Memorial Sloan Kettering
Cancer Center

Variant classification

Developing a knowledge-based approach using IMPACT data

November 8, 2018

Papaemmanuil Lab
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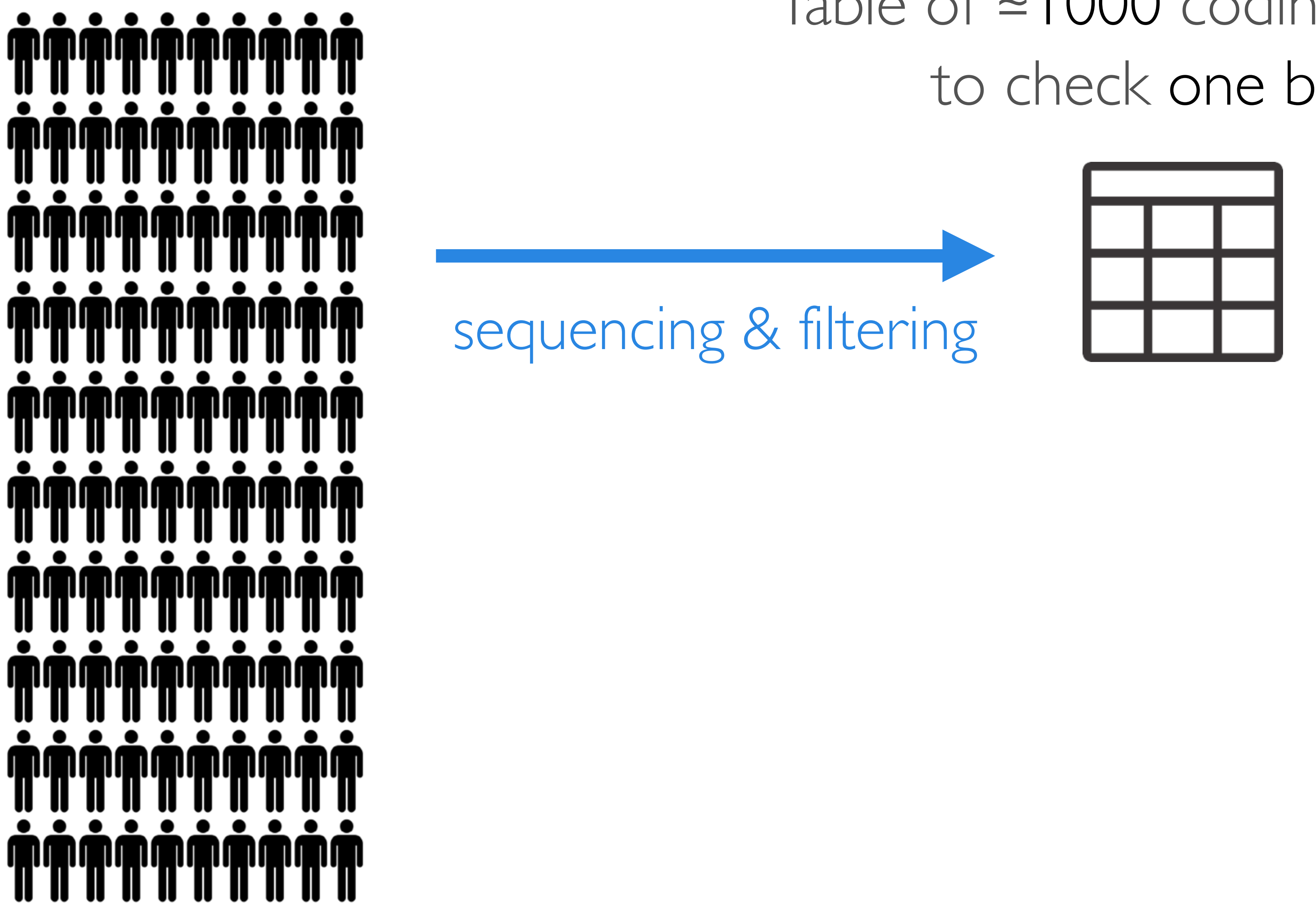
In collaboration with A. Zehir, R. Ptashkin and C. Debyani

A variant classifier, why is it important?



100 patients

sequencing & filtering

Table of ≃1000 coding mutations
to check one by one

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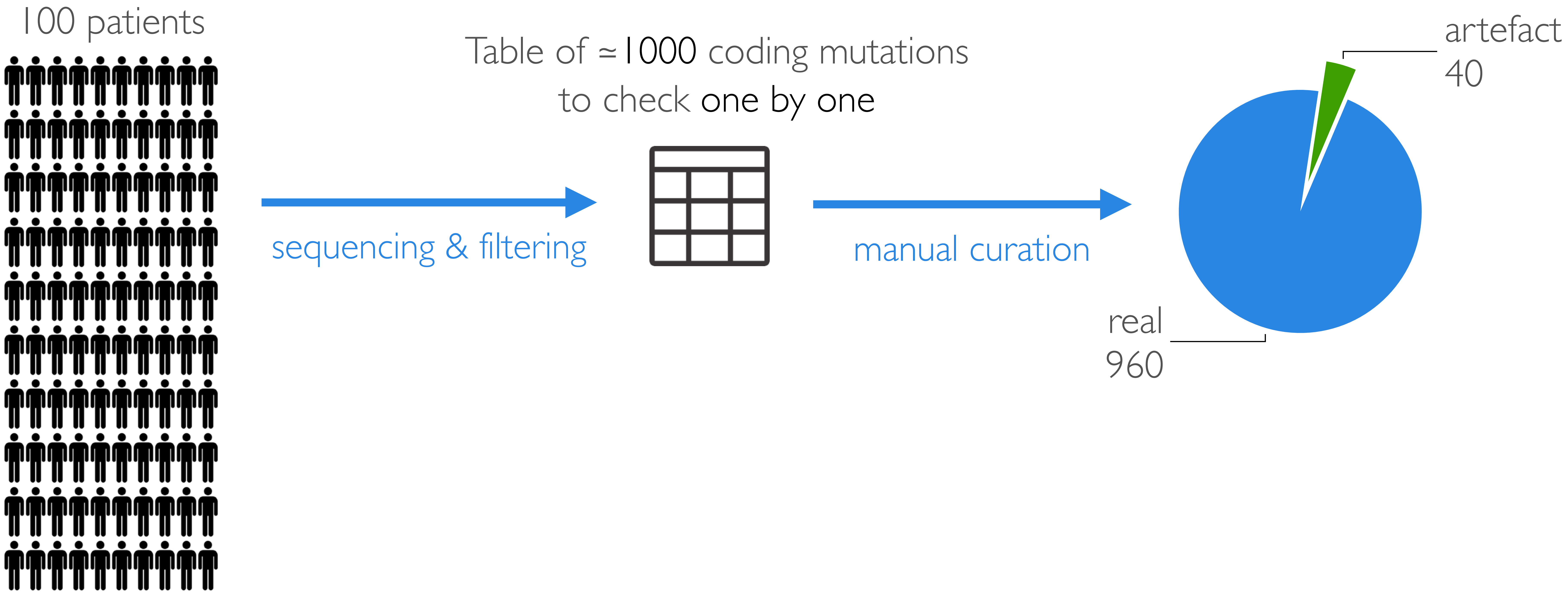

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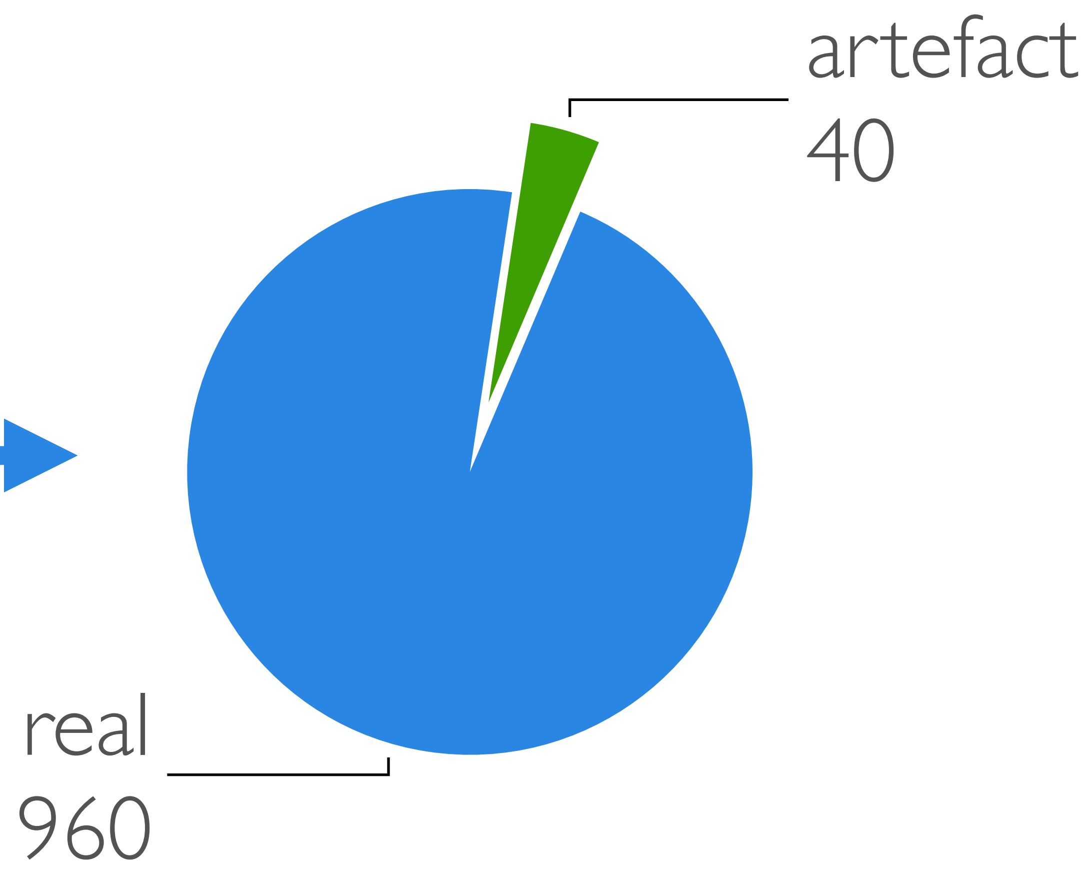
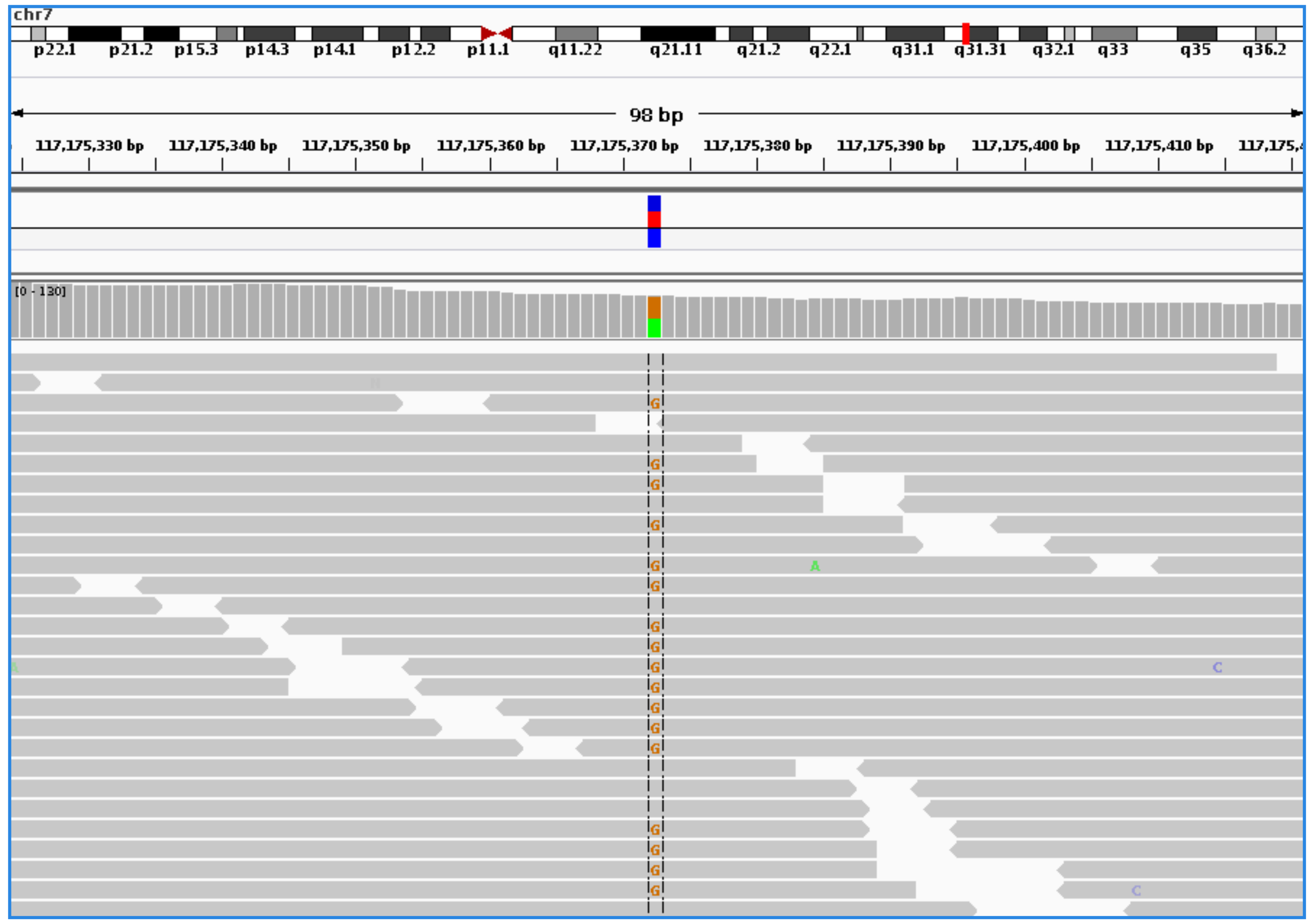


Expert work



IGV snapshot

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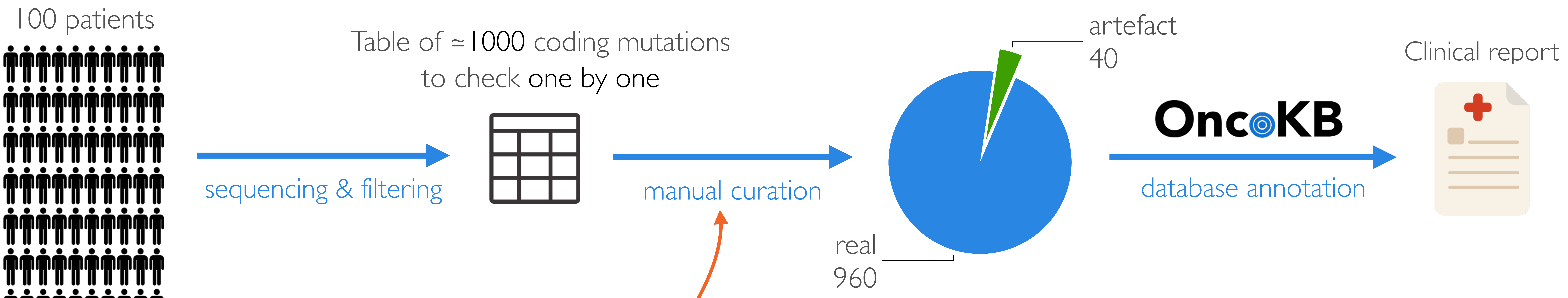

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artefact
40

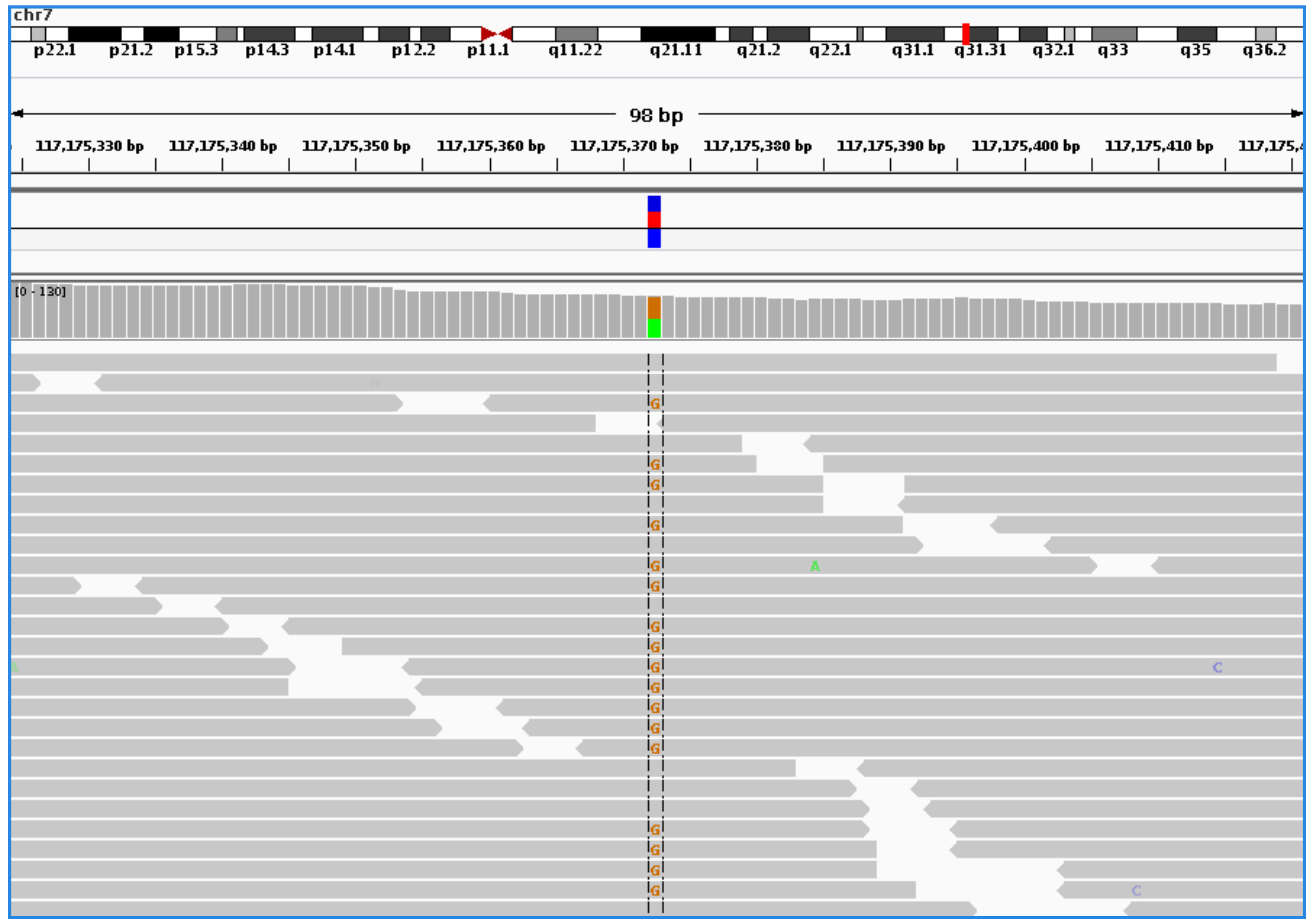
real
960

OncoKB

database annotation

Clinical report

Expert work



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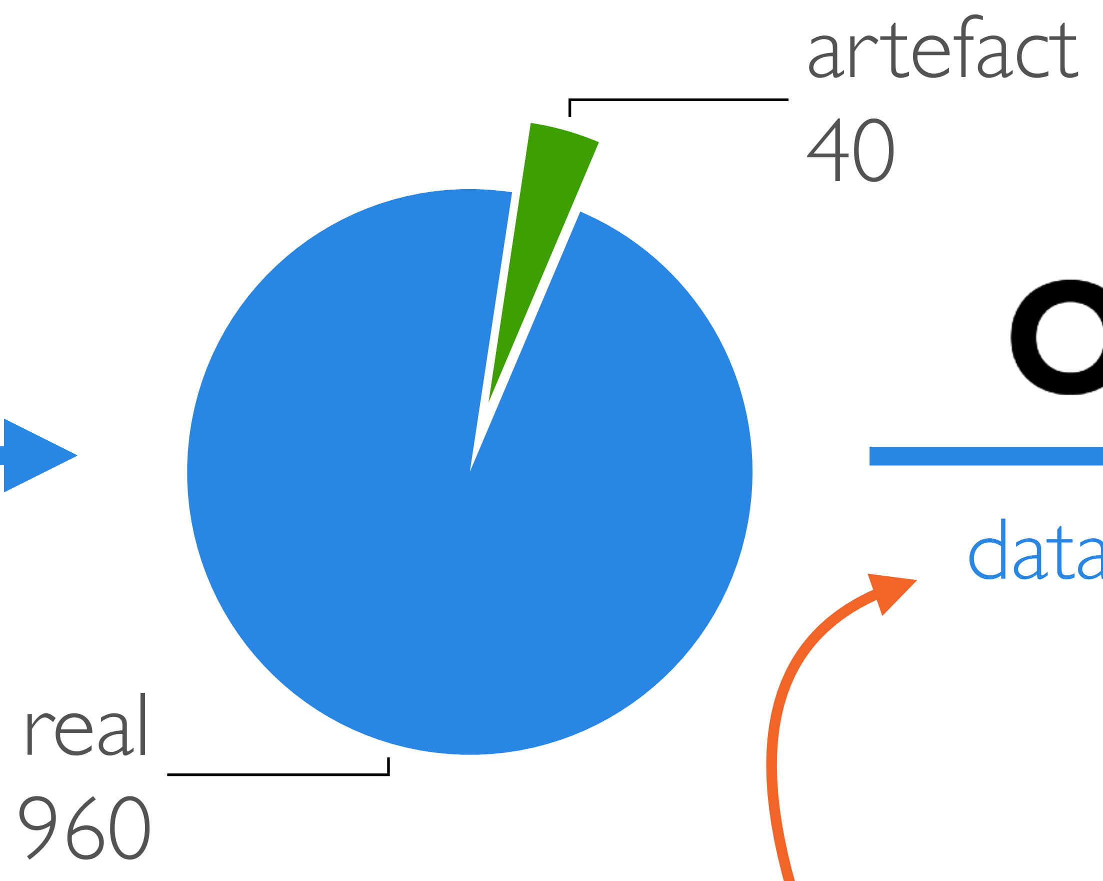

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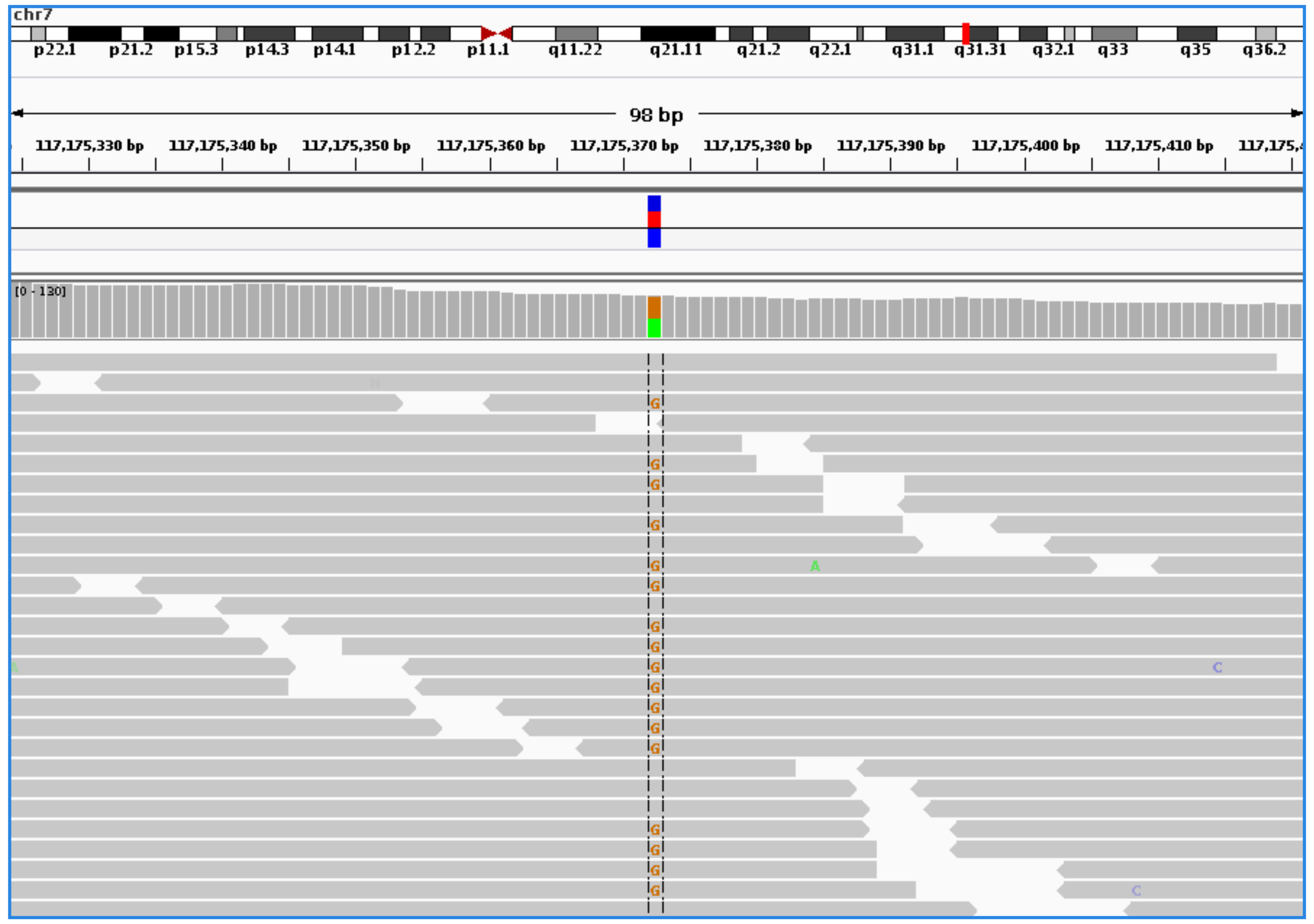
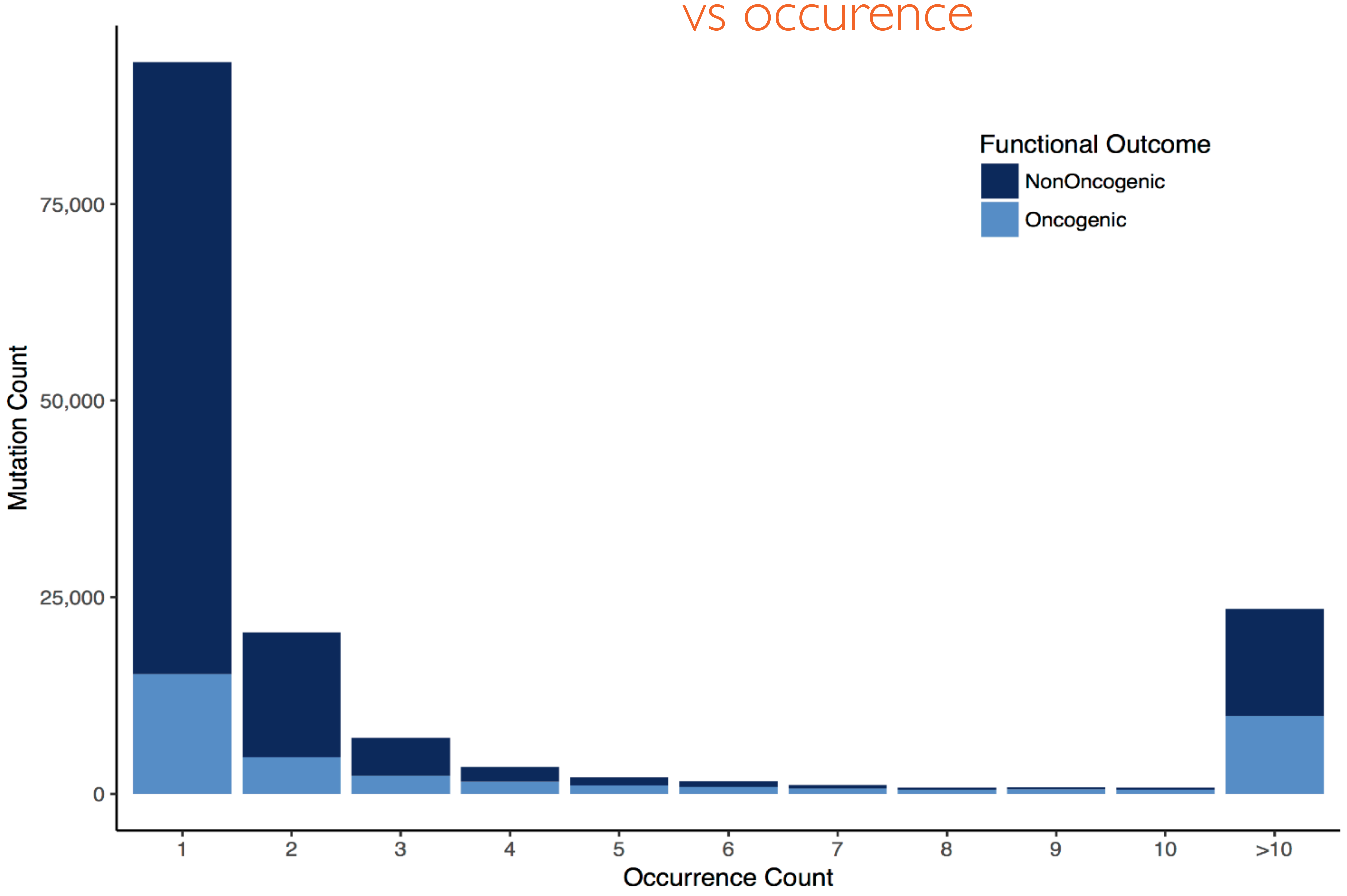


IGV snapshot

MSK-IMPACT: oncogenicity
vs occurence

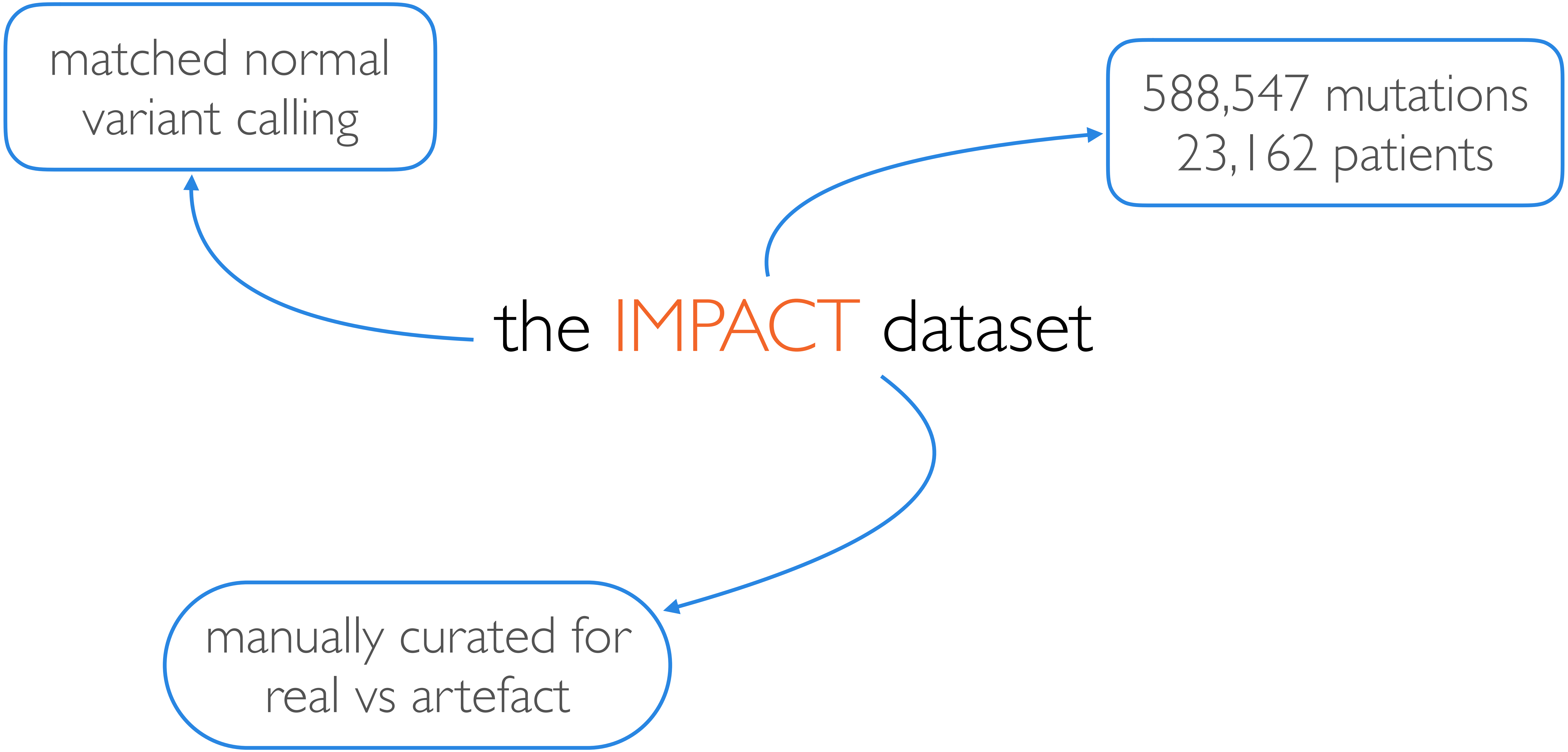


The goal

Create a tool that classifies variant automatically

- real vs artefact OR driver vs passenger
- all cancers, all mutation types
- using Supervised Machine Learning Classification
- on the IMPACT dataset

IMPACT, the dataset



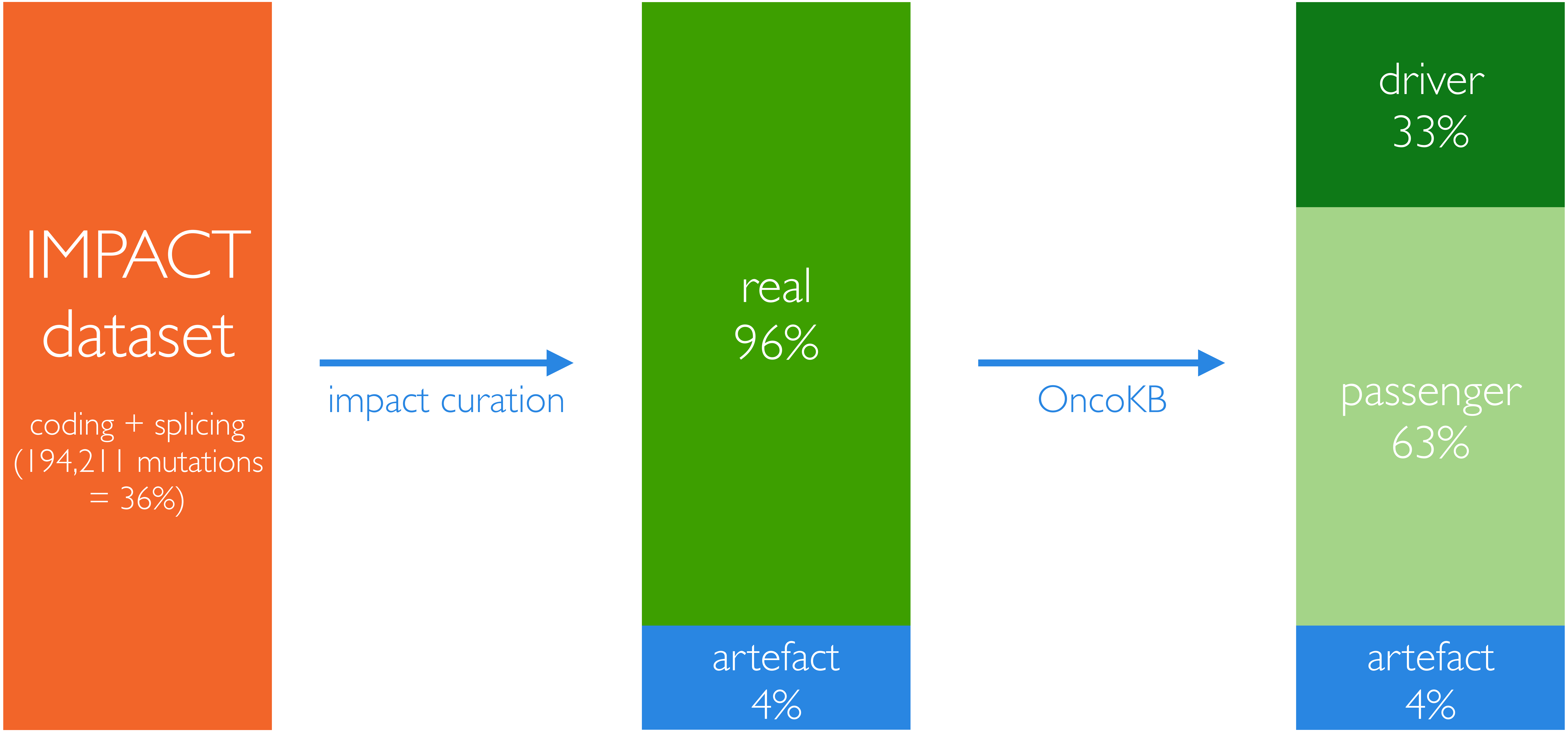
matched normal variant calling

588,547 mutations
23,162 patients

the IMPACT dataset

manually curated for real vs artefact

Two steps classification



IMPACT dataset

coding + splicing (194,211 mutations = 36%)

impact curation

real 96%

artefact 4%

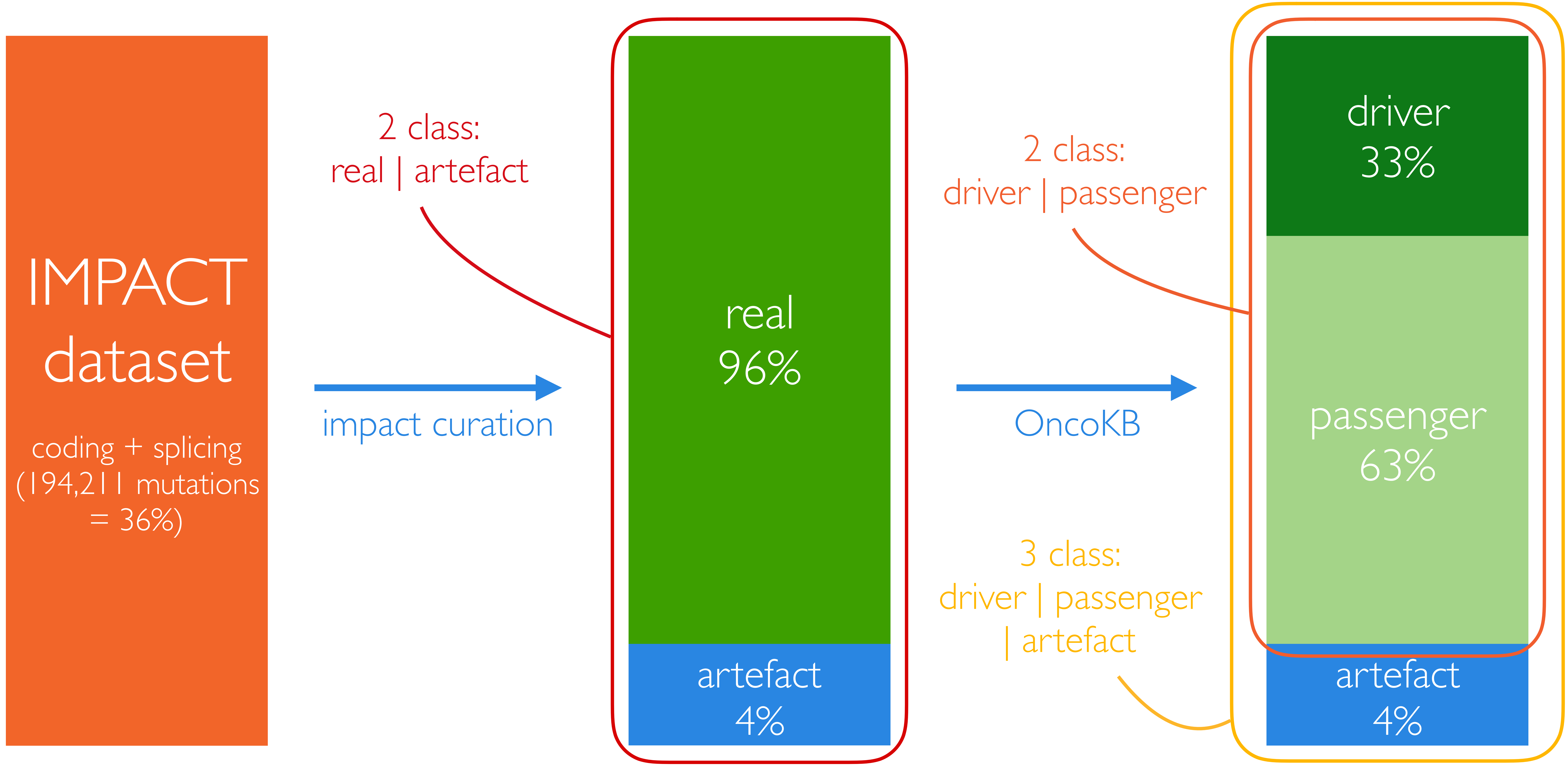
OncoKB

driver 33%

passenger 63%

artefact 4%

Two steps classification



IMPACT dataset

coding + splicing (194,211 mutations = 36%)

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2 class:
real | artefact

real 96%

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OncoKB

2 class:
driver | passenger

3 class:
driver | passenger | artefact

driver 33%

passenger 63%

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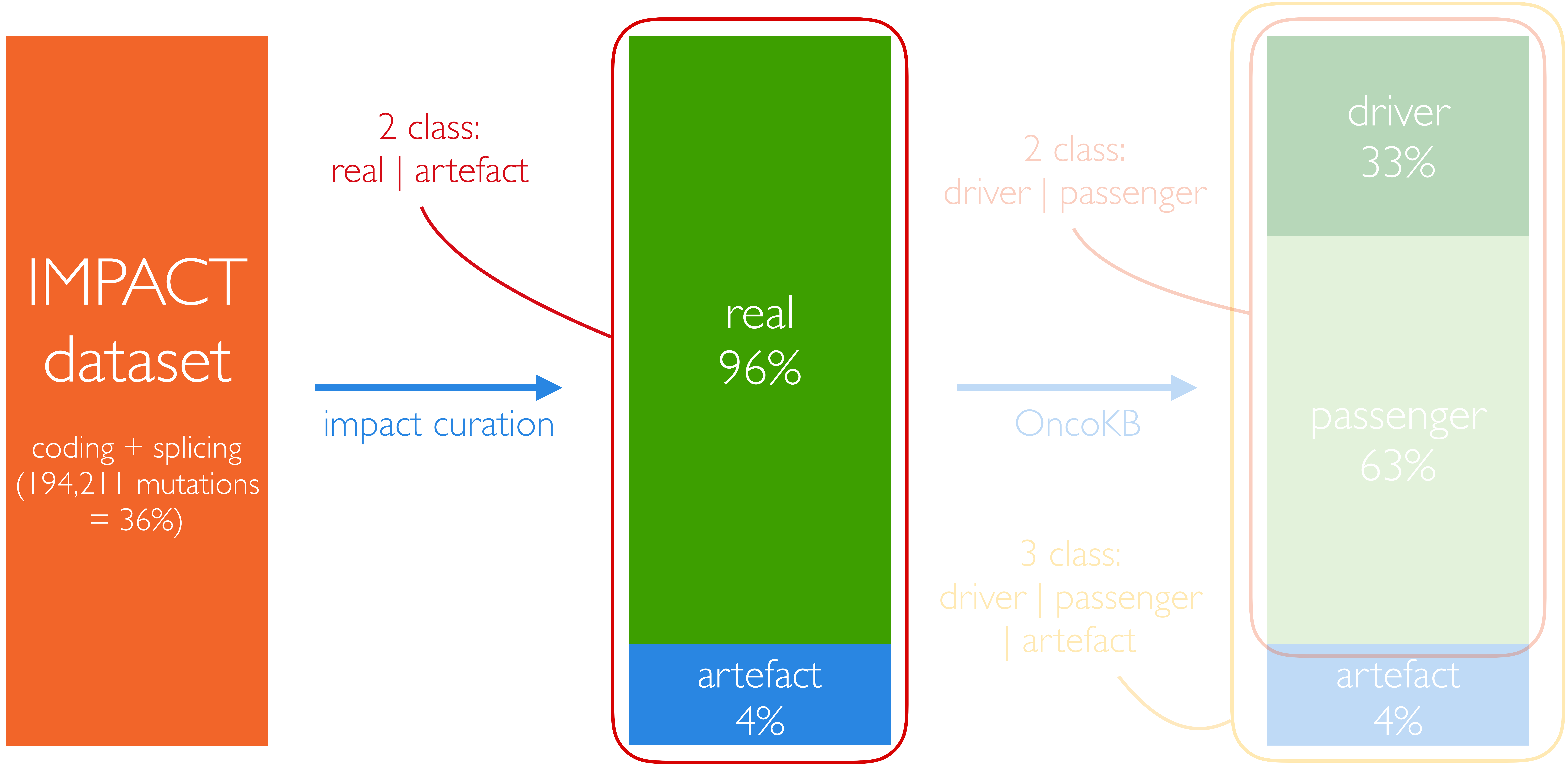
Two steps classification



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The features used in our model

- Sequencing features (n = 11)

  Tumor VAF, tumor depth

- Genomic coordinates (n = 3)

  Chromosome, Hugo Symbol

- Control populations (n = 12)

  Population based
  GnomAD allele frequency

- Cancer populations (n = 4)

  COSMIC, OncoKB

- Normal control (n = 1)

  Frequency in normal control

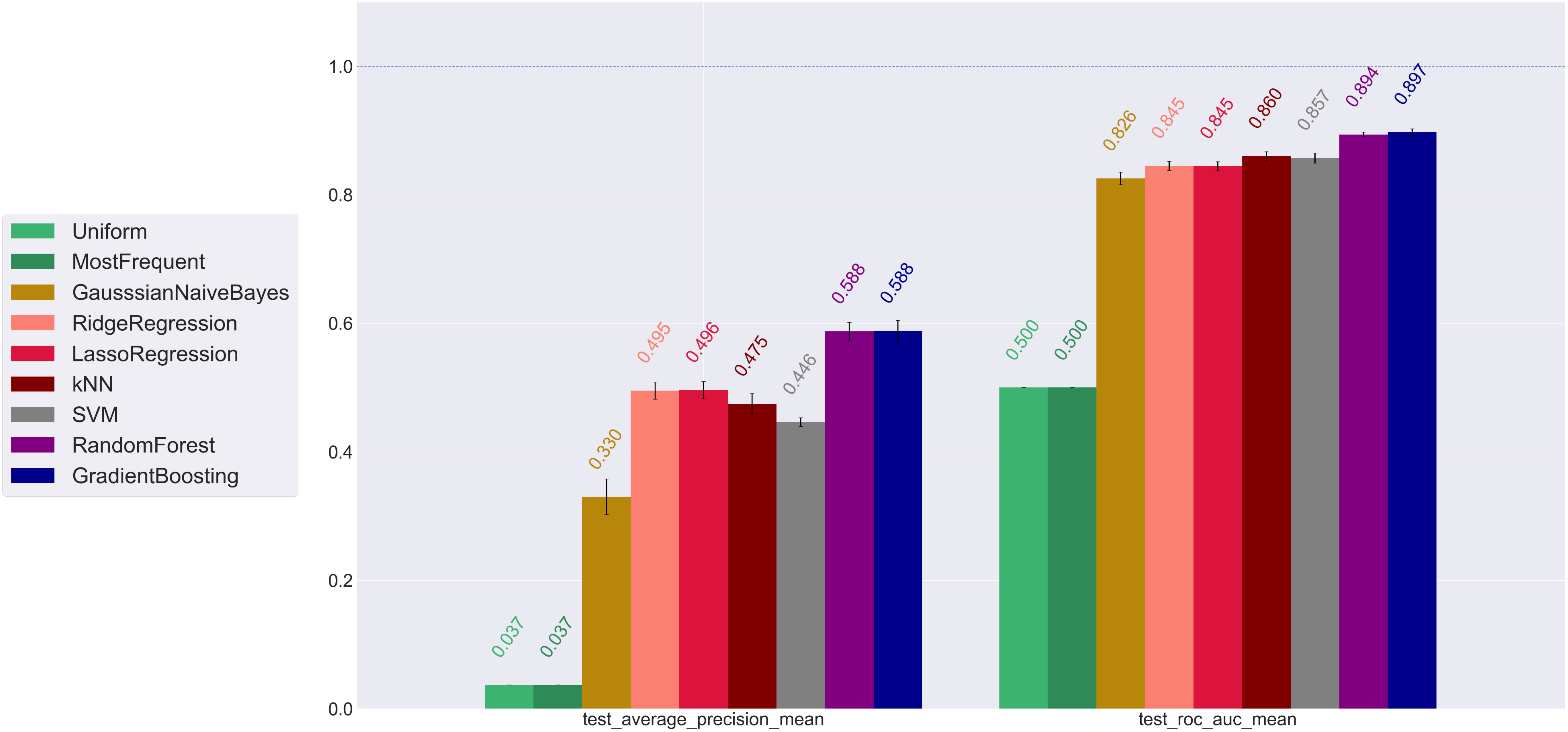
- Mutation consequence (n = 6)

  Protein effect, SIFT & PolyPhen class

Algorithm comparison

- 🟩 Uniform
- 🟩 MostFrequent
- 🟨 GausssianNaiveBayes
- 🟧 RidgeRegression
- 🟥 LassoRegression
- 🟥 kNN
- ⬜ SVM
- 🟪 RandomForest
- 🟦 GradientBoosting

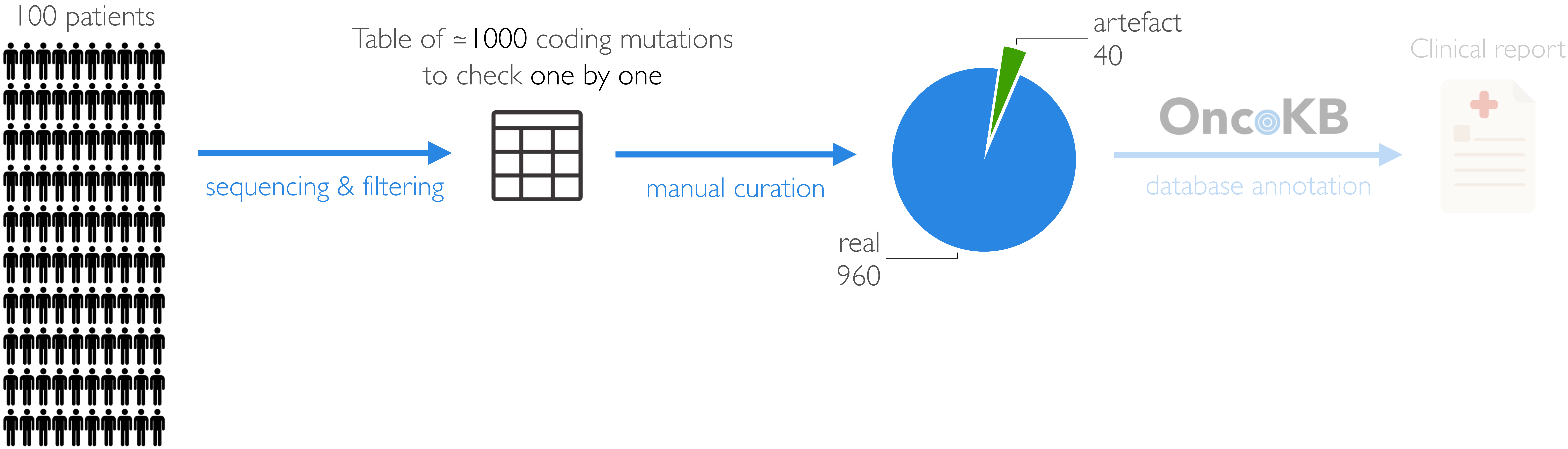
Algorithm comparison



Best algorithm probability output

artefact
real
density
40
30
20
10
0
0.0
0.2
0.4
0.6
0.8
1.0
predicted probability

The variant classifier performances



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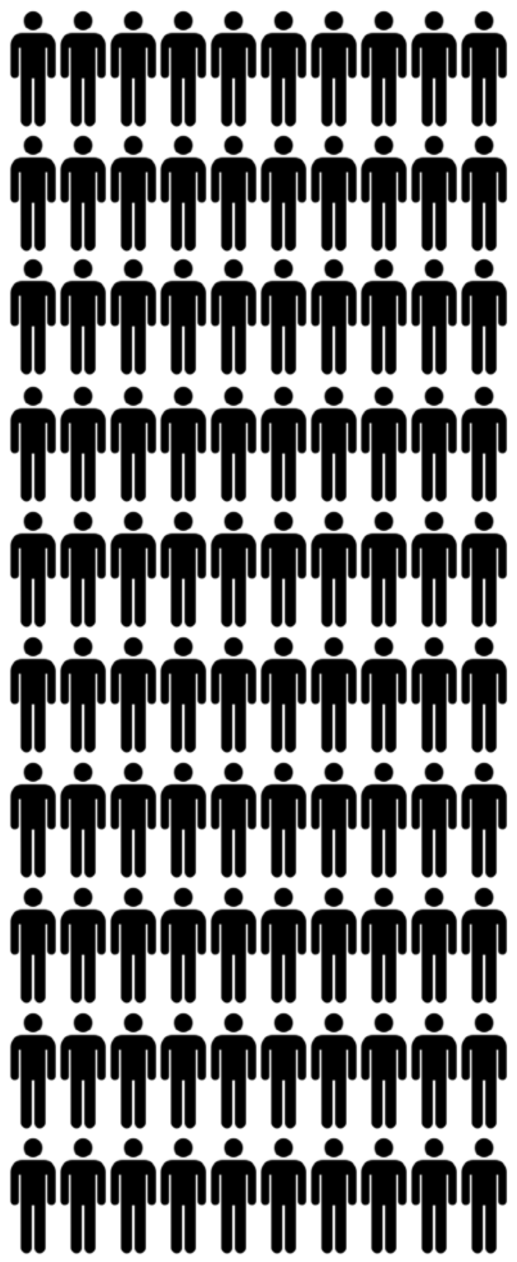

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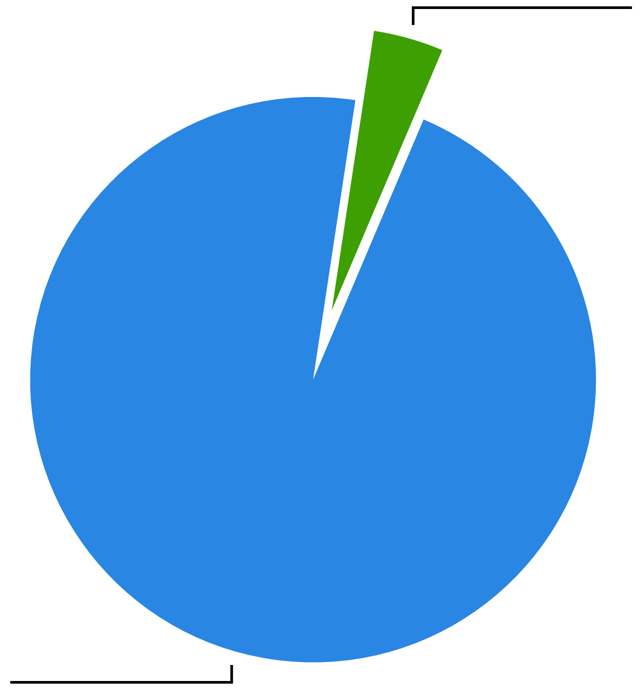

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Clinical report

variant
classifier

960 real

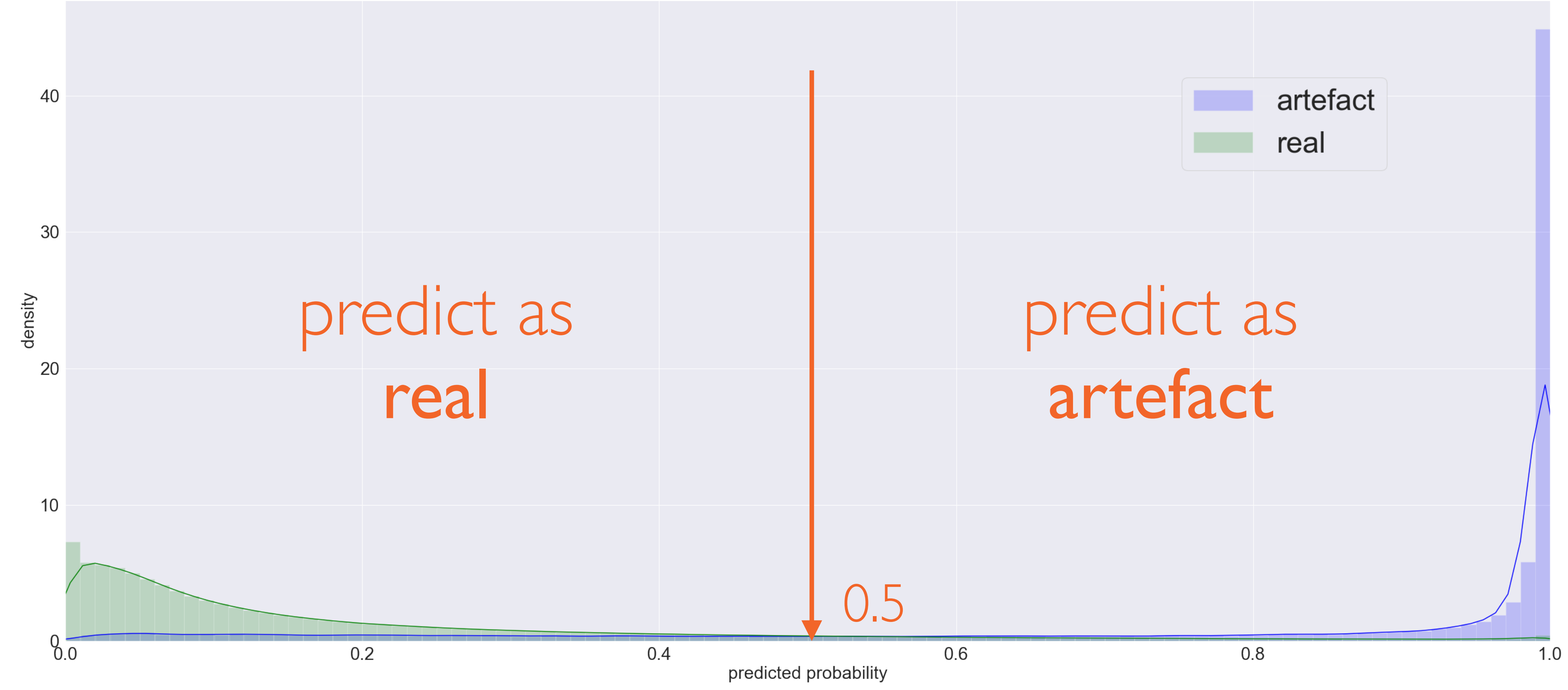
✅ 848 → real

❌ 112 → artefact

40 artefact

✅ 32 → artefact

❌ 8 → real

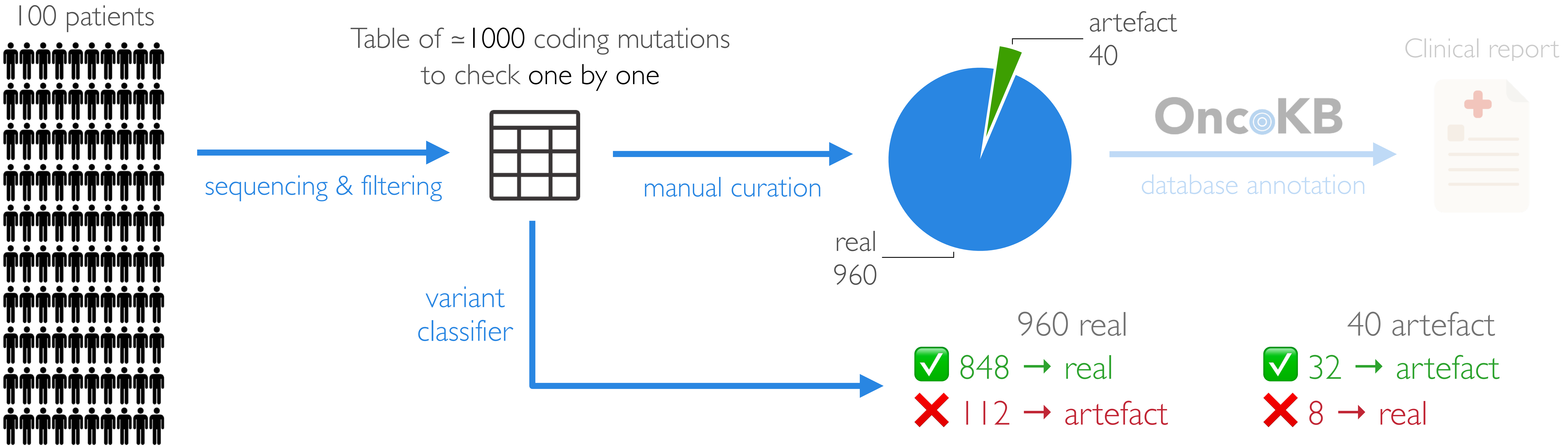


predict as
real

predict as
artefact

0.5

The variant classifier performances



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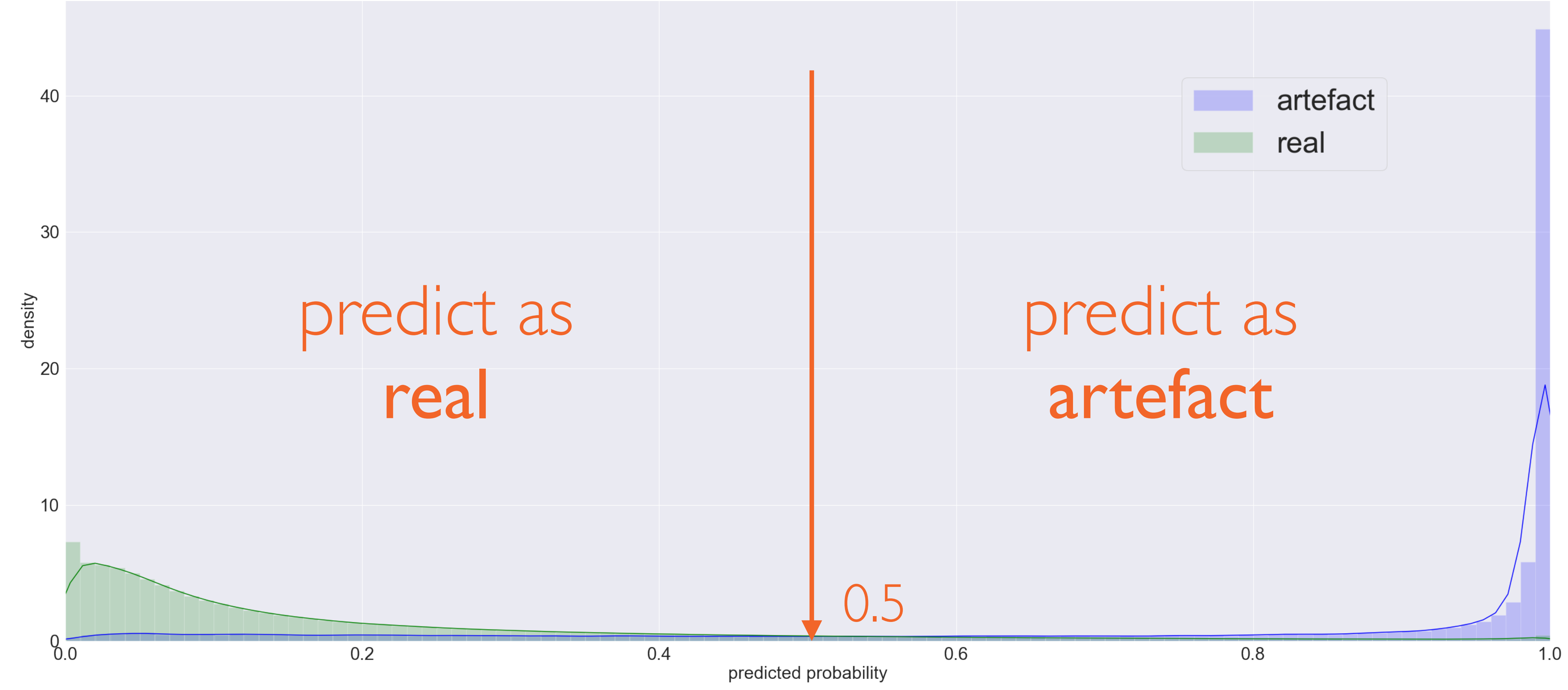


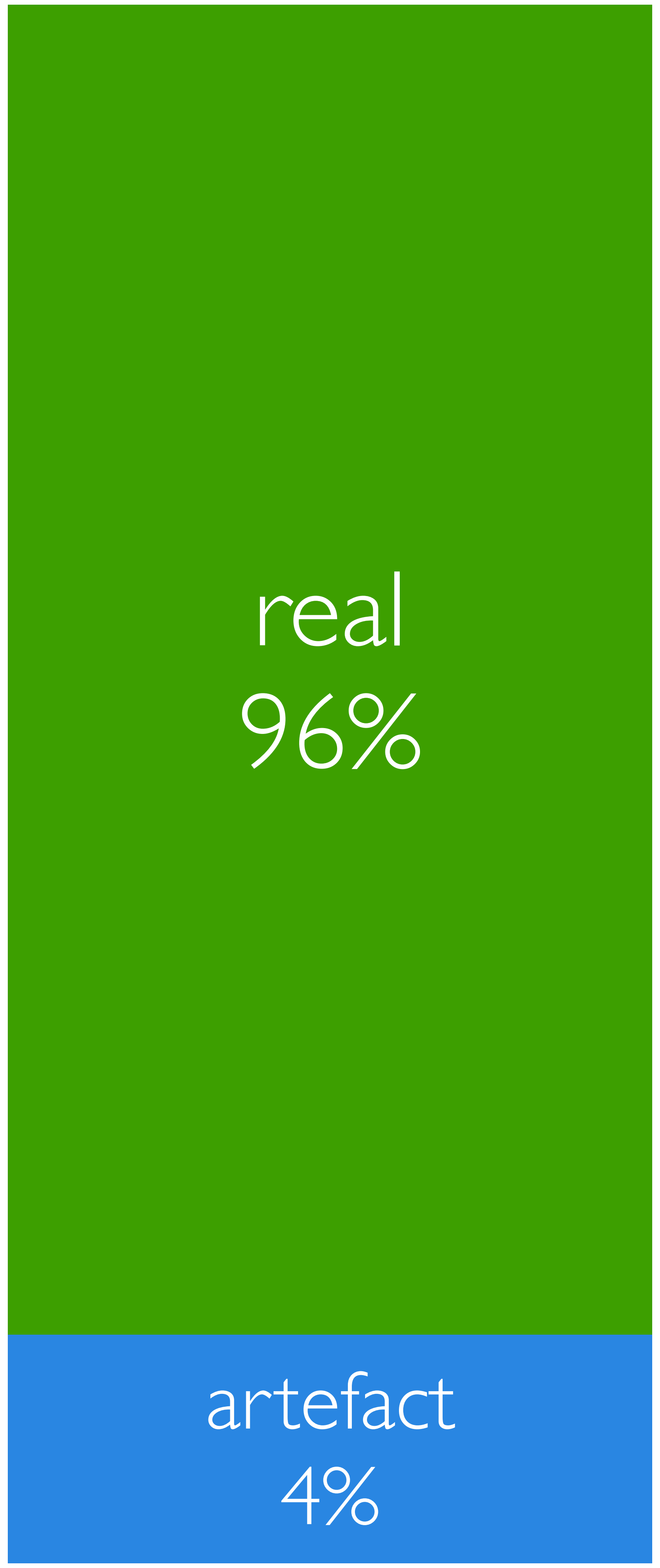
❌ 8/40 artefacts considered as real

📝 8x less work

144/1000 mutations to check one by one instead of 1000/1000

Main challenges

Imbalanced dataset



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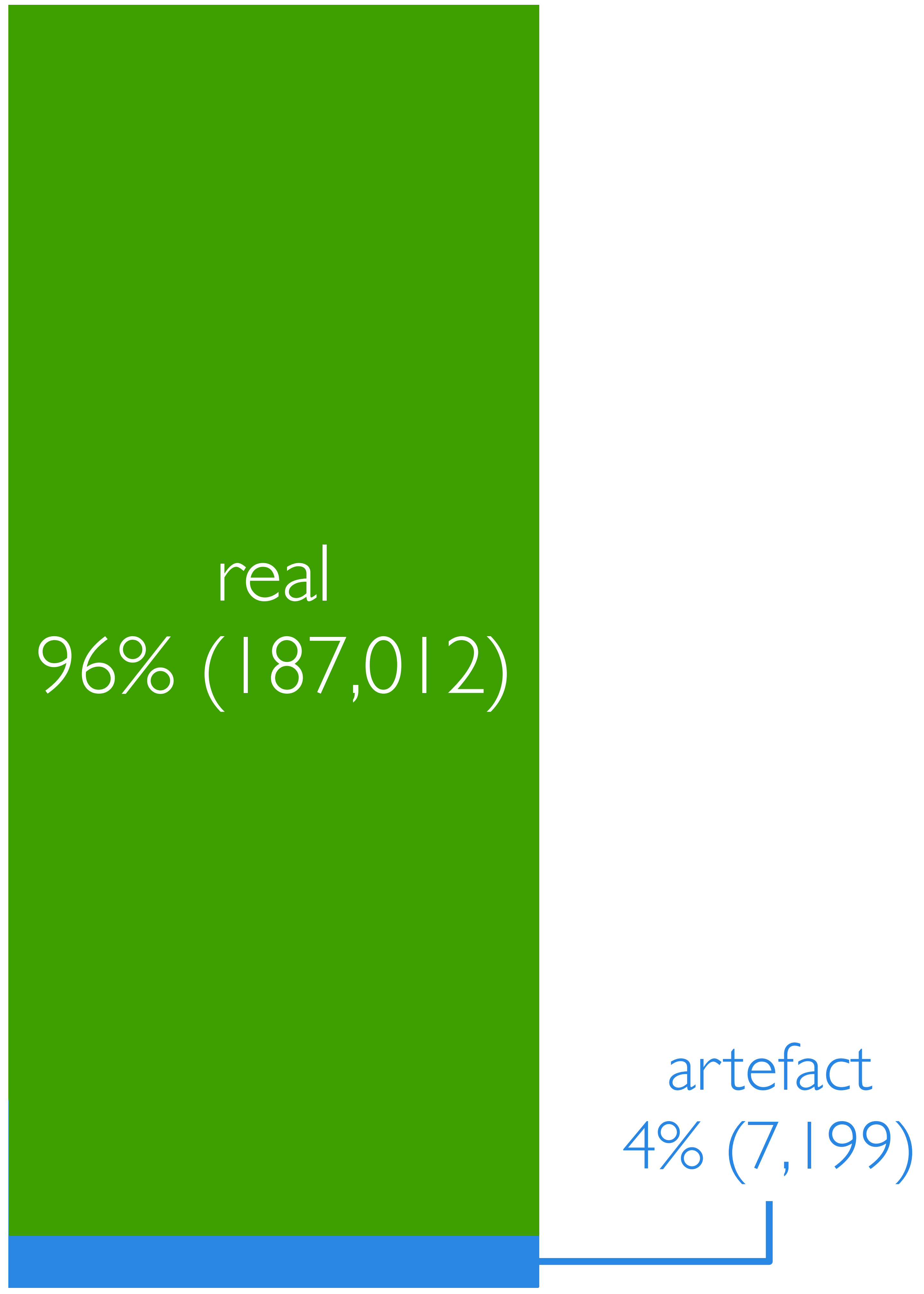

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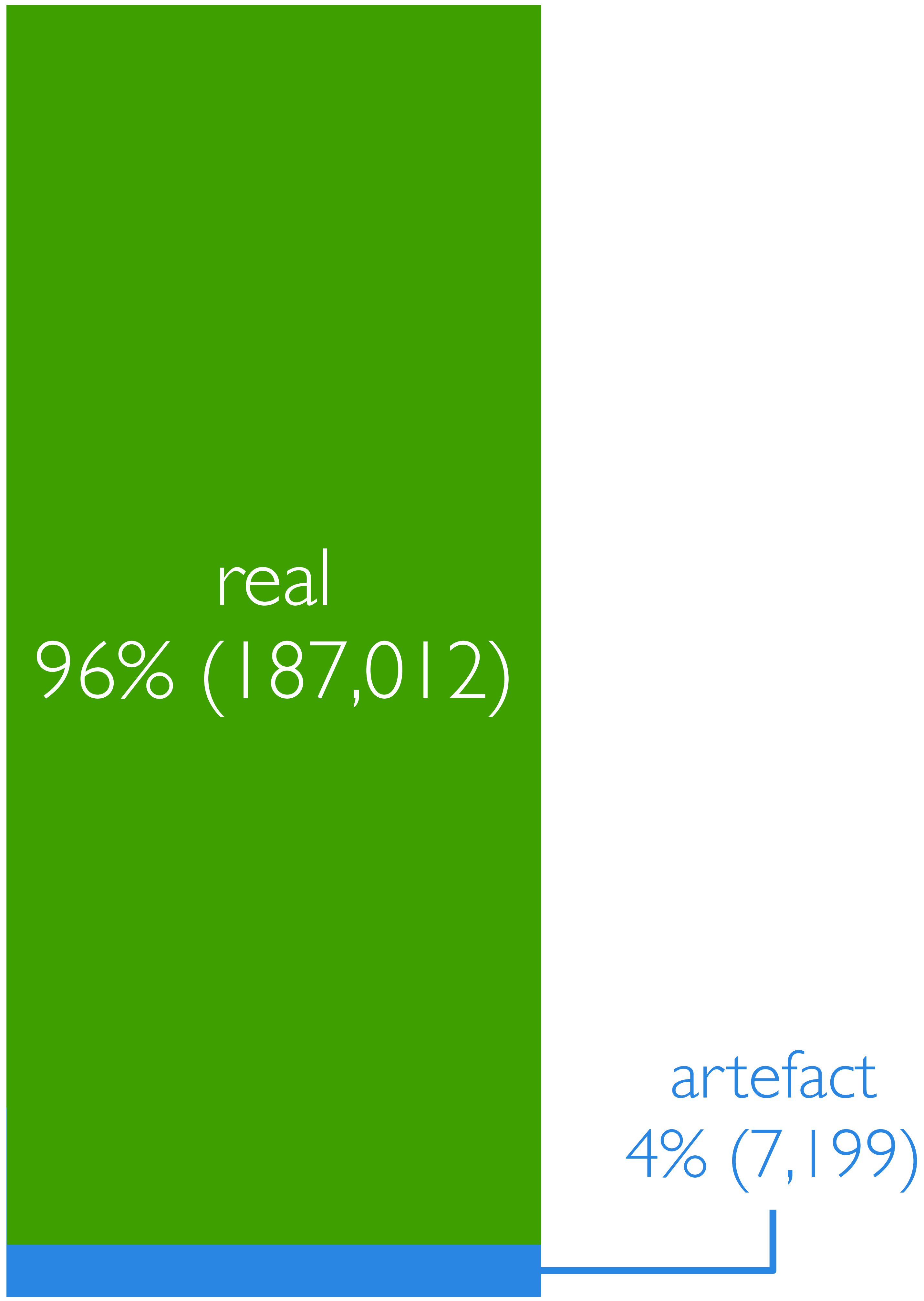
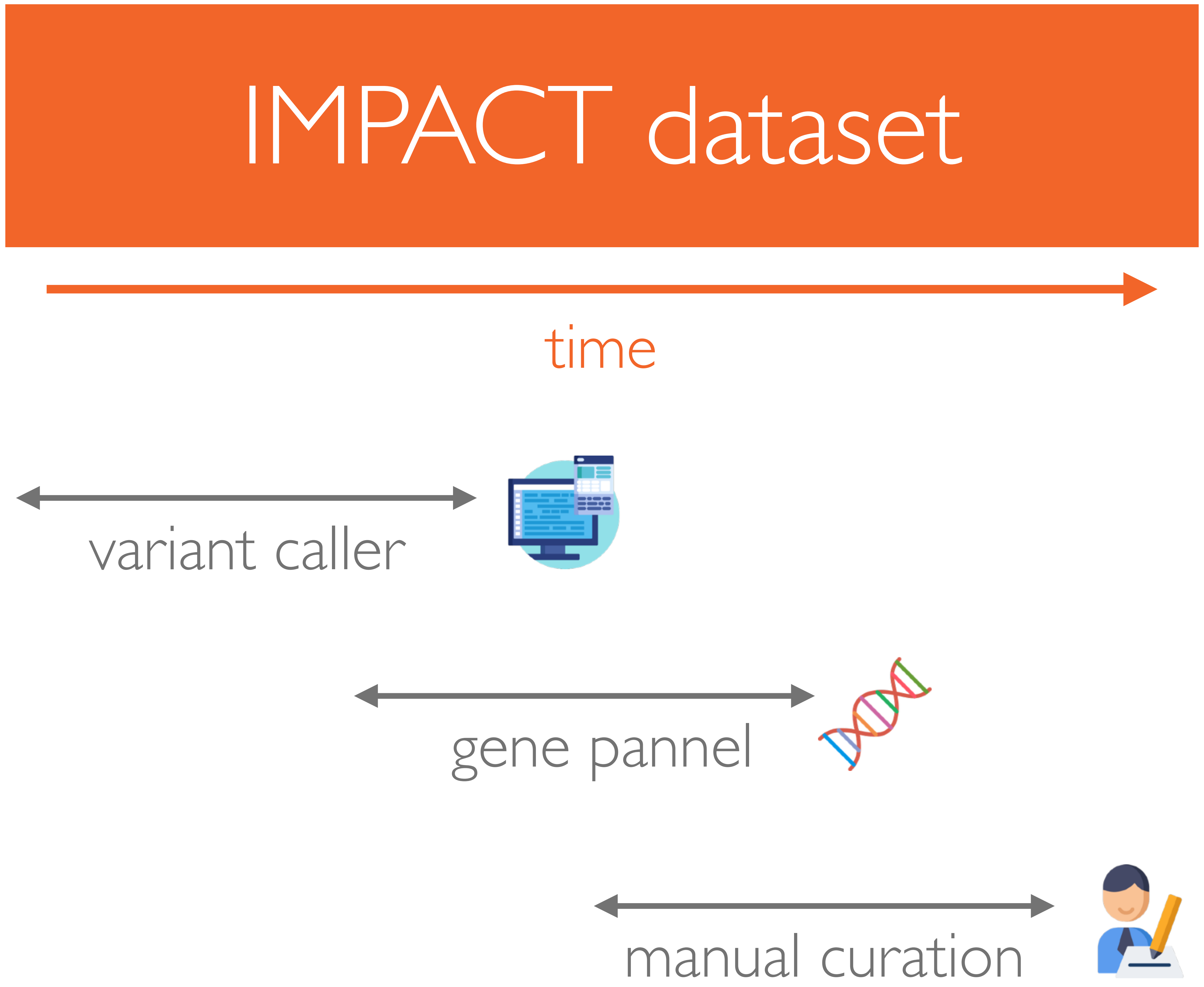


Evolution over time



IMPACT dataset

time

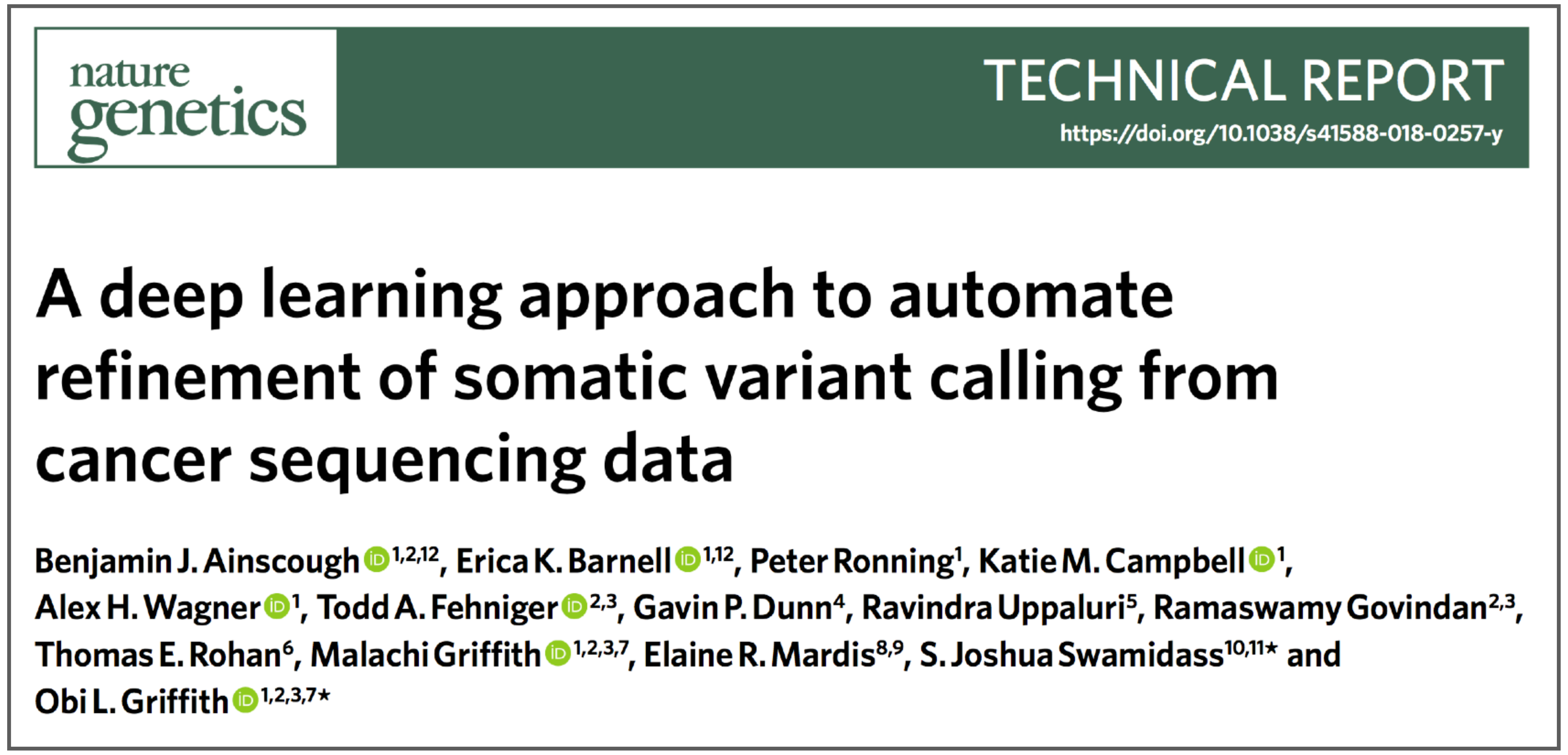
variant caller

gene pannel

manual curation

Next steps

Method comparison



nature genetics

TECHNICAL REPORT

https://doi.org/10.1038/s41588-018-0257-y

A deep learning approach to automate refinement of somatic variant calling from cancer sequencing data

Benjamin J. Ainscough[1,2,12], Erica K. Barnell[1,12], Peter Ronning[1], Katie M. Campbell[1], Alex H. Wagner[1], Todd A. Fehniger[2,3], Gavin P. Dunn[4], Ravindra Uppaluri[5], Ramaswamy Govindan[2,3], Thomas E. Rohan[6], Malachi Griffith[1,2,3,7], Elaine R. Mardis[8,9], S. Joshua Swamidass[10,11*] and Obi L. Griffith[1,2,3,7*]

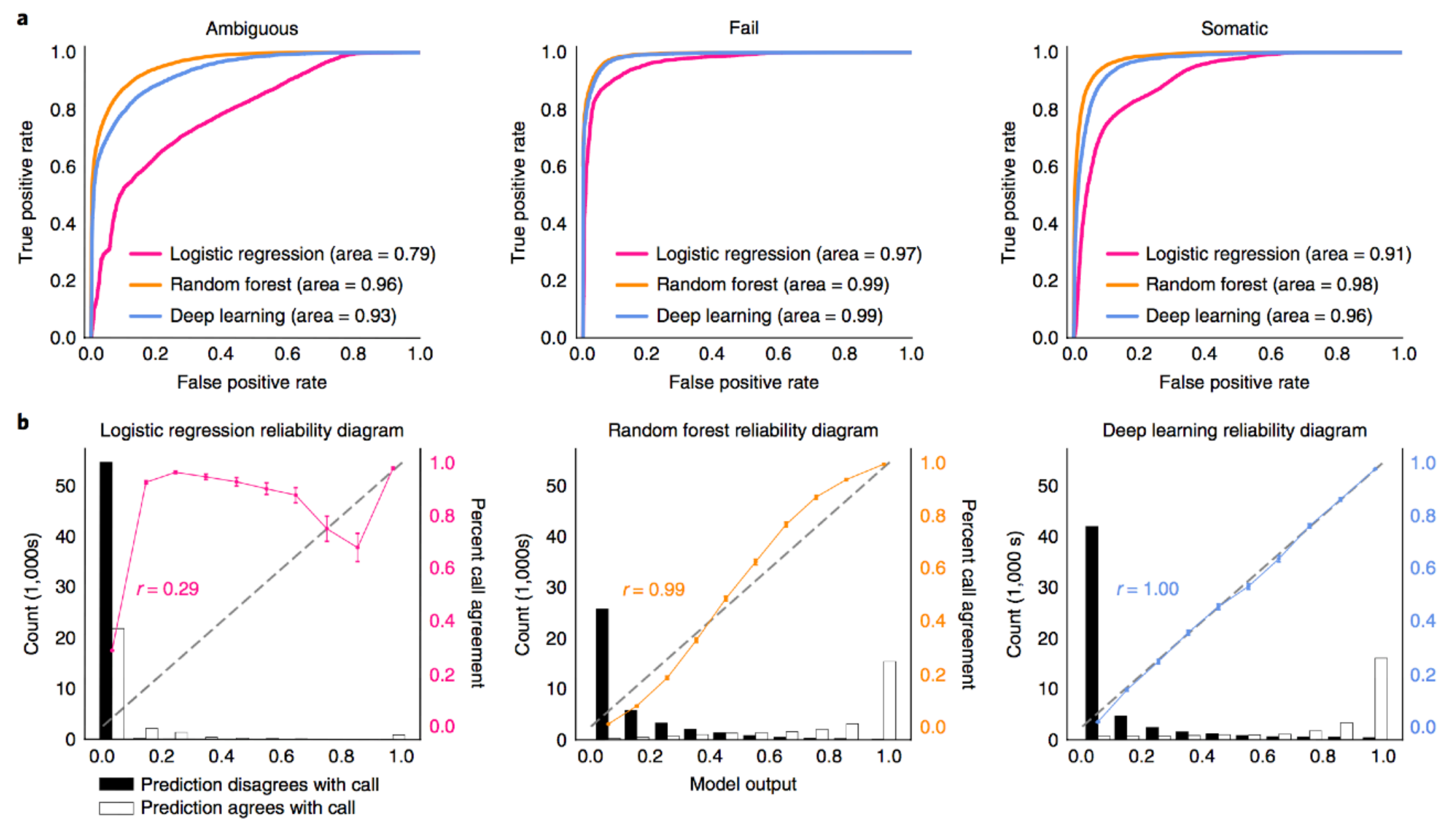
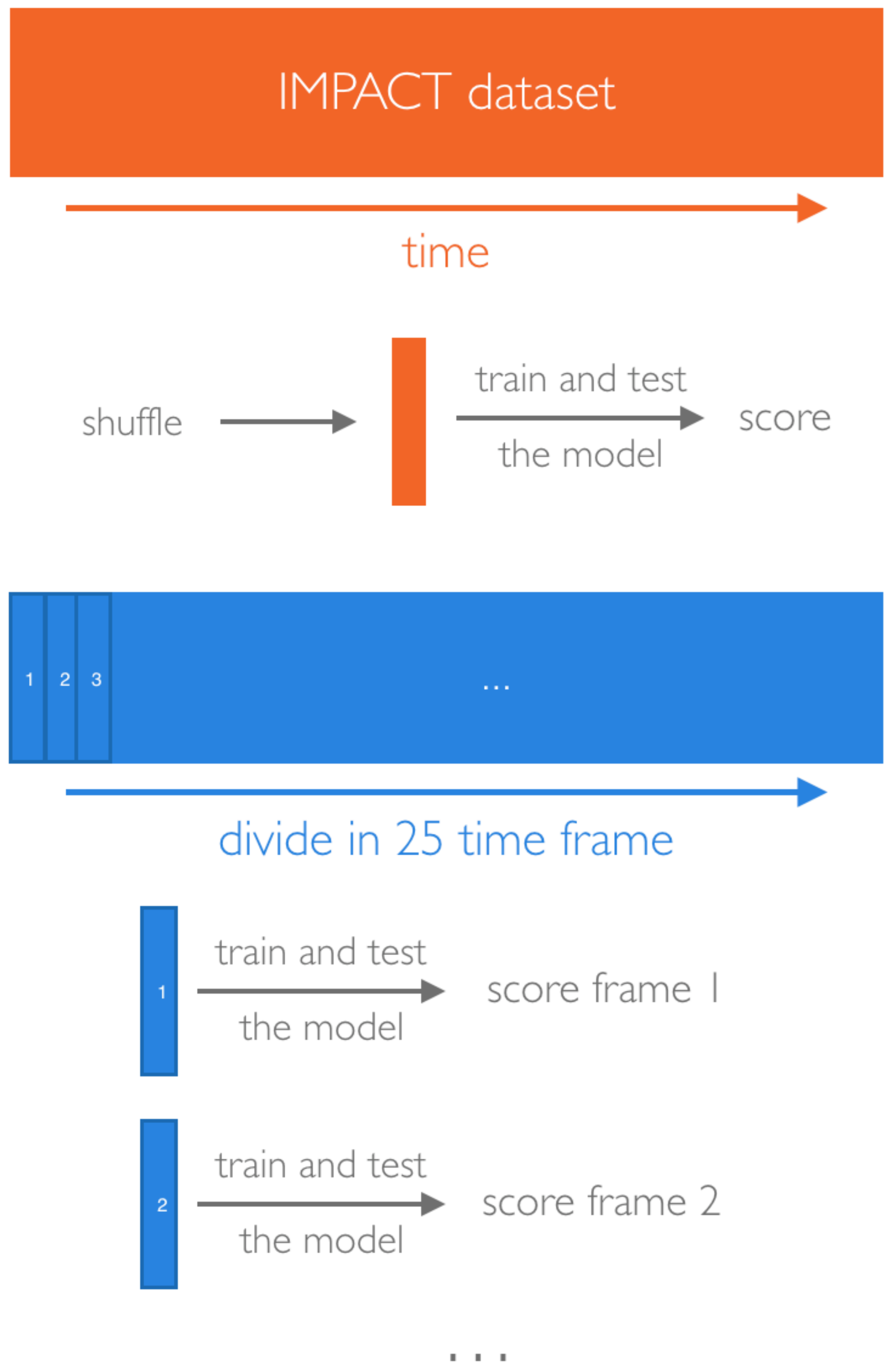
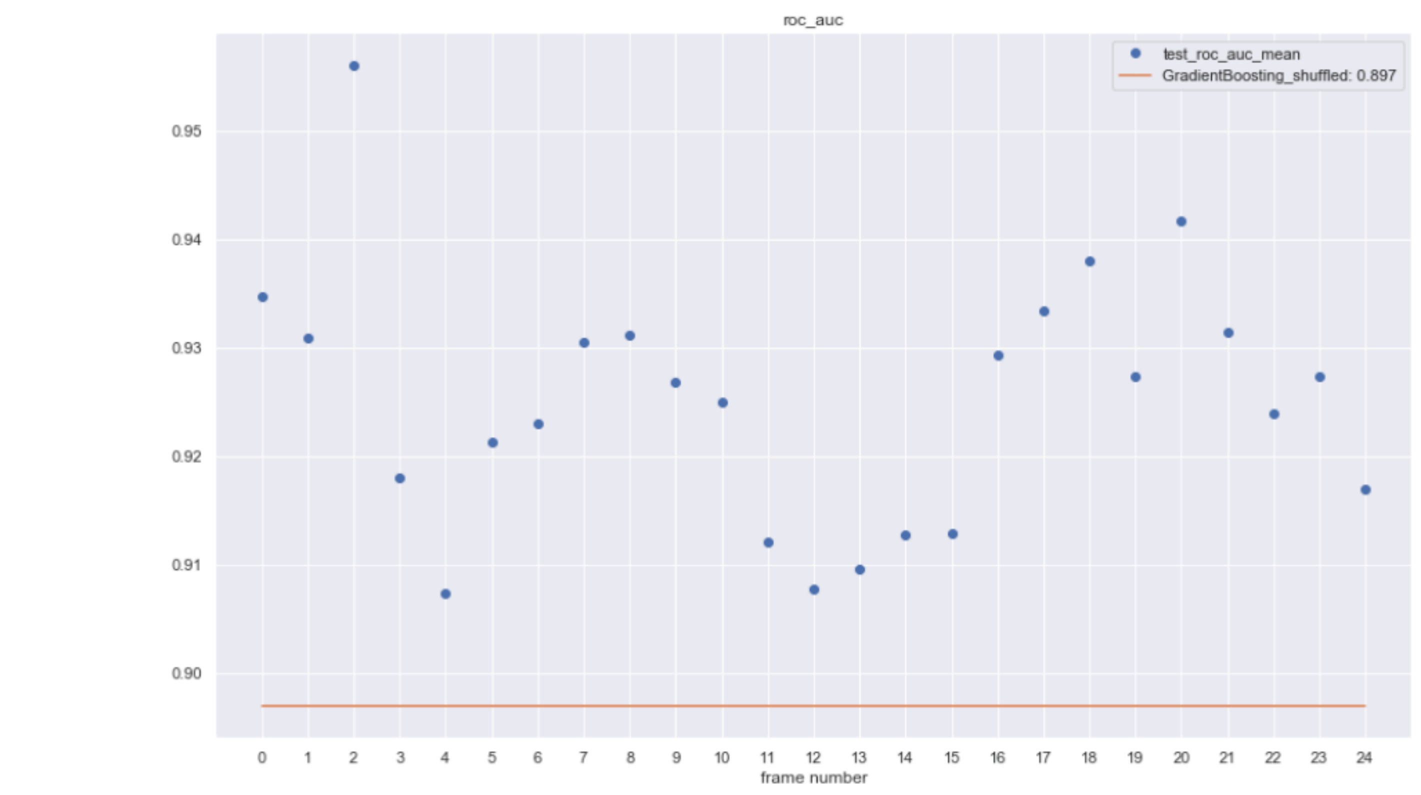
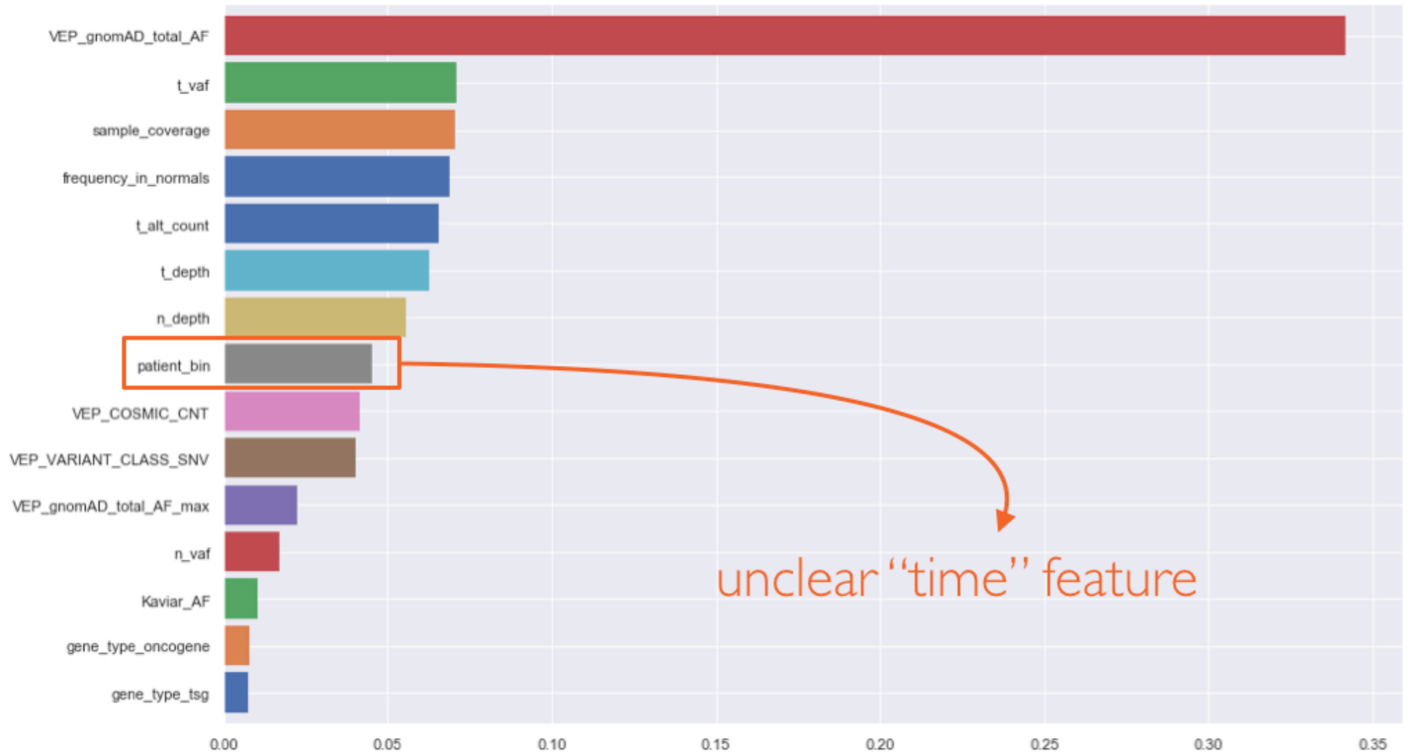


Fig. 1 | Deep learning and random forest models achieved very high manual review classification performance during tenfold cross-validation.

Uniform IMPACT processing?



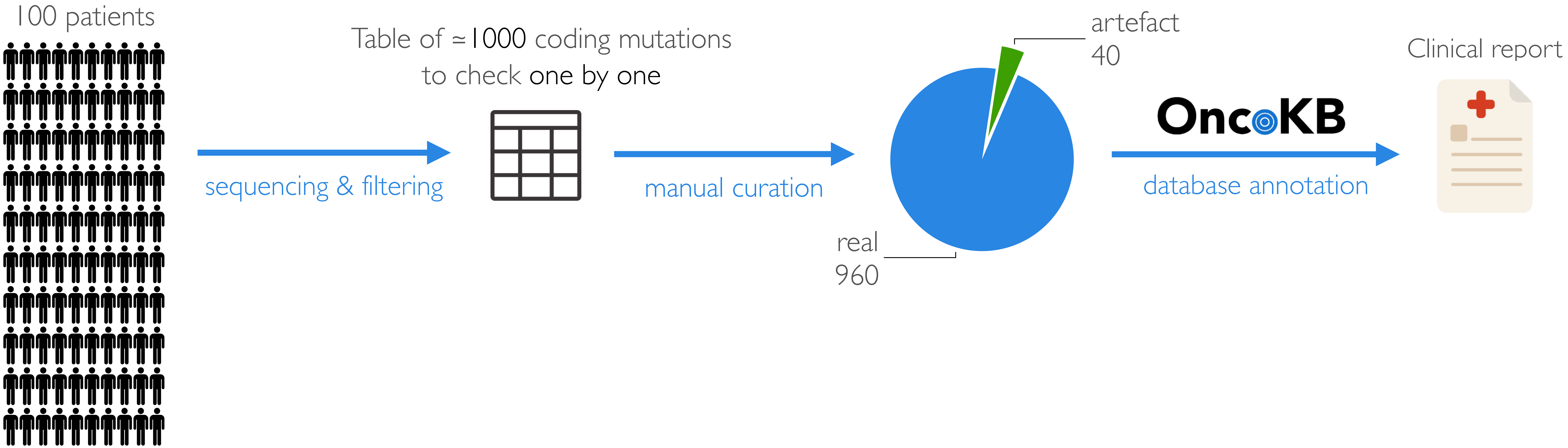




→ Uniform variant callers across time & panels

→ Enable detailed feature extraction | Technical & Flags

Final goal: a two-steps web-based classifier



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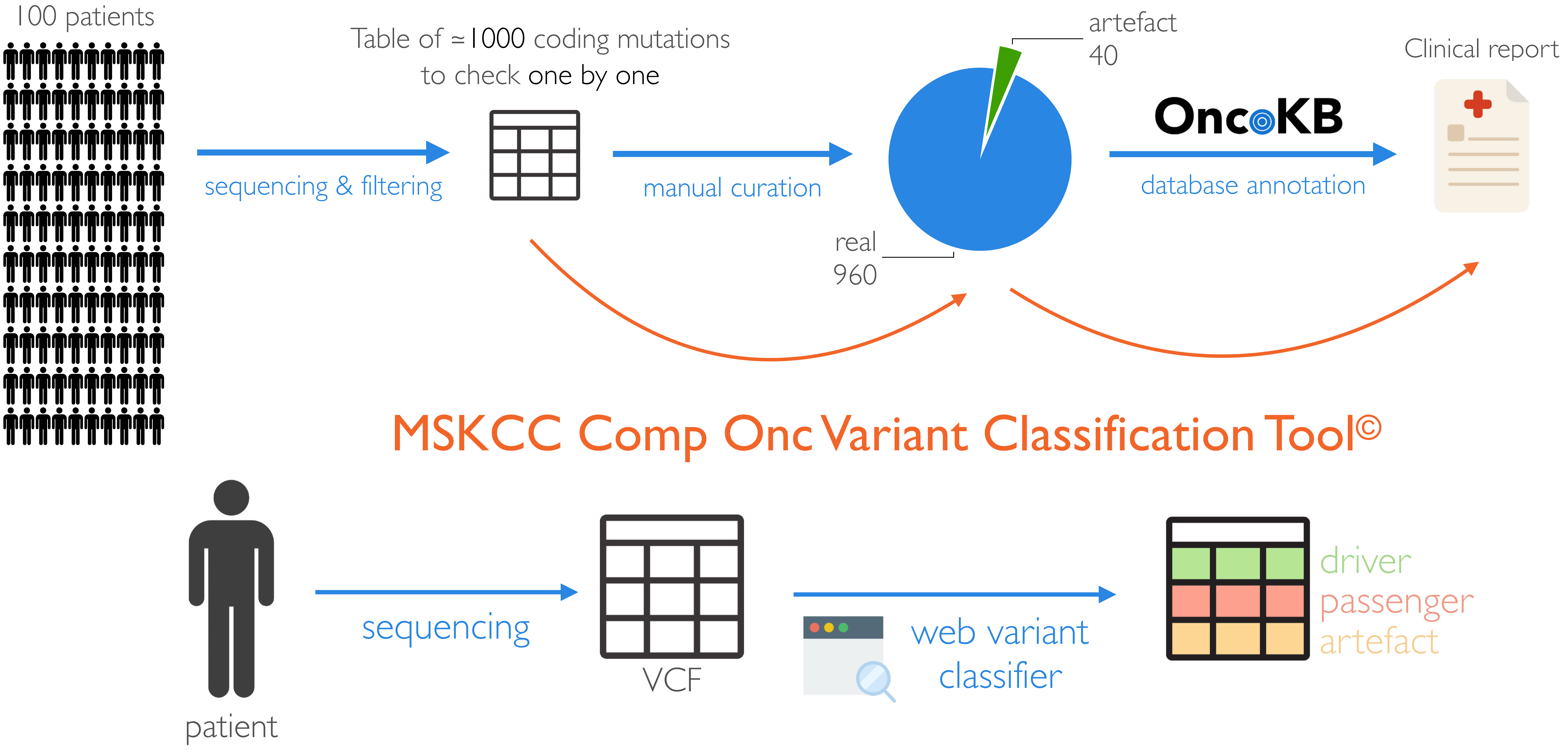

MSKCC Comp Onc Variant Classification Tool©