan FT+ (Foss Electric A/S, Hillerød, Denmark)	ANN with different training algorithms (LM, SCG, BR)	Matlab
Frizzarin et al. 2023a	6,572 (423,532 spectra)	Other	ΔBCS	Continuous	MilkoScan FT6000 (Foss Electric A/S, Hillerød, Denmark)	PLS and NN	R package *pls* and *brnn*
Frizzarin et al. 2023b	80,400 (1,258,766 spectra)	Other	ΔBCS	Continuous	MilkoScan FT+ (Foss Electric A/S, Hillerød, Denmark)	PLS and NN	R package *pls* and *brnn*
Zhao et al. 2023	336 (672 spectra)	Milk	Milk FA profile	Continuous	Bentley spectrometers (Bentley Instruments, Chaska, MN)	RF, PLS, LASSO, RR	–

[1]Studies were selected according to the ability of providing enough information on the characteristics of the spectrometers and the software used for calibration.
[2]The range of spectra is dependent from the analysed trait.
ANN = artificial neural network, BHB = β-hydroxybutyrate, BCS = body condition score, BLUP = best linear unbiased prediction, Bayesian regularisation (BR), BW = body weight, ΔBCS = daily change in BCS, ΔBW = daily change in body weight, DMI = dry matter intake, EB = energy balance, EEI = efficient energy intake, EN = elastic net, packaGBM = gradient boosting machine, LASSO = least absolute shrinkage and selection operator regression, Levenberg-Marquardt (LM), MY = milk yield, NN = neural network, PLS = partial least square regression, RF = random forest, RFI = residual feed intake, RR = ridge regression, scaled conjugate gradient (SCG).

SCC, milk urea nitrogen (MUN; Kawasaki et al. 2006), and milk fatty acids (FA; Nguyen et al. 2011). Attempts have also been made in predicting cheesemaking traits (Mota et al. 2022) and blood metabolites (Giannuzzi et al. 2022), providing promising results.

Thanks to VIS and NIR, farmers can maintain control over the quality of bulk milk (Huang et al. 2008), not only to monitor the quality of the milk supplied to the dairy industry but also to inspect well-being of the herd. Some bulk milk traits like urea are in fact important for evaluating diet appropriateness and excess/lack of protein in the ration. Having milk analysis daily available at farm level provides information regarding animals' efficiency and ration administered. It is also worth mentioning that NIR could allow for milk analysis even at quarter level which is extremely important in contexts where selective dry therapy protocols are in use and blanket therapies prohibited (e.g. in all European countries).

In recent times, significant advancements have occurred in the swiftness of acquiring spectra, signal processing, and transmission, along with enhanced possibilities for superior connections and NIR spectral management. Additionally, instruments have evolved with a marked reduction in size and weight, contributing to the growing utilisation of NIR spectroscopy outside the laboratory and directly on the dairy farm

(Evangelista et al. 2021). For several years, researchers have been actively involved in developing NIR spectroscopy applications suitable for a real-time analysis at milking. This includes efforts in adapting NIR spectroscopy for its use in farms equipped with milking parlour (Kawasaki et al. 2006, Kawamura et al. 2007; Melfsen et al. 2012; Iweka et al. 2016, 2020) and automatic milking systems (AMS; Iweka et al. 2018). Real-time analysis of milk can be either online or in-line with NIR. In the case of online instruments, the measurement is performed continuously but not directly within the process/pipe itself. A dedicated branch, in fact, takes a representative amount of milk to be automatically analysed. Differently, if NIR is implemented in-line, measurements occur directly in the process. At-line analyses, instead, are performed mostly with handled and portable NIR devices (e.g. SCiO, Consumer Physics Inc., Israel) on bulk milk as they require the sample to be taken out from the pool manually and analysed separately.

Overall, accuracy and precision of prediction models for the main cow milk chemical constituents are high or moderate (Table 3). Among the investigated parameters, milk fat content results to be the best predicted trait in all studies, with high coefficients of determination (>0.90) and low standard error of predictions, both in reflectance and transmittance mode.

Table 3. Fitting statistics of near-infrared models developed for the real-time analysis of raw milk.

NIR system	N. samples	VS	Fat (%)	Protein (%)	Lactose (%)	Solid not fat (%)	Urea (mg/dL)	SCS	Milking	References
Transmittance spectra (600-1050 nm)	428-787	R^2	0.91	0.64	0.74	–	0.60	0.57	MP	Kawasaki et al. 2005
		SEP	0.53	0.22	0.14	–	2.58	0.31		
		Bias	−0.03	−0.01	−0.01	–	−0.15	−0.01		
		RPD	–	–	–	–	–	–		
Transmittance spectra (600–1050 nm)	134-151	R^2	0.95	0.91	0.94	–	0.90	0.82	MP	Kawamura et al. 2007
		SEP	0.42	0.09	0.05	–	1.33	0.27		
		Bias	0.01	0.00	0.00	–	−0.03	−0.03		
		RPD	–	–	–	–	–	–		
Transmittance spectra (600–1050 nm)	49-72	R^2	0.95	0.72	0.83	–	0.53	0.68	AMS	Kawasaki et al. 2006
		SEP	0.25	0.15	0.26		1.50	0.28		
		Bias	−0.06	0.00	0.00	–	−0.09	−0.03		
		RPD	–	–	–	–	–	–		
Reflectance spectra (851-1649 nm)	262	R^2	0.998	0.98	0.92	–	0.82	0.85	MP	Melfsen et al. 2012
		SEP	0.09	0.05	0.06	–	19.32	0.18		
		Bias	−0.0004	0.0003	−0.0076	–	−1.6959	−0.0119		
		RPD	21.72	6.44	3.51	–	2.36	2.57		
Absorbance spectra (700-1050 nm)	218	R^2	0.99	0.95	0.91	–	0.94	0.91	MP	Iweka et al. 2016
		SEP	0.17	0.06	0.06	–	0.88	0.09		
		Bias	0.00	−0.00	0.00	–	−0.00	−0.00		
		RPD	9.53	4.31	3.36	–	3.92	3.41		
Absorbance spectra (700-1050 nm)	377	R^2	0.98	0.72	0.54	–	–	0.63	AMS	Iweka et al. 2018
		SEP	0.23	0.25	0.15	–	–	0.48		
		Bias	0.00	0.00	0.00	–	–	0.00		
		RPD	–	–	–	–	–	–		
Absorbance spectra (700-1050 nm)	92	R^2	0.99	0.92	0.79	0.89	0.51	0.59	MP	Iweka a., 2020
		SEP	0.11	0.09	0.22	0.22	1.13	0.20		
		Bias	−0.01	−0.01	−0.02	−0.02	0.06	0.00		
		RPD	8.89	3.58	2.16	3.04	1.42	1.55		

VS = Validation statistics; R^2 = coefficient of determination of validation; SEP = standard error of prediction; RPD = ratio of standard deviation of the validation set to SEP. SCS = somatic cell score calculated as SCS = $3 + \log_2$(somatic cell count/100,000); MP = milking parlour; AMS = automatic milking system.

Table 4. Near-infrared-based instruments for real-time milk analysis commercially available.

Name	Company	Analysed parameters
AfiLab[TM]	Afikim (Israel)	Fat, protein, and lactose content, conductivity, blood presence, somatic cell count
Dairy sensor	Polanes ltd (Poland)	Fat, protein, and lactose content, electrical conductivity
Sabre[TM] Milk	LIC Automation (New Zeland)	Fat, protein, and lactose content, electrical conductivity

For other parameters there are variations in the prediction ability among studies and among different NIR systems. The NIR technology is becoming popular for prediction of complex traits also in species different than cattle, and the models performance models is constantly improving, laying the groundwork for the development of increasingly precise and reliable tools to be installed in the milking systems. In this way, concrete assistance to farmers, nutritionists, and veterinarians is provided. While it's clear that NIR analysis of milk constituents may not reach the precision required by laboratory standards, it is obvious that at-line and in-line instruments can be used more frequently for milk analysis at different levels, offering precious knowledge for herd and/or animals management (Melfsen et al. 2012).

As reported in Table 4, three are the sensors commercially available to date for the real-time analysis of milk. These can be installed in the milking parlour or AMS to analyse fat, protein, and lactose content at cow individual level. In addition, the AfiLab system is also able to detect some anomalies, e.g. the presence of blood traces in milk. AfiLab as well as Sabre Milk and Dairy Sensor (Table 4) provides additional useful information, namely milk SCC and conductivity. Recently, the innovative Afimilk MCS (milk classification service) System has been introduced, aiming at enhancing the value of milk. In fact, this equipment can dynamically separate milk into two fractions based on predefined criteria - such as milk coagulation ability and aptitude. This smart segregation improves the quality of the milk delivered to industries for cheese manufacturing by indirectly maximising casein content and reducing the risk of high SCC and acidity (Leitner et al. 2011, 2013, Todde et al. 2017).

Milk as a source of information for the nutritional and animal health status

Milk composition

Lactose as a mammary gland health indicator trait
In addition to the standard composition of milk related to fat and protein percentage, other components of milk, potentially predictable through infrared spectroscopy (whether FTIR or NIR), prove to be interesting milk biomarkers of nutritional and animal health status. Indeed, lactose is considered an important marker of mammary gland health. Lactose is the most abundant solid of milk. Due to the physiological role of this osmole, lactose content variation is expected to be very low under healthy conditions (Costa et al. 2020a). Within lactation the variability of this milk component is rather low, with no increase in its concentration at the end of lactation – i.e. lactose is not subjected to dilution and concentration effect as protein and fat. Although overlooked for years, lactose can be informative of the udder health of cows, especially if it is possible to trace perturbations.

In dairy cows, lactose naturally decreases with parity due to tissue ageing; however, it also decreases in presence of mammary gland inflammation (Costa et al. 2019, 2020a). In most of dairy species, the correlations between lactose and the majority of the traditional traits (e.g. milk yield and content of fat, protein, casein) are generally weak or around zero, except with SCC, the most popular mastitis marker. Mastitis and SCC are negatively correlated with lactose content at both phenotypic and genetic level due to a damage of the alveolar epithelium during and after inflammation (Bobbo et al. 2016; Costa et al. 2019, 2020a). The tight junctions of the epithelium are impaired by factors/agents related to local inflammation response, indicating that even a single mastitis event can permanently affect milk lactose content of a cow due to lactosemia (Herve et al. 2018; Costa et al. 2019). This interesting aspect has also been confirmed in other species, with a moderate to strong (-0.27 up to −0.48) negative correlation reported in buffalo (Costa et al. 2020b), goat (Bagnicka et al. 2011; Magro et al. 2022), and sheep (Carta et al. 2023).

Apparently, lactose content seems to be therefore a potential robust marker of mastitis, however often the inflammation -with consequent increase in SCC and lactose reduction - is confined to one quarter, making the variation (drop) in the pooled milk lactose content quite difficult to detect. In this context, NIR installed in AMS could open the room for the use of quarter-level lactose content for early mastitis detection which could be used in combination with quarter-level variation in electrical conductivity, milk yield, and SCC (Ebrahimie et al. 2018). In pooled milk, lactose variation is generally low, therefore its within-animal variability should be considered, and it should be

combined with other proxies of subclinical or clinical mastitis easily available, e.g. electrical conductivity, SCC, and Na.

Costa et al. (2020a) demonstrated that there is a cumulative effect of mastitis on both lactose content and milk yield, indicating that repeated inflammation events deteriorate progressively across cow's lifetime not only the concentration of this milk solid (osmole) but also the synthesis capability of the udder. After proper validation, lactose content might be used as indicator of the mammary gland memory of mastitis (Costa et al. 2020a).

Milk urea as indicator of nitrogen utilisation efficiency

In the rumen, dietary amino acids are converted to ammonia by microbiota to produce microbial protein. This process requires energy; thus, a proper level of different fraction of dietary structural and non-structural carbohydrates is fundamental to ensure this conversion. When the dietary energy and protein availability in the rumen is not synchronised, ammonia starts to accumulate in the rumen and to permeate rumen wall, passing in the bloodstream. Subsequently, in the liver, ammonia is converted to urea, which is less toxic and can be eliminated easily from the organism (urine, saliva, milk). Therefore, blood urea nitrogen (BUN) reflects the effects of dietary intake of crude protein and its digestive utilisation; in addition, BUN is related to milk protein secretion, body protein turnover and nitrogen (N) urinary excretion (Kessler et al. 2020). For high-yielding dairy cows, BUN levels below 5 mg/dL (1.7 mmol/L) suggest a potential deficiency of dietary protein, whereas BUN exceeding 19 mg/dL (6.78 mmol/L) may be due to unbalanced diet, Additionally, impairment of the N balance is associated with laminitis and metabolic dysfunction (Nocek 1997), that, in turn, are associated to diminished conception, and pregnancy rates (Hammond 1997). Since BUN cannot be measured routinely at herd level, the MUN is often used as a proxy due to the high phenotypic correlation with cows' ($r = 0.86$; Hof et al. 1997) and small ruminants' BUN ($r = 0.90$; Jelínek et al. 1996). Therefore, MUN can be view as a by-product of the N metabolism; in addition, at herd level the bulk milk MUN can be a useful indicator of protein and energy status of ruminants and dietary balance.

The MUN concentration is affected by many factors. These encompass environmental conditions like season and feed as well as individual factors such as breed, parity, body weight, rumen microbiota, physiological state, and milk yield (Hojman et al. 2004).

Therefore, establishing monitoring protocols and thresholds can be rather difficult. Considering that measurement of MUN via gold standard is costly and time-consuming, FTIR has been tested for predicting milk urea since the 1990s and is now widely used with high accuracy at population level (Bittante 2022). Optimal milk urea values range from 17 and 26 mg/dL in dairy cows bulk milk, with levels below 17 mg/dL (MUN < 7.82 mg/dL) being related to energy excess/protein deficiency and levels greater than 26 mg/dL (MUN > 11.96 mg/dL) being associated to concentration of dietary protein greater than required and/or energy deficiency (Powell et al. 2011). A sharp variation in MUN (± 4 mg/dL) must be considered therefore as an alert for the farmer whose cause(s) should be explored. Predicted milk urea has been mainly employed in bulk milk for evaluating the dietary balance and excess of N, due to concerns related to environmental impact (Bastin et al. 2009, Aguilar et al. 2012). However, its potential extends to exploring novel applications when coupled with other parameters for negative energy balance detection (Andjelić et al. 2022).

Somatic cell count and differential somatic cell count

Milk SCC (n. cells/mL) is the most popular marker of udder health in dairy species, due to phenotypes availability and its quantitative nature which makes SCC easier to monitor/analyse/evaluate compared to binary diagnosis. Genetically and phenotypically, the correlation between SCC and mastitis in dairy cows is moderate to strong (0.60-0.90), likely due to cow's intrinsic factors (immune response activation, health status, etc), form (clinical, subclinical, acute, chronic, etc), severity, and pathogen(s) involved (de Haas, 2003),

When mastitis occurs, in most of the cases the observed increase in SCC has to be attributed to a single sick quarter, suggesting that at quarter level the increase is exponential. SCC are for the 85-90% white blood cells, the remaining part (10-15%) are exfoliated epithelial cells. The magnitude of the increase can therefore differ, suggesting that looking at the SCC pattern is fundamental for an accurate early prediction of mastitis (Bobbo et al. 2016; Rienesl et al. 2022). In addition, detection/prediction accuracy could be boosted if other traits are considered with SCC (see chapter 3.1.4). Machine learning algorithms nowadays can be exploited for this purpose, as they can combine several predictors and consider their longitudinal evolution, i.e. across days in milk (Ebrahimi et al. 2019). The milk spectrum can contain relevant

information that can be potentially useful in prediction (Rienesl et al. 2022). Of course, availability of monthly data per cow is not sufficient for managerial purpose and does not provide support to the farmers because the diagnosis would occur before the milk analysis report reception. In the case of NIR, however, there is potential to use prediction algorithms that integrate spectral data points and cow-related information on a daily basis, possibly accounting for day-to-day variations.

Conventionally, SCC above 200,000 cells/mL in pooled milk is indicative of suboptimal milking practices and udder health issues in the herd (Ruegg and Pantoja 2013). However, sensitivity and specificity of this threshold depend on a multitude of factors, including the cow-specific physiological baseline SCC level. It is not uncommon, in fact, to observe healthy cows with constantly high milk SCC or, vice versa, sick cows – even with a severe inflammation - with milk SCC below 200,000 cells/mL. On the other hand, it is important to remind that rarely data of cows with mastitis are present in the official databases; in presence of severe acute episodes, for example, cows could be not milked at all, or the milk is discarded for presence of antimicrobial residues. Big data generated from bodies like AIA are therefore lacking part of the information (milk yield and composition) necessary to carry out robust and accurate prediction models for mastitis detection. Milk SCC is determined by the official laboratories as part of the official DHI analyses through flow cytometry. Commercial names of most popular machineries are Bentley SomaCount FCM (Bentley Instruments, Chaska, MN, US), Fossomatic (Foss Electric A/S, Hillerød, Denmark), and Somascope (Delta Instruments, Drachten, the Netherlands).

In recent years, the Foss Electric A/S (Hillerød, Denmark), proposed a novel trait for mammary gland inflammation detection and udder health monitoring, particularly useful for subclinical mastitis. The differential somatic cell count (DSCC, cells/mL) is expressed in percentage, as it represents the proportion (%) of polymorphonuclear leukocytes and lymphocytes out of the total SCC. Nowadays, some Italian laboratories under AIA control routinely determine DSCC in individual bovine milk. According to some studies carried out on both sick and healthy cows, the risk of mastitis seems to be high when the pooled milk DSCC is above 65% along with SCC greater than 200,000 cells/mL (Zecconi et al. 2019). In general, several assumptions are made whenever a threshold is defined; hence, in the case of DSCC, it is reasonable to assume that the threshold differs based on the number of sick quarters, baseline SCC, pathogen(s) involved, lactation stage, parity, season and other individual and environmental sources of variation.

Fine composition

Fatty acid profile as fingerprint of the cow's nutritional and metabolic status

Within the fine components of milk, the fatty acid profile serves as a distinctive marker of the cow's nutritional and metabolic condition, making it a valuable indicator of metabolic imbalance at the individual cow level. Bovine milk fat is composed of approximately 400 different fatty acids (FAs), with nearly equal contributions from mammary gland synthesis and transfer from circulating plasma. Short- and medium-chain FAs (C4 to C14), along with about half of the C16 FAs originating from acetate and β-hydroxybutyrate (BHB), result from de novo synthesis in the mammary gland. The remaining C16 and all longer chain FAs are sourced from either dietary lipids or mobilisation of fat depots (Conte et al. 2017). Additionally, as summarised by Buccioni et al. (2012), various studies demonstrated that bacteria during ruminal activity generate odd- and branched-chain FAs. Of great interest for farm animal diagnostics is the determination of the ratios between various milk FAs. Some examples include the determination of the ratio between trans-10 and trans-11 isomers of C18:1 for diagnosing 'the low-fat milk syndrome' (Conte et al. 2018). The measurement of the concentration of de novo FAs synthesised by the mammary gland provides a fairly accurate indication of the efficiency of ruminal fermentations in providing acetate and butyrate to mammary gland. The proportion of FAs de novo synthesised is also a good indicator of the health mammary status, as demonstrated in single udder quarter with different levels of somatic cells count (Turini et al. 2020). Similarly, determining the proportion of long-chain fatty acids (especially the ratio between C16 and the sum of C18:0 and C18:1 cis9) gives insight into the energy balance of the cow, especially after calving (Gross et al. 2011). Milk FA profile is also an excellent source of information of the feeding regimen and diet administered. In fact, through specific milk FA it is possible to reveal if the feeding system is pasture-based or not and if the ration includes certain forages (Mele 2009).

Given the labour-intensive nature of the analytical methods for milk FAs determination, infrared spectroscopy can be a viable alternative, as it is not nondestructive, rapid, cheap and multiparametric. Recently, to estimate some specific FAs (C12:0, C14:0,

C16:0, C16:1 cis9, C18:1 *cis* and *trans* isomers and SFA and MUFA) in cows' milk (Soyeurt et al. 2006). Although the accuracy of FTIR to separate specific geometric and positional isomers of UFA is not comparable to the gold standard analysis (gas-chromatography), the possibility to perform a huge number of samples in a very repeatable and quick way allowed to obtain interesting results by using FTIR for the routine analysis of milk FA profile. In fact, the possibility to routinely predict the main classes and some specific FAs seems effective in the monitoring of nutritional and health status of lactating cows, including ketosis and calcium dynamics in early lactation (Bach et al. 2019; Seely et al. 2022; Seminara et al. 2023).

Detailed milk protein profile as indicator of inflammatory and metabolic disorders

Bovine milk has an average protein content of 35 g/L, mainly composed by casein (CN), which account for almost 80% of the total proteins present in different fractions: α-S1-, α-S2-, β- and κ-CN. Whey proteins represent the remaining 20% of proteins of milk, are found in solution and are mainly composed by β-lactoglobulin (β-LG) and α-lactalbumin (α-LA), followed by lactoferrin (LF), and a traces of serum albumin and immunoglobulins. Besides their impact on milk coagulation and cheese-making properties (Bisutti et al. 2022), changes in CN proportion have been observed in animals having clinical and subclinical mastitis. This implies that monitoring fluctuations in CN fractions could be a useful proxy for udder inflammation (Pegolo et al. 2020). In particular, the decrease of the two most abundant fractions (i.e. α-S1 and β-CN) of caseins was linked to the enhanced activity of proteolytic enzymes released by somatic cells in response to the udder inflammation (Ramos et al. 2015). Other protein fractions could provide useful information pertaining to the health condition of the animal. For instance, LF is an iron binding protein with antimicrobial properties which can also exert a wide range of actions towards the immune system, from the inhibition of the inflammatory process to the modulation of both innate and adaptive immune response (Drago-Serrano et al. 2017; Shimazaki and Kawai 2017). Interestingly, some whey proteins could provide significant insight also in relation to other conditions like ketosis or acidosis. In fact, increase in milk β-LG was recently proposed as a marker for the diagnosis of ketosis, while high concentration of α-LA could be informative for identifying the occurrence of acidosis (Puppel et al. 2021). The identification and quantification of milk protein fractions is typically conducted through analytical methods such as Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis (SDS-PAGE) or High-Performance Liquid Chromatography (HPLC). These methods, while highly efficient, are expensive and time consuming and require expert personnel, and therefore challenging for routine screening at the farm level. In this context, the utilisation of FTIR for milk prediction opens an intriguing avenue. Studies in the past decade have shown challenging results with poor to moderate prediction ability through both NIR and FTIR spectroscopy (Díaz-Carrillo et al. 1993, Bonfatti et al. 2011). Improved accuracy was reported with the implementation of wavelength selection (Niero et al. 2016). Recently, with the advent of new machine learning algorithms for elaborating predictions, a recent study demonstrated that protein fractions can be predicted with high accuracy from milk FTIR spectra, with a few highly significant wavelengths (Mota et al. 2023a). The potential of using this technique in the context of health monitoring need to be further explored.

Mineral profile as marker of mastitis

Minerals constitute a minor fraction of milk components, accounting for approximately 0.7% (Kaufmann and Hagemeister 1987). Mineral content in milk is primarily influenced by dietary mineral intake and environmental factors, but is also partly heritable (Buitenhuis et al. 2015). What's even more significant is that the mineral content is influenced by the cow's physiological and health status. Specifically, decreased levels of Ca, Mg and K in milk, coupled with increased Na concentration, has been regarded as markers of mastitis (Gaucheron, 2005; Nogalska et al. 2020). Moreover, specific trace minerals such as Zn, Cu, and Mn are closely connected to immune system functioning and the overall health of the udder (O'Rourke 2009, Nogalska et al. 2020). A recent study highlighted the positive association between S and macrophages and SCC, highlighting its relationship with whey proteins (Giannuzzi et al. 2024). In the same study, Fe and DSCC were positively associated, remarking the role of Fe in immune regulation during inflammation (Cronin et al. 2019). Regarding cow's metabolic status, given the strong dependence of milk minerals on milk protein, various associations have been observed between macrominerals, such as Ca, and S, and traits related to metabolic changes like BCS, liver ultrasound measures, and blood BHB (Toscano et al. 2023). Gold standards for milk mineral content quantification, such as the inductively coupled plasma atomic emission spectrometry and the X-ray fluorescence, require trained

personnel and investment for the benchtop instrument(s) purchase. Moreover, they are time consuming and expensive, hindering their feasibility for routine analysis. Initial efforts to predict milk mineral content, particularly macrominerals, yielded promising results with good to very good prediction accuracy, except for Na, which posed a particular challenge when it came to accurate prediction (Soyeurt et al. 2009, Visentin et al. 2016, Christophe et al. 2021). Nevertheless, there has been relatively little focus on predicting trace minerals (i.e. Fe, Cu, Zn, Mn, and Se), which, as mentioned earlier, seems to have a vital role in the regulation of the immune system, and could serve as valuable indicators for complementing information in the early detection of health-related issues. Indeed, few researchers have invested some effort into predicting trace minerals, resulting in reduced accuracy (Zaalberg et al. 2021).

Blood biomarkers

Metabolic profile

In dairy cattle, blood biochemistry serves as a support in diagnostic investigations for health management, offering corroborative evidence for suspected diagnoses, functioning as a prognostic marker, and allowing the monitoring of disease progression in animals undergoing treatment (Premi et al. 2021). In addition, evaluating the levels of specific biochemical compounds in a comprehensive list known as the blood metabolic profile enables the assessment of disease risk in clinically healthy dairy cows (Payne et al. 1970). The significance of serum metabolic profiling is particularly pronounced in identifying subclinical disorders, which can affect the welfare and production levels of the cows. Within the blood metabolic profile, non-esterified fatty acids (NEFA) and BHB are extensively investigated as markers of negative energy balance during early lactation. In recent years, a heightened focus has been given to immune metabolic changes starting during late lactation or dry-off period and leading to long-term carryover effects on the subsequent calving and lactation stages (Caixeta and Omontese 2021). Hence, a more comprehensive investigation into blood biomarkers that spans the entire lactation period monitoring metabolic changes related to hepatic overload, systemic inflammation, and oxidative imbalance is essential. Within this framework, hepatic damage enzymes (e.g. ALP, AST, GGT, PON), negative and positive acute-phase proteins, oxidants (e.g. reactive oxygen metabolites), and antioxidant compounds have been demonstrated to provide

additional information regarding metabolic adaptability of cows throughout the lactation period (Premi et al. 2021). While metabolic profiling offers clear benefits, the routinary collection of blood samples involves an invasive and labour-intensive process for large-scale monitoring. Conversely, milk is a ready-to-use matrix, and its collection is non-invasive and easy to implement into traditional milking procedures. As already stated, the composition of milk reflects the health and nutritional status of dairy cows, and disruptions in metabolic homeostasis are evident through changes in its components. In recent years diverse studies have investigated the predictive ability of infrared spectroscopy in the indirect prediction from milk of various blood metabolites (Table 1). Luke et al. (2019) and Ho et al. (2021) using partial least square regression obtained good predictions on BHB, fatty acids and BUN, whereas serum minerals, albumin and globulins achieved poor predictions using milk FTIR in a wide Australian Holstein population. Applying similar statistical approaches to milk FTIR of Holstein Friesian, Brown Swiss, or Simmental cows in Northern Italy yielded similar results, demonstrating good predictability of BHB, BUN and NEFA, but scarce predictive ability for glucose, triglycerides, cholesterol, and AST (Benedet et al. 2019). Grelet et al. (2019) integrated FTIR with on-farm information (i.e. days in milk and parity) and obtained good performance in predicting glucose, BHB, NEFA, and IGF-I within a European dairy cows' population. Recently, using various machine learning algorithms on milk FTIR spectra, and integrating on-farm and genomic information, significant improvement of predictive ability has been achieved on the prediction of a comprehensive metabolic profile, especially for acute phase proteins (globulins, ceruloplasmin, haptoglobin), hepatic enzymes (AST, GGT, and ALP) and oxidative stress markers (Giannuzzi et al. 2023, Mota et al. 2023b). One intriguing point to note is that, while good predictability is achieved when a metabolite is present both in blood and in milk, FTIR spectra can also capture indirect information about blood compounds that are only detectable at trace concentrations in milk, such as minerals and total bilirubin (Giannuzzi et al. 2023). This emphasises the relevance of milk in recording fluctuations in the metabolic status of the cow, irrespective of the direct presence of specific metabolites.

Within this context, the potential to predict blood biomarkers from individual milk using an in-line system could represent a significant advancement in assessing the health and metabolic status of cows and identifying individual susceptibility to metabolic

disorders in a timely manner (Evangelista et al. 2021). Moreover, compared to the FTIR spectra predictions, the additional benefit of real-time NIR predictions lies in their capability to detect alterations irrespective of individual variability. This is achieved by calculating the variance between daily registrations for each animal. To date, only one study has explored the feasibility of indirectly predicting blood biomarkers using milk NIR spectra, obtained from the Afilab equipment, in combination with on-farm information (Giannuzzi et al. 2022). Even if accuracy must be improved for practical daily applications in health status monitoring, the prediction equations for haptoglobin and hepatic enzymes, and for oxidative stress markers have shown promising results.

Milk infrared spectra for nutritional status evaluation

The knowledge of milk composition, as available real-time, with infrared spectra technique, can provide valuable insights for effectively monitoring and managing nutrition (Evangelista et al. 2021). The composition of milk exhibits considerable variability, influenced by the intricate interplay of complex metabolic activities, nutritional factors, and environmental variables. Nutritional composition of the diet directly influences the milk's constituents, including fat and protein levels. A low level of milk protein could indicate a low energy concentration in ration, as a positive linear relationship has been demonstrated between these two factors (Coulon and Rémond 1991). Instead, the urea content, as previously mentioned, may indicate an excessive/deficiency dietary protein, an imbalance between energy/protein ratio or energy deficit. Monitoring the fat-to-protein ratio in milk allows us to identify animals with metabolic disorders. The threshold for this indicator is 1.4, with the optimal range between 1.2 and 1.4 (Brand et al. 2010), with greater levels linked to negative energy balance or ketosis (Toni et al. 2011) and lactose content can serve as an indicator of the health and reproductive status of dairy cow. Monitoring milk fat content during each milking session enables detection of errors in feed preparation and distribution that may contribute to subacute/acute metabolic disorders in dairy cows, such as subacute ruminal acidosis (SARA). SARA is a well-recognised digestive disorder prevalent in high-yielding dairy cows, significantly impacting both animal health and herd profitability (Plaizier et al. 2014). It stands as one of the most significant digestive disorders in intensive farming, with an estimated incidence ranging from 19 to 26% during the early to mid-lactation period (Plaizier et al. 2008).

The milk spectral data obtained by each individual animal offer the possibility of evaluating various phenotypes, including dry matter intake (DMI), energy balance (EB), efficient energy intake (EEI) and nutritional status of the animals (Table 2). Research has been carried out (Table 2) on the predictive capacity of FTIR for the individual parameters relating to EB, EEI, residual feed intake (RFI) and DMI based on milk spectral data information. Of these animal phenotypes, FTIR prediction accuracy is fair and has been shown to be significantly improved when information regarding milk production or animal body weight and BCS is added to the model (McParland et al. 2011; Shetty et al. 2017). Having access to daily data relating to the aforementioned parameters can allow to keep the health, fertility and well-being of individual animals under control and also allow to efficiently and effectively improve the overall management of the farm.

Infrared technologies as a high-throughput phenotyping tool in selective breeding

The Mike Coffey's well-known statement, 'In the age of the genotype [genomics], phenotype is king' (Coffey 2020) found consensus among animal breeders and underscores the essential role of phenomics in the current era. In other words, accurate measurement and recording of novel phenotypes is pivotal for an effective, sustainable, and meaningful genomic selection of dairy breeds. Among the emerging phenotypes, those related to nutritional and animal health status appear to be of primary importance for the sustainability of dairy sector. In this context, all devices currently employed for milk screening, regardless if based on FTIR or NIR, are proving to be promising for generating novel (predicted) phenotypes for selective breeding (Miglior et al. 2017; Cole et al. 2020; Giannuzzi et al. 2023). This is attributed to advancements in both analytical techniques for establishing gold standard phenotypes (i.e. wet-lab reference data) and the statistical approaches, based on machine learning methods, that have increased the predictive capacity of the chemometric models (Zitnik et al. 2019).

Significant differences exist between FTIR benchtop machineries and NIR instruments. Although FTIR demonstrates in general greater predictive power compared to NIR, its effectiveness for the health-related traits monitoring is constrained by two factors: (i) the infrequent storage of spectra, and (ii) fragmented

information available (i.e. approximately one milk test per animal per month in the Italian DHI system). These limitations are particularly important, as animals at risk (e.g. in the transition period) or more susceptible to disease than the others may need more frequent checks. For example, during the postpartum phase (first 30 days in milk), where the incidence of metabolic disorders is maximum, predictions available on a daily basis would boost detection of sick individuals in the herd. Indeed, the possibility of day-by-day monitoring of animals becomes paramount for elucidating novel phenotypes based on longitudinal data, such as the pattern of certain long-chain FAs associated with negative energy balance, body reserve loss process or metabolic adaptations. In addition, there are interesting parameters linked to energy metabolism or inflammation that could be monitored in dairy cows such as BHB, NEFA, urea, ceruloplasmin, and haptoglobin. Despite of the moderate prediction accuracy, infrared-predicted phenotypes still hold potential for exploitation in national breeding programs as indicators of postpartum stress resilience (Giannuzzi et al. 2022), opening the discussion on the possibility to combine these proxies to develop a resilience index. However, although predictable, envisioning the practical use of such biomarkers in selective breeding remains challenging due to the absence of a clear physiological and genetic direction, unknown genetic correlation with traits of major interest (e.g. protein and fat yield), and potential undesired response.

Another crucial aspect to consider when evaluating the utility of infrared technology as a phenotyping tool for breeding purposes is the assessment of the reliability of calibration equations. It is evident that relying solely on the mere fitting statistics such as R^2 and RMSE is insufficient. Researchers have demonstrated that the effectiveness of FTIR calibrations in generating novel phenotypes for indirect selective breeding depends on factors such as the genetic variation of FTIR predictions and the genetic (co)variance between the prediction and the reference (measured) trait, i.e. the true breeding goal (Cecchinato et al. 2009; Costa et al. 2021). In fact, simulations have shown that, while the predictive ability of FTIR data could remain moderate for some traits and insufficient for punctual determination, the genetic response achievable by selecting animals based on FTIR predictions is often comparable to or slightly lower than the response achieved when direct measurements (reference traits) are utilised (Cecchinato et al. 2009; Rutten et al. 2010; Cecchinato et al. 2020). In this scenario, it

becomes evident how large can be the potential of in-line NIR devices. Indeed, for each monitored animal, there is possibility to move from the current 12 yearly FTIR spectra, one per month, up to hundreds of daily NIR spectra. Under twice-a-day milking, in fact, roughly 720 milk scans could be obtained per each animal every year. Currently, no studies have conducted comprehensive comparisons between the two scenarios in terms of genetic gain achievable.

In the era of big data, the substantial volume of data stored by infrared devices, along with individual animal information (i.e. milk yield, days in milk, parity), as well as genotype information, opens the possibility to integrate such information within a unified statistical framework (e.g. multiple kernel learning and multilayer BayesB). These sources have the potential to remove random noise from data and capture the variety of signals affecting phenotypes, enabling their combination to enhance prediction performance (Baba et al. 2021). This approach was recently exploited by Mota et al. (2023b), who used FTIR spectra and on-farm and genomic information for predicting cows' blood markers of metabolic disorders. In addition, a similar study was conducted using NIR spectra recorded by Afilab devices (Mota et al. 2024). While intriguing in terms of predictive capacity, this approach may face limitations due to challenges in routinely, automatically and timely access to all sources of information, including lactating females' genomic data although with the rapid drop in the price of genotyping, there has been a considerable increase in the number of young genotyped females in Italy, as well as in the rest of the world, in the last years. Within DHI recording schemes (i.e. FTIR technology), the potential to generate a substantial number of phenotypes through this approach could prove to be an exceptionally promising solution for selective breeding. Cecchinato et al. (2020) emphasised the importance of phenotypic information collected from daughters of proven bulls at the population level. This collection enhances predictive capacity at a low cost, as, in practice, the cost is constrained to the solely development of the calibration equation. However, the effectiveness of this successful approach relies on the availability of FTIR spectra and in several countries – including Italy – the storage of DHI tests spectrum started to be carried out systematically by milk laboratories only in recent times. In addition, a further bottleneck that may limit the development of this integrated data approach, both for FTIR and NIR technology, is the ownership of data and developed calibration equations.

To address this issue, international and national initiatives have been proposed. In Italy, for instance, the 'Livestock Environment Opendata' (LEO) project, initiated in 2014 and led by the Italian Breeder Association (AIA, Rome, https://opendata.leo-italy.eu/portale/home), was born. This project aimed to establish an open platform where to upload both FTIR infrared spectra (stored by milk laboratories dedicated to official DHI analyses) and measured phenotypes. An international network is also currently working on milk spectra to promote discussion about the prediction of complex traits in dairy species, with the support of the ICAR and the International Dairy Federation (FIL/IDF). In fact, the ExtraMIR ('Extra value from- smart use of- MIR spectra') intitiative was born for a deeper understanding and monitoring of the activities carried out worldwide on FTIR milk spectra(https://www.icar.org/index.php/technical-bodies/sub-committees/milk-analysis-sub-committee-landing-page/extramir-extra-value-from-smart-use-of-mir-spectra-2/).

Other challenges that need to be overcome before infrared technologies can be widely adopted globally include: i) harmonisation of the raw spectral data recorded by FTIR or NIR automated systems (across manufacturers, countries, and years of sampling), ii) encouraging farmers, nutritionists, and veterinarians to consistently record high-quality phenotypes related to nutritional and animal health status (e.g. by introduction of standardised guidelines and free and user-friendly online tools), and iii) addressing the genomic gap for such novel traits.

Lastly, a point to consider is the potential constraints due to patenting. It cannot be excluded, in fact, that the use of FTIR prediction models or of the predicted phenotypes themselves may be restricted. Some models, in fact, have been patented in recent years for commercial reasons and limitations can be therefore applied if used out of the academia for non-research purpose.

Conclusions

The complexity of milk matrix holds immense potential as source of important biomarkers for dairy animals, acting as a mirror for various nutritional and health disorders. However, despite their utility, current analytical methods are costly, time-consuming and impractical to be performed and adopted on a large scale. These challenges have spurred exploration towards alternative (low cost, hi-tech, and rapid) technologies, with FTIR and NIR on the front line. However, hurdles persist, including the need to define

adequate targets for traits related to metabolic diseases and deep understanding the role of specific blood biomarkers. Despite these challenges, the potential of infrared predictions in large-scale applications remains significant.

Finally, in a context of selective breeding, a collaborative and collective effort will be indispensable to achieve extensive and uniform international databases without the constraints of patent protections. Such a collective endeavour would facilitate the comprehensive definition of novel resilience marker in cosmopolitan dairy breeds, laying solid foundations for the genetic improvement of animal health and welfare.

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Data availability statement

Data used in the present review article is available from the corresponding author upon reasonable request.

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