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iBox Scoring System (Composite Biomarker Panel)

The original development of the iBox Scoring System by Loupy et al. 2019[1] in the Paris Transplant Group included time post-transplant to account for varying iBox assessments of an individual patient and to assist in patient care and prognosis estimation. The derivation dataset in this qualification submission represents all 4,000 subjects for the abbreviated iBox Scoring System described in the Loupy et al., 2019 publication. Additional analyses were conducted on this derivation dataset in which the time of evaluation was fixed at one-year post-transplant to assess the performance as a trial endpoint for a typical Phase 3 study. C-Path has evaluated the inclusion of the time post-transplant variable from 6-24 months post-transplant, recognizing the potential use in Phase 2/POC (at 6 months) and Phase 3 trials (at 1 and possibly 2 years). Tables 3-6 below are the calibration and discrimination analyses (external validation) on the qualification validation datasets with varying times post-transplant.

The frequency chart in Figure 1 below shows the distribution of assessment time points for donor-specific antibody (DSA) measurements up to 2 years post-kidney transplant. DSA was selected for illustration since it is collected less frequently than eGFR and/or proteinuria and, therefore, will be the key limiting factor for the availability of iBox measurements at various time points post-transplant across the qualification validation datasets. Helsinki University Hospital only assessed proteinuria and DSA data at one-year post-transplant, and therefore is not included in the 4-month, 6-month, and 2-year time points.

The number of transplant recipients with iBox assessments at varying times post-transplant in the external validation datasets are shown in Tables 1 and 2 below. In addition, the five-year post-transplant discrimination and calibration were assessed and are shown in Tables 3-6 below. The red colour in Tables 3 and 5 highlights c-statistics (c-stat) below 0.7. The green shading in Tables 4 and 6 indicates that the observed events are not significantly different than model predictions. Non-applicable (NA) reflects no assessments in Tables 1-2 or fewer than two events in Tables 3-6.

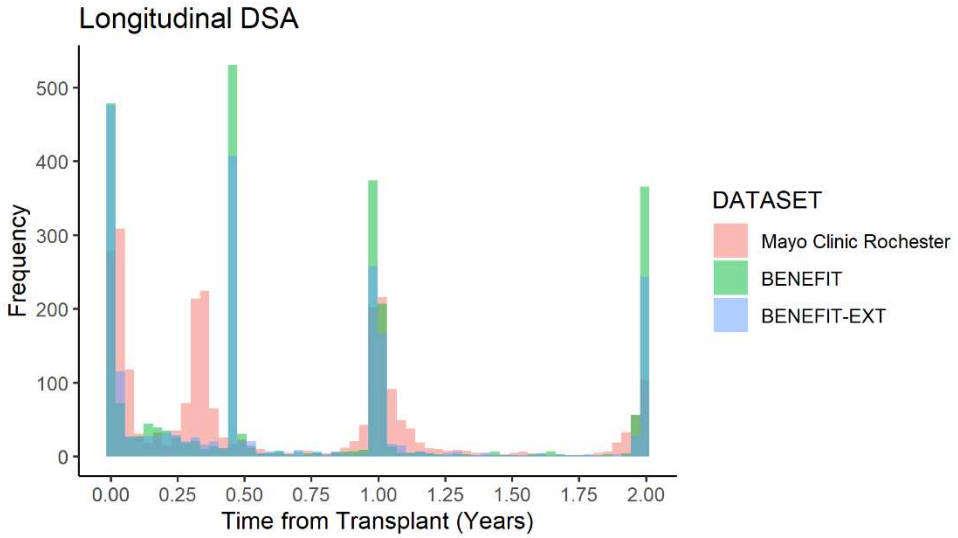

Figure 1. Frequency of DSA measurements across the qualification validation datasets

*Table 1. Number of subjects with **full** iBox Scoring System evaluations at varying time points*

Dataset	Time post-transplant			
	4-months (n)	6-months (n)	1-year (n)	2-years (n)
Helsinki University Hospital*	NA	NA	344	NA
Mayo Clinic Rochester	224	NA	483	NA
BENEFIT RCT	NA	30	416	12
BENEFIT-EXT RCT	NA	31	260	5
Total Subjects	**224**	**61**	**1,503**	**17**

* No longitudinal proteinuria or DSA data
NA reflects no assessments

*Table 2. Number of subjects with **abbreviated** iBox Scoring System evaluations at varying time points*

Dataset	Time post-transplant			
	4-months (n)	6-months (n)	1-year (n)	2-years (n)
Helsinki University Hospital*	NA	NA	344	NA
Mayo Clinic Rochester	231	NA	497	NA
BENEFIT RCT	NA	527	515	476
BENEFIT-EXT RCT	NA	383	357	328
Total Subjects	**231**	**910**	**1,713**	**804**

* No longitudinal proteinuria or DSA data
NA reflects no assessments

*Table 3. Five-year post-transplant c-statistics values for the **full** iBox Scoring System at varying time points*

Dataset	Time post-transplant															
	4-months				6-months				1-year				2-years			
	n	# Graft losses	c-stat	SE	n	# Graft losses	c-stat	SE	n	# Graft losses	c-stat	SE	n	# Graft losses	c-stat	SE
Observational	224	14	0.66	0.08	NA	NA	NA	NA	827	39	0.84	0.04	NA	NA	NA	NA
Helsinki University Hospital	NA	NA	NA	NA	NA	NA	NA	NA	344	21	0.78	0.06	NA	NA	NA	NA
Mayo Clinic Rochester	224	14	0.66	0.08	NA	NA	NA	NA	483	18	0.93	0.03	NA	NA	NA	NA
RCTs	NA	NA	NA	NA	61	8	0.78	0.06	676	24	0.76	0.06	NA	NA	NA	NA
BENEFIT	NA	NA	NA	NA	30	3	0.84	0.07	416	12	0.71	0.09	NA	NA	NA	NA
BENEFIT-EXT	NA	NA	NA	NA	31	5	0.71	0.11	260	12	0.81	0.07	NA	NA	NA	NA

- The red text colour highlights c-statistics < 0.7

- NA reflects fewer than two events

*Table 4. Poisson calibration for the **full** iBox Scoring System at varying time points*

Dataset	Time post-transplant															
	4-months				6-months				1-year				2-years			
	n	Obs	Pred	p value	n	Obs	Pred	p value	n	Obs	Pred	p value	n	Obs	Pred	p value
Observational	224	14	12.67	0.71	NA	NA	NA	NA	827	39	38.74	0.97	NA	NA	NA	NA
Helsinki University Hospital	NA	NA	NA	NA	NA	NA	NA	NA	344	21	14.40	0.08	NA	NA	NA	NA
Mayo Clinic Rochester	224	14	12.67	0.71	NA	NA	NA	NA	483	18	24.34	0.20	NA	NA	NA	NA
RCTs	NA	NA	NA	NA	61	8	5.11	0.20	676	24	27.90	0.46	NA	NA	NA	NA
BENEFIT	NA	NA	NA	NA	30	3	2.03	0.50	416	12	12.93	0.80	NA	NA	NA	NA
BENEFIT-EXT	NA	NA	NA	NA	31	5	3.08	0.28	260	12	14.97	0.44	NA	NA	NA	NA

- The green shading indicates that the observed events are not significantly different than model predictions
- NA reflects fewer than two events

*Table 5. Five-year post-transplant c-statistics values for the **abbreviated** iBox Scoring System at varying time points*

Dataset	Time post-transplant															
	4-months				6-months				1-year				2-years			
	n	# Graft losses	c-stat	SE	n	# Graft losses	c-stat	SE	n	# Graft losses	c-stat	SE	n	# Graft losses	c-stat	SE
Observational	231	14	0.64	0.08	NA	NA	NA	NA	841	41	0.80	0.04	NA	NA	NA	NA
Helsinki University Hospital	NA	NA	NA	NA	NA	NA	NA	NA	344	21	0.77	0.06	NA	NA	NA	NA
Mayo Clinic Rochester	231	14	0.64	0.08	NA	NA	NA	NA	497	20	0.84	0.05	NA	NA	NA	NA
RCTs	NA	NA	NA	NA	910	45	0.73	0.05	872	38	0.75	0.05	804	24	0.75	0.06
BENEFIT	NA	NA	NA	NA	527	19	0.68	0.08	515	15	0.70	0.08	476	11	0.73	0.10
BENEFIT-EXT	NA	NA	NA	NA	383	26	0.72	0.06	357	23	0.78	0.06	328	13	0.76	0.07

- The red text colour highlights c-statistics < 0.7
- NA reflects fewer than two events

*Table 6. Poisson calibration for the **abbreviated** iBox Scoring System at varying time points*

Dataset	Time post-transplant															
	4-months				6-months				1-year				2-years			
	n	Obs	Pred	p value	n	Obs	Pred	p value	n	Obs	Pred	p value	n	Obs	Pred	p value
Observational	231	14	13.90	0.98	NA	NA	NA	NA	841	41	40.61	0.95	NA	NA	NA	NA
Helsinki University Hospital	NA	NA	NA	NA	NA	NA	NA	NA	344	21	16.19	0.23	NA	NA	NA	NA
Mayo Clinic Rochester	231	14	13.90	0.98	NA	NA	NA	NA	497	20	24.41	0.37	NA	NA	NA	NA
RCTs	NA	NA	NA	NA	910	45	51.30	0.38	872	38	39.92	0.76	804	24	32.38	0.14
BENEFIT	NA	NA	NA	NA	527	19	22.01	0.52	515	15	16.95	0.64	476	11	13.61	0.48
BENEFIT-EXT	NA	NA	NA	NA	383	26	29.29	0.54	357	23	22.97	1.00	328	13	18.77	0.19

- The green shading indicates that the observed events are not significantly different than model predictions
- NA reflects fewer than two events

Tables 1 and 2 show the data distribution for the iBox assessments in the qualification validation datasets from 4 months up to 2 years post-transplant. There are 17 and 804 subjects with full and abbreviated iBox assessments at two-years post-transplant, respectively.

Tables 3-6 show the discrimination and calibration analyses and support the inclusion of time post-transplant in the iBox Scoring System from 6 months to 2 years post-transplant.

C-Path envisages that Phase 2/POC studies may include the endpoint at six-months post-transplant, whereas Phase 3 trials would be of 1-2 years duration to assess the endpoint.

References

1. Loupy A, Aubert O, Orandi BJ, Naesens M, Bouatou Y, Raynaud M, et al. Prediction system for risk of allograft loss in patients receiving kidney transplants: international derivation and validation study. BMJ. 2019 Sep 17;l4923.