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From cause and effect to *causes and effects*

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Abstract

It is now—at least loosely—acknowledged that most health and clinical outcomes are influenced by different interacting causes. Surprisingly, medical research studies are nearly universally designed to study—usually in a binary way—the effect of a single cause. Recent experiences during the coronavirus disease 2019 pandemic brought to the forefront that most of our challenges in medicine and healthcare deal with systemic, that is, interdependent and interconnected problems. Understanding these problems defy simplistic dichotomous research methodologies. These insights demand a shift in our thinking from 'cause and effect' to '*causes and effects*' since this transcends the classical way of Cartesian reductionist thinking. We require a shift to a '*causes and effects*' frame so we can choose the research methodology that reflects the relationships between variables of interest—one-to-one, one-to-many, many-to-one or many-to-many. One-to-one (or cause and effect) relationships are amenable to the traditional randomized control trial design, while all others require systemic designs to understand '*causes and effects*'. Researchers urgently need to re-evaluate their science models and embrace research designs that allow an exploration of the clinically obvious multiple '*causes and effects*' on health and disease. Clinical examples highlight the application of various systemic research methodologies and demonstrate how '*causes and effects*' explain the heterogeneity of clinical outcomes. This shift in scientific thinking will allow us to find the necessary personalized or precise clinical interventions that address the underlying reasons for the variability of clinical outcomes and will contribute to greater health equity.

KEYWORDS

heterogeneity, philosophy of science, reductionism, reductionist thinking, systems thinking

1 | INTRODUCTION

While it is—at least loosely—acknowledged that most health and clinical outcomes are influenced by different interacting causes, medical research studies are nearly universally designed to study and investigate—usually in a binary way—the effect of a single cause. However, as recent experiences during the coronavirus disease 2019 (COVID-19) pandemic brought to the forefront, most of our challenges in contemporary medicine and healthcare deal with systemic, that is, interdependent and interconnected problems—the multiple causes of health and disease, the link between health and social systems and their influence on economic system dynamics. Understanding these problems defy simplistic dichotomous research methodologies. These insights demand a shift in our thinking from '*cause and effect*' to '*causes and effects*' since this transcends the classical way of Cartesian reductionist thinking.

This paper calls on researchers to re-evaluate their science models and to embrace research designs that allow an exploration of the clinically obvious multiple '*causes and effects*' on health and disease, and its links to societal well-being and the economy. To facilitate the necessary shift to a '*causes and effects*' frame, the paper, first, describes the development of scientific thinking and its related research methodologies since the 17th century end of the Middle Ages. It provides a brief overview of systems thinking and system methodologies (the figures and their footnotes provide more detail), and lastly, highlights its so far limited application to various clinical conditions. Embracing research based on '*causes and effects*' will allow us to find the necessary personalized or precise clinical interventions that address the underlying reasons for the variability of clinical outcomes, and will contribute to greater health equity.

2 | HOW TO UNDERSTAND THE WORLD: A HISTORICAL PERSPECTIVE

The call for this shift in thinking goes back more than two centuries. At the end of the 18th century, Goethe observed that the laws of physics (the Newtonian worldview) do not apply to the laws of the natural world, and in about 1795 Alexander von Humboldt declared that to understand a phaenomenon in the living world (e.g., the behaviour of an animal) requires a simultaneous understanding of its environmental context. He realized that a researcher's observations of a natural phaenomenon were dependent on the state of many other variables.[1]

From a philosophy of science perspective, what was important in terms of appreciating the environmental context and the complexity such context added to investigating and understanding a natural phenomenon was the introduction of the controlled experiment. In such experiments, the researcher could reasonably conclude with confidence that an independent variable was responsible for or the cause of the change in a dependent variable. Thus, a cause–effect relationship was built into the experimental design itself.

The Newtonian worldview is characterized by two fundamental beliefs, first, that the universe is capable of being completely understood and therefore all phaenomena are universal and time independent, and second, the commitment to a particular method of inquiry known as reductionism. Reductionism entails three steps known as analysis: one, take apart the thing you want to understand; two, understand the behaviour of each part taken separately; and three, aggregate the understanding of the behaviour of each part into an understanding of the whole.[2] Thus, the behaviour of the whole is simply a summation of the behaviour of the parts with no residue left over, that is, no part of the whole system goes without explanation rather the complete phenomenon can be explained without anything going unexplained.

In contrast, the Humboldtian worldview understands the world as interconnected and interdependent. Interconnectedness and interdependencies are the core characteristics of a system. Its three key features are: one, it consists of two or more independent elements (from here on referred to by its system terminology as *agents*); two, each agent can affect the behaviour of the whole, while simultaneously depending on what other agents are doing; and three, the properties of the whole are not necessarily present in its individual parts. These characteristics of a system are often simply referred to as '*a system being bigger and different than its parts*'. Or, in other words, there is a residue that exists when the whole is divided or reduced into its parts.

3 | THE IMPLICATIONS OF THE DIFFERENT WORLDVIEWS

The supposition that one can know all the elements of the universe and that their behaviours result from *cause-and-effect relationships* underpins the *deterministic* worldview. Determinism entails that the world can be precisely explained and predicted. It follows that the repeated and controlled laboratory experiment will always result in precisely the same outcome, as long as the external conditions remain constant. Hence, experiments are conducted in laboratories devoid or severely limited of any context.[2]

The systemic worldview a priori embraces context and accepts that the behaviour of things in the living world results in emergent outcomes, that is, outcomes cannot be precisely predicted [emergence]. Indeed, even the smallest (and often difficult to recognize) differences in context may lead to dramatically different outcomes. That said, these outcomes are neither random nor infinite. The systemic research effort focuses on the description and understanding of observations and aims to identify their purpose and meaning that are not simply deterministic.

The deterministic and systemic worldviews have two very different mathematical distribution patterns. The first reflects the Newtonian world, which is concerned with prediction and precision looking at the reliability of repeated measurement and assuming a symmetrical distribution of measures around the true (mean) value as demonstrated by Gauss. The second involves the contextual world, which is concerned with understanding the natural distributions observed in the living world and follows an inverse power law or 80/20 split distribution pattern as demonstrated by Pareto.[3]

These very different worldviews, in the Kuhnian sense, define distinct paradigms.[4] Figure 1 describes the long road to systems thinking from its historical beginnings over its theoretical and philosophical development towards its application to health and healthcare.

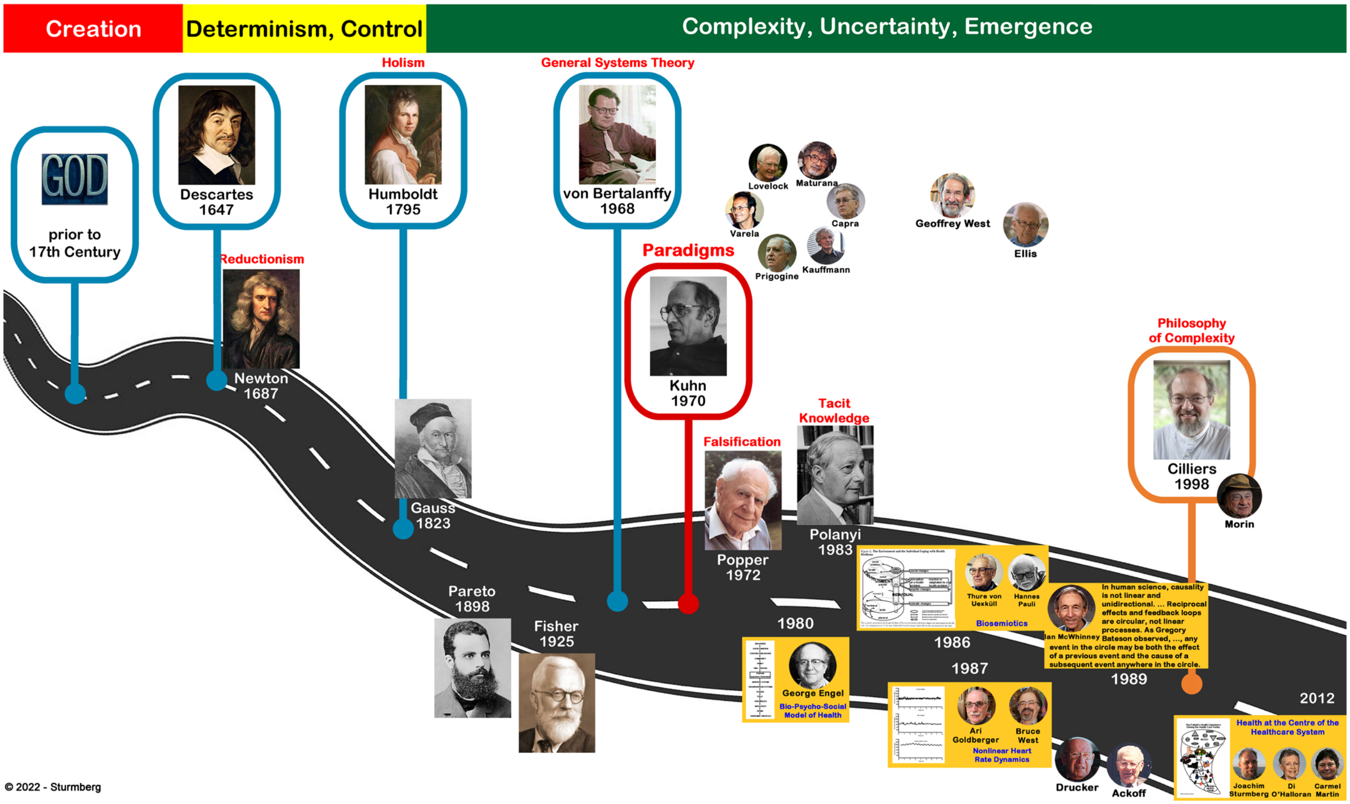

FIGURE 1 The philosophical trajectory from creationism to complexity sciences in health.[5] Modern scientific thought started during the Enlightenment period. Descartes postulated the mind-body split, while Newton introduced the reductionist scientific method of the controlled experiment in the absence of environmental contexts. It was Newton's dream to be able to predict exactly the behaviour of the world (determinism). The end of the enlightenment shifted thinking from reductionism to holism, Humboldt became acutely aware that the living world can only be understood in context (systems thinking/sciences). In 1968, von Bertalanffy synthesized this thinking into *General Systems Theory*, which laid the foundations for modern systems science,[6] whose various strands emerged rapidly from the works of Capra, Ellis, Kaufmann, Lovelock, Maturana, Prigogine, Verala and G. West. The philosophy of post-Newtonian thinking resulted in the exploration of paradigms by Kuhn[4] to indicate semiridged frameworks under which science operates, while Popper introduced the concept of *falsification*[5] and Polanyi the insight that most knowledge is *tacit*.[7] Finally, Cilliers, in 1998, influenced by Morin, formulated a coherent philosophy of systems science.[8] Medical thinking quickly adopted systemic thinking, with Engel postulating the biopsychosocial model of health,[9] while von Uexküll and Pauli[10] introduced the notion of biosemiotics, which involves the translation of physiological signals into experiential understandings. Goldberger and West[11] demonstrated the nonlinear dynamics of physiological behaviours (heart rate variability), and McWhinney[12] described the systemic nature of patients' illnesses. Sturmberg et al.[13] introduced the healthcare vortex as a model to demonstrate the hierarchical interdependencies of personal health within the context of their social, environmental and political context.

4 | HORSES FOR COURSES: WHAT IS THE APPROPRIATE RESEARCH METHOD FOR MY QUESTION?

The answer to this question defines which one of the two research approaches applies to the current project. Does the project examine a one-to-one relationship, or does it examine a one-to-many, many-to-one, or many-to-many relationship issue? Figure 2 illustrates the relationship issue across the scale-free distribution of medical research domains. At the extremes, the research methodology to be applied is clear, but for the majority of issues beyond a certain scale point, systemic methodologies must apply.

One-to-one relationship issues are usually benchtop questions, for example, does this new antibiotic kill a particular organism? However, applying the newly found 'test-tube' effective antibiotic to sick patients constitutes a one-to-many relationship question. The effectiveness of the drug depends on the interactions with many different agents of the patient and the illness, ranging from the microlevel metabolomic/proteomic through the mesolevel tissue/organ to the macrolevel patient and patient context domains. All are interdependent, and hence the treatment outcome will show heterogeneous patterns. In one-to-many, many-to-one or many-to-many relationships, outcomes cannot be precisely predicted, a well-known phaenomenon that clinicians experience daily. Nevertheless, clinicians, fortunately, have a 'gut feeling' or an intuition about what the most likely outcome of their interventions will be. 'Gut feelings' or intuitions reflect their tacit knowledge and accumulated experience[7] in recognizing known patterns of disease dynamics. Just consider the paediatrician who treated a little boy repeatedly for streptococcal throat (one-to-one). He considered his external environment a major

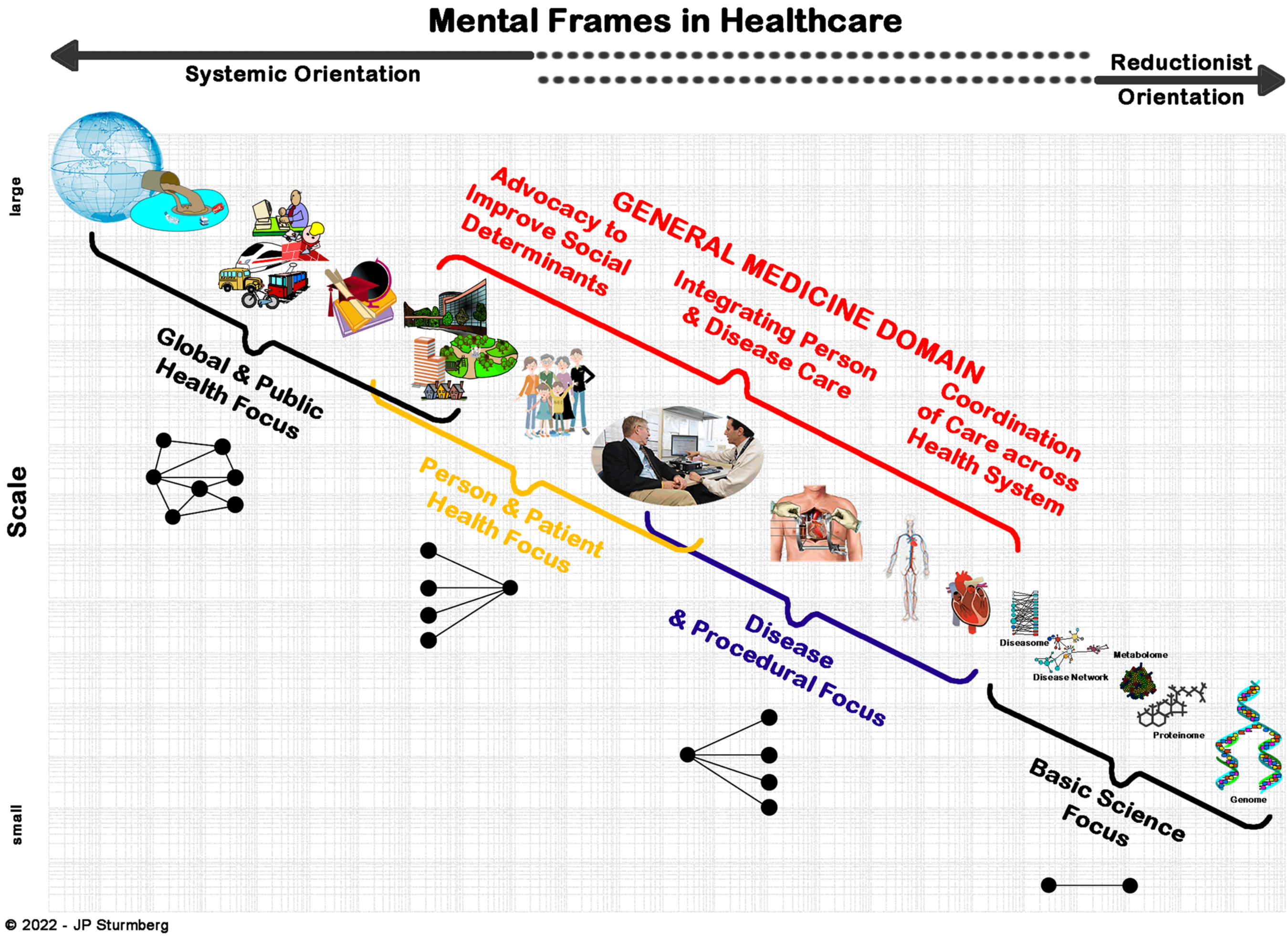

FIGURE 2 The variability of healthcare frames according to the scale of observation and relationships considered. Health covers the continuum from the nanolevel of the biological building blocks through the microlevel of the physiological and cellular building blocks to the mesolevel of organs and the macrolevel of persons in their environment. Of note, each of these levels or scales explores a different but often also overlapping type of relationship; the nanolevel is largely concerned with 'true' one-to-one relationships, whereas the microlevel explores one-to-many and the mesolevel many-to-one relationships. At the macrolevel, issues are invariably of a many-to-many relationship level. Basic 'benchtop' sciences and global health sciences are at the extreme points on the scale, while medical care, in the context of diseases, primarily adopts a one-to-many relationship frame, and at the person-centred care level, a many-to-one relationship frame.

contributing factor, so he visited the boy at home finding him living in absolute squalor (many-to-one/many-to-many).

5 | HEALTH PROBLEMS ARE COMPLEX PROBLEMS …

Figure 3 visually delineates the one-to-one, one-to-many, many-to-one, and many-to-many relationship issues in the clinical context. If a condition consists of one homogeneous pattern, reductionist research methods might be applied, ceteris paribus (or all other conditions remain unchanged or the same). However, many single conditions exhibit a variable pattern amongst affected people, while 'the same' multimorbidity condition affects individuals in highly variable ways. These types of problems require systemic research approaches to be understood at the various levels along the scale distribution. Not only do these problems show multiple outcomes across the somato-psycho-socio-semiotic domains of health,[16,17] they also have many already known causes.

6 | … THAT CAN ONLY BE SOLVED BY SYSTEMIC RESEARCH METHODOLOGIES

Systemic research entails a variety of methods that focus on systemic structures, system dynamics and sense/meaning-making. All have one thing in common, namely, to consider the relational interdependencies amongst the agents and their system-wide activities and consequences on a system of interest. Importantly, these approaches should involve all stakeholder groups affected by the problem being

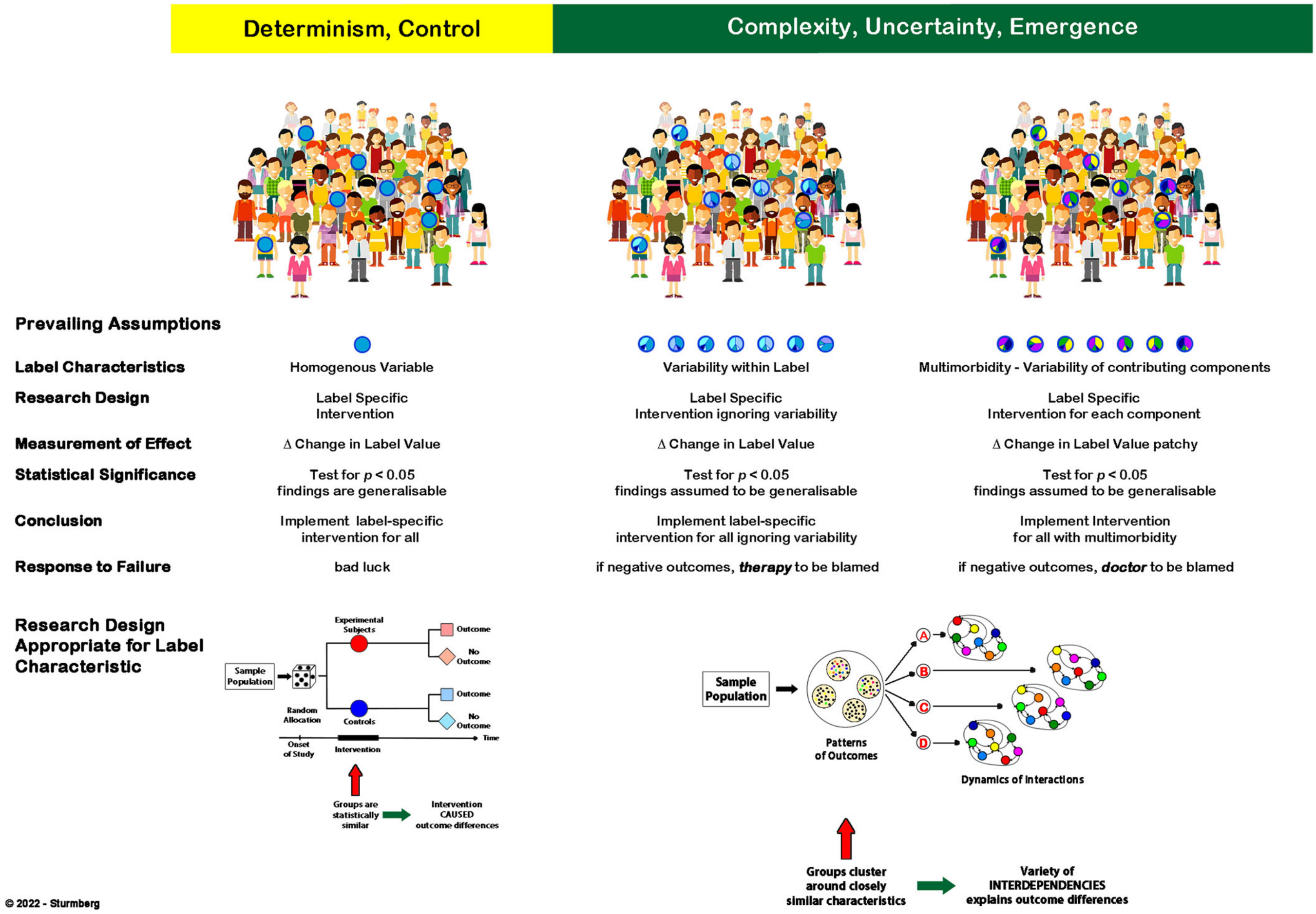

FIGURE 3 Disease and disease distribution rarely follow a one-to-one relationship allowing for a reductionist research approach, while most show a heterogeneous pattern of one-to-many, many-to-one and many-to-many relationships that must be studied with complexity-based research approaches. The figure illustrates the different patterns of disease in the community. Occasionally a disease has the same underlying mechanisms (the common point mutation diseases like cystic fibrosis, sickle cell anaemia or Tay–Sachs disease). However, the majority of common diseases show a great deal of heterogeneity (e.g., diabetes showing five distinct patterns,[14] or glioblastoma showing eight intratumoural subtypes[15]), with multimorbidity showing the greatest variability. Homogenous diseases can be rightly studied with the traditional trial designs, while heterogeneous diseases must be studied with systems methodologies like cluster analysis.

studied, only then can one be reasonably assured that all important issues are considered. Three approaches are described covering in broad terms the structural, dynamic and sense/meaning-making methods.

6.1 | Exploring system structure through systems thinking

System structures are typically thought about and drawn in a stepwise fashion; the narrative of the problem gets firstly drawn as a rich picture diagram. It forms the basis for drawing a systems map, which is the basis for drawing an influence diagram, which in turn is the basis for developing a multiple cause diagram that then gets transformed into a sign graph diagram to indicate the reinforcing or stabilizing relationships between variables. Finally, following the linkages, one will be able to identify reinforcing and balancing feedback loops that underpin a system's dynamics (Figure 4). Clinical care (e.g., see Sturmberg[19]) and clinical research approaches become more rigorous, impactful, and transparent when represented by systems and causal influence diagrams.

6.2 | Exploring system dynamics

System dynamics can be explored from an *outcomes* perspective—what are the patterns produced by the system like in cluster analysis,[20] or what is the network structure and the strength between the variables,[21] or a *predictive* perspective—how do changes in the characteristics of a variable affect the outcomes of other system variables of interest. The three commonly used modelling approaches are discrete event modelling, system dynamic modelling and agent-based modelling.[22–24]

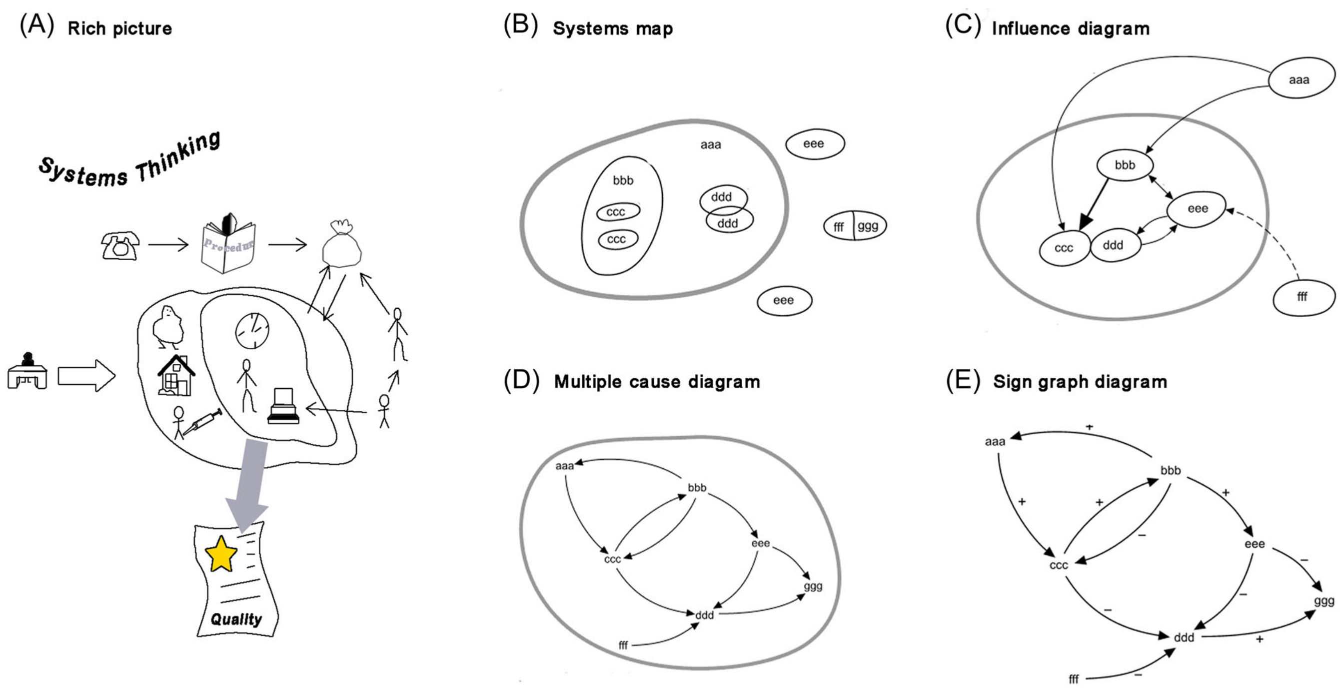

FIGURE 4 The steps of visualizing a systemic problem. Systemic problems are typically visualized in a number of steps. First, one draws a *rich picture* image (A) that broadly describes the issue. A systems map illustrates the groupings of variables within the system and its boundaries (B), before adding arrows to show key influences affecting variables (C). The next step involves the drawing of the multiple relationships, which then get evaluated for their reinforcing (+) or balancing (−) interactions (D). The last step involves the assessment of feedback loops (not shown here) (E).[18]

Any single intervention to a system agent causes effects on many agents or put differently: any intervention into a complex adaptive system has *multiple* consequences that affect multiple agents at multiple system domains. To capture the dynamics and their consequences more fully requires the combination of modelling approaches, a feature that is provided by the more sophisticated modelling applications (Figure 5).

6.3 | Exploring sense- or meaning-making

Sense-making approaches, like the Cynefin framework,[25,26] engage people to share and clarify their understandings and perspectives of a systemic issue. Drawing the various issues according to their level of knowability allows all affected people to understand more clearly where and how they can provide inputs into the development of solutions that consider their contextual constraints. The shared understanding of the system furthermore enables leaders to work with affected people more effectively in finding systemic solutions to the issues of concern (Figure 6).

7 | APPLIED *CAUSES AND EFFECTS* THINKING

There clearly is a large overlap between the described system methodologies, and there equally are research questions at each scale level that can be methodologically explored by a research design that correctly identifies and thinks about the nature of the causal relationships systematically.

Some clinician-researchers have recently realized the importance and impact of heterogeneity among patients, morphological characteristics of a disease and drivers of disease dynamics on patient outcomes.[27–29] In particular, there is no evidence that a small number of identified '*causes*' result in a disease,[29] rather than that disease arises from the interconnections and interdependencies of many '*causes*'.[30] Most '*causes*' of diseases taken individually only have small effects on '*causing*' a disease or '*determining*' its trajectory; it usually is the combination of all the '*causes*' that result in its phaenotypical expression and dynamics[27] (Box 1).

'*Causes and effects thinking*' entails the need for a shift in research design and approach. This needs to start with an explicit description of the context in which a research question arises. It then will require consideration of the variables that are of relevance within the context described, and importantly, where to set their cut-off score between normal and abnormal.[52] Chosen variables require clear definitions,[53] as well as baseline measurements, to assess the dynamical processes that underly the patient's unique condition before the implementation of any intervention. Intervention effects then need to be considered as much in terms of biological as of clinically relevant parameters across the somato-psycho-socio-semiotic domains[16,17,54] and across all levels of scale. Those parameters need to be assessed

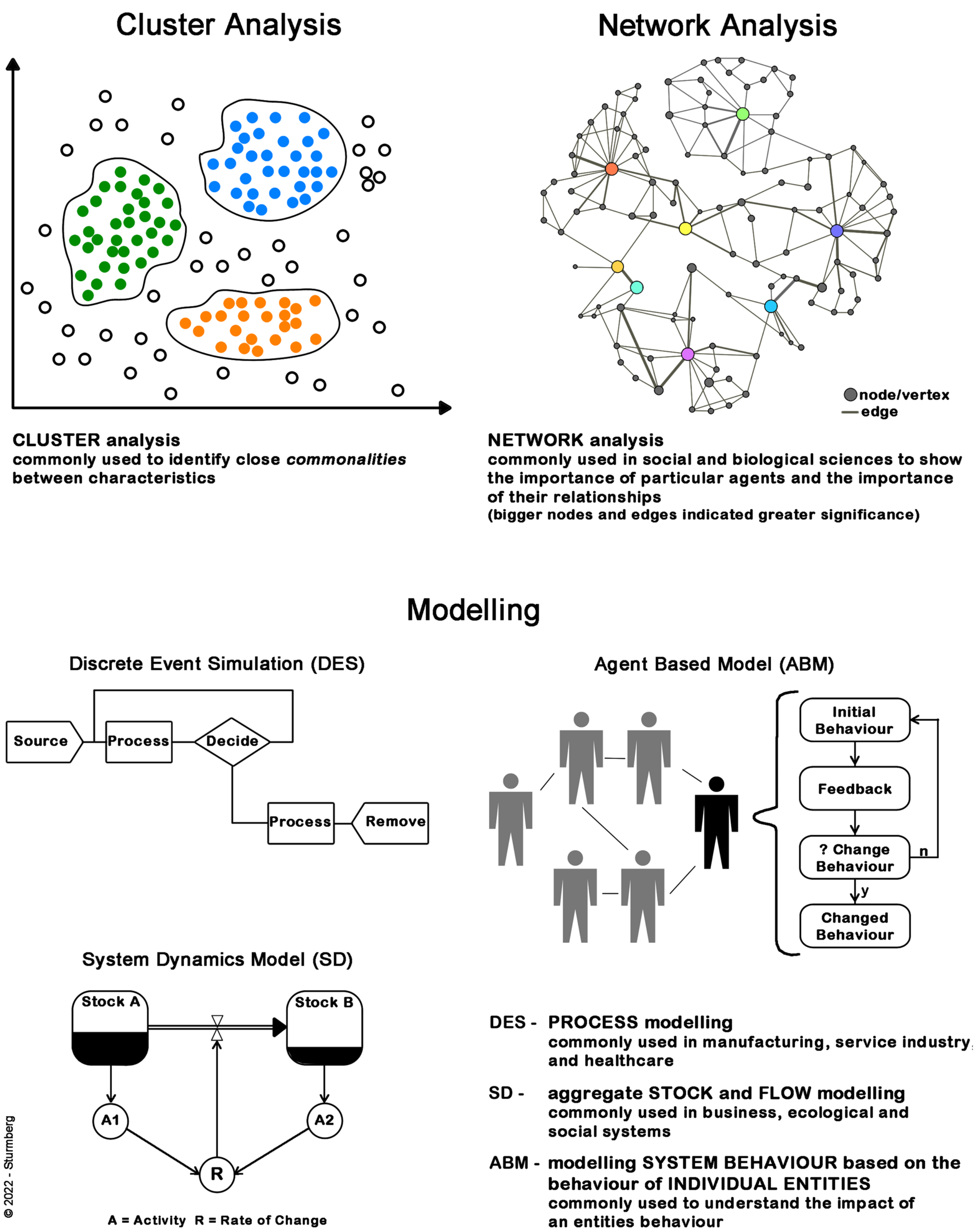

FIGURE 5 (See caption on next page)

regularly during an intervention to capture their dynamics. Equally, observation periods need to be longer as many conditions 'naturally' improve/stabilize in time to be no longer different—or at least clinically different—to observable differences in the short term (regression to the mean),[54–56] and any difference needs to be presented in transparent terms, that is, as *absolute*—rather than relative—*difference*.[57]

Study designs embracing '*causes and effects*' thinking need to consider the multidirectional—across nano- to macrolevel scales—interactions among multiple 'parts' that create the

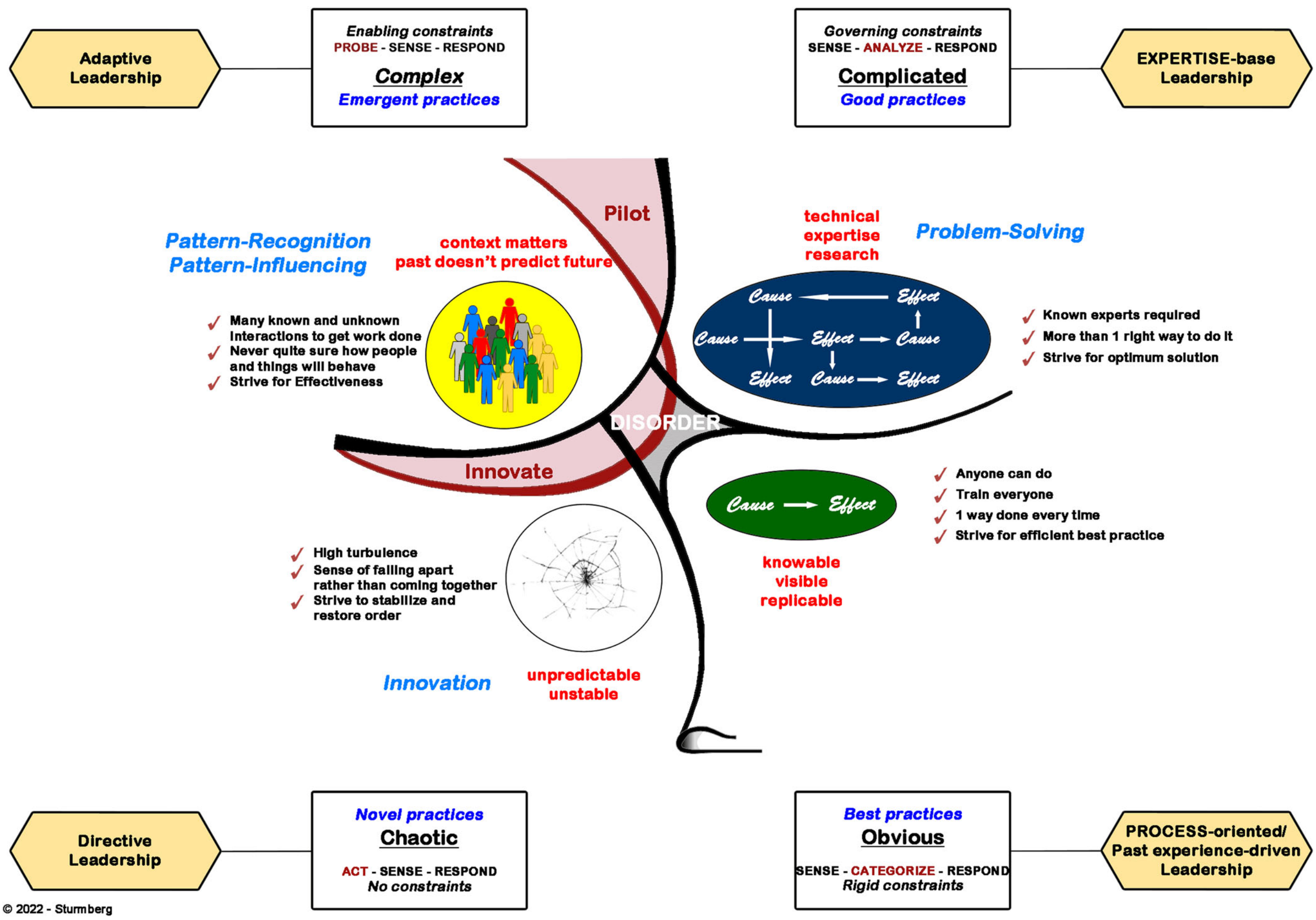

FIGURE 6 The Cynefin framework of sense-making/knowledge management. The Cynefin framework[25] explores five domains of sense-making/knowing—the obvious knowable domain based on clear cause-and-effect relationships, the complicated domain-based causal chains understood by experts, the complex domain characterized by appreciating context where one can sense patterns that are generally not repeatable and the chaotic domain where phaenomena have no appreciable relationship to each other. The fifth domain is that of disorder or confusion—the domain where phaenomena reside that have no clear place of belonging. Each domain tells us HOW we differently *know*, *act* and *lead*. The obvious domain defines *best practices* for acting and is reinforced by *process-oriented* leadership. The complicated domain entails *good practices* that are implemented by *expert* leadership and generally driven by *problem-solving* strategies. The complex domain describes *emergent practices* and requires *adaptive* leadership, one that can facilitate necessary change in light of unexpected developments. A key skill in the complex domain is *pattern recognition* and *pattern influencing*. The chaotic domain allows for the development and implementation of *novel practices* under the oversight of *directive* leadership.

FIGURE 5 Three systems methodologies—cluster analysis, network analysis and modelling. Cluster analysis identifies those variables whose characteristics are very similar (note: not identical), while network analysis aims to identify those variables that have the greatest influence on the behaviour of a system. Modelling is a way to 'predict' the potential behaviour of system behaviours, either in a process way (DES), a system dynamic outcomes way (SD) or in terms of the impact of particular agent characteristics (ABM).

BOX 1 Examples of applied systems thinking approaches to clinical problems

Research methodology	Scale	Examples	Details
Cluster analysis	Macro	Ambulatory care groupings[31,32]	Thirteen major ambulatory care clusters correlating to ambulatory care resource use
		Cancer prevention[33]	Four patterns of cancer prevention behaviours among European Union countries based on known risk factor characteristics (gross domestic product/capita, healthcare spending, years of education, particulate matter in the air, human papillomavirus-vaccination coverage, alcohol consumption, smoking rates, healthy diet, obesity rates, access to sports facilities and sport activity)
	Meso	Patient populations in general practice[34]	Seven distinct clusters of patients based on variables from the health system, individual doctor, individual patient, consultation and consultation outcome domains
		Burnout in nursing staff[35]	Five burnout profiles based on three dimensions (emotional exhaustion, depersonalization, personal accomplishment)
		Coronary artery disease risk[36]	Four phenotypically and prognostically distinct clusters based on variables from medical history (peripheral artery disease, heart failure, arrhythmias, prior stroke, diabetes, triple vessel disease, prior coronary intervention), biological and genetic variables (ankle–brachial index, body mass index, low-density lipoprotein, rs819750, rs9485528, 9p21 variants), and lifestyle (smoking, exercise, educational attainment, medication adherence, socioeconomic status)
	Meso/micro	Coronary artery disease risk[37]	Three phenotype clusters that are associated with variable risk of patient- and device-oriented composite endpoints (1) Inflammatory (high white blood cell counts, high values of C-reactive protein (CRP) and neutrophil-to-lymphocyte ratio), (2) high erythrocyte sedimentation rate (ESR) and (3) noninflammatory Four phenotype clusters in acute coronary symptom patients treated by the percutaneous coronary intervention (high CRP, high ESR, high aspartate-aminotransferase and normal)
	Micro	Diabetes[14,38]	Five distinct clusters defined by six variables (glutamate decarboxylase antibodies, age at diagnosis, body mass index, haemoglobin A1c, B-cell function and insulin resistance) indicating significantly different disease progression and diabetic complications (nephropathy, retinopathy)
		Parkinson's disease[39]	Three subtypes are defined by four domains (motor, autonomic dysfunction, rapid eye movement behaviour disorder and cognitive dysfunction) resulting in distinct patterns of survival, falls, wheelchair use, the onset of dementia and care placement
		Pathophysiology of coronary artery disease[40]	Four clusters defined by degree and level of coronary stenoses, inflammatory markers, metabolic syndrome, troponin levels and cardiovascular disease risk scores
	Nano	Glioblastoma multiforme[15]	Eight intratumoural subtypes based on patterns of nine immune markers that match the pathophysiologically relevant clinical groupings
Network analysis	Macro	Multimorbidity across racial groups[41]	Marked differences in multimorbidity profiles White, African American, Asian, Hispanic, Native American, bi- or multiracial and Pacific Islander

(Continues)

Research methodology	Scale	Examples	Details
	Meso	Subjective well-being[42]	Complex relationship between individual and place characteristics in the context of subjective well-being (influential nodes and edges are *subjective health, financial status, housing conditions, local greenspace, civic agency and neighbourhood cohesion*)
	Micro	Disease networks[43–45]	Gene–disease and disease–disease associations
	Nano	Coronary artery disease[46]	Two hub genes (TLR2, CD14) are associated with higher atherosclerotic plaque vulnerability, and high expression is associated with myocardial infarction
Modelling	Macro	Food taxes/subsidies on population health costs[47]	*Health economics modelling*—Modelling of tax impact on unhealthy foods and subsidies on health food on population health and health system expenditure (significant health gains and significant health expenditure savings over the remaining lifespan per capita)
		Smoking cessation policy option[48]	*Agent-based population health model*—Availability of electronic nicotine delivery systems (ENDS) on outcomes comparing ongoing cigarette smoking versus a modified case of introducing ENDS (37% decrease in smoking prevalence, prevention of 2.5 million premature deaths by 2100 after accounting for mortality impact of both smoking and ENDS)
	Macro/meso	Drink-driving and fatalities[49]	*System-dynamic modelling*—Combination of integrated policy approaches (road safety interventions like education and enforcement) and public health policy approaches (alcohol misuse) are more effective than individual interventions
	Meso/micro	Timing of transcatheter aortic valve replacement in severe aortic stenosis patients[50]	*Discrete-event modelling*—Increasing wait time for procedure substantially increases complications and mortality in severe aortic stenosis patients
	Nano	Inflammation and chronic instability in the aging process[51]	Computational model of the AMPK-NAD+– PGCla–SIRTI signalling pathway (becomes less responsive with age and that this can prime for the accumulation of dysfunctional mitochondria)

emergent outcomes we observe. Hence, it requires a rethinking of trial designs beyond the traditional randomized control trial. Recently suggested approaches, such as basket trials (targeted intervention is evaluated on multiple diseases), umbrella trials (evaluation of multiple targeted interventions on a single disease) and platform trials (evaluation of several interventions against a common control group), are steps in that direction.[58] However, their conception does not articulate the impact of context on the outcomes observed. Taking context into account is paramount as the observed behaviours and outcomes are highly context-dependent, and even minor differences in context can result in very different outcomes (the phaenomenon of *sensitivity to initial conditions*[59]). Hence, analysis and interpretation of study findings need to consider implications at the individual, group, system or prediction/sense-making levels (Figure 7).

8 | CONCLUSIONS

Recent experiences during the COVID-19 pandemic brought to the forefront that most of our challenges in contemporary medicine and healthcare deal with systemic, that is, interdependent and interconnected problems that defy simplistic dichotomous research methodologies. One of the lessons to be learnt from the COVID-19 pandemic must be to embrace the notion of '*causes and effects*'. It still remains unclear what specific causes were responsible for the emergence of the virus. Nevertheless, we now know that multiple causes at different health, social and economic systems resulted in problems and challenges for health, health and social systems, as well as economic system dynamics. Unfortunately, the interactive feedback loops propagated multiple—often incoherent—responses bringing the system as a whole to near collapse.[60–62] COVID-19 also illustrates Peter Drucker's notion of the need to distinguish between '*doing things right and doing the right thing*'.[63]

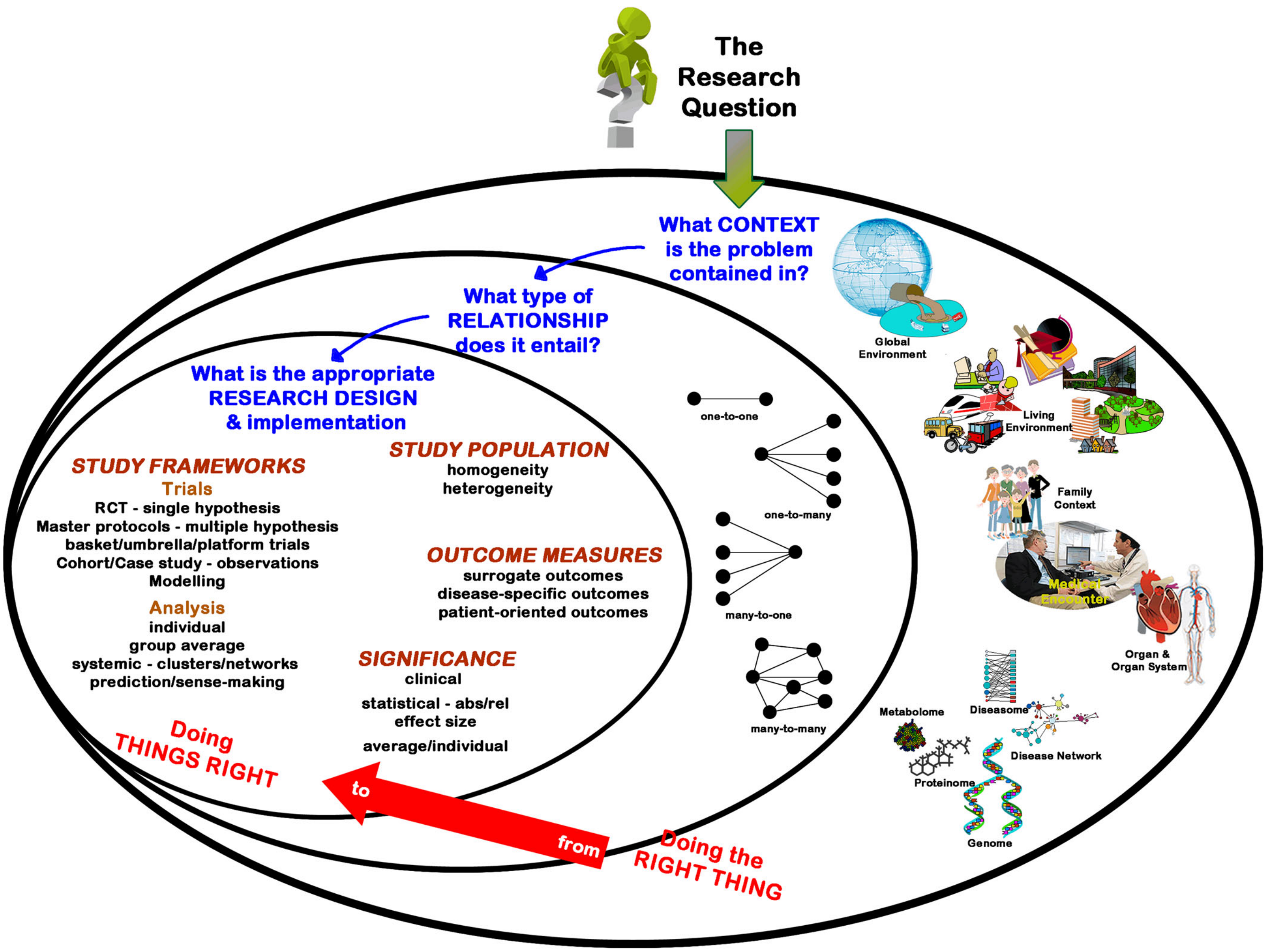

FIGURE 7 Applied '*causes and effects*' thinking. Putting it all together—doing the right thing starts with evaluating the nature of a study question initially in terms of its context, followed by deciding on the relationship/s to be explored. Context and relationship/s together with the nature of the study population and the determination of significance and outcome measures determine the research design, implantation strategy and analysis frame to be chosen.

Doing things right requires a systems understanding out of which arise the things we need to do right. If we fail, we end up '*doing the wrong thing and trying to do them righter*'.[64]

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analysed during the current study.

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