Detailed Analysis of MVT 3

The 9/10 and 10/10 values of algorithms #1, #3, #4 and #5 differing from reference result #2 were determined and compiled into a spreadsheet. The first few rows of this file are shown in Figure S1.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	**pat_id**	**don_id**	**n/10**		**#1**	**#3**	**#4**	**#5**		**reference (#2)**	**max. deviation**		**diplo [pat]**	**diplo [don]**	**pairs**
2	P000001	D001797	10		0	0	0	0		0	0		14	1755	24570
3	P000001	D001797	9		1	1	1	2		1	1		14	1755	24570
4															
5	P000001	D004368	10		0	0	0	0		0	0		14	1014	14196
6	P000001	D004368	9		4	4	4	5		4	1		14	1014	14196
7															
8	P000001	D004457	10		0	0	0	0		0	0		14	1755	24570
9	P000001	D004457	9		1	1	1	2		1	1		14	1755	24570
10															
11	P000003	D000102	10		0	0	0	0		0	0		20	914	18280
12	P000003	D000102	9		44	44	44	45		44	1		20	914	18280
13															
14	P000003	D000613	10		0	0	0	0		0	0		20	1076	21520
15	P000003	D000613	9		43	43	43	50		43	7		20	1076	21520
16															
17	P000003	D001084	10		44	44	44	57		44	13		20	1790	35800
18	P000003	D001084	9		2	2	2	1		2	1		20	1790	35800

Figure S1: Spreadsheet showing the discrepant values for the 9/10 and 10/10 predictions of algorithms #1, #3, #4 and #5 compared to algorithm #2 (reference result) for MVT 3. Deviating values of one and two percentage points are highlighted in yellow and light orange resp.; higher deviations are highlighted in orange. The computational complexity of the considered patient-donor pair is indicated by the number of diplotypes of patient and donor and their product i. e. the resulting number of diplotype pairs.

The individual distribution of the discrepancies for the 9/10 and 10/10 predictions of each algorithm compared to reference result #2 was visualized as bar charts. Figure 2 in the publication shows exemplarily the deviations of algorithm #1. For this case, the small number of deviations higher than 1% could be attributed to a disregarding of the baseline counting for AA-NA and/or AA-BB according to Table S2. This algorithm counted both cases as 1 difference although the first should be treated as a match and the second as having 2 differences. In extreme cases this different counting led to high deviations up to 100%. The deviations of 1% mainly can be classified as floating point arithmetical artifacts as described below.

For each locus the 2/2 predictions and/or the match grade characters of the algorithms #1, #4 and #5 differing from reference result #2 were determined and assembled in a spreadsheet. As explained in the publication, participant #3 is not considered here due to the provided locus specific conditional probability values. The first few rows of the spreadsheet file are shown in Figure S2.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	**pat_id**	**don_id**	**char/prob**		**#1**	**#4**	**#5**		**reference (#2)**	**max. deviation**		**diplo [pat]**	**diplo [don]**	**pairs**
2	P000001	D000266	char		P	P	P		P	N/A		14	2503	35042
3	P000001	D000266	prob		1	1	0		1	1		14	2503	35042
4														
5	P000001	D000408	char		P	P	P		P	N/A		14	253	3542
6	P000001	D000408	prob		3	3	4		3	1		14	253	3542
7														
8	P000001	D000530	char		P	P	P		P	N/A		14	1275	17850
9	P000001	D000530	prob		10	10	9		10	1		14	1275	17850
10														
11	P000001	D000537	char		P	P	P		P	N/A		14	78	1092
12	P000001	D000537	prob		69	69	71		69	2		14	78	1092
13														
14	P000001	D000648	char		P	P	P		P	N/A		14	76	1064
15	P000001	D000648	prob		10	10	12		10	2		14	76	1064
16														
17	P000001	D000674	char		P	P	P		P	N/A		14	1170	16380
18	P000001	D000674	prob		77	77	80		77	3		14	1170	16380

Figure S2: Spreadsheet showing the discrepant values for the HLA-C specific 2/2 predictions and match grade characters of algorithms #1, #4 and #5 compared to algorithm #2 (reference result) for MVT 3. Deviating values of one and two percentage points are highlighted in yellow and light orange resp.; higher deviations are highlighted in orange. The computational complexity of the considered patient-donor pair is indicated by the number of diplotypes of patient and donor and their product i. e. the resulting number of diplotype pairs.

The locus-wise distribution of the discrepancies for the 2/2 predictions of each algorithm compared to reference result #2 was visualized as bar charts. Figure 3 in the publication shows exemplarily the deviations of algorithm #1 observed for locus HLA-C. For this case, the small number of deviations higher than 1% again could be attributed to a disregarding of the baseline counting for AA-NA and/or AA-BB already mentioned above. Analogous, the deviations of 1% mainly can be again classified as floating point arithmetical artifacts.

Unclear disparities found in the analysis process were inspected by means of a tracing tool based on algorithm #2. For a given patient-donor pair this script computes 4 spreadsheets narrowing down the calculations of the haplotype frequency based matching process in detail. Sheet 1 contains the given HLA genotypes of the considered patient and donor i. e. the raw input data. Sheet 2 is showing the patient's computed set of possible diplotypes which includes among other detail information the frequencies and relative probabilities of each diplotype. These cell values are formula based, therefore allowing insights into the computations (see Figure S3). Analogous, sheet 3 contains the diplotype data for the donor. The last sheet contains the pair-wise combinations of the patient's and the donor's diplotypes. For each diplotype pair the number of HLA differences for each locus is counted and the mismatched HLA values are highlighted in red color. This information is completed by the assigned locus specific and overall matching probabilities. The summary line of this sheet shows the computed locus specific 2/2 and the overall 9/10 and 10/10 prediction values. The cell values are also formula based.

O15 =IF(AND(A15=H15;B15=I15;C15=J15;D15=K15;E15=L15);F15*M15;2*F15*M15)

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	H1-A	H1-C	H1-B	H1-DRB1	H1-DQB1	H1-Freq		H2-A	H2-C	H2-B	H2-DRB1	H2-DQB1	H2-Freq		H1-H2-Freq	H1-H2-Prob [%]
2	01:01g	07:02g	07:02g	13:02	06:04g	0,00062		03:01g	07:02g	07:02g	15:01	06:02	0,03547		4,39828E-05	61,33203928
3	01:01g	07:02g	07:02g	15:01	06:02	0,00609		03:01g	07:02g	07:02g	13:02	06:04g	0,00113		1,37634E-05	19,19244317
4	01:01g	07:01g	07:02g	13:02	06:04g	0,00017		03:01g	07:02g	07:02g	15:01	06:02	0,03547		1,20598E-05	16,81684948
5	01:01g	07:02g	07:02g	15:01	06:02	0,00609		03:01g	07:02g	07:02g	13:02	06:09	0,00007		8,526E-07	1,188912409
6	01:01g	07:02g	07:02g	13:02	06:04g	0,00062		03:01g	07:02g	07:02g	15:01	06:03g	0,00039		4,836E-07	0,674358481
7	01:01g	07:02g	07:04	15:01	06:02	0,00009		03:01g	07:02g	07:02g	13:02	06:04g	0,00113		2,034E-07	0,283632165
8	01:01g	07:01g	07:02g	13:02	06:04g	0,00017		03:01g	07:02g	07:02g	15:01	06:03g	0,00039		1,326E-07	0,184904745
9	01:01g	07:02g	07:02g	13:02	06:04g	0,00062		03:01g	07:10	07:02g	15:01	06:02	0,00006		7,44E-08	0,103747459
10	01:01g	07:02g	07:02g	13:02	06:04g	0,00062		03:01g	07:02g	07:02g	15:01	06:04g	0,00005		0,000000062	0,086456216
11	01:01g	07:01g	07:02g	15:01	06:02	0,00002		03:01g	07:02g	07:02g	13:02	06:04g	0,00113		4,52E-08	0,06302937
12	01:01g	07:01g	07:02g	13:02	06:04g	0,00017		03:01g	07:10	07:02g	15:01	06:02	0,00006		2,04E-08	0,028446884
13	01:01g	07:01g	07:02g	13:02	06:04g	0,00017		03:01g	07:02g	07:02g	15:01	06:04g	0,00005		0,000000017	0,023705737
14	01:01g	07:02g	07:04	15:01	06:02	0,00009		03:01g	07:02g	07:02g	13:02	06:09	0,00007		1,26E-08	0,017570134
15	01:01g	07:01g	07:02g	15:01	06:02	0,00002		03:01g	07:02g	07:02g	13:02	06:09	0,00007		2,8E-09	0,003904474
16																
17															SUM(O2:O15)	SUM(P2:P15)
18															7,17126E-05	100

Figure S3: Example of sheet 2 of the trace file used to track down disparities for patient P000001 for MVT 3. The possible 14 pairs of haplotypes H1 and H2 with their respective frequencies are listed. For each of these diplotypes, the computed diplotype frequency and the diplotype probability is shown in columns *O* and *P*.

A finding of the detailed analysis was, that floating point arithmetic in combination with the required rounding can lead to a substantial number of deviations of 1%. Numeric mathematics teaches that first the precision determined by the register size of the floating point unit of the used computer hardware and second the randomly order of summing up floating point numbers generally can impact the obtained total sum (31). For example although the computed floating point values 32.5 (*IEEE 754* double: 0x4040400000000000) and 32.49999999999999 (*IEEE 754* double: 0x40403fffffffffff) are virtually identical, the first is rounded up to 33 and the second is rounded down to 32. For the sake of comparability and reproducibility, in the consensus result for MVT 3 probability values in the range of x.5 $\pm$ $1/10^{12}$ are set to exactly x.5 before rounding. Anyone who wants to compare his own result with the provided consensus file must keep in mind that such disparities likely will occur.