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*Published in:*
Human Mutation

*DOI:*
10.1002/humu.23144

2017

*Document Version:*
Peer reviewed version (aka post-print)

# How to Define Pathogenicity, Health, and Disease?

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Hum Mutat 38:129–136, 2017.

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## ABSTRACT

Scientific and clinical communities produce ever increasing amounts of data and details about health and disease. Our ability to understand and utilize this information is limited because of imprecise language and lack of well-defined concepts. This problem involves also the principal concepts of health, disease, and pathogenicity. Here, a systematic model is presented for pathogenicity, as well as for health and disease. It has three components: extent, modulation, and severity, which jointly define the continuum of pathogenicity. The model is population based, and once implemented, it can be used for numerous purposes such as diagnosis, patient stratification, prognosis, finding phenotype–genotype correlations, or explaining adverse drug reactions. The new model has several benefits including health economy by allowing evidence-based personalized/precision medicine.

KEY WORDS: pathogenicity model; pathogenicity zone; pathogenicity; disease; health; disease severity; disease extent; disease modulation; individual variability

Contract Grant Sponsor: Swedish Research Council; Barncancerfonden.

## BACKGROUND

Pathogenicity is a concept that has several different and even confusing meanings. Traditionally it has been used for describing the quality or state of being pathogenic or capable of producing disease, especially in the case of microbes. Increasingly, pathogenic and pathogenicity have been used also in other meanings, especially related to the phenotypes caused by genetic variations. The terminology has been further puzzled by commonly mixing the individual and population levels.

Genetic variants have been considered as pathogenic or harmful when they appear in patient(s) and cannot be found in a healthy control population, they alter the function of a gene product and/or cosegregate in families. None of these conditions is conclusive. Many variations have variable expressivity and can appear in healthy subjects as well as in those with disease. Functional tests are difficult to interpret even when available, as one need to find out what change level causes disease, a parameter that has personal variation. *De novo* variants are frequent in many diseases reducing the significance of cosegregation. Thus, a new systematic and practical definition of pathogenicity is needed.

To define pathogenicity, we have to start by defining health and disease as they are the two extreme ends of the spectrum. The concept of disease has usually been defined as a negation of health. Even health has not been clearly defined, although several suggestions have been presented. The definition of the World Health Organization (WHO), "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO), has been widely used—and criticized. Different schools of philosophers have tried to define the concept of disease. Normativists argue disease to be a value judgment [Engelhardt, 1975], whereas according to naturalists, especially the biostatistical theory [Boorse, 1975], disease is a deviation from the normal bodily function. The latter is claimed to be objective and a value-free approach referring to a group of individuals with similar age, sex, and ethnicity. Even this approach is value-laden because of the choice of the reference group [Kingma, 2007].

For naturalists, disease is epistemically a measurable situation. A triad of the concepts disease, illness, and sickness has been used for describing the physical, psychological, and social aspects of wellbeing, respectively [Twaddle, 1974; Nordenfeldt, 1987]. Additional aspects of health and disease left outside this triad include cultural, ecological, economical, and political determinants and outcomes of health. Further, legal frameworks, practices, and policies have also an important impact. The choices of the definitions for health and disease have practical implications to healthcare by defining or contributing to decisions on what should be treated, who should be treated and how, the justice of healthcare, contents of health plans, and overall health economics.

A widely accepted, utilized, and applied pathogenicity concept would allow consistent diagnosis and treatment of conditions as well as to permit prognosis and follow-up of disease evolution, likely contributing to improved healthcare and health economy. Additional benefits are related to the increased understanding of diseases and their mechanisms and facilitating development of novel interventions, as well as the possibility to develop better predictive models for prognosis of diseases.

Pathogenicity has been considered to contain or to be based on certain factors, which, however, have been poorly or vaguely defined and without a consensus. Some of the terms and their definitions are discussed here to highlight the imprecise language and the lack of systematics in this field. Virulence has been used as a synonym for pathogenicity, but also as the degree of pathogenicity caused by

pathogens, that is, microorganisms. Expressivity is widely used in the sense of capacity to affect phenotype but also as an extent of pathogenicity caused by a microorganism, whereas severity describes the stage or degree of disease. By penetrance has been meant the probability of a gene or genetic trait to be expressed. Pathogenicity has been presented to be the product of infectivity (ability to establish an infection) and virulence in the case of infectious diseases, but this model has been found to be too simplistic. Still other definitions appear and are often overlapping and contradictory.

To allow systematic description and use of the concept of pathogenicity, a new generic definition applicable to all kinds of conditions is presented. First, we define the components and then present how they jointly describe pathogenicity. The model aims at being a practical tool for clinicians and researchers. It can be used in many areas for descriptive and predictive purposes including pharmacogenomics, public health, epidemiology, diagnosis and treatment, as well as for prediction and prognosis. The new model is presented for pathogenicity on population level, but it can also be applied on individual level once enough data are available to populate the space of variability.

It is essential to distinguish phenotype and pathogenicity, which have sometimes been mixed up. Pathogenicity deals with being diseased (ranging from healthy to severely ill), whereas phenotype characterizes the presence of signs, symptoms, and indications. The importance of structured phenotype data has been pointed out [Deans et al. 2015] and there are on-going projects to define phenotypes including the Human Phenotype Ontology [Robinson et al. 2008]. Systematics is available also for describing the effects and mechanisms of DNA, RNA, and protein variants by using the Variation Ontology [Vihinen, 2014]. Here, a framework for systematic description of pathogenicity is presented.

## COMPONENTS OF PATHOGENICITY

The new pathogenicity model (PM) contains three components: extent, modulation, and severity. Specific and unambiguous terms and definitions are needed for the pathogenicity components. Many existing terms either have several meanings depending on the context and/or they refer to individuals, whereas the PM is for the population level. Unambiguous terms are a necessity for systematics; for problems with muddled terminology in genetics see Vihinen (2015).

The concepts of the pathogenicity components are described in Box 1. A single or even two components are not sufficient determinants of pathogenicity. Pathogenicity is described jointly by the three factors based on the distribution in a large cohort of healthy and diseased individuals. Jointly the three components define pathogenicity in all situations. Severity of the disease indicates the stage or degree to which a disease is expressed. Extent measures the breadth of disease appearance. Modulation means the combined effect of numerous factors that modify the disease phenotype.

The model is intended to be applicable to all types of diseases, all types of genetic variations and inheritance modes, and all types of regulators, modifiers, and so on. This is achieved by collecting and using data for each condition, thus there should be as many implementations as there are diseases with sufficient amounts of cases.

Several terms are related to, but not synonymous with, the three disease components (Box 1). Penetrance is related to morbidity and virulence, but has a different meaning in population biology as

a measure of the proportion of population carrying an allele and expressing phenotype. This is related to extent, but it has the intrinsic assumption of being disease related, whereas extent ranges from healthy non-syndromic cases to those having a fully blown phenotype. In epidemiology, penetrance indicates the proportion of a population found to have a condition, so it has a single value instead of the continuum as in extent. A further problem with the penetrance, and causing confusion, is that it means also the probability of clinical manifestations of trait carriers at the individual level.

Emergence is used for describing the appearance of infectious diseases. Virulence refers to the ability of a microorganism to cause a disease. Similarly, infectivity means the ability to produce infection. In population biological sense, morbidity means the incidence or prevalence of a disease, but it means also the state of being diseased at individual level.

Expressivity is related to severity and is used for describing the degree to which a genotype is phenotypically expressed in individuals. This term includes also the assumption that there is a disease phenotype to express and thus excludes the non-pathogenic end of the spectrum. Expressivity is typically discussed in the context of incomplete or variable expressivity, whereas the severity scale ranges from benign to fatal (depending on the disease).

Numerous studies have already been published on the components of pathogenicity; however, their joint effect has not been investigated. Severity has been presented to be the total effect on organ function and to consist of both irreversible and reversible components [Medsger et al. 2003]. Disease severity schemes and scoring systems have been developed for many conditions. These include the Follicular Lymphoma International Prognostic Index (IPI) [Solal-Celigny et al. 2004], the Japanese severity score for acute pancreatitis [Hamada et al. 2013], several schemes for hidradenitis suppurativa [Martorell et al. 2015], the disease severity scoring system (DS3) for type 1 Gaucher disease [Weinreb et al. 2010], the sepsis-related organ failure assessment (SOFA) score [Vincent et al. 1996], and many others. Staging and grading systems are available for cancers (2010), chronic graft-versus-host disease [Filipovich et al. 2005], idiopathic pulmonary disease [Homma et al. 2015], chronic kidney disease [Levey et al. 2005] and other diseases. Apart from the disease specific scores there are systems for other purposes, such as the intensive care unit (ICU) patient scoring and performance evaluation, which can be used to triage patients. These include the Acute Physiology and Chronic Health Evaluation (APACHE) [Zimmerman et al. 2006], the mortality probability model (MPM) [Higgins et al. 2007], and the simplified acute physiology score (SAPS) [Metnitz et al. 2005]. Scoring systems should be feasible, reliable, and valid to be useful. They are typically developed by expert groups.

Incomplete penetrance and heterogeneous expressivity have usually been linked to diseases with autosomal dominant inheritance, but these features apply to almost all diseases, at least to some extent. Variable expressivity of disease severity is common in many diseases causing the appearance of different phenotypes [Cooper et al. 2013; Zlotogora, 2003]. Pleiotropy refers to multiple phenotypes due to variations in a single gene. Severity is modulated by diverse factors depending on the disease. These include a combination of genetic, environmental, and lifestyle factors.

The extent of disease has been considered in numerous conditions. Depending on the situation, it has meant, for example, the spread of a tumor [Matthay et al. 2010], affected surface area in Crohn's disease [Daperno et al. 2004] or cutaneous T-cell lymphoma [Dippel et al. 1997], or plaque distribution in coronary heart disease [Lin et al. 2008]. Dedicated disease extent indexes have been

developed for Wegener's granulomatosis [Reinhold-Keller et al. 1994] and several for coronary artery plaques [Dash et al. 1977; Califf et al. 1985; Sullivan et al. 1990; Bogaty et al. 1993;Mark et al. 1994].

In here, extent means more generally the extent or degree of disease, details varying for conditions. Differences in phenotypes due to genetic variations are largely influenced by modifiers [Dowell et al. 2010]. The effects of combinations of the modulators on phenotype have seldom been studied, instead the effects of individual factors have been extensively investigated, for a review see Cooper et al. (2013). These factors include age, sex, disease history, nutrition and nutritional history, ethnicity, modifier molecules; genetic factors such as allele dosage, oligogenic variants, copy number variants (CNVs), imprinting, lyonization, and epigenetics; complex genetic and environmental interactions; immune system status and its history; microbiome; alternative splicing; gene/protein expression patterns, and others.

The PMs are applicable to all types of genetic variations, whether nucleotide substitutions or large structural variations, whether affecting DNA, RNA, or protein, independent of inheritance mode and whether the disease is Mendelian or not, or having effects on structure, function, interactions, or other properties of biomolecules. The model describes also non-genetic diseases whether of external or internal causes. The features of pathogenicity are not unique for human conditions, instead apply to all organisms. Penetrance (and consequently extent) and disease severity have been found to bear complex correlations also in plants [Seem, 1984].

## PATHOGENICITY MODEL

Previous definitions of pathogenicity have limitations, so a new model as a sum of three components is introduced. The model can be visualized in a cube, where the three factors are on the axes (Fig. 1). The cube summarizes the situation for a population and is filled with data points representing the pathogenicity profiles of a large number of individuals. The data points form a cloud or zone that ranges from the normal, benign situation to the most severe, in certain diseases to fatal, condition in the other end. Variations in the contributions of the three factors lead to the formation of a more or less thick cushion or layer through the cube and is called for pathogenicity zone (PZ) as it represents the combined variability of the components in the space of pathogenicity.

Population wide studies are needed to obtain comprehensive pathogenicity information. The contributions of the three components depend on the disease and have to be solved case by case. The PZ clearly explains how for example a similar genotype, even for monozygous twins, can lead to different phenotypes because of the combined effect of the pathogenicity components. Different modulation effects due to, for example, environmental factors lead to placement of individuals in different parts of the PZ. It is important to bear in mind that a certain condition caused, for example, by genetic variations only in exceptional cases causes exactly the same phenotype for all carriers. This applies to extremely harmful variants that frequently lead to abortion or death at birth or soon after. The pathogenicity pattern may for a certain disease vary based on ethnicity due to genetic and other differences, thus several population specific PMs may be needed or have to be adjusted.

The shape and position of the PZ varies from disease to disease. The very severe diseases have a very steep and thin PZ, whereas diseases with more variable outcome have a less steep and thicker PZ.

The end for the severest pathogenicity gets narrower as one move toward the maximum of all the three components. The lower end of a non-pathogenic or normal phenotype may under less severe conditions remain in the non-pathogenic region for a large part of the graph. Note that for a disease to be extremely pathogenic, all the three components have to contribute. For example, even a life-threatening disease cannot have a phenotype unless it has an extent above a certain threshold.

In the exceptional case of a fully binary phenotype with two clearly distinct traits without any intervening states, severity and extent mean the same because the expressivity and penetrance are the same at the individual level. The majority of diseases have a continuum of phenotypes and PMs can be applied to them.

To establish the PM for a disease, cohort or population studies are needed. This could be organized or supervised by societies for diseases, major research laboratories and (inter)national consortia. The applied approach depends on how the research and clinical field for a condition is organized, therefore well-studied conditions provide good starting points. Once the pathogenicity profile is defined, it can be used for numerous purposes. How to define the pure contributions of each component independently can sometimes be challenging and is disease specific.

The PMs are independent for each disease and are not directly comparable. Pathogenicity is unique for each condition, for example severity has a different extent depending on the condition; however, the PM ranges always from benign to the most severe form of the condition.

## APPLICATIONS OF THE PM

### Diagnosis

Pathogenicity is a continuum ranging from benign and very mild to most severe, even lethal, forms. It is apparent that many, if not all, diseases have a continuum of severity and pathogenicity. For example, elevated blood pressure is diagnosed as hypertension when a certain threshold value is exceeded. These kinds of thresholds are somewhat arbitrary, still practically useful and originate from evidence based medicine. The pathogenicity continuum has a number of corollaries. In Figure 2A–C, how each of the combinations of two components is variable at a certain, fixed level of the third component is shown. Such cutoffs can be used for various purposes and can appear at any angle necessary in the graph. One such plane can be used for diagnosis of diseases to identify cases that surpass a set threshold. From the PM graph, it is evident that individuals with a diagnosis have widely variable combinations of the values for the pathogenicity components. The plane for diagnosis distinguishes between health and disease, which both are highly variable with regard to the combined effect of the pathogenicity components.

PMs could be integrated with other information to build clinical diagnosis support systems, which are already implemented in some areas [Samarghitean and Vihinen, 2008; Velickovski et al. 2014; Jabez Christopher et al. 2015]. In addition to the diagnostic level of pathogenicity, additional thresholds could be implemented.

### Actionability

Another threshold in the PMof a certain disease can define which cases are actionable. This cutoff can be different from that for diagnosis. Actionable cases are those that can be treated with existing regimes and have a combined pathogenicity so that treatment is both essential and beneficial. In certain conditions, actionability may be missing due to the lack of suitable interventions for treating

patients.

A metric has been presented for the actionability of incidental findings from sequencing [Berg et al. 2015]. According to this scheme, there are five elements including severity and likelihood of the disease outcome, efficacy and burden of intervention, and knowledge base, that is, degree of evidence. This model includes information of intervention that is not used in the PM and provides a single score that is simplistic compared with the PM. Stratified actionable cases can be defined from the PM and then the physician can make a decision with additional information whether there would be expected outcome.

Actionability has recently been discussed largely in the context of incidental or secondary findings from sequencing; however, as the PM indicates, it has a much wider impact and application area. For cancer classification, a system was designed for variants detected in molecular profiling [Sukhai et al. 2016].They have five tiers based on the actionability ranging from not clinically actionable to variants applicable for direct patient care. Widely adapted guidelines are available for the interpretation of sequence variants in general, not only in cancers [Richards et al. 2015].

**Stratification, Pharmacogenetics, and Adverse Drug Effects**

Some diseases have widely variable spectra of pathogenicity even so that variants in one gene can lead to distinct disease forms depending, for example, on how and where the genetic variants have effect. In the case of the Wiskott-Aldrich syndrome protein (WASP), variants in altogether four diseases have been noticed including the intermittent X-linked thrombocytopenia (XLT; MIM#313900), XLT (MIM# 313900), and Wiskott-Aldrich syndrome (MIM# 301000) for decreased protein activity, and congenital neutropenia due to gain-of-function (MIM# 300299) [Ochs and Thrasher, 2006]. The disease-causing variants have clearly distinct characteristics in each disease form[Vihinen, 2014] but all affect the same system. The PM can be used for stratification of patients to disease forms by applying relevant thresholds.

Sickle cell anemia is a classic example of a disease where modulation has great impact. The patients have the same genetic defect, still their phenotypic diversity is very wide ranging from benign to life threatening because of the effect of modulators [Steinberg, 2009]. Depending on the degree of a defect on dystrophin DMD gene, the patients have either Duchenne muscular dystrophy (MIM# 310200) because of completely inactivated gene or protein or Becker muscular dystrophy (MIM#300376) because of partially impaired function [Flanigan, 2014]. Another example of a protein activity degree related disease emerges due to inactivating and activating variants of ret proto-oncogene *RET* gene. Reduced or missing activity leads to Hirschsprung disease whereas increased activity causes multiple endocrine neoplasia type 2 [Amiel et al. 2008].

PMs provide ideal opportunities for deriving genotype–phenotype correlations. Stratified subgroups can be investigated for correlation with genetic features. When such correlations are detected, they

will increase the understanding of the bases of diseases, and allow for the development of novel predictors.

Another example where stratification is useful is related to pharmacogenomics and drug effects. The variability in the PM can explain why some individuals benefit from a certain medication, whereas others do not respond or even have adverse drug reactions (ADRs). Depending on the combination of the pathogenicity components, the drug use outcome may vary. The PM could help in stratifying cases into a sub-cohort where there is maximal efficacy as well as detecting those individuals who should avoid using the drug, thereby maximizing the benefits and minimizing the risks and costs of treatment.

The potency of drugs is measured either as half maximal inhibitory concentration ($IC_{50}$) or half maximal effective concentration ($EC_{50}$) for antagonists and agonists, respectively. The optimal treatment concentration can be achieved by stratifying a target group having benefit of the drug based on the PM. Similarly, the median lethal dose of toxins, radiation, or pathogen ($LD_{50}$) can vary greatly based on the individual variation. By including information for drug absorption, distribution, metabolism, excretion, and toxicity (ADMETox) to the PM the actual reason for the adverse reactions in the stratified populations can be exposed. Even the dosage within the therapeutic window of drugs could be related to the PM for the condition and tailored for individual needs in precision medicine.

ADRs are frequent causes of hospital admissions, morbidity, and mortality. The PM could be used to chart patients with whom certain combinations of the pathogenicity components display ADRs and then to stratify patients based on this information. We can conclude that the PM can contribute toward risk-benefit profiles of medicinal compounds, detection of cohorts having optimal efficacy and minimizing ADRs, all having substantial economical and medical benefits.

**Prognosis and Severity**

Several disease-specific models and predictors have been developed for morbidity and mortality. Many, if not all of them, would benefit from taking the PM into account. Definitions of severity are available for many diseases, even multiple somewhat different definitions, which can lead to different and controversial diagnoses of patients. The severity scores can be replaced or improved by using PM-based thresholds that take into account the variability of the pathogenicity components. The existing severity, staging, and grading scores lack the three component joint effect, thus being simpler and less precise estimates. An example of multiple severity scores is the prediction of coronary artery disease risk by three metabolic syndrome definitions, those from the International Diabetes Federation (IDF), the National Cholesterol Education Program Adult Treatment Panel III (ATPIII), and the WHO criteria [Chang et al. 2012]. When comparing the methods, the overlap for penetrance was only 25% and the ratio of patients diagnosed in the cohort varied from 33.9% to 52.8%. The PM can solve this kind of controversies and provide a consensus because the high variability among the patients can be taken into account and thereby defining a relevant threshold.

Several international organizations and consortia have worked toward defining pathogenicity and grouping cases in certain diseases, including The International Society for Gastrointestinal Hereditary Tumours Incorporated (InSiGHT) that has classified patients with mismatch repair gene defects in gastrointestinal cancers [Thompson et al. 2014]. These classification schemes contain typically five categories such as pathogenic, likely pathogenic, likely benign, benign, and

unclassified variations. It remains to be seen how many categories are required for the best way of classifying diseases when PM models are utilized. Too fine-grained classification is likely not useful and applicable because the model indicates that there is large heterogeneity in the outcome and therefore groups may be somewhat overlapping and thus have poor ability to differentiate classes.

The number of classes has been limited in most variant tolerance (pathogenicity) predictors to two [Niroula and Vihinen, 2016], and even those with three classes have better performance when classes are combined to two (benign/pathogenic) [Thusberg et al. 2011]. Recently, the PON-P2 tool that has a third class for unclassified variants was shown to have good performance [Niroula et al. 2015]. In many diseases, it would be important to detect and predict intermediate cases, as the example of WASP-related diseases depicts, since the different disease forms could be amenable for different treatment, follow-up and prognosis.

The PM allows basis for describing differential morbidity. The combined effect of the three factors is variable as manifested in how sick the patients are and how the pathogenicity varies. The model may prove useful also for explaining epidemies and pandemies as collective population-wide vulnerabilities for disease agents.

The existing severity/morbidity/mortality scoring schemes including, for example [Vincent et al. 1996; Flacker and Kiely, 2003; Solal-Celigny et al. 2004; Porock et al. 2010; Hamada et al. 2013] aim at taking into account uncertainties often by applying fuzzy logic where truth values of variables vary [Watari et al. 2014; Mak, 2015; Miranda and Felipe, 2015]. Fuzzy sets and logic are largely dependent on the initial setup. The cutoffs are somewhat arbitrary and for example calculated grade ranges have been used to deal with the uncertainty [Blanks, 2011]. Fuzzy logic and similar approaches apply cutoffs based on the algorithm without deeper insight into the condition, as when using the PM.

The PM could be applied even to some comorbidities. This could be done, for example, by including comorbidities to the modulation component in sufficiently large datasets. Comorbidity is another example of an unclear concept [Valderas et al. 2009]. Here, it means the combined effect of two or more diseases. Several approaches have been released for estimating the combined effect of coexisting diseases including the Charlson index [Charlson et al. 1987], the Elixhauer index [van Walraven et al. 2009], the Cumulative Illness Rating Scale (CIRS) [Linn et al. 1968], and others. These scores are based on summing the existence of conditions sometimes together with medication information. Unlike the PM, these approaches do not take into account the variability between individuals.

## GENERALIZED EXAMPLE

A generalized example explains how the issues discussed above can be applied to practice. The example refers to Figure 1. The PM is constructed only once and by the clinical community. It would be misleading to have several implementations at different hospitals and clinics. For most diseases, local implementations would not even be possible because a relatively large number of cases covering the entire spectrum are required.

First, the three components are defined by taking into account the specifics of the condition. The clinical community should agree on the definitions. Methods for scoring each of the pathogenicity components have to be implemented. In some instances, this may be straightforward if there already is, for example, a severity or extent scale available. In most diseases, it is likely that many factors should be taken into account and weighed. Then data are collected for a population or cohort of sufficient size. The number of required cases depends on the disease and the definitions of extent, modulation, and severity. Epidemiological data can be used to estimate the number of cases needed to reach sufficient coverage of the space of variation.

Next, the data are organized and presented in the PM cube. The individual cases define the positions of the upper and the lower layers. The cube is useful already as such providing a visualization of the distribution of the variability in the population from benign cases to severely ill ones. However, by applying evidence-based thresholds, it becomes possible to stratify the cases. The distribution of the known disease-causing cases can be used to define the threshold for diagnosis. Figure 2 indicates effects of cutoffs on each of the three axes. Note that the figures present situations at the 70% level. If that is the cutoff for diagnosis, all the cases with the disease are on the gray area and the white area toward to upper right hand corner, where the cases surpassing the threshold are located. The threshold can be at any angle depending on the evidence and does not even have to be in plane. The PM cube makes it possible to define the actual position of the cutoff for diagnosis as it summarizes all the relevant information for the condition.

The evidence-based medicine-originating threshold for diagnosis indicates that patients fulfilling the criteria for diagnosis have widely variable combinations of the three components. This is one of the great strengths of the PM. Additional evidence-based thresholds can be applied for other purposes to find actionable cases, to stratify patients, for example, for pharmacogenetics and ADR assessment, as well as for disease prognosis and severity prediction.

The PM thus facilitates the definition of health, disease, and other related aspects for practical purposes. The PM is essential also for the realization of personalized medicine by providing the full picture of the individual's disease to be captured and understood. Once the PM is established, it will be easy to use, information for the suspected patient case is placed into the three dimensional cube, which allows comprehension of the case in relation to thresholds. The PM could be incorporated into a computer-assisted diagnosis decision support system. Data for patients could be fed directly from electronic health records. The PM requires initial investment to define the components and their distribution and obtaining a representative cohort, but once done it can be applied for several purposes. Further, by feeding data back from clinical diagnoses, themodel can be refined.

## CONCLUSIONS

The novel PM combines effects of three components and describes diseases at the population level. The PM combines both statistical population wide data and evidence-based thresholds thus merging normative and naturalist principles into a practice-oriented pathogenicity description. The PM indicates the high variability between individuals even those having the same condition. Several examples of individual variability are available from genetics. Genetic variants classified as disease-causing have been found from healthy individuals [Cassa et al. 2013] and even when considering that

variant databases contain errors, known disease-causing variants are found from asymptomatic individuals [Chen et al. 2016; Xue et al. 2012] including those in actionable genes [Amendola et al. 2015].

The model will have applications in several fields. Once the PZ is defined for a condition, it can be used for developing prediction methods that can be used for the identification and prioritization of disease-related variants, as well as for the diagnosis and prognosis of disease. To facilitate this, international collaborations and consortia will be needed to collect large enough patient cohorts. It remains to be seen how large patient data sets have to be; however, by utilizing statistical methods and sampling of the pathogenicity space, the amount of required cases can be minimized.

The conceptualization of the pathogenicity provides several benefits even when detailed PMs have not been obtained. The conception of the PM allows one to consider inter-individual differences in diseases and consequences for diagnosis, treatment, drug dosage and choice. The PM allows evidence-based medicine as the uncertainty in response and prognosis can be understood. PMs help to answer the most important questions in healthcare: who to treat, when, how, how long, and with which dose. The scheme is applicable to all kinds of diseases, among genetic diseases both Mendelian and complex disorders can be described with the scheme. The PM facilitates deep understanding of diseases and their progression, and better and more economical treatment and even improved public health.

In systems biology, the PZ could explain the robustness and redundancy of systems for perturbations. Although a PM is intended to be defined separately for each individual disease, there might be cases where it could be used simultaneously for several related diseases that share many signs and symptoms. One application would be in classification and nosology of related diseases [Samarghitean et al. 2009; Fava et al. 2012]. Further, the PM could be coupled to healthcare information systems for diagnostic, prognostic, and demographic purposes. By considering all the aspects that the model explains, it becomes evident that the PM will be a useful tool for personalized/precision medicine and facilitate evidence-based medicine. PMs will likely have additional application areas due to providing an analytical concept of variability for pathogenicity components in individuals and populations.

## ACKNOWLEDGMENTS

*Disclosure statement:* The authors declare no conflict of interest.

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BOX 1. Definition of terms

*Pathogenicity* Capacity or ability to produce disease. Ranges from benign to the most severe condition for a disease. Has previously been used in relation to pathogenic micro-organisms or genetic variations, refers here to pathogenicity in general.

Definitions for the three pathogenicity components. All of them are for individuals forming a population:

*Extent* Degree or breadth of disease appearance.

*Modulation* Extent of modifier effects on disease presentation.

*Severity* Extent or degree of the disease expression.

Definitions for some related concepts:

*Actionability* Ability to treat a medical condition based on individual's pathogenicity presentation.

*Comorbidity* Simultaneous presence of more than one disease entity in an individual. Frequent in chronic medical conditions.

*Expressivity* Extent of signs and symptoms of a phenotype on individuals carrying the genotype for the trait.

*Genotype* Genetic constitution of an individual.

*Penetrance* The frequency with which a heritable trait is manifested by individuals carrying the gene or genes for the condition.

*Phenotype* Physical appearance or biochemical characteristics of an organism as a result of genotype, environment and their interaction.

**FIGURES**

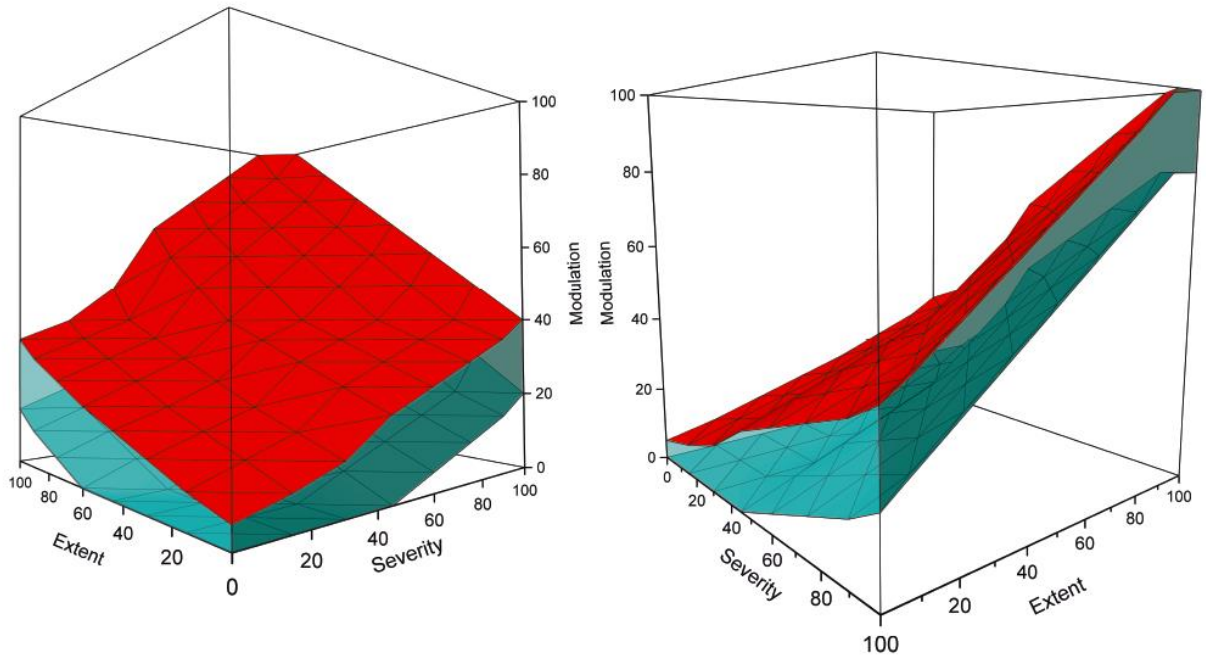


Figure 1. Pathogenicity model indicating the combined effect of extent, modulation and severity. A and B show two projections of the model. Red colored layer indicates the upper boundary and the cyan layer the lower boundary of pathogenicity. The space between the two layers is filled by data points for individual cases representing the variable phenotypes. The meshes on the upper and lower layers of pathogenicity are only for visualization purposes to better highlight the shape of the pathogenicity zone.

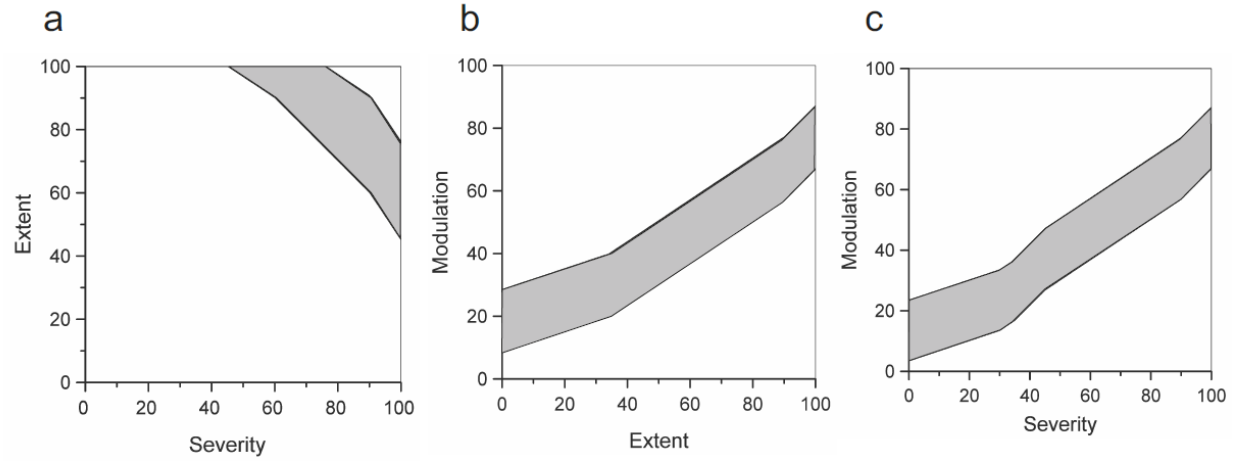


Figure 2. Examples for the implementation of cutoffs to the PM. In all the panels the cutoff is set at 70% of one component, A) modulation, B) extent, C) severity. The shaded areas indicate how variable the cases at a fixed cutoff are and explain many differences between individuals in regards to phenotype and for example adverse drug effects. Note that real life cutoffs for diagnosis and other purposes may be applied at other angles depending on the data.