Computational analysis of clinically actionable genomic features: Precision Heuristics for Interpreting the Alteration Landscape (PHIAL)

Abstract # 558

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Background

Cancer treatment has been revolutionized by the ability to sequence the genomic data of individual patients' tumor tissue. This has led to a **massive increase in the quantity of data available to clinicians**; an increase with potential therapeutic implications if interpreted intelligently. Additionally, cancer researchers would benefit from a standard method of ranking patient sample actionability. We have developed **PHIAL** and **TARGET** to address these unmet needs.

PHIAL

Precision **H**euristics for **I**nterpreting the **A**lteration **L**andscape

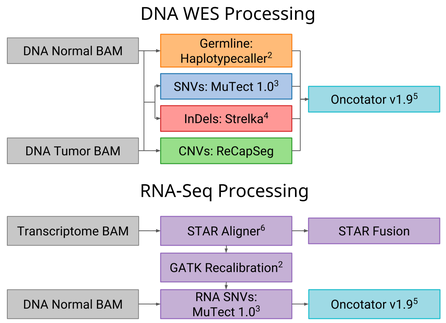
- A heuristic clinical interpretation algorithm created in 2014[1] to identify **clinically actionable or biologically relevant** alterations in patient tumor sequence data.
- Uses cancer alteration databases to generate **personalized treatment reports** (figs. 1 and 3).
- Our most recent revision (PHIAL2) allows:
  - Annotation of new features: including SNVs in the context of RNA-Seq data, InDels, somatic CNVs, fusions, and global features.
  - Use of germline and transcriptome data when estimating clinical utility of somatic alterations.

TARGET

Tumor **A**lterations **R**elevant for **GE**nomics-driven **T**herapy

- Developed concurrently with PHIAL[1] as a manually curated **database of relationships between genetic alterations and potential clinical actions**.
- Our most recent revision (TARGET2) includes:
  - The addition of 404 alteration-action relationships, for a total of 526 relationships.
  - "Predictive implication" estimates, increasing the ability to **qualify putative drug sensitivity, resistance, or prognostic claims.**
  - Creation of a web portal to enable convenient public access to our curated database of alteration-action relationships (fig. 2).

Sample Processing Pipeline



PHIAL uses normal DNA, tumor DNA, and transcriptome data to predict clinical actionability. Several genomics tools are used to convert raw sequence data into annotated results that PHIAL can process.

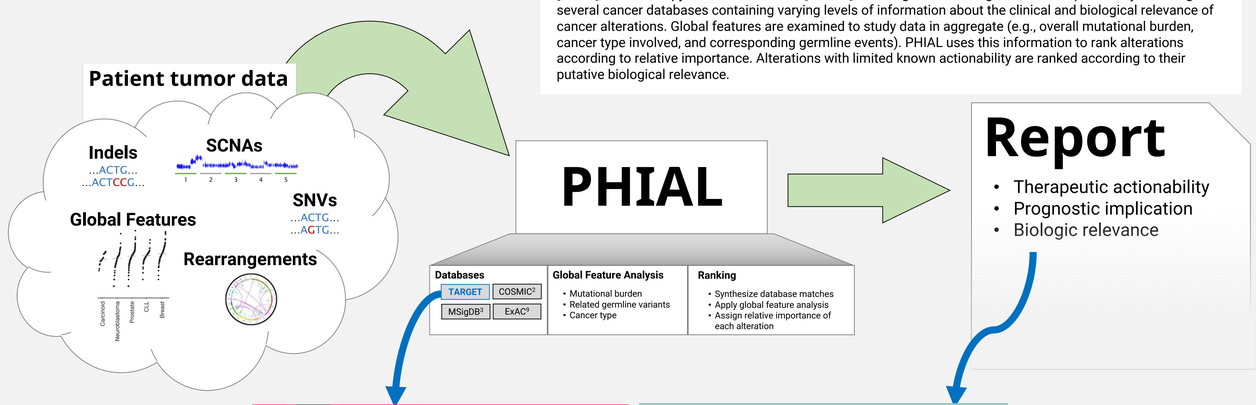


Fig. 1: The PHIAL analysis pipeline. Patient tumor data (single nucleotide variations [SNVs], insertions/deletions [indels], somatic copy number alterations [SCNAs], rearrangements, and global features) are analyzed using several cancer databases containing varying levels of information about the clinical and biological relevance of cancer alterations. Global features are examined to study data in aggregate (e.g., overall mutational burden, cancer type involved, and corresponding germline events). PHIAL uses this information to rank alterations according to relative importance. Alterations with limited known actionability are ranked according to their putative biological relevance.

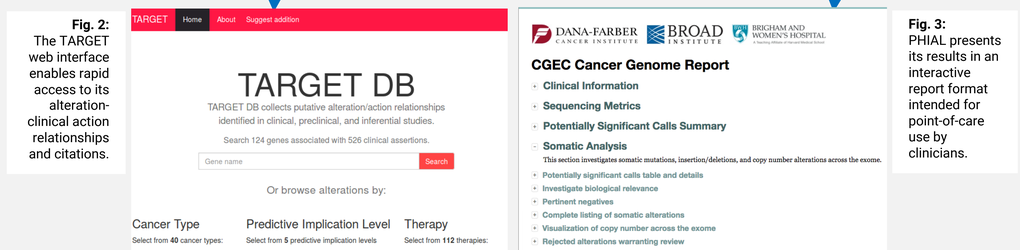


Fig. 2: The TARGET web interface enables rapid access to its alteration-clinical action relationships and citations.

Fig. 3: PHIAL presents its results in an interactive report format intended for point-of-care use by clinicians.

Results

We compared the results of PHIAL2 (with TARGET2) with those of PHIAL1 (with TARGET1) using a 260 patient cohort containing both whole exome and transcriptome sequencing data (110 metastatic melanoma[4] and 150 castration-resistant prostate cancer[5] patients). Importantly, **PHIAL2 associated over 14% of TARGET-related variants with an FDA-approved therapy, and over 9% with a clinical trial**. These associations could have suggested potential treatment options not previously identified for these patients.

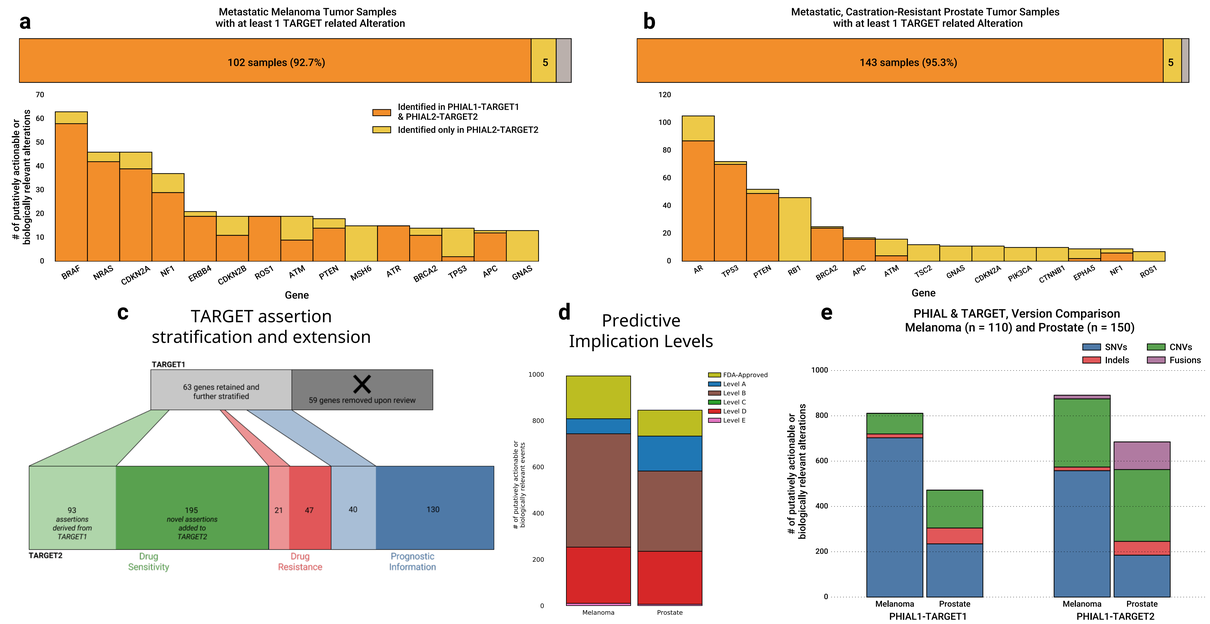


Fig. 4: (a, b) PHIAL2-TARGET2 identifies additional putatively actionable or biologically relevant alterations in two patient cohorts (metastatic melanoma and metastatic castration-resistant prostate cancer. **(a)** At least one TARGET-related alteration was found in an additional 5% of metastatic melanoma samples using PHIAL2+TARGET2; 2.7% of samples had no TARGET-related alteration (gray segment). **(b)** At least one TARGET-related alteration was found in an additional 5% of metastatic castration-resistant prostate tumor samples using PHIAL2-TARGET2; 1.33% of samples had no TARGET-related alteration (gray segment). **(c)** TARGET2 derives several alteration-action relationships from the gene-centric data in TARGET1; these relationships are represented as the lighter-colored segment in each relationship category block. **(d)** Predictive implication levels of alteration-action relationships found by PHIAL2-TARGET2. **(e)** Cross-comparison using PHIAL1 and PHIAL2 with both the TARGET1 and TARGET2 databases.

Conclusions

Our revisions have improved PHIAL's ability to identify and annotate putatively actionable alterations. Additionally, our work has transitioned PHIAL from a variant-based to a feature-based approach. These advances may increase the clinical utility of whole-exome and transcriptome sequencing by providing a rapid method for interpreting these data. Additionally, our modifications to TARGET have resulted in an accessible comprehensive database of alteration-action relationships.

Future Work

We are pursuing several extensions to PHIAL and TARGET:

- Machine-learning based approaches may assist PHIAL's ability to provide a deeper understanding of cases in which there is no clear cause of oncogenesis.
- Greater use of global features, such as mutational signature analysis, could enable PHIAL to consider alterations in the overall context of a patient's tumor, tailoring its analysis to the mutated processes in the individual tumor rather than providing general information linked to common alterations.
- Improved data visualization methods could be used to increase the accessibility and information density of PHIAL's reports. In particular, interactive graphs could be used to illustrate concepts such as the quality of the sampled data, quantity of actionable versus non-actionable events, and the cellular pathways altered in an individual patient's cancer.
- Automated data curation methods could enable TARGET to suggest potential new alteration-action relationships from recent publications, increasing the speed at which relationships can be added to the database.

References

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View our code on GitHub!
github.com/vanallenlab/2017-aacr_phial2