Figure 1

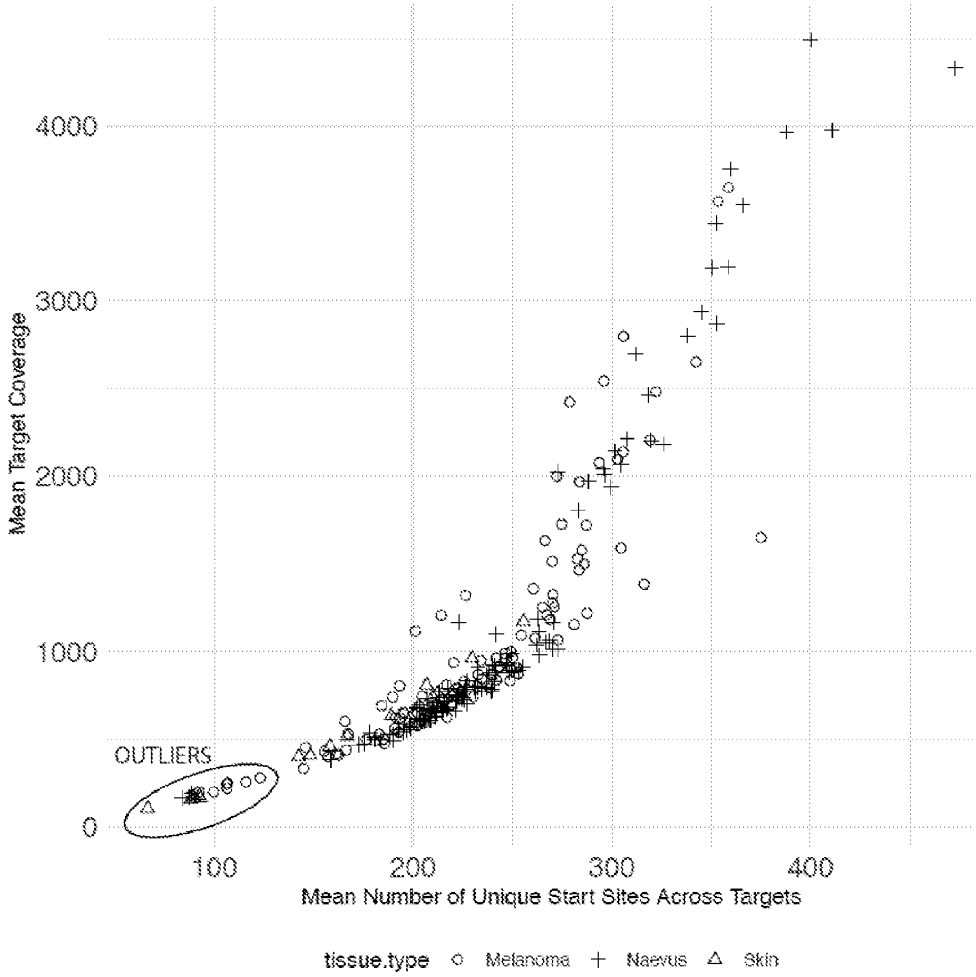

4000
3000
2000
1000
0
Mean Target Coverage
OUTLIERS
100
200
300
400
Mean Number of Unique Start Sites Across Targets
tissue.type
Melanoma
Naevus
Skin

Figure 2

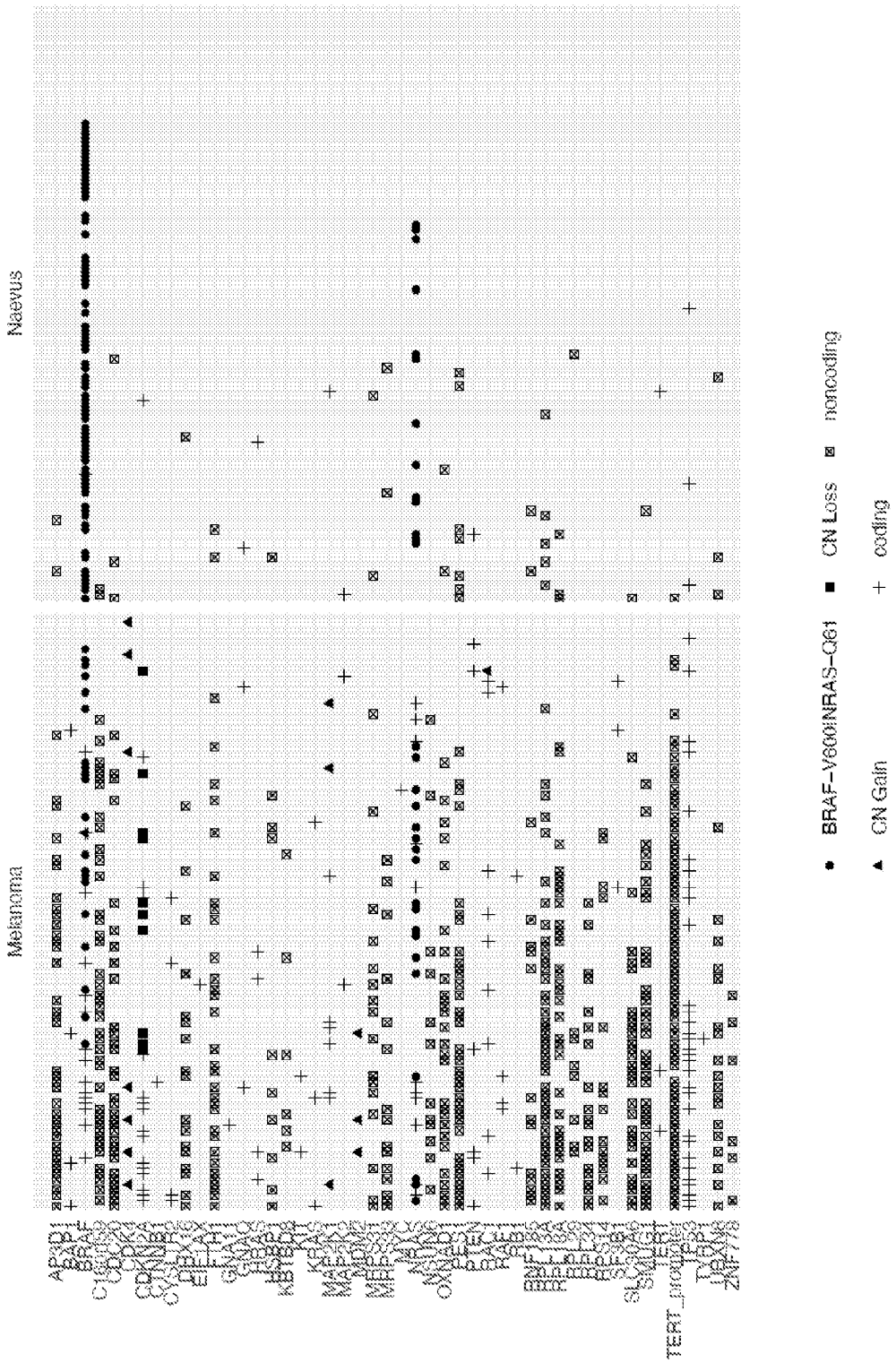

Melanoma
Naevus
BRAF-V600/NRAS-Q61
CN Loss
noncoding
CN Gain
coding

Figure 3

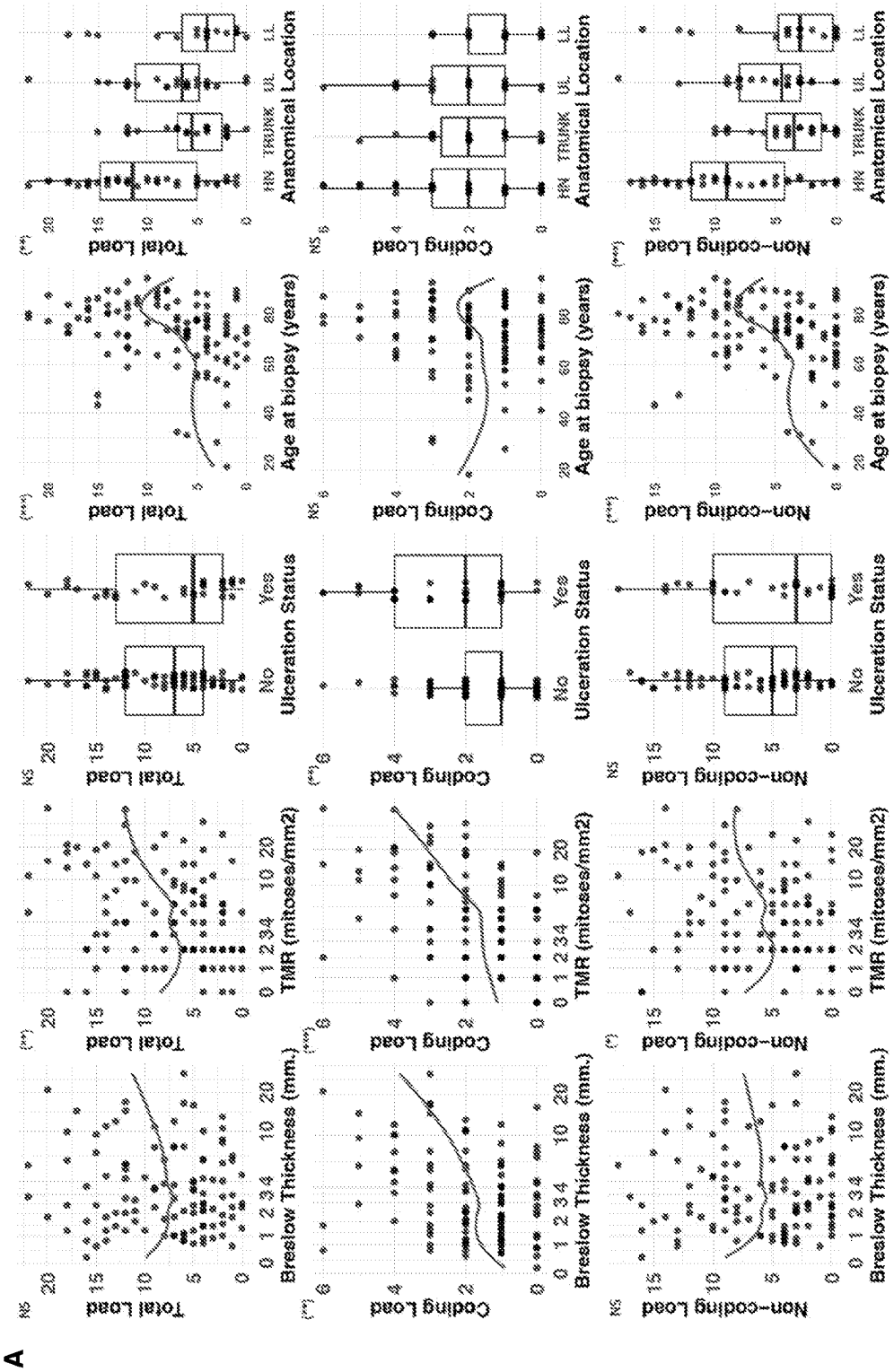

A
Total Load
Coding Load
Non-coding Load
Breslow Thickness (mm.)
TMR (mitoses/mm2)
Ulceration Status
No
Yes
Age at biopsy (years)
Anatomical Location
HN
TRUNK
UL
LL
NS

Figure 3 continued

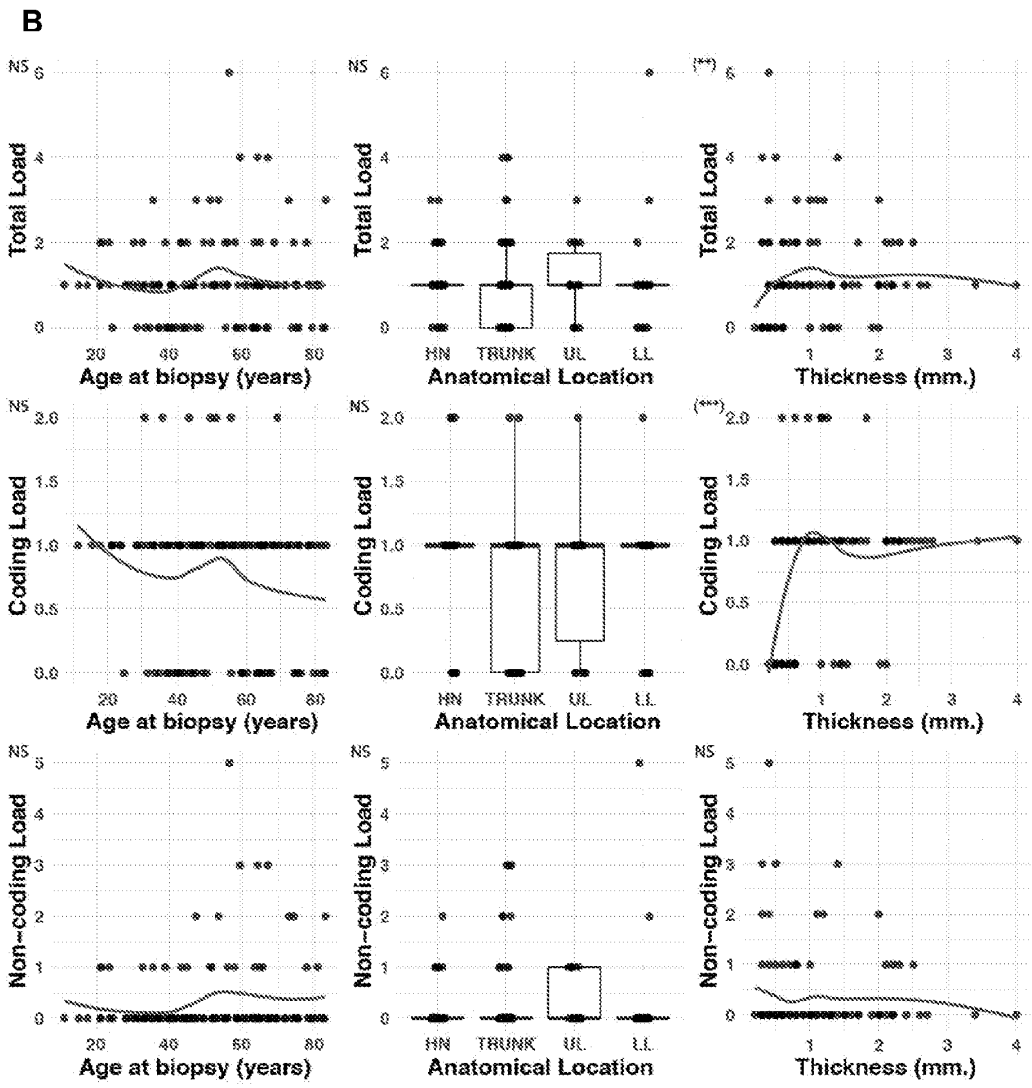


Figure 4

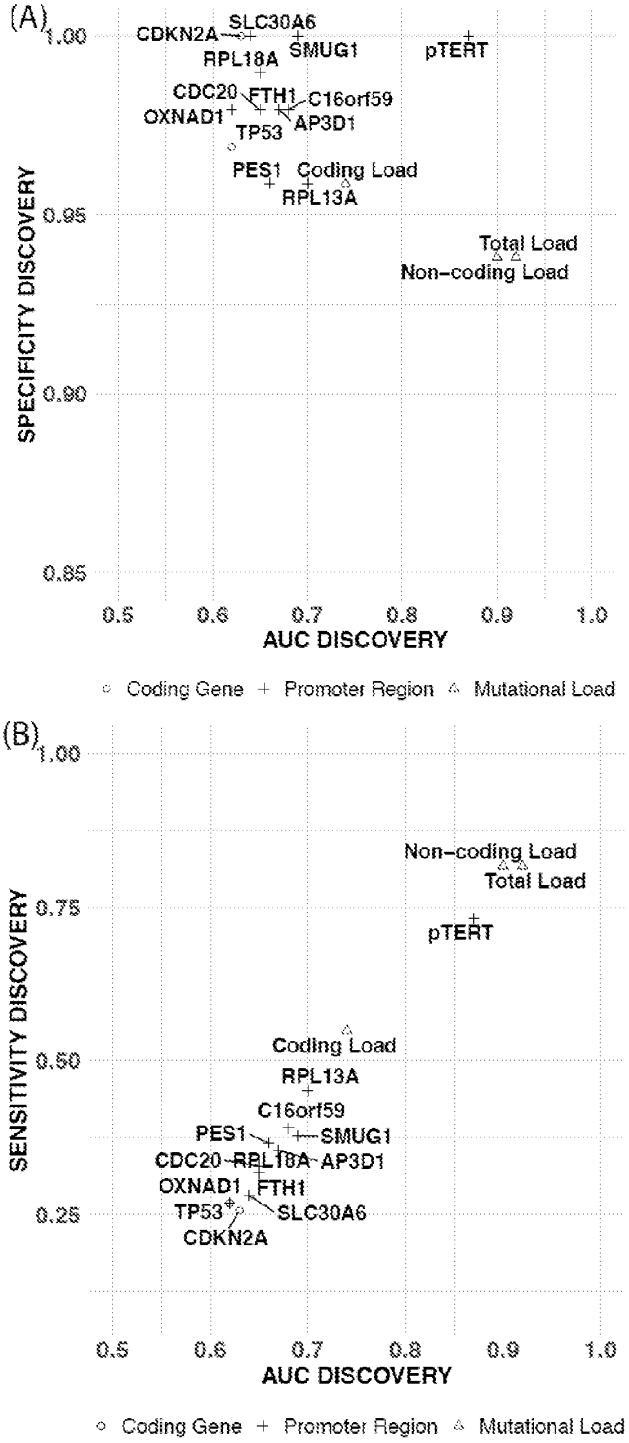

(A)
SPECIFICITY DISCOVERY
AUC DISCOVERY
1.00
0.95
0.90
0.85
0.5
0.6
0.7
0.8
0.9
1.0
CDKN2A
SLC30A6
SMUG1
pTERT
RPL18A
CDC20
FTH1
C16orf59
OXNAD1
AP3D1
TP53
PES1
Coding Load
RPL13A
Total Load
Non−coding Load
Coding Gene
Promoter Region
Mutational Load
(B)
SENSITIVITY DISCOVERY
AUC DISCOVERY
1.00
0.75
0.50
0.25
0.5
0.6
0.7
0.8
0.9
1.0
Non−coding Load
Total Load
pTERT
Coding Load
RPL13A
C16orf59
PES1
SMUG1
CDC20
RPL18A
AP3D1
OXNAD1
FTH1
TP53
SLC30A6
CDKN2A
Coding Gene
Promoter Region
Mutational Load

Figure 5

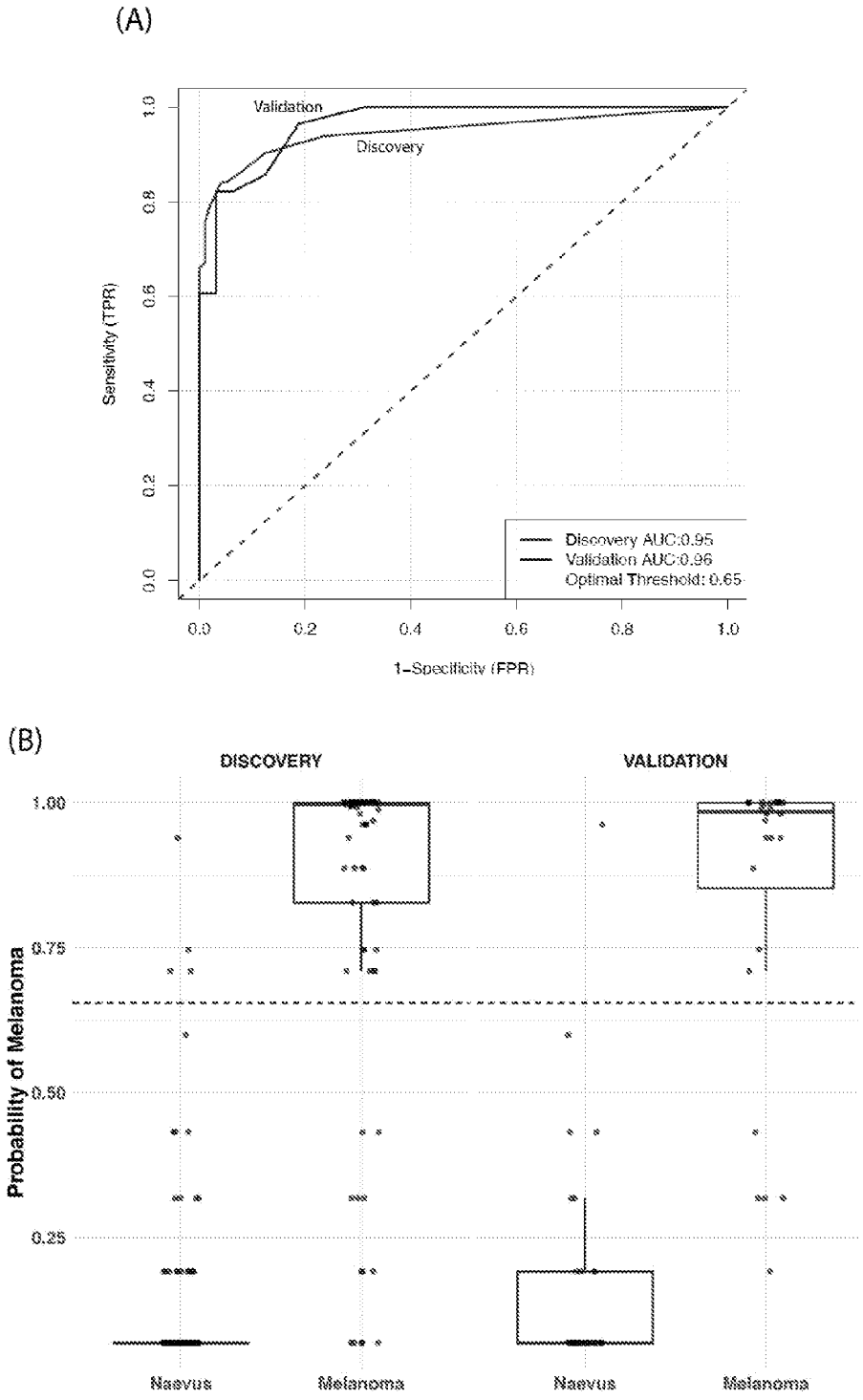

(A)
Validation
Discovery
Sensitivity (TPR)
1−Specificity (FPR)
Discovery AUC:0.95
Validation AUC:0.96
Optimal Threshold: 0.65
(B)
DISCOVERY
VALIDATION
Probability of Melanoma
Naevus
Melanoma
Naevus
Melanoma

Figure 6

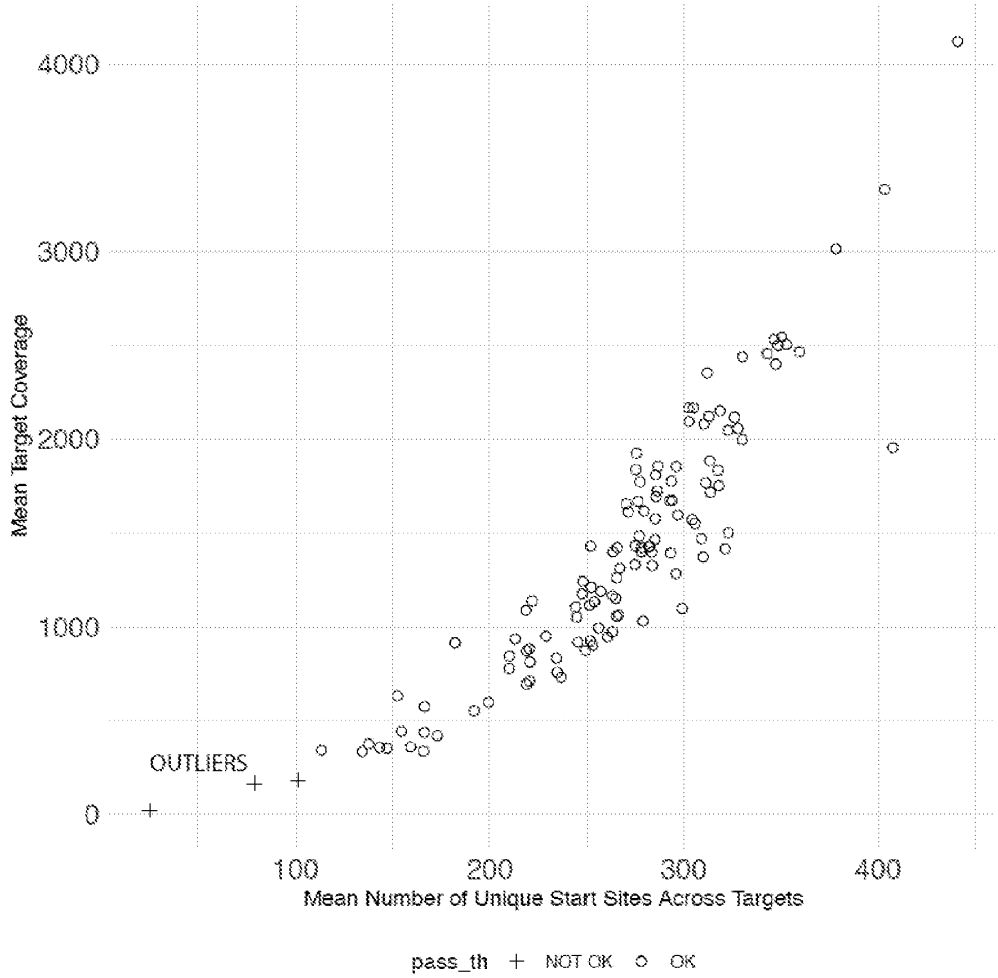

4000
3000
2000
1000
0
Mean Target Coverage
OUTLIERS
100
200
300
400
Mean Number of Unique Start Sites Across Targets
pass_th
NOT OK
OK

Figure 7

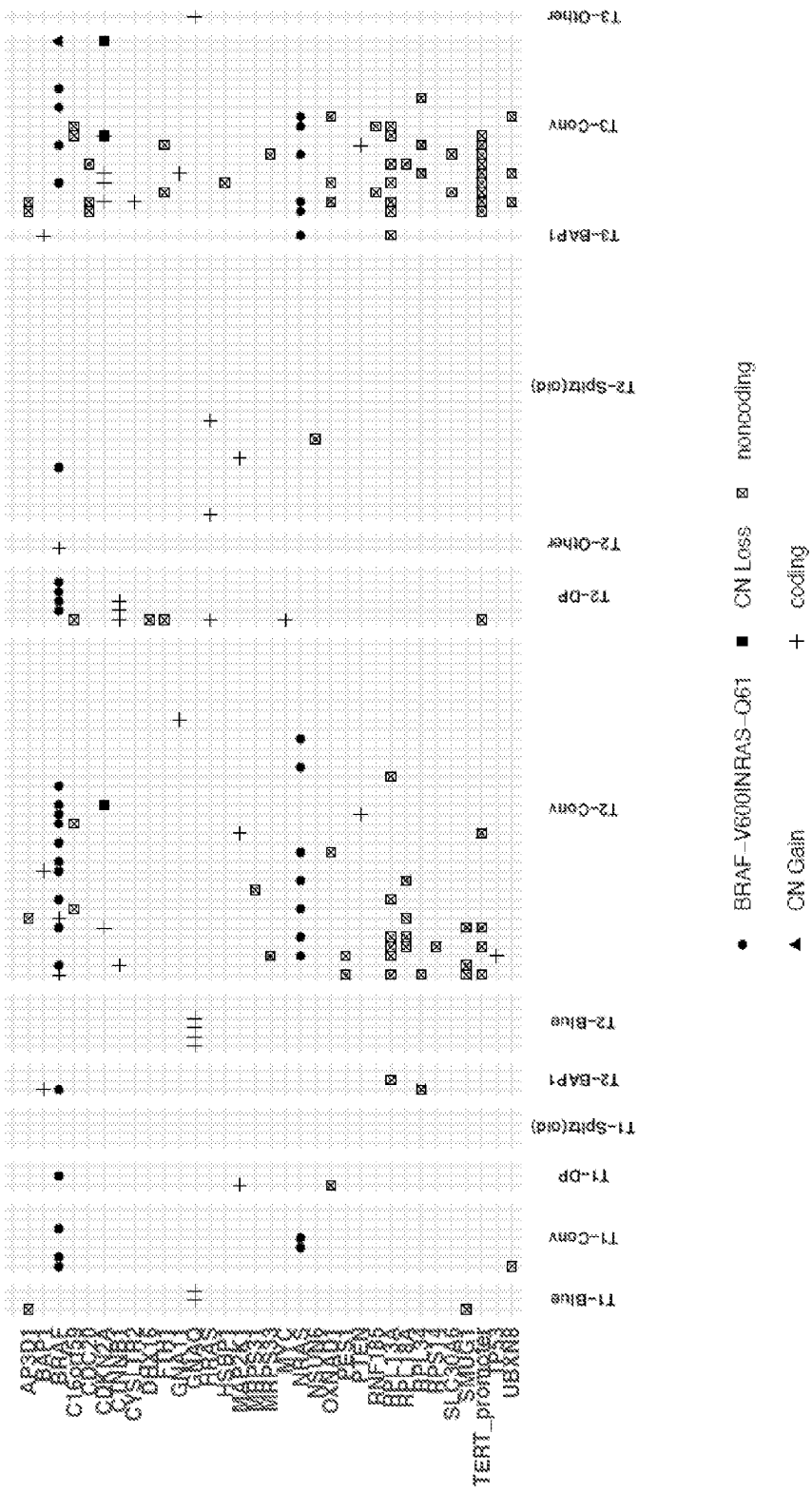

T1-Blue
T1-Conv
T1-DP
T1-Splitz(aid)
T2-BAP1
T2-Blue
T2-Conv
T2-DP
T2-Other
T2-Splitz(aid)
T3-BAP1
T3-Conv
T3-Other
BRAF_V600INRAS_Q61
CN Loss
noncoding
CN Gain
coding

Figure 8

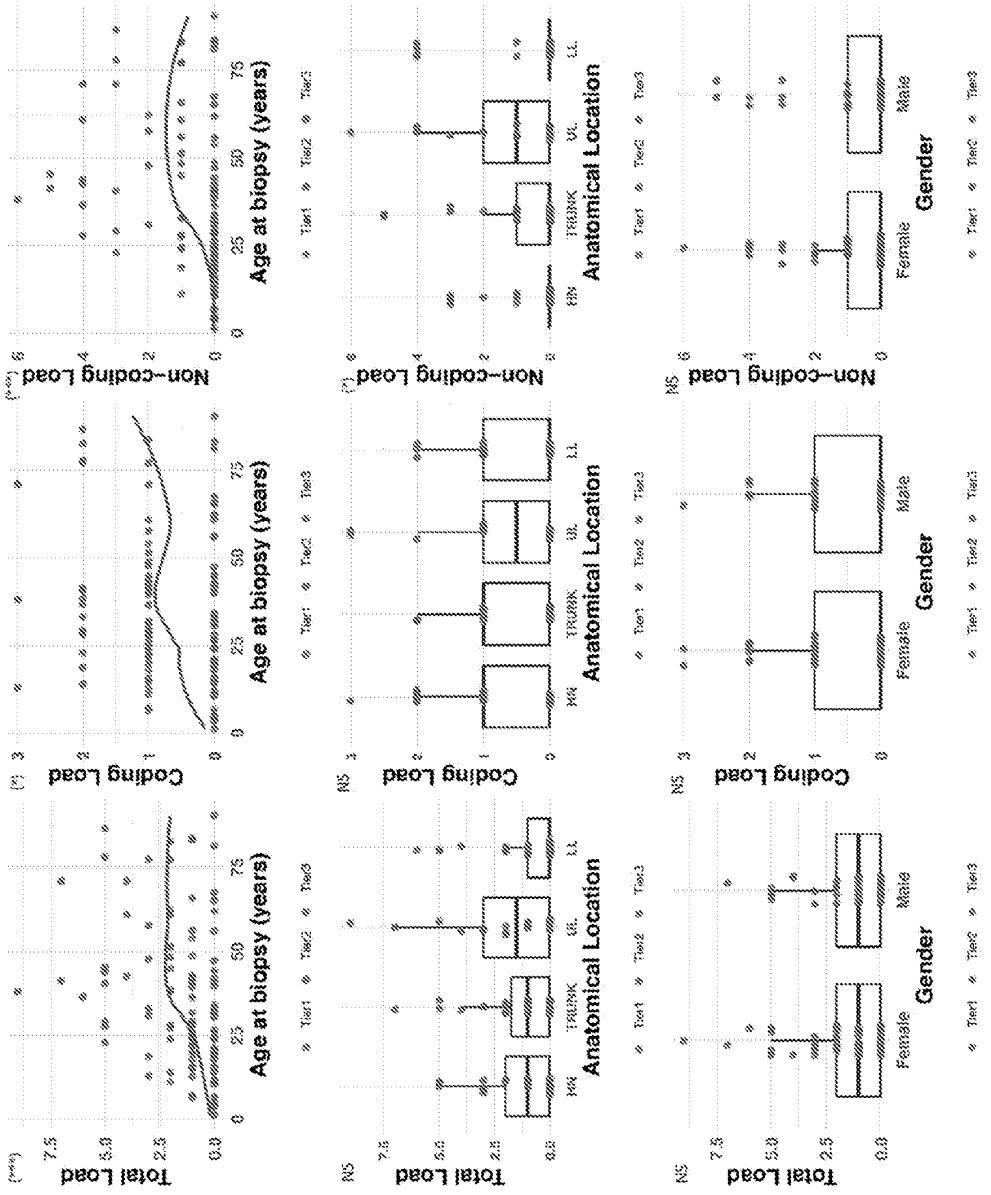

Total Load
Coding Load
Non−coding Load
Age at biopsy (years)
Anatomical Location
Gender
Female
Male
Tier1
Tier2
Tier3
NS

Figure 9

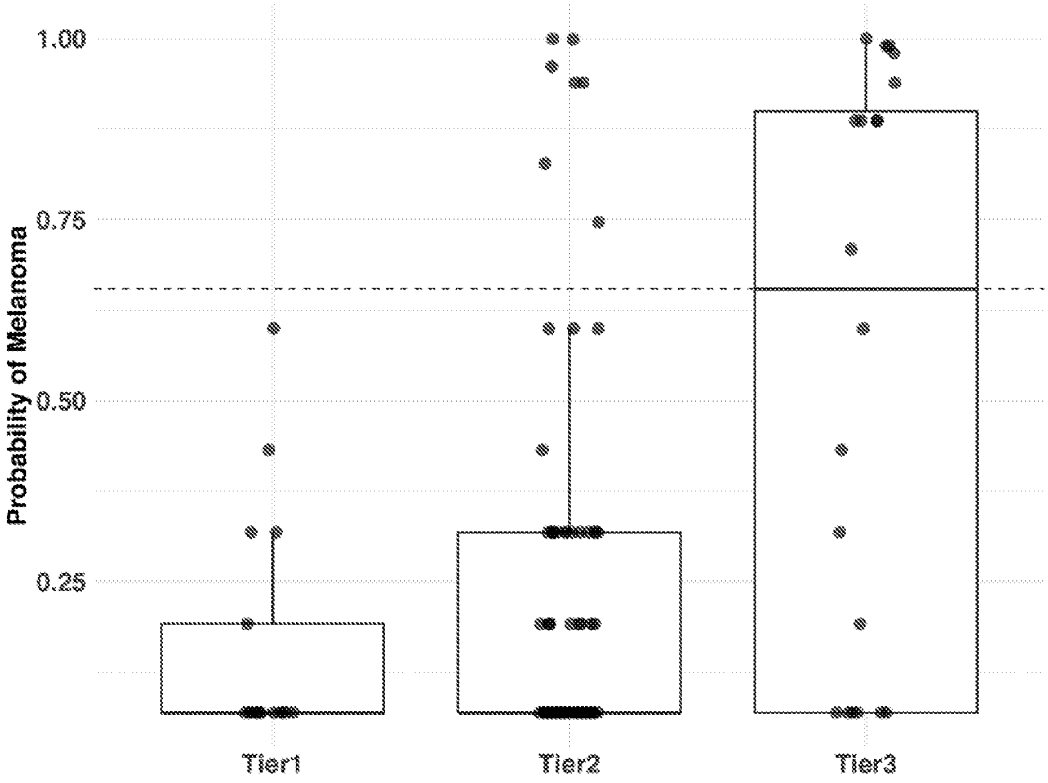


Figure 10

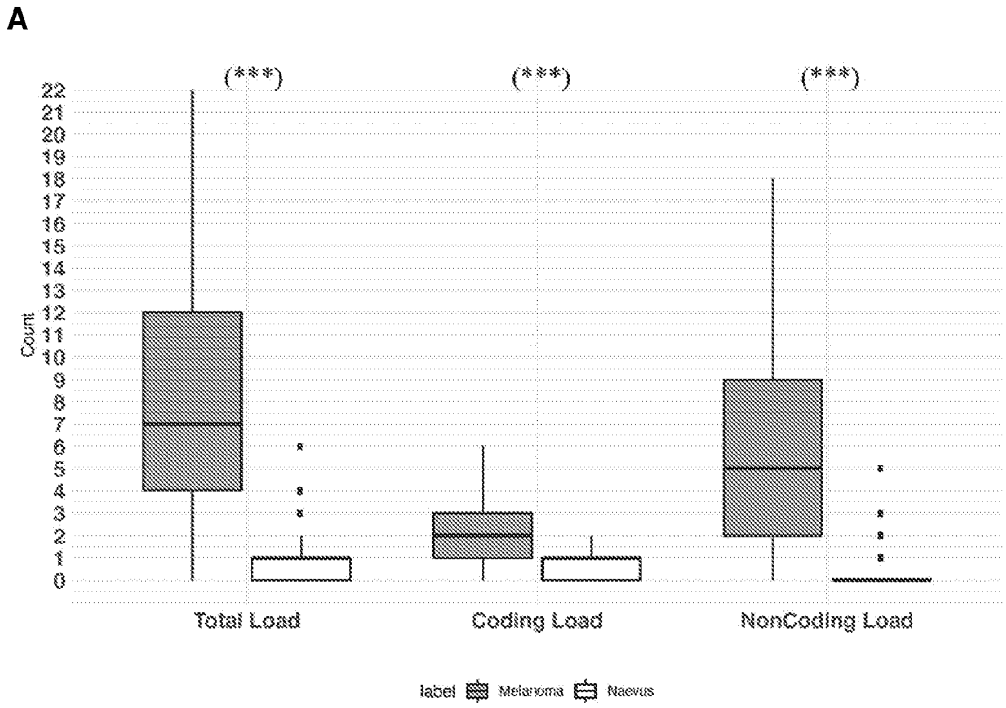

A
(***)
(***)
(***)
Count
Total Load
Coding Load
NonCoding Load
label Melanoma Naevus
B
(ns)
(ns)
(ns)
(ns)
(ns)
(ns)
(*)
(ns)
(*)
Count
Total Load
Coding Load
NonCoding Load
mutant.type BRAF-V600 NRAS-Q61 non-BRAF/non-NRAS

Figure 11

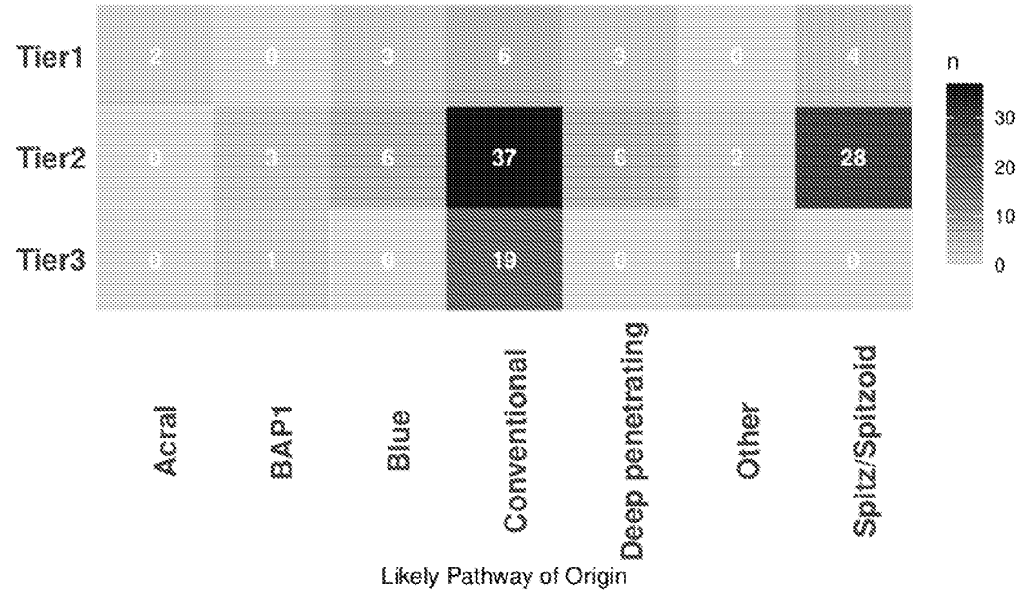

Tier1
Tier2
Tier3
2
0
3
6
3
6
4
3
1
6
37
6
2
28
0
1
0
19
0
1
0
n
30
20
10
0
Acral
BAP1
Blue
Conventional
Deep penetrating
Other
Spitz/Spitzoid
Likely Pathway of Origin

Figure 12

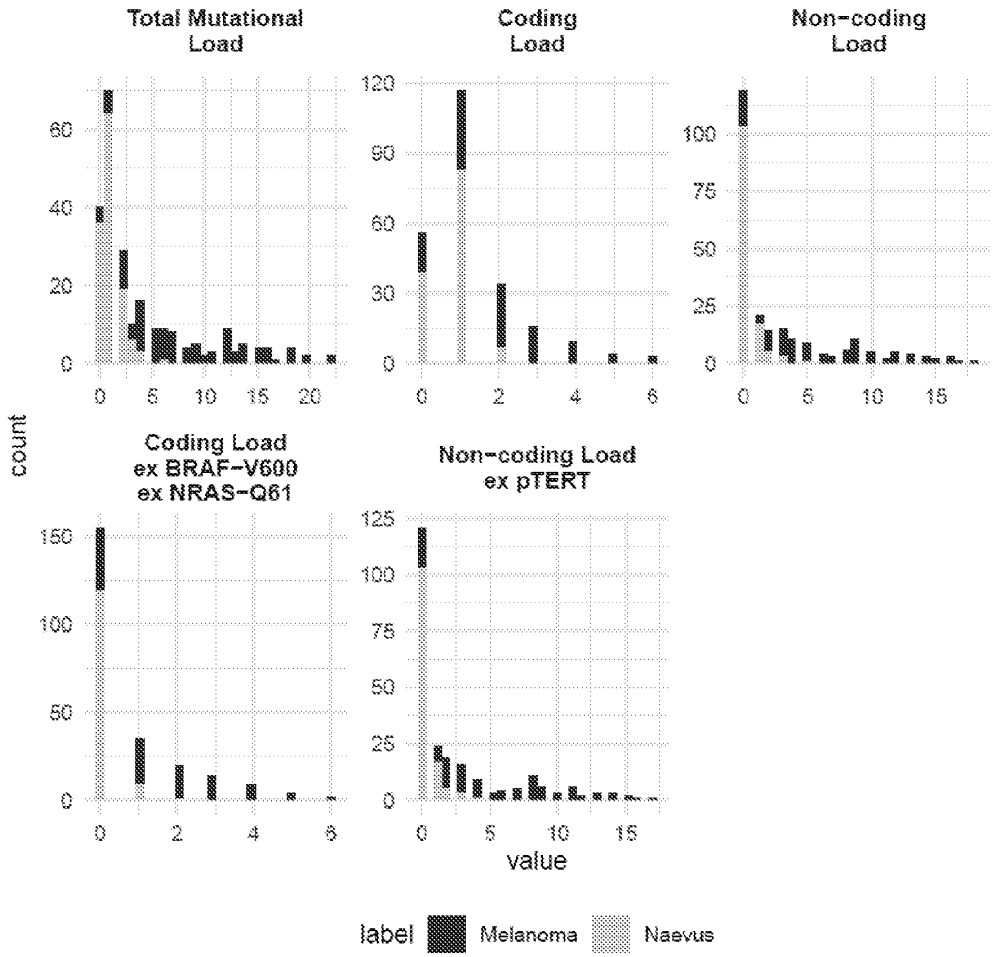

Total Mutational Load
Coding Load
Non−coding Load
Coding Load ex BRAF−V600 ex NRAS−Q61
Non−coding Load ex pTERT
count
value
label
Melanoma
Naevus

Figure 13

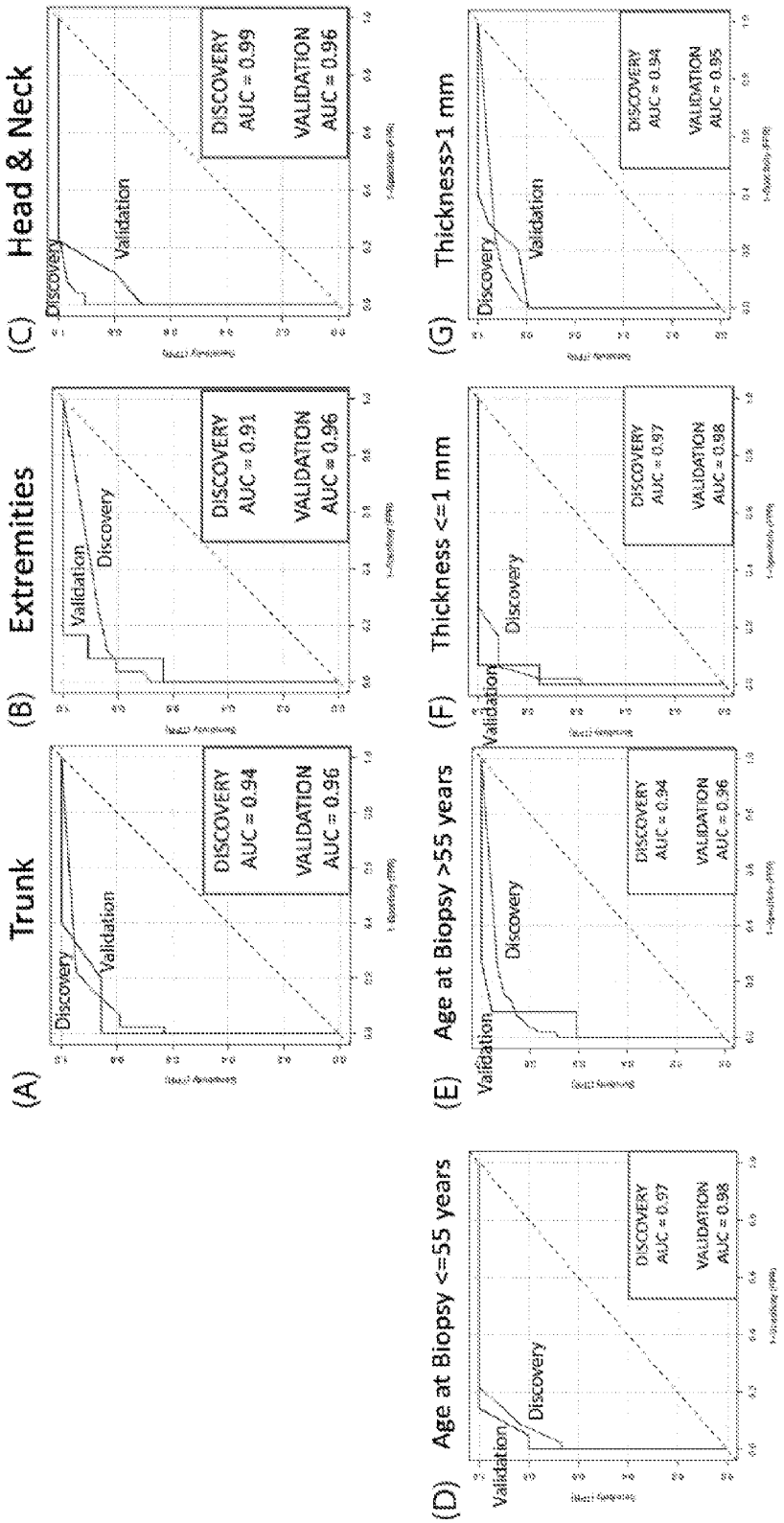

(A) Trunk
Discovery
Validation
DISCOVERY AUC = 0.94
VALIDATION AUC = 0.96
(B) Extremities
Validation
Discovery
DISCOVERY AUC = 0.91
VALIDATION AUC = 0.96
(C) Head & Neck
Discovery
Validation
DISCOVERY AUC = 0.99
VALIDATION AUC = 0.96
(D) Age at Biopsy <=55 years
Validation
Discovery
DISCOVERY AUC = 0.97
VALIDATION AUC = 0.98
(E) Age at Biopsy >55 years
Validation
Discovery
DISCOVERY AUC = 0.94
VALIDATION AUC = 0.96
(F) Thickness <=1 mm
Validation
Discovery
DISCOVERY AUC = 0.97
VALIDATION AUC = 0.98
(G) Thickness>1 mm
Discovery
Validation
DISCOVERY AUC = 0.94
VALIDATION AUC = 0.95

Figure 14

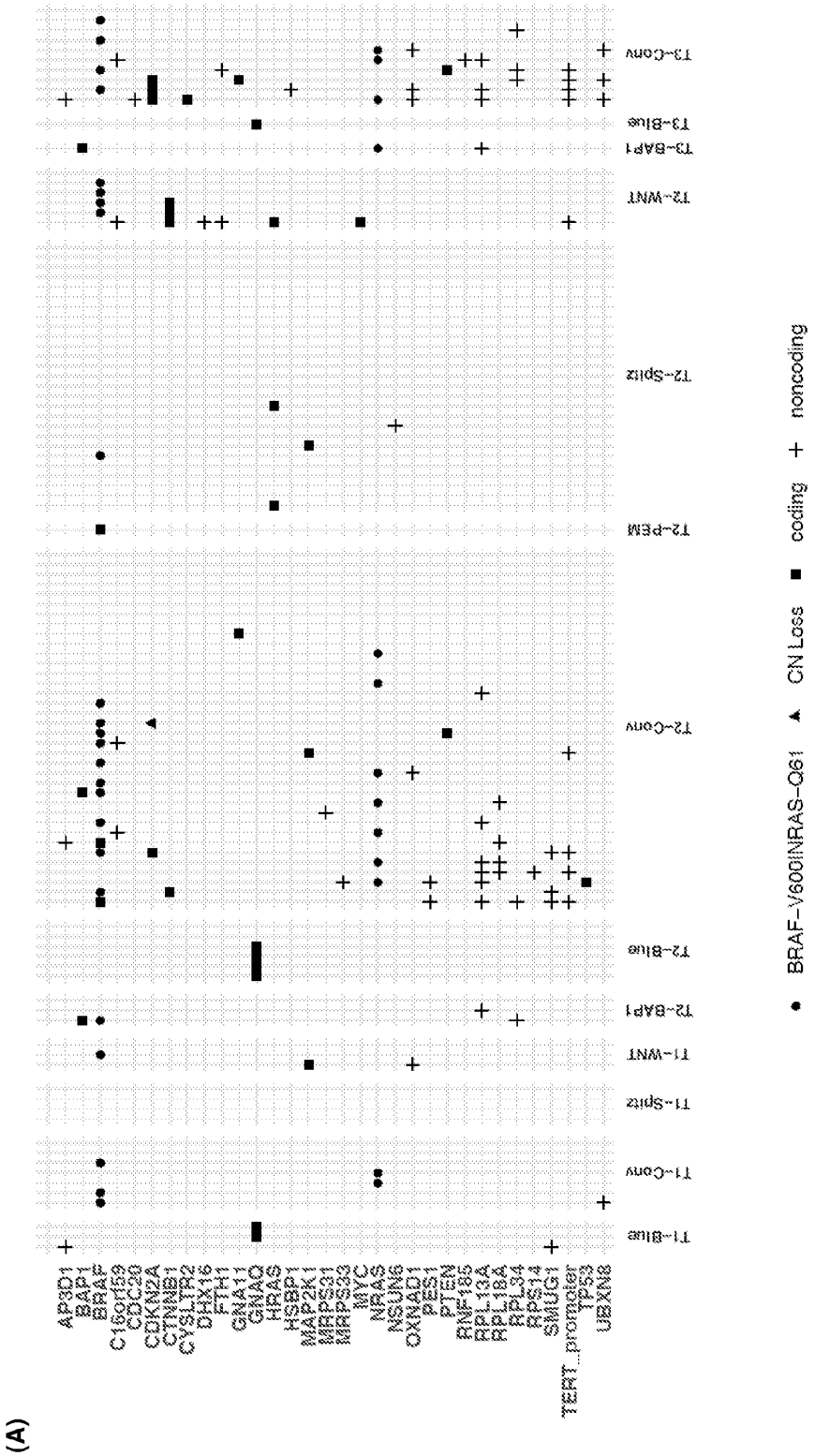

(A)
AP3D1
BAP1
BRAF
C16orf59
CDC20
CDKN2A
CTNNB1
CYSLTR2
DHX16
FTH1
GNA11
GNAQ
HRAS
HSBP1
MAP2K1
MRPS31
MRPS33
MYC
NRAS
NSUN6
OXNAD1
PES1
PTEN
RMP185
RPL13A
RPL18A
RPL34
RPS14
SMUG1
TERT_promoter
TP53
UBXN8
T1~Blue
T1~Conv
T1~Spitz
T1~WNT
T2~BAP1
T2~Blue
T2~Conv
T2~PEM
T2~Spitz
T2~WNT
T3~BAP1
T3~Blue
T3~Conv
BRAF−V600|NRAS−Q61
CN Loss
coding
noncoding

Figure 14 continued

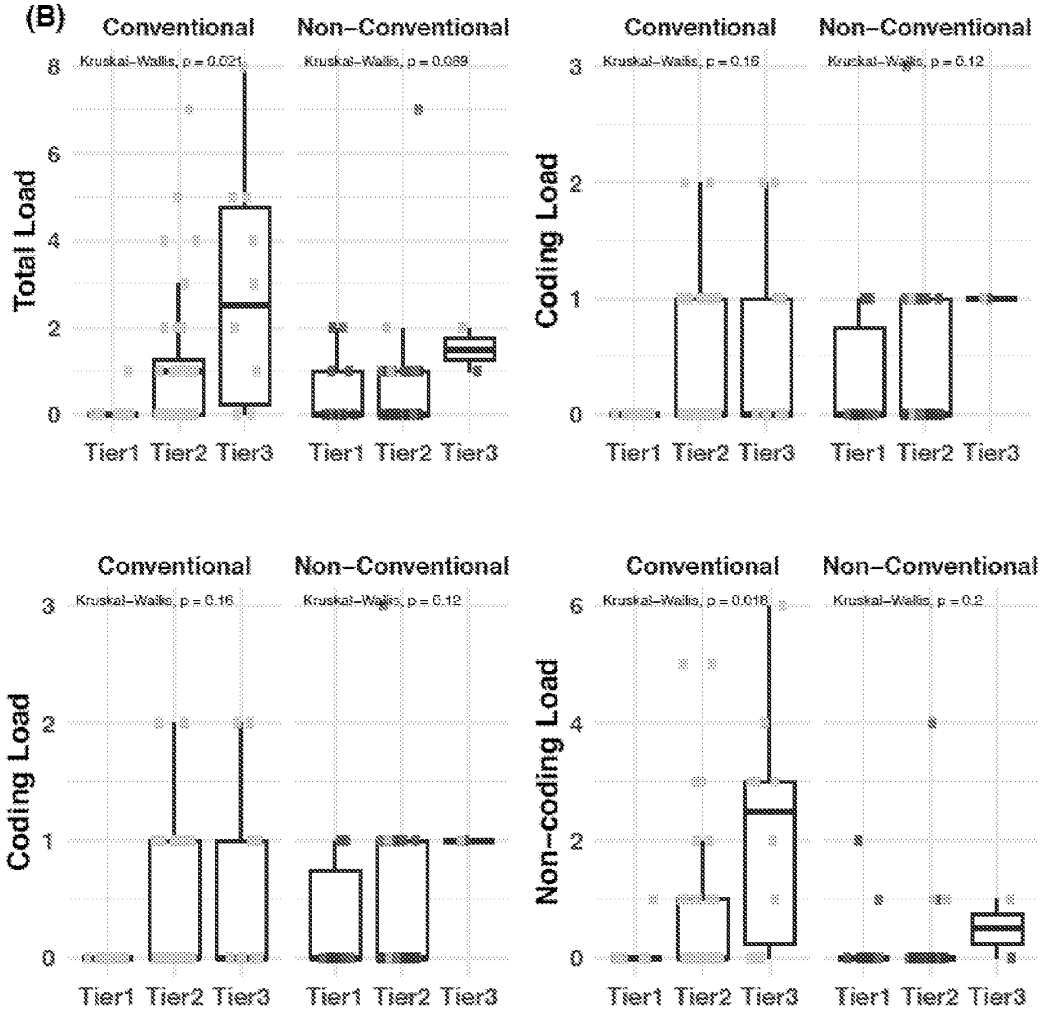


Figure 14 continued

(C)

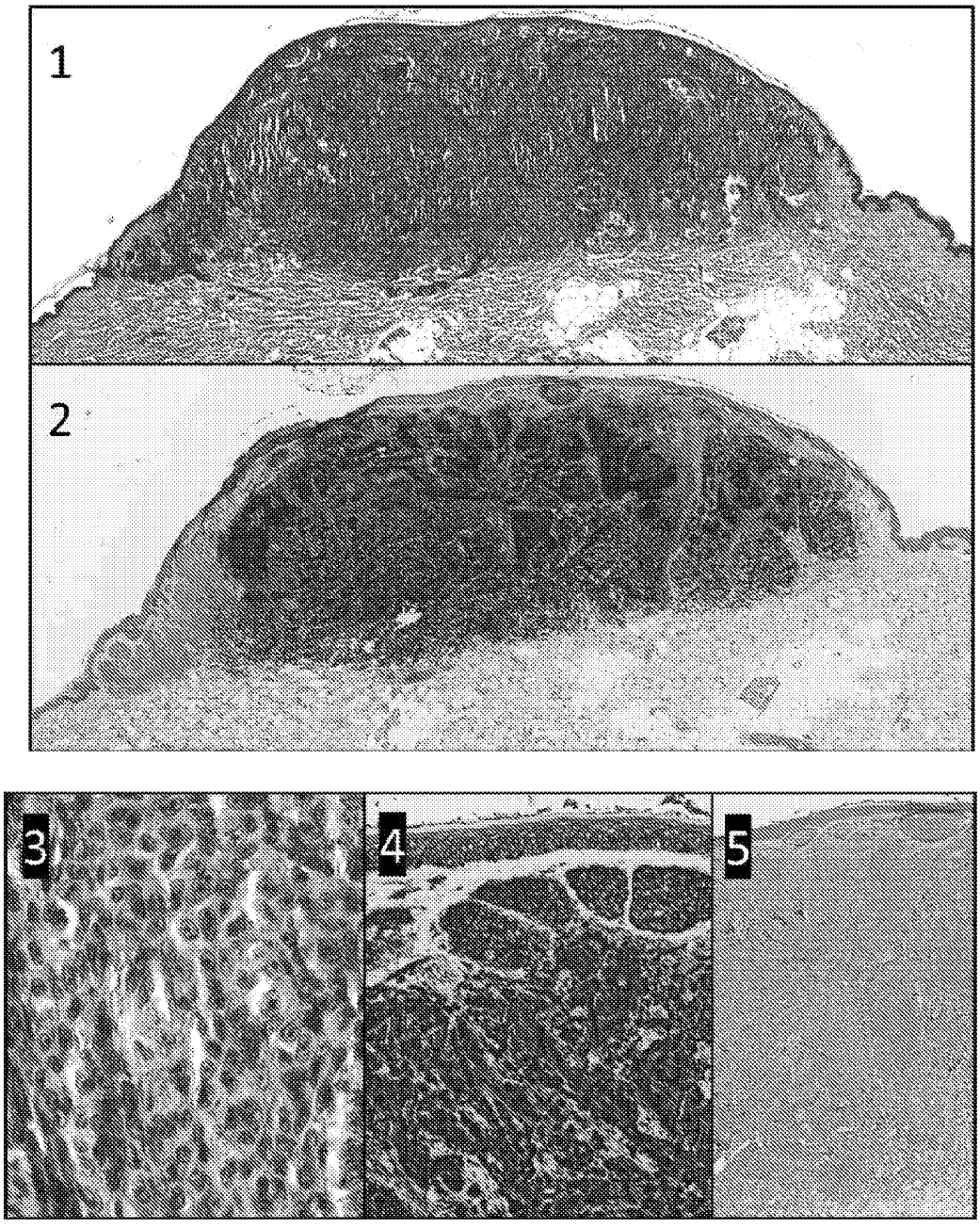
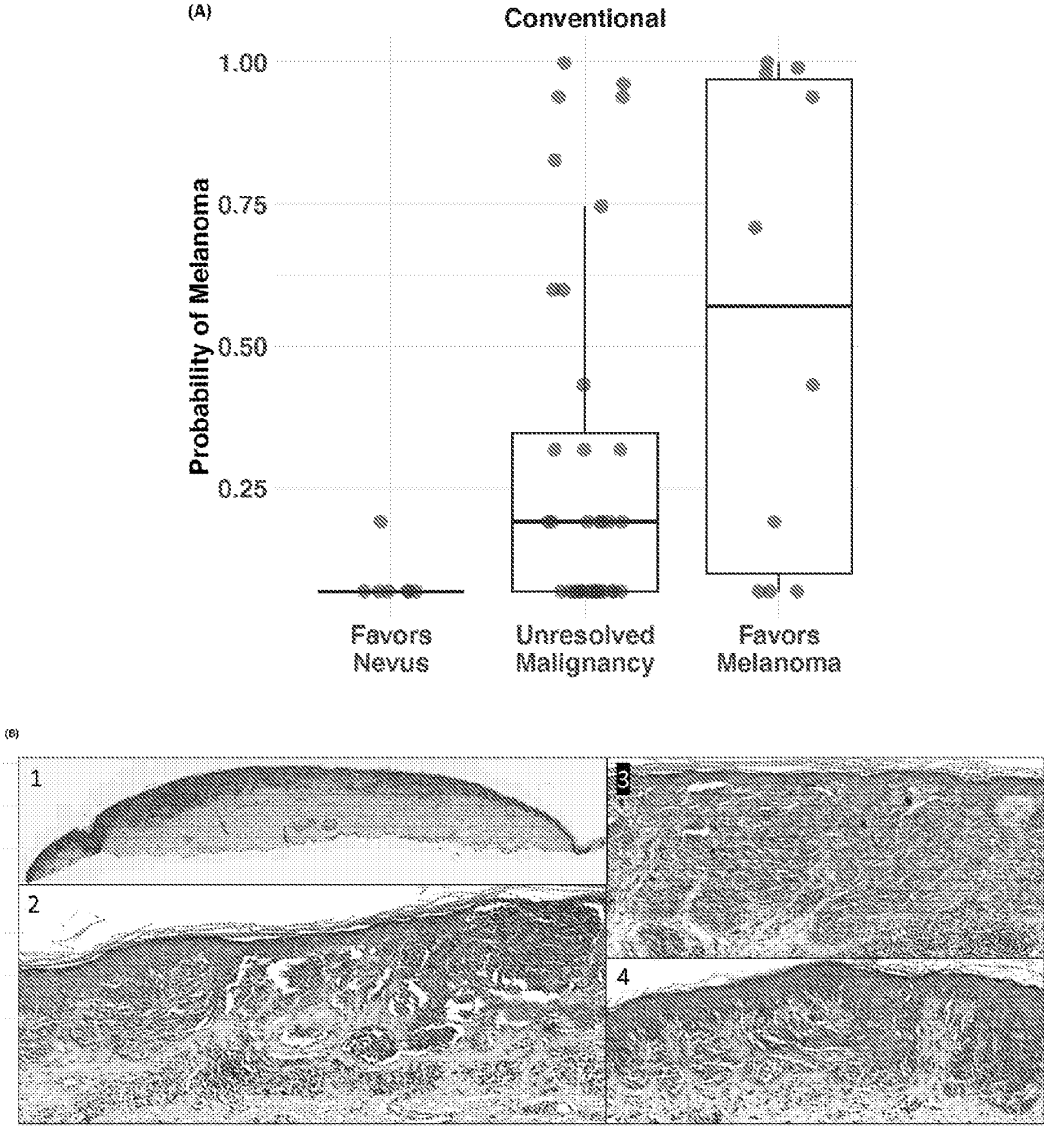


Figure 15


(A)
Conventional
Probability of Melanoma
1.00
0.75
0.50
0.25
Favors Nevus
Unresolved Malignancy
Favors Melanoma
(B)
1
2
3
4