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Patient self-testing of white blood cell count and differentiation: A study of feasibility and measurement performance in a population of Danish cancer patients

Running title: Cancer patients can test own white blood cells

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Conflict of Interest

All authors declare no financial or non-financial competing interests in relation to the work described.

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Setting and ethics

The study was conducted at the Department of Oncology, Odense University Hospital, Denmark, covering the Region of Southern Denmark, one of five highly specialized oncology departments in Denmark with 3.600 admissions and 126.000 ambulatory visits annually (2016). The hospital is part of the Danish tax-funded universal healthcare system. The study was approved by the National Committee on Health Research Ethics project (id S-20160184) and the Danish Data Protection Agency via the Region of Southern Denmark (id 2012-58-0018). The study was performed in accordance with the Declaration of Helsinki.

Additional information

Authorship

TOM, JH and LF-H designed the study. TOM was in charge of the data collection. TOM and JS analysed the data and JH and LF-H provided advice on the data analysis. All authors contributed to the interpretation of data. TOM drafted the manuscript. All authors participated in the revision of the manuscript and all authors have read and approved the final manuscript.

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Article type : Original Article

Title

Patient self-testing of white blood cell count and differentiation: A study of feasibility and measurement performance in a population of Danish cancer patients

Keywords

Medical Oncology, Patient education, Point-of-care testing, febrile neutropenia, antineoplastic agents, aged, patient comfort.

Abstract

1 *Objective*

2 Patients in anticancer treatment with a known side effect of neutropenia are monitored closely with laboratory
3 measurements of white blood cell count (WBC) and differentiation. This study sought to evaluate measurement
4 properties and feasibility of patients' self-testing using a Point-of-care Testing (POCT) device

5
6 *Methods*

7 A prospective feasibility and measurement study comparing standard measurement of cancer patients' WBC and
8 neutrophil count with POCT measurements. The study included 60 outpatients and 22 inpatients from a
9 department of oncology at a university hospital

10
11 *Results*

12 Patients successfully conducted 106 measurements using the POCT device. 46% of the patients were >70 years.
13 Weighted Deming regression analysis showed minimal yet significant proportional bias between methods, with
14 POCT increasingly underestimating both total WBC and neutrophils compared to the standard method the higher
15 the count. Over 90% of patients reported they were willing and considered themselves able to use the POCT
16 device at home

17
18 *Conclusions*

19 The instrument can be used for self-testing of post anticancer leucopenia and has sufficient measurement
20 precision for patient risk stratification. Patients are able and willing to conduct measurements including when in
21 a situation of acute illness. Further studies are needed to confirm safety and value within patients own home

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1 Introduction

2

3 A 30% increase in cancer incidence is anticipated over the next 20 years and more than 90% of the estimated
4 future increase is expected to be in the population of those 70-years- old and older(Ewertz et al., 2016). Hence,
5 with an increasing cancer population and within this an increasing elderly and more vulnerable population, the
6 economic burden of cancer is rapidly increasing(Tangka et al., 2010). One of the resource demanding procedures
7 is keeping patients safe during anticancer treatment. Most patients today are followed in hospital outpatient
8 clinics with multiple blood tests, physical evaluations, registration and treatment of possibly life-threatening
9 adverse effects, all in order to provide a safe antineoplastic treatment and supportive care. Due to increased
10 comorbidity and polypharmacy, elderly patients are at a higher risk of adverse effects(M. Sharma, Loh,
11 Nightingale, Mohile, & Holmes, 2016), including febrile neutropenia(Legrand et al., 2012). Therefore, treatment
12 in this population often requires more extensive monitoring and supportive care, including shorter or longer
13 hospital admissions(Legrand et al., 2012).

14

15 Monitoring the white blood cell (WBC) count is essential in many cancer patients since a low neutrophil count
16 (neutropenia) can be a dose-limiting toxicity of systemic anticancer therapy and life-threatening when
17 complicated by fever and sepsis(Klastersky & Paesmans, 2013; Legrand et al., 2012). All patients in anticancer
18 treatment with a known side effect of neutropenia are therefore monitored closely(Klastersky & Paesmans,
19 2013). A white blood cell count including a neutrophil count is required prior to initiating or continuing
20 treatment or in cases of acute fever with suspected neutropenia. A neutrophil count is currently obtained by
21 venepuncture by a health-care professional, requiring the patient to visit their general practitioner or a hospital
22 laboratory facility. A point-of-care solution for measurement of leucocyte and differentiation may benefit both
23 patients and oncologists in several ways. The main advantage is the possibility of testing without having to go to
24 the nearest hospital i.e. prior to treatment or when experiencing an episode of fever during treatment. In case of
25 fever a normal white blood cell neutrophil count measured by the patient at home, may even prevent an acute
26 hospital admission. Also, a low WBC and neutrophil measured at home could spare the patient an outpatient
27 visit. Hence it would benefit patients and reduce pressure on the hospital outpatient clinics.

28

29 The HemoCue® WBC DIFF is a point-of-care-testing (POCT) instrument for measurement of leucocyte and
30 differentiation. The technology is CE marked and currently approved for use by healthcare personnel, i.e. general
31 practitioners. It has shown acceptable reliability and reproducibility and good correlation when compared to
32 standard measurement methods in different patient populations (Bogers, Bui, Herruer, & Cohen, 2015; Bui,
33 Bogers, Cohen, Njo, & Herruer, 2016; Ivaska, Niemela, Leino, Mertsola, & Peltola, 2015; Karawajczyk, Haile,
34 Grabski, & Larsson, 2017; Spaeth, Shephard, McCormack, & Sinclair, 2015). Yet none of the studies have tested
35 cancer patients or patients with severe neutropenia or febrile neutropenia. Furthermore, the studied WBC DIFF
36 POCT was developed for use by professionals and therefore the solution has not yet been tested for use by
37 patients for self-testing white blood cell count.

38

1 This study aims to 1) evaluate feasibility; including acceptability, demand and practicality of cancer patients
2 using a POCT (WBC DIFF) to self-test white blood cell counts, as well as possible related differences between
3 younger and older cancer patients 2) evaluate the measurement properties of the POCT WBC DIFF unit when
4 used by cancer patients for self-testing, compared to standard laboratory tests.
5

6 **Methods**

7 **Setting and ethics**

8 The study was conducted at the Department of Oncology, Odense University Hospital, Denmark, covering the
9 Region of Southern Denmark, one of five highly specialized oncology departments in Denmark with 3.600
10 admissions and 126.000 ambulatory visits annually (2016). The hospital is part of the Danish tax-funded
11 universal healthcare system. The study was approved by the National Committee on Health Research Ethics
12 project (id S-20160184) and the Danish Data Protection Agency via the Region of Southern Denmark (id 2012-
13 58-0018). The study was performed in accordance with the Declaration of Helsinki.
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16 **Study design**

17 We performed a feasibility and measurement property study of patients' capillary blood self-testing when using
18 a POCT vs. standard laboratory venous blood test to measure total white blood cell count and neutrophil counts.
19 The POCT device was chosen by the test centre of the Innovative high-tech cancer treatment Denmark-Germany
20 project (InnoCan) among other potential POCT devices. The specific POCT unit was chosen for further clinical
21 testing based on its ease of use and the fact that it carried the CE mark for use by professionals. The specific
22 POCT technique is based on cell counting by image analysis on a small volume of capillary blood (10 µl) drawn
23 from e.g. a finger prick. The red blood cells are lysed in the cuvette and the nuclei of the white cells are stained.
24 37 images are taken of the stained white cells and the cells are identified. The number of cells is counted by
25 image analysis in the analyzer and the concentration calculated from the 2 µl (of the 10 µl) volume in which the
26 cells were examined (HemoCue, 2017). The unit also provides analysis of lymphocytes, monocytes, eosinophils
27 and the basophils, yet in this study these were not recorded since counts are considered too low to be measured
28 reliably, and these measures are seldom used in risk stratification of solid tumours. The standard laboratory test
29 to measure total White Blood Cell count and neutrophil count on venous blood sample used is SYSMEX XN-1000.
30 An automated haematology analyser using direct current sheath flow for red cell count, haematocrit and
31 impedance platelet count. Fluorescence flow cytometry is used for leucocyte differential, nucleated red blood
32 cells, reticulocytes and fluorescence platelet count (Briggs, Longair, Kumar, Singh, & Machin, 2012).
33
34
35

36 **Study population**

37 The study included both in- and outpatients to test feasibility, acceptability and measurement properties in both

1 acute and ambulatory settings. In both the inpatient and outpatient groups, the aim was to have a minimum of
2 1/3 of the patients being >70-years-old. Outpatients were recruited when queuing for standard laboratory blood
3 tests as part of monitoring their antineoplastic treatment. All outpatients measured once. Inpatients were
4 included when admitted acute to the department with suspected febrile neutropenia after anticancer treatment.
5 All inpatients measured daily (only weekdays) during their admission. Inclusion criteria were patients aged 18
6 years or above, diagnosed with a solid tumour and in active antineoplastic treatment. Patients were excluded if
7 they were unable to understand or read Danish or if they were unable to handle the lancet and/or the cuvettes.
8 Patients were recruited when visiting for lab test or upon admission to the department.

10 Testing - First test *all patients*

11 After providing informed consent for the study the patients were instructed by the local biomedical laboratory
12 scientist in the use of the POCT instrument. Instruction included a simple stepwise laminated illustrative guide
13 (Figure 1) to use as a table place mat and one guided demonstration by the biomedical laboratory scientist.

14 The illustrated stepwise guide was developed using an iterative design process lead by study personnel from the
15 Design School Kolding, Denmark. When the patient reported ready the self-testing began. The instruction and
16 self-testing were observed by trained study personnel (observer). The observer collected feasibility data on
17 turnaround time (TAT) from test to the results – recorded the WBC diff test result displayed on the POCT for the
18 measurement calculation– and placed a subjective feasibility and acceptability judgment on the patient's ability
19 to perform future self-testing by answering three questions regarding the test, two questions regarding
20 feasibility of using the instrument (Table 1, observers question one and three) and one question regarding
21 patients acceptability of the instrument (Table 1, observers question two). A predefined acceptable average test
22 time limit was set at a maximum of 7 minutes.

24 The POCT either displays the result as a white blood cell count including differentiation, a censored result (if
25 total WBC was outside measurement range of WBC above $30.0 \times 10^9 /L$ or less than $0.3 \times 10^9 /L$ – also if total
26 WBC is below 1 then total WBC is displayed with no differentiation) or as an error code indicating a
27 measurement failure. In all cases the result was noted. In case of error codes, the error was recorded and then
28 the general user instructions were followed to correct the error if possible. A predefined acceptable rate of
29 measurement failure and error codes (in total) was set at a maximum of 10%. After the self-testing, the
30 biomedical laboratory scientist drew the standard venous blood test to be used for comparison. Finally, the
31 observer asked the patient a few questions regarding patients' experience with the instruction and self-testing,
32 including patients' attitude and acceptability toward future self-testing (Table 1, patients questions one and
33 two). Prior to initiating the study, we defined a positive attitude in minimum 75% of the patients as an
34 acceptable rate to initiate further studies within patients' home. Given feasibility and measurement
35 requirements were met.

37 Testing – *Inpatients* following days

38 The inpatients were, after the initial self-testing as described above, asked to store the POCT unit including the

1 instruction material at their bedside. In the following admission days an observer would approach the patient
2 and ask them to perform an observed self-test. These tests were guided by the written material from the initial
3 instruction and with the possibility to ask for assistance from the observer but did not include a prior
4 demonstration. As on the first test day, a biomedical laboratory technician drew the standard venous blood test
5 after the self-testing.

6 7 **Statistical methods**

8 All data were entered to a secure database within the OPEN network using RedCap. All data were analysed using
9 R statistics. Descriptive statistics were used in evaluating demand, acceptability and feasibility. Differences
10 between younger and older patients regarding their subjective POCT experience and their ability to perform the
11 POCT measurements themselves were evaluated using chi-squared tests. The level of agreement between
12 standard laboratory measurements and POCT measures were assessed using Bland-Altman plots of
13 measurement differences (Bland & Altman, 1996). Grading of leucopenia (counts below $3.0 \cdot 10^9/L$) and
14 neutropenia (counts below $1.5 \cdot 10^9/L$) is commonly assessed using the Common Terminology Criteria for
15 Adverse Events (CTCAE) ("Common Terminol. Criteria Advers. Events Version 5.0," 2017) since intervals
16 between grades of leucopenia and neutropenia are respectively 1.0 and 0.5, we defined acceptable limits of
17 agreement as $\pm 1.0 \cdot 10^9/L$ and $\pm 0.5 \cdot 10^9/L$. We used weighted Deming regression to test the statistical significance
18 of systematic- and proportional disagreements between the laboratory and the POCT measurement, considering
19 known measurement error in both methods. The measurement error for each method was quantified using the
20 test-retest coefficient of variation (CV). For the SYSMEX measures, the CVs have been calculated from repeated
21 measurements on the blood samples. From the daily production the samples at concentrations covering the
22 measuring interval were chosen, tested 10 times and mean and CV calculated: 2.7% @ $2.9 \cdot 10^9/L$, 2.0% @ 6.8
23 $10^9/L$ and 1.5% @ $16.1 \cdot 10^9/L$. For the POCT, the CVs reported by the manufacturer was used. Repeated
24 measurements on inpatients from day two until discharge were omitted from the analysis to meet the
25 independence assumption of the Deming regression. Measures of leucocytes below 0.3 and above 30 were
26 removed due to the censoring function of the POCT device.

27 28 **Results**

29 The study included 60 outpatients and 22 inpatients, 36 female and 46 male patients. 38 (46%) patients were
30 older than 70 years and 44 (54%) younger. Patients' mean age was 67 years, range 39-86 years. All patients
31 were diagnosed with solid tumours and receiving active anticancer treatment within the department. No
32 patients were excluded due to inability to handle the lancet or the cuvettes, but one patient was excluded due to
33 insufficient Danish language skills.

34 35 **User observations and feasibility**

36 Outpatients measured once and inpatients once a day (weekdays only), this resulting in 46 single POCT
37 measurements by inpatients and 106 single POCT measures in total. None of the patients failed to complete the

1 filling and placement within the instrument of the of the lancet. 95 of 106 (90%) measures were successful on
2 the first try the other 11 (10%) measures yielded an error code. All error codes were non-critical, with the most
3 common error being code 04 (Acceptable light cannot be achieved – suggested solution; repeat measurement). In
4 six cases a second measure yielded a result (yet these results were disregarded in the analysis). No significant
5 difference was observed between younger and elderly patients on the number of POCT error codes, hence
6 successful tests. Mean test time was 4 minutes and 19 seconds, (range 1-16 minutes). Table 1 show the
7 subjective judgments placed by the observer on the patients' ability to conduct self-testing and the patients'
8 answers on their own ability to conduct self-testing within their own home, as well as patients' previous
9 experience with self-testing.

10
11 A majority of the patients were judged comfortable conducting the test (93%) and 57% were able to conduct
12 self-testing by using the illustrative guide without any other help after just *one* demonstration. The other 43%
13 needed guidance: oral instructions from the project staff or direct assistance in opening the cuvette, using the
14 lancet or operating the device. 87% of the patients were judged able to conduct self-testing within their own
15 home following further instruction, and 96% of patients reported they were willing and considered themselves
16 able to do so following further instruction. Again, there was no significant difference between the elderly and
17 younger patients regarding judgment by observer or answers on patients' ability and willingness to perform the
18 test. Also, there was no significant difference between elderly and younger patients in their prior experience
19 with self-testing.

21 Measurement properties

22 Point-of-care measurements of the POCT WBC DIFF unit of total number of WBC were compared to standard
23 measurement of the hospital lab unit.

24 A total of 106 single measurements were conducted. The standard white blood cell measures from the SYSMEX
25 XN-1000 unit ranged from $0.61 \times 10^9/L$ to $53.7 \times 10^9/L$ with a mean of $5.8 \times 10^9/L$. We registered 43 measures
26 below normal, 48 measures within the normal range (3.5-8.7) and 15 above normal. Standard measures of
27 neutrophil counts ranged from $0 \times 10^9/L$ to $15.5 \times 10^9/L$ with a mean of $3.1 \times 10^9/L$.

28 The analysis of measurement properties requires independent, non-censored measurement pairs. Among the 82
29 independent measurement pairs (60 outpatients plus 22 inpatients) ten pairs were excluded due to error of the
30 POCT device and seven pairs due to censoring of high and low measurements by the device, leaving 65 complete
31 and independent measurement pairs suitable for analysis. All censored results were correctly censored when
32 comparing the POCT result with the SYSMEX result.

33
34 The Bland-Altman analysis of differences between all complete pairs of leucocytes measures showed a small but
35 significant systematic disagreement between methods, with point-of-care yielding measures which on average
36 are lower by -0.37 (95% CI -0.63, -0.13) (Figure 2a). When examining the below average ($<3.5 \times 10^9/L$) measures
37 of leucocytes there is a small, non-significant systematic disagreement between methods with POCT yielding
38 measurements which on average are lower by -0.11 (95% CI -0.3, 0.09) (Figure 2b). Limits of agreement are

1 within the predefined accepted range of $\pm 1.0 \times 10^9/L$ (Fig 2b), with no significant trend or inconsistency of
2 variability across the plot.

3
4 Weighted Deming regression analysis on total WBC showed minimal yet significant proportional bias of 0.92
5 (0.86, 0.97) between methods (Figure 3b), with POCT increasingly underestimating the WBC compared to the
6 standard method the higher the count (Figure 3a). When examining the below average ($< 3.5 \times 10^9/L$) we found
7 no significant proportional bias or difference (Figure 3c).

8
9 Bland-Altman plots for the neutrophil counts revealed a small significant systematic disagreement between both
10 methods with POCT yielding measurements which on average are lower by -0.38 (-0.64, -0.13) compared to
11 standard measures (Figure 4a). When examining the below average neutrophil counts ($< 1.5 \times 10^9/L$) we found a
12 non-significant systematic difference of 0.05 (-0.11, 0.21) (Figure 4b). Limits of agreement are within the
13 accepted range of $\pm 0.5 \times 10^9/L$, with no significant trend or inconsistency of variability across the plot (Figure
14 4b).

15
16 Weighted Deming regression analysis on neutrophil counts showed a significant systematic difference of 0.23
17 (0.13, 0.40) and proportional bias of 0.86 (0.79, 0.91) between methods (Figure 5b) with increasing
18 underestimation of the higher the neutrophil count (Figure 5a). The regression analysis conducted on the
19 neutrophil counts below average ($< 1.6 \times 10^9/L$) showed significant systematic difference of 0.23 (0.11, 0.66) and
20 a non-significant proportional bias of 0.84 (0.37, 1.11) (Figure 5c).

21 22 **Discussion**

23 Total WBC count and, absolute Neutrophil Count (ANC) are monitored following induction of anticancer therapy
24 to adjust doses and plan treatment course but are also used to assess the risk of neutropenic fever. All cancer
25 patients at risk are therefore closely monitored especially when they experience fever and prior to initiating new
26 treatment cycles. Monitoring currently takes place at planned visits to outpatient clinics, or as acute admissions
27 in the case of fever episodes, and all blood samples are examined at hospital laboratories.

28
29 We found that patients, using a small POCT analyser, can obtain clinically useful and reliable WBC- and
30 neutrophil counts and data that are just as useful as those produced by larger hospital analysers, to assess if
31 patients have normal or below normal WBC and neutrophil counts. Hence, ability to stratify patients for further
32 examination prior to initiating /reinitiating antineoplastic treatment or treatment of suspected infection.

33
34 Our study showed the total WBC measurements and neutrophil counts of the POCT on average are respectively
35 lower by -0.37 and $-0.38 \times 10^9/L$ compared to the standard measurements with increasing underestimation for
36 measurements in the higher range. This increasing underestimation is in accordance with what is reported by
37 the manufacturer (HemoCue, 2017) and prior studies of the specific POCT WBC DIFF measurement
38 properties (Bui et al., 2016; Heffler, Crimi, & Crimi, 2017; Ivaska et al., 2015; Karawajczyk et al., 2017; Osei-

1 Bimpong, Jury, McLean, & Lewis, 2009; Spaeth et al., 2015).

2

3 Leucocyte and neutrophil counts are used through the entire measuring range, but identification and grade of
4 leucopenia/neutropenia are of greatest importance for cancer patients, as this is used for risk stratification when
5 receiving antineoplastic treatment. We therefore closely examined the below average counts: WBC range 0-3.5 x
6 $10^9/L$ and neutrophil range 0-1.5 $\times 10^9/L$. The measurements of WBC below 3.5 $\times 10^9/L$ are not significantly
7 different from the standard measures and has acceptable variability. Data show neutrophil measures in the
8 lower regions, especially below 1 are quite unreliable, yet this is also the case with standard measurement
9 methods for WBC differentiation(Briggs et al., 2012). One of the factors contributing to this is, that the immature
10 granulocytes in the samples make up a greater fraction of cells when measures are low and, in this case, the two
11 different measurement technologies (POCT is based on image recognition and standard lab on flowcytometry)
12 also have slightly different cut offs for the different classes of cells. But in a clinical setting, patients with fever
13 and measures of WBC below 3.5 $\times 10^9/L$ would likely be evaluated in hospital, with standard laboratory
14 measures and physical evaluation by a physician. The use of the POCT will therefore be for stratification of
15 patients with normal WBC counts vs. low counts. Since, patients with fever and normal counts are at lower risk
16 and may be treated within their homes with oral antibiotics(Talcott et al., 2011). In the case of measurement
17 prior to antineoplastic treatment even a WBC count of below normal in combination of a normal neutrophil
18 count would be acceptable.

19

20 At neutrophil counts above 1.5 we found reliable results, yet the POCT starts underestimating as with WBC.
21 There could be several reasons for this underestimation. One could be due to sampling/pre-analytical conditions
22 that are known to influence the measurements. For instance, the techniques used, and the order of the blood
23 drops has also been shown to affect measurements(Yang et al., 2001). Furthermore the chosen reference
24 instruments could also affect the comparison as there are minor differences in ANL and ANC(Meintker,
25 Ringwald, Rauh, & Krause, 2013).

26

27 However, a slight systematic underestimation of the WBC and neutrophil counts during leucopenia will not
28 expose the patients to any danger as it will lead to a slight overestimation of the risk and subsequently admission
29 to the hospital for physical examination and lab re-evaluation(Klustersky & Paesmans, 2013)(Talcott et al.,
30 2011). On the contrary, an overestimation could be a potential safety hazard with a risk of overlooking
31 neutropenia and therefore underestimating the need for treatment of side effects or the risk of continuing the
32 anticancer treatment.

33

34 Our study is lacking samples with elevated WBC and neutrophil counts. In contrast, a measuring error in
35 leucocytosis or neutrocytosis will have minor or no clinical importance in the clear majority of the clinical
36 settings and is often a result of treatment with leucocyte stimulating agents or a corticosteroid.

37

38 Some of the challenges regarding the random variability presumably are due to that the instrument has been

1 developed for doctors' offices in order to diagnose infections in non-leucopenic patients. Therefore, the
2 instrument has been developed with a 10 µl chamber for the sample. However, only cells 2 µL are counted. In
3 severe leucopenia e.g. $1.0 \times 10^9/L$ only 300 cells will be counted and less at lower leucocyte counts. At this low
4 number the statistically uncertainty begins to be a major component. Therefore, it may be an advantage in the
5 future if POCT instruments for home monitoring of post chemotherapy patients counted the cells in a larger
6 volume.

7
8 We found that given proper instructions both younger and elderly cancer patients were able to deliver safe and
9 high-quality self-monitoring of WBC DIFF within the hospital. For many years self-monitoring has been the
10 backbone of diabetes treatment, helping patients achieve and maintain target blood glucose levels to reduce the
11 risk of diabetes related complications(Bailey et al., 2016). Also, self-monitoring of anti-coagulation therapy(P.
12 Sharma et al., 2015) and more recently, irritable bowel disease(Vinding et al., 2016) has become feasible.

13
14 We found, in this study that cancer patients are eager to learn how to use the POCT instrument, and more than
15 90% expressed immediate interest and a positive attitude towards evaluating the benefit of taking the
16 instrument home. Meeting our predefined acceptability measure of minimum 75% by far. Patients in the study
17 were able to measure using the POCT, both in the calm ambulatory setting and in the acute setting when
18 experiencing acute illness, this with no difference in success rate, and within an acceptable time of 4 minutes on
19 average. Meeting our pre-set acceptability measures. This is again similar to what has been seen for other self-
20 monitoring programs including point-of-care self-monitoring of blood sugar levels(Bailey et al., 2016) and
21 coagulation status(P. Sharma et al., 2015).

22 Yet future trials need to explore if this can be translated into safe home monitoring of hematologic toxicity and
23 even into full management of antineoplastic therapy within the patients' homes.

24
25 One concern is that the error rate of 10% on first measures by this POCT, reported in this study, could potentially
26 be a barrier towards efficient home measurement causing patients distress and extra trips to the hospital for
27 evaluation of the POCT instrument.

28
29 Our study has also uncovered an unexpected challenge. Currently all instruments are only approved to be
30 handled by healthcare professionals. Therefore, even though our study has clearly demonstrated that the
31 instruments delivers an acceptable analytical quality and that measurement is feasible and acceptable by
32 patients, there are major regulatory challenges that need to be addressed and solved, before this technology can
33 be implemented in routine setting.

34
35 Thus, it seems likely that self-monitoring of WBC Diff post anti-cancer treatment can be introduced. Initially this
36 must be done as part of carefully designed trials under strict surveillance and constant monitoring, so that the
37 safety of these regimes can be evaluated. However, it seems likely that like the above-mentioned programs self-
38 monitoring in oncology will be beneficial for both patient and hospital. For the patient and or the relatives, it

1 could be empowering to self-manage the blood test and the responsibility hereof and maybe provide a feeling of
2 control of their disease and treatment. Furthermore, reducing the time spent on patients commuting back and
3 forth to blood sampling/outpatient clinics will allow them to live a more *normal* life, less impacted by their
4 disease. It may also play into other initiatives such as “home anticancer therapy”. For the hospitals, only
5 admitting those in need could free up time in the outpatient clinics in cases where therapy can be postponed
6 prior to the patients' appointment.
7
8

9 **Conclusion**

10 The POCT studied can be used for self-testing of leucopenia induced by antineoplastic therapy. The instrument
11 has sufficient precision for patient risk stratification when operated by patients. Measurement is both feasible
12 and acceptable in younger and elderly patients. Further studies are needed to confirm acceptability, feasibility
13 and value of self-monitoring within patients own homes as well as assess unforeseen drawbacks associated with
14 patients' in-home self-monitoring.

15 **Additional information**

16 **Authorship**

17 TOM, JH and LF-H designed the study. TOM was in charge of the data collection. TOM and JS analysed the data
18 and JH and LF-H provided advice on the data analysis. All authors contributed to the interpretation of data. TOM
19 drafted the manuscript. All authors participated in the revision of the manuscript and all authors have read and
20 approved the final manuscript.
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Reference List

Bailey, T. S., Grunberger, G., Bode, B. W., Handelsman, Y., Hirsch, I. B., Jovanovic, L., ... American College of, E. (2016). American Association of Clinical Endocrinologists and American College of Endocrinology 2016 Outpatient Glucose Monitoring Consensus Statement. *Endocr Pract*, 22(2), 231–261. <https://doi.org/10.4158/EP151124.CS>

Bland, J. M., & Altman, D. G. (1996). Measurement error and correlation coefficients. *BMJ (Clinical Research Ed.)*. <https://doi.org/10.1136/bmj.313.7048.41>

Bogers, J. P., Bui, H., Herruer, M., & Cohen, D. (2015). Capillary compared to venous blood sampling in clozapine treatment: patients and healthcare practitioners experiences with a point-of-care device. *Eur Neuropsychopharmacol*, 25(3), 319–324. <https://doi.org/10.1016/j.euroneuro.2014.11.022>

Briggs, C., Longair, I., Kumar, P., Singh, D., & Machin, S. J. (2012). Performance evaluation of the Sysmex haematology XN modular system, 1024–1030. <https://doi.org/10.1136/jclinpath-2012-200930>

Bui, H. N., Bogers, J. P., Cohen, D., Njo, T., & Herruer, M. H. (2016). Evaluation of the performance of a point-of-care method for total and differential white blood cell count in clozapine users. *Int J Lab Hematol*, 38(6), 703–709. <https://doi.org/10.1111/ijlh.12561>

Common Terminology Criteria for Adverse Events Version 5.0. (2017).

Ewertz, M., Christensen, K., Engholm, G., Kejs, A. M., Lund, L., Matzen, L. E., ... Academy of Geriatric Cancer, R. (2016). Trends in cancer in the elderly population in Denmark, 1980-2012. *Acta Oncol*, 55 Suppl 1, 1–6. <https://doi.org/10.3109/0284186X.2015.1114678>

Heffler, E., Crimi, C., & Crimi, N. (2017). The accuracy of the HemoCue WBC DIFF in assessing blood eosinophils depends on the clinical setting and medical condition. *Acta Paediatr*, 106(10), 1706. <https://doi.org/10.1111/apa.13979>

HemoCue. (2017). No Title. Retrieved from <https://www.hemocue.dk/da-dk/produkter/white-blood-cell-count/wbc-diff>

Ivaska, L., Niemela, J., Leino, P., Mertsola, J., & Peltola, V. (2015). Accuracy and feasibility of point-of-care white blood cell count and C-reactive protein measurements at the pediatric emergency department. *PLoS One*, 10(6), e0129920. <https://doi.org/10.1371/journal.pone.0129920>

Karawajczyk, M., Haile, S., Grabski, M., & Larsson, A. (2017). The HemoCue WBC DIFF system could be used for leucocyte and neutrophil counts but not for full differential counts. *Acta Paediatr*, 106(6), 974–978. <https://doi.org/10.1111/apa.13790>

Klastersky, J., & Paesmans, M. (2013). The Multinational Association for Supportive Care in Cancer (MASCC) risk index score: 10 years of use for identifying low-risk febrile neutropenic cancer patients. *Support Care Cancer*, 21(5), 1487–1495. <https://doi.org/10.1007/s00520-013-1758-y>

Legrand, M., Max, A., Peigne, V., Mariotte, E., Canet, E., Debrumetz, A., ... Azoulay, E. (2012). Survival in

- 1 neutropenic patients with severe sepsis or septic shock. *Crit Care Med*, 40(1), 43–49.
2 <https://doi.org/10.1097/CCM.0b013e31822b50c2>
- 3 Meintker, L., Ringwald, J., Rauh, M., & Krause, S. W. (2013). Comparison of automated differential blood cell counts
4 from abbot sapphire, siemens advia 120, beckman coulter DxH 800, and sysmex XE-2100 in normal and
5 pathologic samples. *American Journal of Clinical Pathology*. <https://doi.org/10.1309/AJCP7D8ECZRXXGWCG>
- 6 Osei-Bimpong, A., Jury, C., McLean, R., & Lewis, S. M. (2009). Point-of-care method for total white cell count: an
7 evaluation of the HemoCue WBC device. *Int J Lab Hematol*, 31(6), 657–664. <https://doi.org/10.1111/j.1751->
8 [553X.2008.01093.x](https://doi.org/10.1111/j.1751-553X.2008.01093.x)
- 9 Sharma, M., Loh, K. P., Nightingale, G., Mohile, S. G., & Holmes, H. M. (2016). Polypharmacy and potentially
10 inappropriate medication use in geriatric oncology. *J Geriatr Oncol*, 7(5), 346–353.
11 <https://doi.org/10.1016/j.jgo.2016.07.010>
- 12 Sharma, P., Scotland, G., Cruickshank, M., Tassie, E., Fraser, C., Burton, C., ... Brazzelli, M. (2015). The clinical
13 effectiveness and cost-effectiveness of point-of-care tests (CoaguChek system, INRatio2 PT/INR monitor and
14 ProTime Microcoagulation system) for the self-monitoring of the coagulation status of people receiving long-term
15 vitamin K antagonist t. *Health Technol Assess*, 19(48), 1–172. <https://doi.org/10.3310/hta19480>
- 16 Spaeth, B. A., Shephard, M. D., McCormack, B., & Sinclair, G. (2015). Evaluation of HemoCue white blood cell
17 differential counter at a remote health centre in Australia's Northern Territory. *Pathology*, 47(1), 91–95.
18 <https://doi.org/10.1097/PAT.0000000000000202>
- 19 Talcott, J. A., Yeap, B. Y., Clark, J. A., Siegel, R. D., Loggers, E. T., Lu, C., & Godley, P. A. (2011). Safety of early
20 discharge for low-risk patients with febrile neutropenia: A multicenter randomized controlled trial. *Journal of*
21 *Clinical Oncology*, 29(30), 3977–3983. <https://doi.org/10.1200/JCO.2011.35.0884>
- 22 Tangka, F. K., Trogdon, J. G., Richardson, L. C., Howard, D., Sabatino, S. A., & Finkelstein, E. A. (2010). Cancer
23 treatment cost in the United States: Has the burden shifted over time? *Cancer*. <https://doi.org/10.1002/cncr.25150>
- 24 Vinding, K. K., Elsberg, H., Thorkilgaard, T., Belard, E., Pedersen, N., Elkjaer, M., ... Munkholm, P. (2016). Fecal
25 Calprotectin Measured By Patients at Home Using Smartphones--A New Clinical Tool in Monitoring Patients
26 with Inflammatory Bowel Disease. *Inflamm Bowel Dis*, 22(2), 336–344.
27 <https://doi.org/10.1097/MIB.0000000000000619>
- 28 Yang, Z. W., Yang, S. H., Chen, L., Qu, J., Zhu, J., & Tang, Z. (2001). Comparison of blood counts in venous, fingertip
29 and arterial blood and their measurement variation. *Clinical and Laboratory Haematology*.
30 <https://doi.org/10.1046/j.1365-2257.2001.00388.x>

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Tables

Table 1

Observations and patient answers to post test questions by younger and elderly patients

Observers questions and judgment at each test (N=106)				
	Age			p-value for age-effect
	All (%)	0-70	>70	
<i>1. Was the patient able to conduct the test without any help?</i>				
Yes	60 (57%)	37	23	
No	46 (43%)	25	21	
				0.45
<i>2. Did the patient seem comfortable with the self-testing?</i>				
Yes	99 (93%)	58	41	
No	7 (7%)	4	3	

				0.94
<i>3. Do you think the patient at this point would be able to conduct self-testing in their home?</i>				
Yes	93 (87%)	54	39	
No	13 (12%)	8	5	
				0.81
Patients questions and answers (N=82)				
<i>1. Do you think you could do self-testing within your own home following this instruction?</i>				
Yes	79 (96%)	44	35	
No/(maybe)	2/(1) (4%)	0	2(1)	
				0.09
<i>2. Do you have any experience with self-testing using other point-of-care technologies e.g. blood sugar testing etc.?</i>				
Yes	20 (24%)	10	10	
No	62 (76%)	34	28	
				0.71

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Legends to Figures

Fig. 1

Laminated illustrative guide for patient instruction and use

Fig. 2ab

Bland-Altman plots of differences between point-of-care and standard measures of leucocytes, including separate analysis of counts below $3.5 \times 10^9/L$ (fig. b)

1 **Fig. 3abc**

2 Weighted Deming regression analysis on the total number of white blood cells.

3

4 **Fig. 3b**

5 Point-of-care leucocyte measurements versus standard measurements with added Deming regression line.

6

7 **Fig. 3c**

8 Point-of-care leucocyte measurements versus standard measurements with added Deming regression line. Sub-
9 group analysis for below average leucocyte counts $<3.5 \times 10^9/L$.

10

11 **Fig. 4ab**

12 Bland-Altman plots of differences between point-of-care and standard measures of neutrophil counts, including
13 separate analysis of counts below $1.5 \times 10^9/L$ (fig. 4b)

14

15 **Fig. 5abc**

16 Weighted Deming regression analysis on the total number of white blood cells, including separate analysis of the
17 neutrophil counts below $1.6 \times 10^9/L$

18

19 **Fig. 5b**

20 Figure 5b. Point-of-care leucocyte measurements versus standard measurements with added Deming regression
21 line.

22

23 **Fig. 5c**

24 Point-of-care leucocyte measurements versus standard measurements with added Deming regression line. Sub-
25 group analysis for below average leucocyte counts $<3.5 \times 10^9/L$.

YOU NEED...

HOW TO TEST...

1 - Disinfection wipes



1. Wipe down your hands thoroughly



2. Use 100% alcohol wipe



3. Cover the palm with the disinfection wipe

2 - Lint-free



4. Use 100% cotton or paper towel from the base to the top



5. Turn out the side of the finger tip



6. Press the back of the hand to the palm and to wrist

3 - Tissue paper



7. Wipe along the front and back of the hand

4 - Microcuvette



8. Apply liquid to cover the finger from the base to the tip



9. Wipe down the side of the hand to the wrist

5 - Tissue paper



10. Wipe off excess liquid from base of hand to wrist



11. Check for an infection in the hand environment



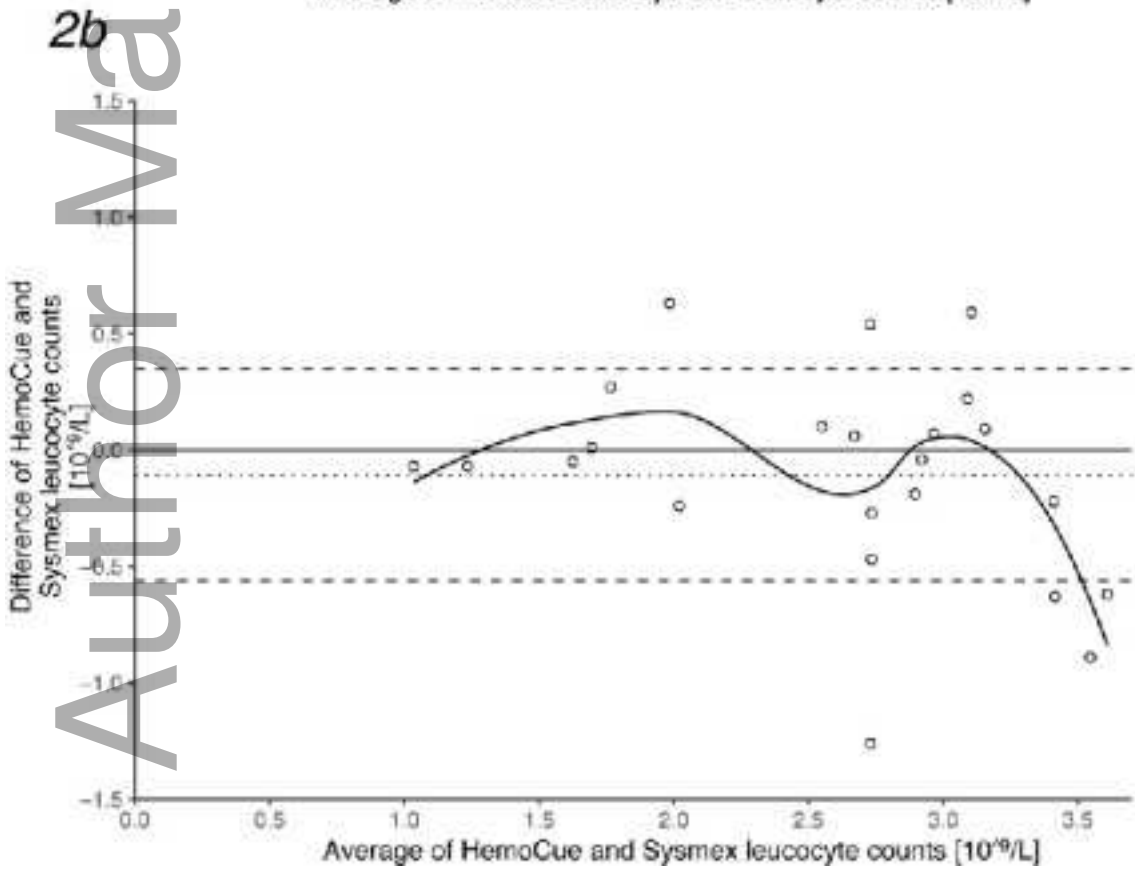
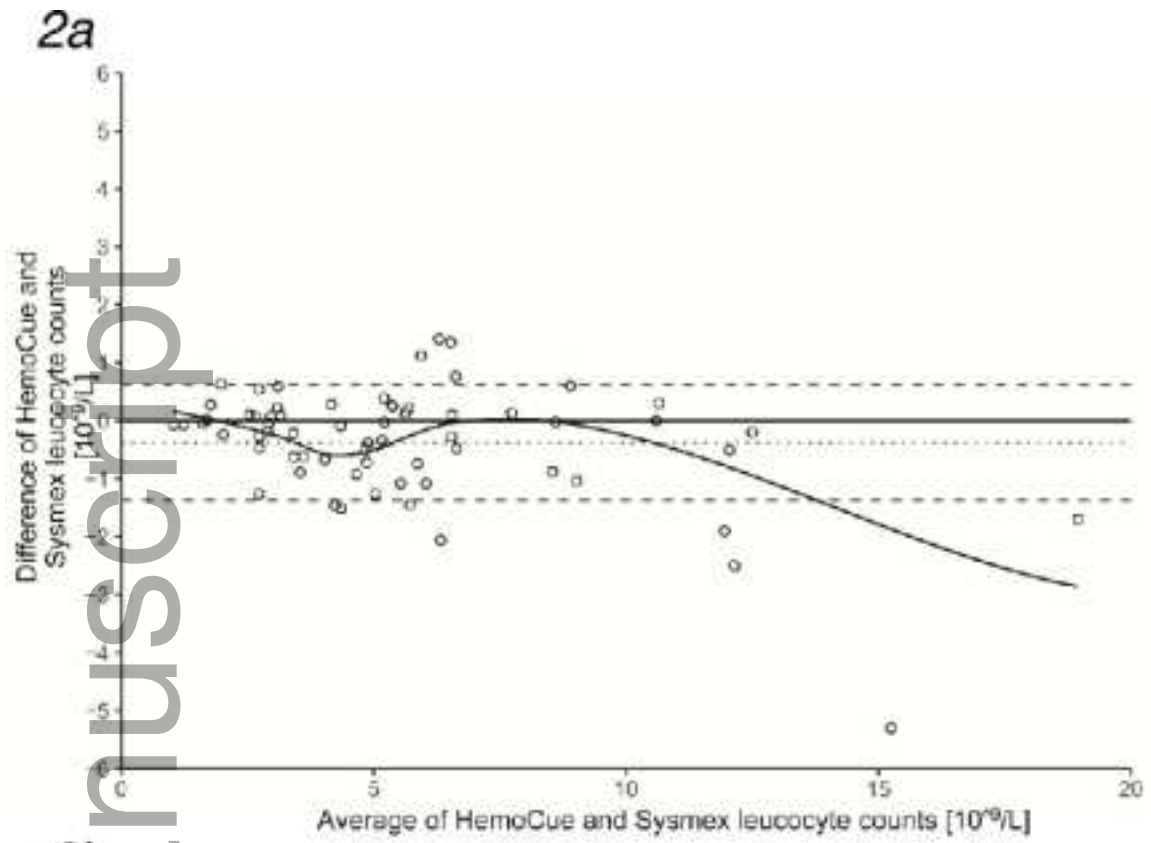
12. Clean the microcuvette in the case of a failure



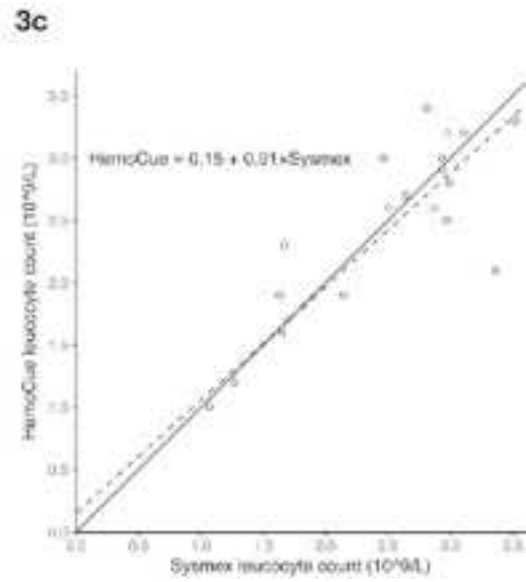
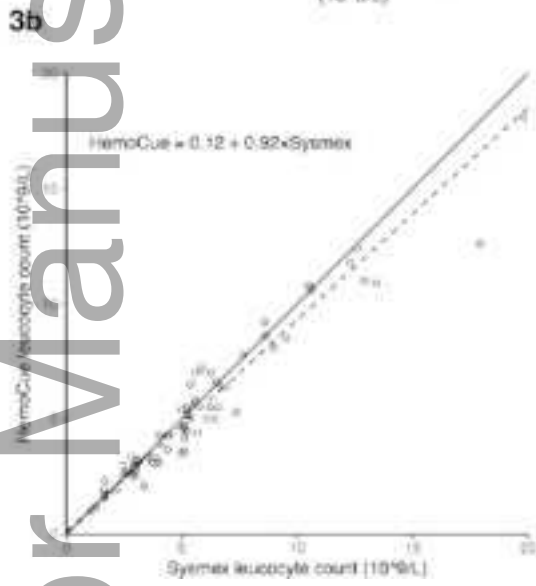
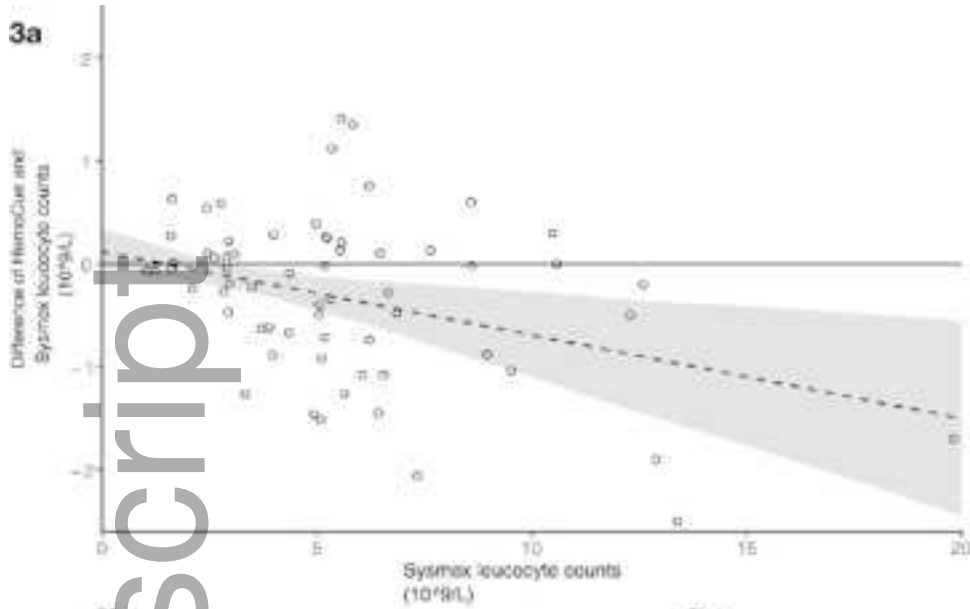
13. Carry out the test according to the procedure

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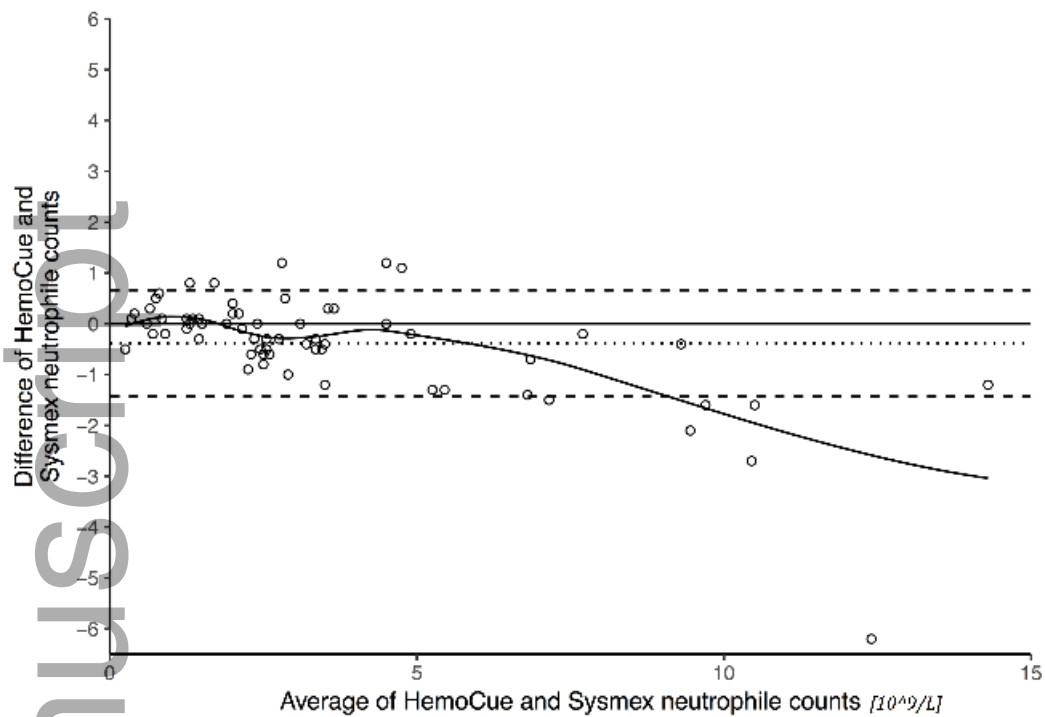


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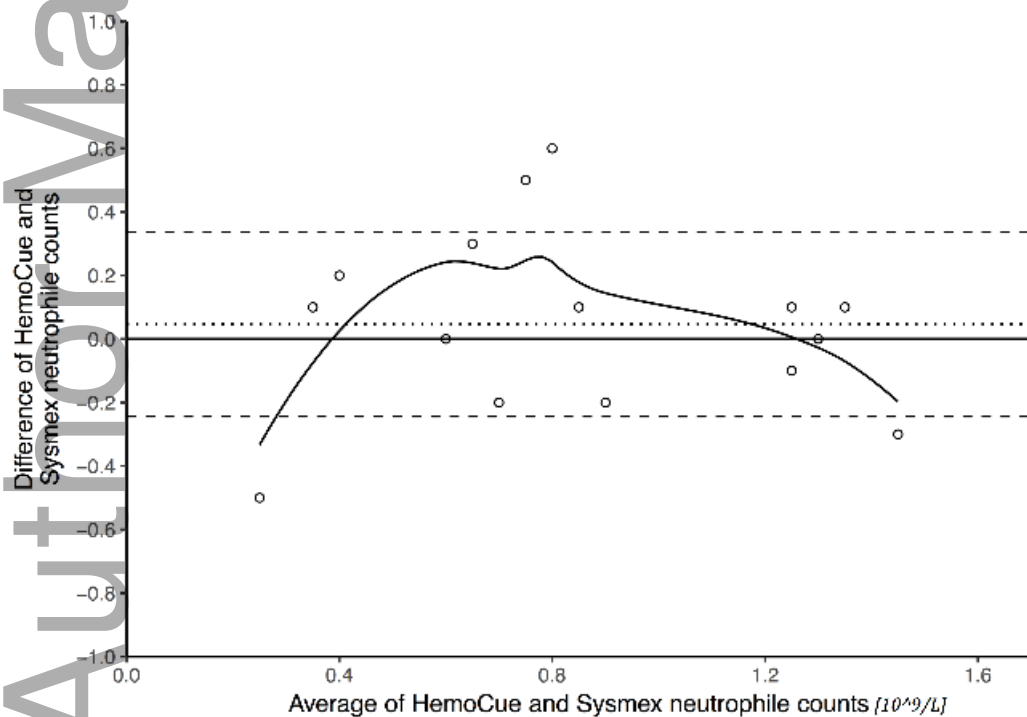


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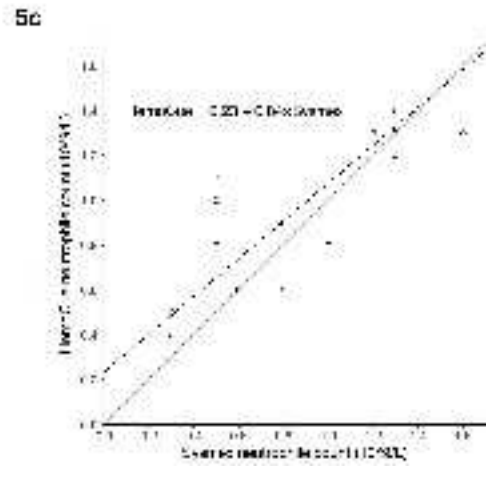
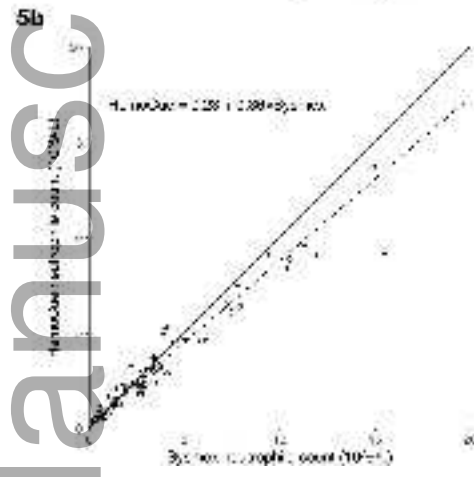
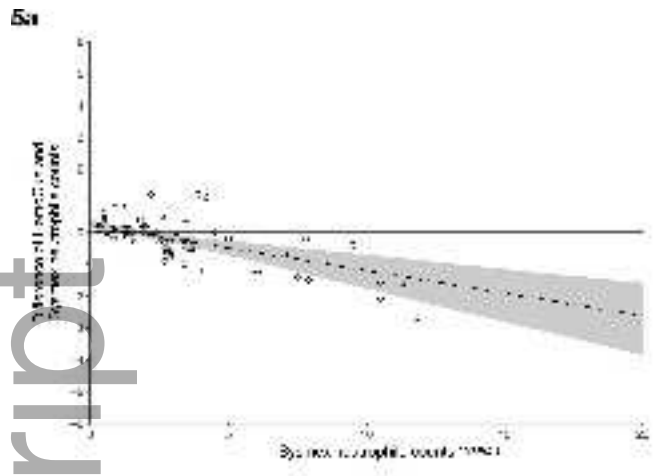
4a



4b



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