# Volatile organic compounds for early detection of prostate cancer from urine

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## ARTICLE INFO

## ABSTRACT

Prostate cancer (PCa) is one of the most common cancers in men worldwide. Early diagnosis of PCa is extremely challenging due to the lack of effective diagnostic methods. The study presented here aims to evaluate whether urine volatile organic compounds (VOCs) can be used as an emerging diagnostic biomarker for PCa. Gas chromatography-ion mobility spectrometry (GC-IMS) was used to detect VOCs in urine samples from 66 patients with PCa and to comparatively analyze samples from 87 patients with non-cancerous controls (NCs). A total of 86 substance peak heights were detected in urine samples from all patients. Analysis using four machine learning algorithms suggested that the diagnosis of PCa could be effectively facilitated. Ultimately, diagnostic models were constructed based on the four VOCs selected. The AUC for the RF and SVM model were 0.955 and 0.981, respectively. Both the NN and DT diagnostic models also achieved an AUC of 0.8 or more, but their sensitivity or specificity was poor compared to the RF and SVM models.

## 1. Introduction

Prostate cancer (PCa) is the second most common cancer and fifth leading cause of cancer death among men worldwide [1]. In 2020, PCa is estimated to be responsible for 1,400,000 new cases and 375,000 deaths worldwide. Current PCa diagnosis and monitoring consists of PSA testing, abnormal digital rectal examination, and histopathological evaluation of prostate biopsy samples. Nevertheless, a high number of false positive results are associated with PSA screening in the diagnosis of PCa due to its lack of specificity. Furthermore, most abnormal PSA results are false positive results caused by benign prostatic hyperplasia (BPH), prostatitis, or cystitis, and the normal PSA can't exclude PCa either [2,3]. The resulting unnecessary prostate biopsy often leads to fever, infection and pain in patients [4]. The survival time of PCa patients is closely related to the malignant tumor stage at clinical diagnosis. Although the progression of PCa is slow, most newly diagnosed cases of PCa are in advanced stage due to insidious onset, resulting in poor overall prognosis of PCa patients. Therefore, screening for PCa in high-risk groups, diagnosis of early PCa, and standardized treatment are

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important means to improve the prognosis of patients with PCa.

Within the framework of genome-transcriptome-proteome-metabolome systems biology, Metabonomic in the downstream, the closest to the biological phenotype. By investigating the composition and content changes of all small molecular metabolites (molecular weight less than 1500 Da) before and after stimulation or disturbance of biological system in a specific period, the relative relationship between metabolites and physiological and pathological changes was sought [5]. VOCs are widely present in the human body as an important component of metabolites and can be detected in a variety of biological samples. Meanwhile, urine metabolomics is the most common and preferred choice for metabolomics work as urine is available in large quantities through non-invasive sampling [6]. Although markers of VOCs are still not used in medical practice, many studies to date have confirmed the important role of urinary VOCs in the diagnosis of tumors. Urinary VOCs analysis has a potential role in the colorectal cancer screening pathway, reducing the need for invasive colonoscopy, with the highest clinical utility for colorectal cancers and polyps compared to controls, with sensitivities and specificities of 87.8% and 88.2% respectively [7]. VOCs detected in urine can be applied by a combination of statistical analysis and machine learning algorithms to construct effective diagnostic models to help differentiate between breast cancer patients and controls, where sensitivity of 100% and specificity of 85.71% was achieved [8]. In addition, a diagnostic model based on the detection of VOC in urine was also reported in pancreatic cancer with a sensitivity of 84.0% and a specificity of 94.0% [9].

In a previous study, Tyagi et al. also used GC-IMS to test urine samples from prostate cancer patients [10]. Compared to their study, we collected a larger number of samples, used four different machine learning algorithms for model building, and obtained good diagnostic performance.

## 2. Materials and methods

### 2.1. Study population

Patients aged 18 years or older with a histological diagnosis of PCa were recruited from September 2021 to August 2022 in Qilu Hospital of Shandong University. Inclusion criteria were as follows: 1) patients without any other malignancy or history of anti-cancer treatment, 2) patients who could provide fresh urine samples and complete medical records, and 3) patients who underwent radical surgery and reported PCa by pathological examination. Urine samples from NC patients were used as controls. The overall study design is demonstrated in Fig. 1. The overall study protocol was approved by the Ethics Committee of Qilu Hospital of Shandong University and informed consent was obtained from all participating patients and their families. This study was carried out in accordance with the Declaration of Helsinki.

### 2.2. Sample preparation

All urine samples were obtained preoperatively. Approximately 10 mL of urine samples were collected from each subject using sterile containers and stored in a −80 °C refrigerator within 3 h.
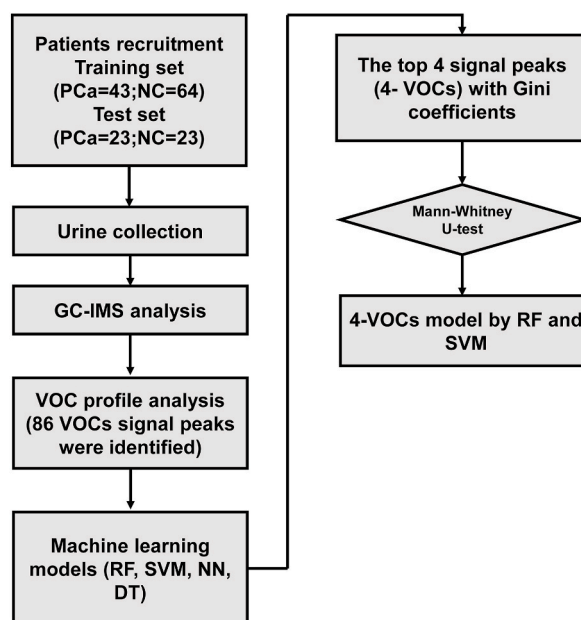


**Fig. 1.** Flowchart of study design.

## 2.3. Analysis of the VOCs in urine

GC-IMS ("FlavorSpec" brand, Dortmund, Germany) was used for VOCs analysis in urine samples. All samples were fed using a static headspace. GC-IMS first pre-separates the complex VOC fraction in urine by GC and then in series with IMS, and then achieves a secondary separation based on the mass of the molecular ion of the substance to be measured and the one-dimensional collision cross-sectional area. Therefore, two-dimensional characterisation can be performed based on the retention index (RI) of the GC and the drift time (Dt) of the IMS, and quantification is based on the signal response intensity. All samples were treated homogenously. Briefly, 2 mL of urine (with 0.2 g of aspartic acid powder) was placed in each headspace vial and incubated at 100 °C for 5 min. Subsequently, 1000 μL of gas was extracted from the headspace vials for analysis. Nitrogen was used as the carrier gas. The subsequent operating parameters were: IMS drift gas was maintained at 150 mL/min and the carrier gas gradient was as follows: 0 min: 2 mL/min; 1 min: 2 mL/min; 8 min: 100 mL/min; 10 min: 150 mL/min; 15 min: 150 mL/min. Other main parameters were as follows: T1 drift tube temperature: 45 °C; T2 GC column temperature: 80 °C; T3 inlet temperature: 80 °C; T4 connection line 1: 80 °C and T5 connection line 2: 45 °C. Each experiment was performed in triplicate.

## 2.4. Statistical analysis

The GC RI and IMS relative Dt were cross-characterised from the NIST database for RI and from the self-built IMS database for Dt. The peak positions of the compounds were confirmed by comparison with the peak positions of the standards, and the RI and Dt of the compounds to be tested had to agree with the data of the standards at the same time. By manually selecting the signal of the compound on the spectrum, the three-dimensional signal on the spectrum should have a regular peak shape, when the peak height is at least 3 times greater than the baseline noise. Bias in the absolute ion drift time is removed by normalising the RIP. The nomenclature of all compounds has been taken from the purchased NIST spectral library and has not been modified. Chemically these nomenclatures are also canonical and can be accurately defined by CAS number. The different VOCs were compared between NC and PCa using the Mann-Whitney $U$ test. The receiver operating characteristic (ROC) curve of the prediction model was calculated and compared with MedCalc 9.3.9.0. The data were analyzed using a 10-fold cross-validation, undertaken using R program ($\times$64 4.2.0). Based on identified VOCs, random forests (RF), neural network (NN), support vector machines (SVM), decision trees (DT) were used for diagnostic model building.

## 3. Results

### 3.1. Participant characteristics

A cohort of 153 patients with a definite pathological diagnosis, including 66 PCa patients and 87 NC patients, was included in this study. In addition, recruited subjects were randomized into a training set (n = 43 PCa and n = 64 NC) and a test set (n = 23 PCa and n = 23 NC). There were no significant differences in age, height, weight and lifestyle habits (smoking, alcohol consumption) between the two groups. More detailed clinical characteristics of these patients are presented in Table 1.

**Table 1**
Patient characteristics.

| Characteristics | PCa ($N = 66$) | | NC ($N = 87$) | |
| --- | --- | --- | --- | --- |
| | Training set | Test set | Training set | Test set |
| Cases | **43** | **23** | **64** | **23** |
| **Demographic data** | | | | |
| Age, years, means ± SD | 68.3 ± 6.5 | 66.0 ± 6.8 | 65.0 ± 11.9 | 65.5 ± 7.9 |
| Body height, cm, means ± SD | 170.4 ± 6.0 | 169.0 ± 5.5 | 170.2 ± 5.3 | 170.7 ± 5.5 |
| Weight, means ± SD | 72.6 ± 10.4 | 69.2 ± 9.7 | 69.5 ± 8.8 | 69.9 ± 11.1 |
| Smoking history | 20 (46.5) | 10 (43.5) | 29 (45.3) | 10 (43.5) |
| Current smoking | 4 (9.3) | 3 (13.0) | 12 (18.8) | 7 (30.4) |
| Alcohol history | 24 (55.8) | 11 (47.8) | 33 (51.6) | 13 (56.5) |
| Current alcohol drinking | 16 (37.2) | 9 (39.1) | 15 (23.4) | 12 (52.2) |
| **Comorbidities** | | | | |
| Diabetes | 11 (25.6) | 5 (21.7) | 9 (14.1) | 5 (21.7) |
| Cardiovascular disease | 9 (20.9) | 2 (8.7) | 16 (25.0) | 3 (13.0) |
| Respiratory disease | 2 (4.7) | 0 | 2 (3.1) | 2 (8.7) |
| **Gleason score** | | | | |
| low-risk ($\leq$6) | 1 (2.4) | 2 (8.7) | | |
| intermediate-risk (7) | 21 (48.8) | 9 (39.1) | | |
| high-risk ($\geq$8) | 21 (48.8) | 12 (52.2) | | |

Data are the mean ± standard deviation or number (%).
N: number.

## 3.2. VOC profile analysis in NC and PCa patients

Characterization of VOC using molecular gas chromatography retention indices. For each urine sample, we will generate 3D data (retention index, drift time and peak intensity). The VOC data are selected from the 2D spectra, with each point representing a signal peak (Fig. 2). The compounds are characterized by retrieving the 2D coordinates (retention index x drift time) of the location of the signal peaks, and boxing the integration region to integrate the signal peaks to obtain the peak height values. In total, 86 VOC peaks were selected from the urine samples. Fig. 2 shows that we can visualize the difference in VOC between the PCa and NC samples, with red representing the higher concentrations of the substance in the urine and blue representing the lower concentrations.

## 3.3. Diagnostic performance of urine VOCs with machine learning algorithms

Peak height data from the 86 VOCs mentioned above were modelled analytically using four types of machine learning (RF, NN, SVM, DT). The test set results show that all four models can distinguish PCa from NC well. The RF and SVM models both have an AUC of 0.9 or more in the study. The AUC for the NN and DT models is only between 0.7 and 0.8. Table 2 shows the detailed diagnostic performance of the four models. The AUC for the RF method was 0.945 with a sensitivity of 87.0% and specificity of 91.3%, while the AUC for the SVM method was 0.919 with a sensitivity of 87.0% and specificity of 95.7%. The specificity of both the NN and DT diagnostic models reached over 90%, but their sensitivity was only about 50%, which was far from that of the SVM and RF models.

## 3.4. Identification of urine VOCs using RF & SVM analysis

Fig. 3A shows the top four peak heights of VOCs in the Gini coefficient ranking obtained through the model analysis. Fig. 3B reveals the differences between the peak heights of the top 4 VOCs for PCa patients and NC. These include one up-regulated VOC (Furan-3-methanol) and three down-regulated VOCs ((E, E)-Octadeca-2,4-dienal, 2-Ethylhexan-1-ol, 2-Undecen-1-al). The four VOCs were modelled using RF and SVM algorithms, respectively. The results are shown in Fig. 4 (A, B), with AUC of 0.955 for the RF model and 0.981 for the SVM model. Detailed results for all models are shown in Supplementary Table 1.

## 3.5. Urine biomarkers and pathological parameters

ROC curve analysis showed that Furan-3-methanol, (E, E)-Octadeca-2,4-dienal, 2-Ethylhexan-1-ol, 2-Undecen-1-al were significant in differentiating PCa from NC patients, with AUCs >0.70 (Supplementary Table 2). Among them, the AUC of (E, E)-Octadeca-2,4-dienal reached 0.915. Examining the clinical data we collected on the population revealed that PCa patients were mostly at intermediate-risk to high-risk at the time of diagnosis, so we compared the differences between the four VOCs at low risk and intermediate to high risk. Supplementary Fig. 1 shows that Furan-3-methanol differed between the three subgroups, while the other three VOCs were not statistically significant.

## 4. Discussion

This study used GC-IMS to explore the urinary VOC profile of patients with PCa. In the urine of PCa and NC patients, we found differential trends and statistically significant differences in four VOCs. Based on this, we constructed and evaluated a diagnostic model for VOCs in PCa.
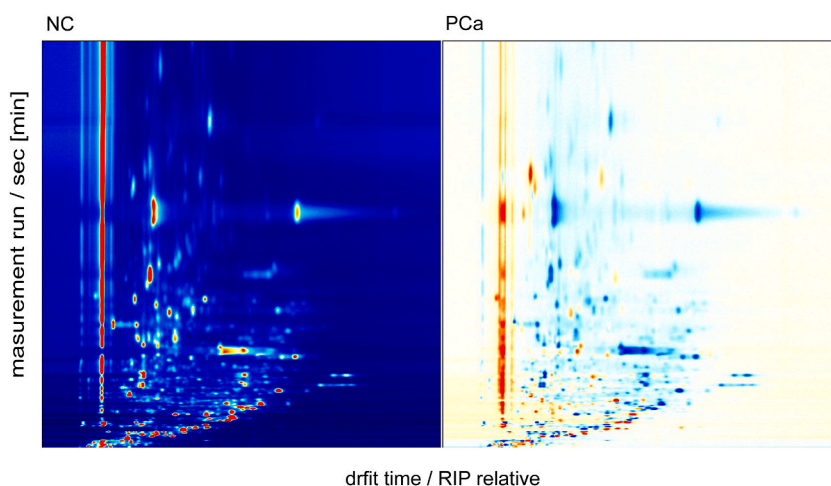


**Fig. 2. Urine VOCs profile detected in NC and PCa.** (A) 3D spectral map of VOC generated by GC-IMS. (B) A 2D map showed the difference in the VOCs when comparing an NC sample and an PCa sample so that the drift time and retention index of different VOCs can be intuitively observed.

**Table 2**
Diagnostic performance of VOCs with machine learning algorithm.

| Model | Accuracy | Precision | Recall | F1 | Specificity | AUC |
|-------|----------|-----------|--------|-------|-------------|-------|
| RF | 0.891 | 0.909 | 0.870 | 0.889 | 0.913 | 0.945 |
| SVM | 0.913 | 0.952 | 0.870 | 0.909 | 0.957 | 0.919 |
| NN | 0.761 | 0.929 | 0.565 | 0.703 | 0.957 | 0.771 |
| DT | 0.717 | 0.857 | 0.522 | 0.649 | 0.913 | 0.768 |

Note: Recall is equivalent to sensitivity.
RF: random forests; NN: neural network; SVM: support vector machines; DT: decision trees; AUC: area under the curve.
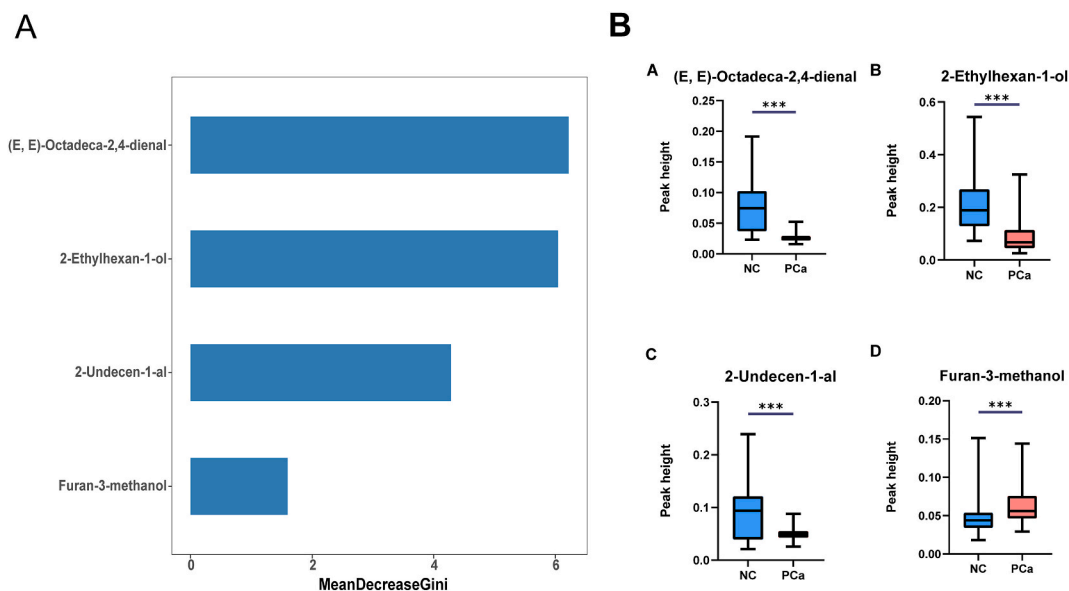


**Fig. 3. Identification of urinary VOCs using Random forests analysis.** (A) The top four VOCs with Gini coefficients by RF. (B) Comparisons of peak height of volatile organic compounds in patients with NC and PCa. The peak height of (E, E)-Octadeca-2,4-dienal (A), 2-Ethylhexan-1-ol (B), 2-Undecen-1-al (C), Furan-3-methanol (D). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (Mann-Whitney $U$ test).
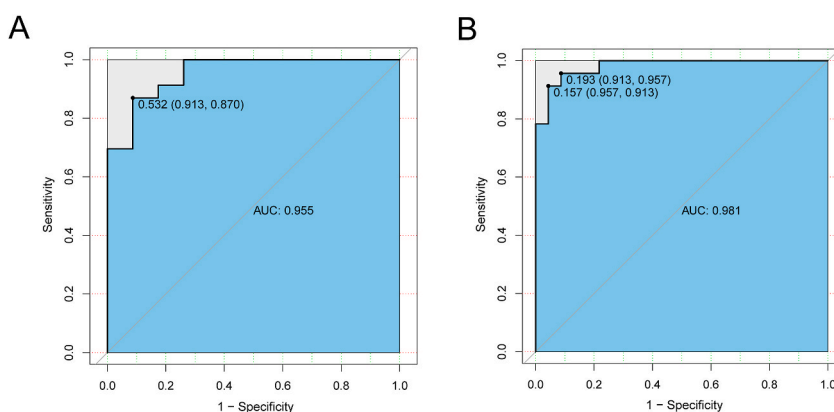


**Fig. 4. ROC curves analysis for RF & SVM machine learning model.** (A) The AUC area of 4-VOCs model by RF in validation study. (B) The AUC area of 4-VOCs model by SVM in validation study.

An increasing number of studies have focused on VOCs from metabolites of oncology patients, of which urine, exhaled breath, bile, and feces are of potential diagnostic value for tumors. Exhaled breath was one of the first sample types to be used for VOCs due to its ease of collection and storage. A prediction model constructed by Princivalle et al. based on 10 VOCs in alveolar air VOCs could well distinguish between pancreatic ductal adenocarcinoma and normal controls [11]. Navaneethan et al. found that detecting volatile organic compounds in bile may help diagnose cholangiocarcinoma in patients with primary sclerosing cholangitis [12]. Additionally,

VOCs may improve the use of fecal immunochemical testing in colorectal cancer detection, and VOCs can also be a good test method for excluding the presence of CRC in people with negative Faecal immunochemical test (FIT) symptoms [13]. Besides, VOC alone or a combination of VOC and FIT can be used as a triage tool for patients awaiting colonoscopy in the polyp surveillance population, VOC is superior to FIT in detecting patients with high-risk findings [14]. Lett and George et al. illustrated that significant trends in urinary volatile organic compounds can identify some but not all urothelial bladder cancer samples from clinically relevant controls and can assist in the diagnosis and monitoring of UBC [15]. In our study, we collect midstream urine samples from patients uniformly in the early morning, followed immediately by centrifugation and separation and final storage in a $-80\,^\circ$C refrigerator, and we try to ensure that the freezing time of each urine sample is consistent before proceeding with the topping up, a measure that effectively avoids differences due to degradation and changes in the metabolites in the urine.

Previously, some teams have studied PCa VOCs using other detection platforms. Khalid et al. collected urine samples from 59 PCa patients and 43 cancer-free controls, analyzed VOCs in the urine headspace by gas chromatography/mass spectrometry, and constructed a diagnostic model based on alcohols, aldehydes, and ketones VOCs. However, prior to statistical modeling, the authors removed compounds that were found to be relatively rare as well as relatively common in both groups from the data set, a manipulation that may have resulted in the absence of diagnostic VOCs species in the model [16]. Similarly, Gao et al. tested urine headspace VOCs by Gas chromatography-mass spectrometry (GC-MS) in a group of 108 biopsie-confirmed PCa positive and negative patients, resulting in a diagnostic model of 11 VOCs that was subsequently validated with another group of samples. The resulting AUC was 0.86 [17]. Compared to Khalid et al.'s study, Gao's team tested a larger number of urine VOCs samples and further validated the model using an external patient cohort after the training group had constructed the model, which improved the reliability of the diagnostic model. Tyagi et al. examined urinary headspace VOC in patients with PCa and bladder cancer using GC-IMS and gas chromatography time-of-flight mass spectrometry (GC-TOF-MS) and found differences between the two types of tumor patients, in addition to differences between tumor patients and controls differences. In particular, the AUC reached 0.89 and 0.95 for the PCa and bladder cancer versus control groups respectively, while the AUC for the PCa and bladder cancer groups was 0.97, according to GC-IMS discrimination.

Despite the above studies describing the role of VOCs in oncology, unfortunately, there are few studies on the mechanisms of production of metabolite VOCs. It has been reported that tumor cells are usually accompanied by elevated acetaldehyde dehydrogenase (ALDH) activity and that ALDH catalyzes the oxidation of exogenous and endogenous aldehyde substrates to their corresponding carboxylic acids [18,19]. These findings expound the decreased aldehyde levels in PCa patients in our study. 2-Ethyl-1-hexanol is a metabolite of Diethylhexyl phthalate (DEHP) that exhibits characteristic induction of apoptosis, and apoptosis induction can further trigger tumor cell death [20,21]. In the present study, 2-Ethylhexan-1-ol was reduced in VOCs, so we speculate that this may attenuate PCa cell apoptosis thereby promoting prostate cancer progression. However, the detailed mechanism of metabolite production in VOCs and its role in tumors still needs further exploration.

Thanks to the non-invasive nature of urine collection, the use of VOCs in urine for early screening and diagnosis of tumors is a good option. Compared to the current clinical use of blood screening, urine samples are well suited to improve patient acceptability. In addition, urine is rich in exogenous and endogenous metabolites that are filtered through the kidneys and can reflect rapid changes in the local environment of the genitourinary tract and the body's metabolic pathways, and even have the potential to suggest the onset of disease [22], making it a good sample for the study of urological tumor VOCs.

PSA is one of the tumor markers used by clinicians to make the initial diagnosis of PCa. However, it provides only limited sensitivity and poor specificity for the diagnosis of PCa. To ensure the reliability of a small set of conclusions drawn, we constructed diagnostic models using four machine learning algorithms, which were also validated using external data. The diagnostic accuracy of the RF and SVM models reached over 95%. Therefore, we concluded that urinary VOCs can be used as a valid biomarker for PCa diagnosis.

## Author contribution statement

## Ethics approval and consent to participate

## Data availability

## Funding

Innovation Project of Shandong Province (2021CXGC010603, 2021CXGC011105), and Taishan scholar program of Shandong Province.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

Not applicable.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e16686.

## References

[1] H. Sung, J. Ferlay, R.L. Siegel, et al., Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, Ca - Cancer J. Clin. 71 (3) (2021) 209–249, https://doi.org/10.3322/caac.21660.
[2] H. Van Poppel, T. Albreht, P. Basu, et al., Serum PSA-based early detection of prostate cancer in Europe and globally: past, present and future, Nat. Rev. Urol. 19 (9) (2022) 562–572, https://doi.org/10.1038/s41585-022-00638-6.
[3] W.J. Catalona, D.S. Smith, T.L. Ratliff, et al., Measurement of prostate-specific antigen in serum as a screening test for prostate cancer, N. Engl. J. Med. 324 (17) (1991) 1156–1161, https://doi.org/10.1056/nejm199104253241702.
[4] D.J. Rosario, J.A. Lane, C. Metcalfe, et al., Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study, BMJ 344 (2012) d7894, https://doi.org/10.1136/bmj.d7894.
[5] Y. Chen, E.M. LiL, Y. Xu, Guide to metabolomics analysis: a bioinformatics workflow, Metabolites 12 (4) (2022), https://doi.org/10.3390/metabo12040357.
[6] D. Kumar, K. Nath, H. LalA. Gupta, Noninvasive urine metabolomics of prostate cancer and its therapeutic approaches: a current scenario and future perspective, Expert Rev. Proteomics 18 (11) (2021) 995–1008, https://doi.org/10.1080/14789450.2021.2011225.
[7] C.E. Boulind, O. Gould, B. de Lacy Costello, et al., Urinary volatile organic compound testing in fast-track patients with suspected colorectal cancer, Cancers 14 (9) (2022), https://doi.org/10.3390/cancers14092127.
[8] J. Giró Benet, M. Seo, M. Khine, et al., Breast cancer detection by analyzing the volatile organic compound (VOC) signature in human urine, Sci. Rep. 12 (1) (2022), 14873, https://doi.org/10.1038/s41598-022-17795-8.
[9] E. Daulton, A.N. Wicaksono, A. Tiele, et al., Volatile organic compounds (VOCs) for the non-invasive detection of pancreatic cancer from urine, Talanta 221 (2021), 121604, https://doi.org/10.1016/j.talanta.2020.121604.
[10] H. Tyagi, E. Daulton, A.S. Bannaga, R.P. ArasaradnamJ, A. Covington, Urinary volatiles and chemical characterisation for the non-invasive detection of prostate and bladder cancers, Biosensors 11 (11) (2021), https://doi.org/10.3390/bios11110437.
[11] A. Princivalle, L. Monasta, G. Butturini, C. BassiL. Perbellini, Pancreatic ductal adenocarcinoma can be detected by analysis of volatile organic compounds (VOCs) in alveolar air, BMC Cancer 18 (1) (2018) 529, https://doi.org/10.1186/s12885-018-4452-0.
[12] U. Navaneethan, M.A. Parsi, V. Lourdusamy, et al., Volatile organic compounds in bile for early diagnosis of cholangiocarcinoma in patients with primary sclerosing cholangitis: a pilot study, Gastrointest. Endosc. 81 (4) (2015) 943–949.e941, https://doi.org/10.1016/j.gie.2014.09.041.
[13] S. Chandrapalan, S. Bosch, J. Cubiella, et al., Systematic review with meta-analysis: volatile organic compound analysis to improve faecal immunochemical testing in the detection of colorectal cancer, Aliment. Pharmacol. Ther. 54 (1) (2021) 14–23, https://doi.org/10.1111/apt.16405.
[14] S. Chandrapalan, F. Khasawneh, B. Singh, et al., A multi-centre study to risk stratify colorectal polyp surveillance patients utilising volatile organic compounds and faecal immunochemical test, Cancers 14 (19) (2022), https://doi.org/10.3390/cancers14194951.
[15] L. Lett, M. George, R. Slater, et al., Investigation of urinary volatile organic compounds as novel diagnostic and surveillance biomarkers of bladder cancer, Br. J. Cancer 127 (2) (2022) 329–336, https://doi.org/10.1038/s41416-022-01785-8.
[16] T. Khalid, R. Aggio, P. White, et al., Urinary volatile organic compounds for the detection of prostate cancer, PLoS One 10 (11) (2015), e0143283, https://doi.org/10.1371/journal.pone.0143283.
[17] Q. Gao, X. Su, M.H. Annabi, et al., Application of urinary volatile organic compounds (VOCs) for the diagnosis of prostate cancer, Clin. Genitourin. Cancer 17 (3) (2019) 183–190, https://doi.org/10.1016/j.clgc.2019.02.003.
[18] A. Ahmed LaskarH. Younus, Aldehyde toxicity and metabolism: the role of aldehyde dehydrogenases in detoxification, drug resistance and carcinogenesis, Drug Metab. Rev. 51 (1) (2019) 42–64, https://doi.org/10.1080/03602532.2018.1555587.
[19] B. Jackson, C. Brocker, D.C. Thompson, et al., Update on the aldehyde dehydrogenase gene (ALDH) superfamily, Hum. Genom. 5 (4) (2011) 283–303, https://doi.org/10.1186/1479-7364-5-4-283.
[20] K. Rios, C. VélezB. Zayas, Cell death effects of the phthalate 2-ethyl-1-hexanol on human linfoblast cells, Open J. Apoptosis 8 (2019) 1–15, https://doi.org/10.4236/ojapo.2019.81001.
[21] R.G. Uzzo, N.B. Haas, P.L. CrispenV, M. Kolenko, Mechanisms of apoptosis resistance and treatment strategies to overcome them in hormone-refractory prostate cancer, Cancer 112 (8) (2008) 1660–1671, https://doi.org/10.1002/cncr.23318.
[22] Q. Wen, P. Boshier, A. Myridakis, I. BelluomoG, B. Hanna, Urinary volatile organic compound analysis for the diagnosis of cancer: a systematic literature review and quality assessment, Metabolites 11 (1) (2020), https://doi.org/10.3390/metabo11010017.