Clinical Trials and Reductionist Approach Preclude Cures for Chronic Diseases Due to Flawed Presumptions

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ABSTRACT

Modern medicine adopted four presumptions when it evolved from an-
20   cient experienced-based mind-body medicine. To understand its failure in find-ing cures for chronic diseases, we examined four presumptions, and found that statistical population of health properties does not exist for most research pur-poses, mathematical models are misused to model intensive properties, syn-thetic drugs are inherently more dangerous than nature-made medicines un-
25   der their respective application conditions, and reductionist treatments are in-ferior and inherently dangerous. We found that clinical trials are valid only for research where treatment effect is much stronger than the total effects of all interfering or co-causal factors or errors introduced by misused mathematical models can be tolerated. In all other situations, clinical trials introduce exces-
30   sive errors and fail to detect treatment effects, or produce biased, incorrect or wrong results. We further found that chronic diseases are manifestation of small departures in multiple process attributes in distinctive personal biologi-cal pathways networks, that modern medicine lacks required accuracy for ac-curately characterizing chronic diseases, and that reductionist treatments are
35   good at controlling symptoms and safe for short term uses. For all stated rea-sons, as long as modern medicine continues relying on the flawed presump-

tions, it can never find predictable cures for chronic diseases. By implication, predictable cures to chronic diseases are adjustments to lifestyle, dietary, emotional, and environmental factors to slowly correct departures in process attributes responsible for chronic diseases.

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INTRODUCTION

The systematic failure of medicine in chronic diseases was extensively discussed as early as 1875 [1], and often the subjects of critique by media [2-4]. As today, most chronic diseases have no predictable cure in medicine [5]. Population-based treatments have failed in cancer, heart diseases, mental disease, etc. [6-8]. Chronic diseases are the biggest economic burdens in the U.S. [7] and are predicted to consume about $3.5 trillion by 2050 [8]. From medical performance, we see two distinctively patterns: treatments for acute diseases are successful, but treatments for chronic diseases and cancer consistently fail. Thus, we suspect that the failure in chronic diseases must be of systematic nature that might have precluded cures for chronic diseases.

In our prior study, we found that controlled trials are improper methods for studying weak health factors when many interfering factors (equivalent to covariates in statistics) normally exist in clinical trials [9]. Our findings support the conclusions that all controlled clinical trials are biased [10]. Our prior model study shows a common scenario where each weak treatment or factor cannot be resolved or accurately determined if it is interfered by at least one to thousands of other factors that have similar degrees of effects. If a weak factor is studied in a clinical trial, it is improperly rejected as experimental errors. Most assumptions used in clinical trials and statistical analysis have not been considered [9].

To understand how weak factors affect disease outcomes, we need to examine biological pathways and disease-controlling mechanisms. We have shown that randomized controlled trials do not have the power to overcome sensitivity limits [9]. This insufficient-accuracy problem cannot be seen from the outcomes of clinical trials. When the validity of research model is challenged, such a challenge cannot be resolved by examining outcomes of research using the model. Moreover, due to complexity of health problems and a massive number of interfering factors that exist in clinical trials, it is impossible to find problems by examining the data of clinical trials. To find research model flaws we are required to consider all kinds of evidence other than clinical trial outcomes.

Presumptions are part of foundation of medicine and taken as truth so that their validity has never been questioned or examined. When medicine evolved from ancient medicines into the modern medicine, it changed natural medicines into synthetic drugs, changed populations into statistical popula-

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tions, introduced mathematical models as universal tools for medical research, and used the binary scale to model health properties. To find the cause of the systematic failure in chronic diseases, we will examine all presumptions and assumptions. The oldest presumption was that "medicine can cure disease".

5 While this presumption existed in the early history, medicine used in Yellow River Civilization is not the same as "medicine" prescribed in doctor offices today. We will consider what is wrong to use a population to study chronic diseases and what problems mathematical models can create. In addition, we will examine each of the assumptions used in clinical trials and statistical anal-

10 ysis to show additional flaws from biological points of view.

MATERIALS AND METHODS

We collects from medical literature published data and research findings

15 which tend to support or refuse challenged presumptions and assumptions. We rely on data from four sources: one of the sources is research findings that establish the existence of interfering factors and their degrees of effects. Due to an extremely large set of study findings, we will cite only selected references, and treat others as common knowledge. We must use this unique approach be-

20 cause no single set of data or any particular findings can ever resolve this challenge. This is why conducting one or more experiments is meaningless because the data of each study is like a drop of water in a bucket. The second source of data we rely on is media stories, reports from health care providers, personal stories, and our own observations. When the validity of controlled tri-

25 als is under challenge, we give more weights to those sources of evidence. Based on our prior studies [9], we ignore negative findings from controlled trials directed to weak factors.

Other data considered includes biochemical pathways, cellular or structural data, disease mechanisms, host responses to stressors, immune re-

30 sponses, factor-factor interactions, organ-organ interactions, rational explanations based on body structural compartment, rate balance among different biological pathways, and balance between disease process and healing process. Due to the large scope, we do not cite all contributors directly. The third source of data is data from simple mathematical models to refute or support

35 concepts or mechanisms. Such a method is used only to show that clinical trials with current data analysis can produce inaccurate, biased, or wrong results, but not used to establish that the use of mathematical method is right. As we show, that use of mathematical models is often improper if research purpose is assessing treatment benefits and finding cures. If use of mathemati-

40 cal models is refuted, clinical trials, as a research method, fall for this reason without regarding the propriety of mathematical models. The fourth source of data is the performance data in treating diseases. However, since most performance studies are based on clinical trials by various degrees, we must read

them to offset potential inaccuracies. In general, the treatment benefits of weak factors are underestimated based on our prior study [9] and obvious logic.

5 FAILURE OF CLINICAL TRIALS IN CHRONIC DISEASES

To show why clinical trials are invalid for most research purposes, we studied its development history provided in medical literature [11]. To understand mathematical models, we study biological pathways and their interactions, the multiple interactive disease mechanisms, factor-factor interactions, and the structural effects of tissues and organs, etc. In addition, we will show that treatment unit additivity assumption and an implied random error assumption fail to hold in nearly all clinical trials for studying chronic diseases.

A. Errors Reflected in the Development History of Clinical Trials

The development history of clinical trials reveals that clinical trials were developed by adding components piece by piece by different contributors in several centuries [11]. When clinical trial was first used, there was no need to examine statistical population because statistical analysis was not a part of analysis method for clinical trials. Population used in the early human history just means a collection of members, and early medical researchers naturally used population to study diseases because it always created a false impression that a treatment capable of curing more persons must be better than one that does not. This is still a reason for convincing researchers today. In the early days, there was never a need to examine the population of biological properties or health and disease properties. The controlled trial on scurvy conducted by James Lind in 1747 contained most elements. By 1946, all components of randomized controlled trials have been added. It is fair to infer that the clinical trials have gained general acceptance before the 60's [11] without using statistical analysis. Before about 1980s, medical researchers did not know the massive biological properties concerning diseases initiation, development and reversal, the complex human immune system, and the role of Central Nervous System. They did not have a vantage to see how personal genomes, environmental factors, emotional states, etc. affect health and disease properties. It was natural to presume that any health property in different people is similar so that the values of the property from different people can be treated as a statistical population.

Decades after clinical trials gained general acceptance, researchers started looking into human genome, biochemical pathways, environmental fac-

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tors, and lifestyle factors, emotional problems, etc. The effects of a large number of primitive factors on diseases have been established by tens of thousands of studies mainly after 1980 [See some references in Section E]. Even though, a good portion of studies is conducted by using population approach,
5   affirmative findings in those studies suffer inaccuracy by various degrees. Nevertheless, those positive findings have firmly established that differences in health and disease properties cannot be treated as random errors, and there is no statistical population as far as health and disease properties are concerned. Unfortunately, massive discoveries have not prompted medical researchers to
10   revisit the presumption of statistical population in the last a few decades. We have shown that effects of massive interfering factors are responsible for trial outcome uncertainty. When the nature of interfering factors was not understood, it was natural to attribute trial outcome uncertainty and conflicting findings to experimental errors. It is natural to try to solve this problem by using
15   misapplied statistical analysis.

Misuse of statistical analysis in clinical trials is clearly reflected in the development history of statistics. Statistical analysis was added to clinical trails as one of a few last components. The origins of statistical theory lie in the 18th-century, but improved experimental design, hypothesis testing meth-
20   ods, etc. were developed in the 1910s and 20s by William Sealy Gosset, and Ronald Fisher, and further refinement was made in the 1930s [12]. Hypothesis tests are used to determine whether positive outcomes in clinical trials are really caused by the treatment effect or due to uncontrollable experimental error. Use of hypothesis tests in clinical trials started centuries after the initial
25   use of clinical trials and more than a decade after the formation of modern clinical trials. Statistical analysis was added as additional analysis step to clinical trials from the 30s to about 60s. When statistical analysis is added, the traditional concept *population* was changed into *statistical population*. No published study has seriously discussed whether health properties of human be-
30   ings can be treated as a statistical population and their numbers can be added and divided like fungible properties.

B. Flaws in Past Statistical Studies

35   Past studies including those done by Altman, Senn, Zhao and Berger [13-18] have made a presumption that any health properties such as survival times, process attributes such as conversion rate and intermediate concentrations, etc. in human bodies can be treated as a statistical population [13-18]. They did so without exploring the effects of all interfering and co-causal fac-
40   tors normally exist in clinical trials. This presumption had been accepted for several centuries before. It had been beyond challenges. By using this presumption, even extremely complex health and disease properties such as survival time and emotional health can be studied like statistical population,

where outcome uncertainty can be attributed to random processes like rolling a dice or blowing colored balls from a lottery machine. After examining disease mechanisms and existing risk-disease data, we found that no disease happens like flipping a coin and blowing colored balls.

5   Due to a historical development reason, early researchers could not pay attention to biological properties and their affects on health properties. Flaws in those studies can be summarized as follows: first they made a presumption that disease and health properties can be studied like drawing events and that health properties of human beings in a treatment group can be treated as a
10 statistical population. They then made an assumption that disease or health properties can be mathematically added up and divided to yield a mean for the presumed population. In doing so, they actually made another assumption that health properties are fungible and exchangeable, and all uncontrollable interfering factors do not exist or can be neglected as random errors, and failed to
15 examine whether treatments have different effects on different persons, how interfering factors affect health properties, and how their plus and minus effects distort analysis outcomes.

          In the early years, they did not have the vantage to see the irrefutable evidence that most so-called errors are not truly random errors that are seen
20 in statistical trials, but a combination effect of hundreds to thousands of interfering or co-casual factors. They did not consider abundant evidence that treatments often have different levels of effects and different-sign effects on different persons, that magnitude of measured errors due to interfering factors can be larger than treatment effects; the interaction between a treatment
25 and any of potential interfering factors is distinctive in each person; that interfering factors can distort treatment effects by their positive and negative effects, with sufficient magnitudes to distort trial outcomes, and that personal biological properties are distinctive. Without considering external evidence, they were not in a position to compare the effects of a treatment with effects
30 of interfering factors, and naturally attributed all differences among individual persons to experimental errors.

          Past studies by Altman, Senn, Zha and Burger [13-18] share several common errors: They treated health and disease properties of human beings as population. They assumed that the differences among individual persons hap-
35 pen like those in statistical sampling, but never discussed external evidence about health properties such as process attributes [19]. By failing to look into the nature of all interfering factors, they bundle all contributions caused by different process attributes in the biological pathway networks into experimental errors. They concluded that there is no need to concern the baseline
40 balance. They never proved that health properties of people can be treated as a statistical population. If statistical analysis can fix the overwhelming problems, we could reach absurd conclusions that controlled trials have the power to resolve contributory effects of any weak factors; valid scientific research does not depend on separation method and detection technologies; and re-

search sensitivity limits can be overcome by running bigger clinical trials followed by doing a statistical analysis. Each of those conclusions must fall automatically.

5   What is wrong is that "statistical population" has been taken as granted for any research purpose. This is plainly reflected nearly all medical studies that never even attempt to determine whether a statistical population of a health property exists for intended research purpose. When a clinical trial is used to study a chronic disease, it is required that all persons must be similar in their chances of getting or resisting the same disease. Due to the massive

10 interfering factors in clinical trials, clinical trials tend to produce different outcomes. Early researchers could not understand the sources of uncertainty, and naturally assumed that trial uncertainty is caused by experimental errors beyond human control. Naturally, statistical analysis was used to solve this problem. When statistical analysis was added, *population* was silently changed into

15 *statistical population*. Medical researchers have made a presumption that a statistical population exists for any health property and any research purpose. This is evidenced by the widespread abuse of statistical analysis in medical research publications.

          While hypothesis tests are not wrong for all research purposes, they can

20 address only experimental uncertainties that are truly caused by uncontrollable random errors that happen like flipping a coin, blowing colored balls out of a lottery machine, or rolling a dice. The massive medical findings have firmly refuted that trial outcome uncertainty is caused by uncontrollable random processes but systematic errors. An implied requirement for classical sta-

25 tistical trials is that the coin must have identical weights on two sides to have the unbiased chance to produce each outcome, all numbered balls in a lottery chamber must have same weight, same shape, same size, and uniform internal density, and the dice must be a cubic with same area on all six faces, and has same density at every inner locality within the dice. If the rim or density near

30 two surfaces of a coin is altered, it will introduce systematic errors that cannot be treated as random error. A coin with altered feature may produce outcome ratio other than 1:1. The ball sizes and densities among different balls can be changed to result in different outcome probabilities. In clinical trials, systematic errors cannot be determined from trial results. Systematic biases cannot

35 be corrected without understanding the nature of the biases. The systematic biases can be established in reality by external evidence other than trial results. All interfering factors in clinical trials can have systematical impacts on trial outcomes. Inability to control interfering factors is not the reason to ignore their existence.

40   A vast number of the primitive factors such as nutrition, toxins, heavy metals, exercise, emotion issues, etc. are not really uncontrollable. Each of those factors is weak and hidden among the rest of the factors. It is like a situation where the effect of each factor cannot be determined but the collective effects of all factors are responsible for diseases. Even intermediate factors

such as glucose or triglycerides levels in blood can be altered by adjustment to lifestyle. None of those factors work like an uncontrollable driving force that makes a spinning coin to take one particular outcome.

Misuse of statistical analysis could not remove the trial outcome uncertainty. Great uncertainty in trial outcomes provides a great room for manipulation of experiments. Instead investigating the inherent flaws, medicine has tried to address this uncertainty problem by controlling selection biases and conflict interests as remedies. Thus, we see massive ethical regulations established after 1946 [11]. While selection biases can cure uncertainty caused by identifiable factors such as age, sex, overall health, disease stages, etc, it cannot do away with outcome uncertainty caused by a large number of other uncontrolled interfering factors. Conflict-of-interest measures can never do away with outcome uncertainty except that it is has become a scapegoat for the flaws of clinical trials. Such measures create massive administrative burdens which are rarely seen in other fields such as bridge design, aviation, automobile, etc.

C. Statistical Populations of Health Properties Do Not Exist for Most Research Purposes

While the population concept can be used for various purposes, the population, as used in statistical analysis in clinical trials for diseases, can be refuted by relying on observed health properties and known analytical data. Boys, girls, men, women, healthy persons, and persons with unidentified diseases, etc, are expected to have different baselines. For example, a healthy young person may have a baseline survival time of five thousand days while an old patient may have a baseline survival time of fifty days. Among the persons in a trial, besides the term "person", they are different in biological age, physical strength, shape and look, size and weight, etc. They differ in physical check-up data and laboratory analysis data [20]. Differences in local concentrations of intermediate compounds of some biological pathways in tissue cells between different persons could be more striking even though few studies were done to understand such differences at the cellular level. Even if assuming that diseases were realized in a manner like blowing human physical entities out of a lottery machine, some persons might be "drawn" at much higher probabilities. There is no population which would meet statistical distribution except by approximation in studies concerning body weight and head count. In most clinical trials, the baseline health property for each person cannot be accurately measured and determined. This present inability is not a valid basis for treating differences in health properties as random errors.

As a general rule, when a treatment in a trial is sufficiently strong while experimental errors are relatively small, two experiments with two measure-

ments in each would be enough without using statistical analysis. Statistical analysis is never required in most experiments in analytical chemistry. In a drug trial with the endpoint being survival time, real experimental errors are small because survival time, treatment dates, and drug doses can be deter-
5   mined and recorded accurately. But for the interfering or co-causal factors, clinical trials repeated in the same condition are expected to produce consistent results without need to use statistical analysis. In a trial involving a poorly defined treatment such as a stress-relieving method, part of outcome uncertainty is caused by the uncertainty in treatment definition; and part of the out-
10   come uncertainty is caused by interfering factors. Statistics is not a suitable method for taking care of interfering factors and definition uncertainty of treatments.

D. Several Model Problems Defeat the Population Presumption

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We will discuss several model problems that make population presumption fail.

1. The averaging of positive and negative effects of a treatment

A first problem is that a factor or treatment can have positive effect or
20   negative effect on different persons. For example, to improve vitamin D supply, its levels in blood for a sample of a population can be determined together with the mean and a standard deviation. This mean may be used to determine the total amount of Vitamin D required for correcting vitamin deficiency for the population. Since vitamin levels actually vary among persons, the amounts
25   of supplement intakes cannot be determined on the basis of the population mean but on actual vitamin level in each person. If the same amount of vitamin supplement is indiscriminately used by all persons, the amount is insufficient to those with low vitamin levels but may intoxicate those with high vitamin levels. This treatment will have both positive effects on some persons and nega-
30   tive effect on others. If we assume that 50% persons need to increase vitamin D while other 50% of persons do not, vitamin supply may happen to show a net zero. An overwhelming number of factors can have both positive effects, no effect and negative effects on different persons for any health problem. Each of all nutrients, physical exercises, measures to reduce toxic pollutants, etc. is
35   expected to have positive effect, no effect, and negative effects. The averaging operation used in clinical trials always produce meaningless results. A lack of effect is false because it is an improper average; a negative mean is wrong because at least some persons need the vitamin; and a positive mean may be underestimated because the values have been brought down by those who ex-
40   hibit toxic reactions. Thus findings based clinical trials are meaningless and cannot be used as treatment guidance.

2. The treatment effect is distorted by the positive and negative effects of each of a large number interfering factors.

Even if the treatment or the treatment factor has a fixed positive effect on a health property on all subjects, this constant number cannot be accurately determined. This constant-effect assumption must be false, but we use it to show that a large number of interfering factors can distort the treatment effect. All interfering factors have positive or negative effects on different persons. Assuming that treatment T has a fixed treatment effect on all persons, the positive and negative effect of an interfering fact can distort its effect so that it may produce a false result. This problem is caused by the inability to resolve contribution of the treatment and contribution of the interfering factor on each specific person. This can be shown in the following table:

Table 1. How An Interfering Factor Affects the Treatment Effects of a Treatment of Similar Strength.

	Person ID	1	2	3	4	5	6	7	8	9	10	Mean
1	TX	1	1	1	1	1	1	1	1	1	1	1
2	IF (Ctl)	+1	-1	+1	-1	+1	-1	+1	-1	+1	-1	0
3	TX Obs.	2	0	2	0	2	0	2	0	2	0	1

In Table 1, the treatment has a fixed effect of 1 on all persons. One interfering factor in row 2 has positive or negative effects, and raises the variances of the observed data in row 3. The net interfering factor in row 2 could be viewed as a control. If no interfering factor, all values in row 2 would be near zero, all measured values would be 1, and the mean could be determined without any uncertainty. The interfering factor dramatically raises the variances of the treatment in row 3, and thus raises the threshold of rejecting the null hypothesis. The trial most probably fails to find the true benefit of the treatment. When hundreds of interfering factors exist, the variances seen for the treatment must be larger even if the interfering factors follow complex or unknown distributions.

Table 2. How a Strong Interfering Factor Distorts the True Effect of a Weak Treatment.

No	Person ID	1	2	3	4	5	6	7	8	9	10	Mean
1	TX	1	1	1	1	1	1	1	1	1	1	1
2	IF (Ctl)	+10	-10	+10	-10	+10	-10	+10	-10	+10	-10	0
3	TX Obs.	11	-9	11	-9	11	-9	11	-9	11	-9	1

In Table 2, a single strong interfering factor dramatically increases the variances of the observed data. The massive variations of the interfering factor find its way into the values of the treatment group relative to a control. Due to the massive variances between individual persons within the treatment group, true treatment effect in row 1 may be completely hidden in the interfering ef-

fect. Although the treatment mean is detected as unbiased, the enlarged variances will result in a much higher threshold for rejecting the null hypothesis. Based on other observational data, we must say that the variances from different persons are very high and result in failure to reject the null hypothesis. We suspect that strong interfering factors are very common in studies intended to study weak and slow-delivery environmental and lifestyle factors. In such situations, clinical trials always produce false negative findings.

Table 3. Strong Biased Interfering Factor Overrides a Weak Treatment

	Person ID	1	2	3	4	5	6	7	8	9	10	"Mean"
1	TX	1	1	1	1	1	1	1	1	1	1	1
2	IF (Ctl)	+10	-10	-10	+10	-10	-10	+10	-10	-10	-10	-4.0
3	TX obs.	11	-9	-9	11	-9	-9	11	-9	-9	-9	-3

In Table 3, a single strong interfering factor has a biased affect on the measured health property of both treatment and control. This kind of interfering factors include fears, development stage, aging, seasonable effects, exposure to bad news etc, that strike all subjects in both the treatment and control groups. It can dramatically increase the variances of the observed data. In addition, it also moves the measured values as well as the mean to negative side. Even though the treatment has a net effect of 1 on each person, the observed data may be still negative. In addition, aging, development stage, seasonal factor, or exposure to bad news may interact with the treatment. A treatment may have curative benefit, but negative news may make all subjects so sad that the news might have suppressed the immune system or the whole body health. Due to the massive variances and negative interactions, true treatment effects are most probably rejected as errors.

In clinical trials, there are hundreds to thousands of interfering factors. Their variances can be added up for well known distributions [9]. For unknown distributions, the final variances depend on the number of interfering factors and their effect on variances within the treatment group. This results in systematically rejection of weak treatment effects.

3. Treatment effects are distorted by interactions between the treatment and interfering factors.

The impact of interfering factors in clinical trials cannot be corrected by achieving baseline balance between the treatment group and the control group. This can be shown by the interactions between the treatment and interfering factors. Assuming that treatment T is under the influences of uncontrollable interfering factors (H_1, H_2..., H_n), the detectable treatment value for a person is $AT_i = \Sigma(T_i + T_i - H_{j=1} + T_i - H_{j=2} + ..., T_i - H_{j=n})$. Each interfering factor H_j causes plus and minus affects ($T - H_j$) over an imagined treatment T_i. Some interfering factor may raise treatment effect by various degrees while other interfering

factors may depress treatment effect by various degrees. The net effect of the treatment on a person depends on the treatment and all interaction effects. Thus, net treatment effect on a particular person must be different from the net treatment on another person. In the control, the correspondent term is zero. We ignore each of the interfering factors. All interaction terms (T_i-$H_{j=1}$+T_i-$H_{j=2}$+...,T_i-$H_{j=n}$) would depend on the treatment. It is possible that a treatment is predicted to have beneficial effects on a disease, but the interactions with other factors might have brought the predicted effect down to nothing or negative value. Because the number and impact degree of interfering factors are unique in each person, the effect of treatment will be altered by different degrees in different persons. This might be the reason many drugs do not deliver intended benefits.

The total treatment's effect for the treatment group is the sum of all treatment effects on all persons (Ignoring the problem in additivity for the time being). A large number of interfering factors interact with the treatment. If they interact with the treatment in an unpredictable way, the average of treatment effect is meaningless. The nature of interactions is determined by the treatment OR interfering factors. For example, calcium supplement is predicted to benefit bone health, but high sodium daily intake promotes calcium loss. The sodium's effect on calcium balance depends on persons who have different sodium intakes. Similarly, exercise can beneficially affect innate immunity, acquired immunity, etc, and people vary in doing exercises. Exercise can dramatically raise the beneficial role of other treatments such as nutrition and detoxification of heavy metals intended to improve the immune system. Upper and down shifts of baselines cannot be determined for a specific person. Thus, the knowledge of baseline upper or down shifts by interfering factors can provide a better strategy for formulating treatments.

In the above example, simple mathematical model is used to characterize treatment effect and its interactions with interfering factors. However, accurate interactions cannot be characterized accurately due to multiple layers o complex healing and disease mechanisms.

2. Treatment effect is realized at a very slow speed

One unique problem with human health is that many lifestyle factors affect health and diseases slowly. This problem is an additional reason for the failure of clinical trials. Even if a treatment is relatively strong, it cannot be detected in a short trial. The treatment may be unable to trump the effects of random and unpredictable interfering factors. Exercise is a very weak factor if it is examined in a short-term trial. No benefits can be detected for a short time trial. If exercise is examined in a long-term trial, its true benefit is interfered by certain factors that also have systematic impacts. Those factors include ages, aging, development stage, menopause stage, hospital isolation, etc. For people at advanced ages, part of the long-term treatment effects are interfered by those factors.

E. A Massive Number of Interfering Factors and Their Nature

Each person is a unique being by genome [22]. The typical difference between the genomes of two individuals was estimated at 20 million base pairs (or 0.6% of the total of 3.2 billion base pairs) [22]. Moreover, even identical twin can become different beings by epigenetic changes that have an effect of turning on or off gene expressions [23-24]. Each disease like cancer is a distinctive product of personal genome, diet, living environment, etc. [25-26].

1. Evidence showing the effects of interfering factors

All factors a person exposed to can affect the person's health. Emotional shock, chronic stress and social isolation, etc. can affect inflammation [26-28], the immune system [29-32], influenza and respiratory infection [34-36], cancer development and metastasis [37-40], heart diseases [41-42] and drug metabolism [43]. Since the brain controls hormonal actions and biological processes, disorders in the brain must affect correspondent tissue ecosystems. This critical role was described in 1875 [1]. Nutrition affects immunity to viral infection [44-46], infection [47-49], viral pathogenicity [50], etc. Selenium affects viral mutations [51]; and Zink affects risk of pneumonia in the elderly [54]. Obesity affects immunity to infection, inflammation, and immune responses [55-62]. Excessive cell phone usage increases risks of brain tumor [62-65].

Metals, including lead, cadmium, mercury, arsenic, chromium, copper, selenium, nickel, silver, and zinc, and other metallic contaminants including aluminum, cesium, cobalt, manganese, molybdenum, strontium, and uranium are found in living organism, plants, contaminated vegetables, industrial materials and polymers, soil and land resource, and air and water pollution [66]. Most heavy metals such as aluminum, arsenic, beryllium, cadmium, lead, mercury, nickel, and radium increase risks of cancers including lung, kidney, liver, stomach, intestines, bladder, colon, gastric, nasopharyngeal, pancreatic, breast, gallbladder, esophagus, prostate, testes, gastrointestinal skin cancer and non-Hodgkin's lymphoma [67-69]. Exposure to arsenic, lead, cadmium, and copper is associated with an increased risk of cardiovascular diseases and coronary heart disease [70, 71]. Heavy metals can damage cells [74], disturb the Redox balance [72, 74], and suppress the immune system often at very low concentrations [73, 74]. Many heavy metals can damage liver, kidneys, and brain and nerves [74]. Alteration of homeostasis of metals could cause the overproduction of reactive oxygen species and induce DNA damage, lipid peroxidation, and alteration of proteins, thus increase risks of developing brain tumors [75]. Metals such as lead, mercury, cadmium, and arsenic may be important contributors to neurodevelopmental disorders and disabilities [76]. The findings in those studies firmly establish that heavy metals can cause specific diseases, but they must be viewed as having global adverse health effects

because they can interfere with enzymatic reactions that control reaction rates of all biological pathways.

Inorganic and organic substances can have adverse health effects. Sodium, the most common flavor is the number-one silent worldwide killer due to its role of raising blood pressure [77]. Habitual dietary salt intake is positively associated with the risk of gastric cancer [78]. Besides cardiovascular diseases, high salt intake increases risks of gastric and some other cancers, obesity, Meniere's disease, worsening of renal disease, triggering an asthma attack, osteoporosis, exacerbation of fluid retention, renal calculi, etc. [79]. High sodium intake is associated with obesity [80]. Moderately high salt intakes affect calcium metabolism and bone health [81]. Reduction of sodium intake can reduce both systolic and diastolic pressures [82]. Exposure to common quaternary ammonium disinfectants may decrease fertility based on animal models [83-85]. Hydrogen peroxide may cause poisoning [86]. Lack of exercise and physical inactivity are found to the substantial causes of chronic diseases [87-88]. From the benefits of exercises on cancer survival [89-100], it is expected that reduced exercise and increased inactivity has adverse impacts on survival among cancer patients. People have different organ reserve capacities [101-103], which are presumed to be the most important factor that affects patients' ability to survive from diseases.

Available spaces in the thoracic cages affect their ability to accommodate tissue swelling in lungs [104]. Obesity is found to be a high risk factor for COVID-19 disease [105, 153]. Information stored on the CNS neurons is different, and it, like computer programs, affects emotional health and CNS regulatory functions over the body. Lack of medical findings is not a reason to deny its role and importance. Full details of those factors can be presented only in a searchable database. Even environmental factors such as oxygen [147], humidity [148], and temperature [149] affect immunity and pathological responses to infection. Massive organic compounds, industrial materials, industrial chemicals, pesticides, herbicides, fungicides, etc. will be discussed elsewhere.

Many factors exhibit non-linear complex effects and may interact with each other. The CNS interacts with bone, marrow, and the micro-environment [151]. Enteric microbiota, central and enteric nervous systems interact though the gut-brain axis [152]. Sodium also exhibits different effects under different use conditions. High salt (4% NaCl as well as 1% NaCl enriched tap water feed mice for 2 weeks) inhibits tumor growth by enhancing anti-tumor immunity [82] contrary to the long term adverse effects. Like glucose level that has both good and bad roles, sodium's short-term effect may be realized by influencing blood viscosity and fluid ionic strength while its long-term affects are most probably realized by affecting blood pressure and the vascular system. Any factor affecting viral diseases could also depend on a large number of other factors that affect innate immunity, host responses, acquired immunity, micro-circulation, and structure features of target tissues. The cited findings

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provide irrefutable proof that none of interfering factors can be ignored in the mission to find cures.

2. Slow effects of weak factors

To understand the nature of interfering factors, it is important to understand event timing. Some treatments such as consuming glucose to raise blood glucose can show immediate benefits. Other treatments or factors will affect the biological pathways networks without immediately causing symptoms. It may take time to distort the biological networks. The distorted network then slowly alters the structure of the body. This is similar to the development of chronic diseases. Altered biological network and altered body structure also interact with the Central Nervous system by the mind-body interactions [112-113]. The mind-body interactions may be a mechanism for stabilizing the physical body. Most departures in biological networks in tissue cells cannot be directly determined in clinics because reference ranges of chemical analysis data for normal ranges are very large. Chronic diseases are often diagnosed by examining blood compositions, changes in cellular structures and disease biomarkers. It is difficult to determine the effects of weak primitive factors by monitoring blood compositions, cellular structures and disease biomarkers.

F. Flaws of Using Mathematical Models

In modern medicine, another presumption is that every health problem can be represented by a mathematical model. Now, a super majority of medical studies include statistical analysis. We refute this presumption.

1. Flawed assumption of linear effect of a treatment

The assumption of linear effect of treatment is widely used in medical research, but fails in nearly all situations. Most interfering factors influence health properties by a complex manner. For example, nutritional intake, physical activities, sleep duration, thinking activities, environmental factors such as temperature, atmospheric pressure, and humidity, etc. affect personal health often by quadratic functions (if we do not resolve precise effects at a finer scale). A low nutrient intake has negative effects, its beneficial effect increases with intake amount, and hits an imagined optimal point; after this point, further increased intake causes a reduced beneficial effect, and results in progressively increasing toxic effects. The point of the optimal value for any factor is not static. The shape of effect-concentration curve depends on personal genome, health condition, age, physical activities, lifestyle, diets, and emotional states, etc. This rough quadratic pattern is true even for physical activities. Too little sleep can hurt due to insufficient rest time and too much sleep time may result in excessive fat accumulation. It is even true for things like usage levels of body parts such as hands, feet or joints. Long inactivity hurts,

and overuse also hurts. Thus, relationship between two variables is unique in each person. Regression cannot be done for a population.

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Mathematical models cannot model complex interactions of health properties and primitive factors. Health properties such as glucose level, triglycerides levels, oxygen saturation, etc. may work like influencing factors for other health and disease properties. They also affect other high-level health properties such as disease risks, death rates, survival time, etc. Due to complex interactions, we found that most health properties must be multiple complex functions of a large number of primitive factors. There is no best nutritional profile, no best diet, no best copper intake, no best environment, etc. because the effect of each factor also depends on other factors and personal activities. There are no objective criteria for determining what is best. There is no best amount of exercise, and nor best kind of exercises for all people in a population. Even for a given person, there is no static best value. An imagined best value may exist only under certain conditions with respect to arbitrary evaluation criteria, and must change with age, health condition, activity levels, emotional health and other personal, environmental and lifestyle factors. The notion of best value such as best sleep duration for a population is flawed. The linear models used in statistics can model only simple properties like crop weights and production yields when research purpose concerns a fungible property.

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The unique nature of process attributes implies that health properties are not the types of properties for mathematical operations. Moreover, interactions between disease initiation and multiple layers of disease defense mechanisms also refute this assumption completely. Disease mechanisms are further influenced by a large number of primitive lifestyle and environmental factors. Clinical trials can produce unpredictable and inconsistent results due to effects of influencing factors at different layers. A factor for diseases may be found to have no effect if a strong defensive mechanism in most human subjects can overcome initiated diseases; and in another trial, the same factor effecting disease initiation may be found to be a strong controlling factor if the defensive mechanism in most subjects is compromised.

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2. Mathematical average of health properties generally has no meaning.

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The notion of equating average of a population as the best value was formed from a false perception of comparative results in clinical trial. By using a comparison, clinical trials always produce a false impression that the positively determined treatment must be good for the population. Thus, treatments developed from clinical trials have been regarded as the best in practice for centuries. The validity of controlled trails has been presumed for centuries but has not been proved. The purpose of a clinical trial is determining whether a treatment is better than a control often by using statistical analysis. In conducting statistical analysis, measurement values from all persons in the treatment group are added up to yield an average. There is no scientific proof that such health properties can be added and that a determined average can repre-

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sent all persons in the treatment population. This presumption holds only if all persons in the population actually had a mean, and the averaging operation is merely to remove truly random experimental errors.

Most health properties are process attributes such as conversion rate, the concentrations of intermediate, or the matrix of those things. In the treatment group, a mean determined by mathematical averaging can represent none of the members in the treatment group. If a treatment is found to have positive effects over a control group, what is proved is that the treatment has sufficiently positive effects on the members of the treatment group over the control. Such a positive value can be detected if the treatment effect is stronger than the sum of all interfering factors in the treatment group, the treatment produces beneficial effects on more persons than it produces adverse effects of same degrees on others within the treatment group, or the treatment has a net beneficial effect on the treatment group over the control for whatever reasons. It does not prove that the treatment is effective for the treatment group, is effective for treating the disease, or is the best for all persons with the disease.

The notion that "an average represents a population" is generally wrong unless a statistical population can be established by independent evidence. In politics, number-based representation is a principle imposed by will, but not natural law. In a statistical population, the members must share enough similarity so that the members can be used to investigate a treatment. This requirement is entirely relative to the investigation purpose. Computed average can represent a population only if a statistical population actually exists. The existence of a statistical population cannot be proved by mathematical operation itself, reasonable data pattern or a computed average value. Mathematics can be used to determine average weight of a sesame seed and a fighter carrier or the average heart output of an elephant and a bird. Such averages can represent neither the weight of the sesame or the carrier, and nor the heart output of the elephant or the bird. While the values in those two examples are extreme, similar data values do not provide a basis for finding a statistical population. Similar reaction rates in certain tissue cells in tigers and turtles do not make the rates a statistical population (even though turtle's mean may be used to estimate the tiger's mean in practice). It is possible that apple tree data might nicely fit into human data purely by accident.

Existence of a statistical population must be established by examining individual members and the purpose of investigation. If an identical nutrient intake has a beneficial effect on one person but a toxic effect on another person, the average value, which has the same value, does not represent a beneficial effect for both, and nor a toxic effect for both. On the contrary, apple, orange, and plum in a compartment mixture could be treated as a reasonable statistical population if the investigation purpose is to estimate packaging volume. Even abstract concepts may become a statistical population if their differences do not defeat the investigation purpose. Similarly, deformed coin, ir-

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regular balls, and non-cubic dice with varying inner densities cannot be used in drawing sampling for classical statistical trials. In the vast medical research articles, research purposes and accuracy requirements have been ignored. This single error makes many study findings meaningless.

5   The permissible use of mathematical operations for population-based study depends mainly on the purpose of research. Grain weights may be added and divided if research purpose is to study grain supply and demand. In this situation, grain weight is fungible because mathematics does not differentiate sources just like market demand. However, if the research purpose is to in-
10 crease individual seed weights by using a new treatment, grain weight is not a fungible property. We must consider if the treatment has the same effect on each individual seed. If the same treatment can have different effects on differ-ent seeds with different genetic compositions, a mathematical model that re-gards the treatment having the same effect must fail. Lifespan is partially con-
15 trolled by complex biological pathways, and thus is not fungible: extending 20 years for a boy is not the same as extending 20 years for an elderly person. However, survival time could meet statistical population if research purpose is to determine total community life spans for the purpose of getting a financial reward under a lifespan-based reward program. If a mathematical model
20 treats positive and negative effects of influencing factors as experimental er-rors, the errors must be sufficiently smaller than the treatment effect so that study validity can be justified by approximation. Based on this rational, mathe-matical operations cannot be used to find best treatments for persons who have distinctive biological properties.

25   Mathematical averaging of process attributes is improper also because most process attributes have no standalone meaning. One class of properties is intensive property that reflects local physical property of a system. Exam-ples of intensive properties include temperature, pressure, refractive index, density. Extensive properties such as the mass and volume are additive. Tem-
30 perature is not additive because heat absorbed at different temperature would be different, and temperature at different systems such as water and gas means completely different things. Process attributes and health properties are similar to intensive properties. A Civic uses fuel at the rate of 1 gal/time (where time is a suitable time unit) and an Accord consumes fuel at 2 gal/time.
35 Their average would be 1.5 gal/time. This number may indicate average usage of fuel from fuel supplies. However, this number cannot be used to study the performance of the cars because the performance of each car depends on a large number of other variables such as driving distance and weight of carried goods. The average, 1.5 gal/time, has no meaning if it is viewed out of context.
40 Fuel injection rate can be evaluated only against criteria such as shipping weight and running distance. We can infer that all process attributes such as fuel injection rate, coolant flow rate, heat dissipating rate, etc. from individual cars or planes cannot be added and averaged across individual model, and then applied to any specific unit.

Direct mathematical average is proper only for fungible properties such as crop weight and production volume. For such properties, the significance of each unit of weight or volume does not depend on other variables. However, direct averaging without using weights is improper for computing average for
5   alcohol of 99% purity and alcohol of 30% purity. The net weight of alcohol depends on their purity which is an additional variable. For nearly all health properties, the significance of process attributes always depends on other variables. Mathematical operations used in classical probability trials do not violate the fungible requirement. In probability trials, events are defined accu-
10   rately. The appearance of a numbered ball, a dice position, or coin face is not subject to additional variables. Each outcome has the same significance as any of other outcomes. That is the basis for adding them up to get a sum. Observing examples in statistical books, we found that an intensive property may be used as a statistical population only for the same system or similar systems.
15   For example, daily production rate of a machine can be added up and averaged for different days because all other variables are fixed and thus the number of product pieces is the only variable. Whether production rate from different machines can be summed and averaged depends on the purpose of mathematical operations.

20   Contrarily, process attributes are generally not the kind of properties that can be summed up and divided. The specific values of process attributes do not have standalone meaning. They are incapable of determining system performance like health or disease states. Glucose level, a process attribute, affects health by interacting with other factors or variables. When the glucose
25   level is low, it is vital to survival. If it increases, its benefit reaches a plateau. Further increase in the glucose level will cause negative effects by damaging the vascular system. Thus, the 15 mg/liter in the low end and 15 mg/liter in the high end have different benefits even for the same person; and 10 mg/liter in diabetes patients and 10 mg/liter in hypoglycemia patients have different
30   meanings. Averaging glucose levels for diabetes patients and hypoglycemia patients would result in a "healthy" mean, which is clearly contrary to reality. We can find that all process attributes share this same problem.

Any process attribute as well as unit change to an attribute such as glucose level (mg/liter), red blood cells (no/liter), white blood cells (no/liter), en-
35   zyme activity (in any units), etc. have no standalone meaning unless it is considered for a specific person under a set of specific conditions. Thus, a computed mean of any health property has no meaning. If the reaction rate of a specific biological pathway in a person is X while that for another person is 2X, the mathematical average can represent neither. Intermediate concentrations
40   also have no meaning. A low glucose concentration would imply low conversion speed only if the rate constant for the biological process is same. However, in reality, 110 mg/liter in an obese person may reflect even lower of conversion speed than 70 mg/liter in a young person. Similarly, rate constant or activity level of an enzyme has no meaning unless it is considered in context.
45   The high concentration in an obese person might be caused by excessively

slow conversion rate so that more of absorbed glucose is backed up in the blood. In addition, net conversion rate must be influenced by physical structural features of the body.

Each process attribute in the biological network [106-108] of a person is
5   distinctive and this nature bars approximations. Given the long development time of chronic disease, departure in any process attribute in the biological network is very small [Sup. A]. Thus, computed mean cannot be imposed on to any individual person because the mean must be different from the correspondent value for the person. Based on above discussion, we find that all process
10   attributes have non-linear, complex effects on personal health, and that their effects on personal health depend on many other personal factors. Personal health values cannot be added up across individual persons except in situations where research purposes can tolerate such errors.

Many large-scale clinical trials such as TAILORx trial [109] reveal mis-
15   use of representation principle. It attempted to get better "representation" from people by running a multiple national trial. Since findings from clinical trials always had some kind of average of personal numbers, they cannot represent a super majority of the persons other than lucky persons whose numbers luckily fall on the average (which may happen by the chance of winning a
20   lottery). The average is not the optimal value of any person in the trial subjects. Since the mean of a health property derived from a population cannot represent individual persons, a treatment on the basis of such health property cannot be valid for any of participant persons except the abstract person that does not exist. There is no basis to find that such a treatment is best for other
25   patients outside the trial. The flawed logic is that the validity of the treatment for persons in the U.S. depends on how good the treatment is to persons in Brazil.

3. Use of the binary scale and classify properties by categories

Another problem arises from using the binary scale. Most of health prop-
30   erties are continuous properties except a few things like gender and death. Many health properties actually exhibit 0 and 1 states, with 1 state further comprising values in non-linear continuous profile. One obvious example is exposure to a virus. Exposure can be classified as no and yes. Among exposures, infection risk would depend on the number of viral copies exposed. However,
35   nearly all health properties or process attributes of biological pathways are continuous. They differ in amount or degree. Conversion of such properties into the binary states introduces excessive errors. By common sense, digitizing a sound by two-bit digital scheme can introduce great distortions. Conversion of data into the binary scale can introduce as much as 50% relative error. The
40   49.9% will become zero while 50.1% will become one, but each of the two numbers could get a different binary value. The binary scale has been widely used to characterize health conditions, disease definitions, blood pressure, selection of control groups, etc. The binary scale is not used in nature, but imposed by human will (e.g., normal blood pressure). The normal and abnormal

system is widely used for chemical analysis data, and thus introduces excessive errors relative to the required accuracy for correcting chronic diseases. Categories are also used in classifying side effects, cancer stages, etc in an attempt to break continuous properties into categories by human wills. The binary scale does not provide precision required to characterize chronic diseases.

4. Other assumptions used in statistical models

The unit treatment additivity assumption is used in regression and variance analysis. Most weak factors, if they are studied as treatment, defeat this assumption because they have positive and negative effects on different persons. Human body always has several layers of disease mechanisms including innate, host response, acquired immune responses, resolution of inflammation, and recovery of damage. Whether a treatment shows its effects would depend on the roles of this mechanism targeted by a treatment relative to other mechanisms. A weak mechanism must be hidden within a strong mechanism. Exercise may have negative effects on some people whose blood vessels are severely damaged, but positive effect on others. Finally, even if the treatment effect is constant, interfering factors can distort their values; and a large number of nutrients, physical properties, environmental factors, etc. can distort treatment effects by interacting with the treatment, making this assumption fail.

G. Altering the Presumption That Medicines Can Cure Diseases

"Medicine can cure diseases" is the oldest presumption that everyone takes it for granted. The first synthetic drug, chloral hydrate, was discovered in 1832 by Justus von Liebig in Gießen and introduced as a sedative-hypnotic in 1869 [110]. Before the start of new drug industry, all medicines, referred in old medical literature, are natural products comprising mixture of natural compounds, and most medicines are even formulations of natural products like herbs. After 1869, medicine definition was changed without examining is validity into active synthetic components [111]. There are several important changes to the original meaning. Old medicines work like multiple-component diets with much milder effects while synthetic drugs are used at higher concentrations. Second, early medicines are things that once worked as selection pressure in evolution. For example, the compounds from herbs, plants, and natural products might have found their ways to human bodies through the food chain. It is reasonable to infer that human body can tolerate them in low concentrations. Fecundity phenotype will not be passed on to the next generation if the individual person cannot tolerate natural compounds at low concentrations, and die before reaching reproductive age. In comparison, most human beings are not exposed to synthetic drugs, and thus selection will start

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upon ingesting such compounds. Those two things affect drug side effects and the ability to restore the biological pathway networks.

FAILURE OF REDUCTIONIST TREATMENT MODEL

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The flaws in clinical trials and failure of reductionist treatments are two different things but share some common elements. We have proved that treatments derived from clinical trials are deemed to be poor or inherently dangerous due to mismatched application [9]. Besides the mismatch of treatment, the poor performance of population-based treatments can be attributed to reductionist approach, which is found to be poor or unworkable in nutrition [114-115], lower back pain [116], neuroscience and brain research [117-118], diagnostics [119], exercise [120], patient care [121-132], public health programs [124], and holistic medicine [125-127, 150]. The evidence, taken as whole, has firmly established that reductionist treatments are inferior. Those findings in combination of our simulation study [9] prove that reductionism is a wrong approach to chronic diseases.

A. The Limitation of Reductionist Treatment Approach

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Most medical treatments are developed according to reductionist thinking. The reductionist idea is that human body is like a machine, and any fault can be fixed by targeting the fault part. This notion has been proved in some aspects such as organ transplant. However, we also see severe limitations. For example, after a person has died for some time, there is no way to revive the dead person like restarting a repaired car. The human ability to intervene brain is very limited. A reductionist treatment always has two components: a treatment is developed from a population and applied to the patient in treatment of a disease. Both components are responsible for the failure of reductionist treatments.

1. Population-based reductionist treatment cannot cure diseases.

It is generally believed that a treatment developed from a population must be good for persons A, B, C, etc. While this idea formed in old history, it can be summarily rejected by using a car repairing model. Automobiles made by Honda, Nissan, and Ford cannot be repaired by using a common method or common specification because they are distinctively designed. We now know that each human body is also distinctively designed. Second, even for cars, many process attributes cannot be altered without changing the whole car. For example, the cooling system and exhaustion system for each model of car must be matched to the rest of the car. Even the wheels for a given model of car

cannot be replaced by average sizes of the wheels used in the auto industry. The average of fuel consumption rates from a Civic and a Mercedes-Benz G550 cannot be imposed on either the car. We can imagine that if auto repair and plane repair industries have used a population approach, mechanical
5   problem in automobiles and planes must be incurable. All planes will crash.

A treatment derived by clinical trials is mismatched to patients. For example, John Doe suffers Vitamin A deficiency but Jack Doe suffers Vitamin A poisoning. Both are sick even though their average is perfect. If a treatment is developed from such a population, the treatment reflects impermissible trans-
10 fer of process attributes in the biological networks. The treatment cannot be valid for both of them. This is not an isolated problem but a universal problem in treatments for chronic diseases. Most, if not all, of nutrients, pollutants, activities levels, etc. are expected to have both positive and negative effects. If a treatment is used to affect one of such factors, the treatment must be im-
15 proper for a considerable portion of persons. Even if a treatment has a constant treatment effect, the interfering factors affect the treatment (see Tables 1, 2, and 3). Mathematics makes impermissible average in finding treatments and such treatments cannot be good for anyone except by accident.

Treatments derived from population trials always make improper trade
20 harmful to patients. In a mini trial comprising a 90-year old man, a 40-year old man, a 40-year female, and a 10-year old boy, their health and disease properties must vary greatly. We acquire data and find an averaged value in a health property for this population. The data does not form a statistical population. If we impose the averaged value onto all of them by imagined measure, we
25 should anticipate that the measure most probably will kill all of them in a long run. Obviously, to develop a treatment by the population approach, attempts are made to balance age effect and sex effects. Treatment of the old man is balanced by the need to offer benefits to the young boy. A treatment for the man is balanced by the need to offer benefits to the female. This mathematical
30 averaging violates our observed principle that health property cannot be altered arbitrarily and cannot be transferred from a person to another person. Any treatment based on the representation principle must be detrimental to all persons if the treatment is used for a long term. This flaw cannot be cured by increasing the number of participants in the trial.

35 Even responsive rate used in medicine is a poor concept. Two treatments with 5% curative rates are considered in mathematics as same. However, they mean completely different things if one treatment cures only females while another cures only males. The population model makes an assumption that all persons are treated in the same way, but in reality, they cannot. What is really
40 important is who will survive and who will die. Treatments determined by using mathematical model are insensitive to personal differences and cannot be used to formulate the best treatments for all persons. Two treatments respectively with responsive rates of 50% and 40% lack comparison basis and cannot be compared. If they work on entirely different persons, they would treat 90%

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of the population if they are matched to right persons. If their joint responsive rate is 20%, they would benefit 70% of the population.

2. Reductionist treatments cannot correct departures in human biological pathways networks.

Each person has a unique biological pathway network [106-108], and chronic diseases are manifestation of a large number of departures in process attributes in the network. All attributes in one person's biological pathway network are different from those in another person's network. This distinctiveness is implied by well known variations of chemical analysis data [128]. The distinctiveness of physical check-up profile of each person is a common knowledge. If a treatment is used on different persons, changes caused by the treatment in process attributes in one person's network must be different from changes in other personal pathways networks. Even if the treatment is derived from a population, it cannot be matched to any person because the personal network is different from that of the averaged person. If a treatment is the best for one person, it cannot be best for another person.

If a treatment is to alter a single process attribute in the biological network, such a treatment cannot correct all departures in the biological pathways network. One well known example is the alteration of biochemical and cellular pathways in cancer patients: attributes of six categories of biological properties (growth signaling, cell apoptosis, anti-growth signaling, angiogenesis, tissue invasion and metastasis, and cell replication limits) are changed in cancer patients [108]. Those process attributes are shown in P1, P2.... Pn in Figure 2. The top diagram shows a plurality of process attributes. Fault environmental, dietary, emotional, and lifestyle factors slowly cause many process attributes to depart from healthy values. It is highly unlikely that the disturbed biological networks can be corrected by using one single synthetic drug. This may be the reason why drugs deliver results that are poorer than what is predicted in theory. It is anticipated that application of a number of primitive factors can have better chances to correct the departures in process attributes responsible for chronic diseases.

3. Reductionist treatment cannot correct problems in CNS

The mathematical models cannot characterize interactions between the Central Nervous System and the body running biological pathways. The role of CNS was known even 1875 [1]. It is well known that the CNS and body constantly exchange neuronal signals but little about the signals are understood. It is expected that any changes caused by emotional interventions will invite the CNS to respond. We reasonably assume that the CNS-body interactions are to resist changes in the body. Mind and body interactions are like a gearbox containing two gears. One gear cannot be freely altered without making correspondent adjustment to the other.

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4. Reductionist treatments lack force to correct existing departures or further disturb process attributes in other attributes.

     All process attributes in personal biological networks are caused by a large number of interfering factors. Correction of problems in personal biolog-
5 ical networks cannot be made by targeting only one or a few steps in the net-work. This is shown in Figure 1. For example, the immune system can be sup-pressed by sad emotion and chronic stress, toxins and heavy metals, nutri-tional imbalance, poor vascular system attributed to lack of exercise, toxic mi-cro-organic byproducts, etc. The actual causes may comprise a large number
10 of primitive environmental, dietary, and lifestyle factors. Simultaneous correc-tion of hundreds of fault factors is more powerful than doing one single thing which may completely miss the target.

     A treatment targeted to one attribute such as P2 of one pathway lacks sufficient driving force. Such a treatment cannot correct all departures in
15 process attributes but most probably disturb other process attributes. If a treatment is to alter the rate of one biological pathway, it is impossible to tell how the treatment might alter other pathways. Besides, responses in other pathways might depend on personal variations. Thus, one should find that dis-eases cannot be cured by correcting one seemingly fault pathway. It is possible
20 some unexpected changes in other process attributes may make personal health or disease worse. This is one reason that synthetic drugs fail to work.

     Figure 1 may be used to interpret cancer treatment model. In this case, P1 to Pn could mean, respectively, genetic mutations, foreign matter, micro-biota, pollutants and toxins, nutrition, heavy metals, vascular condition, organ
25 functional capacities, inflammation biomakers, micro-circulation condition, in-nate immunity, CNS condition, nerve health, glucose level, emotional states, etc. Microbiota affects metabolic byproducts which may damage cells; foreign matter such fiber grass and asbestos may affect tissue's local environment. P1 to Pn may denote process attributes (e.g., the glucose level) or anything that
30 can directly or indirectly affect the process attributes of local biological path-way networks. Each of the P1 to Pn bars may mean a large number of primi-tive factors. Foreign matter may mean anything that could disturb the biologi-cal pathways with an effect to promote cancer. Toxins may mean one or more of potentially thousands of known and unknown compounds. With the massive
35 variations in mind, Figure 2 may represent completely different process at-tributes for the same disease for two different persons. Two colon cancer pa-tients may have completely different process attributes in Figure 2, and natu-rally require different lifestyle prescriptions. Considering their lifestyles, one may be caused by using a large amount of salty, hot, fried snacks while the
40 other might be caused by excessive stress, distinctive microbiota, and lack of exercise. While they may share some common things, they must be treated differently to achieve better results.

5. Reductionist approach could not address highly complex health problems.

We will consider how mathematical model might perform when it is used to predict disease outcome of COVID-19 disease for a person. Infection diseases are mainly controlled by (1) exposures to the virus, (2) viral reproduction ability, (3) innate immune responses and host responses, (4) acquired immune response, and (5) the capacity to withstand tissue swelling [104, 137-142]. Thus, disease severity such as risk of death could be expressed as multiple functions of a large number of influencing factors under various conditions. If the virus exposure is well controlled, the contribution from (2) to (5) will appear to have no role to the disease outcome. If acquired immune response is fast and powerful, all of the effects from (1) to (3) and (5) may appear to have no role. From those large contributory ranges, we expect to establish a mathematical model having multiple component equations with various conditions as switches. Each of the component equations may include linear equation, polynomial equation, power law, etc, which has tens to thousands primitive lifestyle, personal, dietary, emotional, and environmental factors. Disease severity also depends on aging or development stage, information in neurons, hormonal regulation, eptigetic changes in cells, menopause status, personal activities, etc. Many of the factors (e.g., the independent variables) are random variables so that some of the component equations are random variables. For a population, disease severity is just viewed as the sum of all functions for all individual persons. No solution could be found to such complex function, there is no way to combine all personal functions for the population, and there is no way to solve a combined function for the population.

A mathematical model developed for a person cannot be used to predict disease severity for other persons unless they are close to the person. The model may tell how to change dependent variables to achieve a better outcome. We must find that current epidemiological models [143-146] are irrelevant to the disease and humans. An articulation like "temperature or oxygen can cure the disease" has far more science than a mathematical model. Epidemiological models contain almost none of the biological factors. Manipulation of twenties to a hundred factors, most of which are conceived out of imagination, will not help solve the pandemic. Medicine needs to far more attention to human disease biology and personal health, rather than coins, dices, lotteries, etc. It is a wrong strategy to jump onto the population health while forgetting basic disease biology.

Strong treatment that is not matched to the patient condition must produce drug side effects if the treatment is used for a long time [129-136].

DISCUSSION

1. Flawed presumptions in the foundation of medicine

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When medicine evolved from experienced-based ancient mind-body per-
sonalized medicine to drug-based reductionist modern medicine, medicine
silently changed multi-component natural mild medicines into highly concen-
trated synthetic drugs, changed the holistic mind-body medicine into reduc-
tionist treatments, turned health properties of human beings into statistical
populations, and started using mathematical models for most research sub-
jects. Those four presumptions have been accepted as foundation of medicine,
without ever being validated. Our analysis using massive data produced by
tens of thousands of medical studies firmly refute the presumptions. The big-
gest flaw in modern medicine is the use of mathematical model to add up
process attributes, which are intensive properties, across individual persons.
While this presumption is not always wrong for all research purposes, it is al-
ways wrong in a trial to study chronic diseases. Chronic diseases are manifes-
tation of distinctive biological pathway networks in humans often with very
small departures in multiple process attributes, addition of intensive proper-
ties across different persons produce meaningless results except for a strong
treatment. Without overhauling the foundation, modern medicine lacks re-
quired accuracy for accurately characterizing chronic diseases and will never
find predictable cures for chronic diseases.

2. Limitations in Clinical Trials

In assessing treatment effect, (1) clinical trail is useful in a study when a
strong treatment T is against N interfering factors Fi, where T is much and
much stronger than the sum of all interfering factors ΣFi. In this situation, sta-
tistical population exits by approximation while all interfering factors can be
viewed as experimental errors, and if the treatment is not intended to disturb
the biological networks, the treatment is only for short term use; (2) clinical
trail may be able to detect the effect of treatment T among N interfering fac-
tors Fi, if the accumulated effect of the treatment in a sufficiently long period
can stand out accumulated interfering factors ΣFi. This is why some long-term
trials can result in useful estimates; (3) clinical trail cannot produce right re-
sult if a treatment T in the study is used only for a brief time so that its treat-
ment effects are hidden among N interfering factors Fi. A brief exercise, brief
diet and brief emotional invention show no detectable benefit; and (4) clinical
trial produces a false result if treatment T in a study does not have the same
or similar effect on all subjects, or if all interfering factors have different im-
pacts on different subjects, or both. In those situations, the positive effect of
the treatment T on some subjects are nullified by negative effects on other
subjects, or distorted by randomly interfering factors. Moreover, treatment ef-
fects on all subjects must be compared with differences attributable to differ-
ent subjects in light of the accuracy requirement of investigation purposes.

Clinical trials are invalid for studying drug side effects that are realized
slowly while the measured health properties are interfered by a large number
of interfering factors. Among the massive medical studies, only one class of
studies directed to strong treatment effects are correct by approximation as

far as treatment effects are concerned. However, those studies may still fail to produce correct results for the side effects of treatments.

Root flaws in clinical trials include (1) misuse of statistical population as presumption without considering research purposes and required accuracy; (2) failure to study the massive interfering factors and co-causal factors; (3) misuse of mathematical models with attempts to change process attributes as if they were fungible properties; (4) use of mathematical model that is remote from realty; (5) misuse of representative principle when there is no statistical population and no approximation is allowed; (6) failure to determine required accuracy relative to interfering factors; and (7) failure to address one-way biases caused by interfering factors. Each of those problems can make study findings inaccurate, biased or even completely meaningless.

Due to widespread use of clinical trials, all studies involving weak environmental, dietary, emotional, lifestyle factors are most probably wrong if findings are negative. This flawed method creates a worst risk to civilization. Each of the potentially thousands of harmful and toxic substances is found to be harmless because it is interfered by a large number of other interfering factors. Those harmful substances strike human health slowly. We regard the misused clinical trials as well as population-based studies as the main reasons for human inability to protect the ecosystem and provide lame excuses for abusive use of avoidable toxic substances such as food additives, synthetic flavors, text modifiers, etc. Now, cancer, infertility, mental diseases, infection diseases, etc. are striking mankind with unprecedented impacts. The risk of getting cancer in a person lifetime rises from 0.04 to 0.4 and will soon reach a unity. Stories like six cancer patients in a family and three cancer deaths in a year will become more frequent. There is no way to find causes, and nothing could be attempted to arrest many bad trends. Problems like infertility will become civilization crises.

4. Problems in Reductionist Treatments

Reductionist treatments cannot cure chronic diseases for all of following reasons: The treatment (1) is based on clinical trials that attempt to make impermissible trades in health properties between different persons; (2) is mismatched to individual persons' biological network; (3) fails to address the interlock role of CNS; (4) lacks force to alter departures of process attributes in the biological networks; (5) cannot deal with multiple layers of mechanisms concerning disease initiation, progression, innate immune response, adoptive immune response, resolution of inflammation, and resolution of damages; and (6) has too strong force to distort intervened biological network and thus causing drug side effects by further distorting the biological networks. This proves why medicine fails for centuries.

Population-derived treatments should be presumed to be dangerous if they are used to directly affect a step in the biological pathways network for a long term. Biological pathways in each person must be maintained as a dis-

tinctive pattern in terms of intermediate species concentrations and conversion rates. Each person's values cannot be changed into the population averages or the values of another person because the person's values are constrained by upper-stream, coupled and downstream biological pathways in the
5   pathways network. It is impossible to alter just one single or a few steps in the network without altering others. Intervention by using a strong drug must distort other process attributes and thus cause new diseases. This distinctiveness nature implies that mathematical averages of the values have no meaning, that chronic diseases cannot be cured by intervening one single or a few steps in
10 the network.

      Immediate cures for chronic diseases lie in use of primitive factors to slowly alter the personal biological network. Use of evolution-compatible life style factors are presumed to the safest cures. Most biological properties (except genes and age) can be altered by using lifestyles, foods, exercise, emotion
15 management, and avoidance of toxic substances. Even certain genetic properties can be altered in limited extent by changing epigentics. The effects of many primitive factors have been found in studies; and effects of weak factors such as activity habits, cellular phone use, etc. cannot be determined under current research models but may be established by studying disease mecha-
20 nisms or disease risks. The adverse effects of lack of exercise and inactivity can be seen in elevated disease risks among obese people, people having vascular diseases, and people who are sedentary. However, negative findings in clinical trials should not be read to preclude potential benefits of weak factors on specific persons.

25   Most diseases progress from altering primitive factors, altering the biological networks, altering the structure, and altering the CNS function. The severity of chronic diseases is almost always manifested in functional impairment caused by structural changes. Changes in each of those phases may take considerable time, and disease development and disease reversal would take
30 considerable time. Preventive measures may be used in any of those phases, and there is no difference in mechanism between curative measures and preventive measures except that reversing diseases is more difficult.

      The democratic representation principle used in research harm minorities. Treatments developed in clinical trials can have severer adverse impacts
35 on minorities. Genetics are more similar between persons within a race than between members in different races. Computed average of health property for a population of a majority race is expected to be different from that for a population of a minority race. If a treatment is developed by a clinical trial containing persons of both races according to their population ratio, the average will
40 be closer to the average of the majority race. This implies that the treatment for the minority race is poorer or more dangerous than it is for the majority race.

      The problems in clinical trials are found by studying its theory, basic assumptions, biological pathways, disease initiation and defense mechanisms,

factor-factor interactions, body structure, etc. Treatments developed by using population approach are inherently invalid except by accident and inherently dangerous if they are used in long term. All four presumptions -- treating health property as a population, using synthetic drugs, using mathematical and statistical method, and using reductionist treatments -- are refuted. The flawed foundation precludes finding predictable cures for chronic diseases and cancer.

5. Impacts of this study

The findings of this study will affect lives of ten of million of people who are dying from chronic diseases in the world each year, the use of a good part of $41 billion federal research funds administered by NIH, the use of more than a hundred of billion private research fund in the U.S., the trillion of medical spending in the U.S., validity and accuracy of conclusions in a large number of published medical studies, and risk to civilization. The worst effect of those flaws is that it creates incurable notion to justify failure of medicine. By trusting the flawed research model and treatments, medicine fails to study hundreds of well documented cancer miracles and makes no attempt to discover millions of undocumented miracles in cancer, heart diseases and mental diseases. The ruined health wisdom among patients suffering "terminal" diseases is a strong aggravating factor that causes patient deaths because patients are misled by propagation that diseases are incurable. If one truly understands all flawed presumptions and all flaws in research and treatment models, one should see that diseases are curable among patients with willpower to change. Unfortunately, the medical establishment has built a highly sophisticated protective system to discriminate against, preclude, and suppress any research findings that challenge the foundation of medicine.

CONFLICT OF INTERESTS

None.

ADDITIONAL INFORMATION

Additional information is provided in a supplemental document and additional factual information will be stored in igoosa.com online database.

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Figures
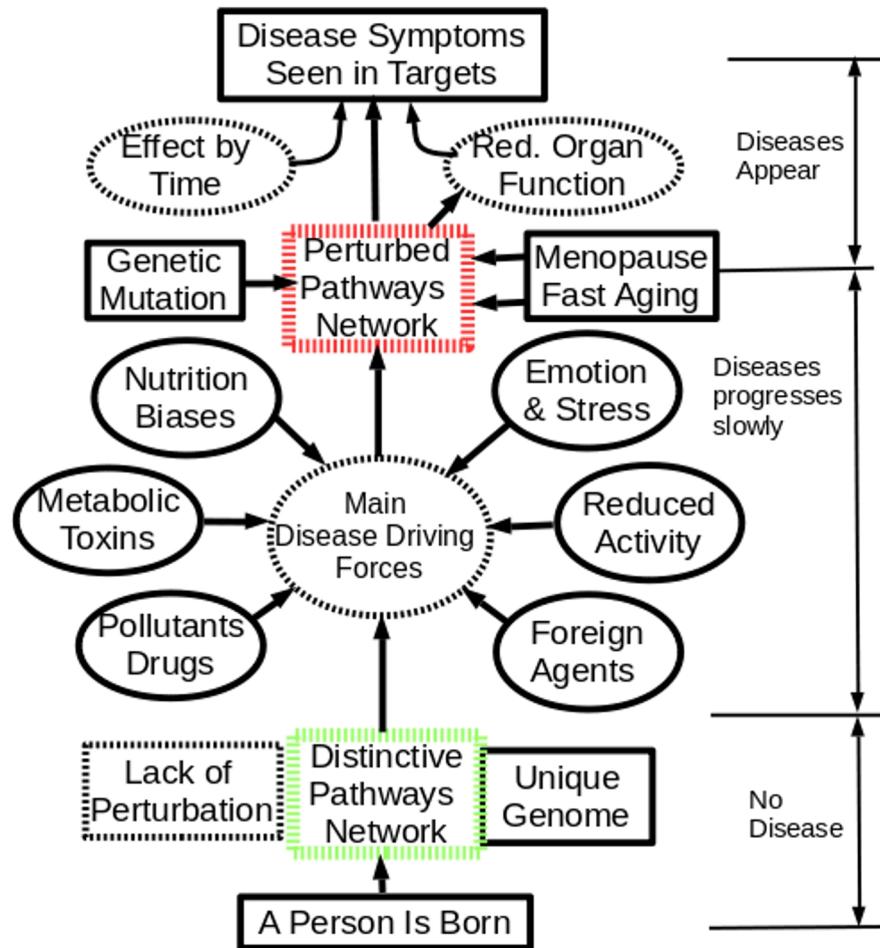
Figure 1. Environmental, Dietary, Emotional and Lifestyle Factors Slowly To Cause the Biological Pathways Network to Depart from A Healthy State.
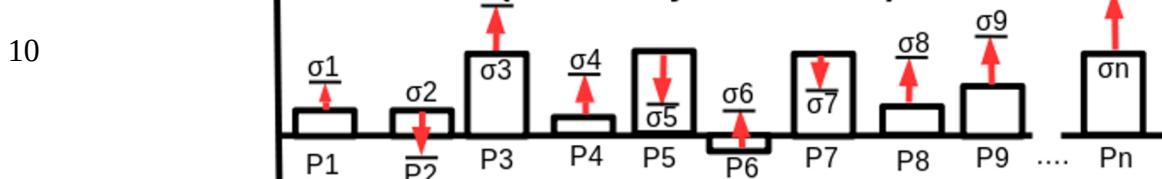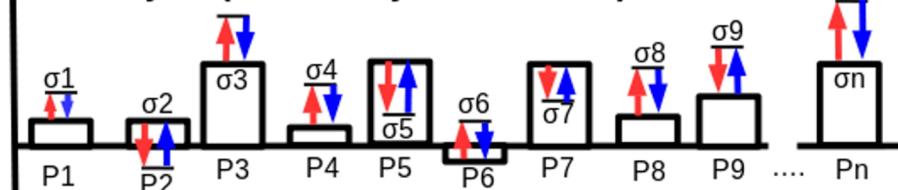
Figure 2. How the Process Attributes Profile of the Biological Pathway Network Is Disturbed by Fault Environmental, Dietary, Emotional and Lifestyle Factors and How It Is Corrected by Adjustment to the Lifestyle.