Clinical Interpretation Analysis

The goal of a clinical analysis is to identify, from millions of patient's variants, a few ones that may explain the disease. Once selected a few variants, they are classified according to a pathogenicity or clinical significance criteria.

For each selected variant, OpenCGA creates a clinical variant that mainly, consists of a list of clinical variant evidences. And each evidence classifies the variant according to a tier, ACGM value, clinical significance, drug response, trait association and functional effect and more.

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Useful Links

- ACMG standards and guidelines
- GEL tiering algorithm
- TEAM tool

Clinical analysis classification

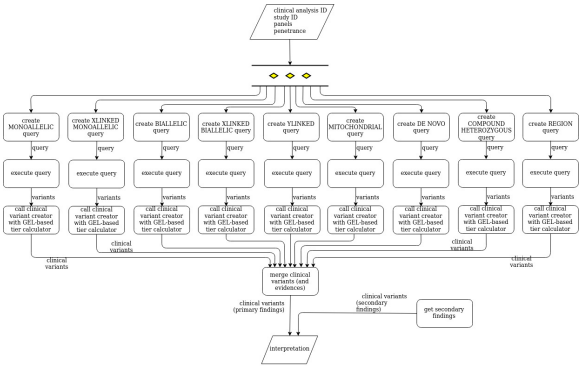
OpenCGA provides two types of clinical analysis depending on the outcome:

- Analysis that return a list of clinical variants:
  - Primary finding analysis
  - Secondary finding analysis
- Analysis that return a clinical analysis interpretation.
  An interpretation consists of two lists of clinical variants (one for primary findings, and one for secondary findings), a list of panels and the low-coverage regions for that panel genes. OpenCGA implements different interpretation analysis for both rare disease and cancer.
  - Interpretation analysis for rare diseases:
    - Tiering interpretation analysis based on GEL tiering algorithm
    - Zetta interpretation analysis
    - TEAM interpretation analysis
  - Interpretation analysis for cancer:
    - Interpretation analysis based on GEL cancer tiering algorithm.

Tiering interpretation analysis based on GEL tiering algorithm

The tiering interpretation analysis creates and executes, in parallel (multithreaded execution), a variant query for each mode of inheritance (family segregation), those queries filter by a set of consequence types, protein coding biotype and population frequencies and calls the clinical variant creator in order to create clinical variants. In addition, it executes a secondary findings analysis. The tiering interpretation analysis returns a clinical analysis interpretation.

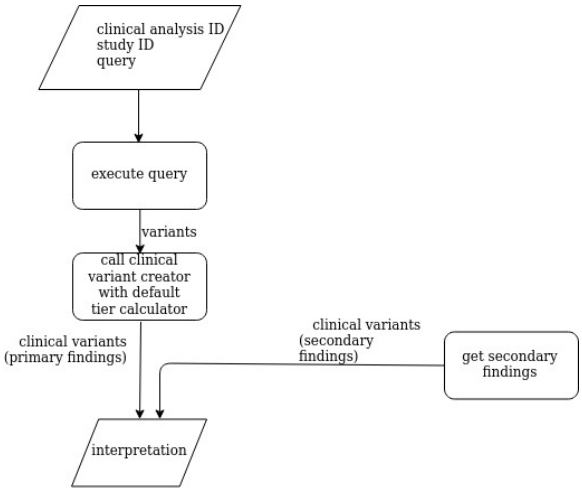
The following diagram shows how the tiering interpretation analysis:



Zetta interpretation analysis

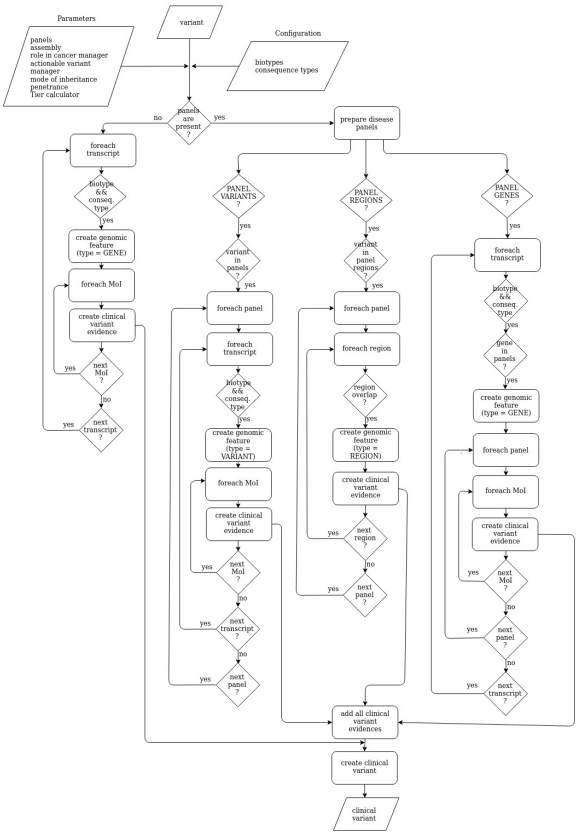
The Zetta interpretation analysis executes an user-defined query in order to retrieve the variants that are processed by the clinical variant creator in order to create clinical variants. In addition, it executes a secondary findings analysis an. The Zetta interpretation analysis returns a clinical analysis interpretation.

The following diagram shows how the Zetta interpretation analysis:



Clinical variant creator

The clinical variant creator creates clinical variant(s) from the input variant(s) according to certain parameters and configuration options. A clinical variant evidence is created for each combination of mode of inheritance, panel and trascript. See diagram below:



Tier calculator

To assign the tier value of a selected variant is crucial in clinical analysis. OpenCGA considers three values:

- Tier 1, variants with strong clinical significance
- Tier 2, variants with potential clinical significance
- Tier 3, other findings

OpenCGA implements two algorithms to assign tier values:

- Default tier calculator
- GEL-based tier calculator

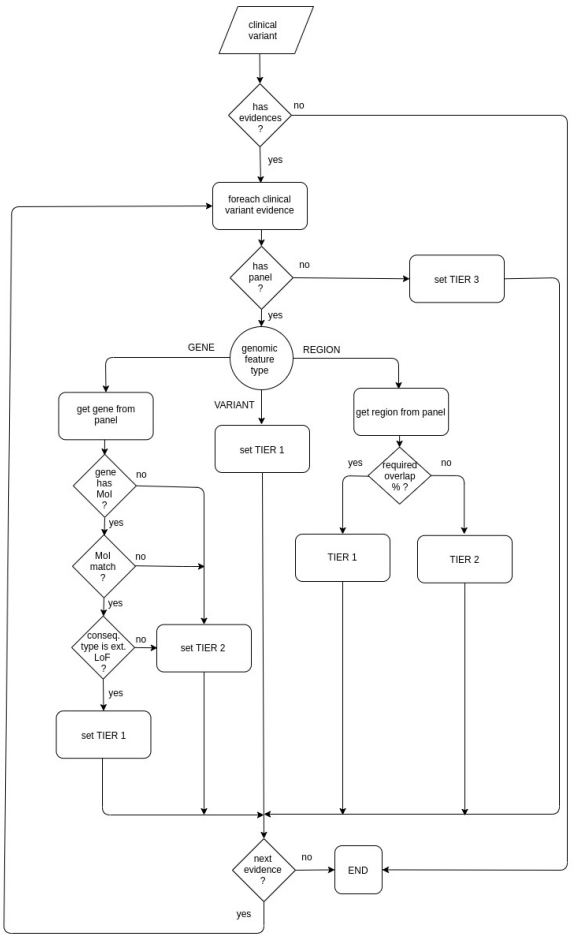
Default tier calculator

Default tier calculator sets the tier score for each clinical variant evidence taking into account:

1. the genomic feature type (VARIANT, GENE or REGION)
2. the mode of inheritance (MoI) and
3. the overlap percentage.

The default tier calculator is used by the primary findings, secondary findings, Zetta interpretation and TEAM-based interpretation analysis.

The following diagram shows how the default tier calculator assigns a tier value:



GEL-based tier calculator

GEL-based tier calculator sets the tier value for each reported event of a given reported variant taking into account:

1. the genomic feature type (GENE or REGION),
2. the mode of inheritance (MoI) and
3. the overlap percentage.

The GEL-based tier calculator is used by the interpretation analysis based on GEL algorithms.

The following diagram shows how the GEL-based tier calculator assigns a tier value: