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A co-occurrence framework conceptualized for bridging the gap between basic science, clinical research and clinical practices

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A CO-OCCURRENCE FRAMEWORK CONCEPTUALIZED FOR BRIDGING THE GAP BETWEEN BASIC SCIENCE, CLINICAL RESEARCH AND CLINICAL PRACTICES

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ABSTRACT

The intellectual impulsiveness of man to understand the unknown and the continual need of the society to improve healthcare have encouraged extensive investigation on numerous and diverse cause-and-effect relationships. The nature of this endeavor, however, renders the inability of investigator at all levels to escape beyond the narrow conceptual boundary described by an early French philosopher as the vicious cycle. To enjoy the theoretically plausible benefits of refined labor division, data-driven healthcare management, and real-time evidence-based practices, it must first be acknowledged that co-occurrence is better than cause-and-effect in explaining how an observation takes place at a particular time. This paper details a co-occurrence framework, and discusses its implications for the global healthcare system.

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LIST OF ABBREVIATIONS

DNA……...…….Deoxynucleic Acid

EBM…….....Evidence-based Medicine

IE…….Independent Enrollment

MRC……...……..Medical Research Council

PCR…….……..Polymerase Chain Reaction

QB……..……Quadruple Blinding

RCT…….....Randomized Controlled Trial

STD……..……..Sexually Transmitted Disease

VS…….……Variable Shuffling

INTRODUCTION

Although technology has advanced rapidly over the past decades, the quest of mankind to sort out the relationships between the plentiful variables observable in life is not new. The struggle in qualifying and quantifying those relationships has been precisely described by Michel de Montaigne in *The Essays of Montaigne*: one requires a procedure to distinguish the true appearances from the false ones, but one cannot know whether the procedure is surely successful in making that distinction unless it is already known what is true and what is false (Montaigne, 1933). In order to understand something, a method is required. One cannot know if the method succeeds in achieving that aim, unless sufficient knowledge on that something has already been gained. This problem, also known as the vicious cycle, has been pervasive in both the practical and investigational aspects of medicine.

Basic Science

Basic science is the foundation of the technological advancement in medicine. Recent breakthroughs in molecular medicine and medical genetics is known to originate from the work of Johann Gregor Mendel, who performed a series of plant artificial hybridization experiments from 1857 to 1864. Mendel found simple mathematical patterns in the heredity of traits in *Pisum*, the garden pea; the fortunate selection of which as his experimental model is thought to be a key factor leading to his success. Particularly, certain characteristics of the model are helpful: the natural existence in diverse pure strains, the hermaphroditic nature that makes both self- and cross fertilization feasible, and the annual and short-term growth pattern that permit large-scale artificial breeding (Dunn, 2003). Despite the difficulty and hard work in the case of Mendel, son of a poor peasant farmer, and despite his efforts to publicize his research, it had largely been ignored by the scientific community until 1900, sixteen years since his death, after other scientists

reproduced his experiments (Dunn, 2003; Weling, 1991; Sorsby, 1965; Walsh, 1966). Mendel demonstrated his ingeniousness by applying statistical methods in the context of the biological inheritance, a novel attempt at the time. The scientific community, however, was stuck in a vicious cycle, and was therefore not ready to acknowledge Mendel's work.

The isolation and identification of nucleic acid took place in 1871, but it was not until 1944 that the research group of Oswald Avery performed an experiment that revealed the clue that DNA is the material that contribute to the Mendelian pattern of inheritance. Avery *et al.* demonstrated that the agent that was delivered into pneumococcus bacteria via the process of transformation is deoxynucleic acid (DNA) but not protein. However, their conclusion was only modestly made as at that time because certain alternative hypotheses still needed to be ruled out in order to fully understand the mechanism of transformation. Those hypotheses included: 1. the transforming agent may be a mutagen which alters the actual hereditary material, and 2. There may be minute amount of other substances, like a virus, intimately associated with deoxyribonucleic acid that drives the process of transformation instead (Avery *et al*., 1944). Although much doubt remained, Avery was clear that a crucial next-step for his work was to determine the chemical structure of DNA, a task to which he must retract due to personal reasons (Dubos, 1976). Avery performed the well-controlled experiment to demonstrate that the agent responsible for transformation was likely DNA, but one could not be certain whether his work indeed proved it because there was not sufficient insight into the transformation mechanism and the structures of the components involved.

In 1953, Francis Crick and James Watson proposed a structure of DNA, which is considered a milestone in the history of modern molecular biology and genetic medicine. Much insight has been gained and recognition awarded for their proposed double-helix, anti-parallel structure, with nitrogenous bases on the interior and sugar phosphate backbone on the exterior (Watson and

Crick, 1953). It was made clear in their paper that the two key factors leading to their conclusion were: 1. the ruling out of a similar structure proposed by other colleagues, which was a triple-helix, and 2. the unpublished x-ray image from Dr. Rosalind E. Franklin and co-workers at King's College in London, which made the elimination conclusive (Platt, 1964). In the paper, they explained that the conception of the double-helix structure occurred prior to their awareness of the x-ray data, but a crucial fact was ignored in their statement: in science, the experimental evidence which rules out the wrong hypothesis is as important, if not more important, than the production of multiple hypotheses within which one may better represent the truth (Platt, 1964; Watson and Crick, 1953). To understand the chemical structure of DNA, Francis Crick and James Watson proposed a model, and yet they cannot know whether that model truly resembles the actual structure, unless they have already had a sufficient confidence that it is the case. In their particular case, it was found in the works of other colleagues.

The identification of DNA structure and the extensive public interest over the subject have led to the invention of many techniques used to characterize DNA at different levels - on the levels of the chromosome through karyotyping, on portions of chromosomes through hybridization with complementary DNA, and on nucleotides through sequencing (Alpman *et al*., 2015). Polymerase chain reaction (PCR) is a landmark technique that is still widely applied in research, and its capacity to amplify a DNA segment up to thousands of nucleotides in length proves the success of the scientific community in overcoming two major obstacles while working with DNA, which are the low quantitative output and the insufficient purity (Mullis and Faloona, 1987; Saiki *et al*., 1985; 1987). The key components of PCR that allow its successful operation are two primers, each binding to regions flanking the DNA segment of interest, specific temperature alternating cycle that facilitates the process of DNA annealing, denaturation and amplification, and the use of heat-resistant DNA polymerase (Saiki *et al*., 1987). The availability of these ideas and physical

components individually, however, were not invented by Kary B. Mullis, the scientist widely recognized for his creation of PCR in 1987; Mullis did not create but instead, he only put together existing techniques or concepts. First documentation on the annealing and denaturation process was dated back to as early as 1959, the use of the heat sensitive bacterial DNA polymerase, which was used in the PCR prototype, was first reported in 1957, and the successful isolation and characterization of the heat-resistant DNA polymerase from *Thermus aquaticus* took place in 1976 (Marmur *et al*., 1963; Marmur and Doty, 1959; Doty *et al*., 1959; Mandel and Marmur, 1968; Lehman *et al*., 1958; Chien *et al*., 1976). Montaigne's vicious cycle is again at work: Mullis could not have known whether or not the PCR protocol was a valid method for DNA amplification, unless a sufficient understanding regarding each of its parts had already been gained.

Everything exists in a context, and basic science is no exception. Always, one thing leads to the next. Without prior existing techniques or ideas, new techniques could not be created, and novel ideas could not be formed. These statements also apply to the technological advancements in basic science after PCR. They apply to DNA sequencing, the Human genome project, massive parallel sequencing, and next generation sequencing. They apply to genetic screening, genetic fingerprinting, and gene therapy. They also apply to every single field under or related to basic science - they apply to targeted medication, biostatistics, and bioengineering, they apply to immunology, anatomy, and pathology, and they apply to physiology, immunology, and pharmacology.

Clinical Research

Research conducted on human subjects is crucial to understand the effect of any organic or inorganic agent on the human body. The first, if not one of the earliest, clinical trial, was

documented in the Bible. In the Book of Daniel, the prophet Daniel, was given the opportunity to train in the palace of a Babylonian king, and he was asked to eat the royal food and wine as his regular diet (International Bible Society, 1984). However, Daniel, determined not to be defiled by the royal food, asked the official to compare the appearance of his group, who were to consume vegetables and water only, to the appearance of others who were to consume the royal food and wine after ten days (International Bible Society, 1984). The better appearance of his group after ten days convinced the official to provide vegetables and water as their regular diet (International Bible Society, 1984). Alternative explanations remain to be ruled out in order to fully understand the relationship between the diet of Daniel's group and the observed outcome in appearance, but it was Daniel's divine conviction prior to the implementation of the clinical trial that the royal food was defiled makes the story seem especially convincing to the officials.

Although the idea of clinical trial is by no mean recent, modern elements of design widely applied in clinical trial carried out nowadays, which include double-blinding, placebo-control, and random allocation, were not seen until the 1940s; the Medical Research Council (MRC) of the United Kingdom first utilized these elements to evaluate the treatment effects of Penicillin extract and streptomycin on the common cold and pulmonary tuberculosis, respectively (Bhatt, 2010; Hart, 1999; MRC Streptomycin in Tuberculosis Trials Committee, 1948). The ability of the design to eliminate confounding and biases led the scientific community to adoption of the randomized controlled trial (RCT) as the gold standard in clinical research. Following a series of events and the advent of regulations governing clinical research, posting clinical trial information on a publicly accessible database prior to the enrollment of subjects has become a common practice believed to enhance trial integrity, and one could, by surveying the database, appreciate the expansion of the number of RCTs conducted over the past decade.

Table 1 was accessed from ClinicalTrial.gov (March8, 2015), and it describes the numbers and the types of studies registered in the database. Interestingly, only about nine percent of the studies registered have posted results (ClinicalTrial.gov, 2015). Among the different types of interventions, the percentage values for the trials with posted results vary, and they are thirteen percent, six percent and five percent for drug/biologic, behavioral/other and surgical procedure, respectively (ClinicalTrial.gov, 2015). It is uncertain whether such a low percentage is due to social, regulatory and/or technical reasons, but there is no doubt that hindrance of the trial's initiation and completion exists, even if the research is well-planned and submitted for display in the public database. Especially, the trial that seeks to evaluate intervention imposing a higher potential risk like surgical procedure, seems to suffer from even greater hindrance.

Although RCT is considered the gold standard in clinical research, it is not without its flaws. It has, however, been shown through comparative analysis that RCTs do themselves have fewer methodological flaws than non-RCTs (Steen and Dager, 2013). Examples of characteristic flaws in RCTs include incomplete data, compromised randomization and imperfect blinding, and certainly, not all RCTs hold the same merit depending on the presence and extent of those problems (Steen and Dager, 2013). It has been widely accepted that an inherent drawback of RCT is limited generalizability, but it has also been recognized that RCTs tend to show contradictory results with other RCT and/or meta-analysis (Baker et al., 2013; Concato, 2013). It is unsurprising that it is recognized that RCT alone is insufficient to guide clinical decision-making (Concato, 2013; Gugiu, 2015).

RCT provides the medical field a fine tool to evaluate the effect of an intervention, but for practical reasons, other means are also used for the purpose despite the fact that the extent of their technical drawbacks may be more significant. To classify the levels of evidence and thereby determine the worth of clinical research evidence in affecting clinical decision making, the

Canadian Task Force on the Periodic Health Examination first proposed in 1979 a system, which rates evidence derived from at least one RCT, case-control or cohort study, dramatic results from uncontrolled studies or time series comparison, and professional opinions, from the strongest to the weakest, as level I , level II.1, level II.2, and level III evidences, respectively (The Periodic Health Examination, 1979). Another model was described in 1989, which rates large RCTs, small RCTs, case-control or cohort studies, historical case-control or cohort studies, and uncontrolled studies, as, from the strongest to the weakest, level I, level II, level III, level IV, and level V evidences, respectively (Sackett DL, 1989). These proposed systems are based on the rational beliefs that: 1. Controlled is better than uncontrolled, 2. RCT is better than Observational studies, 3. Larger sample size is better than smaller sample size, 4. Results from any research is better than expert opinions. The above authors created the model seeking to distinguish strong evidence from weak evidence in clinical research, and they base the worth of the model itself on, at the very least, the described four points.

The model has been modified in the past decade, and the result is a more comprehensive model encompassing both basic science and human subject research (Schottinger, 2006; Burns *et al*., 2011). Recognizing the previously described drawbacks of RCT, the modern hierarchy places systemic reviews and meta-analyses on top of individual RCTs as the most robust evidence (Schottinger, 2006; Burns *et al*., 2011). One could clearly observe that the influence of the vicious cycle is at work. The field started with the conviction that the subjective judgment of experts is inferior to any human subject research carried out, and yet, due to the inherit drawback of each clinical research design and the technical flaw in its conduct, it is, in a roundabout manner, again acknowledged that the expert's opinions made based on the prior published clinical research may suffice in providing the best conclusion. Much uncertainty remains concerning

whether the effect of an intervention is true, and concerning whether the method to quantify the effect is valid.

Clinical Practices

Clinical practice is based on professional guidelines, which are made in governmental or non-governmental agencies. Out of many treatment options for a particular condition, one could, in no way, predict the exact effect of all potential interventions on an individual with a particular condition. As a consequence, clinical practice is a realm of following trends, which are defined by a combination of factors including, but not limited to, the availability of technology, the willingness of people to market a certain treatment, its safety and effectiveness, and the readiness of the community to adopt it. It is undoubtedly, a field made up of diverse individuals pursuing different interests.

The burden of responsibility to keep up with the availability of new treatments on the market as well as understanding their implications, lie directly on the shoulders of the healthcare providers and their institutions. It is, therefore, not surprising that increased labor division in healthcare has been observed over the past decades; it reflects the simple truth that the burden of responsibility is too large to handle, and it will only become even larger in the future if the foundation in theory and practice behind the current healthcare system is unchanged.

The Aim of This Work

A problem exists when theory put into practice does not align perfectly with reality. The extent of the problem depends on the size of that gap. Modern medicine has maneuvered its way toward holistic and personalized services, and this trend reflects the flaws in the traditional approach

built on the logical fallacy of cause-and-effect and the unrealistic hunt for a panacea. The aim of this paper is to discuss the concept of co-occurrence, an idea that better aligns with the context-oriented and mechanism-driven nature of life. The implication of it on the healthcare system once implemented will also be discussed.

Proposed Framework

Co-occurrence Framework

A key difference between the proposed framework in this paper and the current system is that the proposed one has a data-driven and bottom-up backbone. The co-occurrence formula should be applied to all the variables that could be recorded concerning an individual, and each unique individual should be assigned a unique identifier; a simple formula is the Q-value described elsewhere (Nguyen *et al*, 2013). The categorical variables like the binary sex should be broken two different variables – male or not and female or not. The continuous variables should be broken into however many binary variables that are clinically meaningful. For example, a variable describing a vital sign may be converted to a binary variable that describes whether or not the value is within the normal range. In this way, all the variables could be converted to the same format, which allows meaningful comparison.

The proposed framework is conceived to encompass the full spectrum of variables relating to healthcare, which will be described shortly. Figure 1 summarizes the co-occurrence backbone. To manage the huge variety of variables and to clearly define them for universalized usage, there must be a database that is recognized by all, from which a common language for data collection could be agreed upon. In Figure 1A, the green box describes such a starting point. After the

database is sufficiently established, the variables defined could be implemented in the recording system in the participating healthcare and healthcare-related institutions (orange box). If the computer software is designed so that the information captured by the recording systems could be automatically converted to the co-occurrence format (black box and the table), those information is added to the proposed database backbone, and they could be analyzed accordingly (blue box).

Figure 1B describes the extent of the variety of institutions and professional fields that could participate in the co-occurrence system on a local level, which could include public health, environmental measure, basic science, clinical care, clinical research and consumer's behavioral pattern. Information in basic science that could be collected includes the presence of a particular allele in the genome. If the alleles of each gene could be properly categorized and the genome sequenced, information about each gene could be put in the co-occurrence database. If not, information on the key genes could be collected, and the rest added in the future. Clinical research could also be easily implemented in the co-occurrence backbone. While the backbone itself could be considered a comprehensive observational study, RCT could also be implemented in the system. Using the model, if one seeks to examine the effect of a drug on a patient population, the interventional variable (i.e. intervention or placebo) and the outcome variable could be defined and proposed to the committee managing the global variable database. Once safety and effectiveness is suggested on a local scale, the international committee could allow interested party on a global scale to test the drug, and if efficacy more frequently co-occurs with the drug relative to the placebo to a significant extent, the drug could be recognized as such. Information in clinical care could include all the information collectible in a hospital visit or periodic health examination. There should overlap between public health, environmental measures and consumer's behavior. Overall, information could be collected ranging from diet, physical exercise, use of recreational drugs, purchase of particular cosmetic or cleaning products,

the presence of electricity generators close to a residence, the extent of traffic within the neighborhood and, the presence of particular indoor plants.. Once the information is collected on a regional level, it could be passed to the higher levels. As illustrated in figure 1C, all the regional data should gather to form the national database, and all the national data should gather to form the single international database.

Figure 2 summarizes the work flow of the co-occurrence model on a global scale. As already described, individual-centered data is collected on a regional level from a variety of platforms, including the electronic medical record system in healthcare. All of the data collected in this manner form the regional database. The means through which the personal data is collected, however, could be modified for enhancement according to recommendations made by the international, national and regional committees governing the work. For example, new variables or novel definitions of variables could be implemented in the data collection process through the described public international database, and the information concerning the variables could be collected and thus contribute to the personal data. The recommendations from the different levels should be made depending on the need of the institutions operating at each level.

As illustrated also in figure 2, the personal data, once collected and converted to the co-occurrence format, is interpreted and further enhanced on a regional level to form the regional data. The personal data in enhanced so that they collectively become meaningful on the regional level. For example, residence in a particular district should be annotated with zip code. By doing so, another layer of variables is added to the database. Interpretation and enhancement should also be done on both the national and international levels, so that variables meaningful on those levels could be added for analysis.

As shown on the right side of figure 2, the international data, enhanced from the national data, is analyzed on the international level. Policy and recommendation are made based on the analysis of the data. Recommendation should also be made to guide how committees on the national levels should interpret their data. Using the national data, each national committee is, likewise, devise customized policy and makes recommendation to committees on the regional level concerning how their data should be interpreted. Finally, the regional committees, using its regional data and the recommendations from the higher levels, devise their policies.

Variable Shuffling, Independent Enrollment and Quadruple Blinding

In addition to the overall framework, certain novel elements of clinical research should be brought to the attention of the readers. Theoretically, they could be implemented in either the co-occurrence or the present systems. Practically, they could be used to qualify and quantify the hidden interactions that the present system may be incapable to evaluate. They include variable shuffling (VS), independent enrollment (IE) and quadruple blinding (QB):

Figure 3 illustrates the concept of IE. In IE, it's crucial to create a list of numbers representing the order at which the subjects in the study will be enrolled (A). The list is then randomly assigned into the different experimental groups (B). As each subject is enrolled, that subject is given the intervention assigned based on its order of enrollment (C, D). After the subject is given the intervention, the subject is to be followed individually until the pre-determined study duration has passed (E). It is recommended that IE be accompanied by proper blinding procedure in order that the prior randomization assignment does not encourage biases.

QB is a method proposed to complement IE to eliminate any likelihood of bias. QB involves five parties, which include the subject, the personell to provide the personell to enroll the subject based on the enrollment criteria, the personell to deliver the assigned intervention to the subject,

the personell to provide outcome assessment(s), and the coordinator who, unlike the other four parties, is not blinded with respect to the randomization results. The coordinator acts behind the scenes and is the only party knowing both the list for the order of enrollment and its randomization outcome. He or she assigns the personell who are to make a diagnosis and enroll the subject based on the enrollment criteria.. Once the subject is identified, the personell reports to the coordinator and the order the subjects will be enrolled in the study is known. The subject is then referred to the personell delivering the assigned intervention. Additional parties may be used to provide support to the subject during the follow-up, but they must also be blinded and report any significant issues to the coordinator. After the follow-up period, the subject is assigned to the last party, the personell responsible for assessing the outcome.

Figure 4 illustrates the concept of VS. Like the randomization for single-treatment trial (A), VS performs randomization on each individual treatment, albeit the fact that VS deals with multiple interventions tested on the same pool of subjects. For the multiple interventions, it is conventional to adopt a factorial design, with which subjects are randomly assigned into a multiple number of groups (B). If, regarding intervention 1, the subjects could be assigned to receive either intervention 1 or the control, and regarding intervention 2, the subjects could be assigned to receive either intervention 2 or the control, that number is the multiple of two and two, which is four. Although factorial design could be used to evaluate the combined effect of multiple variables, it is often impractical as randomization into multiple groups while maintaining the ability to evaluate the effects demands greater sample size. By treating each intervention as an independent event and performing randomization based on it, it is theoretically plausible that with the equivalent demand for sample size, VS could evaluate the effect of an intervention with any other intervention tested in the trial.

DISCUSSION

The Essence of Co-occurrence

A phrase that has been commonly used in the science education is "correlation does not equal causation," and the statement commonly implies that the former is inferior to the latter. If much emphasis is placed on the search for cause, however, one could easily fall into the trap of Montaigne's vicious cycle. Always, a single method cannot suffice in characterizing the cause of an event, and confidence in its reliability only depends on the extent of the background knowledge or evidence through other channels. This has been the case, and examples for clarification have already been provided elsewhere.

Since the discerning of cause depends on the extent of other knowledge, it is fair to state that unless the available knowledge is perfect, one cannot reach a perfect understanding on the cause of an observation. As the sequence of events that lead to the formation of the observation are numerous, unless one can identify all the events, one cannot have perfect knowledge. Since one cannot capture all those events, a perfect understanding of the cause cannot be gained.

The reason why the vicious cycle is present and pervasive is that the mentality to search for the cause of an effect does not align perfectly with nature. Naturally, the occurrence of an event, which perplexed mankind and prompted them to search for its cause, is made possible only when specific prior events have occurred, and for those prior events to occur, particular events that take place even earlier are necessary for them to happen. Mechanism has to be understood in order to fully understand why an event happens. Mechanism, however, differs on a case-by-case basis. Often, confidence is obtained for understanding the microscopic or biochemical pattern of a medical observation, but the lack of understanding on the historical and social context which made the observation happen destroys that confidence. In many cases where nothing could be

done to reverse an undesired effect, despite the effort and genuine passion of the healthcare professional and the resources invested, the course of the condition is so unchanging that it is essentially trivial. There is little knowledge on the sequence of events leading to that effect in those helpless cases, but they have likely occurred elsewhere in the world or throughout the history, and lessons could have been gained from it.

The key question is to what extent we have captured the numerous events defined socially, culturally, geographically, biochemically, clinically and genetically that can lead to the occurrence of an effect. Have we understood all the different mechanisms that can individually lead to its occurrence or the reversal of its occurrence, both short-term and long-term? Have we done our best capturing those knowledge given the available technology?

Although correlation does not imply causation, causation does not imply comprehensive knowledge of the mechanism. Different entities have their different approaches to solving a problem, but each is not necessarily a reflection of comprehensive knowledge. Suppose there is a person possessing allele A, B and C in the genetic background, living in an indoor environment with airborne carcinogens coming from the sewage system, working in a physically relaxing work-place where certain past traumatic events would sometimes be remembered, having a well-rounded diet but once a week dine at a restaurant serving food inducing oxidative stress, having a habit to sleep in a particular posture, having a sexual partner frequenting a barber shop also frequented by sexually transmitted disease (STD) carriers and where its equipment is not thoroughly cleaned every Tuesday when the hired personell is distracted by a soap opera, having a religion that requires fasting on the 15th day of every month, having biological ancestors mostly living in cold climate zone, and living in a warm region inhabited by mosquitos where the wind blows mostly eastward in the summer time.

The complex interactions between the many different variables in the case of the person are here described (Figure 5A). In a regular day in summer, the person wakes up exhausted and inhaled some carcinogens circulating in the air of the room, which alone would regularly be cleared through the immune system. Last night, the person did not close the window on the west side of his room intentionally in order to enjoy the summer air. Several mosquitos flew in, riding the eastward summer wind flowing from a breeding pond located west, and they persistently disturbed his sleep throughout the night. He was bitten. A particular chemical released from the saliva of the insect led to reduced activity of the gene product encoded by allele C, which normally enhances, when needed, the ability of the gene product of allele B in clearing the oxidative stress within his body. Tired, he went to the work place, and yet the exhaustion aided his recalling of the past traumatic memory to which a particular person in his office is an unrelated trigger. Feeling burdened, he called his partner after work to arrange a dinner at his favorite restaurant and consumed the oxidative stress-induced food more than he normally would. The gene product of allele B is unable cope with the oxidative stress due to the decreased activity of the gene product of allele C. In conjunction with the carcinogen which has not been cleared through his immune system in his distressed state, leads to the mutation transforming a proto-oncogene to an oncogene in one of his bone marrow precursor blood cells.

After dinner, he slept with his partner in his bedroom, but unfortunately her immune system was currently fighting the STD pathogen delivered into her body via an accidental cut from the contaminated scissors used in the barber shop last Wednesday. She normally visited the barber shop on the weekend, but she had a free week because her boss went on a vacation. The cleaning staff at the barber shop left the scissors unwashed due to distraction from the soap opera every Tuesday, and an STD carrier visited the barber shop and was cut by the same scissors. As a consequence, the person became infected with the STD pathogen, further adding burden onto her

partner's immune system. His regular posture in sleep made his left leg extend to the side of his partner, and his partner, overweight, turned her body and compressed his left leg leading to reduced blood flow in the lower extremity for the entire night. A significant amount of muscle cells were destroyed, and their content released into the blood stream.

The STD infection and the content from the damaged cells activated his bone marrow precursor cells to produce more white blood cells. The mutated blood cell precursor with the oncogene was also replicated, and each daughter white blood cell contained the same oncogene. The person felt sick after waking up, and it is the 15th day of the month. The gene product of allele A in his genome would normally use a particular essential nutrient from the diet to enhance a molecular pathway that could fight against the abnormal cells like the mutated white blood cells circulating in the blood stream. However, the person decided to fast for two days straight because he felt his sickness may be related to his failure to adhere to the ritual in the past two weeks. The failure to have an adequate amount of the essential nutrients available immediately from his diet reduced the likelihood of successful clearance of the mutated white blood cells, which were instead continuously reproduced. By chance, a tumor suppressor gene mutation occurs in one of the mutated white blood cells, and it became an early tumor cell. Subsequent exposure to the indoor carcinogen, post-traumatic stress, diet-induced oxidative stress, problematic partner and/or religious ritual compromised his immune system, and the tumor cell is proliferated to the point that it posed a threat to the health of the person.

The person, sick, distressed and confused, went to the hospital. The strong air-conditioning in the hospital somehow triggered his genetic inclination for a cold environment, which is a result of his biological ancestry in the cold climate. He became especially talkative in front of his doctor and was open-minded discussing about his stories including his past traumatic experiences. The novice doctor then diagnosed him with a psychological disorder. After the blood tumor became

detectable, he was diagnosed of leukemia. When the criteria were met, he was given chemotherapy, which although cleared the detectable biomarkers but, compromised his immune system even further. Discharged from the hospital, the person resumed his regular life influenced by the described persisting and problematic factors, and the patient passed away from sepsis and multiple organ failure eventually.

Detailed is the case of a chronic disease, but it is not radically different from the acute condition concerning the matter of comprehensive knowledge. Suppose there is a person living next to a neighborhood known for its higher crime rate where there were recent incidences of robbery. The person is a minority female teenager, and she lived with her parents who are unidentified classical narcissists. . Her father is the primary supporter for the family but suffered from a cerebellar injury in his young adulthood. He has, however, found a career niche as a company manager though personal connection and was successful in his career. The father, however, displays impulsive and self-centered behaviors. The teenager grew up to comply with the demand of her parents, and was conditioned to maintain a meek and complying disposition. She has, however, made friends at school who could provide the means for her to escape from her stressful family relationship when the chance became available.

After a stressful conversation with her parents, on a peaceful night, the teenager called her friends to attend an overnight party located in the neighborhood with high crime rate. She was asked to pick up a few bottles of alcohol at a local store managed by a family of refugee immigrants from Asia. Being aware of the recent incidences of robbery, the shop clerk was given a pistol to protect the shop when necessary. Suspicion was thrown on the teenager as a shoplifter.When confronted, the teenager intended to invert her pant pockets to demonstrate her innocence, but the act was misunderstood as an attempt to draw a weapon. The teenager was shot on the spot and died later in the hospital.

In the case of the male working professional, the ideal solution should be a comprehensive one that includes: 1. Fix the sewage system and eliminate the source of carcinogens circulating in the room, 2. Propose to the local government to release mosquitofish into every dead water to eliminate the pest, 3. When physical discomfort occurs, take a half day off work, 4. Consult a mental health specialist to resolve the post-traumatic response, 5. Refrain from consuming particular oxidative stress-inducing food at his favorite restaurant, 6. Tell his partner to change barber shops, 7. Avoid sleeping next to his partner, 8. When sick, do not limit food consumption, 9. Carry a lucky charm, and 10. Take the chemotherapy as a last resort. In an ideal co-occurrence system where every one of these events is captured (Figure 5B), as long as there are other cases that demonstrate the relevance of the observed sequence(s) of events that lead to the observed outcome(s), this complex mechanism could be suggested based on their high co-occurrence scores. Theoretically, the co-occurrence score of an event against another event will be high when they are in a causal pathway, and the causal pathway for an outcome of interest could be suggested by comparing the difference in the co-occurrence patterns between the subgroup having that outcome of interest and those without that outcome of interest. The mechanism specific to a particular subgroup of the population could be suggested by finding the difference in the co-occurrence patterns only using the data from that subgroup. By zooming in, the mechanism leading to the condition in the case of the individual could be better understood. To illustrate further, the pattern obtained by using the broader data could suggest the more universal sequence of events leading to an outcome of interest, but the pattern obtained by using the narrower data could suggest the more specific and yet relevant mechanism that is applicable only to the subgroup where the data is drawn. To illustrate even further, the transformation of the proto-oncogene to an oncogene and the mutation of the tumor suppressor gene may be universal events

leading to the development of cancer. However, only among those having allele C can a mosquito bite co-occur more significantly with the development of cancer.

Figure 5C demonstrates the events that should be captured in the person's hospital visit, assuming that the current medical system is used but not the co-occurrence system. Since there is a relatively long incubation period for the condition, some events in the past are only captured by the current system at imperfect odds (presented in yellow boxes). By encompassing the fields of basic science (Figure 5D), clinical research (Figure 5E), and public health/environmental measure/consumer pattern/personal behavior (Figure 5E), all events directly, partially and/or indirectly contributing to the progression of the condition of the person can be captured (orange box).

Likewise, in the acute case of the minority female teenager, the best actions to take in order to help with her situation include: 1. Provide social support to help her cope with narcissistic parents, 2. Make understood the implication of past brain injury as relevant to betterment of current life, 3. Advise the teenager not to go out late at night, especially in the nearby neighborhood, 4. Encourage the refugee family to better involve with the local community and the local culture, 5. Ask the local government to devise material to minimize temptations for illegal behaviors, and 6. Ask the local government to break the fear and distrust within the neighborhood by implementing relevant programs. The events in her case that could be captured by the current system are very likely the superficial ones, which include gunshot wound, misbehavior as a teenager and a well-off family background.

The co-occurrence framework targets the complex mechanism behind an event and its associated events, and it does not limit its source of information on a particular perspective but all perspectives worthy of investigation. Obviously, the quality of the framework should depend on

the ability of the current technology and human resources to discover, define and measure variables. Since improvement of the public database of variables, which has already been described, is part of the framework, the system itself can grow as the technology improves- it is basically a living system. The bottom line that could be drawn is that if the system is implemented, the quantity and quality of the information obtained should be much greater than the sum of all the health-related researches carried out in the present system.

Shift of Responsibility for the Burden of Proof, the Direction toward Lower Skills and Better Specializations, and the Encouragement for Diverse Medical Solutions

The Co-occurrence formula is a highly sensitive mean to detect the effect of a medical intervention, even for those that have not been accepted by the mainstream. Suppose a mushroom extract is found to be a cure for a persisting chronic condition.. The extract is passed to another person experiencing the same condition, who passed it to the third. It does not require a huge number of subjects to show that the treatment is effective or not: the co-occurrence value will remain high as long as the consumption of the extract more frequently occurs with elimination of the symptom, as compared to a reference group. If the co-occurrence value is not significantly high in the general population, one can obtain a comparative analysis, among the subgroup of subjects who had the condition and had consumed the extract, between those who demonstrated success and those who demonstrated failure. With the result, insight could be gained about why a particular intervention works in a certain context but not the other, and how that knowledge could be utilized to improve healthcare.

There is no doubt that with a global data collection backbone like the proposed co-occurrence framework, there will be many possible mechanisms documented, which relate to many variables

of diverse interest. Since the data collection could solely depend on this backbone, it is then possible for responsibility for the burden of proof to shift from the individual investigators or the research institutions to the data committee of the system. The current system is a paradoxical one where clinical research yields benefits like career advancement, financial benefits, and/or social prestige, and yet conflict of interest is deemed a risk factor for compromising the quality of research, neglecting the fact that with significant conflict of interest, research could be of high quality and integrity if appropriately conducted. Through the shift of responsibility, the committee could break down the tasks involved in clinical research, much like the described QB and IE. Then, through the labor division, perfect blinding, and access to global network, RCT of high quality could be implemented and documented in the co-occurrence database.

Lastly, medical training requires much investment of time and resources to complete. Due to advancing technology, changing regulations and the uncompromised emphasis on the patient'srighrs, more and more demands are placed on healthcare professionals. It is foreseeable, however, that such growing demands will finally become impractical when the volume of information surpasses what the human brain could handle. If the co-occurrence model is implemented, it could be understood from the system how frequently the prescription of a treatment is associated with its desired outcome, and whether or not the patient visiting the hospital fits the criteria for a medical treatment. If these sequences of events are clearly understood, the services involved could be provided by different recognized parties, and for the intervention that demands less skills, the services involved could be passed to those healthcare workers traditionally and customarily deemed less qualified than the medical doctors.

The present trend has allowed avoiding labor intensive and high-risk treatments, although they may be safe and effective if properly handled. There are incidences where complications result due to lack of experience with a procedure.. Ideally, as long as the intervention is proven to be

safe and effective, as long as it is provided by those who can master and deliver the procedure, and as long as the patients needing the intervention can be properly screened and referred to those people, treatment can be delivered. Likewise, as long as the criteria for prescribing a medication are met, as long as there is a robust system/human resources to determine whether those criteria are met, and as long as the safety and effectiveness of the treatment can be monitored, the medication can be prescribed. The co-occurrence framework could provide a layer of support that safeguards the safety and effectiveness of treatment, and because of this additional and fine-tuned system of support, prescription of certain treatments and the delivery of those treatment could be subject to finer labor division that decreases the demand for skill and workload in the party involved in healthcare, as long as the same outcome is achieved.

Global Inequality, Personalized Healthcare, and Simultaneous Feedback Loop

The inability of the current healthcare system to account for all the factors involved in the development of a medical condition at hand and the explosion of new information that is inaccessible due to the limitation on technology just a few decades ago led to the current emphasis on holistic medicine and personalized medicine. There is an enormous amount of data in the various databases that need to be analyzed in order for meaningful insights to be extracted. However, what could be achieved once those databases are fully analyzed? Suppose a regional hospital has used an electronic medical system, which allows all information involved in healthcare to be captured. Even if that information is fully utilized, the insight gained would be limited to the context in which that particular hospital operates: the majority of their patients may only come from a particular ethnicity, and there may be factors influencing the residents in the city where the hospital resides that make a particular treatment more or less useful for a particular

condition. Due to practical reasons, the current system established itself as a top-down one, where many social resources are invested in training professionals, encouraging support for the large institutions, and maintaining regulatory organizations which are given the power to devise and enforce policies. One should always be conscious, however, that even the least impressive entity in the society to whom the medical service is provided by the healthcare system is worthy of full respect, because the historical, cultural, social, molecular and physiological contexts in which a certain medical condition is brought to the attention of the experts involves intricate and delicate interactions between numerous variables that the current system and the professional mind are incapable to detect, but the knowledge of them could have helped the patient in the most customized and suitable way.

Doubtless, if evenness is defined by equal distribution of resources, the current world is largely unfair. The question, however, is whether distribution of the resources could be done so that each individual on earth could experience the quality of physical, social and psychological wellness fundamental to a healthy life. Obviously, the living standard in different part of the world varies, and the requirements leading to a healthy life must vary on a case by case basis. However, there is no doubt that certain lines exist that can differentiate between the healthy and the unhealthy, and between the thriving and the suffering, which have their foundation in the significant commonalities, biological, social and psychological, in the human experience. If this line is crossed, the healthcare system should be able to detect and resolve the contributing causes.

By using a framework that focuses on the individual while being able to use experience from other mankind to characterize the effect of the external and internal characteristics relating to the person contributing to a particular problem of interest allows true personalized care to be delivered. Such a framework can also allow, on a data-driven basis, higher authorities to determine whether the unequal distribution of resources among the lower entities deserves

attention and subsequently act to resolve it. Since the co-occurrence database comes from recording the variables previously defined using computer software, it is possible to, in turn, use the information from the database to enhance the human experience that those variables came from.

The feedback loop of the co-occurrence framework could manifest in healthcare. Suppose a patient comes to the hospital for a specific medical problem. With the existing information on the person in the database and the new information concerning the present hospital visit, this information could be compared against the information in the database, and after computer processing, treatment options can be recommended as well as the corresponding predicted outcomes. Because the database is comprehensive, the treatment options can be diverse in scope. The data could show, among those with similar genetic background, adoption of which particular life habits could ameliorate the condition over time, it can show whether or not a traditional herbal therapy could help with the condition based on patients with the same condition who underwent them, and it could show the potential side effects of a particular medicine in both the short-term and the long-term, as well as what life habits could minimize those side effects. It could suggest the most suitable and personalized treatment based on the comprehensive data collected, and the unique information concerning the individual.

The Breakdown of Support Barrier, the Promotion of World Peace, and the Celebration for Diversity

Suppose there is a homeless person wandering around the street and asking for financial support. The majority of the responses that the person would receive from the public is perhaps rejection to lend him the support, but that rejection is normally not only harsh to that person but also to those who reject. The failure to lend support is due to the lack of comprehensive knowledge of the person's circumstances, and some would even go further and resort to a

defensive mentality, subjectively attributing the person's begging deed as a direct result of drug use or laziness. Whether or not it is righteous to reject lending the support depends on the actual circumstances of the person, and the outcome of that financial support. If the story depicted with the defensive mentality is correct, lending the support would only facilitate the drug addiction and personal laziness that led to these circumstances. . In that case, failure to lend the trivial financial support may be free of the influence of the perfectionist's guilt.

If, however, the person was a hardworking, professional newcomer who has little connection in the area. He came out of his professional training full of debt. Divorced from his partner and with a dear first-degree relative passed away overseas, there is much regret for coming to the foreign land to pursue his career in the first place, and the guilt severely affects the quality of his work. One day his apartment with a defective smoke detectorwas broken into by a burglar, and the burglar left a cigarette butt on the wooden floor. Dismissed by his indifferent boss for his absent-mindedness at work from his job, he received a notification that his apartment was on fire. Running back to his apartment and with diminished attention to the surroundings, he was hit by a car and sent to the hospital. After a week of stay at the hospital, he was discharged with an overall situation incapable of working. Having spent all his immediate financial resources on food, he was forced by the situation to go to the street to beg.

In the latter described case, the person does seem to deserve the support as it can be an important one at the moment to aid him to get on his track again. However, no entity would assume responsibility unless the comprehensive knowledge on his background is known. The lack of it, and the unavailability of a system to provide data-driven analysis to both explain a particular phenomenon in the society and justify the sequence of steps to solve problems associated with that phenomenon is what constitutes the barrier to support. The barrier, which was explained in an individual level, also exists in the regional and national levels. The problems

present on those higher levels also have the complex context in which they develop and even persist. With the data-driven, co-occurrence system, insight on the complex mechanism could be gained, and likewise, understandings on the best course of actions to support the entity in trouble and to fix the associated problems could be sorted out.

On the national and international level, conflicts could lead to devastating outcomes that result in the loss of lives and/or the quality of lives. Historically, wars occur due to conflict of interest, difference in beliefs, and/or destructive ambition. Overall, they all have a fundamental reason, which is an isolated mind set. When that mind set developed in the certain persons who, given their resources of any kind, can in turn affects the behaviors and thinking of other individuals, devastating outcomes could result. Under the current top-down system, entities with the isolated and skewed mind sets are subject to law reinforcement. On the national scale, the nation with those mind sets are subject to stigmatization and threat of military actions. Ideally, however, thorough explanations on the perspectives of the different entities could have helped eliminate any conflict incipient. Political marriage, free trade and international guidelines in different areas have helped bridged the gap throughout the history. Nevertheless, what is fundamentally needed is a common platform where the different entities can communicate, negotiate and collaborate. The paper proposed that the co-occurrence framework could be such a platform that not only connects the different nations but the numerous diverse entities within each nation. With it, the different entities could perfectly understand the contexts involved in any topic of interest. When addressing an issue, they could make data-driven comparison, which determines the necessity of the proposed action. Resources could be distributed so that the baseline standards leading to rewarding human experiences in each unique case could be met. If every human being could be guaranteed with the customized basic, each is not vulnerable to manipulation by the isolated and

the skewed. The world could then focus more on enriching the global civilization but not the internal conflict.

Colonization on the Extraterrestrial Planets and the Maintenance of Humanity

As it is true for any medical condition that its occurrence requires that certain prior events have taken place, historical landmark of the mankind is true in the same manner. Without the available technology in boat building and the navigation methods, the America could not have been discovered by the Europeans. Unless certain catastrophic event occurs along the way to halt the process, it is inevitable that the mankind will colonize the extraterrestrial planets. The more cautious-minded might start to panic when picturing a reality where the mankind is distributed across the galaxy. What would happen if a certain planet is governed by the problematic mind, and it determines to develop weapon to destroy other planets? When physical contact is difficult and infrequent, and when the living environments largely varies, will the mankind diverges into multiple biological species? How to control and maintain inter-planet guidelines for healthcare when the living environments are so diverse? Most importantly, how to monitor the need and to guarantee its satisfaction in each unique individual living in different colonies in an efficient manner?

Clearly, with the current top-down approach, what would happen in that future is perhaps the declaration of independence one planet after another, modeling after the events throughout the history and prompted by their unique and yet unfulfilled need? As the co-occurrence framework could be applied at all different levels, including level as small as the molecular level -the timing of molecular action and the interaction between the different gene products can also be examined with that mechanism-driven and context-directed approach-, it could be expanded further to cover level even above the international level. With the same proposed framework, data would be

drawn from each individual living in different planets, and following the analytic and policy-making process already described, the policy made at any higher level will respect and account for the need of their lower counterparts in the hierarchy.

CONCLUSION

The concept of cause-and-effect has been applied by humankind to explain the unknown, but it does not perfectly align with reality. Failure to understand the weakness of this concept would let one easily fall into the trap known as the “vicious cycle.” The context-based and mechanism-driven co-occurrence concept excels over cause-and-effect, primarily due to the fact that it aligns better with the reality. By examining the complex healthcare structure with this corrected angle, one may be able to see way to completely revitalize the present system and to unite all its components.

TABLES AND FIGURES

Table 1. Types of Registered Studies. Numerical and percentage breakdown for the study and intervention types registered at Clinical Trial.gov. Adapted from ClinicalTrial.gov (accessed March 8, 2015).

Study and Intervention Type (as of March 08, 2015)		Number of Registered Studies and Percentage of Total	Number of Studies With Posted Results and Percentage of Total***
Total		185,690	16,461
Interventional		149,747 (80%)	15,433 (93%)
Type of Intervention*	**Drug or biologic**	95,884	12,698
	Behavioral, other	40,286	2,271
	Surgical procedure	16,296	789
	Device**	15,125	1,618
Observational		35,097 (18%)	1,028 (6%)
Expanded Access		289	N/A

A

Subject	V.1	V.2	V.3	V.4	V.5	V.6	V.7	V.8	...
1	1	0	1		1	1	1	0	...
2	0	1	0	1	1		0		...
3	1	1		1		0		1	...
4		1	1		0	1	0	1	...
5	1	0	1	0	1		1		...
6	1	1	1	0	0	1	0	1	...
...	0	0	1		0	1	0	1	...

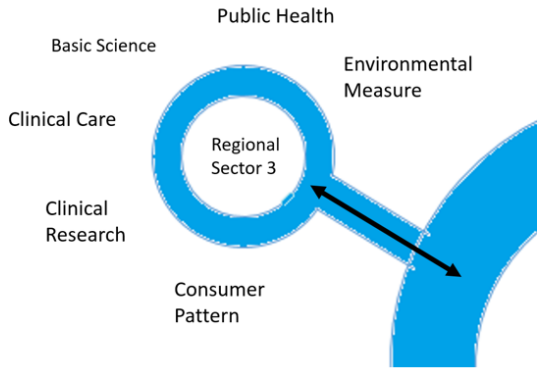
Q-Value Calculation, Combinatorial Analysis, Data Interpretation

Public International Database: Classification and Annotation of Variables

Instruments and facilities to measure values

Conversion to Co-occurrence format

B



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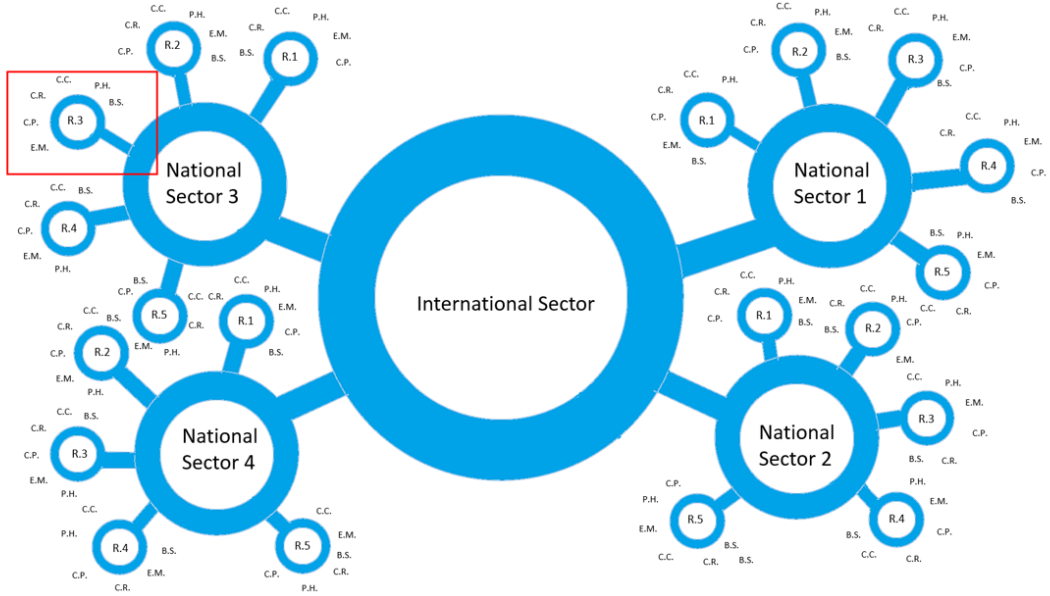


Figure 1. The Global Co-occurrence Backbone. Described is the co-occurrence database backbone. (A). All the variables directly or indirectly relating to healthcare is defined and annotated in a public database (green box), implemented in the building of computer software supporting the data recording hard wares (orange box), subsequently converted to the co-occurrence format (black box and the table), and analyzed (blue box). (B). data collection could be made on the local level encompassing a variety of fields, including environmental measure, public health, basic science, clinical care, clinical research and consumer pattern. (C). Data collected on the regional level gather to form the national database, and all the national database gather to form the international database; the regional sector boxed in red was described in B. R. = regional sector; B.S. = basic science; P.H. = public health; E.M. = environmental measure, C.C. = clinical care, C.R. = clinical research, C.P. = consumer pattern.

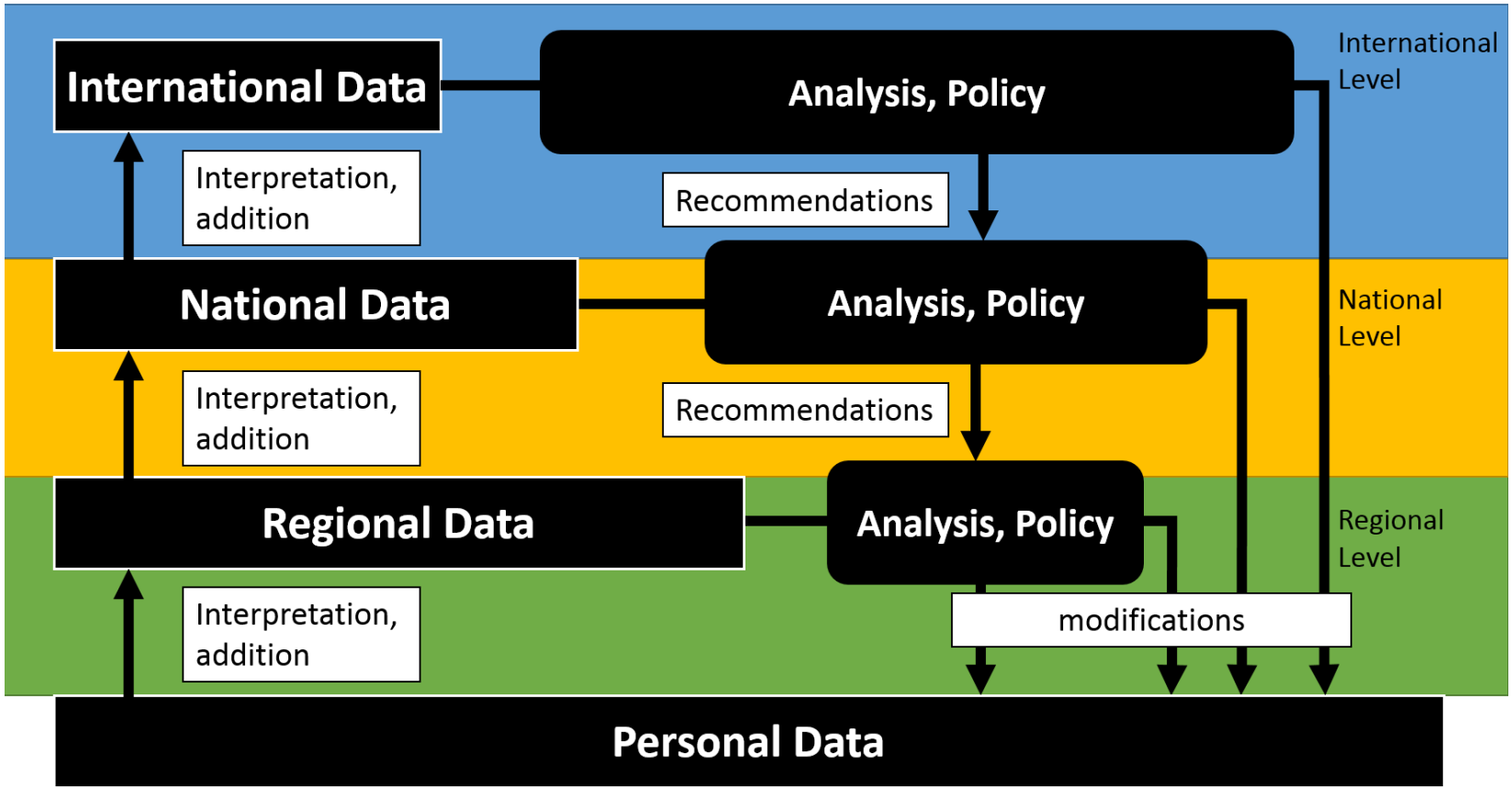

International Data
Analysis, Policy
International Level
Interpretation, addition
Recommendations
National Data
Analysis, Policy
National Level
Interpretation, addition
Recommendations
Regional Data
Analysis, Policy
Regional Level
Interpretation, addition
modifications
Personal Data

Figure 2. The Global Co-occurrence Operation. Information is collected on an individual basis primarily through healthcare electronic records. All information in the format of co-occurrence as described in the text, is interpreted and enhanced by regional committee based on the regional needs. The database is then passed to national committee, and it is likewise interpreted and enhanced based on the national needs. The further enhanced database in then passed to the international committees and it is also interpreted and enhanced based on the international needs. Once the international committees have received the final database, analysis is done to provide recommendations for policymaking. The recommendations made on the international level is passed to the national institutions, and the national institutions use the international recommendation as template and the database to devise recommendations most suitable to the national needs. The regional institutions then use the recommendation from the national institutions as template and the database to devise recommendation most suitable to its regional needs. All committees, either on the international, national or regional levels, could influence how data is collect on the individual level, and the mean shall be collaborative.

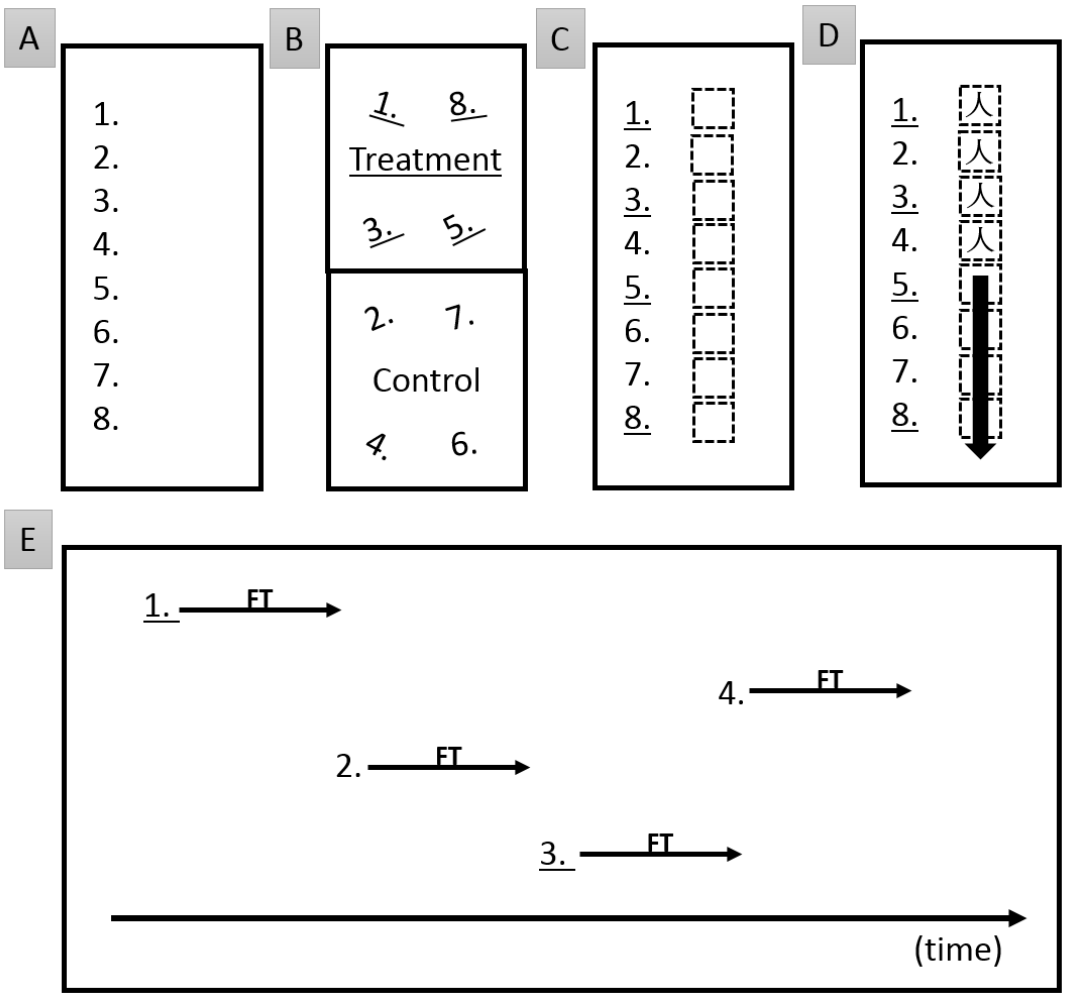


Figure 3. Independent Enrollment and Randomization by Order. (A) An imaginary list of subjects with each number representing the order of enrollment is obtained. (B) The number from (A) is randomized and assigned into the treatment or control groups. (C) The list from A is annotated with the randomization results. (D) Subject is enrolled one by one. (E) As soon as a subject is enrolled, either the intervention or the control procedure could be provided, and the subject is individually followed for the assessment of safety and study outcome until the fixed study duration passes.

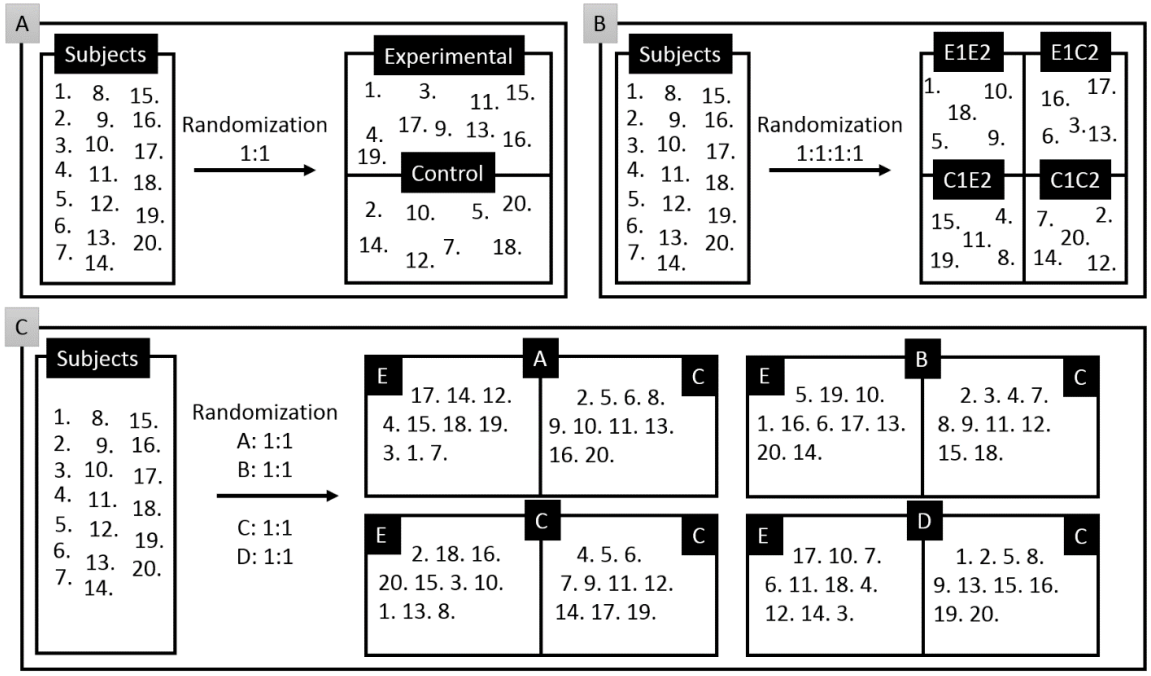
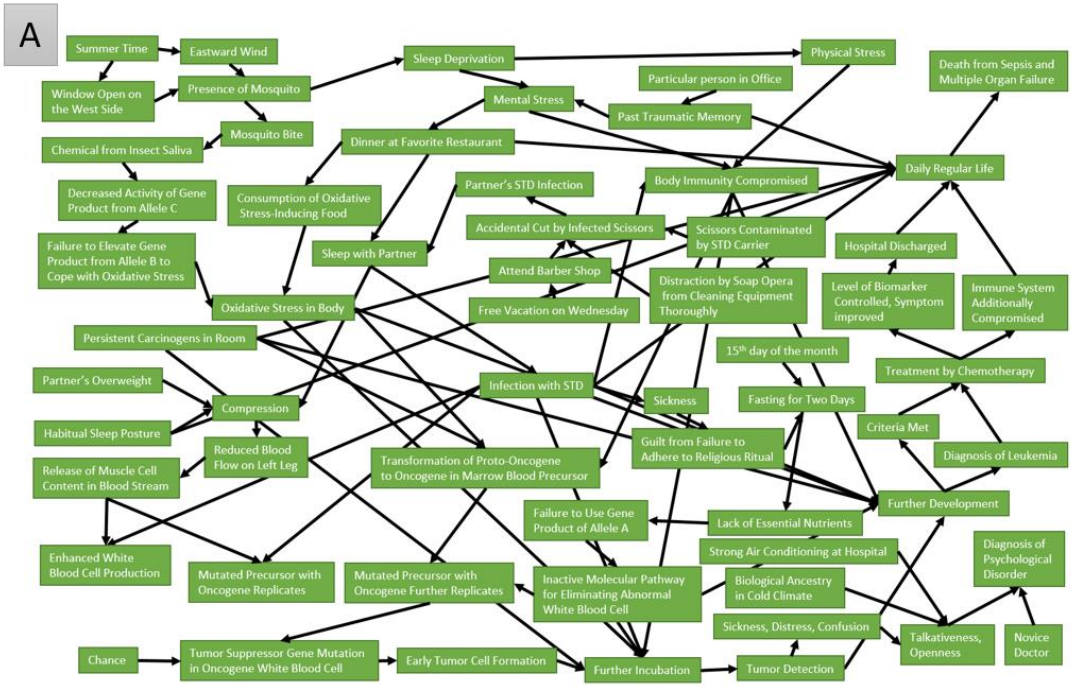


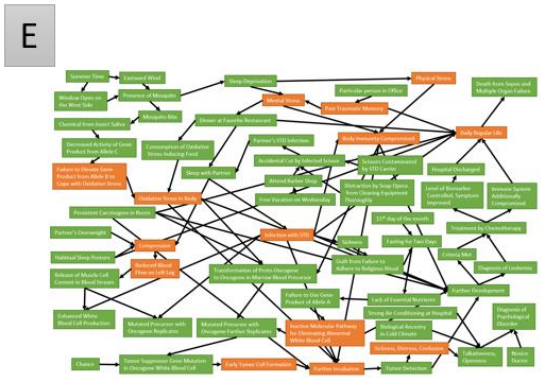
Figure 4. Comparison between the Classical Randomization, Randomization for a Factorial Design and Randomization for a Variable Shuffling Design. (A) Illustrated is the classical 1:1 randomization that distributes the subjects into the experimental and control groups. (B) Illustrated is a 1:1:1:1Randomization for a two-intervention factorial design that distributes the subjects into four groups: E1E2, which received both intervention 1 and intervention 2, E1C2, which receives intervention 1 and control 2, C1E2, which receives control 1 and intervention 2, and C1C2, which receives control 1 and control 2. (C) Illustrated is randomization for a variable shuffling design that involves four different interventions that are treated as independent events during randomization, and each randomization is performed on the same pool of subjects.


A
Summer Time
Eastward Wind
Window Open on the West Side
Presence of Mosquito
Mosquito Bite
Chemical from Insect Saliva
Decreased Activity of Gene Product from Allele C
Failure to Elevate Gene Product from Allele B to Cope with Oxidative Stress
Consumption of Oxidative Stress-Inducing Food
Sleep Deprivation
Mental Stress
Dinner at Favorite Restaurant
Partner's STD Infection
Sleep with Partner
Oxidative Stress in Body
Persistent Carcinogens in Room
Partner's Overweight
Compression
Habitual Sleep Posture
Reduced Blood Flow on Left Leg
Release of Muscle Cell Content in Blood Stream
Enhanced White Blood Cell Production
Mutated Precursor with Oncogene Replicates
Mutated Precursor with Oncogene Further Replicates
Chance
Tumor Suppressor Gene Mutation in Oncogene White Blood Cell
Early Tumor Cell Formation
Physical Stress
Particular person in Office
Past Traumatic Memory
Body Immunity Compromised
Accidental Cut by Infected Scissors
Scissors Contaminated by STD Carrier
Attend Barber Shop
Free Vacation on Wednesday
Infection with STD
Sickness
Transformation of Proto-Oncogene to Oncogene in Marrow Blood Precursor
Guilt from Failure to Adhere to Religious Ritual
Failure to Use Gene Product of Allele A
Inactive Molecular Pathway for Eliminating Abnormal White Blood Cell
Further Incubation
Tumor Detection
Death from Sepsis and Multiple Organ Failure
Daily Regular Life
Hospital Discharged
Distraction by Soap Opera from Cleaning Equipment Thoroughly
Level of Biomarker Controlled, Symptom improved
Immune System Additionally Compromised
15th day of the month
Fasting for Two Days
Criteria Met
Treatment by Chemotherapy
Diagnosis of Leukemia
Further Development
Lack of Essential Nutrients
Strong Air Conditioning at Hospital
Biological Ancestry in Cold Climate
Sickness, Distress, Confusion
Talkativeness, Openness
Diagnosis of Psychological Disorder
Novice Doctor


B


C


D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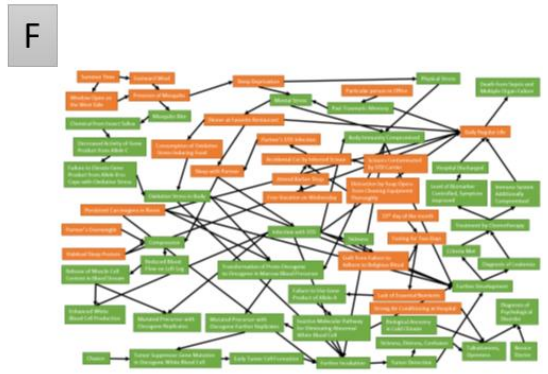
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Figure 5. The Complex Interplay of Different Variables Involved in the Progression of A Story From A Summer Breeze to Leukemia to Death from Sepsis and Multiple Organ Failure. (A) The story detailed in the article is summarized. (B) Events presented in orange boxes are those detectable an ideal co-occurrence system that leads to leukemia and/or death. (C) The events presented in orange box represent those highly likely detectable in hospital visit, and presented in yellow box represents those likely detectable in hospital visit. (D) The events presented in orange box are those related to the area of basic science. (E) The events presented in orange box are those related to the area of clinical research. (F) The events presented in orange box are those related to the area of public health, environmental measure, consumer pattern, or personal behavior.

LIST OF JOURANL ABBREVIATIONS

Am J Med Genet----------American Journal of Medical Genetics

Am J Respir Crit Care Med--American Journal of Respiratory and Critical Care Medicine

Arch Dis Child Fetal Neonatal Ed---Archives of Disease in Childhood-Fetal and Neonatal Edition

BioMed Res Int ----------BioMed research international

BMJ----------British Medical Journal

BML----------Biomedicolegal Journal

Can Med Assoc J----------Canadian Medical Association Journal

Eval Program Plann ----------Evaluation and Program Planning

FASEB----The Journal of the Federation of American Societies for Experimental Biology

J. Bacteriol----------Journal of Bacteriology

J Biol Chem----------The Journal of Biological Chemistry

JEM----------The journal of experimental medicine

Med J Austr----------Medical Journal of Australia

Methods Enzymol----------Methods in Enzymology

Perm J----------The Permanente Journal

Perspect Clin Res----------Prospective in clinical research

Plast Reconstr Surg----------Plastic and Reconstruction Surgery

PNAS----------Proceedings of the National Academy of Sciences of the United States of America

Prog. Nucleic Acid Res----------Progress in Nucleic Acid Research and Molecular Biology

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EDUCATION AND CERTIFICATION

High School	**Nei-Hu Senior High School**, Taipei, Taiwan
	Guitar Club (President) 2005, 2006
	Los Altos High School, Hacienda Heights, CA
	Diploma, 2007
College	**Mount San Antonio College**, Walnut, CA
	Outstanding Student in Chemistry, 2009
	University of California Los Angeles, Los Angeles, CA
	Scholar Recognition Awards, 2009
	Dean's Honors List, 2009-2012
	B.S. in molecular, cell and developmental biology, 2012
	Departmental honors, 2012
	Summa cum laude, 2012
Graduate School	**Boston University Medical Center**, Boston, MA
	Clinical Investigation Graduate Certificate, 2014
	M.S. in Medical Sciences, 2016 (anticipated)

APPOINTMENTS

Researcher (2012-2014)	**Hsu's Andrology**, Taipei City, Taiwan Microsurgical Potency Reconstruction and Research Center Venogenic Erectile Dysfunction
Graduate Research Trainee (2013-2014)	**Brigham and Women's Hospital**, Boston, MA Department of Emergency Medicine Acute Respiratory Distress Syndrome
Undergraduate Researcher (2011-2012)	**David Geffen School of Medicine**, Los Angeles, CA Department of Pathology and Laboratory Medicine Ataxia Telangiectaxia
Teaching Assistant (2010-2012)	**University of California Los Angeles**, Los Angeles, CA Department of Molecular, Cell and Developmental Biology Genetics, Molecular Biology Laboratory
Undergraduate Researcher (2010)	**David Geffen School of Medicine**, Los Angeles, CA Department of Neurology Duchenne Muscular Dystrophy
Tutor (2008)	**School on Wheels**, Los Angeles, CA Whittier Homeless Shelter Domestic Violence Shelter

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PUBLICATIONS

1. Lee, P. Y., Costumbrado, J., **Hsu, C.** Y., Kim, Y. H. Agarose Gel Electrophoresis for the Separation of DNA Fragments. *J. Vis. Exp.* 2012 Apr 20; (62), e3923, doi:10.3791/3923. Pub Med PMID: 22546956.

2. Hsu, G., Hung, Y., Tsai, M., Chang, H., Liu, S., Molodysky E., **Hsu, M. C.** The Venous Drainage of the Corpora Cavernosa in the Human Penis. *Arab J. Urol*. Epub 2013 May 20. http://dx.doi.org/10.1016/j.aju.2013.04.002.

3. Hsu, G., Molodysky E., Liu S., Chang H., Hsieh C., **Hsu C**. Reconstructive Surgery for Idealising Penile Shape and Restoring Erectile Function in Patients with Penile Dysmorphology and Erectile Dysfunction. 2013 September 17. DOI: 10.1016/j.aju.2013.08.009.

4. Hsu, G., Hill, J. W., Hsieh C., Liu S., **Hsu, C**. Venous Ligation: A Novel Strategy for Glans Enhancement in Penile Prosthesis Implantation. *Biomed Res Int*. 2014 August 7. http://dx.doi.org/10.1155/2014/923171.

5. Hsieh, C., Tsai, H., Hsu, G., Chen, C., **Hsu, C**. Herb Formula Enhances Treatment of Impotent After Penile Venous Stripping: A Randomized Clinical Trials. 2015 Dec. 20. doi: 10.1111/and.12508.

PRESENTATIONS

1. Huynh, C., Hsu G., Hills J., Hsieh C., Liu S., **Hsu C**. Venous Ligation: A Novel Strategy for Glans Enhancement in Penile Prosthesis Implantation. The European Congress of Andrology. ECA Barcelona, 2014.

PATENT

1. Erection promoting device by pressurizing penis veins. Intellectual Property Office MOEA R.O.C. Publication No. M496464.