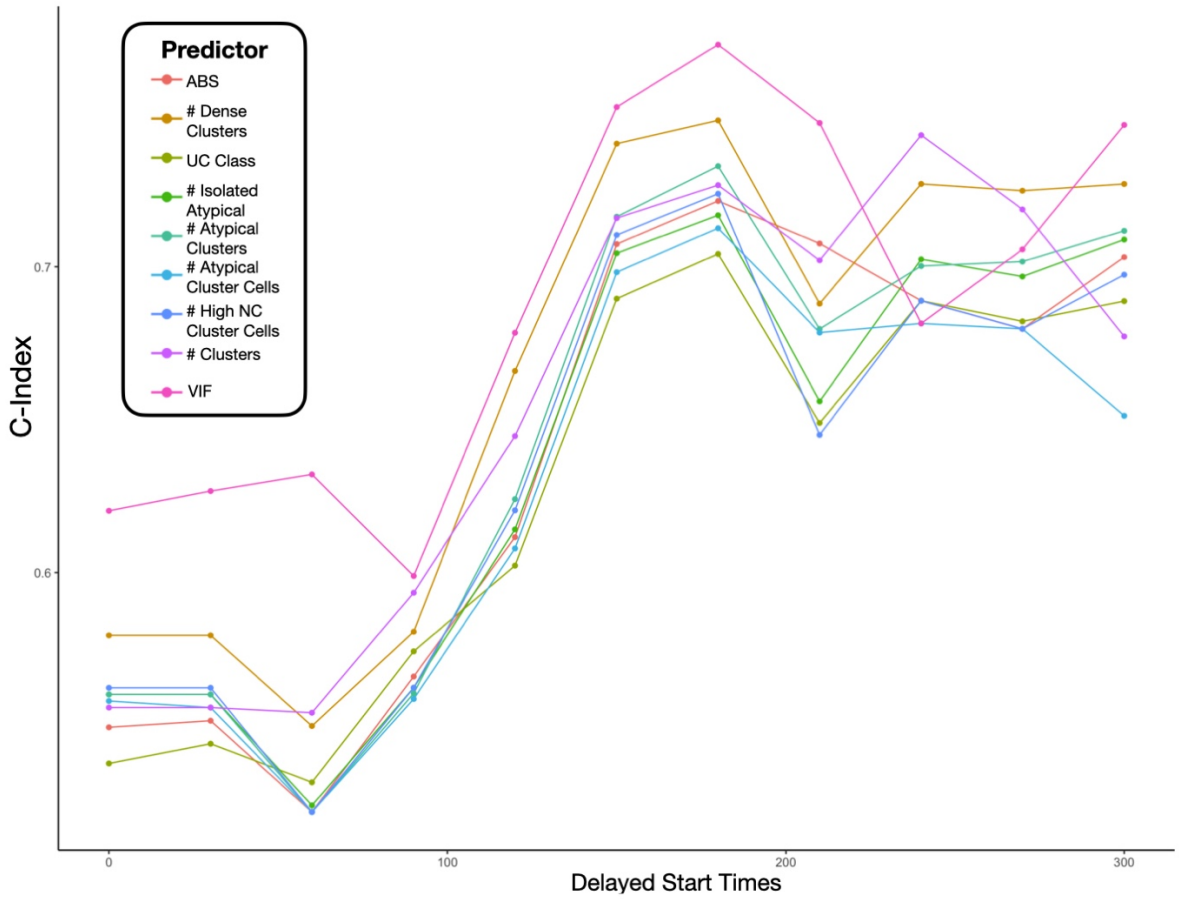
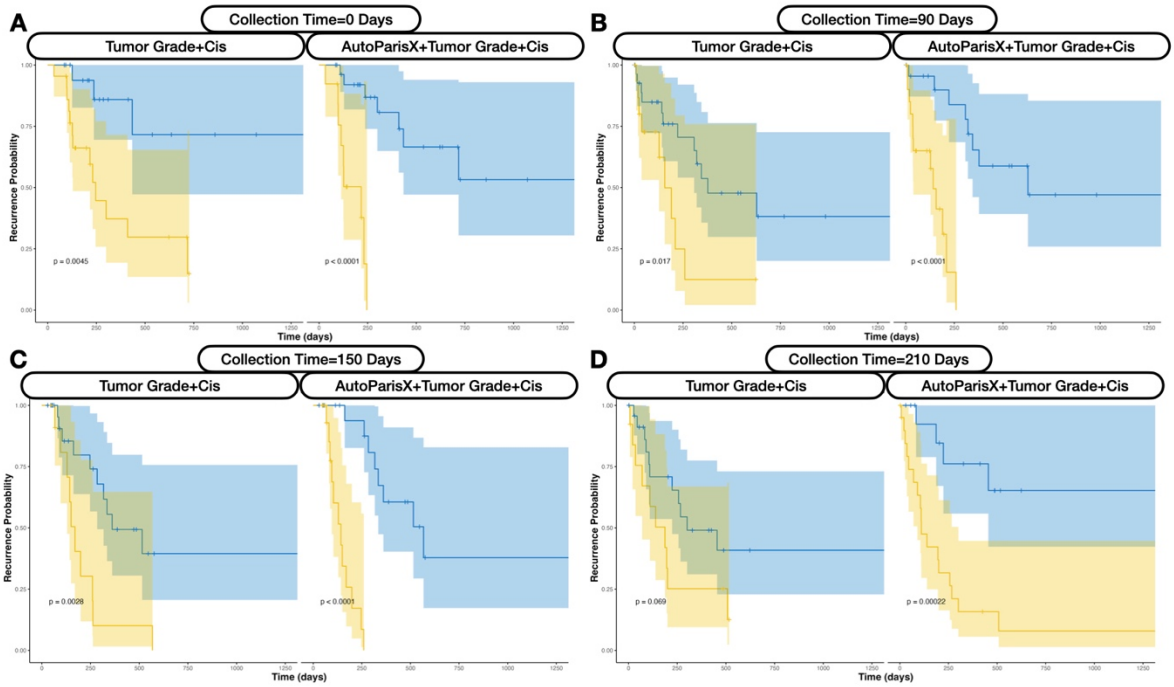
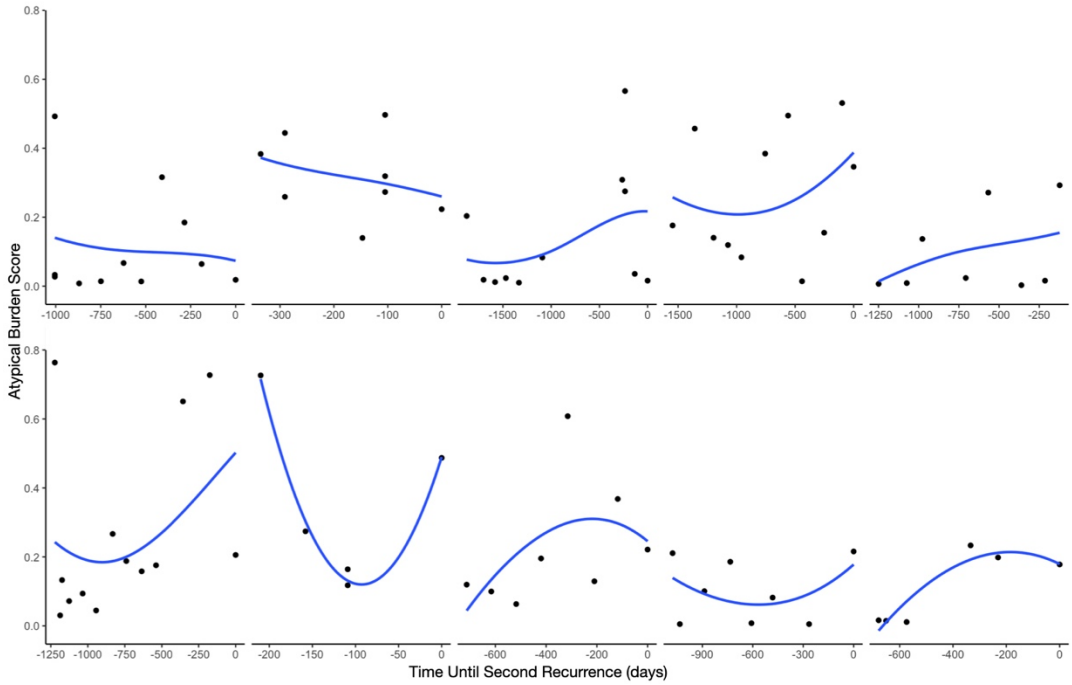
Appendix



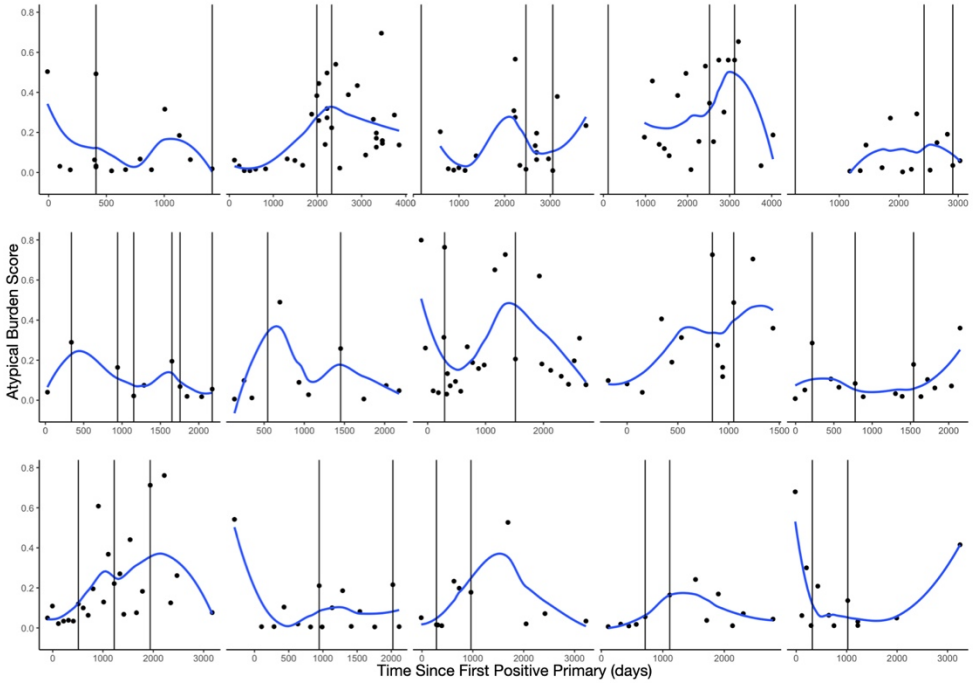
Supplementary Figure 1: C-index for specific imaging / manual cytology exam results, reported based on different collection periods/times (days) prior to the recurrence risk follow-up period; only select AutoParis-X measurements of interest were reported



Supplementary Figure 2: Comparison of KM plots for Imaging versus Histological Predictors, for cytological information collected across the following collection time periods after the first positive primary: **A)** 0 days**, B)** 90 days**, C)** 150 days**, D)** 210 days



Supplementary Figure 3: Atypia Burden Score Versus Time Until Second Recurrence: Reported for 10 patients with at least 4 repeat exams across the period between their first and second recurrence



Supplementary Figure 4: Atypia Burden Score Versus Time Across Multiple Recurrence Events for Select Patients: Each recurrence date is represented with the vertical line

Supplementary Table 1: **Description of Slide Level predictors of Recurrence**

Level	Predictor	Algorithm	Description
Cell	Urothelial cell score	UroNet	Predicted probability of urothelial cell from convolutional neural network, used to dynamically isolate urothelial cells in specimen
	Atypia score	AtyNet	Predicted probability of presence of atypical features in urothelial cell (e.g., hyperchromasia, irregular nuclear membrane, etc.), determined using convolutional neural network
	NC Ratio	UroSeg	Nuclear to cytoplasm area ratio derived from pixelwise segmentation of nucleus and cytoplasm using segmentatio neural network
	Morphometric measures	Custom	Complements binning of urothelial cells and assignment of atypia score, features: 1) area; 2) convex area; 3) eccentricity; 4) equivalent diameter; 5) extent; 6) Feret's diameter; 7) maximum diameter; 8) filled area; 9) major axis length; 10) minor axis length; 11) perimeter; and 12) solidity
Cluster	Dense Area	BorderDet	Whether cluster contains dense architecture of overlapping and indistinguishable cytoplasmic borders
	Number urothelial cells	BorderDet/ UroNet	Whether cluster contained urothelial cells, determined by counting cells with high urothelial cell score
	Number atypical urothelial cells (atypia score)	BorderDet/ UroNet/AtyNet	Whether cluster contained abnormal urothelial cells, determined by counting cells with high atypia score
	Number atypical urothelial cells (NC ratio)	BorderDet/ UroNet/UroSeg	Whether cluster contained abnormal urothelial cells, determined by counting cells with high NC ratio
	Dense & Atypical	BorderDet/ UroNet/AtyNet/UroSeg	Whether cluster contained both dense architecture and atypical cellular features

Slide	Patient characteristics	Supplied	Includes age, sex, history of hematuria, specimen source (e.g., voided), presence of specimen artifact
	Isolated Cell-SIF Scores	Bayesian Optimization	Counting the number of cells with the following features from cells not associated with clusters: 1) cellularity (urothelial score), 2) atypia (atypia score), 3) atypia (NC ratio), 4) other morphometric measures
	Cluster Cell-SIF Scores	Bayesian Optimization	Counting the number of cells with the following features from cells associated with clusters: 1) cellularity (urothelial score), 2) atypia (atypia score), 3) atypia (NC ratio), 4) other morphometric measures
	All Cell-SIF Scores	Bayesian Optimization	Combines Isolated Cell-SIF Scores and Cluster Cell-SIF Scores
	Cluster-SIF	Bayesian Optimization	Counting the number of clusters with the following features: 1) number of urothelial clusters, 2) atypical urothelial clusters (atypia score), 3) atypical clusters (NC ratio), 4) dense clusters, 5) dense and atypical clusters
	Atypia Burden Score	Mixed effects machine learning	Integrates all slide-level predictors using machine learning model to calculate a score between 0-1 reflecting overall specimen atypia, correlated with UC diagnostic category

Supplemental Table 2: Concordance statistics for *fixed predictors* at the following collection time periods; also included are performance statistics for *dynamic predictors* from the *time-varying covariate* cox model; the percentage of imaging variables which outperform manual examination is represented as "% Outperform UC Class"

Collection Time (days)	**0**		**30**		**60**		**90**		**120**		**150**	
Predictors	**C**	**SE**	**C**	**SE**	**C**	**SE**	**C**	**SE**	**C**	**SE**	**C**	**SE**
ABS	0.549	0.075	0.552	0.075	0.522	0.076	0.566	0.06	0.615	0.065	0.707	0.047
# Dense Clusters	0.62	0.069	0.62	0.069	0.6	0.069	0.581	0.061	0.666	0.066	0.74	0.051
UC Class	0.544	0.081	0.548	0.08	0.536	0.079	0.575	0.059	0.614	0.058	0.701	0.065
Eccentricity	0.558	0.084	0.564	0.088	0.515	0.078	0.557	0.059	0.662	0.059	0.716	0.048
# Isolated Atypical Cells	0.56	0.077	0.56	0.077	0.524	0.077	0.562	0.059	0.615	0.064	0.704	0.042
# Atypical Clusters	0.56	0.076	0.56	0.076	0.522	0.078	0.563	0.06	0.626	0.065	0.716	0.054
# Overall Atypical Cells	0.562	0.079	0.56	0.077	0.524	0.076	0.565	0.059	0.623	0.063	0.701	0.047
# Cluster Atypical Cells	0.558	0.076	0.556	0.075	0.522	0.076	0.561	0.059	0.623	0.062	0.698	0.047
% Clusters Dense/Atypical	0.554	0.076	0.554	0.076	0.519	0.077	0.564	0.06	0.631	0.051	0.683	0.054
# Isolated Cells High NC	0.558	0.081	0.558	0.081	0.522	0.076	0.564	0.058	0.617	0.063	0.713	0.047
# Overall Cells High NC	0.56	0.08	0.56	0.08	0.526	0.077	0.566	0.059	0.616	0.063	0.713	0.047
# Cluster Cells High NC	0.562	0.077	0.562	0.077	0.522	0.08	0.562	0.059	0.62	0.062	0.71	0.046
LASSO	0.59	0.084	0.603	0.073	0.578	0.069	0.584	0.06	0.654	0.058	0.74	0.051
# Cells	0.558	0.08	0.558	0.08	0.524	0.078	0.573	0.065	0.628	0.065	0.71	0.048
# Clusters	0.567	0.073	0.571	0.072	0.582	0.07	0.593	0.061	0.645	0.067	0.716	0.05
Overall	0.672	0.073	0.725	0.055	0.714	0.056	0.707	0.061	0.81	0.074	0.824	0.045
VIF	0.62	0.073	0.627	0.071	0.632	0.066	0.614	0.055	0.7	0.051	0.752	0.058
% Outperform UC Class	1.000	0.000	1.000	0.000	0.278	0.106	0.278	0.106	1.000	0.000	0.889	0.074

Collection Time (days)	**180**		**210**		**240**		**270**		**300**		**Time Varying Covariates**	
Predictors	**C**	**SE**	**C**	**SE**	**C**	**SE**	**C**	**SE**	**C**	**SE**	**C**	**SE**
ABS	0.722	0.048	0.708	0.051	0.689	0.063	0.68	0.067	0.703	0.06	0.652	0.039
# Dense Clusters	0.748	0.05	0.688	0.058	0.727	0.057	0.725	0.055	0.727	0.066	0.603	0.038
UC Class	0.724	0.062	0.673	0.063	0.689	0.06	0.682	0.059	0.689	0.059	0.579	0.05
Eccentricity	0.724	0.048	0.697	0.059	0.665	0.073	0.639	0.076	0.699	0.068	0.607	0.034

# Isolated Atypical Cells	0.717	0.043	0.692	0.056	0.702	0.065	0.697	0.066	0.709	0.061	0.612	0.039
# Atypical Clusters	0.733	0.053	0.716	0.062	0.7	0.067	0.702	0.064	0.712	0.06	0.62	0.039
# Overall Atypical Cells	0.715	0.048	0.679	0.062	0.685	0.069	0.682	0.068	0.663	0.067	0.638	0.04
# Cluster Atypical Cells	0.713	0.048	0.681	0.064	0.685	0.069	0.68	0.069	0.651	0.068	0.637	0.042
% Clusters Dense/Atypical	0.701	0.055	0.695	0.066	0.641	0.069	0.649	0.072	0.669	0.071	0.588	0.041
# Isolated Cells High NC	0.724	0.046	0.664	0.061	0.709	0.066	0.69	0.066	0.689	0.063	0.588	0.039
# Overall Cells High NC	0.727	0.047	0.655	0.054	0.707	0.066	0.685	0.065	0.709	0.062	0.564	0.042
# Cluster Cells High NC	0.724	0.047	0.645	0.057	0.697	0.068	0.68	0.066	0.699	0.068	0.541	0.044
LASSO	0.734	0.056	0.723	0.054	0.707	0.061	0.691	0.051	0.726	0.064	0.657	0.038
# Cells	0.724	0.045	0.705	0.052	0.707	0.058	0.692	0.063	0.712	0.059	0.631	0.039
# Clusters	0.727	0.049	0.702	0.053	0.743	0.051	0.719	0.056	0.677	0.067	0.6	0.039
Overall	0.827	0.046	0.849	0.051	0.927	0.035	0.92	0.036	0.911	0.03	0.659	0.041
VIF	0.773	0.058	0.747	0.057	0.731	0.061	0.743	0.074	0.746	0.06	0.682	0.036
% Outperform UC Class	0.611	0.115	0.722	0.106	0.667	0.111	0.611	0.115	0.667	0.111	0.778	0.098

Supplemental Table 3: Comparison between Cytological Imaging Predictors Versus Histology: Hazard ratios, 95% confidence intervals and p-values, specifically after adjusting for tumor grade/type, reported for a variable constructed from the imaging predictors alone; also includes p-values from partial likelihood ratio test assessing whether imaging cytological exams improves on histological predictors; reports for *fixed predictors* collected across various collection time periods

Collection Time (days)	log(HR)	2.5% CI	97.5% CI	p-value	p-value– H1: Imaging> Grade+Cis	p-value– H1: Imaging+Grade+Cis> Grade+Cis
0	1.258	0.569	1.947	0.00035	0.220	0.048
30	1.199	0.533	1.865	0.00042	0.220	0.054
60	0.980	0.429	1.531	0.00049	0.060	0.042
90	0.982	0.319	1.646	0.00370	0.144	0.130
120	1.003	0.519	1.488	0.00005	0.115	0.102
150	1.019	0.538	1.499	0.00003	0.055	0.059
180	1.051	0.563	1.539	0.00002	0.060	0.060
210	1.081	0.542	1.621	0.00009	0.026	0.028
240	0.962	0.455	1.470	0.00020	0.024	0.017
270	0.974	0.517	1.432	0.00003	0.020	0.022
300	1.021	0.452	1.589	0.00044	0.016	0.017

Supplementary Table 4: C-indices for Imaging Predictors from *Time-Varying Effects* Models

Predictor	C	SE
ABS	0.65	0.039
Age	0.614	0.046
# Dense Clusters	0.578	0.037
UC Class	0.616	0.047
Eccentricity	0.563	0.049
Sex	0.54	0.041

# Isolated Atypical Cells	0.554	0.042
# Atypical Clusters	0.572	0.041
# Overall Atypical Cells	0.599	0.043
% Clusters Dense/Atypical	0.568	0.043
# Isolated Cells High NC	0.558	0.039
# Overall Cells High NC	0.557	0.04
# Cells	0.603	0.044
# Clusters	0.627	0.042
Overall	0.728	0.043

Supplementary Table 5: Hazard Ratios for Imaging Predictors from Time Varying Effects Models; Predictor effect size and significance is reported for every half year, which was used as the time periods to assess recurrence risk

Predictor	Time	log(HR)	2.5% CI	97.5% CI	z	Pr(>|z|)
# Overall Atypical Cells	0-180	1.39E-04	8.58E-05	1.93E-04	1.77E+00	7.63E-02
	180-360	3.08E-04	1.90E-04	4.26E-04	1.51E+00	1.32E-01
	360-540	4.60E-04	3.12E-04	6.07E-04	1.50E+00	1.33E-01
	540-720	7.25E-04	1.53E-04	1.30E-03	6.43E-01	5.20E-01
	720-900	-6.14E-04	-1.84E-03	6.08E-04	-6.91E-01	4.89E-01
	>900	1.38E-03	8.03E-04	1.95E-03	1.10E+00	2.69E-01
# Overall Cells High NC	0-180	2.03E-04	-2.87E-05	4.35E-04	6.93E-01	4.89E-01
	180-360	8.75E-04	4.99E-04	1.25E-03	2.35E+00	1.89E-02
	360-540	1.52E-03	9.92E-04	2.05E-03	1.29E+00	1.98E-01
	540-720	1.09E-03	-1.20E-04	2.30E-03	5.60E-01	5.75E-01
	720-900	-5.97E-05	-2.13E-03	2.01E-03	-3.43E-02	9.73E-01
	>900	8.15E-03	6.09E-03	1.02E-02	3.97E+00	7.23E-05
# Cells	0-180	4.72E-05	3.32E-05	6.11E-05	1.73E+00	8.39E-02
	180-360	5.16E-05	3.65E-05	6.66E-05	1.65E+00	9.90E-02
	360-540	-4.94E-06	-3.29E-05	2.31E-05	-1.32E-01	8.95E-01
	540-720	7.06E-05	4.95E-05	9.17E-05	2.49E+00	1.28E-02
	720-900	-1.07E-04	-2.38E-04	2.33E-05	-1.41E+00	1.58E-01
	>900	2.03E-04	1.43E-04	2.63E-04	1.58E+00	1.14E-01
Eccentricity	0-180	4.30E+00	1.89E+00	6.70E+00	8.73E-01	3.83E-01
	180-360	-1.60E+00	-3.89E+00	6.87E-01	-5.49E-01	5.83E-01
	360-540	3.97E+00	4.59E-01	7.47E+00	4.50E-01	6.53E-01
	540-720	1.72E+01	1.12E+01	2.31E+01	1.15E+00	2.49E-01
	720-900	6.20E+00	-2.94E+00	1.53E+01	3.73E-01	7.09E-01
	>900	5.72E+00	-1.11E+00	1.25E+01	4.22E-01	6.73E-01
# Isolated Atypical Cells	0-180	1.21E-04	-1.75E-04	4.17E-04	3.89E-01	6.98E-01
	180-360	4.85E-04	1.04E-04	8.67E-04	8.19E-01	4.13E-01
	360-540	2.02E-03	1.60E-03	2.44E-03	3.47E+00	5.22E-04
	540-720	1.15E-04	-2.23E-03	2.46E-03	2.37E-02	9.81E-01
	720-900	-4.80E-03	-9.49E-03	-1.21E-04	-7.92E-01	4.29E-01
	>900	2.19E-03	1.24E-04	4.25E-03	5.51E-01	5.82E-01
# Isolated Cells High NC	0-180	3.20E-04	-3.19E-04	9.60E-04	3.78E-01	7.05E-01
	180-360	2.70E-03	1.86E-03	3.54E-03	3.79E+00	1.51E-04
	360-540	2.33E-03	1.48E-03	3.18E-03	1.19E+00	2.34E-01
	540-720	4.15E-03	2.00E-03	6.30E-03	1.24E+00	2.13E-01
	720-900	-2.49E-03	-7.73E-03	2.75E-03	-6.05E-01	5.45E-01
	>900	1.43E-02	1.09E-02	1.77E-02	2.95E+00	3.15E-03
# Dense Clusters	0-180	2.85E-04	-5.81E-04	1.15E-03	2.38E-01	8.12E-01
	180-360	2.08E-03	1.54E-03	2.61E-03	4.87E+00	1.12E-06
	360-540	9.12E-03	7.59E-03	1.06E-02	4.20E+00	2.64E-05
	540-720	-1.02E-02	-1.91E-02	-1.20E-03	-9.38E-01	3.48E-01
	720-900	-4.12E-03	-1.39E-02	5.63E-03	-3.27E-01	7.44E-01
	>900	-3.12E-03	-1.12E-02	4.96E-03	-2.68E-01	7.89E-01

# Clusters	0-180	8.60E-05	5.55E-05	1.16E-04	1.56E+00	1.20E-01
	180-360	1.39E-04	1.10E-04	1.69E-04	3.66E+00	2.50E-04
	360-540	4.19E-05	-9.12E-06	9.29E-05	4.55E-01	6.49E-01
	540-720	4.93E-05	-1.16E-05	1.10E-04	4.64E-01	6.43E-01
	720-900	-5.40E-04	-8.79E-04	-2.02E-04	-1.85E+00	6.48E-02
	>900	5.93E-05	-2.11E-05	1.40E-04	3.87E-01	6.99E-01
% Clusters Dense/Atypical	0-180	8.25E+00	5.08E+00	1.14E+01	1.93E+00	5.30E-02
	180-360	5.06E+00	-2.06E+00	1.22E+01	3.65E-01	7.15E-01
	360-540	2.56E+01	1.99E+01	3.14E+01	2.64E+00	8.39E-03
	540-720	-2.20E+01	-4.32E+01	-7.23E-01	-6.85E-01	4.93E-01
	720-900	3.74E+01	2.15E+01	5.34E+01	1.67E+00	9.44E-02
	>900	2.29E+01	7.72E+00	3.81E+01	1.02E+00	3.07E-01
# Atypical Clusters	0-180	7.07E-04	2.25E-04	1.19E-03	1.39E+00	1.65E-01
	180-360	2.89E-03	1.76E-03	4.02E-03	1.53E+00	1.26E-01
	360-540	3.58E-03	2.71E-03	4.45E-03	2.12E+00	3.40E-02
	540-720	3.22E-03	-5.21E-04	6.96E-03	3.99E-01	6.90E-01
	720-900	-6.12E-03	-1.40E-02	1.74E-03	-5.87E-01	5.57E-01
	>900	4.81E-03	9.55E-04	8.67E-03	6.08E-01	5.43E-01
ABS	0-180	2.74E+00	2.17E+00	3.31E+00	3.00E+00	2.69E-03
	180-360	2.22E+00	1.57E+00	2.86E+00	1.72E+00	8.51E-02
	360-540	-1.86E-01	-1.22E+00	8.45E-01	-1.30E-01	8.96E-01
	540-720	8.28E-01	-5.97E-01	2.25E+00	2.75E-01	7.84E-01
	720-900	2.39E+00	6.42E-01	4.15E+00	9.43E-01	3.46E-01
	>900	7.96E+00	6.45E+00	9.47E+00	3.31E+00	9.41E-04
UC Class	0-180	1.61E+00	1.35E+00	1.88E+00	3.10E+00	1.96E-03
	180-360	8.31E-01	5.37E-01	1.13E+00	1.38E+00	1.68E-01
	360-540	-2.07E-01	-7.32E-01	3.19E-01	-2.03E-01	8.39E-01
	540-720	4.70E-01	-7.19E-02	1.01E+00	4.38E-01	6.61E-01
	720-900	1.29E+00	6.80E-01	1.91E+00	1.39E+00	1.64E-01
	>900	1.49E+00	1.00E+00	1.98E+00	1.55E+00	1.21E-01

Supplementary Table 6: Results from beta regression models comparing recurrence risk to ABS scores during distinct time periods; Coefficients **B** represents differences in ABS scores between low and high risk patients at specific time periods; the final coefficient represents how ABS scores are changing over time between the first and second recurrences

Comparison	Time Period	B	2.5% CI	97.5% CI	p-value
High vs low risk, days since positive primary	**0-113**	-0.297	-1.169	0.575	0.506
	114-204	0.134	-1.212	1.479	0.846
	205-295	-0.806	-1.849	0.238	0.133
	295-412	-1.038	-1.888	-0.187	0.019
	413-690	-1.186	-1.957	-0.416	0.003
High vs low risk, days until first recurrence	**>752**	-0.070	-0.645	0.505	0.812
	752-391	0.122	-0.438	0.683	0.669
	390-227	-0.496	-1.086	0.095	0.102
	226-114	0.093	-0.459	0.645	0.742
	113-0	-0.595	-1.193	0.003	0.053
Days until second recurrence, starting from first recurrence	**Time in days (continuous)**	0.001	0.000	0.001	0.018