Rapid COVID-19 MS-based diagnostic test work plan

Summary

The aim of this project is to develop a rapid COVID-19 mass spectrometry-based diagnostic test that can be implemented at Schiphol airport or other places of need.

The project is divided into two phases: in phase 1 we will demonstrate the validity of the MS-based diagnostic approach, in phase 2 we will realize the MS-based platform at Schiphol airport for rapid COVID-19 diagnosis and upscale the throughput.

The platform does not require critical reagents and will be significantly faster and more cost-efficient than current PCR tests that currently cost 5.1.2b Euro/sample.

Work plan for Phase 1

Objectives/deliverables

Optimization of an integrated MS-based COVID-19 instrumentation and method suitable for use at Schiphol Airport for the two-step screening of 5.1.1c samples / hour. The instrumentation includes a DESI-RDa swab analyser device (Instrument I) introducing nasal swabs into the device automatically, analysing them, separating the positive swabs from the negative ones and preparing the positive ones for confirmatory analysis with a second instrument. The second instrument (Instrument II) is an MS/MS analyser with an automated sample preparation unit comprising sample clean-up (liquid extraction and solid-phase extraction), electrospray ionization and triple quadrupole mass analyser.

In phase 2, Instrument I will be deployed at the place where the swabs will be collected by medical professionals from the individual travellers selected based on certain criteria (flight, etc). Based on the results, the heads of the positive swabs will be cut off and placed into vials. The capped vials will be taken to the sample preparation unit of Instrument II.

In Instrument II, after solvent precipitation and extraction, trypsin-digestion will be performed at accelerated conditions for 10 min. Next, SPE clean-up is applied and then the extract directly analzyed with electrospray-MS/MS analysed using a qTRAP. Peptides of NCAP and SPIKE protein are monitored, and a human protein included for quality control purposes.

Response time

The negative result in estimated 90% of the cases will be available in principle within a minute following the sampling procedure. For the other cases, the result will be available within 20-25 minutes.

Such a rapid test will allow to provide rapid feedback to the passengers, still before boarding, or leaving the airport and travelling home.

Diagnostic accuracy

The recall rate of first tier testing is expected to be 10% (i.e., requiring measurement with Instrument II as second tier) at <1% false negative rate. The diagnostic accuracy of the second tier testing is expected to be >95% using nasopharyngeal PCR as a reference method.

Expected throughput

The initial throughput is estimated to be at least 5.1.1c samples/hour after installation at the airport in phase 2. We expect to be able to increase the throughput to more than 5.1.1c amples/hour within 2-4 weeks after installation. The costs per sample are estimated to be 5.1.1c Euro, and the results of the first tier.

Steps of work plan phase 1

1. *Sample collection at Amsterdam RAI test street and Charing Cross Hospital, London*

In addition to the swab used for diagnosis, a second, additional nasal/nasopharyngeal swab will be collected from subjects visiting test centers using knitted polyester swabs in a parallel fashion with COVID-19 RT-PCR screening. Currently ethical permission of duplicate swab collection and retrieving the screening data for anonymized samples at London is obtained, and for Amsterdam RAI requested via the Erasmus MC. The daily capacity of Amsterdam is > 5.1.1c samples/day (and expecting to include 5.1.1c 0/day), while London is approx 5.1.1c day. We aim to collect up to 5.1.1c samples in Amsterdam to have at least 5.1.1c positive nasal sabs, and 5.1.1c amples in London for initial tests and validation of our platform, of which we want to have significant part available by September 16, depending on ethical approval and the percentage of persons volunteering for a second nose swab.

2. *Analysis of swabs by DESI-MS metabolic profiling for validation of the method for instrument I*

Minimally 5.1.1c swabs containing at least 5.1.1c COVID-19 positive samples will be analysed by DESI-MS (note: numbers will vary with persons participating in study and by infection rate). The samples collected in London will be analyzed by DESI-MS at Imperial College London/Imperial College Healthcare NHS Trust (Charing Cross Hospital). The same DESI-MS system as in London will be installed at Leiden University to analyze samples collected at the RAI test street; London will serve as backup for samples from Amsterdam. The sensitivity, selectivity and between center stability will evaluated and method performance demonstrated.

3. *Analysis of swabs by targeted analysis of selected SARS-CoV-2 proteins for validation of the method for instrument II*

At least 5.1.1c swabs containing at least 5.1.1c COVID-19 positive cases will be analysed using a method comprising combined protein extraction and tryptic digestion followed by MS/MS analysis. Peptides derived from SPIKE and NCAP protein specific for SARS-CoV-2 protein will be analyzed, and a human albumin related peptide will be used for quality control. The results obtained will serve as a basis for validation and improving cut-off values. The method validation will demonstrate the correlation of protein signal with qPCR as the gold standard and report the sensitivity of this method compared to PCR.

4. *Development of swab introduction system*

An automated swab introduction system will be designed and the building of it initiated in phase 1. The system will feature one or more swab holder units, which will be automatically moved by the system for DESI analysis and – depending on the outcome of the first-tier assay – will be transferred for the second analysis of SARS-CoV-2 peptides.

Steps in the sample processing for the peptide analysis will also be automated, but may have steps that still require human intervention and will be further optimized for speed in phase 2.

5. *Software package*

The software will comprise data harvesting from the external PC of the analytical systems and matching this data with the data collected by the GGD. The software package will perform pre-processing and evaluation of the analytical data including the implementation of quality assurance and quality control measures. The system will feed the results into a platform agreed upon with the GGD. The software development will be initiated in phase 1.

Deliverables of phase 1:

Analysis platform for rapid COVID-19 MS-based diagnostic test comprising two steps, a metabolic profile and a targeted analysis of two SARS-CoV-2 proteins.

Validation of the COVID-19 MS diagnostic test of nose swabs with regards to false negative and false positive rate using PCR as reference; we will report accuracy, sensitivity and specificity of the method.

A time planning and budget plan for the of set-up and implementation at Schiphol airport will be delivered, including the initial expected throughput after installation, and the throughput 2-4 weeks later. Also, the and estimation of the costs per sample initially and after 2-4 weeks will be provided.

After approval of phase 2, the system will be set-up at Schiphol airport within 3-5 weeks. The system will be run at the beginning semi-automated, and will be during operation further automated, in various steps within 6-12 weeks after installations further automation will be achieved. The budget for phase 2 to realize the COVID-19 test at Schiphol airport is estimated to be 3 million Euro's.

The validation of the samples collected can be reported in the third week of September if we have enough dry swabs available of persons with SARS-CoV-2. We will do our utmost best to get dry swabs for validation as soon as possible and to finish validation as soon as possible.

Budget plan of phase 1

Items required for phase 1	kEuro
Salaries	5.1.2b
Materials	
Reference analysis	
Robot for LC-MS/MS	
Design and first part of robot for swabs	
Start automation of swab analysis	
Software integration & validation (part 1)	
Total	

In phase 1 several investments will be started to be able to set up the diagnostic COVID MS test at Schiphol airport.

The DESI-MS system will be supplied by Waters to Leiden University, and the system will be only paid in phase 2.

Project team

The project is led by [5.1.2e], Leiden Academic Centre for Drug Research, Leiden University, and members of his group will optimize the peptide profiling and implement and validate the DESI-MS method.

[5.1.2e] Imperial College, is sub-contractor for this project, and will optimize and validate the DESI-MS method with his team in London.

GGD Amsterdam (dr [5.1.2e], Dr. [5.1.2e] [5.1.2e] is the partner for sampling the swabs at RAI and to support the interpretation of the MS-based results obtained, and will supervise the planning of the implementation at Schiphol airport. Erasmus MC (dr. [5.1.2e] [5.1.2e], [5.1.2e]) is partner for supplying samples, and advising on the results obtained.

Intellectual property

The proposed MS-based COVID-19 diagnostic test is partly making use of a patent with prof. [5.1.2e] as lead and owned by [5.1.2e] [5.1.2h]
https://patents.google.com/[5.1.2h]

All IP necessary to realize and implement the set-up at Schiphol airport is available.