

eMethods

Cluster derivation

We applied an unsupervised ML approach to develop clinical phenotypes of very elderly (age ≥ 80 at time of transplant) kidney transplant recipients in the UNOS/OPTN database by conducting unsupervised consensus clustering.^[1] We performed consensus clustering analysis on the whole study population. We initially assessed the distribution and missingness in phenotyping variables. Subsequently, missing data were imputed through multiple imputation using multivariate imputation by chained equations (MICE),^[2] and non-normal data were z-score normalized. Multiple imputation is a widely used approach to estimate variables when data are missing at random. MICE is optimal when less than 30% of a variable's data are missing.^[3-8] All of the extracted variables in our study had missing data less than 5% (Table S1). We subsequently applied clustering using the consensus cluster algorithm. The algorithm begins by subsampling a proportion of items and a proportion of features from a data matrix. Each subsample is then partitioned into up to groups (k) by a user-specified clustering algorithm. This process is repeated for a specified number of times. Pairwise consensus values, defined as 'the proportion of clustering runs in which two items are grouped together', are calculated and stored in a consensus matrix (CM) for each cluster. Clustering settings used were as follows: maximum number of clusters, 10; number of iterations, 100; subsampling fraction, 0.8; clustering algorithm, partitioning around medoids (PAM) with Gower distance matrix).^[1] The number of potential clusters ranges from 2 to 10, to avoid producing an excessive number of clusters that would not be clinical useful. Pairwise consensus values, defined as 'the proportion of clustering runs in which two items are [grouped] together'^[1], are calculated and stored in a CM for each k. Then for each k, a final agglomerative hierarchical consensus clustering using distance of 1-consensus values is completed and pruned to k groups, which are called consensus clusters.

The clustering algorithm is to maximize the potential number of clusters while maintaining high cluster consensus. The optimal number of clusters was determined by examining the CM heat map, cumulative distribution function, cluster-consensus plots with the within-cluster consensus scores, and the proportion of ambiguously clustered pairs (PAC).^[9, 10] The within-cluster consensus score, ranging between 0 and 1, is defined as the average consensus value for all pairs of individuals belonging to the same cluster.^[10] A value closer to one indicates better cluster stability.^[10] PAC, ranging between 0 and 1, is calculated as the proportion of all sample pairs with consensus values falling within the predetermined boundaries.^[9] A value closer to zero indicates better cluster stability.^[9] To examine the cluster profile, we calculated and graphically displayed the standardized mean differences of the variables between each cluster and the overall study population. Calculation of the standardized difference of each parameter used the cutoff of ± 0.3 to show subgroup features with the key features for each cluster.

All cluster derivation analyses were performed using R, version 4.0.3 (RStudio, Inc., Boston, MA; <http://www.rstudio.com/>), with the packages of ConsensusClusterPlus (version 1.46.0)^[10]. We imputed missing data through multivariable imputation by chained equation (MICE) method.^[2] All analyses were two-tailed, and P value < .05 was considered statistically significant.

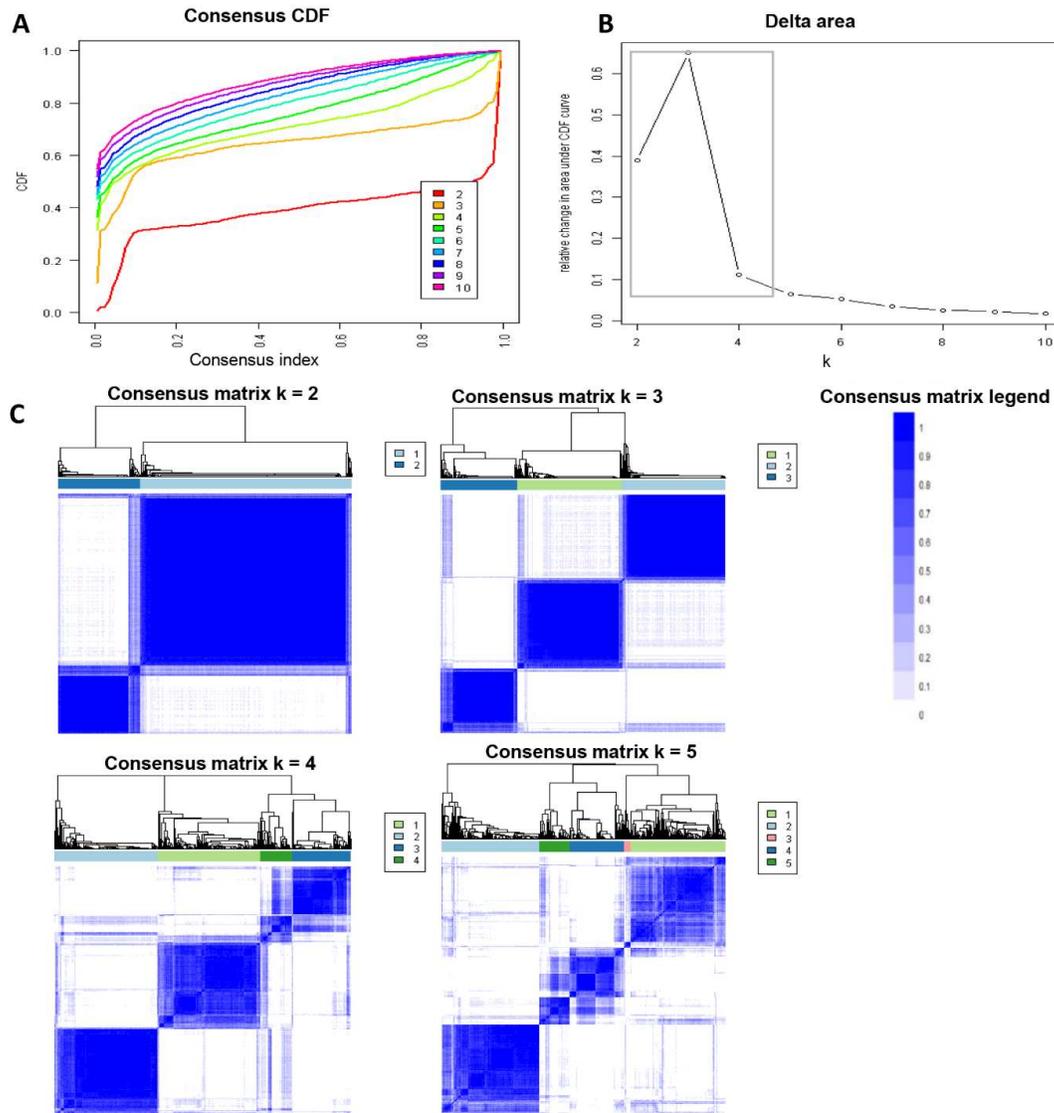
eTable 1 the number and percentages of missing data

	Missing data (total=419)
Recipient Age	0 (0)
Recipient male sex	0 (0)
ABO blood group	0 (0)
Body mass index	0 (0)
Kidney retransplant	0 (0)
Kidney donor status	0 (0)
Dialysis duration	5 (1)
Cause of end-stage kidney disease	0 (0)
Comorbidity	
- Diabetes mellitus	0 (0)
- Malignancy	0 (0)
- Peripheral vascular disease	4 (1)
PRA (%)	11 (3)
Positive HCV serostatus	0 (0)
Positive HBs antigen	0 (0)
Positive HIV serostatus	0 (0)
Functional status	13 (3)
Working income	14 (3)
Public insurance	1 (0.2)
US resident	0 (0)
Undergraduate education or above	17 (4)
Serum albumin	15 (4)
Donor age	0 (0)
Donor male sex	0 (0)
Donor race	0 (0)
History of hypertension in donor	0 (0)
KDPI	0 (0)
HLA mismatch	0 (0)
Cold ischemia time	6 (1)
Kidney on pump	0 (0)
Delay graft function	0 (0)
Allocation type	0 (0)
EBV status	20 (5)
CMV status	0 (0)
Induction immunosuppression	
- Thymoglobulin	0 (0)
- Alemtuzumab	0 (0)
- Basiliximab	0 (0)
- Other	0 (0)
- No induction	0 (0)
Maintenance Immunosuppression	
- Tacrolimus	0 (0)
- Cyclosporine	0 (0)
- Mycophenolate	0 (0)
- Azathioprine	0 (0)
- mTOR inhibitors	0 (0)
- Steroid	0 (0)

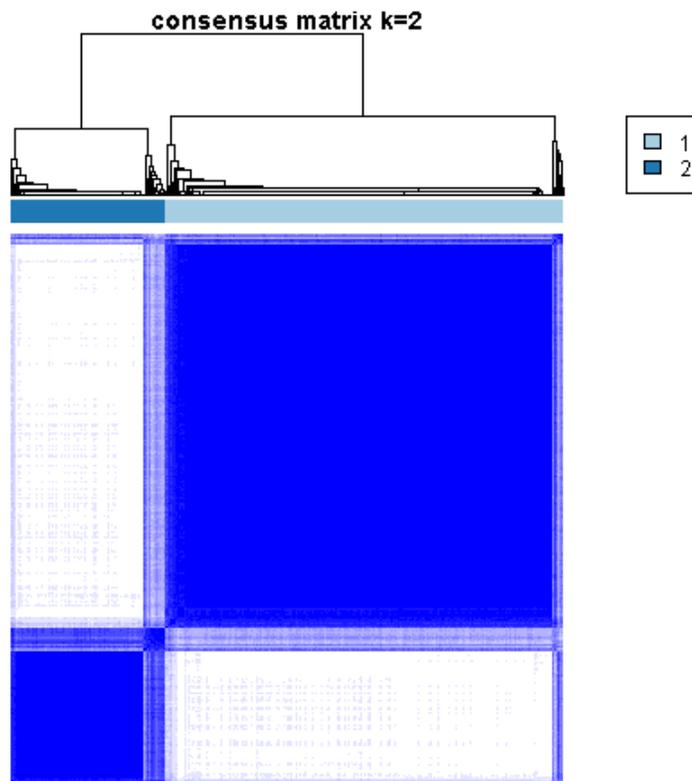
eTable 2. Proportion of clusters according to the OPTN Regions

Region	N	Cluster 1	Cluster 2	Cluster 3
1	17	2 (12)	10 (59)	5 (29)
2	79	38 (48)	26 (33)	15 (19)
3	55	27 (49)	17 (31)	11 (20)
4	27	10 (37)	7 (26)	10 (37)
5	58	15 (26)	26 (45)	17 (29)
6	17	9 (53)	6 (35)	2 (12)
7	26	8 (31)	7 (27)	11 (42)
8	49	16 (33)	16 (33)	17 (35)
9	56	18 (32)	20 (36)	18 (32)
10	19	7 (37)	9 (47)	3 (16)
11	16	4 (25)	8 (50)	4 (25)

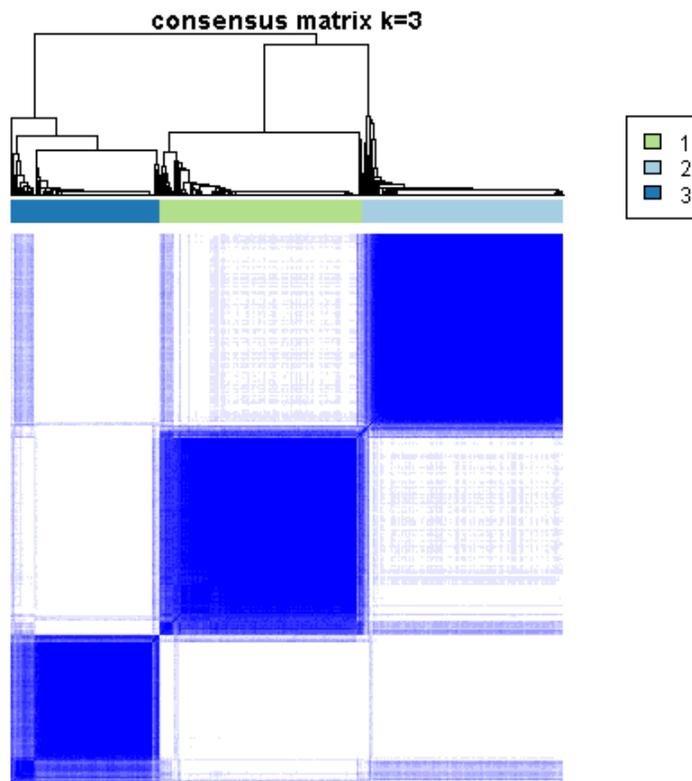
eFigure 1. CDF plot displaying consensus distributions for each k ; B. Delta area plot reflecting the relative changes in the area under the CDF curve. C. Consensus matrix heat map depicting consensus values on a white to blue color scale of each cluster.



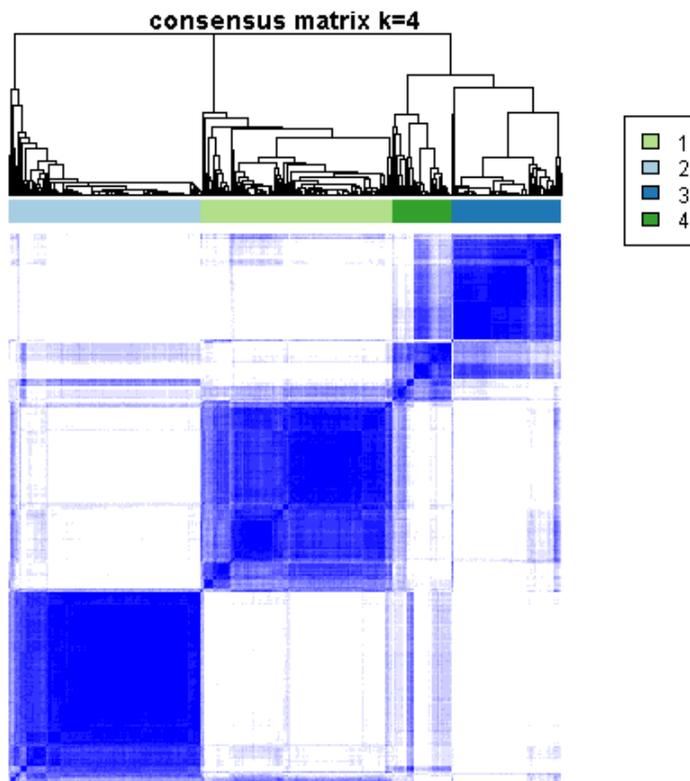
eFigure 2. Consensus matrix heat map ($k = 2$) depicting consensus values on a white to blue color scale of each cluster



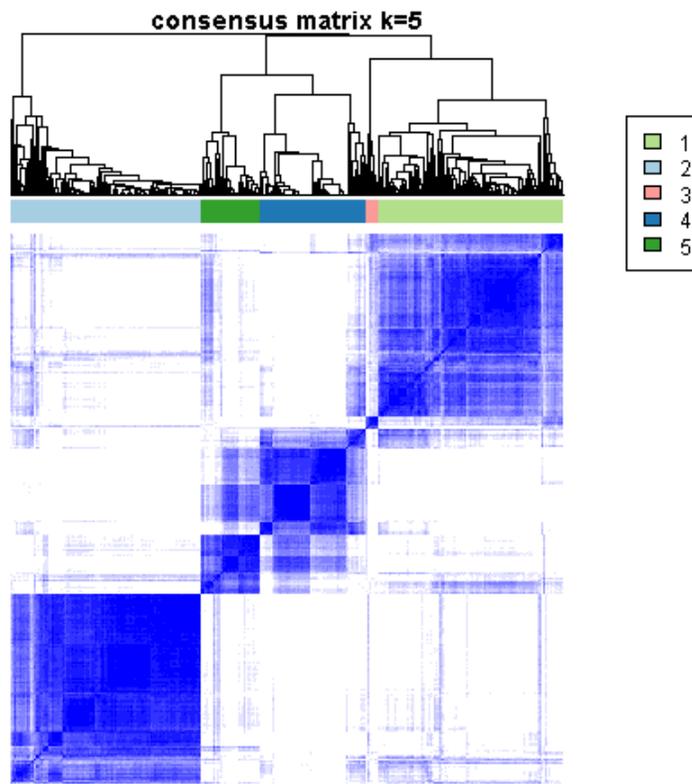
eFigure 3. Consensus matrix heat map ($k = 3$) depicting consensus values on a white to blue color scale of each cluster



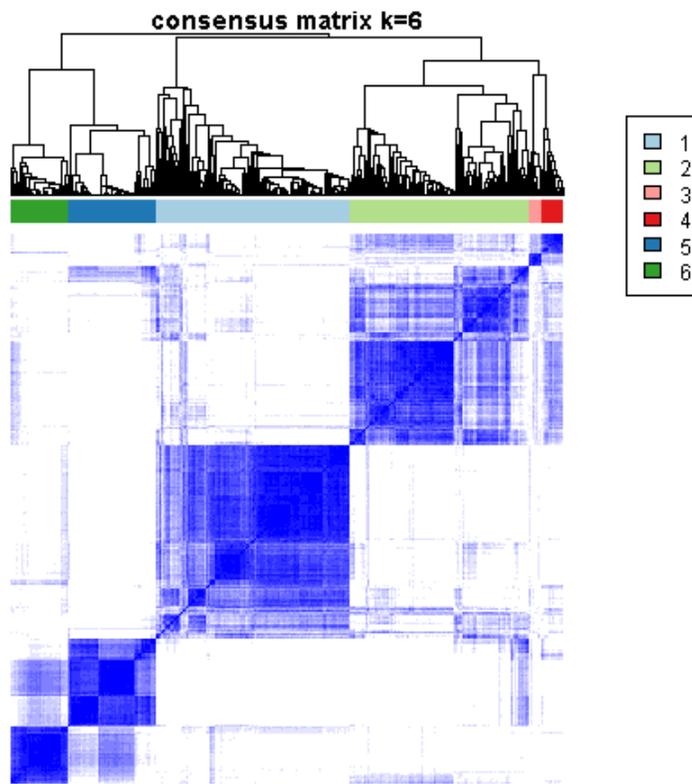
eFigure 4. Consensus matrix heat map ($k = 4$) depicting consensus values on a white to blue color scale of each cluster



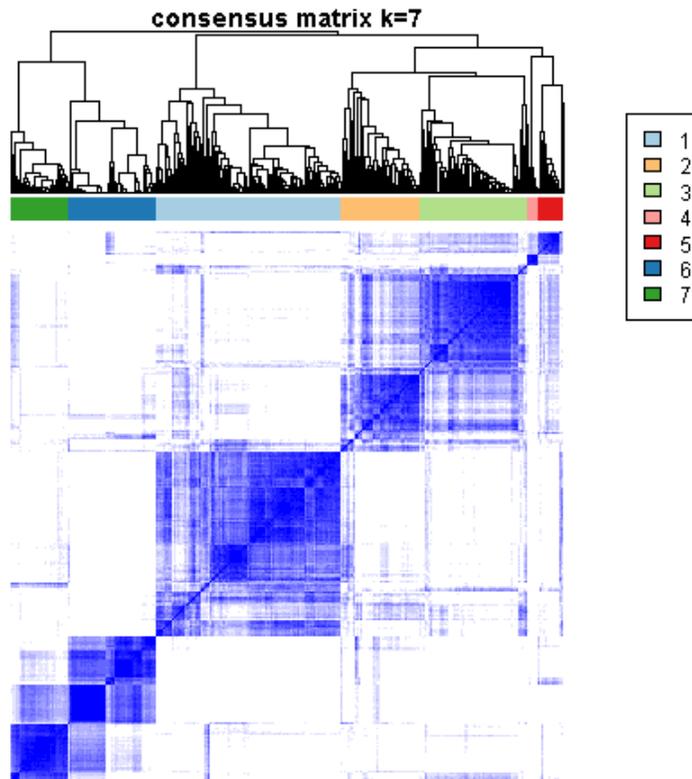
eFigure 5. Consensus matrix heat map (k = 5) depicting consensus values on a white to blue color scale of each cluster



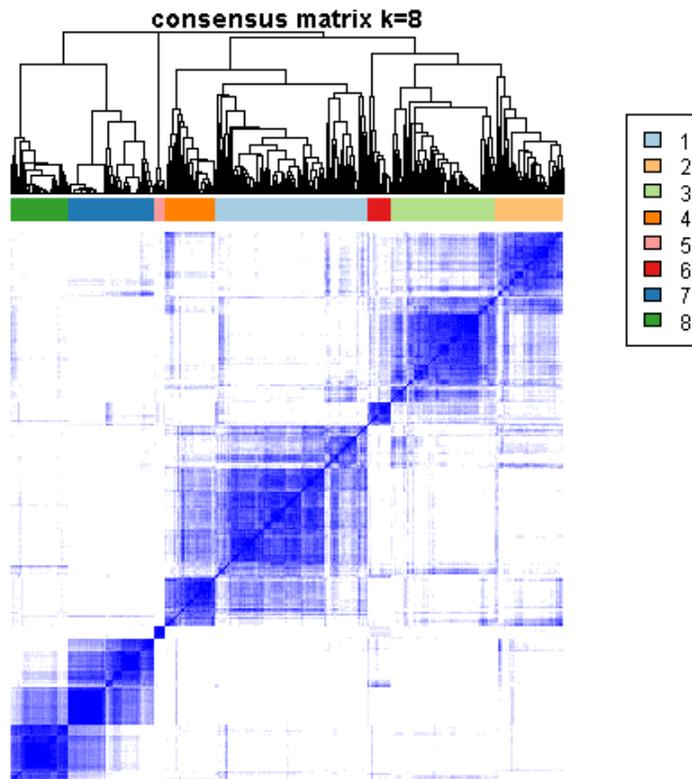
eFigure 6. Consensus matrix heat map (k = 6) depicting consensus values on a white to blue color scale of each cluster



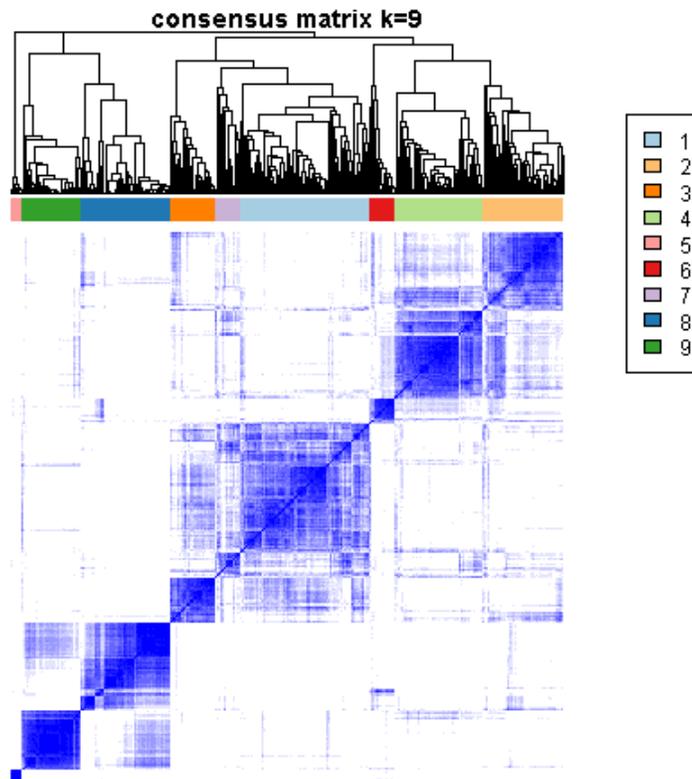
eFigure 7. Consensus matrix heat map ($k = 7$) depicting consensus values on a white to blue color scale of each cluster



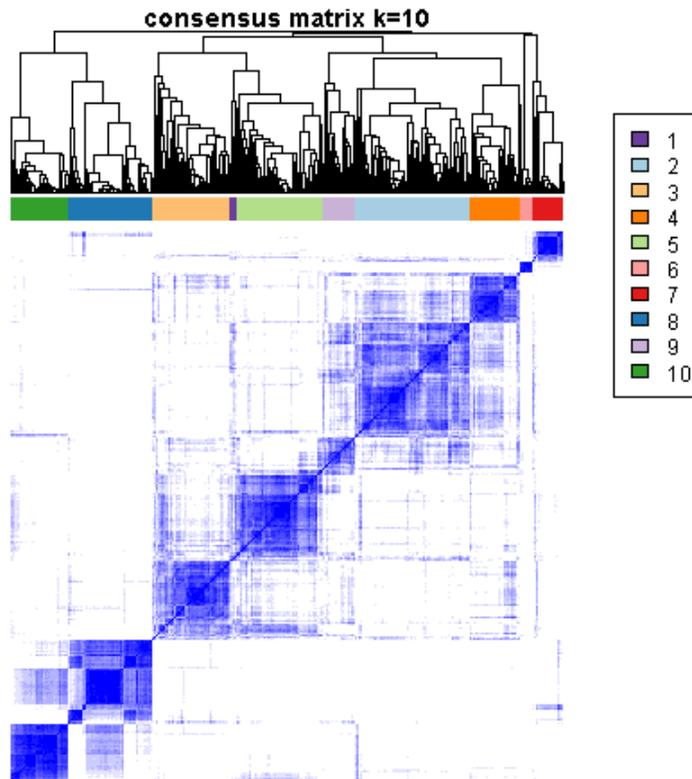
eFigure 8. Consensus matrix heat map ($k = 8$) depicting consensus values on a white to blue color scale of each cluster



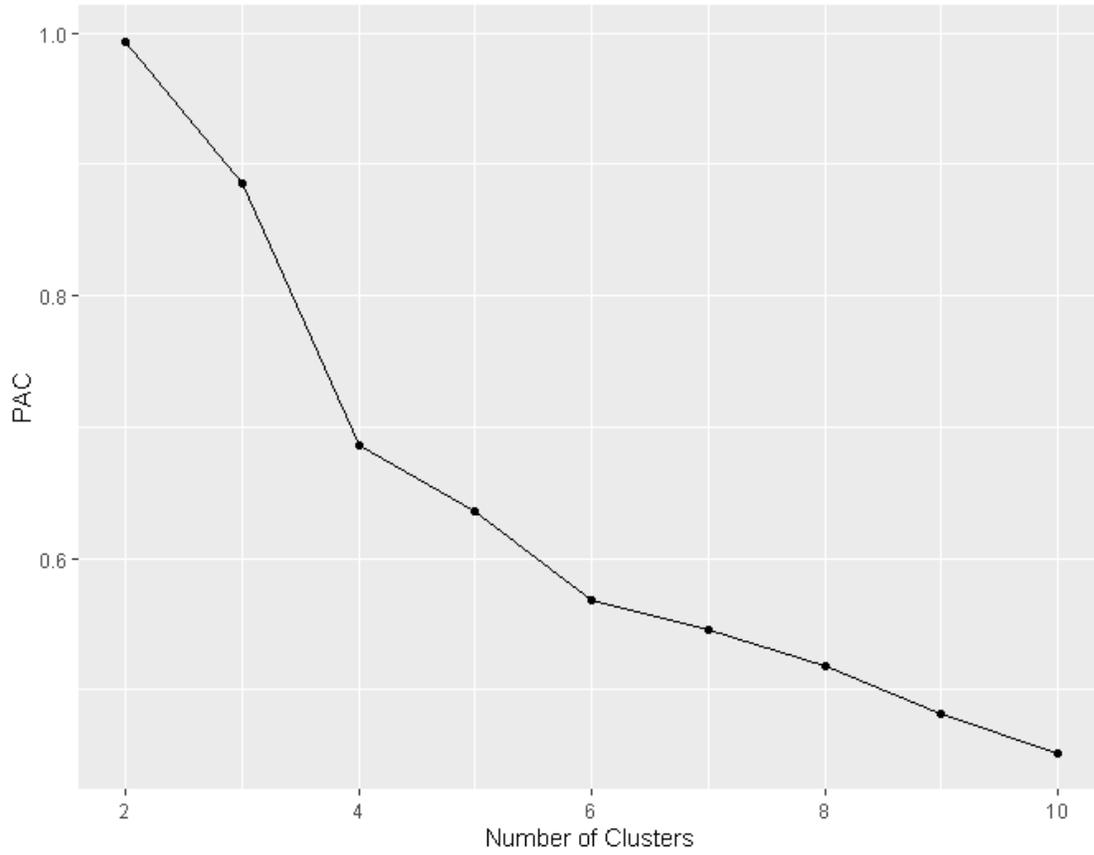
eFigure 9. Consensus matrix heat map ($k = 9$) depicting consensus values on a white to blue color scale of each cluster



eFigure 10. Consensus matrix heat map (k = 10) depicting consensus values on a white to blue color scale of each cluster

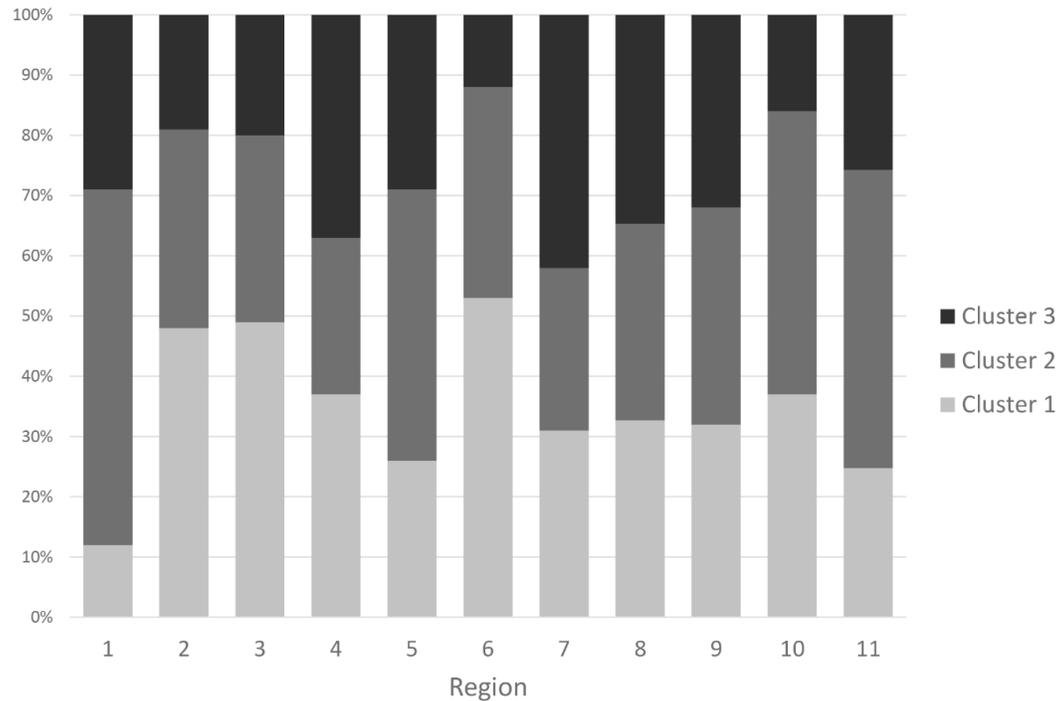


eFigure 11. The PAC values assess ambiguously clustered pairs.



eFigure 12.

Proportion of clusters according to the OPTN regions



References

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