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How Accurate and Reliable (Certain) Are Medical Predictions?

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Abstract

Unpredictability and uncertainty reigns over most of medicine. Should women be screened for mammography and men for prostate cancer? The answer is not obvious as a growing number of researchers and doctors assert that the harm of preventive measures is greater than the benefits. Can patients trust the diagnoses of their doctors? Awkwardly, research has shown that the chance of a correct diagnosis of difficult cases to be as low as 5.8% and worse that the doctors involved were 64% certain that they were right. Further, a new study estimates as many as 400,000 deaths a year in the USA caused by medical errors. In addition, assuming a correct diagnosis the wrong treatment can be applied, an inappropriate dosage of the prescribed medicine can be given, while patients may not consume the recommended dosages correctly. Moreover, there can be harmful side effects from medication, "never events" and infections by superbugs while in hospitals. These occurrences increase the chance that something can go wrong, enlarging uncertainty and decreasing the predictability that a cure will be successful. In medicine as in other fields, forecasts are needed to improve our decisions regarding future events and medical decisions are not exceptions. In the great majority of cases, the higher their accuracy and the lower their uncertainty the greater their value and the higher our confidence that our decisions will be correct. As most medical decisions require predictions about future, uncertain events, it is of interest to know their accuracy and correctly appreciate their level of uncertainty, or their reliability. This paper is organized in two parts. It uses a forecasting perspective and considers how accurately we can predict first the consequences of preventive and second those of curative medicine while also discussing the uncertainty involved when making such predictions. There is also a concluding section summarizing the findings and proposing some actions to improve the accuracy and reduce the uncertainty in medical decisions.

Keywords: Medical Predictions, Diagnostic Accuracy, Medical Errors, Prescription Errors, Superbugs, Preventive Screening, Medical Research, Correct Treatment

HOW ACCURATE AND RELIABLE (CERTAIN) ARE MEDICAL PREDICTIONS?

Spyros Makridakis[1]

It appears to me a most excellent thing for the physician to cultivate Prognosis; for by foreseeing and foretelling, in the presence of the sick, the present, the past, and the future, and explaining the omissions which patients have been guilty of, he will be the more readily believed to be acquainted with the circumstances of the sick.

***Hippocrates**, Book of Prognostics*

Forecasts are needed to improve our decisions regarding future events. In the great majority of cases, the higher their accuracy and the lower their uncertainty (or alternatively the greater their reliability), the bigger their value and the more superior our confidence that our decisions will be correct. As most medical decisions require predictions about future, uncertain events, it is of interest to know their accuracy and be able to appreciate their level of uncertainty or reliability. This paper is organized in two parts. It uses a forecasting perspective and considers how accurately we can predict first the consequences of preventive and second those of curative medicine while also discussing the uncertainty involved when making such predictions. There is also a concluding section summarizing the findings and proposing some actions to improve the accuracy and reduce the uncertainty in medical decisions.

Some typical medical situations requiring forecasting are the following:

- I am well and I consider undertaking some preventive health care, will such care increase my life expectancy and improve the quality of my life?
- I feel sick and I visit a doctor to diagnose what is wrong with me. What is the chance that the diagnosis will be correct?
- Once the diagnosis of my disease has been made and assuming that it is correct, the doctor must come up with the most appropriate treatment. What is the probability that such treatment will cure my disease without complications?
- Answering the above three questions involves a good amount of uncertainty as the benefits and harm of preventive medicine are debatable while the correct diagnosis as well as the choice and the implementation of the most appropriate treatment can go wrong, as the research findings supporting the treatment can be reversed by new research.

Exhibit 1 is a schematic presentation of the stages of medical forecasting indicating the correct outcomes as well as what could go wrong in the process of preventive and curative medicine.

The Forecasts of Preventive Medicine

According to the American College of Preventive Medicine (ACPM, 2015) the goal of such medicine is ***"to protect, promote, and maintain health and well-being and to prevent disease, disability, and death".*** Preventive health measures can be general, covering all aspects of a person's health, or specific aimed at preventing a specific disease. The time interval for both the general and the specific preventive checkups is usually a year or some other fixed interval.

According to the independent Cochrane Foundation:

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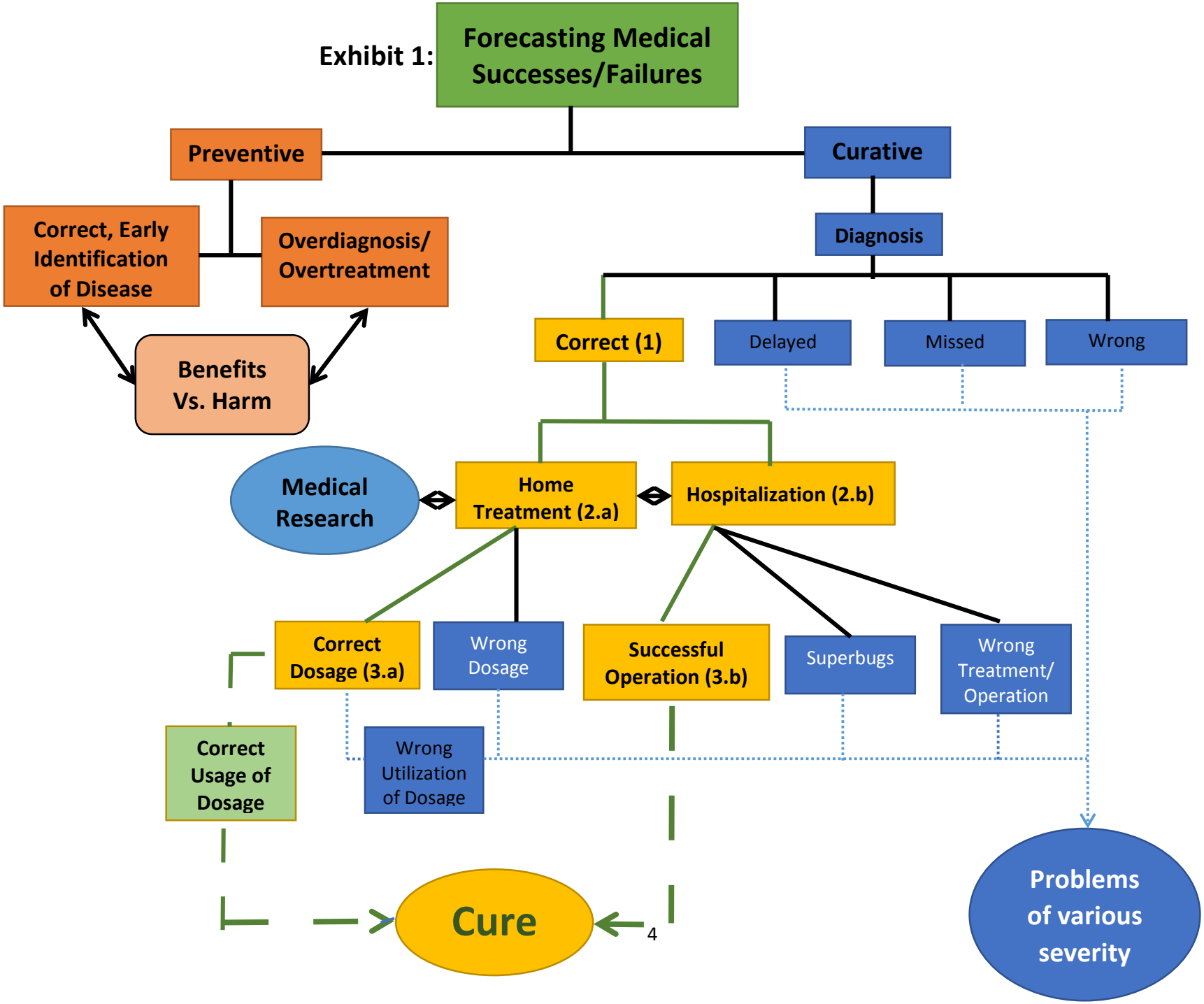
"General health checks involve multiple tests in a person who does not feel ill with the purpose of finding disease early, preventing disease from developing, or providing reassurance. . . . To many people, health checks intuitively make sense, but experience from screening programs for individual diseases have shown that the benefits may be smaller than expected and the harms greater. A possible harm from health checks is the diagnosis and treatment of conditions that were not destined to cause symptoms or death" (Cochrane Library, 2015, p. 2).

Exhibit 1:


Forecasting Medical Successes/Failures
Preventive
Curative
Correct, Early Identification of Disease
Overdiagnosis/ Overtreatment
Benefits Vs. Harm
Diagnosis
Correct (1)
Delayed
Missed
Wrong
Medical Research
Home Treatment (2.a)
Hospitalization (2.b)
Correct Dosage (3.a)
Wrong Dosage
Successful Operation (3.b)
Superbugs
Wrong Treatment/ Operation
Correct Usage of Dosage
Wrong Utilization of Dosage
Cure
Problems of various severity

General annual, health examinations started in the early 1920s and have continued since then, although studies going back to the 1960s have shown no benefits from them apart from some psychological ones related to decreased patient worries (Boulware LE, Marinopoulos S, et al., 2007). Krogsboll et al., (2012) concluded: ***"General health checks did not reduce morbidity or mortality, neither overall nor for cardiovascular or cancer causes, although the number of new diagnoses was increased"*** (p*. 2).* For these reasons, general health checks are not recommended by national expert panels. Since 1979 the Canadian Task Force on the Periodic Health Examination advised against the annual general health tests (Canadian Task Force, 1979), and similar guidance from the United States Preventative Service Task Force (1989) is in force since 1989. Yet, despite evidence against annual routine examinations, many family physicians recommend them (Mehrotra, Zaslavsky and Ayanian, 2007) exploiting the *"illusion of reassurance"* (see Makridakis and Moleskis, 2015) that a preventive test will catch health problems early, reducing disease and increasing life expectancy. In reality, however, there is great uncertainty surrounding the value of such checks as their benefits have been exaggerated while their harm has been ignored. In a recent book, Welch (2015) asserts the following seven popular assumptions and the disturbing truths about preventive medicine and the harm it can cause:

No.	**Assumption**	**Disturbing Truth**
1	All risks can be lowered	Risks can't always be lowered–and trying creates risks of its own
2	It's always better to fix the problem	Trying to eliminate a problem can be more dangerous than managing one
3	Sooner is always better	Early diagnosis can needlessly turn people into patients
4	It never hurts to get more information	Data overload can scare patients and distract your doctor from what's important
5	Action is always better than inaction	Action is not reliably the "right" choice
6	Never is always better	New interventions are typically not well tested and often wind up being judged ineffective (even harmful)
7	It's all about avoiding death	A fixation on preventing death diminishes life

Breast Cancer Screening: A frequently recommended preventive test for breast cancer is mammography. Since 2003 the US Cancer Society (2015) recommends such screening on a yearly basis for all women older than 40 for as long as they are healthy. The US Preventive Service Task Force (2009) now recommends biannual mammography tests only for women between 50 and 74 years of age while also advising women to avoid self-examinations. There is not, therefore, an agreement concerning the age or the interval of screening while those opposing it claim there is strong evidence that the potential harm from screening is considerably greater than the benefits. Furthermore, screening is done at a huge cost that according to O'Donoghue et al., (2014) was $7.8 billion in 2010 with an estimated 70% of all USA women participating in mammography tests.

Gøtzsche (2012) in his book "***Mammography Screening: Truth, Lies and Controversy***" states:

> ***"If we wish to reduce the incidence of breast cancer, there is nothing as effective as avoiding getting mammograms. It reduces the risk of getting breast cancer by one-third."*** (p.349)

A recent study by (Miller et al., 2014) concluded:

> ***"Annual mammography in women aged 40-59 does not reduce mortality from breast cancer beyond that of physical examination or usual care when adjuvant therapy for breast cancer is freely available. Overall, 22% (196/484) of screen detected invasive cancers were over-diagnosed, representing one over-diagnosed breast cancer for every 424 women who received mammography screening in the trial.***

Another 2015 study (Harding et al., 2015) of almost 60,000 women across US counties stated, when directed toward the general US population: **"the most prominent effect of screening mammography is overdiagnosis"** quantifying it as ***"an increase of 10 percentage points in screening was associated with a 25% increase in the incidence of small breast cancers and a 7% increase in the incidence of larger breast cancers"*** (p.E1). Furthermore, the authors concluded:

> **Nonetheless, we do not believe that the right rate of screening mammography is zero. As is the case with screening in general, the balance of benefits and harms is likely to be most favorable when screening is directed to those at high risk, provided neither too frequently nor too rarely, and sometimes followed by watchful waiting instead of immediate active treatment"** (p.E6).

There are numerous other studies in medical literature some showing small absolute gains in mortality as the result of screening and others, like those mentioned above, indicating the potential harm due to overdiagnosis and overtreatment. Taking into account these studies, the Swiss Medical Board (Biller-Andorno and Jüni, 2014) recommended that "no new systematic mammography screening programs be introduced and that a time limit be placed on existing programs" (p. 1966). The reasons we mention this is that ***"For every breast-cancer death prevented in U.S. women over a 10-year course of annual screening beginning at 50 years of age, 490 to 670 women are likely to have a false positive mammogram with repeat examination; 70 to 100, an unnecessary biopsy; and 3 to 14, an over diagnosed breast cancer that would never have become clinically apparent"*** (p.1966).

But there is additional uncertainty as to the best preventive decision once a woman has been diagnosed with cancer and must choose between prophylactic mastectomy and lumpectomy with radiation (Lagnado, 2015) given the evidence from a new study by Kurian et al., 2104 that concludes:

> **"Use of bilateral mastectomy increased significantly throughout California from 1998 through 2011 and was not associated with lower mortality than that achieved with breast-conserving surgery plus radiation. Unilateral mastectomy was associated with higher mortality than were the other 2 surgical options" (**p. 902**).**

From a forecasting point of view the obvious conclusion is: "too much uncertainty" and no way to come up with rational decisions aided by accurately forecasting, assuring increases in life expectancy and/or improvements in the quality of life. The great uncertainty is due to the conflicting evidence and the inability to assure that such evidence will not change over time.

Prostate Cancer: Prostate cancer tests for men are also common as it is estimated that close to 52% of men are tested annually at a cost exceeding half a billion for Medicare patients alone in the USA (Wang et al., 2014). As with breast cancer, there are numerous studies about the benefits and harm of screening for prostate cancer with practically the same conclusions as those of breast cancer mentioned above. This section only refers to the book by Richard Ablin, the inventor of the PSA test being used to diagnose prostate cancer, as the conclusions of the numerous studies for prostate cancer available in the medical literature are practically the same as those of breast cancer.

Ablin (2014) in his book "The Great Prostate Hoax" states:

> ***"The ability of the PSA test to identify men with prostate cancer is slightly better than that of flipping a coin. And its continued use as a routine screening tool is nothing short of a national health disaster"*** (p. 6).

Albin concludes that the screening is done because of financial interests as it increases the number of additional tests and prostatectomies. He asserts that ***"Without radical prostatectomies, more than half of all the urology practice in the United States would go belly-up"*** (p. 42). It is a harsh assertion by the person who invented the PSA test and who claims, in the subtitle of his book, that "Big Medicine Hijacked the PSA Test and Caused a Public Health Disaster". Yet, 52% of men are tested for prostate cancer every year at a huge cost and inconvenience because their

doctors persuade them that such a test will contribute to avoiding death from prostate cancer. May be it is time to use the advice of epidemiologist McPherson that *"**reducing incidence (diagnosis of cancers) must be the primary goal, with reducing mortality an important but secondary end point**"* (p. 233-5, referenced in Gotzsche p. 361).

Recently, Medicare in the USA is considering penalizing doctors for ordering prostate (PSA) tests in order to improve the quality of health care, as such tests reduce the risk of death from prostate cancers only minimally, if at all, as most grow so slowly they are effectively harmless, while many men diagnosed with prostate cancer undergo surgery and radiation, which can have lifelong side effects. Meanwhile, about 28,000 U.S. men die annually from aggressive prostate cancers, often despite getting regular PSA tests and fast treatment. As expected the reaction to such a proposal is drawing heavy response from doctors vehemently opposing it (Beck, 2015).

An Aspirin a Day: The following quote is from ***Time*** Magazine's March 21, 2012 issue: ***"Many people take a daily aspirin to reduce their risk of heart attack, but now fresh evidence suggests that the over-the-counter pain reliever may be a powerful tool in cancer prevention as well. In three new studies published in the Lancet, researchers from the University of Oxford say a daily dose of aspirin can reduce people's risk of developing a variety of cancers and also lower the chance of their cancer spreading"*** (Park, 2012). Given such favorable reports, millions of people around the world take a low dose of aspirin daily to benefit from this wonder drug that, in addition, costs just a few cents.

But practically concurrently with the ***Time***'s article another one appears in the ***Archives of Internal Medicine*** (Seshasai, 2012) that concluded: ***"Despite important reductions in nonfatal MI, aspirin prophylaxis in people without prior CVD does not lead to reductions in either cardiovascular death or cancer mortality. Because the benefits are further offset by clinically important bleeding events, routine use of aspirin for primary prevention is not warranted and treatment decisions need to be considered on a case-by-case basis"*** *(p.209).* Furthermore a new article (Hira, 2015) concludes that the risks associated with regular aspirin use outweigh the benefits while a report by Mayo Clinic describes the benefits and risks involved (Mayo Clinic, 2015). What is the solution? Is it to ask a doctor? But can he or she know any better, given the conflicting research evidence? Unfortunately, any attempt to forecast the benefits/harm of the daily dose of aspirin is filled with uncertainty given the conflicting research evidence.

Drinking Coffee: Similar reversals have been observed with coffee too. Originally, research findings were negative, concluding to an association of coffee drinking with coronary heart disease that was increasing with higher coffee consumption (LaCroix et al., 1986) as well as an increase in the risk of death (Freedman et al., 2012). Later findings, however, showed benefits that ranged from a longer life expectancy (Butt and Sultan, 2011) to reducing ovarian cancer (Tworoger, et al., 2008). So should people enjoy their daily cup of coffee or will the most recent findings be reversed again by some new ones concluding that drinking coffee provides no benefits or harm?

Obesity as the No. 1 Killer: In 2004, USA Today (Hellmich, 2004) typified the press coverage of a major study about obesity in America with a story entitled "Obesity on Track as No.1 Killer" by citing a study from the Journal of the American Medical Association (Mokland et al., 2004) stating that poor diet and physical inactivity had accounted for 400,000 deaths in 2000 compared with 435,000 deaths from tobacco. However, just one year later, a study by different researchers also appeared in the Journal of the American Medical Association, (Flegal et al., 2005) estimating that the effect of obesity was only 26,000 more deaths per year. So should overweight and obese people lose weight to increase their life expectancy? In a meta-analysis Flegal and colleagues (2013) concluded that relative to normal weight, grade 1 (mild) obesity ***"was not associated with higher mortality, and overweight was associated with significantly lower all-cause mortality"*** (p. 71) while they also stated that their results ***"are broadly consistent with 2 previous meta-analyses by McGee and Janseen and Mark***" (p.76).

In addition to the few examples mentioned above, there is numerous advice on how to increase life expectancy and improve quality of life by both medical and general wellness sources. These range from following the right diet, taking suitable vitamin supplements, being fit, sleeping well but not too much, avoiding stress and adopting positive thinking. Some of these may be useful but there are no assurances that they will indeed increase life expectancy or improve the quality of life. At least no research has proven any of this beyond reasonable doubt and worse there is no way to know whether or not future research will come up with conflicting conclusions related to those of existing ones. Uncertainty prevail and accurate forecasting cannot be assured.

Preventive testing is a medical area requiring fundamental rethinking. The question is if vested interests from both doctors and pharmaceutical firms would allow any changes in established preventive medicine practices? In the meantime the uncertainty of the benefits versus the harm is and will remain enormous for those who must decide whether or not the benefits exceed the harm of overdiagnosis and overtreatment.

The Forecasts of Curative Medicine

In curative medicine there are three types of forecasts required (see Exhibit 1 above). The first relates to whether the doctor will make the correct diagnosis. The second, is if the correct diagnosis will be matched with the most appropriate treatment, including hospitalization, by determining the best therapy, based on published research findings that are often presented in the form of guidelines written by professional committees of doctors. The third is if the correct dosage will be prescribed, or if a hospital treatment will be carried out successfully. Finally, there are several factors beyond the control of the doctor such as the patient being inflicted by a superbug while in hospital or if she does not take the prescribed dosage correctly. This section looks at each of these three stages of the medical process, describes what can go wrong and discusses the implications in terms of lost lives or harm to patients.

M*edical Diagnoses:* The diagnosis of disease has progressed a great deal with the wide availability of laboratory tests (e.g. blood and urine), equipment like x-rays, ultrasound and MRI machines and PET and CT scanners but still diagnostic errors seem to abound. Such errors ***"are defined as those in which diagnosis was unintentionally delayed (sufficient information was available earlier), wrong (another diagnosis was made before the correct one), or missed (no diagnosis was ever made), as judged from the eventual appreciation of more definitive information"*** (Singh et al., 2007, p.489). Table 1 (Graber, 2013, p. ii22) shown below lists the research approaches used to estimate the incidence of various types of diagnostic errors. Such errors are in the range of 10% to 15% according to Elstein (1995) while it seems that from 1,000 hospital deaths 5% were considered preventable. In the Harvard Medical Practice Study (Leape et al., 1991) of 30,195 hospital records, diagnostic errors accounted for 17% of adverse events. In a recent study that reported in a WSJ article Singh (2014), the foremost expert in diagnostic errors and how they could be prevented, concludes that around 5% of the US population, close to 12 million, is misdiagnosed each year, with the resulting errors killing close to 100,000 people a year. A study conducted by Johns Hopkins Medicine researchers (2013) concluded that diagnostic errors are more common, costly and harmful than treatment mistakes, resulting to permanent injury or death of between 80,000 and 160,000 a year in the USA. In addition they count for the greatest number of insurance claims and the highest proportion of payments. Another study reports that diagnostic errors account for 63% of all claims against GPs in the UK and for about a third of negligent adverse events in the US primary care (Kostopoulou, Delaney and Munro, 2008). No doubt, therefore, incorrect diagnosis is a major factor influencing the accuracy of forecasting and greatly increasing the associated uncertainty for patients seeking medical care.

Table 1 Research approaches used to estimate the incidence of diagnostic error

Research approach	Findings—examples	Suitable for evaluating incidence	Suitable for evaluating aetiology
Autopsies	Major unexpected discrepancies that would have changed the management are found in 10–20%[8 9]	Yes	No
Patient and provider surveys	One-third of patients relate a diagnostic error that affected themselves, a family member, or close friend[10]; Over half the surveyed paediatricians report making a diagnostic error at least once or twice a month[11]	Limited	Limited
Standardised patients	Internists misdiagnosed 13% of patients presenting with common conditions to clinic (COPD, RA, others)[12]	Yes	Yes
Second reviews	10–30% of breast cancers are missed on mammography[13]; 1–2% of cancers are misread on biopsy samples[14]	Yes	No
Diagnostic testing audits	Errors related to laboratory testing are the most common reason for a diagnostic error[15 16]	Very limited	Limited
Malpractice claims	Problems relating to diagnostic error are the leading cause for paid malpractice suits in every large system	Very limited	Limited
Case reviews (cross-sectional studies by symptom, disease, or condition); (may be enriched by trigger tools)	Patients with asthma—median delay in making the correct diagnosis was 3 years, or 7 visits[17]; 12–51% of patients with subarachnoid haemorrhage are misdiagnosed in the emergency department.[18] Of 1000 hospital deaths, 5% were considered preventable, and the most frequent aetiology was diagnostic error.[19]	Yes	Limited
Voluntary reports	1674 reports of diagnostic error were submitted to the UK's National Reporting and Learning System over a 2-year period, 0.5% of all incidents reported[20]	Yes	Yes

COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis.

The statistics about diagnostic errors refer to the average of all disease. However, there is a clear distinction between easy and difficult cases. Fink, Lipatov and Konitzer (2009) claim that less than 20% of the most frequent diagnoses account for more than 80% of consultations and that only 10% of all the diagnoses can be confirmed as certain (p.784) while the diagnostic accuracy of the most difficult ones (e.g., uncharacteristic febrile syndrome) can be more than 240 times less than the less difficult ones. In a 2013 article, Ashley et al., came up with similar findings pointing out the substantial uncertainty involved in the diagnostic process. They state their conclusions as follows:

> ***"A total of 118 physicians with broad geographical representation within the United States correctly diagnosed 55.3% of easier and 5.8% of more difficult cases (P < .001) (making an overall average of a 31% success rate). Despite a large difference in diagnostic accuracy between easier and more difficult cases, the difference in confidence was relatively small (7.2 vs 6.4 out of 10, for easier and more difficult cases, respectively) (P < .001) and likely clinically insignificant. Overall, diagnostic calibration was worse for more difficult cases (P < .001) and characterized by overconfidence in accuracy" (p. 1952).***

An average 5.8% correct diagnosis rate for the difficult cases (meaning a correct diagnosis in only one out of seventeen patients) is terrifyingly low and raises the question of why such information is not clearly communicated to patients to be aware of their extremely low chance of being diagnosed correctly so that they ask for a second opinion or avoid the recommended treatment.

Another major, and equally disturbing finding of the Ashley's et al. study, was how little the physicians' level of confidence changed from the easy to the hard cases (7.2 out of 10 for the easy ones and 6.4 out of 10 for the hard ones). This means that with an accuracy rate of only 5.8%, the physicians were still 64% confident that they had come up with the right diagnosis! In terms of decision making, a low diagnostic accuracy of 5.8% could have been tolerated if the physician was, say, only 10% confident of being right. In that case he/she could have been ordering more tests, reevaluating the symptoms, or asking for a second opinion from another doctor in order to improve the chance of a correct diagnosis. However a 64% confidence probably excludes such actions, convincing the doctor to proceed with a treatment, based on the wrong diagnosis, the consequences of which would be harmful for the patient.

Berner and Graber (2008) further discussed how overconfidence results in medical errors in general and diagnostic ones in specific and what needs to be done to reduce them. Fink, Lipatov and Konitzer (2009) attribute the reasons for such overconfidence in the doctors' judgment to the well-known "expert" problem saying that ***"most practitioners believe that they have valuable experience and precious intuition. However, simple logic shows that all of their experience is still only a small (often biased!) sample"*** (p. 792). Thus, it seems that the common problem of overconfidence encountered in the field of forecasting is also present in medical diagnoses with detrimental negative outcomes and an urgent need for concrete steps to correct it as people's wellbeing and lives are seriously affected.

The Most Appropriate Treatment (after the Diagnosis): Once a diagnosis has been made, the doctor needs to come up with the most appropriate treatment by consulting the medical literature, including the available guidelines, on the best way to cure the diagnosed disease or to recommend hospitalization. A problem when searching for the most appropriate treatment, however, is that research findings change over time as new ones replace and even invalidate old ones. Some of these changes in preventive medicine research findings were mentioned above. However, Ioannidis has published widely on the deficiencies of medical research (see Ioannidis 2005 and Ioannidis 2005). In his PLoS Medicine article he states ***"There is increasing concern that in modern research, false findings may be the majority or even the vast majority of published research claims"*** (p. 696). In his article in ***JAMA*** (2005), he concludes ***"Contradiction and initially stronger effects are not unusual in highly cited research of clinical intervention and their outcomes"*** (p. 218). In a 2010 article in the ***Atlantic*** featuring Ioannidis, Freedman (2010) quotes him saying "***that as much as 90 percent of the published medical information that doctors rely on is flawed and that he worries that the field of medical research is so pervasively flawed, and so riddled with conflicts of interest, that it might be chronically resistant to change—or even to publicly admitting that there's a problem"***. So the application of the right treatment, assuming a correct diagnosis, is also uncertain lowering the accuracy of forecasting that a patient will be cured.

Going back and forth between aspirins and coffee, as discussed above, may not involve life threatening situations but a *bone marrow transplant* definitely does. In addition to involving an extremely painful procedure, it is also downright expensive, with costs ranging upwards to $150,000 and reaching the million marks in complicated cases (Brawley, 2012). The idea behind the marrow transplant was to harvest and store it in order to avoid the toxic effects of chemotherapy and then re-introduce it once the chemotherapy was completed. Well, randomized trials found that the procedure did not improve survival and it was, therefore, abandoned (Brawley, 2011, p.35) as another failed recommended therapy. Unfortunately, the marrow transplant disaster which caused great pain and huge medical costs to patients is not unique in medical research. People in general and doctors in specific, driven by personal interest (money or fame) are "doctoring" their findings (Kendrick, 2015) to achieve their objectives, not caring much about the implications of their conclusions to people's wellbeing and lives.

From an epistemological point of view the critical question is how medical research findings can be utilized to base treatment when unknown, future ones could reverse or invalidate existing recommendations? Is there something fundamentally wrong, requiring a major rethinking of medical research and how medical guidelines should be applied? In addition, is it possible to ensure that conflicts of interests aimed at increasing the revenues of doctors and pharmaceutical companies, or even to avoid fraud will not influence the diagnostic process and the recommended therapy? A great deal needs to be done to answer these questions in a scientific and objective manner by accepting the actual uncertainty of medical decisions, the judgmental limitations of doctors and the inadequacies of medical research.

Medical Mistakes in Hospitals: The article "How Many Die from Medical Mistakes in U.S. Hospitals?" (Scientific American, Allen, 2013) mentions that the numbers come out worse as time passes. They were estimated at 98,000 a

year back in 1999 when in 2000 the Book "To Err Is Human" was published. They were then raised to 180,000 in 2010 by the Office of Inspector General for Health and Human Services for Medicare patients alone (Wilson, 2010). A new study published in 2013 (James, 2013) further raises the number to a low of 210,000, with a more realistic level of more than 400,000 patients who suffer some kind of preventable harm contributing to their death. Moreover, the study reports that serious harm seems to be 10 to 20 times greater than the lethal one. Some of the serious harm and deaths in hospitals is caused by "never events", such as (a) surgical instruments, unintentionally left behind in the patient, (b) a wrong procedure performed, (c) a wrong surgical site is operated upon, and (d) surgery is done on the wrong patient altogether.

Superbugs and Antibiotic Resistance Threats in Hospitals: According to CDC (2014) ***"On any given day, approximately one in 25 U.S. patients has at least one infection contracted during the course of their hospital care, adding up to about 722,000 infections in 2011"*** adding that ***"Although there has been some progress, today and every day, more than 200 Americans with healthcare-associated infections will die during their hospital stay".*** In an updated report "Antibiotic Resistance Threats in the United States, 2013" CDC raises to more than two million the number of people sickened in hospitals every year with antibiotic-resistant infections. According to the Consumers Union (2010) this puts hospital-acquired infections to the top-ten category of leading causes of death. A limitation of the CDC and other studies is that they focused on hospitals, excluding other health care facilities such as skilled-nursing facilities and other long-term care ones, thus underestimating the numbers which, are according to CDC "based on conservative assumptions and are likely minimum estimates".

Correct Dosage*:* According to the FDA a medication error is any preventable event that may cause or lead to inappropriate medication use or harm to a patient while the medication is in the control of a health care professional. Such errors can occur both in general practice and in hospitals (thus some of the numbers being reported in this section may overlap those of "Medical Mistakes in Hospitals"). According to Medicine Net (Stoppler, et al., 2014) approximately 1.3 million people are injured annually in the United States following so-called "medication errors". From those the greatest part, around 70%, are prescription ones, with about half of the errors caused by the wrong dose selection (Velo and Minuz, 2009) who also report that the great majority of errors, up to 51.4%, is attributable to junior doctors, mentioning that inappropriate prescriptions are most often instigated from lack of knowledge or inadequate training while Phillips and colleagues (2001) reported that about 10% of the medication errors were fatal.

Incorrect Usage of Prescribed Medication: The right medication dosage must also be utilized correctly by the patient to be effective. However, for various reasons (Medicine Safety, 2015), ranging from forgetfulness to take it to reducing the dose for economic reasons or to avoid side effects. This results in negative consequences that in some instances can be fatal, particularly in patients over 60 years old that are the most vulnerable to wrong usage (Phillips et al., 2001). There are suggestions for avoiding the adverse outcomes by educating and better communicating to patients the dangers involved and providing a "medication check-up", in particular for patients taking several medicines in order to determine whether they are all needed, making sure that they are used correctly and determining potential negative drug interactions (Medicine Safety, 2015).

The Forecasting Factor in Medicine

Both preventive and curative medical decisions as they refer to future, uncertain events require forecasting. In preventive medicine the individual involved must decide if the benefits are greater than the harm by taking into account his/her age, risk factors as well as his/her and his/her family's medical history. At present this is not an easy decision as there is an intense debate about such benefits/harm and no agreement even among the experts. A letter written by a prominent UK doctor, Professor Susan Bewley (2011), to England's cancer tsar pinpoints the issue and the difficulty in making a decision.

> ***"Approaching 50, with a family history of the cancer (grandmother, aunt, and sister) and risk factors (late childbearing, low parity, obesity), I had to consider screening mammography for myself. It is natural to fear cancer and its treatments and understandable to think "better safe than sorry"—that the promise of early detection could offer me a much better chance of life and health.***
> ***I declined screening when it was offered, as the NHS breast screening programme was not telling the whole truth"*** (p. 1).

Given the uncertainty, the need to better understand the balance of benefits and harm becomes important while following the advice of Harding and colleagues (2015) that ***"positive diagnoses to be followed by watchful waiting instead of immediate active treatment"***, until additional, indisputable research evidence can prove in one way or another if the benefits are greater than the harm or the other way around.

Similarities between Medical and General Forecasting: A major conclusion in the field of forecasting is that uncertainty is seriously underestimated. The same is true in medicine where doctors are overconfident that their diagnostic and other predictions are correct when in reality they are not. Another finding is the value of intuitive, versus clinical judgment. Going back to the mid-1950s, Meehl (1954) published a little book comparing the accuracy of clinical psychologists to those of simple statistical models and he found that the latter were more accurate than the former. Many subsequent studies (Sawyer, 1966 and Kleinmuntz, 1990) have reinforced Meehl's original findings and have cast doubts on the unaided value of expertise. It is obvious that medical doctors will not accept Meehl's conclusion the same way that clinical psychologists have yet to accept it. But the evidence that has been accumulating (Grove, 2000) must be considered by the medical profession, as it is highly relevant to the practice of medicine.

In a recent book, Philip Tetlock (2005) explored the issue of expertise using information from a mammoth study analyzing more than 82,000 decisions from experts in the field of political science. His findings are similar to those of Meehl. Simple models turn out to be more accurate than human forecasters. In addition, he concluded that experts are rarely more accurate in predicting than informed individuals. Moreover, the political experts Tetlock studied were not as good as non-experts at modifying their forecasts in the light of new information, as they felt they knew all the relevant facts. They were also overconfident about the accuracy of their predictions, as in the other forecasting fields mentioned earlier. It seems that the only exception to that rule is among meteorologists whose forecasts are perfectly calibrated (Makridakis and Bakas, 2015) as they have available and utilize frequently objective feedback to improve the calibration of their predictions. These findings can be valuable to medical doctors.

The above does not aim to diminish the value of medical expertise which comes from many years of intensive education, internships and practice but to find ways to diminish, or even eliminate the biases and limitations of human judgment (Kanheman, 2011) that inevitably apply to doctors as well. For instance robotic surgery does not substitute the doctor, rather it allows her to perform more complex procedures with greater precision and higher level of control than using conventional techniques. The same is true with computer assisted diagnoses that can search large data bases and come up with additional, rare diagnoses that cannot be considered by the doctor. There are suggestions that technology can considerably improve medicine (Khosla, 2012) although it may take some time to develop full proof technologies and have them accepted and utilized by the medical profession.

Preventive and Curative Medical Decisions: There is one of three strategies to be followed, given the inaccuracy of forecasts and the high degree of uncertainty for deciding whether or not to undertake some preventive health test(s):

- If a person is classified in a high risk category because of her personal or family medical history preventive health tests should be considered, although care should be taken to avoid, as much as

possible, the negative consequences of overdiagnosis and overtreatment and of understanding their potential harm.

- The person is healthy and not in a high risk category but still chooses preventive medical health care, fully understanding the benefits and risks involved. In this case she should follow the advice of Esserman and colleagues (2014) and have the tests neither too frequently nor too rarely while if the test is positive it should be followed by watchful waiting instead of immediate active treatment.
- Refuse any preventive testing, given the uncertainty in predicting the benefits versus the harm, and in doing so avoiding, the costs and inconvenience of testing.

In curative medicine making the right decision is more complicated, depending upon several extra factors and even greater uncertainty. First and most importantly is the urgency of getting cured. If the patient cannot wait going to a doctor the cure cannot be postponed. Otherwise, there could be time for more deliberations and getting a second or even a third opinion. In both cases, however, forecasting accuracy will depend on the probability that (a) the diagnosis will be correct, (b) the treatment (either at home or in the hospital) will be successful, (c) the medication dosage will be the right one, and finally (d) the prescribed dosage will be consumed appropriately (see Exhibit 1). Estimating the probabilities entails a great deal of uncertainty as the estimated numbers could vary, sometimes considerably, depending upon the individual, the type of her disease, what findings from the many available to use, the difficulty of the diagnosis as well as the medical and other errors that may affect the treatment. Assuming a diagnosis of medium difficulty, with a probability of being right of 0.667, the chance of a correct treatment around 0.85 and the probability of correct dosage and its appropriate usage of around 0.9, then the probability of a successful cure is around 50% (see Exhibit 2), a rather high percentage that could get worse with more difficult diagnostic cases and realizing that the probabilities of the various stages may not be independent of one another, as a wrong diagnosis will affect the remaining curative stages.

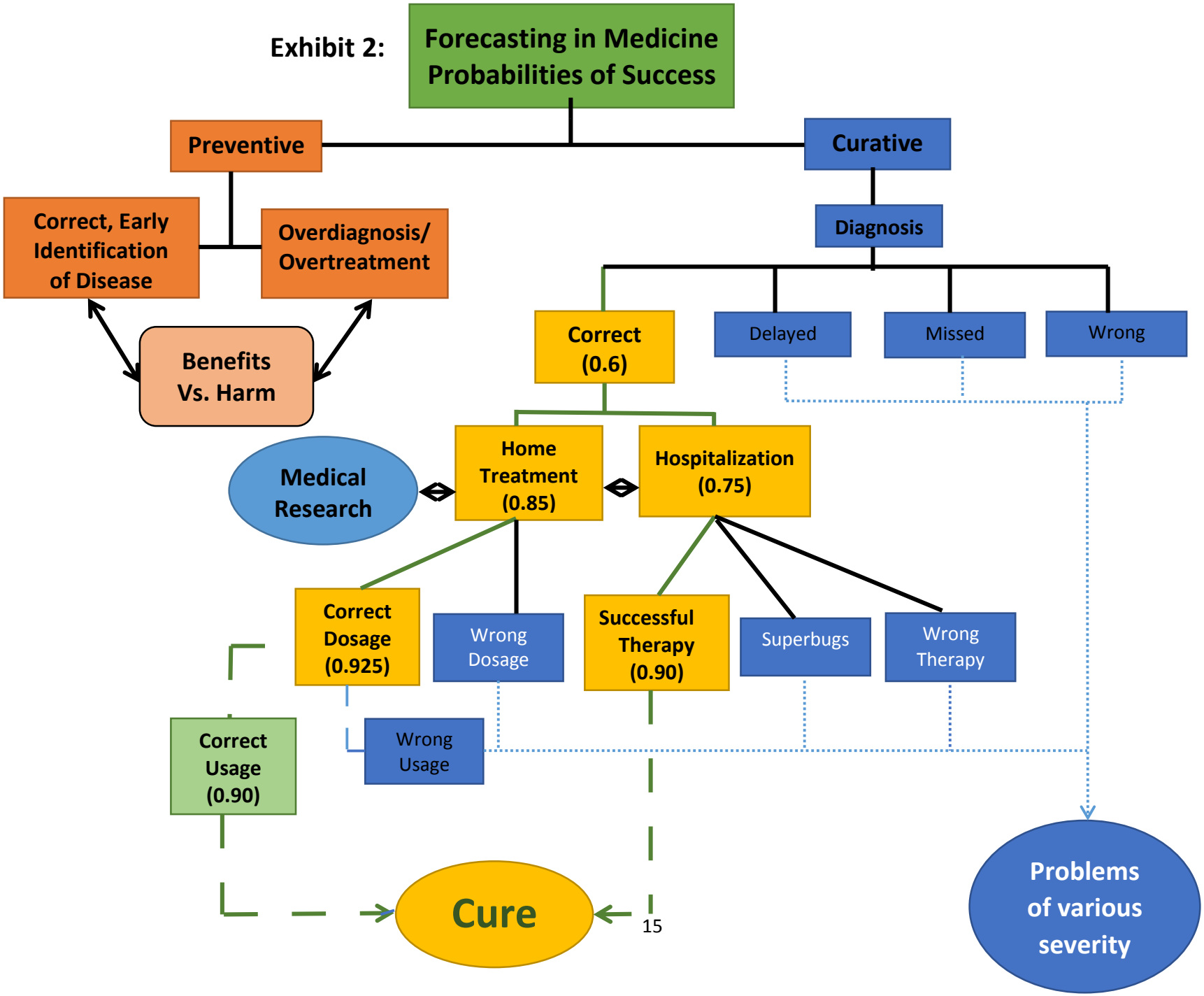
Conclusions and Directions for Future Actions/Research

The medical area is characterized by low predictive accuracy and great uncertainty as harm can come from preventive tests, the wrong diagnosis, inappropriate treatment (assuming the correct diagnosis) based on incorrect research findings that can be invalidated by new studies, severe and fatal medical errors, hospital superbugs, or the wrong usage of medication. In surveys 38% of people in the EU perceive medical mistakes as very important and that something must be done to avoid them (Medical Errors, 2006) while 42% in USA say they had experienced a medical mistake in their own care or in the care of a family member (Goldstein, J., 2002). Clearly, the situation is far from ideal as many doctors are unable or unwilling to appreciate the level of uncertainty concerning their patients and consequently do not communicate such uncertainty to them (see below).

Karl Popper (1972) has advanced the notion of ‘falsification’ of existing scientific theories, arguing that no theory can ever be considered as a ‘universal truth’ since it is usually only a matter of time before it will be rejected by becoming inconsistent with empirical data. This has been happening in medicine for some time now and is explained by Kuhn (1962)who went an important step further than Popper by showing that scientists tend to continue working within their maintained paradigm, even after empirical evidence has accumulated, suggesting considerable anomalies between the deductions derived from the espoused theory and what is observed in practice. He, therefore, postulated that science does not evolve slowly under the impact of new evidence but instead such evidence is ignored for as long as possible, in particular if it is in conflict with the basic tenets of the accepted paradigm. Science, he argues, progresses in revolutionary steps only when the anomalies become so strong that no ad hoc modifications in the accepted theory can explain the empirical findings. But even in such cases, fundamental changes do not take root until the “old guard” is replaced by a new generation of scientists whose minds are open to new theories. Fildes and Makridakis (1995), showed that this has been the case in the field of forecasting where

new findings have been ignored by the established academics who have continued applying the old theories.

Exhibit 2:


Forecasting in Medicine Probabilities of Success
Preventive
Curative
Correct, Early Identification of Disease
Overdiagnosis/ Overtreatment
Benefits Vs. Harm
Diagnosis
Correct (0.6)
Delayed
Missed
Wrong
Medical Research
Home Treatment (0.85)
Hospitalization (0.75)
Correct Dosage (0.925)
Wrong Dosage
Successful Therapy (0.90)
Superbugs
Wrong Therapy
Correct Usage (0.90)
Wrong Usage
Cure
Problems of various severity

In addition to the Cochrane collaboration that has been spearheading the need for fundamental changes in the medical profession, a new generation of doctors have started questioning the accepted dogmas. The issue of how long it will take for the revolution to spread to the entire profession is hard to answer but the process has at least started. In his new book Doctor Welch (2015) writes: ***"You might think that the biggest problem of medical care is that it costs too much. Or that medical insurance is too expensive . . . But the central problem is that too much medical care has too little value"*** (p. xii). Similarly, Doctor Gawande (2015) in a New Yorker article states: ***"Millions of people are receiving drugs that aren't helping them, operations that aren't going to make them better, and scans and tests that do nothing beneficial for them, and often cause harm."*** In addition the book "Doctoring Data: How to Sort out Medical Advice from Medical Nonsense" by Doctor Kendrick (2014) is, as its subtitle indicates, a serious effort on how to avoid medical nonsense and escape what can go wrong in medicine. These and similar books like "How We Do Harm: A Doctor Breaks Ranks About Being Sick in America" by Doctor Otis Brawley (2012) are demystifying medicine and helping people make better informed decisions by revealing the vested interests of doctors and pharmaceutical firms. But still much more needs to be done.

Although medical doctors study for many years that are followed by long internships, medicine is still not a science. This is clear by the estimated 400,000 deaths caused by medical errors, the unnecessary mastectomies deforming women, the pointless radical prostatectomies causing impotence and incontinence to men or the tiny 5.8% success rate in difficult diagnoses. Thus, the critical question is what can be done to improve the field of medicine and reduce needless deaths, misery, and pointless, not to mention expensive, care? In the opinion of this author the first and most important thing is that doctors accept the problems, limitations and possible harm caused by their actions and take concrete steps to improve the situation. Perhaps the time will soon come that a new generation of doctors will replace the "old guard" by accepting the problems and limitations in their fields and adopt a realistic approach in dealing with the new reality even though such an approach may reduce their revenues.

Uncertainty in Medicine: Renée Fox (1980), in his exceptional article on "The Evolution of Medicine" states: **"our great twentieth-century progress in medical science and technology has helped to reveal how ignorant, bewildered, and mistaken we still are in many ways about health and illness, life and death**" (p. 1). The same theme is echoed 29 years later by Wallis (2009), who also talks about the fear that uncertainty provokes in both patients but also doctors who pay lip service acknowledging it but continue to ignore it in their practice (Katz, 1984) and worse by their unwillingness to disclose it to their patients. Doctors are not unique in ignoring uncertainty. The same is true in all areas of forecasting where, as it has been mentioned, uncertainty is seriously underestimated as decision makers are unwilling to accept and act on conceivable, future threatening events. There is, however, a major difference concerning the disclosure of uncertainty in medicine and other areas where the worst outcome would be loss of money while in medicine could involve matters of life and death.

Uncertainty abounds in all aspects of medicine: from diagnosis to treatment and to cure. It must first be accepted by the doctors and then communicated effectively to their patients. Medical doctors must be trained in the most appropriate way of both realistically assessing uncertainty and how to best communicate it to their patients. In addition, doctors must also be exposed to the biases and limitations that characterize their judgments that are the same as those of the general population, and consequently adopt ways to minimize their damaging impact (Kahneman, 2011). Accepting that uncertainty is present and that doctors are also subject to judgmental biases and limitations may seem hard to admit as the perception of a doctor is to be certain about her advice and not wanting to create doubts about her recommendations. But is there an alternative? Patients need to be told in a clear and truthful manner the full range of uncertainty that must include not only the benefits but also the dangers involved, in order to decide if they should follow the doctor's advice, ask for a second opinion or postpone or avoid the recommended therapy.

Reducing Medical Errors: There is little being done to reduce fatal medical errors given that it is the third largest cause of deaths, after hearth disease and cancer. For instance there are innumerable articles published each year aimed at decreasing the around 150,000 deaths from Alzheimer and diabetes while there are a small number of publications about reducing deaths caused by medical errors. The 1980s and 1990s witnessed the strong expansion of the total quality movement in Japan and the Western world that dramatically decreased defective products to less than one in a million using the six sigma approach. May be the time has come to apply the knowledge and experience from such movement to medicine (De Jonge, et al., 2011). The major problem in doing so is that medical errors must be identified and accepted before an effort to reduce them can start. The problem, however, is the fear of litigation that compels doctors not to report their mistakes. Moreover, doctors are not eager to identify mistakes made by other doctors not wanting to "betray" their colleagues. Blendon, a professor at the Harvard School of Public Health who designed the survey and analyzed the results (Goldstein, 2002) said that doctors "are supersensitive to the malpractice problem which makes them supersensitive to the reporting of errors" and that only 14 percent of those surveyed said there should be public disclosure of serious errors, and just 23 percent supported reporting such mistakes to a state agency. Furthermore, Blendon reported that "One of the striking findings of his survey was that physicians disagree with national experts on the effectiveness of many of the proposed solutions to the problem of medical errors." Thus, some way must be found in order to report errors before any major progress to reduce them can start.

There are several classifications of the medical errors being reported. One proposed by Graber and co-authors (Graber et al., 2002) considers three major categories (No-fault, System and Cognitive) and propose ways of reducing them, or eliminating at least a good number of them. In order to reduce them they propose system improvements, second opinions, decision support systems, enhanced access to specialists and training to debias the doctors. This is also the approach advocated by Croskerry (2003), specializing in diagnostic errors, who suggests an approach called "cognitive disposition to respond" that involves stepping back from the immediate problem to examine and reflect on the thinking process. The same idea is advanced by Vickrey and co-authors (2010) who use a cognitive perspective to improve neurological diagnoses.

Other schemes (Elder and Dovey, 2002) classify errors as diagnostic, treatment, preventive and process ones which include judgmental, communicative, administrative and regulatory. They conclude by suggesting that inputs from patients, consumers and health care providers will be needed to complete the puzzle and provide a better picture of medical errors. Other studies provide more specific advice; Gawande (2010), for instance, suggests a checklist that can guide a doctor through the key steps in any complex procedure. The same suggestion is made by Haynes et al., (2009) who propose a surgical safety checklist to reduce errors. Further, in a book Marcucci, Moritz and Chen (2005) provide specific advice to avoid common surgical errors in various categories. In addition, Chiozza and Ponzetti (2009) proposes a model used in the aerospace industry based on reducing the prospective risk of high-risk processes while Sax et al. (2009) recommend team training of medical personnel to improve their performance and reduce errors. Finally, Ioannidis and Lau (2001) has published a meta-analysis of intervention studies aimed at reducing medical errors. Their conclusions was: **"Medical errors were very frequent in the studies we identified, arising sometimes in more than half the cases where there is an opportunity for error. Relative simple interventions may achieve large reductions in error rates"** (p. 325). The challenge is, therefore, to identify and implement such simple interventions to substantially reduce medical errors giving greater emphasis to serious ones.

Improving Medical Research: The articles of Ioannidis cited above leave little doubt about the pressing need to substantially improve the value of medical research in order to guide in a truly scientific way the practice of medicine. The present situation as portrayed by Ioannidis "***that as much as 90 percent of the published medical information that doctors rely on is flawed"*** can be explained by one of three factors.

First, there is what the Economist (2013) in an editorial calls the publication bias, stating that "science has changed the world but now it needs to change itself" by taming careerism that encourages "massaging" the results to come up with new, interesting findings most likely to be published in high impact journals. Second, the scientific method utilized can be wrong or ill executed either by error or on purpose. In an article co-authored by this author (Makridakis and DiNicolantonio, 2014) it was concluded "There are significant conflicts in the conclusions of hypertension studies that cannot be explained statistically as these studies are based on large sample sizes. The reasons for the conflicts are due to the methodological, epistemological and statistical deficiencies of the hypertension studies" (p. 1). The last reason is vested interests on the part of those publishing the findings that could be financial or increasing the reputation of the authors. These vested interests are covered next.

Minimizing Vested Interests: Gøtzsche (2013) shows the undue influence of pharma firms in recommending therapy and drugs and the potential dangers of such drugs that often exceed their assumed benefits. He quotes a former vice-president of Pfizer saying "The mob makes obscene amounts of money, as does this industry". The book by Goldacre (2012) is along the same lines describing the great influence of pharmaceutical firms whose main purpose is to increase their profits. Lastly, the book "Medicine, Money, and Moral: Physicians' Conflicts of Interest", by Rodwin (1993) covers seven activities: kickbacks; referral to facilities in which physicians have a financial interest; the selling of medical products that they themselves prescribe; hospital purchases of private practices; payments by hospitals for patient referrals; gifts by pharmaceutical firms; and risk-sharing in health-maintenance organizations (HMOs) leading to significant conflicts of interest that influence doctors' decisions at the detriment of patients. A number of the books quoted in this article (Ablin, 2014; Brawley and Goldberg, 2012; Gotzsche 2012; Gotzsche 2013; Kendrick, 2014; Welch, 2015) also confirm how doctors' decisions are influenced by vested interests, urging that something must be done to prevent or at least minimize them.

Caesarean sections are probably the most flagrant example driven by the direct motive to increase the revenues of those involved. Although, it is well known that caesareans above the 10-15% rates recommended by the WHO (2015) are associated with higher infant mortality and no benefits for the mother or the child (Sevelsted et al, 2014) (Xie, et al., 2015, Nature Medicine, 2008). There is a growing trend over time as doctors recommend them to natural births for both monetary and convenience reasons as they can schedule them at suitable times one after the other in a manner of a production line. The end result is that caesarians are many times the recommended level (Nature Medicine, 2008) and in some countries like Brazil they are as high as 85% for all women and must extend to every single one giving birth in a private hospital as the average rate for public hospitals is 45% (Ye, J., et al., 2014). A similar situation also applies to Greece (Balezdrova, A., 2011) where practically all women covered by health insurance give birth by caesarean.

Given the indisputable evidence of the iatrogenic damage caused by caesareans it is hard to explain their extremely high rates in most developed countries. Doctors do not seem to follow the Hippocratic Oath of "no harm" in the interest of profits. The big surprise that indicates the power of the medical lobby is that government agencies have been doing nothing to regulate the caesarean epidemic even though they are well-aware of the harm caused to the mother and newborns.

The Doctor as a Healer: The opposite of a doctor driven by vested interests is that of a healer following the old Hippocratic tradition of aiding the natural resistance of her patient to avoid disease and achieve a harmonic balance. In Kahneman's (2011) terms the doctor ought to listen attentively to her patient, and use "System 2" thinking rather than accepting unconsciously what "System 1" dictates. The problem is that "System 2" requires time and effort that is not always available in busy doctors. Its advantage is, however, that it minimizes biases as it requires deliberate effort, after a careful evaluation of all the evidence. It may be that "System 2" thinking could substantially reduce medical errors and improve the quality of care.

Clearly, more research and experimentation will be needed to establish its value. But in the opinion of this author the grand commercialization of medicine must be controlled for the benefit of everyone and the education of doctors to utilize “System 2” thinking could contribute positively towards this direction.

What Next?

Medicine is unique in its potential ability to improve the quality of our lives and to prolong life expectancy. This ability creates a huge psychological dependence as practically all people strive to enhance living and delay death and are, therefore, predisposed to listen to their doctors for achieving these objectives. And although the contributions of modern medicine cannot be denied, there are serious problems as those being raised by this paper. The harm of preventive medicine, the fatal medical mistakes being the third leading cause of death, high rates of diagnostic errors, new research findings invalidating older ones, among others, cannot be sidestepped as they affect a great number of people. The critical question is how these problems can be substantially reduced or even eliminated and how vested interests will be overcome in doing so. On the positive side there is an increasing number of doctors and researchers advocating the need for change. On the negative vested interests supported by powerful lobbies resist to even small changes.

Change will depend on government and non-profit organizations to intervene and educate the general public about the benefits and disadvantages of medical practices, including the possible harm from preventive medicine. In addition, governmental agencies must intervene to regulate certain aspects of medicine, some examples being a vast reduction in caesarean births, or the unnecessary operations and the more effective usage of new drugs. Hopefully, medical professional bodies will become more active in self-regulating their members so that the need for governments to intervene will be avoided.

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