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Prediction of clinical outcomes using RNA velocity of the blood transcriptome

A method to predict the trajectory of acute illness or response to treatment using measurements of spliced and unspliced RNAs

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A method to predict the trajectory of acute illness or response to treatment using measurements of spliced and unspliced RNAs at a single point in time to predict future gene expression and thereby future clinical status.

Proposed Uses

Predicting trajectory of acute illness is one of the biggest challenges faced by clinicians and underlies many clinical decisions. It is essential to recognise patients who will rapidly deteriorate towards severe illness, but it is also important to avoid overtreatment and unnecessary hospital admission for those who are not at risk. This technology is likely to be commercialised as a method to triage / risk-stratify patients with a variety of acute illnesses to support clinical decision making, such as need for hospital admission and type of treatment. It may also be used to determine whether a given treatment is being effective.

Problem addressed

Clinicians are good at determining the current state and severity of illness in their patients. However, they are not so good at predicting what will happen to their patients over subsequent hours and days. Consequently, emergency departments and hospital wards are filled with patients with acute illnesses, admitted for close monitoring and empirical treatments whilst waiting to see if they get better or worse. A cautious approach is taken to avoid risk of missing patients who will deteriorate, but this overburdens healthcare systems and patients with unnecessary admissions and treatment. An RNA velocity-based test to accurately predict the trajectory of illness from a single blood sample at the time of initial presentation will provide objective evidence to support triage and clinical decisions in common acute illnesses like infections. Clinicians will be able to identify patients at highest risk of deterioration and provide early interventions, likely leading to better outcomes. Clinicians will also be able to identify patients at low risk of deterioration, suitable for discharge and outpatient management.

Technology Overview

Different illnesses, and different stages and severities of the same illness, are associated with differences in the expression of messenger RNA (mRNA) in cells and tissues. Nascent mRNA contains introns which are removed by splicing. Both unspliced and spliced transcripts are detectable in the transcriptome, and the ratio of unspliced to spliced transcripts for a particular gene can indicate whether the gene's expression is increasing or decreasing over timeframes of hours to days. Therefore, analysis of spliced and unspliced transcripts in sample at a single point in time can indicate the current state of an individual, and the rate of change (so called RNA-velocity) towards the expression profile of other clinical states.

We have shown that the blood transcriptome can be used to define disease and severity states of interest, and RNA-velocity can be calculated to predict future gene expression and future clinical state (https://doi.org/10.21203/rs.3.rs-5764288/v1). We have shown that it is possible to select small numbers of genes which are most informative and use only these as the basis for prediction. This opens the way to feasible translation onto platforms which can rapidly measure transcript abundance, and to clinical application as a precision medicine tool to predict disease trajectories for individual patients and to support clinical management decisions. Since differences in gene expression also exist between successfully treated and untreated conditions, the same principle can be applied to predict responses to treatment before they become clinically apparent.

Publication:

Full details of the method and initial evidence of application are available in this pre-print: https://doi.org/10.21203/rs.3.rs-5764288/v1

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Benefits

- Prediction of disease trajectories without the need for serial sampling or monitoring
- Potential for implementation on rapid laboratory or point of care test platforms
- Decision support for triage and management of acute illnesses
- Early recognition of patients at high risk of deterioration
- Identification of low-risk patients who can be managed more conservatively
- Early monitoring of response to treatment