

Supplementary Material

A Process for the Emulation of Comparative Oncology Trials with Real-world Evidence (ENCORE)

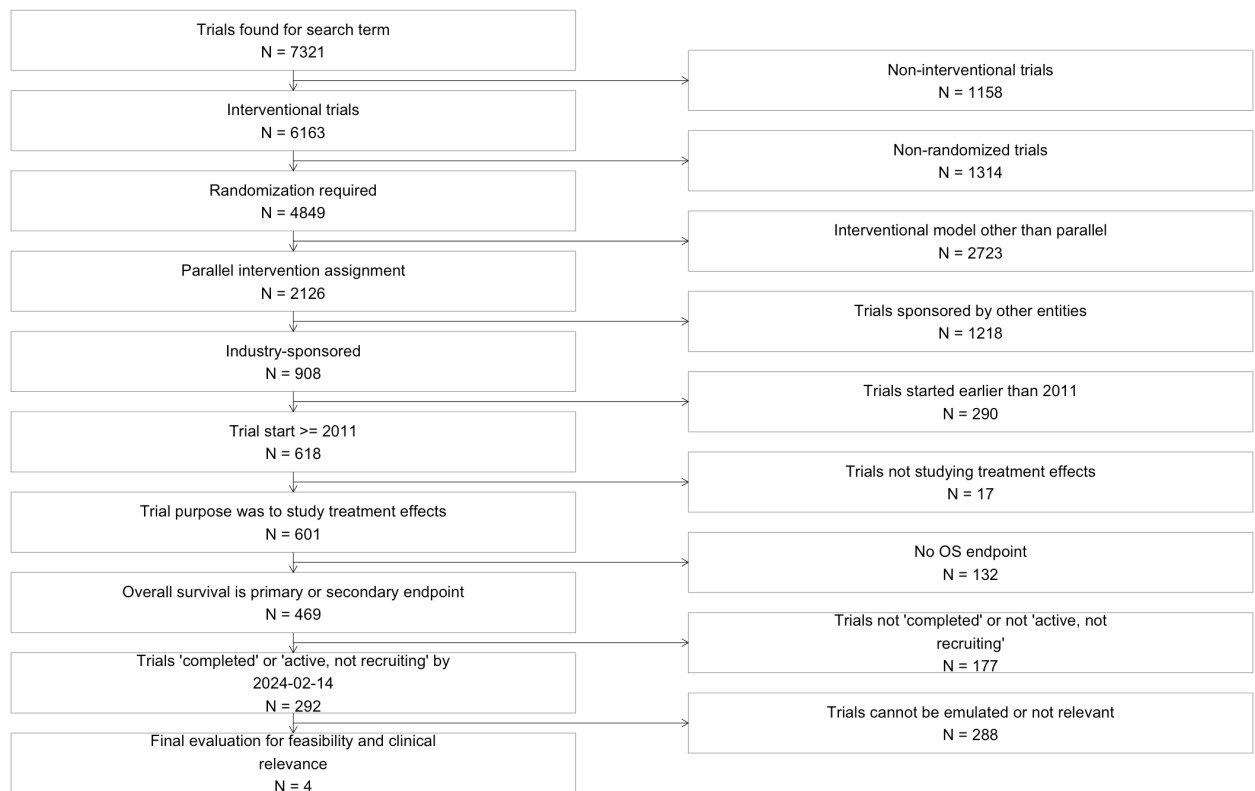
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Supplementary Figures

Supplementary Figure 1: CONSORT diagram for non-small cell lung cancer (NSCLC) top candidate trials.

Final trial selection step - NSCLC



Results snapshot on 2024-02-14.

Note that Supplementary Figure 1 results in four shortlisted candidates because both Check-Mate017/057 have been both shortlisted and only differ in the squamous versus nonsquamous histological eligibility of the trial population.

Supplementary Figure 2: CONSORT diagram for breast cancer (BC) top candidate trials.

Final trial selection step - BC



Results snapshotted on 2024-02-14.

Supplementary Figure 3: CONSORT diagram for colorectal cancer (CRC) top candidate trials.

Final trial selection step - CRC



Results snapshot on 2024-02-29.

Supplementary Figure 4: CONSORT diagram for multiple myeloma (MM) top candidate trials.

Final trial selection step - MM



Results snapshot on 2024-02-14.

R package documentation

The following documentation for the internal `encore.io` packages describes and details reproducible functions to query analytic cohorts consistently across trial emulations.

! Important

The `encore.io` package will be continually developed throughout the ENCORE project and the following documentation is a version-controlled snapshot at the time of this publication. Updated versions will be published with the corresponding protocols for each trial emulation separately.

Package ‘encore.io’

December 14, 2024

Type Package

Title Functions and Wrappers To Streamline Analytics For The ENCORE Trial Emulation Project

Version 0.2.0

Description This package contains important functions to streamline the analytics for the ENCORE trial emulation project. This includes the query of eligible trials to emulate and most analytical steps to emulate these trials.

BugReports <https://gitlab.partners.org/drugepi/encore/encore.io>

License Apache License (>= 2)

Encoding UTF-8

LazyData true

Imports arrow,
assertthat,
data.table,
dplyr,
forcats,
glue,
ggplot2,
gt,
gtsummary,
parallel,
stringr,
survival,
tibble,
tidyr,
lifecycle,
lubridate,
magrittr,
MatchIt,
mice,
pROC,
WeightIt

RoxygenNote 7.3.1

Suggests anesrake,
cobalt,
devtools,
DT,
here,

knitr,
 locfit,
 MatchThem,
 rmarkdown,
 scales,
 simsurv,
 smdi,
 testthat ($\geq 3.0.0$)

Config/testthat/edition 3

Roxygen list(markdown = TRUE)

VignetteBuilder knitr

Depends R (≥ 2.10)

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create_table1	<i>Wrapper around gtsummary::tbl_summary() to create a beautiful Table 1 quickly</i>
---------------	--

Description

Create a table 1 fast

Usage

```
create_table1(
  x = NULL,
  covariates = NULL,
  covariates_labels = NULL,
  treat = "treat",
  explicit_na_categorical = TRUE
)
```

Arguments

<code>x</code>	dataframe queried from edbx with treatment stratification variable and covariates to be displayed in the Table 1
<code>covariates</code>	character vector of columns/covariate names to be displayed in Table 1
<code>covariates_labels</code>	named character vector or list of formulas specifying variables labels of covariate-label pairs to display in table
<code>treat</code>	character specifying column name of treatment variable
<code>explicit_na_categorical</code>	logical, should missings in categorical variables be explicitly included as a separate category (default is TRUE)

Details

...

Value

object of class "tbl_summary" "gtsummary"

Examples

```
## Not run:
library(encore.io)
set global option to make gtsummary tables more compact
theme_gtsummary_compact()
table1 <- ard |>
  create_table1(
    covariate = table1_covariates$covariate,
    treat = "treat")

## End(Not run)
```

c_statistics

*Calculates c-statistics for mimids/wimids objects***Description**

[Experimental] Calculates the propensity score c-statistics (= area under the curve) for imputed and unmatched/all and matched datasets resulting from `MatchThem::matchthem` (mimids objects)

Usage

```
c_statistics(
  object = NULL,
  exposure = "treat",
  weights = "weights",
  ps = "distance"
)
```

Arguments

object	mimids or data.frame object from <code>complete(..., action = 'long', all = TRUE, ...)</code>
exposure	character, quoted name of the exposure/treatment variable (must be of class factor)
weights	character, quoted name of the variable indicating the matching weights (usually 0: unmatched and 1: matched)
ps	character, quoted name of the variable with the distance measure (e.g., propensity score)

Details

The object input needs to be a mimids object or a data.frame object coming from `MatchThem::matchthem()`. If the mimids object is already converted to a long data.frame of stacked imputed datasets, the `MatchThem::complete()` function needs to be completed using `action = "long"` and `all = TRUE` arguments.

The function computes the c-statistic by computing the AUC in each imputed dataset and then summarizing the average and min/max c-statistic by matching group. This aims to describe how well treatment can be predicted given a patient's propensity score. The idea is that in well-matched or weighted datasets, the c-statistic should be close to 0.5, i.e., we can't infer treatment propensity anymore given a patient's baseline covariates.

Value

tibble with summary c-statistics across imputed datasets

See Also

Franklin JM, Rassen JA, Ackermann D, Bartels DB, Schneeweiss S. Metrics for covariate balance in cohort studies of causal effects. *Stat Med*. 2014 May 10;33(10):1685-99. doi: 10.1002/sim.6058. Epub 2013 Dec 9. PMID: 24323618.

Examples

```
## Not run:
library(encore.io)

c_statistics(
  object = edb1_mimids,
  exposure = "treat",
  ps = "distance"
)

## End(Not run)
```

```
edb1_3_4_compute_ropro
```

Derive ROPRO prognostic score

Description

This function computes ROPRO prognostic score (Becker, Weberpals, et al., Ann Oncol 2020) for a given inception cohort.

Usage

```
edb1_3_4_compute_ropro(
  x = NULL,
  cancer = c("aNSCLC", "MetastaticBreast", "EarlyBreast", "MetastaticCRC",
    "MultipleMyeloma")
)
```

Arguments

x	dataframe with inception cohort and required ROPRO covariates
cancer	character, what cancer-specific ROPRO should be computed ("aNSCLC", "MetastaticBreast", "EarlyBreast", "MetastaticCRC", "MultipleMyeloma")

Details

This function takes in a dataframe with all required variables to compute the general and cancer-specific ROPRO (specified in cancer). The variables need to be queried and transformed before which can be done through the `edb(x)_query_ropro` functions (specific for each database).

Important: This function is only valid for data coming from EDB1, EDB3 and EDB4. Since EDB2 does not have all required variables, please use the `edb2_compute_ropro` function for this database to compute a reduced ROPRO model.

Value

The function returns x with the final general and cancer-specific ROPRO

Examples

```
## Not run:
library(encore.io)

x_ropro <- x |>
  edb_4_query_ropro(
    index_date = "dt_index",
    path = Sys.getenv("path_edb4"),
    cancer = "NSCLC",
    max_lookback = -90,
    verbose = TRUE
  ) |>
  edb_1_3_4_compute_ropro(
    cancer = "aNSCLC"
  )

## End(Not run)
```

edb1_cohorts

*System data used to streamline functions and analysis***Description**

System data used to streamline functions and analysis

Usage

```
edb1_cohorts
```

Format

edb1_cohorts:

A tibble with edb1-specific mappings

cancer Abbreviated cancer types

cohort Cancer type sub-directory

biomarker Cancer type biomarker tables

special_biomarker_cols Special biomarker columns to select ...

edb1_get_biomarker

*Query biomarker information for a given inception cohort***Description**

Function queries biomarker tables and curates information on alterations in defined driver genes.

Usage

```
edb1_get_biomarker(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb1"),
  cancer = NULL,
  biomarker_name = NULL,
  from = -90,
  to = 0,
  label_name = FALSE
)
```

Arguments

x	dataframe queried with at least patient ids and index date of inception cohort
index_date	character, variable/column name with the patient's index_date
path	character string, path to directory where EDB1 data/files are located
cancer	character, one of "aNSCLC", "CRC", "EarlyBreast", "EarlyNSCLC", or "MetastaticBreast"
biomarker_name	character, name of biomarker/gene alteration (see details)
from	integer, left boundary of biomarker measurement window relative to index date (e.g., -90, indicating biomarker should be measured not before 90 days before index date)
to	integer, right boundary of biomarker measurement window relative to index date (e.g., 0, indicating biomarker should be measured until day of index date (inclusive))
label_name	logical, should variable name carry information about the measurement window

Details

The function queries and categorizes a certain biomarker that was collected and curated as part of the database as either positive or negative. The categorization happens according to if the biomarker mutation/alteration is a clinically actionable one. For example, patients with any mutation in the EGFR gene or MSI-H/dMMR status would be classified as positive. In case there are multiple measurements per biomarker and patient, the time point of measurement is defined as the non-missing biomarker result in the covariate ascertainment window given by 'from' and 'to' that is closest to the index date. The biomarker date (dt_(biomarker)) in this database is defined as the earliest of specimen collected date, specimen received date or result date.

Depending on the cancer type, the biomarker names can be: ALK, BRAF, EGFR, HER2/ERBB2, KRAS, MET, NTRK1, NTRK2, NTRK3, PDL1, RET, ROS1, NTRK - unknown gene type, NTRK - other, MMR/MSI, NRAS, ER, HER2, Ki-67, PR, BRCA, ESR1, Oncotype, Mammaprint, PIK3CA

Value

x with all additional biomarker variables joined, that is:

- c_(biomarker_name)_status_(from)_(to) (binary, biomarker mutation status positive or negative)
- c_(biomarker_name)_detail_(from)_(to) (character string, more details about selected measurement)

- `c_(biomarker_name)_detail_all_(from)_(to)` (character string, this provides details about all results and details for this biomarker if there were multiple tests in the measurement window (from, to))
- `c_(biomarker_name)_distance_(from)_(to)` (numeric, relative distance between date of measurement and index date in days)
- `dt_(biomarker_name)_(from)_(to)` (date, date of selected biomarker measurement)

Examples

```
## Not run:
library(encore.io)

## End(Not run)
```

`edb1_get_demographics` *Query demographic variables for an inception cohort*

Description

Function queries all available demographic variables from a given inception cohort.

Usage

```
edb1_get_demographics(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb1"),
  cancer = NULL
)
```

Arguments

<code>x</code>	dataframe queried with at least patient ids and index date of inception cohort
<code>index_date</code>	character, variable/column name with the patient's index_date
<code>path</code>	character string, path to directory where EDB1 data/files are located
<code>cancer</code>	character, one of "aNSCLC", "CRC", "EarlyBreast", "EarlyNSCLC", "MetastaticBreast" or "MultipleMyeloma"

Details

Some important data curation details include:

- Race and Ethnicity are combined into a new combined variable 'dem_race_ethnicity' with five mutually exclusive groups as defined by SEER. However, EDB1 has a larger "Other" race category since "American Indian or Alaska Native" seems to be not coded as such, i.e., as opposed to other datasets, "Other" is an explicit group in this case
- The date of birth DOB is given on year granularity level and is hence imputed to the mid of the year as `<dt_dob_imputed>`, e.g. 1955 becomes 1955-07-02. This affects all variables which are derived from the date of birth such as all age variables
- Smoking history is assessed as a history of current or former (= smoking history) or never (= no smoking history). There is no date associated with the measurement of smoking history.

Value

x with all additional demographic variables joined, that is, ADD NEW VARIABLE NAMES

- dem_age_initial_diagnosis (categorical, categorized age measured at initial cancer diagnosis: <60, 60-69, 70-79, 80+)
- dem_age_le_18_flag (logical, indicating if patients was at least (larger/equal; le) 18 years of age at index date)
- dem_age_index_cont (continuous, age measured at index date; note: date of birth has only year-granularity, hence age is imprecise)
- dem_age_index (nominal, categorized age measured at index date: <60, 60-69, 70-79, 80+)
- dem_sex (binary, Male, Female)
- dem_race (nominal)
- dem_ethnicity (binary)
- dem_race_ethnicity (categorical, classification into five mutually exclusive groups according to SEER)
- dem_state (character, US state of the center/network the patient is receiving care at)
- dem_region (nominal, region of the center/network the patient is receiving care at, can be Midwest, Northeast, South, West)
- dem_practice (nominal, setting patient is receiving care at, i.e. Academic, Community or both)
- dem_ses (nominal, socioeconomic status (SES) index based on residence area of patient; can be from '1 - Lowest SES' through '5 - Highest SES')
- c_smoking_history (logical, history of smoking; TRUE = History of smoking, FALSE = No history of smoking)

Examples

```
## Not run:
library(encore.io)

analysis_cohort <- x |>
  edb1_get_demographics(
    index_date = "dt_index",
    cancer = "aNSCLC"
  )

## End(Not run)
```

edb1_get_diagnosis_heme

Query diagnostic details for heme tumors in EDB1 database

Description

Function queries diagnosis details including ISS staging information.

Usage

```
edb1_get_diagnosis_heme(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb1"),
  cancer = "MultipleMyeloma"
)
```

Arguments

x	dataframe queried from edb1 with at least patient ids and index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB1 data/files are located
cancer	character, so "MultipleMyeloma"

Details

Function queries diagnosis details for all patients in .

- ISS stage (c_stage_initial_dx) is curated for multiple myeloma patients and "Unknown/not documented" is mapped to NA
- M protein IgG is derived and if the patient's immunoglobulin class of M protein is not documented, an NA is assigned
- Light chain Kappa and Lambda information is derived and if the patient's involved light chain is not documented, an NA is assigned
- Experimental: The number and location of secondary malignancies is inferred by C79.x ICD-10 codes (and corresponding ICD-9 mappings). The c_number_met_sites is inferred by counting the unique number of sites as given by a C79.x granularity in the secondary diagnosis table. For more see icd_metastases system file.

Value

x with all additional diagnosis variables joined, that is:

- dt_initial_dx (date, date of diagnosis or first documented diagnosis date for tumor)
- c_stage_initial_dx (nominal, summary ISSS stage at initial diagnosis)
- c_time_dx_to_index (continuous, time between initial diagnosis and index date (in days))
- c_m_protein_igg (logical, whether the patient's immunoglobulin class of M protein is IgG)
- c_light_chain_kappa (logical, whether the patient's involved light chain is Kappa)
- c_light_chain_lambda (logical, Whether the patient's involved light chain is Lambda)

Experimental:

- c_number_met_sites (integer, number of metastatic sites for a given patient anytime before/on index date (inferred from ICD codes, see icd_metastases system file)
- c_met_sites (character string, description of anatomical locations of metastatic sites for a given patient patient's index date)

Examples

```
## Not run:
library(encore.io)

ard <- x |>
  edb1_get_diagnosis_heme(
    index_date = "dt_index",
    path = Sys.getenv("path_edb1"),
    cancer = "MultipleMyeloma"
  )

## End(Not run)
```

edb1_get_diagnosis_solid

Query initial and metastatic diagnosis dates for EDB1 database

Description

Function queries diagnosis details including staging information.

Usage

```
edb1_get_diagnosis_solid(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb1"),
  cancer = NULL
)
```

Arguments

x	dataframe queried from edb1 with at least patient ids and index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB1 data/files are located
cancer	character, one of "aNSCLC", "CRC", "EarlyBreast", "EarlyNSCLC", "MetastaticBreast" or "MultipleMyeloma"

Details

Function queries diagnosis details for all patients in .

- Summary group stage (c_stage_initial_dx) is curated for advanced and metastatic enhanced cohorts and "Not documented", "Occult", "Unknown", "Group stage is not reported" is mapped to NA
- For early cohorts (early NSCLC and breast), summary group stage (c_stage_initial_dx) is derived from the pathological group stage or from clinical group stage if the pathological is not available

- For aNSCLC, the metastatic diagnosis date (dt_met_dx) is derived as the the of initial diagnosis for patients with stage IV diagnosis or the machine learning-derived metastatic diagnosis date. All other solid tumor for which the metastatic diagnosis date is available, this variable was used
- The number and location of metastatic sites is inferred by C79.x ICD-10 codes (and corresponding ICD-9 mappings). The c_number_met_sites is inferred by counting the unique number of sites as given by a C79.x granularity in the secondary diagnosis table. For more see icd_metastases system file.

The function also returns <c_met_pre_index> which is a helper variable that is TRUE in case there is any evidence of at least one distant metastatic diagnosis before or on the index date. This captures both de novo metastatic patients and those with a metastatic diagnosis date before/on the index date. Note: if neither group stage nor metastatic diagnosis date are available, we set <c_met_pre_index> to NA because we can't make say they're FALSE either

Value

x with all additional diagnosis variables joined, that is:

- dt_initial_dx (date, date of diagnosis or first documented diagnosis date for tumor)
- c_stage_initial_dx (nominal, summary group stage at initial diagnosis, if available)
- dt_met_dx (date, date of earliest evidence of distant metastasis)
- c_de_novo_mets_dx (binary logical, evidence of presence of one or multiple metastases at/before initial diagnosis)
- c_time_dx_to_index (continuous, time between initial diagnosis and index date (in days))
- c_time_adv_dx_to_index (continuous, time between advanced diagnosis and index date (in days; advanced NSCLC only))
- c_time_met_dx_to_index (continuous, time between earliest evidence of a metastatic diagnosis and index date (in days; not in early NSCLC))
- c_met_pre_index (binary logical, evidence of any metastasis before/on index date; includes de novo metastatic patients and progressors (overlap with c_de_novo_mets_dx possible))
- c_number_met_sites (integer, number of metastatic sites for a given patient anytime before/on index date (inferred from ICD codes, see icd_metastases system file))
- c_met_sites (character string, description of anatomical locations of metastatic sites for a given patient patient's index date)

Examples

```
## Not run:
library(encore.io)

ard <- x |>
  edb1_get_diagnosis_solid(
    index_date = "dt_index",
    path = Sys.getenv("path_edb1"),
    cancer = "aNSCLC"
  )

## End(Not run)
```

edb1_get_ecog

*Query performance status information for an inception cohort***Description**

Function queries ECOG performance status tables and curates derived variables

Usage

```
edb1_get_ecog(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb1"),
  cancer = NULL,
  from = -90,
  to = 0,
  ties = "lower",
  label_name = FALSE,
  verbose = TRUE
)
```

Arguments

x	dataframe queried with at least patient ids and index date of inception cohort
index_date	character, variable/column name with the patient's index_date
path	character string, path to directory where EDB1 data/files are located
cancer	character, one of "aNSCLC", "CRC", "EarlyBreast", "EarlyNSCLC", "MetastaticBreast" or "MultipleMyeloma"
from	integer, left boundary of ECOG measurement window relative to index date (e.g., -90, indicating ECOG should be measured not before 90 days before index date)
to	integer, right boundary of ECOG measurement window relative to index date (e.g., 0, indicating ECOG should be measured until day of index date (inclusive))
ties	character, one of "lower" or "higher" to choose either the lower (default) or higher ECOG measurement if there are two measurements on the same day
label_name	logical, should variable name carry information about the measurement window
verbose	logical, print query progress and informative meta information

Details

The function considers both NLP-extracted and structured ECOG measurements (to enhance the availability of ECOG measurements). All ECOG measurements are identified within the baseline measurement window, then the closest measurement relative to the index date is selected. If there are two measurements within the same closest distance, the lower (default) or higher (depending on how ties is specified) is prioritized.

Value

x with all additional ECOG variables joined, that is:

- c_ecog_{from}_{to}, ECOG value measured in the specified measurement window
- c_ecog_{from}_{to}, distance of the date the ECOG value was measured relative to the index date

Note: if from or to is a negative integer, the resulting covariate name will contain a "min" for "minus" preceding the integer to comply with the tidy variable naming rules

Examples

```
## Not run:
library(encore.io)

ard <- x |>
  edb1_get_ecog(
    cancer = "aNSCLC",
    from = -180,
    to = 0,
    ties = "lower"
  )

## End(Not run)
```

edb1_get_histology	<i>Query histology information for an inception cohort</i>
--------------------	--

Description

Function queries histology information for a given inception cohort.

Usage

```
edb1_get_histology(
  x = NULL,
  path = Sys.getenv("path_edb1"),
  cancer = NULL,
  histology_match = NULL
)
```

Arguments

x	dataframe with at least patient ids and index date of inception cohort
path	character string, path to directory where EDB1 data/files are located
cancer	character, one of "aNSCLC", "CRC", "EarlyBreast", "EarlyNSCLC", "MetastaticBreast" or "MultipleMyeloma"
histology_match	character, string match to categorize and identify patients with a certain histology for the indicated tumor site, e.g. "non-squamous cell carcinoma".

Details

Some patients may have more than one histology recording across cohorts since they can have multiple primaries. However, this function is designed to query histology information for one cancer type at a time. That means, there is just one recording per patient. For general frequency descriptives, see vignettes for EDB1.

Note that the search string defined in argument `histology_match` is not case sensitive.

Value

x with all additional histology variables joined, prepended with "c_"

- `c_histology` (nominal, histology recorded for given patient)
- `c_(histology_match)` (logical, there is a string match for histology specified by `histology_match`. FALSE may also include "unknowns" or "NOS" whose information was just not granular enough to be able to determine the histological subtype with absolute certainty

Examples

```
## Not run:
library(encore.io)

ard <- x |>
  edb1_get_histology(
    cancer = "aNSCLC",
    histology_match = "Non-squamous cell carcinoma"
  )

## End(Not run)
```

edb1_get_labs

Query lab information for a given inception cohort

Description

Function queries the lab table and standardizes according to a reference measurement unit.

Usage

```
edb1_get_labs(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb1"),
  cancer = NULL,
  lab_name = NULL,
  from = -90,
  to = 0,
  ties = "lower",
  set_implausible_na = TRUE,
  label_name = FALSE,
  verbose = TRUE
)
```

Arguments

x	dataframe queried from EDB1 with at least patient ids and therapy index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB1 data/files are located
cancer	character, "aNSCLC", "CRC", "EarlyBreast", "EarlyNSCLC", "MetastaticBreast" or "MultipleMyeloma"
lab_name	character, curated name of lab (see details)
from	integer, left boundary of lab measurement window relative to index date (e.g., -90, indicating lab should be measured not before 90 days before index date)
to	integer, right boundary of lab measurement window relative to index date (e.g., 0, indicating lab should be measured not later than the day of the index date (inclusive))
ties	character, in case of ties (two equi-distant measurements), should the "higher" or "lower" lab measurement be prioritized
set_implausible_na	logical, should implausible values (outliers) be automatically be set NA? Lower and upper thresholds are documented in labs_mapping_edb1
label_name	logical, should variable name carry information about the measurement window
verbose	logical, print query progress and informative meta information

Details

The function queries and cleans supported lab measurements. In detail, the function selects measurements in a from - to measurement window relative to the index date. The date of the lab test is derived as the earliest of the test date or result date. In case that there are multiple measurements in this window, the function uses the measurement that has the smallest absolute distance relative to the index date. If there are two equi-distant measurements, the lower (default) or higher measurement can be prioritized.

Note: Only selected labs are supported by this function which were taken from the ROPRO prognostic score (Becker T et al., Ann Oncol 2020).

The supported and available labs are:

- c_albumin_g_l (albumin mass/volume in serum or plasma)
- c_alp_u_l (alkaline phosphatase enzymatic activity/volume in serum or plasma)
- c_alt_u_l (alanine aminotransferase enzymatic activity/volume in serum or plasma)
- c_ast_u_l (aspartate aminotransferase enzymatic activity/volume in serum or plasma; used to compute ast-alt ratio)
- c_bilirubin_mg_dl (total bilirubin mass/volume in serum or plasma)
- c_calcium_mg_dl (calcium mass/volume in serum or plasma)
- c_chloride_mmol_l (chloride moles/volume in serum or plasma)
- c_eosinophils_leukocytes_ratio (eosinophils/100 leukocytes in blood)
- c_glucose_mg_dl (glucose mass/volume in serum or plasma)
- c_granulocytes_leukocytes_ratio (granulocytes/100 leukocytes in blood)
- c_hemoglobin_g_dl (hemoglobin mass/volume in blood)

- c_ldh_u_l (lactate dehydrogenase enzymatic activity/volume in serum or plasma)
- c_lymphocyte_10_9_l (lymphocytes #/volume in blood; used to compute neutrophil/lymphocyte ratio)
- c_lymphocyte_leukocyte_ratio (lymphocytes/100 leukocytes in blood)
- c_monocytes_10_9_l (monocytes #/volume in blood)
- c_neutrophil_10_9_l (neutrophils #/volume in blood; used to compute neutrophil/lymphocyte ratio)
- c_platelets_10_9_l (platelets #/volume in blood)
- c_protein_g_l (protein mass/volume in Serum or Plasma)
- c_urea_nitrogen_mg_dl (urea nitrogen mass/volume in serum or plasma)

The following labs are part of ROPRO but are not supported yet:

- c_light_chain_kappa (Light Chain Kappa; dichotomous; >0 vs. 0)
- c_light_chain_lambda (Light Chain Lambda; dichotomous; >0 vs. 0)
- c_m_protein_igg (M protein IgG (dichotomous; >0 vs. 0)

Value

x with all additional labs variables joined, that is:

- c_(lab_name)_distance_(from)_(to) - days from date of lab measurements to index date
- c_(lab_name)_(unit)_(from)_(to) - binary lab result indicating if lab was within ("normal") the reference range or outside ("abnormal")
- c_(lab_name)_(unit)_(from)_(to)_cont - quantitative lab result after unit harmonization/conversion

Note: if from or to is a negative integer, the resulting covariate name will contain a "min" for "minus" preceding the integer to comply with the tidy variable naming rules

Examples

```
## Not run:
library(encore.io)

ard <- x |>
  edb1_get_labs(
    cancer = "aNSCLC",
    lab_name = "c_albumin_g_l",
    set_implausible_na = TRUE,
    verbose = TRUE
  )

## End(Not run)
```


edb1_get_os

*Query overall survival outcome for a given inception cohort***Description**

Function queries mortality and other information to derive a righ-censored time to all-cause mortality endpoint

Usage

```
edb1_get_os(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb1"),
  cancer = NULL,
  data_cut_off_date = lubridate::ymd("2024-04-30"),
  verbose = TRUE
)
```

Arguments

x	dataframe queried from edb1 with at least patient ids and index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where data/files are located
cancer	character, one of "aNSCLC", "CRC", "EarlyBreast", "EarlyNSCLC", "MetastaticBreast" or "MultipleMyeloma"
data_cut_off_date	date of database lock; the data cut-off for this delivery (May 30, 2024) is April 30, 2024. This parameter can be changed if a grace period of x months before database lock is desired.
verbose	logical, print query progress and informative meta information

Details

The function queries and curates intention-to-treat (ITT) overall survival endpoint. The ITT follow up time is defined as the time from index date (dt_index) to date of death. If a patient did not decease during follow-up, the patient will be censored at the last observed clinical activity (including visits and treatment information) or data cut-off date whichever is earlier.

Note that in EDB1, the granularity of the date of death variable is given as month-year and (in rare cases) year only. In these cases, the date of death is imputed to the mid/15th of the month and the mid/July 2 of the year, respectively. This can lead to negative/implausible follow-up times if the index date is after the imputed date of death.

Value

x with all endpoint information joined, that is:

- death_itt (binary, event indicator for all-cause mortality)
- fu_itt_days (numeric, ITT follow-up time in days)

- fu_itt_months, (numeric, ITT follow-up time in months (i.e., fu_itt_days / 30.417))
- fu_itt_years, (numeric, ITT follow-up time in years)

Examples

```
## Not run:
library(encore.io)

ard <- x |>
  edb1_get_os(
    cancer = "aNSCLC"
  )

## End(Not run)
```

edb1_get_vitals

Query vital sign measurements for a given cohort

Description

Function queries vitals sign measurements

Usage

```
edb1_get_vitals(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb1"),
  cancer = NULL,
  vital_name = NULL,
  from = -90,
  to = 0,
  ties = "lower",
  set_implausible_na = TRUE,
  label_name = FALSE,
  verbose = TRUE
)
```

Arguments

x	dataframe queried from EDB1 with at least patient ids and therapy index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB1 data/files are located
cancer	character, "aNSCLC", "CRC", "EarlyBreast", "EarlyNSCLC", "MetastaticBreast" or "MultipleMyeloma"
vital_name	character, curated name of vital sign (see details)
from	integer, left boundary of lab measurement window relative to index date (e.g., -90, indicating lab should be measured not before 90 days before index date)

to	integer, right boundary of lab measurement window relative to index date (e.g., 0, indicating lab should be measured not later than the day of the index date (inclusive))
ties	character, in case of ties (two equi-distant measurements), should the "higher" or "lower" lab measurement be prioritized
set_implausible_na	logical, should implausible values (outliers) be automatically be set NA (default is TRUE)? Lower and upper thresholds are documented in <code>vitals_mapping_edb1</code>
label_name	logical, should variable name carry information about the measurement window
verbose	logical, print query progress and informative meta information

Details

The function queries and cleans all available vital sign measurements. In detail, the function removes measurements that are character strings and only considers quantitative results. In EDB1, unit-cleaned vital sign measurements are provided. However, due to frequent missing units, unit-cleaned vital sign measurements can exhibit high missingness. To mitigate this missingness, the function also considers "raw" vital sign measurements if no unit-cleaned measurement is observed. Hence, it is recommended to set `set_implausible_na` to TRUE to remove implausible values. The function further only selects measurements in a from - to measurement window relative to the index date. In case that there are multiple measurements in this window, the function uses the measurement that has the smallest absolute distance relative to the index date. If there are two equi-distant measurements, the lower (default) or higher measurement can be prioritized.

The available and supported vitals are:

- `c_sbp` (systolic blood pressure in mmHg)
- `c_dbp` (diastolic blood pressure in mmHg)
- `c_bmi` (body mass index in kg/m² directly measured)
- `c_height` (height in m)
- `c_hr` (heart rate/pulse in beats/min)
- `c_oxygen` (oxygen saturation; taken from O2 sat and pulse oximetry)
- `c_weight` (weight in kg)

Value

x with all additional labs variables joined, that is:

- `c_(vital_name)_distance_(from)_(to)` - days from date of vital sign measurements to index date
- `c_(vital_name)_(unit)_(from)_(to)_cont` - quantitative vital sign measurement

Note: if from or to is a negative integer, the resulting covariate name will contain a "min" for "minus" preceding the integer to comply with the tidy variable naming rules

Examples

```
## Not run:
library(encore.io)

ard <- x |>
  edb1_get_vitals(
```

```

    cancer = "aNSCLC",
    vital_name = "c_oxygen",
    set_implausible_na = TRUE,
    verbose = TRUE
  )

## End(Not run)

```

edb1_query_ropro

Query and curate all relevant ROPRO variables

Description

This function queries, cleans and transforms all necessary covariates needed to compute the ROPRO prognostic score in EDB1.

Usage

```

edb1_query_ropro(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb1"),
  cancer = NULL,
  from = -90,
  to = 0,
  verbose = TRUE
)

```

Arguments

x	dataframe queried from EDB1 with at least patient ids and therapy index date of inception cohort
index_date	character, variable/column name with the patient's index date, default is dt_index
path	character string, path to directory where EDB1 data/files are located
cancer	character, one of "aNSCLC", "CRC", "EarlyBreast", "EarlyNSCLC", "MetastaticBreast" or "MultipleMyeloma"
from	integer, left boundary of measurement window for time-dependent variables relative to index date (e.g., -90, indicating variables should be measured not before 90 days before index date)
to	integer, right boundary of measurement window for time-dependent variables relative to index date (e.g., 0, indicating variables should be measured not later than the day of the index date (inclusive))
verbose	logical, print progress of query

Details

Wrapper around major functions to query required covariates to compute ROPRO. Selected covariates are log transformed or log-log transformed. More details, see Becker, Weberpals, et al., Ann Oncol 2020.

Value

x with all required ROPRO covariates joined. All general and cancer type-specific (as specified in cancer argument) covariates are returned.

Note that:

- there is no specific ROPRO for EarlyNSCLC, so only the covariates for the general pan-tumor ROPRO will be returned
- there is only a ROPRO for metastatic CRC (no early CRC)
- covariates for EarlyBreast are identical to the the general pan-tumor ROPRO, just the weights are different

Examples

```
## Not run:
library(encore.io)

x_ropro <- x |>
  edb1_query_ropro(
    index_date = "dt_index",
    path = Sys.getenv("path_edb1"),
    cancer = "aNSCLC",
    from = -90,
    to = 0,
    verbose = TRUE
  )

## End(Not run)
```

edb2_assign_date	<i>Helper function to assign an actual date for a xxx_timedelta variable in edb2</i>
------------------	--

Description

In the edb2 database, time differences (timedelta) are assigned for clinical events. These timedeltas are always relative to the initial cancer diagnosis for which a given patient sampled into the database. This function helps to assign actual dates based on on those time differences.

Usage

```
edb2_assign_date(
  x = NULL,
  path = Sys.getenv("path_edb2"),
  cancer = c("MM", "NSCLC")
)
```

Arguments

x	dataframe queried from edb2 with at least the patient id column and columns that end on "timedelta"
path	string, path to edb2 root directory
cancer	character, either "NSCLC" or "MM"

Details

CAVEAT: both the date of initial diagnosis and other dates come with imprecision (_imp). There are 3 possibilities: 0: There is no imprecision. precise date (MM/DD/YYYY) associated with this event. 15: There is imprecision. imprecise date (MM/YYYY) associated with this event. 182: There is imprecision.imprecise date (YYYY) associated with this event.

Value

x including the date colum(s) of all timedelta columns (.col) with naming convention dt_{.col}"

Examples

```
## Not run:
library(encore.io)

## End(Not run)
```

edb2_compute_ropro	<i>Derive ROPRO prognostic score</i>
--------------------	--------------------------------------

Description

This function computes ROPRO prognostic score (Becker, Weberpals, et al., Ann Oncol 2020).

Usage

```
edb2_compute_ropro(x = NULL, cancer = c("NSCLC", "MM"))
```

Arguments

x	dataframe with inception cohort and required ROPRO covariates
cancer	character, what cancer-specific ROPRO should be computed ("NSCLC", "MM")

Details

This function takes in a dataframe with all required variables to compute the general and cancer-specific ROPRO (specified in cancer). The variables need to be queried and transformed before which can be done through the edb2_query_ropro functions (specific for each database).

Important: Since EDB2 does not have all required variables, please use the edb2_compute_ropro function before use of this function to compute a reduced ROPRO model.

Value

The function returns x with the final general and cancer-specific ROPRO

Examples

```
## Not run:
library(encore.io)

x_ropro <- x |>
  edb2_query_ropro(
    index_date = "dt_index",
    path = Sys.getenv("path_edb2"),
    cancer = "NSCLC",
    from = -90,
    to = 0,
    verbose = TRUE
  ) |>
  edb2_compute_ropro(
    cancer = "NSCLC"
  )

## End(Not run)
```

edb2_get_biomarker	<i>Query biomarker information for a given solid tumor inception cohort</i>
--------------------	---

Description

Function queries biomarker tables and curates information on alterations in defined driver genes.

Usage

```
edb2_get_biomarker(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb2"),
  cancer = c("MM", "NSCLC"),
  biomarker_name = NULL,
  from = -90,
  to = 0,
  label_name = FALSE
)
```

Arguments

x	dataframe queried from edb2 with at least patient ids and therapy index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB2 data/files are located
cancer	character, one of MM or NSCLC

biomarker_name	character, name of biomarker/gene alteration (see details)
from	integer, left boundary of biomarker measurement window relative to index date (e.g., -90, indicating biomarker should be measured not before 90 days before index date)
to	integer, right boundary of biomarker measurement window relative to index date (e.g., 0, indicating biomarker should be measured until day of index date (inclusive))
label_name	logical, should variable name carry information about the measurement window

Details

The function queries and categorizes a certain biomarker that was collected and curated as part of the database as either positive or negative. The categorization happens according to if the biomarker mutation/alteration is a clinically actionable one. For example, patients with any mutation in the EGFR gene or MSI-H/dMMR status would be classified as positive. In case there are multiple measurements per biomarker and patient, the time point of measurement is defined as the non-missing biomarker result in the covariate ascertainment window given by 'from' and 'to' that is closest to the index date.

The biomarker date (dt_(biomarker)) in this database is defined as the earliest of specimen collection, result report or documented date. There can be imprecisions to the date of measurement on the month or year granularity level.

Depending on the cancer type, the biomarker names can be: 1p, 1q, ALK, BRAF, Complex Cytogenetics/Karyotype, DDR2, del(13), del(17), del(17p), Diploid, EGFR, FGFR1, HER2 (ERBB2), Hyperploid, Hypoploid, KEAP1 (INRF2), KRAS, MEK1(MAP2k1), MEK2 (MAP2K2), MET, MLH1, MMR, MSH2, MSH6, MSI/Microsatellite Instability, Normal Cytogenetics/Karyotype, NRAS, NTRK1, NTRK2, NTRK3, PD-L1, PIK3CA, PMS2, RET, ROS1, STK11 (LKB1), t(11;14), t(14;16), t(14;20), t(4;14), t(6;14), TMB/Tumor Mutational Burden, TP53

Value

x with all additional biomarker variables joined, that is:

- c_(biomarker_name)_status_(from)_(to) (binary, biomarker mutation status positive or negative)
- c_(biomarker_name)_detail_(from)_(to) (character string, more details about selected measurement)
- c_(biomarker_name)_detail_all_(from)_(to) (character string, this provides details about all results and details for this biomarker if there were multiple tests in the measurement window (from, to))
- c_(biomarker_name)_distance_(from)_(to) (numeric, relative distance between date of measurement and index date in days)
- dt_(biomarker_name)_(from)_(to) (date, date of selected biomarker measurement)

Note: if from or to is a negative integer, the resulting covariate name will contain a "min" for "minus" preceding the integer to comply with the tidy variable naming rules

Examples

```
## Not run:
library(encore.io)
analysis_cohort <- x |>
```



```

edb2_get_biomarker(
  cancer = "NSCLC",
  biomarker_name = "egfr",
  from = -180,
  to = 0)

## End(Not run)

```

edb2_get_demographics *Query demographic variables for an inception cohort*

Description

Function queries all available demographic variables from the EDB2 database, curates them and joins them to the inception cohort x.

Usage

```

edb2_get_demographics(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb2"),
  cancer = c("MM", "NSCLC")
)

```

Arguments

x	dataframe queried from edb2 with at least patient ids and index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB2 data/files are located
cancer	character, one of MM or NSCLC

Details

Some important data curation details include:

- race and ethnicity are combined into a new combined variable 'dem_race_ethnicity' with five mutually exclusive groups as defined by SEER https://seer.cancer.gov/seerstat/variables/seer/race_ethnicity/#:~:text=
- the age at initial diagnosis and index date is categorized; note: in edb2, age is truncated after age >89; also, many dates come with imprecision and are therefore imputed
- Age at index date is calculated as the age at diagnosis + time difference (in years) between age at diagnosis and treatment initiation date
- Smoking history is assessed as any evidence of tobacco history on or before index date

Value

x with all additional demographic variables joined, that is, ADD NEW VARIABLE NAMES

- dem_age_initial_diagnosis (categorized age measured at initial cancer diagnosis: <60, 60-69, 70-79, 80+)
- dem_age_le_18_flag (logical indicating if patients was at least (larger/equal; le) 18 years of age at index date)
- dem_age_index_cont (continuous age measured at index date, CAVE: edb2 truncates age to 89 years for all patients >89, which means that dem_age_index_cont will show NA for these patients)
- dem_age_index (categorized age measured at index date: <60, 60-69, 70-79, 80+)
- dem_sex (binary, Male, Female, NA)
- dem_race (categorical, "", "Declined" and "Other" are converted to NA)
- dem_ethnicity (binary, "" and "Declined" are converted to NA)
- dem_race_ethnicity (categorical, classification into five mutually exclusive groups according to SEER)
- c_smoking_history (binary, history of any tobacco use on or before index date, TRUE = yes, FALSE = no)

Examples

```
## Not run:
library(encore.io)
ard <- x |>
  edb2_get_demographics(
    index_date = "dt_index",
    cancer = "BC"
  )

## End(Not run)
```

edb2_get_diagnosis_solid

Query initial and metastatic diagnosis dates for EDB2 database

Description

Function queries diagnosis details including staging information.

Usage

```
edb2_get_diagnosis_solid(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb2"),
  cancer = "NSCLC"
)
```

Arguments

x	dataframe queried from edb4 with at least patient ids and index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB4 data/files are located
cancer	character, NSCLC (default)

Details

Function queries diagnosis details for all patients in . Summary group stage and TNM staging information as recorded in EBD2.

A de novo metastatic status variable <c_de_novo_mets_dx> is derived and is TRUE if the group stage (<c_stage_initial_dx>) indicates any stage IV diagnosis, the TNM staging (<c_tnm_initial_dx>) indicates an M1 value, or if the date of earliest evidence of a distant metastasis is earlier or coincides with the date of initial diagnosis (<dt_initial_dx>).

Note: if both group and TNM staging variables are missing, <c_de_novo_mets_dx> will be missing, too.

The function also returns <c_met_pre_index> which is a helper variable that is TRUE in case there is any evidence of at least one distant metastasis at any time before the index date (inclusive). This captures both de novo metastatic patients and those who progressed/developed metastases before/on the index date. Note: if neither group stage nor tnm stage are available, we set <c_met_pre_index> to NA because we can't make say they're FALSE either

Value

x with all additional diagnosis variables joined, that is:

- dt_initial_dx - Date of diagnosis or first documented diagnosis date for tumor (de-identified to week)
- dt_staging - Date stage was recorded, if available (de-identified to week)
- dt_met_dx - Date of earliest evidence of distant metastasis (de-identified to week)
- c_stage_initial_dx - First summary group stage at initial diagnosis, if available
- c_tnm_initial_dx - Individual TNM staging values/stages at initial diagnosis
- c_de_novo_mets_dx - Evidence of presence of one or multiple metastases at/before initial diagnosis
- c_time_dx_to_index - Time between initial diagnosis and index date (in days)
- c_time_met_dx_to_index - Time between earliest evidence of a metastatic diagnosis and index date (in days)
- c_met_pre_index - Evidence of any metastasis between initial diagnosis and index date (logical); includes initial diagnosis date (overlap with c_de_novo_mets_dx possible)
- c_number_met_sites - number of metastatic sites for a given patient anytime before/on index date (inferred from provided metastatic site description)
- c_met_sites - description of anatomical locations of metastatic sites for a given patient patient's c_number_met_sites

Examples

```
## Not run:
library(encore.io)
analysis_cohort <- x |>
  edb4_get_diagnosis(cancer = "NSCLC")

## End(Not run)
```

edb2_get_ecog	<i>Query performance status information for a given cohort</i>
---------------	--

Description

Function queries performance status (ECOG, Karnofsky) tables and curates derived variables

Usage

```
edb2_get_ecog(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb2"),
  cancer = c("MM", "NSCLC"),
  from = -90,
  to = 0,
  ties = "lower",
  label_name = FALSE
)
```

Arguments

x	dataframe queried from edb2 with at least patient ids and index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB4 data/files are located
cancer	character, one of MM or NSCLC
from	integer, left boundary of ECOG measurement window relative to index date (e.g., -90, indicating ECOG should be measured not before 90 days before index date)
to	integer, right boundary of ECOG measurement window relative to index date (e.g., 0, indicating ECOG should be measured until day of index date (inclusive))
ties	character, one of "lower" or "higher" to choose either the lower (default) or higher ECOG measurement if there are two measurements on the same day
label_name	logical, should variable name carry information about the measurement window #treat character, column indicating binary exposure status (needed for measurement summary statistics by treatment status)

Details

The function queries all ECOG and Karnofsky measurements, then maps the Karnofsky measurement to an ECOG value according to Oken et al. (Am J Clin Oncol 1982), then filters for all measurements within the indicated time window specified by `from` and `to`. It then chooses the measurement closest to the index date (closest relative distance). In case of ties, the user has the option to choose the lower or higher (`ties`) measurement.

Value

`x` with all additional ECOG variables joined, that is:

- `c_ecog_{from}_{to}`, ECOG value measured in the specified measurement window
- `c_ecog_{from}_{to}`, distance of the date the ECOG value was measured relative to the index date

Note: if `from` or `to` is a negative integer, the resulting covariate name will contain a "min" for "minus" preceding the integer to comply with the tidy variable naming rules

Examples

```
## Not run:
library(encore.io)

analysis_cohort <- x |>
  edb2_get_performance(
    cancer = "NSCLC",
    from = -180,
    to = 0,
    ties = "lower"
  )

## End(Not run)
```

edb2_get_histology	<i>Query histology information from edb2</i>
--------------------	--

Description

Function queries and binarizes information for a provided histologiccal subtype from the EDB2 database.

Note: This function does not apply to multiple myeloma

Usage

```
edb2_get_histology(
  x = NULL,
  path = Sys.getenv("path_edb2"),
  cancer = "NSCLC",
  histology_match = NULL,
  return_all = FALSE
)
```

Arguments

x	dataframe queried from edb4 with at least patient ids and index date of inception cohort
path	character string, path to directory where EDB2 data/files are located
cancer	character, NSCLC
histology_match	character, string match to categorize and identify patients with a certain histology for the indicated tumor site, e.g. "adenocarcinoma"
return_all	logical, should a variable be returned that summarizes all recorded histology measurements? default is FALSE

Details

column information includes: Many patients can have more than one histological subtype recorded. In this function, the user must provide the desired cancer type and histological subtype and returns a binary TRUE/ FALSE if any of the histological recordings match the histology subtype provided in as well as a summary of all recorded histological subtypes (optional).

Tip: the function can also be stacked/executed multiple times with different histological subtypes.

Note that the search string defined in argument histology_match is not case sensitive.

Value

x with all additional histology variables joined, prepended with "c_"

- c_histology_match): A TRUE/FALSE if the histological subtype was observed for a given patient. FALSE may also include "unknowns" whose information was just not granular enough to be able to determine the histological subtype with absolute certainty
- c_histology_all: All observed histology recording for a given patient (optional if return_all = TRUE)

Examples

```
## Not run:
library(encore.io)

analysis_cohort_histology <- x |>
  edb2_get_histology(cancer = "NSCLC", histology_match = "adenocarcinoma")

## End(Not run)
```

edb2_get_labs

Query lab information for a given cohort

Description

Function queries the lab table and standardizes according to a reference measurement unit.

Usage

```
edb2_get_labs(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb2"),
  cancer = c("MM", "NSCLC"),
  lab_name = NULL,
  from = -90,
  to = 0,
  ties = "lower",
  set_implausible_na = TRUE,
  label_name = FALSE,
  verbose = TRUE
)
```

Arguments

x	dataframe queried from EDB2 with at least patient ids and therapy index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB2 data/files are located
cancer	character, one of MM or NSCLC
lab_name	character, curated name of lab (see details)
from	integer, left boundary of lab measurement window relative to index date (e.g., -90, indicating lab should be measured not before 90 days before index date)
to	integer, right boundary of lab measurement window relative to index date (e.g., 0, indicating lab should be measured not later than the day of the index date (inclusive))
ties	character, in case of ties (two equi-distant measurements), should the "higher" or "lower" lab measurement be prioritized
set_implausible_na	logical, should implausible values (outliers) be automatically be set NA (default is TRUE)? Lower and upper thresholds are documented in labs_mapping_edb2
label_name	logical, should variable name carry information about the measurement window
verbose	logical, print query progress and informative meta information

Details

The function queries supported labs in the given from - to measurement window, selects the closest measurement to the index date, prioritizes one measurement in case of ties and standardizes the quantitative result to 1. a binary "normal" vs. "abnormal" variable (depending on if the measurement is inside or outside a given physiological reference range) and 2. standardizes the quantitative lab result according to a reference measurement unit (e.g., a result in g/dL is converted to a result in g/L, latter of which is the reference unit).

Note: Only selected labs are supported by this function which were taken from the ROPRO prognostic score (Becker T et al., Ann Oncol 2020).

The supported and available labs are:

- c_albumin_g_l (albumin mass/volume in serum or plasma)

- `c_alp_u_l` (alkaline phosphatase enzymatic activity/volume in serum or plasma)
- `c_alt_u_l` (alanine aminotransferase enzymatic activity/volume in serum or plasma)
- `c_ast_u_l` (aspartate aminotransferase enzymatic activity/volume in serum or plasma; used to compute ast-alt ratio)
- `c_bilirubin_mg_dl` (total bilirubin mass/volume in serum or plasma)
- `c_calcium_mg_dl` (calcium mass/volume in serum or plasma)
- `c_hemoglobin_g_dl` (Hemoglobin)
- `c_ldh_u_l` (lactate dehydrogenase enzymatic activity/volume in serum or plasma)
- `c_neutrophil_10_9_l` (neutrophils #/volume in blood; used to compute neutrophil/lymphocyte ratio)
- `c_platelets_10_9_l` (platelets #/volume in blood)
- `c_protein_g_l` (protein Mass/volume in Serum or Plasma)

The following labs are part of ROPRO but are either not available in EDB2 or not supported yet:

- `c_chloride_mmol_l` (chloride moles/volume in serum or plasma)
- `c_eosinophils_leukocytes_ratio` (eosinophils/100 leukocytes in blood)
- `c_glucose_mg_dl` (Glucose)
- `c_glucose_mg_dl` (glucose mass/volume in serum or plasma)
- `c_light_chain_kappa` (Light Chain Kappa; dichotomous; >0 vs. 0)
- `c_light_chain_lambda` (Light Chain Lambda; dichotomous; >0 vs. 0)
- `c_lymphocyte_10_9_l` (lymphocytes #/volume in blood; used to compute neutrophil/lymphocyte ratio)
- `c_lymphocyte_leukocyte_ratio` (lymphocytes/100 leukocytes in blood)
- `c_m_protein_igg` (M protein IgG (dichotomous; >0 vs. 0)
- `c_monocytes_10_9_l` (monocytes #/volume in blood)
- `c_urea_nitrogen_mg_dl` (urea nitrogen mass/volume in serum or plasma)

Value

x with all additional labs variables joined, that is:

- `c_(lab_name)_distance_(from)_(to)` - days from date of lab measurements to index date
- `c_(lab_name)_(unit)_(from)_(to)` - binary lab result indicating if lab was within ("normal") the reference range or outside ("abnormal")
- `c_(lab_name)_(unit)_(from)_(to)_cont` - quantitative lab result after unit harmonization/conversion

Note: if from or to is a negative integer, the resulting covariate name will contain a "min" for "minus" preceding the integer to comply with the tidy variable naming rules

Examples

```
## Not run:
library(encore.io)

ard <- x |>
  edb2_get_labs(
    cancer = "NSCLC",
    lab_name = "c_albumin_g_l",
    from = -90,
    to = 0
  )

## End(Not run)
```

edb2_get_os

Query overall survival outcome for a given cohort

Description

Function queries mortality and other information to derive a right-censored time to all-cause mortality endpoint

Usage

```
edb2_get_os(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb2"),
  cancer = c("MM", "NSCLC"),
  data_cut_off_date = lubridate::ymd("2023-02-24"),
  verbose = TRUE
)
```

Arguments

x	dataframe queried from edb2 with at least patient ids and index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where data/files are located. Default is path_edb2 environment variable if available.
cancer	character, one of MM or NSCLC
data_cut_off_date	date of database lock; according to vendor communication the data cut-off for the Q3 2023 delivery is Feb 24, 2023. This parameter can be changed if a grace period of x months before database lock is desired.
verbose	logical, print query progress and informative meta information

Details

The function queries and intention-to-treat (ITT) overall survival endpoint. The ITT follow-up time is defined as the time interval from index date (dt_index) to the date of death (if death event occurred), or the date of a patient's last structured clinical activity or database cut-off, whichever is earlier. Upon advice by the EDB2 vendor, the documented or reported days were not used (except for ECOG) as this is not a good indicator if a patient was truly alive by that time or not. All tables with dates were used except for tumor grading as here only reported and documented dates were available.

Note: for a fraction of patients, only month-level or year-level granularity is provided for the dates used to compute follow-up. This can result in implausible/negative follow-up times if the index date is after the imputed date of death.

Value

x with all endpoint information joined, that is:

- death_itt, event indicator for all-cause mortality
- fu_itt_days, ITT follow-up time in days
- fu_itt_months, ITT follow-up time in months (i.e., fu_itt_days / 30.417)
- fu_itt_years, ITT follow-up time in years

Examples

```
## Not run:
library(encore.io)

ard <- x |>
  edb2_get_os(
    cancer = "NSCLC"
  )

## End(Not run)
```

edb2_get_vitals

Query vital sign measurements for a given cohort

Description

The function queries vital sign measurements in a specified measurement window and converts standardized measurements to SI units (e.g., meters for height and kg for weight).

Usage

```
edb2_get_vitals(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb2"),
  cancer = c("MM", "NSCLC"),
  vital_name = NULL,
  from = -90,
```

```

    to = 0,
    ties = "lower",
    set_implausible_na = TRUE,
    label_name = FALSE,
    verbose = FALSE
  )

```

Arguments

x	dataframe queried from EDB2 with at least patient ids and therapy index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB2 data/files are located
cancer	character, one of MM or NSCLC
vital_name	character, curated name of vital sign measurement (see details)
from	integer, left boundary of vital signs measurement window relative to index date (e.g., -90, indicating vital should be measured not before 90 days before index date)
to	integer, right boundary of vital signs measurement window relative to index date (e.g., 0, indicating vital should be measured until day of index date (inclusive))
ties	character, in case of ties (two equi-distant measurements), should the "higher" or "lower" lab measurement be prioritized?
set_implausible_na	logical, should implausible values (outliers) be automatically be set NA (default is TRUE)? Lower and upper thresholds are documented in vitals_mapping_edb2
label_name	logical, should variable name carry information about the measurement window
verbose	logical, print query progress and informative meta information

Details

The function queries and cleans all available vital sign measurements. In detail, the function selects measurements in a from - to measurement window relative to the index date. In case that there are multiple measurements in this window, the function uses the measurement that has the smallest absolute distance relative to the index date. If there are two equi-distant measurements, the lower (default) or higher measurement can be prioritized.

The available and supported vitals are:

- c_height (height in m)
- c_weight (weight in kg)

To compute BMI, query both c_height and c_weight and compute c_bmi as c_weight/c_height^2

Value

x with all additional labs variables joined, that is:

- c_(vital_name)_distance_(from)_(to) - days from date of vital sign measurements to index date
- c_(vital_name)_(unit)_(from)_(to)_cont - quantitative vital sign measurement

Note: if from or to is a negative integer, the resulting covariate name will contain a "min" for "minus" preceding the integer to comply with the tidy variable naming rules

Examples

```
## Not run:
library(encore.io)

ard <- x |>
  edb2_get_vitals(
    cancer = "NSCLC",
    vital_name = "c_height",
    from = -180,
    to = 0
  )

## End(Not run)
```

edb2_path_helper	<i>Helper function to assign correct paths based on cancer entity in EDB2</i>
------------------	---

Description

Use this helper function to assign the correct paths based on the cancer entity

Usage

```
edb2_path_helper(path = Sys.getenv("path_edb2"), cancer = c("MM", "NSCLC"))
```

Arguments

path	string, path to edb2 root directory
cancer	character, either "NSCLC" or "MM"

Details

lot_path in MM also contains the imwg.csv table

Value

paths to line of therapy (lot_path) and all other data files (data_files_path)

Examples

```
## Not run:
library(encore.io)

nscclc_paths <- edb2_path_helper(cancer = "NSCLC")

## End(Not run)
```

edb2_query_ropro	<i>Query and curate all relevant ROPRO variables</i>
------------------	--

Description

This function queries, cleans and curates all necessary covariates from EDB2 as they are used to compute the ROPRP prognostic score (Becker, Weberpals, et al., Ann Oncol 2020).

Usage

```
edb2_query_ropro(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb2"),
  cancer = NULL,
  from = -90,
  to = 0,
  verbose = TRUE
)
```

Arguments

x	dataframe queried from EDB2 with at least patient ids and therapy index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB2 data/files are located
cancer	character, one of MM or NSCLC
from	integer, left boundary of measurement window for time-dependent variables relative to index date (e.g., -90, indicating variables should be measured not before 90 days before index date)
to	integer, right boundary of measurement window for time-dependent variables relative to index date (e.g., 0, indicating variables should be measured not later than the day of the index date (inclusive))
verbose	logical, print progress of query

Details

Wrapper around major functions to query required covariates to compute ROPRO. Selected covariates are log transformed or log-log transformed. More details, see Becker, Weberpals, et al., Ann Oncol 2020.

Note that EDB2 does not provide all covariates to compute the full ROPRO model. Hence, this function queries all available covariates for a reduced model.

Value

x with all required ROPRO covariates joined. All general and cancer type-specific (as specified in cancer argument) covariates are returned.

Examples

```
## Not run:
library(encore.io)

x_ropro <- x |>
  edb2_query_ropro(
    index_date = "dt_index",
    path = Sys.getenv("path_edb2"),
    cancer = "NSCLC",
    from = -90,
    to = 0,
    verbose = TRUE
  )

## End(Not run)
```

edb3_get_demographics *Query demographic variables for an inception cohort in EDB3*

Description

Function queries all available demographic variables from the EDB3 database, curates them and joins them to the inception cohort x.

Usage

```
edb3_get_demographics(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb3")
)
```

Arguments

x	dataframe queried from edb3 with at least patient ids and index date of inception cohort
index_date	character, variable/column name with the patient's index_date
path	character string, path to directory where edb3 data/files are located

Details

Some important data curation details include:

- race and ethnicity converted to <dem_race> and <dem_ethnicity> are cleaned for missing values, i.e., "", "Other or Unknown Race" and "Unknown" are explicitly changed to NA
- race and ethnicity are combined into a new combined variable 'dem_race_ethnicity' with five mutually exclusive groups as defined by SEER https://seer.cancer.gov/seerstat/variables/seer/race_ethnicity/#:~:text=
- The date of birth DOB is given on year granularity level and is hence imputed to June 30th in <dt_dob_imputed>

- The date of death DOD is suppressed to the closest Sunday within 4 days of the date of death and is sourced from curation, EMR, and third-party death data (in this hierarchical order) <dt_dod_imputed>
- Smoking history is assessed as a history of current or former (= smoking history) or never (= no smoking history) on or before index date

Value

x with all additional demographic variables joined, that is, ADD NEW VARIABLE NAMES

- dem_age_initial_diagnosis (categorized age measured at initial cancer diagnosis: <60, 60-69, 70-79, 80+)
- dem_age_le_18_flag (logical indicating if patients was at least (larger/equal; le) 18 years of age at index date)
- dem_age_index_cont (continuous age measured at index date; derived from dt_index and dt_dob_imputed)
- dem_age_index (categorized age measured at index date: <60, 60-69, 70-79, 80+)
- dem_sex (binary, Male, Female, NA)
- dem_race (categorical, "", "Declined" and "Other" are converted to NA)
- dem_ethnicity (binary, "" and "Declined" are converted to NA)
- dem_race_ethnicity (categorical, classification into five mutually exclusive groups according to SEER)
- dem_institution_type (academic/community hospital patients receives care)
- dem_region (categorical, Northeast, South, West, Midwest, Multiple)
- dem_state (categorical, state patients receives care)
- c_smoking_history (binary, history of smoking on or before index date, 1 = current or former, 0 = never)

Examples

```
## Not run:
library(encore.io)
analysis_cohort <- inception_cohort |>
  edb3_get_demographics(cancer = "NSCLC")

## End(Not run)
```

edb3_get_labs

Query lab information for a given cohort

Description

Function queries the lab table and standardizes according to a reference measurement unit.

Usage

```
edb3_get_labs(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb3"),
  lab_name = NULL,
  from = -90,
  to = 0,
  ties = "lower",
  set_implausible_na = TRUE,
  label_name = FALSE,
  verbose = TRUE
)
```

Arguments

x	dataframe queried from EDB3 with at least patient ids and therapy index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB3 data/files are located
lab_name	character, curated name of lab (see details)
from	integer, left boundary of lab measurement window relative to index date (e.g., -90, indicating lab should be measured not before 90 days before index date)
to	integer, right boundary of lab measurement window relative to index date (e.g., 0, indicating lab should be measured not later than the day of the index date (inclusive))
ties	character, in case of ties (two equi-distant measurements), should the "higher" or "lower" lab measurement be prioritized
set_implausible_na	logical, should implausible values (outliers) be automatically be set NA (default is TRUE)? Lower and upper thresholds are documented in labs_mapping_edb3
label_name	logical, should variable name carry information about the measurement window
verbose	logical, print query progress and informative meta information

Details

The function queries and cleans supported lab measurements. In detail, the function selects measurements in a from - to measurement window relative to the index date. In case that there are multiple measurements in this window, the function uses the measurement that has the smallest absolute distance relative to the index date. If there are two equi-distant measurements, the lower (default) or higher measurement can be prioritized.

Note: Only selected labs are supported by this function which were taken from the ROPRO prognostic score (Becker T et al., Ann Oncol 2020).

The supported and available labs are:

- c_albumin_g_l (albumin mass/volume in serum or plasma)
- c_alp_u_l (alkaline phosphatase enzymatic activity/volume in serum or plasma)
- c_alt_u_l (alanine aminotransferase enzymatic activity/volume in serum or plasma)

- `c_ast_u_l` (aspartate aminotransferase enzymatic activity/volume in serum or plasma; used to compute ast-alt ratio)
- `c_bilirubin_mg_dl` (total bilirubin mass/volume in serum or plasma)
- `c_calcium_mg_dl` (calcium mass/volume in serum or plasma)
- `c_chloride_mmol_l` (chloride moles/volume in serum or plasma)
- `c_eosinophils_leukocytes_ratio` (eosinophils/100 leukocytes in blood)
- `c_glucose_mg_dl` (glucose mass/volume in serum or plasma)
- `c_granulocytes_leukocytes_ratio` (granulocytes/100 leukocytes in blood)
- `c_hemoglobin_g_dl` (hemoglobin mass/volume in blood)
- `c_ldh_u_l` (lactate dehydrogenase enzymatic activity/volume in serum or plasma)
- `c_lymphocyte_10_9_l` (lymphocytes #/volume in blood; used to compute neutrophil/lymphocyte ratio)
- `c_lymphocyte_leukocyte_ratio` (lymphocytes/100 leukocytes in blood)
- `c_monocytes_10_9_l` (monocytes #/volume in blood)
- `c_neutrophil_10_9_l` (neutrophils #/volume in blood; used to compute neutrophil/lymphocyte ratio)
- `c_platelets_10_9_l` (platelets #/volume in blood)
- `c_protein_g_l` (protein mass/volume in Serum or Plasma)
- `c_urea_nitrogen_mg_dl` (urea nitrogen mass/volume in serum or plasma)

The following labs are part of ROPRO but are either not available in EDB3 or not supported yet:

- `c_light_chain_kappa` (Light Chain Kappa; dichotomous; >0 vs. 0)
- `c_light_chain_lambda` (Light Chain Lambda; dichotomous; >0 vs. 0)
- `c_m_protein_igg` (M protein IgG (dichotomous; >0 vs. 0)

Value

x with all additional labs variables joined, that is:

- `c_(lab_name)_distance_(from)_(to)` - days from date of lab measurements to index date
- `c_(lab_name)_(unit)_(from)_(to)` - quantitative lab result after unit harmonization/conversion

Note: if from or to is a negative integer, the resulting covariate name will contain a "min" for "minus" preceding the integer to comply with the tidy variable naming rules

Examples

```
## Not run:
library(encore.io)
```

```
ard <- x |>
  edb3_get_labs(
    lab_name = "c_albumin_g_l",
    from = -90,
    to = 0
  )
```

```
## End(Not run)
```

edb3_get_vitals

*Query vital sign measurements for a given inception cohort***Description**

Function queries vitals sign measurements

Usage

```
edb3_get_vitals(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb3"),
  vital_name = NULL,
  from = -90,
  to = 0,
  ties = "lower",
  set_implausible_na = TRUE,
  label_name = FALSE
)
```

Arguments

x	dataframe queried from EDB3 with at least patient ids and therapy index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB3 data/files are located
vital_name	character, curated name of vital sign measurement (see details)
from	integer, left boundary of lab measurement window relative to index date (e.g., -90, indicating lab should be measured not before 90 days before index date)
to	integer, right boundary of lab measurement window relative to index date (e.g., 0, indicating lab should be measured not later than the day of the index date (inclusive))
ties	character, in case of ties (two equi-distant measurements), should the "higher" or "lower" lab measurement be prioritized?
set_implausible_na	logical, should implausible values (outliers) be automatically be set NA (default is TRUE)? Lower and upper thresholds are documented in vitals_mapping_edb3
label_name	logical, should variable name carry information about the measurement window

Details

The function queries and cleans supported vital sign measurements. In detail, the function selects measurements in a from - to measurement window relative to the index date. In case that there are multiple measurements in this window, the function uses the measurement that has the smallest absolute distance relative to the index date. If there are two equi-distant measurements, the lower (default) or higher measurement can be prioritized.

The supported vitals are:

- c_sbp (systolic blood pressure in mmHg)
- c_dbp (diastolic blood pressure in mmHg)
- c_bmi (body mass index in kg/m² directly measured or derived from weight/height²)
- c_height (height in m)
- c_hr (heart rate/pulse in beats/min)
- c_oxygen (oxygen saturation; taken from O2 sat and pulse oximetry)
- c_resp (respiration in breaths/min)
- c_weight (weight in kg)

Value

x with all additional labs variables joined, that is:

- c_(vital_name)_distance_(from)_(to) - days from date of vital sign measurements to index date
- c_(vital_name)_(unit)_(from)_(to)_cont - quantitative vital sign measurement

Note: if from or to is a negative integer, the resulting covariate name will contain a "min" for "minus" preceding the integer to comply with the tidy variable naming rules

Examples

```
## Not run:
library(encore.io)

ard <- x |>
  edb3_get_vitals(
    vital_name = "c_weight",
    from = -90,
    to = 0
  )

## End(Not run)
```

edb4_get_biomarker	<i>Query biomarker information for a given inception cohort</i>
--------------------	---

Description

Function queries biomarker tables and curates information on alterations in defined driver genes.

Usage

```
edb4_get_biomarker(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb4"),
  cancer = c("BC", "CRC", "MM", "NSCLC"),
  biomarker_name = NULL,
  from = -90,
```

```

    to = 0,
    label_name = FALSE
  )

```

Arguments

x	dataframe queried from edb4 with at least patient ids and index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB4 data/files are located
cancer	character, one of BC, CRC, MM or NSCLC
biomarker_name	character, name of biomarker/gene alteration (see details)
from	integer, left boundary of biomarker measurement window relative to index date (e.g., -90, indicating biomarker should be measured not before 90 days before index date)
to	integer, right boundary of biomarker measurement window relative to index date (e.g., 0, indicating biomarker should be measured until day of index date (inclusive))
label_name	logical, should variable name carry information about the measurement window

Details

The function queries and categorizes a certain biomarker that was collected and curated as part of the database as either positive or negative. The categorization happens according to if the biomarker mutation/alteration is a clinically actionable one. For example, patients with any mutation in the EGFR gene or MSI-H/dMMR status would be classified as positive. In case there are multiple measurements per biomarker and patient, the time point of measurement is defined as the non-missing biomarker result in the covariate ascertainment window given by 'from' and 'to' that is closest to the index date.

The biomarker recorded date (dt_(biomarker)) in this database is defined as the date documented or result date. Note that the biomarker date is de-identified to week (date documented or result date) and is converted to ymd format.

Depending on the cancer type, the biomarker names can be: alk, braf, brca1, brca2, egfr, er, esr1, her2neu, kras, met, mmr, msi, nras, ntrk1, ntrk2, ntrk3, pd-l1, pik3ca, pr, ret, ros1, tmb

Value

x with all additional biomarker variables joined, that is:

- c_(biomarker_name)_status_(from)_(to) (binary, biomarker mutation status positive or negative)
- c_(biomarker_name)_detail_(from)_(to) (character string, more details about selected measurement)
- c_(biomarker_name)_detail_all_(from)_(to) (character string, this provides details about all results and details for this biomarker if there were multiple tests in the measurement window (from, to))
- c_(biomarker_name)_distance_(from)_(to) (numeric, relative distance between date of measurement and index date in days)
- dt_(biomarker_name)_(from)_(to) (date, date of selected biomarker measurement)

Note: if from or to is a negative integer, the resulting covariate name will contain a "min" for "minus" preceding the integer to comply with the tidy variable naming rules

Examples

```
## Not run:
library(encore.io)
analysis_cohort <- inception_cohort |>
  edb4_get_biomarker(
    cancer = "NSCLC",
    biomarker_name = "egfr",
    from = -180,
    to = 0)

## End(Not run)
```

edb4_get_demographics *Query demographic variables for an inception cohort*

Description

Function queries all available demographic variables from the EDB4 database, curates them and joins them to the inception cohort x.

Usage

```
edb4_get_demographics(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb4"),
  cancer = c("BC", "CRC", "MM", "NSCLC")
)
```

Arguments

x	dataframe queried from edb4 with at least patient ids and index date of inception cohort
index_date	character, variable/column name with the patient's index_date
path	character string, path to directory where EDB4 data/files are located
cancer	character, one of BC, CRC, MM or NSCLC

Details

Some important data curation details include:

- RACE and ETHNICITY are combined into a new combined variable 'dem_race_ethnicity' with five mutually exclusive groups as defined by SEER https://seer.cancer.gov/seerstat/variables/seer/race_ethnicity
- The date of birth DOB is given on year granularity level and is hence imputed to the mid of the year as <dt_dob_imputed>, e.g. 1955 becomes 1955-07-02. This affects all variables which are derived from the date of birth such as all age variables
- Smoking history is assessed as a history of current or former (= smoking history) or never (= no smoking history) on or before index date

Value

x with all additional demographic variables joined, that is, ADD NEW VARIABLE NAMES

- dem_age_initial_diagnosis (nominal, categorized age measured at initial cancer diagnosis: <60, 60-69, 70-79, 80+)
- dem_age_le_18_flag (logical, indicating if patients was at least (larger/equal; le) 18 years of age at index date)
- dem_age_index_cont (continuous, age measured at index date; note: date of birth has only year-granularity, hence age is imprecise)
- dem_age_index (nominal, categorized age measured at index date: <60, 60-69, 70-79, 80+)
- dem_sex (binary, Male, Female)
- dem_family_history (binary, TRUE, FALSE)
- dem_race (nominal, "", "Declined" and "Other" are converted to NA)
- dem_ethnicity (binary, "" and "Declined" are converted to NA)
- dem_race_ethnicity (nominal, classification into five mutually exclusive groups according to SEER)
- dem_region (nominal, region of the center/network the patient is receiving care at, can be Midwest, Northeast, South, West)
- c_smoking_history (logical, history of smoking on or before index date, TRUE = current or former, FALSE = never)

Examples

```
## Not run:
library(encore.io)

analysis_cohort <- x |>
  edb4_get_demographics(
    index_date = "dt_index",
    cancer = "NSCLC")

## End(Not run)
```

```
edb4_get_diagnosis_solid
```

Query initial and metastatic diagnosis dates for EDB4 database

Description

Function queries diagnosis details including staging information.

Usage

```
edb4_get_diagnosis_solid(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb4"),
  cancer = c("BC", "CRC", "MM", "NSCLC")
)
```

Arguments

x	dataframe queried from edb4 with at least patient ids and index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB4 data/files are located
cancer	character, one of BC, CRC, MM or NSCLC

Details

Function queries diagnosis details for all patients in . Summary group stage and TNM staging information as recorded in EBD4 ("Other" and "Unknown" categories are mapped to NA).

A de novo metastatic status variable <c_de_novo_mets_dx> is derived and is TRUE if the group stage (<c_stage_initial_dx>) indicates any stage IV diagnosis, the TNM staging (<c_tnm_initial_dx>) indicates an M1 value, or if the date of earliest evidence of a distant metastasis is earlier or coincides with the date of initial diagnosis (<dt_initial_dx>).

Note: if both group and TNM staging variables are missing, <c_de_novo_mets_dx> will be missing, too.

The function also returns <c_met_pre_index> which is a helper variable that is TRUE in case there is any evidence of at least one distant metastasis at any time before the index date (inclusive). This captures both de novo metastatic patients and those who progressed/developed metastases before/on the index date. Note: if neither group stage nor tnm stage are available, we set <c_met_pre_index> to NA because we can't make say they're FALSE either

Value

x with all additional diagnosis variables joined, that is:

- dt_initial_dx - Date of diagnosis or first documented diagnosis date for tumor (de-identified to week)
- dt_staging - Date stage was recorded, if available (de-identified to week)
- dt_met_dx - Date of earliest evidence of distant metastasis (de-identified to week)
- c_stage_initial_dx - First summary group stage at initial diagnosis, if available
- c_tnm_initial_dx - Individual TNM staging values/stages at initial diagnosis
- c_de_novo_mets_dx - Evidence of presence of one or multiple metastases at/before initial diagnosis
- c_time_dx_to_index - Time between initial diagnosis and index date (in days)
- c_time_met_dx_to_index - Time between earliest evidence of a metastatic diagnosis and index date (in days)
- c_met_pre_index - Evidence of any metastasis before/on index date (logical); includes de novo metastatic patients and progressors (overlap with c_de_novo_mets_dx possible)
- c_number_met_sites - number of metastatic sites for a given patient anytime before/on index date (inferred from mets_location as provided by the vendor)
- c_met_sites - description of anatomical locations of metastatic sites for a given patient patient's c_number_met_sites

Examples

```
## Not run:
library(encore.io)
analysis_cohort <- x |>
  edb4_get_diagnosis(cancer = "NSCLC")

## End(Not run)
```

edb4_get_ecog

Query performance status information for an inception cohort

Description

Function queries performance status (ECOG, Karnofsky) tables and curates derived variables

Usage

```
edb4_get_ecog(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb4"),
  cancer = c("BC", "CRC", "MM", "NSCLC"),
  from = -90,
  to = 0,
  ties = "lower",
  label_name = FALSE
)
```

Arguments

x	dataframe queried from edb4 with at least patient ids and index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB4 data/files are located
cancer	character, one of BC, CRC, MM or NSCLC
from	integer, left boundary of ECOG measurement window relative to index date (e.g., -90, indicating ECOG should be measured not before 90 days before index date)
to	integer, right boundary of ECOG measurement window relative to index date (e.g., 0, indicating ECOG should be measured until day of index date (inclusive))
ties	character, one of "lower" or "higher" to choose either the lower (default) or higher ECOG measurement if there are two measurements on the same day
label_name	logical, should variable name carry information about the measurement window

Details

The function queries all ECOG and Karnofsky measurements, then maps the Karnofsky measurement to an ECOG value according to Oken et al. (Am J Clin Oncol 1982), then filters for all measurements within the indicated time window specified by `from` and `to`. It then chooses the measurement closest to the index date (closest relative distance). In case of ties, the user has the option to choose the lower or higher (`ties`) measurement.

Value

`x` with all additional ECOG variables joined, that is:

- `c_ecog_{from}_{to}`, ECOG value measured in the specified measurement window
- `c_ecog_{from}_{to}`, distance of the date the ECOG value was measured relative to the index date

Note: if `from` or `to` is a negative integer, the resulting covariate name will contain a "min" for "minus" preceding the integer to comply with the tidy variable naming rules

Examples

```
## Not run:
library(encore.io)

analysis_cohort <- x |>
  edb4_get_ecog(
    cancer = "NSCLC",
    from = -180,
    to = 0,
    ties = "lower"
  )

## End(Not run)
```

edb4_get_histology	<i>Query histology information from edb4</i>
--------------------	--

Description

Function queries and binarizes information for a provided histological subtype from the EDB4 database. Note: This function does not apply to multiple myeloma

Usage

```
edb4_get_histology(
  x = NULL,
  path = Sys.getenv("path_edb4"),
  cancer = c("BC", "CRC", "NSCLC"),
  histology_match = NULL,
  return_all = FALSE
)
```

Arguments

x	dataframe queried from edb4 with at least patient ids and index date of inception cohort
path	character string, path to directory where EDB4 data/files are located
cancer	character, one of BC, CRC or NSCLC
histology_match	character, string match to categorize and identify patients with a certain histology, e.g. "adenocarcinoma"
return_all	logical, should a variable be returned that summarizes all recorded histology measurements? default is FALSE

Details

column information includes: Many patients can have more than one histological subtype recorded. In this function, the user must provide the desired cancer type and histological subtype and returns a binary TRUE/FALSE if any of the histological recordings match the histology subtype provided in histology_match as well as a summary of all recorded histological subtypes (optional). Tip: the function can also be stacked/executed multiple times with different histological subtypes.

CAVE: EDB4 does not provide any information about the specimen/tissue type for which the histology was determined!

Note that the search string defined in argument histology_match is not case sensitive.

Value

x with all additional histology variables joined, prepended with "c_"

- c_(histology_match): A TRUE/FALSE if the histological subtype was observed for a given patient. FALSE may also include "unknowns" whose information was just not granular enough to be able to determine the histological subtype with absolute certainty
- c_histology_all: All observed histology recording for a given patient (optional if return_all = TRUE)

Examples

```
## Not run:
library(encore.io)
analysis_cohort_histology <- x |>
  edb4_get_histology(cancer = "NSCLC", histology_match = "adenocarcinoma")

## End(Not run)
```

edb4_get_labs

Query lab information for a given inception cohort

Description

Function queries the lab table and standardizes according to a reference measurement unit.

Usage

```
edb4_get_labs(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb4"),
  cancer = c("BC", "CRC", "MM", "NSCLC"),
  lab_name = NULL,
  from = -90,
  to = 0,
  ties = "lower",
  set_implausible_na = TRUE,
  label_name = FALSE,
  verbose = TRUE
)
```

Arguments

x	dataframe queried from EDB4 with at least patient ids and therapy index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB4 data/files are located
cancer	character, one of BC, CRC, MM or NSCLC
lab_name	character, curated name of lab (see details)
from	integer, left boundary of lab measurement window relative to index date (e.g., -90, indicating lab should be measured not before 90 days before index date)
to	integer, right boundary of lab measurement window relative to index date (e.g., 0, indicating lab should be measured not later than the day of the index date (inclusive))
ties	character, in case of ties (two equi-distant measurements), should the "higher" or "lower" lab measurement be prioritized
set_implausible_na	logical, should implausible values (outliers) be automatically be set NA (default is TRUE)? Lower and upper thresholds are documented in labs_mapping_edb4
label_name	logical, should variable name carry information about the measurement window
verbose	logical, print query progress and informative meta information

Details

The function queries and cleans supported lab measurements. In detail, the function selects measurements in a from - to measurement window relative to the index date. In case that there are multiple measurements in this window, the function uses the measurement that has the smallest absolute distance relative to the index date. If there are two equi-distant measurements, the lower (default) or higher measurement can be prioritized.

Note: Only selected labs are supported by this function which were taken from the ROPRO prognostic score (Becker T et al., Ann Oncol 2020).

The supported and available labs are:

- c_albumin_g_l (albumin mass/volume in serum or plasma)
- c_alp_u_l (alkaline phosphatase enzymatic activity/volume in serum or plasma)

- c_alt_u_l (alanine aminotransferase enzymatic activity/volume in serum or plasma)
- c_ast_u_l (aspartate aminotransferase enzymatic activity/volume in serum or plasma; used to compute ast-alt ratio)
- c_bilirubin_mg_dl (total bilirubin mass/volume in serum or plasma)
- c_calcium_mg_dl (calcium mass/volume in serum or plasma)
- c_chloride_mmol_l (chloride moles/volume in serum or plasma)
- c_eosinophils_leukocytes_ratio (eosinophils/100 leukocytes in blood)
- c_glucose_mg_dl (glucose mass/volume in serum or plasma)
- c_granulocytes_leukocytes_ratio (granulocytes/100 leukocytes in blood)
- c_hemoglobin_g_dl (hemoglobin mass/volume in blood)
- c_ldh_u_l (lactate dehydrogenase enzymatic activity/volume in serum or plasma)
- c_lymphocyte_10_9_l (lymphocytes #/volume in blood; used to compute neutrophil/lymphocyte ratio)
- c_lymphocyte_leukocyte_ratio (lymphocytes/100 leukocytes in blood)
- c_monocytes_10_9_l (monocytes #/volume in blood)
- c_neutrophil_10_9_l (neutrophils #/volume in blood; used to compute neutrophil/lymphocyte ratio)
- c_platelets_10_9_l (platelets #/volume in blood)
- c_protein_g_l (protein mass/volume in Serum or Plasma)
- c_urea_nitrogen_mg_dl (urea nitrogen mass/volume in serum or plasma)

The following labs are part of ROPRO but are either not available in EDB4 or not supported yet:

- c_light_chain_kappa (Light Chain Kappa; dichotomous; >0 vs. 0)
- c_light_chain_lambda (Light Chain Lambda; dichotomous; >0 vs. 0)
- c_m_protein_igg (M protein IgG (dichotomous; >0 vs. 0)

Value

x with all additional labs variables joined, that is:

- c_(lab_name)_distance_(from)_(to) - days from date of lab measurements to index date
- c_(lab_name)_(unit)_(from)_(to)_cont - quantitative lab result after unit harmonization/conversion

Note: if from or to is a negative integer, the resulting covariate name will contain a "min" for "minus" preceding the integer to comply with the tidy variable naming rules

Examples

```
## Not run:
library(encore.io)

ard <- x |>
  edb4_get_labs(
    cancer = "NSCLC",
    lab_name = "c_albumin_g_l",
    from = -90,
    to = 0
```

```
)

## End(Not run)
```

edb4_get_os

Query overall survival outcome for a given inception cohort

Description

Function queries mortality and other information to derive a righ-censored time to all-cause mortality endpoint

Usage

```
edb4_get_os(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb4"),
  cancer = NULL,
  data_cut_off_date = lubridate::ymd("2024-09-30"),
  verbose = TRUE
)
```

Arguments

x	dataframe queried from edb4 with at least patient ids and index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where data/files are located
cancer	character, one of BC, CRC, MM or NSCLC
data_cut_off_date	date of database lock; the data cut-off for this delivery is Sep 30, 2024. This parameter can be changed if a grace period of x months before database lock is desired.
verbose	logical, print query progress and informative meta information

Details

The function queries and curates intention-to-treat (ITT) overall survival endpoint. The ITT follow-up time is defined as the time interval from index date (dt_index) to the date of death (if death event occurred), or the last date of proof that the patient was alive at that time (date de-identified to week).

Note that in EDB4, the granularity of the date of death variable is given as month-year. In these cases, the date of death is imputed to the mid/15th of the month. This can in rare circumstances lead to negative/implausible follow-up times if the index date is after the imputed date of death.

Value

x with all endpoint information joined, that is:

- death_itt, event indicator for all-cause mortality
- fu_itt_days, ITT follow-up time in days
- fu_itt_months, ITT follow-up time in months (i.e., fu_itt_days / 30.417)
- fu_itt_years, ITT follow-up time in years

Examples

```
## Not run:
library(encore.io)

ard <- x |>
  edb4_get_os(
    cancer = "NSCLC"
  )

## End(Not run)
```

edb4_get_vitals

Query vital sign measurements for a given cohort

Description

Function queries vitals sign measurements

Usage

```
edb4_get_vitals(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb4"),
  cancer = c("BC", "CRC", "MM", "NSCLC"),
  vital_name = NULL,
  from = -90,
  to = 0,
  ties = "lower",
  set_implausible_na = TRUE,
  label_name = FALSE,
  verbose = TRUE
)
```

Arguments

x	dataframe queried from EDB4 with at least patient ids and therapy index date of inception cohort
index_date	character, variable/column name with the patient's index_date, default is dt_index
path	character string, path to directory where EDB4 data/files are located

cancer	character, one of BC, CRC, MM or NSCLC
vital_name	character, curated name of vital sign measurement (see details)
from	integer, left boundary of lab measurement window relative to index date (e.g., -90, indicating lab should be measured not before 90 days before index date)
to	integer, right boundary of lab measurement window relative to index date (e.g., 0, indicating lab should be measured not later than the day of the index date (inclusive))
ties	character, in case of ties (two equi-distant measurements), should the "higher" or "lower" lab measurement be prioritized?
set_implausible_na	logical, should implausible values (outliers) be automatically be set NA (default is TRUE)? Lower and upper thresholds are documented in <code>vitals_mapping_edb4</code>
label_name	logical, should variable name carry information about the measurement window
verbose	logical, print query progress and informative meta information

Details

The function queries and cleans all available vital sign measurements. In detail, the function removes measurements that are character strings (e.g., "BMI < 21") and only considers quantitative results. The function further only selects measurements in a from - to measurement window relative to the index date. In case that there are multiple measurements in this window, the function uses the measurement that has the smallest absolute distance relative to the index date. If there are two equi-distant measurements, the lower (default) or higher measurement can be prioritized.

The available and supported vitals are:

- c_sbp (systolic blood pressure in mmHg)
- c_dbp (diastolic blood pressure in mmHg)
- c_bmi (body mass index in kg/m² directly measured or derived from weight/height²)
- c_bsa (body surface area in m²)
- c_height (height in m)
- c_hr (heart rate/pulse in beats/min)
- c_oxygen (oxygen saturation; taken from O2 sat and pulse oximetry)
- c_pain (pain scale in ?)
- c_resp (respiration in breaths/min)
- c_temp (temperature in fahrenheit)
- c_weight (weight in kg)

Value

x with all additional labs variables joined, that is:

- c(vital_name)_distance_(from)_(to) - days from date of vital sign measurements to index date
- c(vital_name)_(unit)_(from)_(to)_cont - quantitative vital sign measurement

Note: if from or to is a negative integer, the resulting covariate name will contain a "min" for "minus" preceding the integer to comply with the tidy variable naming rules

Examples

```
## Not run:
library(encore.io)

ard <- x |>
  edb4_get_vitals(
    cancer = "NSCLC",
    vital_name = "c_bmi",
    from = -90,
    to = 0
  )

## End(Not run)
```

edb4_query_ropro

Query and curate all relevant ROPRO variables

Description

This function queries, cleans and transforms all necessary covariates needed to compute the ROPRO prognostic score in EDB4.

Usage

```
edb4_query_ropro(
  x = NULL,
  index_date = "dt_index",
  path = Sys.getenv("path_edb4"),
  cancer = NULL,
  from = -90,
  to = 0,
  verbose = TRUE
)
```

Arguments

x	dataframe queried from EDB4 with at least patient ids and therapy index date of inception cohort
index_date	character, variable/column name with the patient's index date, default is dt_index
path	character string, path to directory where EDB4 data/files are located
cancer	character, one of "BC", "CRC", "MM" or "NSCLC"
from	integer, left boundary of measurement window for time-dependent variables relative to index date (e.g., -90, indicating variables should be measured not before 90 days before index date)
to	integer, right boundary of measurement window for time-dependent variables relative to index date (e.g., 0, indicating variables should be measured not later than the day of the index date (inclusive))
verbose	logical, print progress of query

Details

Wrapper around major functions to query required covariates to compute ROPRO. Selected covariates are log transformed or log-log transformed. More details, see Becker, Weberpals, et al., Ann Oncol 2020.

Value

x with all required ROPRO covariates joined. All general and cancer type-specific (as specified in cancer argument) covariates are returned.

#' Note that:

- covariates for EarlyBreast are identical to the the general pan-tumor ROPRO, just the weights are different. That means, if cancer = "BC" is specified, the function also returns covariates for the metastatic breast cancer-specific ROPRO.

Examples

```
## Not run:
library(encore.io)

x_ropro <- x |>
  edb4_query_ropro(
    index_date = "dt_index",
    path = Sys.getenv("path_edb4"),
    cancer = "NSCLC",
    from = -90,
    to = 0,
    verbose = TRUE
  )

## End(Not run)
```

ess	<i>Calculates the averaged effective sample sizes for mimids/wimids objects</i>
-----	---

Description

[Experimental]

Calculates the averaged effective sample sizes for imputed and matched or weighted datasets resulting from `MatchThem::matchthem(mimids objects)` or `MatchThem::weightthem(wimids objects)`

Usage

```
ess(object = NULL, decimals = 2)
```

Arguments

object	mimids or data.frame object from <code>complete(..., action = 'long', all = TRUE, ...)</code>
decimals	decimals to round for averaged effective sample size (default is 2 decimals)

Details

Matching or weighting across imputed datasets with partially observed covariates leads to slightly differenmatched or weighted cohorts with different sample sizes for each imputed dataset.

To account for this in the descriptive reporting of the effective sample size used in our analysis, this function computes the averaged effective sample sizes across all matched or weighted cohorts.

This function is a wrapper around the [bal.tab](#) function of the cobalt R package which performs these computations. For more information on how the effective sample sizes are computed.

Value

tibble with sample size information by treatment indicator

See Also

[bal.tab](#)

<https://ngreifer.github.io/cobalt/reference/bal.tab.html>

Examples

```
## Not run:

if(require("smdi") & require("MatchThem")){

  library(smdi)
  library(mice)
  library(MatchThem)
  library(encore.io)

  mids <- mice(smdi_data, printFlag = F)

  fit <- as.formula(exposure ~ age_num + female_cat + ecog_cat + egfr_cat + pdl1_num)
  wimids <- weightthem(fit, mids)

  ess(wimids, decimals = 1)

}

## End(Not run)
```

gt_tbl_compact

Utility function for a more compact look of gt tables

Description**[Experimental]**

Is a convenience utility function to make gt tables look more compact as compared to the default size and spacing.

#' @seealso [gt theme_gtsummary_compact](#)

Usage

```
gt_tbl_compact(gt_tbl = NULL, font_size = 13)
```

Arguments

```
gt_tbl      gt table object
font_size   numeric, desired font size (default is 13)
```

Value

gt table in compact format

Examples

```
library(encore.io)
library(gt)

head(iris) |>
gt() |>
gt_tbl_compact()
```

icd_metastases	<i>ICD-10-CM to ICD-9-CM equivalence crosswalk table</i>
----------------	--

Description

ICD-10-CM to ICD-9-CM equivalence crosswalk table

Usage

```
icd_metastases
```

Format

```
icd_metastases:
ICD-10-CM to ICD-9-CM equivalence crosswalk for secondary malignancy codes taken from
NBER
icd10cm ICD-10-CM code
icd9cm Mapped ICD-9-CM code
approximate Approximate map flag - identifies entries where the complete meaning of the source
system code and that of the target system code are not considered equivalent
no_map No map flag - distinguishes entries where the source system code has at least one trans-
lation from entries where the source system code has no target system translation
sites Organ site description ...
```

Source

<https://www.nber.org/research/data/icd-9-cm-and-icd-10-cm-and-icd-10-pcs-crosswalk-or-general-6>

imputation_workflow	<i>Streamlines the imputation workflow</i>
---------------------	--

Description

This function streamlines the imputation workflow from an eligible cohort with missings to an imputed mids object with only a subset of the key covariates and computed ropro

Usage

```
imputation_workflow(
  ard_eligible = NULL,
  database = NULL,
  cancer = NULL,
  covars_for_imputation = NULL
)
```

Arguments

ard_eligible	data frame with all eligible patients and covariates needed for imputation
database	character, which database is used ("edb1", "edb2", "edb3" or "edb4")
cancer	character, which cancer is investigated ("aNSCLC", "MetastaticBreast", "Early-Breast", "MetastaticCRC", "MultipleMyeloma")
covars_for_imputation	character vector with covariates for imputation (should include covariates for propensity score, treatment, outcome and optionally other auxiliary covariates)

Details

...

Value

imputed mids object with ROPRO

Examples

```
## Not run:
if(require("smdi")){

  library(encore.io)

  mids_data <- imputation_workflow(
    ard_eligible,
    database = "edb1",
    cancer = "aNSCLC",
    covars_for_imputation = c("dem_age_index", "dem_sex")
  )

}

## End(Not run)
```

km_pooling

*Pooled Kaplan-Meier estimate and survival curve***Description**

Computes pooled median survival Kaplan-Meier estimates using Rubin's rule and outputs corresponding Kaplan-Meier curve across imputed and matched/weighted datasets

Usage

```
km_pooling(
  object = NULL,
  surv_formula = as.formula(survival::Surv(eventtime, status) ~ exposure)
)
```

Arguments

`object` imputed and matched (mimids) or weighted (wimids) object
`surv_formula` specification of survival model formula to be fitted

Details

The function requires an object of class mimids or wimids, which is the output of a workflow that requires imputing multiple (m) datasets using mice or amelia and matching or weighting each imputed dataset via the MatchThem package (see examples).

The function fits the pre-specified survfit model (`surv_formula`) to compute survival probabilities at each individual time point according to the Kaplan-Meier method. For matched and weighted datasets, weights, cluster membership (matching only) and robust variance estimates are considered in the `survfit` call by default.

Since survival probabilities typically don't follow normal distributions, these need to be transformed to approximate normality first before pooling across imputed datasets and time points. To that end, survival probabilities are first transformed using a complementary log-log transformation ($\log(-\log(1-\text{pr}(\text{surv})))$) as recommended by multiple sources (Marshall, Billingham, and Bryan (2009)).

To pool the transformed estimates across imputed datasets and time points, the `pool.scalar` function is used to apply Rubin's rule to combine pooled estimates (\bar{q}) according to formula (3.1.2) Rubin (1987) and to compute the corresponding total variance (t) of the pooled estimate according to formula (3.1.5) Rubin (1987).

The pooled survival probabilities are then back-transformed via $1-\exp(-\exp(\bar{q}))$ for pooled survival probability estimates and $1-\exp(-\exp(\bar{q} \pm 1.96\sqrt{t}))$ for lower and upper 95% confidence intervals. As the formula indicates, the pooled standard error is computed as the square root of the total variance. The vertically stacked table with transformed and backtransformed estimates is returned with the `km_survival_table` table.

Finally, the median survival time is extracted from the `km_survival_table` table by determining the time the survival probability drops below .5 for the first time. For this a sub-function of Terry M. Therneau's `print.survfit` function is used. Therneau also considers some edge cases/nuisances ($x = \text{time}$, $y = \text{surv}$):

- Nuisance 1: if one of the y's is exactly .5, we want the mean of the corresponding x and the first x for which y<.5. We need to use the equivalent of all.equal to check for a .5 however: `survfit(Surv(1:100)~1)` gives a value of .5 + 1.1e-16 due to roundoff error.
- Nuisance 2: there may be an NA in the y's
- Nuisance 3: if no y's are <=.5, then we should return NA
- Nuisance 4: the obs (or many) after the .5 may be censored, giving a stretch of values = .5 +- epsilon

More references:

- <https://stefvanbuuren.name/fimd/sec-pooling.html>
- <https://link.springer.com/article/10.1007/s10198-008-0129-y>
- <https://bmcmmedresmethodol.biomedcentral.com/articles/10.1186/s12874-015-0048-4>

Value

list with pooled median survival estimate and pooled Kaplan-Meier curve `km_median_survival`:

- `strata` = stratum
- `t_median` = median survival time
- `t_lower` = lower 95% CI of median survival time
- `t_upper` = upper 95% CI of median survival time

`km_survival_table`:

- `strata` = stratum
- `time` = observed time point
- `m` = number of imputed datasets
- `qbar` = pooled univariate estimate of the complementary log-log transformed survival probabilities, see formula (3.1.2) Rubin (1987)
- `t` = total variance of the pooled univariate estimate of the complementary log-log transformed survival probabilities, formula (3.1.5) Rubin (1987)
- `se` = total standard error of the pooled estimate (derived as `sqrt(t)`)
- `surv` = back-transformed pooled survival probability
- `lower` = Wald-type lower 95% confidence interval of back-transformed pooled survival probability
- `upper` = Wald-type upper 95% confidence interval of back-transformed pooled survival probability

`km_plot`: `ggplot2` object with Kaplan-Meier curve

See Also

[survfit.pool.scalar.matchthem.weightthem](#)

Examples

```

if(require("MatchThem")){

  library(smdi)
  library(mice)
  library(MatchThem)
  library(encore.io)

  # impute data
  set.seed(42)
  mids <- mice(smdi_data[1:500, ], m = 2, printFlag = FALSE)

  # fit a propensity score model
  fit <- as.formula(exposure ~ age_num + female_cat + ecog_cat + egfr_cat + pdl1_num)

  # weight (or alternatively match) patients within each imputed dataset
  wimids <- weightthem(
    formula = fit,
    datasets = mids,
    approach = "within",
    method = "glm",
    estimand = "AT0"
  )

  # specify survival model
  km_fit <- as.formula(survival::Surv(eventtime, status) ~ exposure)

  # estimate and pool median survival times and Kaplan-Meier curve
  km_out <- km_pooling(
    object = wimids,
    surv_formula = km_fit
  )

  # median survival time
  km_out$km_median_survival

  # KM curve
  km_out$km_plot
}

```

labs_mapping_edb1

Lookup table for unique lab test observations

Description

Lookup table for unique lab test observations

Usage

```
labs_mapping_edb1
```

Format

labs_mapping_edb1:
 Lookup table for unique lab test and unit combinations in EDB1

test Test name as found in data
testunitscleaned Harmonized test unit
n N observed
ropro Is vital sign deemed to be prognostic
lab_name_clean Harmonized variable name
unit_clean Harmonized variable unit
lower_implausible_li Lower implausible threshold
upper_implausible_li Upper implausible threshold ...

labs_mapping_edb2	<i>Lookup table for unique lab test observations</i>
-------------------	--

Description

Lookup table for unique lab test observations

Usage

labs_mapping_edb2

Format

labs_mapping_edb2:
 Lookup table for unique lab test and unit combinations in EDB2

database Database
lab_name Test name as found in data
unit Unit for test name as found in data
n N observed
ropro Is vital sign deemed to be prognostic
lab_name_clean Harmonized variable name
unit_clean Harmonized variable unit
conversion_factor Conversion factor to multiply with to get standardized unit
comment Comment
lower_implausible_li Lower implausible threshold
upper_implausible_li Upper implausible threshold ...

labs_mapping_edb3	<i>Lookup table for unique lab test observations</i>
-------------------	--

Description

Lookup table for unique lab test observations

Usage

labs_mapping_edb3

Format

labs_mapping_edb3:
Lookup table for unique lab test and unit combinations in EDB3
database Database
lab_name Test name as found in data
unit Unit for test name as found in data
n N observed
ropro Is vital sign deemed to be prognostic
lab_name_clean Harmonized variable name
unit_clean Harmonized variable unit
comment Comment
lower_implausible_li Lower implausible threshold
upper_implausible_li Upper implausible threshold ...

labs_mapping_edb4	<i>Lookup table for unique lab test observations</i>
-------------------	--

Description

Lookup table for unique lab test observations

Usage

labs_mapping_edb4

Format

labs_mapping_edb4:
Lookup table for unique lab test and unit combinations in EDB4
database Database
lab_name Test name as found in data
n N observed
unit Unit for test name as found in data
ropro Is vital sign deemed to be prognostic

lab_name_clean Harmonized variable name
unit_clean Harmonized variable unit
conversion_factor Conversion factor to multiply with to get standardized unit
comment Comment
lower_implausible_li Lower implausible threshold
upper_implausible_li Upper implausible threshold ...

labs_mapping_implausible_values

Threshold table for plausible value ranges for selected labs

Description

Threshold table for plausible value ranges for selected labs

Usage

labs_mapping_implausible_values

Format

labs_mapping_implausible_values:

Thresholds for plausible value ranges for selected labs in a given unit; list was developed as part of the ENCORE project together with physicians from Dana-Farber Cancer Institute and MassGeneralBrigham

lab_name_clean Harmonized lab variable name as derived in the fh_get_labs() function

lower_implausible_limit Lower implausible threshold

upper_implausible_limit Upper implausible threshold ...

n_fmt

Quickly format numbers

Description

format raw numeric numbers into formatted characters including large decimal "," and small decimal "."

Usage

n_fmt(x, n_digits = 2)

Arguments

x number

n_digits integer, number of digits after comma

Details

...

Value

a character of the formatted numbers

Examples

```
## Not run:
library(encore.io)
n_fmt(12345678)

## End(Not run)
```

power_survival	<i>Power analysis for proportional hazards models</i>
----------------	---

Description

Function computes implementations of sample-Size Formula for the Proportional-Hazards Regression Model for the statistical power of a two arm treatment comparison as described by David A. Schoenfeld (Biometrika 1983)

Usage

```
power_survival(
  beta = NULL,
  alpha = NULL,
  p_exposed = NULL,
  n_events = NULL,
  hr = NULL
)
```

Arguments

beta	numeric, beta percentiles of the normal distribution (type II error rate;)
alpha	numeric, 1-alpha percentiles of the normal distribution (type I error rate)
p_exposed	numeric, proportion of exposed patients
n_events	numeric, number of events
hr	numeric, hazard ratio

Details

One parameter can be left undefined (except p_exposed) which is the computed using an implementation of David A. Schoenfeld's (Biometrika 1983) formula.

Value

integer representing the undefined parameter

See Also

Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. *Biometrics* 1983;39:499-503.

<https://www.jstor.org/stable/2531021>

Examples

```
library(encore.io)

power_survival(
  alpha = 0.05,
  beta = 0.2,
  p_exposed = 0.5,
  hr = 0.8
)
```

ps_balance_plot

Computes and visualizes the overlap for distance measures between exposure groups

Description

#' **[Deprecated]** Calculates the the overlap for distance measures (e.g., propensity or prognostic scores) between exposure groups for multiple imputed and matched datasets.

Usage

```
ps_balance_plot(
  object = NULL,
  exposure = "treat",
  weights = "weights",
  ps = "distance"
)
```

Arguments

object	mimids or data.frame object from complete(..., action = 'long', all = TRUE, ...)
exposure	character, quoted name of the exposure/treatment variable
weights	character, quoted name of the variable indicating the matching weights (usually 0: unmatched and 1: matched)
ps	character, quoted name of the variable with the distance measure (e.g., propensity score)

Details

The object input needs to be a mimids object or a data.frame object coming from MatchThem::matchthem(). If the mimids object is already converted to a long data.frame of stacked imputed datasets, the MatchThem::complete() function needs to be completed using action = "long" and all = TRUE arguments.

The function then creates two stacked datasets (unmatched/all and matched only) patients and combines the propensity score across all imputed datasets into a single graph.

Value

ggplot object

Examples

```
## Not run:
library(encore.io)

ps_balance_plot(
  object = edbl_mimids,
  exposure = "treat",
  ps = "distance"
)

## End(Not run)
```

 qc_assertive_line_check

Assertive line of therapy checks

Description

Assertive line of therapy checks to make sure that patients in an advanced line of treatment also received a previous line. Important: input dataframe needs to have a one line per patient per line of therapy format.

Usage

```
qc_assertive_line_check(
  data = NULL,
  id_col = NULL,
  linenummer_col = NULL,
  linename_col = NULL
)
```

Arguments

data	dataframe including line number and line treatment
id_col	quoted character specifying the column name of the patient identifier
linenummer_col	quoted character specifying the column name of the line number
linename_col	quoted character specifying the column name of the line name/treatment

Details

...

Value

a table/dataframe with the logical results (TRUE/FALSE) of the assertive checks.

Examples

```
## Not run:
library(encore.io)

## End(Not run)
```

re_weight	<i>Custom function to perform matching/weighting and re-weighting to match a target patient population</i>
-----------	--

Description

Custom function to perform matching/weighting and re-weighting to match a target patient population

Usage

```
re_weight(x, targets = NULL, matching_weighting = NULL, ...)
```

Arguments

x	data.frame or mild object/list of data.frames if used in combination with lapply
targets	named list of all target values for the raking procedure (see anesrake)
matching_weighting	character, one of "matching" or "weighting"
...	other arguments and specifications to propagate on to matchit or weightit , depending on chosen method (matching_weighting).

Details

This function is a wrapper for [matchit](#) and [weightit](#) in combination with [anesrake](#).

The function performs any matching algorithm supplied in [matchit](#) or any weighting algorithm in [weightit](#). The specific arguments can be propagated to the respective functions using the ... argument.

If nothing is specified for targets, the function will simply return the [matchit](#) or [weightit](#) object.

If a list of target distributions is specified for targets, the function will perform a corresponding re-weighting of matched patients or patients with weights greater than 0, respectively.

In case of an already weighted datasets (e.g., via propensity score-derived weights), those weights are accounted for (weightvec argument) in the [anesrake](#) call.

Value

an object of type [matchit](#) or [weightit](#) with included sampling weights (s.weights) if re-weighting was performed.

See Also

[matchit](#) [weightit](#) [anesrake](#)

Examples

```

if(require("MatchThem") & require("mice")){

  library(encore.io)
  library(dplyr)
  library(mice)
  library(MatchThem)

  data_miss <- simulate_flaura(
    n_total = 3500,
    seed = 41,
    include_id = FALSE,
    imposeNA = TRUE,
    propNA = .33
  ) |>
  # anesrake works best with factor variables
  # convert c_smoking_history into a factor
  mutate(c_smoking_history = factor(ifelse(c_smoking_history == TRUE, "Current/former", "Never")))

  # impute data
  data_imp <- mice(
    parallelseed = 42,
    n.core = 7,
    data = data_miss,
    m = 5,
    print = FALSE
  )

  # define covariates for propensity score model
  covariates <- data_miss |>
    select(starts_with("c_"), starts_with("dem_")) |>
    colnames()

  # define propensity score model
  ps_form <- as.formula(paste("treat ~", paste(covariates, collapse = " + ")))

  # create a mild object containing lists of data.frames
  data_mild <- mice::complete(data = data_imp, action = "all", include = FALSE)

  smoker_target <- c(.35, .65)
  names(smoker_target) <- c("Current/former", "Never")

  # summarize target distributions in a named list vector -----
  targets <- list(smoker_target)
  names(targets) <- c("c_smoking_history")

  # create a mild object containing lists of data.frames
  data_mild <- mice::complete(data = data_imp, action = "all", include = FALSE)

  # call re-weight
  matchit_out_list <- lapply(
    X = data_mild,
    FUN = re_weight,
    targets = targets,
    matching_weighting = "matching",
    # arguments passed on to matchit

```

```

    formula = ps_form,
    ratio = 1,
    method = "nearest",
    distance = "glm",
    link = "logit",
    caliper = 0.01,
    replace = FALSE
  )

  # convert the output back into a mimids object
  data_mimids_from_function <- MatchThem::as.mimids(
    x = matchit_out_list,
    datasets = data_imp
  )

  # print
  data_mimids_from_function
}

```

ropro_aNSCLC_covars *aNSCLC-specific ROPRO covariate vector*

Description

aNSCLC-specific ROPRO covariate vector

Usage

ropro_aNSCLC_covars

Format

ropro_aNSCLC_covars:
Covariate vector with harmonized covariate names for aNSCLC-specific ROPRO

ropro_covars_log_log_transform
Covariate vector of covariates that are log-log-transformed

Description

Covariate vector of covariates that are log-log-transformed

Usage

ropro_covars_log_log_transform

Format

ropro_covars_log_log_transform:
Covariate vector of covariates that are log-log-transformed

ropro_covars_log_transform

Covariate vector of covariates that are log-transformed

Description

Covariate vector of covariates that are log-transformed

Usage

ropro_covars_log_transform

Format

ropro_covars_log_transform:

Covariate vector of covariates that are log-transformed

ropro_earlyBreast_covars

early Breast-specific ROPRO covariate vector

Description

early Breast-specific ROPRO covariate vector

Usage

ropro_earlyBreast_covars

Format

ropro_earlyBreast_covars:

Covariate vector with harmonized covariate names for early Breast-specific ROPRO

ropro_mBreast_covars *metastatic Breast-specific ROPRO covariate vector*

Description

metastatic Breast-specific ROPRO covariate vector

Usage

ropro_mBreast_covars

Format

ropro_mBreast_covars:

Covariate vector with harmonized covariate names for metastatic Breast-specific ROPRO

ropro_mCRC_covars	<i>metastatic CRC-specific ROPRO covariate vector</i>
-------------------	---

Description

metastatic CRC-specific ROPRO covariate vector

Usage

ropro_mCRC_covars

Format

ropro_mCRC_covars:

Covariate vector with harmonized covariate names for metastatic CRC-specific ROPRO

ropro_MM_covars	<i>MM-specific ROPRO covariate vector</i>
-----------------	---

Description

MM-specific ROPRO covariate vector

Usage

ropro_MM_covars

Format

ropro_MM_covars:

Covariate vector with harmonized covariate names for MMspecific ROPRO

ropro_pan_tumor_covars	<i>Pan-tumor ROPRO covariate vector</i>
------------------------	---

Description

Pan-tumor ROPRO covariate vector

Usage

ropro_pan_tumor_covars

Format

ropro_pan_tumor_covars:

Covariate vector with harmonized covariate names for pan-tumor ROPRO

ropro_pan_tumor_covars_categorical

Pan-tumor ROPRO covariate vector (modified for categorical covariates)

Description

Pan-tumor ROPRO covariate vector (modified for categorical covariates)

Usage

```
ropro_pan_tumor_covars_categorical
```

Format

ropro_pan_tumor_covars_categorical:

Covariate vector with harmonized covariate names for pan-tumor ROPRO. Age, sex and ECOG are included as a trurly categorical (factor) variable

simulate_flaura

Simulates and artifical FLAURA EHR-derived dataset

Description

Parameterized function to quickly create an artificial FLAURA EHR-derived analytic cohort for analytic code development.

Usage

```
simulate_flaura(
  n_total = 3500,
  seed = 42,
  include_id = TRUE,
  imposeNA = TRUE,
  propNA = NULL
)
```

Arguments

n_total	integer, number of total patients
seed	integer, seed for reproducibility
include_id	logical, include a generated patientid variable
imposeNA	logical, set covariates to missing
propNA	numeric, proportion of missingness, needs to be between 0 and 1

Details

...

Value

data frame with simulated analytic cohort

Examples

```
## Not run:
library(encore.io)

data_miss <- simulate_flaura(
  n_total = 3500,
  seed = 41,
  include_id = FALSE,
  imposeNA = TRUE,
  propNA = .33
)

head(data_miss)

## End(Not run)
```

state_region_mapping *A mapping between US States and geographical regions*

Description

A mapping between US States and geographical regions

Usage

```
state_region_mapping
```

Format

```
state_region_mapping:
A mapping between US States and geographical regions
state US State
dem_region Mapped geographical region ...
```

vitals_mapping_edb1 *Lookup table for unique lab test observations*

Description

Lookup table for unique lab test observations

Usage

```
vitals_mapping_edb1
```

Format

vitals_mapping_edb1:
 Lookup table for unique lab test and unit combinations in EDB1
test Test name as found in data
testunitscleaned Harmonized test unit
n N observed
ropro Is vital sign deemed to be prognostic
vital_name_clean Harmonized variable name
unit_clean Harmonized variable unit
conversion_factor Factor to convert vital sign measurement to harmonized unit
comment Comment
lower_implausible_li Lower implausible threshold
upper_implausible_li Upper implausible threshold ...

vitals_mapping_edb2 *Lookup table for unique lab test observations*

Description

Lookup table for unique lab test observations

Usage

vitals_mapping_edb2

Format

vitals_mapping_edb2:
 Lookup table for unique lab test and unit combinations in EDB2
vital_name Vital test name as found in data
vital_name_clean Harmonized variable name
lower_implausible_li Lower implausible threshold
upper_implausible_li Upper implausible threshold ...

vitals_mapping_edb3 *Lookup table for unique lab test observations*

Description

Lookup table for unique lab test observations

Usage

vitals_mapping_edb3

Format

vitals_mapping_edb3:

Lookup table for unique lab test and unit combinations in EDB3

database Database

test_category Test category

vital_name Test name as found in data

vital_unit Harmonized test unit

n N observed

ropro Is vital sign deemed to be prognostic

vital_name_clean Harmonized variable name

unit_clean Harmonized variable unit

conversion_factor Factor to convert vital sign measurement to harmonized unit

comment Comment

lower_implausible_li Lower implausible threshold

upper_implausible_li Upper implausible threshold ...

vitals_mapping_edb4	<i>Lookup table for unique lab test observations</i>
---------------------	--

Description

Lookup table for unique lab test observations

Usage

vitals_mapping_edb4

Format

vitals_mapping_edb4:

Lookup table for unique lab test and unit combinations in EDB4

vital_name Test name as found in data

vital_name_clean Harmonized variable name

unit_clean Harmonized variable unit

lower_implausible_li Lower implausible threshold

upper_implausible_li Upper implausible threshold ...

`vitals_mapping_implausible_values`*Threshold table for plausible value ranges for selected vital sign measurements*

Description

Threshold table for plausible value ranges for selected vital sign measurements

Usage

```
vitals_mapping_implausible_values
```

Format

```
vitals_mapping_implausible_values:
```

Thresholds for plausible value ranges for selected labs in a given unit; list was developed as part of the ENCORE project together with physicians from Dana-Farber Cancer Institute and MassGeneralBrigham

vital_name_clean Harmonized vitals variable name as derived in the `fh_get_vitals()` function

lower_implausible_limit Lower implausible threshold

upper_implausible_limit Upper implausible threshold ...

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