

Overview of the Molecular Oncology Almanac for variant interpretation

Brendan Reardon

Cancer Genomics Consortium workshop, 2023 August 13

Find us at
moalmanac.org

Find these slides at
github.com/vanallenlab/2023-cgc

Interpretation workflows are labor intensive

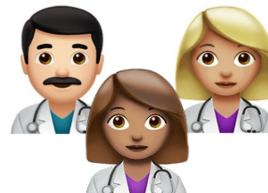
Annotation

Variants are **annotated** for clinical and biological significance using curated knowledge bases and guidelines

CiViC, OncoKB,
MetaKB, and so many more!

Interpretation

Variants are **interpreted** for actionability and relevance in the context of an individual patient's unique cancer



Delivery

Results are **delivered** from molecular pathologist or molecular tumor board to a provider or patient in the form of a report



We think that integrated computational systems can help

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Patient DNA

Somatic and germline mutations
Copy number alterations

Patient RNA

Somatic mutations
Fusions

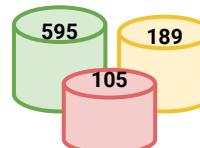
9 Established
Databases



Annotate & interpret
first-order genomic relationships

Molecular Oncology Almanac

894 alteration-action relationships
asserting **sensitivity**, **resistance**, and
prognostic claims

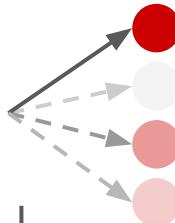


Annotate & interpret
second-order genomic relationships

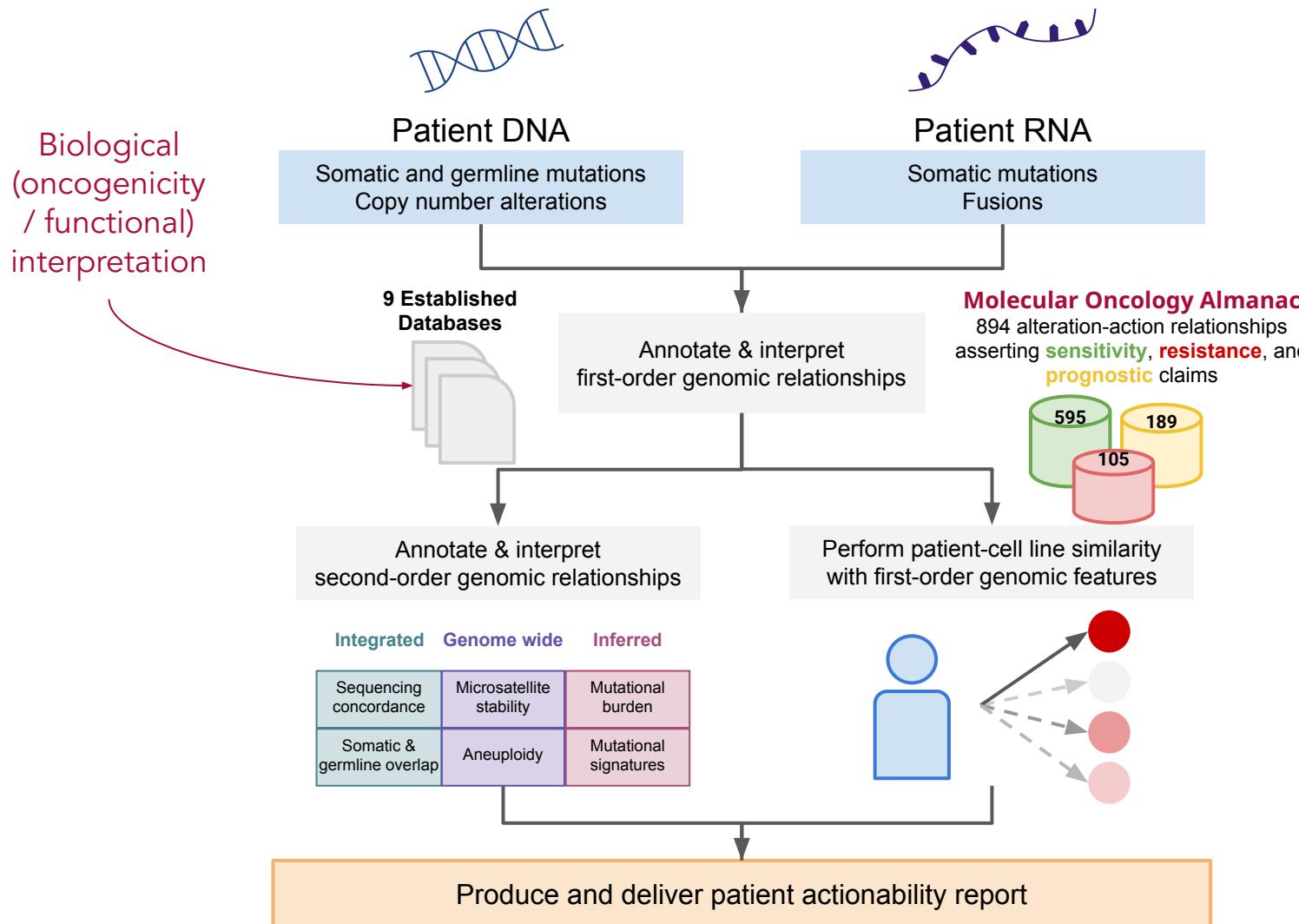
Perform patient-cell line similarity
with first-order genomic features

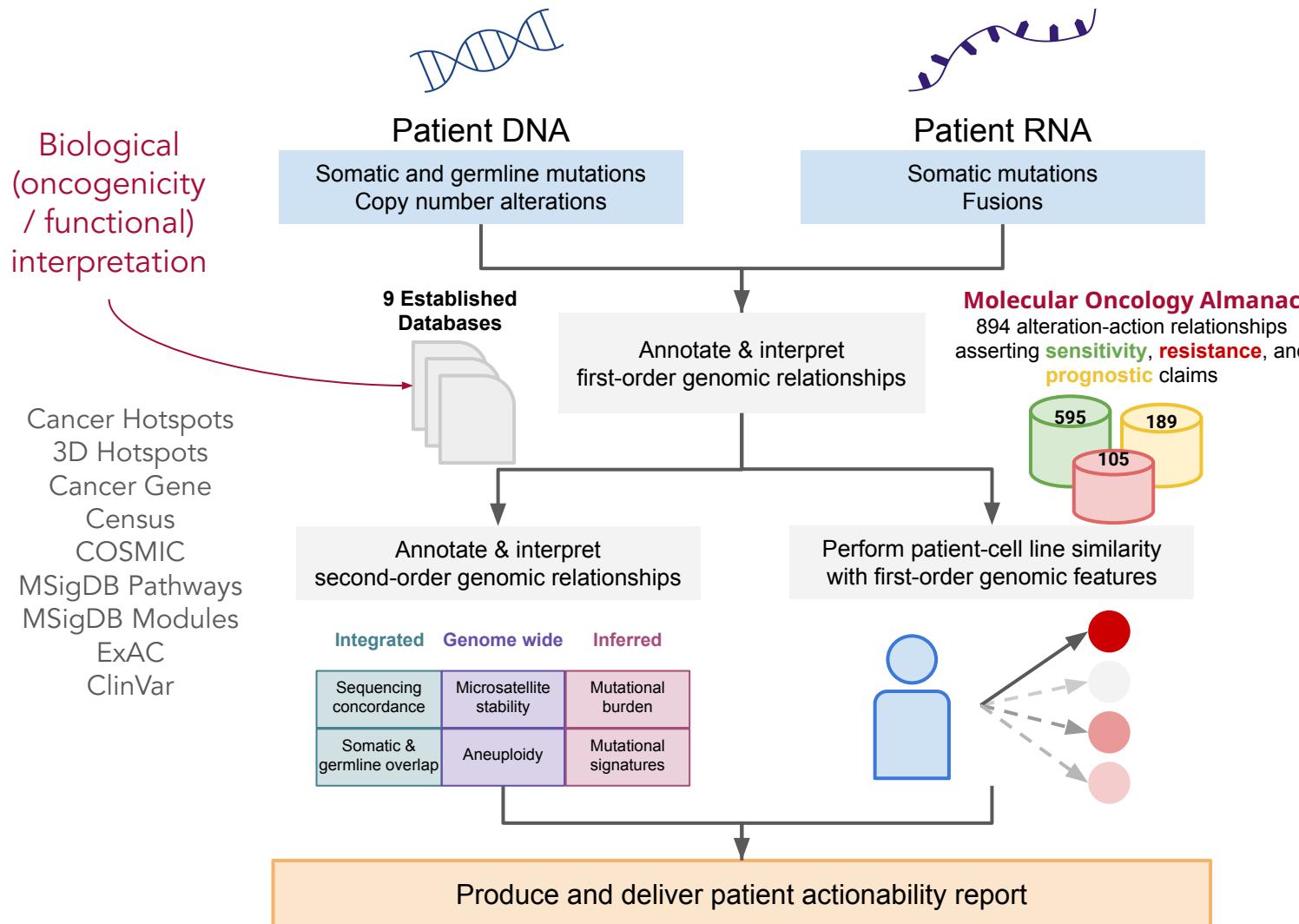
Integrated Genome wide Inferred

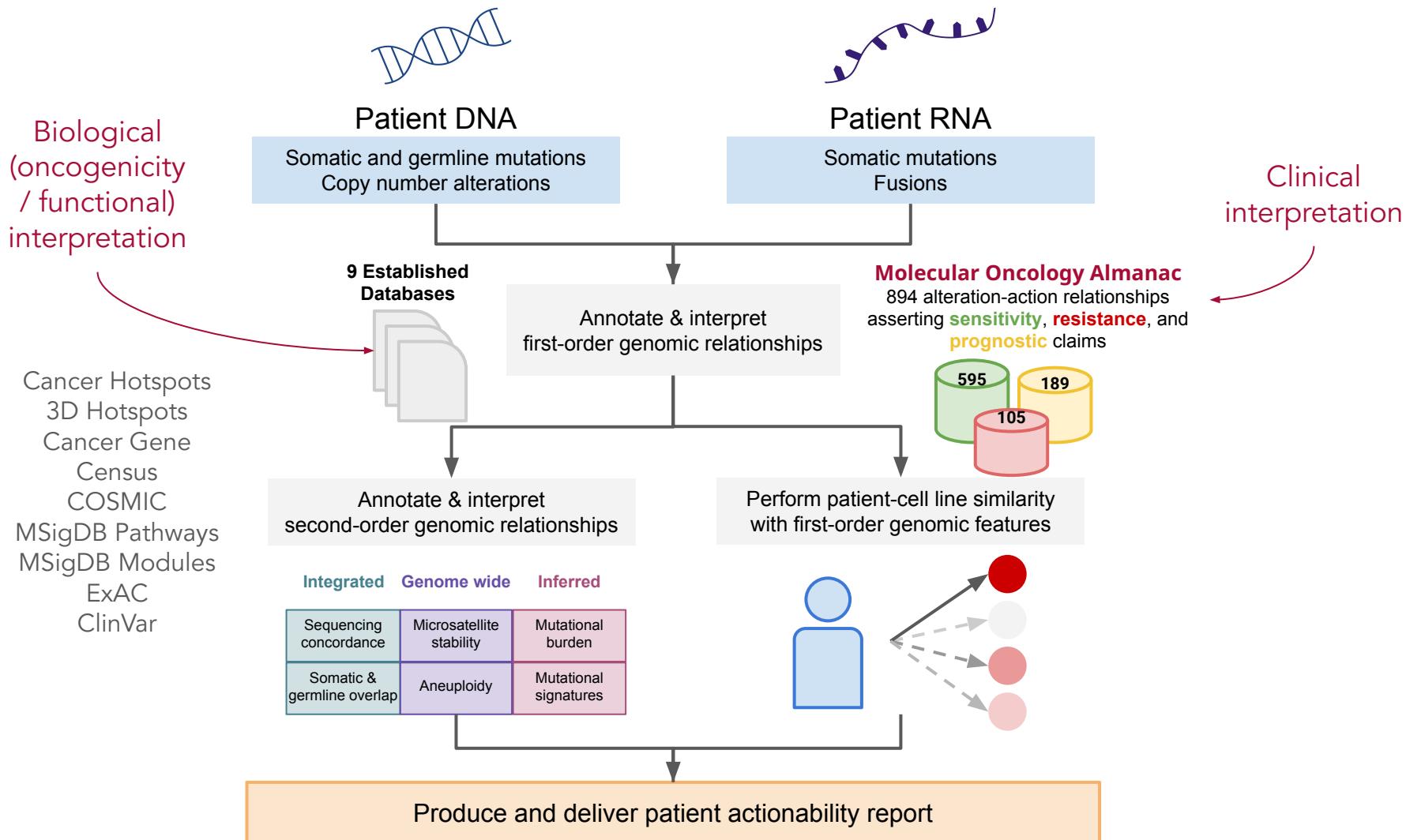
Sequencing concordance	Microsatellite stability	Mutational burden
Somatic & germline overlap	Aneuploidy	Mutational signatures



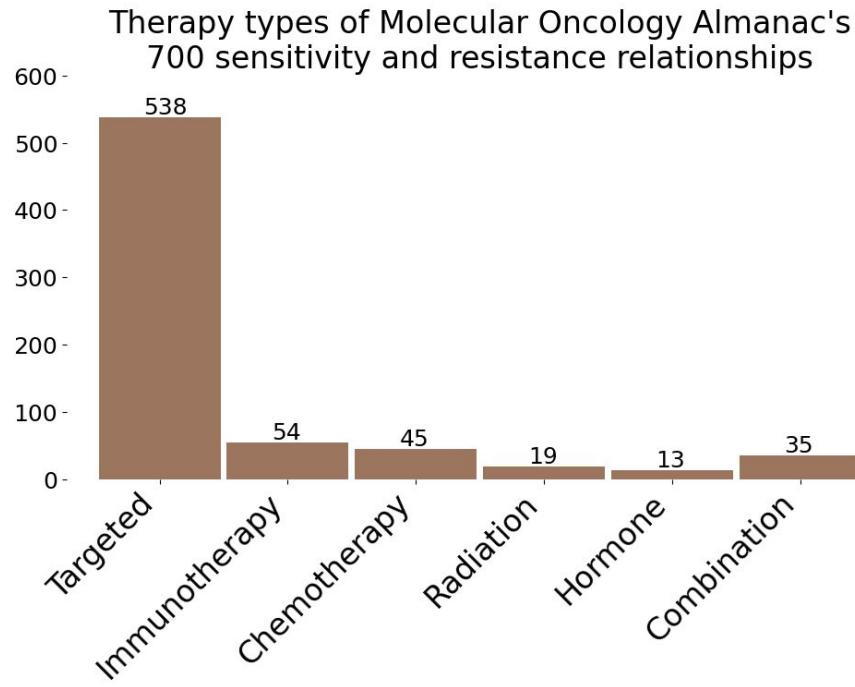
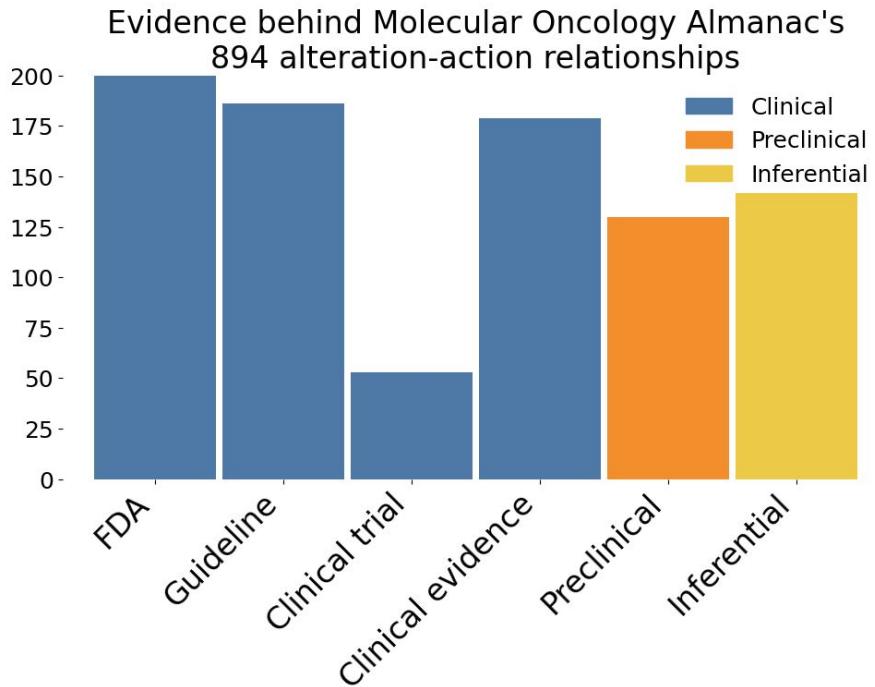
Produce and deliver patient actionability report





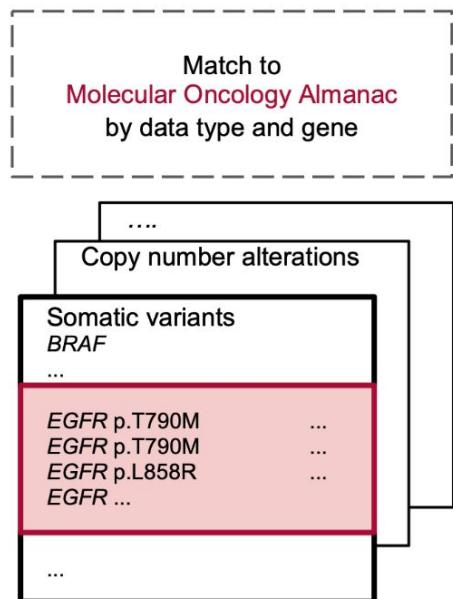


Number of alteration-action relationships



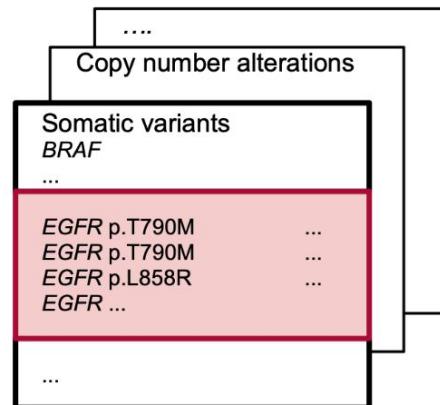
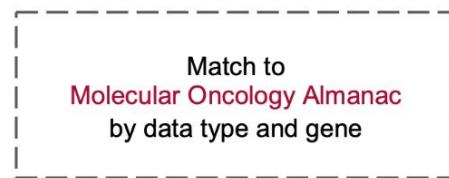
Matching a clinically relevant somatic variant to catalogued assertions

a NSCLC profile harboring
somatic variant *EGFR* p.T790M

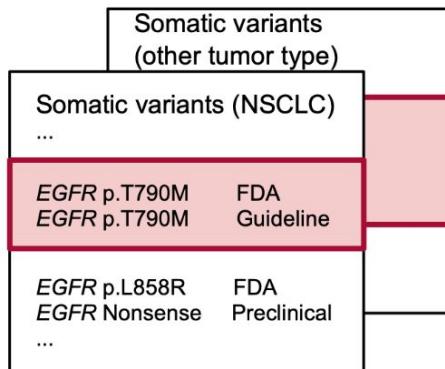
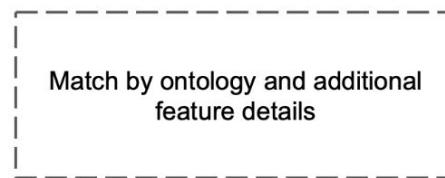


Matching a clinically relevant somatic variant to catalogued assertions

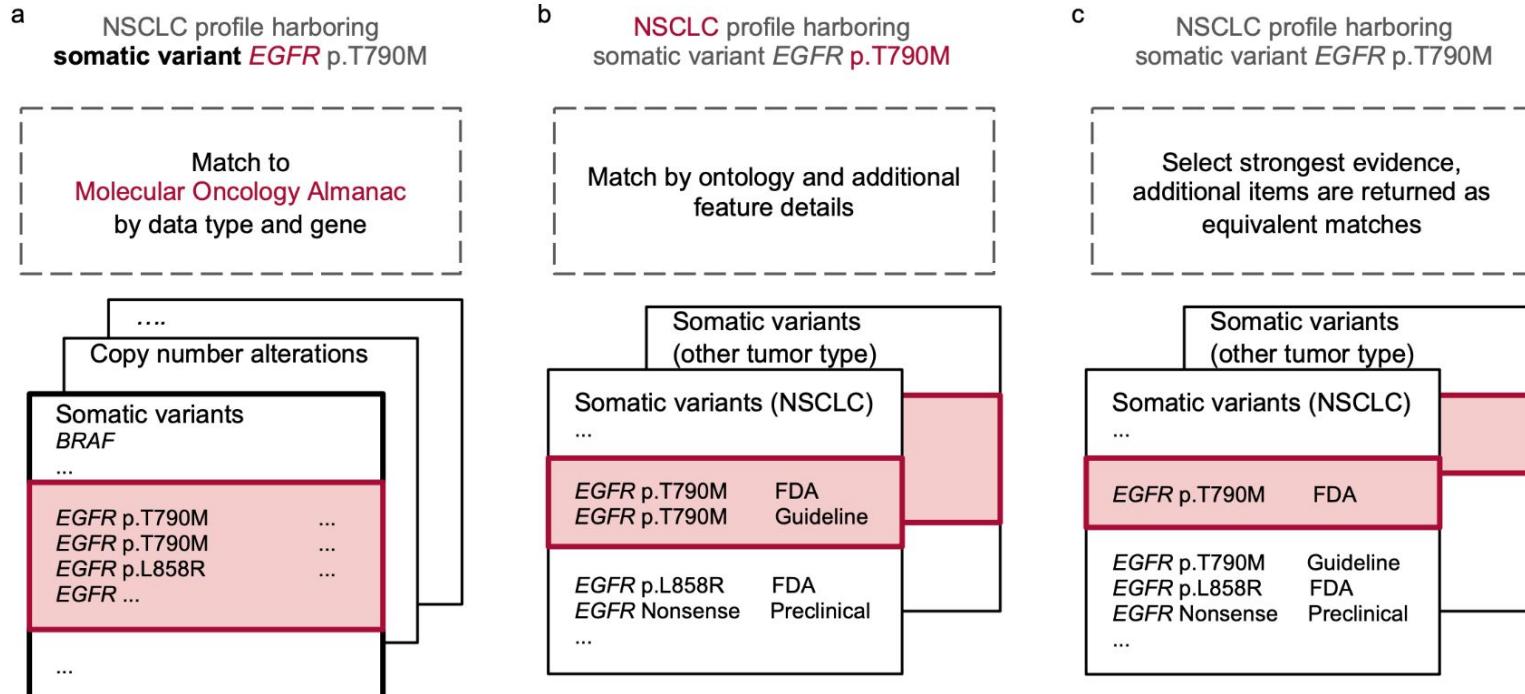
a NSCLC profile harboring
somatic variant *EGFR* p.T790M



b **NSCLC** profile harboring
somatic variant ***EGFR* p.T790M**



Matching a clinically relevant somatic variant to catalogued assertions





Some updates since publication

- 104 relationships added to our underlying database
 - 790 in September 2021 and currently have 894, with 19 currently pending
- Added simplified input to allow usage without having genomic alterations in standard data types (e.g., Mutation Annotation Format, MAF)
- Refactored algorithm codebase to support parallelization
- Expanded algorithm configuration to enable or disable several features
 - Preclinical comparisons, signature analysis, sample similarity, and report generation
- Released secondary code to assist with cohort-wide analyses of interpretations
- Nurtured collaborations
 - All Island Cancer Research (University of Limerick and Queen's University Belfast), Institute for Cancer Research (London), VarSome, Veteran Affairs, Participant Engagement and Cancer Genome Sequencing, Osteosarcoma Count Me In, GA4GH / VICC!, IRB Barcelona, cBioPortal
 - AMIA 2023 - Theodore "Ted" Feldman at Veteran Affairs will be presenting on interpretation performed on ~1,600 veterans

Guiding principles for development

Open source

All code for the Molecular Oncology Almanac's algorithm, underlying database, web resources, and supporting code are [publicly available on GitHub](#) with permissive licensing (GNU GPL 2.0).

Containerized

The algorithm is available on [Docker Hub](#) with all external data sources and is not dependent on APIs.

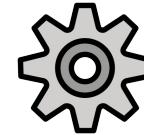
Configurable

The algorithm contains configuration files to modify several properties. You may deploy it with a modified database, disable or enable features, adjust considered thresholds, column names, etc.

Privacy

Our web services do not utilize cookies and we do not see, receive, or have access to any of your data.

There are many ways to use Molecular Oncology Almanac!

	Programming not required	Programming required
Few variants	Browse our database moalmanac.org 	Programmatically access our database moalmanac.org/api/assertions 
Many variants	Annotate and interpret individual profiles with our algorithm on portal.moalmanac.org 	Annotate and interpret individual profiles with our algorithm directly via GitHub and/or Docker 

Molecular Oncology Almanac

Browser

A collection of putative alteration/action relationships identified in clinical, preclinical, and inferential studies.

Search 149 molecular features associated with 894 assertions.

Multiple search terms may be combined. [Click here for search help.](#)

Or browse alterations by:

Cancer Type

Select from 65 cancer types:

Evidence

Select from 6 types of evidence sources:

Therapy

Select from 155 therapies:

Database version: 1.0.0

Content release: [2023-07-06](#)

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vanallenlab / moalmanac-db

Type ⌘ to search



Code

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Jul 6



brendanreardon

v.2023-07-06

-o 746da24 ✓

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2023 July 6 release

Latest



Added entries:

- (FDA) *BRCA1* and *BRCA2* somatic and germline variants and sensitivity to olaparib in combination with abiraterone and prednisone or prednisolone for patients with metastatic castration-resistant prostate cancer.
- (FDA) *BRCA1* and *BRCA2* germline variants and sensitivity to olaparib for patients with metastatic pancreatic adenocarcinoma.
- (FDA) *BRCA1* and *BRCA2* germline variants and sensitivity to olaparib for the treatment of adult patients with HER2-negative high risk early breast cancer.
- (FDA) *ATM*, *ATR*, *BRCA1*, *BRCA2*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, and *RAD51C* somatic variants and sensitivity to talazoparib in combination with enzalutamide for patients with metastatic castration-resistant prostate cancer.

Revised entries:

- (FDA) *BRCA1* and *BRCA2* germline variants and sensitivity to olaparib in breast cancer. Revised description to add additional approval details from FDA drug label.



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Cancer Type

Select from 65 cancer types:

Select cancer type

Evidence

Select from 6 types of evidence sources:

✓ FDA-Approved

- Guideline
- Clinical trial
- Clinical evidence
- Preclinical
- Inferential

Therapy

Select from 155 therapies:

Select therapy

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Therapies

Osimertinib

Durvalumab + Osimertinib

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Select from 65 cancer types:

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Select from 6 types of evidence sources:

Therapy

Select from 155 therapies:

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Select therapy

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Gene:EGFR Erlotinib Afatinib Osimertinib
Durvalumab + Osimertinib

Search

Multiple search terms may be combined. [Click here for search help.](#)

Click on any alteration below to view more details about the alteration-actionability relationship.

Show 25 entries

Feature type	Feature	Therapy	Response	Cancer Type	Predictive Level
Somatic Variant	EGFR p.T790M (Missense)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved
Somatic Variant	EGFR	Afatinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved
Somatic Variant	EGFR (Nonsense)	Afatinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved
Somatic Variant	EGFR p.L858R (Missense)	Afatinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved
Somatic Variant	EGFR Exon 19 (Deletion)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved
Somatic Variant	EGFR p.L858R (Missense)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved
Somatic Variant	EGFR	Erlotinib	Sensitivity	Non-Small Cell Lung Cancer	Guideline
Somatic Variant	EGFR	Afatinib	Sensitivity	Non-Small Cell Lung Cancer	Guideline
Somatic Variant	EGFR p.T790M (Missense)	Durvalumab + Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	Clinical trial
Somatic Variant	EGFR p.T790M (Missense)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	Clinical trial
Somatic Variant	EGFR Exon 19 (Nonsense)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	Clinical trial
Somatic Variant	EGFR p.L858R (Missense)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	Clinical trial
Somatic Variant	EGFR p.T790M (Missense)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	Clinical evidence
Somatic Variant	EGFR p.T790M (Missense)	Erlotinib	Resistance	Non-Small Cell Lung Cancer	Clinical evidence
Somatic Variant	EGFR p.T790M (Missense)	Afatinib	Resistance	Non-Small Cell Lung Cancer	Clinical evidence

Showing 1 to 15 of 15 entries

Previous 1 Next

x Gene:EGFR x Erlotinib x Afatinib x Osimertinib
x Durvalumab + Osimertinib x FDA-Approved x Clinical trial

 Search

Multiple search terms may be combined. [Click here for search help.](#)

Click on any alteration below to view more details about the alteration-actionability relationship.

Show 25 ▾ entries

Feature type	Feature	Therapy	Response	Cancer Type	Predictive Level	View
Somatic Variant	EGFR p.T790M (Missense)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved	
Somatic Variant	EGFR	Afatinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved	
Somatic Variant	EGFR (Nonsense)	Afatinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved	
Somatic Variant	EGFR p.L858R (Missense)	Afatinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved	
Somatic Variant	EGFR Exon 19 (Deletion)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved	
Somatic Variant	EGFR p.L858R (Missense)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved	
Somatic Variant	EGFR	Erlotinib	Sensitivity	Non-Small Cell Lung Cancer	Guideline	
Somatic Variant	EGFR	Afatinib	Sensitivity	Non-Small Cell Lung Cancer	Guideline	
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Somatic Variant	EGFR p.L858R (Missense)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	Clinical trial	
Somatic Variant	EGFR p.T790M (Missense)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	Clinical evidence	
Somatic Variant	EGFR p.T790M (Missense)	Erlotinib	Resistance	Non-Small Cell Lung Cancer	Clinical evidence	
Somatic Variant	EGFR p.T790M (Missense)	Afatinib	Resistance	Non-Small Cell Lung Cancer	Clinical evidence	

Showing 1 to 15 of 15 entries

Previous

1

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x Gene:EGFR x Erlotinib x Afatinib x Osimertinib

x Durvalumab + Osimertinib x FDA-Approved x Clinical trial

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Click on any alteration below to view more details about the alteration-actionability relationship.

Show 10 entries

Feature type	Feature	Therapy	Response	Cancer Type	Predictive Level	
Somatic Variant	EGFR p.T790M (Missense)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved	
Somatic Variant	EGFR	Afatinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved	
Somatic Variant	EGFR (Nonsense)	Afatinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved	
Somatic Variant	EGFR p.L858R (Missense)	Afatinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved	
Somatic Variant	EGFR Exon 19 (Deletion)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved	
Somatic Variant	EGFR p.L858R (Missense)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	FDA-Approved	
Somatic Variant	EGFR p.T790M (Missense)	Durvalumab + Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	Clinical trial	
Somatic Variant	EGFR p.T790M (Missense)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	Clinical trial	
Somatic Variant	EGFR Exon 19 (Nonsense)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	Clinical trial	
Somatic Variant	EGFR p.L858R (Missense)	Osimertinib	Sensitivity	Non-Small Cell Lung Cancer	Clinical trial	

Showing 1 to 10 of 10 entries

Previous 1 Next

Assertion: Sensitivity to Osimertinib (in Non-Small Cell Lung Cancer)

FDA-Approved

Somatic Variant: EGFR p.T790M (Missense)

Osimertinib is a kinase inhibitor indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation positive non-small cell lung cancer (NSCLC), as detected by an FDA approved test, whose disease has progressed on or after EGFR TKI therapy.

Citations:

- AstraZeneca Pharmaceuticals, LP. Tagrisso (osimertinib) [package insert]. U.S. Food and Drug Administration website.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208065s016lbl.pdf. Revised May 2020. Accessed November 12, 2020.

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Citations:

- AstraZeneca Pharmaceuticals, LP. <https://www.accessdata.fda.gov/drugatf/cder/OSIMERTINIB.html>

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use TAGRISSO safely and effectively. See full prescribing information for TAGRISSO.

TAGRISSO® (osimertinib) tablets, for oral use

Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Dosage and Administration (2.4)

12/2019

Warnings and Precautions (5.5)

12/2019

INDICATIONS AND USAGE

TAGRISSO is a kinase inhibitor indicated for

- the first-line treatment of patients with metastatic NSCLC whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test. (1.1, 2.1)
- the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy. (1.2, 2.1)

DOSAGE AND ADMINISTRATION

Recommended dosage: 80 mg orally once daily, with or without food. (2.2)

DOSE FORMS AND STRENGTHS

Tablets: 80 mg and 40 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- **Interstitial Lung Disease (ILD)/Pneumonitis:** Occurred in 3.9% of patients. Permanently discontinue TAGRISSO in patients diagnosed with ILD/Pneumonitis. (5.1)
- **QTc Interval Prolongation:** Monitor electrocardiograms and electrolytes in patients who have a history or predisposition for QTc prolongation, or those who are taking medications that are known to prolong the QTc

FULL PRESCRIBING INFORMATION: CONTENTS***1 INDICATIONS AND USAGE**

- 1.1 First-line Treatment of EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)
- 1.2 Previously Treated EGFR T790M Mutation-Positive Metastatic

interval. Withhold then restart at a reduced dose or permanently discontinue TAGRISSO. (2.4, 5.2)

- **Cardiomyopathy:** Occurred in 2.6% of patients. Conduct cardiac monitoring, including left ventricular ejection fraction (LVEF) assessment in patients with cardiac risk factors. (2.4, 5.3)
- **Keratitis:** Promptly refer patients with signs and symptoms of keratitis to an ophthalmologist for evaluation. (5.4)
- **Erythema Multiforme and Stevens-Johnson Syndrome:** Withhold TAGRISSO if erythema multiforme major (EMM) or Stevens-Johnson syndrome (SJS) is suspected and permanently discontinue if confirmed. (2.4, 5.5)
- **Embryo-Fetal Toxicity:** TAGRISSO can cause fetal harm. Advise females of potential risk to the fetus and to use effective contraception during treatment with TAGRISSO and for 6 weeks after final dose. Advise males to use effective contraception for 4 months, after the last dose of TAGRISSO. (5.6, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 20\%$) were diarrhea, rash, dry skin, nail toxicity, stomatitis, fatigue and decreased appetite. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or www.TAGRISSO.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Strong CYP3A Inducers: Avoid if possible. If not possible, increase TAGRISSO to 160 mg daily in patients receiving a strong CYP3A4 inducer. (2.4, 7.1)

USE IN SPECIFIC POPULATIONS

Lactation: Do not breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2020

7.3 Drugs That Prolong the QTc Interval

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation



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For more information on our curation process, please view our [standard operating procedure for data curation](#). Entries can also be recommended through the [Molecular Oncology Almanac connector](#), a Google Chrome extension.

Source*

DOI, e.g. 10.1126/science.1062538

Cancer Type*

Select cancer type:

Select a disease**Feature Type***

Select the feature asserted in the source:

Select a feature**Predictive Implication Level***

Select a predictive implication level

Select a predictive implication level**Therapy**

Select or enter a therapy:

Select a therapy**Email Address***

We may contact you to ask you about your experience with this portal.

Submit

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Source*

DOI, e.g. 10.1126/science.1062538

Cancer Type*

Select cancer type:

Feature Type*

Select the feature asserted in the source:

Direction**Gene****Cytoband****Predictive Implication Level***

Select a predictive implication level

Therapy

Select or enter a therapy:

Email Address*

We may contact you to ask you about your experience with this portal.

**Submit**

Submit Entry to The Molecular Oncology Almanac

Success

Entry was submitted for review:

Email: breardon@broadinstitute.org

Therapy: Abiraterone

Implication: Guideline

Feature: copy_number

Source: 10.1126/science.1062538

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Select the feature asserted in the source:

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Gene

Cytoband

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Source*

DOI, e.g. 10.1126/science.1062538

**Cancer Type***

Select cancer type:

Prostate Adenocarcinoma

Feature Type*

Select the feature asserted in the source:

Copy Number

Direction**Gene****Cytoband**

Molecular Oncology Almanac

Algorithm

API

Browser

Extension

Portal

Recommend entry

Submit Entry to The Molecular Oncology Almanac

Success

Entry was submitted for review:

Email: breardon@broadinstitute.org

Therapy: Abiraterone

Implication: Guideline

Feature: copy_number

Source: [10.1126/science.1062538](https://doi.org/10.1126/science.1062538)

For more information on our curation process, please view our [standard operating procedure for data curation](#) or our [Molecular Oncology Almanac connector](#), a Google Chrome extension.

Source*

DOI, e.g. 10.1126/science.1062538

10.1126/science.1062538

Feature Type*

Select the feature asserted in the source:

Submit Entry to MOA

Source*

DOI, e.g. 10.1126/science.1062538

Feature Type*

Select feature

Cancer Type*

Select cancer type

Predictive Implication Level*

Select predictive implication level

Therapy

Select therapy

Email Address*

We may contact you to ask you about your experience with MOA.

Submit

Molecular Oncology Almanac

Browser

A collection of putative alteration/action relationships identified in clinical, preclinical, and inferential studies.

Search 149 molecular features associated with 894 assertions.

Multiple search terms may be combined. [Click here for search help.](#)

Or browse alterations by:

Cancer Type

Select from 65 cancer types:

Evidence

Select from 6 types of evidence sources:

Therapy

Select from 155 therapies:

Database version: 1.0.0

Content release: [2023-07-06](#)

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Molecular Oncology Almanac

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Getting Molecular Oncology Almanac

The codebase is available for download through this GitHub repository, [Dockerhub](#), and [Terra](#). The method can also be run on Terra, without having to use Terra, by using [our portal](#). Accessing Molecular Oncology Almanac through GitHub will require building some of the [datasources](#) but they are also contained in the Docker container.

Installation

Molecular Oncology Almanac is a Python application using Python 3.11 but also utilizes R to run [deconstructSigs](#) as a subprocess. This application, datasources, and all dependencies are packaged on Docker and can be downloaded with the command

```
docker pull vanallenlab/moalmanac
```



Alternatively, the package can be built from this GitHub repository. To download via GitHub,

```
git clone https://github.com/vanallenlab/moalmanac.git
```



We recommend using a [virtual environment](#) and running Python with either [Anaconda](#) or [Miniconda](#). After installing Anaconda or Miniconda, you can set up by running

```
conda create -n moalmanac python=3.11 -y  
source activate moalmanac  
pip install -r requirements.txt
```



Usage

Usage documentation can be found within the [moalmanac/](#) directory of this repository.

How to contribute

Please follow [our contribution instructions](#) if you are interested in contributing to this project.

Citation

If you find this tool or any code herein useful, please cite:

Reardon, B., Moore, N.D., Moore, N.S., et al. Integrating molecular profiles into clinical frameworks through the Molecular Oncology Almanac to prospectively guide precision oncology. *Nat Cancer* (2021).
<https://doi.org/10.1038/s43018-021-00243-3>

Standard usage

Molecular Oncology Almanac may be executed on any combination of input data but does require a patient_id to label output files.
Additional settings can be set by modifying the [config.ini](#) file and column names may be modified by editing the [colnames.ini](#) file.

Required arguments:

--patient_id	<string>	patient identifier	
--------------	----------	--------------------	--

Optional arguments:

--tumor_type	<string>	tumor ontology, default=Unknown	
--stage	<string>	tumor stage, default=Unknown	
--snv_handle	<string>	handle for MAF file of somatic single nucleotide variants	
--indel_handle	<string>	handle for MAF file of somatic insertions and deletions	
--bases_covered_handle	<string>	handle for text file which contains the number of calcable somatic bases	
--called_cn_handle	<string>	handle for text file which contained genes and copy number calls, will be used for fusion detection	
--cnv_handle	<string>	handle for annotated seg file for somatic copy number	
--fusion_handle	<string>	handle for STAR fusion output, .final.abridged	
--germline_handle	<string>	handle for MAF file of germline single nucleotide variants and insertions and indels	
--validation_handle	<string>	handle for MAF file of somatic single nucleotide variant called from validation	
--ms_status	<string>	microsatellite status as deemed by MSI sensor, MSI or MSS, default=Unknown	
--purity	<float>	tumor purity	
--ploidy	<float>	tumor ploidy	
--wgd	<boolean>	specify the occurrence of whole genome duplication	
--disable_matchmaking	<boolean>	remove patient-to-cell line matchmaking from report	
--description	<string>	description of patient	
--output-directory	<string>	specify location of produced outputs	

Example:

```
python moalmanac.py \
    --patient_id "example" \
    --tumor_type "SKCM" \
    --stage "Metastatic" \
```

Simplified input

A simplified input of a single file for somatic variants, germline variants, called copy number alterations, and fusions may also be used for a minimal interpretation. This mode also allows for [MSI status](#) and [whole-genome doubling](#) to be considered. With this format, MOAlmanac will be unable to annotate with any datasources that rely on nucleotide position.

As with the [standard usage](#), additional settings can be set by modifying the [config.ini](#) file and column names may be modified by editing the [colnames.ini](#) file.

Input for simplified input is a tab delimited file with one genomic alteration per row based on MOAlmanac's [standardized feature columns](#). In short the following columns are expected,

1. `feature_type`, the data type of the molecular features and accepts `Somatic Variant`, `Germline Variant`, `Copy Number`, or `Rearrangement`. These strings can be customized in the `feature_types` section of [config.ini](#).
2. `gene` or `feature`, the gene name of the genomic alteration.
3. `alteration_type`, classification or consequence of the genomic alteration
 - For somatic and germline variants: `Missense`, `Nonsense`, `Nonstop`, `Splice_Site`, `Frame_Shift_Ins`, `Frame_Shift_Del`, `In_Frame_Ins`, or `In_Frame_Del`
 - For copy number alterations: `Amplification` or `Deletion`
 - For rearrangements: `Fusion` or `Translocation`
4. `alteration`, specific genomic alteration,
 - For somatic and germline variants: the protein change with [1-letter amino acid codes](#), `p.HGVSp_Short`
 - For copy number alterations: Leave blank
 - For rearrangements: the full fusion separated by two dashes, `--`

For example,

<code>feature_type</code>	<code>feature</code>	<code>alteration_type</code>	<code>alteration</code>
Somatic Variant	BRAF	Missense	p.V600E
Copy Number	CDK4	Amplification	
Rearrangement	COL1A1	Fusion	COL1A1--CITED4
Germline Variant	BRCA2	Frameshift	p.S1982fs

Configuration

MOAlmanac can be customized by modifying the [config.ini](#) file and column names may be modified by editing the [colnames.ini](#) file.

config.ini

The configuration file [config.ini](#) lets users change settings, thresholds, and input string values. The file contains the following sections,

- `function_toggle` allows users to enable or disable the [actionability report](#), [model_similarity](#), [mutational signature](#), and [preclinical efficacy](#) functions.
- `versions` are string inputs to describe the MOAlmanac algorithm and database versions
- `exac` allows users to specify a threshold for [Allele frequency in ExAC](#) to identify common variants
- `fusion` allows users to specify the minimum spanning fragments required for fusions
- `mutation` allows users to specify minimum values for coverage and allelic fraction for evaluation of somatic and germline variants
- `seg` allows users to specify thresholds for total copy number
- `signatures` allows users to specify the minimum required contribution to consider mutational signatures
- `validation_sequencing` allows users to specify minimum power and allelic fraction to consider for variants from validation sequencing
- `feature_types` allows users to specify strings for considered feature types
- `databases` specifies file paths for databases used for annotation, found in the `moalmanac/databases/` folder
- `preclinical` specifies file paths for datasources used for preclinical functions, [model_similarity](#) and [preclinical efficacy](#)

colnames.ini

The configuration file [colnames.ini](#) lets users change strings associated with column names for input and output files. The file contains the following relevant sections,

- `input_data` , allows users to change column names for input data

Other sections in this configuration file are used internally to MOAlmanac for processing.

Molecular Oncology Almanac

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Or browse alterations by:

Cancer Type

Select from 65 cancer types:

Evidence

Select from 6 types of evidence sources:

Therapy

Select from 155 therapies:

Database version: 1.0.0

Content release: [2023-07-06](#)

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New analysis

Upon clicking "Begin analysis", a **Terra workspace** will be created under your specified Terra Billing Project and your provided files will be uploaded to the corresponding Google bucket. The google account associated with submitting this analysis will have access to the workspace and further access can be delegated from within Terra. You can also manually create a workspace and run **the method** yourself. Click [here](#) to view an example report generated by Molecular Oncology Almanac.

Neither Dana-Farber Cancer Institute nor the Van Allen Laboratory will have access to your data, whether uploaded or produced by this portal. The Broad Institute of MIT & Harvard's Terra is compliant with NIST-800-53 and has been audited as per FISMA Moderate, read more on [Terra's privacy policy](#) and [security posture](#).

You also agree to the [Van Allen Laboratory](#) contacting you via e-mail requesting feedback on your experience using the Molecular Oncology Almanac and the Molecular Oncology Almanac Portal.

Required fields

Add your de-identified sample name, tumor type from Oncotree, and select a billing project. The following inputs are required.

De-identified sample name:

Tumor type: ⓘ

Terra billing project: ⓘ

Only letters, numbers, underscores, and dashes allowed.

Optional fields

Add a description or upload any combination of the file types below. The following inputs are optional.

Analysis description: ⓘ

Single nucleotide variants: ⓘ

 No file selected.

Suggested method: MuTect 1.0

Insertions or deletions: ⓘ

 No file selected.

Suggested method: Strelka

Somatic bases covered: ⓘ

 No file selected.

Suggested method: MuTect 1.0

New analysis

Upon clicking Google bucket can also manually upload.

Neither Dana-Farber nor MIT & Harvard

You also agree to the terms of the Molecular Oncology Almanac.

Required fields

Add your de-identified sample ID

De-identified sample ID

de-identified sample ID

Only letters, numbers, underscores, and dashes allowed.

Optional fields

Add a description or upload any combination of the file types below. The following inputs are optional.

Analysis description: ⓘ

Single nucleotide variants: ⓘ

Browse... No file selected.

Suggested method: MuTect 1.0

Copy number alterations: ⓘ

Insertions or deletions: ⓘ

Browse... No file selected.

Suggested method: Strelka

Fusions from RNA: ⓘ

Somatic bases covered: ⓘ

Browse... No file selected.

Suggested method: MuTect 1.0

Single nucleotide variants (RNA): ⓘ

Optional Field: Single Nucleotide Variants

If providing single nucleotide variants (SNVs) for upload, they should follow the guidelines set by either the TCGA or NCI's [Mutation Annotation Format \(MAF\)](#). We recommend MuTect and Oncotator to generate this file. The Molecular Oncology Almanac specifically requires the following columns:

Hugo_Symbol, NCBI_Build, Chromosome, Start_position, End_position, Reference_Allele, Tumor_Seq_Allele1, Tumor_Seq_Allele2, Variant_Classification, Protein_Change, Tumor_SampleBarcode, Matched_Norm_SampleBarcode, Annotation_Transcript, t_ref_count, t_alt_count

Example upload file for SNVs using required columns:

Hugo_Symbol	NCBI_Build	Chromosome	Start_position	End_position	Reference_Allele	Tumor_Seq_Allele1	Tumor_Seq_Allele2
BRAF	37	7	140453136	140453136	A	T	A
MSH2	37	2	47739466	47739466	G	A	G
STAG2	37	X	123191810	123191810	A	T	A

Close

Molecular Oncology Almanac

Portal

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Please review our [Privacy Policy](#) and [Terms of Use](#) before use.

[Begin new analysis](#)[View workspaces on Terra](#)

Browse previous analyses

Example-profile-B NON-SMALL CELL LUNG CANCER (NSCLC)

Created on: October 31, 2022 3:25 PM

[View the Report](#)[View Terra Workspace](#)

67 year old man with history of 40 pack per year smoking history diagnosed with metastatic NSCLC to adrenals now s/p carbo-pemetrexed with good response and maintenance pemetrexed with continued disease control at 6 months. Tumor sample from diagnostic adrenal biopsy.

Molecular Oncology Almanac

Patient Report

Generated on: Oct 31 2022

Patient Information

Identifiers

Patient ID: Example-profile-B
Tumor Barcode: example_tumor_profile
Normal Barcode: example_normal_profile

Disease

Code: NSCLC
Ontology: Non-Small Cell Lung Cancer
Stage: Unknown

Metrics

Tumor Purity: Unknown
Tumor Ploidy: Unknown
Microsatellite Stability: Unknown

Actionability Report

About: Predictive Implication

Bins

Datasources

Variants and Features associated with Therapeutic Sensitivity

Predictive Implication	Feature Type	Feature	Therapy & Rationale
FDA-Approved Putatively Actionable [More details]	Somatic Variant	BRAF p.V600E (Missense)	Dabrafenib + Trametinib The U.S. Food and Drug Administration (FDA) granted approval to dabrafenib in combination with trametinib for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E, as detected by an FDA-approved test. [source] [Preclinical evidence]
Clinical evidence Investigate Actionability - Low [More details]	Somatic Variant	MSH2 p.D887N (Missense)	Pembrolizumab Patients with defects in DNA mismatch repair genes may have enhanced sensitivity to immune checkpoint blockade. [source]

Molecular Oncology Almanac

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Clinical evidence Investigate Actionability - Low [More details]	Somatic Variant	MSH2 p.D887N (Missense)	Pembrolizumab Patients with defects in DNA mismatch repair genes may have enhanced sensitivity to immune checkpoint blockade. [source]

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Tumor Barcode: example_tumor_profile
Normal Barcode: example_normal_profile

Disease

Code: NSCLC
Ontology: Non-Small Cell Lung Cancer
Stage: Unknown

Metrics

Tumor Purity: Unknown
Tumor Ploidy: Unknown
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Generated on: Oct 31 2022

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Disease

Code: NSCLC
Ontology: Non-Small Cell Lung Cancer
Stage: Unknown

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Tumor Purity: Unknown
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Predictive Implication	Feature Type	Feature	Therapy & Rationale
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Datasources

Variants and Features associated with Therapeutic Sensitivity

Predictive Implication	Feature Type	Feature	Therapy & Rationale
FDA-Approved Putatively Actionable [More details]	Somatic Variant	BRAF p.V600E (Missense)	Dabrafenib + Trametinib The U.S. Food and Drug Administration (FDA) granted approval to dabrafenib in combination with trametinib for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E, as detected by an FDA-approved test. [source] [Preclinical evidence]
Clinical evidence Investigate Actionability - Low [More details]	Somatic Variant	MSH2 p.D887N (Missense)	Pembrolizumab Patients with defects in DNA mismatch repair genes may have enhanced sensitivity to immune checkpoint blockade. [source]



Molecular Oncology Assertion

Evidence for Somatic Variant: BRAF p.V600E (Missense)

on: Oct 31 2022

The following assertion was the strongest match to the observed molecular feature.

Evidence: FDA-Approved

Molecular feature: BRAF p.V600E (Missense)

Assertion: Sensitivity to Dabrafenib + Trametinib in Non-Small Cell Lung Cancer (NSCLC)

The U.S. Food and Drug Administration (FDA) granted approval to dabrafenib in combination with trametinib for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E, as detected by an FDA-approved test. [\[source\]](#)

Unknown
Unknown
Unknown

The following assertions are equivalent matches within this patient's ontology or stronger in another cancer type.

Molecular feature & evidence

BRAF p.V600E (Missense)

FDA-Approved

Assertion & rationale

Sensitivity to Dabrafenib + Trametinib in Melanoma (MEL)

The U.S. Food and Drug Administration (FDA) granted approval to dabrafenib in combination with trametinib for the treatment of patients with unresectable or metastatic melanoma (MEL) with BRAF V600E or V600K mutation, as detected by an FDA-approved test. [\[source\]](#)

DataSources

Patient Information

Identifiers

Patient ID:

Tumor Barcode:

Normal Barcode:

Actionability Report

About: Predictive

Variants and Features

Molecular Oncology Almanac

Patient Report

Generated on: Oct 31 2022

Patient Information

Identifiers

Patient ID: Example-profile-B
Tumor Barcode: example_tumor_profile
Normal Barcode: example_normal_profile

Disease

Code: NSCLC
Ontology: Non-Small Cell Lung Cancer
Stage: Unknown

Metrics

Tumor Purity: Unknown
Tumor Ploidy: Unknown
Microsatellite Stability: Unknown

Actionability Report

About: Predictive Implication Bins

Datasources

Variants and Features associated with Therapeutic Sensitivity

Predictive Implication	Feature Type	Feature	Therapy & Rationale
FDA-Approved Putatively Actionable [More details]	Somatic Variant	BRAF p.V600E (Missense)	<p>Dabrafenib + Trametinib The U.S. Food and Drug Administration (FDA) granted approval to dabrafenib in combination with trametinib for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E, as detected by an FDA-approved test. [source]</p> <p>[Preclinical evidence]</p>
Clinical evidence Investigate Actionability - Low [More details]	Somatic Variant	MSH2 p.D887N (Missense)	<p>Pembrolizumab Patients with defects in DNA mismatch repair genes may have enhanced sensitivity to immune checkpoint blockade. [source]</p>



Molecular Oncology Almanac

Patient Report

Generated on: Oct 31 2022

Patient Information

Identifiers

Disease ORIGINAL ARTICLE

Metrics

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Dung T. Le, M.D., Jennifer N. Uram, Ph.D., Hao Wang, Ph.D., Bjarne R. Bartlett, B.S., Holly Kemberling, R.N., Aleksandra D. Eyring, M.Pharm., Andrew D. Skora, Ph.D., Brandon S. Luber, Sc.M., Nilofer S. Azad, M.D., Dan Laheru, M.D., Barbara Biedrzycki, Ph.D., C.N.R.P., Ross C. Donehower, M.D.,
et al.

Article Figures/Media

Metrics

June 25, 2015

N Engl J Med 2015; 372:2509-2520

DOI: 10.1056/NEJMoa1500596

54 References 6227 Citing Articles Letters

Clinical evidence
Investigate Actionability - Low
[More details]

Somatic Variant

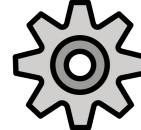
MSH2 p.D887N (Missense)

[Preclinical evidence]

Pembrolizumab
Patients with defects in DNA mismatch repair genes may have enhanced sensitivity to immune checkpoint blockade. [source]



Try it out and let us know what you think

	Programming not required	Programming required
Few variants	Browse our database moalmanac.org 	Programmatically access our database moalmanac.org/api/assertions 
Many variants	Annotate and interpret individual profiles with our algorithm on portal.moalmanac.org 	Annotate and interpret individual profiles with our algorithm directly via GitHub and/or Docker 

Brendan Reardon
@brendan_reardon
brendan_reardon@dfci.harvard.edu

Van Allen laboratory
@vanallenlab
vanallenlab.dana-farber.org

Thank you!

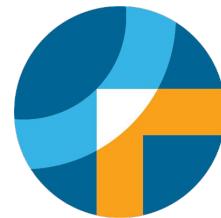
Eliezer Van Allen	Alanna Church	Tali Mazor
Caroline Canning	Lynette Sholl	Ken Kehl
Maha Shady	Krishna Patel	Aedin Culhane
Nathanael Moore	Ethan Cerami	Ted Feldman
Nicholas Moore	Jenny Mack	Paul Marcantonio
Eric Kofman	Katie Janeway	CGC organizers!

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