# Data-aware metacaller for improved gene fusion detection in RNA-seq

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## 1 INTRODUCTION

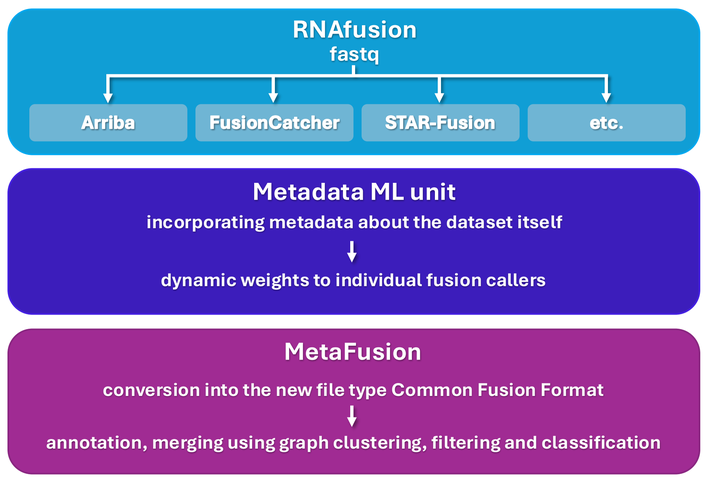
Gene fusions are critical drivers of tumorigenesis and serve as important diagnostic and therapeutic targets in oncology [1,2]. Detecting these events from RNA-seq data remains a complex bioinformatics task due to variable performance of existing tools and the influence of dataset-specific factors, such as sequencing protocol, read length, and cancer type [3, 4]. Current multi-caller and aggregation approaches improve robustness but do not account for dataset characteristics, resulting in suboptimal accuracy. To address this gap, we propose a **data-aware metacaller** that dynamically adapts fusion detection to the properties of the input data.

## 2 METHODS

We conducted a meta-analysis of **10 independent benchmarking studies**, identifying dataset-level features that strongly impact fusion caller performance. Based on these insights, we designed a hybrid system combining two established frameworks:

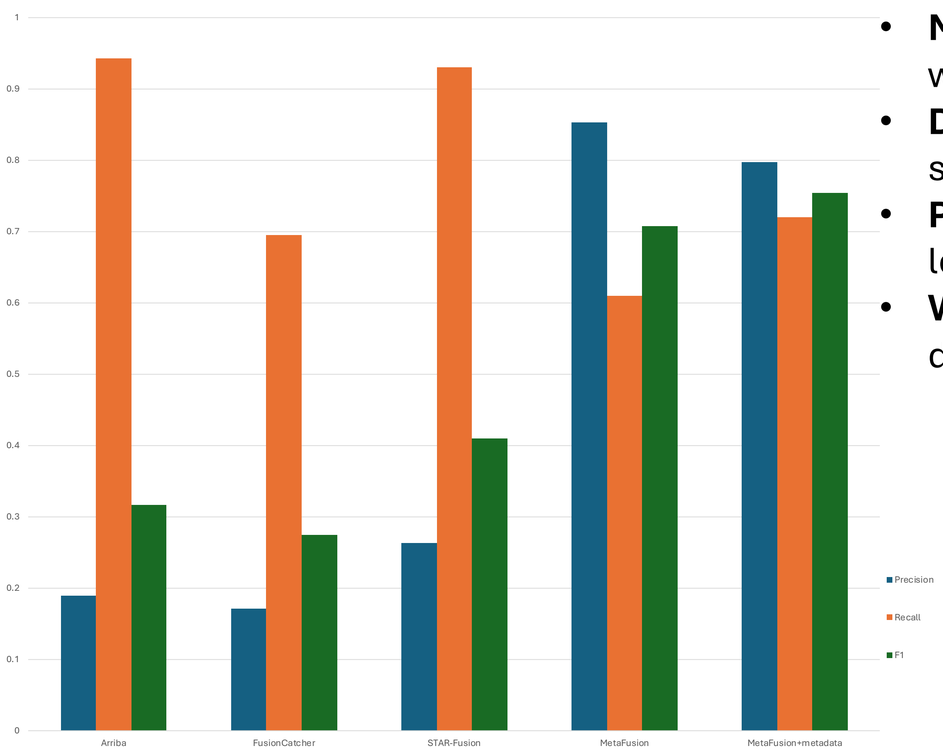
- **RNAfusion [5] (nf-core/rnafusion)**, a reproducible multi-caller pipeline for detecting gene fusions
- **MetaFusion [6]**, a graph-based ensemble method for result aggregation.

Our innovation introduces an additional metadata-aware layer that incorporates information such as sample type, sequencing characteristics, and quality metrics. We train a **machine learning model** on curated datasets from published studies to learn optimal weighting schemes for individual fusion callers, enabling adaptive prioritization according to dataset context.




The model was trained on real-world data comprising **56 cell lines representing multiple cancer types**, ensuring biological diversity and robustness of the learned weighting strategies.

## 3 RESULTS




- **Metadata-aware aggregation** improved both precision and recall compared to uniform-weighted approaches.
- **Dynamic weighting** consistently prioritized callers that performed best under dataset-specific conditions, reducing false positives while maintaining sensitivity.
- **PyCaret-based model selection** enabled identification of the most suitable machine learning algorithms, ensuring robust performance and reproducibility.
- **Workflow compatibility**: the system integrates seamlessly with existing RNA-seq fusion detection pipelines and scales across diverse cancer types.

| Model | Recall | Prec. | F1 |
|---|---|---|---|
| Random Forest Classifier | 0,7199 | 0,7973 | 0,7542 |
| Extra Trees Classifier | 0,7193 | 0,7960 | 0,7531 |
| K Neighbors Classifier | 0,7134 | 0,7671 | 0,7355 |
| Logistic Regression | 0,6375 | 0,8395 | 0,7212 |
| Decision Tree Classifier | 0,6892 | 0,7487 | 0,7156 |

## 4 DISCUSSION

Our findings demonstrate the importance of dataset-aware strategies in complex genomic analyses. By explicitly modeling the relationship between data characteristics and caller performance, the proposed framework overcomes limitations of current ensemble methods that treat all tools equally. Notably, incorporating cancer type and read-level features such as the number of split and junction reads led to encouraging improvements in F1-score, highlighting the value of feature-driven weighting. These results motivate further extensions of the system to include additional metadata, such as sequencing read length, sample size, or other specimen-specific parameters. Expanding the feature set may enable even greater adaptability across diverse experimental contexts and improve generalization to novel datasets.

## 5 CONCLUSSION

We present a **data-aware metacaller** that leverages metadata-driven machine learning to optimize gene fusion detection from RNA-seq data. This adaptive framework improves robustness, interpretability, and applicability across research and clinical contexts. By bridging benchmarking insights with predictive modeling, our system sets the stage for more reliable and customizable bioinformatics pipelines.

## REFERENCES

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