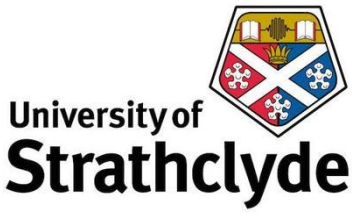

Vibrational Spectroscopy in the analysis of Human Blood for Cancer Diagnosis - a Systematic Review; Protocol

Version 1

05/10/18

Title: Vibrational Spectroscopy in the analysis of Blood for Cancer Diagnosis - a Systematic Review

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Step 1: Prepare the Topic

Introduction

Review Question: Can the novel use of Vibrational Spectroscopy in the analysis of human blood diagnose cancer?

Rationale:

Early recognition and detection of cancer improves survival(1, 2) and is essential for both optimal treatment and quality of life. It is easily demonstrable from population statistics that the detection and treatment of cancers at an earlier stage will improve survival outcomes for patients(3-5). Ideally then, a minimally invasive, cost effective diagnostic tool would be available to allow all cancers to be detected and treated at the earliest possible opportunity.

Current pathways for cancer diagnosis are often invasive (tissue biopsy) and require histopathological analysis by the pathologist under the microscope. This can result in morbidity(6), and requires significant sample processing and staining(7), is time consuming(8, 9) and is subject to inter-operator variability in interpretation(10, 11), rendering the diagnostic process expensive and resource heavy.

The potential use of cancer DNA blood detection or "liquid biopsy" has been widely reported in the mainstream media recently, with the prospective of early diagnosis lauded as a potential "holy grail" in cancer diagnosis. It has been demonstrated that Vibrational Spectroscopy is a valid and powerful tool in the analysis of biological fluids and tissues(12-15). By providing a unique "biological fingerprint" of the whole sample of fluid or tissue under analysis, detectable variations within that fingerprint can be used to detect and diagnose different disease pathologies(13, 16) through identification of specific "spectral biomarkers" of disease. It is effective at detecting and developing such disease biomarkers from tiny volumes of blood(17, 18). New analytical techniques allow for these "Biomarkers" for diseases to be identified for cancers(19-21). There is a wide array of studies published in this area, but to date no systematic review has occurred to evaluate the quality of the research to date and assess the viability of the technique with a view to translatability to the clinical setting.

To help assess the science in this area, we conduct a systematic review to evaluate the use of vibrational spectroscopy in the analysis of human blood for cancer diagnosis, based on the growth in the literature on the subject over the past years, and increasing public interest in the topic. To our knowledge no systematic review on this topic has been conducted to date.

Objectives:

To summarise the available literature on the novel use of Vibrational Spectroscopy in the analysis of Human Blood for cancer detection and diagnosis.

Specific Aims:

- Provide a summary of the literature and rate our confidence in studies that assess the novel use of Vibrational Spectroscopy in the analysis of Human Blood for cancer detection and diagnosis
- Evaluate the evidence for the plausibility of the use of Vibrational Spectroscopy in the clinical setting for the diagnosis of cancer in the general population based on current available evidence

Methods

Eligibility Criteria:

Types of studies

Only studies with a cancer and control population group with 75 participants or over will be included. Studies on non-blood samples (tissue, cells), Animal studies and studies without a concurrent control will be excluded. Review articles, opinion papers and commentaries will be excluded. Studies looking at identification of existing tumour markers were excluded.

Types of participants and model systems

Studies of humans, with *ex vivo,* vibrational spectroscopic analysis of blood or constituents (serum/plasma) for the detection of cancer. There are no restrictions based on demographic statistics.

Types of exposures/intervention/investigation

Blood samples must undergo laboratory analysis by vibrational spectroscopy (Raman/Infrared). No discrimination will be made for subtypes of spectroscopy (FTIR, SERS etc...). No discrimination will be made for blood samples analysed (whole blood/serum/plasma).

Types of outcomes

Publications must include an indicator of the diagnostic capability of Vibrational Spectroscopy (in the form of sensitivity, specificity, ROC AUC etc...). Standard diagnostic criteria for the cancer under investigation must have been applied to those in the cancer group for inclusion.

Types of publications

Publications must be peer-reviewed articles. An English language restriction was applied. No date range restrictions apply.

Table 1: Criteria for Inclusion of Studies within the Systematic Review

Criteria for Inclusion of Studies within the Systematic Review	
1. Population, or participants and conditions of interest	Human population with histopathologically confirmed cancer diagnosis
2. Intervention/Exposure/Investigation	Application of Vibrational Spectroscopy to the analysis of Human Blood with the specific aim of cancer diagnosis
3. Comparisons/Control Groups	Non-cancer population as control group
4. Outcomes of Interest	Descriptors of diagnostic potential (sensitivity, specificity, accuracy, Positive Predictive Value (PPV), Negative Predictive Value (NPV), Kappa Values, ROC Curve
5. Setting	Laboratory analysis of Human Blood with Vibrational Spectroscopy
6. Study Design	Any Study Design fitting the above criteria

Table 2: Exclusion Criteria

Criteria for Exclusion of Studies within the Systematic Review, not detailed in inclusion criteria above
1. Studies with less than 75 participants in each arm (Cancer and Control) will be excluded* **2.** Not an original paper examining the use of Vibrational Spectroscopy in the analysis of Human Blood for Cancer detection/diagnosis (Review article/Opinion/Commentaries) **3.** Method other than vibrational spectroscopy as the primary method of analysis **4.** Non-human studies **5.** Analysis primarily of non-blood based analyte (tissue, cell) **6.** English Language Restriction will apply ***Existing literature(22) identifies that in order for an effective model to be constructed for classification and diagnosis, a dataset of 75 patients or greater is required, justifying our lower limit of patients for inclusion in the systematic review.*

Step 2: Search for and Select Studies for Inclusion

Search Methods – Electronic Databases

- The following databases will be searched from inception to the present:
- MEDLINE
- EMBASE
- PubMed
- TRIP
- Web of Science
- Cochrane Library

Search Strategy

The search strategy outlined below was employed in the MEDLINE electronic database. A similar strategy was used for each electronic database, being adapted for use with other bibliographic databases in combination with database-specific filters, where these are available. No Date Limit will be applied. The search terms were identified by (1) reviewing Medical Subject Headings for relevant and appropriate terms and (2) extracting key terminology/keywords from reviews and a sample of potentially relevant primary data studies. A test set of potentially relevant studies was used to ensure the search terms retrieve 100% of the test set.

1. cancer* OR neoplas* OR tumour OR tumor OR malignan*[Title/Abstract] n= 4233257
2. spectroscopy AND (infared OR IR OR FTIR OR fourier transform OR ATR OR attenuated total reflectance OR ATR-FTIR OR raman OR SERS OR surface enhanced raman OR optical OR absorption)[Title/Abstract] n=90389
3. (diagnosis OR diagnostic OR detect* OR identify OR identification OR diagnose OR classification OR classify)[Title/Abstract] AND (blood OR serum OR plasma OR sera)[Title/Abstract] n = 967615
4. 1 + 2 n=12015
5. 2+3 n=2168
6. 1+2+3 n= 1443

Duplicate citations

The results of the literature search will be downloaded into Endnote X8 software. Exact article duplicates will be removed using Endnote X8 software.

Screening studies for eligibility

Identified articles from the literature search will first be independently reviewed at the title and abstract level by two members of the review team. Disagreements between the 2 screeners will be review and arbitration with a third independent reviewer. A copy of articles that appear to meet the inclusion criteria based on the title and abstract screen will be obtained for full-text review unless the article is not available after an attempt has been made to obtain it. Copies of articles that cannot be assessed for relevance based on the title and abstract screen will also be obtained to determine eligibility based on full-text review. Studies will not be considered further when the title and abstract clearly indicate that the study does not meet the inclusion criteria described above.
Full-text eligibility review will also be independently by two members of the review team with reasons for exclusion recorded. The primary reason for excluding studies will be if the article does not contain original data relevant to our eligibility criteria, or if it fits our exclusion criteria. If the full text of an article is not in English then it will be excluded. Flow of information through the different phases of the review will be documented in a schematic similar to that represented in Figure 1 as recommended in the PRISMA statement on preferred reporting items for systematic reviews and meta-analyses(23).
One member of the review team will independently scan the bibliographies of the included studies, and relevant reviews for relevant references that were not identified from the database searches. Eligibility will be confirmed by a second screener in order to be included.

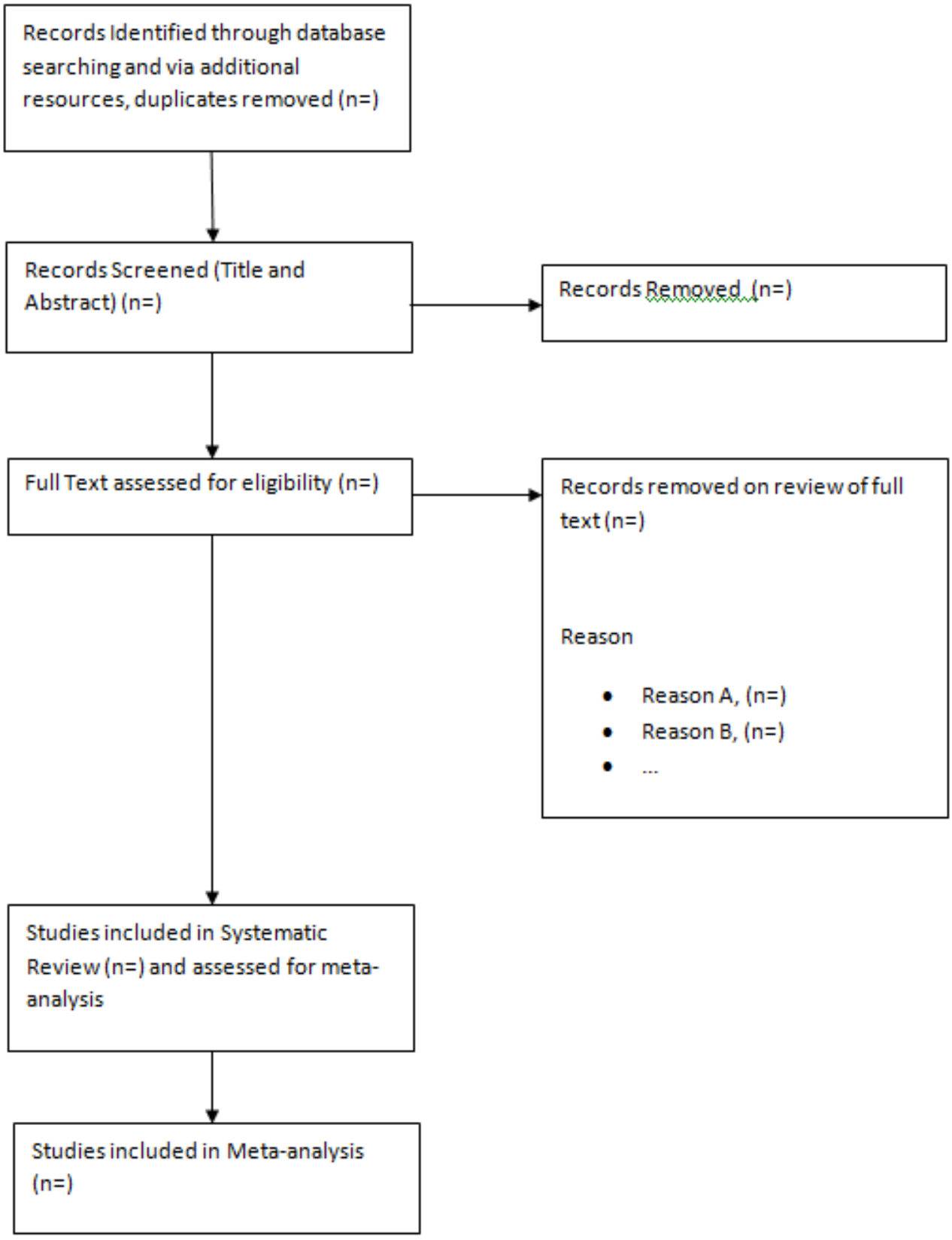
Valid studies will then be assessed for their quality before any retrieval of information

If no, or few (<3), studies are identified that meet our inclusion criteria, then we will characterise the evidence base as "insufficient to conduct a systematic review." Although unlikely, if a systematic review in this area is identified during the literature search/review, we would revisit whether there was still a need to proceed with the proposed evaluation or a portion of the objectives that are not duplicative with the published systematic review.

Table 3: Search Methods

Search Methods	
1. Electronic Database	MEDLINE EMBASE PubMed TRIP Cochrane Library Web of Science
2. Other Methods for Identifying Relevant Research	Augmentation by review of the reference list/bibliography of identified studies
3. Journals Hand Searched	Not carried out for any specific journal

Figure 1: Flow of Information through the different phases of the Review



Step 3: Quality Assessment of Individual Papers

Quality assessment

Two reviewers will independently check each selected article to minimise bias. All selected articles will be judged for their quality based on the CEBM Diagnostic Study Appraisal Tool (CEBM, University of Oxford) and the QADAS tool for quality of diagnostic accuracy (University of Bristol). Any areas of conflict will be resolved with discussion, and by review and arbitration with a third reviewer if necessary.

Step 4: Data Extraction

Data extraction

Data will be extracted on review of each individual article, and stored in Excel format. The data extracted will include all details specific to the review question and fulfils the requirements for both the narrative synthesis of outcomes and potential meta-analysis. We will contact corresponding authors for key information when data are ambiguous or missing from the published study wherever possible. Data extraction will be independently cross-checked.

Outcomes

The outcomes of the review will be grouped under the following headings:

- Sensitivity
- Specificity
- Accuracy
- Positive Predictive Value
- Negative Predictive Value
- Kappa Value
- Area under Receiver Operating Curve

Step 5: Data Analysis

Descriptive analysis

A narrative synthesis of the outcomes of the selected studies will be presented in the final review. This will include the following:

1. Sample and control group size
2. Population characteristics; age, sex, disease
3. Outcomes: Diagnostic ability reported including sensitivity, specificity, Positive and Negative Predictive Values, Accuracy, Kappa Values and Area under Receiver Operating Curve

Statistical analysis

Given the likely heterogeneous nature of the included studies, we anticipate a limited ability to run a meta-analysis for this review. However, in studies which used the same end point measurements we will (where possible) perform meta-analysis to assess the efficacy of vibrational spectroscopy in blood based cancer diagnosis. Potential publication and small sample size bias will be assessed by visual inspections of funnel plots.

Conclusion

This systematic review will provide evidence in support or against the hypothesis that Vibrational Spectroscopy in the analysis of Human Blood can be used for cancer diagnosis. This conclusion will stem from measurements of diagnostic ability as outlined above. Where sufficient data are available, we will conduct a meta-analysis. Overall, the review will complement the evidence base on the use of Vibrational Spectroscopy in the diagnosis of cancer from analysis of blood.

References

1. World Health Organisation. Cancer: Early Diagnosis 2018 [cited 2018 26 February]. Available from: http://www.who.int/cancer/prevention/diagnosis-screening/en/.
2. Department of Health. Improving Outcomes: A Strategy for Cancer 2011 [cited 2018 26 February]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213785/dh_123394.pdf.
3. Cancer Research UK. Bowel Cancer Survival Statistics [cited 2018 26 February]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/survival#heading-Two.
4. Cancer Research UK. Breast Cancer Survival Statistics [cited 2018 26 February]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/survival#heading-Two.
5. Cancer Research UK. Prostate Cancer Survival Statistics [cited 2018 26 February]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/survival#heading-Two.
6. Nazir B. Pain during Transrectal Ultrasound-Guided Prostate Biopsy and the Role of Periprostatic Nerve Block: What Radiologists Should Know. Korean Journal of Radiology. 2014;15(5):543-53.
7. Kumar RS, R. Srivastava, S. Detection and Classification of Cancer from Microscopic Biopsy Images Using Clinically Significant and Biologically Interpretable Features. Journal of Medical Engineering. 2015;2015:14.
8. Backhaus J, Mueller R, Formanski N, Szlama N, Meerpohl H-G, Eidt M, et al. Diagnosis of breast cancer with infrared spectroscopy from serum samples. Vibrational Spectroscopy. 2010;52(2):173-7.
9. Backhaus J, Mueller R, Formanski N, Szlama N, Meerpohl H-G, M. E. Diagnosis of breast cancer with infrared spectroscopy from serum samples. Vibrational Spectroscopy. 2010;52(2):173-7.
10. Kendall C, Stone N, Shepherd N, Geboes K, Warren B, Bennett R, et al. Raman spectroscopy, a potential tool for the objective identification and classification of neoplasia in Barrett's oesophagus. The Journal of pathology. 2003;200(5):602-9.
11. Stamey TA, Caldwell M, McNeal JE, Nolley R, Hemenez M, Downs J. The prostate specific antigen era in the United States is over for prostate cancer: what happened in the last 20 years? The Journal of urology. 2004;172(4 Pt 1):1297-301.
12. Bellisola G, Sorio C. Infrared spectroscopy and microscopy in cancer research and diagnosis. American journal of cancer research. 2012;2(1):1-21.
13. Byrne HJ, Baranska M, Puppels GJ, Stone N, Wood B, Gough KM, et al. Spectropathology for the next generation: quo vadis? The Analyst. 2015;140(7):2066-73.
14. Diem M, Romeo M, Boydston-White S, Miljkovic M, Matthaus C. A decade of vibrational micro-spectroscopy of human cells and tissue (1994-2004). The Analyst. 2004;129(10):880-5.
15. Kumar S, Srinivasan A, Nikolajeff F. Role of infrared spectroscopy and imaging in cancer diagnosis. Current medicinal chemistry. 2018;25(9):1055-72.
16. Baker MJ, Hussain SR, Lovergne L, Untereiner V, Hughes C, Lukaszewski RA, et al. Developing and understanding biofluid vibrational spectroscopy: a critical review. Chemical Society Reviews. 2016(45):1803-18.
17. Kong K, Kendall C, Stone N, Notingher I. Raman spectroscopy for medical diagnostics--From in-vitro biofluid assays to in-vivo cancer detection. Advanced drug delivery reviews. 2015;89:121-34.

18. Lacombe C, Untereiner V, Gobinet C, Zater M, Sockalingum GD, Garnotel R. Rapid screening of classic galactosemia patients: a proof-of-concept study using high-throughput FTIR analysis of plasma. The Analyst. 2015;140(7):2280-6.
19. Hands JR, Clemens G, Stables R, Ashton K, Brodbelt A, Davis C, et al. Brain tumour differentiation: rapid stratified serum diagnostics via attenuated total reflection Fourier-transform infrared spectroscopy. Journal of Neuro-Oncology. 2016;127:463-72.
20. Elmi F, Movaghar AF, Elmi MM, Alinezhad H, Nikbakhsh N. Application of FT-IR spectroscopy on breast cancer serum analysis. Spectrochimica acta Part A, Molecular and biomolecular spectroscopy. 2017;187:87-91.
21. Li Q, Hao C, Kang X, Zhang J, Sun X, Wang W, et al. Colorectal Cancer and Colitis Diagnosis Using Fourier Transform Infrared Spectroscopy and an Improved K-Nearest-Neighbour Classifier. Sensors (Basel, Switzerland). 2017;17(12).
22. Beleites C, Neugebauer U, Bocklitz T, Krafft C, Popp J. Sample size planning for classification models. Analytica Chimica Acta. 2013;760:25-33.
23. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6(7):e1000097.