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Comprehensive molecular characterization of mitochondrial genomes in human cancers

Yuan Yuan ^{1,16}, Young Seok Ju ^{2,3,16}, Youngwook Kim ^{4,5,16}, Jun Li ¹, Yumeng Wang^{1,6}, Christopher J. Yoon³, Yang Yang⁷, Inigo Martincorena², Chad J. Creighton ⁸, John N. Weinstein ^{1,9}, Yanxun Xu¹⁰, Leng Han ¹¹, Hyung-Lae Kim¹², Hidewaki Nakagawa¹³, Keunchil Park ¹⁴ , Peter J. Campbell ^{2,15} , Han Liang ^{1,6,9}  and PCAWG Consortium*

¹Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. ²Cancer Genome Project, Wellcome Trust Sanger Institute, Hinxton, UK. ³Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology, Daejeon, Korea. ⁴Department of Health Science and Technology, Samsung Advanced Institute for Health Science and Technology, Sungkyunkwan University School of Medicine, Seoul, Korea. ⁵Samsung Genome Institute, Samsung Medical Center, Seoul, Korea. ⁶Quantitative and Computational Biosciences Graduate Program, Baylor College of Medicine, Houston, TX, USA. ⁷Division of Biostatistics, The University of Texas Health Science Center at Houston School of Public Health, Houston, TX, USA. ⁸Department of Medicine and Dan L. Duncan Cancer Center Division of Biostatistics, Baylor College of Medicine, Houston, TX, USA. ⁹Department of Systems Biology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. ¹⁰Department of Applied Mathematics and Statistics, Johns Hopkins University, Baltimore, MD, USA. ¹¹Department of Biochemistry and Molecular Biology, The University of Texas Health Science Center at Houston McGovern Medical School, Houston, TX, USA. ¹²Department of Biochemistry, Ewha Womans University School of Medicine, Seoul, Korea. ¹³Laboratory for Cancer Genomics, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. ¹⁴Division of Hematology/Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea. ¹⁵Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK. ¹⁶These authors contributed equally: Yuan Yuan, Young Seok Ju, Youngwook Kim. *A list of members and affiliations appears in the Supplementary Note. e-mail: kpark@skku.edu; pc8@sanger.ac.uk; hliang1@mdanderson.org

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¹²Laboratory for Cancer Genomics, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. ¹³Division of Hematology/Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea. ¹⁴Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.

¹⁵These authors contributed equally: Yuan Yuan, Young Seok Ju, Youngwook Kim. *A list of members and affiliations appears in the Supplementary Note.

 e-mail: kpark@skku.edu; pc8@sanger.ac.uk; hliang1@mdanderson.org

Supplementary Information

Comprehensive Molecular Characterization of the Mitochondrial Genomes in Human Cancers

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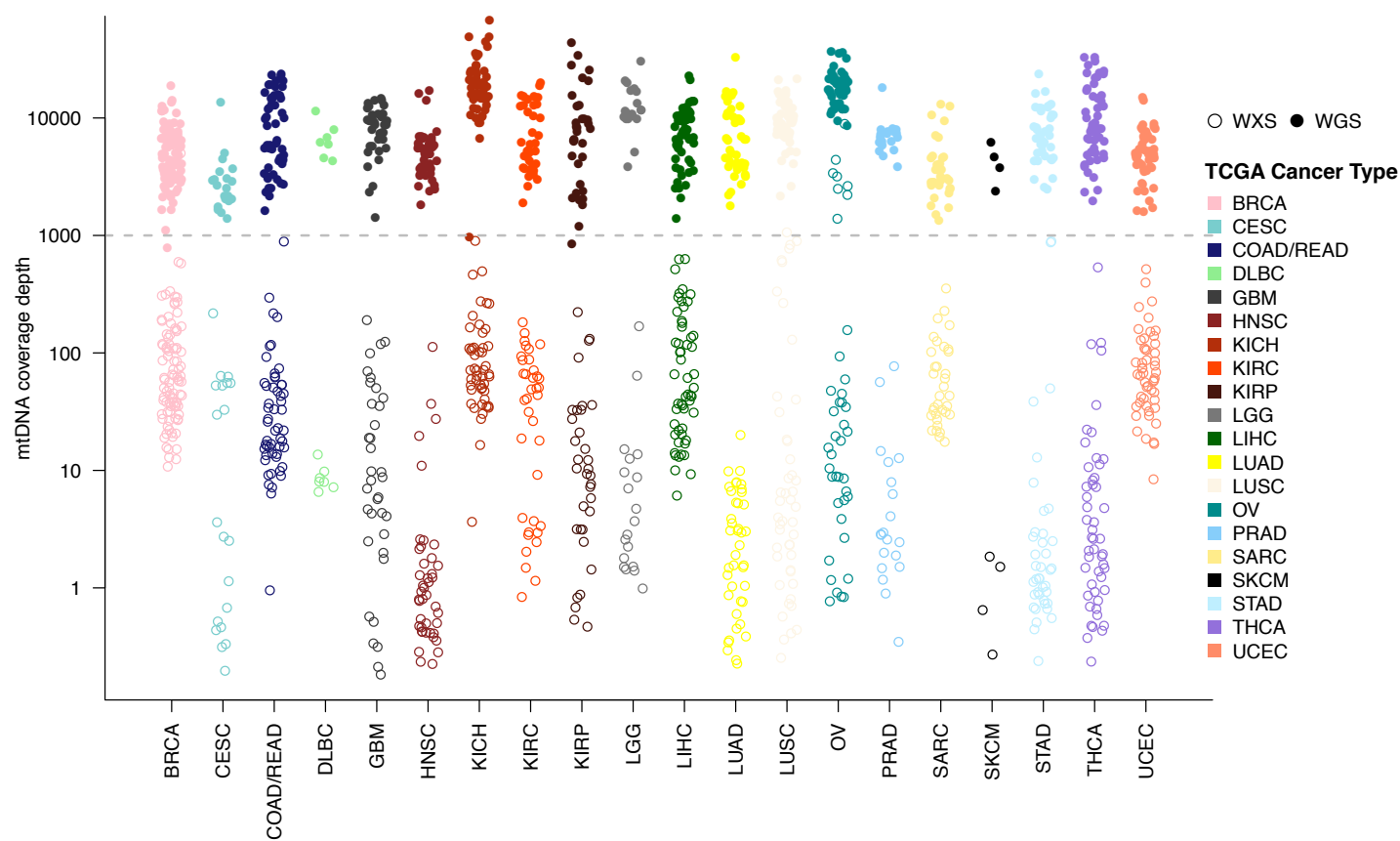
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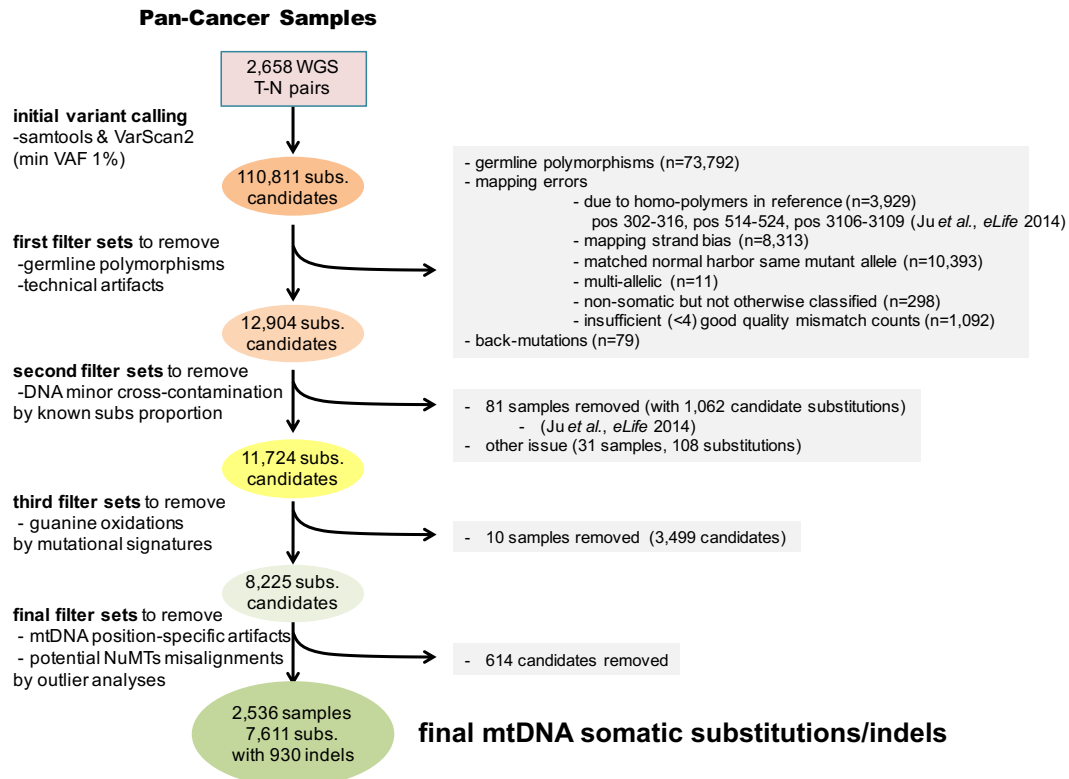
Supplementary Figure 1



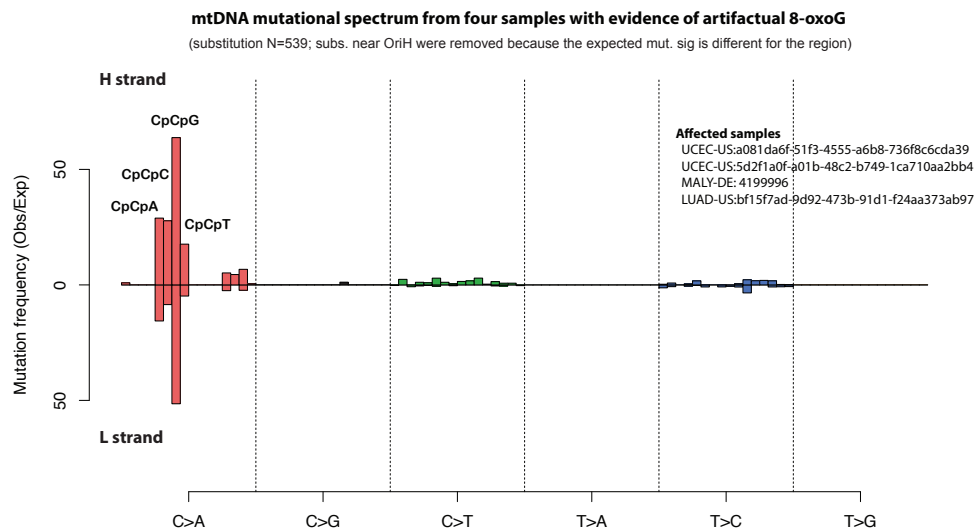
Comparison of mtDNA coverage depth for samples with both WGS and WGS data

Supplementary Figure 2

a



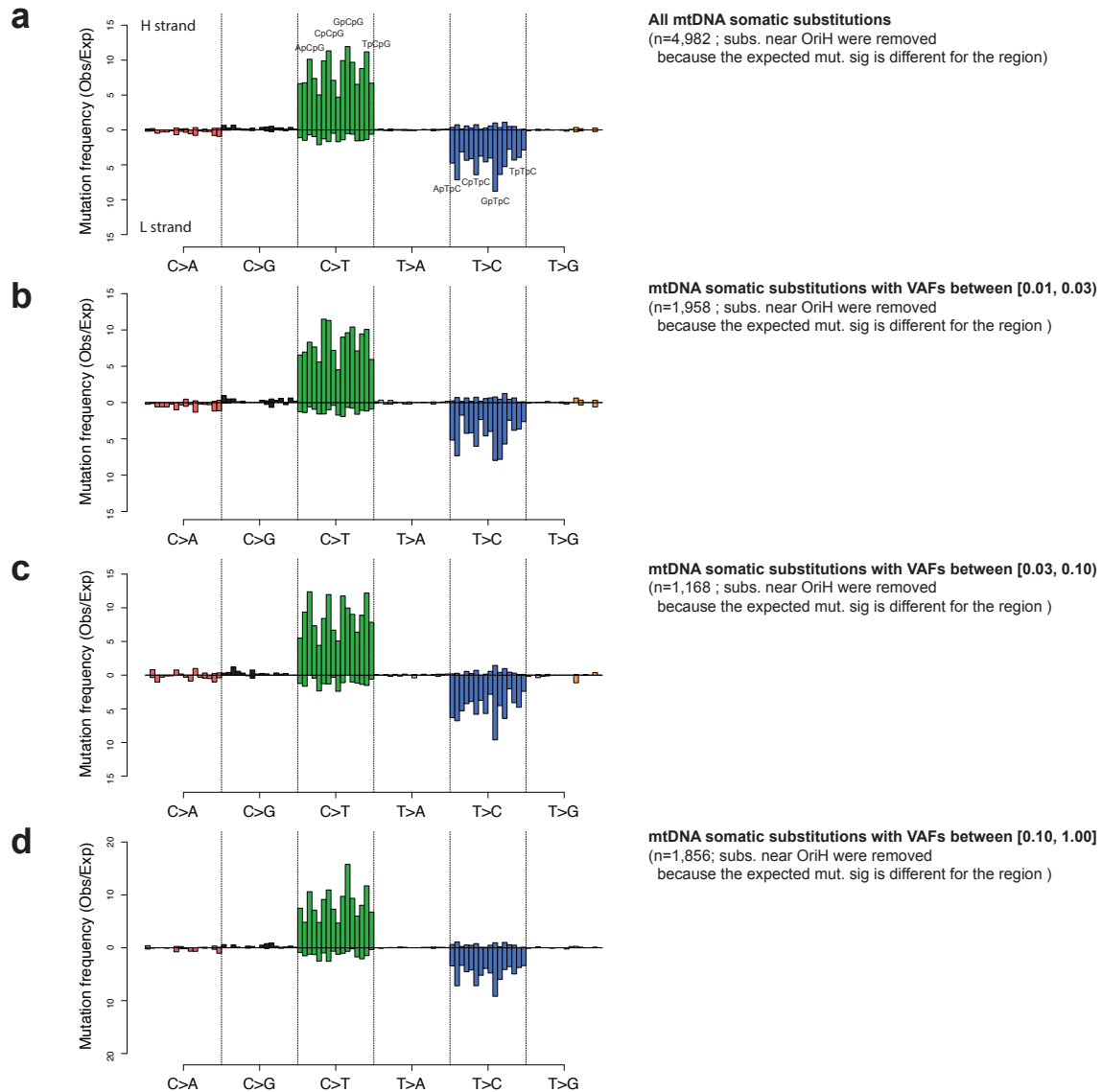
b



Filters to obtain sensitive and specific mtDNA somatic mutations

(a) A schematic diagram which summarizes the filters used in variant calling in this study. (b) Mutational spectrum from mutation candidates from four samples with evidence of artifactual guanine oxidation during library preparation step. The mutation spectrum is not consistent with that of mtDNA somatic mutations, but that of false positives due to artifacts (8-oxoGuanine) generated during library preparation steps (Costello et al., Nuc Acids Res 2012).

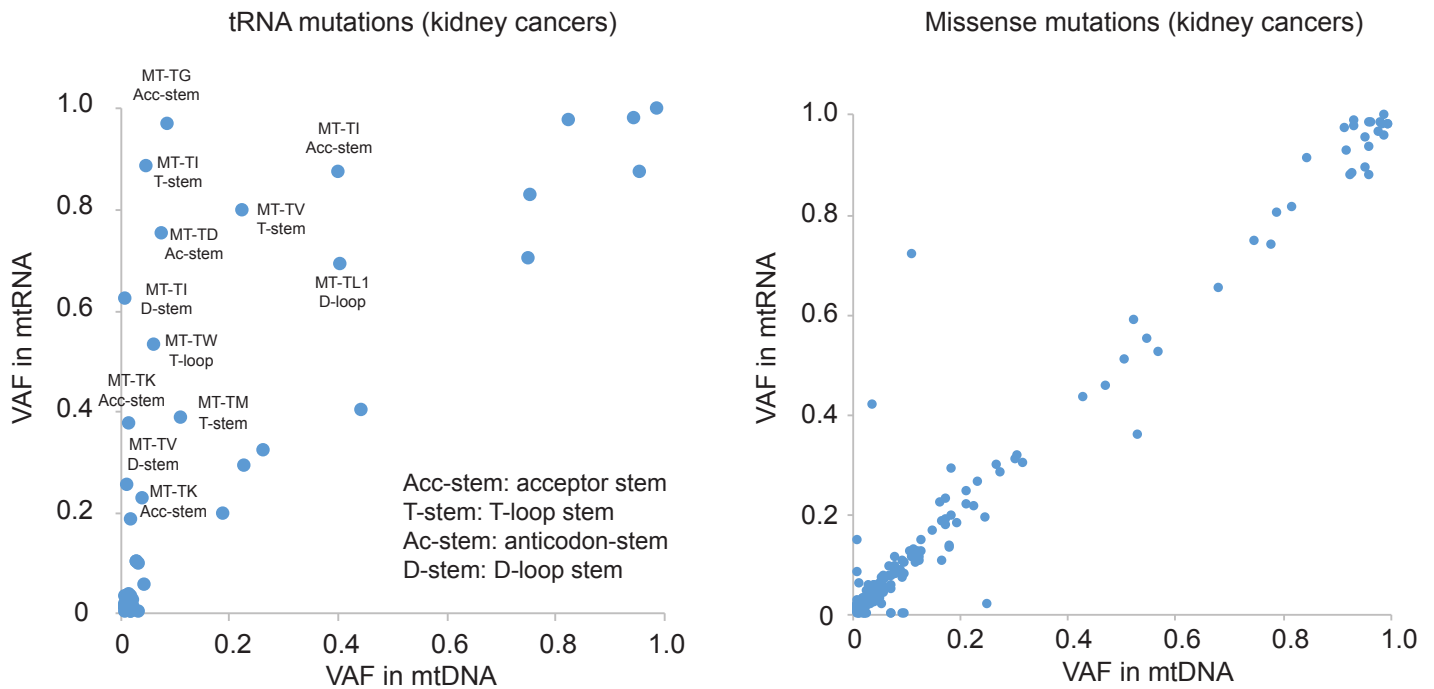
Supplementary Figure 3



Consistent mtDNA mutation spectrum for substitutions at VAF between 1%-3%

We compared mutation signatures for four different groups of substitutions: ones at VAF 1%-3%, 3%-10%, 10%-100% and overall (1%-100%). The 1%-3% VAF somatic substitutions (n=1,958; substitutions at D-Loop were not included) show unique mtDNA somatic mutation signature, suggesting they are mostly true positives.

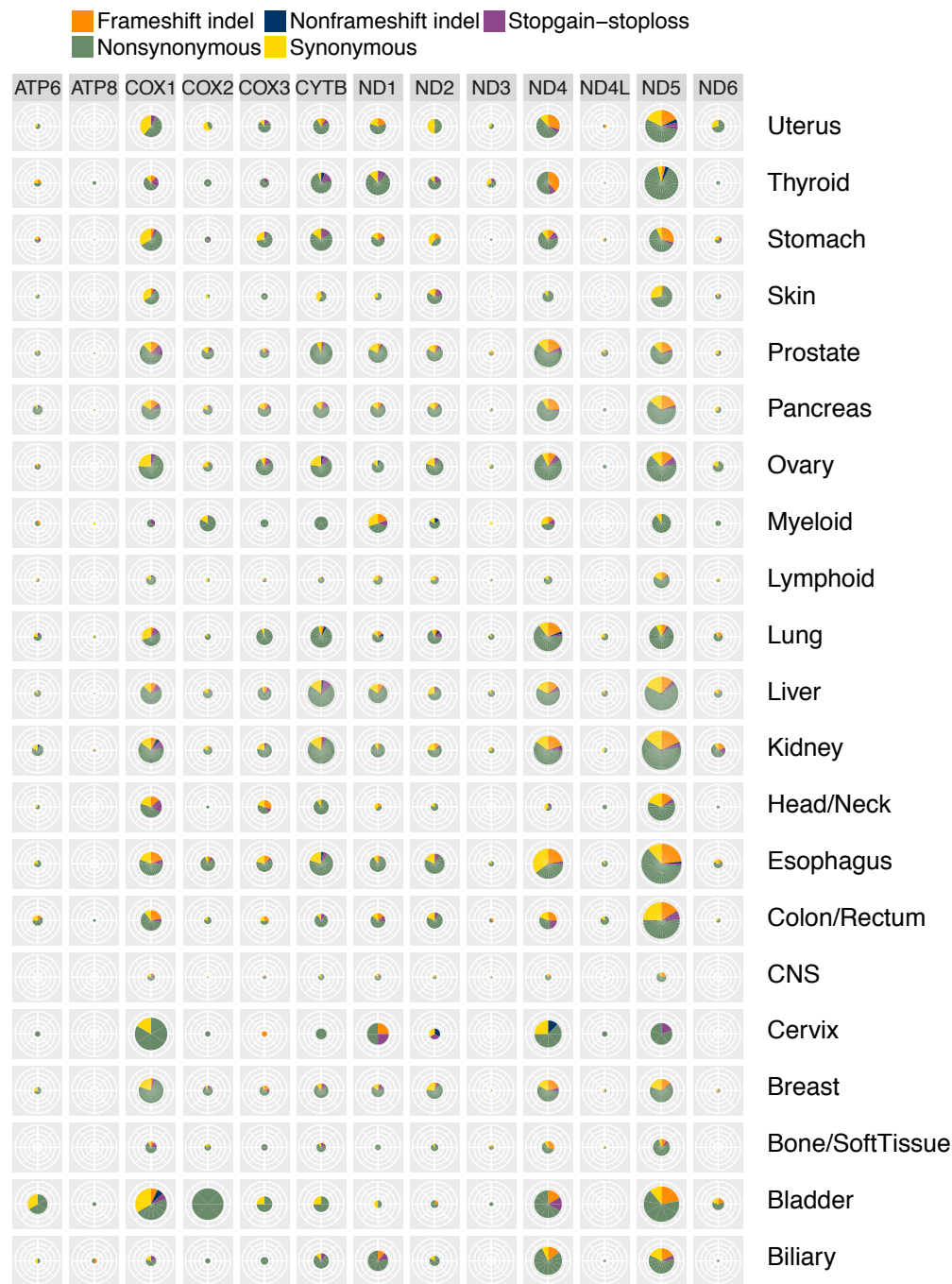
Supplementary Figure 4



Comparison of mtDNA somatic mutations at DNA and mRNA level

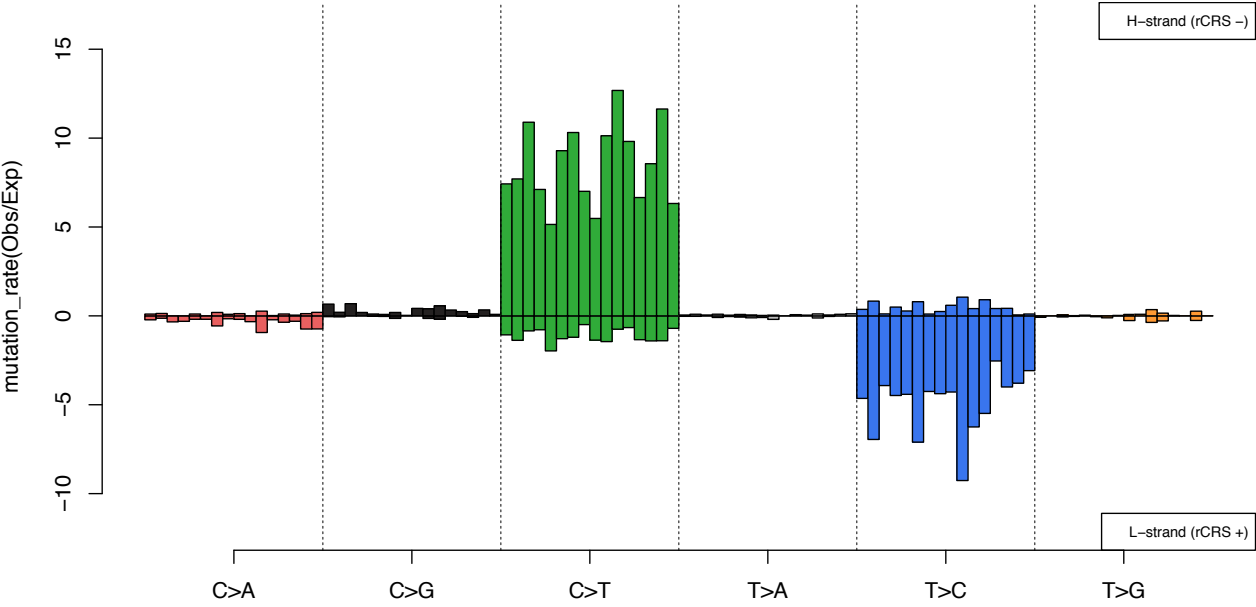
Left panel: the variant allele frequency (VAF) of the same mutation in mitochondrial tRNA and its DNA. Several mutations affecting the secondary structure of tRNA resulted in accumulation of mutant tRNA. Right Panel: missense mutations of mitochondrial coding genes demonstrated proportional relationship between mtDNA and mtRNA VAF.

Supplementary Figure 5



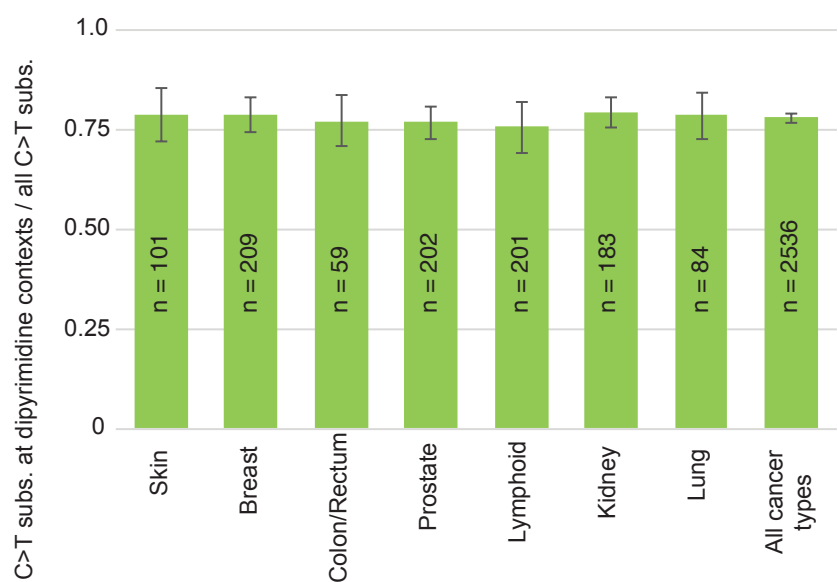
An overview of the mutation frequency of the 13 mtDNA coding genes across cancer tissue types
Pie chart sizes are proportional to overall mutation frequency; slice colors correspond to variant types.

Supplementary Figure 6



Replicative strand-specific mutational spectrum of mtDNA substitutions

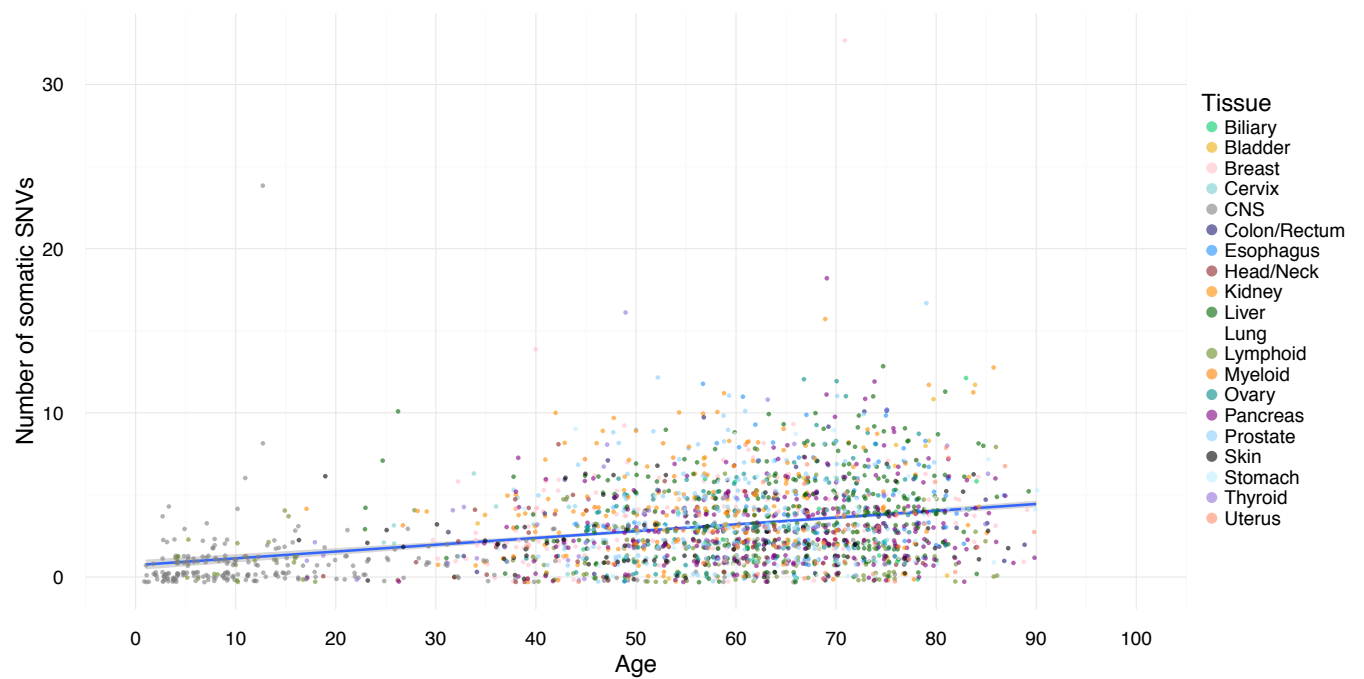
Supplementary Figure 7



The proportion of C→T substitutions at dipyrimidine contexts (where UV light frequently generates mutations)

n = number of samples with mtDNA mutation information available. The error bars represent the 95% confidence intervals of the proportions calculated using binomial distribution.

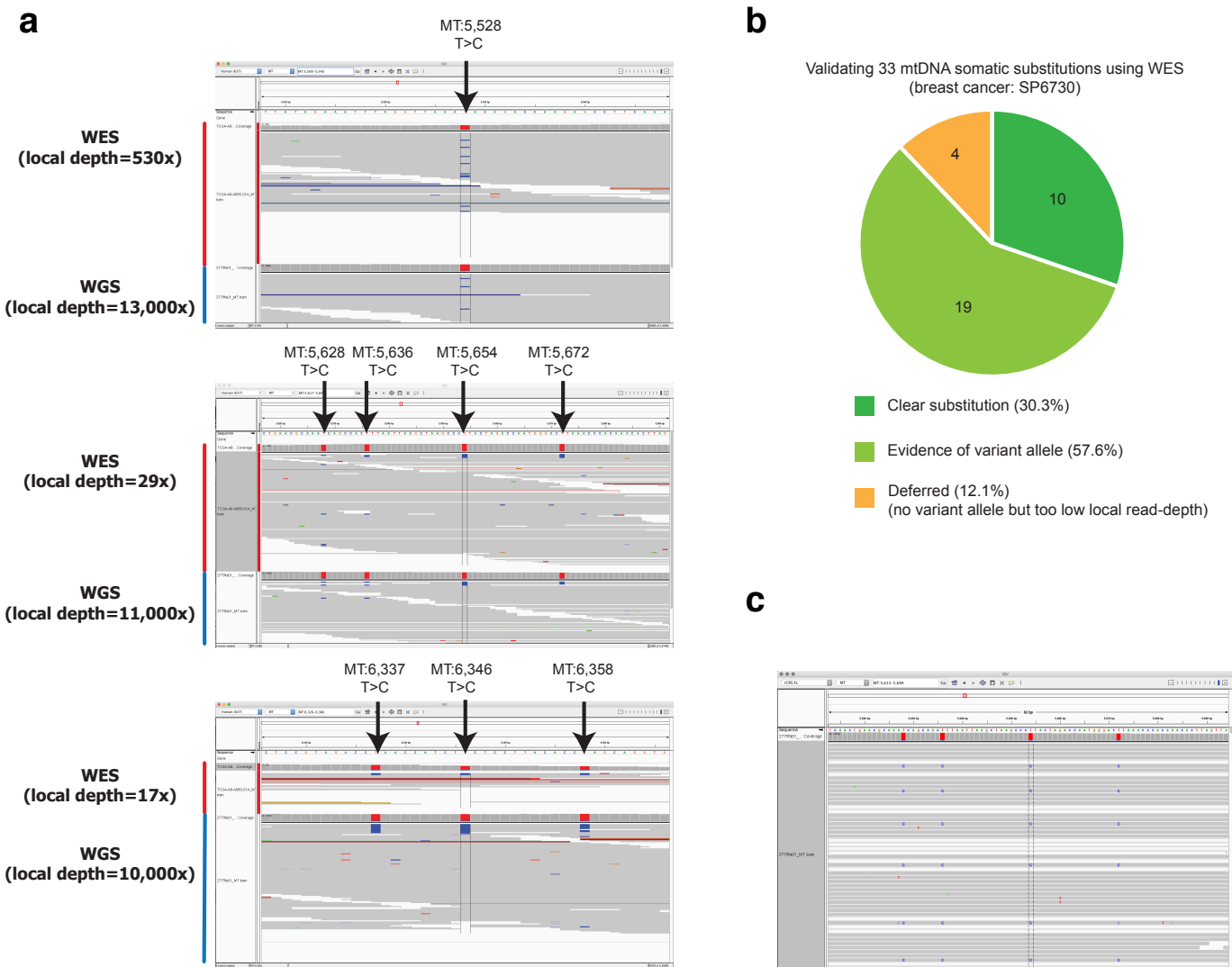
Supplementary Figure 8



The correlation between the number of mtDNA somatic SNVs and patient age

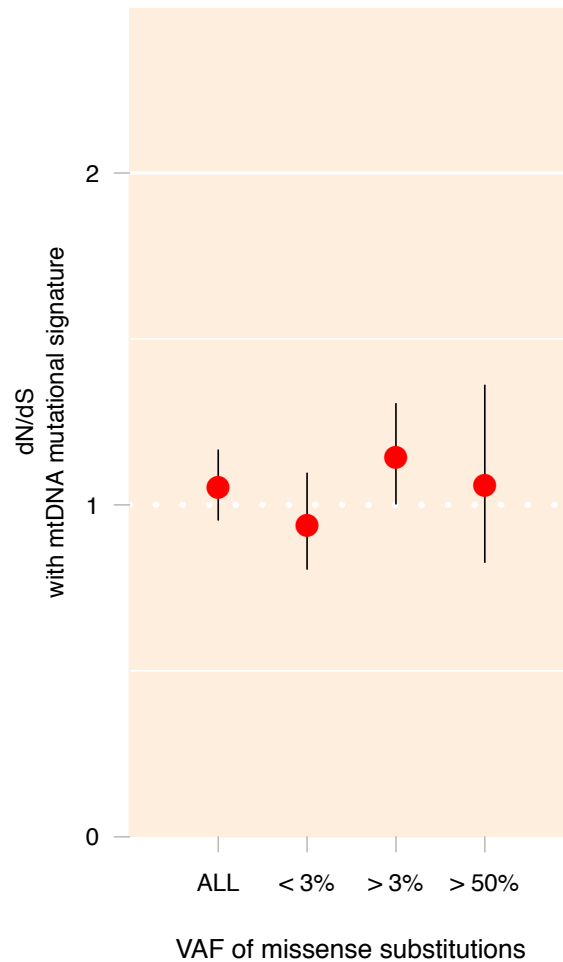
The correlation was determined based on the 2,414 patients with both age and somatic SNV information available. The shaded region represents the 95% confidence interval for the predictions from a linear model with the number of somatics VAFs as the response variable and patient age as the explanatory variable.

Supplementary Figure 9



Hypermutated sample validated by WXS

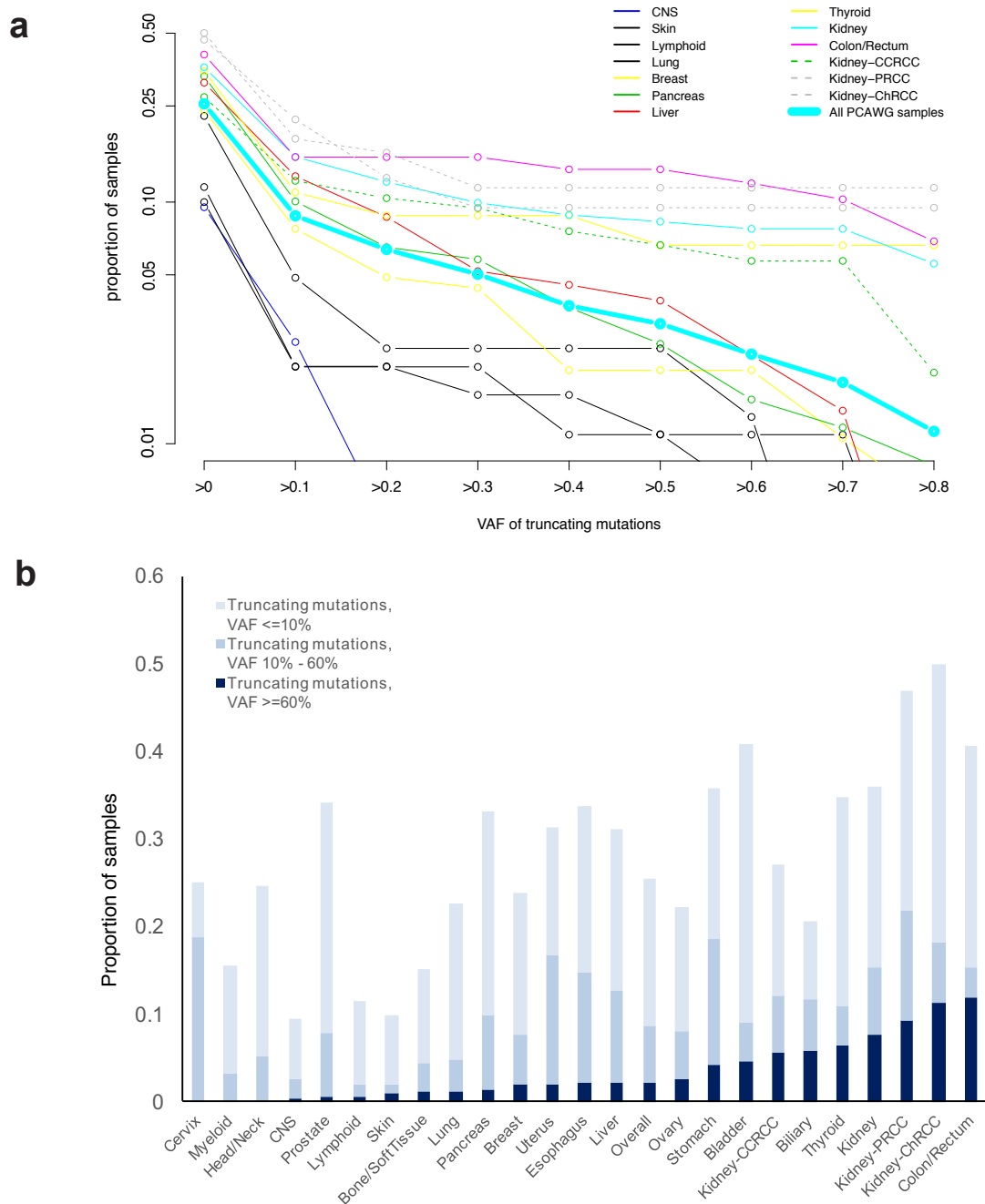
Supplementary Figure 10



dN/dS ratio from mtDNA somatic missense substitutions

All VAF: 3521 missense vs 874 silent; VAF <3%: 1392 missense vs 366 silent ;VAF >3% 2129 missense vs 508 silent ; VAF >50%: 565 missense vs 132 silent mutations. The error bars represent the 95% confidence intervals of the dN/dS ratio (likelihood).

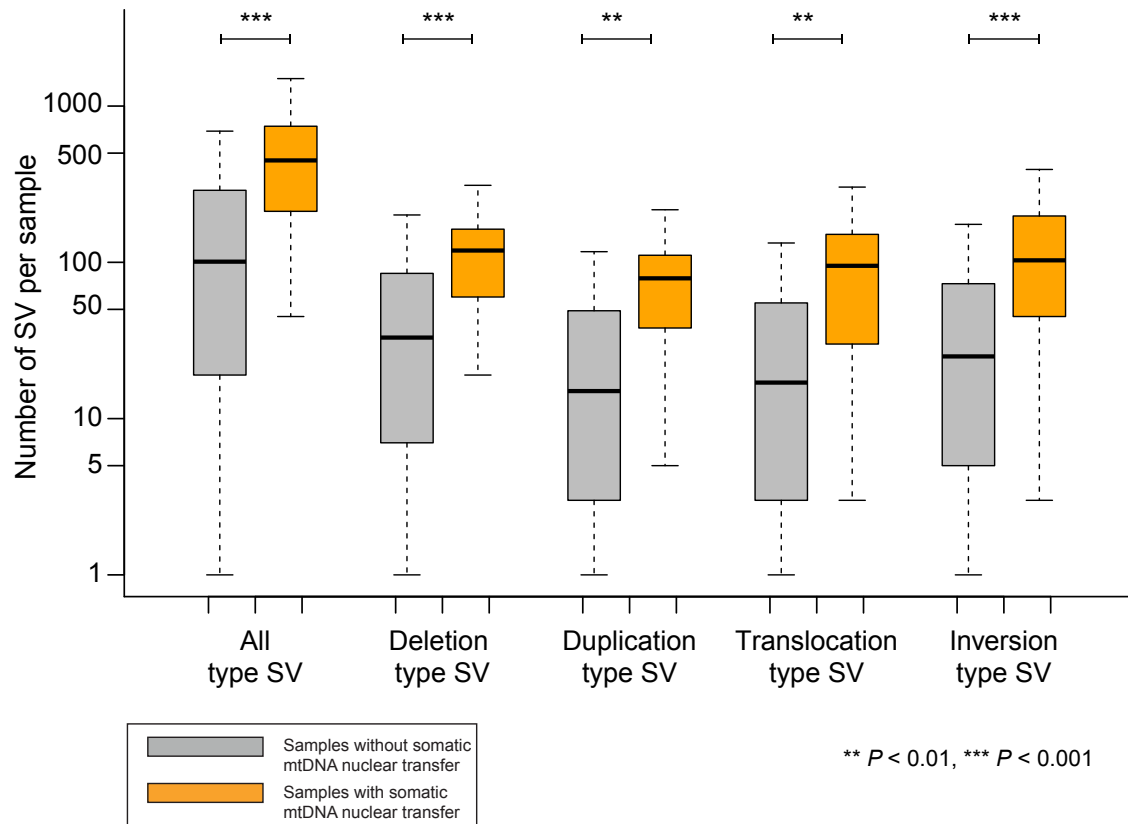
Supplementary Figure 11



The proportion of samples with truncating mutations by cancer types

(a) The proportion of samples (y-axis) that harbor truncating mutations with VAF above specified cutoff (x-axis) within each cancer type. (b) The proportion of samples that harbor truncating mutations, grouped (in color) by their maximum VAF ($\leq 10\%$, 10%-60%, $\geq 60\%$) within each cancer type.

Supplementary Figure 12

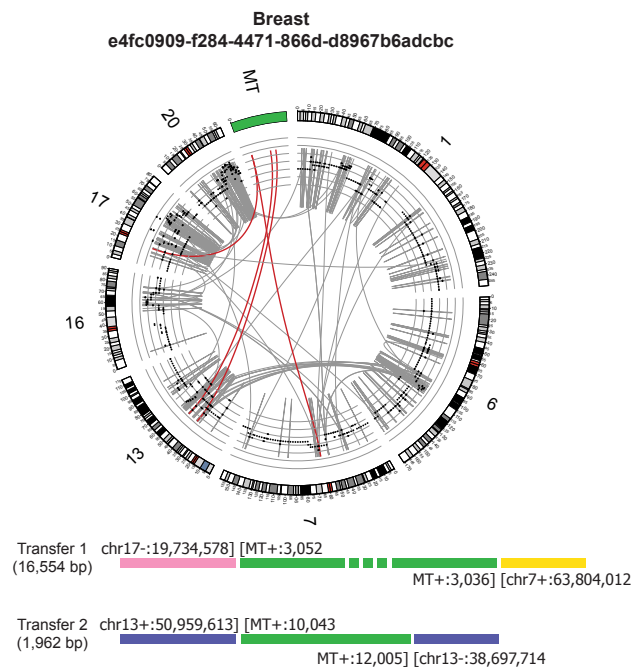


The numbers of SV breakpoints in samples with and without somatic mtDNA nuclear transfers (SMNT) by SV types

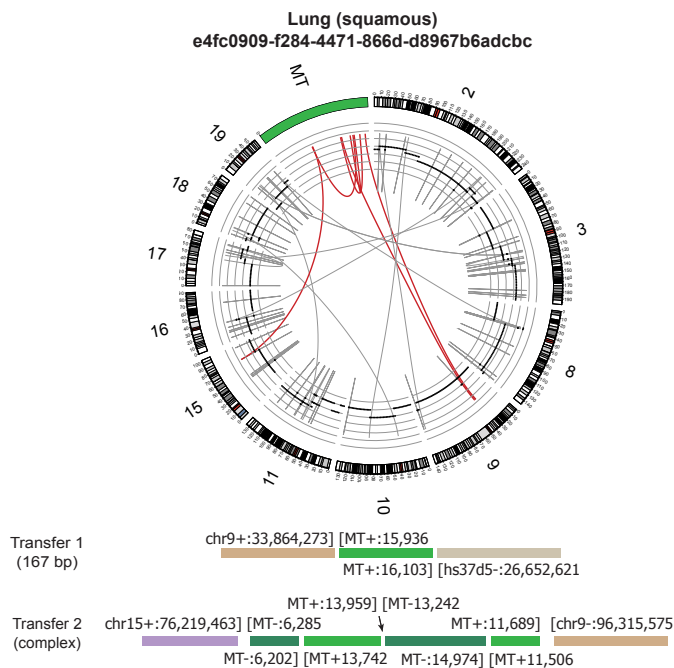
Samples without mtDNA transfer (gray) = 2603, with mtDNA transfer (orange) = 55. The p-values were based on two-sided t-test without multiple comparison adjustment. The boundaries of the boxes mark the first and third quartile, with the median in the center, and whiskers extending to 1.5 interquartile range from the boundaries.

Supplementary Figure 13

a



b

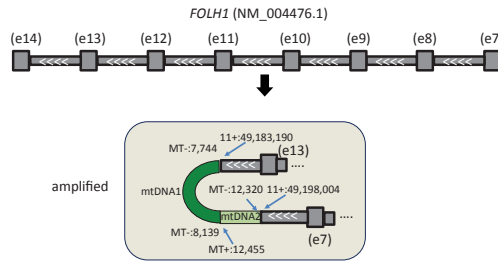


Somatic nuclear transfer of mtDNA

(a) A Circos plot representing two long-segment mtDNA nuclear transfers in a breast cancer genome. (b) A Circos plot representing two mtDNA nuclear transfers in a lung cancer genome. One mtDNA segment transferred has three inversion-type rearrangements as depicted.

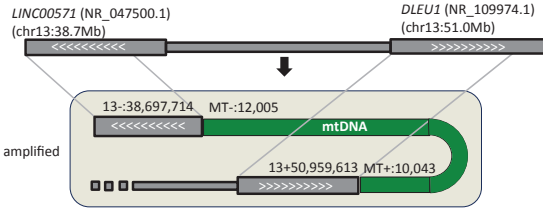
Supplementary Figure 14

a Breast [174850b4-5ec2-462b-a890-89bd1716b3c2]



b Breast [e4fc0909-f284-4471-866d-d8967b6adcbc]

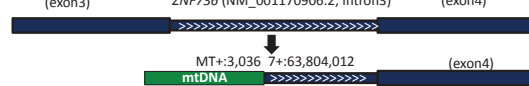
mtDNA nuclear transfer event #1



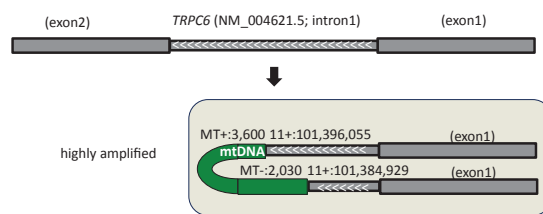
mtDNA nuclear transfer event #2



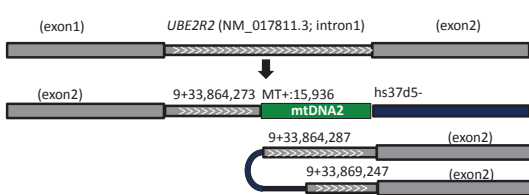
mtDNA nuclear transfer event #3 (or #2)



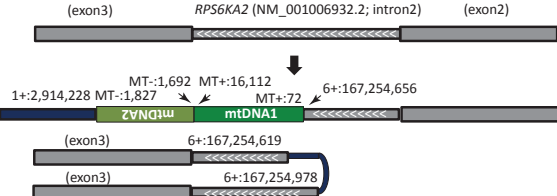
c Lung [037c57d1-b4a5-45dc-bda4-0550461d321b]



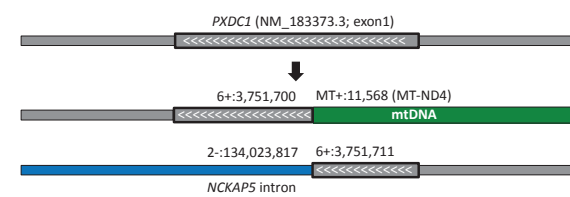
d Lung [87ac0ad4-8c9d-409e-9a86-1d201d01769d]



e Lung [9293e197-e38a-4e19-a7d0-1b45d1ad48bd]

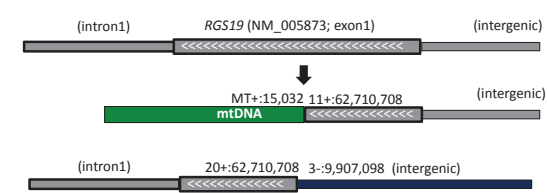


f Skin [01ad975d-c2ed-4e4d-bd3b-c9512fc9073c]

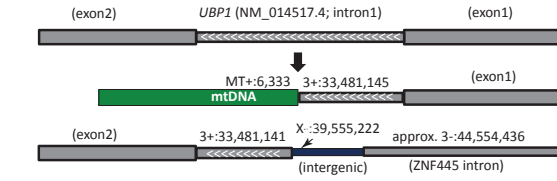


g Skin [81cedb9e-ee43-476b-9ed9-8d0fdb346065]

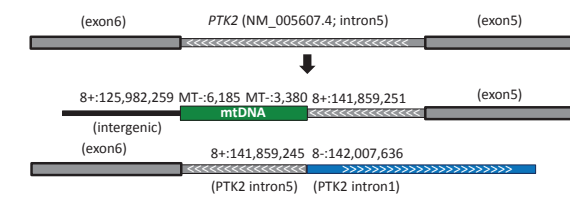
mtDNA nuclear transfer event #1



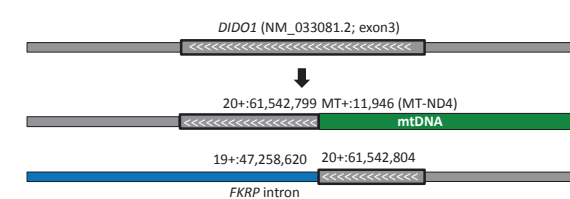
mtDNA nuclear transfer event #2



h Skin [MELA-0259]

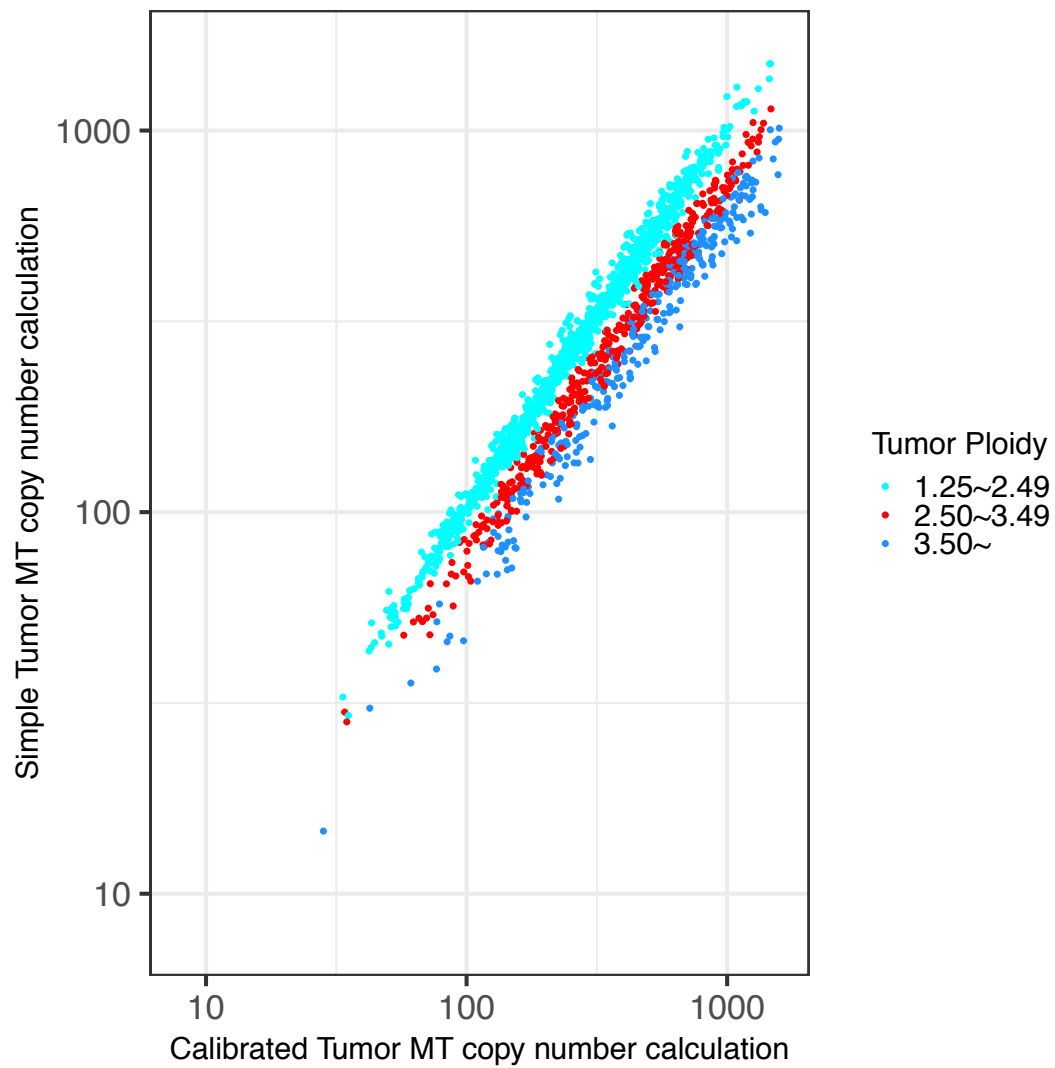


i Skin [c2948fe9-5798-43bc-a743-511e94e417f8]



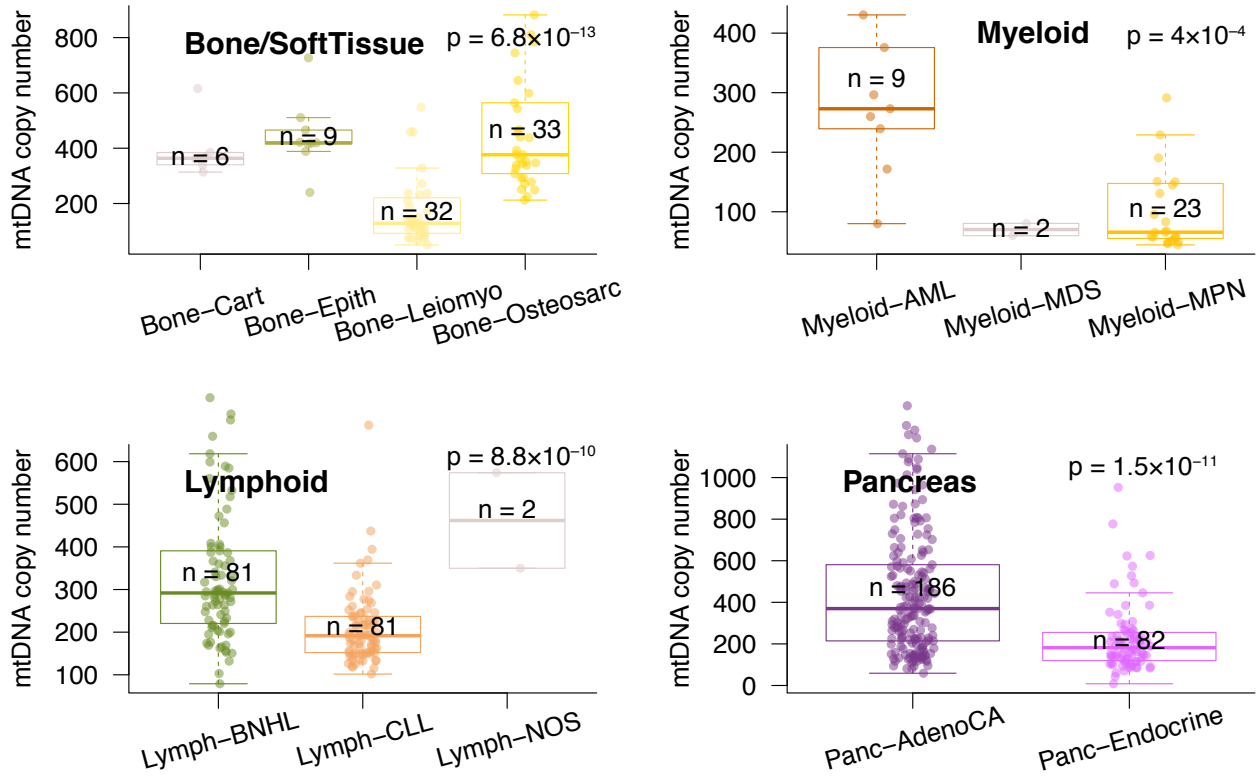
The functional consequence of the SMNT events

Supplementary Figure 15



The comparison of mtDNA copy number calculated from simple estimation (using only coverage depth information) vs. our method (incorporating coverage depth, tumor purity and ploidy)

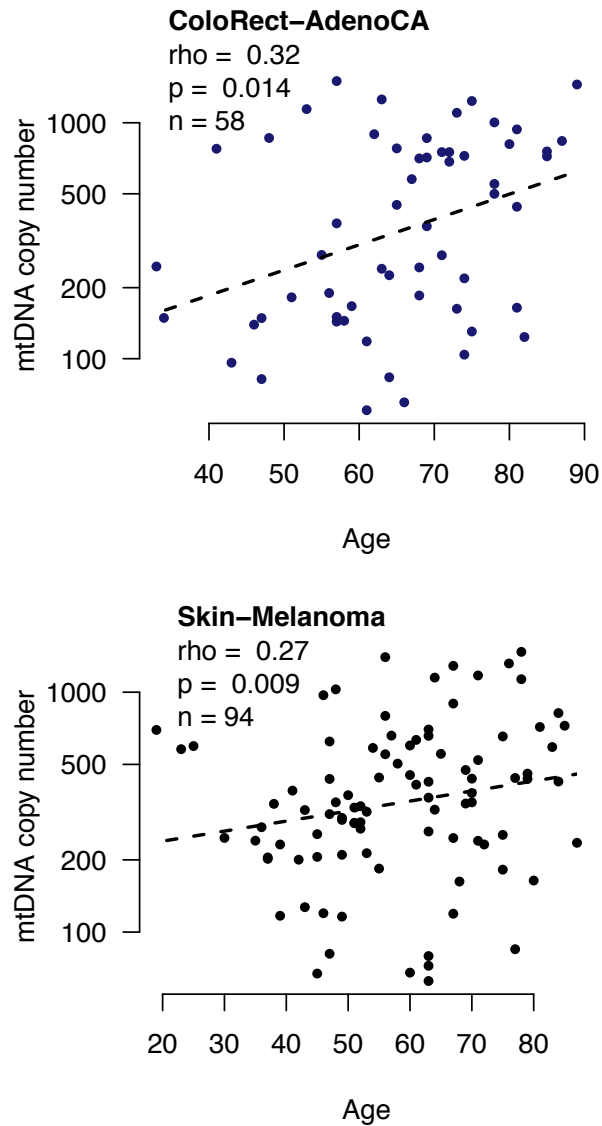
Supplementary Figure 16



The copy number distributions of mtDNA in multiple cancers derived from the same tissue type

n = number of samples with cancer mtDNA information available. The p-values were either generated by t-test (for two cancer types) or ANOVA (for > two cancer types). The boundaries of the boxes mark the first and third quartile, with the median in the center, and whiskers extending to 1.5 interquartile range from the boundaries.

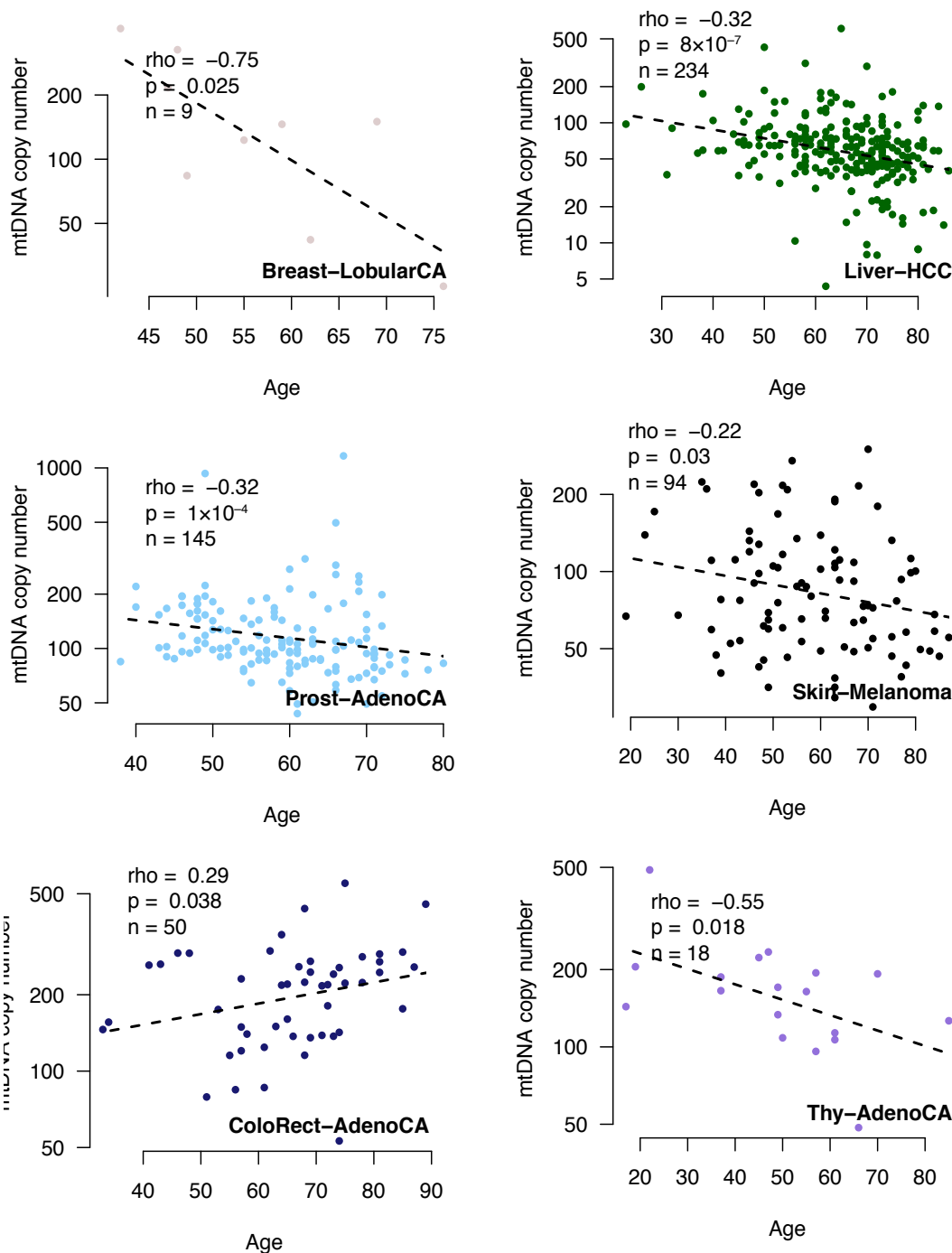
Supplementary Figure 17



The correlation between mtDNA copy number and patient age

n = number of samples with cancer mtDNA copy number and patient age information available. The correlation and p-value were determined using Spearman's rank correlation.

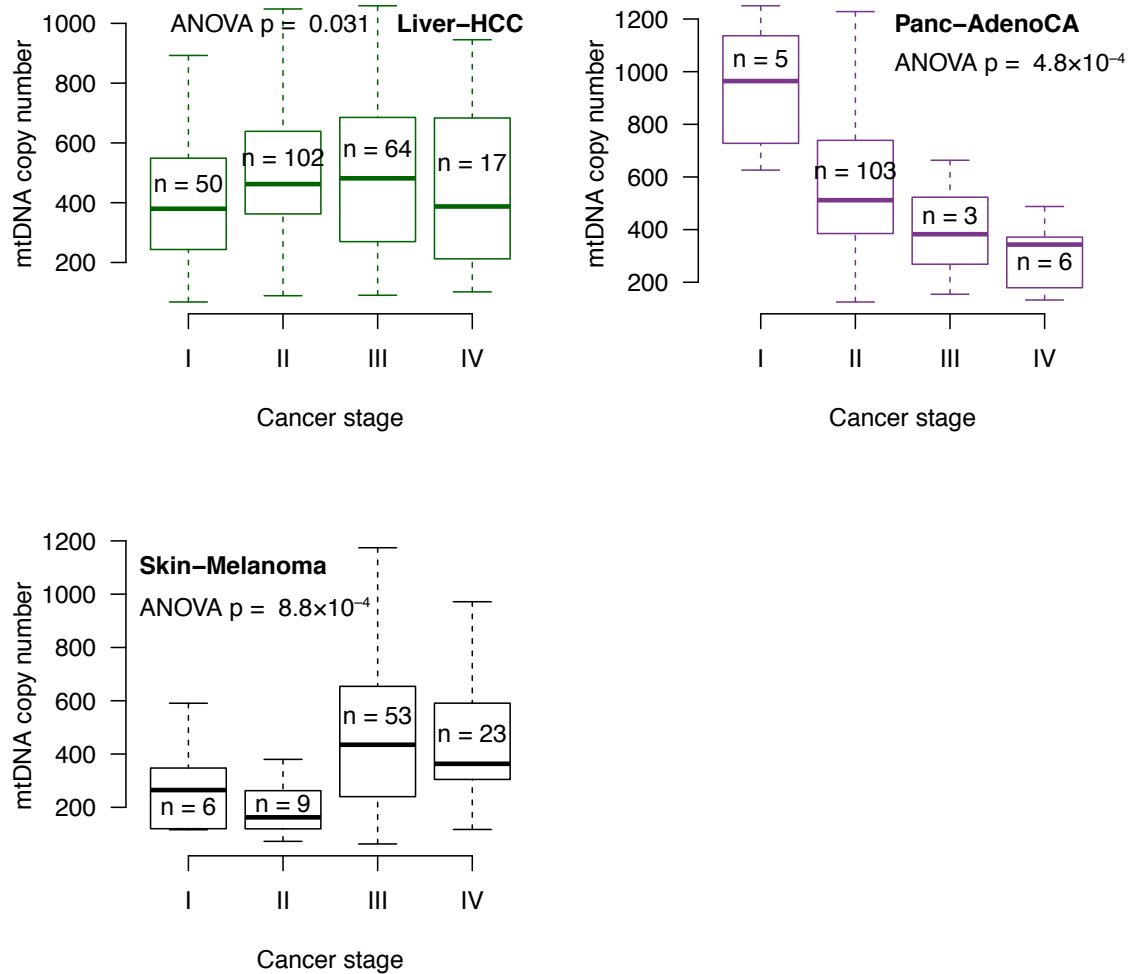
Supplementary Figure 18



The correlation between normal blood mtDNA copy number and patient age

n = number of samples with normal blood mtDNA copy number and patient age information available. The correlation and p-value were determined using Spearman's rank correlation.

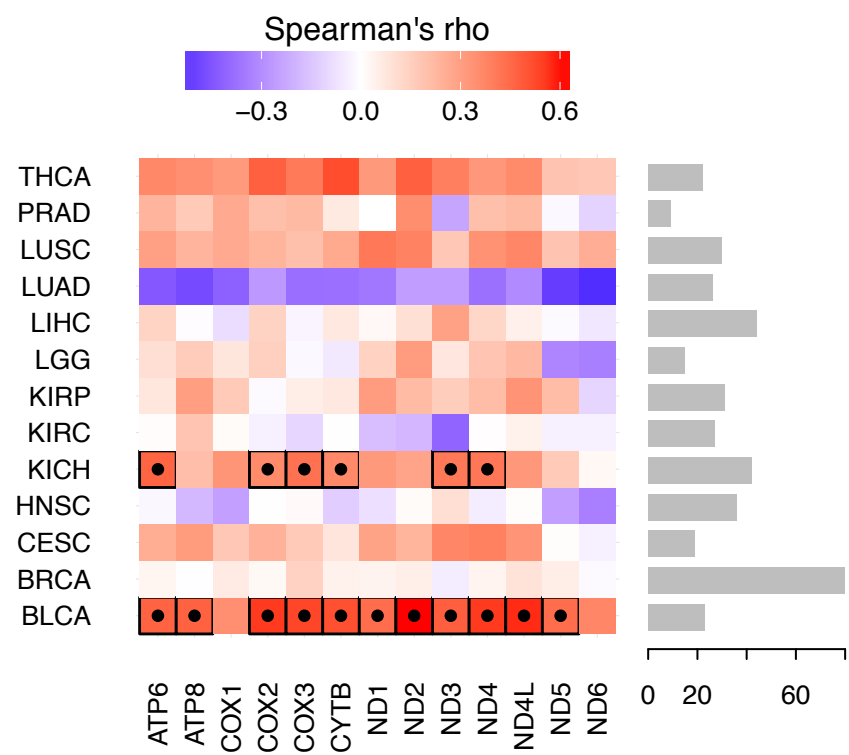
Supplementary Figure 19



The correlation between mtDNA copy number and patient cancer stage

n = number of samples with cancer mtDNA copy number and stage information available. the boundaries of the boxes mark the first and third quartile, with the median in the center, and whiskers extending to 1.5 interquartile range from the boundaries.

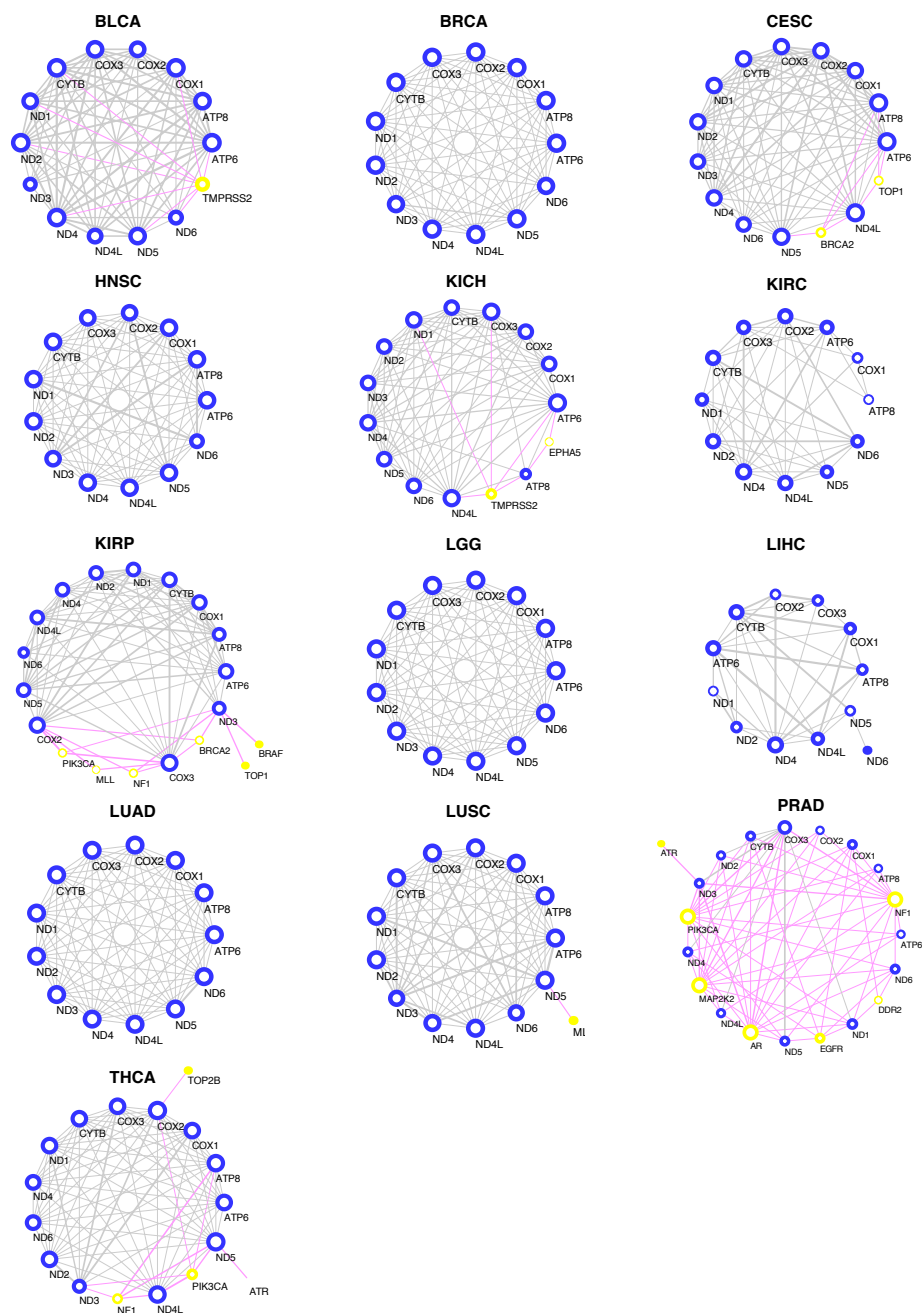
Supplementary Figure 20



The correlation between mtDNA copy number and gene expression.

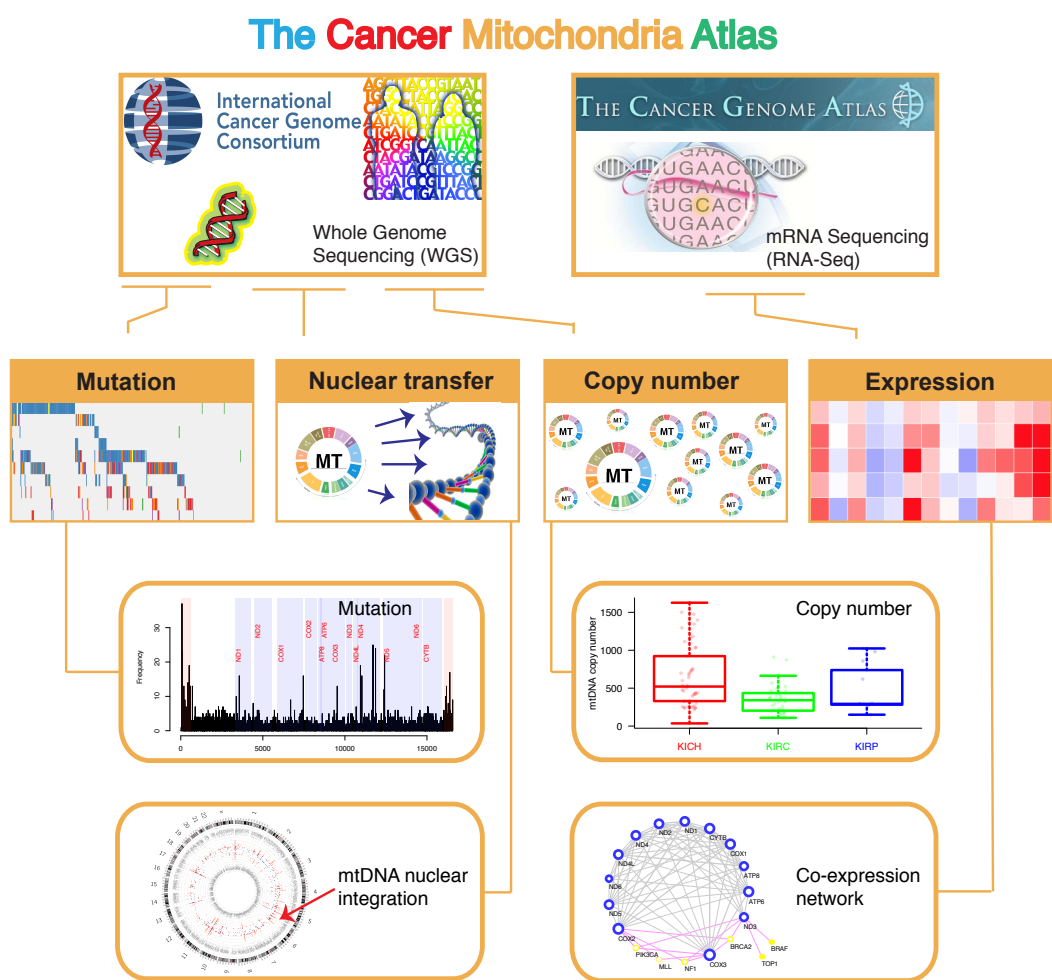
The left panel shows the heatmap of Spearman's rho, with the significant cases (with FDR < 0.05) boxed and marked with black dots. The right panel shows the sample sizes (the number of samples with both mtDNA copy number and gene expression data available for each cancer type) in barplot.

Supplementary Figure 21



The gene co-expression network seeded on mtDNA genes

The size of the node is proportional to the number its direct neighbors (connectivity). The thickness of the edge is proportional to the connection strength between nodes. Further, the nodes were colored based on the gene: mtDNA genes in blue, nuclear genes in yellow; the edges were colored based on the connection type: mtDNA gene - mtDNA gene connection in gray, mtDNA gene - nuclear gene connection in magenta.



An overview of the TCMA data portal

Supplementary Table 1. An overview of the mtDNA whole-genome sequencing (WGS) data

Cancer tissue	Cancer (ICGC)	Sample #	Average mtDNA coverage
Biliary	Biliary-AdenoCA	34	10591.4
Bladder	Bladder-TCC	23	3201.2
Bone/SoftTissue	Bone-Benign, Bone-Epith, Bone-Osteosarc, SoftTissue-Leiomyo, SoftTissue-Liposarc	98	8160.8
Breast	Breast-AdenoCA, Breast-DCIS, Breast-LobularCA	214	9724.1
Cervix	Cervix-AdenoCA, Cervix-SCC	20	3211.9
CNS	CNS-GBM, CNS-Medullo, CNS-Oligo, CNS-PiloAstro	294	5766.3
Colon/Rectum	ColoRect-AdenoCA	60	10374.3
Esophagus	Eso-AdenoCA	98	6546.4
Head/Neck	Head-SCC	57	6765.3
Kidney	Kidney-ChRCC (Kidney-Chromophobe), Kidney-RCC (Kidney-Clear Cell, Kidney-Papillary)	189	13213.0
Liver	Liver-HCC	317	11542.0
Lung	Lung-AdenoCA, Lung-SCC	86	9146.9
Lymphoid	Lymph-BNHL, Lymph-CLL	202	5289.8
Myeloid	Myeloid-AML, Myeloid-MDS, Myeloid-MPN	38	3706.1
Ovary	Ovary-AdenoCA	113	16960.4
Pancreas	Panc-AdenoCA, Panc-Endocrine	324	12629.9
Prostate	Prost-AdenoCA	210	14533.1
Skin	Skin-Melanoma	107	10812.5
Stomach	Stomach-AdenoCA	75	7014.7
Thyroid	Thy-AdenoCA	48	12104.8
Uterus	Uterus-AdenoCA	51	5313.7
21 tissue types	38 Cancer types	*2658	9959.1

*Samples used in mutation analysis: 2,536; samples used in nuclear transfer analysis: 2,658; samples used in copy number analysis: 2,157.

Supplementary Table 2. The high-allele-frequency mtDNA mutations (VAF > 50%) identified in KICH by our pipeline vs. those by LR-PCR method

(a) All high-allele-frequency mtDNA mutations (VAF > 50%) identified in KICH by our pipeline can be validated by LR-PCR method

TCGA barcode	Chr	Substitution /Indel	Position	Ref	Var	Region	VAF	In LR-PCR results
TCGA-KL-8327	MT	Indel	65	T	+G	D-Loop	59%	Yes
TCGA-KL-8328	MT	Substitution	16355	C	T	D-Loop	72%	Yes
TCGA-KL-8328	MT	Substitution	16399	A	G	D-Loop	57%	Yes
TCGA-KL-8333	MT	Substitution	5767	C	T	TRNC	75%	Yes
TCGA-KL-8341	MT	Substitution	14159	C	A	ND6	78%	Yes
TCGA-KL-8344	MT	Indel	13127	A	-C	ND5	91 %	Yes
TCGA-KM-8438	MT	Indel	65	T	+G	D-Loop	87%	Yes
TCGA-KM-8438	MT	Substitution	4569	G	A	ND2	82%	Yes
TCGA-KM-8438	MT	Substitution	5738	G	C	L-strand origin	83%	Yes
TCGA-KM-8441	MT	Indel	13230	C	-A	ND5	88%	Yes
TCGA-KM-8477	MT	Substitution	4429	G	A	TRNM	99%	Yes
TCGA-KM-8477	MT	Substitution	4969	G	C	ND2	99%	Yes
TCGA-KM-8477	MT	Substitution	10806	G	A	ND4	99%	Yes
TCGA-KM-8477	MT	Indel	12384	T	-C	ND5	80%	Yes
TCGA-KN-8419	MT	Indel	12417	C	+A	ND5	82%	Yes
TCGA-KN-8422	MT	Indel	65	T	+G	D-Loop	67%	Yes
TCGA-KN-8432	MT	Substitution	6490	T	C	COX1	96%	Yes
TCGA-KN-8434	MT	Substitution	3922	G	A	ND1	68%	Yes
TCGA-KN-8434	MT	Substitution	9651	C	T	COX3	80%	Yes
TCGA-KN-8435	MT	Substitution	16156	G	A	D-Loop	53%	Yes
TCGA-KN-8437	MT	Indel	13230	C	-A	ND5	90%	Yes

(b). Our pipeline captured 21/26 of the high-allele-frequency mtDNA mutations (VAF > 50%) previously identified in KICH by LR-PCR method

TCGA barcode	Chr	Substitution /Indel	Position	Ref	Var	Region	VAF	In WGS results
TCGA-KL-8326	MT	Indel	11866	A	+C	ND4	82%	Filtered
TCGA-KL-8327	MT	Indel	65	T	+G	D-Loop	59%	Yes
TCGA-KL-8331	MT	Indel	451	A	-T	D-Loop	51%	Yes
TCGA-KL-8331	MT	Substitution	16426	C	A	D-Loop	51%	No
TCGA-KL-8333	MT	Substitution	5767	C	T	TRNC	73%	Yes
TCGA-KL-8341	MT	Substitution	14159	C	A	ND6	81%	Yes
TCGA-KL-8343	MT	Indel	3565	A	+C	ND1	79%	No
TCGA-KL-8344	MT	Indel	13127	A	-C	ND5	86%	Yes
TCGA-KM-8438	MT	Indel	65	T	+G	D-Loop	93%	Yes
TCGA-KM-8438	MT	Substitution	4569	G	A	ND2	82%	Yes
TCGA-KM-8438	MT	Substitution	5738	G	C	L-strand origin	86%	Yes
TCGA-KM-8441	MT	Indel	13230	C	-A	ND5	90%	Yes

TCGA-KM-8442	MT	Indel	3105	A	-C	RNR2	93%	No
TCGA-KM-8476	MT	Substitution	16426	C	A	D-Loop	51%	No
TCGA-KM-8477	MT	Substitution	4429	G	A	TRNM	99%	Yes
TCGA-KM-8477	MT	Substitution	4969	G	C	ND2	99%	Yes
TCGA-KM-8477	MT	Substitution	10806	G	A	ND4	99%	Yes
TCGA-KM-8477	MT	Indel	12384	T	-C	ND5	76%	Yes
TCGA-KN-8419	MT	Indel	12417	C	+A	ND5	72%	Yes
TCGA-KN-8422	MT	Indel	65	T	+G	D-Loop	71%	Yes
TCGA-KN-8428	MT	Substitution	1900	A	G	RNR2	93%	No
TCGA-KN-8432	MT	Substitution	6490	T	C	COX1	95%	Yes
TCGA-KN-8434	MT	Substitution	3922	G	A	ND1	67%	Yes
TCGA-KN-8434	MT	Substitution	9651	C	T	COX3	76%	Yes
TCGA-KN-8435	MT	Substitution	16156	G	A	D-Loop	51%	Yes
TCGA-KN-8437	MT	Indel	13230	C	-A	ND5	89%	Yes

Supplementary Table 3. Somatic mtDNA nuclear transfer (SMNT) predicted to interrupt the open reading frames

Sample	MT Chr	MT Strand	MT Position	Nuclear Chr	Nuclear Strand	Nuclear Position	Orientation (1: MT-nuclear, 0: nuclear-MT)	Genes	Genetic impact
BLCA:9c274536-3ca1-4f0e-93a8-1688074d862f	MT	+	16,525	3	+	161,285,798	1	intergenic	-
BLCA:9c274536-3ca1-4f0e-93a8-1688074d862f	MT	+	16,113	10	+	131,401	0	intergenic	-
BLCA:9c274536-3ca1-4f0e-93a8-1688074d862f	MT	+	11,468	11	-	67,592,693	1	intergenic	-
BLCA:9c274536-3ca1-4f0e-93a8-1688074d862f	MT	+	11,140	11	-	67,593,978	0	intergenic	-
BLCA:9c274536-3ca1-4f0e-93a8-1688074d862f	MT	+	16,115	15	-	93,433,461	0	CHD2(intron)	not remarkable
BLCA:9c274536-3ca1-4f0e-93a8-1688074d862f	MT	+	27	15	-	93,433,460	1	CHD2(intron)	not remarkable
BOCA:CGP_donor_1691150	MT	+	16,106	4	+	82,052,576	0	PRKG2(intron)	indeterminable
BOCA:CGP_donor_1691150	MT	+	16,108	20	+	51,370,057	0	intergenic	-
BOCA:CGP_donor_1691217	MT	+	14,405	9	+	22,816,364	1	FLJ35282(intron)	indeterminable
BRCA:174850b4-5ec2-462b-a890-89bd1716b3c2	MT	+	12,320	11	-	49,198,004	0	FOLH1(intron)	truncation
BRCA:174850b4-5ec2-462b-a890-89bd1716b3c2	MT	-	7,744	11	+	49,183,190	1	FOLH1(intron)	truncation
BRCA:4da999a0-cf41-4a0b-b1d1-446b39cc855a	MT	+	1,358	8	+	37,433,689	0	intergenic	-
BRCA:4da999a0-cf41-4a0b-b1d1-446b39cc855a	MT	+	2,838	16	+	11,905,542	1	intergenic	-
BRCA:a9b7d7fe-be31-4f71-afee-c1bfd511888	MT	+	1,579	3	+	11,755,134	0	VGLL4(intron)	not remarkable
BRCA:a9b7d7fe-be31-4f71-afee-c1bfd511888	MT	+	1,671	16	+	64,385,169	1	intergenic	-
BRCA:b094e8b2-8ece-4b36-8025-18073a8b873c	MT	-	3,284	3	+	51,848,724	0	IQCF1(intron)	truncation
BRCA:b094e8b2-8ece-4b36-8025-18073a8b873c	MT	-	846	3	-	51,848,760	1	IQCF1(intron)	truncation
BRCA:b094e8b2-8ece-4b36-8025-18073a8b873c	MT	+	9,775	3	+	84,640,033	0	intergenic	-
BRCA:b094e8b2-8ece-4b36-8025-18073a8b873c	MT	+	10,364	3	+	84,640,058	1	intergenic	-
BRCA:c0892598-1f7b-4f23-9cd8-731f797753d5	MT	+	3,711	1	-	163,302,499	0	NUF2(intron)	truncation
BRCA:c0892598-1f7b-4f23-9cd8-731f797753d5	MT	+	80	16	+	61,521,078	1	intergenic	-
BRCA:CGP_donor_1232859	MT	+	109	X	-	17,546,722	1	NHS(intron)	indeterminable
BRCA:CGP_donor_1337226	MT	+	16,247	15	+	53,349,620	0	intergenic	-
BRCA:CGP_donor_1337226	MT	+	16,455	15	+	53,349,509	1	intergenic	-
BRCA:CGP_donor_1353432	MT	+	16,127	7	-	96,923,230	0	intergenic	-
BRCA:CGP_donor_1353432	MT	+	12,736	X	-	14,944,763	1	intergenic	-
BRCA:CGP_donor_1353432	MT	+	63	7	-	96,680,019	0	intergenic	-
BRCA:CGP_donor_1363963	MT	+	10,060	8	+	89,726,912	0	intergenic	-
BRCA:CGP_donor_1363963	MT	+	12,584	8	+	77,053,130	0	intergenic	-
BRCA:d67cd793-2931-429a-9084-2f3c4c8be7ad	MT	+	8,643	9	-	96,752,532	0	intergenic	-
BRCA:d67cd793-2931-429a-9084-2f3c4c8be7ad	MT	+	10,203	9	-	96,752,475	1	intergenic	-
BRCA:d8d7a6c2-6427-4f47-968c-6c3affba4617	MT	+	4,915	17	+	37,882,252	0	ERBB2(intron)	truncation
BRCA:d8d7a6c2-6427-4f47-968c-6c3affba4617	MT	+	5,344	17	+	37,871,155	1	ERBB2(intron)	truncation
BRCA:e4fc0909-f284-4471-866d-d8967b6adcbc	MT	+	10,043	13	+	50,959,613	0	DLEU1(intron)	fusion_transcript
BRCA:e4fc0909-f284-4471-866d-d8967b6adcbc	MT	+	12,005	13	-	38,697,714	1	LINC00751(intron)	fusion_transcript
BRCA:e4fc0909-f284-4471-866d-d8967b6adcbc	MT	+	3,052	17	-	19,734,578	0	ULK2(intron)	truncation
BRCA:e4fc0909-f284-4471-866d-d8967b6adcbc	MT	+	3,036	7	+	63,804,012	1	ZNF736(intron)	truncation
HNSC:4cfea0b-90a7-4c86-a73f-bb8feca3ada7	MT	+	92	11	+	113,976,595	1	ZBTB16(intron)	not remarkable
HNSC:7de19081-d5fd-468c-ad0d-f6c3e8b2ad70	MT	+	5,763	8	+	115,373,838	0	intergenic	-
HNSC:7de19081-d5fd-468c-ad0d-f6c3e8b2ad70	MT	+	5,804	8	-	115,373,630	1	intergenic	-

HNSC:90a8d2cb-1f31-45f9-8575-eed3cb9a7798	MT	+	16,454	9	+	137,950,628	0	intergenic	-
HNSC:90a8d2cb-1f31-45f9-8575-eed3cb9a7798	MT	+	1,403	15	+	101,262,248	1	intergenic	-
LUAD:bfl5f7ad-9d92-473b-91d1-f24aa373ab97	MT	+	522	7	-	64,473,632	0	intergenic	-
LUAD:cc4bd56a-25c5-4c48-b583-ac3aeb778ca6	MT	+	1,931	14	+	40,799,718	1	intergenic	-
LUAD:cc4bd56a-25c5-4c48-b583-ac3aeb778ca6	MT	+	15,955	14	-	72,230,011	1	intergenic	-
LUAD:cc4bd56a-25c5-4c48-b583-ac3aeb778ca6	MT	+	15,196	14	-	72,439,511	0	intergenic	-
LUAD:cc4bd56a-25c5-4c48-b583-ac3aeb778ca6	MT	+	2,253	14	-	72,618,504	1	intergenic	-
LUAD:cc4bd56a-25c5-4c48-b583-ac3aeb778ca6	MT	+	11,325	14	-	72,618,020	1	intergenic	-
LUAD:cc4bd56a-25c5-4c48-b583-ac3aeb778ca6	MT	+	6,126	14	-	72,623,601	1	intergenic	-
LUAD:cc4bd56a-25c5-4c48-b583-ac3aeb778ca6	MT	+	3,898	14	-	72,626,341	0	intergenic	-
LUAD:cc4bd56a-25c5-4c48-b583-ac3aeb778ca6	MT	+	693	21	+	9,827,144	1	intergenic	-
LUSC:037c57d1-b4a5-45dc-bda4-0550461d321b	MT	+	2,030	11	-	101,384,929	0	TRPC6(intron)	truncation
LUSC:037c57d1-b4a5-45dc-bda4-0550461d321b	MT	+	3,600	11	+	101,396,055	1	TRPC6(intron)	truncation
LUSC:220be009-8f1e-4a77-ab04-3220b5f87ea6	MT	+	9,815	13	+	108,054,362	0	FAM155A(intron)	truncation
LUSC:3edf933a-be1a-46e8-bfb0-acdf3f30e64a0	MT	+	1,344	12	-	94,816,065	1	CCDC41(intron)	not remarkable
LUSC:585e6487-b0a3-4828-8a06-46bee01dff74	MT	+	16,110	1	+	84,517,869	0	intergenic	-
LUSC:585e6487-b0a3-4828-8a06-46bee01dff74	MT	+	49	21	+	22,236,786	1	intergenic	-
LUSC:87ac0ad4-8c9d-409e-9a86-1d201d01769d	MT	+	11,689	9	-	36,315,575	1	intergenic	-
LUSC:87ac0ad4-8c9d-409e-9a86-1d201d01769d	MT	+	15,936	9	+	33,864,273	0	UBE2R2(intron)	truncation
LUSC:87ac0ad4-8c9d-409e-9a86-1d201d01769d	MT	+	16,103	hs37d5	-	26,652,621	1	intergenic	-
LUSC:87ac0ad4-8c9d-409e-9a86-1d201d01769d	MT	+	6,285	15	-	76,219,463	1	FBXO22(intron)	truncation
LUSC:9293e197-c38a-4e19-a7d0-1b45d1ad48bd	MT	-	1,827	1	+	2,914,228	0	intergenic	-
LUSC:9293e197-c38a-4e19-a7d0-1b45d1ad48bd	MT	+	72	6	+	167,254,656	1	RPS6KA2(intron)	truncation
LUSC:e58e8850-154f-4695-bee0-005c76410327	MT	+	7,998	1	-	39,786,349	0	MACF1(intron)	truncation
LUSC:e58e8850-154f-4695-bee0-005c76410327	MT	+	8,139	1	+	39,786,037	1	MACF1(intron)	truncation
MALY:4150895	MT	+	11,170	4	+	137,895,166	0	intergenic	-
MALY:4159421	MT	+	5,248	2	-	145,091,202	0	intergenic	-
OV:7ca97692-0bf5-4bbd-81ce-10a051d04bd5	MT	+	12,488	11	-	72,613,495	1	FCHSD2(intron)	truncation
OV:c435627c-159d-4a6d-a819-30abac24bf4d	MT	+	16,113	16	+	60,469,789	0	intergenic	-
PACA:ICGC_0543	MT	+	16,083	4	-	157,262,727	0	intergenic	-
PACA:ICGC_0543	MT	+	32	5	+	131,561,359	1	P4HA2(intron)	not remarkable
PBCA:MBRep_T27	MT	+	16,114	9	+	95,506,702	0	BICD2(intron)	not remarkable
PBCA:MBRep_T27	MT	+	191	9	+	95,506,708	1	BICD2(intron)	not remarkable
SARC:b85e2156-d5ae-486c-93e1-86525ea41a64	MT	+	1,372	10	-	30,823,230	0	intergenic	-
SKCM:01ad975d-c2ed-4e4d-bd3b-c9512fc9073c	MT	+	11,568	6	+	3,751,700	0	PXDC1(exonic)	truncation
SKCM:01ad975d-c2ed-4e4d-bd3b-c9512fc9073c	MT	-	11,557	6	-	63,951,719	1	intergenic	-
SKCM:81cedb9e-ee43-476b-9ed9-8d0fdb346065	MT	+	5,081	8	+	90,465,476	0	intergenic	-
SKCM:81cedb9e-ee43-476b-9ed9-8d0fdb346065	MT	+	6,333	3	+	33,481,145	0	UBP1(intron)	truncation
SKCM:81cedb9e-ee43-476b-9ed9-8d0fdb346065	MT	+	15,032	20	+	62,710,708	1	RGS19(exonic)	truncation
UCEC:24118b8f-59fe-482a-aed3-7b1bde1571b7	MT	+	3,767	8	-	38,766,339	0	PLEKHA2	truncation
UCEC:24118b8f-59fe-482a-aed3-7b1bde1571b7	MT	+	4,287	8	-	36,603,622	1	intergenic	-
UCEC:748c38b1-2ead-4a0a-8881-d640617b856b	MT	+	16,186	22	-	48,182,869	0	AK093107(intron)	not remarkable
UCEC:748c38b1-2ead-4a0a-8881-d640617b856b	MT	+	16,274	22	-	48,181,913	0	AK093107(intron)	not remarkable
UCEC:7b9947d5-e86b-4006-8890-ea5209584a88	MT	+	8,033	9	+	12,816,690	1	intergenic	-

UCEC:7b9947d5-e86b-4006-8890-ea5209584a88	MT	+	13,424	9	-	12,841,745	1	intergenic	-
BRCA:CGP_donor_1475202	MT	+	16,323	1	-	197,335,986	1	intergenic	-
BRCA:CGP_donor_1475202	MT	+	approx. 1,693	hs37d5	+	approx. 4,907,000	0	intergenic	-
BRCA:CGP_donor_1475202	MT	+	approx. 1,770	hs37d5	-	approx. 28,645,400	1	intergenic	-
ESAD:OCCAMS-AH-196	MT	+	approx. 38	9	-	94,218,789	1	intergenic	-
LIRI:RK004	MT	+	7,673	5	+	93,303,764	1	FAM12A(intron)	indeterminable
LIRI:RK082	MT	+	14,850	11	+	125,083,145	0	PKNOX2(intron)	not remarkable
LIRI:RK082	MT	+	approx. 15,182	11	+	125,083,160	1	PKNOX2(intron)	not remarkable
LIRI:RK243	MT	+	1,315	12	+	64,095,441	0	intergenic	-
LIRI:RK243	MT	+	7,709	12	+	64,096,484	1	intergenic	-
MELA:MELA-0001	MT	+	14,906	9	-	44,776,871	1	intergenic	-
MELA:MELA-0001	MT	+	286	11	-	39,777,366	1	intergenic	-
MELA:MELA-0001	MT	+	16,105	16	-	50,038,448	0	intergenic	-
MELA:MELA-0002	MT	-	10,296	13	+	88,692,225	0	intergenic	-
MELA:MELA-0002	MT	+	13,807	13	-	88,709,481	1	intergenic	-
MELA:MELA-0002	MT	+	13,988	15	+	54,192,579	0	intergenic	-
MELA:MELA-0002	MT	+	6,933	15	+	54,168,518	1	intergenic	-
MELA:MELA-0167	MT	+	10,789	11	-	3,172,598	0	OSBPL5(intron)	truncation
MELA:MELA-0167	MT	+	2,936	15	+	28,354,949	1	intergenic	-
MELA:MELA-0167	MT	+	16,335	11	-	12,718,261	0	TEAD1(intron)	not remarkable
MELA:MELA-0167	MT	+	16,504	11	-	12,718,337	1	TEAD1(intron)	not remarkable
MELA:MELA-0167	MT	+	12,450	11	-	3,850,705	0	RHOG(intron)	indeterminable
MELA:MELA-0167	MT	+	41	17	+	48,554,863	1	intergenic	indeterminable
MELA:MELA-0174	MT	+	16,119	6	-	14,734,925	0	intergenic	-
MELA:MELA-0174	MT	+	151	3	+	33,188,139	1	CRTAP(3UTR)	not remarkable
MELA:MELA-0174	MT	+	3,921	15	-	31,338,568	0	TRPM1(intron)	not remarkable
MELA:MELA-0174	MT	+	6,767	15	-	31,338,588	1	TRPM1(intron)	not remarkable
MELA:MELA-0203	MT	+	14,549	6	+	98,286,935	0	intergenic	-
MELA:MELA-0203	MT	+	9,625	6	+	120,503,724	1	intergenic	-
MELA:MELA-0213	MT	+	16,197	9	+	20,945,617	1	FOCAD(intron)	indeterminable
MELA:MELA-0259	MT	+	3,380	8	-	141,859,251	0	PTK2(intron)	truncation
MELA:MELA-0259	MT	+	6,185	8	-	125,982,259	1	intergenic	-
PACA:PCSI_0250	MT	+	1,252	15	+	101,848,527	0	PCSK6(intron)	not remarkable
PACA:PCSI_0250	MT	+	22400	15	+	101,848,646	1	PCSK6(intron)	not remarkable
PRAD:CPCG0098	MT	+	11,624	11	-	70,026,819	0	ANO1(intron)	truncation
PRAD:CPCG0098	MT	+	11,972	11	+	69,523,432	1	intergenic	-
SARC:cd73a55f-03c1-4da0-9fa7-1ae4a263664e	MT	+	4,939	12	+	112,788,982	0	HECTD4(intron)	truncation
SARC:cd73a55f-03c1-4da0-9fa7-1ae4a263664e	MT	+	4,478	12	-	112,793,558	1	HECTD4(intron)	truncation
SKCM:c2948fe9-5798-43bc-a743-511e94e417f8	MT	+	14,122	20	-	61,976,332	0	CHRNA4(3UTR)	not remarkable
SKCM:c2948fe9-5798-43bc-a743-511e94e417f8	MT	+	11,946	20	+	61,542,799	0	DIDO1(exonic)	truncation

Supplementary Table 4. An overview of the mtDNA RNA-sequencing (RNA-seq) data

Cancer (TCGA)	Description	Cancer tissue	Sample #	Average # mappable reads
BLCA	Bladder Cancer	Bladder	252	10.9M
BRCA	Breast Cancer	Breast	837	8.3M
CESC	Cervical Squamous Cell Carcinoma	Cervix	196	7.4M
LGG	Brain Lower Grade Glioma	CNS	486	13.3M
HNSC	Head and Neck Squamous Cell Carcinoma	Head/Neck	426	4.9M
KICH	Kidney Chromophobe	Kidney	66	43.3M
KIRC	Kidney Renal Clear Cell Carcinoma	Kidney	448	17.0M
KIRP	Kidney Renal Papillary Cell Carcinoma	Kidney	198	17.9M
LIHC	Liver Hepatocellular carcinoma	Liver	200	11.1M
LUAD	Lung Adenocarcinoma	Lung	488	6.1M
LUSC	Lung Squamous Cell Carcinoma	Lung	220	4.8M
PRAD	Prostate Adenocarcinoma	Prostate	374	8.8M
THCA	Head and Neck Thyroid Carcinoma	Thyroid	498	13.6M
Total	13 cancer types	11 tissue types	4689	10.7M

The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes (PCAWG) Consortium Working Groups

PCAWG Steering committee

Peter J Campbell^{#1,2}, **Gad Getz**^{#3,4,5,6}, **Jan O Korbel**^{#7,8}, **Lincoln D Stein**^{#9,10} and **Joshua M Stuart**^{#11,12}

PCAWG Head of project management

Jennifer L Jennings¹³

PCAWG Executive committee

Sultan T Al-Sedairy¹⁴, Axel Aretz¹⁵, Cindy Bell¹⁶, Miguel Betancourt¹⁷, Christiane Buchholz¹⁸, Fabien Calvo¹⁹, Christine Chomienne²⁰, Michael Dunn²¹, Stuart Edmonds²², Eric Green²³, Shailja Gupta²⁴, Carolyn M Hutter²³, Karine Jegalian²⁵, Jennifer L Jennings¹³, Nic Jones²⁶, Hyung-Lae Kim²⁷, Youyong Lu^{28,29,30}, Hitoshi Nakagama³¹, Gerd Nettekoven³², Laura Planko³², David Scott²⁶, Tatsuhiro Shibata^{33,34}, Kiyo Shimizu³⁵, **Lincoln D Stein**^{#9,10}, Michael R Stratton¹, Takashi Yugawa³⁵, Giampaolo Tortora^{36,37}, K VijayRaghavan²⁴, Huanming Yang³⁸ and Jean C Zenklusen³⁹

PCAWG Ethics and Legal Working Group

Don Chalmers^{#40}, Yann Joly⁴¹, **Bartha M Knoppers**^{#41}, Fruzsina Molnár-Gábor⁴², Mark Phillips⁴¹, Adrian Thorogood⁴¹ and David Townend⁴³

PCAWG Technical Working Group

Brice Aminou⁴⁴, Javier Bartolome⁴⁵, Keith A Boroevich^{46,47}, Rich Boyce⁷, Alvis Brazma⁷, Angela N Brooks^{3,11,12,48}, Alex Buchanan⁴⁹, Ivo Buchhalter^{50,51,52}, Adam P Butler¹, Niall J Byrne⁴⁴, Andy Cafferkey⁷, Peter J Campbell^{1,2}, Zhaohong Chen⁵³, Sunghoon Cho⁵⁴, Wan Choi⁵⁵, Peter Clapham¹, Brandi N Davis-Dusenbery⁵⁶, Francisco M De La Vega^{57,58,59}, Jonas Demeulemeester^{60,61}, Michelle T Dow⁵³, Lewis Jonathan Dursi^{9,62}, Juergen Eils^{63,64}, Roland Eils^{50,52,63,64}, Kyle Ellrott⁴⁹, Claudiu Farcas⁵³, Nodirjon Fayzullaev⁴⁴, Vincent Ferretti^{44,65}, Paul Flicek⁷, Nuno A Fonseca^{7,66}, Josep L L Gelpi^{45,67}, Gad Getz^{3,4,5,6}, Robert L Grossman⁶⁸, Olivier Harismendy^{69,70}, Allison P Heath⁷¹, Michael C Heinold^{50,52}, Julian M Hess^{3,72}, Oliver Hofmann⁷³, Jongwhi H Hong⁷⁴, Thomas J Hudson^{75,76}, Barbara Hutter^{77,78,79}, Carolyn M Hutter²³, Daniel Hübschmann^{52,63,80,81,82}, Seiya Imoto⁸³, Sinisa Ivkovic⁵⁶, Seung-Hyup Jeon⁵⁵, Wei Jiao⁹, Jongsun Jung⁸⁴, Rolf Kabbe⁵⁰, Andre Kahles^{85,86,87,88,89}, Jules NA Kerssemakers⁵⁰, Hyung-Lae Kim²⁷, Hyunghwan Kim⁵⁵, Jihoon Kim⁹⁰, Youngwook Kim^{91,92},

Kortine Kleinheinz^{50,52}, Jan O Korbel^{7,8}, Michael Koscher⁹³, Antonios Koures⁵³, Milena Kovacevic⁵⁶, Chris Lawrenz⁶⁴, Ignaty Leshchiner³, Jia Liu⁹⁴, Dimitri Livitz³, George L Mihaiescu⁴⁴, Sanja Mijalkovic⁵⁶, Ana Mijalkovic Mijalkovic-Lazic⁵⁶, Satoru Miyano⁸³, Naoki Miyoshi⁸³, Hardeep K Nahal-Bose⁴⁴, Hidewaki Nakagawa⁴⁷, Mia Nastic⁵⁶, Steven J Newhouse⁷, Jonathan Nicholson¹, **Brian D O'Connor**^{#44,95}, David Ocana⁷, Kazuhiro Ohi⁸³, Lucila Ohno-Machado⁵³, Larsson Omberg⁹⁶, BF Francis Ouellette^{44,97}, Nagarajan Paramasivam^{50,78}, Marc D Perry^{44,98}, Todd D Pihl⁹⁹, Manuel Prinz⁵⁰, Montserrat Puiggròs⁴⁵, Petar Radovic⁵⁶, Keiran M Raine¹, Esther Rheinbay^{3,6,100}, Mara Rosenberg^{3,100}, Romina Royo⁴⁵, Gunnar Rätsch^{85,86,87,88,89,101}, Gordon Saksena³, Matthias Schlesner^{50,102}, Solomon I Shorser⁹, Charles Short⁷, Heidi J Sofia²³, Jonathan Spring¹⁰³, **Lincoln D Stein**^{#9,10}, Adam J Struck¹⁰⁴, Grace Tiao³, Nebojsa Tijanic⁵⁶, David Torrents^{45,105}, Peter Van Loo^{60,61}, Miguel Vazquez^{45,106}, David Vicente⁴⁵, Jeremiah A Wala^{3,6,48}, Zhining Wang³⁹, Sebastian M Waszak⁸, Joachim Weischenfeldt^{8,107,108}, Johannes Werner^{50,109}, Ashley Williams⁵³, Youngchoon Woo⁵⁵, Adam J Wright⁹, Qian Xiang⁴⁴, **Sergei Yakneen**^{#8}, Liming Yang³⁹, Denis Yuen⁹, **Christina K Yung**^{#44} and **Junjun Zhang**^{#44}

PCAWG Reference Annotations Working Group

Angela N Brooks^{3,11,12,48}, Ivo Buchhalter^{50,51,52}, Peter J Campbell^{1,2}, Priyanka Dhingra^{110,111}, Lars Feuerbach¹¹², Mark Gerstein^{113,114,115}, Gad Getz^{3,4,5,6}, Mark P Hamilton¹¹⁶, Henrik Hornshøj¹¹⁷, Todd A Johnson⁴⁶, Andre Kahles^{85,86,87,88,89}, Abdullah Kahraman^{118,119,120}, Manolis Kellis^{3,121}, **Ekta Khurana**^{#110,111,122,123}, Jan O Korbel^{7,8}, Morten Muhlig Nielsen¹¹⁷, Jakob Skou Pedersen^{117,124}, Paz Polak^{3,4,6}, Jüri Reimand^{9,125}, Esther Rheinbay^{3,6,100}, Nicola D Roberts¹, Gunnar Rätsch^{85,86,87,88,89,101}, Richard Sallari³, Nasa Sinnott-Armstrong^{3,59}, Alfonso Valencia^{45,105}, Miguel Vazquez^{45,106}, Sebastian M Waszak⁸, Joachim Weischenfeldt^{8,107,108} and Christian von Mering^{120,126}

PCAWG Quality-Control Working Group

Sergi Beltran^{127,128}, Ivo Buchhalter^{50,51,52}, Peter J Campbell^{1,2}, Roland Eils^{50,52,63,64}, Daniela S Gerhard¹²⁹, Gad Getz^{3,4,5,6}, **Ivo G Gut**^{#127,128}, Marta Gut^{127,128}, Barbara Hutter^{77,78,79}, Daniel Hübschmann^{52,63,80,81,82}, Kortine Kleinheinz^{50,52}, Jan O Korbel^{7,8}, Dimitri Livitz³, Marc D Perry^{44,98}, Keiran M Raine¹, Esther Rheinbay^{3,6,100}, Mara Rosenberg^{3,100}, Gordon Saksena³, Matthias Schlesner^{50,102}, Miranda D Stobbe^{127,128}, Jean-Rémi Trotta¹²⁷, Johannes Werner^{50,109} and Justin P Whalley¹²⁷

PCAWG SNV Calling Working Group

Matthew H Bailey^{130,131}, Beifang Niu¹³², Matthias Bieg^{78,133}, Paul C Boutros^{9,125,134,135}, Ivo Buchhalter^{50,51,52}, Adam P Butler¹, Ken Chen¹³⁶, Zechen Chong¹³⁷, **Li Ding**^{#130,131,138}, Oliver Drechsel^{128,139}, Lewis Jonathan Dursi^{9,62}, Roland Eils^{50,52,63,64}, Kyle Ellrott⁴⁹, Shadrielle MG Espiritu⁹, Yu Fan¹⁴⁰, Robert S Fulton^{130,131,138}, Shengjie Gao³⁸, Josep L L Gelpi^{45,67}, Mark Gerstein^{113,114,115}, Gad Getz^{3,4,5,6}, Santiago Gonzalez^{7,8}, Ivo G Gut^{127,128}, Faraz Hach^{141,142}, Michael C Heinold^{50,52}, Julian M Hess^{3,72}, Jonathan Hinton¹, Taobo Hu¹⁴³, Vincent Huang⁹, Yi Huang^{144,145}, Barbara Hutter^{77,78,79},

David R Jones¹, Jongsun Jung⁸⁴, Natalie Jäger⁵⁰, Hyung-Lae Kim²⁷, Kortine Kleinheinz^{50,52}, Sushant Kumar^{114,115}, Yogesh Kumar¹⁴³, Christopher M Lalansingh⁹, Ignaty Leshchiner³, Ivica Letunic¹⁴⁶, Dimitri Livitz³, Eric Z Ma¹⁴³, Yosef E Maruvka^{3,72,100}, R Jay Mashl^{131,147}, Michael D McLellan^{130,131,138}, Andrew Menzies¹, Ana Milovanovic⁴⁵, Morten Muhlig Nielsen¹¹⁷, Stephan Ossowski^{128,139,148}, Nagarajan Paramasivam^{50,78}, Jakob Skou Pedersen^{117,124}, Marc D Perry^{44,98}, Montserrat Puiggròs⁴⁵, Keiran M Raine¹, Esther Rheinbay^{3,6,100}, Romina Royo⁴⁵, S Cenk Sahinalp^{142,149,150}, Gordon Saksena³, Iman Sarrafi^{142,150}, Matthias Schlesner^{50,102}, **Jared T Simpson**^{#9,151}, Lucy Stebbings¹, Chip Stewart³, Miranda D Stobbe^{127,128}, Jon W Teague¹, Grace Tiao³, David Torrents^{45,105}, Jeremiah A Wala^{3,6,48}, Jiayin Wang^{131,145,152}, Wenyi Wang¹⁴⁰, Sebastian M Waszak⁸, Joachim Weischenfeldt^{8,107,108}, Michael C Wendt^{131,138,153}, Johannes Werner^{50,109}, David A Wheeler^{154,155}, Zhenggang Wu¹⁴³, Hong Xue¹⁴³, Sergei Yakneen⁸, Takafumi N Yamaguchi⁹, Kai Ye^{152,156}, Venkata D Yellapantula^{138,157}, Christina K Yung⁴⁴ and Junjun Zhang⁴⁴

PCAWG Drivers and Functional Interpretation Working Group

Federico Abascal¹, Samirkumar B Amin^{158,159,160}, Gary D Bader¹⁰, Pratiti Bandopadhyay^{3,161,162}, Jonathan Barenboim⁹, Rameen Beroukhim^{3,6,163}, Johanna Bertl^{117,164}, Keith A Boroevich^{46,47}, Søren Brunak^{165,166}, Peter J Campbell^{1,2}, Joana Carlevaro-Fita^{167,168,169}, Dimple Chakravarty¹⁷⁰, Calvin Wing Yiu Chan^{50,171}, Ken Chen¹³⁶, Jung Kyoon Choi¹⁷², Jordi Deu-Pons^{173,174}, Priyanka Dhingra^{110,111}, Klev Diamanti¹⁷⁵, Lars Feuerbach¹¹², J Lynn Fink^{45,176}, Nuno A Fonseca^{7,66}, Joan Frigola¹⁷³, Carlo Gambacorti-Passerini¹⁷⁷, Dale W Garsed¹⁷⁸, **Mark Gerstein**^{#113,114,115}, **Gad Getz**^{#3,4,5,6}, Qianyun Guo¹²⁴, Ivo G Gut^{127,128}, David Haan¹¹, Mark P Hamilton¹¹⁶, Nicholas J Haradhvala^{3,100}, Arif O Harmanici^{115,179}, Mohamed Helmy¹⁸⁰, Carl Herrmann^{50,52,181}, Julian M Hess^{3,72}, Asger Hobolth^{124,164}, Ermin Hodzic¹⁵⁰, Chen Hong^{112,171}, Henrik Hornshøj¹¹⁷, Keren Isaev^{9,125}, Jose MG Izarzugaza¹⁸², Rory Johnson^{168,183}, Todd A Johnson⁴⁶, Malene Juul¹¹⁷, Randi Istrup Juul¹¹⁷, Andre Kahles^{85,86,87,88,89}, Abdullah Kahraman^{118,119,120}, Manolis Kellis^{3,121}, Ekta Khurana^{110,111,122,123}, Jaegil Kim³, Jong K Kim¹⁸⁴, Youngwook Kim^{91,92}, Jan Komorowski^{175,185}, Jan O Korbel^{7,8}, Sushant Kumar^{114,115}, Andrés Lanzós^{168,169,183}, Erik Larsson⁸⁵, **Michael S Lawrence**^{#3,46,100}, Donghoon Lee¹¹⁵, Kjong-Van Lehmann^{85,86,87,88,89}, Shantao Li¹¹⁵, Xiaotong Li¹¹⁵, Ziao Lin^{3,186}, Eric Minwei Liu^{110,111,187}, Lucas Lochovsky^{114,115,160}, Shaoke Lou^{114,115}, Tobias Madsen¹¹⁷, Kathleen Marchal^{188,189}, Iñigo Martincorena¹, Alexander Martinez-Fundichely^{110,111,123}, Yosef E Maruvka^{3,72,100}, Patrick D McGillivray¹¹⁴, William Meyerson^{115,190}, Ferran Muiños^{174,191}, Loris Mularoni^{174,191}, Hidewaki Nakagawa⁴⁷, Morten Muhlig Nielsen¹¹⁷, Marta Paczkowska⁹, Keunchil Park^{192,193}, Kiejung Park¹⁹⁴, **Jakob Skou Pedersen**^{#117,124}, Tirso Pons¹⁹⁵, Sergio Pulido-Tamayo^{188,189}, **Benjamin J Raphael**^{#196}, Jüri Reimand^{9,125}, Iker Reyes-Salazar¹⁹¹, Matthew A Reyna¹⁹⁶, Esther Rheinbay^{3,6,100}, Mark A Rubin^{183,197,198,199,200}, Carlota Rubio-Perez^{174,191,201}, S Cenk Sahinalp^{142,149,150}, Gordon Saksena³, Leonidas Salichos^{114,115}, Chris Sander^{85,202,203}, Steven E Schumacher^{3,204}, Mark Shackleton¹⁷⁸, Ofer Shapira^{3,205}, Ciyue Shen^{203,206}, Raunak Shrestha¹⁴², Shimin Shuai^{9,10}, Nikos Sidiropoulos¹⁰⁸, Lina Sieverling^{112,171}, Nasa Sinnott-Armstrong^{3,59}, Lincoln D Stein^{9,10}, **Joshua M Stuart**^{#11,12}, David Tamborero^{174,191}, Grace Tiao³, Tatsuhiko Tsunoda^{46,207,208,209}, Husen M Umer^{175,210}, Liis Uusküla-Reimand^{211,212}, Alfonso Valencia^{45,105}, Miguel Vazquez^{45,106}, Lieven PC Verbeke^{189,213}, Claes Wadelius²¹⁴, Lina Wadi⁹, Jiayin Wang^{131,145,152}, Jonathan Warrell^{114,115}, Sebastian M Waszak⁸, Joachim Weischenfeldt^{8,107,108}, **David A Wheeler**^{#154,155}, Guanming Wu²¹⁵, Jun Yu²¹⁶, Jing Zhang¹¹⁵, Xuanping Zhang^{145,217}, Yan Zhang^{115,218,219}, Zhongming Zhao²²⁰, Lihua Zou²²¹ and Christian von

PCAWG Transcriptome Working Group

Samirkumar B Amin^{158,159,160}, Philip Awadalla^{9,10}, Peter J Bailey²²², **Alvis Brazma**^{#7}, **Angela N Brooks**^{#3,11,12,48}, Claudia Calabrese^{7,8}, Aurélien Chateigner⁴⁴, Isidro Cortés-Ciriano^{223,224,225}, Brian Craft¹², David Craft^{3,226}, Chad J Creighton²²⁷, Natalie R Davidson^{85,86,87,88,101}, Deniz Demircioğlu^{228,229}, Serap Erkek⁸, Nuno A Fonseca^{7,66}, Milana Frenkel-Morgenstern²³⁰, Mary J Goldman¹², Liliana Greger⁷, Jonathan Göke^{228,231}, Yao He²³², Katherine A Hoadley^{233,234}, Yong Hou^{38,235}, Matthew R Huska²³⁶, Andre Kahles^{85,86,87,88,89}, Ekta Khurana^{110,111,122,123}, Helena Kilpinen²³⁷, Jan O Korbel^{7,8}, Fabien C Lamaze⁹, Kjong-Van Lehmann^{85,86,87,88,89}, Chang Li^{38,235}, Siliang Li^{38,235}, Xiaobo Li^{38,235}, Xinyue Li³⁸, Dongbing Liu^{38,235}, Fenglin Liu^{232,238}, Xingmin Liu^{38,235}, Maximillian G Marin¹¹, Julia Markowski²³⁶, Matthew Meyerson^{3,6,48}, Tannistha Nandi²³⁹, Morten Muhlig Nielsen¹¹⁷, Akinyemi I Ojesina^{240,241,242}, BF Francis Ouellette^{44,97}, Qiang Pan-Hammarström^{38,243}, Peter J Park^{223,225}, Chandra Sekhar Pedamallu^{3,6,163}, Jakob Skou Pedersen^{117,124}, Marc D Perry^{44,98}, **Gunnar Rättsch**^{#85,86,87,88,89,101}, Roland F Schwarz^{7,81,236,244}, Yuichi Shiraishi⁸³, Reiner Siebert^{245,246}, Cameron M Soulette¹¹, Stefan G Stark^{86,88,247,248}, Oliver Stegle^{7,8,249}, Hong Su^{38,235}, Patrick Tan^{239,250,251,252}, Bin Tean Teh^{250,251,252,253,254}, Lara Urban^{7,8}, Jian Wang³⁸, Sebastian M Waszak⁸, Kui Wu^{38,235}, Qian Xiang⁴⁴, Heng Xiong^{38,235}, Sergei Yakneen⁸, Huanming Yang³⁸, Chen Ye^{38,235}, Christina K Yung⁴⁴, Fan Zhang²³², Junjun Zhang⁴⁴, Xiuqing Zhang³⁸, Zemin Zhang^{232,255}, Liangtao Zheng²³², Jingchun Zhu¹² and Shida Zhu^{38,235}

PCAWG Epigenome Working Group

Hiroyuki Aburatani²⁵⁶, **Benjamin P Berman**^{#257,258,259}, Hans Binder^{260,261}, **Benedikt Brors**^{#79,112,262}, Huy Q Dinh²⁵⁷, Lars Feuerbach¹¹², Shengjie Gao³⁸, Ivo G Gut^{127,128}, Simon C Heath^{127,128}, Steve Hoffmann^{260,261,263,264}, Charles David Imbusch¹¹², Ekta Khurana^{110,111,122,123}, Helene Kretzmer^{261,264}, Peter W Laird²⁶⁵, Jose I Martin-Subero^{105,266}, Genta Nagae^{256,267}, **Christoph Plass**[#], Paz Polak^{3,4,6}, Hui Shen²⁶⁹, Reiner Siebert^{245,246}, Nasa Sinnott-Armstrong^{3,59}, Miranda D Stobbe^{127,128}, Qi Wang⁹³, Dieter Weichenhan²⁶⁸, Sergei Yakneen⁸ and Wanding Zhou²⁶⁹

PCAWG Structural Variation Working Group

Kadir C Akdemir¹³⁶, Eva G Alvarez^{270,271,272}, Adrian Baez-Ortega²⁷³, **Rameen Beroukhi**^{#3,6,163}, Paul C Boutros^{9,125,134,135}, David D L Bowtell¹⁷⁸, Benedikt Brors^{79,112,262}, Kathleen H Burns^{274,275}, John Busanovich^{3,276}, **Peter J Campbell**^{#1,2}, Kin Chan²⁷⁷, Ken Chen¹³⁶, Isidro Cortés-Ciriano^{223,224,225}, Ana Dueso-Barroso⁴⁵, Andrew J Dunford³, Paul A Edwards^{278,279}, Xavier Estivill^{139,280}, Dariush Etemadmoghadam¹⁷⁸, Lars Feuerbach¹¹², J Lynn Fink^{45,176}, Milana Frenkel-Morgenstern²³⁰, Dale W Garsed¹⁷⁸, Mark Gerstein^{113,114,115}, Dmitry A Gordenin²⁸¹, David Haan¹¹, James E Haber²⁸², Julian M Hess^{3,72}, Barbara Hutter^{77,78,79}, Marcin Imielinski^{283,284}, David TW Jones^{285,286}, Young Seok Ju^{1,172}, Marat D Kazanov^{287,288,289}, Leszek J Klimczak²⁹⁰, Youngil Koh^{291,292}, Jan O Korbel^{7,8}, Kiran Kumar³, Eunjung Alice Lee²⁹³, Jake June-Koo Lee^{223,225}, Yilong Li¹, Andy G Lynch^{278,279,294}, Geoff

Macintyre²⁷⁸, Florian Markowetz^{278,279}, Iñigo Martincorena¹, Alexander Martinez-Fundichely^{110,111,123}, Satoru Miyano⁸³, Hidewaki Nakagawa⁴⁷, Fabio CP Navarro¹¹⁴, Stephan Ossowski^{128,139,148}, Peter J Park^{223,225}, John V Pearson^{295,296}, Montserrat Puiggròs⁴⁵, Karsten Rippe⁸¹, Nicola D Roberts¹, Steven A Roberts²⁹⁷, Bernardo Rodriguez-Martin^{270,271,272}, Steven E Schumacher^{3,204}, Ralph Scully²⁹⁸, Mark Shackleton¹⁷⁸, Nikos Sidiropoulos¹⁰⁸, Lina Sieverling^{112,171}, Chip Stewart³, David Torrents^{45,105}, Jose MC Tubio^{270,271,272}, Izar Villasante⁴⁵, Nicola Waddell^{295,296}, Jeremiah A Wala^{3,6,48}, Joachim Weischenfeldt^{8,107,108}, Lixing Yang²⁹⁹, Xiaotong Yao^{284,300}, Sung-Soo Yoon²⁹², Jorge Zamora^{1,270,271,272} and Cheng-Zhong Zhang^{3,301}

PCAWG Mutational Signatures Working Group

Ludmil B Alexandrov^{1,70,302}, Erik N Bergstrom^{70,303}, Arnoud Boot^{251,304}, Paul C Boutros^{9,125,134,135}, Kin Chan²⁷⁷, Kyle Covington¹⁵⁵, Akihiro Fujimoto⁴⁷, Gad Getz^{3,4,5,6}, Dmitry A Gordenin²⁸¹, Nicholas J Haradhvala^{3,100}, Mi Ni Huang^{251,304}, S. M. Ashiqul Islam⁵³, Marat D Kazanov^{287,288,289}, Jaegil Kim³, Leszek J Klimczak²⁹⁰, Michael S Lawrence^{3,46,100}, Iñigo Martincorena¹, John R McPherson^{251,304}, Sandro Morganello¹, Ville Mustonen^{305,306,307}, Hidewaki Nakagawa⁴⁷, Alvin Wei Tian Ng³⁰⁸, Serena Nik-Zainal^{1,309,310,311}, Paz Polak^{3,4,6}, Stephenie D Prokopec⁹, Steven A Roberts²⁹⁷, **Steven G Rozen**^{251,252,304}, Radhakrishnan Sabarinathan^{174,191,312}, Natalie Saini²⁸¹, Tatsuhiro Shibata^{33,34}, Yuichi Shiraishi⁸³, **Michael R Stratton**¹, **Bin Tean Teh**^{250,251,252,253,254}, Ignacio Vázquez-García^{1,157,313,314}, Yang Wu^{251,304}, Fouad Yousif⁹ and Willie Yu³¹⁵

PCAWG Germline Cancer Genome Working Group

Ludmil B Alexandrov^{1,70,302}, Eva G Alvarez^{270,271,272}, Adrian Baez-Ortega²⁷³, Matthew H Bailey^{130,131}, Mattia Bosio^{45,128,139}, G Steven Bova³¹⁶, Alvis Brazma⁷, Alicia L Bruzos^{270,271,272}, Ivo Buchhalter^{50,51,52}, Carlos D Bustamante^{58,59}, Atul J Butte³¹⁷, Andy Cafferkey⁷, Claudia Calabrese^{7,8}, Peter J Campbell^{1,2}, Stephen J Chanock³¹⁸, Nilanjan Chatterjee^{319,320}, Jieming Chen^{115,321}, Francisco M De La Vega^{57,58,59}, Olivier Delaneau^{322,323,324}, German M Demidov^{128,139,148}, Anthony DiBiase³²⁵, Li Ding^{130,131,138}, Oliver Drechsel^{128,139}, Lewis Jonathan Dursi^{9,62}, Douglas F Easton^{326,327}, Serap Erkek⁸, Georgia Escaramis^{139,328,329}, **Xavier Estivill**^{139,280}, Erik Garrison¹, Mark Gerstein^{113,114,115}, Gad Getz^{3,4,5,6}, Dmitry A Gordenin²⁸¹, Nina Habermann⁸, Olivier Harismendy^{69,70}, Eoghan Harrington³³⁰, Shuto Hayashi⁸³, Seong Gu Heo³³¹, José María Heredia-Genestar³³², Aliaksei Z Holik¹³⁹, Eun Pyo Hong³³¹, Xing Hua³¹⁸, Kuan-lin Huang^{131,333}, Seiya Imoto⁸³, Sissel Juul³³⁰, Ekta Khurana^{110,111,122,123}, Hyung-Lae Kim²⁷, Youngwook Kim^{91,92}, Leszek J Klimczak²⁹⁰, **Jan O Korbel**^{7,8}, Roelof Koster³³⁴, Sushant Kumar^{114,115}, Ivica Letunic¹⁴⁶, Yilong Li¹, Tomas Marques-Bonet^{105,127,332,335}, R Jay Mashl^{131,147}, Simon Mayes³³⁶, Michael D McLellan^{130,131,138}, Lisa Mirabello³¹⁸, Francesc Muias^{128,139,148}, Hidewaki Nakagawa⁴⁷, Arcadi Navarro^{105,127,332}, Steven J Newhouse⁷, Stephan Ossowski^{128,139,148}, Ji Wan Park³³¹, Esa Pitkänen⁸, Aparna Prasad¹²⁸, Raquel Rabionet^{128,139,337}, Benjamin Raeder⁸, Tobias Rausch⁸, Steven A Roberts²⁹⁷, Bernardo Rodriguez-Martin^{270,271,272}, Vasilisa A Rudneva⁸, Gunnar Rätsch^{85,86,87,88,89,101}, Natalie Saini²⁸¹, Matthias Schlesner^{50,102}, Roland F Schwarz^{7,81,236,244}, Ayellet V Segre^{3,338}, Tal Shmaya⁵⁷, Suyash S Shringarpure⁵⁹, Nikos Sidiropoulos¹⁰⁸, Reiner Siebert^{245,246}, Jared T Simpson^{9,151}, Lei Song³¹⁸, Oliver Stegle^{7,8,249}, Hana Susak^{128,139}, Tomas J Tanskanen³³⁹, Grace Tiao³, Marta Tojo²⁷², Jose MC

Tubio^{270,271,272}, Daniel J Turner³³⁶, Lara Urban^{7,8}, Sebastian M Waszak⁸, David C Wedge^{1,340,341}, Joachim Weischenfeldt^{8,107,108}, David A Wheeler^{154,155}, Mark H Wright⁵⁹, Dai-Ying Wu⁵⁷, Tian Xia³⁴², Sergei Yakneen⁸, Kai Ye^{152,156}, Venkata D Yellapantula^{138,157}, Jorge Zamora^{1,270,271,272} and Bin Zhu³¹⁸

PCAWG Pathology and Clinical Correlates Working Group

Fatima Al-Shahrour³⁴³, Gurnit Atwal^{9,10,344}, Peter J Bailey²²², **Andrew V Biankin**^{#222,345,346,347}, Paul C Boutros^{9,125,134,135}, Peter J Campbell^{1,2}, David K Chang^{222,345}, Susanna L Cooke²²², Vikram Deshpande¹⁰⁰, Bishoy M Faltas¹⁰¹, William C Faquin¹⁰⁰, **Levi Garraway**^{#48}, Gad Getz^{3,4,5,6}, **Sean M Grimmond**^{#348}, Syed Haider⁹, **Katherine A Hoadley**^{#233,234}, Wei Jiao⁹, Vera B Kaiser³⁴⁹, Rosa Karlić³⁵⁰, Mamoru Kato³⁵¹, Kirsten Kübler^{3,6,100}, Alexander J Lazar^{158,352}, Constance H Li^{9,125}, David N Louis¹⁰⁰, Adam A Margolin¹⁰⁴, Sancha Martin^{1,353}, Hardeep K Nahal-Bose⁴⁴, G Petur Nielsen¹⁰⁰, Serena Nik-Zainal^{1,309,310,311}, Larsson Omberg⁹⁶, Christine P'ng⁹, Marc D Perry^{44,98}, Paz Polak^{3,4,6}, Esther Rheinbay^{3,6,100}, Mark A Rubin^{183,197,198,199,200}, Colin A Semple³⁴⁹, Dennis C Sgroi¹⁰⁰, Tatsuhiro Shibata^{33,34}, Reiner Siebert^{245,246}, Jaclyn Smith³⁵⁴, **Lincoln D Stein**^{#9,10}, Miranda D Stobbe^{127,128}, Ren X Sun⁹, Kevin Thai⁴⁴, Derek W Wright^{222,355}, Chin-Lee Wu¹⁰⁰, Ke Yuan^{278,353,356} and Junjun Zhang⁴⁴

PCAWG Evolution & Heterogeneity Working Group

David J Adams¹, Pavana Anur³⁵⁷, Rameen Beroukhim^{3,6,163}, Paul C Boutros^{9,125,134,135}, David D L Bowtell¹⁷⁸, Peter J Campbell^{1,2}, Shaolong Cao¹⁴⁰, Elizabeth L Christie¹⁷⁸, Marek Cmero^{358,359,360}, Yupeng Cun³⁶¹, Kevin J Dawson¹, Jonas Demeulemeester^{60,61}, Stefan C Dentro^{1,60,340}, Amit G Deshwar³⁶², Nilgun Donmez^{142,150}, Ruben M Drews²⁷⁸, Roland Eils^{50,52,63,64}, Yu Fan¹⁴⁰, Matthew W Fittall⁶⁰, Dale W Garsed¹⁷⁸, Moritz Gerstung^{7,8}, Gad Getz^{3,4,5,6}, Santiago Gonzalez^{7,8}, Gavin Ha³, Kerstin Haase⁶⁰, Marcin Imielinski^{283,284}, Lara Jerman^{8,363}, Yuan Ji^{364,365}, Clemency Jolly⁶⁰, Kortine Kleinheinz^{50,52}, Juhee Lee³⁶⁶, Henry Lee-Six¹, Ignaty Leshchiner³, Dimitri Livitz³, Geoff Macintyre²⁷⁸, Salem Malikić^{142,150}, Florian Markowetz^{278,279}, Iñigo Martincorena¹, Thomas J Mitchell^{1,279,367}, Quaid D Morris^{344,368}, Ville Mustonen^{305,306,307}, Layla Oesper³⁶⁹, Martin Peifer³⁶¹, Myron Peto³⁵⁷, Benjamin J Raphael¹⁹⁶, Daniel Rosebrock³, Yulia Rubanova^{151,344}, S Cen Sahinalp^{142,149,150}, Adriana Salcedo⁹, Matthias Schlesner^{50,102}, Steven E Schumacher^{3,204}, Subhjit Sengupta³⁷⁰, Ruian Shi³⁶⁸, Seung Jun Shin²⁴⁸, **Paul T Spellman**^{#357}, Oliver Spiro³, Lincoln D Stein^{9,10}, Maxime Tarabichi^{1,60}, **Peter Van Loo**^{#60,61}, Shankar Vembu^{368,371}, Ignacio Vázquez-García^{1,157,313,314}, Wenyi Wang¹⁴⁰, **David C Wedge**^{#1,340,341}, David A Wheeler^{154,155}, Jeffrey A Wintersinger^{151,180,344}, Tsun-Po Yang³⁶¹, Xiaotong Yao^{284,300}, Kaixian Yu³⁷², Ke Yuan^{278,353,356} and Hongtu Zhu^{372,373}

PCAWG Portals and Visualization Working Group

Fatima Al-Shahrour³⁴³, Elisabet Barrera⁷, Wojciech Bazant⁷, Alvis Brazma⁷, Isidro Cortés-Ciriano^{223,224,225}, Brian Craft¹², David Craft^{3,226}, Vincent Ferretti^{44,65}, Nuno A Fonseca^{7,66},

Anja Füllgrabe⁷, Mary J Goldman¹², **David Haussler**^{#12,374}, Wolfgang Huber⁸, Maria Keays⁷, Alfonso Muñoz⁷, Brian D O'Connor^{44,95}, Irene Papatheodorou⁷, Robert Petryszak⁷, Elena Piñeiro-Yáñez³⁴³, Alfonso Valencia^{45,105}, **Miguel Vazquez**^{#45,106}, John N Weinstein^{375,376}, Qian Xiang⁴⁴, Junjun Zhang⁴⁴ and **Jingchun Zhu**^{#12}

PCAWG Mitochondrial Genome and Immunogenomics Working Group

Peter J Campbell^{1,2}, Yiwen Chen¹⁴⁰, Chad J Creighton²²⁷, Li Ding^{130,131,138}, Akihiro Fujimoto⁴⁷, Masashi Fujita⁴⁷, Gad Getz^{3,4,5,6}, Leng Han²¹⁷, Takanori Hasegawa⁸³, Shuto Hayashi⁸³, Seiya Imoto⁸³, Young Seok Ju^{1,172}, Hyung-Lae Kim²⁷, Youngwook Kim^{91,92}, Youngil Koh^{291,292}, Mitsuhiro Komura⁸³, Jun Li¹⁴⁰, **Han Liang**^{#140}, Iñigo Martincorena¹, Satoru Miyano⁸³, Shinichi Mizuno³⁷⁷, **Hidewaki Nakagawa**^{#47}, Keunchil Park^{192,193}, Eigo Shimizu⁸³, Yumeng Wang¹⁴⁰, John N Weinstein^{375,376}, Yanxun Xu³⁷⁸, Rui Yamaguchi⁸³, Fan Yang³⁶⁸, Yang Yang²¹⁷, Christopher J Yoon¹⁷², Sung-Soo Yoon²⁹², Yuan Yuan¹⁴⁰, Fan Zhang²³² and Zemin Zhang^{232,255}

PCAWG Pathogens Working Group

Malik Alawi^{379,380}, Ivan Borozan⁹, Daniel S Brewer^{381,382}, Colin S Cooper^{382,383,384}, Nikita Desai⁴⁴, Roland Eils^{50,52,63,64}, Vincent Ferretti^{44,65}, Adam Grundhoff^{380,385}, Murat Iskar³⁸⁶, Kortine Kleinheinz^{50,52}, **Peter Lichter**^{#77,386}, Hidewaki Nakagawa⁴⁷, Akinyemi I Ojesina^{240,241,242}, Chandra Sekhar Pedamallu^{3,6,163}, Matthias Schlesner^{50,102}, Xiaoping Su³⁵² and **Marc Zapatka**^{#386}

Providers of tumour-sequencing data

PCAWG Tumour-specific providers (ovarian cancer) in Australia

Kathryn Alsop¹⁷⁸, Australian Ovarian Cancer Study Group^{295,387,388}, **David D L Bowtell**^{#178}, Timothy JC Bruxner¹⁷⁶, Angelika N Christ¹⁷⁶, Elizabeth L Christie¹⁷⁸, Stephen M Cordner³⁸⁹, Prue A Cowin³⁸⁷, Ronny Drapkin³⁹⁰, Dariush Etemadmoghadam¹⁷⁸, Sian Fereday¹⁷⁸, Dale W Garsed¹⁷⁸, Joshy George¹⁶⁰, Sean M Grimmond³⁴⁸, Anne Hamilton³⁸⁷, Oliver Holmes^{295,296}, Jillian A Hung³⁹¹, Karin S Kassahn^{176,392}, Stephen H Kazakoff^{295,296}, Catherine J Kennedy^{391,393}, Conrad R Leonard^{295,296}, Linda Mileshekin¹⁷⁸, David K Miller^{176,345}, Gisela Mir Arnau³⁸⁷, Chris Mitchell¹⁷⁸, Felicity Newell^{295,296}, Katia Nones^{295,296}, Ann-Marie Patch^{295,296}, John V Pearson^{295,296}, Michael C Quinn^{295,296}, Mark Shackleton¹⁷⁸, Darrin F Taylor¹⁷⁶, Heather Thorne¹⁷⁸, Nadia Traficante¹⁷⁸, Ravikiran Vedururu³⁸⁷, Nick M Waddell²⁹⁶, Nicola Waddell^{295,296}, Paul M Waring³⁹⁴, Scott Wood^{295,296}, Qinying Xu^{295,296} and Anna deFazio^{391,393,395}

PCAWG Tumour-specific providers (pancreatic cancer) in Australia

Matthew J Anderson¹⁷⁶, Davide Antonello³⁹⁶, Andrew P Barbour^{397,398}, Claudio Bassi³⁹⁶, Samantha Bersani³⁹⁹, **Andrew V Biankin**^{#222,345,346,347}, Timothy JC Bruxner¹⁷⁶, Ivana Cataldo^{399,400}, David K Chang^{222,345}, Lorraine A Chantrill^{345,401}, Yoke-Eng Chiew^{391,393}, Angela Chou^{345,393}, Angelika N Christ¹⁷⁶, Sara Cingarlini³⁶, Nicole Cloonan⁴⁰², Vincenzo Corbo^{400,403}, Maria Vittoria Davi⁴⁰⁴, Fraser R Duthie^{222,405}, J Lynn Fink^{45,176}, Anthony J Gill^{345,406}, Janet S Graham^{222,407}, **Sean M Grimmond**^{#348}, Ivon Harliwong¹⁷⁶, Oliver Holmes^{295,296}, Nigel B Jamieson^{222,347,408}, Amber L Johns³⁴⁵, Karin S Kassahn^{176,392}, Stephen H Kazakoff^{295,296}, James G Kench^{345,406,409}, Luca Landoni³⁹⁶, Rita T Lawlor⁴⁰⁰, Conrad R Leonard^{295,296}, Andrea Mafficini⁴⁰⁰, Neil D Merrett^{396,410}, David K Miller^{176,345}, Marco Miotto³⁹⁶, Elizabeth A Musgrove²²², Adnan M Nagrial³⁴⁵, Felicity Newell^{295,296}, Katia Nones^{295,296}, Karin A Oien^{394,411}, Marina Pajic³⁴⁵, Ann-Marie Patch^{295,296}, John V Pearson^{295,296}, Mark Pinese³⁴⁵, Andreia V Pinho⁴¹², Michael C Quinn^{295,296}, Alan J Robertson¹⁷⁶, Ilse Rooman³⁴⁵, Borislav C Rusev⁴⁰⁰, Jaswinder S Samra^{396,413}, Maria Scardon³⁹⁹, Christopher J Scarlett^{345,414}, Aldo Scarpa⁴⁰⁰, Elisabetta Sereni³⁹⁶, Katarzyna O Sikora⁴⁰⁰, Michele Simbolo⁴⁰³, Morgan L Taschuk⁴⁴, Christopher W Toon³⁴⁵, Giampaolo Tortora^{36,37}, Caterina Vicentini⁴⁰⁰, Nick M Waddell²⁹⁶, Nicola Waddell^{295,296}, Scott Wood^{295,296}, Jianmin Wu³⁴⁵, Qinying Xu^{295,296} and Nikolajs Zeps^{415,416}

PCAWG Tumour-specific providers (skin cancer) in Australia

Lauri A Aaltonen⁴¹⁷, Andreas Behren⁴¹⁸, Hazel Burke⁴¹⁹, Jonathan Cebon⁴¹⁸, Rebecca A Dagg⁴²⁰, Ricardo De Paoli-Iseppi⁴¹⁹, Ken Dutton-Regester²⁹⁵, Matthew A Field⁴²¹, Anna Fitzgerald⁴²², Sean M Grimmond³⁴⁸, **Nicholas K Hayward**^{#295,419}, Peter Hersey⁴¹⁹, Oliver Holmes^{295,296}, Valerie Jakrot⁴¹⁹, Peter A Johansson²⁹⁵, Hojabr Kakavand⁴¹⁹, Stephen H Kazakoff^{295,296}, Richard F Kefford⁴²³, Loretta MS Lau⁴²⁴, Conrad R Leonard^{295,296}, Georgina V Long⁴¹⁹, **Graham J Mann**^{#393,419,419}, Felicity Newell^{295,296}, Katia Nones^{295,296}, Ann-Marie Patch^{295,296}, John V Pearson^{295,296}, Hilda A Pickett⁴²⁴, Antonia L Pritchard²⁹⁵, Gulietta M Pupo³⁹³, Robyn PM Saw⁴¹⁹, Sarah-Jane Schramm³⁹³, **Richard A Scolyer**^{#409,413,419}, Mark Shackleton¹⁷⁸, Catherine A Shang⁴²², Ping Shang⁴¹⁹, Andrew J Spillane⁴¹⁹, Jonathan R Stretch⁴¹⁹, Varsha Tembe³⁹³, John F Thompson⁴¹⁹, Ricardo E Vilain⁴²⁵, Nick M Waddell²⁹⁶, Nicola Waddell^{295,296}, James S Wilmott⁴¹⁹, Scott Wood^{295,296}, Qinying Xu^{295,296} and Jean Y Yang⁴²⁶

PCAWG Tumour-specific providers (pancreatic cancer) in Canada

John Bartlett^{427,428}, Prashant Bavi⁴²⁹, Ivan Borozan⁹, Dianne E Chadwick⁴³⁰, Michelle Chan-Seng-Yue⁴²⁹, Sean Cleary^{429,431}, Ashton A Connor^{431,432}, Karolina Czajka⁷⁶, Robert E Denroche⁴²⁹, Neesha C Dhani⁴³³, Jenna Eagles⁷⁶, Vincent Ferretti^{44,65}, Steven Gallinger^{429,431,432}, Robert C Grant^{429,432}, David Hedley⁴³³, Michael A Hollingsworth⁴³⁴, **Thomas J Hudson**^{#75,76}, Gun Ho Jang⁴²⁹, Jeremy Johns⁷⁶, Sangeetha Kalimuthu⁴²⁹, Sheng-Ben Liang⁴³⁰, Ilinca Lungu^{429,435}, Xuemei Luo⁹, Faridah Mbabaali⁷⁶, **John D McPherson**^{#476,429,436}, Treasa A McPherson⁴³², Jessica K Miller⁷⁶, Malcolm J Moore⁴³³, Faiyaz Notta^{429,437}, Danielle Pasternack⁷⁶, Gloria M Petersen⁴³⁸, Michael H A Roehrl^{125,429,430,439,440,441}, Michelle Sam⁷⁶, Iris Selander⁴³², Stefano Serra³⁹⁴, Sagedeh Shahabi⁴³⁰, **Lincoln D Stein**^{#9,10}, Morgan L Taschuk⁴⁴, Sarah P Thayer⁴³⁴, Lee E Timms⁷⁶, Gavin W Wilson^{9,429}, Julie M Wilson⁴²⁹ and Bradly G Wouters¹²⁵

PCAWG Tumour-specific providers (prostate cancer) in Canada

Timothy A Beck^{44,442}, Vinayak Bhandari⁹, **Paul C Boutros**^{#9,125,134,135}, **Robert G Bristow**^{#125,443,444,445,446}, Colin C Collins¹⁴², Shadrielle MG Espiritu⁹, Neil E Fleshner⁴⁴⁷, Natalie S Fox⁹, Michael Fraser⁹, Syed Haider⁹, Lawrence E Heisler⁴⁴, Vincent Huang⁹, Emilie Lalonde⁹, Julie Livingstone⁹, John D McPherson^{76,429,436}, Alice Meng⁴⁴⁸, Veronica Y Sabelnykova⁹, Adriana Salcedo⁹, Yu-Jia Shiah⁹, Theodorus Van der Kwast⁴⁴¹ and Takafumi N Yamaguchi⁹

PCAWG Tumour-specific providers (gastric cancer) in China

Shuai Ding⁴⁴⁹, Daiming Fan⁴⁵⁰, Yong Hou^{38,235}, Yi Huang^{144,145}, Lin Li³⁸, Siliang Li^{38,235}, Dongbing Liu^{38,235}, Xingmin Liu^{38,235}, **Youyong Lu**^{#28,29,30}, Yongzhan Nie^{450,451}, Hong Su^{38,235}, Jian Wang³⁸, Kui Wu^{38,235}, Xiao Xiao¹⁴⁵, Rui Xing³⁰, **Huanming Yang**^{#38}, Shanlin Yang⁴⁴⁹, Yingyan Yu⁴⁵², Xiuqing Zhang³⁸, Yong Zhou³⁸ and Shida Zhu^{38,235}

PCAWG Tumour-specific providers (renal cancer) in the EU & France

Rosamonde E Banks⁴⁵³, Guillaume Bourque^{454,455}, Alvis Brazma⁷, Paul Brennan⁴⁵⁶, **Mark Lathrop**^{#455}, Louis Letourneau⁴⁵⁷, Yasser Riazalhosseini⁴⁵⁵, Ghislaine Scelo⁴⁵⁶, **Jörg Tost**^{#458}, Naveen Vasudev⁴⁵⁹ and Juris Viksna⁴⁶⁰

PCAWG Tumour-specific providers (breast cancer) in the EU & United Kingdom

Sung-Min Ahn⁴⁶¹, Ludmil B Alexandrov^{1,70,302}, Samuel Aparicio⁴⁶², Laurent Arnould⁴⁶³, MR Aure⁴⁶⁴, Shriram G Bhosle¹, Ewan Birney⁷, Ake Borg⁴⁶⁵, Sandrine Boyault⁴⁶⁶, Arie B Brinkman⁴⁶⁷, Jane E Brock⁴⁶⁸, Annegien Broeks⁴⁶⁹, Adam P Butler¹, Anne-Lise Børresen-Dale^{464,470}, Carlos Caldas^{278,471}, Peter J Campbell^{1,2}, Suet-Feung Chin^{278,471}, Helen Davies^{1,309,310}, Christine Desmedt^{472,473}, Luc Dirix⁴⁷⁴, Serge Serge¹, Anna Ehinger⁴⁷⁵, Jorunn E Eyfjord⁴⁷⁶, Aquila Fatima²⁰⁴, John A Foekens⁴⁷⁷, P Andrew Futreal⁴⁷⁸, Øystein Garred^{479,480}, Moritz Gerstung^{7,8}, Dilip D Giri⁴⁸¹, Dominik Glodzik¹, Dorte Grabau⁴⁸², Holmfridur Hilmarsdottir⁴⁷⁶, Gerrit K Hooijer⁴⁸³, Jocelyne Jacquemier⁴⁸⁴, Se Jin Jang⁴⁸⁵, Jon G Jonasson⁴⁷⁶, Jos Jonkers⁴⁸⁶, Hyung-Yong Kim⁴⁸⁴, Tari A King^{487,488,489}, Stian Knappskog^{1,490}, Gu Kong⁴⁸⁴, Savitri Krishnamurthy^{352,491}, Sunil R Lakhani⁴⁹², Anita Langerød⁴⁶⁴, Denis Larsimont⁴⁹³, Hee Jin Lee⁴⁸⁵, Jeong-Yeon Lee⁴⁹⁴, Ming Ta Michael Lee⁴⁷⁸, Yilong Li¹, Ole Christian Lingjærde⁴⁹⁵, Gaetan MacGrogan⁴⁹⁶, John WM Martens⁴⁷⁷, Sancha Martin^{1,353}, Iñigo Martincorena¹, Andrew Menzies¹, Sandro Morganella¹, Ville Mustonen^{305,306,307}, Serena Nik-Zainal^{1,309,310,311}, Sarah O'Meara¹, Iris Pauporté²⁰, Sarah Pinder⁴⁹⁷, Xavier Pivot⁴⁹⁸, Elena Provenzano⁴⁹⁹, Colin A Purdie⁵⁰⁰, Keiran M Raine¹, Manasa Ramakrishna¹, Kamna Ramakrishnan¹, Jorge Reis-Filho⁴⁸¹, Andrea L Richardson²⁰⁴, Markus Ringnér⁵⁰¹, Javier Bartolomé

Rodriguez⁴⁵, F Germán Rodríguez-González⁵⁰², Gilles Romieu⁵⁰³, Roberto Salgado³⁹⁴, Torill Sauer⁴⁹⁵, Rebecca Shepherd¹, Anieta M Sieuwerts⁴⁷⁷, Peter T Simpson⁴⁹², Marcel Smid⁴⁷⁷, Christos Sotiriou⁵³, Paul N Span⁵⁰⁴, Lucy Stebbings¹, Ólafur Andri Stefánsson⁵⁰⁵, Alasdair Stenhouse⁵⁰⁶, **Michael R Stratton**^{#1}, Henk G Stunnenberg^{235,507}, Fred Sweep⁵⁰⁸, Benita Kiat Tee Tan⁵⁰⁹, Jon W Teague¹, Gilles Thomas⁵¹⁰, Alastair M Thompson⁵⁰⁶, Stefania Tommasi⁵¹¹, Isabelle Treilleux^{512,513}, Andrew Tutt²⁰⁴, Naoto T Ueno⁵¹⁴, Steven Van Laere⁴⁷⁴, Peter Van Loo^{60,61}, Gert G Van den Eynden⁴⁷⁴, Peter Vermeulen⁴⁷⁴, Alain Viari⁴⁰⁰, Anne Vincent-Salomon⁵⁰⁷, David C Wedge^{1,340,341}, Bernice H Wong⁵¹⁵, Lucy Yates¹, Xueqing Zou¹, Carolien HM van Deurzen⁵¹⁶, Marc J van de Vijver³⁹⁴ and L van't Veer⁵¹⁷

PCAWG Tumour-specific providers (malignant lymphoma) in Germany

Ole Ammerpohl^{518,519}, Sietse Aukema^{520,521}, Anke K Bergmann⁵²², Stephan H Bernhart^{260,261,264}, Hans Binder^{260,261}, Arndt Borkhardt⁵²³, Christoph Borst⁵²⁴, Benedikt Brors^{79,112,262}, Birgit Burkhardt⁵²⁵, Alexander Claviez⁵²⁶, Roland Eils^{50,52,63,64}, Maria Elisabeth Goebler⁵²⁷, Andrea Haake⁵¹⁸, Siegfried Haas⁵²⁴, Martin Hansmann⁵²⁸, Jessica I Hoell⁵²³, Steve Hoffmann^{260,261,263,264}, Michael Hummel⁵²⁹, Daniel Hübschmann^{52,63,80,81,82}, Dennis Karsch⁵³⁰, Wolfram Klapper⁵²⁰, Kortine Kleinheinz^{50,52}, Michael Kneba⁵³⁰, Jan O Korbel^{7,8}, Helene Kretzmer^{261,264}, Markus Kreuz⁵³¹, Dieter Kube⁵³², Ralf Küppers⁵³³, Chris Lawerenz⁶⁴, Dido Lenze⁵²⁹, Peter Lichter^{77,386}, Markus Loeffler⁵³¹, Cristina López^{246,518}, Luisa Mantovani-Löffler⁵³⁴, Peter Möller⁵³⁵, German Ott⁵³⁶, Bernhard Radlwimmer³⁸⁶, Julia Richter^{518,520}, Marius Rohde⁵³⁷, Philip C Rosenstiel⁵³⁸, Andreas Rosenwald⁵³⁹, Markus B Schilhabel⁵³⁸, Matthias Schlesner^{50,102}, Stefan Schreiber⁵⁴⁰, **Reiner Siebert**^{#245,246}, Peter F Stadler^{260,261,264}, Peter Staib⁵⁴¹, Stephan Stilgenbauer⁵⁴², Stephanie Sungalee⁸, Monika Szczepanowski⁵²⁰, Umut H Toprak^{52,543}, Lorenz HP Trümper⁵³², Rabea Wagener^{246,518} and Thorsten Zenz⁷⁹

PCAWG Tumour-specific providers (paediatric brain cancer) in Germany

Ivo Buchhalter^{50,51,52}, Juergen Eils^{63,64}, Roland Eils^{50,52,63,64}, Volker Hovestadt³⁸⁶, Barbara Hutter^{77,78,79}, David TW Jones^{285,286}, Natalie Jäger⁵⁰, Christof von Kalle⁸¹, Marcel Kool^{93,285}, Jan O Korbel^{7,8}, Andrey Korshunov⁹³, Pablo Landgraf^{454,545}, Chris Lawerenz⁶⁴, Hans Lehrach⁵⁴⁶, **Peter Lichter**^{#77,386}, Paul A Northcott⁵⁴⁷, Stefan M Pfister^{93,285,548}, Bernhard Radlwimmer³⁸⁶, Guido Reifenberger⁵⁴⁵, Matthias Schlesner^{50,102}, Hans-Jörg Warnatz⁵⁴⁶, Joachim Weischenfeldt^{8,107,108}, Stephan Wolf⁵⁴⁹, Marie-Laure Yaspo⁵⁴⁶ and Marc Zapatka³⁸⁶

PCAWG Tumour-specific providers (prostate cancer) in Germany

Yassen Assenov⁵⁵⁰, Benedikt Brors^{79,112,262}, Juergen Eils^{63,64}, Roland Eils^{50,52,63,64}, Lars Feuerbach¹¹², Clarissa Gerhauser²⁶⁸, Jan O Korbel^{7,8}, Chris Lawerenz⁶⁴, Hans Lehrach⁵⁴⁶, Sarah Minner⁵⁵¹,

Christoph Plass²⁶⁸, **Guido Sauter**^{#552}, Thorsten Schlomm^{107,553}, Nikos Sidiropoulos¹⁰⁸, Ronald Simon⁵⁵², **Holger Sültmann**^{#79,554}, Hans-Jörg Warnatz⁵⁴⁶, Dieter Weichenhan²⁶⁸, Joachim Weischenfeldt^{8,107,108} and Marie-Laure Yaspo⁵⁴⁶

PCAWG Tumour-specific providers (oral cancer) in India

Nidhan K Biswas⁵⁵⁵, Luca Landoni³⁹⁶, Arindam Maitra⁵⁵⁵, **Partha P Majumder**^{#555} and **Rajiv Sarin**^{#556}

PCAWG Tumour-specific providers (pancreatic cancer) in Italy

Davide Antonello³⁹⁶, Stefano Barbi⁴⁰³, Claudio Bassi³⁹⁶, Samantha Bersani³⁹⁹, Giada Bonizzato⁴⁰⁰, Cinzia Cantù⁴⁰⁰, Ivana Cataldo^{399,400}, Sara Cingarlini³⁶, Vincenzo Corbo^{400,403}, Maria Vittoria Davi⁴⁰⁴, Angelo P Dei Tos⁵⁵⁷, Matteo Fassan⁵⁵⁸, Sonia Grimaldi⁴⁰⁰, Luca Landoni³⁹⁶, Rita T Lawlor⁴⁰⁰, Claudio Luchini³⁹⁹, Andrea Mafficini⁴⁰⁰, Giuseppe Malleo³⁹⁶, Giovanni Marchegiani³⁹⁶, Michele Milella³⁶, Marco Miotto³⁹⁶, Salvatore Paiella³⁹⁶, Antonio Pea³⁹⁶, Paolo Pederzoli³⁹⁶, Borislav C Rusev⁴⁰⁰, Andrea Ruzzenente³⁹⁶, Roberto Salvia³⁹⁶, Maria Scardoni³⁹⁹, **Aldo Scarpa**^{#400}, Elisabetta Sereni³⁹⁶, Michele Simbolo⁴⁰³, Nicola Sperandio⁴⁰⁰, Giampaolo Tortora^{36,37} and Caterina Vicentini⁴⁰⁰

PCAWG Tumour-specific providers (biliary tract cancer) in Japan

Yasuhito Arai³³, Natsuko Hama³³, Nobuyoshi Hiraoka⁵⁵⁹, Fumie Hosoda³³, Mamoru Kato³⁵¹, Hiromi Nakamura³³, Hidenori Ojima⁵⁶⁰, Takuji Okusaka⁵⁶¹, **Tatsuhiko Shibata**^{#33,34}, Yasushi Totoki³³ and Tomoko Urushidate³⁴

PCAWG Tumour-specific providers (gastric cancer) in Japan

Hiroyuki Aburatani^{#256}, Yasuhito Arai³³, Masashi Fukayama⁵⁶², Natsuko Hama³³, Fumie Hosoda³³, Shumpei Ishikawa⁵⁶³, Hitoshi Katai⁵⁶⁴, Mamoru Kato³⁵¹, Hiroto Katoh⁵⁶³, Daisuke Komura⁵⁶³, Genta Nagae^{256,267}, Hiromi Nakamura³³, Hirofumi Rokutan³⁵¹, Mihoko Saito-Adachi³⁵¹, **Tatsuhiko Shibata**^{#33,34}, Akihiro Suzuki^{256,565}, Hirokazu Taniguchi³⁴, Kenji Tatsuno²⁵⁶, Yasushi Totoki³³, Tetsuo Ushiku⁵⁶², Shinichi Yachida^{33,566} and Shogo Yamamoto²⁵⁶

PCAWG Tumour-specific providers (liver cancer) in Japan

Hiroyuki Aburatani²⁵⁶, Hiroshi Aikata⁵⁶⁷, Koji Arihiro⁵⁶⁷, Shun-ichi Ariizumi⁵⁶⁸, Keith A Boroevich^{46,47}, Kazuaki Chayama⁵⁶⁷, Akihiro Fujimoto⁴⁷, Masashi Fujita⁴⁷, Mayuko Furuta⁴⁷, Kunihiro Gotoh⁵⁶⁹, Natsuko Hama³³, Takanori Hasegawa⁸³, Shinya Hayami⁵⁷⁰, Shuto Hayashi⁸³, Satoshi Hirano⁵⁷¹, Seiya Imoto⁸³, Mamoru Kato³⁵¹, Yoshiiku Kawakami⁵⁶⁷, Kazuhiro Maejima⁴⁷,

Satoru Miyano⁸³, Genta Nagae^{256,267}, **Hidewaki Nakagawa**^{#47}, Hiromi Nakamura³³, Toru Nakamura⁵⁷¹, Kaoru Nakano⁴⁷, Hideki Ohdan⁵⁶⁷, Yasushi Rino⁵⁷², Aya Sasaki-Oku⁴⁷, **Tatsuhiro Shibata**^{#33,34}, Yuichi Shiraishi⁸³, Hiroko Tanaka⁸³, Yasushi Totoki³³, Tatsuhiko Tsunoda^{46,207,208,209}, Masaki Ueno⁵⁷⁰, Rui Yamaguchi⁸³, Masakazu Yamamoto⁵⁶⁸ and Hiroki Yamaue⁵⁷⁰

PCAWG Tumour-specific providers (biliary tract cancer) in Singapore

Su Pin Choo⁵⁷³, Ioana Cutcutache^{251,304}, Narong Khuntikeo^{396,574}, John R McPherson^{251,304}, Choon Kiat Ong⁵⁷⁵, Chawalit Pairojkul³⁹⁴, Irinel Popescu⁵⁷⁶, **Steven G Rozen**^{#251,252,304}, **Patrick Tan**^{#239,250,251,252} and **Bin Tean Teh**^{#250,251,252,253,254}

PCAWG Tumour-specific providers (blood cancer) in South Korea

Keun Soo Ahn⁵⁷⁷, Hyung-Lae Kim²⁷, Youngil Koh^{291,292} and **Sung-Soo Yoon**^{#292}

PCAWG Tumour-specific providers (chronic lymphocytic leukaemia) in Spain

Marta Aymerich⁵⁷⁸, **Elias Campo**^{#579,580}, Josep L L Gelpi^{45,67}, Ivo G Gut^{127,128}, Marta Gut^{127,128}, Armando Lopez-Guillermo⁵⁸¹, Carlos López-Otín⁵⁸², Xose S Puente⁵⁸², Romina Royo⁴⁵ and David Torrents^{45,105}

PCAWG Tumour-specific providers (bone cancer) in the United Kingdom

Fernanda Amary⁵⁸³, Daniel Baumhoer⁵⁸⁴, Sam Behjati¹, Bodil Bjerkehagen^{584,585}, **Peter J Campbell**^{#1,2}, **Adrienne M Flanagan**^{#586}, P Andrew Futreal⁴⁷⁸, Ola Myklebost⁴⁹⁰, Nischalan Pillay⁵⁸⁷, Patrick Tarpey⁵⁸⁸, Roberto Tirabosco⁵⁸⁹ and Olga Zaikova⁵⁹⁰

PCAWG Tumour-specific providers (chronic myeloid disorders) in the United Kingdom

Jacqueline Boulton⁵⁹¹, David T Bowen¹, Adam P Butler¹, **Peter J Campbell**^{#1,2}, Mario Cazzola⁵⁹², Carlo Gambacorti-Passerini¹⁷⁷, Anthony R Green²⁷⁹, Eva Hellstrom-Lindberg⁵⁹³, Luca Malcovati⁵⁹², Sancha Martin^{1,353}, Jyoti Nangalia¹, Elli Papaemmanuil² and Paresh Vyas^{295,594}

PCAWG Tumour-specific providers (oesophageal cancer) in the

United Kingdom

Yeng Ang⁵⁹⁵, Hugh Barr⁵⁹⁶, Duncan Beardsmore⁵⁹⁷, Matthew Eldridge²⁷⁸, **Rebecca C Fitzgerald#**³¹⁰, James Gossage⁵⁹⁸, Nicola Grehan³¹⁰, George B Hanna⁵⁹⁹, Stephen J Hayes^{600,601}, Ted R Hupp⁶⁰², David Khoo⁶⁰³, Jesper Lagergren^{593,604}, Laurence B Lovat²³⁷, Shona MacRae³⁷⁵, Maria O'Donovan³¹⁰, J Robert O'Neill⁶⁰⁵, Simon L Parsons⁶⁰⁶, Shaun R Preston⁶⁰⁷, Sonia Puig⁶⁰⁸, Tom Roques⁶⁰⁹, Grant Sanders²³⁴, Sharmila Sothi⁶¹⁰, Simon Tavaré²⁷⁸, Olga Tucker⁶¹¹, Richard Turkington⁶¹², Timothy J Underwood⁶¹³ and Ian Welch⁶¹⁴

PCAWG Tumour-specific providers (prostate cancer) in the United Kingdom

Daniel M Berney⁶¹⁵, Johann S De Bono³⁸³, G Steven Bova³¹⁶, Daniel S Brewer^{381,382}, Adam P Butler¹, Declan Cahill⁶¹⁶, Niedzica Camacho³⁸³, **Colin S Cooper#**^{382,383,384}, Nening M Dennis⁶¹⁶, Tim Dudderidge^{616,617}, Sandra E Edwards³⁸³, **Rosalind A Eeles#**^{383,616}, Cyril Fisher⁶¹⁶, Christopher S Foster^{618,619}, Mohammed Ghori¹, Pelvender Gill⁵⁹⁴, Vincent J Gnanapragasam^{367,620}, Gunes Gundem¹⁸⁷, Freddie C Hamdy⁵⁹⁴, Steve Hawkins²⁷⁸, Steven Hazell⁶¹⁶, William Howat³⁶⁷, William B Isaacs⁶²¹, Katalin Karaszi⁵⁹⁴, Jonathan D Kay²³⁷, Vincent Khoo⁶¹⁶, Zsofia Kote-Jarai³⁸³, Barbara Kremeyer¹, Pardeep Kumar⁶¹⁶, Adam Lambert⁵⁹⁴, Daniel A Leongamornlert^{1,383}, Naomi Livni⁶¹⁶, Yong-Jie Lu^{615,622}, Hayley J Luxton²³⁷, Andy G Lynch^{278,279,294}, Luke Marsden⁵⁹⁴, Charlie E Massie²⁷⁸, Lucy Matthews³⁸³, Erik Mayer^{616,623}, Ultan McDermott¹, Sue Merson³⁸³, Thomas J Mitchell^{1,279,367}, David E Neal^{278,367}, Anthony Ng⁶²⁴, David Nicol⁶¹⁶, Christopher Ogden⁶¹⁶, Edward W Rowe⁶¹⁶, Nimish C Shah³⁶⁷, Jon W Teague¹, Sarah Thomas⁶¹⁶, Alan Thompson⁶¹⁶, Peter Van Loo^{60,61}, Clare Verrill^{594,625}, Tapio Visakorpi³¹⁶, Anne Y Warren^{367,626}, David C Wedge^{1,340,341}, Hayley C Whitaker²³⁷, Jorge Zamora^{1,270,271,272}, Hongwei Zhang⁶²² and Nicholas van As⁶¹⁶

PCAWG Tumour-specific providers (TCGA) in the United States

Adam Abeshouse¹⁸⁷, Nishant Agrawal⁶²⁷, Rehan Akbani^{310,376}, Hikmat Al-Ahmadie¹⁸⁷, Monique Albert⁴²⁸, Kenneth Aldape^{352,628}, Adrian Ally⁶²⁹, Yeng Ang⁵⁹⁵, Elizabeth L Appelbaum^{131,237}, Joshua Armenia⁶³⁰, Sylvia Asa^{441,606}, J Todd Auman⁶³¹, Matthew H Bailey^{130,131}, Miruna Balasundaram⁶²⁹, Saianand Balu²³⁴, Jill Barnholtz-Sloan^{632,633}, Hugh Barr⁵⁹⁶, John Bartlett^{427,428}, Oliver F Bathe^{634,635}, Stephen B Baylin^{320,617}, Duncan Beardsmore⁵⁹⁷, Christopher Benz⁶³⁶, Andrew Berchuck⁶³⁷, Benjamin P Berman^{257,258,259}, Rameen Beroukhi^{3,6,163}, Mario Berrios⁶³⁸, Darell Bigner⁶³⁹, Michael Birrer¹⁰⁰, Tom Bodenheimer²³⁴, Lori Boice⁶⁰⁸, Moiz S Bootwalla⁶³⁸, Marcus Bosenberg⁶⁴⁰, Reanne Bowlby⁶²⁹, Jeffrey Boyd⁶⁴¹, Russell R Broaddus³⁵², Malcolm Brock⁶⁴², Denise Brooks⁶²⁹, Susan Bullman^{3,163}, Samantha J Caesar-Johnson³⁹, Thomas E Carey⁶⁴³, Rebecca Carlsen⁶²⁹, Robert Cerfolio⁶⁴⁴, Vishal S Chandan⁶⁴⁵, Hsiao-Wei Chen^{595,630}, Andrew D Cherniack^{3,48,163}, Jeremy Chien⁶⁴⁶, Juok Cho³, Eric Chuah⁶²⁹, Carrie Cibulskis³, Kristian Cibulskis³, Leslie Cope³²⁰, Matthew G Cordes^{131,609}, Kyle Covington¹⁵⁵, Erin Curley⁶⁴⁷, Bogdan Czerniak^{352,603}, Ludmila Danilova³²⁰, Ian J Davis⁶⁴⁸, Timothy Defreitas³, John A Demchok³⁹, Noreen Dhalla⁶²⁹, Rajiv Dhir⁶⁴⁹, Li Ding^{130,131,138}, HarshaVardhan Doddapaneni¹⁵⁵, Adel El-Naggar^{352,603}, Ina Felau³⁹, Martin L Ferguson⁶⁵⁰, Gaetano

Finocchiaro⁶⁵¹, Kwun M Fong⁶⁵², Scott Frazer³, William Friedman⁶⁵³, Catrina C Fronick^{131,609},
 Lucinda A Fulton¹³¹, Robert S Fulton^{130,131,138}, Stacey B Gabriel³, Jianjiong Gao⁶³⁰, Nils
 Gehlenborg^{3,654}, Jeffrey E Gershenwald^{655,656}, Gad Getz^{3,4,5,6}, Ronald Ghossein⁴⁸¹, Nasra H
 Giamia⁶⁵⁷, Richard A Gibbs¹⁵⁵, Carmen Gomez⁶⁵⁸, James Gossage⁵⁹⁸, Ramaswamy Govindan¹³⁰,
 Nicola Grehan³¹⁰, George B Hanna⁵⁹⁹, D Neil Hayes^{234,659,660}, Stephen J Hayes^{600,601}, Apurva M
 Hegde^{375,376}, David I Heiman³, Zachary Heins¹⁸⁷, Austin J Hepperla²³⁴, Katherine A Hoadley^{233,234},
 Andrea Holbrook⁶³⁸, Robert A Holt⁶²⁹, Alan P Hoyle²³⁴, Ralph H Hruban³²⁰, Jianhong Hu¹⁵⁵, Mei
 Huang⁶⁰⁸, David Huntsman⁶⁶¹, Ted R Hupp⁶⁰², Jason Huse¹⁸⁷, **Carolyn M Hutter**^{#23}, Christine A
 Iacobuzio-Donahue⁴⁸¹, Michael Ittmann^{662,663,664}, Joy C Jayaseelan¹⁵⁵, Stuart R Jefferys²³⁴, Corbin
 D Jones⁶⁶⁵, Steven JM Jones⁶²⁹, Hartmut Juhl⁶⁶⁶, Koo Jeong Kang⁶⁶⁷, Beth Karlan⁶⁶⁸, Katayoon
 Kasaian⁶²⁹, Electron Kebebew^{669,670}, David Khoo⁶⁰³, Hark Kyun Kim⁶⁷¹, Jaegil Kim³, Tari A
 King^{487,488,489}, Viktoriya Korchina¹⁵⁵, Ritika Kundra^{595,630}, Jesper Lagergren^{593,604}, Phillip H Lai⁶³⁸,
 Peter W Laird²⁶⁵, Eric Lander³, Michael S Lawrence^{3,46,100}, Alexander J Lazar^{158,352}, Xuan Le⁶⁷²,
 Darlene Lee⁶⁷³, Douglas A Levine^{187,674}, Lora Lewis¹⁵⁵, Tim Ley⁶⁷⁵, Haiyan Irene Li⁶⁷³, Pei Lin³, W M
 Linehan⁶⁷⁶, Eric Minwei Liu^{110,111,187}, Fei Fei Liu³⁶⁸, Laurence B Lovat²³⁷, Yiling Lu³⁷⁶, Lisa Lype⁶⁷⁷,
 Yussanne Ma⁶⁷³, Shona MacRae³⁷⁵, Dennis T Maglinte^{638,678}, Elaine R Mardis^{131,641,679}, Jeffrey
 Marks^{396,680}, Marco A Marra⁶⁷³, Thomas J Matthew¹¹, Michael Mayo⁶⁷³, Karen McCune⁶⁸¹,
 Michael D McLellan^{130,131,138}, Samuel R Meier³, Shaowu Meng²³⁴, Matthew Meyerson^{3,6,48}, Piotr A
 Mieczkowski²³³, Tom Mikkelsen⁶⁸², Christopher A Miller¹³¹, Gordon B Mills⁶⁸³, Richard A
 Moore⁶⁷³, Carl Morrison^{394,684}, Lisle E Mose²³⁴, Catherine D Moser⁶⁵⁷, Andrew J Mungall⁶⁷³, Karen
 Mungall⁶⁷³, David Mutch⁶⁸⁵, Donna M Muzny¹⁵⁵, Jerome Myers⁶⁸⁶, Yulia Newton¹¹, Michael S
 Noble³, Peter O'Donnell⁶⁸⁷, Brian Patrick O'Neill⁶⁸⁸, Angelica Ochoa¹⁸⁷, Akinyemi I Ojesina^{240,241,242},
 Joong-Won Park⁶⁸⁹, Joel S Parker⁶⁹⁰, Simon L Parsons⁶⁰⁶, Harvey Pass⁶⁹¹, Alessandro Pastore⁸⁵,
 Chandra Sekhar Pedamallu^{3,6,163}, Nathan A Pennell⁶⁹², Charles M Perou^{234,690,693}, Gloria M
 Petersen⁴³⁸, Nicholas Petrelli⁶⁹⁴, Olga Potapova⁶⁹⁵, Shaun R Preston⁶⁰⁷, Sonia Puig⁶⁰⁸, Janet S
 Rader⁶⁹⁶, Suresh Ramalingam⁶⁹⁷, W Kimryn Rathmell⁶⁹⁸, Victor Reuter⁴⁸¹, Sheila M Reynolds⁶⁷⁷,
 Matthew Ringel⁶⁹⁹, Jeffrey Roach⁷⁰⁰, Lewis R Roberts⁶⁵⁷, A Gordon Robertson⁶⁷³, Tom Roques⁶⁰⁹,
 Mark A Rubin^{183,197,198,199,200}, Sara Sadeghi⁶⁷³, Gordon Saksena³, Charles Saller⁷⁰¹, Francisco
 Sanchez-Vega^{595,630}, Chris Sander^{85,202,203}, Grant Sanders²³⁴, Dirk Schadendorf^{77,702}, Jacqueline E
 Schein⁶⁷³, Heather K Schmidt¹³¹, Nikolaus Schultz⁶³⁰, Steven E Schumacher^{3,204}, Richard A
 Scolyer^{409,413,419}, Raja Seethala⁷⁰³, Yasin Senbabaoglu⁸⁵, Troy Shelton⁶⁴⁷, Yan Shi²³⁴, Juliann
 Shih^{3,163}, Ilya Shmulevich⁶⁷⁷, Craig Shriver⁷⁰⁴, Sabina Signoretti^{163,168,705}, Janae V Simons²³⁴, Samuel
 Singer^{396,706}, Payal Sipahimalani⁶⁷³, Tara J Skelly²³³, Karen Smith-McCune⁶⁸¹, Nicholas D Socci⁸⁵,
 Heidi J Sofia²³, Matthew G Soloway⁶⁹⁰, Anil K Sood^{707,708,709}, Sharmila Sothi⁶¹⁰, Angela Tam⁶⁷³,
 Donghui Tan²³³, Roy Tarnuzzer³⁹, Nina Thiessen⁶⁷³, R Houston Thompson⁷¹⁰, Leigh B Thorne⁶⁰⁸,
 Ming Tsao^{437,606}, Olga Tucker⁶¹¹, Richard Turkington⁶¹², Christopher Umbricht^{274,597,711}, Timothy J
 Underwood⁶¹³, David J Van Den Berg⁶³⁸, Erwin G Van Meir⁷¹², Umadevi Veluvolu²³³, Douglas
 Voet³, Jiayin Wang^{131,145,152}, Linghua Wang¹⁵⁵, Zhining Wang³⁹, Paul Weinberger⁷¹³, John N
 Weinstein^{375,376}, Daniel J Weisenberger⁶³⁸, Ian Welch⁶¹⁴, David A Wheeler^{154,155}, Dennis Wigle⁷¹⁴,
 Matthew D Wilkerson²³³, Richard K Wilson^{131,715}, Boris Winterhoff⁷¹⁶, Maciej Wiznerowicz^{717,718},
 Tina Wong^{131,673}, Winghing Wong⁷¹⁹, Liu Xi¹⁵⁵, Liming Yang³⁹, Christina Yau⁶³⁶, Venkata D
 Yellapantula^{138,157}, **Jean C Zenklusen**^{#39}, Hailei Zhang³, Hongxin Zhang⁶³⁰ and Jiashan Zhang³⁹

Denotes **working group or project co-leader**

Author Affiliations

1. Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton CB10 1SA, UK.
2. Department of Haematology, University of Cambridge, Cambridge CB2 2XY, UK.
3. Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA.
4. Center for Cancer Research, Massachusetts General Hospital, Boston, MA 02129, USA.
5. Department of Pathology, Massachusetts General Hospital, Boston, MA 02115, USA.
6. Harvard Medical School, Boston, MA 02115, USA.
7. European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Cambridge CB10 1SD, UK.
8. Genome Biology Unit, European Molecular Biology Laboratory (EMBL), Heidelberg 69117, Germany.
9. Computational Biology Program, Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada.
10. Department of Molecular Genetics, University of Toronto, Toronto, ON M5S 1A8, Canada.
11. Department of Biomolecular Engineering, University of California Santa Cruz, Santa Cruz, CA 95064, USA.
12. UC Santa Cruz Genomics Institute, University of California Santa Cruz, Santa Cruz, CA 95064, USA.
13. International Cancer Genome Consortium (ICGC)/ICGC Accelerating Research in Genomic Oncology (ARGO) Secretariat, Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada.
14. King Faisal Specialist Hospital and Research Centre, Al Maather, Riyadh 12713, Saudi Arabia.
15. DLR Project Management Agency, Bonn 53227, Germany.
16. Genome Canada, Ottawa, ON K2P 1P1, Canada.
17. Instituto Carlos Slim de la Salud, Mexico City, Mexico.
18. Federal Ministry of Education and Research, Berlin 10117, Germany.
19. Institut Gustave Roussy, Villejuif 94805, France.
20. Institut National du Cancer (INCA), Boulogne-Billancourt 92100, France.
21. The Wellcome Trust, London NW1 2BE, UK.
22. Prostate Cancer Canada, Toronto, ON M5C 1M1, Canada.
23. National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892, USA.
24. Department of Biotechnology, Ministry of Science and Technology, Government of India, New Delhi, Delhi 110003, India.
25. Science Writer, Garrett Park, MD 20896, USA.
26. Cancer Research UK, London EC1V 4AD, UK.
27. Department of Biochemistry, College of Medicine, Ewha Womans University, Seoul 07895, South Korea.
28. Chinese Cancer Genome Consortium, Shenzhen 518083, China.
29. Department of Medical Oncology, Beijing Hospital, Beijing 100730, China.
30. Laboratory of Molecular Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital and Institute, Beijing 100142, China.
31. National Cancer Center, Tokyo 104-0045, Japan.

- 32.** German Cancer Aid, Bonn 53113, Germany.
- 33.** Division of Cancer Genomics, National Cancer Center Research Institute, National Cancer Center, Tokyo 104-0045, Japan.
- 34.** Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, University of Tokyo, Tokyo 108-8639, Japan.
- 35.** Japan Agency for Medical Research and Development, Tokyo 100-0004, Japan.
- 36.** Medical Oncology, University and Hospital Trust of Verona, Verona 37134, Italy.
- 37.** University of Verona, Verona 37129, Italy.
- 38.** BGI-Shenzhen, Shenzhen 518083, China.
- 39.** National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
- 40.** Centre for Law and Genetics, University of Tasmania, Sandy Bay Campus, Hobart, TAS 7001, Australia.
- 41.** Centre of Genomics and Policy, McGill University and Génome Québec Innovation Centre, Montreal, QC H3A 1A4, Canada.
- 42.** Heidelberg Academy of Sciences and Humanities, Heidelberg 69120, Germany.
- 43.** CAPHRI Research School, Maastricht University, Maastricht, ER 6200MD, The Netherlands.
- 44.** Genome Informatics Program, Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada.
- 45.** Barcelona Supercomputing Center (BSC), Barcelona 08034, Spain.
- 46.** Laboratory for Medical Science Mathematics, RIKEN Center for Integrative Medical Sciences, Yokohama 230-0045, Japan.
- 47.** RIKEN Center for Integrative Medical Sciences, Yokohama 230-0045, Japan.
- 48.** Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA.
- 49.** Biomedical Engineering, Oregon Health and Science University, Portland, OR 97239, USA.
- 50.** Division of Theoretical Bioinformatics, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.
- 51.** Heidelberg Center for Personalized Oncology (DKFZ-HIPO), German Cancer Research Center, Heidelberg 69120, Germany.
- 52.** Institute of Pharmacy and Molecular Biotechnology and BioQuant, Heidelberg University, Heidelberg 69120, Germany.
- 53.** University of California San Diego, San Diego, CA 92093, USA.
- 54.** PDXen Biosystems Inc, Seoul 4900, South Korea.
- 55.** Electronics and Telecommunications Research Institute, Daejeon 34129, South Korea.
- 56.** Seven Bridges Genomics, Charlestown, MA 02129, USA.
- 57.** Annai Systems, Inc, Carlsbad, CA 92013, USA.
- 58.** Department of Biomedical Data Science, Stanford University School of Medicine, Stanford, CA 94305, USA.
- 59.** Department of Genetics, Stanford University School of Medicine, Stanford, CA 94305, USA.
- 60.** The Francis Crick Institute, London NW1 1AT, UK.
- 61.** University of Leuven, Leuven B-3000, Belgium.
- 62.** The Hospital for Sick Children, Toronto, ON M5G 0A4, Canada.
- 63.** Heidelberg University, Heidelberg 69120, Germany.
- 64.** New BIH Digital Health Center, Berlin Institute of Health (BIH) and Charité - Universitätsmedizin Berlin, Berlin 10117, Germany.
- 65.** Department of Biochemistry and Molecular Medicine, University of Montreal, Montreal, QC

H3C 3J7, Canada.

66. CIBIO/InBIO - Research Center in Biodiversity and Genetic Resources, Universidade do Porto, Vairão 4485-601, Portugal.

67. Department Biochemistry and Molecular Biomedicine, University of Barcelona, Barcelona 08028, Spain.

68. Department of Medicine, Section of Hematology/Oncology, University of Chicago, Chicago, IL 60637, USA.

69. Department of Medicine, Division of Biomedical Informatics, UC San Diego School of Medicine, San Diego, CA 92093, USA.

70. UC San Diego Moores Cancer Center, San Diego, CA 92093, USA.

71. Children's Hospital of Philadelphia, Philadelphia, PA 19146, USA.

72. Massachusetts General Hospital Center for Cancer Research, Charlestown, MA 02129, USA.

73. University of Melbourne Centre for Cancer Research, Melbourne, VIC 3010, Australia.

74. Syntekabio Inc, Daejeon 34025, South Korea.

75. AbbVie, North Chicago, IL 60064, USA.

76. Genomics Research Program, Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada.

77. German Cancer Consortium (DKTK), Heidelberg 69120, Germany.

78. Heidelberg Center for Personalized Oncology (DKFZ-HIPO), German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.

79. National Center for Tumor Diseases (NCT) Heidelberg, Heidelberg 69120, Germany.

80. Department of Pediatric Immunology, Hematology and Oncology, University Hospital, Heidelberg 69120, Germany.

81. German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.

82. Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM), Heidelberg 69120, Germany.

83. Institute of Medical Science, University of Tokyo, Tokyo 108-8639, Japan.

84. Genome Integration Data Center, Syntekabio, Inc, Daejeon, 34025, South Korea.

85. Computational Biology Center, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA.

86. Department of Biology, ETH Zurich, Zürich 8093, Switzerland.

87. Department of Computer Science, ETH Zurich, Zurich 8092, Switzerland.

88. SIB Swiss Institute of Bioinformatics, Lausanne 1015, Switzerland.

89. University Hospital Zurich, Zurich 8091, Switzerland.

90. Health Sciences Department of Biomedical Informatics, University of California San Diego, La Jolla, CA 92093, USA.

91. Department of Health Sciences and Technology, Sungkyunkwan University School of Medicine, Seoul 06351, South Korea.

92. Samsung Genome Institute, Seoul 06351, South Korea.

93. Functional and Structural Genomics, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.

94. Leidos Biomedical Research, Inc, McLean, VA 22102, USA.

95. Center for Biomolecular Science and Engineering, University of California Santa Cruz, Santa Cruz, CA 95064, USA.

96. Sage Bionetworks, Seattle, WA 98109, USA.

- 97.** Department of Cell and Systems Biology, University of Toronto, Toronto, ON M5S 3G5, Canada.
- 98.** Department of Radiation Oncology, University of California San Francisco, San Francisco, CA 94518, USA.
- 99.** CSRA Incorporated, Fairfax, VA 22042, USA.
- 100.** Massachusetts General Hospital, Boston, MA 02114, USA.
- 101.** Weill Cornell Medical College, New York, NY 10065, USA.
- 102.** Bioinformatics and Omics Data Analytics, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.
- 103.** Institute for Genomics and Systems Biology, University of Chicago, Chicago, IL 60637, USA.
- 104.** Computational Biology Program, School of Medicine, Oregon Health and Science University, Portland, OR 97239, USA.
- 105.** Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona 08010, Spain.
- 106.** Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim 7030, Norway.
- 107.** Department of Urology, Charité Universitätsmedizin Berlin, Berlin 10117, Germany.
- 108.** Finsen Laboratory and Biotech Research and Innovation Centre (BRIC), University of Copenhagen, Copenhagen 2200, Denmark.
- 109.** Department of Biological Oceanography, Leibniz Institute of Baltic Sea Research, Rostock 18119, Germany.
- 110.** Department of Physiology and Biophysics, Weill Cornell Medicine, New York, NY 10065, USA.
- 111.** Institute for Computational Biomedicine, Weill Cornell Medicine, New York, NY 10021, USA.
- 112.** Division of Applied Bioinformatics, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.
- 113.** Department of Computer Science, Yale University, New Haven, CT 06520, USA.
- 114.** Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, CT 06520, USA.
- 115.** Program in Computational Biology and Bioinformatics, Yale University, New Haven, CT 06520, USA.
- 116.** Department of Internal Medicine, Stanford University, Stanford, CA 94305, USA.
- 117.** Department of Molecular Medicine (MOMA), Aarhus University Hospital, Aarhus N 8200, Denmark.
- 118.** Clinical Bioinformatics, Swiss Institute of Bioinformatics, Geneva 1202, Switzerland.
- 119.** Institute for Pathology and Molecular Pathology, University Hospital Zurich, Zurich 8091, Switzerland.
- 120.** Institute of Molecular Life Sciences, University of Zurich, Zurich 8057, Switzerland.
- 121.** MIT Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology, Cambridge, MA 02139, USA.
- 122.** Controlled Department and Institution, New York, NY 10065, USA.
- 123.** Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, NY 10065, USA.
- 124.** Bioinformatics Research Centre (BiRC), Aarhus University, Aarhus 8000, Denmark.
- 125.** Department of Medical Biophysics, University of Toronto, Toronto, ON M5S 1A8, Canada.

- 126.** Institute of Molecular Life Sciences and Swiss Institute of Bioinformatics, University of Zurich, Zurich 8057, Switzerland.
- 127.** CNAG-CRG, Centre for Genomic Regulation (CRG), Barcelona Institute of Science and Technology (BIST), Barcelona 08028, Spain.
- 128.** Universitat Pompeu Fabra (UPF), Barcelona 08003, Spain.
- 129.** Office of Cancer Genomics, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
- 130.** Alvin J. Siteman Cancer Center, Washington University School of Medicine, St Louis, MO 63110, USA.
- 131.** The McDonnell Genome Institute at Washington University, St Louis, MO 63108, USA.
- 132.** Computer Network Information Center, Chinese Academy of Sciences, Beijing 100190, China.
- 133.** Center for Digital Health, Berlin Institute of Health and Charité - Universitätsmedizin Berlin, Berlin 10117, Germany.
- 134.** Department of Human Genetics, University of California Los Angeles, Los Angeles, CA 90095, USA.
- 135.** Department of Pharmacology, University of Toronto, Toronto, ON M5S 1A8, Canada.
- 136.** University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
- 137.** Department of Genetics, Informatics Institute, University of Alabama at Birmingham, Birmingham, AL 35294, USA.
- 138.** Department of Medicine and Department of Genetics, Washington University School of Medicine, St. Louis, St Louis, MO 63110, USA.
- 139.** Centre for Genomic Regulation (CRG), The Barcelona Institute of Science and Technology, Barcelona 08003, Spain.
- 140.** Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
- 141.** Department of Urologic Sciences, University of British Columbia, Vancouver, BC V5Z 1M9, Canada.
- 142.** Vancouver Prostate Centre, Vancouver, BC V6H 3Z6, Canada.
- 143.** Division of Life Science and Applied Genomics Center, Hong Kong University of Science and Technology, Clear Water Bay, Hong Kong, China.
- 144.** Geneplus-Shenzhen, Shenzhen 518122, China.
- 145.** School of Computer Science and Technology, Xi'an Jiaotong University, Xi'an 710048, China.
- 146.** Biobyte solutions GmbH, Heidelberg 69126, Germany.
- 147.** Division of Oncology, Washington University School of Medicine, St Louis, MO 63110, USA.
- 148.** Institute of Medical Genetics and Applied Genomics, University of Tübingen, Tübingen 72076, Germany.
- 149.** Indiana University, Bloomington, IN 47405, USA.
- 150.** Simon Fraser University, Burnaby, BC V5A 1S6, Canada.
- 151.** Department of Computer Science, University of Toronto, Toronto, ON M5S 1A8, Canada.
- 152.** School of Electronic and Information Engineering, Xi'an Jiaotong University, Xi'an 710048, China.
- 153.** Department of Genetics, Washington University School of Medicine, St Louis, MO 63110, USA.

- 154.** Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA.
- 155.** Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX 77030, USA.
- 156.** The First Affiliated Hospital, Xi'an Jiaotong University, Xi'an 710048, China.
- 157.** Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA.
- 158.** Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
- 159.** Quantitative and Computational Biosciences Graduate Program, Baylor College of Medicine, Houston, TX 77030, USA.
- 160.** The Jackson Laboratory for Genomic Medicine, Farmington, CT 06032, USA.
- 161.** Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA 02215, USA.
- 162.** Department of Pediatrics, Harvard Medical School, Boston, MA 02115, USA.
- 163.** Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02115, USA.
- 164.** Department of Mathematics, Aarhus University, Aarhus 8000, Denmark.
- 165.** Center for Biological Sequence Analysis, Department of Bio and Health Informatics, Technical University of Denmark, Lyngby 2800, Denmark.
- 166.** Novo Nordisk Foundation Center for Protein Research, University of Copenhagen, Copenhagen 2200, Denmark.
- 167.** Department for BioMedical Research, University of Bern, Bern 3008, Switzerland.
- 168.** Department of Medical Oncology, Inselspital, University Hospital and University of Bern, Bern 3010, Switzerland.
- 169.** Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern 3012, Switzerland.
- 170.** Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.
- 171.** Faculty of Biosciences, Heidelberg University, Heidelberg 69120, Germany.
- 172.** Korea Advanced Institute of Science and Technology, Daejeon 34141, South Korea.
- 173.** Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, Barcelona 8003, Spain.
- 174.** Research Program on Biomedical Informatics, Universitat Pompeu Fabra, Barcelona 08002, Spain.
- 175.** Department of Cell and Molecular Biology, Science for Life Laboratory, Uppsala University, Uppsala SE-75124, Sweden.
- 176.** Queensland Centre for Medical Genomics, Institute for Molecular Bioscience, University of Queensland, St Lucia, Brisbane, QLD 4072, Australia.
- 177.** University of Milano Bicocca, Monza 20052, Italy.
- 178.** Sir Peter MacCallum Department of Oncology, Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, VIC 3000, Australia.
- 179.** Center for Precision Health, School of Biomedical Informatics, The University of Texas Health Science Center, Houston, TX 77030, USA.
- 180.** The Donnelly Centre, University of Toronto, Toronto, ON M5S 3E1, Canada.
- 181.** Health Data Science Unit, University Clinics, Heidelberg 69120, Germany.
- 182.** Technical University of Denmark, Lyngby 2800, Denmark.

- 183.** Department for Biomedical Research, University of Bern, Bern 3008, Switzerland.
- 184.** Research Core Center, National Cancer Centre Korea, Goyang-si 410-769, South Korea.
- 185.** Institute of Computer Science, Polish Academy of Sciences, Warsaw 01-248, Poland.
- 186.** Harvard University, Cambridge, MA 02138, USA.
- 187.** Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA.
- 188.** Department of Information Technology, Ghent University, Ghent B-9000, Belgium.
- 189.** Department of Plant Biotechnology and Bioinformatics, Ghent University, Ghent B-9000, Belgium.
- 190.** Yale School of Medicine, Yale University, New Haven, CT 06520, USA.
- 191.** Institute for Research in Biomedicine (IRB Barcelona), Barcelona 08028, Spain.
- 192.** Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 06351, South Korea.
- 193.** Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University School of Medicine, Seoul 06351, South Korea.
- 194.** Cheonan Industry-Academic Collaboration Foundation, Sangmyung University, Cheonan 31066, South Korea.
- 195.** Spanish National Cancer Research Centre, Madrid 28029, Spain.
- 196.** Department of Computer Science, Princeton University, Princeton, NJ 08540, USA.
- 197.** Bern Center for Precision Medicine, University Hospital of Bern, University of Bern, Bern 3008, Switzerland.
- 198.** Englander Institute for Precision Medicine, Weill Cornell Medicine and New York Presbyterian Hospital, New York, NY 10021, USA.
- 199.** Meyer Cancer Center, Weill Cornell Medicine, New York, NY 10065, USA.
- 200.** Pathology and Laboratory, Weill Cornell Medical College, New York, NY 10021, USA.
- 201.** Vall d'Hebron Institute of Oncology: VHIO, Barcelona 08035, Spain.
- 202.** cBio Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, USA.
- 203.** Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA.
- 204.** Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, MA 02215, USA.
- 205.** Dana-Farber Cancer Institute, Boston, MA 02215, USA.
- 206.** cBio Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02215, USA.
- 207.** Core Research for Evolutional Science and Technology (CREST), JST, Tokyo 102-8666, Japan.
- 208.** Department of Biological Sciences, Laboratory for Medical Science Mathematics, Graduate School of Science, University of Tokyo, Yokohama 230-0045, Japan.
- 209.** Department of Medical Science Mathematics, Medical Research Institute, Tokyo Medical and Dental University (TMDU), Tokyo 113-8510, Japan.
- 210.** Department of Oncology-Pathology, Science for Life Laboratory, Karolinska Institutet, Stockholm 17121, Sweden.
- 211.** Department of Gene Technology, Tallinn University of Technology, Tallinn 12616, Estonia.
- 212.** Genetics and Genome Biology Program, SickKids Research Institute, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada.
- 213.** Department of Information Technology, Ghent University, Interuniversitair Micro-Electronica Centrum (IMEC), Ghent B-9000, Belgium.

- 214.** Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Uppsala University, Uppsala SE-75108, Sweden.
- 215.** Department of Medical Informatics and Clinical Epidemiology, Division of Bioinformatics and Computational Biology, OHSU Knight Cancer Institute, Oregon Health and Science University, Portland, OR 97239, USA.
- 216.** Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Shatin, NT, Hong Kong, China.
- 217.** The University of Texas Health Science Center at Houston, Houston, TX 77030, USA.
- 218.** Department of Biomedical Informatics, College of Medicine, The Ohio State University, Columbus, OH 43210, USA.
- 219.** The Ohio State University Comprehensive Cancer Center (OSUCCC – James), Columbus, OH 43210, USA.
- 220.** The University of Texas School of Biomedical Informatics (SBMI) at Houston, Houston, TX 77030, USA.
- 221.** Department of Biochemistry and Molecular Genetics, Feinberg School of Medicine, Northwestern University, Chicago, IL 60637, USA.
- 222.** Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow, Glasgow G61 1BD, UK.
- 223.** Department of Biomedical Informatics, Harvard Medical School, Boston, MA 02115, USA.
- 224.** Department of Chemistry, Centre for Molecular Science Informatics, University of Cambridge, Cambridge CB2 1EW, UK.
- 225.** Ludwig Center at Harvard Medical School, Boston, MA 02115, USA.
- 226.** Physics Division, Optimization and Systems Biology Lab, Massachusetts General Hospital, Boston, MA 02114, USA.
- 227.** Department of Medicine, Baylor College of Medicine, Houston, TX 77030, USA.
- 228.** Computational and Systems Biology, Genome Institute of Singapore, Singapore 138672, Singapore.
- 229.** School of Computing, National University of Singapore, Singapore 117417, Singapore.
- 230.** The Azrieli Faculty of Medicine, Bar-Ilan University, Safed 13195, Israel.
- 231.** National Cancer Centre Singapore, Singapore 169610, Singapore.
- 232.** Peking University, Beijing 100871, China.
- 233.** Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA.
- 234.** Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA.
- 235.** China National GeneBank-Shenzhen, Shenzhen 518083, China.
- 236.** Berlin Institute for Medical Systems Biology, Max Delbrück Center for Molecular Medicine, Berlin 13125, Germany.
- 237.** University College London, London WC1E 6BT, UK.
- 238.** School of Life Sciences, Peking University, Beijing 100180, China.
- 239.** Genome Institute of Singapore, Singapore 138672, Singapore.
- 240.** Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL 35294, USA.
- 241.** HudsonAlpha Institute for Biotechnology, Huntsville, AL 35806, USA.
- 242.** O'Neal Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham,

AL 35294, USA.

243. Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm 14183, Sweden.

244. German Cancer Consortium (DKTK), Partner site Berlin.

245. Human Genetics, University of Kiel, Kiel 24118, Germany.

246. Institute of Human Genetics, Ulm University and Ulm University Medical Center, Ulm 89081, Germany.

247. Computational and Systems Biology Program, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA.

248. Korea University, Seoul 02481, South Korea.

249. Division of Computational Genomics and Systems Genetics, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.

250. Cancer Science Institute of Singapore, National University of Singapore, Singapore 169609, Singapore.

251. Programme in Cancer and Stem Cell Biology, Duke-NUS Medical School, Singapore 169857, Singapore.

252. SingHealth, Duke-NUS Institute of Precision Medicine, National Heart Centre Singapore, Singapore 169609, Singapore.

253. Institute of Molecular and Cell Biology, Singapore 169609, Singapore.

254. Laboratory of Cancer Epigenome, Division of Medical Science, National Cancer Centre Singapore, Singapore 169610, Singapore.

255. BIOPIC, ICG and College of Life Sciences, Peking University, Beijing 100871, China.

256. Genome Science Division, Research Center for Advanced Science and Technology, University of Tokyo, Tokyo 153-8904, Japan.

257. Center for Bioinformatics and Functional Genomics, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA.

258. Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA.

259. The Hebrew University Faculty of Medicine, Jerusalem 91120, Israel.

260. Department of Computer Science, Bioinformatics Group, University of Leipzig, Leipzig 04109, Germany.

261. Interdisciplinary Center for Bioinformatics, University of Leipzig, Leipzig 04109, Germany.

262. German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.

263. Computational Biology, Leibniz Institute on Aging - Fritz Lipmann Institute (FLI), Jena 07745, Germany.

264. Transcriptome Bioinformatics, LIFE Research Center for Civilization Diseases, University of Leipzig, Leipzig 04109, Germany.

265. Center for Epigenetics, Van Andel Research Institute, Grand Rapids, MI 49503, USA.

266. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona 08036, Spain.

267. Research Center for Advanced Science and Technology, University of Tokyo, Tokyo 108-8639, Japan.

268. Cancer Epigenomics, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.

269. Van Andel Research Institute, Grand Rapids, MI 49503, USA.

270. Centre for Research in Molecular Medicine and Chronic Diseases (CiMUS), Universidade de Santiago de Compostela, Santiago de Compostela 15706, Spain.

- 271.** Department of Zoology, Genetics and Physical Anthropology, (CiMUS), Universidade de Santiago de Compostela, Santiago de Compostela 15706, Spain.
- 272.** The Biomedical Research Centre (CINBIO), Universidade de Vigo, Vigo 36310, Spain.
- 273.** Department of Veterinary Medicine, Transmissible Cancer Group, University of Cambridge, Cambridge CB3 0ES, UK.
- 274.** Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.
- 275.** McKusick-Nathans Institute of Genetic Medicine, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA.
- 276.** Foundation Medicine, Inc, Cambridge, MA 02141, USA.
- 277.** Department of Biochemistry, Microbiology and Immunology, Faculty of Medicine, University of Ottawa, Ottawa, ON K1H 8M5, Canada.
- 278.** Li Ka Shing Centre, Cancer Research UK Cambridge Institute, University of Cambridge, Cambridge CB2 0RE, UK.
- 279.** University of Cambridge, Cambridge CB2 1TN, UK.
- 280.** Quantitative Genomics Laboratories (qGenomics), Barcelona 08950, Spain.
- 281.** Genome Integrity and Structural Biology Laboratory, National Institute of Environmental Health Sciences (NIEHS), Durham, NC 27709, USA.
- 282.** Brandeis University, Waltham, MA 02254, USA.
- 283.** Institute for Computational Biomedicine, Weill Cornell Medical College, New York, NY 10065, USA.
- 284.** New York Genome Center, New York, NY 10013, USA.
- 285.** Hopp Children's Cancer Center (KiTZ), Heidelberg 69120, Germany.
- 286.** Pediatric Glioma Research Group, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.
- 287.** A.A. Kharkevich Institute of Information Transmission Problems, Moscow 127051, Russia.
- 288.** Oncology and Immunology, Dmitry Rogachev National Research Center of Pediatric Hematology, Moscow 117997, Russia.
- 289.** Skolkovo Institute of Science and Technology, Moscow 121205, Russia.
- 290.** Integrative Bioinformatics Support Group, National Institute of Environmental Health Sciences (NIEHS), Durham, NC 27709, USA.
- 291.** Center For Medical Innovation, Seoul National University Hospital, Seoul 03080, South Korea.
- 292.** Department of Internal Medicine, Seoul National University Hospital, Seoul 03080, South Korea.
- 293.** Division of Genetics and Genomics, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA.
- 294.** School of Medicine/School of Mathematics and Statistics, University of St Andrews, St Andrews, Fife KY16 9SS, UK.
- 295.** Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD 4006, Australia.
- 296.** Institute for Molecular Bioscience, University of Queensland, St Lucia, Brisbane, QLD 4072, Australia.
- 297.** School of Molecular Biosciences and Center for Reproductive Biology, Washington State University, Pullman, WA 99164, USA.

- 298.** Cancer Research Institute, Beth Israel Deaconess Medical Center, Boston, MA 02215, USA.
- 299.** Ben May Department for Cancer Research and Department of Human Genetics, University of Chicago, Chicago, IL 60637, USA.
- 300.** Tri-Institutional PhD Program in Computational Biology and Medicine, Weill Cornell Medicine, New York, NY 10065, USA.
- 301.** Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA 02215, USA.
- 302.** Department of Cellular and Molecular Medicine and Department of Bioengineering, University of California San Diego, La Jolla, CA 92093, USA.
- 303.** Department of Cellular and Molecular Medicine and Department of Bioengineering, University of California, San Diego, La Jolla, CA 92093, USA.
- 304.** Centre for Computational Biology, Duke-NUS Medical School, Singapore 169857, Singapore.
- 305.** Department of Computer Science, University of Helsinki, Helsinki 00014, Finland.
- 306.** Institute of Biotechnology, University of Helsinki, Helsinki 00014, Finland.
- 307.** Organismal and Evolutionary Biology Research Programme, University of Helsinki, Helsinki 00014, Finland.
- 308.** Programme in Cancer and Stem Cell Biology, Centre for Computational Biology, Duke-NUS Medical School, Singapore 169857, Singapore.
- 309.** Academic Department of Medical Genetics, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK.
- 310.** MRC Cancer Unit, University of Cambridge, Cambridge CB2 0XZ, UK.
- 311.** The University of Cambridge School of Clinical Medicine, Cambridge CB2 0SP, UK.
- 312.** National Centre for Biological Sciences, Tata Institute of Fundamental Research, Bangalore 560065, India.
- 313.** Department of Applied Mathematics and Theoretical Physics, Centre for Mathematical Sciences, University of Cambridge, Cambridge CB3 0WA, UK.
- 314.** Department of Statistics, Columbia University, New York, NY 10027, USA.
- 315.** Duke-NUS Medical School, Singapore 169857, Singapore.
- 316.** Faculty of Medicine and Health Technology, Tampere University and Tays Cancer Center, Tampere University Hospital, Tampere FI-33014, Finland.
- 317.** Bakar Computational Health Sciences Institute and Department of Pediatrics, University of California, San Francisco, CA 94158-2549, USA.
- 318.** Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
- 319.** Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD 21205, USA.
- 320.** Department of Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA.
- 321.** Integrated Graduate Program in Physical and Engineering Biology, Yale University, New Haven, CT 06520, USA.
- 322.** Department of Computational Biology, University of Lausanne, Lausanne 1015, Switzerland.
- 323.** Department of Genetic Medicine and Development, University of Geneva Medical School, Geneva CH 1211, Switzerland.

- 324.** Swiss Institute of Bioinformatics, University of Geneva, Geneva CH 1211, Switzerland.
- 325.** Independent Consultant, Wellesley 02481, USA.
- 326.** Department of Oncology, Centre for Cancer Genetic Epidemiology, University of Cambridge, Cambridge CB1 8RN, UK.
- 327.** Department of Public Health and Primary Care, Centre for Cancer Genetic Epidemiology, University of Cambridge, Cambridge CB1 8RN, UK.
- 328.** CIBER Epidemiología y Salud Pública (CIBERESP), Madrid 28029, Spain.
- 329.** Research Group on Statistics, Econometrics and Health (GRECS), UdG, Barcelona 8041, Spain.
- 330.** Oxford Nanopore Technologies, New York, NY 10013, USA.
- 331.** Department of Medical Genetics, College of Medicine, Hallym University, Chuncheon 24252, South Korea.
- 332.** Department of Experimental and Health Sciences, Institute of Evolutionary Biology (UPF-CSIC), Universitat Pompeu Fabra, Barcelona 08003, Spain.
- 333.** Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.
- 334.** Laboratory of Translational Genomics, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
- 335.** Institut Català de Paleontologia Miquel Crusafont, Universitat Autònoma de Barcelona, Barcelona 08193, Spain.
- 336.** Applications Department, Oxford Nanopore Technologies, Oxford OX4 4DQ, UK.
- 337.** Department of Genetics, Microbiology and Statistics, University of Barcelona, IRSJD, IBUB, Barcelona 08028, Spain.
- 338.** Department of Ophthalmology and Ocular Genomics Institute, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA 02114, USA.
- 339.** Department of Medical and Clinical Genetics, Genome-Scale Biology Research Program, University of Helsinki, Helsinki 00100, Finland.
- 340.** Big Data Institute, Li Ka Shing Centre, University of Oxford, Oxford OX3 7LF, UK.
- 341.** Oxford NIHR Biomedical Research Centre, University of Oxford, Oxford OX4 2PG, UK.
- 342.** School of Electronic Information and Communications, Huazhong University of Science and Technology, Wuhan 430074, China.
- 343.** Bioinformatics Unit, Spanish National Cancer Research Centre (CNIO), Madrid 28029, Spain.
- 344.** Vector Institute, Toronto, ON M5G 0A3, Canada.
- 345.** Cancer Division, Garvan Institute of Medical Research, Kinghorn Cancer Centre, University of New South Wales (UNSW Sydney), Sydney, NSW 2010, Australia.
- 346.** South Western Sydney Clinical School, Faculty of Medicine, University of New South Wales (UNSW Sydney), Liverpool, NSW 2170, Australia.
- 347.** West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, Glasgow G31 2ER, UK.
- 348.** Centre for Cancer Research, Victorian Comprehensive Cancer Centre, University of Melbourne, Melbourne, VIC 3010, Australia.
- 349.** MRC Human Genetics Unit, MRC IGMM, University of Edinburgh, Edinburgh EH4 2XU, UK.
- 350.** Department of Biology, Bioinformatics Group, Division of Molecular Biology, Faculty of Science, University of Zagreb, Zagreb 10000, Croatia.
- 351.** Department of Bioinformatics, Division of Cancer Genomics, National Cancer Center Research Institute, Tokyo 104-0045, Japan.

- 352.** Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
- 353.** University of Glasgow, Glasgow G61 1BD, UK.
- 354.** Oregon Health and Science University, Portland, OR 97239, USA.
- 355.** MRC-University of Glasgow Centre for Virus Research, Glasgow G61 1QH, UK.
- 356.** School of Computing Science, University of Glasgow, Glasgow G12 8RZ, UK.
- 357.** Molecular and Medical Genetics, OHSU Knight Cancer Institute, Oregon Health and Science University, Portland, OR 97239, USA.
- 358.** Department of Surgery, University of Melbourne, Parkville, VIC 3010, Australia.
- 359.** The Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, VIC 3052, Australia.
- 360.** Walter and Eliza Hall Institute, Parkville, VIC 3052, Australia.
- 361.** University of Cologne, Cologne 50931, Germany.
- 362.** The Edward S. Rogers Sr. Department of Electrical and Computer Engineering, University of Toronto, Toronto, ON M5S 3G4, Canada.
- 363.** University of Ljubljana, Ljubljana 1000, Slovenia.
- 364.** Department of Public Health Sciences, University of Chicago, Chicago, IL 60637, USA.
- 365.** Research Institute, NorthShore University HealthSystem, Evanston, IL 60201, USA.
- 366.** Department of Statistics, University of California Santa Cruz, Santa Cruz, CA 95064, USA.
- 367.** Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, UK.
- 368.** University of Toronto, Toronto, ON M5G 2M9, Canada.
- 369.** Department of Computer Science, Carleton College, Northfield, MN 55057, USA.
- 370.** Center for Psychiatric Genetics, NorthShore University HealthSystem, Evanston, IL 60201, USA.
- 371.** Argmix Consulting, North Vancouver, BC V7M 2J5, Canada.
- 372.** Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
- 373.** Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA.
- 374.** Howard Hughes Medical Institute, University of California Santa Cruz, Santa Cruz, CA 95064, USA.
- 375.** Cancer Unit, MRC University of Cambridge, Cambridge CB2 0XZ, UK.
- 376.** Department of Bioinformatics and Computational Biology and Department of Systems Biology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
- 377.** Department of Health Sciences, Faculty of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan.
- 378.** Department of Applied Mathematics and Statistics, Johns Hopkins University, Baltimore, MD 21218, USA.
- 379.** Bioinformatics Core Facility, University Medical Center Hamburg, Hamburg 20246, Germany.
- 380.** Heinrich Pette Institute, Leibniz Institute for Experimental Virology, Hamburg 20251, Germany.
- 381.** Earlham Institute, Norwich NR4 7UZ, UK.
- 382.** Norwich Medical School, University of East Anglia, Norwich NR4 7TJ, UK.
- 383.** The Institute of Cancer Research, London SW7 3RP, UK.

- 384.** University of East Anglia, Norwich NR4 7TJ, UK.
- 385.** German Center for Infection Research (DZIF), Partner Site Hamburg-Borstel-Lübeck-Riems, Hamburg, Germany.
- 386.** Division of Molecular Genetics, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.
- 387.** Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, VIC 3000, Australia.
- 388.** QIMR Berghofer Medical Research Institute, Brisbane, QLD 4006, Australia.
- 389.** Victorian Institute of Forensic Medicine, Southbank, VIC 3006, Australia.
- 390.** University of Pennsylvania, Philadelphia, PA 19104, USA.
- 391.** Department of Gynaecological Oncology, Westmead Hospital, Sydney, NSW 2145, Australia.
- 392.** Genetics and Molecular Pathology, SA Pathology, Adelaide, SA 5000, Australia.
- 393.** Centre for Cancer Research, Westmead Institute for Medical Research, University of Sydney, Sydney, NSW 2145, Australia.
- 394.** Department of Clinical Pathology, University of Melbourne, Melbourne, VIC 3052, Australia.
- 395.** Faculty of Medicine and Health, University of Sydney, Sydney, NSW 2145, Australia.
- 396.** Department of Surgery, Pancreas Institute, University and Hospital Trust of Verona, Verona 37134, Italy.
- 397.** Department of Surgery, Princess Alexandra Hospital, Brisbane, QLD 4102, Australia.
- 398.** Surgical Oncology Group, Diamantina Institute, University of Queensland, Brisbane, QLD 4102, Australia.
- 399.** Department of Diagnostics and Public Health, University and Hospital Trust of Verona, Verona 37134, Italy.
- 400.** ARC-Net Centre for Applied Research on Cancer, University and Hospital Trust of Verona, Verona 37134, Italy.
- 401.** Illawarra Shoalhaven Local Health District L3 Illawarra Cancer Care Centre, Wollongong Hospital, Wollongong, NSW 2500, Australia.
- 402.** School of Biological Sciences, University of Auckland, Auckland 1010, New Zealand.
- 403.** Department of Pathology and Diagnostics, University and Hospital Trust of Verona, Verona 37134, Italy.
- 404.** Department of Medicine, Section of Endocrinology, University and Hospital Trust of Verona, Verona 37134, Italy.
- 405.** Department of Pathology, Queen Elizabeth University Hospital, Glasgow G51 4TF, UK.
- 406.** University of Sydney, Sydney, NSW 2006, Australia.
- 407.** Department of Medical Oncology, Beatson West of Scotland Cancer Centre, Glasgow G12 0YN, UK.
- 408.** Academic Unit of Surgery, School of Medicine, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow Royal Infirmary, Glasgow G4 0SF, UK.
- 409.** Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Sydney, NSW 2050, Australia.
- 410.** Discipline of Surgery, Western Sydney University, Penrith, NSW 2751, Australia.
- 411.** Institute of Cancer Sciences, College of Medical Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8QQ, UK.
- 412.** Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW 2109,

Australia.

413. Sydney Medical School, University of Sydney, Sydney, NSW 2050, Australia.

414. School of Environmental and Life Sciences, Faculty of Science, The University of Newcastle, Ourimbah, NSW 2258, Australia.

415. Eastern Clinical School, Monash University, Melbourne, VIC 3128, Australia.

416. Epworth HealthCare, Richmond, VIC 3121, Australia.

417. Applied Tumor Genomics Research Program, Research Programs Unit, University of Helsinki, Helsinki 00290, Finland.

418. Olivia Newton-John Cancer Research Institute, La Trobe University, Heidelberg, VIC 3084, Australia.

419. Melanoma Institute Australia, University of Sydney, Sydney, NSW 2065, Australia.

420. Children's Hospital at Westmead, University of Sydney, Sydney, NSW 2145, Australia.

421. Australian Institute of Tropical Health and Medicine, James Cook University, Douglas, QLD 4814, Australia.

422. Bioplatforms Australia, North Ryde, NSW 2109, Australia.

423. Melanoma Institute Australia, Macquarie University, Sydney, NSW 2109, Australia.

424. Children's Medical Research Institute, Sydney, NSW 2145, Australia.

425. Discipline of Pathology, Sydney Medical School, University of Sydney, Sydney, NSW 2065, Australia.

426. School of Mathematics and Statistics, University of Sydney, Sydney, NSW 2006, Australia.

427. Diagnostic Development, Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada.

428. Ontario Tumour Bank, Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada.

429. PanCuRx Translational Research Initiative, Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada.

430. UHN Program in BioSpecimen Sciences, Toronto General Hospital, Toronto, ON M5G 2C4, Canada.

431. Hepatobiliary/Pancreatic Surgical Oncology Program, University Health Network, Toronto, ON M5G 2C4, Canada.

432. Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON M5G 1X5, Canada.

433. Division of Medical Oncology, Princess Margaret Cancer Centre, Toronto, ON M5G 2M9, Canada.

434. University of Nebraska Medical Center, Omaha, NE 68198-6880, USA.

435. Transformative Pathology, Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada.

436. Department of Biochemistry and Molecular Medicine, University California at Davis, Sacramento, CA 95817, USA.

437. University Health Network, Princess Margaret Cancer Centre, Toronto, ON M5G 1L7, Canada.

438. Department of Health Sciences Research, Mayo Clinic, Rochester, MN 55905, USA.

439. Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON M5S 1A8, Canada.

440. Department of Pathology, Human Oncology and Pathogenesis Program, Memorial Sloan

Kettering Cancer Center, New York, NY 10053, USA.

441. Department of Pathology, University Health Network, Toronto General Hospital, Toronto, ON M5G 2C4, Canada.

442. Human Longevity Inc, San Diego, CA 92121, USA.

443. CRUKManchester Institute and Centre, Manchester M20 4GJ, UK.

444. Department of Radiation Oncology, University of Toronto, Toronto, ON M5S 1A8, Canada.

445. Division of Cancer Sciences, Manchester Cancer Research Centre, University of Manchester, Manchester M20 4GJ, UK.

446. Radiation Medicine Program, Princess Margaret Cancer Centre, Toronto, ON M5G 2M9, Canada.

447. Department of Surgical Oncology, Princess Margaret Cancer Centre, Toronto, ON M5G 2M9, Canada.

448. STTARR Innovation Facility, Princess Margaret Cancer Centre, Toronto, ON M5G 1L7, Canada.

449. Hefei University of Technology, Anhui 230009, China.

450. State Key Laboratory of Cancer Biology, and Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Shaanxi 710032, China.

451. Fourth Military Medical University, Shaanxi 710032, China.

452. Department of Surgery, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200025, China.

453. Leeds Institute of Medical Research, University of Leeds, St James's University Hospital, Leeds LS9 7TF, UK.

454. Canadian Center for Computational Genomics, McGill University, Montreal, QC H3A 0G1, Canada.

455. Department of Human Genetics, McGill University, Montreal, QC H3A 1B1, Canada.

456. International Agency for Research on Cancer, Lyon 69008, France.

457. McGill University and Genome Quebec Innovation Centre, Montreal, QC H3A 0G1, Canada.

458. Centre National de Génomique, CEA - Institut de Génomique, Evry 91000, France.

459. Leeds Institute of Medical Research @ St James's, University of Leeds, St James's University Hospital, Leeds LS9 7TF, UK.

460. Institute of Mathematics and Computer Science, University of Latvia, Riga LV 1459, Latvia.

461. Department of Oncology, Gil Medical Center, Gachon University, Incheon 405-760, South Korea.

462. Department of Molecular Oncology, BC Cancer Research Centre, Vancouver, BC V5Z 1L3, Canada.

463. Los Alamos National Laboratory, Los Alamos, NM 87545, USA.

464. Department of Cancer Genetics, Institute for Cancer Research, Oslo University Hospital-Radiumhospitalet, Oslo O310, Norway.

465. Department of Clinical Sciences, Lund, Division of Oncology and Pathology, Skåne University Hospital, Lund University, Lund 223 62, Sweden.

466. Translational Research Lab, Centre Léon Bérard, Lyon 69373, France.

467. Department of Molecular Biology, Faculty of Science, Radboud Institute for Molecular Life Sciences, Radboud University, Nijmegen 6500 HB, The Netherlands.

468. Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.

- 469.** Department of Molecular Pathology, The Netherlands Cancer Institute, Amsterdam 1066 CX, The Netherlands.
- 470.** Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo O310, Norway.
- 471.** Department of Oncology, University of Cambridge, Cambridge CB2 1TN, UK.
- 472.** Breast Cancer Translational Research Laboratory JC Heuson, Institut Jules Bordet, Brussels 1000, Belgium.
- 473.** Department of Oncology, Laboratory for Translational Breast Cancer Research, KU Leuven, Leuven 3000, Belgium.
- 474.** Translational Cancer Research Unit, GZA Hospitals St.-Augustinus, Center for Oncological Research, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp 2000, Belgium.
- 475.** Department of Laboratory Medicine, Translational Cancer Research, Lund University Cancer Center at Medicon Village, Lund University, Lund SE-221 85, Sweden.
- 476.** Icelandic Cancer Registry, Icelandic Cancer Society, Reykjavik 125, Iceland.
- 477.** Department of Medical Oncology, Josephine Nefkens Institute and Cancer Genomics Centre, Erasmus Medical Center, Rotterdam 3015 CN, The Netherlands.
- 478.** National Genotyping Center, Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan.
- 479.** Department of Pathology, Oslo University Hospital Ulleval, Oslo 0450, Norway.
- 480.** Faculty of Medicine and Institute of Clinical Medicine, University of Oslo, Oslo NO-0316, Norway.
- 481.** Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA.
- 482.** Department of Pathology, Skåne University Hospital, Lund University, Lund SE-221 85, Sweden.
- 483.** Department of Pathology, Academic Medical Center, Amsterdam 1105 AZ, The Netherlands.
- 484.** Department of Pathology, College of Medicine, Hanyang University, Seoul 133-791, South Korea.
- 485.** Department of Pathology, Asan Medical Center, College of Medicine, Ulsan University, Songpa-gu, Seoul 05505, South Korea.
- 486.** The Netherlands Cancer Institute, Amsterdam 1066 CX, The Netherlands.
- 487.** Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, Boston, MA 02115, USA.
- 488.** Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA.
- 489.** Division of Breast Surgery, Brigham and Women's Hospital, Boston, MA 02115, USA.
- 490.** Department of Clinical Science, University of Bergen, Bergen 5020, Norway.
- 491.** Morgan Welch Inflammatory Breast Cancer Research Program and Clinic, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
- 492.** The University of Queensland Centre for Clinical Research, Royal Brisbane and Women's Hospital, Herston, QLD 4029, Australia.
- 493.** Department of Pathology, Institut Jules Bordet, Brussels 1000, Belgium.
- 494.** Institute for Bioengineering and Biopharmaceutical Research (IBBR), Hanyang University, Seoul 133-791, South Korea.

- 495.** University of Oslo, Oslo 0316, Norway.
- 496.** Institut Bergonié, Bordeaux 33076, France.
- 497.** Department of Research Oncology, Guy's Hospital, King's Health Partners AHSC, King's College London School of Medicine, London SE1 9RT, UK.
- 498.** University Hospital of Minjoz, INSERM UMR 1098, Besançon 25000, France.
- 499.** Cambridge Breast Unit, Addenbrooke's Hospital, Cambridge University Hospital NHS Foundation Trust and NIHR Cambridge Biomedical Research Centre, Cambridge CB2 2QQ, UK.
- 500.** East of Scotland Breast Service, Ninewells Hospital, Aberdeen AB25 2XF, UK.
- 501.** Department of Clinical Sciences, Lund, Division of Oncology and Pathology, Lund University, Lund 223 62, Sweden.
- 502.** University of Copenhagen, Copenhagen 2200, Denmark.
- 503.** Oncologie Sénologie, ICM Institut Régional du Cancer, Montpellier 34298, France.
- 504.** Department of Radiation Oncology, Radboud University Nijmegen Medical Centre, Nijmegen 6525 GA, The Netherlands.
- 505.** University of Iceland, Reykjavik 101, Iceland.
- 506.** Dundee Cancer Centre, Ninewells Hospital, Dundee DD2 1SY, UK.
- 507.** Institut Curie, INSERM Unit 830, Paris 75248, France.
- 508.** Department of Laboratory Medicine, Radboud University Nijmegen Medical Centre, Nijmegen 6525 GA, The Netherlands.
- 509.** Department of General Surgery, Singapore General Hospital, Singapore 169608, Singapore.
- 510.** Université Lyon, INCa-Synergie, Centre Léon Bérard, Lyon 69008, France.
- 511.** Giovanni Paolo II / I.R.C.C.S. Cancer Institute, Bari BA 70124, Italy.
- 512.** Department of Biopathology, Centre Léon Bérard, Lyon 69008, France.
- 513.** Université Claude Bernard Lyon 1, Villeurbanne 69100, France.
- 514.** Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
- 515.** NCCS-VARI Translational Research Laboratory, National Cancer Centre Singapore, Singapore 169610, Singapore.
- 516.** Department of Pathology, Erasmus Medical Center Rotterdam, Rotterdam 3015 GD, The Netherlands.
- 517.** Division of Molecular Carcinogenesis, The Netherlands Cancer Institute, Amsterdam 1066 CX, The Netherlands.
- 518.** Institute of Human Genetics, Christian-Albrechts-University, Kiel 24118, Germany.
- 519.** Institute of Human Genetics, Ulm University and Ulm University Medical Center of Ulm, Ulm 89081, Germany.
- 520.** Hematopathology Section, Institute of Pathology, Christian-Albrechts-University, Kiel 24118, Germany.
- 521.** Institute of Human Genetics, University of Ulm and University Hospital of Ulm, Ulm 89081, Germany.
- 522.** Department of Human Genetics, Hannover Medical School, Hannover 30625, Germany.
- 523.** Department of Pediatric Oncology, Hematology and Clinical Immunology, Heinrich-Heine-University, Düsseldorf 40225, Germany.
- 524.** Department of Internal Medicine/Hematology, Friedrich-Ebert-Hospital, Neumünster 24534, Germany.
- 525.** Pediatric Hematology and Oncology, University Hospital Muenster, Muenster 24534,

Germany.

526. Department of Pediatrics, University Hospital Schleswig-Holstein, Kiel 24105, Germany.

527. Department of Medicine II, University of Würzburg, Würzburg 97070, Germany.

528. Senckenberg Institute of Pathology, University of Frankfurt Medical School, Frankfurt 60596, Germany.

529. Institute of Pathology, Charité – University Medicine Berlin, Berlin 10117, Germany.

530. Department for Internal Medicine II, University Hospital Schleswig-Holstein, Kiel 24105, Germany.

531. Institute for Medical Informatics Statistics and Epidemiology, University of Leipzig, Leipzig 04109, Germany.

532. Department of Hematology and Oncology, Georg-Augusts-University of Göttingen, Göttingen 37073, Germany.

533. Institute of Cell Biology (Cancer Research), University of Duisburg-Essen, Essen D-45147, Germany.

534. MVZ Department of Oncology, PraxisClinic am Johannisplatz, Leipzig 04109, Germany.

535. Institute of Pathology, Ulm University and University Hospital of Ulm, Ulm 89081, Germany.

536. Department of Pathology, Robert-Bosch-Hospital, Stuttgart, Germany, Stuttgart 70376, Germany.

537. University Hospital Giessen, Pediatric Hematology and Oncology, Giessen 35392, Germany.

538. Institute of Clinical Molecular Biology, Christian-Albrechts-University, Kiel 24118, Germany.

539. Institute of Pathology, University of Würzburg, Würzburg 97070, Germany.

540. Department of General Internal Medicine, University Kiel, Kiel 24118, Germany.

541. Clinic for Hematology and Oncology, St.-Antonius-Hospital, Eschweiler D-52249, Germany.

542. Department for Internal Medicine III, University of Ulm and University Hospital of Ulm, Ulm 89081, Germany.

543. Neuroblastoma Genomics, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.

544. Department of Pediatric Oncology and Hematology, University of Cologne, Cologne 50937, Germany.

545. University of Düsseldorf, Düsseldorf 40225, Germany.

546. Department of Vertebrate Genomics/Otto Warburg Laboratory Gene Regulation and Systems Biology of Cancer, Max Planck Institute for Molecular Genetics, Berlin 14195, Germany.

547. St. Jude Children's Research Hospital, Memphis, TN 38105-3678, USA.

548. Heidelberg University Hospital, Heidelberg 69120, Germany.

549. Genomics and Proteomics Core Facility High Throughput Sequencing Unit, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.

550. Epigenomics and Cancer Risk Factors, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.

551. Institute of Pathology, University Medical Center Hamburg-Eppendorf, Hamburg 20246, Germany.

552. Institute of Pathology, University Medical Center Hamburg-Eppendorf, Hamburg 20251, Germany.

553. Martini-Clinic, Prostate Cancer Center, University Medical Center Hamburg-Eppendorf, Hamburg 20095, Germany.

- 554.** Division of Cancer Genome Research, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.
- 555.** National Institute of Biomedical Genomics, Kalyani 741235, West Bengal, India.
- 556.** Advanced Centre for Treatment Research and Education in Cancer, Tata Memorial Centre, Navi Mumbai, Maharashtra 410210, India.
- 557.** Department of Pathology, General Hospital of Treviso, Department of Medicine, University of Padua, Treviso 31100, Italy.
- 558.** Department of Medicine (DIMED), Surgical Pathology Unit, University of Padua, Padua 35121, Italy.
- 559.** Department of Pathology and Clinical Laboratory, National Cancer Center Hospital, Tokyo 104-0045, Japan.
- 560.** Department of Pathology, Keio University School of Medicine, Tokyo 160-8582, Japan.
- 561.** Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo 104-0045, Japan.
- 562.** Department of Pathology, Graduate School of Medicine, University of Tokyo, Tokyo 113-0033, Japan.
- 563.** Preventive Medicine, Graduate School of Medicine, University of Tokyo, Tokyo 113-0033, Japan.
- 564.** Department of Gastric Surgery, National Cancer Center Hospital, Tokyo 104-0045, Japan.
- 565.** Department of Gastroenterology and Hepatology, Yokohama City University Graduate School of Medicine, Kanagawa 236-0004, Japan.
- 566.** Department of Cancer Genome Informatics, Graduate School of Medicine, Osaka University, Osaka 565-0871, Japan.
- 567.** Hiroshima University, Hiroshima 734-8553, Japan.
- 568.** Tokyo Women's Medical University, Tokyo 162-8666, Japan.
- 569.** Osaka International Cancer Center, Osaka 541-8567, Japan.
- 570.** Wakayama Medical University, Wakayama 641-8509, Japan.
- 571.** Hokkaido University, Sapporo 060-8648, Japan.
- 572.** Department of Surgery, Yokohama City University Graduate School of Medicine, Kanagawa 236-0004, Japan.
- 573.** Division of Medical Oncology, National Cancer Centre, Singapore 169610, Singapore.
- 574.** Cholangiocarcinoma Screening and Care Program and Liver Fluke and Cholangiocarcinoma Research Centre, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
- 575.** Lymphoma Genomic Translational Research Laboratory, National Cancer Centre, Singapore 169610, Singapore.
- 576.** Center of Digestive Diseases and Liver Transplantation, Fundeni Clinical Institute, Bucharest 022328, Romania.
- 577.** Department of Surgery, Division of Hepatobiliary and Pancreatic Surgery, School of Medicine, Keimyung University Dongsan Medical Center, Daegu 41931, South Korea.
- 578.** Pathology, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona 8034, Spain.
- 579.** Anatomia Patològica, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona 8036, Spain.
- 580.** Spanish Ministry of Science and Innovation, Madrid 28046, Spain.
- 581.** Hematology, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer

(IDIBAPS), University of Barcelona, Barcelona 8034, Spain.

582. Department of Biochemistry and Molecular Biology, Faculty of Medicine, University Institute of Oncology-IUOPA, Oviedo 33006, Spain.

583. Royal National Orthopaedic Hospital - Bolsover, London W1W 5AQ, UK.

584. Department of Pathology, Oslo University Hospital, The Norwegian Radium Hospital, Oslo O310, Norway.

585. Institute of Clinical Medicine and Institute of Oral Biology, University of Oslo, Oslo O310, Norway.

586. Department of Pathology (Research), University College London Cancer Institute, London WC1E 6BT, UK.

587. Research Department of Pathology, University College London Cancer Institute, London WC1E 6BT, UK.

588. East Anglian Medical Genetics Service, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, UK.

589. Royal National Orthopaedic Hospital - Stanmore, Stanmore, Middlesex HA7 4LP, UK.

590. Division of Orthopaedic Surgery, Oslo University Hospital, Oslo O379, Norway.

591. Radcliffe Department of Medicine, University of Oxford, Oxford OX3 9DU, UK.

592. University of Pavia, Pavia 27100, Italy.

593. Karolinska Institute, Stockholm SE-171 76, Sweden.

594. University of Oxford, Oxford OX3 9DU, UK.

595. Salford Royal NHS Foundation Trust, Salford M6 8HD, UK.

596. Gloucester Royal Hospital, Gloucester GL1 3NL, UK.

597. Royal Stoke University Hospital, Stoke-on-Trent ST4 6QG, UK.

598. St Thomas's Hospital, London SE1 7EH, UK.

599. Imperial College NHS Trust, Imperial College, London W2 INY, UK.

600. Department of Histopathology, Salford Royal NHS Foundation Trust, Salford M6 8HD, UK.

601. Faculty of Biology, Medicine and Health, University of Manchester, Manchester M13 9PL, UK.

602. Edinburgh Royal Infirmary, Edinburgh EH16 4SA, UK.

603. Barking Havering and Redbridge University Hospitals NHS Trust, Romford RM7 0AG, UK.

604. King's College London and Guy's and St Thomas' NHS Foundation Trust, London SE1 7EH, UK.

605. Cambridge Oesophagogastric Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, UK.

606. Nottingham University Hospitals NHS Trust, Nottingham NG7 2UH, UK.

607. St Luke's Cancer Centre, Royal Surrey County Hospital NHS Foundation Trust, Guildford GU2 7XX, UK.

608. University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA.

609. Norfolk and Norwich University Hospital NHS Trust, Norwich NR4 7UY, UK.

610. University Hospitals Coventry and Warwickshire NHS Trust, Coventry CV2 2DX, UK.

611. University Hospitals Birmingham NHS Foundation Trust, Birmingham B15 2GW, UK.

612. Centre for Cancer Research and Cell Biology, Queen's University, Belfast BT9 7AB, UK.

613. School of Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton SO17 1BJ, UK.

614. Wythenshawe Hospital, Manchester M23 9LT, UK.

- 615.** Barts Cancer Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London EC1M 6BQ, UK.
- 616.** Royal Marsden NHS Foundation Trust, London and Sutton SW3 6JJ, UK.
- 617.** University Hospital Southampton NHS Foundation Trust, Southampton SO16 6YD, UK.
- 618.** HCA Laboratories, London W1G 8AQ, UK.
- 619.** University of Liverpool, Liverpool L69 3BX, UK.
- 620.** Department of Surgery, Academic Urology Group, University of Cambridge, Cambridge CB2 0QQ, UK.
- 621.** Department of Urology, James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA.
- 622.** Second Military Medical University, Shanghai 200433, China.
- 623.** Department of Surgery and Cancer, Imperial College, London W2 1NY, UK.
- 624.** The Chinese University of Hong Kong, Shatin, NT, Hong Kong, China.
- 625.** Nuffield Department of Surgical Sciences, John Radcliffe Hospital, University of Oxford, Oxford OX3 9DU, UK.
- 626.** Department of Histopathology, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, UK.
- 627.** Department of Surgery, University of Chicago, Chicago, IL 60637, USA.
- 628.** Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892, USA.
- 629.** Canada's Michael Smith Genome Sciences Centre, BC Cancer Agency, Vancouver, BC V5Z 4S6, Canada.
- 630.** Center for Molecular Oncology, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA.
- 631.** Department of Pathology and Laboratory Medicine, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA.
- 632.** Department of Population and Quantitative Health Sciences, Case Western Reserve University School of Medicine, Cleveland, OH 44016, USA.
- 633.** Research Health Analytics and Informatics, University Hospitals Cleveland Medical Center, Cleveland, OH 44106, USA.
- 634.** Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB T2N 4N2, Canada.
- 635.** Departments of Surgery and Oncology, University of Calgary, Calgary, AB T2N 4N2, Canada.
- 636.** Buck Institute for Research on Aging, Novato, CA 94945, USA.
- 637.** Duke University Medical Center, Durham, NC 27710, USA.
- 638.** USC Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA 90033, USA.
- 639.** The Preston Robert Tisch Brain Tumor Center, Duke University Medical Center, Durham, NC 27710, USA.
- 640.** Departments of Dermatology and Pathology, Yale University, New Haven, CT 06510, USA.
- 641.** Fox Chase Cancer Center, Philadelphia, PA 19111, USA.
- 642.** Department of Surgery, Division of Thoracic Surgery, The Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA.
- 643.** University of Michigan Comprehensive Cancer Center, Ann Arbor, MI 48109, USA.
- 644.** University of Alabama at Birmingham, Birmingham, AL 35294, USA.
- 645.** Division of Anatomic Pathology, Mayo Clinic, Rochester, MN 55905, USA.

- 646.** Division of Experimental Pathology, Mayo Clinic, Rochester, MN 55905, USA.
- 647.** International Genomics Consortium, Phoenix, AZ 85004, USA.
- 648.** Departments of Pediatrics and Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA.
- 649.** Department of Pathology, UPMC Shadyside, Pittsburgh, PA 15232, USA.
- 650.** Center for Cancer Genomics, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
- 651.** Department of Neuro-Oncology, Istituto Neurologico Besta, Milano 20133, Italy.
- 652.** The University of Queensland Thoracic Research Centre, The Prince Charles Hospital, Brisbane, QLD 4032, Australia.
- 653.** Department of Neurosurgery, University of Florida, Gainesville, FL 32610, USA.
- 654.** Center for Biomedical Informatics, Harvard Medical School, Boston, MA 02115, USA.
- 655.** Department of Cancer Biology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
- 656.** Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
- 657.** Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN 55905, USA.
- 658.** Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL 33136, USA.
- 659.** Department of Internal Medicine, Division of Medical Oncology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA.
- 660.** University of Tennessee Health Science Center for Cancer Research, Memphis, TN 38163, USA.
- 661.** Centre for Translational and Applied Genomics, British Columbia Cancer Agency, Vancouver, BC V5Z 1L3, Canada.
- 662.** Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX 77030, USA.
- 663.** Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX 77030, USA.
- 664.** Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX 77030, USA.
- 665.** Carolina Center for Genome Sciences, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA.
- 666.** Indivumed GmbH, Hamburg 20251, Germany.
- 667.** Department of Surgery, Division of Hepatobiliary and Pancreatic Surgery, School of Medicine, Keimyung University Dong-san Medical Center, Daegu 41931, South Korea.
- 668.** Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA.
- 669.** Department of Surgery, The George Washington University, School of Medicine and Health Science, Washington, DC 20052, USA.
- 670.** Endocrine Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
- 671.** National Cancer Center, Gyeonggi 10408, South Korea.
- 672.** ILSbio, LLC Biobank, Chestertown, MD 21620, USA.
- 673.** Canada's Michael Smith Genome Sciences Centre, BC Cancer Agency, Vancouver, BC V5Z 4S6, Canada.

- 674.** Gynecologic Oncology, NYU Laura and Isaac Perlmutter Cancer Center, New York University, New York, NY 10016, USA.
- 675.** Division of Oncology, Stem Cell Biology Section, Washington University School of Medicine, St. Louis, MO 63110, USA.
- 676.** Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
- 677.** Institute for Systems Biology, Seattle, WA 98109, USA.
- 678.** Department of Pathology and Laboratory Medicine, Center for Personalized Medicine, Children's Hospital Los Angeles, Los Angeles, CA 90027, USA.
- 679.** Institute for Genomic Medicine, Nationwide Children's Hospital, Columbus, OH 43215, USA.
- 680.** Department of Surgery, Duke University, Durham, NC 27710, USA.
- 681.** Department of Obstetrics, Gynecology and Reproductive Services, University of California San Francisco, San Francisco, CA 94143, USA.
- 682.** Departments of Neurology and Neurosurgery, Henry Ford Hospital, Detroit, MI 48202, USA.
- 683.** Precision Oncology, OHSU Knight Cancer Institute, Oregon Health and Science University, Portland, OR 97239, USA.
- 684.** Department of Pathology, Roswell Park Cancer Institute, Buffalo, NY 14263, USA.
- 685.** Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Washington University School of Medicine, St. Louis, MO 63110, USA.
- 686.** Penrose St. Francis Health Services, Colorado Springs, CO 80907, USA.
- 687.** Department of Medicine, University of Chicago, Chicago, IL 60637, USA.
- 688.** Department of Neurology, Mayo Clinic, Rochester, MN 55905, USA.
- 689.** Center for Liver Cancer, Research Institute and Hospital, National Cancer Center, Gyeonggi 410-769, South Korea.
- 690.** Department of Genetics, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA.
- 691.** NYU Langone Medical Center, New York, NY 10016, USA.
- 692.** Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH 44195, USA.
- 693.** Department of Pathology and Laboratory Medicine, University of North Carolina, Chapel Hill, NC 27599, USA.
- 694.** Helen F. Graham Cancer Center at Christiana Care Health Systems, Newark, DE 19713, USA.
- 695.** Cureline, Inc, South San Francisco, CA 94080, USA.
- 696.** Department of Obstetrics and Gynecology, Medical College of Wisconsin, Milwaukee, WI 53226, USA.
- 697.** Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA 30322, USA.
- 698.** Vanderbilt Ingram Cancer Center, Vanderbilt University, Nashville, TN 37232, USA.
- 699.** Ohio State University College of Medicine and Arthur G. James Comprehensive Cancer Center, Columbus, OH 43210, USA.
- 700.** Research Computing Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA.

- 701.** Analytical Biological Services, Inc, Wilmington, DE 19801, USA.
- 702.** Department of Dermatology, University Hospital of Essen, Essen 45122, Germany.
- 703.** University of Pittsburgh, Pittsburgh, PA 15213, USA.
- 704.** Murtha Cancer Center, Walter Reed National Military Medical Center, Bethesda, MD 20889, USA.
- 705.** Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.
- 706.** Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA.
- 707.** Center for RNA Interference and Noncoding RNA, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
- 708.** Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
- 709.** Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
- 710.** Department of Urology, Mayo Clinic, Rochester, MN 55905, USA.
- 711.** Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.
- 712.** Departments of Neurosurgery and Hematology and Medical Oncology, Winship Cancer Institute and School of Medicine, Emory University, Atlanta, GA 30322, USA.
- 713.** Georgia Regents University Cancer Center, Augusta, GA 30912, USA.
- 714.** Thoracic Oncology Laboratory, Mayo Clinic, Rochester, MN 55905, USA.
- 715.** Institute for Genomic Medicine, Nationwide Children's Hospital, Columbus, OH 43205, USA.
- 716.** Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Mayo Clinic, Rochester, MN 55905, USA.
- 717.** International Institute for Molecular Oncology, Poznań 60-203, Poland.
- 718.** Poznan University of Medical Sciences, Poznań 61-701, Poland.
- 719.** Edison Family Center for Genome Sciences and Systems Biology, Washington University, St. Louis, MO 63110, USA.