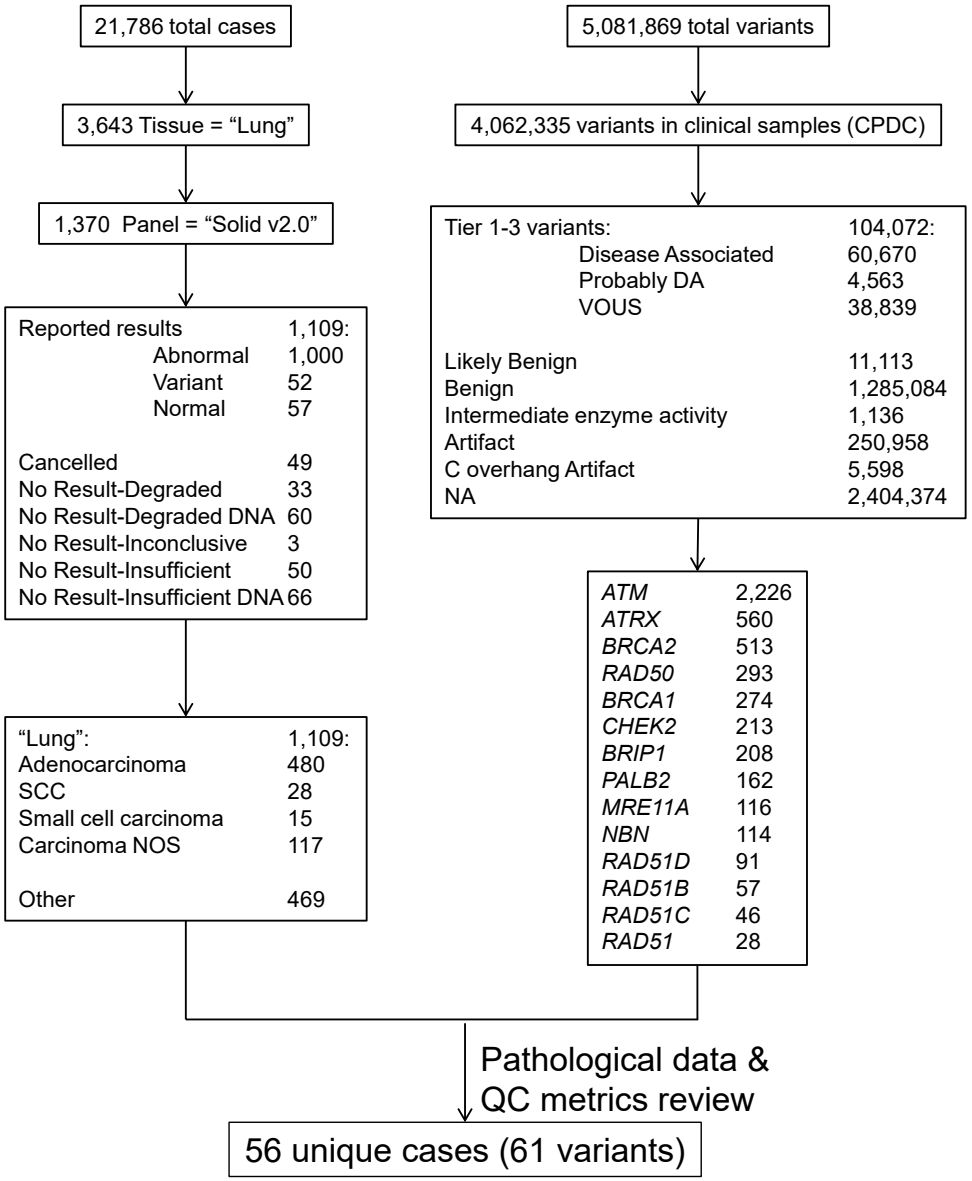

Figure S1 Algorithm used for filtering of cases of interest. All cases were sequenced at the Center for Personalized Diagnostics (CPD; University of Pennsylvania), from September 2016 to October 2019. DA, disease associated; VOUS (VUS), variant of uncertain significance; NA, not available/applicable; SCC, squamous cell carcinoma; NOS, not otherwise specified; QC, quality control.

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Table S1 Lung cancer family history and somatic testing results

Age/sex (smoking)	Somatic alteration (amino acid change, VAF, classification)	Family cancer history[#]
60F (42 PY)	*ATM* NM_000051.4: c.192delAinsTG (p.L64Ffs*36, 39%, DA)	Lung (father@55, sister@59)
72F (36 PY)	*ATM* NM_000051.4: c.8545C>T (p.R2849*, 82%, DA)	Prostate (father), lung (brother, nephew)
62M (PY unknown)	*ATM* NM_000051.4: c.7181C>T (p.S2394L, 62%, probably DA)	Lung (sister)
65F (98 PY)	*CHEK2* NM_001005735.2: c.1412C>T (p.S471F, 51%, probably DA)	Kidney (brother), lung (father), colon (maternal GF, maternal GM, 2 maternal uncles), breast (maternal GM), lymphoma (mother), leukemia (sister)
45M (never)	*ATM* NM_000051.4: c.2179G>C (p.G727R, 47%, VUS)	Breast (mother@56, paternal GM), pancreas (mother@56), lung (paternal GM)
67F (17 PY)	*ATM* NM_000051.4: c.2930G>T (p.C977F, 45%, VUS)	Lung (father), breast (mother), cervix (mother), thyroid (mother)
52F (15 PY)	*ATM* NM_000051.4: c.5489T>C (p.M1830T, 59%, VUS)	Lung (NOS)
65M (27 PY)	*ATM* NM_000051.4: c.6998C>T (p.T2333I, 70%, VUS)	Lung (son-small cell), colon (father, maternal GF, paternal GF), prostate (father, paternal GF)
55F (35 PY)	*ATM* NM_000051.4: c.9031A>G (p.M3011V, 52%, VUS)	Lung (2 brothers, father)
54F (40 PY)	*ATRX* (NM_000489.6): c.2933C>T (p.S978F, 52%, VUS)	Lung (father), skin (sister), breast (paternal GM), colorectal (maternal GM)
56F (34 PY)	*BRCA2* NM_000059.4: c.2716A>G (p.T906A, 60%, VUS)	Lung(mother), breast (maternal GM)
41F (38 PY)	*BRCA2* NM_000059.4: c.4436G>C (p.S1479T, 40%, VUS)	Lung (2 maternal aunts), GYN (maternal aunt)
54F (never)	*BRCA2* NM_000059.4: c.8732C>G (p.A2911G, 33%, VUS)	Lung (father), colon (maternal GF), lymphoma (maternal GM)
62F (never)	*BRCA2* NM_000059.4: c.9391T>C (p.S3131P, 75%, VUS)	Breast (paternal cousin@53, paternal aunt@85), lung (maternal aunt@82), leukemia (mother@39), head and neck cancer (brother@62)
55M (PY unknown)	*CHEK2* NM_001005735.2: c.1556C>T (p.T519M, 44%, VUS)	Kidney (father), lung (father)
72F (50 PY)	*MRE11A* NM_005591.4: c.1972A>G (p.T658A, 48%, VUS)	Lung(father), ovary(mother)

[#], ages at diagnosis are indicated, where known. @: diagnosed at age. VAF, variant allele fraction; PY, pack-year cigarette smoking; F, female; M, male; DA, disease-associated genetic variant; GF, grandfather; GM, grandmother; VUS, variant of unknown significance; NOS, not otherwise specified; GYN, unspecified gynecological cancer.

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Table S2 152 genes sequenced at the Center for Personalized Diagnostics

ABL1
APC
ATM
BRCA1
CCND1
CDK4
CRKL
DNMT3A
ERBB3
ESR2
FGFR2
GATA3
H3F3A
JAK2
KDR
MAP2K2
MCL1
MET
MSH6
NF1
NKX2-1
EP300
PIK3CA
PTPN11
RAD51B
RET
SLIT2
SRC
SYK
TSC1
WT1
AKT1
AR
ATRX
BRCA2

Table S2 (*continued*)

CCND2
CDK6
CSF1R
EGFR
ERBB4
EZH2
FGFR3
GNA11
IDH1
JAK3
KIT
MAP2K4
MDM2
MITF
MTOR
NF2
NOTCH1
PAK1
PIK3CB
RAB35
RAD51C
RHOA
SMAD4
STAG2
TET2
TSC2
XRCC2
AKT2
ARAF
AURKA
BRIP
CCND3
CDKN2A
CTNNB1
EIF1Ax

Table S2 (*continued*)

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Table S2 (*continued*)

ERCC2
FBXW7
FGFR4
GNAQ
IDH2
KDM5A
KMT2C
MAPK1
MDM4
MLH1
MYC
NTRK1
NOTCH2
PALB2
PIK3R1
RAC1
RAD51D
RNF43
SMARCA4
STK11
TGFBR2
TSHR
AKT3
ARID1A
BAP1
BTK
CCNE1
CHEK2
DAXX
EPHA3
ERG
FGF3
FLT3
GNAS
IGF1R

Table S2 (*continued*)

Table S2 (*continued*)

KDM5C
KRAS
MAPK3
MED12
MRE11A
MYCN
NTRK2
NOTCH3
PBRM1
PTCH1
RAD50
RAF1
SETD2
SMO
SUFU
TP53
U2AF1
ALK
ARID2
BRAF
CBP
CDH1
CIC
DDR2
ERBB2
ESR1
FGFR1
FUBP1
HRAS
JAK1
KDM6A
MAP2K1
MAX
MEN1
MSH2

Table S2 (*continued*)

https://dx.doi.org/10.21037/tlcr-22-749

Table S2 (*continued*)

NBN
NTRK3
NRAS
PDGFRA
PTEN
RAD51
RB1
SF3B1
SPOP
SUZ12
TRAF7
VHL

Table S3 55 gene targets for fusion transcript panel assay

AKT1
CALCA
EGFR3
EWSR1
FUS
KRT7
NRG1
PIK3CA
RAF1
STAT6
TFG
ALK
CAMTA1
EPC1
FGFR1
GLI1
MEAF6
NTRK1
PLAG1
RET

Table S3 (*continued*)

TAF15
THADA
AXL
CCNB3
ERBB2
FGFR2
HMGA2
MET4
NTRK2
PMS2
ROS1
TCF12
TMPRSS2
BCOR
CCND1
ERG
FGFR3
JAZF1
MKL2
NTRK3
PPARG
SLC5A5
TERT
USP6
BRAF
CIC
ESR1
FOXO1
KRT20
NCOA2
PDGFB
PTH
SS18
TFE3
YWHAE

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