Supplemental Appendix Index

Supplemental Figure 1: Principle component analysis of normalized nanoString gene expression data of tumour samples collected at diagnosis compared to matched recurrences according to the following subgroups: **A)** SHH, **B)** Group 3, and **C)** Group 4 and D) NMF consensus clustering of primary and recurrent medulloblastoma (k=3, cophenetic coefficient=1).

Supplemental Figure 2: Secondary high grade glioma in the tumour bed of a previously irradiated Group 4 patient. **A)** H&E staining at diagnosis showing densely packed sheets of small round nuclei with scant cytoplasm consistent with classic histology medulloblastoma. **B)** H&E staining at second surgery showing markedly different morphology with pleomorphic nuclei and more abundant cytoplasm consistent with a high grade glioma. **C)** Heatmap of relative gene expression of 22 nanoString probes normalized to three housekeeping genes (*ACTB*, *GAPDH*, *LDHA*) the sample in **A)** at diagnosis, and **B)** at second surgery. Relative gene expression is plotted on a blue-red gradient where red indicates high expression and blue low expression. Note the paucity of Group 4 markers in the sample from second surgery

Supplemental Figure 3: Subgroup specific recurrence free survival across three non-overlapping cohorts of recurrent medulloblastoma. Kaplan Meier Survival estimates of recurrence free survival for the **A)** Discovery Cohort, **B)** Validation Cohort 1, and **C)** Validation Cohort 2. p-values were determined using the generalized Wilcoxon test across the three subgroups.

Supplemental Figure 4: Median overall survival post-recurrence for all recurrent medulloblastoma. Kaplan Meier Survival estimates of survival post-recurrence for the A) Discovery Cohort, B) Validation Cohort 1 and C) Validation Cohort 2.

Supplemental Figure 5: Incidence of metastatic recurrences across medulloblastoma subgroups. Stacked column graph of local *vs*. metastatic recurrences in the three subgroups across all three cohorts. P-values determined by the Fisher's exact test. Solid areas of the graph represent local recurrence, and diagonally striped areas represent metastatic recurrences.

Supplemental Figure 6: Pattern of recurrence stratified by treatment across medulloblastoma subgroups in Validation Cohort 1 and 2. Validation Cohort 1: **A)** SHH, **B)** Group 3, **C)** Group 4; Validation Cohort 2: **E)** SHH, **F)** Group 3, **G)** Group 4. p-values determined by the Fisher's exact test. Solid areas of the graph represent local tumour bed recurrence and diagonally striped areas represent metastatic recurrences. Note: Two patients in Validation Cohort 1 received focal RT with chemotherapy, one SHH with a metastatic recurrence and one Group 4 with a metastatic recurrence. Both cases are included in the chemotherapy only category.

Supplemental Figure 7: Pattern of recurrence stratified by age across SHH medulloblastomas in the **A)** Discovery Cohort, **B)** Validation Cohort 1, and **C)** Validation Cohort 2. p-values represent Fisher's exact test. p-values determined by the Fisher's exact test. Solid areas of the graph represent local tumour bed recurrence and diagonally striped areas represent metastatic only recurrence.

Supplemental Table 1: Compilation of reports on recurrent medulloblastoma reporting the location of recurrence

	Number of Recurrent Medulloblastoma	Clinical Annotation	Molecular Annotation	Matched Tissue from Diagnosis and Recurrence
Current Study 2013	203	✔	✔	✔
Tarbell et al. 2013[1]	19	✔		
Friedrich et al, 2013[2]	18	✔		
Lannering et al. 2012[3]	66	✔		
Pizer et al. 2011[4]	40	✔		
Dunkel et al. 2010[5]	25	✔		
Chargari et al. 2010[6]	19	✔		
Srikantha et al. 2010[7]	33	✔		
Warmuth-Metz et al. 2010[8]	40	✔		
von Hoff et al, 2009[9]	107	✔		
Riffaud et al. 2009[10]	11	✔		
Massimino et al. 2009[11]	17	✔		
Gandala et al. 2008[12]	8	✔		
Gururangan et al. 2008[13]	30	✔		
Korshunov et al. 2008[14]	28		✔	✔
Padovani et al. 2007[15]	74	✔		
Bowers et al. 2007[16]	46	✔		
Abe et al. 2006[17]	12	✔		
Paulino et al. 2006[18]	31	✔		
Tabori et al. 2006[19]	22	✔		
Gajjar et al. 2006[20]	26	✔		
Packer et al. 2006[21]	62	✔		
Grill et al. 2005[22]	51	✔		
Rutkowski et al. 2005[23]	9	✔		
Herrlinger et al. 2005[24]	12	✔		
Oyharcabal-Bourden et al. 2005[25]	47	✔		
Saunders et al. 2003[26]	53	✔		
Taylor et al. 2003[27]	56	✔		
Yalcin et al. 2002[28]	31	✔		
Chan et al. 2000[29]	17	✔		
Bouffet et al, 1998[30]	46	✔		
Prados et al. 1995[31]	22	✔		
Frost et al. 1995[32]	24	✔		
Torres et al. 1994[33]	23	✔		
Wara et al. 1994[34]	54	✔		

Belza et al. 1991[35]	36	✔		
Silverman and Simpson 1982[36]	31	✔		

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Supplemental Table 2: Subgroup-specific median time to recurrence and survival post-recurrence across all three cohorts

	Discovery Cohort	Validation Cohort 1	Validation Cohort 2	p-value
Time to Recurrence (years + 95% CI)				
All Subgroups	1·49 (95% 1·09-1·9)	1·65 (95% 1·3-2·0)	1 (95% 0·91-1·09)	**0·0038**
SHH	0·96 (95% 0·85-1·08)	1·34 (95% 0·8-1·9)	1 (95% 0·81-1·19)	0·58
Group 3	1·5 (95% 0-3·2)	1·1 (95% 0·6-1·6)	0·92 (95% 0·78-1·06)	0·36
Group 4	3·9 (95% 3·3-4·5)	2·18 (95% 1·5-2·8)	1·17 (95% 0·68-1·66)	**0·00018**
Survival post-recurrence (years + 95% CI)				
All Subgroups	0·63 (95% 0-1·39)	1·68 (95% 0·8-2·6)	1·67 (95% 0·65-2·7)	**0·11**
SHH	0·14 (95% 0·08-0·2)	0·98 (95% 0·8-1·4)	0·92 (95% 0·04-1·8)	**0·0025**
Group 3	0·3 (95% 0·14-0·42)	1·1 (95% 0-2·7)	1·75 (95% 0·47-3·03)	**0·023**
Group 4	2·14 (95% 0·99-3·29)	3·7 (95% 2-5·5)	1·75 (95% 0·5-3)	0·89

Times to recurrence reported as Years (95% confidence intervals). p-values for time to recurrence are calculated using the generalized Wilcoxon test and p-values for survival post-recurrence are calculated using the log-rank method.

Supplemental Table 3: Subgroup Specific Location of Metastatic Dissemination

	SHH	Group 3	Group 4	p-value
Toronto Discovery Cohort				0.17
Diffuse Leptomeningeal	2	5	2	
Isolated Supratentorial Metastatic	0	1	6	
Spine Only	0	1	0	
Tumour Bed + Metastatic	1	1	1	
Validation Cohort				0.60
Diffuse Leptomeningeal	4	2	6	
Isolated Supratentorial Metastatic	1	5	7	
Spine Only	2	3	5	
Tumour Bed + Metastatic	2	2	2	
Extraneural	1	2	0	
DKFZ Validation Cohort				0.37
Metastatic	1	26	22	
Tumour Bed + Metastatic	2	10	11	

Supplemental Table 4: Subgroup specific clinical Characteristics by craniospinal irradiation at diagnosis for all 3 cohorts

	Chemo Only	CSI +	p-value
WNT	0	3	
Male Gender		2 (66%)	
Age (years)		10 (6·5-11)	
Histology			
Classic		3	
M+ at Diagnosis		0	
Incomplete Resection		0	
Pattern of Recurrence			
Local		1	
Metastatic		2	
SHH	20	38	
Male Gender	12 (63%)	12 (39%)	0·15
Age (years)	2 (1·4-2·5)	12 (7·2-18·4)*	**<0·0001**
Histology			0·051
LCA	1 (5·6%)	9 (27%)	
Classic	7 (39%)	17 (50%)	
Desmoplastic	10 (56%)	8 (23%)	
M+ at Diagnosis	4 (20%)	6 (19%)	1
Incomplete Resection	3 (21%)	7 (28%)	0.72
Pattern of Recurrence			1
Local	14 (70%)	26 (68%)	
Metastatic	6 (30%)	12 (32%)	
Group 3	20	47	
Male Gender	11 (61%)	36 (78%)	0·21
Age (years)	3 (2·2-3·3)	6 (4·2-10)	**<0·0001**
Histology			0·54
LCA	7 (35%)	21 (46%)	
Classic	12 (60%)	24 (52%)	
Desmoplastic	1 (5%)	1 (2%)	
M+ at diagnosis	12 (60%)	23 (52%)	0·60
Incomplete Resection	5 (33%)	13 (34%)	1
Pattern of Recurrence			0·6
Local	2 (10%)	4 (9%)	
Metastatic	18 (90%)	43 (92%)	
Group 4	9	58	
Male Gender	5 (57%)	41 (75%)	0·41
Age (years)	4.9 (3·4-5·4)	9 (7-11)	**<0·0001**
Histology			1
LCA	1 (20%)	10 (19%)	
Classic	4 (80%)	43 (80%)	
Desmoplastic	0	1 (2%)	
M+ at diagnosis	1 (11%)	22 (41%)	0·24
Incomplete Resection	1 (33%)	17 (35%)	1
Pattern of Recurrence			**0·032***
Local Only	3 (38·5%)	4 (6·8%)	
Metastatic	5 (62·5%)	55 (93·2%)	

p-values – Fisher exact test for categorical variables and Mann-Whitney U test for continuous variables. Age represented by median (IQR). *p<0·05 considered significant. Percentages are within columns. LCA=Large Cell/Anaplastic Histology

Notes: *One infant received 18Gy CSI at diagnosis.

Gender missing in 24 cases; Histology missing in 23 cases; M+ Dissemination at diagnosis missing in 22 cases; Extent of Resection missing in 56 cases;

Supplemental Table 5: Clinical Characteristics by pattern of recurrence for all three cohorts

	Local Recurrence	Metastatic Recurrence	p-value
WNT	1	2	
Male Gender	1	1 (50%)	
Age	10, 11	6·5	
Histology			
Classic	1	2	
M+ at Diagnosis	0	0 (0%)	
Incomplete Resection	0	0 (0%)	
Treatment at Diagnosis			
Chemo Only	0	0	
RT +/- Chemo	1	2	
SHH	44	18	
Male Gender	17 (46%)	7 (50%)	1
Age	8·04 (2·3-16·8)	6·1 (2·4-15·4)	0·98
Histology			0·12
LCA	6 (16%)	5 (31%)	
Classic	21 (55%)	4 (25%)	
Desmoplastic	11 (29%)	7 (44%)	
M+ at Diagnosis	6 (16%)	3 (33%)	0·25
Incomplete Resection	8 (28%)	2 (20%)	1
Treatment at Diagnosis			1
Chemo Only	14 (35%)	6 (29%)	
RT +/- Chemo	26 (65%)	12 (71%)	
Group 3	6	62	
Male Gender	5 (83%)	43 (73%)	1
Age	6·3 (3·1-10·5)	4·6 (3·2-7·1)	0·64
Histology			0·36
LCA	1 (17%)	27 (42%)	
Classic	5 (83%)	32 (54%)	
Desmoplastic	0	2 (3%)	
M+ at diagnosis	0	36 (61%)	**0·0058***
Incomplete Resection	1 (25%)	17 (33%)	1
Treatment at Diagnosis			1
Chemo Only	2 (33%)	18 (29%)	
RT +/- Chemo	4 (67%)	43 (71%)	
Group 4	7	63	
Male Gender	5 (83%)	41 (72%)	1
Age	5 (4-10)	8 (6·2-11)	0·35
Histology			1
LCA	1 (20%)	10 (18%)	
Classic	4 (80%)	46 (80%)	
Desmoplastic	0	1 (2%)	
M+ at diagnosis	0	24 (42%)	**0·039***
Incomplete Resection	2 (67%)	16 (39%)	0·27
Treatment at Diagnosis			**0·032***
Chemo Only	3 (43%)	5 (8%)	
RT +/- Chemo	4 (57%)	55 (92%)	

p-values – Fisher exact test for categorical variables and Mann-Whitney U test for continuous variables. Age represented by median (IQR).
*p<0·05 considered significant. Percentages are within columns.
CSI=craniospinal irradiation. LCA=Large Cell/Anaplastic Histology

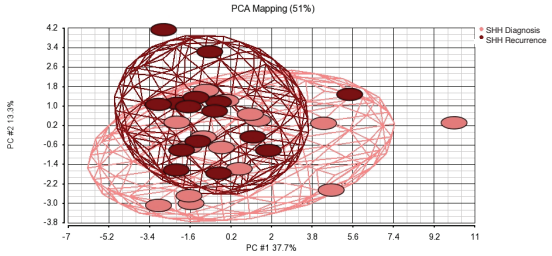
Supplemental Table 6: Treatment at diagnosis for all three cohorts

	Local Recurrence	Metastatic Recurrence	p-value
WNT	2	1	N/A
Chemo + RT	2	1	
CSI Dose			N/A
18-24	0	1	
36	1	1	
SHH	44	18	
Chemo Only	14 (36%)	5 (28%)	0·53
Chemo + CSI	21 (54%)	11 (61%)	
CSI Only	4 (10%)	1 (6%)	
Chemo + Focal RT	0	1 (6%)	
Missing	5	0	
CSI Dose			0·44
0 Gy	14 (38%)	6 (33%)	
18-24 Gy	4 (11%)	4 (27%)	
36 Gy	18 (50%)	6 (40%)	
>18Gy dose unk	3[a]	2	
Group 3	6	62	
Chemo Only	2 (40%)	18 (30%)	0·67
Chemo + CSI	3 (60%)	42 (69%)	
CSI Only	0	1 (2%)	
Focal RT + Chemo	0	0	
Missing	1[b]	1	
CSI Dose			0·33
0 Gy	2 (50%)	18 (32%)	
18-24 Gy	1 (25%)	6 (11%)	
36 Gy	1 (25%)	33 (57%)	
>18Gy dose unk	1		
Group 4	7	63	
Chemo Only	3 (43%)	3 (5%)	**0·022***
Chemo + CSI	4 (57%)	55 (93%)	
CSI Only	0	0	
Focal RT + Chemo	0	1 (2%)	
Missing	0	4[c]	
CSI Dose			**0·014***
0 Gy	3 (43%)	4 (7%)	
18-24 Gy	2 (29%)	12 (21%)	
36 Gy	2 (29%)	40 (71%)	
>18Gy dose unk	0	2	

p-values – Fishers exact test *p<0·05 considered significant. Percentages are within columns. CSI=craniospinal irradiation. RT=Radiation Therapy. a-3 cases are known to have received CSI but dose and chemo unknown b- 1 case known to have received CSI but dose and chemo unknown c – 2 cases known to have received CSI but dose and chemo unknown

Supplementary Figure 1

A



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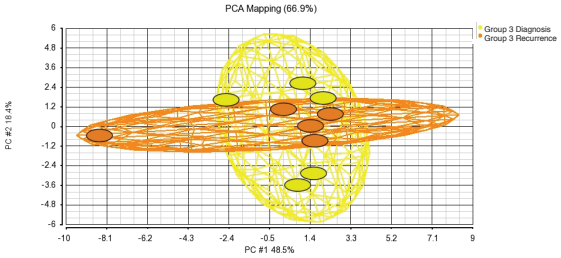

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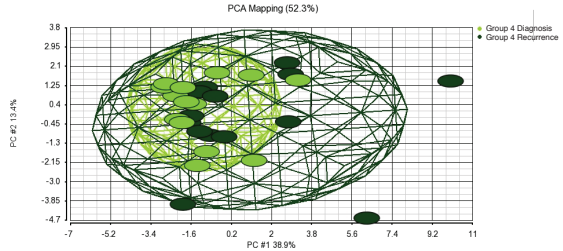

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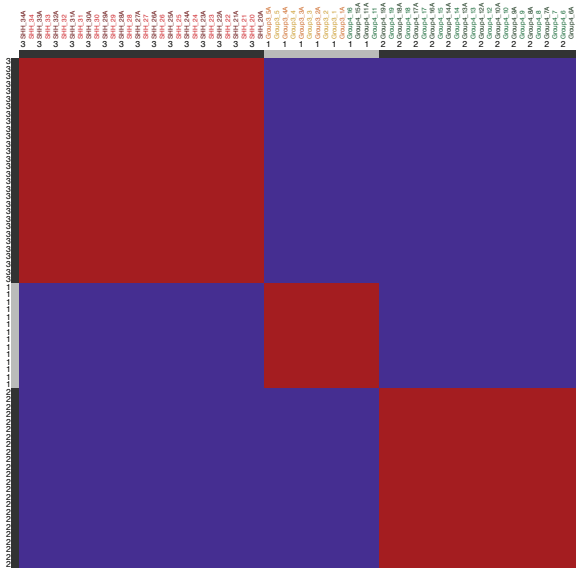

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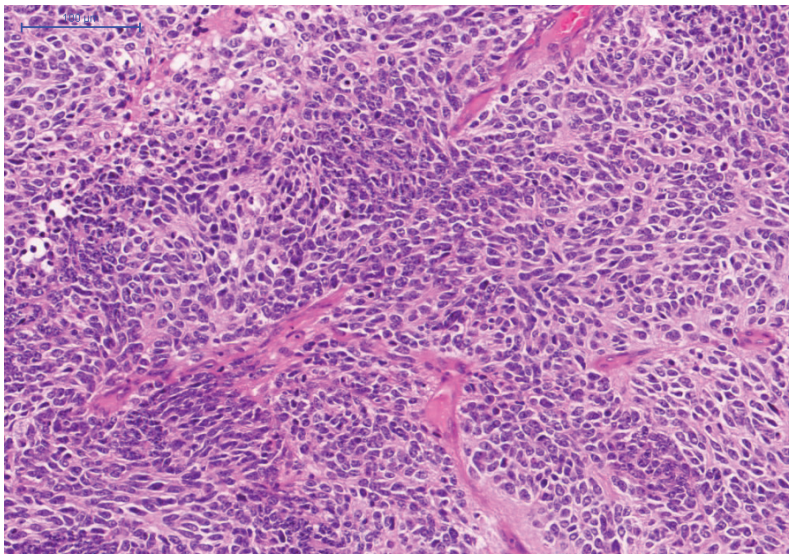

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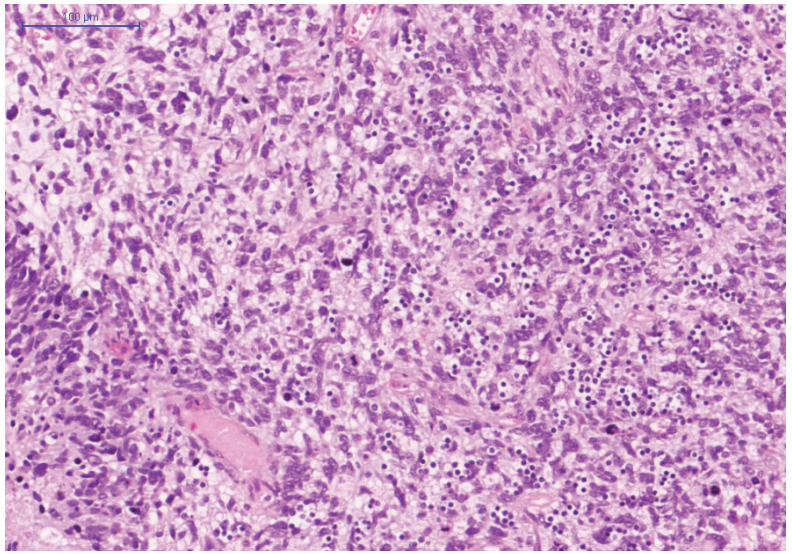

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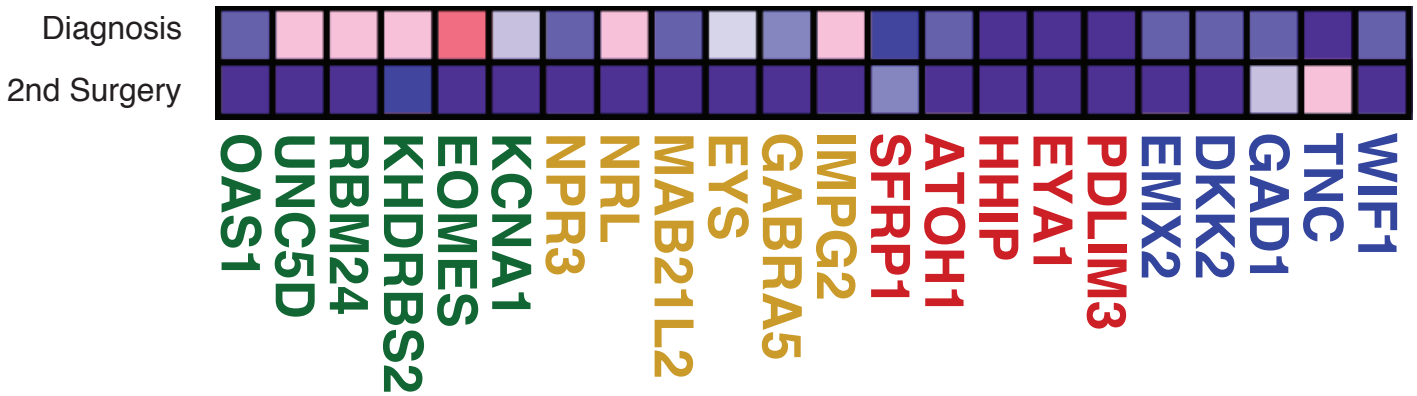
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UNC5D
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GABRA5
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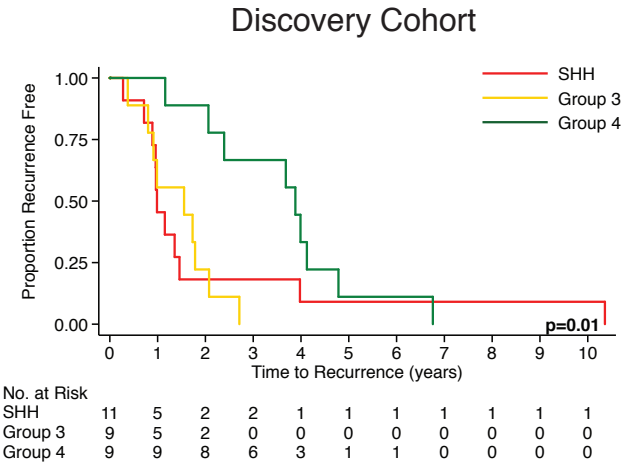
TNC
WIF1

Supplemental Figure 3

A



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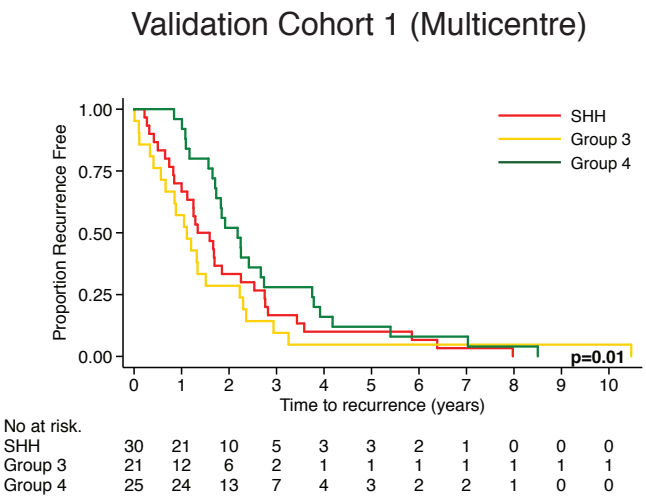

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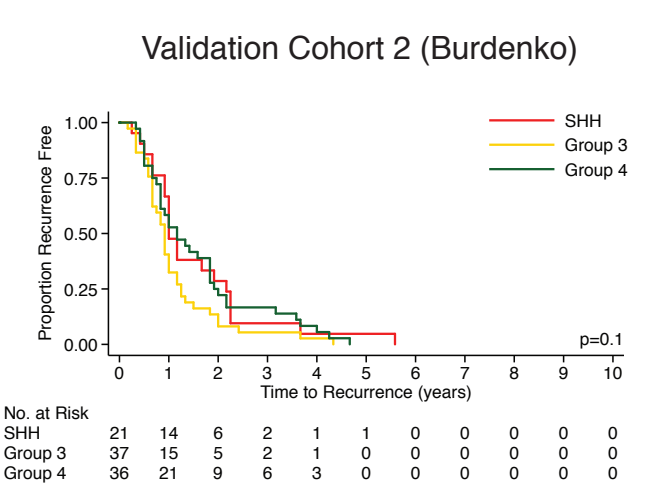
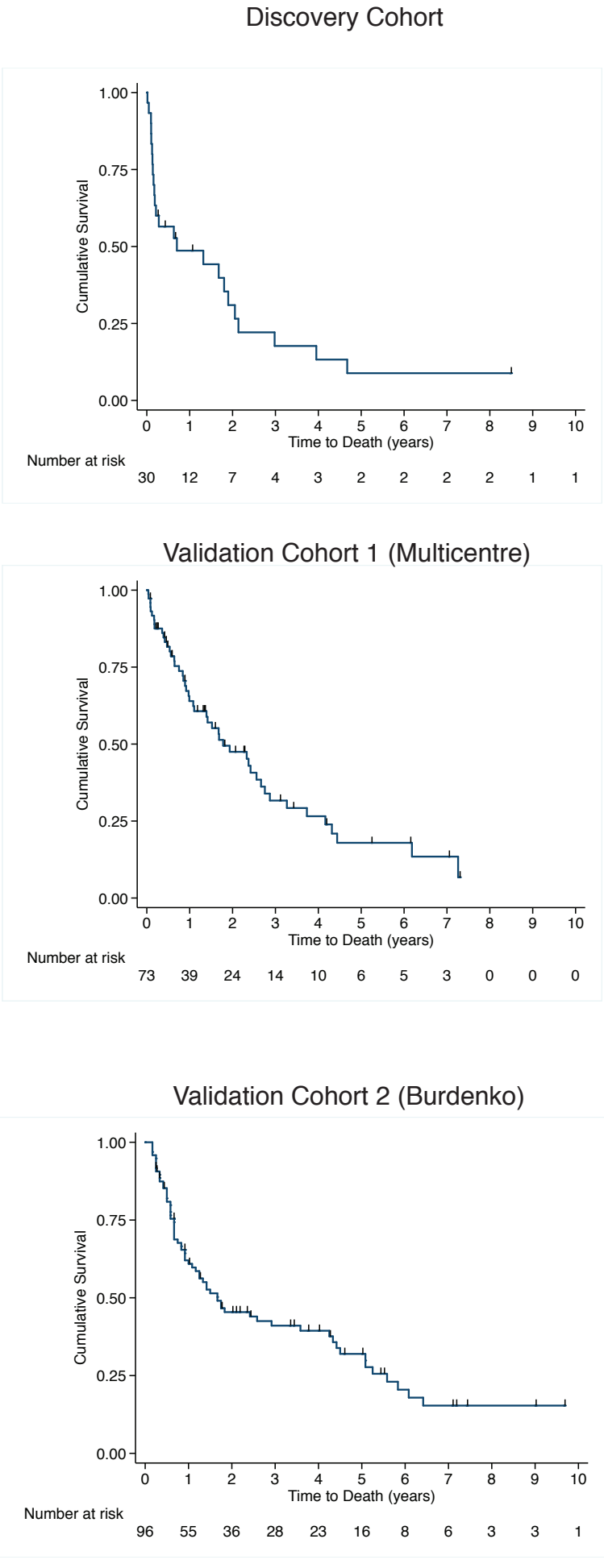
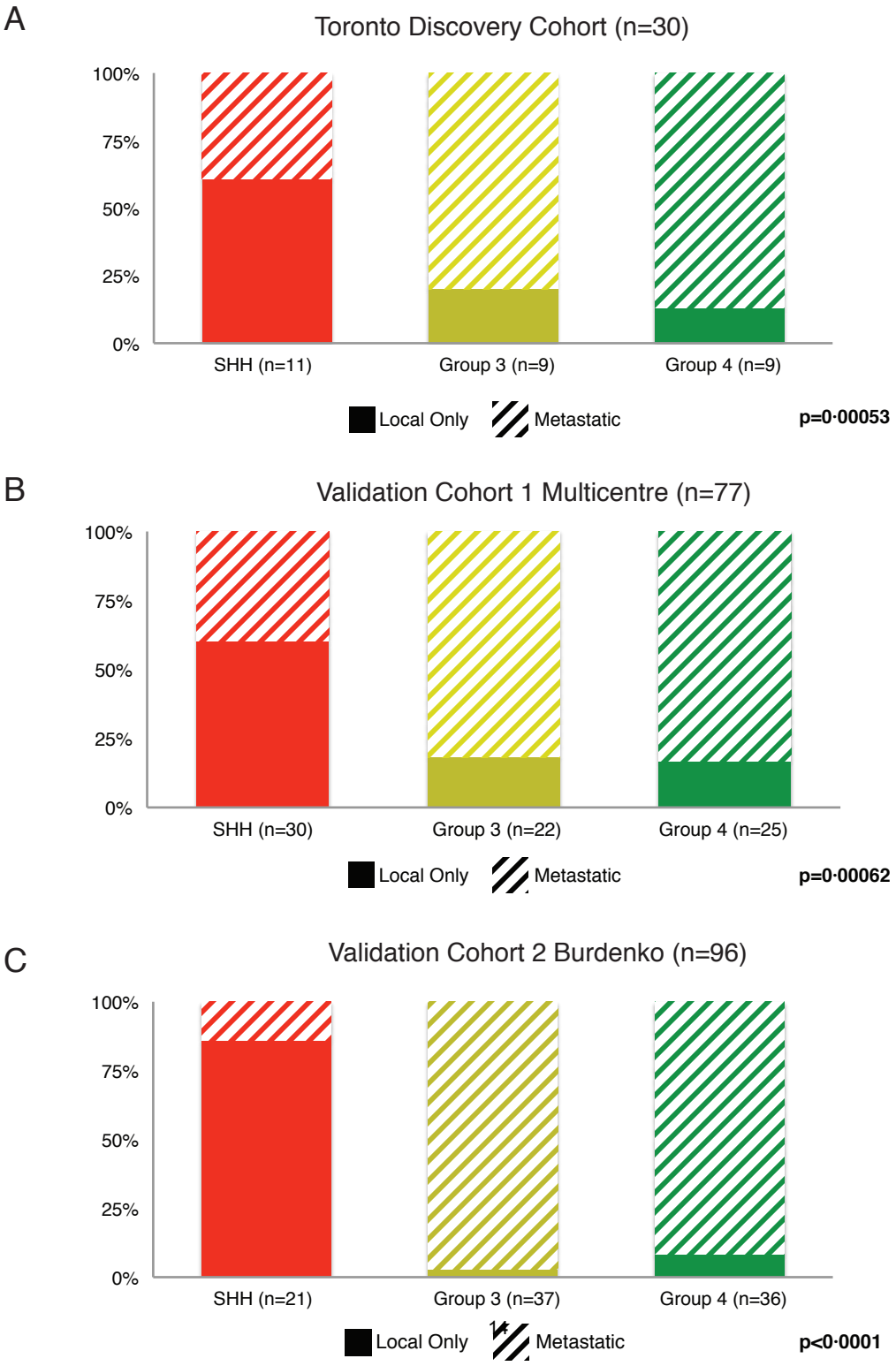


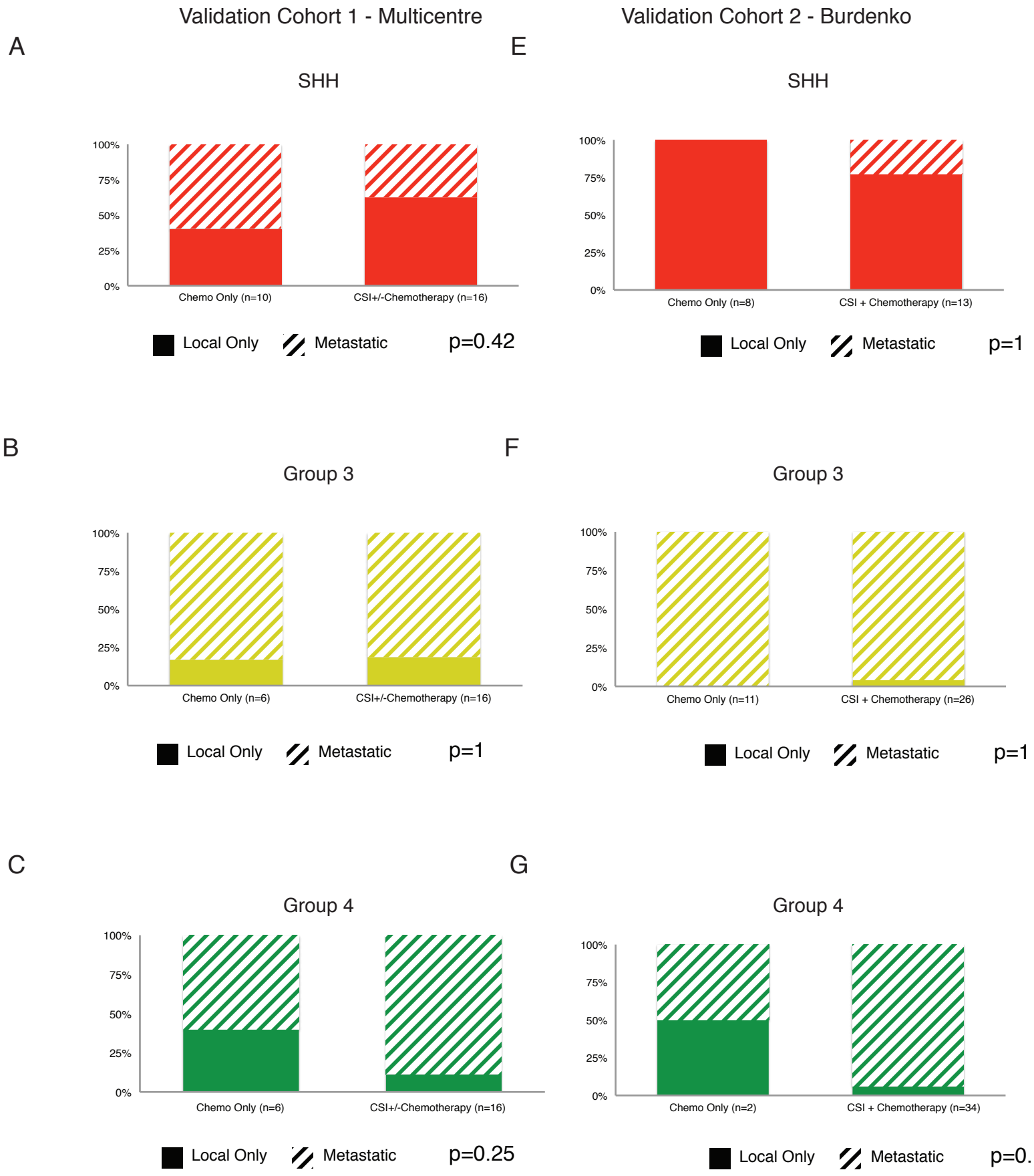
Supplemental Figure 4



Supplemental Figure 5



Supplemental Figure 6



Supplementary Figure 7