NDRS
NATIONAL DISEASE REGISTRATION SERVICE

NHS England

Counting Haematological Malignancies and Haematological Malignancy Transformations

An NDRS Standard Operating Procedure (SOP)

2023-05-17

Version 2.0

About the NDRS

The National Disease Registration Service (NDRS) is part of NHS England. Its purpose is to collect, collate and analyse data on patients with cancer, congenital anomalies, and rare diseases. It provides robust surveillance to monitor and detect changes in health and disease in the population. NDRS is a vital resource that helps researchers, healthcare professionals and policy makers make decisions about NHS services and the treatments people receive.

The NDRS includes:

- the National Cancer Registration and Analysis Service (NCRAS) and
- the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

Healthcare professionals, researchers and policy makers use data to better understand population health and disease. The data is provided by patients and collected by the NHS as part of their care and support. The NDRS uses the data to help:

- understand cancer, rare diseases, and congenital anomalies
- improve diagnosis
- plan NHS services
- improve treatment
- evaluate policy
- improve genetic counselling

NDRS
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1. Summary of how to count haematological malignancies

In general for most cancers, when counting the incidence of cancer we count the number of rows in AT_TUMOUR. Usually one new diagnosis of cancer is the same as one new primary tumour and is also the same as one row in the table.

This does not currently work for haematological malignancies because of the existence of transformations. 'What are transformations and why is our data confused around them' is explained in more detail in Section 4, but broadly some patients have haematological malignancies that are initially diagnosed as one type of malignancy but then develop over time into a nastier / more aggressive malignancy. These subsequent malignancies are not an independent new malignancy, but 'transformations' of the earlier malignancy. In our data some rows in AT_TUMOUR are primary haematological malignancies, and some are haematological transformations. If you just count the rows you inflate the count by counting the transformations as well as the true primary malignancies.

To count the number of new primary haematological malignancies (which is the number you usually want for incidence rates and similar) you need to take all the haematological malignancies in AT_TUMOUR, but exclude the rows that are transformations. Code to do this is given in Appendix A. 'How to define a haematological malignancy' is explained in more detail in Section 3.

To count the number of haematological transformations you need to use the table, AT_TRANSFORMATION_HAEM. One row in this table is one transformation and it can be counted straightforwardly. Code to do this is given in Appendix B. The code that creates the table, including comments that explain how it works, is given in Appendix C.

We hope to be able to work with the CAS team to take the secondary tumours resulting from a transformation out of AT_TUMOUR, which will make counting primary haematological tumours easier again, but until this is done this SOP should be followed.

This problem is largest for years prior to 2018 (when a change in how we record transformations happened, see section 4 for more details). Following this SOP correctly makes a difference of approximately 3% to the total number of primary haematological malignancies for 2017 (there are 36,003 haematological malignancies recorded from CAS counts, 34,914 excluding transformations). The main differences are for Acute myeloid leukaemia (AML) (2,862 from CAS counts, 2,246 excluding transformations, a reduction of 27%) and Diffuse large B-cell lymphoma (DLBCL) (4,918 from CAS counts, 4,564 excluding transformations, a reduction of 8%) [Numbers run on CAS2210.]

The purpose of this SOP is to provide a method of counting primary haematological malignancies, and haematological malignancy transformations separately for diagnoses

from 2013. We believe the transformations table *AT_TRANSFORMATION_HAEM* is working well for identifying transformations from 2013 onwards, and have published 2013-2020 numbers in the Get Data Out publication. If you want to count haematological malignancies for years before the creation of a single NDRS (i.e., pre 2013) we recommend you talk to the haematology lead.

2. An aside on terminology

This SOP talks about 'haematological malignancies'. The term 'blood cancers' is often commonly used by organisations such as Cancer Research UK. The National Statistics talk about 'new diagnoses of cancer' or 'incidence of cancer' and many of the other NDRS documentation talks about 'new primary tumours'.

'Tumour' v's 'Cancer' v's 'Malignancy'

Most cancers are solid tumours. This is not the case for haematological cancers. Cancers like leukaemia are characterised by an abnormally large number of white blood cells, but they do not form a solid lump or growth like a breast tumour or a lung tumour. Therefore referring to 'tumours' when talking about haematological malignancies can be misleading.

Some of the conditions included in 'haematological malignancies' are behaviour 1 in ICD O3 rev 2011[1] and may not be generally referred to as 'cancer' (e.g., mastocytomas)

In general 'malignancies' can be a more accurate term than 'tumours' or 'cancers' for these conditions.

'Haematological' v's 'blood'

The two terms can be used fairly interchangeably, but 'haematological' is preferred in NDRS work. Some of the conditions do form solid tumours (e.g., lymphomas) – although these are a type of blood cancer, some people use 'blood cancer' to mean cancer that does not form a solid tumour, so 'haematological' is felt to be clearer.

[1] Fritz A, Percy C, Jack A, et al. (2013) *International Classification of Diseases for Oncology*. 3rd ed. First revision. Geneva: WHO Press

3. Defining haematological malignancies

After working with clinicians and coding experts, a standard list of morphology and behaviour codes that define 'haematological malignancies' has been produced.

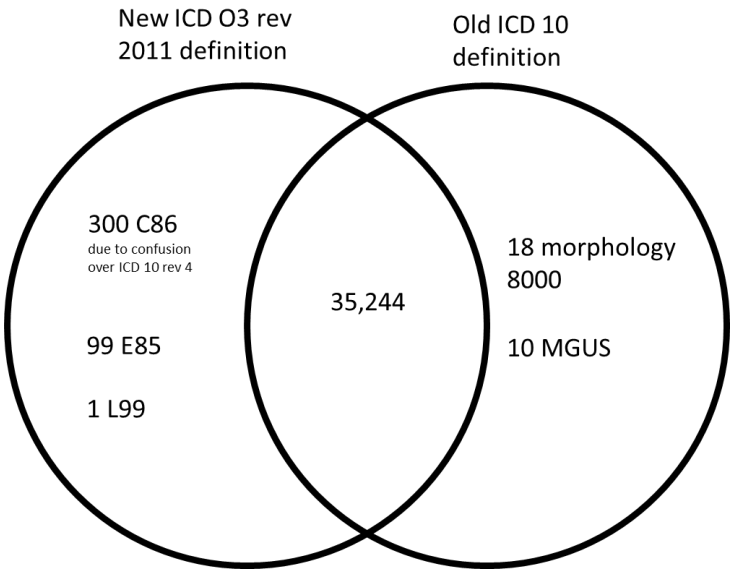
This is a list of 157 pairs of codes (a morphology code and a behaviour code, making a unique pair) coded in ICD O3 rev 2011. These codes can be found in the table ANALYSISHANHUALIU.GDO_MORPH_HAEM@CASREF01 (which we expect to move to GDO.MORPH_HAEM@CASREF01 soon). They are repeated in Appendix D.

These codes are in agreement with the WHO definitions of haematological malignancies.

To find a cohort of all haematological malignancies, take all the registered malignancies from the CAS, apply the usual counting cancer cases SOP rules for age, gender, geography etc, and inner join to this table on morphology and behaviour so only the haematological ones remain. Do not limit your cohort to only malignancies that are C codes in ICD 10, as some of the haematological malignancies are D codes (and a few are E and L codes!).

This method gives very similar answers to the old method of defining haematological malignancies using ICD 10 codes. This used to define All Blood Cancer as ICD 10 C81-C85, C88, C90-C96, D45-D47.

Comparing these definitions we see that the differences are very small (numbers run for 2019 on CAS2210 as the most recent finalised year not affected by the pandemic).



The new definition remembers to include C86, which only exists as a code in ICD 10 rev 4. It also picks up about 100 cancers that do not get C or D codes in ICD 10, but are haematological malignancies – these are immunoglobulin deposition disease. The new definition excludes 18 poorly coded tumours, which have the very generic morphology code 8000 for 'neoplasm' and so we do not truly know what they are, and also excludes 10 Monoclonal gammopathy of undetermined significance (MGUS; ICD O3 rev 2011 9765/1) tumours (which are not registrable conditions and should not be on the cancer registry at all).

The table ANALYSISHANHUALIU.GDO_MORPH_HAEM@CASREF01 also puts these codes into smaller meaningful groups for analysis of different types of haematological malignancies such as 'Acute myeloid leukaemia (AML)' and 'Hodgkin Lymphoma'. A more detailed description of what these groups are can be found in the document 'Haematological Malignancy Descriptions.docx'. These groupings should be the standard groupings used for any sub-analysis of haematological malignancies.

Once this cohort has been identified by ICD O3 rev 2011 morphology and behaviour codes, you will need to remove transformations to get a clean cohort of *primary* haematological cases. (See Section 4 and the code in Appendix A).

The code in Appendix A shows how to identify and count all haematological malignancies using this table, and also how to put them into the main groups of sub-types and remove transformations.

4. Transformations

Why is there a SOP on how to count haematological malignancies? The main answer is because of 'transformations' and because of a change that happened in registration in 2018.

Generally, for all cancers, cancer registration tries to register the primary tumour. For example if a patient has a lung cancer, and it sadly spreads to their brain, they are not registered with a lung cancer *and* a brain cancer, because the tumour in their brain is not a primary brain cancer. They are registered with one lung cancer, as that was the primary cancer. Similarly, if a patient has a breast cancer, and it is treated but sadly grows back five years later, the patient is registered with one breast cancer, not two breast cancers. Most relevantly, if a patient was diagnosed with a stage 1 cancer, and despite treatment it kept growing and became a stage 3 cancer, we would not make two registrations, one for the stage 1 cancer and one for the stage 3 cancer, because it would be the same cancer.

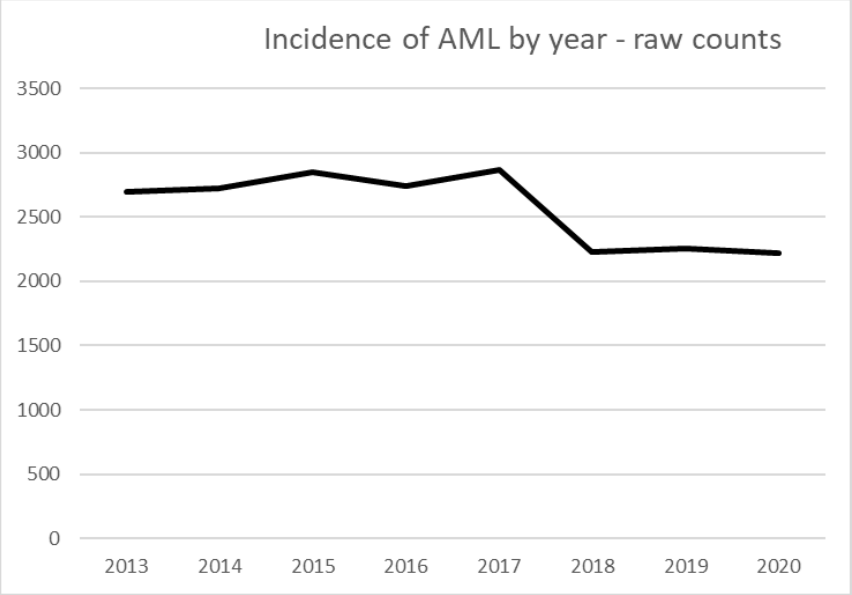
This causes problems with haematology, where malignancies can 'get worse' and get new names, but are still broadly the same malignancy. The most common example of this is Myelodysplastic syndrome (MDS) transforming to Acute myeloid leukaemia (AML). These are both diseases where there is a problem with immature blood cells, 'blasts', in the bone marrow. AML is generally diagnosed when there is involvement of more than 20% of the blood and/or bone marrow by leukaemic myeloblasts. Not all MDS transforms to AML, and not all AML is preceded by a diagnosis of MDS, but sometimes MDS can 'get worse' and it can transform to AML. In this case it makes more sense to think of this as the earlier MDS diagnosis transforming / progressing than it does to think of the patient as having two independent unrelated malignancies.

Because of this we changed the way the registry records haematological transformations in 2018. For diagnosis years before 2018, if a patient had MDS *and* AML, we would make two registrations for two malignancies, as though they were separate unrelated malignancies.

In 2018, following European Network of Cancer Registry guidelines[2] and an improved understanding of transformations, we stopped registering these cases as two separate malignancies. This means that for patients with a haematological malignancy transformation (e.g., MDS followed by AML) if two patients had an identical pair of malignancies, the number of tumours reported in AT_TUMOUR made a sudden change in 2018:

First tumour	Second tumour	Number of rows in AT_TUMOUR
Before 2018	Before 2018	2 rows
Before 2018	2018 onwards	1 row
2018 onwards	2018 onwards	1 row

You can see the effect of this if you do a naïve count of the number of cases of AML by year in the AT_TUMOUR table, there is a large drop between 2017 and 2018.



The transformation is still registered, but it is not registered as a new tumour – it is registered as a 'transformation event' on the primary tumour. This event is recorded in the SPRINGMVC3.TRANSFORMATION table.

[2] Gavin A, Rous B, Marcos-Gragera R, et al. Towards optimal clinical and epidemiological registration of haematological malignancies: Guidelines for recording progressions, transformations and multiple diagnoses. European Journal of Cancer 2015; 51: 1109–1122.
https://doi.org/10.1016/j.ejca.2014.02.008
https://encr.eu/sites/default/files/Recommendations/Gavin_2015_HM_coding.pdf

To correct for this, we have attempted to identify all transformations in a unified table for analysts to use: AT_TRANSFORMATION_HAEM. We have done this in two ways:

- Any transformation event registered as a transformation event is included in AT_TRANSFORMATION_HAEM
- For any pair of malignancies where the second malignancy appears to be a transformation from the first malignancy (e.g., AML following MDS), the second malignancy is included in the transformation table. The definition of which pairs of tumours count as a transformation is taken from the Gavin et al paper *'Towards optimal clinical and epidemiological registration of haematological malignancies: Guidelines for recording progressions, transformations and multiple diagnoses'*

The second part of this requires knowing what both registered malignancies are. We have a definition of haematological transformations in both ICD O2 and ICD O3 rev 2011. This allows us to find pairs of malignancies that impute a transformation when the earlier malignancy has been registered any time from 1995 onwards. However, prior to 1995 our data is only coded in ICD 9. We do not have a look up for valid first malignancies (precursor conditions) in ICD 9, and so our table does not capture these transformations. This has two main effects on the table

- Data for the years very near to the coding change will be very incomplete, and the majority of transformations will be missing. This is a major driver of why we do not recommend analysis of transformations before 2013.
- Transformations which have taken a very long time will be missing from our imputed transformations in later years. For example, if a malignancy first diagnosed in 1994 transforms in 2017, it is expected that this will be missing from the transformation table and miscounted as a new primary tumour. For 2018 onwards where transformations have been manually registered, whether or not transformations where the precursor condition was registered pre-1995 are recorded as a transformation will depend on how registration officers have recorded them, but good practice would now be to add these to the original primary tumour.

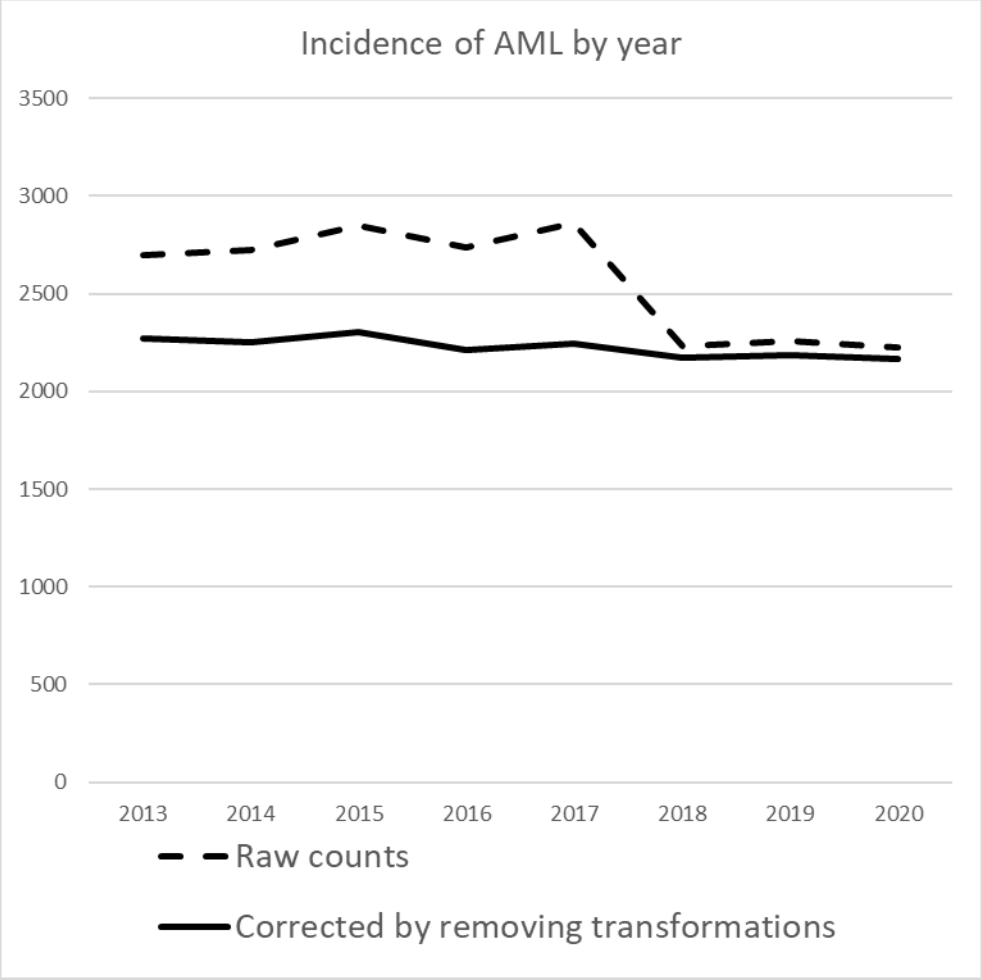
When building the AT_TRANSFORMATION_HAEM table, we discovered that for some patients the same transformation appeared to be recorded more than once. For example if there was a patient with MDS registered in 2014, and then AML registered in 2016 and AML registered again in 2017. Because of this we have added a flag to identify duplicates to the transformation table – the DEDUP flag. Transformations we believe are genuine are flagged '1' and duplicates are flagged '0'. This mirrors the DEDUP flag in the main AT_TUMOUR table.

We could not remove the duplicate transformations from this table entirely, as this table is used to remove transformations from the primary malignancies count in the code in Appendix A. If the duplicate transformations were removed from this table, the code to

count primary malignancies would not take them out, and so they would reappear inaccurately as primary malignancies.

The majority of transformations from 2018 are identified using the transformation event table. Because registering transformations is new and difficult and a manual process, currently there appear to be some cases in 2018 onwards where two tumours have been registered, but only one tumour should have been registered according to the rules. We are sending these to the QA team to review and fix, but we are also continuing to remove them as transformations in the code for the time being, as after discussions with Brian Rous this was felt to make the most accurate time series. If this was not the case, we would only need to apply the code to remove transformations for the years 2013-2017, but currently we are applying it for all years 2013 onwards.

If the transformations in the transformation table are removed from the count of AML (i.e., following the code in Appendix A) the timeseries is much steadier.



Full details of how the transformation table was built and the assumptions made can be found in the code in Appendix C.

Appendix A: Code to count primary haematological malignancies

Please note that at the time this SOP was written, some tables were still in personal tablespaces on the CAS. We will aim to update this SOP when these tables are moved, but if this code does not run, this would be the first thing I would check. We expect the following moves:

- The definition of haematological malignancies ANALYSISHANHUALIU.GDO_MORPH_HAEM@CASREF01 to move from Hanhua's space to the GDO space and become GDO.MORPH_HAEM@CASREF01
- The transformations table ANALYSISPOLLYJEFFREY.AT_TRANSFORMATION_HAEM@CAS2210 to move from Polly's space to the general analysis space ANALYSISNCR.AT_TRANSFORMATION_HAEM@CAS2210 or AV2020.AT_TRANSFORMATION_HAEM@CASREF01

Code

This is sample code to count the number of primary haematological malignancies in 2017 based on CAS2210 / av2020.

The main features are:

- an 'inner join' to define the haematological malignancies by the MORPH_HAEM table
- a 'not exists' to take out the transformations defined by the AT_TRANSFORMATION_HAEM table.

```
select
count(*)
from av2020.at_tumour_england@casref01 avt
inner join analysishanhualiu.gdo_morph_haem@casref01 hl on
avt.morph_icdo3rev2011=hl.morph_icdo3rev2011 and
avt.behaviour_icdo3rev2011=hl.behaviour --using the haem lookup
where
avt.diagnosisyear >= 2013 -- restrict to diagnoses of 2013 onwards
--excluding transformation events
and not exists (
select
ht.transformed_tumourid
from analysispollyjeffrey.at_transformation_haem@cas2210 ht
where
avt.tumourid=ht.transformed_tumourid
)
```

```
--below are CAS_SOP_Counting_cancer_cases.pdf rules
and avt.ctry_code ='E' -- England residents using country code
and avt.statusofregistration ='F' -- Finalised cases
and avt.dedup_flag=1 -- Excluding duplicates
and avt.age between 0 and 200 --Sensible age:age between 0 and 200
and avt.sex in (1,2) -- Known sex
and diagnosisyear = 2017 --restrict to diagnoses of 2017
;
```

The code can be tweaked for different years/different snapshots.

If you want to count more granular groups than 'all haematological malignancies' the 'SPLIT' columns can be used in the MORPH_HAEM table.

```
select
nvl(split_4, nvl (split_3, nvl (split_2, split_1))) as haem_type
, count(*)
from av2020.at_tumour_england@casref01 avt
inner join analysishanhualiu.gdo_morph_haem@casref01 hl on
avt.morph_icdo3rev2011=hl.morph_icdo3rev2011 and
avt.behaviour_icdo3rev2011=hl.behaviour --using the haem lookup
where
avt.diagnosisyear >= 2013 -- restrict to diagnoses of 2013 onwards
--excluding transformation events
and not exists (
select
ht.transformed_tumourid
from analysispollyjeffrey.at_transformation_haem@cas2210 ht
where
avt.tumourid=ht.transformed_tumourid
)
--below are CAS_SOP_Counting_cancer_cases.pdf rules
and avt.ctry_code ='E' -- England residents using country code
and avt.statusofregistration ='F' -- Finalised cases
and avt.dedup_flag=1 -- Excluding duplicates
and avt.age between 0 and 200 --Sensible age:age between 0 and 200
and avt.sex in (1,2) -- Known sex
and diagnosisyear = 2017 --restrict to diagnoses of 2017
group by nvl(split_4, nvl (split_3, nvl (split_2, split_1)))
order by count(*) desc
;
```

Appendix B: Code to count haematological transformations

Please note that at the time this SOP was written, some tables were still in personal tablespaces on the CAS. We will aim to update this SOP when these tables are moved, but if this code does not run, this would be the first thing I would check. We expect the transformations table ANALYSISPOLLYJEFFREY.AT_TRANSFORMATION_HAEM@CAS2210 to move from Polly's space to the general analysis space ANALYSISNCR.AT_TRANSFORMATION_HAEM@CAS2210 or AV2020.AT_TRANSFORMATION_HAEM@CASREF01

Also note that the haematological transformations table was designed to produce a cohort of English transformations. This means that currently this code has no restriction on geography (and the transformation table has no geography field). If we were to extend the transformations table to Welsh cases we would need to review how to identify these in the table.

Code

This is sample code to count the number of haematological transformations in 2017 based on CAS2210 / av2020.

```
select
count(*)
from analysispollyjeffrey.at_transformation_haem@cas2210
where
transformation_year = 2017 --restrict to transformations of 2017
and dedup_flag=1 -- Excluding duplicates
;
```

The main features are

- A dedup flag that removes duplicate transformations
- The implicit knowledge that all transformations are for English residents

The code can be tweaked for different years/different snapshots.

If you want to count more granular groups than 'all haematological transformations' the 'TRANSFORMATION_SPLIT' columns can be used. Transformation split 1 is what the haematological malignancy has transformed into (secondary malignancy), transformation split 2 is what the haematological malignancy transformed from (primary/precursor malignancy).

```
select
transformation_split_1, transformation_split_2, count(*)
from analysispollyjeffrey.at_transformation_haem@cas2210
where
transformation_year = 2017 --restrict to transformations of 2017
and dedup_flag=1 -- Excluding duplicates
group by transformation_split_1, transformation_split_2
order by transformation_split_1, transformation_split_2
;
```

Appendix C: Code to create the table of haematological transformations - AT_TRANSFORMATION_HAEM table

Generally we recommend you just *use* the table of transformations and do not try and rebuilt it from scratch unless you really need to. It was developed by Sally Vernon, Andrew Bacon, Charlotte Eversfield and Hanhua Liu, so if there are things in it you want to understand and don't, please feel free to ask them. The code is included here for transparency and in case someone needs to understand it in more detail in the future.

The code currently lives in the analysis svn in Analytical code repository\Haematology\AT_TRANSFORMATION_HAEM although we expect it to move into the standard CAS build soon.

There are comments in the code which should explain what it is doing and the assumptions it is making.

```
/*------------------------------------------------------------------------------
                            at_transformation_haem
------------------------------------------------------------------------------

    Creating a standard haematological transformations table for analysis

   By imputing transformations from 1995 onwards using the Gavin paper and
   counting transformations registered in the transformation table by NDRS

------------------------------------------------------------------------------

Development:
Tables were developed by Andrew Bacon, with clinical and pathological input from
Mark Bishton and Brian Rous. QA was performed by Sally Vernon.

This code is designed to produce a transformation table on any standard CAS
snapshot. Table was developed on CAS2109 and CAS2210. Producing this table on
end of year snapshots is important for correcting reporting incidence of
haematological malignancies.

------------------------------------------------------------------------------
--                                 Overview
------------------------------------------------------------------------------
--                          Motivation for this table

To date there is no uniform definition of the transformation of haematological
malignancies (Okosun et al., 2018). However, the basic principle of a
transformation is that a tumour cell, subject to a complex combination of
genetic mutations, can undergo a process of clonal evolution that profoundly
changes the architecture of the cell and results in a transformation to a
different tumour type (Gavin et al., 2015).
```

```
The key question is whether this transformed tumour is a new primary tumour
or a natural progression of the earlier tumour.If it is a new tumour, then two
tumour registrations would be made. If it is a progression of the earlier
tumour, then only one tumour registration would be made.

Prior to 2018 two tumour registrations were always made. From 2018 onwards, best
practice is to make one tumour registration and one transformation registration:

Changes to COSD rules and recording transformation events:
Following consultation with Laboratory Information Management System Suppliers
and the Chair of the Royal College of Pathologists (Working Group on Cancer
Services), alterations were made to the structure and contents of the COSD
dataset. Changes included the recording of transformation events, to conform to
the recommendations established by the European Network of Cancer Registration,
published in February 2014.

Previously, the national cancer registration and analysis service recorded a
transformation event as a new primary malignancy. As part of COSD v9.0, due for
release in April 2020, with full conformance expected by the 1st of July; the
option now exists to record a transformation event, in addition to recording a
relapse or new tumour. A transformation event can be recorded if the
haematological malignancy transforms into a new morphological entity (different
diagnostic group) three-months after the initial registration.

This change in practice causes a noticeable reduction in some primary tumours,
particularly AML (20% reduction in registered AML between 2017 and 2018)
In order to provide reliable haematolgoical time series
cases that would now be registered as transformations must be identified
so they can be removed from the primary tumour time series

This code produces a table of transformations and likely transformations.
Transformations can be counted annually and should be removed from the primary
tumour cohort.

--------------------------------------------------------------------------------
--                      Top level guide to the code
--------------------------------------------------------------------------------

Transformations are identified in one of two ways:

1) They are imputed from a pair of primary tumours
2) They are extracted from the ENCORE Transformations table

To do (1), we need to agree which pairs of primary tumours
suggest a transformation

For example, MDS followed by AML

We want to follow the transformation rules specified in the National Cancer
Registration and Analysis Service (NCRAS) Haematology guidance
as much as possible to do this

These rules come from the Gavin et al., (2015) paper. We have coded the Gavin et
al. paper up into a table:

            analysisandrewbacon.gdo_transformation_haem@casref01;

If a single patients has a pair of tumours defined as a transformation by the
Gavin paper. The first one is assumed to be the primary tumour and the second is
included in the transformation table.

The Gavin paper defines transformations in ICD O3. ICD O3 codes were only used
consistently from 2013 onwards. Given that there is no defined time to
transformation (could be a month, could be 20+ years) we need to extend our
current ICD-O-3 methodology to ICD-O-2.

--------------------------------------------------------------------------------
--                       Overview of tables used / created
--------------------------------------------------------------------------------
Table 1:
                analysishanhualiu.gdo_morph_haem@casref01

Table defining which cases count as a haematological cancer, based on
icdO3rev2011. Any case with morphology and behaviour in this table is
classified as a haem malignancy. The table also puts all haematological cases
into subtypes according to cell lineage.
```

```
Table 2:
            analysisandrewbacon.gdo_transformation_haem@casref01

Table defining when a registered tumour is counted as a precursor condition /
transformation if a patient has multiple tumours registered before 2018
based on Gavin et al. paper.

Table 3:
                analysisandrewbacon.at_transformation_haem

The output of this script, with one row per transformation

--------------------------------------------------------------------------------
--                              Table creation
--------------------------------------------------------------------------------*/
-- Make the framework of the table to insert data into.


DROP TABLE at_transformation_haem PURGE;

CREATE TABLE at_transformation_haem
(
 transformationid VARCHAR2(30) NOT NULL
, patientid VARCHAR2(10) NOT NULL
, precursor_tumourid VARCHAR2(10) NOT NULL
, precursor_diagnosis_date DATE
, precursor_year NUMBER(4)
, precursor_morphology VARCHAR2(4)
, precursor_behaviour VARCHAR2(1)
, precursor_description VARCHAR2(256)
, precursor_subtype VARCHAR2(256)
, precursor_broad_subtype VARCHAR2(256)
, precursor_lineage VARCHAR2(70)

, transformed_tumourid VARCHAR2(10) NOT NULL
, transformation_date DATE
, transformation_year NUMBER(4)
, transformation_morphology VARCHAR2(4)
, transformation_behaviour VARCHAR2(1)
, transformation_description VARCHAR2(256)
, transformation_subtype VARCHAR2(256)
, transformation_broad_subtype VARCHAR2(256)
, transformation_lineage VARCHAR2(70)

, trans_source VARCHAR2(70)
, gavin_flag VARCHAR2(70)
, dedup_flag VARCHAR2(70)
, transformation_split_1 VARCHAR2(256)
, transformation_split_2 VARCHAR2(256)
)
NOLOGGING COMPRESS BASIC
;

/*--------------------------------------------------------------------------------
--          Insert the transformations into the transformation table
--------------------------------------------------------------------------------
Imputing transformations using the Gavin paper.
Section 1a: Finding precursor conditions. Any valid ICD-O-3 precursor code, of
which there are 44 at the moment.
--------------------------------------------------------------------------------*/

INSERT /*+ append */ INTO at_transformation_haem
--CREATE TABLE at_transformation_haem_test NOLOGGING COMPRESS AS
WITH gdo_precursors_o3 AS
(SELECT DISTINCT precursor_morph_o3
      , precursor_behaviour_o3
      , precursor_description_o3
 FROM analysisandrewbacon.gdo_transformation_haem@casref01
)

-- Guidance:
-- Select all of the verified ICD-O-2 codes for precursor conditions. There are
-- 34 of these codes at the moment (o2 is less granular than o3).

, gdo_precursors_o2 AS
(SELECT DISTINCT precursor_morph_o2
      , precursor_behaviour_o2
      , precursor_description_o2
```

```
 FROM analysisandrewbacon.gdo_transformation_haem@casref01
)

-- Guidance:
-- Select all of the verified ICD-O-3 codes for precursor conditions.

-- Notes:
-- Unique pairs of ICD-O-3 codes that define a transformation event. Both  the
-- precursor conditions and transformations are recordede in ICD-O-3. To date
-- there are 771 possibilities. This is basically the heart of how we impute
-- transformations, everything else is simply about aligning classfication
-- systems.

, gdo_transformations_o3_o3 AS
(SELECT DISTINCT precursor_morph_o3
      , precursor_behaviour_o3
      , precursor_description_o3
      , transformation_morph_o3
      , transformation_behaviour_o3
      , transformation_description_o3
 FROM analysisandrewbacon.gdo_transformation_haem@casref01
)

-- Guidance:
-- The section of code below, identifies unique pairs of codes that define a
-- transformation across multiple classifications (ICD-O-2; ICD-O-3). There are
-- 522 possibilities.

-- Notes:
-- There are two ICD-O-3 transformations where their ICD-O-2 mapping has been
-- deliberately excluded, as the O-3 code is very specific and the O-2 is very
-- vague. These are:
-- ICD-O-3 9817/3 B lymphoblastic leukaemia/lymphoma with t(5;14)(q31;q32); IL3-IGH is o2 9821/3
Acute lymphoblastic leukaemia NOS
--  ICD-O-3 9898/3 Myeloid leukemia associated with Down Syndrome in o2 is sometimes 9960/1
Chronic myeloproliferative disease

-- It is also the forward mapping from O-2 to O-3
-- There is also an o2 transformation where the mapping to o3 depends on the
-- precursor condition! o2 9685/3    Malignant lymphoma, lymphoblastic - the
-- precursor condition can show it is a B cell or not. So o3 can be 9728/3
-- Precursor B-cell lymphoblastic lymphoma or 9727/3 Precursor cell
-- lymphoblastic lymphoma, NOS. This is why we can't do a transformation lookup
-- without the precursor conditions.

, gdo_transformations_o3_o2 AS
(SELECT DISTINCT precursor_morph_o3
      , precursor_behaviour_o3
      , precursor_description_o3
      , transformation_morph_o2
      , transformation_behaviour_o2
      , transformation_description_o2
      , transformation_morph_o3
      , transformation_behaviour_o3
      , transformation_description_o3
 FROM analysisandrewbacon.gdo_transformation_haem@casref01
 WHERE transform_o2_o3_mapping_flag = 1
)

-- Notes:
-- gdo_transformation_haem includes a flag (precursor_o2_o3_mapping_flag = 1)
-- that allows us to map O-2 defintions to O-3. These mappings were devised
-- using the mega mapping table. There are ll precursor conditions in ICD-O-2
-- that have been mapped to a preferred ICD-O-3 code.

, precursor_mapping AS
(SELECT DISTINCT precursor_morph_o2
      , precursor_behaviour_o2
      , precursor_description_o2
      , precursor_morph_o3
      , precursor_behaviour_o3
      , precursor_description_o3
 FROM analysisandrewbacon.gdo_transformation_haem@casref01
 WHERE precursor_o2_o3_mapping_flag = 1
)

-- Guidance:
-- ICD-O-2 was used by the registries between 1995-2012. Tumours registered from
```

```
-- 2013 are captured using ICD-O-3.

-- Notes:
-- ICD-O-2 definitions for transformations have been added, despite being
-- outside of the GDO date range because we need to correctly map
-- transformations over the years - a transformation in 2015 could have a
-- precursor condition back in 2001.

-- The following table includes all patients diagnosed with a precursor
-- condition between 1995-2012, as defined in gdo_transformation_haem. It also
-- includes January 2013 to allow one month of follow-up for transformation
-- recorded in 2012. This is not needed for GDO but is useful in general.

-- The subtyping and cell lineage of each precursor condition is listed in
-- analysishanhualiu.gdo_morph_haem. Here our output will consist of one row per
-- tumour / precursor condition. There were 247,153 rows when run on CAS2109 and
-- 247,421 when run on CAS2210. Which is approximately 12,000 precursor
-- conditions a year. however, it is worth stating that there are around 9,000
-- cases in 1995 compared to 19,000 in 2012. There are a number of factors that
-- will have contributed to the dramatic rise in transformations, but mainly
-- it is because of:
-- 1. Introduction of electronic records
-- 2. Merger of 8 regional registries, to one unified registry, with unified
--    standards for data collection.

, o2_precursor_conditions AS
(SELECT /*+ use_hash (t tr)*/
        t.patientid
      , t.tumourid                                AS precursor_tumourid
      , t.diagnosisdatebest                       AS precursor_diagnosis_date
      , t.diagnosisyear                           AS precursor_year
      , p.precursor_morph_o3                      AS precursor_morphology
      , p.precursor_behaviour_o3                  AS precursor_behaviour
      , p.precursor_description_o3                AS precursor_description
      , hlp.split_3                               AS precursor_subtype
      , hlp.split_2                               AS precursor_broad_subtype
      , hlp.split_1                               AS precursor_lineage
 FROM                              analysisncr.at_tumour_england                                t
-- Most recent annual snapshot was chosen to help capture any registry creep
  INNER    JOIN    gdo_precursors_o2    tr    ON    t.morph_icd10_o2    =    tr.precursor_morph_o2
-- Match on morphology (ICD-O-2)
         AND            t.behaviour_icd10_o2           =           tr.precursor_behaviour_o2
-- Match on behaviour for those cases where the behaviour distinguishes the type of disease
  LEFT OUTER JOIN precursor_mapping p ON p.precursor_morph_o2 = tr.precursor_morph_o2
              AND p.precursor_behaviour_o2 = tr.precursor_behaviour_o2
  LEFT  OUTER  JOIN  analysishanhualiu.gdo_morph_haem@casref01  hlp  ON  p.precursor_morph_o3  =
hlp.morph_icdo3rev2011
              AND p.precursor_behaviour_o3 = hlp.behaviour
 WHERE dedup_flag = 1                                                                          -
- Mandatory restrictions
   AND age BETWEEN 0 AND 200
   AND                     statusofregistration                     =                     'F'
-- Finalised Registrations
   AND diagnosisdatebest BETWEEN TO_DATE('1995-01-01', 'YYYY-MM-DD') AND TO_DATE('2013-01-31',
'YYYY-MM-DD')          -- ICDO3 implemented in 2013. Allowing for 31 days in Jan for patients
with synchronous presentation
)

-- Guidance:
-- The table below includes descriptions of all precursor conditions described
-- in the Cancer Analysis System (CAS) from 2013 onwards, as defined by Gavin et
-- al. This table lists each precursor condition on a single row. There were
-- 154,092 rows when run on CAS2109 and 173,115 when the table is run on
-- CAS2210. Which is approximately 20,000 precursor conditions a year. Counts of
-- precursor conditions remain pretty steady over the years, with exception to
-- 2020 which is likely to have been impacted by COVID-19.

, o3_precursor_conditions AS
(SELECT /*+ use_hash (t tr)*/
        t.patientid
      , t.tumourid                          AS precursor_tumourid
      , t.diagnosisdatebest                 AS precursor_diagnosis_date
      , t.diagnosisyear                     AS precursor_year
      , tr.precursor_morph_o3               AS precursor_morphology
      , tr.precursor_behaviour_o3           AS precursor_behaviour
      , tr.precursor_description_o3         AS precursor_description
      , hlp.split_3                         AS precursor_subtype
      , hlp.split_2                         AS precursor_broad_subtype
```

```
      , hlp.split_1                          AS precursor_lineage
 FROM                            analysisncr.at_tumour_england                                t
-- Most recent annual snapshot was chosen to help capture any registry creep
  INNER   JOIN   gdo_precursors_o3   tr   ON   t.morph_icdo3rev2011   =   tr.precursor_morph_o3
-- Match on morphology (ICD-O-3)
         AND           t.behaviour_icdo3rev2011           =           tr.precursor_behaviour_o3
-- Match on behaviour for those cases where the behaviour distinguishes the type of disease
  LEFT  OUTER  JOIN analysishanhualiu.gdo_morph_haem@casref01  hlp  ON  tr.precursor_morph_o3  =
hlp.morph_icdo3rev2011
             AND tr.precursor_behaviour_o3 = hlp.behaviour
 WHERE dedup_flag = 1
   AND age BETWEEN 0 AND 200
   AND statusofregistration = 'F'
   AND         diagnosisdatebest         >=         TO_DATE('2013-01-01',         'YYYY-MM-DD')
-- ICDO3 implemented in 2013
--                               AND               ctry_code               =               'E'
-- No restriction on England. If we know they had a precursor condition we don't care if it was
in England or some other country as long as the transformation was recorded in England.
)

--------------------------------------------------------------------------------
-- Section 1b: Finding transformations
--------------------------------------------------------------------------------
-- Three tables to do this:
-- O2-O2 for when both precursor condition and tranformation are 1995-2012
-- O2-O3 for when precursor is 1995-2012 and transformation is 2013 onwards
-- O3-O3 for when both precursor condition and tranformation are 2013 onwards
--------------------------------------------------------------------------------

-- Guidance:
-- The following table is used to identify all transformation events recorded in
-- ICD-O-2, where both the precursor condition and the transformation are
-- recorded between 01/01/1995 and 31/12/2012 as defined by
-- gdo_transformation_haem.

-- Diagnosis dates are recorded according to either the date the diagnosis was
-- agreed at MDT; or, the day the diagnosis was signed off by the senior
-- pathologist. We therefore routinely allow a 31 day window to accunt for
-- flexibility in reporting. This sentiment has been adopted here too, whereby a
-- precursor_condition can be captured up to 31 days after the transformation.
-- The general rules is that a precursor condition should be before a
-- transformation, but cannot be more than a month after and still be counted.

-- Multiple O3 lookups are avoided by using the precursor_o2_o3_mapping_flag = 1
-- One row is one unique pair of precursor_tumourid and tranformed_tumourid.
-- There were 4,689 rows when run on CAS2109 (4,691 on CAS2210). This is about
-- 300 transformations a year. Counts in 1995 are low because there is no data
-- from the years before for precursor conditions. Counts rise to 561 a year in
-- 2012).

-- The subtyping and lineage of the transformed neoplasm
-- are determined using analysishanhualiu.gdo_morph_haem.

, o2_o2_transformations AS
(SELECT /*+ use_hash (pc t) use_hash (t tr)*/
        pc.patientid

      , pc.precursor_tumourid
      , pc.precursor_diagnosis_date
      , pc.precursor_year
      , pc.precursor_morphology
      , pc.precursor_behaviour
      , pc.precursor_description
      , pc.precursor_subtype
      , pc.precursor_broad_subtype
      , pc.precursor_lineage

      , t.tumourid                           AS transformed_tumourid
      , t.diagnosisdatebest                  AS transformation_date
      , t.diagnosisyear                      AS transformation_year
      , tr.transformation_morph_o3           AS transformation_morphology
      , tr.transformation_behaviour_o3       AS transformation_behaviour
      , tr.transformation_description_o3     AS transformation_description
      , hlt.split_3                          AS transformation_subtype
      , hlt.split_2                          AS transformation_broad_subtype
      , hlt.split_1                          AS transformation_lineage
 FROM o2_precursor_conditions pc
```

```
  INNER JOIN analysisncr.at_tumour_england t ON pc.patientid = t.patientid          -- Matching
on patient ID to ensure we pull all related tumours
  INNER JOIN gdo_transformations_o3_o2 tr ON pc.precursor_morphology = tr.precursor_morph_o3
         AND pc.precursor_behaviour = tr.precursor_behaviour_o3                     -- Joining
converted o2 precursors on to o3 definitions of disease
         AND t.morph_icd10_o2 = tr.transformation_morph_o2
         AND t.behaviour_icd10_o2 = tr.transformation_behaviour_o2                  -- Extra
level of linkage needed to minimise cross matching
  LEFT OUTER JOIN analysishanhualiu.gdo_morph_haem@casref01 hlt ON tr.transformation_morph_o3
= hlt.morph_icdo3rev2011
              AND tr.transformation_behaviour_o3 = hlt.behaviour
 WHERE t.diagnosisdatebest - pc.precursor_diagnosis_date >= -31
   AND pc.precursor_tumourid != t.tumourid                                          --
Registration would capture some transformations AS new primaries, so lets make sure the tumourids
dont match
   AND t.ctry_code = 'E'                                                            -- NDRS
Mandatory restrictions
   AND t.dedup_flag = 1
   AND t.statusofregistration = 'F'
   AND t.age BETWEEN 0 AND 200
   AND t.diagnosisyear BETWEEN 1995 AND 2012                                        -- ICD-O-2
wAS the princple coding system between 1995 and 2012
)

-- Notes:
-- The following table includes all tumour-pairs that could be a transformation,
-- where the precursor is recorded between 1995-2012 and the transformation
-- reported from 2013 onwards, as defined by gdo_transformation_haem
-- O3-precursors and O3-transformations. Please note that a precursor condition
-- should be before a transformation, but we have allowed a 31 day window either
-- side of the precursor diagnosis date to allow for differences in reporting.

-- Subtyping and lineage are determined by analysishanhualiu.gdo_morph_haem.
-- Multiple O3 lookups are avoided by using the precursor_o2_o3_mapping_flag = 1
-- One row is one unique pair of precursor_tumourid and tranformed_tumourid.
-- There were 2,418 rows when run on CAS2109 (2,410 on CAS2210)
-- This is about 400 transformations a year for 2013-2018 (662 in 2013, falling
-- annually to 350 in 2017, as 2012 gets further away. There should be none 2018
-- onwards, but we have 92,26,12 on CAS2210 which is an improvement on 92,41,13
-- on CAS2109).

, o2_o3_transformations AS
(SELECT /*+ use_hash (pc t) use_hash (tr t)*/
        pc.patientid
      , pc.precursor_tumourid
      , pc.precursor_diagnosis_date
      , pc.precursor_year
      , pc.precursor_morphology
      , pc.precursor_behaviour
      , pc.precursor_description
      , pc.precursor_subtype
      , pc.precursor_broad_subtype
      , pc.precursor_lineage

      , t.tumourid                          AS transformed_tumourid
      , t.diagnosisdatebest                 AS transformation_date
      , t.diagnosisyear                     AS transformation_year
      , tr.transformation_morph_o3          AS transformation_morphology
      , tr.transformation_behaviour_o3      AS transformation_behaviour
      , tr.transformation_description_o3    AS transformation_description
      , hlt.split_3                         AS transformation_subtype
      , hlt.split_2                         AS transformation_broad_subtype
      , hlt.split_1                         AS transformation_lineage
 FROM o2_precursor_conditions pc
  INNER JOIN analysisncr.at_tumour_england t ON pc.patientid = t.patientid          -- Match on
patient ID to get all related tumours
  INNER JOIN gdo_transformations_o3_o3 tr ON pc.precursor_morphology = tr.precursor_morph_o3
         AND pc.precursor_behaviour = tr.precursor_behaviour_o3                  -- Precursors
were converted from o2, so matching on o3
         AND t.morph_icdo3rev2011 = tr.transformation_morph_o3                      --
Transformations defined in ICD-O-3
         AND t.behaviour_icdo3rev2011 = tr.transformation_behaviour_o3              -- Extra
level of linkage needed to minimise cross matching
  LEFT OUTER JOIN analysishanhualiu.gdo_morph_haem@casref01 hlt ON tr.transformation_morph_o3
= hlt.morph_icdo3rev2011
              AND tr.transformation_behaviour_o3 = hlt.behaviour
 WHERE t.diagnosisdatebest - pc.precursor_diagnosis_date >= -31
```

```
   AND pc.precursor_tumourid != t.tumourid                                          -- Lets
make sure the tumourids don't match
   AND t.ctry_code = 'E'                                                          -- Mandatory
restrictions
   AND t.dedup_flag = 1
   AND t.statusofregistration = 'F'
   AND t.age BETWEEN 0 AND 200
   AND t.diagnosisyear >= 2013                                                     -- Changes
to ENCR guidelines means that transformations are recorded in a seperate table from 2018
   AND pc.precursor_year <= 2012                                                  -- Take out
the January 2013 tumours or would get same transformation in o2o3 and o3o3
)

-- The table below includes all tumour-pairs that could be a transformation,
-- where the precursor and the transformation were diagnosed from 2013 onwards,
-- as defined by gdo_transformation_haem O3-precursors and O3-transformations.

-- One row is one unique pair of precursor_tumourid and tranformed_tumourid
-- There were 2,728 rows when run on CAS2109 (2,660 on CAS2210). This is about
-- 500 transformations a year, although there are very few in 2013 (only 165,
-- this because there isnt a long follow-up period). Counts rise a lot year on
-- year to 755 in 2017 (also as expected). Then in the 2018-2020 when imputing
-- transformations should no longer be required, we have 68/168/44 CAS2109 and
-- 38/75/61 CAS2210). We hope that as registration staff become more familiar
-- with the recording of transformations the need for imputation wont be
-- necessary in later years.

, o3_o3_transformations AS
(SELECT /*+ use_hash (pc t) use_hash (t tr)*/
        pc.patientid
      , pc.precursor_tumourid
      , pc.precursor_diagnosis_date
      , pc.precursor_year
      , pc.precursor_morphology
      , pc.precursor_behaviour
      , pc.precursor_description
      , pc.precursor_subtype
      , pc.precursor_broad_subtype
      , pc.precursor_lineage

      , t.tumourid                          AS transformed_tumourid
      , t.diagnosisdatebest                 AS transformation_date
      , t.diagnosisyear                     AS transformation_year
      , tr.transformation_morph_o3          AS transformation_morphology
      , tr.transformation_behaviour_o3      AS transformation_behaviour
      , tr.transformation_description_o3    AS transformation_description
      , hlt.split_3                         AS transformation_subtype
      , hlt.split_2                         AS transformation_broad_subtype
      , hlt.split_1                         AS transformation_lineage
 FROM o3_precursor_conditions pc
  INNER JOIN analysisncr.at_tumour_england t ON pc.patientid = t.patientid         -- Match on
patient to get all related tumours
  INNER JOIN gdo_transformations_o3_o3 tr ON pc.precursor_morphology = tr.precursor_morph_o3
         AND pc.precursor_behaviour = tr.precursor_behaviour_o3
         AND t.morph_icdo3rev2011 = tr.transformation_morph_o3
         AND t.behaviour_icdo3rev2011 = tr.transformation_behaviour_o3               -- Extra
level of linkage needed to ensure there is no cross matching
  LEFT OUTER JOIN analysishanhualiu.gdo_morph_haem@casref01 hlt ON tr.transformation_morph_o3
= hlt.morph_icdo3rev2011
             AND tr.transformation_behaviour_o3 = hlt.behaviour
 WHERE t.diagnosisdatebest - pc.precursor_diagnosis_date >= -31
   AND pc.precursor_tumourid != t.tumourid                                          --
Registration would class transformations as new primaries, so lets make sure the tumourids dont
match
   AND t.ctry_code = 'E'                                                          -- Mandatory
restrictions
   AND t.dedup_flag = 1
   AND t.statusofregistration = 'F'
   AND t.age BETWEEN 0 AND 200
   AND t.diagnosisyear >= 2013
)

/*-------------------------------------------------------------------------------
-- Section 2 - finding transformations from the transformation table
-------------------------------------------------------------------------------

European Network of Cancer Registries: Recommendations for Registration of
Haematological Malignancies.
```

```
1. Multiple data sources such as blood, bone marrow, flow cytometry, molecular
   and cytogenetic tests from haematology and designated molecular laboratories
   in addition to histopathology, cytology, clinical records and death
   notifications should be used to register haematological malignancies (HM).

2. When additional information is received on the same HM patient the option
   exists to record as a transformation, same tumour or new tumour

   a. Allocate as Transformation if first HM transforms into a new morphological
      entity (different diagnostic group) after a three month window of first
      registration:
      - Only the first tumour's morphology and date of diagnosis to be
        considered as incident for analysis and reporting
      - The transformed tumour must not be counted as a new tumour and
        therefore not be included in the incidence statistics.

   b. Allocate as same tumour with more specific /revised morphology,
      - if within same diagnostic group, date of diagnosis remains unchanged.
      - if a transformation occurs within three months after the incidence date,
        the morphology code of the transformed malignancy should replace that
        of the first tumour and be recorded as the first primary and not a
        transformation. Date of diagnosis remains unchanged as that of the first
        tumour.

   c. Allocate as a new tumour registration with new incident date when
      - HM with malignant behaviour (code /3) occurs after a previous
        haematological disease with uncertain behaviour (code /1) or
      - The change is not a transformation or a revised diagnosis of an
        existing tumour; or,
      - Clinical opinion regarding a new tumour is available and the detail of
        that decision is recorded.

3. Regular survival analysis methods do not necessarily apply in the case of
   patients with HM where transformations have occurred as the patient has to be
   alive until the diagnosis of multiple tumour or transformation occurs. The
   information of these changes may be used as time-dependent covariates. There
   are special methods for such multiple tumour analyses.

4. The ENCR recommendations for coding of incidence date should be followed.
5. Basis of diagnosis should follow the ENCR recommendations.
6. Record all dates and diagnoses of transformations in the registry.

--------------------------------------------------------------------------------*/

-- This table has one row for each tranformation in the transformations table.
-- It finds the details of the precursor condition from the tumour table and
-- puts this in to definitions of ICDO3_rev2011 as much as possible. It finds
-- the details of the transformation from the transformations table and assumes
-- they are in ICDO3_rev2011 (there are a few hacks to clean this).

-- There are 4,552 transformations on CAS2210 (2,973 on CAS2109). It is about
-- 1,031 in 2018, 1,223 in 2019, and 1,437 in 2020.

, reg_transformations_raw AS
(SELECT t.patientid
      , t.tumourid          AS precursor_tumourid
      , t.diagnosisdatebest AS precursor_diagnosis_date
      , t.diagnosisyear     AS precursor_year

-- This is a hack; we want all tumours in ICDO3_rev2011 if possible, so if they
-- are, we take that. If they aren't, we use Andrew's mapping table from O2 to
-- O3 to put them in O3. If they still aren't, we hard code four values that we
-- know map directly. If that fails, we take the ICD10_O2 field when it exists.
-- If that fails, we take the ICD-O-2 field when it exists.

      , CASE WHEN morph_icdo3rev2011 IS NOT NULL THEN morph_icdo3rev2011
             WHEN p.precursor_morph_o2 IS NOT NULL THEN p.precursor_morph_o3
                WHEN morph_icd10_o2 IN ('9699','9689','9590','9702') AND behaviour_icd10_o2 =
'3' THEN morph_icd10_o2
             WHEN morph_icd10_o2 IS NOT NULL THEN morph_icd10_o2
             WHEN coding_system_desc = 'ICD-O-2' THEN morph_coded
        END AS precursor_morphology

      , CASE WHEN behaviour_icdo3rev2011 IS NOT NULL THEN behaviour_icdo3rev2011
             WHEN p.precursor_morph_o2 IS NOT NULL THEN p.precursor_behaviour_o3
                WHEN morph_icd10_o2 IN ('9699','9689','9590','9702') AND behaviour_icd10_o2 =
'3' THEN behaviour_icd10_o2
```

```
            WHEN behaviour_icd10_o2 IS NOT NULL THEN behaviour_icd10_o2
            WHEN coding_system_desc = 'ICD-O-2' THEN behaviour_coded
       END AS precursor_behaviour

     , CASE WHEN morph_icdo3rev2011 IS NOT NULL THEN 'ICD-O-3 (2011)'
            WHEN p.precursor_morph_o2 IS NOT NULL THEN 'ICD-O-3 (2011)'
               WHEN morph_icd10_o2 IN ('9699','9689','9590','9702') AND behaviour_icd10_o2 =
'3' THEN 'ICD-O-3 (2011)'
            WHEN morph_icd10_o2 IS NOT NULL THEN 'ICD-10/O-2'
            WHEN coding_system_desc = 'ICD-O-2' THEN 'ICD-10/O-2'
       END AS precursor_coding

     , transformationid                       AS transformed_tumourid
     , transformation_date                    AS transformation_date
     , EXTRACT(YEAR FROM(transformation_date)) AS transformation_year
--     , tr.transformation_icdo                  AS transformation_icdo

-- Guidance:
-- The transformation_icdo field is free text and therefore includes codes,
-- words, and M's and /s. As such this needs to be cleaned. You take out
-- anything that is not a number, and then take the first 5 numbers. The first
-- four chracters are usually the morphology and the fifth is the behaviour
-- code.

--     , REGEXP_REPLACE(tr.transformation_icdo,'[^0-9]', NULL) AS transformation_icdo_clean

-- Notes:
-- We are starting to get ICDO3_rev2019 codes in this column. This manually
-- maps them both back to ICDO3_rev2011.

        ,  CASE  WHEN  SUBSTR(REGEXP_REPLACE(tr.transformation_icdo,'[^0-9]',  NULL),1,4)  IN
('9877','9878') THEN '9861'
                  ELSE SUBSTR(REGEXP_REPLACE(tr.transformation_icdo,'[^0-9]', NULL),1,4)
       END AS transformation_morphology

-- This case statement manually fixes two weird things on 2109, but they are
-- fixed by 2210. We've left it in to future proof the query.

        ,  CASE  WHEN  SUBSTR(REGEXP_REPLACE(tr.transformation_icdo,'[^0-9]',  NULL),1,4)  IN
('9861') AND SUBSTR(REGEXP_REPLACE(tr.transformation_icdo,'[^0-9]', NULL),5,1) IS NULL THEN '3'
           WHEN SUBSTR(REGEXP_REPLACE(tr.transformation_icdo,'[^0-9]', NULL),1,4) IN ('9896')
AND SUBSTR(REGEXP_REPLACE(tr.transformation_icdo,'[^0-9]', NULL),5,1) = '1' THEN '3'
           ELSE SUBSTR(REGEXP_REPLACE(tr.transformation_icdo,'[^0-9]', NULL),5,1)
      END AS transformation_behaviour
    , RANK() OVER (PARTITION BY t.patientid ORDER BY tr.transformation_date, tr.transformationid
)   as trans_rank

 FROM springmvc3.transformation tr
  LEFT OUTER JOIN springmvc3.event e ON tr.transformationid = e.eventid
  LEFT OUTER JOIN springmvc3.tumourevents te ON e.eventid = te.eventid
  LEFT OUTER JOIN analysisncr.at_tumour_england t ON te.tumourid = t.tumourid
  LEFT OUTER JOIN tumour t1 ON te.tumourid = t1.tumourid
  LEFT  OUTER  JOIN  precursor_mapping  p  ON  p.precursor_morph_o2  =  nvl(t.morph_icd10_o2,
t.morph_coded)
            AND p.precursor_behaviour_o2 = nvl(t.behaviour_icd10_o2, t.behaviour_coded)
 WHERE t.statusofregistration = 'F'
   AND t.ctry_code = 'E'
   AND t.diagnosisyear >= 1995
)

-- Some patients are registered with multiple transformations
-- For example they have a essential thrombocytemia which transforms
-- to MDS which transforms to AML
-- Talking with clinicians, we want the MDS to be the precursor to the AML
-- Not the ET.
-- So we need to take patients with more than one transformation
-- and make earlier transformations into precursor conditions of later transformations

-- There are 335 transformations on CASREF01 which are created by this method

, reg_transformations_multiples
as
(
SELECT
tr1.patientid as patientid
, tr2.transformed_tumourid as precursor_tumourid
, tr2.transformation_date as precursor_diagnosis_date
, tr2.transformation_year as precursor_year
```

```
, tr2.transformation_morphology as precursor_morphology
, tr2.transformation_behaviour as precursor_behaviour
, 'ICD-O-3 (2011)' as precursor_coding
, tr1.transformed_tumourid as transformed_tumourid
, tr1.transformation_date as transformation_date
, tr1.transformation_year as transformation_year
, tr1.transformation_morphology as transformation_morphology
, tr1.transformation_behaviour

FROM reg_transformations_raw tr1
left outer join reg_transformations_raw tr2
-- transformation is for the same patient
on tr1.patientid = tr2.patientid
-- transformation happened earlier than this transformation
and tr2.trans_rank <  tr1.trans_rank
-- an earlier transformation actually exists
where tr2.patientid is not null
-- transformations on the same day are not precursors to each other
and tr1.transformation_date != tr2.transformation_date
)

-- We then need to add in the extra multiple transformations to the main
-- table of registration transformations:

,reg_transformations_raw_all
as
(
select
patientid
, precursor_tumourid
, precursor_diagnosis_date
, precursor_year
, precursor_morphology
, precursor_behaviour
, precursor_coding
, transformed_tumourid
, transformation_date
, transformation_year
, transformation_morphology
, transformation_behaviour
from reg_transformations_raw
UNION
select
patientid
, precursor_tumourid
, precursor_diagnosis_date
, precursor_year
, precursor_morphology
, precursor_behaviour
, precursor_coding
, transformed_tumourid
, transformation_date
, transformation_year
, transformation_morphology
, transformation_behaviour
from reg_transformations_multiples

)



-- Guidance:
-- Get rid of about 247 transformations that are not haem malignancis (brain
-- etc) by joining to the haem table. This takes us down to 4,305
-- transformations. Also take out 59 where the transformed morphology is the
-- same as the precursor morphology, which takes us down to 4,246
-- transformations.

-- Check they are all in ICDO3_REV2011 at this point - they are on CAS2210.
-- 4,185 are transformations recognised in the Gavin paper (on CAS2210), 61 are
-- weird ones (on CAS2210).




, reg_transformations_haem AS
(SELECT patientid
      , precursor_tumourid
```

```
      , precursor_diagnosis_date
      , precursor_year
      , precursor_morphology
      , precursor_behaviour
      , precursor_coding
          , h2.morph_icdo3rev2011_desc      AS precursor_description
      , h2.split_3                        AS precursor_subtype
      , h2.split_2                        AS precursor_broad_subtype
      , h2.split_1                        AS precursor_lineage
      , transformed_tumourid
      , transformation_date
      , transformation_year
      , transformation_morphology
      , transformation_behaviour
      , h.morph_icdo3rev2011_desc      AS transformation_description
      , h.split_3                      AS transformation_subtype
      , h.split_2                      AS transformation_broad_subtype
      , h.split_1                      AS transformation_lineage
      , CASE WHEN tr.precursor_morph_o3 IS NOT NULL THEN 1
             ELSE 0
        END AS gavin_flag
 FROM reg_transformations_raw_all r

-- Only haem transformations
  LEFT OUTER JOIN analysishanhualiu.gdo_morph_haem@casref01 h ON r.transformation_morphology =
h.morph_icdo3rev2011
              AND r.transformation_behaviour = h.behaviour
-- Talked to Brian R, and the transformation where the precursor is not haem,
-- but the transformation is haem is valid and should be counted as a haem
-- transformation. Only haem precursors (only takes out one extra tumour over
-- the above condition).
  LEFT OUTER JOIN analysishanhualiu.gdo_morph_haem@casref01 h2 ON r.precursor_morphology =
h2.morph_icdo3rev2011
              AND r.precursor_behaviour = h2.behaviour
  LEFT OUTER JOIN gdo_transformations_o3_o3 tr ON r.precursor_morphology = tr.precursor_morph_o3
              AND r.precursor_behaviour = tr.precursor_behaviour_o3
              AND r.transformation_morphology = tr.transformation_morph_o3
              AND r.transformation_behaviour = tr.transformation_behaviour_o3
WHERE h.morph_icdo3rev2011 IS NOT NULL
  AND                       (precursor_morphology||precursor_behaviour                      !=
transformation_morphology||transformation_behaviour)
)


--------------------------------------------------------------------------------
-- Combining the transformations, with a record of where they came from
--------------------------------------------------------------------------------
-- I make this 14,007 transformations on CAS2210 (12632 on CAS2109)

, at_transformation_base AS
(SELECT patientid
      , precursor_tumourid
      , precursor_diagnosis_date
      , precursor_year
      , precursor_morphology
      , precursor_behaviour
        , precursor_description
      , precursor_subtype
      , precursor_broad_subtype
      , precursor_lineage
      , transformed_tumourid
      , transformation_date
      , transformation_year
      , transformation_morphology
      , transformation_behaviour
      , transformation_description
      , transformation_subtype
      , transformation_broad_subtype
      , transformation_lineage
        , 'Imputed o2-o2' as trans_source
      , 1 as gavin_flag
 FROM o2_o2_transformations

 UNION

 SELECT patientid
      , precursor_tumourid
      , precursor_diagnosis_date
```

```
      , precursor_year
      , precursor_morphology
      , precursor_behaviour
         , precursor_description
      , precursor_subtype
      , precursor_broad_subtype
      , precursor_lineage
      , transformed_tumourid
      , transformation_date
      , transformation_year
      , transformation_morphology
      , transformation_behaviour
      , transformation_description
      , transformation_subtype
      , transformation_broad_subtype
      , transformation_lineage
         , 'Imputed o2-o3' as trans_source
      , 1 as gavin_flag
 FROM o2_o3_transformations

 UNION

 SELECT patientid
      , precursor_tumourid
      , precursor_diagnosis_date
      , precursor_year
      , precursor_morphology
      , precursor_behaviour
         , precursor_description
      , precursor_subtype
      , precursor_broad_subtype
      , precursor_lineage
      , transformed_tumourid
      , transformation_date
      , transformation_year
      , transformation_morphology
      , transformation_behaviour
      , transformation_description
      , transformation_subtype
      , transformation_broad_subtype
      , transformation_lineage
         , 'Imputed o3-o3' as trans_source
      , 1 as gavin_flag
 FROM o3_o3_transformations

 UNION

 SELECT patientid
      , precursor_tumourid
      , precursor_diagnosis_date
      , precursor_year
      , precursor_morphology
      , precursor_behaviour
         , precursor_description
      , precursor_subtype
      , precursor_broad_subtype
      , precursor_lineage
      , transformed_tumourid
      , transformation_date
      , transformation_year
      , transformation_morphology
      , transformation_behaviour
      , transformation_description
      , transformation_subtype
      , transformation_broad_subtype
      , transformation_lineage
         , 'Reg_transform' as trans_source
      , gavin_flag
 FROM reg_transformations_haem
)

-- Exactly the same table as at_transformation_base, but with the
-- transformations in GDO tree groups.
, at_transformation_mapped AS
(SELECT patientid
      , precursor_tumourid
      , precursor_diagnosis_date
      , precursor_year
```

```
      , precursor_morphology
      , precursor_behaviour
         , precursor_description
      , precursor_subtype
      , precursor_broad_subtype
      , precursor_lineage
      , transformed_tumourid
      , transformation_date
      , transformation_year
      , transformation_morphology
      , transformation_behaviour
      , transformation_description
      , transformation_subtype
      , transformation_broad_subtype
      , transformation_lineage
         , trans_source
      , gavin_flag

-- Warning this code is fragile to changes in names of groups in master tables

      , CASE WHEN  transformation_broad_subtype LIKE '%Hodgkin%'  THEN 'Diffuse large B-cell
lymphoma (DLBCL), Hodgkin, and other high grade'
             WHEN  transformation_subtype LIKE '%DLBCL%'  THEN 'Diffuse large B-cell lymphoma
(DLBCL), Hodgkin, and other high grade'
             WHEN  transformation_broad_subtype LIKE '%AML%'  THEN 'Acute myeloid leukaemia
(AML)'
             ELSE 'Other transformations'
        END AS transformation_split_1

         , CASE WHEN transformation_broad_subtype LIKE '%AML%' AND precursor_broad_subtype =
'Myelodysplastic syndromes (MDS)' THEN 'Transformation from myelodysplastic syndromes (MDS)'
                WHEN transformation_broad_subtype LIKE '%AML%' AND precursor_broad_subtype =
'Myeloproliferative neoplasms (MPN)' THEN 'Transformation from myeloproliferative neoplasms
(MPN)'
             WHEN transformation_broad_subtype LIKE '%AML%' THEN 'Transformation from other
myeloid neoplasms'
             WHEN transformation_broad_subtype LIKE '%Hodgkin%' and precursor_subtype LIKE
'%CLL%' THEN 'Richter transformation to diffuse large B-cell lymphoma (DLBCL) or Hodgkin lymphoma
from chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)'
             WHEN transformation_subtype LIKE '%DLBCL%' AND precursor_subtype LIKE '%CLL%' THEN
'Richter transformation to diffuse large B-cell lymphoma (DLBCL) or Hodgkin lymphoma from
chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)'
             WHEN  transformation_subtype  LIKE  '%DLBCL%'  AND  precursor_subtype  LIKE
'%ollicular%' THEN 'Transformation to diffuse large B-cell lymphoma (DLBCL) from Follicular
lymphoma'
             WHEN transformation_subtype LIKE '%DLBCL%' AND precursor_subtype LIKE '%arginal%'
THEN 'Transformation to diffuse large B-cell lymphoma (DLBCL) from Marginal lymphoma'
             WHEN transformation_subtype LIKE '%DLBCL%' THEN 'Transformation to diffuse large
B-cell lymphoma (DLBCL) or Hodgkin lymphoma from other precursors'
             WHEN transformation_broad_subtype LIKE '%Hodgkin%' THEN 'Transformation to diffuse
large B-cell lymphoma (DLBCL) or Hodgkin lymphoma from other precursors'
             ELSE NULL
        END AS transformation_split_2

 from  at_transformation_base
)

-- Need to clean duplicates. Start by working out which patients have
-- duplicates, by grouping by patient ID and measuring some useful stuff.

, at_tran_patient AS
(SELECT patientid
      , COUNT(*)                                                AS row_count
      , COUNT(DISTINCT precursor_tumourid)                      AS prec_count
      , COUNT(DISTINCT transformed_tumourid)                    AS tran_count
      , MAX(transformation_split_1)                             AS max_t1
      , MIN(transformation_split_1)                             AS min_t1
      , MAX(transformation_split_2)                             AS max_t2
      , MIN(transformation_split_2)                             AS min_t2
      , MAX(transformation_morphology||transformation_behaviour) AS max_tm
      , MIN(transformation_morphology||transformation_behaviour) AS min_tm
      , MAX(transformation_date)                                AS max_td
      , MIN(transformation_date)                                AS min_td
      , MAX(precursor_diagnosis_date)                           AS max_pd
      , MIN(precursor_diagnosis_date)                           AS min_pd
      , MAX(precursor_morphology||precursor_behaviour)          AS max_pm
      , MIN(precursor_morphology||precursor_behaviour)          AS min_pm
      , MAX(precursor_subtype)                                  AS max_ps
```

```
      , MIN(precursor_subtype)                                    AS min_ps
 FROM at_transformation_mapped
 GROUP BY patientid
)

,  at_tran_rank AS
(SELECT t.*
      , row_count
      , prec_count
      , tran_count
      , max_t1
      , min_t1
      , max_t2
      , min_t2
      , max_tm
      , min_tm
      , max_td
      , min_td
      , max_pm
      , min_pm
      , max_ps
      , min_ps
      , max_td - min_td AS datedifft
      , max_pd - min_pd AS datediffp
      ,   RANK()   OVER   (PARTITION   BY   t.patientid   ORDER   BY   t.transformation_date,
t.transformed_tumourid)                                                    AS trans_rank
      ,   RANK()   OVER   (PARTITION   BY   t.patientid,   t.transformation_split_1   ORDER   BY
t.transformation_date, t.transformed_tumourid)                           AS trans_rank_2
      ,  RANK()  OVER  (PARTITION  BY  t.patientid  ORDER  BY  t.precursor_diagnosis_date  DESC,
t.precursor_tumourid )                                                   AS prec_rank
      , RANK() OVER (PARTITION BY t.patientid, t.transformation_split_1, t.transformed_tumourid
ORDER BY t.precursor_diagnosis_date desc, t.precursor_tumourid) AS prec_rank_2
 FROM at_transformation_mapped t
  LEFT OUTER JOIN at_tran_patient f ON f.patientid = t.patientid
)

, at_transformation AS
(SELECT t.*
-- When there's only one transformation per patient, just take it
      , CASE WHEN row_count = 1 THEN 1
-- Two transformations in different groups, take both
             WHEN row_count = 2 AND tran_count = 2 AND max_t1 != min_t1 THEN 1

-- When there are two transformations AND they are the same precursor with two
-- transformation endpoints, and one of them is 99303 (myeloid sarcoma) and one
-- of them is 98613 (AML), take the AML if it is within 92 days.

             WHEN row_count = 2 AND tran_count = 2 AND prec_count = 1 AND max_tm='99303' AND
min_tm = '98613' AND datedifft <= 92 AND transformation_morphology = '9930' THEN 0
             WHEN row_count = 2 AND tran_count = 2 AND prec_count = 1 AND max_tm='99303' AND
min_tm = '98613' AND datedifft <= 92 AND transformation_morphology = '9861' THEN 1

-- When there are two transformations in the same group but one is earlier than
-- the other take the earlier one.

             WHEN row_count = 2 AND tran_count = 2 AND datedifft > 0 AND max_t1 = min_t1  AND
trans_rank = 1 THEN 1
             WHEN row_count = 2 AND tran_count = 2 AND datedifft > 0 AND max_t1 = min_t1  AND
trans_rank = 2 THEN 0

-- When there are two transformations, and they are the same precursor with two
-- transformation end points and they are on the same day, and one is 9840 (AML
-- M6 type) and one is 9861 (AML NOS) take the M6 type.

             WHEN row_count = 2 AND tran_count = 2 AND prec_count = 1 AND max_tm='98613' AND
min_tm = '98403' AND datedifft <= 0 AND  transformation_morphology = '9861' THEN 0
             WHEN row_count = 2 AND tran_count = 2 AND prec_count = 1 AND max_tm='98613' AND
min_tm = '98403' AND datedifft <= 0 AND  transformation_morphology = '9840' THEN 1

-- When there are two transformations, and they are the same precursor with two
-- transformation end points and they are on the same day with different
-- histology take the higher histology.

             WHEN row_count = 2 AND tran_count = 2 AND prec_count = 1  AND datedifft = 0 AND
max_t1 = min_t1 AND max_tm!= min_tm AND transformation_morphology||transformation_behaviour =
max_tm THEN 1
```

```
            WHEN row_count = 2 AND tran_count = 2 AND prec_count = 1  AND datedifft = 0 AND
max_t1 = min_t1 AND max_tm!= min_tm AND transformation_morphology||transformation_behaviour !=
max_tm THEN 0

-- When there are two transformations, andthey are the same precursor with two
-- transformation end points and they are on the same day with the same
-- histology use tumourID as a tie-break, take the lowest tumour ID.

            WHEN row_count = 2 AND tran_count = 2 AND prec_count = 1  AND datedifft = 0 AND
max_tm= min_tm AND trans_rank = 1  THEN 1
            WHEN row_count = 2 AND tran_count = 2 AND prec_count = 1  AND datedifft = 0 AND
max_tm= min_tm AND trans_rank = 2  THEN 0

-- When there are two transformations and they are on the same day with the same
-- histology but with different precursors take the latest precursor.

            WHEN row_count = 2 AND tran_count = 2 AND prec_count = 2  AND datedifft = 0 AND
max_tm= min_tm AND prec_rank = 1  THEN 1
            WHEN row_count = 2 AND tran_count = 2 AND prec_count = 2  AND datedifft = 0 AND
max_tm= min_tm AND prec_rank = 2  THEN 0

-- When there is one transformation but two possible precursor conditions and
-- the precursor conditions are in the same precursor_subtype (ie are basically
-- the same) take the precursor condition that is earliest (ie happened first).

            WHEN row_count = 2 AND tran_count = 1 AND prec_count = 2  AND datediffp > 0 AND
min_ps = max_ps AND prec_rank = 2 THEN 1
            WHEN row_count = 2 AND tran_count = 1 AND prec_count = 2  AND datediffp > 0 AND
min_ps = max_ps AND prec_rank = 1 THEN 0

-- When there is one transformation but two possible precursor conditions and
-- the precursor conditions are in different precursor_subgroups take the
-- precursor condition that is latest in time (ie nearest to the tumour).

            WHEN row_count = 2 AND tran_count = 1 AND prec_count = 2  AND datediffp > 0 AND
prec_rank = 1 THEN 1
            WHEN row_count = 2 AND tran_count = 1 AND prec_count = 2  AND datediffp > 0 AND
prec_rank = 2 THEN 0

-- When there is one transformation but two possible precursor conditions, but
-- they're both on the same day, take the one with the higher morphology code.

            WHEN row_count = 2 AND tran_count = 1 AND prec_count = 2  AND datediffp = 0 AND
max_pm != min_pm AND precursor_morphology||precursor_behaviour = max_pm THEN 1
            WHEN row_count = 2 AND tran_count = 1 AND prec_count = 2  AND datediffp = 0 AND
max_pm != min_pm AND precursor_morphology||precursor_behaviour != max_pm THEN 0

-- When there is one transformation but two possible precursor conditions but
-- they're both on the same day with the same morphology code, take the one with
-- the lowest tumourID as a tie break.

            WHEN row_count = 2 AND tran_count = 1 AND prec_count = 2  AND datediffp = 0 AND
max_pm = min_pm AND prec_rank = 1  THEN 1
            WHEN row_count = 2 AND tran_count = 1 AND prec_count = 2  AND datediffp = 0 AND
max_pm = min_pm AND prec_rank != 1  THEN 0

-- When there is a person with more than two transformations. Divide the
-- transformations into fundametally different types (using the three top level
-- GDO groups). Take the earliest transformation in each group. Take the latest
-- precursor condition that was allowed for that transformation.

            WHEN row_count >2 AND trans_rank_2 = 1 AND prec_rank_2 = 1 THEN 1
            WHEN row_count >2 AND trans_rank_2 != 1 THEN 0
            WHEN row_count >2 AND trans_rank_2 = 1 AND prec_rank_2 != 1 THEN 0
            ELSE 9999
      END AS dedup_flag
FROM at_tran_rank t
)

-- Tidy up the final table.  This makes 14,067 transformations on CAS2210,
-- of which 13,694 are not duplicates

SELECT precursor_tumourid||'.'||transformed_tumourid AS transformationID
     , patientid
     , precursor_tumourid
     , precursor_diagnosis_date
     , precursor_year
     , precursor_morphology
```

```
     , precursor_behaviour
        , precursor_description
     , precursor_subtype
     , precursor_broad_subtype
     , precursor_lineage
     , transformed_tumourid
     , transformation_date
     , transformation_year
     , transformation_morphology
     , transformation_behaviour
     , transformation_description
     , transformation_subtype
     , transformation_broad_subtype
     , transformation_lineage
        , trans_source
     , gavin_flag
     , dedup_flag
     , transformation_split_1
     , transformation_split_2
FROM at_transformation
;

GRANT SELECT ON at_transformation_haem TO analysisncr;
GRANT SELECT ON at_transformation_haem TO analysisuserid;

--------------------------------------------------------------------------------
--                                  FIN
--------------------------------------------------------------------------------
```

Appendix D: ICD O3 rev 2011 codes to define haematological malignancies – MORPH_HAEM table

This table is the master list of which ICD O3 rev 2011 codes of morphology and behaviour combinations should be counted as haematological malignancies. It is used by the code in Appendix A to define 'all haematological malignancies'. It also has columns for which sub-groups they should be assigned to. It is a copy of the ANALYSISHANHUALIU.GDO_MORPH_HAEM@CASREF01 table.

It can be found in the word document version of this SOP, which is available from the haematology lead, or on-line at *https://www.cancerdata.nhs.uk/getdataout* inside the grouping document for haematological cancers.

Appendix E: Codes to define haematological transformations according to the Gavin paper

This table is the master list of which pairs of malignancies should be counted as haematological malignancy transformations. It is used by the code in Appendix C to define 'haematological malignancy transformations' and create the transformation table. It follows the Gavin et al paper '*Towards optimal clinical and epidemiological registration of haematological malignancies: Guidelines for recording progressions, transformations and multiple diagnoses*. It is a copy of the ANALYSISANDREWBACON.GDO_TRANSFORMATION_HAEM@CASREF01 table.

It can be found in the word document version of this SOP, which is available from the haematology lead, or on-line at *https://www.cancerdata.nhs.uk/getdataout* inside the grouping document for haematological cancers.