Ontological Model of Abnormal States and its Application in the Medical Domain

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ABSTRACT

Exchanging medical data and information is important in the medical domain. This paper discusses abnormal states in the definition of diseases. First, we introduce our unified representation framework of abnormal states in a property-decomposed manner, which enables interoperability between clinical data and abnormal states in the definition of diseases. Next, we propose our ontological model of abnormal states. In our model, common concepts can be kept distinct from specific ones. By applying this to causal chains of diseases, we can capture the commonalities of abnormal states across clinical divisions. This work will contribute to various applications for understanding knowledge about abnormal states with no ambiguity.

1 INTRODUCTION

In clinical medicine, medical data and information exchange are essential for many applications, such as electronic health records (EHR). We focus on abnormal states in the definitions of diseases which should be referred to in many applications and discuss a consistent manner of representing various abnormal states based on ontological theory.

Understanding abnormal states is a hard task. Among the many issues involved, one is the heterogeneity and the variety of grain sizes, from the level of cells, tissue, and organs, to the entire human body, resulting in diverse representations with little uniformity.

Another issue is that usually abnormal states in the definitions of diseases are a bit too conceptual (e.g., hyperglycemia in diabetes) to be compatible with clinical test data.

To tackle these issues, we have been systematically developing an ontological model of abnormal states from generic to specific levels with the aim of providing a unified, consistent framework. Currently, we are assessing the effectiveness of our model in our medical ontology and are looking into various possible applications.

This paper is organized as follows. In Section 2, we define abnormal states and introduce our representation model. In Section 3, we introduce our ontology of abnormalities. In Section 4, we show an application of our work. We built a disease ontology and captured a disease as one or more causal chains of abnormal states in the human body (Mizoguchi et al., 2011). Currently, clinicians describe causal chains of 17,000 abnormal states of 6,000 diseases across 12 clinical divisions, and use of our ontology will contribute to various clinical applications. Then, in Section 5, we discuss some related work, followed by concluding remarks.

2 DEFINITION OF ABNORMAL STATES

2.1 What is an Abnormal State?

In the human body, abnormal states are highly diverse and involve various grain sizes, from the level of cells, tissue, and organs, to the entire human body. Therefore, to systematize knowledge about abnormal states, it is important to clearly capture the essential characteristics of the abnormal states and to conceptualize them in a consistent manner.

In this section, we define abnormal states used in the definitions of diseases. *State* is modeled as an abstraction of a characteristic possessed by an individual, having the value of an attribute that changes with time (Mizoguchi, 2005), and usually corresponds to a time-indexed *Property*. For example, imagine a hunger state. It is represented by "being hungry", or not, at some time point it time. We define *Property* as an abstraction of a characteristic inhered in an entity and having an attribute, together with its value, such as "being red", that is, <color, red>. Properties are distinct from attribute values, for example, a property such as "tall", as in "He is tall", is differentiated from an attribute value such as "large", as in "His height is large"[1].

In many textbooks and dictionaries, diseases are defined in terms of abnormal states. For example, diabetes is explained as "Diabetes mellitus is characterized by chronic hyperglycemia with disturbances of..." (Kahn et al., 2005). Therefore, we can say that a disease is defined in terms of an assertion about the patient "being in abnormal states or not".

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[1] We discuss the differences in representation rather than reality.

In the medical domain, various types of representations for abnormalities are used, and we conceptualize these representations into three categories:

- Quantitative representation (e.g., blood pressure is 180 mmHg, blood glucose concentration is 135 mg/dL).
- Qualitative representation (e.g., blood pressure is high, blood glucose concentration is high).
- Property representation (e.g., hypertension, hyperglycemia).

Since the upper ontology YAMATO (Mizoguchi, 2010) is carefully designed to cover property, quality, and quantity ontologies, it supports our work on abnormalities.

A quantitative representation is important for diagnosis, since a concrete value for each patient should be identified by clinical examination. However, in the definition of a disease, among the above three kinds of representation, rather than quantitative data, a property such as "being hypertensive" or "being hyperglycemic" is essential.

Thus, as our basic policy, first, we capture abnormal states as properties, represented by a tuple like <Property (P), Property Value (Vp)>. Basically, Property Value takes a binary value, i.e., <existence / non-existence>. For example, if the state "stenosis" exists, it is described as <stenosis, existence> In addition, when necessary, a degree value can also be used for describing the degree of the Property Value, such as <stenosis, severe>[2].

Some readers may think that a property represented in the above way is too conceptual to be of practical use due to the lack of a representation giving concrete meaning to data. Therefore, we specify a property by decomposing it into a tuple: <Attribute (A), Attribute Value (V)>. Attribute Value can take either a Qualitative Value (Vql) or a Quantitative Value (Vqt). This approach contributes to promoting consistency in representation, as well as interoperability between quantitative raw data and generic/conceptual abnormality knowledge (see Section 2.3).

In clinical medicine, some properties cannot be decomposed, because the precise mechanisms in the human body have not been completely uncovered yet. For example, in the case of nausea, the property representation could remain undecomposed. Whether such abnormal states can be decomposed into a known attribute and its value will depend on advances in medicine.

A property representation has several advantages. First, it can capture the essentials of each disease easily because of its conceptual nature. Second, it is relatively insusceptible to small parameter modification. Third, it allows distinction between a definition of a disease and a diagnostic task that requires a quantitative representation.

[2] Since the stenosis can be further decomposed into < cross-sectional area (A), small (V)> (described later) that "severe stenosis" can be also described as <stenosis (P), severe (Vp), cross-sectional area (A), small (V)>.

Here, it should be noted that an abnormality can be explained as some bodily feature that is not part of the human life plan (unlike pregnancy) (Scheuermann et al., 2009); however, making a decision about whether or not a particular state is “abnormal” is the job not of ontologists but of medical experts, who must make the decision based on medical knowledge. For example, answering a question about whether or not a high HDL cholesterol level is an "abnormal state" is not the task of ontologists but that of medical experts; therefore, we do not discuss this issue in the present study.

2.2 Representation of Abnormal States

2.2.1 Standard Representation In this section, we introduce our representation model for clinical abnormal states and examine whether we can appropriately represent them in a consistent manner.

Because an attribute cannot exist by itself but always inheres in an independent object, we should identify the object (hereinafter referred to as “target object”). For example, in the case of "gastric dilatation", the target object of its attribute “volume” is nothing but the stomach. Accordingly, we introduce "Object" to represent the target object of an attribute and decompose a property into a triple: <Object (O), Attribute (A), Attribute Value (V)>. This is our standard representation model of abnormalities. For example, "gastric dilatation" is decomposed into <stomach, volume, large> (Table 1(a), row 1).

2.2.2 Advanced Representation We understand that some properties are difficult to decompose into the standard triple representation, such as a ratio and what we call a meta-attribute, discussed below. Accordingly, we introduce a "Sub-Object" (SO) to represent a focused object (see next paragraph) as an advanced representation, so that a property can be decomposed into a quadruple: <Object (O), Sub-Object (SO), Attribute (A), Attribute Value (V)>.

In the case of a ratio, in addition to identifying the target object having the ratio, it should represent what is focused on ("focused object"). Therefore, we represent it by a Sub-Object (SO). For example, the representation of "hyperglycemia" is a quadruple, <blood (O), glucose (SO), concentration (A), high (V)>, where Object is blood and Sub-Object is glucose (Table 1(a), row 3).

There seem to be different kinds of ratio depending on what is focused on. So, Object and Sub-Object vary according to the kind of ratio. Our representation model can represent all of them, as shown in Table 1(b). A detailed discussion can be found in (Yamagata et al., 2012).

Next, we show the representation of a meta-attribute. In the case of the property "gastric polyposis", color and size are attributes of polyps. However, "many polyps" is not an attribute of "polyps" since it is not inhered in each polyp. Following the meta-attribute approach in YAMATO, where, in the case of "the road is curvy", “number of curves” is identified as a meta-attribute of a road which has many

(a)

	Abnormal states (Property: (P))	Property Value (Vp)	Attribute (A)	Attribute Value (V)	Object (O)	Sub-Object (So)
Standard representation	Gastric dilatation Nausea	existence existence	volume	large	stomach Patient	
Advanced representation	Hyperglycemia Gastric polyposis	existence existence	concentration number	high many	blood stomach	Glucose Polyp

(b)

Variant of Ratio	Abnormal states (Property: (P))	Property Value (Vp)	Attribute (A)	Attribute Value (V)	Object (O)	Sub-Object (So)	Ratio
m/n (no unit)	high m ratio	existence	ratio	high	the whole blood	focused	m/n
example	Hyperglycemia	existence	concentration	high	blood	Glucose	Glucose/Blood
m/n (focused on m of same object)	high m ratio	existence	ratio	high	object	m	m/n
example	high Albumin ratio	existence	concentration	high	urine	Albumin	Albumin/Creatinine
m/n (focused on the ratio of same object)	high m/n ratio	existence	ratio	high	object		m/n
example	increased A/G ratio	existence	A/G ratio	high	blood		Albumin/Globulin

Table 1. Representations of abnormal states. (a): Standard and Advanced representations. (b): Representations of ratios.

curves, we regard "the number of polyps" as a meta-attribute of the stomach. By introducing "Sub-object", the property "gastric polyposis" is decomposed into a quadruple <stomach (O), polyps (SO), number (A), many (V)>, where stomach is identified as Object, and polyps are described as Sub-object, which collectively represent "number of polyps" (Table 1(a), row 4).

2.3 Interoperability between Properties and Attributes

Large amounts of clinical test data are collected in hospitals, most of which are quantitative data, e.g., blood glucose concentration of 140 mg/dL. Here, a threshold based on a generic value used in the domain is given, and a qualitative value can be obtained by comparing the threshold value with a quantitative value in the data. For example, a quantitative value (e.g., 230 mg/dL) is converted to the qualitative value "high" with a threshold (e.g., 126 mg/dL).

In this study, we do not deal with what concrete value is to be set for the threshold, because thresholds tend to change as time passes; for example, the cutoff value of Fasting plasma glucose (FPG) level was revised to 140 in 1980 and to 126 in 1999 (WHO, 1999). Therefore, we can change the threshold freely, and to do so is intrinsic. Nevertheless, even if the threshold changes, hyperglycemia always means <glucose concentration, high>.

Our representation model can transform raw data to a quantitative representation in the form <Object (O), (Sub-Object (SO), Attribute (A), Quantitative Value (Vqt)>. For example, the quantitative raw data "blood glucose concentration level of 260 mg/dL" is represented by <blood (O), glucose (SO), concentration (A), 260 mg/dL (Vqt)> as a quantitative representation, and can be further transformed to <blood (O), hyperglycemia (P), severe (Vp)>. As a result, it can be judged whether or not this constitutes "being an abnormality". Thus, it is demonstrated that our approach overcomes the interoperability problem between quantitative clinical test data and conceptual knowledge about abnormal states.

3 *IS-A* HIERARCHY OF ABNORMALITY ONTOLOGY

Clinicians work with strongly domain-specific knowledge, which causes difficulties in finding common and generic knowledge. What we need to do is to make a clear distinction between basic/generic concepts and specific concepts. To this end, we propose the following three levels of abnormal states (Fig. 1):

(1) Level 1: Generic abnormal states
(2) Level 2: Object-dependent abnormal states
(3) Level 3: Specific context-dependent abnormal states

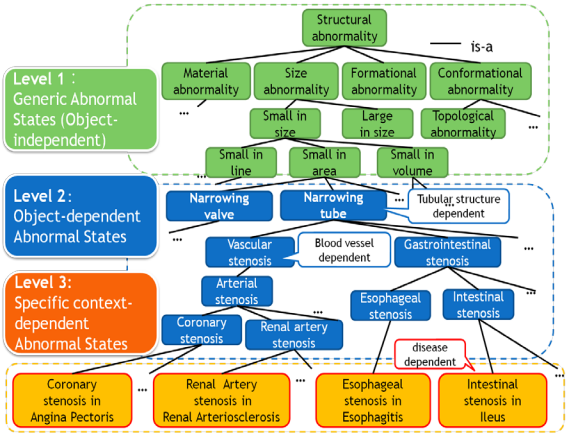

Fig. 1. Three-levels ontological model of abnormal states.

3.1 Level 1: Generic Abnormal States

Level 1 defines very basic (or generic) concepts, which do not depend on any structures, i.e., object-independent states. Examples include deformation, adduct formation, translocation, dysfunction, and so on, which are commonly found in several objects and are usable in many more domains besides medicine, such as machinery, materials, and aviation.

The top-level category of generic abnormal states has three subclasses: "structural abnormality", "functional abnormality", and "other abnormality" (Fig. 2). A structural abnormality is defined as an abnormal state associated with structure. It has sub-categories of material abnormality (e.g., degeneration), shape abnormality (e.g., deformation), size abnormality, and conformational abnormality, such as topological abnormality (e.g., translocation), struc-

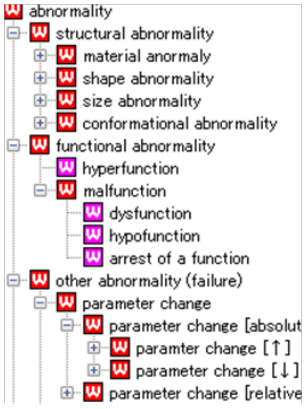

Fig. 2. Top-level categories related to abnormal states.

tural defects (e.g., adduct/loss of parts) etc., while still retaining the identity of the structural body in question.

A functional abnormality is defined as an abnormal state related to impaired function and is classified into hyperfunction and malfunction. Malfunction is subcategorized into dysfunction, function arrest, and hypofunction.

Other abnormal states include parameter abnormalities, which are classified into increased or decreased parameter, depending on whether or not the attribute has a higher or lower value than a threshold level. For example, increased/decreased pressure, increased/decreased weight, etc.

Our model has a recursive structure, in which generic abnormal states at Level 1 are referred to by Level 2 object-dependent abnormal states.

3.2 Level 2: Object-dependent Abnormal States

Level 2 defines object-dependent abnormal states. Top level concepts at Level 2 are dependent on generic structures, such as "wall-type structure", "tubular structure", "bursiform structure", etc., which are common and are used in many domains. Level 2 has been developed by identifying the target object and specializing generic abnormal states at Level 1 with consistency. For example, by specializing "small in area" at Level 1, "narrowing tube", where the cross-sectional area has become narrowed, is defined at Level 2, and this is further specialized in the definitions "oil pipe narrowing", "tracheal stenosis", and so on.

In the lower layer of Level 2, abnormal states that are dependent on the medical domain-specific objects, i.e., human anatomical structures, are defined and designed to represent concepts at all required granularities in the medical domain. Here, in general, one problem arises concerning the level of granularity that we need to support in our ontology. In the case of "stenosis", "coronary arterial stenosis" in a specific organ (the coronary artery) might be redundant. However, note here that abnormal states in one anatomical object influence the adjacent objects, which causes other abnormal states. For example, although both are stenosis, coronary arterial stenosis is different from rhinostenosis because the former causes myocardial ischemia and ischemic heart disease, whereas the latter causes sleep apnea. Therefore, there is a need for distinct abnormal states at specific organ levels.

From an ontological engineering point of view, our framework for modeling abnormal states is intended to capture abnormal states from generic to specific levels, so as to provide abnormal states at the required granularity of specific organ / tissue / cell layers in the medical domain.

Here, abnormal states of a specific object defined at Level 2 should be distinct from the disease-dependent concepts at Level 3. For example, hyperglycemia is defined in a context-independent manner at Level 2, and this is referred to in Level 3 concepts in various diseases, such as diabetes, metabolic syndrome, lipodystrophy, and so on.

3.3 Level 3: Specific Context-dependent Abnormal States

Level 3 consists of context-dependent abnormal states, which refer to Level 2 abnormal states and are specialized into specific disease-dependent ones. For example, "rectal stenosis", which is dependent on the rectum at Level 2, is defined as a constituent of Crohn's disease at Level 3, which is also defined as a cause or a result of other diseases, such as rectal cancer, Hirschsprung disease, intestinal tuberculosis, etc.

3.4 Specialization of an Abnormal State

We illustrate an example of specialization of an abnormal state from a generic level to a specific level. The generic abnormal state "Small in area" at Level 1 is defined by <area (Attribute), small (Qualitative Value)>. Next, at the top level concepts of Level 2, by identifying the target object as "tubular structure", and specializing it into <cross-sectional area, small>", we can define "narrowing tube", where the cross-sectional area of tube has become narrowed. Lower concepts at Level 2 are specialized to represent abnormal states specific to human anatomical structures. For example, "vascular stenosis", which is dependent on "blood vessels", is further specialized into "coronary stenosis", which is dependent on "coronary artery". Furthermore, "coronary stenosis" at Level 2 is specialized into a disease-dependent one at Level 3, for example, angina pectoris-dependent. In angina pectoris, coronary stenosis causes myocardial ischemia.

In this way, our ontology can distinguish common concepts from specific ones. Such an ontological approach contributes to finding commonalities not only across diseases in one division but also across divisions. For example, in cardiovascular medicine, "coronary stenosis" in ischemic heart disease has a commonality with "aortal stenosis" in aorta syndrome in that they have the same upper abnormal state "arterial stenosis", and also has a commonality with "cerebrovascular stenosis" in brain infarction in cerebral surgery in that they have the same upper abnormal state "vascular stenosis". A further commonality can be found with "intestinal stenosis" in the ileus in gastroenterological medicine in that they have the same generic structure-dependent abnormal state "narrowing tube". Therefore, finding commonalities across clinical divisions gives a multidisciplinary perspective, allowing our method to be applied to a wide range of research.

4 APPLICATION WORK

(1) Causal chains of disease

As mentioned in the introduction, we have been developing a disease ontology in which a disease is defined as a causal chain of abnormal states (Mizoguchi et al., 2011). We introduce an *is-a* relation between diseases using the chain-inclusion relationship between causal chains. If the core causal chain of disease A is included in that of disease B, then disease A is a super type of disease B. This judgment is

based on the inclusion of abnormal states, and an *is-a* relation between the abnormal states should be considered, as well as sameness of the abnormal states. Currently, clinicians describe causal chains of diseases and abnormal states. We have been using these abnormal states to develop an *is-a* hierarchy of abnormalities.

Abnormal states used in disease definitions in the ontology are defined as abnormal states at Level 3, where clinicians defined diseases in the respective clinical divisions. We collected all causal relationships from all disease concepts defined in the 12 divisions and combined causal chains including the same abnormal states. As a result, generic causal chains that contain all causal relationships including the 17,000 abnormal states from 12 medical departments can be generated (Kozaki et al., 2012). For example, assume that a cardiovascular specialist in the division of cardiovascular medicine describes "coronary stenosis" and its causal chain <coronary stenosis → myocardial ischemia → myocardial hypoxia> in ischemic cardiac disease. This can be linked with "coronary stenosis" in other diseases (e.g., hyperlipidemia) in other divisions (metabolic medicine). As a result, a generic causal chain <accumulation of cholesterol → coronary stenosis → myocardial ischemia → myocardial hypoxia> of hyperlipidemia can be obtained as a possible causal relationship of abnormal states in the disease.

In this way, across the 12 divisions, all 17,000 abnormal states can be captured with both the *is-a* hierarchical structure of the abnormality ontology, i.e., a vertical relation view, and with a causal chain as a relationship between different classes of abnormal states influenced by each other at the same level, i.e., a horizontal relation view. This allows us to integrate fragmented knowledge of abnormal states, which might allow the application of various kinds of medical knowledge, as follows.

(2) Conceptualization with no ambiguity

There are quite a few ambiguous medical terms that have the same name but different meanings. One reason behind this is that clinicians use each term in the context of specific diseases in their own divisions. For instance, the medical term "cardiac hypertrophy" is used in both cardiovascular medicine and metabolic medicine. On the one hand, in cardiovascular medicine, it means the thickness of the heart muscle, which results from pressure overload, i.e., hypertension in the context of the heart. On the other hand, in metabolic medicine, it implies glycogen accumulation in the heart muscle in glycogenosys, which is caused by metabolic dysfunction. Since our model can provide appropriate upper levels of concepts and can give contextual information, it is possible to clarify their difference.

In such a way, our model can reveal the context of the meanings that is usually hidden in the implicit background knowledge of clinicians and will contribute to making a clear distinction between different types of concepts.

(3) Management of attributes by unified representation

If we allow clinicians to freely express various attributes/abnormalities, it would lead to a lack of consistency and interoperability. Our model solves this problem by giving a unified representation model of attributes/abnormal states, discussed in Section 2, in which differentiation between attributes and properties is clearly made, and properties are decomposed into <attribute, attribute value>, as well as the advanced representation for ratios, meta-attributes, etc.

(4) Quantitative assessment of commonality

Traditionally, abnormal states have been dealt with in a manner specific to each disease in a particular medical division. Here, our model enables us to capture abnormal states common to many diseases, i.e., those that are at the first two levels and that are disease-independent, which allows clinicians to look over all abnormal states across clinical divisions.

As a result, we can quantify and assess the degree of commonality of abnormal states between different clinical divisions. It is also possible to verify the commonality of generic concepts by abstracting, or to find disease-specific abnormal states with no commonality to any disease in other divisions. For example, "esophagostenosis", which is a subclass of "narrowing tube", might demonstrate that it is specific to esophageal disease by showing no commonality with other diseases, whereas vascular stenosis can be confirmed as being more common by showing a higher rate of commonality across multiple diseases. Furthermore, our model might find commonalities of abnormal states that have always been treated as quite different abnormal states in different divisions.

Clinicians' treatment of abnormal states in a manner specific to a disease and/or particular clinical division might have caused fragmentation of the same concept into different concepts that are treated as different ones. Since our approach finds commonalities of organ-independent abnormal states, we can clean up and deal with abnormal states more simply.

Thus, our ontology will provide a clue to revealing the context embedded as background knowledge, which will allow us to compare abnormal states and evaluate their commonalities across clinical divisions.

(5) Commonality of the relationships between abnormal states

Assuming that we find commonality of a single abnormal state, we can find further commonalities of the relationships of abnormal states. As stated above in section (1), we can obtain generic causal chains across divisions. Since each abnormal state in the generic chain can also be generalized by using an *is-a* hierarchy of abnormal states, we can build layers of generic causal chains. We would like to find upper-level commonalities of causal relationships and examine whether or not they have any scientific significance. In our preliminary work, we found some causal chains at the conceptual level, such as <narrowing tube → decrease in flow rate → lack of supply>. In addition, the possible causes of

"decrease in flow rate" are summarized as the following three cases:

- <decrease in input flow of a tube → decrease in output flow rate>. In this case, the tube is normal.
- <adduct formation inside tube→ tubal occlusion → decrease in output flow rate>.
- <contraction movement of tube → decrease in output flow rate>.

Verifying the differences of causal chains and clarifying the specificity will help to identify which state is influenced. Our study might give insights into the basic principles underlying the processes, such as extending or branching, and furthermore, might provide insights into pathogenesis and identify the therapeutic target of diseases.

(6) Infrastructure of Integrated System for Abnormality Knowledge

Since our representation model has interoperability between qualitative data and the properties of abnormalities, it will contribute to developing an integrated system for clinical test databases, interoperable processors for quantitative, qualitative and property representations, and knowledge space for abnormal states in diseases.

5 RELATED WORK

Upper ontologies such as BFO (Grenon et al., 2004), DOLCE (Gualiano, 1998), and Galen (Rector et al., 1996) also deal with qualities; however, each of these ontologies has its own formalism. BFO uses <Entity, Property> (e.g., <rose, red>), whereas DOLCE uses <Entity, Attribute, Value> (e.g., <rose, color, red>), and Galen uses <Entity, Property, Value>, (e.g., <rose, redness, high>).

The YAMATO ontology offers interoperability among all of these descriptions, thereby allowing us to handle all three kinds of description in our representation model.

Phenotypic Quality (PATO) (Gkoutos et al., 2004) is an ontology of phenotypic qualities, in which the description was changed from <Entity, Attribute, Value> to <Entity, Property (Quality)> (e.g., <eye, red>) when they employed BFO. Our representation model has interoperability with both descriptions (Masuya et al., 2011).

In the medical domain, many communities have developed their own ontologies, such as OGMS (Scheuermann et al., 2009) and DO (Osborne et al., 2009). However, they do not have causal relationships between abnormal states in one disease. Our strategy will contribute to providing useful information about the causes of diseases from the viewpoint of the causal relationships of abnormal states.

6 CONCLUSION

We discussed a representation model of abnormal states designed in a unified manner. Currently, we apply this model to 17,000 abnormal states from 6000 diseases. We demonstrated that our model has interoperability between quantitative and qualitative data and the abnormal states. With this model, we developed an ontology of abnormal states from generic to specific levels. In the application we considered, we built disease chains consisting of causal relationships of abnormal states. By combining disease chains (horizontal relations) and the ontology (vertical structure), we can capture all causal relations of the 17,000 abnormal states in the 6,000 diseases across 12 clinical divisions.

While abnormal states have traditionally been thought to be specific to each disease in a particular clinical division, our approach is able to find commonalities among abnormal states across clinical divisions. This work might give insights that will lead to medical progress.

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