Memorial Sloan Kettering Cancer Center

IMPACT annotator

September 11, 2018

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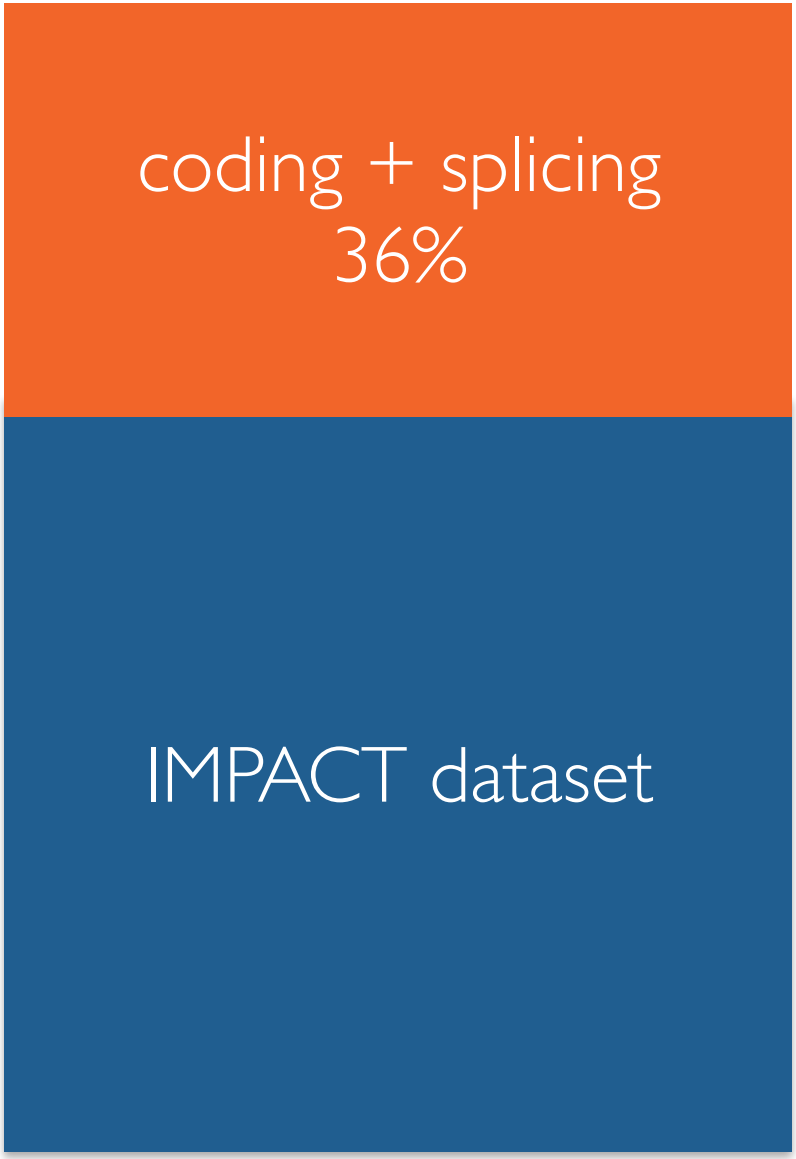
Recurrent synonymous mutations

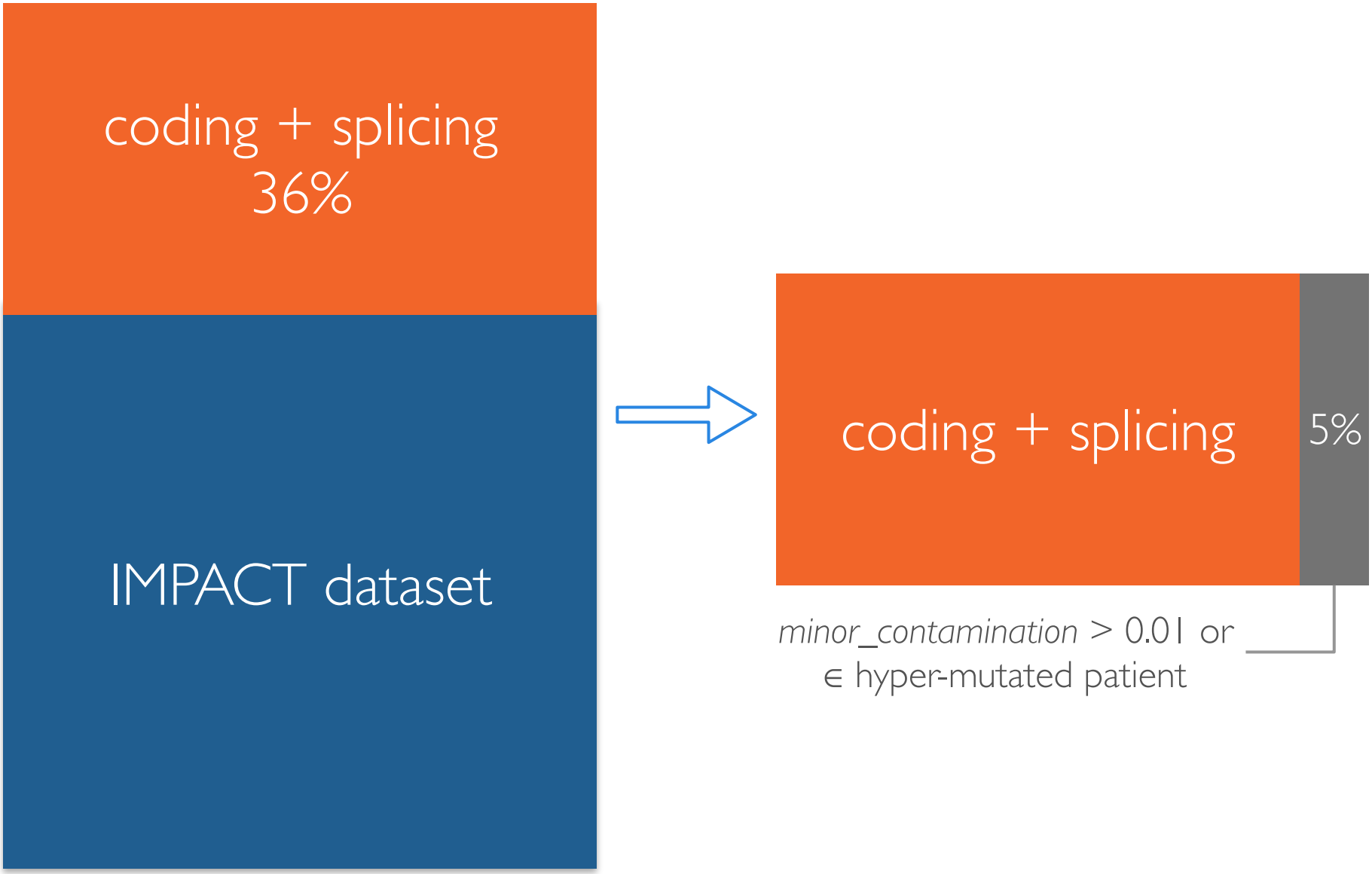
# of patients	Description	Gene	Gene Type	HGVSp	COSMIC count
64	17:7579312 C/T (30) & C/A (29) & C/G (5)	TP53	Tumor suppressor	p.T125T	71 (30 & 37 & 4)
21	18:60985833 & 18:60985834 G/A (11) & C/T (10)	BCL2	Oncogene	p.K22K & p.L23L	19 (13 & 6)
18	6:26056117 C/T	HIST1H1C	Unknown	p.A180A	8
13	20:41101171 G/A	PTPRT	Tumor suppressor	p.I395I	6
11	20:40790142 C/T	PTPRT	Tumor suppressor	p.T863T	0
11	17:7578177 C/T	TP53	Tumor suppressor	p.E224E	15
11	20:9525085 C/T	PAK5	Unknown	p.R600R	0
10	21:39795342 G/A	ERG	Oncogene	p.I126I	0

last exon base

The IMPACT sub-dataset used

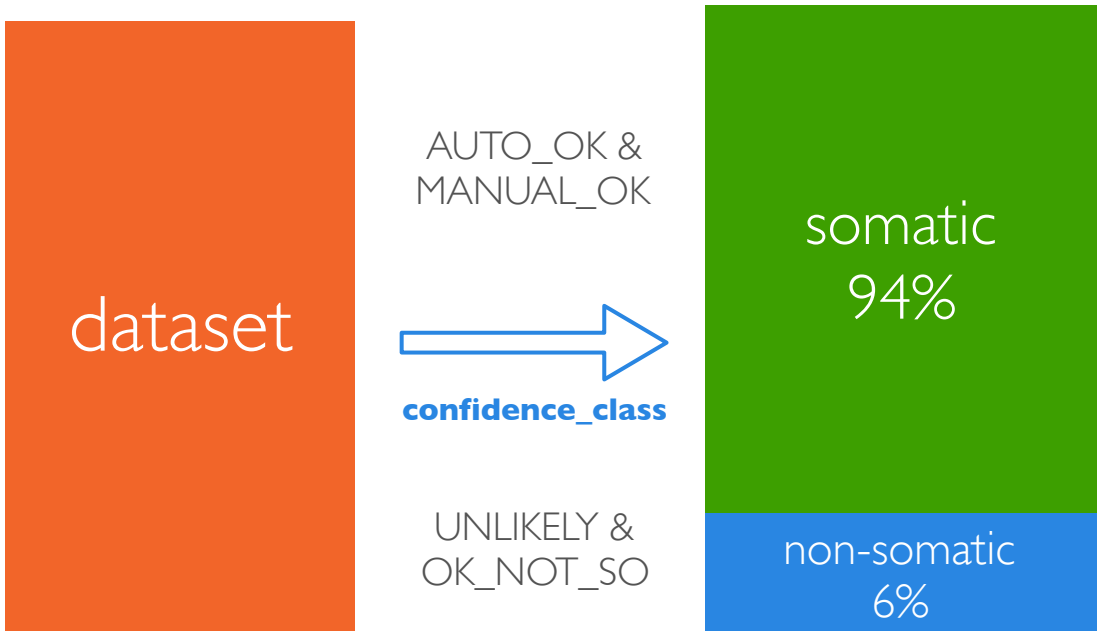


The IMPACT sub-dataset used



Different classes

Different classes



Different classes

dataset

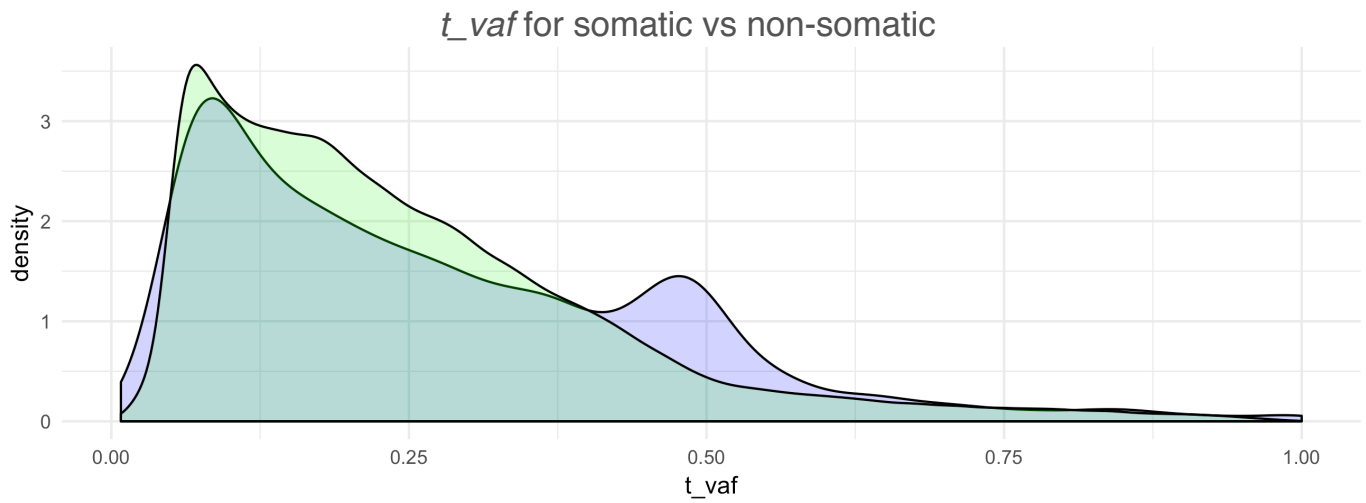
AUTO_OK &
MANUAL_OK

confidence_class

UNLIKELY &
OK_NOT_SO

somatic
94%

non-somatic
6%



non-somatic = artefact + germline

Different classes

dataset

AUTO_OK &
MANUAL_OK

confidence_class

UNLIKELY &
OK_NOT_SO

somatic
94%

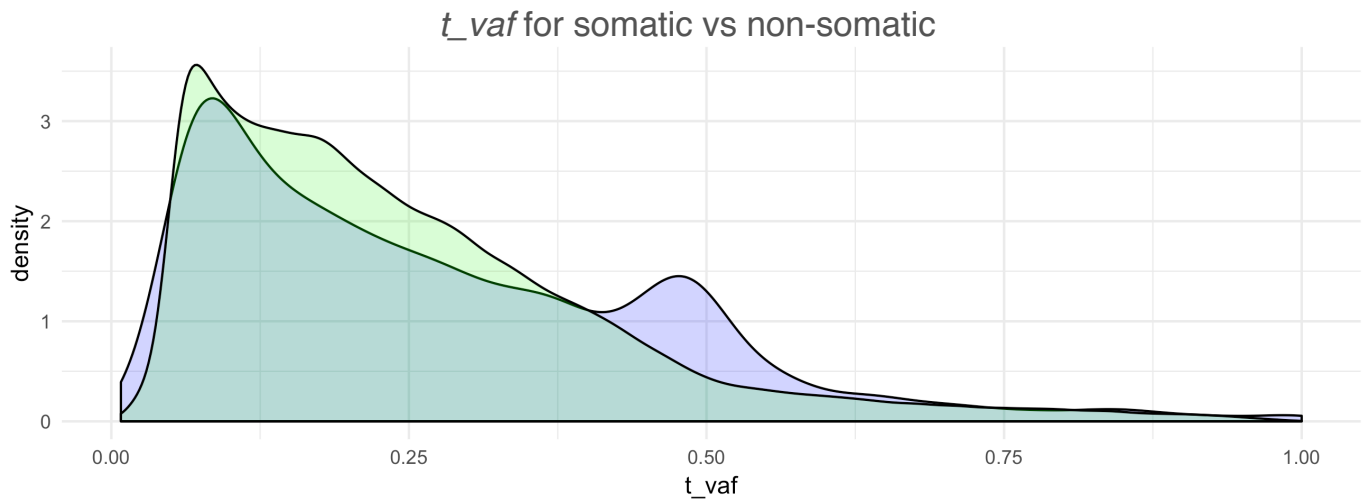
non-somatic
6%

oncokb-annotator

driver
32%

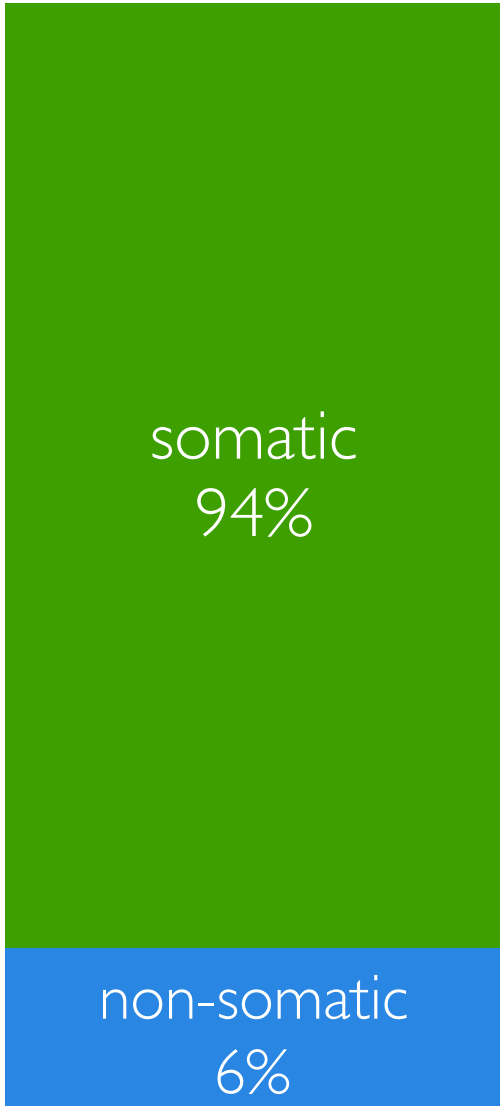
passenger
62%

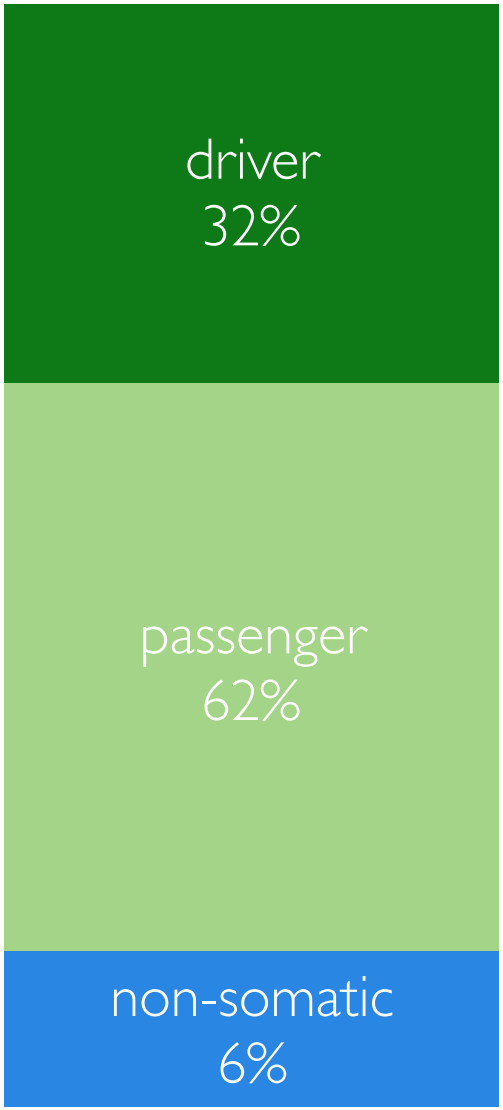
non-somatic
6%



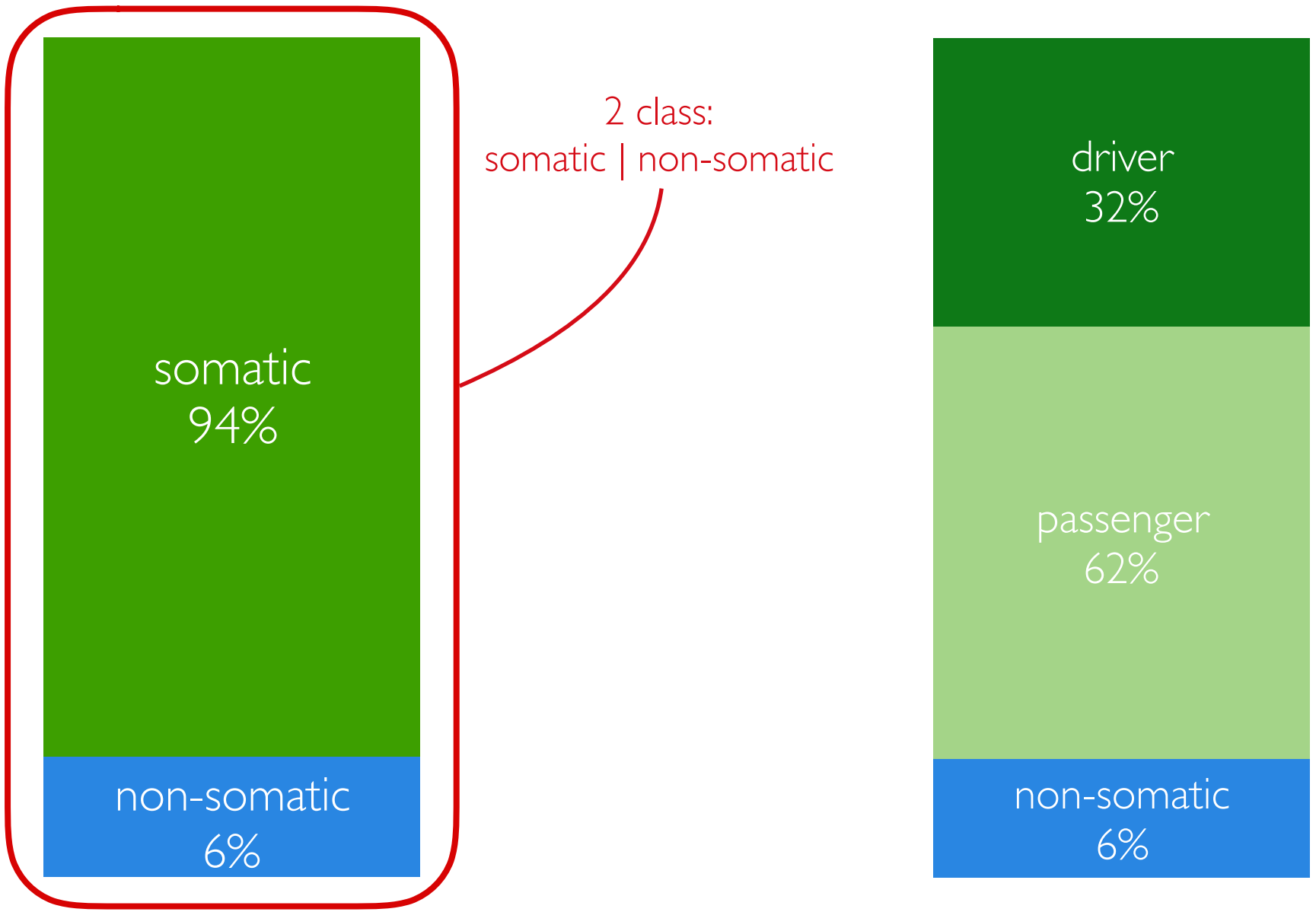
non-somatic = artefact + germline

Supervised learning

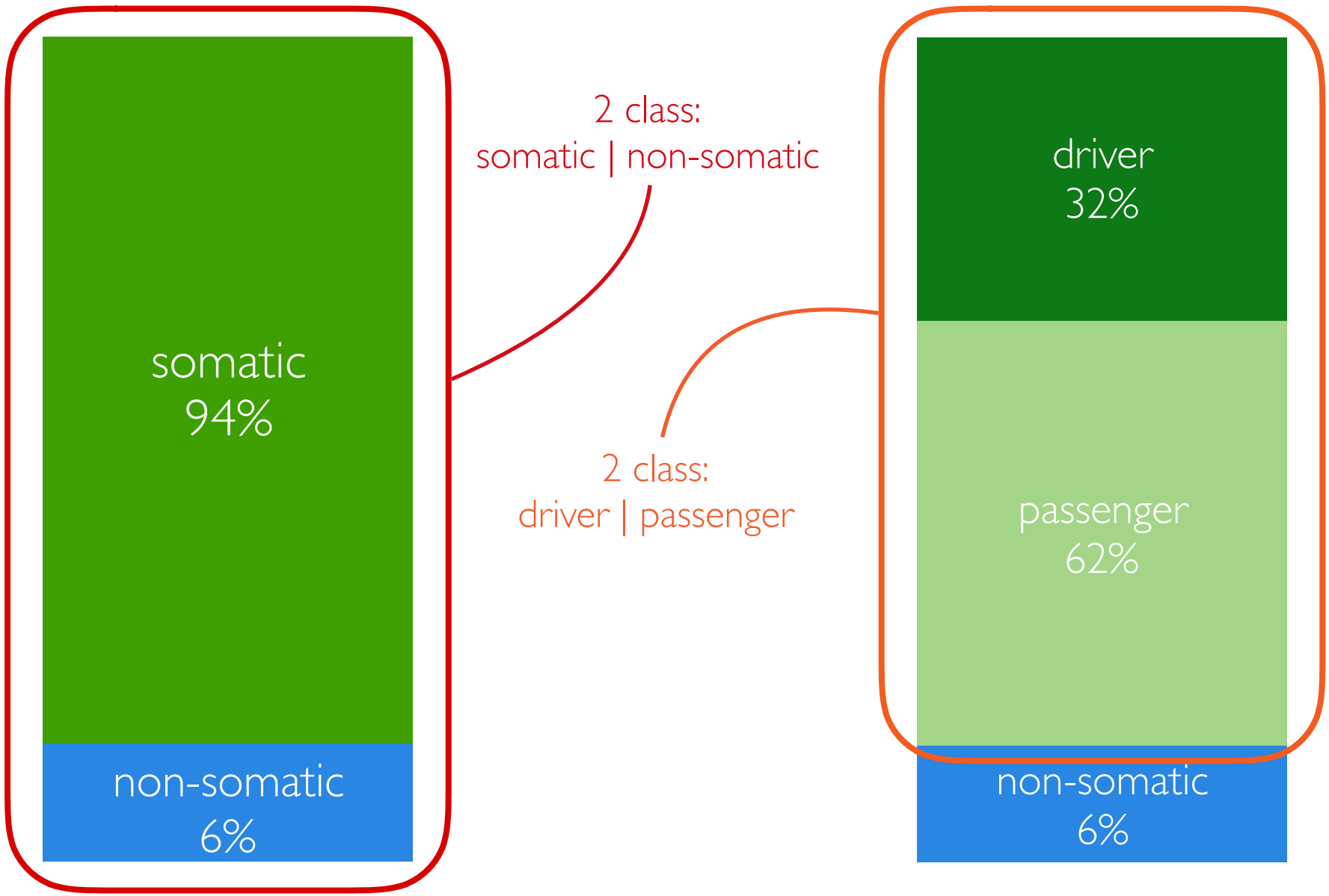




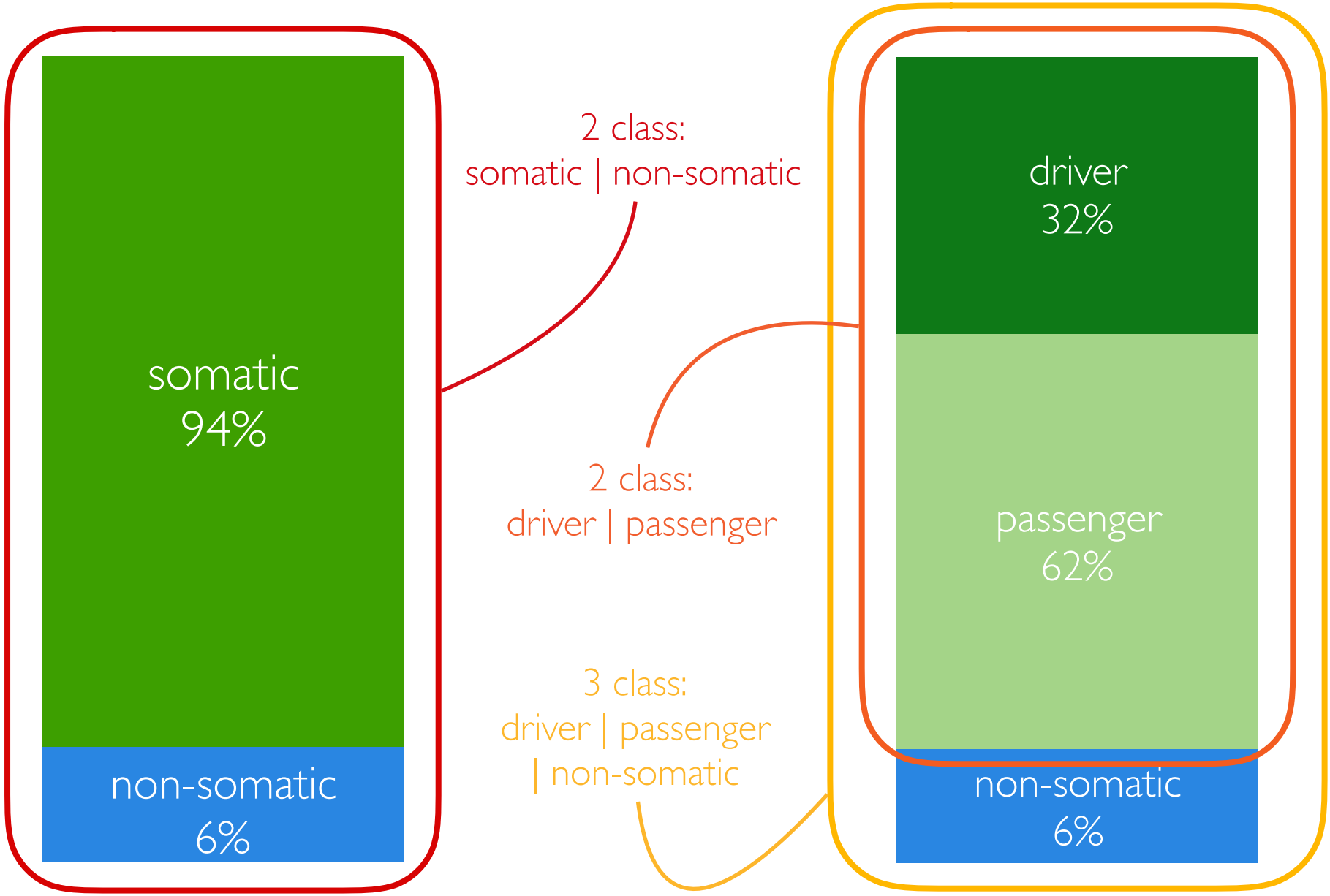
Supervised learning



Supervised learning

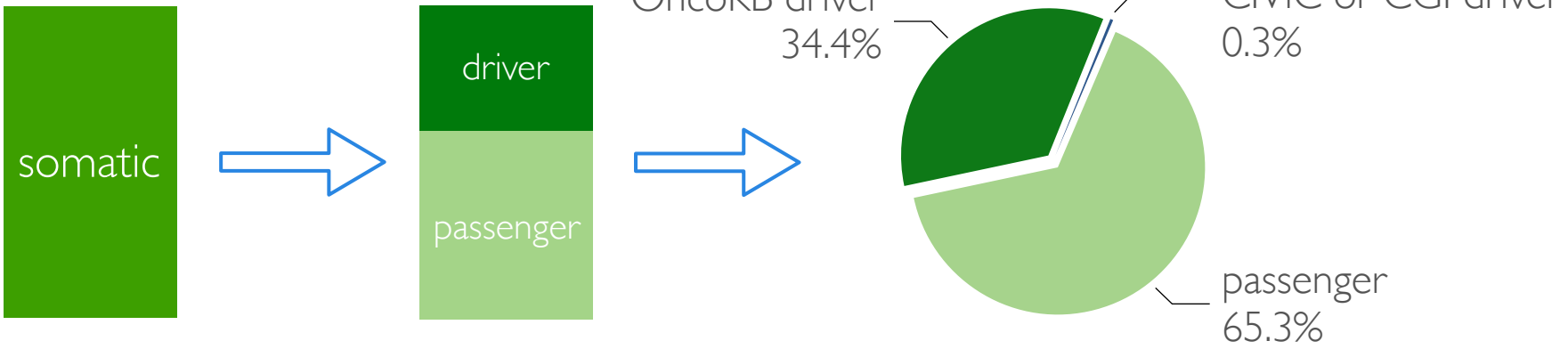


Supervised learning



Literature

Variant annotation databases



Existing algorithms

→ SIFT, PolyPhen-2: predicts whether an amino-acid substitution affects protein function
- not cancer specific

→ CHASM, FATHMM, CanDrA, CScape, rDriver, …: supervised learning for driver classification
- no sequencing features
- non-synonymous SNVs only
- smaller and not "real" dataset
- never done on somatic vs non-somatic

The features

NGS features

- vaf
- strand ratio
- …

Frequency in normals

Population AF

- Kaviar
- GnomAD

COSMIC score

Impact scores

- SIFT
- PolyPhen-2
- …

Genetic features

- gene and gene type
- mutation effect
- …

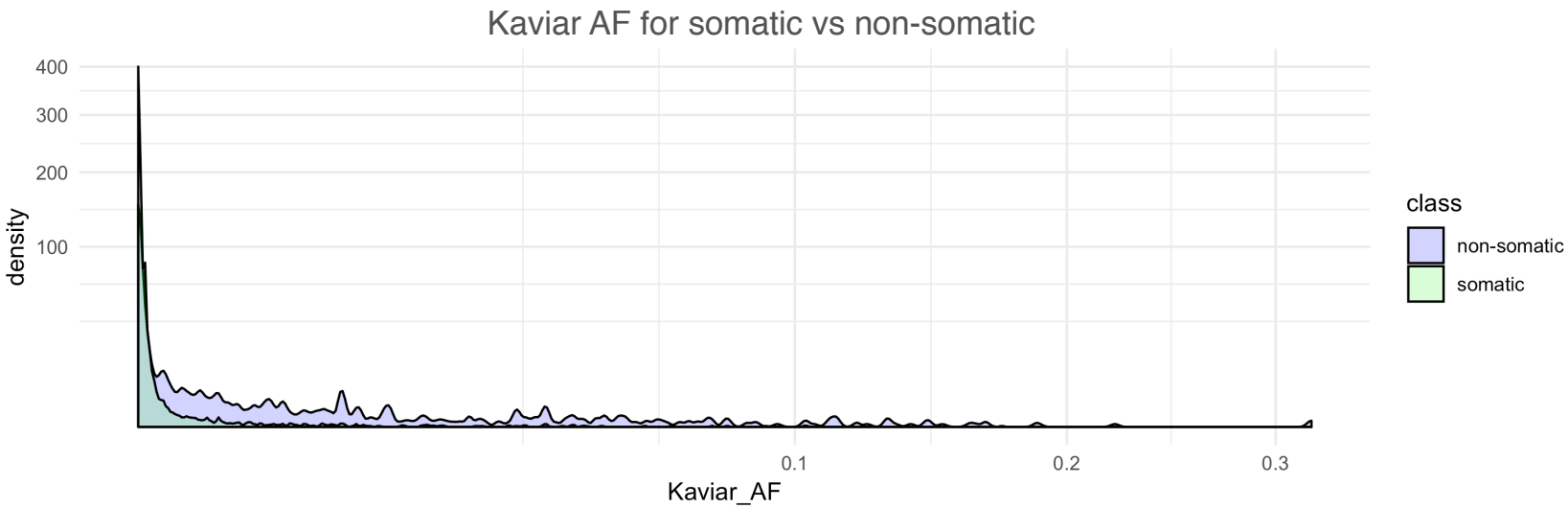
Cancer type?

Any ideas?

Example of informative feature

somatic

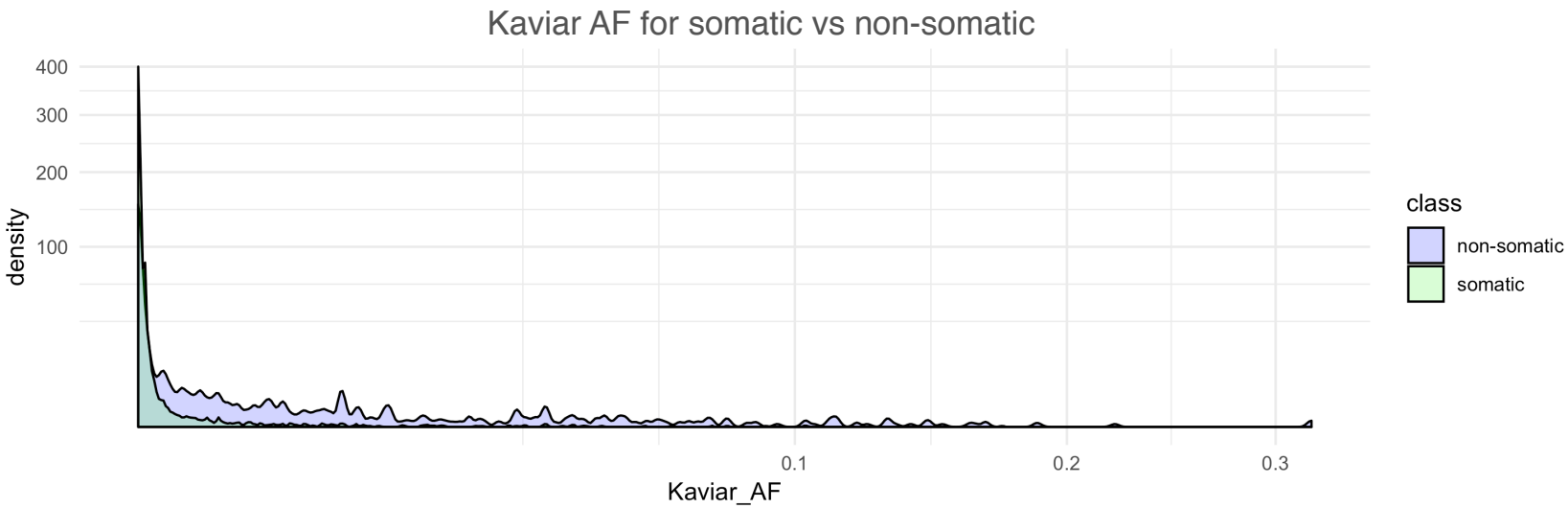
non-somatic



Example of informative feature

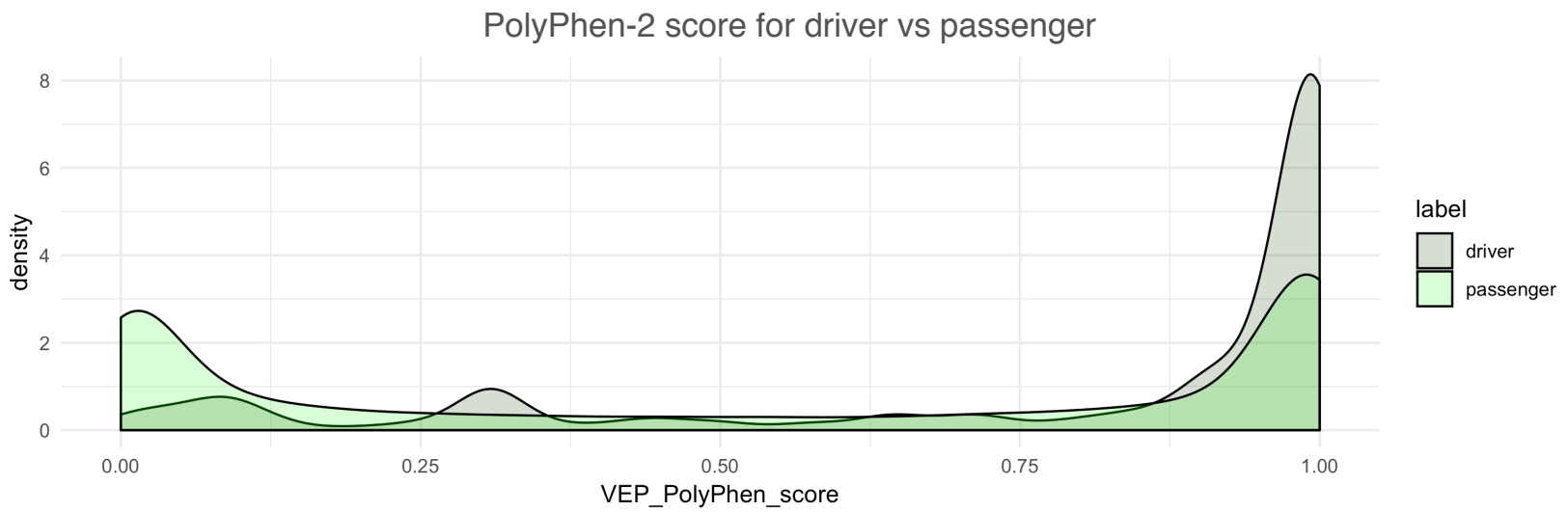
somatic

non-somatic

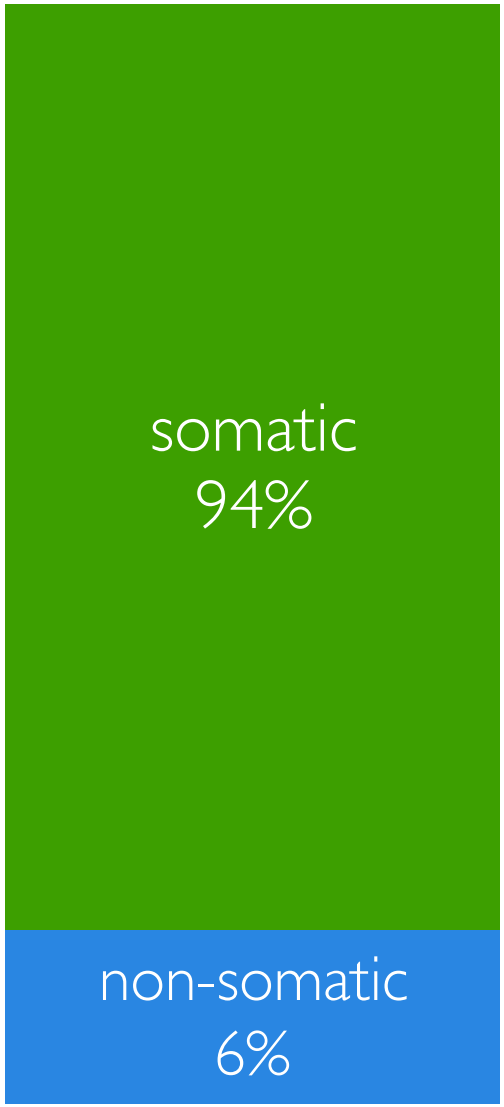


driver

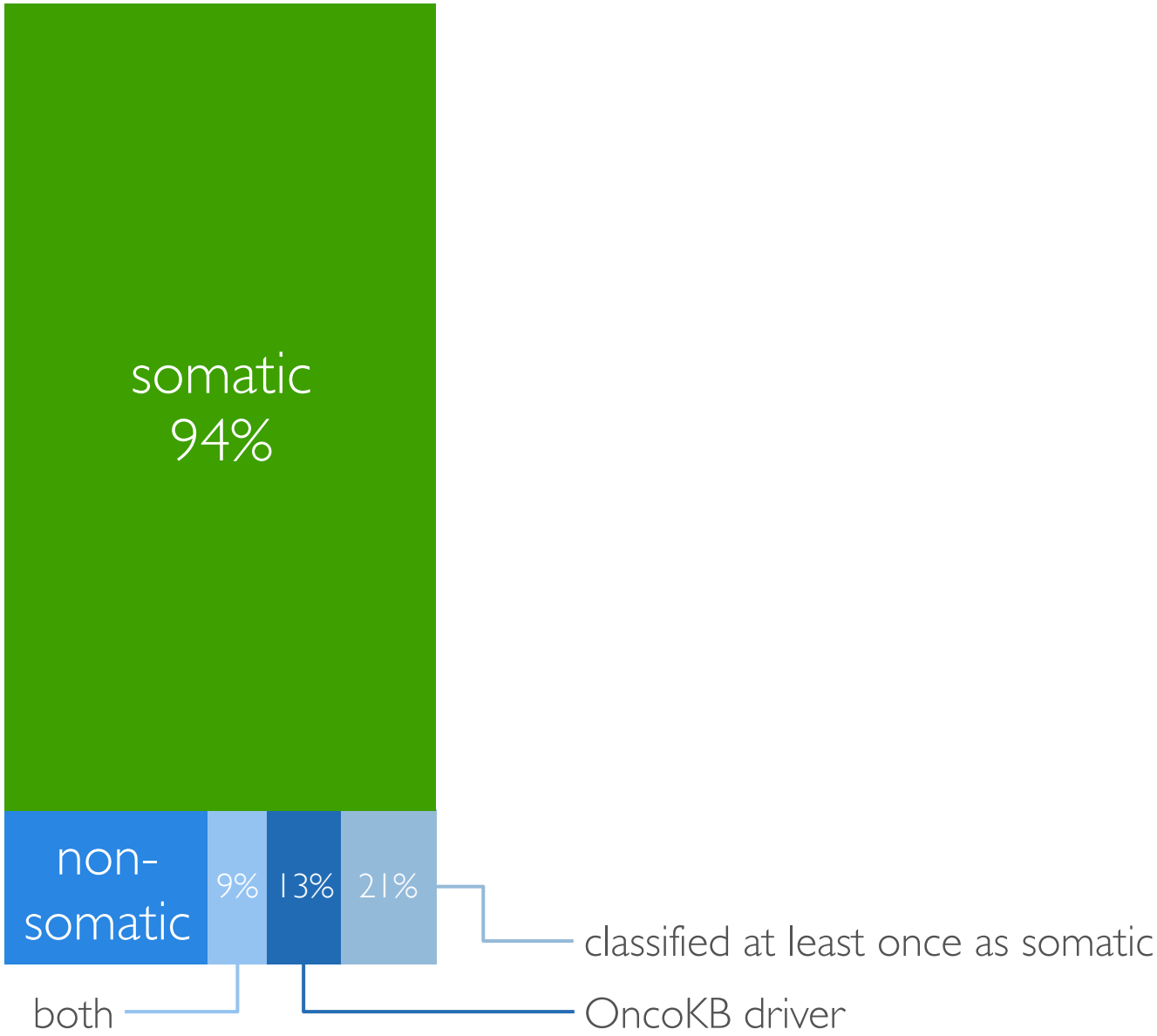
passenger



somatic vs non-somatic



somatic vs non-somatic



somatic vs non-somatic

somatic
94%

non-somatic

9%

13%

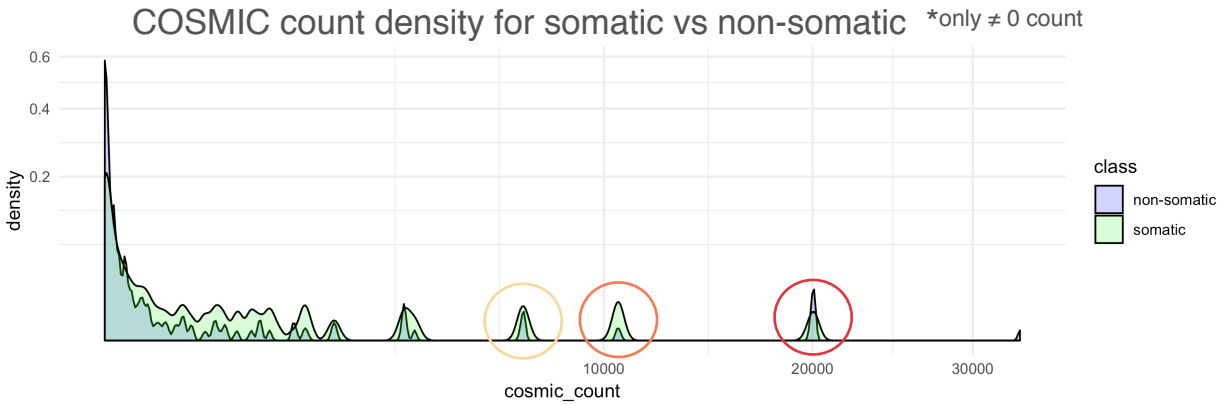
21%

both

classified at least once as somatic

OncoKB driver

Ex: hotspots classified as non-somatic



Description	Gene	HGVSp	COSMIC count	somatic count	non-somatic count	OncoKB driver
7:140453136 A/T	BRAF	p.V600E	20034	622	32	✓
12:25398284 C/T	KRAS	p.G12D	10579	1110	2	✓
12:25398284 C/A	KRAS	p.G12V	7055	896	10	✓

Inconsistent somatic vs non-somatic metrics