How to Think About "Risk" Part 1

Introduction

Hello and welcome to the n-Lorem podcast series, a podcast series devoted to nano-rare patients. I am Stan Crooke, founder, chairman and CEO of n-Lorem, and your host for the podcast series.

Today, we begin a complex, but extremely important topic: risk. In fact, we will discuss a number of topics related to risk. We will talk about how scientists and risk experts think about risk, how risks are perceived by most people, the factors that influence our reactions to perceived risks and how our failure to think logically about risk harms us. I will then do my best to provide a framework that we can all use to consider risks more effectively. Lastly, I will explain why it is important for nano-rare patients and families to be thoughtful in their approach to thinking about risk. Having a pathogenic nano-rare mutation imposes a harsh high-risk reality on patients and families that forces complex risk/benefit decisions that can include the decision to be treated with an experimental ASO. I know that the topic we are tackling can be daunting, and most think they understand risks and how to think about what risks to take. I would tell you that it is in your interest to accept the possibility that the way you perceive risk and that way you think about risk may be flawed, and a failure to develop a more logical approach to risk could do you and your loved ones harm.

Why Nano-Rare Patients and Families Need to Think Effectively About Risk

So, why do nano-rare patients and their families need to think more effectively about risk? All humans face the hazard of a pathogenic mutation. A hazard is an event that can do harm. A risk is the likelihood

of a hazard occurring and a consequence is the impact on a person, organization, system, of a risk that is realized.

In the case of a nano-rare patient, the hazard of a pathogenic mutation that is extraordinarily unlikely has been realized and the consequence of that unlikely risk is substantial. Though different people have different ways of thinking about such things, the truth is that nano-rare mutations are simply the laws of probability at work-just bad luck really. But the realization of that extremely unlikely probability means that many negative consequences are likely to be encountered and we see those as symptoms that worsen and change over time. Tragically, the patient and family must deal with these consequences as they manifest and though they all derive from a single piece of genetic bad luck, all the symptoms demand individual decisions and responses.

At the most fundamental level then, a pathogenic nano-rare mutation forces multiple risk/benefit decisions on the patient and family. Do I just give up? Do I try to find out what is wrong? Do I invest in diagnostic and therapeutic efforts? Which approaches offer the best hope for diagnosis and treatment? All of these types of decisions are fraught with risk and intense emotions, but at some point, the person accountable for these decisions must try to separate from these intense emotions and make the best decision as logically as possible. And everything is harder and worse because most people have no idea how their body works or how medicines work. Then, we must put our fate and the fates of our loved ones in the hands of people we really do not know, just because those people have credentials that give them the right and the obligation to help patients and families through these terrible, terrifying decisions and processes.

In previous “lectures”, I have tried to build your knowledge base from the ground up. From what is a chemical, to what is a disease, and beyond. All of that was to help you prepare to be thoughtful, rational,

informed decision makers. My goals for the Risk and Risk Management lectures are to help you better understand risk assessment and to provide a framework that I hope helps you make better, more rational decisions.

Key Point: The risk of an extraordinarily unlikely pathogenic mutation that all of us face is actually realized in nano-rare patients.

Key Point: The consequences of a pathogenic nano-rare mutation are severe and result in the need to make multiple complex risk benefit decisions.

Risk Vignettes

To demonstrate how we think about risks, and how the way we think is influenced by experience and many other factors, and how much harm humans have done to themselves because they think poorly about risk, I will walk you through several historical risk vignettes.

Infectious Diseases

Given our recent experience with Covid, let's begin with infectious disease.

Throughout most of human history, infectious diseases accounted for a sizeable fraction of all deaths and most deaths in childhood. In the U. S. in 1900, infectious diseases accounted for 800 deaths per 100,000 people, slightly less than the total deaths per 100,000 people from all other causes, that is to say that infectious diseases accounted for about half of the people who died in the US in 1900. As a result of advances in public health, including clean water, draining swamps, sewage control, and all of those sorts of things that we take for granted today, the deaths from infectious diseases declined by 3% a year for the next few

decades. Then, beginning in the late 1940s, the introduction of scores of new anti-infectives and better diagnostic methods led to a decline of almost 9% a year in infectious disease deaths. Today, it is a rare tragedy to lose an otherwise healthy child to an infectious disease, but historically, two out of every five children born died of infectious disease before they became an adolescent. But infectious agents are constantly evolving and there can be unexpected epidemics, even today. For example, in 1918, deaths due to infections spiked because about 675,000 Americans died of the Spanish flu, which actually began in Leavenworth Kansas. At that time, the US population was 105 million. Then again, in 1957- 1959, infectious disease deaths spiked because 1.1 million Americans died due to the flu pandemic in those years. Covid deaths during the most recent epidemic also accounted for about 1.1 million deaths in the U. S., but our population was about 340 million. So, on a per capita basis, both the Spanish flu of 1917-18 and the 1957-59 flu accounted for more American deaths than Covid. Moreover, till vaccines became available, viruses like polio, measles, RSV and others terrified families.

Despite the obvious menace of infectious diseases through the ages and two particularly lethal flu epidemics, not until the Covid epidemic, did we initiate a policy of quarantining the healthy that led to the world's economy being shut down for almost two years. Nor did the notion of wearing masks to avoid infection, staying home from work and school to protect others or special hand wash stations assume any prominence. Why was our response to Covid different when we have been living with infectious disease throughout our human history?

Smoking

Humans often choose to engage in activities that harm them, and there is no more lethal example than smoking.

In 1950, half of American men and about one third of American women smoked, and many, if not most, were heavy smokers. Over the next three decades or more, a war raged between scientists and physicians and the tobacco industry, lobbyists, and many individuals. Mountains of data showing that smoking is catastrophically bad for health, and that about two thirds of smokers would actually die from a smoking related disorders were presented. Anecdotal evidence of how bad smoking is for humans was and is as available today as then, all you have to do is think about the next person you run into who has "smoker's cough." Nevertheless, smoking increased through the 70s and 80s. In 1980 when I became head of R&D at SKB, which is now GSA, in my first all employee address, I was asked by a PhD chemist about my position on worker safety. Of course, I replied that I was committed to worker safety and then said that the single most important thing I could do to protect workers would be to ban smoking in all SKB buildings. Even amongst trained medical scientists who worried about their exposure to toxic chemicals, my comments on smoking precipitated an outraged response. Why? Even today, with taxes driving the cost of smoking through the roof and smokers having to huddle outside buildings to smoke, about 480,000 Americans will die this year due to smoking related illnesses. Why?

Automobile Deaths

Another interesting example is auto safety.

In 1950, there were about 22 deaths per 100,000 Americans due to car accidents. By 1970, the death rate due to car accidents peaked at almost 26 per 100,000, accounting for 53,000 deaths – about equal to deaths due to infectious disease in that year. Despite these terrible statistics, throughout these and the next decade, a war raged between scientists and car safety advocates and auto manufacturers, lobbyists and others. Just as with smoking, the war on one side was fought with

data and common sense and on the other with outright lies, half-truths and inane arguments like “it’s my right to die in a car if I don’t want to wear seatbelts”. Why?

Of course, I could cite other similar controversies such as climate change, or gun control, but I think you get the message.

In my view, the answer to all these whys is that we do not think rationally about risks, and we respond to many influences on our emotions including “official positions”, the emotional content of events, current vogues, news coverage, and irrational comments that facilitate our adoption of positions that are actually harmful to us and our loved ones.

A Rational Way to Think About Risk

Let’s begin with a few simple definitions.

Hazard: A hazard is an event that could be harmful.

Risk: A risk is the likelihood that a hazard will actually be encountered. So, a risk is a probabilistic statement.

Consequence: A consequence is the impact of a risk on the person, population, or system caused by a risk that is actually realized.

One of the most difficult challenges as a scientist and a physician that I have faced is to address a sort of schism in communication.

It has often been said that non-scientists seek certainty and scientists are only comfortable with uncertainty. This is often said because it is almost always true. This dichotomy is at the core of the challenges in communications between scientists and non-scientists. And in no area

are emotions more intense, the stakes higher and the failure to communicate well greater that we discuss medical issues and science. So, if we are going to have an effective conversation about risk/benefit decisions, we have the bridge that gap caused by this schism in thought processes.

Once again, I want to build from the most basic to the most complex. So, let's first agree that we are complex systems, and that when we treat diseases, we are altering complex systems called human beings. As a general rule, complex systems are constructed from less complex building blocks, and the appearance and behavior of a complex system is a composite of the appearance and behaviors of the smallest units or building blocks. What that means is that since an atom is comprised of sub-atomic particles, its appearance and behaviors must reflect the properties of the sub-atomic particles. Or on a larger scale, since we are made up of cells, our appearance and behaviors must reflect the properties of cells. Said simply: complex systems are the sums of their parts, the interacting networks established by the smallest units, and the mathematical and physical laws that govern our universe.

At the sub-atomic level, modern science teaches that particles (or waves) are really just probability statements. The higher the probability of a particle being at some spot moving at some speed, the more likely the particle will be there moving at the predicted speed when we look, but it is entirely uncertain that at the particular moment we look, the particle will be where is most often is traveling at the speed it most often travels at. At more macro levels, all mutations in genes can happen, but the likelihood of a mutation occurring varies from very common to nano-rare. In short, your genetic library is a result of the probability that your parents got together, the genetic information they shared and a dizzying array of events that might happen, the likelihood of which varies from almost always to almost never.

Key Point: Our universe is governed by the laws of probability. Though it is often said that "things happen for a reason", I think good people take what life gives them and make the best of it. Irrespective of what one may believe, when assessing risk, one needs to think probabilistically. There are no guarantees, there are only high and low probability events.

Key Point: The phenotype we display at any moment is a probabilistic outcome reflecting current environmental conditions and all the phenotypes we have displayed in the past.

The 80/20 Rule

The 80/20 rule posits that the return on investment to achieve 80% of a maximum effect is usually justified, but the investment to achieve greater than 80% rises exponentially, making the return on investment unattractive for greater than 80% of max. Though emotionally we all want zero risk, trying to zero risk any system is simply not justified, and in fact, not possible. Even for control of infectious disease, the goal is not to immunize 100% of humans, but to immunize a sufficient fraction of the population to achieve herd immunity.

Key Point: Zero risking anything is essentially impossible. We must be comfortable with reducing the risk as much as possible with a sensible investment.

Consequences

Consequences also must be considered probabilistically. Any mutation may have consequences that range from no effect on health to death. Of course, a single mutation may result directly in several consequences, but effects that are secondary to the basic consequences can also happen. To help you understand this, let's take a specific

example. Let's say that a pathogenic nano-rare mutation occurred in an ion channel. Based on experience with mutations in ion channels, it is probable that symptoms such as epilepsy and movement disorders will manifest. Therefore, in a patient with a mutation in an ion channel, we would guess that it is almost certain that the patient will experience both seizures and movement disorders and the consequences will be severe. Once again, based on experience with ion channel mutations, it seems that there may be about a 50% chance that G.I. issues will manifest and that, though they will not be life threatening, they will have a negative impact on the quality of life of the patient and family.

Once again based on experience, it is highly likely that the patient will manifest developmental delays, so we would probabilize developmental delays at more than 90%, but we would have a difficult time guessing how severe they will be and what type of developmental issues will manifest. Nor do we know whether developmental delays are directly due to the mutation or are secondary to seizures, or both.

Now, let's dissect what we just did. First, we gathered all the information or evidence available about the risks posed by the mutation. Then we created a knowledge base in which we assembled the basic information in an organized fashion that facilitates our ability to make judgements about consequences. Then, based on what we learned, we made probabilistic predictions about the likelihood and severity of various risks. We can now begin to predict the future in a way that helps us decide how severely affected the patient will be, how rapidly the manifestations will progress, which manifestations are most likely to have the greatest impact and determine if there is risk of death in the near term. In short, we now understand the patient and the likely course of events in the future. This then supports an informed judgement about how desperate the need for treatment is and how much risk we are willing to take to have the patient treated.

Key Point: The process we follow to assess risk is to gather as much information as possible, organize the information in a way that helps us make risk benefit decisions, define the probabilities of various risks as well as possible, given what we know, define the potential consequences of each risk, and define the likely severity of each risk and probablize the consequences.

The process we just went through should make you uncomfortable. All of us want certainty about our health and our future, or the health and futures of our loved ones, but futures and health are uncertain and difficult to predict. And a pathogenic nano-rare mutation makes health and the future even more unpredictable. Nor do any of us enjoy picking between several bad choices, but a pathogenic nano-rare mutation leaves us only choices that are unattractive. Nor is it easy for any of us to separate emotion from reason when our health or the health of a loved one is at issue. Nevertheless, if we are to make the best decisions available, we must be data-centered and rational, and we have to weigh a wide range of factors. For example, suppose one “expert” told you that he could have an ASO ready in 12 months guaranteed, but the acknowledged father of the technology said that he could not guarantee an optimized ASO that was maximally likely to work and be safe at all, and certainly not in 12 months. Which choice would you make and why? Well, that might depend on whether you think finding an optimal ASO is easy or complex and what you think of the credentials of the two “experts” and their track records.

Key Point: Given that certainty cannot be achieved, and the presence of a nano-rare mutation presents only unattractive options, to make effective decisions, we must get comfortable with uncertainty, and we must endeavor to separate emotions from what may be achievable rationally.

Now how do you handle the decision to treat? Exactly the same way. Gather facts, collect the facts about the potential treatment into a format that you can use, ask appropriate questions and make a judgement about the risks and potential benefits, being as unemotional as you can be.

Getting Serious About Risk Benefit Evaluations

Now, let's begin to dig deeper. Consider this example. Out of 100 patients treated with an experimental medicine for a year, one experienced a drug related adverse event. Then, in the next study, a higher dose was used, and three patients experienced the adverse event. One could say that side effects were three times greater in the second study or one could say that in the first study, one patient experienced an adverse event, while in the second study three experienced the adverse event. The former provides accurate information, but totally misleads attitudes about the risk, while the latter provides equally accurate information that informs about risk in a sensible way. However, neither is really complete. Neither approach discusses evidence of benefit or the seriousness of the adverse event. So, let's think and communicate about the results of these studies in a more effective fashion.

The parameters of interest are what is the intended therapeutic use of the new agent, what was the design of the trial, what was the dose and how long was the dosing intended, what fraction of patients took all the intended doses, what is the evidence of benefit, what was the side effect and how serious was it.

Key Point: If you are to understand the results of clinical trials whether they are in a population of patients or a single patient, you must understand a number of parameters.

Risk/Benefit Judgements

To be simple, let's say the therapeutic purpose of our new agent was to lower blood pressure. The design was a placebo-controlled trial in which 50 hypertensive patients were randomly treated with placebo, while 50 were treated with five milligrams a day of our new agent, and our goal was to treat all patients for 52 weeks. Of the 50 placebo patients, all took 52 weeks of doses, but in the treated group, one patient stopped dosing at 26 weeks for reasons unknown. The average blood pressure change from baseline in the placebo group was zero mmHg, while in the treated group, the average blood pressure dropped by 5 mmHg and the difference was statistically significant. In the placebo group, no patients experienced nausea, but in the treated group, one patient was mildly nauseated once. We may conclude that we have a pretty decent hypertensive agent. Now in the next study, the design is the same, but the dose is 10mg daily. The blood pressure in the placebo group increased by 5mmHg while the average BP in the treated group dropped by 10mmHg, so there was a 15mmHg difference between the two groups that was highly statistically significant. However, three treated patients experienced nausea once and two of those vomited, compared to zero in the placebo group. Which dose is better? Well, it sort of depends doesn't it on how high your blood pressure is and how desperate you are to lower it. Suppose that there was another new drug that lowered BP equally well, was not associated with nausea, but two patients passed out when they stood up after the second dose, but no other time. Which drug is better? What drug would you use on which patient? These are the sort of risk/benefit decisions physicians must make many times a day.

Key Point: Risk/benefit judgements are extremely complex, and they are unequivocally context dependent.

Before we leave this, let's be sure you know what statistically significant means. We want to know whether the results of these studies represent true results or could have happened by chance, and believe me, many good and bad looking results can happen by chance. To estimate how much, we should believe a result, we use statistics. Conventionally, we have decided that if 95 out of 100 times that we run an experiment that we get the same result, that is probably good enough. So statistically significant typically means that we are 95% confident that we will get the same result if we run the experiment again. Very often you will see something called a p value. A p value of 0.05 means we are 95% certain that the result is real. The lower the p value, the more certain we are. Once again, science is probabilistic. There is no absolute certainty in science.

Key Point: We use statistics to help us understand the likelihood that a result represents an approximation of biological truth. The lower the p value, the more probable the result is "true."