Increased Chance for Recovery vs. Risk Reduction

Lev S Sverdlov, M.D., Ph.D, D.M.Sci.
Redmond Analytics LLC

Abstract. Indices of risk reduction are commonly used to assess the effectiveness of treatment. Increase in chance of recovery is a logically equivalent counterpart to risk reduction. The recovery model emphasizes the distinction between capability of spontaneous recovery and sensitivity to compared treatments. Exploiting this may help improve prediction of treatment response, facilitate search for biomarkers, and reduce risk for adverse effects via eliminating unnecessary prescriptions. Spontaneous and treatment-induced recoveries are not phenotypically distinguishable; thus we introduce a hidden variable model. The (unobservable) proportion of patients sensitive to treatment is not equal to the (observable) proportion of "responders"; we introduce a logical framework for this relationship, which constrains the priors for Bayesian analysis. Clinical, experimental, and epidemiological data will be presented to motivate the hidden variable architecture. We focus on the interface between the clinical and statistical aspects of effectiveness assessment, and on the development of a conceptual, structural, and logical framework.

Key words: Chance for recovery, Risk reduction, Sensitivity to treatment, Spontaneous recovery, Biomarkers, Hidden variable

Every case of anthrax may be regarded as a grave illness, but cases of spontaneous recovery are not altogether uncommon."

James Cornelius Wilson (1909). A Handbook of Medical Diagnosis: For the Use of Practitioners and Students

Introduction

Traditionally, the effect of treatment is measured as its ability to reduce risk of "bad events," such as symptoms, disorders, diseases, disability, deaths, etc. The indices of "absolute risk reduction" and "relative risk reduction" are commonly used in studies assessing the effects of treatment, as well as in pharmacogenetic studies examining the association between genetic markers and response to treatment. Important studies on the heterogeneity in treatment effect and individualization of treatment have also been conducted within the framework of this approach. [i]

Although the increase in chance of recovery is a logically equivalent counterpart to risk reduction ("risk reduction" = "increase in chance for recovery") it is rarely analyzed in clinical and pharmacogenetic studies. Focusing on chance for recovery is not, however, just an exercise in logic.

The assessment of the benefit of treatment via increasing chance for recovery makes us face the rarely mentioned fact that some patients recover spontaneously, i.e., without treatment or regardless of treatment. Recognition of this phenomenon leads to a chain of logical consequences and subsequently to the creation of a new logical model for the assessment of treatment effect, which is our first objective.

Another objective is exploring the phenomena of spontaneous recovery and sensitivity of a patient to treatment. Nowadays these old clinical concepts are rarely used. We will investigate their relationships with each other and with observed outcomes.

Our model creates a framework for statistical analysis of treatment effects accounting for spontaneous recovery and sensitivity to treatment. Classical statistical methods are not sufficient for this analysis. In our opinion - the opinion of a content scientist - the concept of Bayesian networks with hidden variables (e.g., Pearl, 1988)[ii] is a

promising approach to studying these phenomena, although the final selection of a general approach, as well as addressing all theoretical, methodological, and technical challenges of statistical analysis, is the prerogative of statisticians.

One of the crucial yet challenging decisions to be made in the frame of this approach is model selection. It involves choosing a number of hidden variables and their cardinalities, as well as dependencies between them and the observed entities of the domain, which is a problem having received surprisingly little attention in literature.[iii] Our study is intended to help fill this gap.

Also we will sketch a heuristic for searching candidates for markers for a capacity for spontaneous recovery and sensitivity to treatment.

The development of a model requires making necessary simplifying assumptions, and our model will be unavoidably oversimplified. Still we hope it will be useful.

1. Clinical trial model. The core of our approach is analysis and interpretation of the results of a virtual randomized clinical trial on the efficacy of experimental treatment E compared to control treatment C. The outcome of the treatment was either recovery (Y) or death (Z) such that

$$P\left(Y^{(E)}\right) + P\left(Z^{(E)}\right) = 1;$$
$$P\left(Y^{(C)}\right) + P\left(Z^{(C)}\right) = 1.$$

The subjects recruited from the population of patients suffering from a target disorder were randomly assigned to the experimental or control treatment. Each patient from the trial population is described with a vector of binary variables $V = V_1, V_2, \ldots, V_i, \ldots, V_n$. Each of the variables V_i, including clinical, demographic, biological, genetic, treatment, etc., characteristics may have a value 1 or 0.

The hypothesis of the study is that treatment E reduces risk of death more than control treatment C.

The model of a clinical trial we use consists of four major components: treatment population, treatment, outcomes, and covariates expressed in a form of binary variables following a terminological and methodological tradition for clinical trials on the effects of treatment on morbidity and mortality. A positive outcome vs. negative one, i.e., having a heart attack vs. not having it, recovery vs. death, are the most clear-cut clinical presentations of this dichotomy. Analysis of continuous outcomes may require more complex models, but the principles of the approach will remain the same. Also it is natural for the compared modalities of treatment to be expressed as binary or categorical variables.

2. Heterogeneity in treatment effects. The most complex issues are related to the homogeneity/heterogeneity of the treatment population. In the early stages of the development of the theory of randomized clinical trial, the treatment population was assumed to be homogenous. The homogeneity was thought to be reached via recruitment of patients using strict selection criteria.

The understanding that even most thoroughly selected population is still heterogeneous regarding the treatment effect is becoming more popular in clinical research. In our opinion, the very fact that virtually any treated population has positive and negative outcomes is the first evidence of the heterogeneity. Essentially, exploring the underlying layers of the heterogeneity, i.e., the variations of patients' properties determining the treatment response in individual patients and in group of patients, is the way to individualized treatment.

In the article synthesizing results of studies on the individualization of treatment Kent and coauthors (2010) presented a proposal for assessing heterogeneity in treatment effects. The authors refer to growing evidence that in virtually any population of treated patients there is a considerable variation in risk of the outcome of interest. The "average"

benefit observed in the summary trial result of a clinical trial may even be non-representative of the treatment effect for a typical patient in the trial, to the extent that some subgroups of patients can benefit when aggregate results of trials are negative. The authors consider the effects of treatment traditionally, using the indices characterizing risk for a negative outcome ("bad events," i.e., disorders, diseases, disability, or death). In our opinion, the logic of analysis of reducing risk of "bad events" by Kent, et al., could be equally applied to the increase in chance of a positive outcome, and if we switch focus to the increase in chance for recovery, we inevitably come to a conclusion about a considerable variation in chance for recovery, and that some subgroups of patients might have high chance for recovery whether aggregate results of trials are positive or negative.

3. Chance for recovery vs. risk for "bad events." Traditionally, in clinical and epidemiological studies, the benefit of treatment for patients is defined using indices as reduction of risk of death:

- absolute risk reduction: $ARR = P\left(Z^{(E)}\right) - P\left(Z^{(C)}\right)$;
- relative risk reduction: $RRR = \frac{P\left(Z^{(E)}\right) - P\left(Z^{(C)}\right)}{P\left(Z^{(C)}\right)}$ and
- number needed to treat: $NNT = 1/\left[P\left(Z^{(E)}\right) - P\left(Z^{(C)}\right)\right]$.

Almost identically, the benefits of treatment can be expressed using a logically equivalent system of indices defining increasing chance for recovery as follows.

$$ARR = P\left(Z^{(E)}\right) - P\left(Z^{(C)}\right) = ACI;$$
$$NNT = 1/\left[P\left(Z^{(E)}\right) - P\left(Z^{(C)}\right)\right] = NNT';$$

where ACI is the absolute chance increase, and NNT' is the number needed to treat to have one more recovery. The absolute risk reduction and the absolute chance increase are symmetrical and equal, i.e., in the context of the assessment of the effect of treatment they can be used interchangeably.

The relative risk reduction index (RRR) and the relative chance increase index (RCI) are not equal. Their numerators are equal, but their denominators are different.

$$RRR = \frac{P\left(Z^{(E)}\right) - P\left(Z^{(C)}\right)}{P\left(Z^{(C)}\right)} \neq \frac{P\left(Y^{(C)}\right) - P\left(Y^{(E)}\right)}{P\left(Y^{(C)}\right)} = RCI.$$

In the RRR index, the numerator, i.e., absolute risk reduction is related to the proportion of deaths among controls. In the RCI index, the absolute chance increase is related to the proportion of recoveries among controls, which is consistent with the meaning of the RCI index. With this reservation, all operations performed on the indices of risk reduction also formally may be performed with the chance increase indices. However, in such a case there are important content issues.

4. "Responders" vs. "Non-responders." The patients having recovered after being exposed to treatment often are labeled as "responders" as opposed to "non-responders," i.e., those who have not recovered. The term "non-responders" does not call for any objections, but the patients with positive outcomes are not necessarily the "responders" in the proper meaning of this term. Some fraction of them could recover regardless of treatment.[iv] The problem is that, so long as a patient exposed to treatment has recovered it is hardly possible to determine whether the recovery has been induced by the treatment or it was spontaneous, i.e., spontaneous recovery and treatment-induced recovery are not phenomenologically, phenotypically distinguishable. Apparently, this is one of the reasons why in modern clinical research the effect of treatment is usually assessed as a capacity of treatment to reduce risk of a negative outcome rather than increase in chance for recovery, and the old clinical term "spontaneous recovery" is rarely used.

5. Spontaneous recovery. Recovery as one of possible outcomes in a natural course of most disorders has been described by physicians long before modern treatments

have been discovered. Although there are some disorders in which a lethal outcome occurs inevitably regardless of any treatment, in most known disorders the rate of spontaneous recovery is substantial. It is true even for diseases notorious for very high mortality. It varies across disorders and across the forms of the disorders, but even in severe infections which have taken millions of human lives during epidemics and pandemics, recovery has been observed in a substantial proportion of the affected populations.

For instance, Ebola Virus Disease (EVD) is known as one of the most dangerous infections. As of today, there is no treatment for this disease except for life support system in most sophisticated medical facilities, but this treatment was not available in many areas affected by the most recent epidemics. The case fatality rates for EVD have varied from 25% to 90% in past outbreaks,[v] i.e., from 10% to 75% patients (on average about 50%) survived.

A substantial survival rate without treatment is reported in other most dangerous infectious disorders, such as smallpox (75% on average),[vi] bubonic plague (50%), [vii] cholera (40–50%),[viii] cutaneous anthrax (80%), gastrointestinal anthrax (60%), inhalational anthrax (10%),[ix] typhus[x] (40-90%) and so on.

In myocardial infarction, which is dubbed as the "#1 killer," the survival rate is in the vicinity of 90% depending on multiple factors[xi,xii]. In cancer, which is a group of diverse malignant disorders with very different paces of progression, the overall fatality rate is 60%, i.e. approximately 40% survive.[xiii] While many chronic progressive disorders have a clear long-term trend to deterioration, debilitation and even death, a natural course of most of them is characterized by fluctuations of severity, sometimes remissions or even intermissions, at least in a substantial proportion of patients.

This list can be expanded indefinitely, and for most of the disorders listed in medical and public health classifications and manuals spontaneous recovery (or remission, or intermission) is not a rare event due to some accidental confluence of biological and social factors. Rather, we understand the capability for spontaneous recovery as a property reflecting an existence of an evolutionarily developed protective system in response to a specific hazard (the history of plague epidemics in Europe[xiv] can be an example). Hereafter, this property will be designated as Sp, and a lack of this property as $\overline{Sp}$.

6. Observed outcomes and hypothetical properties: Logical model of treatment.

Let us consider the results of a randomized placebo-controlled trial assessing the efficacy of treatment E on a population of patients suffering from a disorder of interest. It is assumed that a number of observations is large enough and a proportion of a positive outcome among patients treated with experimental treatment $P(Y^{(E)})$ was greater than among those treated with placebo $P(Y^{(Pl)})$.

6.1 Property. Hereafter, under the property we mean an attribute, quality, characteristic, ability or trait of a patient determined by a single factor inherent to a relevant category of patients (e.g., polymorphism), or by a confluence of multiple factors, either prevalent or rare. Note that in a randomized trial these factors and the properties determined by them are thought to be equally prevalent in the compared cohorts.

6.2 Model. Two alternative outcomes (recovery vs. death) have been observed. Speaking of the experimental cohort, the only reasonable explanation for the different response to standard treatment in standard environment is that patients differed by some of their properties. It is also the case for the placebo cohort.

A historical, clinical, and epidemiological data show that some unknown proportion of the trial population ought to have recovered regardless of treatment. The appreciation of the phenomenon of spontaneous recovery in a fraction of patients exposed to treatment leads to a chain of logical consequences. The statement that some patients have recovered without or regardless of treatment is equivalent to the statement that these patients possessed a property making them able to recover spontaneously $P(Sp)$. While being randomly assigned to a *placebo control* (Pl), i.e., not being treated with any active medicine, the patients with the ability for spontaneous recovery have comprised the group of those with positive outcome such that

$$Sp^{Pl} = Y^{(Pl)}; \text{ and } Z^{Pl} = \overline{Sp^{Pl}};$$

i.e., all patients with the property Sp^{Pl} were the members of the set of patients with a positive outcome and neither patient without this property is the member of this set.

Apparently, because of randomization, among the patients assigned to the *experimental cohort* there was an equal proportion of those with the property Sp:

$$P\left(Sp^{(E)}\right) = P\left(Sp^{(Pl)}\right); \text{ but}$$
$$P(Y^{(E)}) > P(Sp^{E}).$$

All patients of this cohort with the property Sp were the members of the set $Y^{(E)}$

$$Sp^{(E)} \subset Y^{(E)}; \text{ but}$$
$$Y^{(E)} - Sp^{(E)} = R$$

members of the set $Y^{(E)}$ did not possess the property $Sp^{(E)}$.

Apparently, the members of the set R possessed another property making them responding positively to treatment E, i.e., a property $St^{(E)}$of *sensitivity* to treatment E. The term "responders" can be justly applied only to this set of patients (R).

It is possible that the patients with ability for spontaneous recovery $Sp^{(E)}$ (all of them, part of them, or neither of them) also could have the property $St^{(E)}$. It means that among the patients with a positive outcome $\left(Y^{(E)}\right)$ there are three subsets:

$$Y^{(E)} = Sp^{(E)} \cap \overline{St^{(E)}},\ Sp^{(E)} \cap St^{(E)}, \overline{Sp^{(E)}} \cap St^{(E)}.$$

With regard to the patients possessing both Sp and $St^{(E)}$, it cannot be unambiguously stated whether they have recovered spontaneously or due to the effect of treatment. In our further speculations we will consider recovery in such cases as spontaneous assuming that the patient would have recovered if he/she was not exposed to treatment. This is an arbitrary decision. A researcher focused on specific problems may be guided by other logic. For instance, it can be assumed that if a patient capable of spontaneous recovery and sensitive to treatment was exposed to treatment, then his or her recovery should be qualified as treatment-induced. It may change some quantitative characteristics, but it will not change logic of analysis in general.

The patients with a negative outcome had possessed neither the property of sensitivity to treatment, nor ability for spontaneous recovery - otherwise they would have a positive outcome:

$$Y^{(E)} = \overline{Sp}, \overline{St^{(E)}}.$$

The quantitative relationships between the observed outcome and hypothetical properties in the treated population can be described as follows.

$$P\left(Y^{(E)}\right) = P(Sp) + P\left(St^{(E)}\right) - P(Sp)P\left(St^{(E)}\right);$$
$$P\left(Z^{(E)}\right) = [1 - P(Sp)] \times \left[1 - P(St^{(E)})\right];$$

which is true only under an assumption that properties Sp and $St^{(E)}$ are not related to each other in an individual patient and are independent in the treatment population. This is a strong assumption. As soon as any factual data indicating otherwise are available, a relevant model can be substituted.

7. Sensitivity to treatment. The term "sensitivity" is used in a number of disciplines (statistics, psychology, physiology, biology, microbiology, allergology, physics, engineering, etc.) in various contexts and with different meanings. In statistics, the term sensitivity is used in different contexts, primarily those of sensitivity analysis and sensitivity in binary classification.

We understand the sensitivity of an individual patient to a specified treatment as his or her ability to develop a positive outcome in response to a certain dose of this treatment. We call a patient sensitive to a specified treatment $St^{(Tx)}$ if this treatment has imposed a positive outcome, whereas there are reasons to believe that the outcome would be negative if a specified treatment was not applied.

The capacity of a population to respond to a defined treatment can be meaningfully (although not exclusively) characterized by the proportion of patients sensitive to a specified treatment.

7.1 Sensitivity to specified treatments. Let us assume that a patient has responded positively to treatment *A,* but did not respond to treatment *B*. This can be expressed using two logically equivalent statements: 1) *A* was effective and *B* was not effective in this patient, or 2) the patient was capable of responding positively, i.e., the patient was sensitive to *A* and not sensitive (resistant) to *B*.

In this paper we consider sensitivity to experimental $St^{(E)}$ and control $St^{(C)}$ treatment. The patterns of relationships between $St^{(E)}$ and $St^{(C)}$ in individual patients and within a treatment population are diverse. It requires special analysis, which is beyond the objectives of this paper. Here we will limit our analysis to two models to illustrate the critical importance of adequately modeling these relationships for the assessment of effectiveness.

7.2 Independence. In the first model $\left(St^{(C)} \leftrightarrow St^{(E)}\right)$**,** it is assumed that the properties $St^{(E)}$and $St^{(C)}$ are not related to each other, i.e., in an individual patient each of the properties can exist or not exist regardless of the presence or absence of another one. We will also designate sets of patients within the treatment population Tx.An individual patient can have any combinations of these properties, implying membership in exactly one of $St^{(E)} \cap St^{(C)}$, $\overline{St^{(E)}} \cap St^{(C)}$, $St^{(E)} \cap \overline{St^{(C)}}$, or $\overline{St^{(E)}} \cap \overline{St^{(C)}}$. We write $P\left(St^{(E)}\right)$ for $P\left(tx \in St^{(E)}\right)$ for tx randomly sampled from Tx. Note that $P(St^{(E)}) = P(St^{(C)})$ does not mean $St^{(E)} = St^{(C)}$; likewise, the statement $P(St^{(E)}) > P(St^{(C)})$ does not mean that $St^{(C)} \subset St^{(E)}$ although such special cases can exist. For the purpose of this model, we assume statistical independence of the two properties; that is $P\left(St^{(E)} \cap St^{(C)}\right) = P\left(St^{(E)}\right)P\left(St^{(C)}\right)$, and likewise for other combinations.

Although we did not find systematic data on this matter in available literature, clinical experience provides numerous examples that while one patient reacts positively to medicine A and does not react to medicine B, another patient reacts positively to B and does not react to A; the third patient reacts positively to each of them, and the fourth one reacts positively to neither of them. This can be observed, for instance, in the treatment of hypertension, diabetes, depression, schizophrenia, Parkinson's disease and many other

disorders treated with various medications belonging to different pharmacological classes.

7.3 "Matryoshka" The second model $\left(St^{(C)} \subset St^{(E)}\right)$ assumes that each individual patient sensitive to treatment C is also sensitive to treatment E, but not each individual patient sensitive to treatment E also is sensitive to treatment C. The treatment population consists of patient sets $St^{(E)} \cap \overline{St^{(C)}}$, $St^{(E)} \cap St^{(C)}$, and $\overline{St^{(E)}} \cap \overline{St^{(C)}}$. For example, typically (although not necessarily), the patients who react positively to a low dose of a medication also react positively to a higher dose, but not all of those positively reacting to a high dose of the medication also react positively to a low dose.

8. Spontaneous recovery and sensitivity to treatment: a structure of the properties. Spontaneous recovery is an empirically known phenomenon. Its existence has been confirmed by historical descriptions, clinical observations, epidemiological and experimental evidence. The concepts of treatment induced recovery, capacity for spontaneous recovery, and sensitivity to treatment are hypothetical concepts emerging with logical necessity as a consequence of recognition of existence of the phenomenon of spontaneous recovery. They will remain hypothetical concepts, akin to statistical hidden variables, until their biochemical or physiological substrate and/or their markers and population parameters are found.

The capacity for spontaneous recovery can be determined by polymorphism, inborn or acquired immunity, anatomical, physiological factors, etc., or by a relatively stable assembly of biological and social components and including nonspecific resilience factors, often considered in the context of internal and external environments. The response of this evolutionary system to the hazard can be modified by additional non-random (for instance, treatment) and random factors. In a statistical sense these random factors create a variability of the mortality/survival in the population exposed to the hazard.

Whether recovery was determined by a single factor (for instance, inborn immunity to the disease) or a combination of several factors, the patient who is observed to have recovered without treatment had at least one property which was sufficient to imply recovery.

Similarly, sensitivity to a specific treatment can be determined by a single factor (for instance, presence or absence of a specific enzyme) or by a combination of several factors (e.g., absorption, metabolization, elimination, accumulation, etc.).

Our model deals with the analysis of the results of a clinical trial. In this retrospective exploratory analysis of sensitivity to a specific treatment and capacity for spontaneous recovery, we are inclined to learn first whether the patient (or patients) under our observation did or did not have this integral functional ability, assuming that further steps of analysis will explore the structure and mechanisms of this property.

9. Prospective view on outcomes. If the presence or absence of the properties Sp and $St^{(E)}$ in an individual patient was known, it would be possible to predict an outcome for either treated or untreated patient (Table 1).

Table 1. The Expected Outcome by Treatment, by $St^{(Tx)}$, by Sp.

Tx	$St^{(Tx)}$	Sp	$Y;\ Z$
0	0	0	Z
0	1	0	Z
0	0	1	Y
0	1	1	Y
1	0	0	Z
1	1	0	Y
1	0	1	Y
1	1	1	Y

10. Retrospective view on outcomes. The outcomes of treatment are known from observation. Patients with the properties Sp and/or $St^{(E)}$ are distributed differently in the groups with observed positive and negative outcomes in the populations exposed and not exposed to treatment. This makes possible hypothesizing if the patient was in a possession of the properties of sensitivity to treatment and capability for spontaneous recovery.

Table 2. Possible Combinations of Properties $Sp, St^{(Tx)}, \overline{Sp}, \overline{St^{(Tx)}}$ among Patients, by Treatment, by Outcome

\ **Outcome** **Treatment** \	Y	Z
0	$Sp, St^{(Tx)}; Sp, \overline{St^{(Tx)}}$	$\overline{Sp, St^{(Tx)}}; \overline{Sp}, St^{(Tx)}$
1	$Sp, \overline{St^{(Tx)}};\ Sp, St^{(Tx)}; \overline{Sp}, St^{(Tx)}$	$\overline{Sp, St^{(Tx)}}$

11. Comparing treatment effects. Retrospectively, i.e., having observed the outcome of the trial, the proportions of the outcomes in a randomized study comparing two active treatments can be generally described in our model as

$$P\left(Y_{Sp}^{(E)}\right) + P\left(Y_{R}^{(E)}\right) + P\left(Z^{(E)}\right) = 1;$$
$$P\left(Y_{Sp}^{(C)}\right) + P\left(Y_{R}^{(C)}\right) + P\left(Z^{(C)}\right) = 1.$$

Here the superscripts indicate both outcome classification and randomization arm membership; that is $P\left(Z^{(E)}\right) = P\left(tx \in Z^{(E)}\right)$ for tx randomly chosen among patients assigned to treatment arm E.

The intra-arm outcome proportions $P\left(Y_{Sp}^{(E)}\right)$ and $P\left(Y_{R}^{(E)}\right)$ are not known and they are not phenotypically distinguishable within the set of positive outcomes, as well as $P\left(Y_{Sp}^{(C)}\right)$ and $P\left(Y_{R}^{(C)}\right)$. We know only that $P\left(Y_{Sp}^{(E)}\right) = P(Sp)$. Note that a placebo-controlled trial is a special case where control treatment is intentionally ineffectual (placebo) and therefore $P(Sp^{(C)})$ is known from observation as the proportion of recovery in the placebo arm.

Under an assumption of independence of $St^{(E)}$ and Sp, in the cohort exposed to experimental treatment, the expected mortality is

$$P\left(Z^{(E)}\right) = \left[1 - P\left(Sp^{(E)}\right)\right] \times \left[1 - P\left(St^{(E)}\right)\right]$$
$$= [1 - P(Sp)] \times \left[1 - P\left(St^{(E)}\right)\right];$$

i.e., those not capable of spontaneous recovery and not sensitive to experimental treatment die. The expected rate of recovery is

$$P\left(Y^{(E)}\right) = P(Sp) + P\left(St^{(E)}\right) - P(Sp)P\left(St^{(E)}\right).$$

Similarly, in the *active control cohort* of the trial

$$P\left(Z^{(C)}\right) = \left[1 - P\left(Sp^{(C)}\right)\right] \times \left[1 - P\left(St^{(C)}\right)\right];$$

where C is control treatment, and $P\left(Sp^{(C)}\right) = P(Sp)$. The expected rate of recovery is

$$P\left(Y^{(C)}\right) = P(Sp) + P\left(St^{(C)}\right) - P(Sp)P\left(St^{(C)}\right).$$

These relationships can be expressed as a system of equations with an infinite number of solutions as follows.

$P\left(Y^{(E)}\right) + P\left(Z^{(E)}\right) = 1;$
$P\left(Y^{(C)}\right) + P\left(Z^{(C)}\right) = 1;$ (in both arms, each patient recovers or dies)
$P(Sp) + P\left(Y_{R}^{(E)}\right) = P\left(Y^{(E)}\right);$
$P(Sp) + P\left(Y_{R}^{(C)}\right) = P\left(Y^{(C)}\right);$ (recovery is spontaneous or due to treatment)
$P\left(Y^{(E)}\right) = P(Sp) + P\left(St^{(E)}\right) - P(Sp)P\left(St^{(E)}\right);$

$$P\left(Y^{(C)}\right) = P(Sp) + P\left(St^{(C)}\right) - P(Sp)P\left(St^{(C)}\right);\ \text{(strong independence)}$$
$$P\left(Z^{(E)}\right) = [1 - P(Sp)] \times \left[1 - P(St^{(E)})\right];$$
$$P\left(Z^{(C)}\right) = [1 - P(Sp)] \times \left[1 - P(St^{(C)})\right];\ \text{(implied by the above)}$$

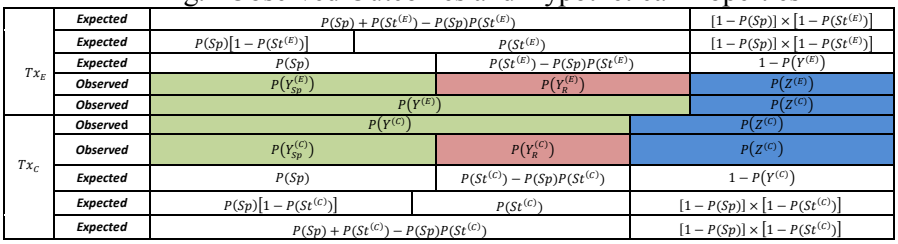
In a trial comparing two active treatments, none of $P(Sp)$, $P\left(St^{(C)}\right)$, and $P\left(St^{(C)}\right)$ can be directly deduced form the observed outcomes. The value of each of these proportions can be found only *relative* to other properties and observed outcomes.

12. Observed Outcomes and Hypothetical Properties: Graphic Presentation. Given $P\left(Sp^{(E)}\right) = P\left(Sp^{(C)}\right) = P(Sp)$, the relationships between the observed outcomes Y and Z and the theoretical proportions

$$P\left(Sp^{(E)}\right); P\left(St^{(E)}\right); P\left(Y_R^{(E)}\right); P\left(Sp^{(C)}\right); P\left(St^{(C)}\right); P\left(Y_R^{(C)}\right);$$

are graphically shown in Fig. 1.

Fig.1 Observed Outcomes and Hypothetical Properties



13. Estimation of the proportion of patients with properties Sp and E. Assuming sample sizes to be large, we will interpret treatment arm population proportions as equivalent to their corresponding probabilities, so as to focus only on the problem of identification. The proportions $P(Y^{(E)})$, $P(Y^{(C)})$, $P(Z^{(E)})$ and $P(Z^{(C)})$ are the known, as they are the observed results of the trial. Given $P\left(Sp^{(E)}\right) = P\left(Sp^{(C)}\right) = P(Sp)$ and, e.g.,

$$P\left(Z^{(E)}\right) = \left[1 - P(Sp^{(E)})\right] \times \left[1 - P(St^{(E)})\right];$$

the relationships between the variables $P(Sp)$, $P\left(Y^{(E)}\right)$ and $P\left(St^{(E)}\right)$ within the trial population can be found as shown in Table 3.

Table 3. Proportion Sensitive to Experimental Treatment, by $P(Sp)$ vs $P\left(Y^{(E)}\right)$

P(Sp)\P(Y$^{(E)}$)	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**
0.1	0.00	0.11	0.22	0.33	0.44	0.56	0.67	0.78	0.89
0.2		0.00	0.13	0.25	0.38	0.50	0.63	0.75	0.88
0.3			0.00	0.14	0.29	0.43	0.57	0.71	0.86
0.4				0.00	0.17	0.33	0.50	0.67	0.83
0.5					0.00	0.20	0.40	0.60	0.80
0.6						0.00	0.25	0.50	0.75
0.7							0.00	0.33	0.67
0.8								0.00	0.50
0.9									0.00

Practically, these computations can be immediately applied only to the results of a randomized placebo-controlled trial. For example, if $P\left(Y^{(Pl)}\right) = 0.4$ and $P(Y^{(E)}) = 0.7$, then assuming that $P(Sp) = P\left(Y^{(Pl)}\right)$ the proportion of patients sensitive to the experimental treatment is $P(St^{(E)}) = 0.5$.

14. Statistical implications. Under these assumptions, if we had a reliable estimate for at least one of the hypothetical properties, it would make it easy to find an estimate for the rest of them, e.g., given a reliable estimate for $P(St^{(C)})$, estimates for $P(Sp)$ and $P\left(St^{(E)}\right)$ can be found from the equations in Section 13, or from Table 3. It may be possible for these purposes to use an external estimate of the proportion of spontaneous

recovery, or the proportion of patients sensitive to one of the treatments, from previous trials or from epidemiological data. However, there are serious concerns regarding the applicability of the imported data. Interpolation of population data to a clinical trial, or extrapolation of data from one trial population to another trial, is always problematic, and this problem is fundamental. Nevertheless these computations can be useful for more robust analysis.

The major obstacle for applying classic statistical methods toward the analysis of treatment effects accounting for the phenomenon of spontaneous recovery is the fact that spontaneously recovered patients are not phenomenologically or phenotypically distinguishable from those with treatment-induced recovery. We have managed to explore the relationships between the hypothetical variables and the observed outcomes. These logical relationships (Section 6), relative quantitative relationships in the form of the system of equations (Section 13), and the restrictions to this system (See below: Section 15.5) constitute a structure and logical model, which sets the groundwork for considering the concept of Bayesian networks with hidden variables (Pearl, 1988) as a promising approach to studying the treatment effects accounting for spontaneous recovery.

Our model, including the hidden variables Sp, $St^{(E)}$ and $St^{(C)}$, as well as the relationships between them and the observed outcomes, represents our beliefs regarding the system. The estimates for the hypothetical variables can be presented in the form of priors. This information has to be complemented with a set of covariates describing the trial population. Given this data and defined relationships, this methodology is capable of finding expectations and variances for $P(Sp)$, $P\left(St^{(E)}\right)$ and $P\left(St^{(C)}\right)$.

The selection of a specific model, as well as addressing all theoretical, methodological, and technical challenges of such analysis is the prerogative of statisticians. The result of such analysis will be a first step on the way to identifying the individual patients possessing these properties.

15. Analytical implications: Exploring markers. Let us assume that satisfactory estimates for the proportions of each of the hidden variables Sp, $St^{(E)}$ and $St^{(C)}$ have been found. Still, we are not able to identify the individual patients possessing and not possessing the properties associated with these variables. Wwe do not discuss possible statistical approaches towards identifying the patients-carriers of the hidden variables (e.g. individuals with the property Sp). Rather, we focus on a search for markers of these properties, which is primarily an empirical process. In the analytical part of this search, we rely primarily on a data mining approach, which is not as straightforward in this case.

15.1 Biomarker. A biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." [xv] In medicine, a biomarker is a measurable characteristic that reflects the severity or presence of some disease state. Generally a biomarker is anything that can be used as an indicator of a particular disease state or some other physiological state of an organism.[xvi] Hereafter, the term biomarker (marker) will be used in this broad sense.

15.2 "Clinical truth." In their search for predictive markers, geneticists and statisticians have to rely upon "clinical truth," which is defined by FDA as "the best clinical evidence for a specific diagnosis or allele assignment." [xvii] In other words, the marker can be effective for a binary classification test, i.e., be sensitive and specific in a statistical sense, only if the state or property designated by the marker (disorder, outcome, functional characteristic, polymorphism, etc.) has a clear clinical definition.

15.3 Marker property and marker function. A marker can be defined as a special case of binary classification. If we consider a variable V_M to be a candidate for the role of a marker for the property *M*, the set of patients with property V_M is the same as that with property M. This description, however, formally fits only a "perfect" marker with maximum sensitivity (in a statistical sense) and specificity. The function of a marker, however, can be carried out not for the entire set M, but only for a subset of it, and not necessarily caused by a single factor. It may be carried out by multiple variables such that
each of them has high specificity ($\cong 1.0$), and (desirably, but not necessarily) high sensitivity. Importantly, these subsets may have elements in common with each other.

Certainly a perfect marker with both maximum sensitivity and specificity would be the most effective for identifying patients possessing a property of interest. The role of potential "partial" markers, i.e., markers with high specificity and low sensitivity, should not be underestimated. The "partial" markers can identify a relatively small segment of the treatment population, maybe just a few patients, possessing a relevant property. For these few individuals, however, it can be of critical importance. Besides, they may have an important exploratory value. The clinical, chemical, morphological, or physiological factors responsible for a positive or negative outcome, and identified with this partial marker, might turn out to be characteristic for the entire population, which can be confirmed or rejected in further studies.

We will define a variable as possessing a *marker property* if it has a capacity to accurately identify an entire segment of a population possessing the property of interest (a "perfect" marker) or part of this segment ("partial" marker).

15.4 Identification of patients - carriers of hypothetical properties. The very idea of finding markers for hidden, hypothetical variables may appear to be invalid. Indeed, a marker has to designate a known, well defined property. In our case the variables $Sp,\ St^{(E)}$ and $St^{(C)}$ are hidden, and neither $Sp,$ nor $St^{(E)}$, nor $St^{(C)}$ are known, i.e. we cannot name or demonstrate a concrete physiological mechanism, or a chemical compound, or any other characteristics firmly associated with these properties.

Under regular circumstances, the patients who are carriers of the property of interest can be identified if a variable marker for this property is known. On the other hand, the variable-marker for this property can be identified if the patients-carriers of the property are known. Because we know neither of them, we have a vicious circle without a finite analytical solution.

Paradoxically, there exist characteristic relationships between the hidden and observed variables, which allow for creating a framework for screening the covariates[1] as candidate markers for the hypothetical properties $Sp,\ St^{(E)}$ and $St^{(E)}$ using a data mining approach and for guiding the empirical search for the marker.

15.5 Constraints (Patterns). In the frame of our model, each of the hypothetical variables $Sp,\ St^{(E)},$ and $St^{(C)}$ has a set of distinctive characteristics, which can be interpreted as constraints for a system of equations with infinite number of solutions (See: Section 11). Also they can be used for screening the set of covariates V for candidates for a role of markers for the properties $Sp,\ St^{(E)}$ and $St^{(C)}$. Note that due

[1] Usually patients included into a clinical trial population are thoroughly investigated and described with a large number of variables, often in the range of several hundred, covering social, biological, clinical, therapeutic, etc., information. Only a small part of selected variables is reported. Most of this valuable information is usually buried in archives (*L.S.*).

to randomization the patients with, for instance, the property $St^{(E)}$ are equally prevalent in each of the compared cohort, but because of exposure to different treatments they may be distributed differently among the segments of relevant observed outcomes ($Y^{(C)}$vs. $Y^{(E)}$ or $Z^{(C)}$ vs. $Z^{(E)}$). The same is true for $St^{(C)}$and Sp. It creates characteristic patterns for the variables $St^{(E)}$, $St^{(C)}$and Sp. Apparently, the markers must have the patterns identical to the relevant hidden variables. Having identified a marker, if exists, we have a possibility of identifying the patients-carriers of the relevant property - $St^{(E)}$, $St^{(C)}$or Sp. The patterns are as follows.

15.5.1 Pattern of sensitivity to control treatment ($\mathbf{St^{(C)}}$). For convenience let us assume that $P(Y^{(C)}) \leq P\left(Y^{(E)}\right)$. By definition, *in the control cohort* all patients sensitive to treatment ($St^{(C)}$) are among those with positive outcome. Due to randomization, the patients sensitive to *control treatment* have to be randomly distributed within the *experimental treatment cohort.* In the large population limit, the proportion of patients *sensitive to control treatment* among patients *exposed to experimental treatment* with a positive outcome has to be equal to the proportion of patients *sensitive to control treatment* among patients with a negative outcome. This is true both under the condition $\left(St^{(C)} \leftrightarrow St^{(E)}\right)$ as well as under the condition $\left(St^{(C)} \subset St^{(E)}\right)$, yielding the following set of equations:

1. $0 \leq P\left(St^{(C)}\right) \leq P\left(Y^{(C)}\right)$;
2. $P\left(St^{(C)}|Z^{(C)}\right) = 0$.
3. $P\left(St^{(C)}|Y^{(E)}\right) = P\left(St^{(C)}|Z^{(E)}\right) = P\left(St^{(C)}\right)$.

Note that the last equation refers to counterfactual conditionals, probabilities that patients would have attained one result had they been assigned by randomization to a different arm than they actually were.

15.5.2 Pattern of sensitivity to experimental treatment ($\mathbf{St^{(E)}}$).
The patients sensitive to *experimental treatment* have to be randomly distributed within the *control treatment cohort* and the proportion of patients *sensitive to control treatment* among patients *exposed to experimental treatment* with a positive outcome has to be equal to the proportion of patients *sensitive to control treatment* among patients with a negative outcome. This is true under the condition $\left(St^{(C)} \leftrightarrow St^{(E)}\right)$.

1. $P(St^{(C)}) \leq P(St^{(E)}) \leq P(Y^{(E)})$;
2. $P\left(St^{(E)}|Y^{(E)}\right) = \frac{P\left(St^{(E)}\right)}{P\left(Y^{(E)}\right)}$;
3. $P\left(St^{(E)}|Z^{(E)}\right) = 0$;
4. $P\left(St^{(E)}|Y^{(C)}\right) = P\left(St^{(E)}|Z^{(C)}\right) = P\left(St^{(E)}\right)$ with counterfactuals as above.

Under the condition $\left(St^{(C)} \subset St^{(E)}\right)$ the relationships are more complex

1. $St^{(C)}) \leq P(St^{(E)}) \leq P(Y^{(E)})$ as assumed above;
2. $P\left(St^{(E)}|Y^{(E)}\right) = \frac{P\left(St^{(E)}\right)}{P\left(Y^{(E)}\right)}$ as above;
3. $P\left(St^{(E)}|Z^{(E)}\right) = 0$ by definition;
4. $P\left(St^{(E)}\right) > P\left(St^{(C)}\right)$ due to the superset condition;

5. $P\left(St^{(E)}|Y^{(C)}\right) = 1$ if a patient recovered spontaneously under the control, they will surely recover under treatment;

$P\left(St^{(E)}|Z^{(C)}\right) = \frac{P\left(Y^{(E)}\right) - P\left(Y^{(C)}\right)}{P\left(Z^{(C)}\right)}$ as any excess recoveries relative to the control are treatment recoveries.

15.5.3 Pattern of spontaneous recovery (Sp).

1. $P\left(Sp^{(C)}\right) = P\left(Sp^{(E)}\right)$
2. $P\left(Sp^{(E)}\right) \leq P(Y^{(E)})$ as above;
3. $P(Sp^{(C)}) = P\left(Y^{(C)}\right)$
4. $P\left(Sp^{(C)}\right) = P\left(Sp^{(E)}\right)$
5. $P(Sp|Z^{(E)}) = 0$;
6. $P\left(Sp\middle|Z^{(C)}\right) = 0$.

If among the set of covariates we identify a variable with a pattern identical to that of the hypothetical property, this variable can be considered a candidate for a role of a marker for the property, which has to be validated in appropriately designed studies. Given an effective marker, it is possible to identify the patients-carriers of this property, thus opening a door to discovering the biological structure of the target property. This would, in turn, have significant clinical implications (See: Section 17).

16. Research implications. In clinical research, epidemiology, and pharmacogenetics, the discovery of genetic, biochemical, physiological, etc., factors critically affecting the effectiveness of treatment requires, in one way or another, contrasting "non-responders" against "responders." The methodology can be sophisticated, but in principle it is always about identifying a factor (let us call it F_E) which is present among "responders" and absent among "non-responders" (or vice versa). This serves a basis for a hypothesis about a causal role of this factor (or its absence) in the treatment response. Our model shows that this approach implicitly contains uncertainty, making the result of analysis potentially imprecise or misleading.

Based on clinical, epidemiological, and experimental data, our model shows that in fact the "responders," i.e., patients with a positive outcome, are a mix of those with treatment-induced recovery ("true responders"), spontaneously recovered, as well as patients with both capability for spontaneous recovery and sensitivity to treatment. Each of these fractions is always smaller than the proportion of "responders," except for special cases when $P(St^E) = P(Y^E)$ and/or $P(Sp) = P(Y^E)$. This situation makes a search for a factor F_E infeasible. In the frame of this approach, a single factor F_E is thought to be associated with a positive outcome, and $\overline{F_E}$ associated with a negative outcome, corresponding to patient sets

$$F_E = Y^E; \text{ and } \overline{F_E} = Z^E.$$

The heterogeneity of "responders" postulated in our model dictates the necessity to seeking for at least two lines of comparison. In the frame of our model

$$F_{Sp} = Sp; \text{ and } \overline{F_{Sp}} = Y^E \cup Z^E - Sp.$$

Note that

$$Y^E - Sp \subset Y^E.$$

The latter is important for screening for markers (See: Section 15). Similarly,

$$F_{St}^E = St^E; \text{ and } \overline{F_{St}^E} = Y^E \cup Z_E - St^E; \text{ and}$$

$$Y^E - St^E \subset Y^E.$$

Space limitations of the paper does not allow for thorough analysis of quantitative aspects of these relationships.

17. Clinical implications. In current clinical practice, if it is known that treatment E is associated with higher percentage of positive outcomes than other treatments, it tends to be prescribed to all patients with a target disorder, except those with contraindications.

Eventually, the discovery of markers for spontaneous recovery Sp_D from a disorder D, and for sensitivity St^E to treatment E, would change the strategy of treatment of this disorder. In a perfect scenario, treatment E should be prescribed only to patients sensitive to it. It should not be prescribed to patients capable of spontaneous recovery and to those for whom this treatment is expected to not be effective. For the latter, it will save precious time and will allow them to be immediately treated with an alternative treatment strategy. The patients prone to spontaneous recovery, as well as the patients for whom treatment E is reliably predicted to be not effective will avoid adverse effects of treatment E because of the elimination of unnecessary treatment.

In reality, clinical practice is much more complex, and there could possibly be important clinical considerations leading to broadening the pool of patients prescribed the treatment, but a primary target for this treatment will be narrowed and defined. This will alleviate the difficulties in making clinical decisions and will be an important step towards individualization of treatment and increasing its effectiveness and safety.

Conclusions

- Switching focus from "risk reduction" to "chance for recovery" unveils new possibilities for studying the effectiveness of treatment. The acknowledgement of the phenomenon of spontaneous recovery leads, with logical necessity, to the concepts of capability for spontaneous recovery and sensitivity to treatment.
- A conceptual, structural and logical model of treatment effect in which an outcome is a function of the capability for spontaneous recovery and sensitivity to treatment is proposed. The model sets a framework for the selection of a statistical approach and models from the family of Bayesian networks with hidden variables.
- The described relationships between the observed outcomes and the hypothetical variables, as well as the constraints required by the model, may reflect our prior knowledge about the system. The estimates for the variables of "capability for spontaneous recovery" and "sensitivity to treatment" obtained through the model can be used as the priors for Bayesian analysis aimed to detect the hypothetical variables.
- The described relationships between the observed outcomes and the hypothetical variables, as well as the constraints required by the model, allow for screening for markers for spontaneous recovery and sensitivity to treatment.
- The proposed model of the treatment effect implies a change in the strategy of prediction of treatment response. Eventually, the implementation of the discussed model will be a further step towards individualization of treatment. It will increase the effectiveness of treatment, reduce risk of adverse effects via eliminating unnecessary prescriptions and facilitate studying the biological and physiological mechanisms of treatment effect and the process of recovery.

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