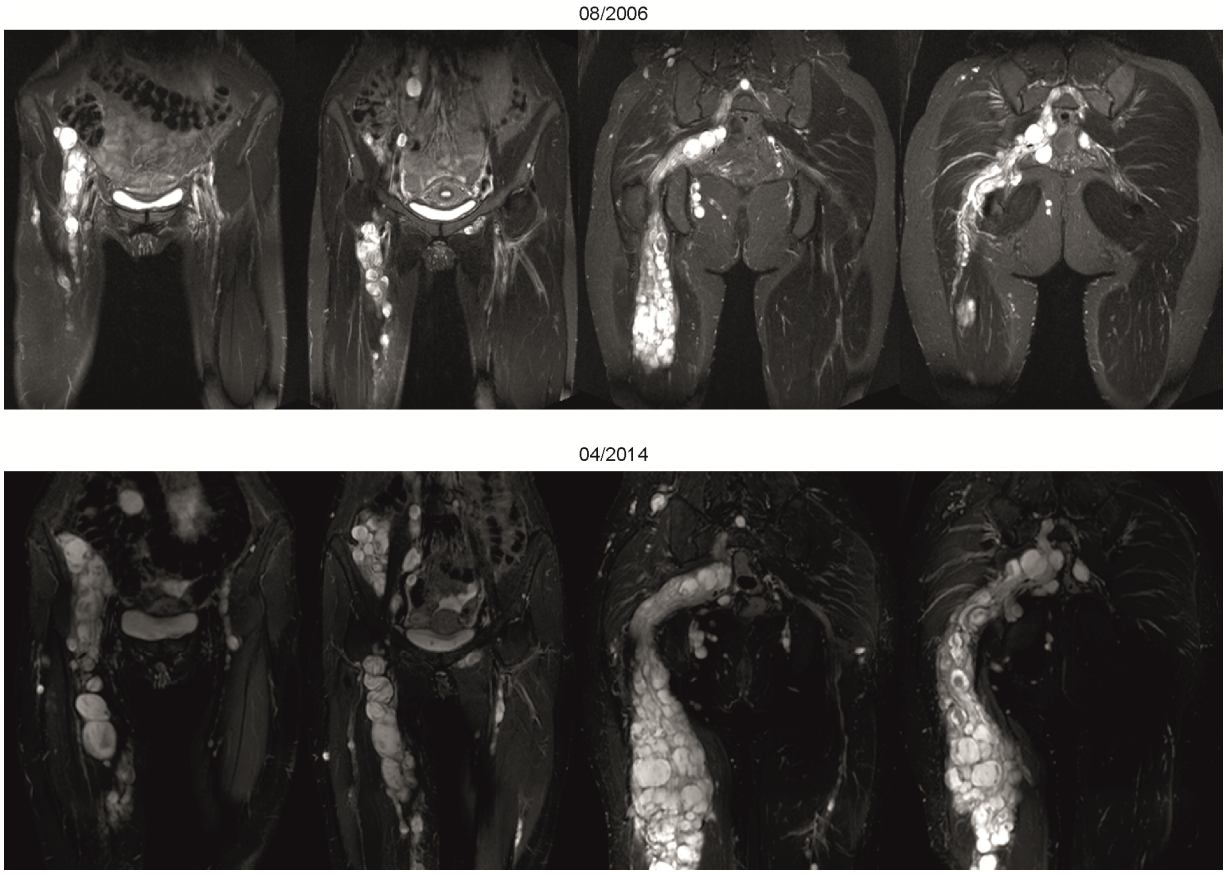
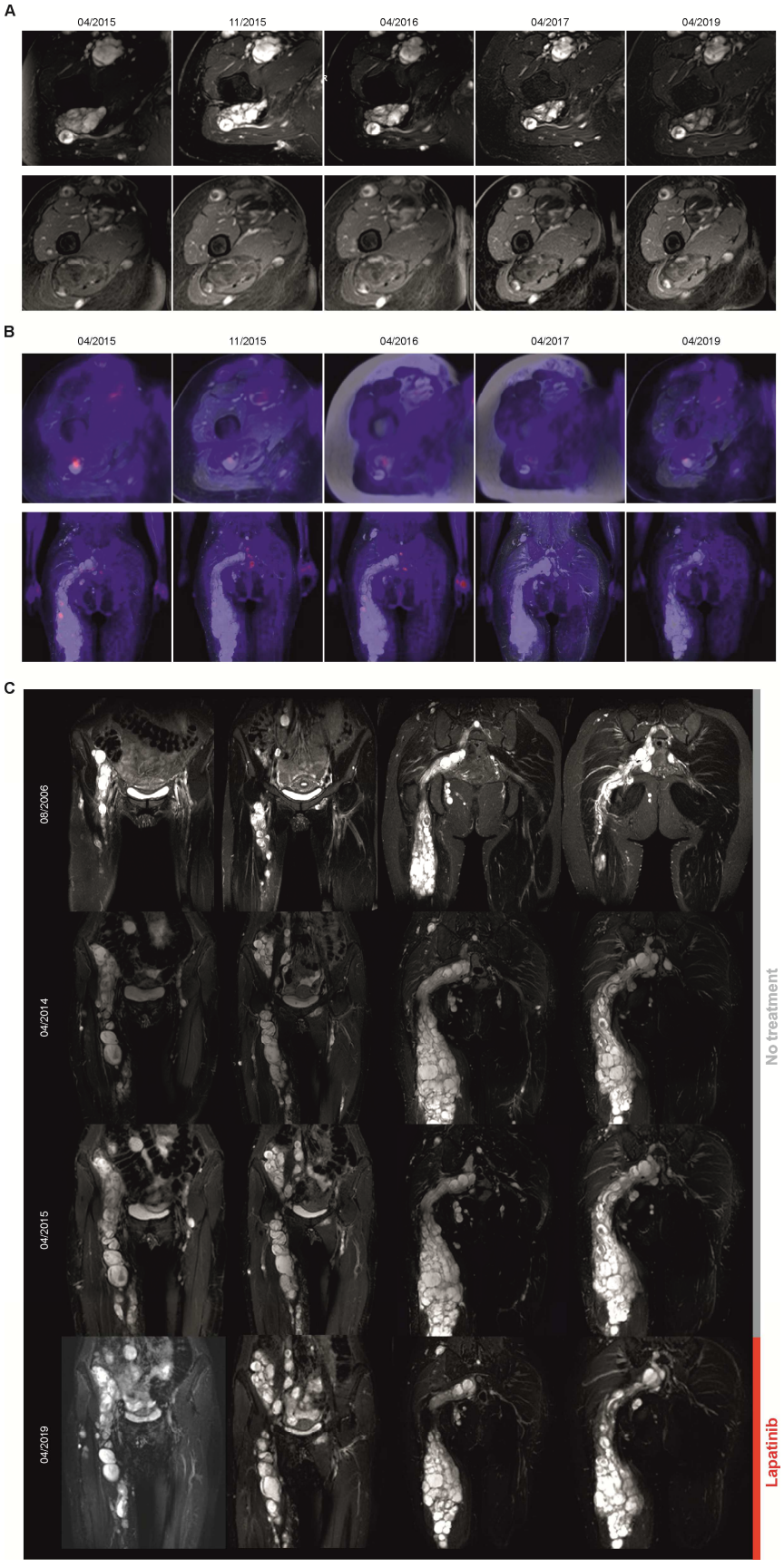
Supplementary Information



Supplementary Figure 1. Tumor growth over time in a patient with N/S HNST. Representative T2-weighted and fat-suppressed coronal MRI studies showing tumor growth along the right femoral nerve and diffusely along smaller peripheral nerves and lumbar and sacral nerve roots over an 8-year period before initiation of lapatinib therapy.

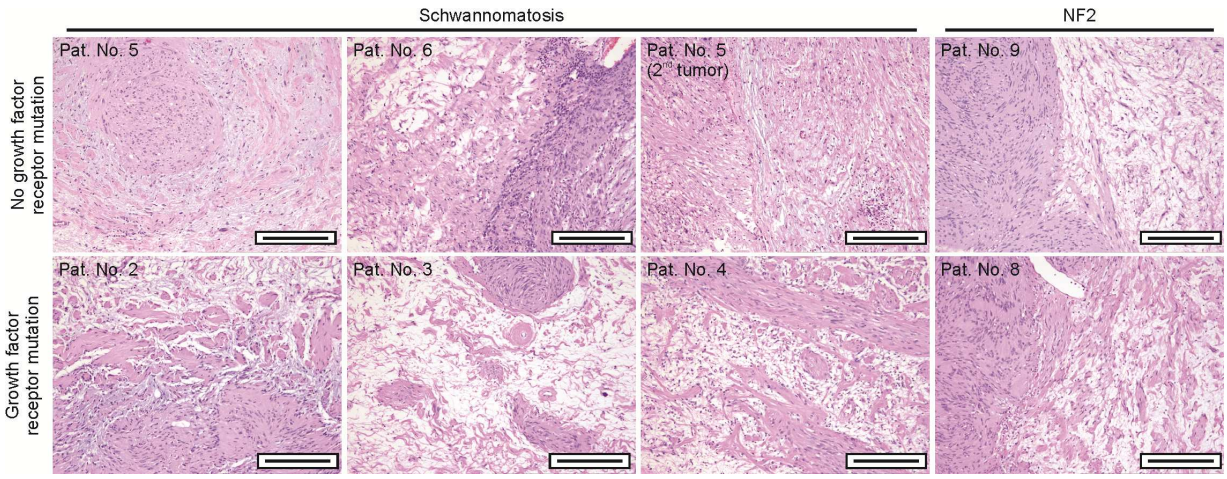

A
04/2015
11/2015
04/2016
04/2017
04/2019
B
04/2015
11/2015
04/2016
04/2017
04/2019
C
08/2006
04/2014
04/2015
04/2019
No treatment
Lapatinib

Supplementary Figure 2. Tumor growth before and after initiation of lapatinib therapy in a patient with N/S HNST.

A: Axial MRI studies showing tumor masses before (04/2015) and after (11/2015 and later) initiation of lapatinib therapy. Upper panel, T2-weighted and fat-suppressed images of hyperintense tumors along the right sciatic and femoral nerves; lower panel, T1-weighted, contrast-enhanced, and fat-suppressed images of slightly and inhomogeneously contrast-enhancing tumors along the right sciatic and femoral nerves. Images from 11/2015 (upper panel) and 04/2017 (upper and lower panel) are reshown from Fig. 1B).

B: FDG-PET/MRI studies showing tracer uptake before (04/2015) and after (11/2015 and later) initiation of lapatinib therapy. Upper row, axial images of tumors along the right sciatic and femoral nerves; lower row, coronal images of tumors along the right sciatic nerve. Images from 04/2017 are reshown from Fig. 1C.

C: Representative T2-weighted and fat-suppressed coronal MRI studies showing tumor growth along the right femoral nerve and diffusely along smaller peripheral nerves and lumbar and sacral nerve roots over a 9-year period before (08/2006-04/2015) and after (04/2019) initiation of lapatinib therapy. Images from 08/2006 and 04/2014 are reshown from Supplementary Fig. 1.



Supplementary Figure 3. Histologic appearance of N/S HNST samples.

Microscopic analysis of HE-stained sections from N/S HNST samples with and without growth factor receptor (ERBB2 or RET) mutations. Scale bar, 200 µm.

Supplementary Table 1. Genes assessed for germline alterations within the NCT MASTER program

AIP	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AML1*	*APC*	*ATM*	*ATR*	*ATRX*	*BAP1*
BARD1	*BMPR1A*	*BRCA1*	*BRCA2*	*BRIP1*	*BUB1B*	*CBFA2*	*CBL*	*CDC73*	*CDH1*	*CDK4*
CDKN1A	*CDKN1B*	*CDKN1C*	*CDKN2A*	*CDKN2B*	*CDKN2C*	*CDKN2D*	*CEBPA*	*CEP57*	*CHEK2*	*CHK2*
CREBBP	*CYLD*	*DAXX*	*DDB2*	*DICER1*	*DIS3L2*	*EGFR*	*EHBP1*	*EPCAM*	*EPHB2*	*ERCC2*
ERCC3	*ERCC4*	*ERCC5*	*EXT1*	*EXT2*	*EZH2*	*FAM175A*	*FANCA*	*FANCB*	*FANCC*	*FANCD1*
FANCD2	*FANCE*	*FANCF*	*FANCG*	*FANCI*	*FANCJ*	*FANCL*	*FANCM*	*FANCN*	*PALB2*	*FANCP*
FH	*FLCN*	*FP*	*GATA2*	*GPC3*	*GPRC5A*	*GSTM1*	*GSTT1*	*HIF2A*	*EPAS1*	*HNF1A*
HORMAD1	*HORMAD2*	*HPC10*	*HPC11*	*HPC12*	*HPC13*	*HPC14*	*HPC15*	*HPC2*	*HPC3*	*HPC4*
HPC5	*HPC6*	*HPC7*	*HPC8*	*HPC9*	*HPCX2*	*HPS1*	*HPT1*	*CDH17*	*HRAS*	*JAK2*
KIF1B	*KIT*	*KITLG*	*MAP3K1*	*MAP3K6*	*MAX*	*MDH2*	*MEN1*	*MET*	*MMS19*	*MLH1*
MLH3	*MN1*	*MRE11A*	*MSH2*	*MSH6*	*MUTYH*	*MYCT1*	*NBN*	*NF1*	*NF2*	*NSD1*
PALLD	*PDGFRA*	*PHD1*	*PHD2*	*EGLN2*	*EGLN1*	*PHOX2B*	*PIK3C2G*	*PIK3CA*	*PIK3R1*	*PIK3R2*
PMS1	*PMS2*	*POLD1*	*POLE*	*PPM1D*	*PRF1*	*PRKAR1A*	*PTCH1*	*PTCH2*	*PTEN*	*RAD50*
RAD51	*RAD51C*	*RAD51D*	*RB1*	*RECQL*	*RECQL2*	*RECQL4*	*RET*	*RHBDF2*	*RINT1*	*RUNX1*
SBDS	*SDH5*	*SDHA*	*SDHAF2*	*SDHB*	*SDHC*	*SDHD*	*SLX4*	*SMAD4*	*SMARCA4*	*SMARCB1*
STK11	*SUFU*	*TACSTD1*	*TMEM127*	*TP53*	*TSC1*	*TSC2*	*VHL*	*WT1*	*XPA*	*XPC*
XRCC2	*XRCC9*	*BLM*	*WRN*							

Supplementary Table 2. Additional patient characteristics

Patient	Age at resection	Gender	Localization
1	37	F	Femoral cutaneous nerve
2	48	F	Femoral nerve
3	30	F	Femoral nerve
4	56	F	Mandibular angle above carotid bifurcation
	55		Paravertebral, level of carotid bifurcation
	52		Cervical area
5	44	F	Axilla
	37	F	Sciatic nerve
6	60	F	Peroneal nerve
7	40	F	Paravertebral, L4/5
8	25	M	Ulnar nerve
	24		Brachial plexus, truncus superior
9	34	M	Parapharyngeal
10	15	F	Supraauricular
11	35	F	Parietal skull
12	11	F	Cerebellopontine angle
13	24	M	Paravertebral, C1/2
14	56	F	Ulnar nerve
15	48	M	Radial nerve

Supplementary Table 3. Genes analyzed by targeted next-generation sequencing

ABL1	*BRD4*	*CUX1*	*FAM175A*	*GATA6*	*IGF1*	*MAP3K13*	*NOTCH4*	*POLE*	*RPTOR*	*TAF1*
ABL2	*BRIP1*	*CXCR4*	*FAM46C*	*GEN1*	*IGF1R*	*MAP3K14*	*NPM1*	*PPARG*	*RUNX1*	*TBX3*
ACVR1	*BTG1*	*CYLD*	*FANCA*	*GID4*	*IGF2*	*MAP3K4*	*NRAS*	*PPM1D*	*RUNX1T1*	*TCEB1*
ACVR1B	*BTK*	*DAXX*	*FANCC*	*GLI1*	*IKBKE*	*MAPK1*	*NRG1*	*PPP2R1A*	*RYBP*	*TCF3*
AKT1	*C11orf30*	*DCUN1D1*	*FANCD2*	*GNA11*	*IKZF1*	*MAPK3*	*NSD1*	*PPP2R2A*	*SDHA*	*TCF7L2*
AKT2	*CALR*	*DDR2*	*FANCE*	*GNA13*	*IL10*	*MAX*	*NTRK1*	*PPP6C*	*SDHAF2*	*TERC*
AKT3	*CARD11*	*DDX41*	*FANCF*	*GNAQ*	*IL7R*	*MCL1*	*NTRK2*	*PRDM1*	*SDHB*	*TERT*
ALK	*CASP8*	*DHX15*	*FANCG*	*GNAS*	*INHA*	*MDC1*	*NTRK3*	*PREX2*	*SDHC*	*TET1*
ALOX12B	*CBFB*	*DICER1*	*FANCI*	*GPR124*	*INHBA*	*MDM2*	*NUP93*	*PRKAR1A*	*SDHD*	*TET2*
ANKRD11	*CBL*	*DIS3*	*FANCL*	*GPS2*	*INPP4A*	*MDM4*	*NUTM1*	*PRKCI*	*SETBP1*	*TFE3*
ANKRD26	*CCND1*	*DNAJB1*	*FAS*	*GREM1*	*INPP4B*	*MED12*	*PAK1*	*PRKDC*	*SETD2*	*TFRC*
APC	*CCND2*	*DNMT1*	*FAT1*	*GRIN2A*	*INSR*	*MEF2B*	*PAK3*	*PRSS8*	*SF3B1*	*TGFBR1*
AR	*CCND3*	*DNMT3A*	*FBXW7*	*GRM3*	*IRF2*	*MEN1*	*PAK7*	*PTCH1*	*SH2B3*	*TGFBR2*
ARAF	*CCNE1*	*DNMT3B*	*FGF1*	*GSK3B*	*IRF4*	*MET*	*PALB2*	*PTEN*	*SH2D1A*	*TMEM127*
ARFRP1	*CD274*	*DOT1L*	*FGF10*	*H3F3A*	*IRS1*	*MGA*	*PARK2*	*PTPN11*	*SHQ1*	*TMPRSS2*
ARID1A	*CD276*	*E2F3*	*FGF14*	*H3F3B*	*IRS2*	*MITF*	*PARP1*	*PTPRD*	*SLIT2*	*TNFAIP3*
ARID1B	*CD74*	*EED*	*FGF19*	*H3F3C*	*JAK1*	*MLH1*	*PAX3*	*PTPRS*	*SLX4*	*TNFRSF14*
ARID2	*CD79A*	*EGFL7*	*FGF2*	*HGF*	*JAK2*	*MLL*	*PAX5*	*PTPRT*	*SMAD2*	*TOP1*
ARID5B	*CD79B*	*EGFR*	*FGF23*	*HIST1H1C*	*JAK3*	*MLLT3*	*PAX7*	*QKI*	*SMAD3*	*TOP2A*
ASXL1	*CDC73*	*EIF1AX*	*FGF3*	*HIST1H2BD*	*JUN*	*MPL*	*PAX8*	*RAB35*	*SMAD4*	*TP53*
ASXL2	*CDH1*	*EIF4A2*	*FGF4*	*HIST1H3A*	*KAT6A*	*MRE11A*	*PBRM1*	*RAC1*	*SMARCA4*	*TP63*
ATM	*CDK12*	*EIF4E*	*FGF5*	*HIST1H3B*	*KDM5A*	*MSH2*	*PDCD1*	*RAD21*	*SMARCB1*	*TRAF2*
ATR	*CDK4*	*EML4*	*FGF6*	*HIST1H3C*	*KDM5C*	*MSH3*	*PDCD1LG2*	*RAD50*	*SMARCD1*	*TRAF7*
ATRX	*CDK6*	*EP300*	*FGF7*	*HIST1H3D*	*KDM6A*	*MSH6*	*PDGFRA*	*RAD51*	*SMC1A*	*TSC1*
AURKA	*CDK8*	*EPCAM*	*FGF8*	*HIST1H3E*	*KDR*	*MST1*	*PDGFRB*	*RAD51B*	*SMC3*	*TSC2*
AURKB	*CDKN1A*	*EPHA3*	*FGF9*	*HIST1H3F*	*KEAP1*	*MST1R*	*PDK1*	*RAD51C*	*SMO*	*TSHR*
AXIN1	*CDKN1B*	*EPHA5*	*FGFR1*	*HIST1H3G*	*KEL*	*MTOR*	*PDPK1*	*RAD51D*	*SNCAIP*	*U2AF1*
AXIN2	*CDKN2A*	*EPHA7*	*FGFR2*	*HIST1H3H*	*KIF5B*	*MUTYH*	*PGR*	*RAD52*	*SOCS1*	*VEGFA*
AXL	*CDKN2B*	*EPHB1*	*FGFR3*	*HIST1H3I*	*KIT*	*MYB*	*PHF6*	*RAD54L*	*SOX10*	*VHL*
B2M	*CDKN2C*	*ERBB2*	*FGFR4*	*HIST1H3J*	*KLF4*	*MYC*	*PHOX2B*	*RAF1*	*SOX17*	*VTCN1*
BAP1	*CEBPA*	*ERBB3*	*FH*	*HIST2H3A*	*KLHL6*	*MYCL1*	*PIK3C2B*	*RANBP2*	*SOX2*	*WISP3*
BARD1	*CENPA*	*ERBB4*	*FLCN*	*HIST2H3C*	*KMT2B*	*MYCN*	*PIK3C2G*	*RARA*	*SOX9*	*WT1*
BBC3	*CHD2*	*ERCC1*	*FLI1*	*HIST2H3D*	*KMT2C*	*MYD88*	*PIK3C3*	*RASA1*	*SPEN*	*XIAP*
BCL10	*CHD4*	*ERCC2*	*FLT1*	*HIST3H3*	*KMT2D*	*MYOD1*	*PIK3CA*	*RB1*	*SPOP*	*XPO1*
BCL2	*CHEK1*	*ERCC3*	*FLT3*	*HLA-A*	*KRAS*	*NAB2*	*PIK3CB*	*RBM10*	*SPTA1*	*XRCC2*
BCL2L1	*CHEK2*	*ERCC4*	*FLT4*	*HLA-B*	*LAMP1*	*NBN*	*PIK3CD*	*RECQL4*	*SRC*	*YAP1*
BCL2L11	*CIC*	*ERCC5*	*FOXA1*	*HLA-C*	*LATS1*	*NCOA3*	*PIK3CG*	*REL*	*SRSF2*	*YES1*
BCL2L2	*CREBBP*	*ERG*	*FOXL2*	*HNF1A*	*LATS2*	*NCOR1*	*PIK3R1*	*RET*	*STAG1*	*ZBTB2*
BCL6	*CRKL*	*ERRFI1*	*FOXO1*	*HNRNPK*	*LMO1*	*NEGR1*	*PIK3R2*	*RFWD2*	*STAG2*	*ZBTB7A*
BCOR	*CRLF2*	*ESR1*	*FOXP1*	*HOXB13*	*LRP1B*	*NF1*	*PIK3R3*	*RHEB*	*STAT3*	*ZFHX3*
BCORL1	*CSF1R*	*ETS1*	*FRS2*	*HRAS*	*LYN*	*NF2*	*PIM1*	*RHOA*	*STAT4*	*ZNF217*

BCR	*CSF3R*	*ETV1*	*FUBP1*	*HSD3B1*	*LZTR1*	*NFE2L2*	*PLCG2*	*RICTOR*	*STAT5A*	*ZNF703*
BIRC3	*CSNK1A1*	*ETV4*	*FYN*	*HSP90AA1*	*MAGI2*	*NFKBIA*	*PLK2*	*RIT1*	*STAT5B*	*ZRSR2*
BLM	*CTCF*	*ETV5*	*GABRA6*	*ICOSLG*	*MALT1*	*NKX2-1*	*PMAIP1*	*RNF43*	*STK11*	
BMPR1A	*CTLA4*	*ETV6*	*GATA1*	*ID3*	*MAP2K1*	*NKX3-1*	*PMS1*	*ROS1*	*STK40*	
BRAF	*CTNNA1*	*EWSR1*	*GATA2*	*IDH1*	*MAP2K2*	*NOTCH1*	*PMS2*	*RPS6KA4*	*SUFU*	
BRCA1	*CTNNB1*	*EZH2*	*GATA3*	*IDH2*	*MAP2K4*	*NOTCH2*	*PNRC1*	*RPS6KB1*	*SUZ12*	
BRCA2	*CUL3*	*FAM123B*	*GATA4*	*IFNGR1*	*MAP3K1*	*NOTCH3*	*POLD1*	*RPS6KB2*	*SYK*	

TREND Statement Checklist

Paper Section/ Topic	Item No	Descriptor	Reported? ✓	Reported? Pg #
Title and Abstract				
Title and Abstract	1	• Information on how unit were allocated to interventions	✓	3,7,8
		• Structured abstract recommended	✓	3
		• Information on target population or study sample	✓	3,7,8
Introduction				
Background	2	• Scientific background and explanation of rationale	✓	3,4,5
		• Theories used in designing behavioral interventions		
Methods				
Participants	3	• Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)	✓	8
		• Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented		
		• Recruitment setting		
		• Settings and locations where the data were collected		
Interventions	4	• Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:	✓	7,8
		○ Content: what was given?	✓	7,8
		○ Delivery method: how was the content given?	✓	7
		○ Unit of delivery: how were the subjects grouped during delivery?	NA	
		○ Deliverer: who delivered the intervention?	NA	
		○ Setting: where was the intervention delivered?	NA	
		○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?	✓	
		○ Time span: how long was it intended to take to deliver the intervention to each unit?	NA	
		○ Activities to increase compliance or adherence (e.g., incentives)	NA	
Objectives	5	• Specific objectives and hypotheses	✓	
Outcomes	6	• Clearly defined primary and secondary outcome measures	NA	7,8
		• Methods used to collect data and any methods used to enhance the quality of measurements	✓	7,8
		• Information on validated instruments such as psychometric and biometric properties	NA	
Sample Size	7	• How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	✓	8
Assignment Method	8	• Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)	NA	
		• Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)	NA	
		• Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)	NA	

TREND Statement Checklist

Blinding (masking)	9	• Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed.	NA	
Unit of Analysis	10	• Description of the smallest unit that is being analyzed to assess intervention effects (e.g., individual, group, or community)	NA	
		• If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)	NA	
Statistical Methods	11	• Statistical methods used to compare study groups for primary methods outcome(s), including complex methods of correlated data	NA	
		• Statistical methods used for additional analyses, such as a subgroup analyses and adjusted analysis	NA	
		• Methods for imputing missing data, if used	NA	
		• Statistical software or programs used	NA	
Results				
Participant flow	12	• Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (a diagram is strongly recommended)	NA	
		○ Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study	NA	
		○ Assignment: the numbers of participants assigned to a study condition	✓	7
		○ Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention	✓	7
		○ Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition	NA	
		○ Analysis: the number of participants included in or excluded from the main analysis, by study condition	NA	
		• Description of protocol deviations from study as planned, along with reasons	NA	
Recruitment	13	• Dates defining the periods of recruitment and follow-up	NA	
Baseline Data	14	• Baseline demographic and clinical characteristics of participants in each study condition	✓	7,8,23,24
		• Baseline characteristics for each study condition relevant to specific disease prevention research	NA	
		• Baseline comparisons of those lost to follow-up and those retained, overall and by study condition	NA	
		• Comparison between study population at baseline and target population of interest	NA	
Baseline equivalence	15	• Data on study group equivalence at baseline and statistical methods used to control for baseline differences	NA	

TREND Statement Checklist

Numbers analyzed	16	• Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible	✓	8
		• Indication of whether the analysis strategy was "intention to treat" or, if not, description of how non-compliers were treated in the analyses	NA	
Outcomes and estimation	17	• For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision	NA	
		• Inclusion of null and negative findings	NA	
		• Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any	✓	7
Ancillary analyses	18	• Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory	✓	7, 8, 23, 24
Adverse events	19	• Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)	NA	
DISCUSSION				
Interpretation	20	• Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	✓	11, 12
		• Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations	✓	11, 12
		• Discussion of the success of and barriers to implementing the intervention, fidelity of implementation	✓	11, 12
		• Discussion of research, programmatic, or policy implications	✓	11, 12
Generalizability	21	• Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues	✓	11, 12
Overall Evidence	22	• General interpretation of the results in the context of current evidence and current theory	✓	11, 12

NA: not applicable

From: Des Jarlais, D. C., Lyles, C., Crepaz, N., & the Trend Group (2004). Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: The TREND statement. *American Journal of Public Health*, 94, 361-366. For more information, visit: http://www.cdc.gov/trendstatement/