A number of diseases exist in which the literature describes the potential for there to exist a recognised set of associated "systemic manifestations". In an attempt to model these systemic manifestations there has been a requirement to identify a modelling pattern which lies somewhere between the concepts of "Co-occurrent" and "Due to".

The issue arose from a discussion on how we should model the systemic manifestation of Sjögren's syndrome and the thread relating to this has been included below as background.

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Potential issues with the use of "Co-occurrence"

Dictionary definitions of 'Co-occurrent' include:
- occurring together or at the same time - "two disorders that are frequently co-occurrent" - Merriam Webster
- the fact of two things happening at the same time - "co-occurrence - the temporal property of two things happening at the same time; "the interval determining the coincidence gate is adjustable" - TheFreeDictionary

The slides suggest the following definition within the context of SNOMED Modelling:

"Use simple co-occurrence for 2 or more conditions without a known causal or temporal relationship associated by a common predisposition"

There are potentially a number of issues with this definition:

- Clearly there is a temporal relationship as we expect the two conditions to be present at the same time
- We are stating that there is no current evidence of a causal relationship BUT
- They are associated by a "common predisposition" - how do we differentiate between a "predisposition" and a "causal relationship"?

In achieving a suitable solution to these issues there are at least 2 use cases which need addressing:

1. The ability to record within the notes the patients current "disease state"
2. The ability to ensure that the modelling within SNOMED CT supports appropriate classification inferences.

Use case 1 requires us to provide sufficient clinical concepts to document both the underlying disorder and its 'manifestations'. For syndromes this will be the name of the syndrome in which the necessary and sufficient manifestations are acknowledged as being present and required for the patient to be said to have that syndrome. In addition, the presence of the genetic mutation which led to the syndrome may predispose that patient to have additional manifestations, each of which must also be recorded separately to gain the full picture of the expression of the disorder in that patient.

Use case 2 requires modelling of both the necessary and sufficient manifestations, currently this modelling does not include YYY (disorder) |Due to| |Deletion of part of XXX chromosome (disorder)| (what is the reason for not adopting |due to|?). However, if we wish to record a manifestation which is predisposed by the presence of the gene abnormality, but is not necessary to classify this as YYY syndrome then I assume we would have to consider the |Due to| modelling pattern and use a description something like "ZZZ with YYY syndrome due to deletion of XXX chromosome".

So, what I am trying to say here is that for syndromes there is a direct causal relationship between the chromosome abnormality and the manifestations, however, some manifestations are necessary in order for it to be "labeled as a syndrome", while there exists a predisposition to other manifestations some of which will be expressed and others that are not. Where we need to record the existence of the additional manifestation I think the use of co-occurrence, if defined as above, does not adequately represent our understanding of the association.
We could also consider diabetes and it's 'complications. I believe the current understanding of the complications is that abnormal blood glucose regulation leads to pathological changes to the microvasculature which in turn leads to damage to the end organs, retina, kidney, nervous system and peripheral vascular system etc. Therefore, having a diagnosis of diabetes mellitus predisposes one to all of the 'complications' as a direct result of the pathological process. However, while the individual may be predisposed to all of these manifestations, a combination of good blood glucose control and lifestyle may result in only some of the complications being manifested. We choose to use |Due to| in modelling in this instance - is there a clear and reproducible difference between diabetes and genetic syndromes which supports us taking a different modelling approach?

And so to Sjögren’s syndrome - There is a considerable amount of literature about Sjögren's syndrome both in the academic press, ClinicalKey (Elsevier) and UpToDate, in addition there has been a small number of large cohort studies which have looked specifically at the extra-glandular manifestations.

In essence and historically Sjögren's syndrome has been divided into "primary" and "secondary" where Primary Sjögren's syndrome is a systemic auto-immune disorder characterised by the presence of dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia) as a consequence of lymphocytic infiltration into the lacrimal and salivary glands. (https://bestpractice.bmj.com/topics/en-gb/175#referencePop1) and Secondary Sjögren's syndrome in which Sjögren's syndrome is present along with another autoimmune disease such as lupus, rheumatoid arthritis and systemic sclerosis. The presence of both Sjögren's syndrome and one of the other autoimmune diseases is a recognised entity, however, as yet there is no clear evidence that the underlying causal factors of each of the disorders is the same except that they are both due to an autoimmune process, however, they do not necessarily share the same autoimmune process. It is suggested that a combination of Sjögren’s syndrome with another autoimmune syndrome may, for some clinicians be useful to record as a single statement, although my personal preference is that they should be recorded separately - (indeed I couldn't find an instance of any concept which include Sjögren's syndrome plus another autoimmune disorder in SNOMED CT!)

If we accept "Co-occurrence" as a useful concept then I would suggest an alternative definition for consideration:

"Co-occurrence" is two or more disorders which are present at the same time in anyone individual, but in which there is currently no evidence that there is a causal relationship between the disorders.

Returning now to Primary Sjögren's syndrome. There is significant literature on the systemic extra-glandular manifestations of Sjögren's syndrome in the absence of a relationship with any other well defined autoimmune disorder with a prevalences of between 10% and 70%. See table below and http:\/\slash\www.medsci.org/v14p0191.pdf

Under normal circumstances, and for many other disorder I think we would call these complications and model them as |Due to|. However, I would accept that the pathogenesis is not well understood and therefore the association between Sjögren's syndrome and its associated systemic manifestations is not as strong as it is for diabetes mellitus and its complications.

What we require is a set of 'associations' which can be used by authors consistently and reproducibly with clear criteria for their definitions. I think we have this for |Due to| and |causative agent|. However, I do not think this is the case for "Co-occurrent" and/or a 4th category in which an association is clearly evidenced but for which, at this moment in time we are unable to evidence the cause.

I would like to suggest that |Associated with| may be a suitable candidate and would suggest the following definitions:

"Co-occurrence" - two or more disorders which are present at the same time in anyone individual, but in which there is currently no evidence that there is a causal relationship between the disorders.

"Associated with" - The presence of systemic manifestations of the primary disorder confirmed by evidence from clinical studies but at this moment in time we are unable to evidence the causal chain.

(I am sure we can come up with more succinct definitions but hopefully the above provides a basis for discussion)

I think the use of 47429007 |Associated with (attribute)| might be appropriate as later clinical studies and evidence may lead to a final decision that the association is either, 42752001 |Due to (attribute)|, 246075003 |Causative agent (attribute)| or |Co-occurrent (attribute)|.

In summary, I think I am saying:

1. We need much better clarity on the distinction between the various forms of "association" to enable consistent and reproducible authoring
2. I think there is an association which sits between |Due to| and my definition of |Co-occurrent| where there is clear evidence for the association without a causal relationship having been fully determined
3. I think the systemic manifestations of Sjögren's syndrome fit into the category which sits between my definition of |Co-occurrent| and |Due to|
4. The association between Sjögren's syndrome and Lupus, SLE RA etc. is currently at best co-occurrent