The Authors suggest that the history of genotype better control subjects in comparative studies reducing noise and bias in studies. In addition, an analysis of phenotype trajectories can be subsequently used to choose factors that might be useful to predict the future phenotypes including the onset of disease. In this perspective, we consider some of these phenotypes to be preferable to others in humans. Accordingly, people with such phenotypes are considered healthy while people with nonpreferable phenotypes are labeled as sick, injured, or disabled.

Scientific consensus stipulates that the development of these nonpreferable phenotypes (i.e., pathologies) may be explained by the combination of genetic constitution and environmental factors.[4] Furthermore, to fully explain the development of pathologies, we also need to factor in aging, because even genetically identical individuals will react differently to identical external stimuli at different ages. In accordance with this line of reasoning, a recent study has shown that even a simple genetic variability in the form of single-nucleotide polymorphisms (SNPs) affects cancer mortality in an age-dependent manner.[10] Therefore, to fully understand the development of any phenotype in a given individual, we need to know the entire genetic constitution as well as the entire life history of environmental interactions and adjust their effect for age.

While this approach may sometimes be feasible in model organisms, it is unattainable in humans. Although we may hypothetically capture the genetic constitution of every studied human individual, we can hardly hope to capture their every interaction with the environment. Thus, in human studies, we are always limited to working with only a subset of environmental interactions for a given individual or population. Likewise, information on environmental interactions, e.g., about chemical exposure, is limited to only a certain time point or, in a best-case scenario, to a certain time period. However, because environmental interactions occurring prior to the beginning of the monitoring period may often play a very important role, this limitation decreases the power of even the best-designed human epidemiological studies aiming to study the disease development and progression.

To overcome this limitation, we propose a novel way of avoiding some of the obstacles encountered in evaluations of genotype–environment interactions. Before presenting the model itself, let us clarify two assumptions that serve as a basis for our reasoning. First, an individual’s phenotype is something of a reflection of the personal history of genotype–environment interactions. Second, possible phenotypes are always interlinked: there is always a preceding and a subsequent phenotype. Before a person develops a phenotype typical of a given pathology, several transient phenotypes can precede (we are not considering injuries due to external forces).
at this point). The order of these phenotypes cannot in principle be random, because they had to originate in the initial “healthy” phenotype and diverge from it only as a result of gradual accumulation of minute changes.

This assumption has several important implications. For example, when conducting longitudinal studies, we should look more closely at the development of phenotypes over time. A plethora of transient phenotypes with potentially significant medical implications (i.e., prediction, prognosis, treatment) may exist between phenotypes manifested at the beginning and end of a study. Phenotypic data were previously used to study genetic and infectious diseases,[5–7] and several studies have even used phenotypic data to identify novel molecular pathways involved in disease etiology based on comparing disease phenotypes between model organisms and humans.[8,9] The approach we suggest takes this approach one step further, examining not only phenotypes associated with diseases and states of health, but also the previous connection of these phenotypes and their longitudinal patterns.

2. What Does It Take to Form a Phenotype?
The sum of the intrinsic properties of a living system, the environmental factors affecting it, and the process of aging may be visualized using a three-dimensional representation, i.e., a cube (Figure 1). The specific position of an individual at a particular moment inside this cube determines their phenotype or, in other words, their state of health or disease. This model, which comprises all of the dimensions involved in the development of disease, might well be termed the pathosome. It is important to highlight that for the purpose of the pathosome, the environment is understood in the widest meaning possible, i.e., as everything, which is not the organism itself. Thus, environmental impulses here also capture the effects of, e.g., the microbiome or social stimuli. Furthermore, in the context of the pathosome, the epigenome results from genotype–environment interactions and is thus also contained by the model.

The pathosome concept implies that, if we possess information about the genotype and age of an individual, we should be able to use phenotype data to estimate their previous interactions with the environment. In principle, such an approach is equivalent to the situation where it is possible to determine that individuals overcome a particular disease or injury due to the presence of a specific lesion. Accordingly, large-scale environmental impulses lead to profound changes in phenotype while small-scale environmental impulses only alter the phenotype to a lesser extent. We can thus assume that the “power” of an environmental impulse is proportional to the

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**Figure 1.** A graphical representation of the pathosome cube. Based on the genetic constitution, an individual may be either predisposed or resistant to a certain pathology (or set of pathologies). Some individuals may be predisposed to such an extent that they will develop the clinical manifestation of a disease without any external stimuli. Examples include, e.g., chromosomal aberrations that are highly likely to result in a typical phenotype irrespective of environmental factors. On the other hand, some individuals may be healthy in a perfect environment but even a small environmental impulse will result in disease onset while still other individuals will remain healthy in most situations and only a great environmental impulse will result in pathology development. However, this situation does not remain static over time. Due to the process of aging, genetically identical older individuals require lesser environmental impulses for a disease to manifest itself. Furthermore, some will even develop a disease without any external stimulus or impact.
extent of phenotype change it inflicts on genetically identical individuals of the same age. For example, if one of monozygotic twins had more childhood infections than the other, it will likely also be the smaller one of the twins in adulthood. However, the difference in height is relatively small, and, e.g., childhood malnutrition would likely result in higher height differences. Thus, childhood malnutrition is likely a stronger environmental impulse than common infections.

3. Phenotypes Develops with Time

As stated above, we assume that a specific phenotype is determined by a combination of the three dimensions of the pathosome cube. By definition, such a phenotype thus does not constitute a static entity, but rather a continuum of dynamically evolving states of health and disease.

The fluent character of phenotypes in time and space can complicate the diagnosis and therapy of disease as well as the promotion of states of health, especially as there is no single “state of health” or “state of disease” but rather an infinite number of states that are continuously and dynamically evolving from the conception of an individual until death. Further complications arise from the highly cross-sectional nature of the current diagnostic methodologies, which is at its very core inherently incapable of including a longitudinal/temporal aspect. A specific disease phenotype is therefore always a static simplification of the actual dynamic process—not unlike the comparison of a still image to a video. As a result, even perfect diagnostic criteria tailored to such a “still image” may turn out to be completely unsatisfactory when applied to a “video”, i.e., individuals belonging to age groups different from those for which the criteria were originally intended.

In order to reflect the dynamic nature of the phenotypic shaping of the pathosome cube introduced above, we present the concept of the dynamic pathosome. The concept is based on the five following presumptions:

1) A continuum of a definite number of health and disease phenotypes exists for each individual in each environmental setting, i.e., the phenotype “shifts” between various states of health and disease and thus continues to evolve.
2) The sum of all possible states of health and disease decreases throughout the process of aging as the adaptation reserves of an organism decline (Figure 2). This reduction of the set of possible phenotypes (SPP) is best illustrated by a hypothetical situation. Let us imagine a young and healthy lumberjack who accidentally cuts his left arm with an axe. Based on several aspects, this accident may have several different outcomes: in the best-case scenario he will end up with only a small scar while in the worst-case scenario he will lose his left hand. One way or another, his SPP decreases. If he gains a scar, he will not be able to achieve phenotypes without this scar anymore and his SPP will thus be somewhat more limited. If he loses a hand he will not be able to achieve any phenotype that includes his left hand; this will naturally massively reduce his SPP. Later in life, this unlucky lumberjack might develop diabetes, which will further reduce his SPP, because he will now be a one‐handed diabetic (or scar‐bearing diabetic); thus, he will no longer be able to attain any of the possible phenotypes that exclude diabetes. Similarly, all illnesses and injuries reduce a person’s SPP, making it smaller and smaller as time progresses.
3) The temporal aspect cannot be separated from the phenotype (the only conceivable exceptions to this rule include ostensibly nonaging organisms, e.g., hydra).
4) Organisms reset certain parameters (e.g., blood pressure) to remain adaptive after achieving a certain threshold. Such a threshold may be characterized by the level of stress.
5) The process of adaptation to the surrounding environment is characterized by the never‐ending negotiation between the costs and gains of adaptation. The cost‐benefit negotiation always exhibits a temporal aspect (the precise timing of an event or process in the context of aging of the organism). The dynamic pathosome may therefore be regarded as the ultimate ordered sum of phenotypes of a given individual at a given time point in life or, even better, the unique phenotype sequence characterizing an individual from conception until death. From a different point of view, it may also be viewed as the unique pattern of phenotypic variability in time and space.

The well-known concept of adaptation through change was proposed in full in 1988 by Sterling and Eyer; it is based primarily on the presumption that efficient regulation is

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Figure 2. The time-dependent reduction of an SPP. At birth, every person has a personal SPP he or she can potentially attain. The birth set possible of phenotypes (BSPP) is thus specific to each individual. The borders of the BSPP of individuals are a result of a specific genetic constitution and events experienced during prenatal development. For every live birth, the BSPP contains an innumerable number of phenotypes. However, the SPP declines with age until it is reduced to the only, but ultimately final, phenotype: death.
anticipatory, i.e., dependent on experience or on learning from past events, and that optimal regulation is achieved by a central command center in the brain. Even, more importantly, Sterling and Eyer[15] viewed allostatic regulation as a system attempting to achieve the optimal and efficient operation of key systems in the body with minimal energy expenditure. McEwen and Stellar[16] later suggested the term “allostatic load” to account for the cost to the response system for maintaining a regulated variable at a value chronically displaced from its previous level by prolonged activation of compensatory effectors.

However, none of the concepts mentioned above operates with the notion of flexible adaptation capacity over time. In contrast, from the perspective of the pathosome, adaptation costs are not static and change profoundly with age. Such a viewpoint is well in agreement with a theory of the homeodynamic space, which is supposed to determine an individual’s chance to survive as well as the ability to maintain a healthy state.[17,18] This similarity is probably best illustrated by the fact that some authors even state that aging is a progressive shrinkage of the homeodynamic space.[18]

The concept of the dynamic pathosome has one important novel implication, namely that future phenotypes are shaped by previous phenotypes—both by their sum and by their order. While this is often intuitive, e.g., in the case of obesity or phenotypes resulting from trauma (missing extremities), it seems to be also true of phenotypes resulting, e.g., from previously encountered inflammatory processes. For example, Naik et al.[19] showed that epithelial tissue has inherent memory properties, facilitating faster and more effective tissue repair following recurring damage. It is likely that this memory component may be defined for other tissues as well. Therefore, even if a phenotype seemingly recurs (e.g., cut wounds may heal without a scar) it still leaves a mark at the molecular level that affects the development of future phenotypes. To give another example, even after women no longer have symptoms of preeclampsia, which is a pregnancy-specific condition characterized by hypertension and proteinuria, they still have a higher risk of future hypertension in comparison to women who never had preeclampsia during their pregnancy.[20]

The assumption that future phenotypes are shaped by preceding phenotypes has much in common with the Developmental Origins of Health and Disease approach (DOHaD), which highlights the role of embryonal development and infant phenotypes (e.g., birthweight) for adult future phenotypes.[21,22] However, the concept of the dynamic pathosome differs from DOHaD as it presumes that all phenotypes, including those of adults, are interlinked and might be theoretically used to predict future phenotypes trajectories.

The concept of dynamic pathosome presented here points out that phenotypes develop over time and suggests that this development is not random but follows certain rules, which can be studied and understood.

4. What Are the Benefits of the Dynamic Pathosome Concept?

The concept of the dynamic pathosome has several practical implications. First, the analysis of the connection between phenotypes (phenotype sequence) in longitudinal studies could provide novel diagnostic tools capable of detecting disease onset prior to its clinical manifestation. In other words, in cases where a “healthy” phenotype is associated with the later onset of a certain disease, it may be used to identify individuals with a high risk of developing the disease.

Second, it is likely that a better appreciation of the association between phenotypes could lead to a better understanding of molecular mechanisms leading to disease onset and progression. To illustrate this point, imagine a study examining the role of, e.g., microRNAs (miRNAs) in breast cancer onset, a study similar to work that has already been conducted.[23–25] Using a current approach, we would collect samples from a group of patients and a group of controls. We would then analyze the expression of miRNA in these two groups and compare them with each other. In the optimistic scenario, we would then find that some miRNAs are differentially expressed in patients and controls and may be interesting for further investigation. However, it is almost certain that some individuals in the control group, particularly if it is big enough to be relevant, will later develop breast cancer as well. Furthermore, even at sample collection, some controls have a phenotype that makes them more likely to develop breast cancer than others, which inevitably leads to further bias as we compare individuals displaying an existing phenotype (i.e., breast cancer) with those who have not developed the phenotype yet but display various degrees of susceptibility to developing it in the future. This inevitably leads to constant noise or even bias in the data as we compare subjects based only on whether they have already developed the phenotype or not.

In order to overcome this problem, we need to create phenotype trajectories linking genetic background, major critical events, and contributing events and previous phenotypes with the manifestation of the phenotype of interest. Some steps in this direction have been already taken by scientists employing group-based trajectory modeling to identify groups of individuals following similar trajectories for a single phenotype.[26,27] The logical next step would be to construct epidemiological studies in such a way that intended comparisons would reflect not only the cross-sectional state, i.e., whether the subject already displays the phenotype or not, but also the likelihood of the development of a given phenotype in the future, i.e., whether or not the trajectory of the subject implies increased risk of the development of the phenotype of interest.

In an ideal scenario, employing the concept of the dynamic pathosome would generate a great amount of data describing existing phenotype trajectories. These phenotype trajectories could then be used to precisely place any well-characterized individual in the pathosome cube for a given disease, thus making it possible for more a precise estimation of the exact individual risk of a disease. This would constitute an important tool for personalized medicine as the exact position of an individual in the pathosome cube could reveal not only how their phenotype will develop in the future but also how it will change in a given environment, provided we are able to describe the environment using a reasonable set of measurable parameters.
However, transforming the concept of dynamic pathosome into a useful tool for personalized medicine or even testing the concept itself requires the specific design of longitudinal studies. First, all gathered phenotypes should be measured as frequently as possible, with an emphasis on the interconnection of the phenotypes in the time. Second and most important, the description of phenotypes needs to be as precise as possible. Currently, it is common practice to assess phenotypes in a simple yes/no fashion based on an arbitrary threshold. Whereas the categorization of the study subjects may be useful in terms of diagnosis and/or therapeutic decision making, it inevitably introduces bias to the studies. First, the routine use of categorization usually leads to multiple hypothesis testing with pairwise comparisons; second, it generally results in loss of power and inaccurate estimates; and third, and most importantly, it makes it difficult to carry out any comparisons of multiple studies.[28] Thus, an ideal longitudinal study would report all investigated traits quantitatively. From this perspective, it is important to emphasize that even classic qualitative traits can frequently be reported in a quantitative fashion. However, such quantizing[29] can be in some cases arbitrary as well and should be, thus, applied with caution.

5. Conclusions and Outlook

To conclude, we here present a novel concept on how to think about, visualize, and study the nature of phenotypic variations. The central presumption of our concept is that phenotypes develop over time in a somewhat predictable pattern.

In this paper, we have outlined the potential implications of the pathosome concept as well as principles by which epidemiological studies based on it could be performed. While such predictions are always speculative to some degree, we truly believe that the existence of phenotypic patterns is very likely and their study would be useful. In an ideal scenario, the concept of the pathosome would achieve the “holy grail” of epidemiology: utilizing data from populations to accurately assess the prognosis of an individual. Hospitals of the future may carefully measure every possible phenotype and use the power of big data to objectively predict future phenotype trajectories based on current “looks” of the patient. In other words, hospitals of the future may do objectively what medical doctors over the centuries had, to the best possible extent, learned from years of experience.

In a more realistic scenario, the concept of the pathosome certainly has the potential to help us design better epidemiological studies by finding the sequence of different phenotypes and evaluating the whole trajectories instead of single cross-sectional phenotypes. Furthermore, the concept of the pathosome could also help to appreciate the importance of phenotypes, which maybe sometimes overlooked in current biomedical science focusing predominantly on everything molecular. We hope this work will encourage others to think about this topic and hopefully also contribute to its experimental validation.

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Conflict of Interest

The authors declare no conflict of interest.

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[1] T. M. Baye, T. Abebe, R. A. Wilke, Pers. Med. 2011, 8, 59.
[2] D. J. Hunter, Nat. Rev. Genet. 2005, 6, 287.
[3] E. Flowers, E. S. Froelicher, B. E. Aouizerat, Eur. J. Cardiovasc. Nurs. 2012, 11, 472.
[4] A. Doherty, Y. Kornogitski, A. M. Kulminski, J. Pedro de Magalhães, Aging 2017, 9, 2117.
[5] R. Hoehndorf, P. N. Schofield, G. V. Gkoutos, Sci. Rep. 2015, 5, 10888.
[6] R. Hoehndorf, P. N. Schofield, G. V. Gkoutos, Interface Focus 2013, 3, 3.
[7] M. A. van Driel, J. Bruggeman, G. Vriend, H. G. Brunner, J. A. M. Leunissen, Eur. J. Hum. Genet. 2006, 14, 535.
[8] R. Hoehndorf, P. N. Schofield, G. V. Gkoutos, Nucleic Acids Res. 2011, 39, e119.
[9] R. Hoehndorf, M. Dumontier, G. V. Gkoutos, Bioinformatics 2012, 28, 2169.
[10] A. E. Hwang, T. M. Mack, A. S. Hamilton, W. James Gauderman, L. Bernstein, M. G. Cockburn, J. Zadnick, K. A. Rand, J. L. Hopper, W. Cozen, Am. J. Epidemiol. 2013, 178, 551.
[11] O. R. Jones, A. Scheuerlein, R. Salguero-Gómez, C. G. Camarda, R. Schaible, B. B. Casper, J. P. Dahigren, J. Ehrlein, M. B. Garcia, E. S. Menges, P. F. Quintana, Nat. Rev. Genet. 2005, 5, 387.
[12] A. Doherty, J. Schermeiner, Arch. Intern. Med. 2012, 172, 238.
[13] D. E. Martinez, Exp. Gerontol. 1998, 33, 217.
[14] O. R. Jones, J. W. Vaupel, Biogerontology 2017, 18, 965.
[15] P. Sterling, J. Eyer, Handbook of Life Stress, Cognition and Health, John Wiley & Sons Ltd., New York 1988, pp. 629–649.
[16] B. S. McEwen, E. Stellar, Arch. Intern. Med. 1993, 153, 2093.
[17] S. I. S. Rattan, Free Radic. Res. 2006, 40, 1230.
[18] D. Demirovic, S. I. S. Rattan, Exp. Gerontol. 2013, 48, 94.
[19] S. Naik, S. B. Larsen, N. C. Gomez, K. Alaverdyan, A. Sendoi, S. Yuan, L. Polak, A. Kulukian, S. Chai, E. Fuchs, Nature 2017, 550, 475.
[20] V. D. Garovic, P. August, Curr. Hypertens. Rep. 2013, 15, 15.
[21] P. Wadhwa, C. Buss, S. Entringer, J. Swanson, Semin. Reprod. Med. 2009, 27, 358.
[22] P. Grandjean, Basic Clin. Pharmacol. Toxicol. 2008, 102, 94.
[23] C. Taslim, D. Y. Weng, T. M. Brasky, R. G. Dumitrescu, K. Huang, B. V. Kallakury, S. Krishnan, A. A. Llanos, C. Marian, J. McElroy, S. S. Schneider, S. L. Spear, M. A. Troester, J. L. Freudenheim, S. Geyer, P. G. Shields, Oncotarget 2016, 7, 86457.

[24] M. V. Iorio, M. Ferracin, C.-G. Liu, A. Veronese, R. Spizzo, S. Sabbioni, E. Magri, M. Pedriali, M. Fabbri, M. Campiglio, S. Ménard, J. P. Palazzo, A. Rosenberg, P. Musiani, S. Volinia, I. Nenci, G. A. Calin, P. Querzoli, M. Negrini, C. M. Croce, Cancer Res. 2005, 65, 7065.

[25] L. F. Sempere, M. Christensen, A. Silahtaroglu, M. Bak, C. V. Heath, G. Schwartz, W. Wells, S. Kauppinen, C. N. Cole, Cancer Res. 2007, 67, 11612.

[26] D. S. Nagin, C. L. Odgers, Annu. Rev. Clin. Psychol. 2010, 6, 109.

[27] D. S. Nagin, B. L. Jones, V. L. Passos, R. E. Tremblay, Stat. Methods Med. Res. 2018, 27, 2015.

[28] C. Bennette, A. Vickers, BMC Med. Res. Methodol. 2012, 12, 21.

[29] M. Sandelowski, C. I. Voils, G. Knaff, J. Mix. Methods Res. 2009, 3, 208.