
An Impossible Decision—the Life Interrupted by Uncertainty

Benjamin Djulbegovic

Department of Medicine. Division of Hematology/Medical Oncology. Medical University of South Carolina. Charleston, USA

Corresponding author: Benjamin Djulbegovic, MD, PhD. Professor of Medicine. Medical University of South Carolina. Department of Medicine. Division of Hematology/Medical Oncology. 39 Sabin St, MSC 635. Charleston, SC 29425. Phone: 843-792-4879. E-mail: djulbegov@musc.edu, djulbegovic@gmail.com. ORCID ID: <http://www.orcid.org/0000-0003-0671-1447>.

The **play** tries to describe making important—life & death—medical decisions under uncertainty. While the overarching goal is to arrive at the most optimal, rational solution, the process of decision-making inherently involves human interactions – here between the patient, her husband, the doctor- fraught with emotions and navigated within immediate familiar and larger social and medical settings in the attempt to provide best possible and compassionate help to a human being afflicted with a life-threatening disease. The play revolves around the optimal choice of treatment for metastatic pancreatic cancer that a young 45-year-old woman and her family face: from not being treated to standard treatment to enrollment in various experimental studies. By covering most scientific concepts using dialogues between the real-life protagonists, the play attempts to show—and educate the broader public—how scientific progress is inevitably made because individuals (“made of flesh and blood”) have consented to participate in medical research while searching for the best solution for them as individuals. It uses a real-life example to answer an elusive ethical “triple aim”- arriving at a decision that respects the right of a person to decide as an autonomous human being, has the best possible chances to personally benefit from the treatments under consideration while contributing to knowledge that can help others in the future.

Act 1: uncertainty about the diagnosis. Act 1, Scene 2: uncertainty about treatment (doctor’s office, after biopsy). Act 2,1: uncertainty about treatment (discussion at home). Act2, 2: decision. The annotations (endnotes) provide further explanations of the theoretical and philosophical concepts that were converted into the real-life drama of a patient facing a life-threatening disease. It attempts to demonstrate the central role of uncertainty that shape these decisions calling on science to help address them. The main goal of the play is to illustrate the **applicability** of many theoretical concepts of the **science of uncertainty to real-life decision-making** to show **that they do matter** to all of us individually and collectively. The author hopes that by converting the scientific, philosophical, and technical writings into this play, the public would benefit more from this text than hundreds of other scientific articles he has written on the topic.

Keywords: Life Interrupted by Uncertainty, real-life decision making, play/drama.

Play/Drama, Received: Nov 30, 2022, Accepted: Dec 28, 2022. doi: 10.5455/ijbh.2022.10.274-302, Int J Biomed Healthc. 2022; 10(4, suppl. 1): 274-302

Real-life medical uncertainties facing a young patient with life-threatening pancreatic cancer presented as a play

Protagonists:

Wife (**Lisa**, age 45, a computer scientist)

Husband (**John**, age 45, a journalist/philosopher)

Children, **Bill** (age 12) and **Jenny** (age 8)

Harley, An adult black cat

Honda, A golden retriever puppy

Doctor, a man with gray hair, experienced looking, in his 60ties

Act 1; Scene 1, house (Setting the scene.)

(**John** and **Lisa** are celebrating their 25th anniversary together with the children and their pets. They have just paid off their home and are planning their

dream family vacation next year. They have out cruise brochures and online videos about vacation hot spots they are sifting through)

John (talking in an upbeat, enthusiastic voice): it feels great to be able to plan our vacation; there are no people I would rather be with than you guys... (**Honda**, the puppy, tugs at his pants leg as if asking if we will be coming too?)

Jenny (daughter) (as if sensing what **Honda** may have on her mind): can we take **Hurley** and **Honda** with us?

Lisa (is remembering her mom who died the year she planned the family vacation with them): I have been thinking of my mom...(Turning to the kids): I still miss grandma... but I know that she would be

happy seeing us on this cruise together...(momentarily she doubles up in pain and then the moment is past) I hope my tummy doesn't act up...over the last few weeks it has increasingly been giving me a hard time.... (**Harley**, the cat, jumps up and snuggles in her lap to distract her from her pain).

Jenny: Maybe you should get that tummy checked out. It was sore last week too.

Lisa: Yes, I have an appointment tomorrow, but I am sure it is nothing; just missing grandma.

Billy: me too... my friend Jimmy's family had a plant to honor the memory of his grandma and grandpa... let's do the same ...to honor the memory of our grandma.....

Jenny: (Nods and then says reassuringly): that would not happen with our mom and dad, right?

John: (smiling): not for a while....

Act 1; Scene 1, house¹

(**Lisa** returns home, takes off her coat, dropping her purse and computer bag softly to the floor. She gazes at her reflection in the hall mirror and then quickly composes her thoughts. The cat, **Harley**, is winding around her legs as if she senses something is about to change).

John: (hears the door open quietly, his wife is home, but something feels different, he puts down the newspaper and ignores the TV in the background):

Honey, you are kind of late today... A tough day at work? Seems that you guys are still struggling with that new software you have been working on....I, too had an unproductive day today....I was working on that piece about uncovering healthcare corruption. Things just don't make sense.²

Lisa (in a forced calm way): Remember that I mentioned I was going to see my doctor?

John (continuing in neutral voice) : Aha...was this for the stomach pain you have been complaining about lately? Is everything OK? What did the doctor say?

Lisa (still in the forced calm way): He did a CT scan...

John: CT scan...right away? Did he say why?

Lisa: He said there appears to be a "mass" in the pancreas...

John: A mass? What does that mean?

Lisa (entering TV room, still in a calm, neutral but slightly raised voice, concealing pent-up anxiety): it means I may have cancer! He sent me to see the oncologist today.

John (jumping to his feet): what!? You are kidding, aren't you?

Lisa: no, that is what the oncologist said. He said he is still not absolutely sure at this point, but to be 100% certain, he arranged for a biopsy... a procedure that consists of using a needle to get a piece of the tissue for examination under the microscope for signs of cancer... likely from the liver because he also

said the CT scan showed some suspicious lesions in the liver...

John: wait a minute! First, you said pancreas, and now you say that your liver is involved...

Lisa: the doctor said that cancer—he called it the "primary"—likely originated in the pancreas and has probably metastasized to the liver³...

John: metastasized? What do you mean?

Lisa (still calm): it means that it has spread to other parts of the body...

John: this is crazy! You are only 45 years old, beautiful, in excellent shape, and you have always maintained a healthy life-style, regularly exercising...

Lisa: well, I have been smoking for a long time, enjoying a glass or two of wine every evening and that is what he thinks may have caused "my" cancer... plus my mother died from pancreatic cancer when she was 60 years old...

John: still... you are only 45 and....you are talking as if your doctor is 100% sure that you have pancreatic cancer that has spread to the liver. Didn't you just say that he said that it is "LIKELY" that the mass he saw on the CT scan is cancer ...and that it has "PROBABLY" spread to your liver? So how exactly sure is he that you have pancreatic cancer?⁴

Lisa: He said more than 90%+sure"...and, I am scared, **John**.

John: Oh, honey (approaching **Lisa**, gently hugging her). Without thinking, I assumed that your doctor's visit was routine. I am so sorry about my obliviousness. But, at the same time, let's not jump into dark pessimism. We have always been able to look at all matters rationally. So, where did your oncologist get his "90%+" number? Out of thin air?

Lisa: No. He said he was that certain because of my stomach pain, family history, and my history of smoking and drinking alcohol... he also had seen the mass in my pancreas and the liver lesions and showed me what he had seen

John: OK, that does not mean it is cancer, though. OK ...let me talk as a philosopher/public health journalist. What about if you did not volunteer your PRIVATE information about yourself? Could that prejudice his interpretation of the CT scan? I often heard that life insurance companies discriminate against individuals who smoke, drink, have positive family cancer history, etc. I know that doctors are in the business of helping, and asking about your personal health habits has a different intent than when the insurance company asks you for the same information. They are indeed there to help, not to discriminate. Still, one has to wonder if he would have drawn the same conclusions if he had looked at your CT scan without knowing any specific information about you. How sure would he be that you have pancreatic cancer?

Lisa: a funny thing, I asked him exactly the same question. In fact, in one of my projects for one of the

large banks, the client asked us to combine specific information about a borrower with the credit score to assess the risk of default. So, I assume the same reasoning must apply in medicine as well. At any rate, he said if he had looked at the CT scan without knowing anything about me, he would be about 20% certain that I had pancreatic cancer.

John: I heard what you just explained, and, despite my educational background, I found it ludicrous. How can he go from 90+% to 20% certainty in diagnosis just because you told him something about yourself? It is as if I am not in the forest, the fallen trees don't make a sound! Shouldn't pancreatic cancer look the same on the CT scan regardless of what you told your doctor about yourself?

Lisa: Yes, I am confused, too, even with my degree in computer science. I am very familiar with risks and probabilities, but I had difficulties following him. Once I heard the word "cancer," I tuned out—all I was thinking was: "this cannot be! Am I going to die? Stay here with and for you, **Bill and Jenny...**?"

John (gently hugging his wife): Oh, honey...I wish I were there with you. I am so sorry I did not realize the seriousness of your stomachache...let's go to future appointments as a team.

Lisa (hugs **John** back gently, buries her head in his chest for a moment, and then looks up at him): the doctor mentioned something about pre and post-test probabilities....He referred to pre-test probability as a chance of having disease, cancer in my case, before even I had a CT scan. Post-test probabilities are probabilities of having a disease after getting test results. He said, for example, if I told him that I had suffered from rheumatoid arthritis, he would have estimated the probability that I had pancreatic cancer to about 50%. This is because he would have reduced his pre-test probability to 5%. But, because I told him that, in addition to my stomach pain, my mom died of pancreatic cancer, I smoked and drank alcohol, he raised his pre-test probabilities to 40-50% to calculate that he was 90% sure that I had pancreatic cancer...

John: Again, this is crazy....it is the SAME scan, but if you told him that you did not smoke or drink, your risk of cancer would drop dramatically. No wonder people lie when they apply for life insurance...rarely admitting that they smoke or drink. And, he talks about HIS pre-test probabilities... Isn't there some OBJECTIVE data that he could offer?

Lisa: I did try to make similar points. He cited some scientific articles to justify his assessment but did say that he updated – this is the term he used—the objective data with his own experience to arrive at HIS pre-test probabilities. He actually made the point that what matters is our subjective probabilities – our, or his, in this case, knowledge or ignorance— more than objective probabilities...⁵ But, he was at pains to explain that this does not mean ev-

erything is willy-nilly ...that he came up with his estimates out of thin air. The doctor tried to assure me that he combined the best scientific—objective knowledge with his subjective assessment...though, he also said that in my case, his subjective assessments are well aligned with objective data reported in the scientific literature.

John: OK?

Lisa: in fact, he showed me how he made the calculations. He used a simple web-based calculator. He first said that CT scan is about 90% true positive and 95% true negative or specific; that is, if we run CT scan on 100 people WITH pancreatic cancers, 90 of them would have the image patterns similar to mine. This also means that in 10 out of 100 patients, cancer may be missed resulting in the so-called false-negative findings. Obviously, this is not our concern, as the CT scan in my case has identified that damned suspicious mass and the liver lesions! Then, he went on to say that in 5 out of 100 patients WITHOUT cancer, their CT would also look like mine...he called these FALSE POSITIVES. This indeed means that the CT scan may have the same features in different diseases. So, when he combined all his data, he came up with the probability of about 90% that I have pancreatic cancer.⁶

He warned me, though, not to confuse what he referred to as the conditional probabilities: the probability of having my CT test considered truly "positive" if I indeed have pancreatic cancer is NOT the same— he stressed this a lot— as the probability that I have pancreatic cancer if CT scan was considered "positive".⁷

John: I see—as the chance that the rain will fall if a day is sunny is not the same as the chance that the day will be sunny if the rain falls. Did he say what other diseases may give similar CT pictures?

Lisa: he mentioned something called "differential diagnosis"— referring to other possible diagnoses that can explain my abdominal pain...He definitely thought cancer was at the top of the list. However, when I pressed him for other diagnostic possibilities, he said that sometimes, particularly in people with autoimmune diseases such as rheumatoid arthritis...

John: I know rheumatoid arthritis—my aunt Karen had it! But you have never shown signs of this before.

Lisa: Apparently...some people with rheumatoid arthritis or other similar conditions can develop a rare condition called IgG4-related disease, which may mimic pancreatic cancer on a CT scan.

John: so, maybe you have one of those conditions, and it is not cancer!? You just said a CT scan can be either true or false positive....so, if it is false positive, you cannot have pancreatic cancer!⁸

Lisa: it is all about probabilities. The doctor said he couldn't say with absolute, 100% certainty that I

had pancreatic cancer. But, he said because he estimated my pre-test probability of pancreatic cancer at 40% when he combined this number with true and false positive numbers of CT scan using the so-called Bayes theorem, he arrived at the probability that I have pancreatic cancer of 92%. If, based on the information I told him, he were to reduce the pre-test probability that I had pancreatic cancer, my final probability–post-test probability– that I have pancreatic cancer would be much lower. For example, if I had never smoked or drunk alcohol, no one in my family had died from pancreatic cancer, nor had I felt any stomach pain, my pre-test probability would be only 1.5%, which would translate into the post-test probability of pancreatic cancer of about 20%–21.5%, to be exact.

John: This all looks to me like a wild guessing game. I am afraid that your doctor is coming up with these numbers– these crazy pre-test probabilities– out of thin air. Why would he say these things before he even does a biopsy?

Lisa: He admitted as much, which is why he arranged for the biopsy. The entire purpose of the biopsy is to increase certainty in diagnosis. In fact, as I was leaving, I overheard him explaining my “case” to his student, saying that in situations like mine, you have to think along the lines: “tumor is a rumor, tissue is an issue, cancer is an answer.” So, it seems that doctors, like the rest of us, use mental shortcuts – heuristics–in their reasoning process. So much for formal probability calculations, we spent so much time fretting about !!⁹

Act 1; Scene 2 , doctor’s office, after biopsy¹⁰

(**John** and **Lisa** in the doctor’s office waiting for the doctor to discuss the results of the liver biopsy...)

John (nervously getting up and sitting back into the chair with the paper and pen in his hands; he will be taking notes throughout the discussion): This is unacceptable...we have been waiting here for more than an hour... it is so humiliating. If it were not for you, I would have left long ago. And, frankly, this is so disrespectful... leaving people so helpless and vulnerable to wait so long... being so blind and deaf to their needs. The news we came to learn are maybe the most important news we will ever face in our lives, and yet I feel they are oblivious to our needs...

Lisa: don’t be so harsh; he is likely too busy helping other people...or there was an emergency

John (cynically): yes, double-booking to make more bucks!

Lisa: don’t be so cynical! He may want earnestly to help as many people as possible, but there are only so many hours a day...

(**Doctor** entering the office)...

Doctor: Hello, I am **Doctor** Williams. Sorry for keeping you waiting, but I had an emergency to address...

John: we understand....thanks. (**Lisa** introduces him and the doctor)

Doctor (in a friendly voice, conveys an impression of understanding of the situation, trying to create as relaxed an atmosphere as possible): Let’s look at the results from your biopsy a few days ago... I’d like us to go over them together.

John/Lisa (almost in the same, raised, anxious voice): Thank you, doctor. What did the biopsy show?

Doctor (sitting in his chair pauses before speaking in a sympathetic voice, looking at and addressing **Lisa**, the patient)¹¹: Unfortunately, I don’t have good news...as we thought it is pancreatic cancer...

Lisa: with spread into the liver?

Doctor: I am afraid that is the case...

(Uncomfortable silence, **Lisa** displaying signs of fear on her face....she is shaking and then shakes her hair and forces a smile)

Doctor: you must have already talked about what you may have, probably read some information on the internet, perhaps talked to your friends... Do you want to share your thoughts with me? How would you like to have this conversation?

Lisa/John (in unison): doc, tell us like it is!

Doctor: before I do it, would you mind telling me what you know about pancreatic cancer?

Lisa: I know it is a death sentence! That I will die soon....(starts crying, raising her hands to her face...)

Doctor (offering a tissue in a compassionate, supportive voice): Let me start by saying that while I will always try to be honest with you in discussing all the issues related to your health care, not all is lost...there is much we can do for you.

Would you like to hear about the available treatment options?

Lisa (composing herself, clearing up tears from her face): yes, please.

Doctor: how much do you want to know? Some patients like to know “everything”; others prefer to learn only key facts of importance for planning their lives ...

Some patients want to know the “numbers,” i.e., estimates of what diagnosis may mean in terms of what, in technical terms, is referred as “prognosis”...

John (in a somewhat angry voice): we know what the “prognosis” means! It means how long **Lisa** is given to live! And, yes, we want to know ALL NUMBERS!

Doctor (calmly addressing **Lisa**): **Lisa**, is that what you want, too? Do you want me to present you with all the available options so we can decide what we think would be best for you?¹²

John (in an angry voice): it is not “we,” doctor. It is **Lisa** and me– and our kids– who are facing these life & death decisions! What do you care!?! (turning his head away)

Lisa (still with tears in her eyes): **John**, please! Let’s have Dr. Williams explain. Dr. Williams, are

you OK if we record this conversation?

Doctor (continues in a calm voice, looking at and, in turn, acknowledging both wife and husband): look, as it may be difficult to appreciate at this moment, I do care...after all, I went into medicine to help people...and trust me, I understand the frustration, predicament, and difficulties of the situation in which both of you and your family unexpectedly found yourself... From living a fulfilling life, looking ahead to raising your kids and all life's excitement to, for no fault of yours, finding yourself in this situation...in the place, you really don't want to be...

And, by all means, please record this conversation and review it later in the comfort of your home...I was about to suggest it myself, too.

(**John** takes iPhone from his pocket to record the conversation)

Lisa: if I only had not smoked¹³...

Doctor: **Lisa**, you cannot blame yourself for getting cancer...while you should immediately quit smoking, there is no way to say that if you had not smoked, you would not have gotten pancreatic cancer. You are not to blame, no one, in particular, is at fault here...I suggest we proceed with the plan to make the best out of this situation that none of us wanted to be in? Please do understand that I will be with you each step of the way, whatever we eventually may decide to make together. Do you want me to tell you about the options you...we are facing?

Lisa (slowly recovering from the stress, looks composed): yes, please

Doctor: a good way to think about this is in terms of 3 options: “what happens if I do nothing, just let disease takes its course...?” What...

John (curtly): of course, we want to do “something”! That is why we are here, doctor!

Doctor (ignoring the husband's remarks):... “what happens if I do something?”

What are the possible “good” (benefits) and “bad” (harms) effects of treatment that we can offer for your pancreatic cancer...

Doctor (addressing **Lisa**): should I go over all options? What happens if you take no treatment...As you have already mentioned, you read about the course of pancreatic cancer and how it affects people's lives...both in quality and longevity...Are you interested in knowing the “numbers”- statistics about people diagnosed with metastatic pancreatic cancer?

Lisa (quietly, whispering, making eye contact with her doctor, and then reaching out to grasp her husband's hand): yes, we want to know¹⁴

Doctor: to place all decisions we are facing in context, let's discuss the first option. When talking about prognosis, it is important to know that we can never know what will happen in individual patients like you. We say prognosis in individual patients is “unknowable.” All we can know is what happens to a

group of patients like you months or years down the line. It is like considering what happens to a group, a cohort of people, when they are born...no one lives longer than 150 years¹⁵, but some will live more than 100 years. Others, unfortunately, die soon after they are born. On AVERAGE, however, people live about 78 years in the USA. But, this is learned only after the fact, by counting who lived, for how long, and who died...At the outset, however, like at the time of diagnosis in your case, we can only talk about the probability of surviving—often expressed as some percentage of survival—for a group of people after a given time period.

Lisa (quietly): hopefully, scientific medicine can offer more assurances than alternative medicine, doc

Doctor: I am trying to be as honest as possible with you, **Lisa**. As you go through the treatment, beware of the guarantees ...you will often be told to try this or that...that all sorts of so-called natural products of so-called alternative medicine can cure your cancer. Scientific medicine, despite its imperfection, uses tools, processes, and methods designed to help us come closer to “evidential truth” than any other way of knowing. If you have to bet, please bet on scientific medicine...

However, and THIS is important, just because I cannot guarantee with the absolute certainty what will happen to you...because such a scientific inference is theoretically impossible... this does not mean that rational and optimal decisions—even under uncertainties- cannot be made. Unfortunately, these days there are a lot of purveyors of mis- and dis-information¹⁶ deliberately spreading misleading or biased information—preying on the people's vulnerability, typically by exploiting legitimate scientific uncertainties.

But, just because we cannot scientifically guarantee that the Sun will rise tomorrow- the theoretical probability is less than 100%- this does not mean that we cannot make rational and pragmatically useful decisions despite all uncertainties we face¹⁷...

John: yes, doc, but you keep talking about probabilities of surviving, uncertainties, group of patients.... Sorry, I am familiar with the probabilities that, in all honesty, I've always found confusing. In the end, the person is either alive or dead. **Lisa** cannot be “probably” alive...like 50% alive?

Doctor: that's a very astute and insightful remark! That is why much of what we are discussing is indeed confusing... But, please understand that, perhaps, paradoxically, by acknowledging uncertainties, science creates a clarifying strategy to help with problem-solving and decision-making¹⁸, including for the situation **Lisa** and you are facing. You have probably heard of paradoxes in science ... One such paradox is the famous Schrodinger's cat.

Lisa, would it be OK for me to explain it? If at any time this—or anything else—I said makes you uncomfortable, please let me know, and I will either stop or reframe the discussion. At the moment, I am assuming that you have allowed me to explain the nature of the problem “like it is.”

Lisa (quietly): yes, please proceed, Dr. Williams.

Doctor: Schrodinger, a quantum physicist, famously imagined a cat in a box and invited us to assess – guess—if the cat in the box is dead or alive. BEFORE the box is opened, Schrodinger argued that we could only estimate the probability that the cat is alive, like the cat is 50% alive, as you suggested.¹⁹ But, once we opened the box, we would know whether the cat was dead or alive. Imagine now 100 cats, or in our case, 100 patients diagnosed with pancreatic cancer. At the diagnosis, it is IMPOSSIBLE to say which INDIVIDUAL patient will be alive or who will die as months or years pass....But, for the GROUP of patients, we can say that about 2% of them will be alive 4–5 years after diagnosis, or that 50% of people will die within 3–6 months of diagnosis if no treatment is given²⁰...So, this is what we can expect if no treatment is offered...again, this is the average for a group of patient like you, but we cannot say what will happen to you with certainty...

Lisa (quietly, with eyes wide open): so, I have only 3–6 months to live if no treatment is given to me?

Doctor: on average....

Lisa: yes, if I am that sort of “average” patient who does not exist! But, I am a real person, made of flesh and blood- I am not interested in “averages”, Dr. Williams.

Doctor: as I said, I will always try to be honest with you...while, of course, I understand where you are coming from, the average estimate is, actually, the best we have...Most if not all, medical decisions are based on evidence obtained from the GROUP of patients medical researchers have studied. Using these group averages²¹, we then extrapolate our inferences from the group of patients to individual patients like you.

John: Yes, but we keep hearing about “personalized medicine” and “precision medicine”—isn’t that one of the scientific initiatives of President Obama—including then Vice-President Biden’s Moonshot Initiative – to develop drugs to target every patient differently according to their specific disease characteristics?²²

Doctor: that is correct, and we are increasingly getting better at accomplishing precisely that- to tailor treatment toward each individual patient. That is, we are increasingly better equipped to slice the large group into smaller groups- subgroups- from the large group of patients with the umbrella disease such as cancer to many more types of cancers. Not so long ago, we could only say that the patient had cancer by looking at the tissue under mi-

croscope...these days we can further differentiate the cancer cells according to their other features... such as molecular and immunological markers...

We use different techniques to individualize our estimates of prognosis and treatment effects, but we always depend on the evidence obtained from studying groups or subgroups of patients similar to you and your cancer. Still, what will happen in any specific INDIVIDUAL patient remains inherently unobservable and uncertain²³...

John (still showing signs of displeasure, almost rudely interrupting): so, what can you tell us about **Lisa**’s disease then, doctor? Is it “inherently unobservable and uncertain”, our flesh-and-blood version of Heisenberg’s famous uncertainty principle – to refer to my college physics day...

Doctor (continuing unperturbed, ignoring increasingly hostile husband): as I said, if **Lisa** decides not to have treatment, but she spends whatever remaining days she- any of us, really, can have- with her family, we are talking about 3–6 months, ON AVERAGE...

John (continuing in a hostile manner): again, average, average ...enough with averages!

Doctor (turning to the husband): I understand why you are upset... This is all hard to process... but I am getting an increasing impression that you are not pleased with how I want to discuss the issues with **Lisa** and you to formulate the management plans. If that is the case, would you want me to refer you to another cancer specialist?²⁴

Lisa (trying to remain calm in the increasingly tense situation): no, Dr. Williams, we are happy with you...it is just, as you can imagine, and to put it mildly, this is not a pleasant situation in which we found ourselves...emotions run high ...I apologize for the way **John** has just reacted. (She hastily rubs away a single tear as she struggles for composure)

Doctor: no need for apologies. Indeed, I should apologize for my limitations in explaining how we might come to an acceptable agreement on the way forward. It is only natural that both of you feel the way you do. When the situation is “unpleasant,” as you say, fraught with uncertainties and scary outcomes, it is only natural to see the world through an emotional lens. My job, however, is to respect your emotions—because they drive a lot of what you value in life- while making sure you make your choice in the most informative and considered ways possible.

John (more composed but still visibly tense): what do you mean by **Lisa** having to make her choice? Can’t you just tell us what is best for **Lisa**?

Doctor: I wish I could.²⁵ And, sometimes, there are obvious choices when it would be foolish – irrational—not to pursue them. But, decisions for many diseases—certainly for pancreatic cancer- are not that obvious. Instead, they involve trade-offs, with some good -beneficial- and some bad -harmful- ef-

facts.

John: well, can't you recommend treatment with benefits outweighing risks? Like, when we applied for the mortgage, we decided the best deal for us based on the financial risk. It seems to me that is how it should work in the case of medical treatment, as well.

Doctor: yes, in principle, this is how it works in medicine, too. But, as you realize, the stakes are much higher, and trade-offs are not single dimensional as in the case of the money – although, I should mention that economists often compare different governmental policies, including health policy, by converting all options and health consequences into dollars....they call it cost-benefit analysis....

John: ah, I think I have heard about it. They even-disgustingly- put the \$ value on the human life. I believe the Congressional Budget Office (CBO) assumes that the life of each of us is worth \$10 million before a particular law, environmental, or other policy the Congress passes is implemented in practice.²⁶At least, that is what I was told by a friend who works in the government.

Doctor: I think you are correct, but as you also implied, policy decisions are different than decisions we make in individual patients like **Lisa**...

John: Really, doc? Let's not kid each other...we all know how huge health care costs are, particularly cancer drugs. Isn't the inability to pay for health care a leading cause of bankruptcy in the US?²⁷ We hope that our insurance company will not create additional problems and that they will approve all treatments that you eventually recommend for **Lisa**. Otherwise, we will have to emigrate to Europe... (trying to make a joke)

Doctor: I sympathize with all your concerns, but let's deal with these issues when and if- they pop up. And, not all is bad about the US health system... for one, we have access to new drugs much earlier than our European colleagues...But, based on our conversation so far, you definitively would like to be treated.

(Turning to **Lisa**): is that correct, **Lisa**?

Lisa: yes.

Doctor: should I then tell you about the available treatment options?

Lisa: yes. Dr. Williams. Please hold nothing back. I need to know all the good and bad aspects of the treatment options that are available to me.

Doctor: thank you for making a job easier for me, **Lisa**. I assume you want **John** to be an active participant in the decision-making?

(After **Lisa** nods affirmatively, the doctor continues) Indeed, I will try to provide you with all information so that when all is said and done, you can make as informed a decision as possible....I will try to respect your autonomy, but I hope you will con-

sider the entire process as a partnership. And allow me to work with you so that together—in what we refer to as “shared decision-making”—we can arrive at the optimal decision by paying close attention to all the things that matter most to you. Would this be ok with both of you?

Lisa/John: both nod affirmatively.

Doctor: Let me start by providing you with some information about your cancer. It is called adenocarcinoma, the most common form of pancreatic cancer. Although, because your mother had it, it is possible that your cancer may have a specific genetic signature ...

Lisa (suddenly becoming more anxious): a genetic signature? Do you mean I inherited it from my mom? Are my kids at risk? Is there something preventative we could do for them now?

Doctor: first, let me explain that all cancers are “genetic” in the sense that it is some mechanism, typically something in our environment—viruses, toxins, tobacco etc—that ultimately affects genes causing them to mutate i.e., change their chemical structure. Most of the time, these changes are acquired because of external conditions and are not inherited. But, occasionally, some affected genes are passed through generations and can cause cancer in offspring...pancreatic cancer, in your case. However, we found no evidence of a specific genetic signature for this in your case.

Lisa: that is a relief—at least one source of the unknown is removed, and we don't have to worry about our kids! Right, **John**?

John: yes, right indeed.

Doctor: to continue, your cancer showed typical features of adenocarcinoma, which, because it has spread to the liver, cannot be surgically removed, which might have been possible if the cancer had not spread to the liver. The consequence of this is that you require what we call “systemic treatment” – that is, treatment with chemotherapy...

Lisa: oh, those poisons...can you explain more?

Doctor: These drugs can kill cancer cells but may also have some unpleasant, adverse effects...

Lisa: like what?

Doctor: I like to outline the benefits and harms of treatment separately ...what do you want to hear about first?

Lisa: let's talk about the bad aspects of treatment first. (**John** nods silently in support of his wife's choice.)

Doctor (rattles in a well-rehearsed, hurried, impersonal, matter-of-fact, almost automatic manner²⁸): ok.

The treatment I recommend for you goes by the acronym FOLFIRINOX, which consists of drugs called (fluorouracil plus leucovorin, irinotecan, and oxaliplatin)²⁹ (hands a brochure to **Lisa** – written information about chemotherapy)

First, to simplify, let me explain that chemotherapy works by interfering with cancer cell growth. However, chemo does not exclusively attack cancer cells. It also may harm normal cells, particularly those that generally grow fast, such as blood cells, hair, and cells in our gut. As a result, the chemotherapy preferentially attacks these cells ...often, but not always, these drugs can cause people to feel sick and have nausea, or, vomiting...because they affect blood cells, your white or “fighter” cells that defend you against infections can drop putting you at risk of developing infections, and these can be serious. To make sure we catch this, we usually test your blood regularly.

Lisa, during treatment, it will be very important that you tell us how you feel. We will ask you to regularly measure your temperature, and if you have a fever, we may give you antibiotics or perhaps even admit you to the hospital. We will provide you with medications to stimulate the growth of white cells to prevent further infections...if your red blood cells drop, we may give you red blood cell transfusions... if your platelets—cells that make blood clot adequately—drop, or if you start to bleed, we may need to give you a transfusion of platelets. You will likely lose your hair...diarrhea can also occur with this chemotherapy, which we will also manage, but if it becomes too severe, we may even stop the chemotherapy...usually only temporarily. This chemo can also damage nerves causing people to feel numbness, pain and tingling of the arms, legs, fingers, and toes... some people may have increased sweating, flushed skin, watering eyes, stuffy nose, or redness, or pain or peeling of palms and soles... other adverse events are also possible...

As you can imagine, treatment is complex. It will require frequent visits to the clinic, perhaps even admission to the hospital if complications occur...In fact, for the foreseeable future, your life will revolve around visiting us...we will be your best new friends (doctor tries to smile as he remembers that he is not alone and need to verify if his monolog is being understood)...But, the most important thing for you to understand is that these are adverse or side effects that COULD happen, not that they WILL necessarily happen...People of your age usually tolerate this treatment well.

Lisa: sorry doc, this is too much to process. Can I die from chemotherapy?

Doctor: possible but unlikely...I suggest you review all the information I briefly outlined for you in detail when you go home...the drugs, side effects...

Lisa: how unlikely?

Doctor: I would say less than 1%— this usually happens to people who are much older than you and are sick from other diseases, so they cannot tolerate chemotherapy well...

Lisa: will my hair grow back?

Doctor (trying awkwardly to make light of it): it will grow back much more vital and be more beautiful than before!

John (interjecting): what about benefits, doc?

Doctor: yes, thanks for asking. Treatment does help people live longer than if you don't receive treatment...

John (tersely): how much longer? Can you cure **Lisa's** disease, doc?

Doctor (continuing in a calm voice): unfortunately, as we noted earlier, we cannot cure pancreatic cancer...but, treatment does help people live longer, on average, for about 6–9 months longer³⁰ over no treatment...or, about 11–12 months vs. 3–6 months with no therapy...

John: only extra 6–9 months! I can't believe you even call this “benefits”, doc! On the top of the long list of those horrible side effects...

Doctor: I understand, and as I said, I am trying honestly to provide you with the most reliable information available so that you— with my help and support— can make a decision that you feel is the best for you... life has placed you in this uncomfortable, precarious situation at no fault of yours ...and all we can do is do the best we can with the cards we have been dealt...

John (still in a hostile manner): it is easy for you to say that, doctor! You are not in **Lisa's** shoes!

Doctor (in a mildly irritant voice but visibly trying to control his emotions not to lash out at the husband): Yes, I am not in **Lisa's** shoes. But—I am sorry to say this —I think everyone understands that it is also not my fault that **Lisa** is affected by this disease...As I said, I have chosen to go into medicine to help people. So, I hope both of you can allow me to try to help you...to do my job to the best of my capabilities.

Lisa: of course, doctor. (turning to **John**): **John**, I need you on my side; I know you are upset and trying to be helpful... it is a lot to process, but let's allow Dr. Williams to do his job...

John: I am sorry, doc; it is just we have known each other since kindergarten, and we counted on growing old together with our family all around us.

Doctor: no problem— let me explain what benefits expressed in terms of average months mean. That does NOT mean that ALL patients treated with chemotherapy for pancreatic cancer like yours will live longer, 6–9 months, COMPARED WITH no treatment...In fact, treatment will work in some patients and it will not work in others...some patients, unfortunately, may not live even three months, but some patients live much longer, and that can sometimes be measured in years...

Lisa: years?

Doctor: yes, some patients can have their cancer controlled for years...again, I want to be honest with you; this does not happen very often...and, there is

no way to say who will be among those lucky few in whom treatment will work...In your case, as in the case of any individual patient, the treatment will or will not work... There is no way to know if the treatment will work until you try it...Nevertheless, the decision to accept or not accept any treatment is always an exercise in COMPARISON. Any time someone tells you this is an excellent treatment, ask “excellent compared to what?”- compared with nothing, treatment A, B or C... so, please compare the odds that you are facing...

Lisa: no much of choice, Dr. Williams...perhaps, the odds of trying treatment beat the odds of not-trying it on paper, but I am not sure if all that hassle you described is going to be worth all that effort... suffering from all those horrible side effects...going back and forth between clinic visits...hardly seeing my kids...What would you do, doc, if you were me or some of your loved ones were in a similar situation?

Doctor: these are real dilemmas, I am not going to lie to you...it is difficult to answer your question, as I am not you, but that is a fair question and I will try to answer it the best I can...I would probably try treatment, as you can always stop it if you don't tolerate it, or don't “like it” for whatever reason...particularly if I were in otherwise good health like you.

Lisa: I desperately want to make that decision, but doubts are accumulating in my mind as the clouds above my head...particularly after hearing about all those chemo toxicities...

Doctor: we have only talked about the so-called “standard” chemotherapy. Perhaps, it would help to discuss all options we can consider, including enrolling you in experimental trials with new treatments?

John: experimental drugs? Do you want Lisa to serve as a guinea pig?

Doctor (somewhat tersely): look, I cannot help you if there is no trust between us. I am aware that the researchers in the past had sometimes exploited the patients who had found themselves in inherently vulnerable situations as you find yourself today. I should like to think that today's oversight of human research is better than in the past, that researchers are better trained in human subject research, more aware of the potential conflict of interest that sometimes creep in the research conduct when doctors and researchers put their interest before the patients'...

John (interrupting with an expression of awe and puzzlement) : what do you mean by doctors being in a conflict of interest? Are you referring to the situations we hear about in the news? When doctors paid by big pharma promote drugs that are not necessarily in the patient's best interests?³¹ Are you saying doctors are also captive of the classic prisoners' dilemma when acting in their interest is more important than in the patients' best interest?

Doctor: I know what you are referring to. And, it is true that the current incentives in the health system...

John: like financial incentives, Doc

Doctor: admittedly, yes- I am not going to lie about that...but other incentives, too ...And, not to appear too defensive of the medical profession, but there is plenty of blame to go around. To illustrate what I am alluding to, let me quote one of the patients who sought opioid medications for his pain: “I am addicted to (opioids), and it's doctors' fault because they prescribed them. But, I'll sue them if they leave me in pain “. The point is that the current incentives often result in the misalignment of interests of doctors and patients, generating the classic prisoners' dilemma you just referred to. It is difficult for me to admit this, but given the current system of incentives, perhaps we should not be too surprised that some physicians sometimes do what is easier for them, as in the case I just mentioned of indiscriminate prescribing the opioid medications³²...

John: and contributing to one of the biggest public health crises in the history of this country...including an unprecedented decline in life expectancy, for the first time since 1900...

Doctor: yes, our profession has a lot to account for. But, the only way we can escape from the prisoners' dilemma is to incentivize the alignment of interests of doctors and patients. One way- perhaps the only way to accomplish this- is to increase trust in the system... and transparency to help clarify the expectations of all interested parties involved.³³ I hope that you will trust me and be assured that I will not abuse it...but rather be honored to take care of Lisa and help you arrive at the best possible decision for Lisa and your family. I take great pride in being able to help my patients.

Lisa: we know that, **Doctor**. Please continue providing me with as transparent and explicit information as possible.

Doctor: Thank you, Lisa. What I want to do is to place issues in perspective. We have already discussed the issues of prognosis- what to expect- if you decide to – or not- to proceed with treatment. However, what I briefly outlined – and provide you with written information–that I want you to review carefully later at your home- is what we refer to as “standard” treatment” that consists of chemotherapy I briefly summarized for you, which is described in further details in the brochure I gave you.

Remember, we do not need and do not want to make the decision today- our objective today is to review all options and then meet next week to go over all the remaining questions and decide what we all agree would be best for you... to respect your wishes and how you want to live your life, regardless of whether you have weeks or years to come...

Lisa: sorry for interrupting, but I forgot to tell you

that in the form they asked me to fill in, I stated that I do not have a living will. Should I make one?

Doctor: yes, absolutely, but we can talk about that next week. Let me first review the remaining options that we can consider ...as you know, medical science makes new advances all the time...new treatments are being developed for many human diseases, including pancreatic cancer...Some of these drugs—not yet FDA-approved—are in the clinical phases of testing....Before I continue, do you understand what it means that “drugs are not yet FDA approved, but are being “clinically tested”?

Lisa: I think so. We need the FDA’s stamp of approval to tell us that drugs work... and are safe.

Doctor: indeed, after they are proven to be “safe and effective”...

John: doc, are you saying that the FDA-approved chemotherapy drugs that you are recommending to **Lisa** as “safe and effective” ...even though you told us that it can only add 3-6 months to **Lisa**’s life with myriad unpleasant things that could happen to her... If so, no wonder why no one trusts the government these days...

Doctor: you are correct that what is “safe and effective” is, to some extent, in the eye of the beholder....

Lisa: in the eye of the beholder, but I thought you said, or at least implied, that the FDA makes decisions based on science...

Doctor: indeed, it does. But, our values and preferences— what makes us essentially humans— cannot be taken out of the picture. What is important to some people may not be important to others. That is why we have already spent this hour discussing how to proceed. Both **John** and you, **Lisa**, have already acknowledged the trade-offs...the same is with the FDA...When the FDA compares outcomes, such as survival in patients with and without treatment, it is also based on judgments. The FDA assesses if the balance of the benefits of treatment it considers for approval outweigh its harms, knowing full well that some people may not agree with the agency, mainly when some of these drugs cost lots of money. Many people criticize the FDA that some of the drugs they approve are not cost-effective, that is, that \$\$\$ spent on some drugs they approve is not worth their benefits...in the US, for example, treatment is considered cost-effective if it costs less than \$200,000/ year life gain³⁴...However, Congress has forbidden the FDA to consider costs, and hence they approve drugs even if the benefits are minimal i.e., considered not that important by many... However, as long as the effects observed in clinical trials testing are scientifically valid, the FDA tends to approve such drugs...

In addition, once the FDA approves the drug for one indication/disease, doctors have the right to use it in the so-called “off-label” setting ...meaning that even if the FDA does not formally approve the par-

ticular drug or drug combination for a specific disease, doctors are at liberty to use it as long as they believe that such treatments would be beneficial for their patients. **Doctors** also make their judgments based on other scientific studies that are not necessarily reviewed by the FDA.

John: but, one or a few studies don’t tell the whole story, do they, Dr Williams?

Doctor: Absolutely; that’s why doctors often rely on the synthesis of all relevant but credible, unbiased studies to assess what we call the totality of evidence on a given question. This is usually done by conducting a systematic review of evidence using specific techniques to synthesize all relevant studies on a given topic. Sometimes, these studies can be further statistically analyzed using a meta-analysis technique. In fact, as you search the internet for information, the best advice I can give you is to first look for systematic reviews/meta-analyses, particularly those published by Cochrane Collaboration³⁵, an international organization devoted to preparing and maintaining research syntheses of scientific evidence. The Collaboration motto is *Trusted evidence, Informed decisions. Better health.* Its reviews typically include a summary in lay language. It is smart first to ask if there is a Cochrane Review on the issue that interests you—that can save you a lot of time and frustration.³⁶

John (writing the information down): will have a look...

Doctor: although evidence is necessary, it is not sufficient for making recommendations and decisions. Often, doctors and their professional or governmental organizations form the so-called clinical practice guideline panels, which then review all evidence and make evidence-based recommendations for doctors and patients to use.

In fact, when I referred to “standard” treatment, that was based on the recommendations developed by my professional organization, which assembled a guidelines panel composed of a most reputable group of world experts who reviewed all existing evidence on the treatment of pancreatic cancer... So another piece of advice I can give you is to ask if the treatments are recommended in evidence-based clinical practice guidelines...

John: you mentioned something that has caught my attention – that studies have to be unbiased. Of course, that goes without saying. Are you saying that doctors can make recommendations based on biased studies?

Doctor: unfortunately, yes. Although often given with the best intentions, medicine is full of examples of the use of unproven or inadequately tested treatments... and despite the best attempts of the agencies like the FDA to assure that truly safe and effective treatments are used in clinical practice...

John: please don’t praise the FDA more than it de-

serves, doc! Everyone knows they are bought by big pharma and are subject to political pressures. Didn't they approve some toxic malaria drug- hydroxy-chloroquine or something- during the COVID19 pandemic³⁷ when then US President Trump twisted their arm to approve it!³⁸ I know that in the meantime, the FDA has reversed its stands, but not because scientific evidence compelled them to do so, but rather because the political climate changed...

Doctor: I am absolutely not going to disagree with you on this one...I also have found the approval of hydroxychloroquine – and some other drugs, by the way, shameful. The same goes for some professionals who distort evidence and spread misinformation and disinformation...often because of misunderstanding how science works... But, without defending the FDA too much- which often found itself between the rock and hard place-trying to adhere to best scientific standards while navigating all sorts of public and political pressures- the hydroxychloroquine case also illustrates the important point how science works...Our knowledge constantly evolves...what we know today will be replaced or modified 1,5 or 10 years down the road... As we answer one question, new questions emerge... some more important than others³⁹...

Lisa (with a smile): Dr. Williams, I can see that you love to teach; I am sure your students are grateful, and if I am not in the position in which I am, I would love to debate with you larger issues of the “truth”, misconception of reality, including misplaced policymaking that we often witness from our government... but can we go back to my case, please? I have a problem here and now, and there is so much unknown...so far, to be frank, the discussion has not helped me reduce my anxiety... as the uncertainty about what to do continues to reign supreme...

Doctor: Thank you, **Lisa**. Without lecturing on scientific theories of knowledge, all I wanted to say is that contemporary medicine is increasingly trying to make sure that treatments are given according to best available evidence that exists at the time of making treatment decisions...this is called practicing evidence-based medicine⁴⁰...and, as surprising, as it may sound, this is not widely accepted by all practitioners and medical scientists...partly, because of disagreement on how we assess what “BEST” evidence is...

Lisa: so, what does “best” evidence say? Which treatment should I be given, Dr. Williams?

Doctor (the earlier irritation in his voice seems to be subsiding, speaking more in accepting, matter-of-fact voice) : as I said, standard, best evidence at this time suggests that you should be given chemotherapy with FOLFIRINOX...

John: and that “best” evidence says that **Lisa** will live about 3–9 months longer than if she were not to take the treatment, on average?

Doctor: because of that, I want to discuss other options, including experimental treatment. May I continue?

Lisa: yes, please.

Doctor: We have established what standard treatment can and cannot do for you. Because, as both of you have clearly noted, this treatment- even if it is considered the best that we currently have- leaves much to be desired. However, medicine continues to improve the effects of the existing treatments to improve patients' health...to enable people to live longer...and hopefully one day cure this disease...

So, I want to discuss the additional alternative treatments we may consider, possibly better options for you, **Lisa**.

First, many oncologists use treatments with different chemotherapies than the “standard” treatment we have discussed. I chose to present “standard” treatment information because the evidence was obtained in the so-called “randomized controlled trials” and recommended by leading professional organizations⁴¹... The evidence shows, rather convincingly, that treatment with the three drugs we discussed is better than with one drug, or no treatment...

Lisa: what is a randomized controlled trial, doc?

John: that is when , instead of a doctor choosing treatment, they let a computer select treatment for you...like rolling a dice...

Lisa: I am a computer scientist, but this sounds rather awful- shouldn't the patient consult you instead of a computer, Dr Williams? Otherwise, what are all those years of training worth?

Doctor: unfortunately, regardless of our rigorous training, experience, and expertise, we can easily be fooled...no individual doctor's experience can match the validity of data that are obtained in well-designed randomized controlled trials⁴², RCT, in short. When we test the effects of treatments in RCTs, we avoid all sorts of pitfalls that may affect our results and possibly mislead us to conclude that treatment works when it doesn't , or that one treatment is better than other, but the opposite is the case.

Remember, assessing if treatment works involve comparison...you can imagine that if we compare the effects of the treatment in young vs. old patients, we may not know if the difference in outcomes we detect, say, in survival between the patients, is because of their age or because of drug effects. The comparison between dissimilar patients may reflect the impact of the biases we discussed earlier. What we want to do to is to make sure that the patients who receive one treatment and the patients who receive the other are similar across all their characteristics except for the treatment given to them... no individual doctor- regardless of how many years h/she/they may have practiced- can meet this requirement. Our personal sample of patients- even in

the busiest possible practice- remains limited. By its very nature, it is “uncontrolled”... and likely biased.

Lisa: I get that. But, why do you need a computer for this? Can’t you make this judgment yourself?

Doctor: well, as I said, doctors are humans, too. Sometimes, we may be tempted to give people with different characteristics- we say with different prognostic factors- different treatments, and hence induce bias. To continue with the example of age-effect, we may be tempted to give more aggressive treatment to younger than to older patients...hence, as I explained, we cannot know if any difference, say, in survival outcomes we observed was due to age of patients, or effects of more or less aggressive therapy...or, sometimes we need to mask, or “blind” doctors or patients to the type of treatment they receive to avoid being fooled due to the so-called “placebo effect”..

Lisa: ...which may make us feel better just because we THINK we are receiving the “right” treatment...

Doctor: precisely...or, sometimes, we may “mask” those who interpret the findings of, say, CT scans when we assess how the tumor is responding to treatment...That is, the radiologists reading your scan should not be aware of what treatment you have received so that this knowledge does not influence their judgments...all, these steps ensure that the results are as reliable and unbiased as possible... Current evidence on “standard treatment” had indeed been collected in rigorous RCTs with built-in procedures against bias...

Lisa: and, yet, for all this extraordinary evidence, this so-called “standard” treatment cannot really help that much...

Doctor: for this reason, many doctors – unsatisfied with our best standard treatment- have started combining different chemotherapy agents, increasingly offering new treatment combinations to their patients with pancreatic cancer. The problem is that these new chemotherapy combination has never been subjected to rigorous testing in RCTs against standard treatment. Some doctors combined drugs approved by the FDA for other diseases in a new way, but without testing this new treatment protocol in a scientifically formal trial. They are allowed to do it as long as they believe that would be in their patient’s best interests. I may have already mentioned that doctors often use drugs in an “off-label” way to treat patients for diseases different from those initially approved by the FDA. Even though critics charged that using drugs off-label is a sort of testing their efficacy in an uncontrolled way, many doctors have increasingly used the new combination of the drugs I mentioned...I call this combination (consisting of two other chemotherapy drugs called gemcitabine and nabpaclitaxe) the protocol GnP for short. Hence, many doctors came to believe that chemotherapy based on the novel combination of

GnP drugs is superior to standard treatment or less toxic. For a good reason, I should admit, they also say that it would be unethical to test the protocol GnP against no therapy or placebo, as these drugs are of a similar class of drugs as a standard treatment and also show activity in preliminary studies against pancreatic cancer...

Nevertheless, no one is sure if the protocol GnP is better than the standard treatment. **Doctors** are equally divided into two camps; some like me, prefer standard treatment, and others like many of my colleagues, favor the protocol GnP. We are uncertain, honestly not sure which treatment is better⁴³. We say we are in equipoise...

Lisa: equipoise?

Doctor: Yes, equipoise⁴⁴. Let me explain...While I may favor the treatment I recommended, other doctors equally strongly favor and recommend their treatment of choice. But, neither of us can claim that we KNOW which treatment is truly better. If we knew this discussion would be superfluous ...professionally and ethically, we would be obliged to recommend treatment that we believe is the best for you. But, as I said, we are divided in our views, uncertain, acknowledging that, in your case the protocol GnP may be better treatment, or the standard treatment, FOLFIRINOX, I recommend may be superior, or that there is no important difference between the effects of these two treatments. Because neither of us knows, the best way- the most rational way- to decide between these two treatments is to randomize- to allow a computer to flip a coin of a sort- between these two treatments.

Lisa: I am slowly grasping what you are talking about...go on, please

Doctor: Asking me- or my colleagues- to make that decision for you is not the best way of choosing treatment for you. When we are uncertain- in equipoise- making a computer randomly select that treatment is a much more superior method of choosing the best treatment. This gives you the most optimal chance to receive the best possible treatment at the time when this decision is made. Of course, after the fact, when the study has been completed, we may find that you have received better or worse treatment, but right now, the best mechanism to choose between these two treatments is to invite you to enroll in an RCT in which we compare effects of the treatment on the protocol GnP with that of standard treatment FOLFIRINOX

Lisa: I see?

Doctor: One advantage of enrolling in this trial is that you will undoubtedly get the treatment that is better than nothing, although, as I explained, I cannot tell which of these treatments will ultimately work better...Right now, we have this trial open, and so far, we have enrolled about 50 patients. We aim to enroll approximately 400 patients. We have also

broadened the so-called eligibility criteria i.e., who can qualify for this trial, to reflect the reality that many patients may have not only pancreatic cancer but suffer from other diseases as well. This is known as undertaking a “pragmatic trial”, which indirectly indicates that we believe that most patients will tolerate treatment with no undue adverse events. Thus, this will allow us to assess what is known as the “effectiveness” problem, which answers the question of whether the treatment works in the real world, for most patients ...

Lisa: ok?

Doctor: We usually do these trials when there are well-established treatments that doctors have used for a while but have not yet figured out which treatment works best. These trials are not often used by the FDA, which typically rely on what we refer as “efficacy” or explanatory trials that attempt to figure out if the treatment works under ideal situations of carefully selected patients to answer the question if the treatment can work under the best of possible circumstances. That is, the way discovery and evaluation of the new drugs work is to address a series of related questions over time- “can” a drug work in an ideal setting, “does” the treatment work in real-life circumstances, and “is it worth” paying for it?²⁵ The “can” question- efficacy question is what the FDA is typically concerned with, but most patients and physicians are concerned with the “does” -effectiveness question, while policy-makers are increasingly interested in “is it ‘worth’” paying for it- i.e., the cost-effectiveness question we touched upon earlier in our conversation..

Lisa: Thanks for your explanation of how drug development works. I am sure the public needs further education on these points and what that means for all of us who find ourselves in situations like these. I think I understand that enrolling in one vs. another type of these studies- RCTs, as you called them- may have different implications or consequences for me....but, sorry, doc, this effectiveness vs. efficacy issue is a bit too much for me... nevertheless, if I am following you correctly, regardless which of these RCTs I decide to participate in, I have 50:50 chance to get better treatment?

Doctor: yes, you understood your chances perfectly well!

Lisa: and the treatment will be made by a computer, not by you- a doctor I trust?

Doctor: that is correct, but as much I appreciate your trust in me, for the scientific reasons I’ve explained, it is actually better for you that the computer makes this decision...

Lisa: It may sound paradoxical to you, as I am a computer scientist, but even I would rather have treatment determined by a trusted human being and not by a computer. After all, I am made of flesh and blood, Dr. Williams! I wanted to be guided by a

doctor I trust and who understands me the way I am without obsessing over scientific minutiae. Frankly, I don’t care about scientific reasons...

Doctor: I understand, but as I was trying to explain...

Lisa: you mentioned that you have already tested the protocol GnP in 50 patients...can you share the experience based on these 50 patients?

Doctor: I am afraid I cannot, even if I wanted. This trial is a multi-center trial between our and 6 other institutions. The data are collected at the Central site in NYC. The trial includes the Data Safety and Monitoring Board, an independent committee of about 10 experts in pancreatic cancer and statistical analysis, which continues to monitor data and will look at the results after 100 patients have been enrolled in the study. They will then decide whether it is worth continuing the trial. This is necessary to ensure the integrity of the research and unbiased results.

John: Doc, you said you are uncertain about the effects of the protocol GnP vs. standard treatment. I presume this also means you are unsure about what maximum longevity either of these treatments can achieve, which is about 9–12 months, on average?

Doctor: that is correct, on average. We often expressed averages using statistical measures such as median, which, as you may recall from your college or high-school days, refers to a value at the midpoint of all possible results. In the case of treatment for cancer such as pancreatic cancer, these values consist of recording data from all patients to construct a distribution of all possible survival times. From there, we determine the midpoint or median at which there is an equal probability of living above or below it. But, please understand that even though the averages provide a correct statistical summary, from Lisa’s perspective, they do not give us the entire story...To paraphrase Professor Gould, a Harvard Professor who personally grappled with another type of aggressive cancer and famously wrote “the median is not your destiny”²⁶some patients will live much longer... Unfortunately, as I have said repeatedly, we cannot predict who will live longer than the median...it is this unpredictability that is a crucial rationale and reason to do the trial...

Lisa: I think I am following you, but would it be possible for you to explain this bit more...

Doctor: sure. The best is if I actually show you some graphs ...(The doctor goes to his bookshelf, picks up a book, and opens a page to show the charts with the survival curve. He then points to the graph and explains...)...I will pick one randomly....just to illustrate the concept... The vertical, Y axis displays survival probability ...the proportion of patients alive at a particular time point...time, as you can see, is presented on the horizontal, X axis, in this case, in years...at time zero, which can be measured from the time of diagnosis, enrollment in the study,

day of randomization, day when person was given treatment etc, everyone- 100% of people- are alive. When the percentage of people who are still alive drops to 50%, you can see that it corresponds to a particular time on the horizontal axis. Let me draw a vertical line from 50% down to time on X axis. In this case, median survival corresponds to the survival of 10 years. So, 50% of people on the left side of the vertical line lived 10 years. But note how this distribution of survival curves is heavily skewed on the right side of the vertical line...in this case, it extends out for years and years, living much longer than 10 years for about 30% of people...

Lisa: I see...but, in the case of pancreatic cancer, as you said, time is measured in months, not in years.... You said that the median is about 6-11 or 12 months, depending on the treatment...

Doctor: true but there is also a tail on the right side of curve in case of the treatments we discussed...

Lisa: so, you are saying I just may be lucky and end up on that tail? Can you show me survival curves that reflect my situation best?

Doctor: (goes to his shelf, look at several books and journals, opens one, and show the graphs to **Lisa** and **John**)...as you can see, the curve extends to the right...

Lisa: X axis seems to show time in months rather than in years, doc? It seems that very few people remain alive after 3.5 years or so? Am I correct?

Doctor (quietly): yes, but...

John: **Lisa**, I don't think this is much of a choice... should we ask Dr. Williams to review other options for us?

Lisa (quietly) : yes.

Doctor: indeed, that is what I was planning to do. Another available option is to think of enrolling in clinical trials testing NEW, experimental treatments. The drugs that are used in the protocol GnP we talked about earlier were individually approved by the FDA but the protocol GnP is yet to be tested against the standard treatment, as we just talked about. So, the combination itself could be considered experimental, but not the drugs themselves. However, more recently, scientists have developed entirely new drugs that the FDA has not yet approved...they show promising activity when used in the animals and cancer cells in laboratory ...

John: Petri dishes?

Doctor: yes, sort of...one of these drugs are being developed for pancreatic cancer and other gastrointestinal cancers...It has not yet been tried in humans, but our IRB- our ethics committee – recently gave us permission to test this new drug in what is called a phase I trial... the drug is so new that it does not even have a proper chemical name...it is called LX567...we have been approved to test it in 30 patients but so far we have used in 3 patients only...

Lisa: what is a phase I trial, Dr. Williams? I know

three patients are not many, but how did these patients fare?

Doctor: all I can tell you is that the patients we have treated so far have tolerated treatment well. But, as you said, 3 is not many patients...it takes many more patients to learn if the treatment is safe...The drug LX567 has been tested in animals and cell cultures but, as I mentioned, has not yet been adequately tested in people...Phase I trials are typically what we call “first-in-human” studies... to be honest, the goal of cancer phase I trial is to learn how well patients tolerate the drug...to determine what the trialists call MTD-“ Maximum Tolerable Dose”- the highest dose of a drug that does not cause unacceptable toxicity or adverse effects ...including potentially lethal effects...

Lisa (very anxiously): you mean I can even die if I take this new drug?

Doctor: we hope not, but it is possible...without testing it in humans, there is no way to know...

Lisa: how do you determine MTD?

Doctor: typically, we keep increasing doses until the highest amount with acceptable adverse effects is found...once the patients start experiencing unacceptable side effects...

Lisa: or, die...

Doctor: yes, unfortunately, or die...we select the dose that was previously tolerated as MTD...

John: Doc, you previously told us about the trade-off we have to make. So, the LX567 may or may not be too toxic, but what about its effect on cancer...benefits, to use your words...

Doctor: yes, I was about to say that even though we always HOPE that the new treatment will work against cancer, the INTENT of phase I trials is to learn about toxicity and assess MTD... Once MTD has been established, the drug is tested in what is referred to as phase II trials to assess its efficacy i.e., how well it works against a particular disease...

John: wait a minute, doc! Are you saying when you enroll the patients in phase I trials, you do it with the purpose to HURT them...perhaps, you may help them, but that is not your primary concern...even though some people can die...

Doctor: I would not put it in such a language, but you are essentially right...the main goal of testing in phase I trial is to determine adequate doses of drugs that people can tolerate...not necessarily efficacious or effective...that is left for phase II and phase III trials...However, and without hyping this too much, it is not uncommon that effects on cancers are noted even in phase I trials...today some diseases that were incurable just a decade ago are highly treatable with the drugs whose effects were noted in early testing ...and confirmed in the later phases of testing...

John: I see...I have a colleague at work whose wife was given one year to live...I am not sure which cancer she had... she went to a well-known cancer center

where she was given what they told was “break-through targeted therapy tailored for her cancer”...5 years later she is alive and well...I think I keep seeing such testimonials and ads on TV as well...

Doctor (speaking somewhat enthusiastically, in an upbeat manner): yes; we talked about chemotherapy, but many other types of treatments have been developed because of testing in clinical trials. In addition to chemotherapy, hormonal therapy, and drugs called tyrosine-kinase inhibitors (TKI), various types of immunotherapy are transforming a landscape of cancer treatments enabling many patients to live long and high-quality lives...For example, imatinib was one of the first TKIs, and it has changed the natural history of a once uniformly deadly type of leukemia ... called chronic myeloid leukemia (CML) ...into a disease with life-expectancy near-normal...many other examples of new drug developments are available...

Lisa: **John**, you are typically more skeptical than me, but I remember when not that long ago, my aunt Mary got metastatic breast cancer and was given stem cell therapy, which she was led to believe would cure her cancer. Unfortunately, the treatment did not work, and she experienced horrible side effects... I am trying to be open-minded toward all experimental options Dr. Williams is discussing with us. Still, aunt Mary’s experience is stuck in my mind...

Doctor: yes, we should be honest about hope vs hype...stem cell transplant for breast cancer is one sordid episode in the history of clinical oncology where inadequately tested treatments unwarrantedly prematurely and inappropriately spread quickly in clinical practice.⁴⁷ Only when valid studies were done did it become clear that stem cell transplant did not work as advertised...it was more harmful than beneficial...unfortunately, your aunt was an unsuspecting victim of too much hype accompanying this treatment at the time. This is one of the reasons that I warned you against paying too much attention to the unwarranted claims that, sadly, are sometimes promoted by medical professionals,⁴⁸ not only those who advocate some sort of alternative medicine...

Lisa: how often does the testing in phase I trials turn out to discover the block-busters you so enthusiastically talked about earlier?

Doctor: admittedly, not very often...less than 2-4% of all testings⁴⁹, but it is certainly not zero...

John: not great odds, doc. Why would anyone enlist in the trial with such low odds?

Doctor: well, lots of people do. Some people even fought to pass so-called the “right to try” law⁵⁰ ...to have access to first-in-human, but unproven treatments...admittedly, a controversial policy as it is not clear if society at large learns anything from such experiences... But, remember, all effective drugs we use today mean that some people had volunteered to participate in trials at some point before...

John: sorry for interrupting, doc, but it is a bit unfair to put pressure on **Lisa** that she owes to society to participate in the trials so that future patients may benefit⁵¹...

Doctor: I apologize- this was not my intention, but knowledge gained from the participation in clinical trials is indeed used to help future patients...people who one day also may develop pancreatic cancer like **Lisa** ...although we always hope that people who consented to participate in any trial- phase I or later phases of the trials- may also benefit... Please do understand that while I am aware of the societal benefits of knowledge gained by undertaking testing in humans- after all, a clinical trial is exactly what it says it is, testing of unproven, EXPERIMENTAL TREATMENTS in humans. I have repeatedly tried to explain that my main concern is **Lisa**’s well-being. But, because we CANNOT KNOW in advance which treatment works in humans we are forced to TEST them IN HUMANS testing serves to sort out unpredictability of hope-for-benefits and unknown harms that is necessary built into new drug development⁵²...

John: Doc, by now, we understand that clinical trials are human experiments...and analytical and moral dilemmas that go with them...although, as a health journalist, I should know better, we slowly appreciate your effort to walk us through the complexity of science and decision-making ...

Doctor: thank you, **John**. I should, however, mention that rationally, under equipoise, one can actually achieve what ethicists call “triple aim”⁵³- respect your right to decide as an autonomous human being about the treatments you are offered, including whether to participate in the experimental trial, have the best possible chances to benefit personally, while contributing to knowledge that can help others in the future. It is like an attempt to find a Goldilocks Zone- an ideal intersection between those who advocate rights-based ethic based on social contract we establish with the rest of society with those who believe that our utmost ethical principle is to help other human beings based on the philosophy...

John: of 18th-century German philosopher Immanuel Kant, famous for his categorical imperatives ...ideas that each one of us has an unconditional moral obligation to “never to act except in such a way that I could also will that my maxim should become a universal law.”⁵⁴

That is, if we perform a particular action, everyone else should also be able to perform it and act accordingly. And, there is nothing more that we all universally accept than our duty to do anything we can to save the life of our fellow human being...

Doctor: correct...but with whom the utilitarian philosophers such as Jeremy Bentham and **John** Stuart Mill disagree by arguing that our actions are

ethically correct only if they are beneficial for a majority of people...

John: “the greatest amount of good for the greatest number of people...”⁵⁵ I have never realized that I would encounter practical application of my philosophy college courses to the situation in which we found ourselves today. Nevertheless, I still don’t see how this ethical discussion will help *Lisa*, doc?

Doctor: well, we have been discussing how our choices about the treatment that *Lisa* ultimately selects can impact *Lisa*, you, as well as the broader society...and, whether we can find some sort of a principle ... a guide of a kind that allows us to find the optimal balance between all potential consequences of *Lisa*’s ultimate decision...and, what I am trying to say, under equipoise these conditions are often met...

Lisa: but, as I understood you, Dr. Williams, equipoise applies only to randomized trials....requiring that dreadful computer to choose for us. You also mentioned phase II trials. Would that be a better option for me?

Doctor: perhaps. There is a new drug, also still without a proper chemical name...currently called MX678, which we are testing with 3 other institutions in patients with metastatic pancreatic cancer... we have been approved to enroll 100 patients, 25 at each site...so, far we have enrolled 10 patients...

Lisa: I presume there is not much experience that you can share with me about these 10 patients? But, how did they fare in the phase I trial?

Doctor: the drug was well tolerated in the phase I trial, and no one has died due to the drug. As we discussed earlier, that does not mean that adverse effects will not emerge as we continue with further testing...in fact, you should know that the testing to date was done in no more than 60 people in total... So, in a phase II trial, we will also continue to monitor for the safety of the treatment but also focus on how well the drug works against your cancer. Also, we want to learn about the mechanism of how the drug works; so, we also take blood samples for biochemical and molecular testing. We may also need to re-biopsy your tumor and get frequent CT scans and other imaging studies ... again to learn how well the treatment works. We will monitor you carefully and might ask you to keep a log of your daily activities and symptoms...

Lisa: how often does the testing in phase II trials turn out to discover new treatments -to use your language, doc- safe and effective treatment that may be a game-changer for me?

Doctor: these are really all insightful questions, but as crucial as your questions are, they are -surprisingly-not well studied. Based on what is known to date, the success rate that drugs tested in phase II trials will turn out to represent genuine therapeutic advances would be about 15%-25%⁵⁶, I would say...

Lisa: again, no great odds. But, you keep telling us that we should go about this most rationally, trying to minimize the role of our emotions (if we can only do it). Would you mind summarizing odds for us – what can we expect if we choose standard treatment vs. if we go with the other route...choosing to become a guinea pig and enroll in phase I vs. phase II vs. phase III trial...I know you cannot predict the future—none of us can—but would it be possible for you to make your best estimate...your best bets on success, so to speak?

Doctor: tough to do, particularly because I worry that when people are given single numbers, we tend to fix on them...

John: regardless, doc- how can we make the best, rational decision, without those best, “average”, as you keep repeating, estimates...

Doctor: a fair point...let me try the best I can to recap what we have discussed so far. As we initially talked about when we were discussing the nature of your diagnosis, it is an inherent characteristic of science and decision-making that absolutely accurate results and decision cannot be guaranteed⁵⁷... As the test and scientific findings can be false-positive and false-negatives, the same goes for the decision choices....You may choose a treatment that will not work, which would be false positives, or decide not to select the treatment that may have worked; these would be false negatives... One strategy to think about this is to ask yourself which choice you would regret more: false negatives, failure to choose the treatment that, in hindsight, would have worked... vs. False-positives, selecting the treatment that, later, proved to be ineffective and possibly harmful...

Lisa: regret⁵⁸, doctor? I thought we were supposed to ignore our emotions when it comes to these life & death decisions.

Doctor: on the contrary, as I pointed out earlier, science alone cannot tell you what to do...we all want to live our lives on our terms, according to what we value most...

John (tersely): well, doctor, *Lisa* would love to be cured of this horrible cancer and live 100 years!

Doctor: of course, but we are constrained by reality...and, the reality is such that we have to choose in the circumstances in which we have found ourselves...the reality boundaries affect our preferences and choices...

John : This is so much to process...how much time is there to make these choices.

Lisa: doc, you were about to summarize the options for me...please continue...

Doctor: thanks, *Lisa*...What I was about to say was that well-tested, available treatment, supported by high-quality evidence, is better than no therapy that, on average, results in median survival of about 9-11 months but some patients can live much longer....about 2% of patients do live 4 to 5-years or

even longerAs we also discussed, there is no way to tell how you would personally fare....Because, admittedly, the odds are not great, we have also discussed offering you experimental treatment....phase I, “first-in-humans”, testing a completely new drug, highly promising in animal studies, but whether it will prove to be beneficial for patients like you is completely unknown...going by experience, what we do know is that, out of 1-2 millions of new compounds that are tested in laboratories every year, 1 out of 250-300 drugs will be tested in humans, of which about 5% -perhaps 2-7%-will hold promise for testing in later phases of testing such as phase II and phase III trials. However, testing in phase I trials does, on rare occasions, about 2-4% of time, result in the discovery of genuinely breakthrough drugs. When it comes to drugs that have progressed to phase II trials, the chance that it will benefit patients is bit higher, probably around 15%-25%and, finally, when you enroll in a RCT, you have about 50:50% chance to get a superior treatment⁵⁹... These are general estimates of our successes in developing new treatments, when one takes all drugs and diseases into account...I hope this summary is helpful. Let me know if I can further clarify any issues...

Lisa: Can you explain again about my chances if I enroll in an RCT?

Doctor: sure. An important point here is that we cannot predict the results of a clinical trial. However, in RCTs, the unpredictability of the results in any particular trial drives the discovery of new treatments in clinical medicine. That is, even though we cannot predict the result in individual trials, we can predict the distribution of treatment successes in such a way that new treatments are better than standard ones just over half of the time.⁶⁰ That’s as it should be...otherwise people would likely not be willing to accept randomization, as their chances for getting better treatment would be reduced. This is how the law of therapeutic discovery works -the pattern of treatment success is not accidental; it is directly related to the moral principle of conduct of clinical trials known as equipoise, or uncertainty principle.⁶¹

John: so, we are dealing with 5% vs. 20% vs. 50% chances, but some include “devils we know” and others we know less about...by the way, I did not realize what it takes to develop a new drug, and how the odds are so small, to begin with...

Doctor: drug development is truly high-risk, high-reward enterprise...nevertheless, we are now developing more drugs than at any time in human history...and as the development of COVID19 vaccines shows, when there is a high level of collaboration, focus, and yes,...money, scientific miracles do happen⁶²

Lisa: let’s chew on this, doc. Can we see you in a few days to discuss this further and hopefully fi-

nalize our decision?

Doctor: yes, of course...that would be the best next step. Please take these brochures, and review them carefully as well as what we have discussed today... Let me see you in about a week. In the meantime, if you have any questions, feel free to call me at any time.

Lisa/John: thank you, doc. Will see you soon then... (Husband ends the recording)

Act 2; Scene 1, discussion at home (Lisa and John, sitting in the living room, somber, reviewing the options for choosing treatment after the conversation with their doctor...)⁶³

Lisa (pensive, displaying calmness and thoughtfulness; the anxiety that dominated the interaction with Dr Williams seems to have subsided) : **John,** you have been tough with the doctor...It is really not his fault that I got sick...also, if we are going forward with this, we don’t want to alienate him... doctors have the means to detach themselves while still doing their job ...I don’t want us to fall in the prisoners’ dilemma situation...we need him as a partner...and fully engaged...

John: I know...sorry, I took it out on him...but all this is so not fair...for you, **Jenny,** **Bill,** me... I often tend to shift between my roles as being a supportive husband and investigative journalist...

Lisa: when will we talk to **Jenny & Bill** about my diagnosis?

John: before we do it, let’s try our best to use the analytical skills that both of us use in our professional lives, as I am afraid the emotional part of our brains will take over if we bring **Jenny & Bill** into the discussion at this time...

Lisa: but, shouldn’t they be a part of the conversation?

John: they are still too young – 8 and 12- to think outside of their emotions and love for you...for us all... and may affect our decisions in a way that does not reflect what you- we all truly want...

Lisa: Ok, let’s go over my- our- odds... We face several choices...to be honest, I have forgotten half what we talked about...you have been taking notes + we have recorded the conversation...let’s review it while **Bill & Jenny** are in school, and then let’s talk with them about all this ordeal...and decision we will have to make...

John: Ok, let’s play the tape (he takes his iPhone from his pocket and starts playing the recorded conversation; the audience hears the opening and the first rude exchange ...and the last few minutes of discussion)

Lisa: I am still dizzy about the intensity of all this and how my cancer diagnosis has suddenly changed our lives... forever....keep thinking about what **John Lennon** said “life is what happens to you while you are busy making other plans”...and, we have indeed been making such wonderful plans for our future...

all suddenly interrupted....(showing tears in her eyes)

John (hugs his wife, gently kissing her on her forehead): we will get through this, **Lisa** ...one way or another...whatever happens, I would never replace what we have had together...if we were to start all over again, I would choose the same life we so wonderfully have built for us...with two amazing kids who will ripple⁶⁴ forever for both of us...

Lisa (smiling through the tears): ...would even let me smoke...

John: even let you smoke...(then in a semi-jokingly way) or, probably find the way to have you smoke some sort of “fake cigars”...if the politicians could have invented the “alternative facts”, why would not scientists be able to invent “fake cigars”?

Lisa (smiling, still with tears, but assuming a decisive voice): Ok, let’s review the REAL -not damned alternative- facts! I do not want us to delude ourselves as the politicians often delude the public...just see what Trump has done with so-called “stolen election”⁶⁵ confusing millions of people making them refuse life-saving COVID19 vaccine. Let’s have all cards on the table, then!

John: Ok, do you want me to summarize it for you – the way I see it, or would you rather try to give your best shot, to sum up what is your understanding of the available options..

Lisa: Let me try... let me review the options as I see them...but, I need your help, so please jump in if you see any hint of my misunderstanding or coloring the information we were given through rosy eyes...I want to avoid seeing what I want to see- confirmation, my side bias⁶⁶- so I need your supportive but also wise voice ...

John: of course, honey

Lisa: The way I see the options Dr. Williams outlined for us is, first, as you said, the choice between the devil we know and the devils we do not. That is, we have a well-tested standard treatment...The treatment is better than doing nothing, but it really sucks...At best, it gives me the advantage of living 6-9 months longer than just sitting at home and doing nothing...while making me awfully sick along the way...

John: on average... remember what Dr. Williams said “median- average- is not your destiny”...some people do live years. It is impossible to know who these lucky people are...it could well be you...

Lisa: yes, but these “some” folks are so rare... didn’t we just hear that only about 2% of people live 4-5 years? Which, while better, is not a great consolation given our kids’ ages...

I think we should also ask the doctor if we decide to enroll in an experimental trial, can we change our minds or are we locked into a decision for the sake of others... If it gets rough, I’d like an option to quit... hoping to regain some quality of life and maybe see

if we could do some travel and make the very best of each day...

John: Also, in 5 years, a lot could happen...didn’t we also just see the news that 100% people with deadly colon cancer had their disease gone...and with immunotherapy alone⁶⁷...without that awful chemotherapy! Haven’t scientists developed the vaccine against COVID19 in less than one year instead of what typically takes them a decade or so... Remember what Dr. Williams said about how progress is accelerating and medicine is now curing previously deadly diseases...

Lisa: Yes, I heard all of it...and that gives me tremendous hope...but, again, I do not want to mislead myself, and I want to choose wisely...But, if I understand you correctly, you seem to be favoring the “devil we do not know”...experimental, so far untested treatments?

John: I did not say that...I was trying to put things in perspective...let’s review all options before, as you said, we make our best possible choice ...

Lisa : Ok, let me continue reviewing the devils we know...while my analytical brain still operates well... Currently, uncertainty about what to choose is huge; it seems that all options are equally- (**Lisa pauses as she tries to express herself**)—unpalatable!

John: I know. Don’t you often remind me when going shopping and with my tendency to consider more options –making me bewildered about what to choose- when the probability of choosing among several options is equal—the entropy, a measure of uncertainty is the largest?⁶⁸

Lisa: indeed, let’s try to reduce our entropic world in which we found ourselves uninvited. I also found it very intriguing that other doctors are using another well-tested treatment...what Dr. Williams said was developed in a sort “off-label” way i.e. not officially approved by the FDA. Interestingly, I thought that the FDA scrutinizes all treatments but apparently not...for better or worse, I might add... It is also surprising to me that doctors have developed the protocol BnP, not in a formal, rigorous study such as an “RCT”, but accumulated their experience in sort of uncontrolled, off-label, testing, which even I know can bias the assessment of the treatment’s true effects...I think Dr. Williams has alluded to the fact that doctors who have developed the BnP protocol continue to give it to ALL their patients. However, for regulatory and scientific purposes, the BnP protocol must be considered an experimental treatment.

John: Indeed

Lisa: So, now, they want to run a formal RCT in which they will require permission to give a drug to HALF of their patients, but, in the first place, they did NOT need any permission to give it to them all⁶⁹! But, then Dr. Williams mentioned that loosely regulated, completely untested treatments can be ac-

cessed via the “right to try”⁷⁰ protocol, which has also surprised me...as it is so clear that desperate people can do desperate things...Perhaps, the initial shock of the diagnosis has not settled yet, but I can see how we can soon become desperate people grasping at any straw of hope. Nothing is worse than putting ourselves in potentially exploitable situations when we want to try everything and anything and then expose ourselves to toxic and deadly stuff. And, in all honesty, I don’t even see what we, or anyone else, can learn if we pursue this route. It is so strange how doctors and scientists develop new drugs. I had no idea...

John (assumes deliberative, thoughtful but somewhat detached attitude) : What insightful comments, **Lisa**. Dr. Williams did not explain the BnP protocol in the exact same words you used, but you are correct- it reminded me of a version of a trolley dilemma we learned in the College ethics classes. Remember, it goes something like this: A trolley is speeding up toward 10 people. You can divert the trolley by pulling a railway switch. If you do nothing, a trolley will kill all 10 people. But, pulling the lever to divert the trolley to another track will kill one person. Which option is more ethically acceptable: intentionally killing one individual or passively allowing 10 to die? So, if we let people choose for themselves- regardless of how bad treatment may be- then the FDA is ok with that as it did not pull the lever and intentionally placed the people in harm’s way even though many people will likely speed up their demise and no one will ever learn much from these last-ditch-ordeals? It seems that well-controlled trials with close FDA supervision and doctors and scientists who have designed new drugs would be a better way to develop new effective treatments.

Lisa: I see that you turned your argument against yourself during our discussion with Dr. Williams when he made you so angry when he started talking about societal benefits. Do you think people should not have their right to try a drug just because the FDA judges that it probably does not work and is likely harmful?

John (continuing with his deliberative, professorial attitude, as if forgetting **Lisa**’s illness) : I understand the difficulties that the FDA faces when they have to make their decision amidst all those uncertainties about drug effects...I also appreciate that uncertainties are irreducible, and cannot be eliminated. As a result, errors are inevitable at the level of how we infer if the drug works and how we eventually make our decisions. And as we repeatedly mentioned, the errors can be of two kinds: false negatives and false positives, and they relate to both benefits and harms.

But, the FDA wants to have both ways: by requiring well-controlled trials, they seem to want to protect society by trying to minimize false positives...

but, because these errors are intricately linked, this comes at the expense of an increase in false negatives. We cannot decrease false positives without raising false negatives and vice versa. The problem is that by attempting to reduce false positives to protect society- which results in increases in false negatives- the FDA hurts individuals like you and me. By saying that the drug “does not work,” we don’t know if it is a truly useless drug or if they acted on false-negative findings. It is impossible to prove “negative”, as you well know. So, “the right to try” advocates are essentially trying to reduce false negatives, but this is done in a rather haphazard unsystematic way...maybe one in million people will benefit, but lots of resources will be squandered.

(**John** suddenly realizes that the issue may well be relevant to **Lisa** and him and changes to a loving-husband mood)

There is something deeply unfair and unjust with the entire process...perhaps, we have to deal with this “unavoidable injustice”⁷¹, but the lack of clear and transparent communication to the public does not help...immediately, it creates distrust and raises all sort of issues of conflict of interest and corruption. As we said to Dr. Williams, just tell us “like it is”- we are adults, we can take it...

Lisa: nevertheless, in all fairness, I now understand the classic dilemma of how to reconcile desperate individual interests vs. societal interests.... Hopefully, I don’t find myself so desperate that my choices do not reflect the real me... I don’t see myself going via the “right-to-try” path...there is something deeply irrational, certainly exploitable, and almost religious about this program that seems to assume that miracles can happen...I do not even know what I would try at this point...but we have digressed in our usual wonderful way of debating the country’s and the world’s -tragedy of commons, unresolvable⁷²- problems...

John: which do affect us, individuals, unfortunately...

Lisa: Regardless, let me finish the line of thought in which I began to summarize the pros and cons of each of the options Dr Williams presented to us.... When it came to the standard treatment vs. the BnP protocol he put the odds at 50:50% that one treatment would beat another...what did he call it? Equipoise? And that allowing a computer to choose for me gives me the most favorable odds to select the best treatment...What I found attractive here is that whatever treatment I get is better than nothing... while contributing to knowledge that can help others....although, even if I get better treatment of the two, we are probably talking of small improvements...certainly not cure, by any stretch of the imagination...

John (in a loving, sweetheart mood): again, you never know if you would be that lucky to go for many

years...or forever, my darling...

Lisa (firming up, visibly focused, less emotional): thank you for being so sweet and supportive, but right now, I need you to stop the bullshit and use the critical part of your brain instead of wishful thinking...

John: no, I am serious...didn't Dr. Williams talk about unknowability...impossibility of predicting who will die who will live at the individual patient level even though prediction at the group level is accurate and, yes, it is not super rosy...

Lisa: Ok... let me now summarize my understanding about the devils we don't know...new, untested treatments but whose developments have progressed from laboratory and animal studies to testing in humans...The chances that these promising drugs will benefit me after testing in what they call phase I, "first-in-humans" studies, are about 1-5% at best...And remember, the benefit here is accidental! The doctors are only focused on those who will be harmed before moving to the next phase—phase II—when they will look for the so-called "efficacy" of treatment- if the drug actually works. Even then, when it comes to treatment that has progressed to phase II trials, the chance that it will benefit patients is only a bit higher, probably around 15-20%...But, these drugs may prove ineffective, and if I forgo standard treatment I don't realize any benefits if the drug did not work...and, I am afraid we could waste our precious time trying a new, experimental treatment as the disease will inevitably progress making more difficult for standard treatment to work...

John: on the other hand, these new drugs MAY work substantially better than standard treatment...

Lisa: at much lower odds...If we forget that the "average" odds reflect our best shot and focus only on the large benefits., have you noticed that the chances of me ending up on that tail where the effects of miraculous treatments seem to concentrate is about the same⁷³- about 2%- regardless of if I play safe and enroll into an RCT- with better average odds- or opt for these new promising treatments that brings hope of cure...

John: interesting, **Lisa**...it was me who was supposed to pay close attention to what Dr. Williams was explaining, but this has escaped me...All I got from him is that it is impossible to predict the effects, whichever option one goes for...

Lisa: also, to be honest, I kept thinking about Dr. Williams's remarks that we enjoy the benefits of today's treatment because someone else before had volunteered to participate in the trials...at some point, every standard treatment was experimental treatment... it would not become standard treatment benefiting millions of people if some people in the past had not consented to then-experimental treatment. Haven't we all you, I, our kids, and family,-

benefited from all those antibiotics and myriad other life-saving drugs because individuals like me- "made of flesh and blood"-have consented to participate in medical research?⁷⁴ Isn't it how medical progress is made, after all? Shouldn't this be my- and all of ours- moral responsibility – as we try to individually gain benefits, think about how we can benefit others, the larger society?

John: **Lisa**, as much as you have always been a moral and ethical person with a deep sense of social responsibility, you should not be factoring this into your decision. It was unfair of Dr. Williams even to mention this...and triggered me to become angry again.

Lisa: Perhaps this should be considered at some level...so that at least someone else can benefit from my experience. It is clear that whatever we choose, we may regret it!

John: what are your thoughts about choosing the treatment that may not work and that ultimately proved to be ineffective and possibly harmful, false positives, as Dr. Williams called it- vs. false negatives, failure to choose the treatment that, with hindsight, would probably have worked?

Lisa: not sure; this is such a wicked problem that even my analytically-prone mind has difficulties grappling with...You are more intuitive than me- what does your intuition say, which way to go?

John (deep in thoughts): we would certainly like to make a decision that we will not regret...or if we do, that the regret is something we can bear...acceptable⁷⁵... I know I sometimes don't regret the consequences of a trivial decision such as, for instance, when the weather forecast indicates that rain is coming and I heeded their advice to take an umbrella even the estimates turned out to be wrong. Can we define which decision we will regret least, or not worry about if we make a bad decision...(John shows apparent signs of grappling with the attempts to create an intimate, reassuring, positive, and helpful atmosphere, but his countenance is not well aligned with the words that he is uttering)

Let's give ourselves some time and let these choices settle. In the meantime, unless we had gone to this doctor, we would not have known which options were available. So, where can we go that is beautiful and celebrates our life while we think about this?

Lisa (hearing noises): it seems that **Jenny** and **Bill** are back from school...

Kidds (B&J) (rushing into a living room, talking in an exciting way)

Jenny: Mommy, mommy, I got an A in math, and **Bill** got C!

Billy: that stupid Math Teacher!

John: Billy, watch your language!

Jenny (sensing some tension in the room): why do you have tears in your eyes, Mommy? Have you been

crying?

Lisa: come here, baby...let me hug you...you, too,
Billy (hugging and kissing her kids)

Billy: what's wrong, mommy? Why are you crying?

Lisa: There is no easy way to say this, but ...your mom is ill.

Jenny: As ill as I had to go see a doctor because of an ear infection?

Lisa: much worse

Billy: how much worse?

Lisa: have you heard of a disease called cancer?

Billy: I think my friend Jim's mom was recently treated for breast cancer...she got something they called "chemotherapy" + something else...she lost her hair, but I saw her yesterday... she is doing just fine...

Lisa: This one is called cancer of the pancreas... and is much more difficult to treat...

Jenny: but it can be cured, cannot it?

Lisa: unfortunately, not...

Billy: what do you mean it cannot be cured? I am sure something can be done...

Lisa: indeed, something can be done... medicine can help me stay without pain; my doctors can try to treat the tumor, which is like a small ball, to make it shrink, but they cannot make it go away for good⁷⁶ ... In fact, there are many treatments that my doctors are offering, and dad and I were discussing how to go about choosing what would work best for me...

Jenny: so, more choices are good, isn't it what dad always says when we go shopping?

Lisa (smiling): you are so right, **Jenny**. This all reminds me of shopping, in this case shopping for the right treatment...but, sometimes, having more choices can make decisions much more difficult⁷⁷...I wish there is a way to tell which treatment will work best...but, we will not exhaust ourselves to go to the extreme only to find that something may not even exist...sufficiently good enough treatment may well be what we need⁷⁸...

Billy: when we bought a car last year, dad kept asking for the track record...I remember him using the words such as "reliability and safety" ...and pestering a salesperson with the questions "how LIKELY is that the car will not break down within next 4-5 years" as he said because we buy a new car every 4-5 years...

Jenny: and I remember how he did not care about the color of the car and the nice seats that the salesperson was talking about...

Lisa: indeed, this is essentially the same process your dad and I have been going through...we are trading good and bad parts of treatment for my cancer...like should we bought a car with a great GPS and color we like, or the car that does not break that easily. Well, we figured at the time that our iPhone GPS is already good enough, and red color, which I really liked, took a back seat to the safety and reli-

ability record...so, we buy a white car, which so far has not broken...My doctor gave us odds, a guess of a sort, how likely is that treatment will help, but from his range of guesses, we now need to decide on one treatment...we are now facing a yes or no decision⁷⁹...

John: Your mom and I need some time to talk about this, and then we can share the decision as a family. (Note: Scene breaks to a place where they dated and remembered going often together as the family)

Billy: Mom and dad, what have you decided about mom's treatment? Do **Jenny** and I have a say?

Lisa: of course you do...nothing will be decided without the two of you guys...but we are still talking...we want to make a decision that we will least regret. We are still not sure if should we go for the treatment, which will almost surely have some good side- benefits as described by Dr. Williams... although probably small ones..., or try to go for a better treatment, better prize, so to say, but with much lower chances that it will work and lots of unpleasant things that we would like to avoid such as the treatment not working and may harm me more. Not sure if small gains are preferable to avoiding larger losses⁸⁰...

Billy: what do you mean "possibly harm you more"...

Lisa: well, as we have been discussing, a lot of things we do in life involve trade-offs....good things or gains...bad things or losses...Didn't we talk several months ago that if you had all straight "As" you will get new bike AND a new play station that you have wanted for sometime...but, if you only have to choose between these two....that is, you can only get EITHER a new bike OR a new play station...

Billy: but, I want both...you promised...it is not fair...

Lisa: and, you may get both...I was just trying to give you an example of the sort of decision process that dad and I are going through...as we try to predict what the future seems to be forcing upon us...

Billy: but what did the doctor say? Don't you always say that I need to listen to the doctor when we go and visit our family physician? (his voice breaks as he senses the gravity of the situation) (The puppy licks his hand. **Jenny** picks up **Harley**, who snuggles into her neck.)

Lisa: so insightful, **Billy**. Yes, we should heed the advice of the people we trust who have spent years trying to learn how to conquer cancer and are supposed to know best. But, in this case, doctors are also not sure. They talk a lot of about uncertainty... and not much about guarantees... As you will eventually learn in school, when there is uncertainty, that is when science⁸¹ is supposed to do its job and help reduce them, minimize what is unknown. And; science is indeed at work to eventually help people like your mom, but at the moment, they don't have all answers for me, and yet we have to CHOOSE...

Jenny: mommy, don't you always say that it is often good not to know everything about the future...because it would leave us without choices and hopes...

Lisa: so wise, **Jenny.** I am so proud of both of you. Perhaps we should not ask for the guarantees... perhaps acknowledging if not embracing, uncertainty⁸² in our choice may provide us with that hope we all need to help us live our lives to the fulness regardless of what the future has in store for us... the trick indeed may be to articulate uncertainty as a clarifying strategy for the decision⁸³ we are facing and then to figure out when uncertainty should be accepted and when we should try to resolve it...

(Lights slowly dimmed down)

ACT 2, act 2: final decision discussion with the doctor

(Arriving at the doctor's office, entering at the same time as the doctor)

Doctor: have you arrived at your decision?

Lisa/John: together, YES, WE HAVE!

The END

- **Acknowledgment:** *The author indebted to Sir Iain Chalmers and Dr Amy Price for reading the text, recommending suggestions for improvement, and making many edits and corrections. The author also, grateful to Prof Izet Masic who saw a value in translating the scientific concepts about uncertainty into Socrates dialog to illustrate how uncertainty touches lives of all our patients as it happens in the real-life encounters.*
- **Author's contribution:** *The author was involved in all steps of preparation of the text of*
- **Play/Drama, including final proofreading.**
- **Conflict of interest:** *None.*
- **Financial support and sponsorship:** *Nil.*

NOTES/REFERENCES

Notes (annotations) are given to provide brief explanations of the real-life issues and theoretical concepts that play a role in and shape the discussion described in the play. The critical point here is that people shift in their reasoning, which can be related to different theoretical frameworks that underpin the dialogues presented in the play. It should be noted that several decision-theoretical concepts are often used in short sequences. The primary intent here is to show that these theoretical concepts that remain cloistered within academic writings profoundly apply to real-life issues and that they matter to all of us individually and collectively. The author hopes that converting the scientific, philosophical, and technical writings into this play may help disseminate these ideas to benefit the public more than all other hundreds of scientific articles he wrote. Scientific references are provided as supporting documentation. (While the universal principles described in the play apply to all settings and

jurisdictions, specific details about treatment and regulatory perspectives are based on the US experience. The latter can be easily modified to other localities as needed).

1. (Note: the first scene attempts to capture the shock of the initial diagnosis of cancer with the focus on uncertainty about establishing diagnosis)
2. the main characters in the play are assumed to have a high educational level so that they can engage in discussion with their doctor about often complex concepts that many people find hard to understand. However, whether the patients can grasp these concepts or not, the dilemmas presented in the play cannot be avoided. The same goes for the potential audience.
3. Metastatic pancreatic cancer was selected because at the time of this writing (2022) this represents one of most deadly diseases with realistically no well-established treatment options that clearly should be favored over others. However, the issues discussed in the play apply to all medical situations even when the stakes do not appear high. As medical science finds its way to eventually cure pancreatic cancer, the future updates of the play may require adaptation to different medical problems. The issue of decision-making under uncertainty will remain inherent in clinical medicine (as indeed is the case for most life decisions).
4. (Note/comment: the exchange is meant to introduce the notions of probability and uncertainty, not being sure, not knowing...it will follow by the discussion of false positives and false negatives...pre-test probabilities, Bayes theorem)
5. Most modern scientists and philosophers consider probability as a measure of "degree of belief". Accordingly, probabilities are states of mind and not states of objects. There is no such thing as an objective probability: a probability reflects a person's knowledge or, equivalently ignorance, about some uncertain distinction. As argued by de Finetti, "The only relevant thing is uncertainty — the extent of our knowledge and ignorance. The actual fact of whether or not the events considered are in some sense determined, or known by other people, is of no consequence". Since there is no such thing as an objective probability, using a term like "subjective probability" only creates confusion. "Probabilities describing uncertainties have no need of adjectives". (for the review see: Djulbegovic B, Hozo I, Greenland S. Uncertainty in Clinical Medicine. In: Gifford F, ed. *Philosophy of Medicine (Handbook of the Philosophy of Science)*. London: Elsevier; 2011:299-356.
6. Web-based Bayes calculator to perform the calculations discussed in the text can be found at: https://ebmcalc.com/BayesianAnalysis_1.htm
The average lifetime risk of pancreatic cancer is about 1 in 64 (~1.5%): <https://www.cancer.org/cancer/pancreatic-cancer/about/key-statistics.html>
The absolute risk for developing pancreatic cancer: Klein AP, Lindström S, Mendelsohn JB, Steplowski E, Arslan

AA, et al. (2013) An Absolute Risk Model to Identify Individuals at Elevated Risk for Pancreatic Cancer in the General Population. *PLoS ONE* 8(9): e72311. doi:10.1371/journal.pone.0072311

At diagnosis, 30–40% of patients report abdominal pain (Koulouris AI, Banim P, Hart AR. Pain in Patients with Pancreatic Cancer: Prevalence, Mechanisms, Management and Future Developments. *Dig Dis Sci.* 2017;62(4):861–70.)

Data for sensitivity and specificity of CT scan for diagnosis of pancreatic cancer: Toft J, Hadden WJ, Laurence JM, Lam V, Yuen L, Janssen A, et al. Imaging modalities in the diagnosis of pancreatic adenocarcinoma: A systematic review and meta-analysis of sensitivity, specificity and diagnostic accuracy. *European Journal of Radiology.* 2017;92:17–23.

Data for sensitivity and specificity of CT scan for diagnosis of pancreatic cancer with liver metastasis:

Alabousi M, McInnes MD, Salameh J-P, Satkunasingham J, Kagoma YK, Ruo L, et al. MRI vs. CT for the Detection of Liver Metastases in Patients With Pancreatic Carcinoma: A Comparative Diagnostic Test Accuracy Systematic Review and Meta-Analysis. *Journal of Magnetic Resonance Imaging.* 2021;53(1):38–48.

As metastasis to the liver typically presents with involvement of the pancreas, the author assumed that CT is 90% sensitive and 95% specific for the diagnosis of metastatic pancreatic cancer to the liver.

Post-test probability for pancreatic cancer using average lifetime risk (i.e., at **15% of pre-test probabilities**)=21.5% (scenario without knowing anything about the patient)

Post-test probability for pancreatic cancer at high risk due to family history, alcohol, and smoking (i.e., at **5% of pre-test probabilities**)=48.6% (scenario at high risk but without symptom of pain)

Post-test probability for pancreatic cancer at high risk but presenting with pain (i.e., at **40% of pre-test probabilities**)=92.3% (scenario at high risk but abdominal pain)

7. Mathematically this is expressed as $P(T+|D+) \neq P(D+|T+)$ meaning that the probability (P) of a positive test (T+) given the presence of disease (D+) is not the same as the probability of having the disease given a positive test.

8. an idea here is to illustrate how often people cling to unlikely, often far-fetched differential-diagnostic possibilities

9. Medical students and physicians are increasingly taught about probabilities and how to communicate them to their patients. The purpose of this exchange is to illustrate how much of doctors' reasoning relies on heuristics (rules-of-thumb) and not so much on the formal probability calculus despite the extensive training that many physicians have about the probabilities, statistics, and likelihoods: Gigerenzer G, Brighton H. Homo heuristics: why biased minds make better inferences. *Top Cogn Sci.* 2009;1(1):107–43. Gigerenzer G, Hertwig

R, Pachur T, eds. *Heuristics. The foundation of adaptive behavior.* New York: Oxford University Press; 2011. Gigerenzer G, Todd P, ABC-Research-Group. *Simple heuristics that make us smart.* 1999.

However, physicians also rely on other reasoning and decision-making strategies such as using both analytical (deductive and inductive-probability-based) and affect-based reasoning such as regret (see also notes below). Djulbegovic B, Beckstead JW, Elqayam S, et al. Evaluation of Physicians' Cognitive Styles. *Med Decis Making.* 2014;34(5):627–37.

10. this scene/Act is about management options, standards, and experimental treatments

11. This section focus on breaking bad news, attempting to mix what goes on in the real life with the ideal communication approach.

12. The doctor tries to send the message that it is **Lisa** the patient- whose views are most relevant

13. The author has seen many patients who blamed themselves or felt shocked when they were diagnosed with cancer despite doing everything they could to keep a healthy lifestyle.

14. This exchange tries to convert the principles of communicating uncertainty toward actionable behavior (Communication is considered effective when it leads to engagement in recommended behavior when the target audience pays attention to the message when it results in the improved acquisition of knowledge, acceptable effects on emotions, and accurate judgments of perceived risks and benefits, and when it results in a message that is credible, accurate, useful, relevant, comprehensive, trustful, clear, and easy to understand).

Communication about uncertainty is all about expectations and managing expectations. One approach illustrated here is to try to establish bounds, anchors of human longevity. This often provides a framework for the expectations and addresses the issues of misinformation and disinformation (see also Djulbegovic B, Hozo I, Greenland S. *Uncertainty in Clinical Medicine.* In: Gifford F, ed. *Philosophy of Medicine (Handbook of the Philosophy of Science).* London: Elsevier; 2011:299–356. Djulbegovic B. Ethics of uncertainty. *Patient Education and Counseling.* 2021;104(11):2628–34.

15. One of the techniques in communicating bad news that I have used is to “normalize” the dismal situation in which patients find themselves by providing some natural anchor that everyone accepts (as no one lives 150 years).

16. misinformation refers to conveying false information, regardless of intent to mislead; disinformation refers to deliberately providing misleading or biased information, manipulated narrative or facts; propaganda.

17. Much of the text in the play is based on the scientific and philosophical debate on inferences, evidence, and rationality: Pinker S. *Rationality. What it is. Why it seems scarce? Why it matters.* New York: Random House; 2021. Stanovich KE. *Rationality and the Reflective Mind.* Oxford: Oxford University Press; 2011.

- Djulbegovic B. Ethics of uncertainty. *Patient Education and Counseling*. 2021;104(11):2628–34. Djulbegovic B. Uncertainty and Equipoise: At Interplay Between Epistemology, Decision Making and Ethics. *Am J Med Sci*. 2011;342(4):282–9. Djulbegovic B, Guyatt GH, Ashcroft RE. Epistemologic inquiries in evidence-based medicine. *Cancer Control*. 2009;16(2):158–68. Djulbegovic B, Guyatt G. EBM and the Theory of Knowledge. In: Guyatt G, Meade M, Cook D, eds. *Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice*. Boston: McGraw-Hill; 2014. Djulbegovic B, Elqayam S. Many faces of rationality: Implications of the great rationality debate for clinical decision-making. *J Eval Clin Pract*. 2017;23(5):915–22. Djulbegovic B, Hamm RM, Mayrhofer T, Hozo I, Van den Ende J. Rationality, practice variation and person-centered health policy: a threshold hypothesis. *J Eval Clin Pract*. 2015;21(6):1121–4. Hozo I, Schell MJ, Djulbegovic B. Decision-making when data and inferences are not conclusive: risk-benefit and acceptable regret approach. *Semin Hematol*. 2008;45(3):150–9. Djulbegovic B, Elqayam S, Dale W. Rational decision making in medicine: Implications for overuse and underuse. *J Eval Clin Pract*. 2018;24(3):655–65
18. See Djulbegovic B. Ethics of uncertainty. *Patient Education and Counseling*. 2021;104(11):2628–34.
19. Djulbegovic B, Ioannidis JPA. Precision medicine for individual patients should use population group averages and larger, not smaller, groups. *European Journal of Clinical Investigation*. 2019;49(1):e13031.
20. Williams S. Pancreatic cancer. pp: 187–191 In: Djulbegovic B, Sullivan DS, eds. *Decision Making in Oncology. Evidence-based management*. New York: Churchill Livingstone, Inc; 1997. In the seminal trial (Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. *New England Journal of Medicine*. 2011;364(19):1817–25.), 2/171 (1.1%; 95%CI 0.14% to 4.10%) patients on FOLFIRINOX (see below) were alive at 42 months from the date of randomization; given that symptoms can precede diagnosis by months and even years in some cases (Nai Q, Luo H, Zhang P, Hossain MA, Gu P, Sidhom IW, et al. How Early Can Pancreatic Cancer Be Recognized A Case Report and Review of the Literature. *Case Reports in Oncology*. 2015;8(1):46–9) the actual survival is longer.
21. Djulbegovic B, Ioannidis JPA. Precision medicine for individual patients should use population group averages and larger, not smaller, groups. *European Journal of Clinical Investigation*. 2019;49(1):e13031. Djulbegovic B, Hozo I, Greenland S. Uncertainty in Clinical Medicine. In: Gifford F, ed. *Philosophy of Medicine (Handbook of the Philosophy of Science)*. London: Elsevier; 2011:299–356. Hill AB. The clinical trial. *N Engl J Med*. 1952(247):113–9.
22. See: <https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative#:~:text=Early%20in%202022%2C%20President%20Biden,with%20cancer%20and%20cancer%20survivors>
- Djulbegovic B, Ioannidis JPA. Precision medicine for individual patients should use population group averages and larger, not smaller, groups. *European Journal of Clinical Investigation*. 2019;49(1):e13031.
23. Djulbegovic B, Ioannidis JPA. Precision medicine for individual patients should use population group averages and larger, not smaller, groups. *European Journal of Clinical Investigation*. 2019;49(1):e13031
24. The intent here is to describe the complexity of decision-making, which involves both emotions, intuitions as well as the analysis/deliberation...the so-called type 1(system 1) vs. type 2(system 2) cognitive processes...experimental design...trade-offs...individual (patients' values and preferences) vs. societal issues). : Djulbegovic B. Ethics of uncertainty. *Patient Education and Counseling*. 2021;104(11):2628–34; Djulbegovic B, Elqayam S. Many faces of rationality: Implications of the great rationality debate for clinical decision-making. *J Eval Clin Pract*. 2017;23(5):915–22. Mellers B, Schwartz A, Ritov I. Emotion-Based Choice *Journal of Experimental Psychology: General*. 1999;128(3):332–45. Evans JSBT, Stanovich KE. Dual-process theories of higher cognition: Advancing the debate. *Perspectives on Psychological Science*. 2013;8(3):223–41. For general texts on these issues, please see: Kahneman D. *Thinking fast and slow*. New York: Farrar, Straus and Giroux; 2011; Hastie R, Dawes RM. *Rational choice in an uncertain world*. 2nd edition. Los Angeles: Sage Publications, Inc.; 2010. Stanovich KE. *Rationality and the Reflective Mind*. Oxford: Oxford University Press; 2011.
25. What follows is one of the key essences of making a rational choice under medical uncertainty – it is inevitably linked to our moral choices. The ethicists and philosophers have long chased an elusive ethical “**triple aim**”- arriving at a decision that respects the right of a person to decide as an autonomous human being, has the best possible chances to personally benefit from the treatments under consideration, while contributing to knowledge that can help others in the future. For an in-depth philosophical treatise on the subject see Parfit, Derek (1984). *Reasons and Persons*. Oxford: Oxford University Press. p. vii. ISBN 019824908X.
26. Sunstein CR. *The cost-benefit revolution*. Cambridge, Massachusetts: The MIT Press; 2018.
27. <https://library.ncl.org/ca/090101>; Daniel Austin, *Medical Debt As a Cause of Consumer Bankruptcy* (Jan. 2014), available at <https://repository.library.northeastern.edu>.
28. This is an attempt to capture real-life presentations. Physicians are required to discuss benefits and harms, typically in a time-constraint setting. While many provide information brochures and/or occasionally use visual decision aids, all of them first verbally explain what is to be expected in terms of benefits and harms. And, often, like a clerk who has been asked many times for some instructions, they just rattle information they have repeated many times.
29. As noted in the first endnote above, this applies to

the treatment of metastatic pancreatic cancer at this time (2022); as science advances, the treatment and assessment of benefits and harms will have to be modified, but the issues that need to be addressed will remain essentially identical

30. The seminal trial that established FOLFIRONOX as the standard of care for metastatic pancreatic cancer (for patients with good performance status) showed median survival on FOLFIRONOX of 11.1 months vs. 6.8 on gemcitabine single agent treatment (Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. *New England Journal of Medicine*. 2011;364(19):1817-25.

Chemotherapy with a single agent is superior to the best supportive care (without chemotherapy) (by improving survival for about 3 months, with median survival of about 6-7 months). Yip D, Karapetis C, Strickland A, Steer CB, Goldstein D. Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD002093. DOI: 10.1002/14651858.CD002093.pub2. Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-Analyses of Chemotherapy for Locally Advanced and Metastatic Pancreatic Cancer. *Journal of Clinical Oncology*. 2007;25(18):2607-15. Williams S. Pancreatic cancer. pp: 187-191 In: Djulbegovic B, Sullivan DS, eds. *Decision Making in Oncology. Evidence-based management*. New York: Churchill Livingstone, Inc; 1997.

31. The association between conflict of interest (defined to exist when professional judgment concerning a primary interest such as patients' welfare, the validity of research, or making practice guideline recommendations) may be influenced by a secondary interest (such as financial gain) and health outcomes in favor of commercial sponsor is a well-established phenomenon that continues to pollute the research results. As a result, the patients are often presented with misleading results. (Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: a systematic review. *BMJ*. 2003;326(7400):1167-70.)

32. It is widely considered that physicians' indiscriminate prescribing of opioids led to one of the major health crises in the history of the US (including a drop in life expectancy for the first time since 1900see; Soelberg CD, Brown REJ, Du Vivier D, Meyer JE, Ramachandran BK. The US Opioid Crisis: Current Federal and State Legal Issues. *Anesthesia & Analgesia*. 2017;125(5):1675-81.

33. When there is a conflict between common and conflicting interests between two 'players' – a doctor and a patient, for example – the situation can be described using game theory. Game theory models situations fraught with conflict and cooperation. It assumes that everyone has 'skin in the game' and that people act strategically to advance their interests. The best-known example of a strategic game is the Prisoners' Dilemma game. **We can escape from the healthcare prisoners' dilemma if**

society incentivizes the alignment of interests of doctors and patients. When the trust in the system is high and the pay-offs of different "players" are similar, the game theory conflict does not apply anymore. This can be accomplished by having a better evidence base, increasing trust in the system, and transparency, which, in turn, will help clarify the expectations of all players involved. **When trust is high, the Prisoner' Dilemma is avoidable.** It is relations built on trust that historically has kept a patient-physician encounter outside of the confines of the game theory. Similar issues apply to both the health system at large and to clinical research conduct. See: Djulbegovic B, Hozo I. When is it rational to participate in a clinical trial? a game theory approach incorporating trust, regret and guilt. *BMC Medical Research Methodology*. 2012;12(1):85. Djulbegovic B, Hozo I, Ioannidis JP. Modern health care as a game theory problem. *Eur J Clin Invest*. 2015;45(1):1-12.

34. This discussion here focuses on the so-called value-based care, cost-effectiveness, and cost-effectiveness i.e. the value(s) from a societal vs personal perspective. In philosophy, **value (singular) refers to worth**, which typically embodies some sort of comparison and exchange (e.g., via economic analyses), while **values (plural) reside in the morality of actions** (i.e., is our deed good or bad?). Value relies to some degree on social consensus, while values relate to those held personally, which may or may not be shared with others. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the \$50,000-per-QALY threshold. *N Engl J Med*. 2014;371(9):796-7. Djulbegovic B. Value-Based Cancer Care and the Excessive Cost of Drugs. *JAMA Oncol*. 2015;1(9):1301-2. Pathak BE, Wieten S, Djulbegovic B. Critical Reflections on Value in Medicine. *J Med Pers* 2013;11:69-72. 2013;11:69-72.

35. <https://www.cochrane.org/> (currently, widely considered the most reliable database of systematic reviews)

36. This is meant to educate the public about the best source of evidence and the importance of systematic reviews.

37. COVID-19 disease is caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus or SARS-CoV-2), which was first detected in China's Hubei Province, in the city of Wuhan, in December of 2019. On March 11, 2020, the WHO declared COVID-19 a pandemic. At the time of this writing, the pandemic is still not over. By October 16, 2022, the worldwide 629,848,573 people died from COVID-19 (<https://coronavirus.jhu.edu/region/united-states>); in the US alone 1,065,108 million people died from COVID19, more than a combined number of deaths reported in all wars the US fought) Deaths from COVID-19 (<https://www.worldometers.info/coronavirus/>). See also the COVID-19 timeline: <https://www.cdc.gov/museum/timeline/covid19.html#:~:text=March%2011%2C%202020,declares%20COVID%2D19%20a%20pandemic..>

38. former US President Trump has promoted the unproven therapy during the COVID-19 pandemic. Three big

- studies dim hopes that hydroxychloroquine can treat or prevent COVID-19 | Science | AAAS; see also Djulbegovic B, Guyatt G. Evidence-based medicine in times of crisis. *Journal of Clinical Epidemiology*. 2020. (<https://doi.org/10.1016/j.jclinepi.2020.07.002>)
39. Djulbegovic M, Djulbegovic B. Implications of the principle of question propagation for comparative-effectiveness and “data mining” research. *JAMA*. 2011;305(3):298-9. Djulbegovic B, Guyatt GH, Ashcroft RE. Epistemologic inquiries in evidence-based medicine. *Cancer Control*. 2009;16(2):158-68.
40. For a review of progress in EBM see Djulbegovic B, Guyatt GH. Progress in evidence-based medicine: a quarter century on. *Lancet*. 2017;390(10092):415-23.
41. “The National Comprehensive Cancer Network® (NCCN®) is a not-for-profit alliance of 32 leading cancer US centers devoted to patient care, research, and education. NCCN is dedicated to improving and facilitating quality, effective, equitable, and accessible cancer care so all patients can live better lives.” https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf; <https://www.nccn.org/patientresources/patient-resources/guidelines-for-patients/guidelines-for-patients-details?patientGuidelineId=33>
42. Silverman WA, Chalmers I. Casting and drawing lots: a time-honoured way of dealing with uncertainty and for ensuring fairness. *BMJ*. 2001;323:1467-8.
43. Justification for randomized trial of FOLFIRINOX against gemcitabine plus nabpaclitaxel (Klein-Brill A, Amar-Farkash S, Lawrence G, Collisson EA, Aran D. Comparison of FOLFIRINOX vs Gemcitabine Plus Nab-Paclitaxel as First-Line Chemotherapy for Metastatic Pancreatic Ductal Adenocarcinoma. *JAMA Network Open*. 2022;5(6):e2216199-e.)
44. Freedman B. Equipose and the ethics of clinical research. *N Engl J Med*. 1987;317:141-5. Mann H, Djulbegovic B. Clinical equipose and the therapeutic misconception. *Hastings Cent Rep*. 2003;33(5):4; author reply -5. Mhaskar R, Bercu B, Djulbegovic B. At what level of collective equipose does a randomized clinical trial become ethical for the members of institutional review board/ethical committees? *Acta Inform Med*. 2013;21(3):156-9. Djulbegovic B. Uncertainty and Equipose: At Interplay Between Epistemology, Decision Making and Ethics. *Am J Med Sci*. 2011;342(4):282-9. Djulbegovic B. Articulating and responding to uncertainties in clinical research. *J Med Philosophy*. 2007;32:79-98.
45. See Djulbegovic B. A Framework to Bridge the Gaps Between Evidence-Based Medicine, Health Outcomes, and Improvement and Implementation Science. *Journal of Oncology Practice*. 2014;10(3):200-2. Djulbegovic B, Paul A. From Efficacy to Effectiveness in the Face of Uncertainty Indication Creep and Prevention Creep *JAMA*. 2011;305(19):2005-6
46. Reference to Stephen Gould’s paper: <https://journalofethics.ama-assn.org/article/median-isnt-message/2013-01>
47. A story of stem cell transplant for breast cancer: Rettig RA, Jacobson PD, Farquhar CM, Aubry WM. False hope. Bone marrow transplantation for breast cancer. New York: Oxford University Press; 2007.
48. Baron RJ, Ejnes YD. Physicians Spreading Misinformation on Social Media — Do Right and Wrong Answers Still Exist in Medicine? *New England Journal of Medicine*. 2022;387(1):1-3.
49. Success rate in early, mostly phase I trials: Djulbegovic B, Glasziou P, Chalmers I. The importance of randomised vs non-randomised trials. *The Lancet*. 2019;394(10199):634-5. Djulbegovic B, Glasziou P, Klocksieben FA, Reljic T, VanDenBergh M, Mhaskar R, et al. Larger effect sizes in nonrandomized studies are associated with higher rates of EMA licensing approval. *Journal of Clinical Epidemiology*. 2018;98:24-32.
50. See <https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try>
51. Mhaskar R, Miladinovic B, Guterbock TM, Djulbegovic B. When are clinical trials beneficial for study patients and future patients? A factorial vignette-based survey of institutional review board members. *BMJ Open*. 2016;6(9):e011150.
52. Silverman WA, Chalmers I. Casting and drawing lots: a time-honoured way of dealing with uncertainty and for ensuring fairness. *BMJ*. 2001;323:1467-8.
53. This discussion was to integrate the argument of how using RCTs to respond to equipose meets criteria for fulfilling what ethicists call “triple aim”- finding the Goldilocks zone between Kantian, utilitarian, and contractualism/right-based ethics; see: Djulbegovic B. Articulating and responding to uncertainties in clinical research. *J Med Philosophy*. 2007;32:79-98. Parfit, Derek (1984). *Reasons and Persons*. Oxford: Oxford University Press. p. vii. ISBN 019824908X.
54. See: <https://plato.stanford.edu/entries/kant-moral/>
55. See: <https://plato.stanford.edu/entries/utilitarianism-history/>
56. See *Nature Biotechnol* 2014;32:40-51
57. Djulbegovic B, Hozo I. When Should Potentially False Research Findings Be Considered Acceptable? *PLoS Medicine*. 2007;4(2):e26.
58. One of our key mechanisms for optimal decision-making is to regulate regret. See: Djulbegovic B, Frohlich A, Bennett CL. Acting on Imperfect Evidence: How Much Regret Are We Ready to Accept? *J Clin Oncol*. 2005;23(28):6822-5. Djulbegovic B, Hozo I. When is it rational to participate in a clinical trial? a game theory approach incorporating trust, regret and guilt. *BMC Medical Research Methodology*. 2012;12(1):85. Djulbegovic B, Hozo I, Schwartz A, McMasters K. Acceptable regret in medical decision making. *Med Hypotheses*. 1999;53:253-9. Djulbegovic M, Beckstead J, Elqayam S, Reljic T, Kumar A, Paidas C, et al. Thinking Styles and Regret in Physicians. *PLoS One*. 2015;10(8):e0134038. Hozo I, Djulbegovic B. When is diagnostic testing inappropriate or irrational? Acceptable regret approach. *Med Decis Making*. 2008;28(4):540-53. Hozo I, Schell MJ, Djulbegovic B. De-

cision-making when data and inferences are not conclusive: risk-benefit and acceptable regret approach. *Semin Hematol.* 2008;45(3):150-9. Tsalatsanis A, Barnes LE, Hozo I, Djulbegovic B. Extensions to Regret-based Decision Curve Analysis: An application to hospice referral for terminal patients. *BMC Medical Informatics and Decision Making.* 2011;11:77. Tsalatsanis A, Hozo I, Djulbegovic B. Acceptable regret model in the end-of-life setting: Patients require high level of certainty before forgoing management recommendations. *Eur J Cancer.* 2017;75:159-66. Tsalatsanis A, Hozo I, Vickers A, Djulbegovic B. A regret theory approach to decision curve analysis: A novel method for eliciting decision makers' preferences and decision-making. *BMC Medical Informatics and Decision Making.* 2010;10(1):51.

59. This pattern of treatment success is not accidental, but is directly related to the moral principle for conduct of clinical trials known as equipoise or uncertainty principle (also dubbed as **the law of therapeutic discovery**) Chalmers I. What is the prior probability of a proposed new treatment being superior to established treatments? *BMJ.* 1997;314:74-5. Djulbegovic B. Articulating and responding to uncertainties in clinical research. *J Med Philosophy.* 2007;32:79-98; Djulbegovic B, Kumar A, Glasziou PP, Perera R, Reljic T, Dent L, et al. New treatments compared to established treatments in randomized trials. *Cochrane Database Syst Rev.* 2012;10:MR000024. Djulbegovic B, Kumar A, Soares HP, Hozo I, Beppler G, Clarke M, et al. Treatment success in cancer: new cancer treatment successes identified in phase 3 randomized controlled trials conducted by the National Cancer Institute-sponsored cooperative oncology groups, 1955 to 2006. *Arch Intern Med.* 2008;168(6):632-42. Djulbegovic B. The paradox of equipoise: the principle that drives and limits therapeutic discoveries in clinical research. *Cancer Control.* 2009;16(4):342-7. Djulbegovic B, Kumar A, Glasziou P, Miladinovic B, Chalmers I. Medical research: Trial unpredictability yields predictable therapy gains. *Nature.* 2013;500(7463):395-6.

60. Djulbegovic B, Kumar A, Glasziou P, Miladinovic B, Chalmers I. Medical research: Trial unpredictability yields predictable therapy gains. *Nature.* 2013;500(7463):395-6. Also, see the previous note

61. **The requirement to uncertainty and subsequently conducting a trial to address such an uncertainty directly links the theory of human experimentation with theory of rational choice.**

62. Effective vaccine against COVID-19 was developed, tested and approved in less than year; see <https://www.cdc.gov/museum/timeline/covid19.html#:~:text=March%2011%2C%202020,declares%20COVID%2D19%20a%20pandemic..>

63. the idea here is to rehearse how actually the patient may have understood the conversation with his/her doctor (presented in somewhat ideal terms that can go between two highly educated individuals). The patients usually forget about 50-75% of the conversation

and taping the discussion is encouraged.

64. "rippling" is a concept describing how can we live forever ...through our kids and other people they know us and love us...

65. On Jan 6, 2021, for the first time in US history peaceful transition of power – from sitting President Trump to newly elected President Biden– was violently threatened. It is widely believed that President Trump orchestrated the riot and the attack on the US Capitol (https://en.wikipedia.org/wiki/January_6_United_States_Capitol_attack)

66. Stanovich KE, West RF, Toplak ME. Myside bias, rational thinking, and intelligence. *Current Directions in Psychological Science.* 2013;22:259-64.

67. Reference to 100% remission in the treatment of colorectal cancer with immune therapy: Remission in Every Patient <https://www.nytimes.com/2022/06/05/health/rectal-cancer-checkpoint-inhibitor.html>; <https://www.nejm.org/doi/full/10.1056/NEJMoa2201445>

68. The concept of entropy is one of the most scientific concepts in the history of science. It originated in the field of thermodynamics and is central to the second law of thermodynamics, which states that the entropy of isolated systems i.e., physical systems that do not interact with other systems always increases toward a state of disorder, randomness, or uncertainty when the entropy is highest. This implies the irreversibility of natural processes, often referred to in the concept of the arrow of time. Entropy is used in diverse scientific disciplines. In information theory, entropy quantifies the amount of uncertainty. It can be shown that when the choices between two or more treatment options are the same, entropy is of the highest value. See: Shannon CE, Weaver W. *The mathematical theory of communication.* Urbana: The University of Illinois Press; 1962; Tsalatsanis A, Hozo I, Djulbegovic B. Research synthesis of information theory measures of uncertainty: Meta-analysis of entropy and mutual information of diagnostic tests. *Journal of Evaluation in Clinical Practice.* 2021;27(2):246-55.

69. "I need permission to give a drug to half of my patients, but not to give it to them all." A famous paradox related to drug development was described by Dr. Smithells in 1975. Smithells RW. Iatrogenic hazards and their effects. *Postgrad Med J* 1975; 15:39-52

70. See: <https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try>

71. This section expands on Hammond's "Irreducible Uncertainty, Inevitable Error, Unavoidable Injustice." Hammond KR. *Human Judgment and Social Policy. Irreducible Uncertainty, Inevitable Error, Unavoidable Injustice.* Oxford: Oxford University Press; 1996. See also; Djulbegovic B, Paul A. From Efficacy to Effectiveness in the Face of Uncertainty Indication Creep and Prevention Creep *JAMA.* 2011;305(19):2005-6; Djulbegovic B. Ethics of uncertainty. *Patient Education and Counseling.* 2021;104(11):2628-34.

72. Hardin famously described the tension between individual vs societal interest (in the setting of population problem) to argue that the problem is technically not solvable. Hardin G. *The Tragedy of the Commons*. *Science*. 1968;162(5364):1243-8.
73. One important question that has received considerable attention in scientific literature refers to the hypothesis that the so-called breakthrough, dramatic, “between-the-eyes-treatment” effects can be so large making use of randomized controlled trials (RCTs) unnecessary. However, an empirical analysis showed that these large effects are about equally concentrated in the tails of distributions of RCTs and non-RCTs. That is, the effect sizes observed in RCTs and nonrandomized trials (including phase I trials) considerably overlap. Large, breakthrough effects are rare and there is no clear threshold for dramatic effects that would obviate future RCTs. The determination of whether a particular effect is “dramatic” or not will always have to be judged on a case-by-case basis- within a context of basic science, preclinical, clinical testing, and analytic framework -statistical and cognitive-of the specific treatment under consideration (Hozo I, Djulbegovic B, Parish AJ, Ioannidis JPA. Identification of threshold for large (dramatic) effects that would obviate randomized trials is not possible. *J Clin Epidemiol*. 2022;145(May 22):101-11.)
74. The World Medical Association (WMA), the Declaration of Helsinki statement of ethical principles for medical research involving human subjects states: “Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects”. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects – WMA – The World Medical Association()
75. Discussion of acceptable regret (which also goes under technical term “robust satisficing”)- a concept that some our wrong decision we don’t regret; see Djulbegovic B, Hozo I, Schwartz A, McMasters K. Acceptable regret in medical decision making. *Med Hypotheses*. 1999;53:253-9. Hozo I, Djulbegovic B. When is diagnostic testing inappropriate or irrational? Acceptable regret approach. *Med Decis Making*. 2008;28(4):540-53. Hozo I, Djulbegovic B. Clarification and corrections of acceptable regret model. *Medical Decision Making* 2009;29:323-4. Hozo I, Schell MJ, Djulbegovic B. Decision-making when data and inferences are not conclusive: risk-benefit and acceptable regret approach. *Semin Hematol*. 2008;45(3):150-9. Tsalatsanis A, Hozo I, Djulbegovic B. Acceptable regret model in the end-of-life setting: Patients require high level of certainty before forgoing management recommendations. *Eur J Cancer*. 2017;75:159-66. Djulbegovic B, Elqayam S. Many faces of rationality: Implications of the great rationality debate for clinical decision-making. *J Eval Clin Pract*. 2017;23(5):915-22. Djulbegovic B, Elqayam S, Dale W. Rational decision making in medicine: Implications for overuse and underuse. *J Eval Clin Pract*. 2018;24(3):655-65.
76. reference to Hippocrates-To cure sometimes, treat often, comfort always
77. Can people feel worse off as the options they face increase? The present studies suggest that some people—maximizers—can. Schwartz B, Ward A, Monterosso J, Lyubomirsky S, White K, Lehman DR. Maximizing versus satisficing: happiness is a matter of choice. *J Pers Soc Psychol*. 2002;83(5):1178-97.
78. The exchange refers that a satisficing (finding a good enough solution) instead of maximizing approach (finding the best possible solution) may be a more rational approach under uncertainty. (Heuristic approach to decision-making is the mechanism of implementation of the so-called theory of bounded rationality which relies on a satisficing process (finding a good enough solution) instead of maximizing approach (finding the best possible solution) under uncertainty. Often these simple strategies can outperform complex statistical models, in a phenomenon known as “less-is-more”) (Gigerenzer G, Brighton H. *Homo heuristics: why biased minds make better inferences*. *Top Cogn Sci*. 2009;1(1):107-43. Gigerenzer G, Hertwig R, Pachur T, eds. *Heuristics. The foundation of adaptive behavior*. New York: Oxford University Press; 2011.;Gigerenzer G, Todd P, ABC-Research-Group. *Simple heuristics that make us smart*. 1999.)
79. While evidence presents at continuum, decisions are categorical: yes or no; this is known as the threshold hypothesis of decision-making: Djulbegovic B, Hamm RM, Mayrhofer T, Hozo I, Van den Ende J. Rationality, practice variation, and person-centered health policy: a threshold hypothesis. *J Eval Clin Pract*. 2015;21(6):1121-4. Djulbegovic B, van den Ende J, Hamm RM, Mayrhofer T, Hozo I, Pauker SG, et al. When is rational to order a diagnostic test, or prescribe treatment: the threshold model as an explanation of practice variation. *Eur J Clin Invest*. 2015;45(5):485-93. Hozo I, Djulbegovic B, Luan S, Tsalatsanis A, Gigerenzer G. Towards theory integration: Threshold model as a link between signal detection theory, fast-and-frugal trees, and evidence accumulation theory. *J Eval Clin Pract*. 2017;23(1):49-65. Djulbegovic B, Hozo I, Mayrhofer T, van den Ende J, Guyatt G. The threshold model revisited. *Journal of Evaluation in Clinical Practice*. 2019;25(2):186-95.
80. This is the perspective of prospect theory: “gains saturate, losses escalate”) Kahneman D, Tversky A. “Prospect theory”: an analysis of decision under risk. *Econometrica*. 1979;47:263-91.. Kahneman D, Tversky A. The psychology of preferences. *Sci American*. 1982;246:160-Tversky A, Kahneman D. *Advances in Prospect Theory: Cumulative Representation of Uncertainty*. *Journal of Risk and Uncertainty*. 1992;5:297-323. Kahneman D. *Thinking fast and slow*. New York: Farrar, Straus and Giroux; 2011.
81. **Science can often be understood as the means to address and resolve some of the uncertainties of interest to a decision-maker** (which can consist of description, explanation, prediction, or intervention related to the phenomena of interest) (Djulbegovic B, Hozo I,

Greenland S. Uncertainty in Clinical Medicine. In: Gifford F, ed. *Philosophy of Medicine (Handbook of the Philosophy of Science)*. London: Elsevier; 2011:299–356)

82. Even though uncertainty is typically abhorred and requires a resolution, there is a paradox in dealing with uncertainty: imagine life without uncertainty, a future that is totally predictable and deterministic, with no choice to be made, no trade-offs to consider, and nothing to hope for. (see: Djulbegovic B, Hozo I, Greenland S. Uncertainty in Clinical Medicine. In: Gifford F, ed. *Philosophy of Medicine (Handbook of the Philosophy of Science)*. London: Elsevier; 2011:299–356; Djulbegovic B.

Well-informed uncertainties about the effects of treatment: Paradox exists in dealing with uncertainty. *BMJ*. 2004;328(7446):1018–; Djulbegovic B. Acknowledgment of uncertainty: a fundamental means to ensure scientific and ethical validity in clinical research. *Curr Oncol Rep*. 2001 Sep;3(5):389–95. doi: 10.1007/s11912-001-0024-5. PMID: 11489238; Djulbegovic B. Articulating and responding to uncertainties in clinical research. *J Med Philosophy*. 2007;32:79–98.

83. Djulbegovic B. Ethics of uncertainty. *Patient Education and Counseling*. 2021;104(11):2628–34.

AFTERWORD

How to make the life and death medical decisions? Using a playwright and Socrates dialogue format to connect the science of uncertainty with personal humanity decision

It has been said that science is about articulating and responding to uncertainties. In clinical medicine, these uncertainties typically revolve around diagnosis, prognosis, and treatment. The science of uncertainty has tremendously advanced during the last couple hundred years, particularly during the previous 20 to 30 years. This has allowed ever better descriptions, explanations, and predictions of the effect of disease and treatment in group and individual patients alike. But uncertainty is theoretically impossible to eliminate. This creates enormous scientific and ethical problems for all our patients –what should the physicians and patients working together do when they face uncertainty, particularly life-threatening events? What is the most rational and ethical way to treat people facing life-and-death decisions? How do we exactly communicate these inevitable uncertainties that all of us will sooner or later face?

Building on decades of the science of uncertainty, Dr Djulbegovic has converted a huge amount of literature into a Socrates dialogue and playwright format to show how the seemingly esoteric multiple theoretical concepts have relevant, real-life implications. The result is a unique text [*An Impossible Decision—the Life Interrupted by Uncertainty*], presented as a drama in two acts where the main protagonist-Lisa, a 45 woman who suddenly finds her life interrupted by pancreatic cancer - has to navigate all unknowns in the face of life-threatening disease.

In this journal, we have published many technical papers offering various mathematical and statistical insights on handling medical uncertainties. However, none of these papers shows real-life relevance to patients often left alone to make these difficult decisions. This is the reason that we decided to publish this text, which brilliantly bridges science with ethics to offer a solution to the ever-elusive "triple ethical aim"- arriving at a decision that respects the right of a person to decide as an autonomous human being, has the best possible chances to personally benefit from the treatments

under consideration, while contributing to knowledge that can help others in the future.

By publishing this text, we hope to reach a much wider audience than it is possible using technical, scientific papers. In particular, we aim to educate the public on how medical advances are made and how inferences and evidence are generated and appraised - in the best tradition of evidence-based medicine while highlighting uncertainties and inevitable trade-offs that accompany science, policies, and personal choices in the attempt to arrive at most satisfactory decisions. The **audience** for this play consists of all people touched by cancer- as patients, their loved ones, healers, or policy-makers- literally millions of people worldwide. In addition to the general public, this play's important audiences are students and faculty in humanities disciplines and medical schools. These students are required to read many dense scientific, philosophical, and technical writings (many of which are referenced/annotated in the Endnotes in the play); The play provides an **exceptional teaching tool** to show how to apply these concepts to decisions relevant to all of us and what shared decision-making entails. We also encourage the theaters and movie producers to enact the play on the stages anywhere in the world and/ or adapt for the movie.

To the best of my knowledge, this is the first editorial attempt to use this format to seek the convergence between the natural sciences and humanities in the great tradition of the search for Consilience- the unity of knowledge. We hope other publishers and journals will follow suit.

Izet Masic, MD, PhD, FWAAS, FEASA, FIAHSI, FEFMI, FACMI
Professor Emeritus of University in Sarajevo, Sarajevo, Bosnia and Herzegovina, President of Academy of Medical Sciences in Bosnia and Herzegovina, Fellow of World Academy of Art and Science, Fellow of European Academy of Sciences and Arts, Fellow of International Academy of Health Sciences Informatics, Fellow of European Federation for Medical Informatics, Fellow of American College of Medical Informatics
E-mail: imasic@lol.ba; izetmasic@gmail.com