Diagnosis and Management of Febrile Illness using RNA Personalised Molecular Signature Diagnosis

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON54367

Source
ToetsingOnline

Brief title
DIAMONDS

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
Febrile illness, fever

Research involving
Human

Sponsors and support

Primary sponsor: Imperial College London
Source(s) of monetary or material Support: Europese Unie; Grant agreement ID: 848196

Intervention

Keyword: Diagnosis, Febrile illness, Infectious diseases, Molecular testing

Outcome measures

Primary outcome

DIAMONDS SEARCH

We will discover and validate RNA-based biomarkers that distinguish children and adults with infectious and inflammatory conditions.

DIAMONDS PILOT DEMONSTRATION

Practicality of personalised molecular signature diagnosis in clinical departments.

Secondary outcome

DIAMONDS SEARCH

We will collect detailed resource-use data on patients presenting to healthcare services with infectious and inflammatory illness. We will capture detailed information on the clinical presentation, patient management and final outcome, and we will correlate this information with biomarker findings.

DIAMONDS PILOT DEMONSTRATION

1. Demonstrate the practical utility of a prototype PMSD device in a real clinical setting, and its robustness

(sensitivity, specificity, predictive value).

2. Demonstrate the potential clinical impact of a PMSD device on time to

diagnosis, accuracy of diagnosis,

resource use, or inappropriate antibiotic use in the patients recruited.

3. Gather pilot data to support the introduction of PMSD testing as part of

clinical care in European countries.

WP9 will use these data to model the impact of PMSD on replacement of current

diagnostics, decision-making

for initial treatment, and admission, thus calculating patient and societal

benefits.

Study description

Background summary

Current management of patients presenting with fever is problematic due to the difficulty in identifying the relatively small number of patients with severe and life-threatening bacterial infections or inflammatory diseases amongst the more common self-limited viral illnesses. The current approach, based on exclusion of bacterial infection using microbiological cultures, presumptive treatment with antibiotics while results are awaited, and consideration of inflammatory conditions only after infection has been treated or excluded, results in delayed and incorrect diagnosis, excessive use of hospital beds and resources during prolonged periods of investigation, and inappropriate administration of antibiotics, contributing to the growing problem of antimicrobial resistance.
We propose a new Personalised Medicine approach to diagnosis of infectious and inflammatory diseases, based on individual RNA signatures detected in blood and will demonstrate the benefit of this approach to individuals and healthcare systems and its economic viability. The study is mainly focused on the pediatric population, but because we aim to also use the newly developed test to diagnose adults and because febrile illness in children often has a different etiology than in adults, we will include children as well as adults.

Study objective

Our proposal builds on 12 years of sustained EU funding, a consortium covering 11 European countries and 27
partners (with non-EU sites in African and two Asian populations to provide a global perspective) and our cuttingedge new research, which has demonstrated that molecular signatures can be used to diagnose a wide variety of
infectious and inflammatory diseases. In this proposal, we extend this work beyond state-of-the-art by developing a
novel molecular taxonomy of infectious and inflammatory disease, which will be used as the basis for
personalised diagnosis by identifying the specific *signature* of each disease using a novel approach, which we term
*Personalised Molecular Signature Diagnosis (PMSD). This approach uses each individual patient*s blood gene
expression to identify RNA signatures, which are specific to individual infectious or inflammatory diseases. In
collaboration with biotechnology and industrial partners, we will develop novel devices to rapidly detect the set of
gene transcripts required for PMSD, and evaluate their impact on improved patient diagnosis and treatment. We will
evaluate in a pilot demonstration the effect of the PMSD approach on health care resource utilization, costs, prediction
of disease severity and outcomes of febrile illness to provide the evidence base for introduction of PMSD in European
health systems.
We will address the following specific objectives:
1. To establish the European Diagnostic Transcriptomic Library based on data from over 15,000 patients with
infectious and inflammatory conditions. This curated RNA expression library will include data on clinical phenotype,
presentation, severity of illness and outcome and will include all ages, sexes, ethnicities, co-morbidities and include
the wide range of infectious and inflammatory conditions.
2. To use the data in the European Diagnostic Transcriptomic Library to develop a comprehensive molecular
taxonomy of infectious and inflammatory diseases based on RNA expression.
3. To use novel computational dimensionality reduction techniques, multinomial variable selection methods and costsensitive approaches to identify a minimal transcript signature for all common infectious and inflammatory
diseases as the basis for PMSD.
4. To evaluate the diagnostic performance of the transcripts required for PMSD using a high throughput
transcriptomic approach in an independent validation cohort of patients presenting with fever and inflammatory
conditions, and including challenging patient subgroups at the extremes of age, and patients with underlying co
morbidities.
5. To develop test platforms for rapid detection of PMSD transcripts in

collaboration with academic, industrial and
small and medium-sized enterprises (SME) partners, and to compare the detection performance of these devices to
existing RNA-detection technologies.
6. To select the best performing device for evaluation in a large-scale pilot demonstration of PMSD as compared
with current diagnostic practices in multiple EU health care settings.
7. To describe current diagnostic practices for febrile patients and preferences of end-users in multiple EU countries
as well as the economic and societal costs and to assess the acceptability and likely uptake of PMSD.
8. To use the data from the pilot demonstration and current practice (objective 7) to model the potential clinical and
health economic impact of PMSD in different EU national health care settings, and determine the impact of PMSD
implementation on health systems across Europe.
9. To disseminate the findings to regional, national and EU policy makers to demonstrate the benefits of a healthcare
model based on PMSD and advocate for widespread implementation of PM.

Study design

DIAMONDS consists of 2 parts using clinical data and/or samples of patients:

DIAMONDS SEARCH
The DIAMONDS consortium will acquire clinical data and RNA samples from subjects with febrile or inflammatory
disease through prospective recruitment of patients attending at the DIAMONDS clinical sites (inpatient and outpatient settings), as part of an observational study. We will supplement new patient recruitment with use of
samples from well-curated collections held by collaborators. In total, an estimated 5,000 samples from adults and
children will be added to the DIAMONDS sample biobank. The main objective of this clinical study is to obtain all
necessary RNA samples and clinical data required for the prototype PMSD device configuration and design.
For the recruiting study, subjects will have samples collected at presentation, at 48 hours and at convalescence
taken for research, taken at the same blood draw alongside their usual clinical tests. Other samples for diagnosis
including nasal secretions and urine will be collected as appropriate. Written consent and assent (if applicable) will
be obtained for all subjects taking part. The prospective data and samples will be merged with existing RNA
expression library and Biobank from previous studies performed by the consortium in which future research has
been agreed by participants, parents or guardian (EUCLIDS, PERFORM, EU-TB,

IRIS, GENDRES).

DIAMONDS PILOT DEMONSTRATION
A pilot demonstration study to evaluate the performance and impact of PMSD on the management of febrile
patients in EU healthcare settings. An observational study will be performed to evaluate whether introduction of
PMSD tests might influence time to diagnosis, accuracy of diagnosis, resource use, or inappropriate antibiotic use.
2,000 febrile patients at 8 selected high-enrolling hospitals, reflecting the spectrum of healthcare settings of the EU
partners will be recruited to test the PMSD platform in real clinical and diagnostic settings, and results will compare
with the standard of care for the diagnosis of febrile diseases.
Patients will have a single set of samples taken for research, taken at the same blood draw alongside their usual
clinical tests. Written consent and assent (if applicable) will be obtained for all subjects taking part.

Study burden and risks

Blood samples will be collected during a routine diagnostic blood sampling from a venapunction or central line. Capillary sampling is not possible. In addition a nasopharyngeal swab or throat swab wil be obtained. When urine or stool sampling is indicated, this will also be collected if leftover material is available. It is estimated that this way the burden for the child is very low and without any risks.

In the majority of the inclusions there will only be one timepoint for blood collection. But, if at 48-72 hours or at 28 days after the hospital visit or at discharge a routine diagnostic blood sampling will be done, then we also want tot collect blood for this study. It is possible that a patient develops multiple separate episodes of fever during admission or treatment, we would like to collect additional blood samples from these episodes, as there may be different underlying causes of fever. In case of early discharge, the patient or patients caregiver will be contacted after a maximum of 28 days to ask about the well-being of the patient.
From patients admitted to the ICU additional blood samples will be collected at t=24; t=48 and once a week after that with a maximum of 5 samples per patient.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

Patients admitted to clinical ward or presenting to the emergency room of one of the participating hospitals presenting with fever or clinical suspicion of infection in whom the attending clinician determines the need for blood sampling.

Exclusion criteria

Patients who do not give consent

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-03-2021
Enrollment:	1800
Type:	Actual

Ethics review

Approved WMO Date:	19-01-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	30-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-07-2022
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	23-08-2023
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT03502993
CCMO	NL75190.041.20