Prediction Algorithms for Cell Therapy Collections

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What kind of prediction algorithms are we talking about?

Mathematical expressions that allow for the calculation of the **whole blood volume** to process to collect a desired cell yield based on the corresponding **cell pre-count**

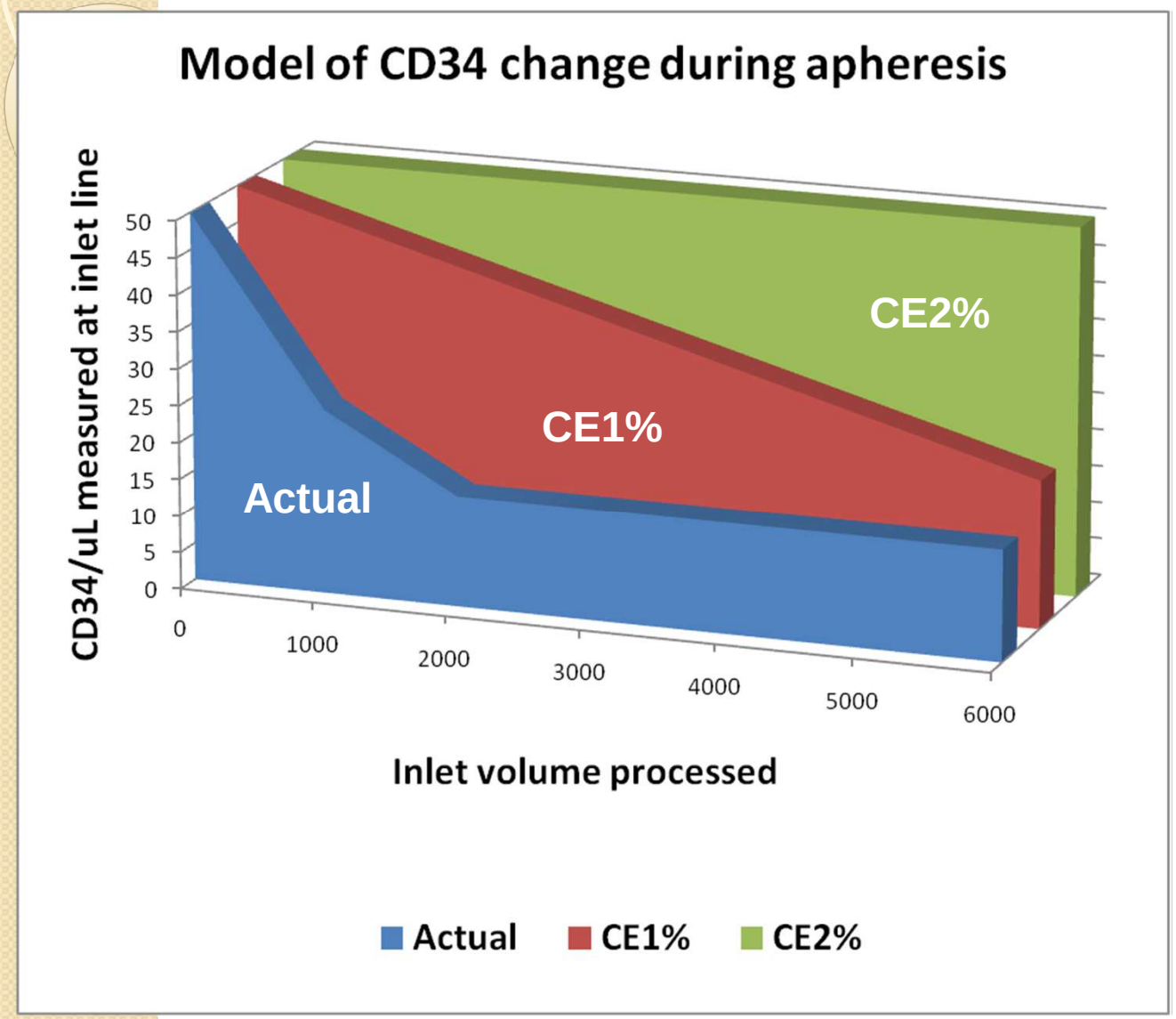
Prediction Algorithms

- Simple
  - Based on average Cell CE2%
  - Empirical
- Complex (statistically calculated)
  - Based on a linear regression

Collection Efficiency - Definition

$$\textbf{Collection Efficiency} = \frac{\text{Cells in the collection bag}}{\text{Cells through the apheresis device}}$$

But how many cells went through the device?



	Collection Efficiency CD34
CE2	54.3%
CE1	66.7%
Actual	89.1%

Borrowed from Richard Smith, Sr. Scientist @ Terumo BCT

Collection Efficiency 1 (CE1)

- It is based on the *average* cell count during the procedure, (pre + post *I* 2), therefore it requires a cell *post* count. It cannot be used to build a prediction algorithm *(Cousins AF et al, JCA 2015).*

$$\textbf{CE1} = \frac{\text{Total Cells collected}}{\text{WB Volume x } \left(\frac{\text{Cell pre- + Cell post-}}{2}\right)}$$

• CE1 is closer to the Actual CE as it assumes correctly that the concentration of CD34+ in peripheral blood is *not* constant.
• CE1 compensates for intra-procedure CD34+ mobilization.
• In general, CE1 > CE2.
• CE1 is not significantly influenced by WB volume processed

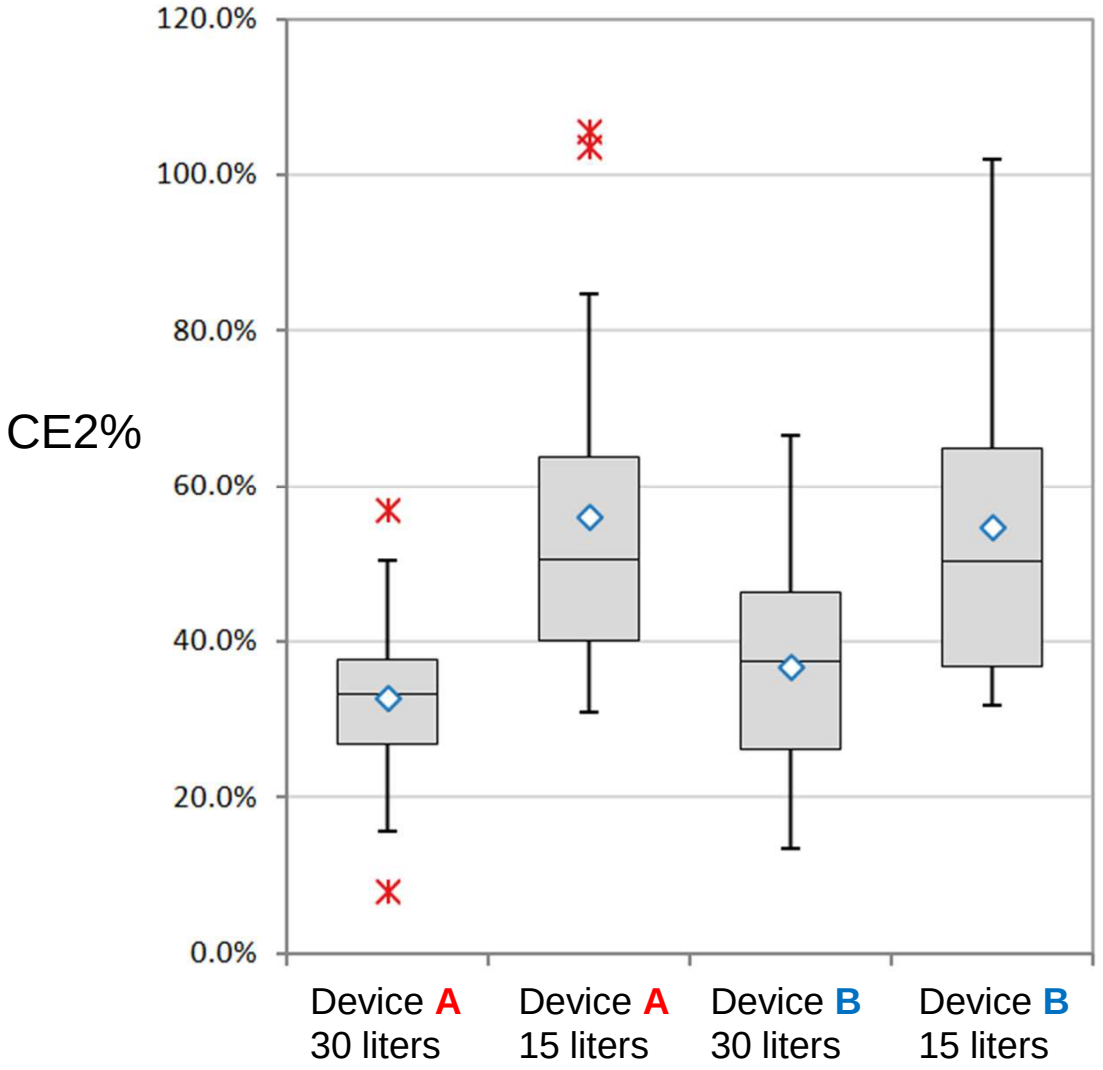
Collection Efficiency 2 (CE2)

Based on cell pre-count *only*. It can be used for prediction purposes. It is the most commonly calculated:

$$\textbf{CE2} = \frac{\text{Total Cells collected}}{\text{WB Volume x Cell pre-}}$$

- Since it wrongly assumes that cell concentration in peripheral blood is constant throughout the procedure, CE2 is not close to the actual CE.
- In general, CE2 < CE1
- The more blood is processed, the lower the CE2 (the assumption about cells going through the apheresis device gets worse)

Dependency of CE2 on WB processed



CE% is device-dependent and institution-dependent

Institution	Device 1	Device 2
1	55%	39%
2	52.7%	46.2%
3	54.2%	48.7%
4	66%	60%
5	42%	35.1%
6	38.3%	27.4%
7	55.5%	38.3%
8	56%	43%
9	56.4%	38.7%
10	67.8%	58.0%
11	55%	46%

Simple prediction algorithm

Based on CE2%

$$CE2\% = \frac{\text{Cell Yield}}{\text{WB volume} \times \text{Cell pre-count}}$$

$$\text{Lymph CE\%} = \frac{\text{Lymphocyte Yield}}{\textbf{WB vol.} \times (\text{WBC pre-count} \times \text{Lymph\%})}$$

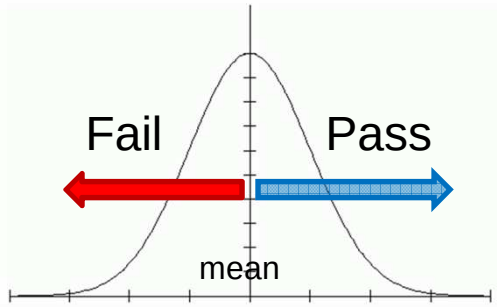
$$\textbf{WB volume} = \frac{\text{Desired Lymph Yield}}{\text{Lymph CE\%} \times (\text{WBC pre-} \times \text{Lymph\%})}$$

Fine tuning a simple algorithm

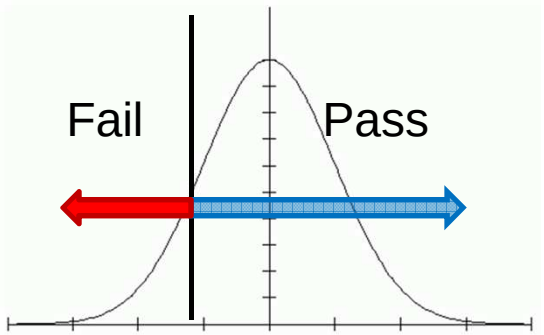
To ensure that we get the desired yield most of the times

WB volume = Desired Cell yield / (Cell pre- x CE%)

- If we use the mean CE% we will fail 50% of the times



- If we use a “pessimistic” CE% we will not fail *most* of the times, but we may over-collect. *(Rosenbaum ER, Cytotherapy 2012)*



Stastistically calculated prediction algorithm

- We need to find a *good* correlation between cells collected and cell pre-count
- But cell yield also depends on WB volume processed, so…
- We need to find a correlation between *normalized* yield (per liter of WB processed) and cell pre-count

Statistically calculated Prediction Algorithm

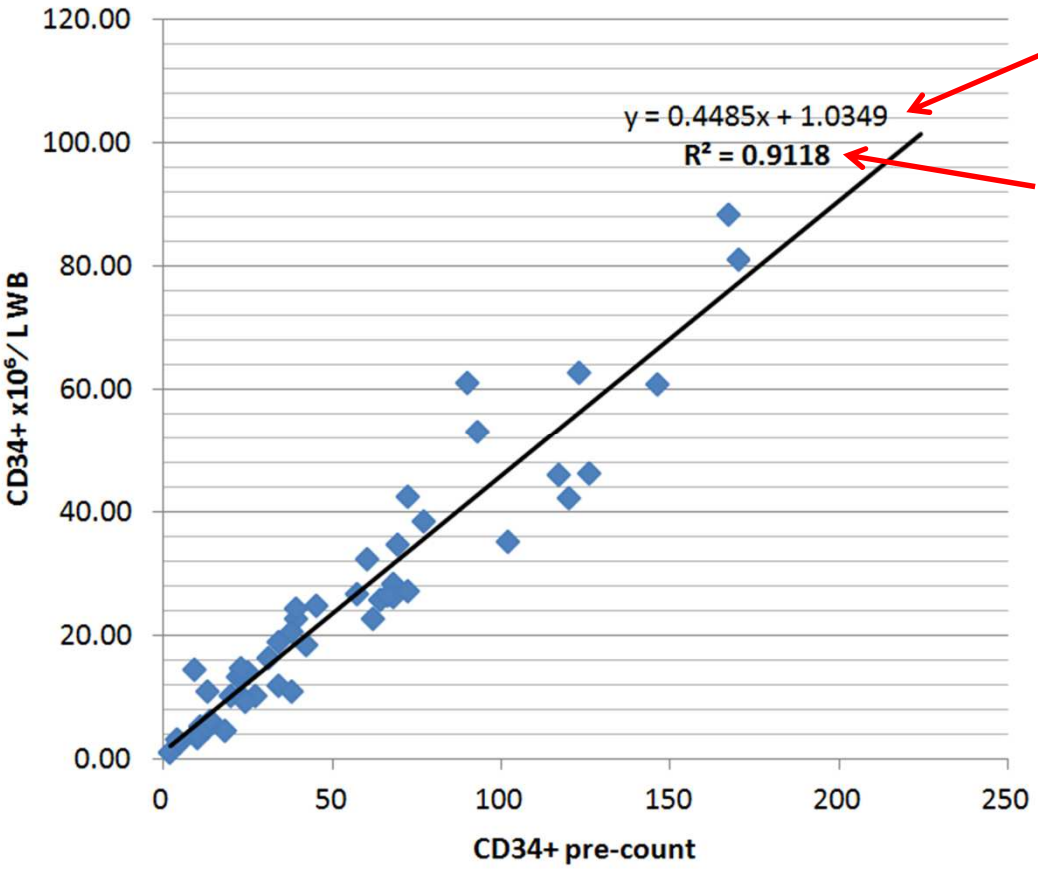
Based on a linear regression – Example

Pre-CD34+/µl	WB processed	Product Volume	Product HCT	Total CD34+	CD34+ CE%	CD34+ / Lit WB
87	27290	339	2.9	1.4E+09	51.9%	5.2E+07
52	21223	454	5.2	5.7E+08	49.9%	2.7E+07
24	13418	365	0	1.6E+08	49.1%	1.2E+07
40	15359	343	1.2	3.0E+08	45.7%	2.0E+07
4	17738	350	4.2	2.9E+07	62.4%	1.6E+06
9	22151	370	1.5	1.3E+08	70.4%	5.8E+06
10	22006	389	2	1.5E+08	76.0%	7.0E+06
46	17954	328	3.9	6.3E+08	33.0%	3.5E+07
21	14552	183	0.8	9.8E+07	57.1%	6.8E+06
13	13902	196	0.7	9.9E+07	51.8%	7.1E+06
34	11050	200	0.8	1.9E+08	73.6%	1.7E+07
20	18673	564	1.6	2.8E+08	66.9%	1.5E+07
19	20099	418	1.2	2.5E+08	61.2%	1.2E+07
41	22603	514	0.8	5.7E+08	39.2%	2.5E+07
42	12607	160	1.3	2.1E+08	65.3%	1.7E+07
54	20201	436	1.3	7.1E+08	43.0%	3.5E+07
45	12741	500	1.3	2.5E+08	57.2%	1.9E+07
40	12829	410	2.1	2.9E+08	38.1%	2.3E+07
36.6	**17846**	**368**	**1.3**	**2.5E+08**	**54.5%**	**1.7E+07**

1. Divide total CD34+ collected by liters of WB to
2. Obtain the CD34+ collected per liter of WB (normalized) and
3. Plot CD34+/ liter WB against pre-CD34+ (see next slide)

Statistically calculated Prediction Algorithm

Can our past help us predict our future?



Linear regression: Used to create prediction algorithm

Regression index: it tells us about our ability to predict the cell yield based on the cell pre-count

- The closer to **1.0** the better the predictability
- Below **0.8** the variation would make the prediction algorithm unreliable

Statistically calculated Prediction Algorithm

Linear regression | ***y* =** *0.4485* ***x*** **+** *1.0349* | *copied from previous chart*

Target CD34+/Kg	5
Kg recipient	75
CD34+ pre-count	50
WB liters to process	16.0

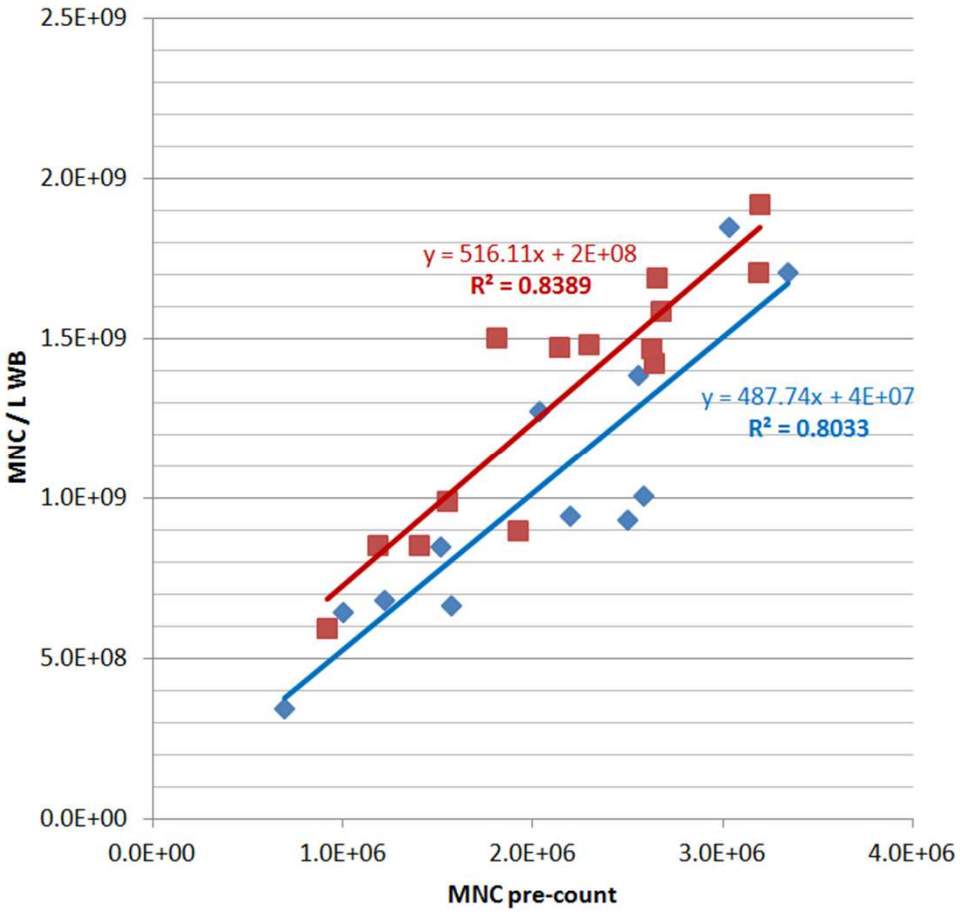
- What the linear regression expression means is, actually:
  CD34+/Liter WB = *0.4485* x CD34+ pre-count + *1.0349*
- Which we can easily turn into:

$$\textbf{Liters WB} = \frac{\text{Target CD34+/Kg x Kg recipient}}{(0.4485 \text{ x CD34+ pre} + 1.0349)}$$

Two devices can be analyzed simultaneously

y =	*516.11*	*x +*	*2.0E+08*
y =	*487.74*	*x +*	*4.0E+07*

Target MNC Yield	1.40E+10
MNC %	28
WBC pre-count	7.0
WB liters to process	11.6
WB liters to process	14.1



- The most efficient device will require you to process less blood to get the same cell yield

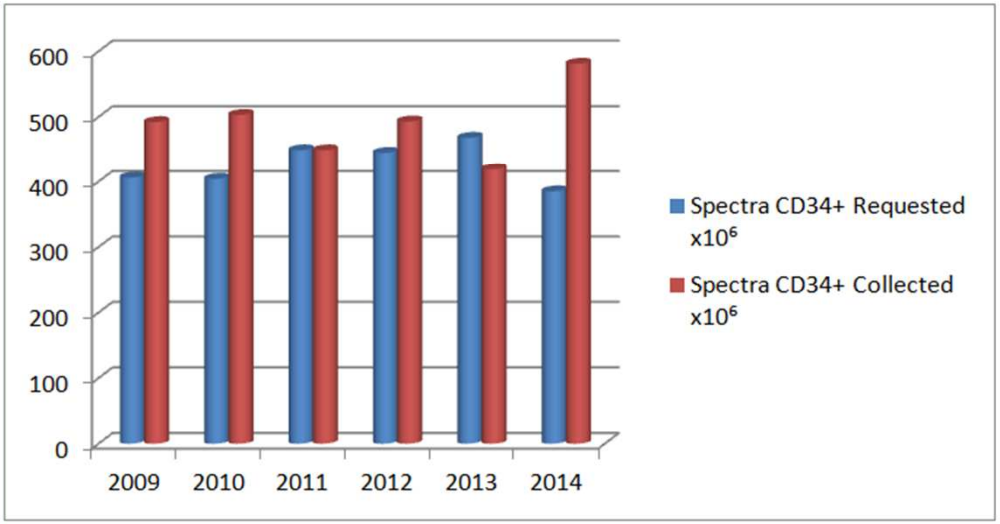
Reasons why we all should consider using prediction algorithms

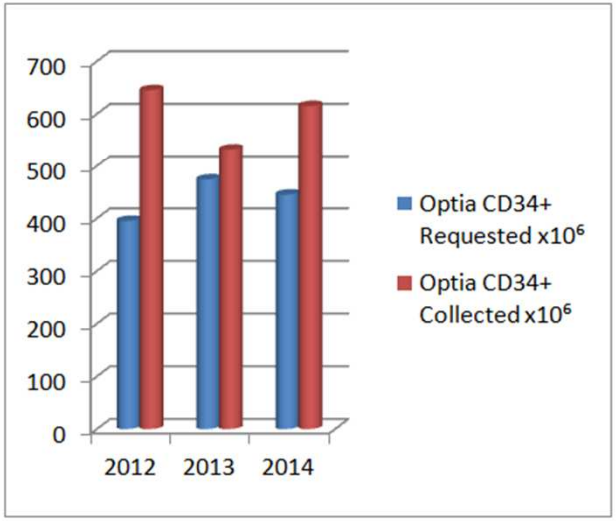
- Collection procedures can be shortened whenever cell pre-counts are average or higher
  - This may improve platelet loss and cross-cellular contamination (less RBC, granulocytes in product)
  - Product volumes will be smaller
  - Over-collecting is not free: consider the cost of freezing and storing the excess of cells ($65 to $100 per bag per year) *(Paolo Perseghin, 2016 WAA Meeting, Paris)*
  - Most adverse effects happen at the end of long collection procedures *(John Miller MD, NMDP – Be The Match Meeting, 2014)*
- If pre-counts are borderline low, the need for additional collections can be confirmed beforehand

Actual results when using a prediction algorithm

Michigan Blood, Grand Rapids, MI

Year	Spectra							Optia						
	WB liters	n	Coll. Time	Spectra CD34+ Requested x10⁶	Spectra CD34+ Collected x10⁶	Second procedure (per year)	Procedures per donor	**WB liters**	n	Coll. Time	Optia CD34+ Requested x10⁶	Optia CD34+ Collected x10⁶	Second procedure (per year)	Procedures per donor
2009	**15.7**	39	6:40	406	492	3	1.08	*na*	*na*	*na*			*na*	*na*
2010	**14.7**	47	6:58	404	503	3	1.06	*na*	*na*	*na*			*na*	*na*
2011	**15.6**	49	5:50	449	449	4	1.08	*na*	*na*	*na*			*na*	*na*
2012	**18.3**	46	5:36	445	493	0	1.00	**16.1**	4	4:47	395	645	0	1.00
2013	**13.3**	26	4:35	468	419	6	1.23	**15.7**	39	6:10	474	532	1	1.03
2014	**14.8**	10	4:06	393	581	1	1.10	**14.9**	26	4:43	445	615	0	1.00





THANK YOU!