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5. SUPPLEMENTARY REFERENCES

1. SUPPLEMENTARY METHODS

Supplementary Method 1: Population in detail, center

The European centers included Necker Hospital, Paris, France (n=1026), Saint-Louis Hospital, Paris, France (n=740), Toulouse Hospital, Toulouse, France (n=432), Bicêtre Hospital, Kremlin Bicêtre, France (n=396), University Hospital, Leuven, Belgium (n=753), University Hospital, Liege, Belgium (n=111), University Hospital Centre Zagreb, Zagreb, Croatia (n=453), Hospital Clínic i Provincial de Barcelona, Barcelona, Spain (n=350), Hospital Vall d'Hebrón, Barcelona, Spain (n=353), and Bellvitge University Hospital, Barcelona, Spain (n=96). The North American centers included the Mayo Clinic, Rochester, MN, USA (n=2933), OneLegacy organ procurement organization, Los Angeles, CA, USA (n=2811), Columbia University Medical Center, New York, NY, USA (n=1332), University of British Columbia, Vancouver, BC, Canada (n=417), and University of Alberta, Edmonton, AB, Canada (n=1161). The Australian center included the Royal Adelaide Hospital, Adelaide, Australia (n=370). The Chinese center included the Sun Yat-sen University, Guangzhou, China (n=298).

Supplementary Method 2: Systematic review

In medicine, tissue biopsies are routinely performed to determine diagnosis and guide therapeutics and prognosis assessment. In kidney transplantation, day-zero biopsies are used as baseline status of the kidney allograft to better contextualize lesions found in subsequent allograft biopsies and guide the decision-making process. However, biopsy remains an invasive and costly procedure that mobilizes human resources, thereby delaying the transplantation procedure. We searched PubMed and MEDLINE from January 2000 to January 2022, using the terms “non-invasive”, “biopsy”, “predict”, and “machine learning” without language restrictions. Our search found overall 164 studies from all medical fields. We removed 12 studies predicting a single disease diagnosis (e.g. cancer). 124 studies used histological images and 28 were related to omics-based diagnoses. Overall, in all medical fields, there was no published study on generating a virtual biopsy to assess the presence and severity of biopsy lesions using a combination of non-invasive parameters.

Supplementary Method 3: Banff grading scheme

The Banff Classification of allograft pathology was created in 1991 and is revised every two years[1]. This is an international standardization of nomenclature and criteria for the histologic diagnosis of kidney allograft rejection and chronic lesion associated with long term outcomes in kidney transplantation. The 9th Banff conference in 2007 then a working group in 2017, approved the application of the Banff criteria to the day-zero biopsy[2,3]. The criteria are as follows:

- arteriosclerosis (Banff "cv" score) as the extent of arterial intimal thickening in the most severely affected artery.
    - cv0—No chronic vascular changes.
    - cv1—Vascular narrowing of up to 25% luminal area by fibrointimal thickening.
    - cv2—Vascular narrowing of 26 to 50% luminal area by fibrointimal thickening.
    - cv3—Vascular narrowing of more than 50% luminal area by fibrointimal thickening
- arteriolar hyalinosis (Banff "ah" score) as the extent of periodic acid Schiff (PAS)-positive arteriolar hyaline thickening.
    - ah0—No PAS-positive hyaline arteriolar thickening.
    - ah1—Mild to moderate PAS-positive hyaline thickening in at least 1 arteriole.
    - ah2—Moderate to severe PAS-positive hyaline thickening in more than 1 arteriole.
    - ah3—Severe PAS-positive hyaline thickening in many arterioles.
- Interstitial fibrosis and tubular atrophy (Banff "IFTA" score) replaced the term of chronic allograft nephropathy (Banff "CAN" score) in the Banff '05[4]. This score is based on the severity of interstitial fibrosis (Banff "ci" score) and tubular atrophy (Banff "ct" score).
    - IFTA0—No Interstitial fibrosis and tubular atrophy. No tubular atrophy (ct0) and interstitial fibrosis in up to 5% of cortical area (ci0).
    - IFTA1—Mild Interstitial fibrosis and tubular atrophy. Tubular atrophy in up to 25% of the area of cortical tubules (ct1) and interstitial fibrosis in 6 to 25% of cortical area (ci1).
    - IFTA2—Moderate Interstitial fibrosis and tubular atrophy. Tubular atrophy involving 26 to 50% of the area of cortical tubules (ct2) and interstitial fibrosis in 26 to 50% of cortical area (ci2).
    - IFTA3—Severe Interstitial fibrosis and tubular atrophy. Tubular atrophy in >50% of the area of cortical tubules (ct3) and/or interstitial fibrosis in >50% of cortical area (ci3).
- Glomerulosclerosis is the percentage defined by the number of sclerotic glomeruli divided by the total number of glomeruli.

Supplementary Method 4: Predictor variables

Eleven candidate predictors of kidney day-zero histological lesions, which were examined and used at donation, were as follows:

1. Donor's age: numeric value (years)
2. Donor's sex: binary value (female or male)
3. Donor type: binary value (deceased or living donor)
4. Donation after cerebrovascular death if deceased: binary value (yes or no)
5. Donation after circulatory death (DCD) if deceased: binary value (yes or no)
6. Donor's history of hypertension: binary value (yes or no)
7. Donor's history of diabetes: binary value (yes or no)
8. Donor's hepatitis C virus status: binary value (yes or no)
9. Donor's body mass index: numeric value (kg/m^2)
10. Donor's serum creatinine lowest at donation: numeric value (mg/dL)
11. Donor's proteinuria status: binary value (yes when dipstick greater than or equal to 1 or urine protein to creatinine ratio (UPCR, g/g) greater than or equal to 0.5 g/g, otherwise no)

In case of multiple donor creatinine for acute kidney injury (AKI), we included the serum creatinine before AKI.

Supplementary Method 5: TRIPOD (adapted to the field of machine learning) checklist

Section/Topic	Checklist Item	Page
Title	Identify the study as developing and/or validating (i.e., testing) a multivariable machine learning model, the target population, and the outcome to be predicted.	1
Abstract	Provide a summary of objectives, study design or data sources, setting, participants, sample size, predictors/features, outcome, machine learning methods, intended use of the model, results, and conclusions.	3
Background and objectives	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable machine learning model, including references to existing models, and the main advantages of the used design and analyses.	4-5
	Explain the intended purpose (e.g., for prognosis or diagnostic predictions) and use for the model in the context of the clinical pathway, including its intended users (e.g., healthcare professionals, patients, public).	4-5
	Specify the study objectives, including whether the study describes the development or validation (e.g., testing) of the model or both.	4-5
Data collection and preparation		
Source of data	Describe the study design or source of data (e.g., randomized trial, cohort, routine care or registry data), separately for the development and validation (test) datasets, if applicable.	16; Supplementary method 1
	Specify the key dates of the collected participant data, including start and of participant/data accrual; and, if applicable, end of follow-up.	16
Participants	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including the number and location of centers or data sources.	Supplementary method 1; Supplementary table 14
	Describe the eligibility criteria for participants or data sources: how, where, and when potentially eligible participants were identified (e.g., symptoms, results from previous tests, inclusion in the registry, patient-care setting, location).	16
Outcome	Clearly define the outcome (e.g., ground truth or reference standard) that is predicted by the machine learning model (including the time horizon), including how and when assessed and the rationale for choosing this outcome measurement (if alternatives exist).	17; Supplementary method 3; Supplementary table 15
Predictors	Clearly define all predictors/features used in developing the multivariable machine learning model, including how and when they were measured. Consider using supplementary material for large numbers of predictors.	18; Supplementary method 4
Machine learning model development		
Participants	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Table 1; Supplementary tables 1 and 9
	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Table 1; Supplementary tables 1, 3, 4, 9, and 10
	For external validation (testing), show a comparison with the development data of the distribution of important predictors/features (demographics, predictors, and outcome).	Supplementary table 8
Data preparation and preprocessing	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	20; Supplementary method 7; Supplementary tables 3 and 4
	Specify data splitting for train (derivation) and test (validation) sets creation.	16
	Describe how unbalanced data were handled, if relevant.	18
Model development	Specify the number of participants and outcome events in each analysis.	Supplementary tables 3 and 4
	Specify which machine learning model(s) is (are) used.	19
	Describe how predictors were handled in the analyses.	Supplementary method 4
	Specify the resampling method used on training or derivation set.	19
Model performance	Specify type of model, all model-building procedures (including any predictor selection), and method for validation.	19-20

	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	19-20
	Report discrimination performance measures (with CIs) for the prediction model.	7-8; Table 2, Figure 2
	Present calibration performance measures for the machine learning model, if relevant.	Supplementary tables 7 and 11
	Present any robustness assessment and durability test used, if relevant.	9-10; Supplementary table 12
Model specification	Present the parameter importance evaluation.	7; Figure 1
	Specify the output of the model (e.g., probabilities, classification, risk grouping).	10
	Explain how to use the prediction model.	10; Figure 3; Supplementary figures 1 and 2; Supplementary video
Findings perspective		
Limitations	Discuss any limitations of the study (such as non-representative sample, few events per predictor, missing data).	13-14
Interpretation	For validation, discuss the results with reference to performance in the cross-validation data, and any other test data.	Supplementary table 6
	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	11-15
Implications	Discuss the potential clinical use of the model and implications for future research.	12-13
Supplementary information	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Supplementary information
Funding	Give the source of funding and the role of the funders for the present study.	28

Supplementary Method 6: Rationale for the cutoffs used to measure the performance metrics

We used Youden's J statistic to calibrate probability score cutoffs of the ensemble models. Each ensemble model was to optimize Youden's statistic, namely, the sum of sensitivity and specificity, based on 3-times repeated 10-folds cross-validations (30 resamples). On each fold, the best cutoff was calculated then 30 cutoffs were averaged. The computed cutoffs were then used for internal and external validations to measure the performance such as sensitivity and specificity.

Supplementary Method 7: Imputation process and included variables

We imputed the missing values with random forest machine learning algorithm, which was implemented in missForest R package[5]. The donor parameters and biopsy findings used in the imputation algorithm were i) age, ii) sex, iii) donor type (living or deceased donor), iv) cerebrovascular cause of death, v) donor after circulatory death (DCD), vi) history of hypertension, vii) diabetes, viii) hepatitis C virus (HCV) status, ix) body mass index (BMI), x), kidney function defined by serum creatinine, xi) proteinuria status, xii) arteriosclerosis (Banff cv score), xiii) arteriolar hyalinosis (Banff ah score), xiv) interstitial fibrosis and tubular atrophy (Banff IFTA score), xv) percentage of sclerotic glomeruli (glomerulosclerosis score). The maximum number of iterations was set to 10 times. Outcome variables (Banff lesions) were not imputed.

2. SUPPLEMENTARY TABLES

Supplementary Table 1 | Baseline donor characteristics of the derivation cohort by center

	Overall (n=12,402)	Mayo Clinic (n=2,933)	OneLegacy OPO (n=2,811)	University of Alberta (n=1,161)	Necker hospital (n=1,026)
Age (years), mean (SD)	46.7 (14.9)	43.4 (12.5)	43.7 (15.0)	40.6 (13.2)	53.2 (16.8)
Sex female, No. (%)	5450 (44.0%)	1602 (54.6%)	979 (34.8%)	565 (48.7%)	434 (42.3%)
Donor type					
Deceased donor, No. (%)	9395 (75.8%)	591 (20.2%)	2811 (100.0%)	765 (65.9%)	1026 (100.0%)
Death from circulatory disease, No. (%)*	1471 (15.7%)	0 (0.0%)	531 (18.9%)	25 (3.3%)	25 (2.4%)
Death from cerebrovascular disease, No. (%)*	4001 (42.8%)	0 (0.0%)	942 (33.5%)	254 (33.2%)	583 (56.8%)
Diabetes mellitus, No. (%)	782 (7.4%)	0 (0.0%)	428 (15.8%)	30 (3.2%)	76 (7.7%)
Hypertension, No. (%)	2375 (21.1%)	0 (0.0%)	916 (33.7%)	103 (11.2%)	257 (26.1%)
BMI (kg/m^2), mean (SD)	26.9 (5.5)	27.7 (5.0)	28.5 (6.7)	26.1 (5.3)	25.0 (4.7)
HCV status, No. (%)	233 (1.9%)	4 (0.1%)	176 (6.3%)	7 (0.7%)	24 (2.3%)
Creatinine (mg/dL), mean (SD)	1.2 (1.0)	1.0 (0.4)	2.0 (1.6)	0.9 (0.6)	1.0 (0.7)
Proteinuria, No. (%)	1904 (20.7%)	0 (0.0%)	317 (11.4%)	122 (33.8%)	558 (56.5%)
Number of Glomeruli, mean (SD)	39.3 (33.5)	21.2 (10.9)	83.9 (34.9)	35.2 (27.7)	18.6 (7.8)
Arteriosclerosis (cv) Banff score, No. (%)					
0	7073 (60.2%)	1714 (60.6%)	1983 (70.5%)	626 (66.2%)	302 (30.6%)
1	3105 (26.4%)	931 (32.9%)	404 (14.4%)	240 (25.4%)	328 (33.2%)
2	1325 (11.3%)	181 (6.4%)	301 (10.7%)	78 (8.2%)	321 (32.5%)
3	252 (2.1%)	2 (0.1%)	123 (4.4%)	2 (0.2%)	36 (3.6%)
Arteriolar hyalinosis (ah) Banff score, No. (%)					
0	8242 (68.8%)	2341 (84.0%)	2516 (89.5%)	624 (55.9%)	323 (31.8%)
1	2546 (21.3%)	391 (14.0%)	157 (5.6%)	334 (29.9%)	398 (39.1%)
2	968 (8.1%)	52 (1.9%)	89 (3.2%)	145 (13.0%)	248 (24.4%)
3	217 (1.8%)	3 (0.1%)	49 (1.7%)	14 (1.3%)	48 (4.7%)
Interstitial fibrosis and tubular atrophy (IFTA) Banff score, No. (%)					
0	7822 (64.4%)	2269 (79.6%)	1803 (64.1%)	571 (56.5%)	660 (65.4%)
1	3647 (30.0%)	576 (20.2%)	653 (23.2%)	395 (39.1%)	297 (29.4%)
2	562 (4.6%)	5 (0.2%)	288 (10.2%)	44 (4.4%)	43 (4.3%)
3	117 (1.0%)	1 (<0.1%)	67 (2.4%)	1 (0.1%)	9 (0.9%)
Glomerulosclerosis, median (interquartile range)	3.0 (0.0-10.0)	2.4 (0.0-8.3)	0.0 (0.0-6.0)	N/A	5.6 (0.0-12.5)

Supplementary Table 1 | Baseline donor characteristics of the population cohort by center (continued)

	KU LEUVEN (n=753)	Saint Louis hospital (n=740)	University Hospital Centre Zagreb (n=453)	Centre Hospitalier Universitaire de Toulouse (n=432)	University of British Columbia (n=417)
Age (years), mean (SD)	46.4 (13.0)	49.1 (15.3)	47.8 (12.2)	49.2 (14.3)	45.8 (13.6)
Sex female, No. (%)	337 (44.8%)	284 (38.4%)	186 (41.1%)	209 (48.4%)	192 (46.0%)
Donor type					
Deceased donor, No. (%)	753 (100.0%)	740 (100.0%)	453 (100.0%)	366 (84.7%)	300 (71.9%)
Death from circulatory disease, No. (%)*	177 (23.5%)	71 (9.6%)	0 (0.0%)	0 (0.0%)	101 (33.7%)
Death from cerebrovascular disease, No. (%)*	375 (49.8%)	429 (58%)	283 (62.5%)	197 (53.8%)	72 (24%)
Diabetes mellitus, No. (%)	N/A	32 (4.4%)	7 (1.5%)	20 (4.8%)	18 (4.6%)
Hypertension, No. (%)	98 (13.0%)	155 (21.2%)	125 (27.6%)	61 (17.3%)	42 (10.9%)
BMI (kg/m^2), mean (SD)	25.2 (4.1)	25.0 (4.6)	26.3 (3.6)	25.4 (4.2)	27.1 (5.3)
HCV status, No. (%)	0 (0.0%)	2 (0.3%)	0 (0.0%)	6 (2.0%)	9 (2.2%)
Creatinine (mg/dL), mean (SD)	0.8 (0.5)	1.0 (0.5)	0.9 (0.4)	1.0 (0.5)	1.0 (0.8)
Proteinuria, No. (%)	N/A	265 (39.5%)	92 (20.3%)	109 (41.4%)	144 (37.2%)
Number of Glomeruli, mean (SD)	N/A	19.1 (7.4)	57.0 (33.9)	16.6 (5.1)	26.6 (12.0)
Arteriosclerosis (cv) Banff score, No. (%)					
0	664 (88.2%)	252 (35.5%)	303 (66.9%)	222 (54.5%)	381 (91.4%)
1	70 (9.3%)	245 (34.5%)	140 (30.9%)	112 (27.5%)	23 (5.5%)
2	19 (2.5%)	186 (26.2%)	6 (1.3%)	54 (13.3%)	11 (2.6%)
3	0 (0.0%)	27 (3.8%)	4 (0.9%)	19 (4.7%)	2 (0.5%)
Arteriolar hyalinosis (ah) Banff score, No. (%)					
0	546 (72.5%)	284 (38.7%)	249 (55.0%)	211 (50.1%)	207 (49.6%)
1	169 (22.4%)	310 (42.2%)	178 (39.3%)	139 (33.0%)	81 (19.4%)
2	35 (4.6%)	105 (14.3%)	23 (5.1%)	60 (14.3%)	106 (25.4%)
3	3 (0.4%)	35 (4.8%)	3 (0.7%)	11 (2.6%)	23 (5.5%)
Interstitial fibrosis and tubular atrophy (IFTA) Banff score, No. (%)					
0	545 (72.4%)	480 (65.0%)	165 (36.4%)	327 (75.7%)	259 (62.1%)
1	191 (25.4%)	204 (27.6%)	256 (56.5%)	99 (22.9%)	154 (36.9%)
2	13 (1.7%)	41 (5.5%)	31 (6.8%)	4 (0.9%)	4 (1.0%)
3	4 (0.5%)	14 (1.9%)	1 (0.2%)	2 (0.5%)	0 (0.0%)
Glomerulosclerosis, median (interquartile range)	0.0 (0.0-8.3)	5.3 (0.0-12.5)	3.3 (0.0-7.7)	6.2 (0.0-14.3)	4.8 (0.0-9.5)

Supplementary Table 1 | Baseline donor characteristics of the population cohort by center (continued)

	Bicêtre hospital (n=396)	Royal Adelaide Hospital (n=370)	Vall d'Hebron University Hospital (n=353)	Hospital Cliníc i Provincial de Barcelona (n=350)	Centre hospitalier universitaire de Liège (n=111)	Hospital Universitari de Bellvitge (n=96)
Age (years), mean (SD)	57.2 (16.4)	46.9 (14.4)	61.3 (11.7)	60.3 (10.2)	44.4 (11.4)	63.2 (12.1)
Sex female, No. (%)	145 (36.6%)	187 (51.9%)	142 (40.2%)	102 (29.1%)	49 (44.1%)	37 (38.5%)
Donor type						
Deceased donor, No. (%)	396 (100.0%)	284 (76.8%)	353 (100.0%)	350 (100.0%)	111 (100.0%)	96 (100.0%)
Death from circulatory disease, No. (%)*	99 (25%)	65 (23%)	103 (29.2%)	187 (53.4%)	48 (43.2%)	39 (40.6%)
Death from cerebrovascular disease, No. (%)*	182 (46%)	113 (40.5%)	207 (58.6%)	269 (76.9%)	58 (52.3%)	37 (38.5%)
Diabetes mellitus, No. (%)	47 (12.0%)	10 (2.7%)	61 (17.3%)	35 (10.0%)	3 (3.3%)	15 (19.2%)
Hypertension, No. (%)	140 (35.7%)	47 (12.8%)	198 (56.2%)	171 (48.9%)	24 (25.3%)	38 (48.7%)
BMI (kg/m^2), mean (SD)	26.0 (5.1)	26.8 (5.7)	27.8 (5.8)	27.5 (4.2)	25.9 (4.3)	27.7 (4.9)
HCV status, No. (%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	3 (0.9%)	0 (0.0%)	0 (0.0%)
Creatinine (mg/dL), mean (SD)	1.0 (0.5)	0.8 (0.3)	0.9 (0.4)	1.2 (0.6)	0.8 (0.4)	0.9 (0.3)
Proteinuria, No. (%)	169 (53.1%)	3 (3.7%)	38 (13.1%)	36 (23.4%)	42 (42.4%)	9 (45.0%)
Number of Glomeruli, mean (SD)	39.2 (30.9)	38.2 (17.4)	N/A	N/A	27.6 (16.7)	N/A
Arteriosclerosis (cv) Banff score, No. (%)						
0	139 (36.9%)	81 (51.3%)	133 (37.7%)	125 (35.8%)	101 (91.0%)	47 (49.5%)
1	133 (35.3%)	48 (30.4%)	184 (52.1%)	210 (60.2%)	6 (5.4%)	31 (32.6%)
2	84 (22.3%)	18 (11.4%)	35 (9.9%)	13 (3.7%)	3 (2.7%)	15 (15.8%)
3	21 (5.6%)	11 (7.0%)	1 (0.3%)	1 (0.3%)	1 (0.9%)	2 (2.1%)
Arteriolar hyalinosis (ah) Banff score, No. (%)						
0	192 (52.3%)	280 (79.3%)	177 (50.4%)	135 (72.6%)	94 (85.5%)	63 (65.6%)
1	103 (28.1%)	63 (17.8%)	136 (38.7%)	51 (27.4%)	9 (8.2%)	27 (28.1%)
2	49 (13.4%)	8 (2.3%)	36 (10.3%)	0 (0.0%)	6 (5.5%)	6 (6.2%)
3	23 (6.3%)	2 (0.6%)	2 (0.6%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Interstitial fibrosis and tubular atrophy (IFTA) Banff score, No. (%)						
0	127 (32.4%)	328 (88.6%)	40 (11.3%)	130 (37.1%)	103 (92.8%)	15 (15.6%)
1	206 (52.6%)	37 (10.0%)	289 (81.9%)	214 (61.1%)	7 (6.3%)	69 (71.9%)
2	43 (11.0%)	4 (1.1%)	24 (6.8%)	6 (1.7%)	1 (0.9%)	11 (11.5%)
3	16 (4.1%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Glomerulosclerosis, median (interquartile range)	8.3 (2.0-15.5)	3.9 (0.0-9.1)	5.1 (2.0-10.0)	7.4 (7.4-7.4)†	0.0 (0.0-6.5)	7.4 (0.0-7.4)†

Supplementary Table 2 | Baseline donor characteristics of the derivation cohort by donor type

	N	Overall (n=12,402)	N	Deceased Donor (n=9,395)	N	Living Donor (n=3,007)	p-value
Age (years), mean (SD)	12402	46.7 (14.9)	9395	47.3 (15.7)	3007	44.8 (12.0)	<0.001
Sex female, No. (%)	12391	5450 (44.0%)	9389	3659 (39.0%)	3002	1791 (59.7%)	<0.001
Donor type							
Deceased donor, No. (%)	12402	9395 (75.8%)	9395	9395 (100.0%)	3007	0 (0.0%)	<0.001
Death from circulatory disease, No. (%)*	9360	1471 (15.7%)	9360	1471 (15.7%)	0	0 (-)	<0.001
Death from cerebrovascular disease, No. (%)*	9354	4001 (42.8%)	9354	4001 (42.8%)	0	0 (-)	<0.001
Diabetes mellitus, No. (%)	10585	782 (7.4%)	7791	779 (10.0%)	2794	3 (0.1%)	<0.001
Hypertension, No. (%)	11274	2375 (21.1%)	8480	2360 (27.8%)	2794	15 (0.5%)	<0.001
BMI (kg/m^2), mean (SD)	11456	26.9 (5.5)	8538	26.7 (5.7)	2918	27.4 (4.9)	<0.001
HCV status, No. (%)	12004	233 (1.9%)	9104	233 (2.6%)	2900	0 (0.0%)	<0.001
Creatinine (mg/dL), mean (SD)	10924	1.2 (1.0)	8583	1.3 (1.1)	2341	0.9 (0.2)	<0.001
Proteinuria, No. (%)	9218	1904 (20.7%)	6609	1904 (28.8%)	2609	0 (0.0%)	<0.001
Number of Glomeruli, mean (SD)	6993	39.3 (33.5)	5903	41.5 (35.3)	1090	27.2 (17.0)	<0.001
Arteriosclerosis (cv) Banff score, No. (%)	11755		8975		2780		<0.001
0		7073 (60.2%)		5334 (59.4%)		1739 (62.6%)	
1		3105 (26.4%)		2228 (24.8%)		877 (31.5%)	
2		1325 (11.3%)		1163 (13.0%)		162 (5.8%)	
3		252 (2.1%)		250 (2.8%)		2 (0.1%)	
Arteriolar hyalinosis (ah) Banff score, No. (%)	11973		9108		2865		<0.001
0		8242 (68.8%)		5918 (65.0%)		2324 (81.1%)	
1		2546 (21.3%)		2097 (23.0%)		449 (15.7%)	
2		968 (8.1%)		878 (9.6%)		90 (3.1%)	
3		217 (1.8%)		215 (2.4%)		2 (0.1%)	
Interstitial fibrosis and tubular atrophy (IFTA) Banff score, No. (%)	12148		9285		2863		<0.001
0		7822 (64.4%)		5606 (60.4%)		2216 (77.4%)	
1		3647 (30.0%)		3014 (32.5%)		633 (22.1%)	
2		562 (4.6%)		549 (5.9%)		13 (0.5%)	
3		117 (1.0%)		116 (1.2%)		1 (<0.1%)	
Glomerulosclerosis, median (interquartile range)	8826	3.0 (0.0-10.0)	8151	3.0 (0.0-10.0)	675	4.2 (0.0-9.1)	0.934

Supplementary Table 3 | Baseline donor characteristics of the derivation cohort before and after imputation comparison

	N	Before Imputation (n=12,402)	N	After Imputation (n=12,402)	p-value
Age (years), mean (SD)	12402	46.7 (14.9)	12402	46.7 (14.9)	1.00
Sex female, No. (%)	12391	5450 (44.0%)	12402	5454 (44.0%)	1.00
Donor type, No. (%)					
Deceased donor, No. (%)	12402	9395 (75.8%)	12402	9395 (75.8%)	1.00
Death from circulatory disease, No. (%)*	9360	1471 (15.7%)	9395	1475 (15.7%)	0.992
Death from cerebrovascular disease, No. (%)*	9354	4001 (42.8%)	9395	4009 (42.7%)	0.900
Diabetes mellitus, No. (%)	10585	782 (7.4%)	12402	809 (6.5%)	0.0108
Hypertension, No. (%)	11274	2375 (21.1%)	12402	2497 (20.1%)	0.0791
BMI (kg/m^2), mean (SD)	11456	26.9 (5.5)	12402	26.8 (5.3)	0.339
HCV status, No. (%)	12004	233 (1.9%)	12402	243 (2.0%)	0.954
Creatinine (mg/dL), mean (SD)	10924	1.2 (1.0)	12402	1.2 (1.0)	0.325
Proteinuria, No. (%)	9218	1904 (20.7%)	12402	3307 (26.7%)	<0.001
Number of Glomeruli, mean (SD)	6993	39.3 (33.5)	6993	39.3 (33.5)	1.00
Arteriosclerosis (cv) Banff score, No. (%)	11755		11755		1.00
0		7073 (60.2%)		7073 (60.2%)	
1		3105 (26.4%)		3105 (26.4%)	
2		1325 (11.3%)		1325 (11.3%)	
3		252 (2.1%)		252 (2.1%)	
Arteriolar hyalinosis (ah) Banff score, No. (%)	11973		11973		1.00
0		8242 (68.8%)		8242 (68.8%)	
1		2546 (21.3%)		2546 (21.3%)	
2		968 (8.1%)		968 (8.1%)	
3		217 (1.8%)		217 (1.8%)	
Interstitial fibrosis and tubular atrophy (IFTA) Banff score, No. (%)	12148		12148		1.00
0		7822 (64.4%)		7822 (64.4%)	
1		3647 (30.0%)		3647 (30.0%)	
2		562 (4.6%)		562 (4.6%)	
3		117 (1.0%)		117 (1.0%)	
Glomerulosclerosis, median (interquartile range)	8826	3.0 (0.0-10.0)	8826	3.0 (0.0-10.0)	1.00

Supplementary Table 4 | Baseline donor characteristics of the external validation cohort before and after imputation comparison

	N	Before Imputation (n=1,630)	N	After Imputation (n=1,630)	p-value
Age (years), mean (SD)	1630	48.0 (13.2)	1630	48.0 (13.2)	1.00
Sex female, No. (%)	1630	723 (44.4%)	1630	723 (44.4%)	1.00
Donor type, No. (%)					
Deceased donor, No. (%)	1630	1124 (69.0%)	1630	1124 (69.0%)	1.00
Death from circulatory disease, No. (%)*	1124	131 (11.7%)	1630	131 (11.7%)	1.00
Death from cerebrovascular disease, No. (%)*	1124	525 (46.7%)	1630	525 (46.7%)	1.00
Diabetes mellitus, No. (%)	1615	215 (13.3%)	1630	223 (13.7%)	0.798
Hypertension, No. (%)	1618	594 (36.7%)	1630	605 (37.1%)	0.839
BMI (kg/m^2), mean (SD)	1624	27.6 (6.3)	1630	27.6 (6.3)	0.979
HCV status, No. (%)	1630	49 (3.0%)	1630	49 (3.0%)	1.00
Creatinine (mg/dL), mean (SD)	1217	1.6 (1.1)	1630	1.5 (1.0)	<0.001
Proteinuria, No. (%)	1623	587 (36.2%)	1630	593 (36.4%)	0.928
Number of Glomeruli, mean (SD)	971	54.7 (45.0)	971	54.7 (45.0)	1.00
Arteriosclerosis (cv) Banff score, No. (%)	1625		1625		1.00
0		453 (27.9%)		453 (27.9%)	
1		551 (33.9%)		551 (33.9%)	
2		590 (36.3%)		590 (36.3%)	
3		31 (1.9%)		31 (1.9%)	
Arteriolar hyalinosis (ah) Banff score, No. (%)	953		953		1.00
0		513 (53.8%)		513 (53.8%)	
1		366 (38.4%)		366 (38.4%)	
2		61 (6.4%)		61 (6.4%)	
3		13 (1.4%)		13 (1.4%)	
Interstitial fibrosis and tubular atrophy (IFTA) Banff score, No. (%)	1630		1630		1.00
0		658 (40.4%)		658 (40.4%)	
1		501 (30.7%)		501 (30.7%)	
2		467 (28.7%)		467 (28.7%)	
3		4 (0.2%)		4 (0.2%)	
Glomerulosclerosis, median (interquartile range)	1629	2.1 (0.0-12.5)	1629	2.1 (0.0-12.5)	1.00

Supplementary Table 5 | Hyperparameters tuning and results

Supplementary Table 5.1 | Arteriosclerosis (Banff cv score)

Machine learning models	Hyperparameters
Random Forest	mtry=4
Gradient Boosting Machine	n.trees=700 interaction.depth=13 shrinkage=0.01 n.minobsinnode=7
Extreme Gradient Boosting Tree	nrounds=54 max_depth=18 eta=0.1852479 gamma=0.02767602 colsample_bytree=0.6063756 min_child_weight=0.9 subsample=0.790576
Linear Discriminant Analysis	-
Model Averaged Neural Network	size=25 decay=0.1 bag=TRUE
Multinomial Logistic Regression	decay=0.001

Supplementary Table 5.2 | Arteriolar hyalinosis (Banff ah score)

Machine learning models	Hyperparameters
Random Forest	mtry=4
Gradient Boosting Machine	n.trees=700 interaction.depth=13 shrinkage=0.01 n.minobsinnode=5
Extreme Gradient Boosting Tree	nrounds=27 max_depth=18 eta=0.06210775 gamma=0.01385926 colsample_bytree=0.8300242 min_child_weight=1.1 subsample=0.8261786
Linear Discriminant Analysis	-
Model Averaged Neural Network	size=15 decay=0.1 bag=TRUE
Multinomial Logistic Regression	decay=0.001

Supplementary Table 5.3 | Interstitial fibrosis and tubular atrophy (Banff IFTA score)

Machine learning models	Hyperparameters
Random Forest	mtry=4
Gradient Boosting Machine	n.trees=700 interaction.depth=13 shrinkage=0.01 n.minobsinnode=7
Extreme Gradient Boosting Tree	nrounds=38 max_depth=15 eta=0.1508891 gamma=0.04430697 colsample_bytree=0.5812269 min_child_weight=1.9 subsample=0.9993576
Linear Discriminant Analysis	-
Model Averaged Neural Network	size=10 decay=0.01 bag=FALSE
Multinomial Logistic Regression	decay=0.01

Supplementary Table 5.4 | Glomerulosclerosis (percentage of sclerotic glomeruli)

Machine learning models	Hyperparameters
Random Forest	mtry=8
Gradient Boosting Machine	n.trees=700 interaction.depth=13 shrinkage=0.01 n.minobsinnode=5
Extreme Gradient Boosting Tree	nrounds=283 max_depth=18 eta=0.01032906 gamma=0.04123139 colsample_bytree=0.5279746 min_child_weight=0.7 subsample=0.6965341
Model Averaged Neural Network	size=10 decay=0.01 bag=FALSE
Ensemble model (linear regression)	-

Supplementary Table 6 | Internal validation of the virtual biopsy system during cross-validation process

Supplementary Table 6.1 | Internal validation of the virtual biopsy system during cross-validation process (cv score)

Resample	Random Forest	Gradient Boosting Machine	Extreme Gradient Boosting Tree	Linear Discriminant Analysis	Model Averaged Neural Network	Multinomial logistic regression	Ensemble model
Fold01.Rep1	0.844	0.806	0.844	0.741	0.760	0.735	0.826
Fold02.Rep1	0.834	0.819	0.839	0.741	0.766	0.740	0.827
Fold03.Rep1	0.834	0.785	0.806	0.757	0.768	0.762	0.815
Fold04.Rep1	0.854	0.820	0.850	0.777	0.798	0.783	0.854
Fold05.Rep1	0.832	0.813	0.820	0.765	0.774	0.770	0.828
Fold06.Rep1	0.823	0.795	0.823	0.755	0.766	0.753	0.817
Fold07.Rep1	0.849	0.820	0.845	0.780	0.783	0.784	0.852
Fold08.Rep1	0.813	0.788	0.818	0.746	0.756	0.750	0.816
Fold09.Rep1	0.850	0.810	0.841	0.764	0.784	0.763	0.849
Fold10.Rep1	0.840	0.825	0.817	0.786	0.791	0.790	0.842
Fold01.Rep2	0.834	0.818	0.833	0.770	0.796	0.772	0.837
Fold02.Rep2	0.838	0.814	0.823	0.781	0.786	0.783	0.839
Fold03.Rep2	0.832	0.815	0.833	0.759	0.771	0.761	0.837
Fold04.Rep2	0.841	0.809	0.844	0.753	0.758	0.750	0.837
Fold05.Rep2	0.833	0.820	0.832	0.760	0.792	0.769	0.835
Fold06.Rep2	0.840	0.798	0.838	0.753	0.765	0.760	0.838
Fold07.Rep2	0.838	0.801	0.827	0.750	0.766	0.751	0.827
Fold08.Rep2	0.819	0.791	0.808	0.763	0.785	0.762	0.827
Fold09.Rep2	0.808	0.780	0.805	0.757	0.749	0.759	0.802
Fold10.Rep2	0.847	0.817	0.827	0.759	0.791	0.761	0.834
Fold01.Rep3	0.824	0.796	0.818	0.757	0.775	0.765	0.824
Fold02.Rep3	0.836	0.808	0.825	0.757	0.778	0.757	0.833
Fold03.Rep3	0.840	0.804	0.837	0.752	0.761	0.747	0.830
Fold04.Rep3	0.821	0.806	0.829	0.764	0.767	0.766	0.828
Fold05.Rep3	0.838	0.797	0.832	0.742	0.781	0.751	0.829
Fold06.Rep3	0.823	0.788	0.814	0.756	0.776	0.757	0.820
Fold07.Rep3	0.844	0.812	0.845	0.766	0.788	0.770	0.849
Fold08.Rep3	0.860	0.828	0.856	0.799	0.813	0.801	0.860
Fold09.Rep3	0.842	0.822	0.848	0.750	0.780	0.749	0.839
Fold10.Rep3	0.835	0.817	0.825	0.771	0.792	0.771	0.838

Supplementary Table 6.2 | Internal validation of the virtual biopsy system during cross-validation process (ah score)

Resample	Random Forest	Gradient Boosting Machine	Extreme Gradient Boosting Tree	Linear Discriminant Analysis	Model Averaged Neural Network	Multinomial logistic regression	Ensemble model
Fold01.Rep1	0.811	0.778	0.794	0.713	0.760	0.714	0.804
Fold02.Rep1	0.785	0.769	0.755	0.736	0.713	0.733	0.800
Fold03.Rep1	0.767	0.755	0.770	0.704	0.718	0.703	0.769
Fold04.Rep1	0.769	0.753	0.769	0.703	0.719	0.706	0.773
Fold05.Rep1	0.747	0.722	0.744	0.684	0.702	0.690	0.745
Fold06.Rep1	0.780	0.754	0.757	0.701	0.753	0.710	0.778
Fold07.Rep1	0.797	0.756	0.772	0.688	0.701	0.690	0.777
Fold08.Rep1	0.743	0.720	0.747	0.686	0.700	0.689	0.745
Fold09.Rep1	0.737	0.732	0.740	0.722	0.704	0.723	0.759
Fold10.Rep1	0.754	0.737	0.751	0.698	0.717	0.708	0.762
Fold01.Rep2	0.810	0.797	0.812	0.734	0.738	0.733	0.813
Fold02.Rep2	0.770	0.746	0.771	0.693	0.690	0.692	0.763
Fold03.Rep2	0.738	0.690	0.741	0.681	0.694	0.686	0.733
Fold04.Rep2	0.755	0.710	0.725	0.707	0.736	0.714	0.756
Fold05.Rep2	0.794	0.773	0.797	0.680	0.713	0.682	0.776
Fold06.Rep2	0.752	0.741	0.763	0.701	0.724	0.708	0.760
Fold07.Rep2	0.760	0.733	0.755	0.697	0.719	0.702	0.769
Fold08.Rep2	0.781	0.752	0.782	0.707	0.722	0.706	0.780
Fold09.Rep2	0.819	0.792	0.807	0.728	0.747	0.729	0.812
Fold10.Rep2	0.784	0.776	0.777	0.703	0.734	0.707	0.784
Fold01.Rep3	0.751	0.741	0.762	0.713	0.736	0.712	0.768
Fold02.Rep3	0.786	0.759	0.784	0.695	0.712	0.700	0.779
Fold03.Rep3	0.779	0.745	0.773	0.701	0.735	0.703	0.772
Fold04.Rep3	0.752	0.732	0.748	0.693	0.699	0.693	0.758
Fold05.Rep3	0.779	0.760	0.770	0.737	0.729	0.739	0.786
Fold06.Rep3	0.780	0.737	0.764	0.672	0.684	0.682	0.755
Fold07.Rep3	0.765	0.729	0.763	0.713	0.737	0.717	0.766
Fold08.Rep3	0.799	0.785	0.788	0.698	0.732	0.692	0.795
Fold09.Rep3	0.797	0.783	0.786	0.718	0.740	0.721	0.799
Fold10.Rep3	0.773	0.737	0.757	0.685	0.706	0.684	0.764

Supplementary Table 6.3 | Internal validation of the virtual biopsy system during cross-validation process (IFTA score)

Resample	Random Forest	Gradient Boosting Machine	Extreme Gradient Boosting Tree	Linear Discriminant Analysis	Model Averaged Neural Network	Multinomial logistic regression	Ensemble model
Fold01.Rep1	0.801	0.749	0.781	0.734	0.717	0.739	0.803
Fold02.Rep1	0.869	0.832	0.855	0.793	0.763	0.790	0.855
Fold03.Rep1	0.843	0.827	0.838	0.779	0.723	0.777	0.840
Fold04.Rep1	0.790	0.764	0.768	0.728	0.748	0.735	0.796
Fold05.Rep1	0.826	0.782	0.832	0.710	0.687	0.708	0.799
Fold06.Rep1	0.862	0.832	0.857	0.763	0.734	0.766	0.851
Fold07.Rep1	0.836	0.815	0.836	0.781	0.782	0.783	0.834
Fold08.Rep1	0.848	0.839	0.856	0.761	0.768	0.768	0.847
Fold09.Rep1	0.788	0.765	0.780	0.715	0.736	0.715	0.805
Fold10.Rep1	0.852	0.851	0.862	0.741	0.808	0.749	0.853
Fold01.Rep2	0.856	0.821	0.850	0.776	0.796	0.775	0.864
Fold02.Rep2	0.836	0.819	0.841	0.767	0.729	0.763	0.837
Fold03.Rep2	0.834	0.811	0.813	0.752	0.772	0.759	0.835
Fold04.Rep2	0.769	0.731	0.777	0.690	0.709	0.695	0.764
Fold05.Rep2	0.813	0.797	0.798	0.763	0.742	0.759	0.817
Fold06.Rep2	0.786	0.762	0.789	0.732	0.732	0.733	0.801
Fold07.Rep2	0.865	0.848	0.865	0.757	0.808	0.756	0.856
Fold08.Rep2	0.826	0.817	0.835	0.753	0.803	0.761	0.842
Fold09.Rep2	0.827	0.790	0.835	0.713	0.742	0.723	0.799
Fold10.Rep2	0.875	0.853	0.856	0.810	0.831	0.807	0.876
Fold01.Rep3	0.814	0.784	0.819	0.741	0.761	0.738	0.811
Fold02.Rep3	0.834	0.813	0.828	0.750	0.738	0.752	0.835
Fold03.Rep3	0.850	0.804	0.851	0.785	0.775	0.782	0.849
Fold04.Rep3	0.859	0.823	0.856	0.783	0.788	0.781	0.858
Fold05.Rep3	0.815	0.806	0.825	0.733	0.770	0.747	0.821
Fold06.Rep3	0.837	0.810	0.837	0.740	0.749	0.750	0.828
Fold07.Rep3	0.822	0.803	0.800	0.717	0.736	0.715	0.816
Fold08.Rep3	0.774	0.753	0.785	0.741	0.736	0.740	0.791
Fold09.Rep3	0.862	0.847	0.859	0.779	0.806	0.788	0.868
Fold10.Rep3	0.839	0.811	0.838	0.725	0.732	0.725	0.833

Supplementary Table 6.4 | Internal validation of the virtual biopsy system during cross-validation process (percentage of sclerotic glomeruli)

Resample	Random Forest	Gradient Boosting Machine	Extreme Gradient Boosting Tree	Model Averaged Neural Network	Ensemble model
Fold01.Rep1	6.050	6.573	6.043	6.714	6.044
Fold02.Rep1	5.734	6.257	5.662	6.479	5.969
Fold03.Rep1	5.606	6.288	5.503	6.313	5.974
Fold04.Rep1	5.624	6.447	5.762	6.548	6.014
Fold05.Rep1	5.797	6.559	5.806	6.760	5.997
Fold06.Rep1	5.889	6.529	5.649	6.483	5.998
Fold07.Rep1	5.591	6.344	5.667	6.535	6.029
Fold08.Rep1	5.905	6.524	5.945	6.492	5.981
Fold09.Rep1	5.995	6.733	5.991	6.670	5.981
Fold10.Rep1	6.084	6.636	5.896	6.680	6.002
Fold01.Rep2	6.109	6.609	5.978	6.699	5.935
Fold02.Rep2	5.592	6.237	5.450	6.281	6.048
Fold03.Rep2	5.551	6.312	5.475	6.465	5.992
Fold04.Rep2	5.813	6.389	5.856	6.477	6.005
Fold05.Rep2	5.644	6.399	5.719	6.599	6.035
Fold06.Rep2	5.922	6.780	5.821	6.865	5.984
Fold07.Rep2	5.918	6.629	5.928	6.793	5.987
Fold08.Rep2	5.907	6.533	5.702	6.549	6.030
Fold09.Rep2	5.730	6.476	5.686	6.582	6.004
Fold10.Rep2	5.670	6.486	5.699	6.451	5.970
Fold01.Rep3	6.143	6.830	6.097	6.873	5.973
Fold02.Rep3	5.938	6.678	5.835	6.751	5.996
Fold03.Rep3	5.641	6.336	5.594	6.394	5.970
Fold04.Rep3	5.792	6.418	5.718	6.508	6.033
Fold05.Rep3	5.768	6.391	5.800	6.493	6.058
Fold06.Rep3	5.909	6.636	5.891	6.711	6.040
Fold07.Rep3	5.877	6.508	5.845	6.627	5.959
Fold08.Rep3	5.494	6.248	5.494	6.269	6.016
Fold09.Rep3	6.031	6.617	6.040	6.825	6.009
Fold10.Rep3	5.473	6.174	5.494	6.306	5.937

Supplementary Table 7 | Calibration confusion matrices of the virtual biopsy system (internal validation)

Supplementary Table 7.1 | Confusion matrix on the arteriosclerosis (cv biopsy lesion score)

Reference	Virtual Biopsy Prediction			
	0	**1**	**2**	**3**
0	5382	1255	327	109
1	945	1481	568	111
2	147	340	741	97
3	4	20	94	134

Supplementary Table 7.2 | Confusion matrix on the arteriolar hyalinosis (ah biopsy lesion score)

Reference	Virtual Biopsy Prediction			
	0	**1**	**2**	**3**
0	6286	1292	361	303
1	875	1118	395	158
2	182	292	381	113
3	21	39	58	99

Supplementary Table 7.3 | Confusion matrix on the interstitial fibrosis and tubular atrophy (IFTA biopsy lesion score)

Reference	Virtual Biopsy Prediction			
	0	**1**	**2**	**3**
0	6071	1475	230	46
1	1086	2175	319	67
2	41	198	286	37
3	8	21	27	61

Supplementary Table 8 | Comparison of donor baseline characteristics between the derivation cohort and the external validation cohort

	N	Overall (n=14,032)	N	Derivation (n=12,402)	N	External (n=1,630)	p-value
Age (years), mean (SD)	14032	46.8 (14.7)	12402	46.7 (14.9)	1630	48.0 (13.2)	<0.001
Sex female, No. (%)	14021	6173 (44.0%)	12391	5450 (44.0%)	1630	723 (44.4%)	0.796
Donor type							
Deceased donor, No. (%)	14032	10519 (75.0%)	12402	9395 (75.8%)	1630	1124 (69.0%)	<0.001
Death from circulatory disease, No. (%)*	10484	1602 (15.3%)	9360	1471 (15.7%)	1124	131 (11.7%)	<0.001
Death from cerebrovascular disease, No. (%)*	10478	4526 (43.2%)	9354	4001 (42.8%)	1124	525 (46.7%)	0.0130
Diabetes mellitus, No. (%)	12200	997 (8.2%)	10585	782 (7.4%)	1615	215 (13.3%)	<0.001
Hypertension, No. (%)	12892	2969 (23.0%)	11274	2375 (21.1%)	1618	594 (36.7%)	<0.001
BMI (kg/m^2), mean (SD)	13080	27.0 (5.6)	11456	26.9 (5.5)	1624	27.6 (6.3)	<0.001
HCV status, No. (%)	13634	282 (2.1%)	12004	233 (1.9%)	1630	49 (3.0%)	0.00610
Creatinine (mg/dL), mean (SD)	12141	1.2 (1.0)	10924	1.2 (1.0)	1217	1.6 (1.1)	<0.001
Proteinuria, No. (%)	10841	2491 (23.0%)	9218	1904 (20.7%)	1623	587 (36.2%)	<0.001
Number of Glomeruli, mean (SD)	7964	41.2 (35.5)	6993	39.3 (33.5)	971	54.7 (45.0)	<0.001
Arteriosclerosis (cv) Banff score, No. (%)	13380		11755		1625		<0.001
0		7526 (56.2%)		7073 (60.2%)		453 (27.9%)	
1		3656 (27.3%)		3105 (26.4%)		551 (33.9%)	
2		1915 (14.3%)		1325 (11.3%)		590 (36.3%)	
3		283 (2.1%)		252 (2.1%)		31 (1.9%)	
Arteriolar hyalinosis (ah) Banff score, No. (%)	12926		11973		953		<0.001
0		8755 (67.7%)		8242 (68.8%)		513 (53.8%)	
1		2912 (22.5%)		2546 (21.3%)		366 (38.4%)	
2		1029 (8.0%)		968 (8.1%)		61 (6.4%)	
3		230 (1.8%)		217 (1.8%)		13 (1.4%)	
Interstitial fibrosis and tubular atrophy (IFTA) Banff score, No. (%)	13778		12148		1630		<0.001
0		8480 (61.5%)		7822 (64.4%)		658 (40.4%)	
1		4148 (30.1%)		3647 (30.0%)		501 (30.7%)	
2		1029 (7.5%)		562 (4.6%)		467 (28.7%)	
3		121 (0.9%)		117 (1.0%)		4 (0.2%)	
Glomerulosclerosis, median (interquartile range)	10455	3.0 (0.0-11.0)	8826	3.0 (0.0-10.0)	1629	2.1 (0.0-12.5)	<0.001

Supplementary Table 9 | Baseline donor characteristics of the external validation cohort by center

	Overall (n=1,630)	Columbia University Medical Center (n=1,332)	Sun-Yat sen university (n=298)
Age (years), mean (SD)	48.0 (13.2)	48.9 (13.3)	44.1 (11.5)
Sex female, No. (%)	723 (44.4%)	628 (47.1%)	95 (31.9%)
Donor type			
Deceased donor, No. (%)	1124 (69.0%)	920 (69.1%)	204 (68.5%)
Death from circulatory disease, No. (%)*	131 (11.7%)	94 (10.2%)	37 (18.1%)
Death from cerebrovascular disease, No. (%)*	525 (46.7%)	472 (51.3%)	53 (26.0%)
Diabetes mellitus, No. (%)	215 (13.3%)	208 (15.8%)	7 (2.3%)
Hypertension, No. (%)	594 (36.7%)	558 (42.3%)	36 (12.1%)
BMI (kg/m^2), mean (SD)	27.6 (6.3)	28.6 (6.4)	23.1 (2.8)
HCV status, No. (%)	49 (3.0%)	44 (3.3%)	5 (1.7%)
Creatinine (mg/dL), mean (SD)	1.6 (1.1)	1.7 (1.1)	1.3 (0.9)
Proteinuria, No. (%)	587 (36.2%)	480 (36.2%)	107 (35.9%)
Number of Glomeruli, mean (SD)	54.7 (45.0)	71.1 (44.9)	17.7 (7.9)
Arteriosclerosis (cv) Banff score, No. (%)			
0	453 (27.9%)	304 (22.9%)	149 (50.3%)
1	551 (33.9%)	412 (31.0%)	139 (47.0%)
2	590 (36.3%)	582 (43.8%)	8 (2.7%)
3	31 (1.9%)	31 (2.3%)	0 (0.0%)
Arteriolar hyalinosis (ah) Banff score, No. (%)			
0	513 (53.8%)	328 (50.1%)	185 (62.1%)
1	366 (38.4%)	274 (41.8%)	92 (30.9%)
2	61 (6.4%)	44 (6.7%)	17 (5.7%)
3	13 (1.4%)	9 (1.4%)	4 (1.3%)
Interstitial fibrosis and tubular atrophy (IFTA) Banff score, No. (%)			
0	658 (40.4%)	532 (39.9%)	126 (42.3%)
1	501 (30.7%)	338 (25.4%)	163 (54.7%)
2	467 (28.7%)	459 (34.5%)	8 (2.7%)
3	4 (0.2%)	3 (0.2%)	1 (0.3%)
Glomerulosclerosis, median (interquartile range)	2.1 (0.0-12.5)	2.0 (0.0-13.8)	2.9 (0.0-9.1)

Supplementary Table 10 | Baseline donor characteristics of the external validation cohort by donor type

	N	Overall (n=1,630)	N	Deceased Donor (n=1,124)	N	Living Donor (n=506)	p-value
Age (years), mean (SD)	1630	48.0 (13.2)	1124	49.9 (13.5)	506	43.7 (11.3)	<0.001
Sex female, No. (%)	1630	723 (44.4%)	1124	428 (38.1%)	506	295 (58.3%)	<0.001
Donor type							
Deceased donor, No. (%)	1630	1124 (69.0%)	1124	1124 (100.0%)	506	0 (0.0%)	<0.001
Death from circulatory disease, No. (%)*	1124	131 (11.7%)	1124	131 (11.7%)	0	0 (-)	<0.001
Death from cerebrovascular disease, No. (%)*	1124	525 (46.7%)	1124	525 (46.7%)	0	0 (-)	<0.001
Diabetes mellitus, No. (%)	1615	215 (13.3%)	1109	215 (19.4%)	506	0 (0.0%)	<0.001
Hypertension, No. (%)	1618	594 (36.7%)	1112	594 (53.4%)	506	0 (0.0%)	<0.001
BMI (kg/m^2), mean (SD)	1624	27.6 (6.3)	1123	28.4 (6.9)	501	25.8 (4.3)	<0.001
HCV status, No. (%)	1630	49 (3.0%)	1124	48 (4.3%)	506	1 (0.2%)	<0.001
Creatinine (mg/dL), mean (SD)	1217	1.6 (1.1)	1123	1.7 (1.1)	94	0.8 (0.2)	<0.001
Proteinuria, No. (%)	1623	587 (36.2%)	1117	587 (52.6%)	506	0 (0.0%)	<0.001
Number of Glomeruli, mean (SD)	971	54.7 (45.0)	877	59.1 (45.2)	94	14.1 (4.3)	<0.001
Arteriosclerosis (cv) Banff score, No. (%)	1625		1123		502		<0.001
0		453 (27.9%)		249 (22.2%)		204 (40.6%)	
1		551 (33.9%)		306 (27.2%)		245 (48.8%)	
2		590 (36.3%)		537 (47.8%)		53 (10.6%)	
3		31 (1.9%)		31 (2.8%)		0 (0.0%)	
Arteriolar hyalinosis (ah) Banff score, No. (%)	953		447		506		<0.001
0		513 (53.8%)		198 (44.3%)		315 (62.3%)	
1		366 (38.4%)		176 (39.4%)		190 (37.5%)	
2		61 (6.4%)		60 (13.4%)		1 (0.2%)	
3		13 (1.4%)		13 (2.9%)		0 (0.0%)	
Interstitial fibrosis and tubular atrophy (IFTA) Banff score, No. (%)	1630		1124		506		<0.001
0		658 (40.4%)		287 (25.5%)		371 (73.3%)	
1		501 (30.7%)		366 (32.6%)		135 (26.7%)	
2		467 (28.7%)		467 (41.5%)		0 (0.0%)	
3		4 (0.2%)		4 (0.4%)		0 (0.0%)	
Glomerulosclerosis, median (interquartile range)	1629	2.1 (0.0-12.5)	1123	9.7 (<0.1-14.4)	506	0.0 (0.0-0.1)	<0.001

Supplementary Table 11 | Calibration confusion matrices of the virtual biopsy system (external validation)

Supplementary Table 11.1 | Confusion matrix on the arteriosclerosis (cv biopsy lesion score)

Reference (external cohort)	Virtual Biopsy Prediction			
	0	**1**	**2**	**3**
0	301	120	20	12
1	256	202	71	22
2	56	132	217	185
3	3	6	10	12

Supplementary Table 11.2 | Confusion matrix on the arteriolar hyalinosis (ah biopsy lesion score)

Reference (external cohort)	Virtual Biopsy Prediction			
	0	**1**	**2**	**3**
0	448	43	20	2
1	266	54	30	16
2	13	13	21	14
3	4	2	3	4

Supplementary Table 11.3 | Confusion matrix on the interstitial fibrosis and tubular atrophy (IFTA biopsy lesion score)

Reference (external cohort)	Virtual Biopsy Prediction			
	0	**1**	**2**	**3**
0	546	102	9	1
1	225	200	64	12
2	6	236	191	34
3	0	3	1	0

Supplementary Table 12 | Internal validation of the virtual biopsy system in various subpopulations and clinical scenarios

Subpopulations / Clinical Scenario		Discrimination			
		Arteriosclerosis (cv)*	Arteriolar hyalinosis (ah)*	Interstitial fibrosis and tubular atrophy (IFTA)*	Glomerulosclerosis†
Region	Europe	0.767	0.711	0.742	7.393
	North America	0.883	0.820	0.884	4.915
	Australia	0.760	0.693	0.837	5.522
Ethnicity‡	African American	0.949	0.861	0.912	4.421
	Caucasian	0.837	0.782	0.875	6.454
	Others§	0.903	0.882	0.909	4.711
Donor criteria	Extended criteria donors (ECD)	0.811	0.769	0.801	9.437
	Standard criteria donors (SCD) OR living donors	0.834	0.758	0.816	4.455
Biopsy type	Preimplantation (before anastomosis)	0.844	0.784	0.842	6.455
	Postreperfusion (after anastomosis)	0.785	0.758	0.679	5.225

Supplementary Table 13 | KDPI as a parameter in predicting day-zero kidney biopsy results

Model	Cohort	Validation	Multi-AUC			Mean Absolute Error
			cv	ah	IFTA	Glomerulosclerosis
KDPI	Internal	Cross-validation	0.688	0.644	0.716	6.647
	External	Columbia University	0.625	0.668	0.638	4.947
		Sun Yat-sen University	0.659	0.552	0.710	4.193

Supplementary Table 14 | Summary of participating centers' biopsy practices and procedures

Country	Center	Performed	Timing	Technique	Tissue processing	Tissue stain	Interpretation
France	PTG (Necker)(SLS)(Toulouse)	Surgeon	Preimplantation (before anastomosis)	Core needle	alcohol–formalin–acetic acid fixed (AFA) and paraffin-embedded (PE)	Periodic acid-Schiff (PAS), Masson's trichrome, Hematoxylin and eosin stain, Jones (methenamine silver)	Renal pathologist
France	Kremlin Bicêtre	Surgeon	Preimplantation (before anastomosis)	Wedge, Core needle	frozen, formalin-fixed paraffin-embedded (FFPE)	Periodic acid-Schiff (PAS), Masson's trichrome, Hematoxylin and eosin stain, Jones (methenamine silver)	General pathologist, Renal pathologist
Belgium	UZ Leuven	Surgeon	Preimplantation (before anastomosis)	Core needle	frozen, formalin-fixed paraffin-embedded (FFPE)	Periodic acid-Schiff (PAS), Masson's trichrome, Hematoxylin and eosin stain, Jones (methenamine silver)	Renal pathologist
Belgium	CHU Liège	Surgeon	Postreperfusion (after the anastomosis)	Wedge	formalin-fixed paraffin-embedded (FFPE)	Periodic acid-Schiff (PAS), Masson's trichrome, Hematoxylin and eosin stain	Renal pathologist
Croatia	University hospital centre Zagreb	Surgeon	Preimplantation (before anastomosis)	Wedge	formalin-fixed paraffin-embedded (FFPE)	Periodic acid-Schiff (PAS), Hematoxylin and eosin stain, Mallory-Weiss stain	Renal pathologist
Spain	Hospital Cliníc i Provincial de Barcelona	Surgeon	Preimplantation (before anastomosis)	Wedge	frozen	Hematoxylin and eosin stain	General pathologist
Spain	Vall d'Hebron University Hospital	Surgeon	Preimplantation (before anastomosis)	Wedge	formalin-fixed paraffin-embedded (FFPE)	Hematoxylin and eosin stain	General pathologist, Renal pathologist
Spain	Hospital Universitari de Bellvitge	Surgeon	Preimplantation (before anastomosis)	Wedge, Core needle	frozen	Periodic acid-Schiff (PAS)	General pathologist

Supplementary Table 14 | Summary of participating centers' biopsy practices and procedures (continued)

Country	Center	Performed	Timing	Technique	Tissue processing	Tissue stain	Interpretation
Canada	University of Alberta	Surgeon	Postreperfusion (after the anastomosis)	Wedge, Core needle	frozen, formalin-fixed paraffin-embedded (FFPE)	Periodic acid-Schiff (PAS), Masson's trichrome, Hematoxylin and eosin stain	Renal pathologist
Canada	University of British Columbia	Surgeon	Postreperfusion (after the anastomosis)	Core needle	formalin-fixed paraffin-embedded (FFPE)	Periodic acid-Schiff (PAS), Masson's trichrome, Hematoxylin and eosin stain	Renal pathologist
United States	Columbia University Medical Center	Surgeon	Postreperfusion (after the anastomosis)	Core needle	formalin-fixed paraffin-embedded (FFPE)	Periodic acid-Schiff (PAS), Masson's trichrome, Hematoxylin and eosin stain, Jones (methenamine silver)	Renal pathologist
United States	Mayo Clinic	Surgeon	Postreperfusion (after the anastomosis)	Core needle	formalin-fixed paraffin-embedded (FFPE)	Periodic acid-Schiff (PAS), Hematoxylin and eosin stain	Renal pathologist
United States	OneLegacy	Surgeon	Preimplantation (before anastomosis)	Wedge	frozen, formalin-fixed paraffin-embedded (FFPE)	Periodic acid-Schiff (PAS), Masson's trichrome, Hematoxylin and eosin stain, Jones (methenamine silver)	Renal pathologist
Australia	Royal Adelaide Hospital	Surgeon	Postreperfusion (after the anastomosis)	Wedge	formalin-fixed paraffin-embedded (FFPE)	Periodic acid-Schiff (PAS), Hematoxylin and eosin stain	Renal pathologist
China	Sun Yat-sen University	Surgeon	Preimplantation (before anastomosis)	Wedge, Core needle	formalin-fixed paraffin-embedded (FFPE)	Periodic acid-Schiff (PAS), Masson's trichrome, Hematoxylin and eosin stain, Jones (methenamine silver)	Renal pathologist

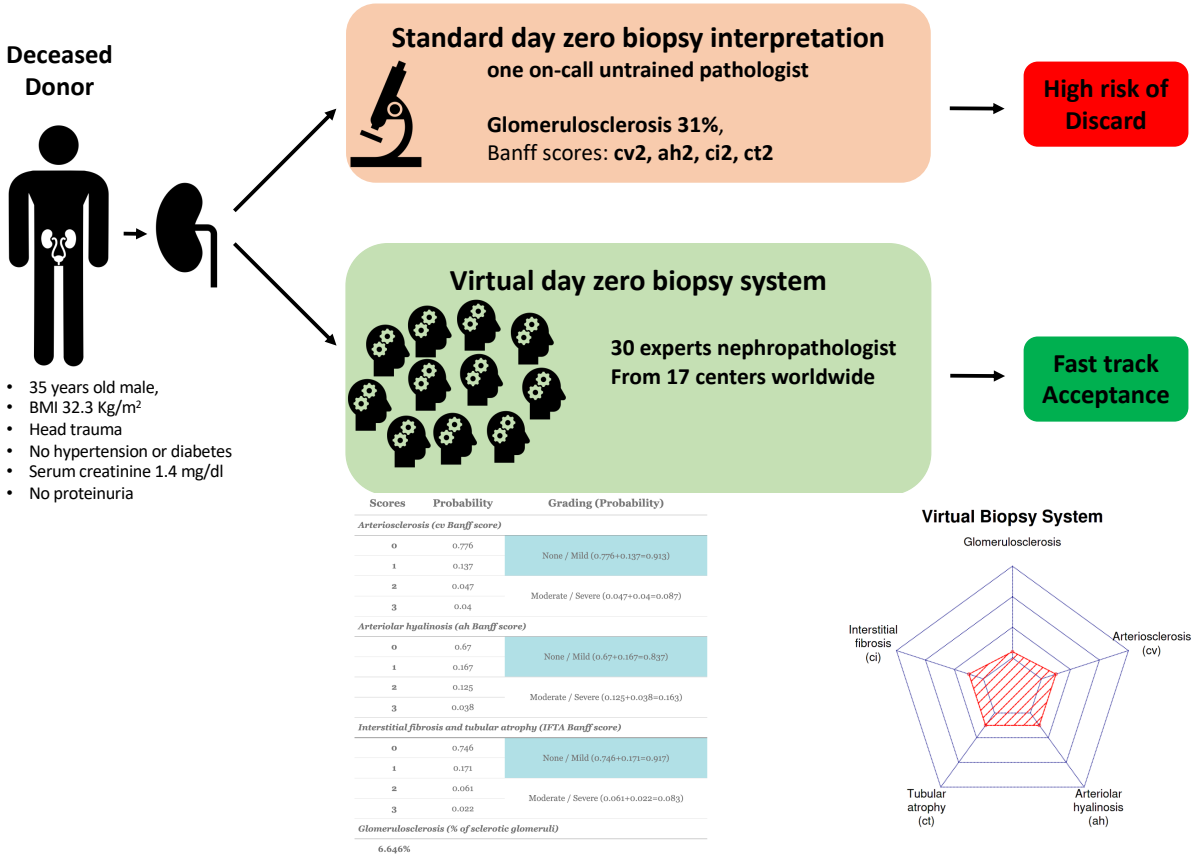
Supplementary Table 15 | Summary of kidney day-zero histological lesion scores (international Banff classification grading scheme)

Banff lesion score	Abbreviation	Grading 0	Grading 1	Grading 2	Grading 3
Vascular fibrous intimal thickening	cv	None	<=25%	26-50%	>50%
Arteriolar hyalinosis	ah	None	Mild to moderate in >=1	Moderate to severe in >1	Severe in many
Interstitial fibrosis	ci	<=5%	6-25%	26-50%	>50%
Tubular atrophy	ct	None	<=25%	26-50%	>50%

3. SUPPLEMENTARY FIGURES

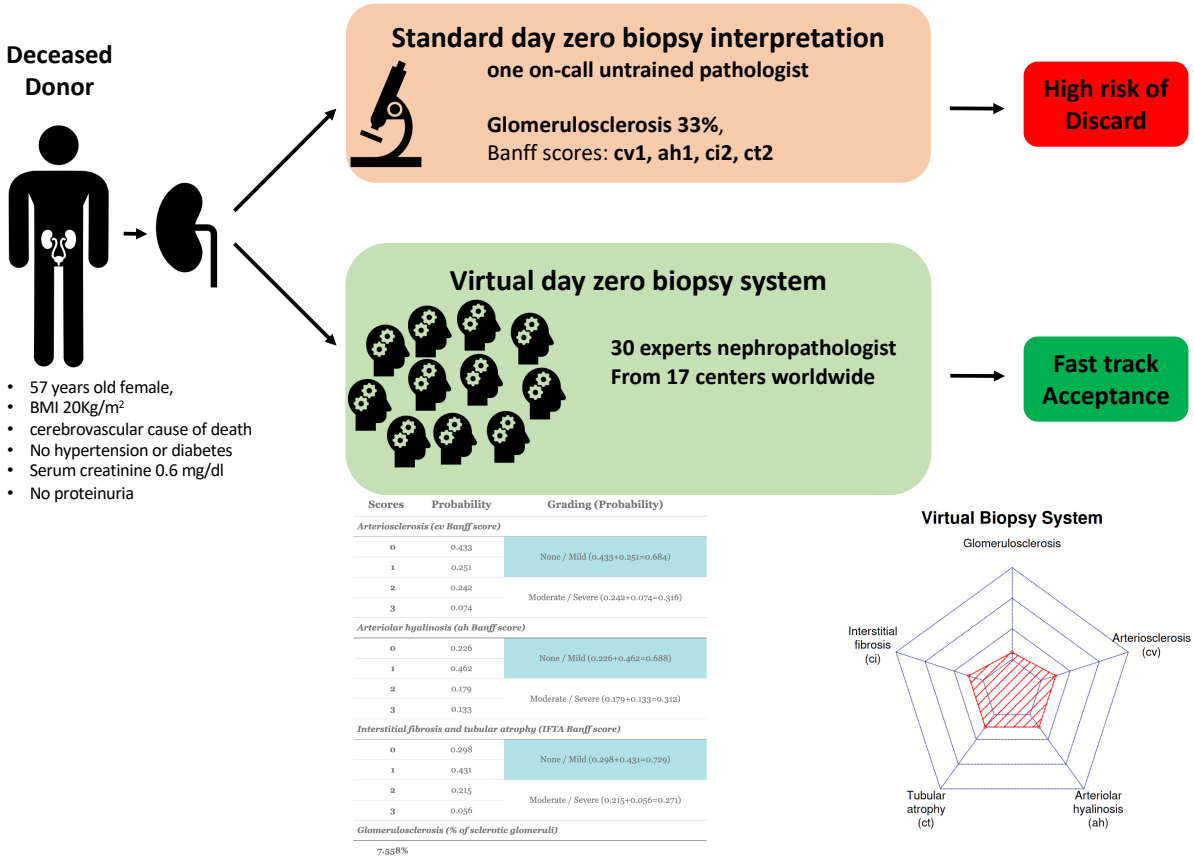
Supplementary Figure 1 | Virtual biopsy system usage in real-life situation and organ allocation

Real clinical case A:



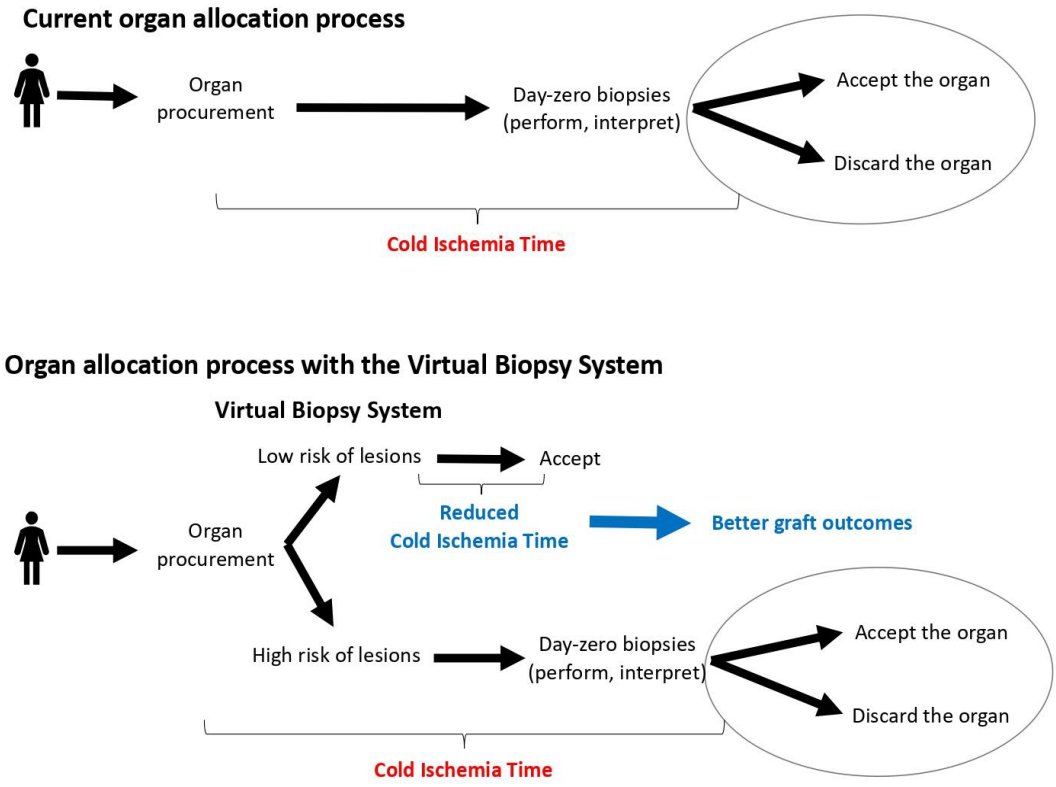
Real clinical case A: in this case based on real life data of a 35-year-old male donor with obesity who died from a head trauma, the day-zero biopsy was performed and interpreted in real life setting by non-nephropathologist showed 31% of glomerulosclerosis, moderate arteriosclerosis (cv2 Banff score), moderate arteriolar hyalinosis (ah2 Banff score) and moderate interstitial fibrosis and tubular atrophy (ci2 and ct2 Banff scores). These results lead to the decision to discard the kidney. The virtual biopsy system based on donor characteristics showed a high probability of None/mild arteriosclerosis (cv0/1 Banff score), None/mild arteriolar hyalinosis (ah0/1 Banff score), None/mild interstitial fibrosis and tubular atrophy (ci0/1 and ct0/1 Banff scores) and a percentage of glomerulosclerosis of 6.646%. In this case, the virtual biopsy might help to not discard the kidney for histological reason.

Real clinical case B:



Real clinical case B: in this case based on real life data of a 57-year-old female donor who died from a stroke, the day zero biopsy performed and interpreted in the real life setting by non-nephropathologists showed 33 % of glomerulosclerosis, mild arteriosclerosis (cv1 Banff score), mild arteriolar hyalinosis (ah1 Banff score) and moderate to severe interstitial fibrosis and tubular atrophy (ci2 and ct2 Banff scores). These results lead to the decision to discard the kidney. The virtual biopsy system based on donor characteristics showed a high probability of None/mild arteriosclerosis (cv0/1 Banff score), None/mild arteriolar hyalinosis (ah0/1 Banff score), None/mild interstitial fibrosis and tubular atrophy (ci0/1 and ct0/1 Banff scores) and a percentage of glomerulosclerosis of 7.558%. In this case the virtual biopsy might help to not discard the kidney for histological reasons.

Supplementary Figure 2 | The potential utility and impact of the virtual biopsy system for organ allocation



4. ADDITIONAL SUPPLEMENTARY MATERIALS

Supplementary Movie 1 | Video of the online application

5. SUPPLEMENTARY REFERENCES

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