Transfusion Medicine and Hemotherapy

Research Article

Transfus Med Hemother 2018;45:341–346
DOI: 10.1159/000486606

Received: October 12, 2017
Accepted: January 3, 2018
Published online: March 9, 2018

Evaluation of the New Lateral Flow Card MDmulticard® Basic Extended Phenotype in Routine Clinical Practice

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Keywords
Duffy antigen · Kidd antigen · Ss antigens · MDmulticard · Lateral flow technology

Summary
Background: Transfusion emergencies and critical situations require specifically designed devices to simplify and optimize the standard procedures. In addition, matching antigens over and above ABO-Rh-K would be beneficial. **Methods:** Routine blood samples were collected in four immunohematology centers and tested with the new MDmulticard Basic Extended Phenotype for the simultaneous detection of the Duffy, Kidd, and Ss antigens, according to the principle of the lateral flow. Results were compared with those obtained using routine serology methods. Discrepancies were analyzed by molecular techniques/genotyping. **Results:** 310 samples were tested (167 donors; 75 patients; 28 subjects with positive direct antiglobulin test (DAT); 15 newborns; 25 previously transfused patients). The 285 samples with non-mixed-field reaction yielded 1,710 antigen results with 8 discrepancies (0.47%) six of which in DAT-positive subjects: three false-positive (Fy^a) for MDmulticard, and two false-positive (Fy^a) plus three false-negative (Fy^b) for the reference methods (MDmulticard PPA for donors/patients/newborns: 99.82%; negative percent agreement: 100%; sensitivity: 100%; specificity: 99.39%, positive predictive value: 99.75%; negative predictive value: 100%). The MDmulticard detected mixed-field in 15 antigen reactions from 13 transfused patients, undetected by the comparative method, with the opposite result in 8 antigens (5 patients). **Conclusion:** The MDmulticard Basic Extended Phenotype met the criteria prescribed for the testing of donor, patient, DAT-positive, and newborn samples in transfusion laboratory routine.

Introduction

Traditional strategies for blood typing in routine clinical analysis include techniques such as slide method, tube testing, microplate technology, and column agglutination technique. Most of the blood typing techniques are based on specific antibody-antigen reactions on the erythrocyte surface [1], and nearly all of them are based on the formation of agglutinates [2]. However, there are limitations associated with conventional methods, including the availability of rare antisera as well as blood typing of recently transfused patients and for those having a positive direct antiglobulin test (DAT-positives), e.g. patients with autoantibodies.

Molecular techniques have become a crucial tool in highlighting occasional blood group phenotyping errors. In particular, a number of weak phenotypes, previously typed false-negative, were discovered in several blood group systems [3]. Even so, blood typing in emergency or life-threatening situations, where patients must be attended to quickly, would require special tools [4].

The Grifols MDmulticard® card, based on the lateral flow technology [5], is specifically designed to simplify standard methods and to optimize the workflow in extreme situations [6]. Unlike conventional methods, the MDmulticard involves little user inter-

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vention; so the possibility of error during processing or interpretation of results is greatly reduced. Preliminary data indicate that the MDmulticard allows determining a patient's ABO group, Rh phenotype and Kell (K) in around 5 min with a single drop of blood [7], with a very low minimum sample volume required (25 µl) which may also be adequate for the typing of newborns.

Even in a transfusion emergency, extending phenotype matching to antigens in addition to ABO, Rh and K would be beneficial in reducing alloimmunization [8–10]. With this aim, the new MDmulticard Basic Extended Phenotype is intended to perform a basic extended phenotype covering additional clinically significant antigens: Duffy (Fy^a, Fy^b), Kidd (Jk^a, Jk^b), and Ss antigens (S, s) [11]. Pilot studies indicate that MDmulticard Basic Extended Phenotype allows for simple and reliable testing of all these antigens together in around 5 min [12]. In addition, MDmulticard Basic Extended Phenotype may be useful to confirm weak phenotypes, including Fy^x, a weak variant of Fy^b [12] as well as for typing patients with a positive DAT [13].

In this study, the performance of the MDmulticard Basic Extended Phenotype was compared to the routine state-of-the-art methods of four reference immunohematology centers.

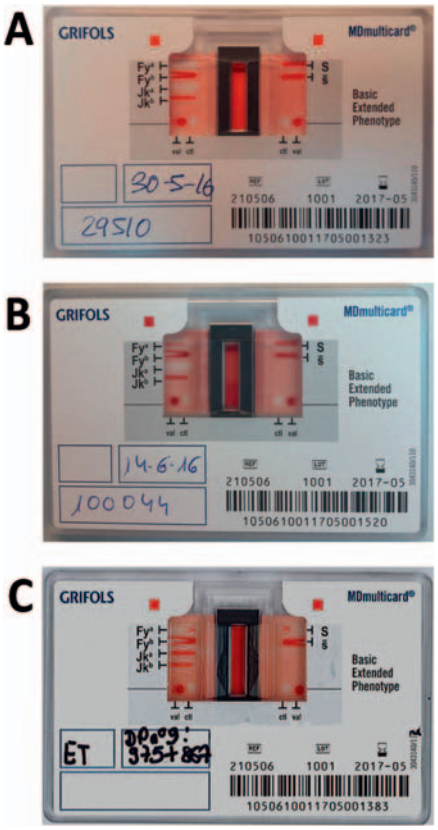

Fig. 1. Positive reactions as they occur in the MDmulticard Basic Extended Phenotype: A) strong reaction 3+ (arrow-shaped band) in Fy^b; B) weak reaction 1+ (weak band) in Fy^a; and C) mixed-field reaction (half band) in Fy^a and S.

Material and Methods

This was a multicenter study conducted at four European immunohematology centers in France (Valenciennes), Germany (Berlin, Ulm) and Spain (Murcia), aimed to evaluate the MDmulticard Basic Extended Phenotype (Medion Grifols Diagnostics, Düdingen, Switzerland) performance, reliability, usability, and adaptability to real-world transfusion laboratory routines. The operators had good knowledge and understanding of the MDmulticard Basic Extended Phenotype product and were well-trained in its use.

The study was conducted in compliance with a clinical protocol, regulatory requirements, good clinical practice (GCP), and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association. All data and information collected during this study was considered and treated as confidential.

Blood Sampling

Anticoagulated samples (whole blood, erythrocyte sediment or clotted blood, as needed) from donors, patients (not transfused within 3 months prior to this study) and newborns (cord blood) were collected and included in the evaluation. Blood samples not used immediately were stored at 2–8 °C. The samples had to have known Duffy, Kidd and Ss antigens, either by being taken from a serum archive or being previously tested with the routine method. A minimum of 240 evaluated samples (±10% accepted) during a period of 3–4 weeks was expected.

Also, a number of complex samples were included: reactive DAT-positive samples collected from patients with known autoantibodies (only samples reacting ≥2+ positive with anti-IgG ± anti-C3d, anti-IgM, anti-IgA were included), and 'mixed-field' samples (two erythrocyte populations) obtained from patients who had been transfused within a few days to 3 months prior to the study with random (not selected for Duffy, Kidd and Ss antigens) red blood cells.

Study Device

The MDmulticard Basic Extended Phenotype is a card reagent formulated using monoclonal antibodies that allows the simultaneous detection of the Duffy (Fya [FY1], Fyb [FY2]), Kidd (Jka [JK1], Jkb [JK2]), and Ss antigens (S [MNS3], s [MNS4]) according to the principle of the lateral flow. The device has a core area of application with two detection fields impregnated with the respective antibodies, as well as two detection zones containing a control spot (ctl) and a process control point (val). Ctl allows for each test to verify whether the red blood cells are reacting with any of the components included in the different antibody formulations, whereas val allows for each test to verify whether i) blood was added, and ii) the flow characteristics of the test are correct. Results are immediately documented as negative reaction (no band) or a positive reaction (red band). Positive reaction strength is graded according to the manufacturer's instructions for use (IFU) of MDmulticard Basic Extended Phenotype: 3+ (arrow-shaped band), 2+ (normal band), 1+ (weak band), and mixed-field reaction (half band). Figure 1 illustrates some of these features in real pictures.

MDmulticard Basic Extended Phenotype Procedures

All MDmulticard Basic Extended Phenotype tests were performed according to the manufacturer's IFU. Suspensions to be read by the MDmulticard Basic Extended Phenotype were prepared as follows:

For whole blood samples, one drop (50 µl) of anticoagulated whole blood was mixed with four drops (200 µl) of Diluent F (Medion Grifols Diagnostics) in a test tube; for erythrocyte sediment samples, one drop (50 µl) of sediment blood was mixed with eight drops (400 µl) of Diluent F in a glass test tube; for clotted blood samples, serum was removed, e.g. by aspirating with a Pasteur pipette, leaving a small amount of serum in the tube. After mild stirring, two drops (100 µl) of liquid from the blood clot were drawn and mixed with two drops (100 µl) of Diluent F in a test tube. In all cases, two drops (100 µl) of the resulting suspension were added to the application zone of the MDmulticard Basic Extended Phenotype. After 30 s, six drops of Diluent F were added to the application zone. After 4 min, six additional drops (300 µl) of Diluent F were added to the application zone. The results were read and recorded after 4 min (8.5 min after application of the suspension to the card).

Comparative Methods

The routine methods used in each of the participating centers were as follows:

Valenciennes laboratory: Erythrocytes Magnetized Technology (E.M.® Technology) on Qwalys® (Diagast, Loos, France) for patient, donor, newborn

Table 1. Antigen test results with MDmulticard Basic Extended Phenotype in non-mixed-field samples and discrepancies with respect to results obtained with reference methods (values in parentheses are results not taking into account two DAT-positive samples with no comparison with reference method available)

Antigen	Reaction result	Sample origin				
		donors	patients	newborns	DAT-positive	total
Fy^a	+	105	53	8	17[c]	183
	–	62	22	7	11 (9)[b]	102
Fy^b	+	129[a]	57	13[a]	27 (25)[a]	226
	–	38	18	2	3 (1)	59
Jk^a	+	127	57	12	22 (21)	218
	–	40	18	3	6 (5)	67
Jk^b	+	117	49	10	19 (17)	195
	–	50	26	5	9	90
S	+	87	44	10	15 (14)	156
	–	80	31	5	13 (12)	129
s	+	149	56	11	24 (22)	240
	–	18	19	4	4	45

[a]1 discrepancy.
[b]2 discrepancies.
[c]3 discrepancies.

and DAT-positive samples; conventional tube test method (Immucor Gamma; Immucor, Norcross, GA, USA) for mixed-field samples.

Ulm laboratory: Conventional tube test method (Immucor Gamma for Fy^a, Fy^b, and s phenotypes; Diagnostic Grifols, Barcelona, Spain, for Jk^a and Jk^b phenotypes; Bio-Rad Laboratories Inc, Hercules CA, USA, for S phenotype). All samples with positive DAT and transfused patient samples were also genotyped using RBC-Ready Gene kits MNS and KKD (Inno-Train Diagnostik GmbH, Kronberg, Germany), DNA extracted with QIAmp DNA Mini Kit (Qiagen GmbH, Hilden, Germany).

Berlin laboratory: Automated blood grouping technology such as solid phase (NEO®; Immucor) for patient and newborn samples; automated (Erytra®) and manual gel column agglutination (Diagnostic Grifols) for donor samples and transfused patient samples, respectively. Samples with positive DAT and with mixed-field reaction were analyzed after DNA extraction by PCR-SSP technology (BAG, Lich, Germany).

Murcia laboratory: Solid-phase microplate (Capture-R® Select®; Immucor) for donor samples. In patients and samples from pipe segments of donation bags, glass beads column agglutination (BioVue®; Ortho-Clinical Diagnostics, Raritan, NJ, USA) were used for samples with Fy^a, Fy^b, s phenotypes; conventional tube testing with liquid antisera (Immucor Gamma) were used for samples with Jk^a, Jk^b and S phenotypes.

Data Analysis

The results obtained with the MDmulticard Basic Extended Phenotype were compared with those obtained with the reference methods. In samples with non-mixed-field reaction (all but those from transfused patients), a difference of interpretation (positive / negative) was considered a discrepancy. In case of discrepancy or unclear results (i.e. doubtful readings, unreadable results, or mixed-field reaction) the test with the MDmulticard Basic Extended Phenotype was repeated to confirm the result. Discrepancies were resolved by molecular techniques/genotyping in favor of one system or another (excepting in those DAT-positive samples already compared to genotyping as the reference method) and were classified as number of false-positives (FP), true-positives (TP), false-negatives (FN) and true-negatives (TN) as appropriated.

Reaction results from donor, patient, and newborn samples comparing MDmulticard Basic Extended Phenotype and reference methods were evaluated in terms of positive percent agreement (PPA), negative percent agreement (NPA), and overall percent agreement (OPA). All matching percentages were followed by the 95% confidence intervals (CI). For phenotyping (donors, patients, and newborns), the acceptance criteria for PPA and NPA were set at the lower 95% confidence bound to be >99%. Results of performance after analysis of discrepancies were evaluated in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

In samples from transfused patients with mixed-field reactions, analysis of the comparison of MDmulticard Basic Extended Phenotype and serology reference methods was descriptive. Differential results between methods were not considered discrepancies, although all samples were also tested with genotyping.

Results

A total of 310 samples were collected (Berlin: 96; Ulm: 95; Murcia: 74; Valenciennes: 45) and were evaluated with MDmulticard Basic Extended Phenotype: 167 (53.9%) from donors, 75 (24.2%) from not previously transfused patients, 25 (8.1%) from previously transfused patients, 28 (9.0%) from DAT-positive patients, and 15 (4.8%) from newborns.

Non-Mixed-Field Samples

Results of the MDmulticard Basic Extended Phenotype test obtained in the 285 samples with non-mixed-field reaction (all but those from previously transfused patients) are shown in table 1. That represented 1,710 antigen results (1,002 from donors, 450 from patients, 90 from newborns and 168 from DAT-positives). Comparison with a reference method was not available in two DAT-positive samples.

A total of eight discrepancies (in eight samples, six of them DAT-positive) between the antigen detection results of MDmulticard Basic Extended Phenotype and the reference method were observed (0.47% of the tests and 2.8% of the samples). Three of the discrepancies were in Fy^a positivity, two in Fy^a negativity, and three in Fy^b positivity (tables 1 and 2).

Table 2. Contingency table of antigen test reaction results with MDmulticard Basic Extended Phenotype and the reference methods in non-mixed-field sample

	Reference methods		
	+	–	total
MDmulticard			
+	1,206	6	1,212
–	2	487	489
Total	1,208	493	1,701

Table 3. Performance results of antigen testing after analysis of discrepancies between MDmulticard Basic Extended Phenotype and the reference methods

	True	False	Total
MDmulticard			
+	1,209	3	1,212
–	489	0	489
Total	1,698	3	1,701
Reference methods			
+	1,205	2	1,207
–	491	3	494
Total	1,696	5	1,701

All three discrepancies in Fy^a positivity were in DAT-positive samples, which showed a weak or very weak positive result with MDmulticard Basic Extended Phenotype (<+1 strength, noted as 'not negative' by the performing technicians) and negative with the reference method (in this case, genotyping). In all three samples, Fy^a was confirmed to be negative, thus resulting in FP for MDmulticard Basic Extended Phenotype.

Of the three discrepancies in Fy^b positivity (one donor, one newborn, one DAT-positive), all of them showed a weak positive result with MDmulticard Basic Extended Phenotype and were negative with the reference method (tube testing). Genotyping revealed the presence of FY*X allele which causes a weak positive Fy^b phenotype. The MDmulticard Basic Extended Phenotype results were therefore correct (TP).

In the two samples typed Fy^a-negative by the MDmulticard Basic Extended Phenotype but positive by the reference method (tube testing), both in DAT-positive samples, genotyping evidenced the lack of the FY*A allele. The MDmulticard Basic Extended Phenotype negative results were therefore correct (TN).

Performance Results

Performance results of both MDmulticard Basic Extended Phenotype and comparison methods are summarized in table 3.

With regard to the phenotyping results from donors, patients and newborns, PPA of MDmulticard Basic Extended Phenotype was 99.82% (95% CI 98.82–99.97%), NPA was 100% (95% CI 99.65–100%) and OPA was 99.87% (95% CI 99.81–99.98%).

Sensitivity of MDmulticard Basic Extended Phenotype was 100% (95% CI 99.68–100%), specificity was 99.39% (95% CI 98.22–99.79%), PPV was 99.75% (95% CI 99.27–99.92%) and NPV was 100% (95% CI 99.22–100%).

Table 4. Results of mixed-field (MF) reactions (double population) using MDmulticard Basic Extended Phenotype in samples from transfused patients (n = 25)

Antigen	Reaction result		
	+	–	MF
Fy^a	21	0	4
Fy^b	22	0	3
Jk^a	19	1	5
Jk^b	23	1	1
S	15	2	8
s	24	0	1
Total	124	4	22

Table 5. Comparison of MDmulticard Basic Extended Phenotype with serology reference methods and genotyping in samples with mixed-field (MF) reactions (n = 22)

Comparison method	MDmulticard			
	+	–	MF	total
Gel column agglutination (n = 12)				
+	49	0	6	55
–	4	0	3	7
MF	7	0	3	10
Total	60	0	12	72
Tube testing (n = 10)				
+	50	0	0	50
–	0	3	6	9
MF	0	1	0	1
Total	50	4	6	60
Genotyping (n = 22)				
+	90	0	1	91
–	20	4	17	41
MF	N/A	N/A	N/A	N/A
Total	110	4	18	132

N/A = Not applicable.

Mixed-Field Samples

Results of the 150 antigen reactions detected in the 25 samples from transfused patients are summarized in table 4. Antigen with most mixed-field (two erythrocyte populations) reactions was S (n = 8/22), whereas Jk^b and s antigens had one mixed-field reaction each.

Three samples had no result available with the reference method and were therefore excluded for comparison. Results are shown in table 5.

In 4 of the 12 samples tested with gel column as comparator, 7 antigens showed mixed-field agglutination that were not detected by the MDmulticard Basic Extended Phenotype (2 Fy^b, 3 Jk^a, 1 Jk^b, and 1 S), with reaction strength from weak to very weak in all cases. On the other hand, MDmulticard Basic Extended Phenotype detected mixed-field agglutination in 9 antigens undetected by gel

column (1 Fy^a, 2 Fy^b, 2 Jk^a, and 4 S) from 8 samples. Mixed-field reaction in 3 antigens (1 Fy^a and 2 Fy^b) from 2 samples was detected by both systems.

In the 10 samples from transfused patients tested with tube technique as comparator, in one case (S) a mixed-field reaction was observed, which was not detected by the MDmulticard Basic Extended Phenotype. By contrast, MDmulticard Basic Extended Phenotype detected 5 mixed-field reactions in 6 antigens undetected by tube testing (1 Fy^b, 2 Jk^a, 1 Jk^b, 1 S, and 1 s) from 5 samples.

When comparing the results of the serological methods with the results of genotyping, full concordance was observed in only 5 samples which were positive for all 6 antigens. Table 5 shows that serological methods tended to detect more positives (n = 110 for MDmulticard Basic Extended Phenotype, n = 105 for both reference methods) and fewer negatives (n = 4 for MDmulticard Basic Extended Phenotype, n = 16 for both reference methods) than true results predicted by genotyping (n = 91 and n = 41, respectively).

Discussion

The development and improvement of tools for rapid and reliable blood typing adequate for use in acute clinical situations is warranted [4]. In a step further to the MDmulticard that determines a patient's main antigens (ABO, Rh phenotype and K) within a few minutes [7], the new MDmulticard Basic Extended Phenotype covers an additional array of clinically significant antigens [11] through the same lateral flow principle. Hence, the combination of typing reagents for Fy, Jk and Ss antigens on one test card would be very helpful for an easy and rapid phenotyping of red cell units or patients when the latter are to be transfused with blood compatible for Fy, Jk and Ss antigens, e.g. patients with warm reactive autoantibodies or patients with sickle cell disease [14–16]. Furthermore, phenotyping is known to be challenging in these patients due to positive DAT and recent transfusions in many cases. We found that the MDmulticard Basic Extended Phenotype was as reliable as the routine reference methods of four immunohematology centers (except molecular techniques/genotyping, as could be expected).

Agreement (PPA, NPA, and OPA) between MDmulticard Basic Extended Phenotype and the reference methods in phenotyping results ranged between 99.8% and 100%. The >99% criteria for the lower 95% confidence bound was met for NPA (99.65%) and was close for PPA (98.82%). However, the two cases of discrepancy (1 weak Fy^b-positive in donors and 1 weak Fy^b-positive in newborn samples) were resolved in favor of MDmulticard Basic Extended Phenotype. Both cases plus one more found in DAT-positives were caused by the presence of FY*X allele, which proved MDmulticard Basic Extended Phenotype to be highly sensitive to weak Fy^b-positive compared to the reference method used (tube testing; E.M. Technology). A remarkable sensitivity of the MDmulticard for the detection of weak Fy^b antigens has been reported recently [17]. The five remaining discrepancies were all observed in the testing of DAT-positive samples. The high sensitivity of the MDmulticard to detect weak Fy^b antigens could be used to confirm the results of red cell units previously typed as Fy^b-negative before transfusions of Fy^b-negative patients.

DAT-positive samples are known to be challenging for most typing systems. The cells of patients with a strong reactive DAT (e.g., patients with autoantibodies and patients with sickle cell disease) often cause false-positive reactions, especially when typing is done by the indirect Coombs test [18]. False-positive reactions are, however, not restricted to IgG antisera. Recent studies revealed that IgM antisera also can be interfered by a reactive DAT [19]. The MDmulticard is based on the lateral flow technique and may, therefore, be less prone to interference by a reactive DAT. That was the case with 2 Fy^a-negative samples that were tested falsely positive by the tube method but truly negative by the MDmulticard Basic Extended Phenotype.

26 samples with reactive DAT were tested with the MDmulticard Basic Extended Phenotype. Two samples negative for Fy^a by PCR were tested falsely positive by the tube method, but reacted truly negative with the MDmulticard Basic Extended Phenotype. Three Fy^a-negative samples showed strongly positive reactions when tested by the gel column agglutination method but only weak or very weak reactions with the MDmulticard Basic Extended Phenotype. Weak reactions of lgG-coated red cells in the MDmulticard Basic Extended Phenotype may occur with the anti-Fy^a, which is the only monoclonal antibody of the IgG type in the MDmulticard Basic Extended Phenotype [20]. These very weak false-positive bands could be easily distinguished from true positive bands or mixed-field bands. Thus, when typing patients with a reactive DAT for their FY phenotype, the MDmulticard Basic Extended Phenotype demonstrated a clear advantage over the indirect antiglobulin test (tube method or gel column method). So far, the only reliable determination of the FY phenotype of such patients can be done by genotyping.

Compared to serological blood grouping, molecular methods still take longer, are more expensive, and are not established in every immunohematological laboratory [21]. The MDmulticard Basic Extended Phenotype might become an equal or even superior alternative for such purposes. Moreover, the MDmulticard system could not only be adequate for blood typing in emergency situations [4, 8–10] and extreme environment conditions [22], but could also be more cost-effective, as it limits the number of genotyping investigations necessary (and therefore the costs) to provide antigen-matched blood, especially for patients with autoantibodies or sickle cell disease. However, this should be confirmed by studies specifically aimed to cost and time analyses [23].

Globally, in all samples with non-mixed-field reaction, performance of MDmulticard Basic Extended Phenotype was very good: 100% sensitivity and NPV (no FN) and >99.3% specificity and PPV (3 FP in Fy^a). Although comparison with several quite different reference methods could be deemed as a limitation of the study, it should be pointed out that genotyping was taken as the focal point for all analyses. In addition, the number of analyzed samples was limited to those evaluable expected from routine practice in the immunohematology centers during the 1-month study period.

Previously transfused patients are also challenging for typing systems. In fact, no routine phenotyping method is able to distin-

guish between autologous and transfused red cells [24]. So far, only genotyping allows the prediction of the phenotype of a transfused patient. Depending on the number of transfused units and depending on the phenotypes of the transfused cells, the patients present with more or less pronounced mixed-field agglutination. In this study, neither the serology reference methods nor the MDmulticard Basic Extended Phenotype were able to overcome the hurdle of mixed-cell populations. Detection of mixed-field reaction in at least one antigen of the investigated samples will help the laboratory to identify transfused patients. In addition, if evidence of mixed-field reaction in one of the antigens is found, none of the other antigens tested by serological methods should be regarded as reliable/valid. Hence, in 15 samples out of the 22 tested and compared, the MDmulticard Basic Extended Phenotype detected antigen-positive mixed-cell populations that were not detected by the comparative method, while the opposite result occurred in 8 samples. Although these results may suggest differential sensitivities of the tested methods for specimens collected from transfused patients, due to the small sample size, the significance of the current evaluation is limited and should be further investigated in a larger study.

Sometimes a method with increased sensitivity may be advantageous, e.g. when transfused cells are searched for. On the other hand, a method with lower sensitivity that overlooks small transfused cell populations may be helpful when the phenotype of a transfused patient is to be estimated. It is suggested that every institution should perform an individual analysis to decide the most appropriate sensitivity of the typing system [25]. Sometimes a negative antigen typing helps to confirm or refuse the specificity of an antibody, even in a transfused patient.

In summary, overall performance and usability of the new MDmulticard Basic Extended Phenotype in transfusion laboratory routine met the criteria prescribed for the testing of donor, patient, and newborn specimens. Moreover, MDmulticard Basic Extended Phenotype could be used in patients with positive DAT and in transfused patients with reliability similar to other routine serological methods.

Disclosure Statement

BM received honorarium from Grifols for being a speaker at the Grifols lunch symposium at the DGTI in 2016. The other authors declare no conflict of interest. This study was funded by Grifols, manufacturer of the MDmulticard Basic Extended Phenotype card. Medical writing and editorial assistance in the preparation of this manuscript was provided by Jordi Bozzo PhD, CMPP (Grifols), under the direction of the authors.

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