AI-Driven Automation of Genetic Variant Interpretation: Enhancing Clinical Reporting with Large Language Models

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I. BACKGROUND | Why are Large Language Models (LLMs) perfectly suited for generating comments in genetic variant interpretation?

Time-consuming

Highly repetitive

Central part of the interpretation report

Bibliography: phenotype, therapeutic, etc.

Genetic variant interpretation is slow and complex
It requires integrating molecular data, clinical phenotypes, literature, and standardized rules such as ACMG guidelines.

Report requirements

Consistent structure

Brief ~~verbose~~

Claude

Gemini

Meta

LLM limitations

Hallucinations

Random format

Large Language Models
can efficiently synthesize these diverse data sources to produce relevant, consistent, and reusable summaries. They are much faster than humans, but they need to be carefully integrated.

II. METHODS | AutoComment: Using LLM with multi-agents, RAG and few-shot prompting techniques.

Retriever — ~~Hallucinations~~

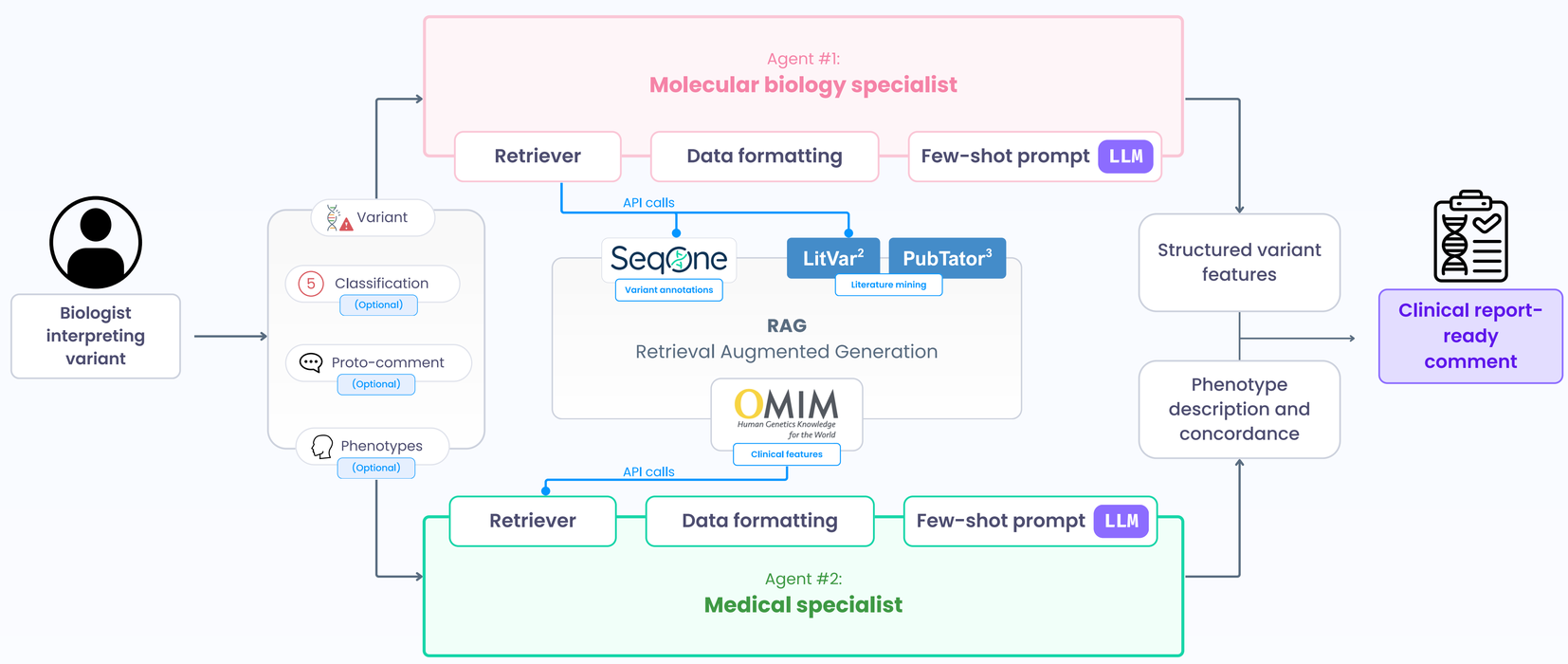
Using RAG scheme, **collect all information necessary for comment generation** to avoid hallucinations and provide all the context to the LLM to generate the comment.

Data formatting — ~~Hallucinations~~

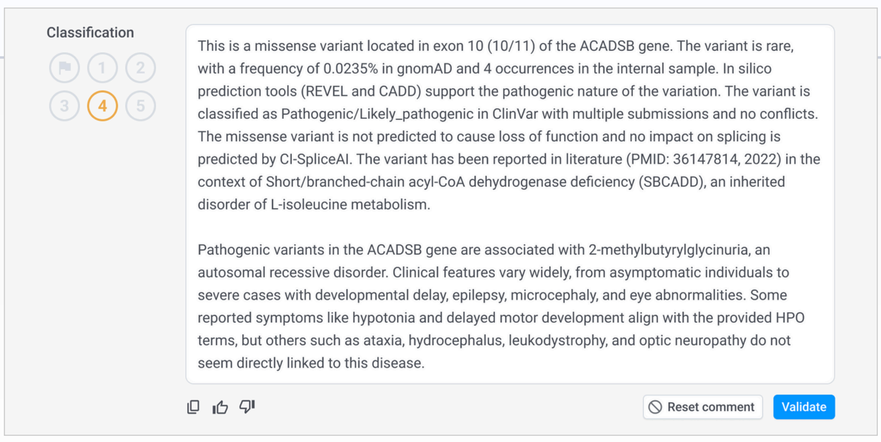
Clear formatting of input data, ex: score AlphaMissense, Value = 0.8, prediction: Likely Pathogenic to guide the LLM and avoid Hallucinations

Few-shot prompt — ~~Random format~~

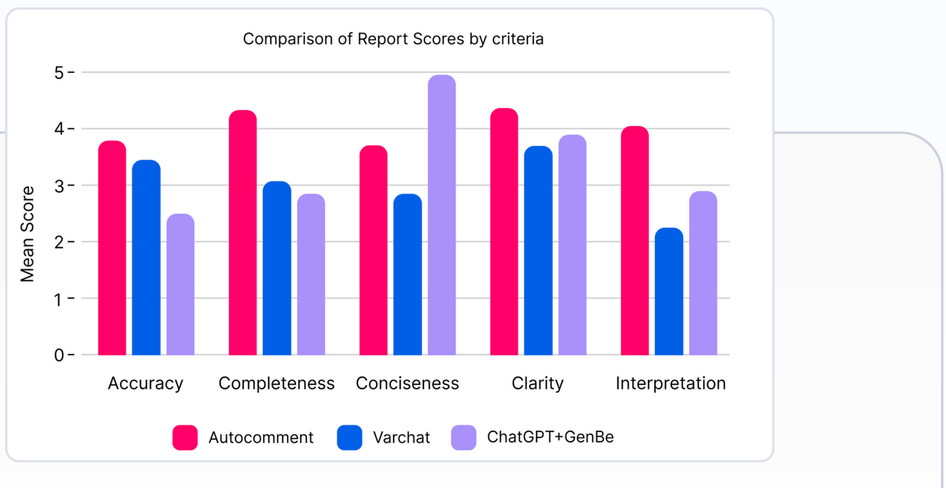
Provide a few examples of output format given the input content to guide the LLM to generate the right output model.



III. RESULTS | Using LLM as a judge approach.



Example of the interface
The interpretation was automatically generated by AutoComment, waiting for user modification / approval.



LLM as a judge
We used Gemini 2.5 pro as an impartial evaluator to assess the quality of outputs, based on a given variant (n=21) generated by AutoComment (SeqOne), VarChat and ChatGPT with a direct input of GeneBe annotations.

IV. DISCUSSION

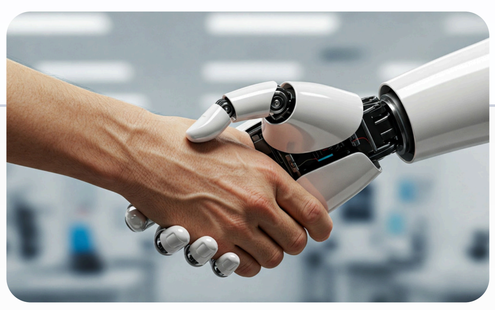
Consistent structure

Brief (~~verbose~~)

~~Hallucinations~~

~~Random format~~

AutoComment is a trusted report generator
Using RAG and few-shot prompting, we present here a tool that improves biologists' efficiency. This work should be further validated and its implementation monitored.



DiagAI Copilot: Long term
This tool is one of many constituting the DiagAI tools suite that will be coordinate by a "controller agent", namely DiagAI Copilot.

SeqOne