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# ACCEPTED MANUSCRIPT

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## Is the hematocrit still an issue in quantitative dried blood spot analysis?

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- 1. Equally contributed

#### **HIGHLIGHTS**

- Hematocrit issues still prevent full acceptance of dried blood spot analysis.
- Many attempts to overcome this hematocrit bias have been proposed
- Whole spot analysis with volumetric application of blood should nullify this bias
- Devices generating dried plasma spots may avoid all hematocrit-related issues
- Strategies to measure the hematocrit of a dried blood spot have been proposed

#### **Abstract**

Hematocrit-related issues remain a major barrier for (regulatory) acceptance of the classical dried blood spot (DBS) analysis in the bioanalytical and clinical field. Lately, many attempts to cope with these issues have been made. Throughout this review, an overview is provided on new strategies that try to cope with this hematocrit effect (going from avoiding to minimizing), on methods estimating a DBS volume, and on methods estimating or measuring the hematocrit of a DBS. Although many successful strategies have been put forward, a combination of different technologies still provides the most complete solution. Therefore, further efforts and the availability of a straightforward guideline for analytical and clinical method validation should help to overcome the hurdles still associated with DBS sampling.

#### **Keywords**

Hematocrit; Dried Blood Spot; Alternative sampling

## 1. Introduction

In the field of quantitative DBS analysis, many attempts to cope with the hematocrit (Hct) issue have been made over the past few years. The lack of a simple, universally applicable approach to overcome the Hct issue has been a main hurdle for the widespread implementation of this sampling technique in the clinical field. The potential applications are numerous and distributed over many different areas, amongst which newborn screening, therapeutic drug monitoring,

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