Milestones in Personalised Medicine: From the ancient time to nowadays - the provocation of COVID-19

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In ancient times, approximately 1550 BC, the first evidence about medicine adapted to individual's health appeared in the *Odyssey* written by Homer [1]: "*Telemachus, the son of Odysseus, visits Menelaus and Helen in search of news about his father, who has still not returned home after the Trojan War. Reminiscence of the absent Odysseus leads to tears and at this moment Helen puts a drug (φάρμακον) into the crater of wine, which eases grief or anger and makes one forget one's woes. This drug came from Egypt: Homer says*" [1]. In fact, according to Homer, Egyptians were considered as "the wisest of men" even from Greek physicians because the Egyptians were descendants of Paeon, the doctor of the gods [1].

The adaptation of that ancient ***"Egyptian medicine"*** to an individual's health status was further elucidated in the Classical period from Herodotus when the practice of medicine was divided into categories and every doctor was a specialist for one disease, one body part [1]. This is the first evidence of personalised medicine, as doctors realised that separating the diseases according to the human body parts can help them to achieve a deeper understanding of illness and consequently attain a better therapeutic outcome. Greeks were fascinated by this approach of medicine and that's why they constantly mention in their treatises the Egyptian medicine with admiration [1]. Only after the appearance of Hippocratic medicine in the fifth century, the Egyptian medicine started to be omitted from the Greek books [1].

Although **"*Hippocratic medicine*"** shares similarities with the Egyptian, the former does not undermine the latter. In contrast, Hippocrates used the knowledge of Egyptian medicine and advanced it by removing the magico-religious part and making it more rational [1]. In fact, at that ancient time, physicians had to think, about the patient's needs and beliefs in order to have a successful treatment [2]. Hippocrates believed that "diseases might be treated from their origin" and "the treatment carried out should be opposed to the cause of the disease". Therefore, they focused more on the personalised approach of the disease and eliminated all the superstition that was

surrounding this time of history [3]. In light of that breakthrough, Hippocrates was ahead of his time, as he managed to give a direction in the understanding of the genomic medicine by suggesting that every human is distinct and this affects both the disease prediction as well as the treatment [3].

During the twenty-five centuries, from the so-called "Father of Western Medicine" Hippocrates to the modern physician, personalised medicine has evolved attracting a lot of attention [3].

However, despite the ancient vision and recommendations, medical therapy employed a very broad approach that was based on clinical and genetic/genomic data from heterogeneous populations instead of focusing on each patient, even in recent decades [4]. Physicians used standardised approaches based on data and knowledge of the earlier patients/diseases to decide on a therapeutic regimen. Clinical trials were only aiming for standarised treatment rooting out 20% of the population that was not going to respond to a treatment or even worse experience adverse effects possibly due to differences in their genetic make-up [2]. This meant that medicine had no room for idiosyncrasy (from ancient Greek ἰδιοσυγκρασία / idiosynkrasia, "a peculiar temperament, habit of the body, e.g. blend of humors". Idiosyncrasy defined the way that physicians conceived diseases in the 19th century [5].) This approach began to change in the 1870s, when discoveries made by researchers in Europe allowed the advent of a ***"scientific medicine"***, a precursor to the evidence-based medicine.

In the early 1950s, scientists started to realise progressively the need for ***"evidence-based medicine"***. The prediction of drug response to ensure the safety of the patient as well as a better outcome gave birth to the field of today's ***"personalised medicine"***. Discoveries in the field of molecular biology contributed to a better understanding of drug response [6]. In this regard, human genome mapping was a breakthrough providing a better understanding of peoples' genetic make-up. Although, individuals are 99.1% identical, the remaining 0.9% of inter-individual genetic variability is responsible for the observed variability within the humans [4].

Overall, the challenge that researchers and physicians face is still immense nowadays. The purpose of personalised medicine is to combine modern medicine with molecular advances in order to target patients separately and improve the efficacy and effectiveness of the therapeutic approach [7]. The realisation that the conventional approach of using candidate genes alone is not sufficient to explain the differences in disease risks between different ethnic groups and also within individuals, led to the whole genome approaches. The evolution of different genotyping technologies over the years has allowed focusing on specific regions of the genome enabling deeper coverage and understanding of the variants. Therefore, it enabled medical practitioners to identify and treat patients based on their unique characteristics.

Today, the four humors of Hippocrates, blood, phlegm, yellow bile, and black bile which determined the treatment of each individual [8] have been replaced with the four building blocks (A, T, G, C) enabling improved medical predictions.

Cutting-edge biochemical advances including single nucleotide polymorphisms (SNPs), genotyping and biochips have made personalised medicine a reality justifying the use of the terminology in the last few decades.

Indeed, the unique identity of every person's genome provides valuable information regarding disease onset and progression along with the response to different therapeutic regimens [9]. Variations such as SNPs, insertions and deletions, structural variants, and copy number variations in the human genome play a distinctive role in the manifestation and progression of diseases such as cancer, diabetes, neurodegenerative and cardiovascular disease [9]. Hence, biomarkers are being investigated as a way of predicting certain diseases and also identifying patient subgroups that respond only to specific drugs. However, environmental factors can also act as triggers and/or co-factors. Therefore, predicting response to drugs as well as treatment based only on genetic information without taking into account the environmental determinants can lead to poor or false results [9].

Combining the human genome, environmental factors, disease assessments, and medication in order to achieve a better therapeutic outcome is the exact vision that personalised medicine is aiming to achieve. For the aforementioned, it is obvious that the journey of personalised medicine, as described in our previous article [10], has not reached its final destination. A mob of problems is still around the patient's needs, which is a challenge for personalised medicine nowadays.

The present review focuses on the major discoveries from the past to the present, points out milestones that helped on personalised medicine's journey, underlines the current problems that physicians still face, and gives insights into the future, assisting thus health care systems globally. *More importantly, it gives direction on how to handle epidemic crises such us coronavirus disease 2019 (COVID-19) that the world is currently facing, regarding diagnostic tools and therapeutic strategies.*

1. Underpinnings of targeted therapy

This chapter points out some important milestones through the history of pharmacotherapy that we must keep in mind and use as a beacon for achieving targeted medicine for individual's needs, which unfortunately, are not yet applied.

1.1. The key treatment of malaria as the beginning - Building knowledge on pandemics

The first evidence of malaria is found in 2700 BC into ancient Chinese medical records. Even today, malaria is an extremely serious and fatal disease [11]. It is estimated that malaria affected 228 million people resulting in 405,000 deaths globally in 2018 [12]. There is still a lot of research regarding diagnosis, prevention, and treatment of this disease all over the world including countries where malaria is even more common like Africa and some Asian countries. In these countries the prevalence of malaria is higher probably due to the tropical climate, which increases the mortality rate from 0.3–2.2 % globally to 11-30% in tropical environments [11].

Several herbs have been used to treat malaria such as Qinghai in the 2nd century BC in China and the Cinchona tree in the 16th century in Peru [11]. In 1926, one of the most effective drugs distributed to treat acute malaria was pamaquine an 8-aminoquinoline. At that time, pamaquine was a groundbreaking discovery because of its effectiveness as an anti-malarial. However, adverse effects observed after its administration raised concerns about its safety [13]. More specifically, between 1930 and 1940 at least 250 cases of acute hemolytic anemia were reported after providing the drug to patients [14]. As a result, in 1943, scientists started investigating alternative therapeutic regimens to encounter the adverse effects of pamaquine. Various compounds were tested, among them primaquine, which also belongs to 8 aminoquinolines [13]. Primaquine, an 8-(4-amino-1-methyl-buty1amino)-6-methoxyquinoline first appeared in the Korean War as an anti-malarial, where soldiers were administered the drug to eliminate the long latency of P. vivax infection [15]. Although primaquine was considered the most appropriate candidate, hemolytic anemia was still observed [13].

The answer to this problem came later, in 1956 when Carson et al. discovered that the side effects of hemolytic anemia were caused by a deficiency in the G6PD enzyme [13]. The G6PD deficiency was well established from 510 BC [16] when Pythagoras, even though he wasn't a physician [17], had observed this side effect after a number of his students consumed fava [16]. The advances in molecular diagnostics revealed that there are a lot of mutations in the gene but people remained asymptomatic and only in a few cases, such as after the administration of primaquine trigger severe side effects [17].

According to WHO primaquine is now used to cure the liver infection caused by malaria (P. vivax and P.ovale) and prevent relapse. To eliminate the hemolytic anemia and achieve a better therapeutic outcome, WHO has published guidelines for primaquine administration to reduce the risk of the adverse effect in people with G6PD deficiency. For example, for the prevention of malaria

in normal adults the therapeutic approach is to administrate 0,25-0,50 mg/kg body weight daily for a duration of 14 days. However, for people with G6PD deficiency, the dosage is differentiated to 0,75mg/kg body weight once a week for 8 weeks with close monitoring of the patient's therapy [18].

The discovery of the association between anti-malarial drugs and G6PD deficiency opened a new perspective regarding the adverse effects of these drugs as well as a more personalised approach to the disease. This was one of the first examples that led to a big step towards the application of a more personalised therapy that was established as a term many years later in 1991 and is currently still quite limited.

But why the reported cases of malaria are still large (228 million globally in 2018) while diseases such as Ebola and Cholera, which were also of a similar magnitude, are being managed properly resulting in a decrease of the infected population [19, 20]? One answer to that question could be that 90% of the population infected by malaria is originated in Africa [12]. For example Ebola appeared in 1976 in central Africa but the outbreak in 2014-2016 was the one that alerted the scientific community as the virus managed to spread quickly from West Africa to urban areas and across borders transforming it into an epidemic [19]. Another aspect could be the inadequacy of resources in developing countries. Lack of food and medical supplies hinders the treatment, proving thus that the environment is also a co-factor in disease progression and cure. So physicians should consider every continent and every patient individually according to his origin and taking into account their environment to achieve improved therapy.

1.2. The pharmacogenetic evolution - an important milestone

Biochemical health sciences started to evolve around the 1940s and 1950s at the same time as the development of instrumentation and new research methods. The scientific field responsible for (1) the research of different patients' responses to the drugs and (2) the minimisation of the adverse effects caused also by variability on the metabolising enzymes is known as pharmacogenetics [21]. After the first appearance of mass spectrometers, science evolved quickly leading to the first observation of cytochrome P450 (CYP450) around 1958. Later, in 1965 the novel drug metabolising enzyme CYP450 was introduced [22]. The constant speculation is the gap between physicians and the knowledge regarding pharmacogenetics in order to achieve personalised medicine [21].

One of the first examples that shifted treatment is CYP2D6, an enzyme that belongs to the CYP450 family and is responsible for the metabolism of 20% of the drugs involving anti-arrhythmic,

antidepressants, antipsychotics, b-blockers and analgesics [23]. CYP2D6 was discovered in 1969 due to different plasma concentrations of nortriptyline observed in patients, indicating differences in its metabolism [24]. Some years later in 1977 it was observed that debrisoquine, an adrenergic-blocking drug, which was used to treat hypertension [25] had also variations in response to treatment [26]. Today debrisoquine is mostly used as a marker to determine the activity of the CYP2D6 enzyme in patients. More specifically, debrisoquine and its 4-OH-metabolite are measured in urine with gas chromatography and high-performance liquid chromatography (HPLC) methods [27] in order to find the individual's CYP2D6 genotype. Therefore, by predicting the phenotype of each patient it can give insight into their response to specific drugs metabolised by the CYP2D6 enzyme.

Although nowadays, important evidence about the multiple variants in CYP2D6 exist, there are still not a lot of applications in medicine where the administration of several drugs in patients is depending on the occurrence of specific SNPs on their DNA. This is a future challenge in this field that will bring us a step forward to personalised therapy.

Another important advancement regarding the application of personalised medicine in cancer therapy is the discovery of the HER-2 gene. Breast cancer is a disease that can be divided into different subtypes depending on the tumor as well as on the patients' genetic background predisposition [28]. More specifically, HER-2 gene (Human Epidermal Growth Factor Receptor 2) encodes a tyrosine kinase receptor that takes part in signaling pathways both in normal and malignant breast cells and is strongly associated with a lower response to cancer treatment and survival rate [29].

The *HER-2* gene became clinically relevant in 1987 when Salmon et al. reported a lower survival rate in women with breast cancer carrying the mutated gene [30]. It was discovered that in the majority of patients carrying the mutation, overexpression of this gene was associated with chemotherapy resistance, poor patient prognosis [31], high risk of cancer progression, and a low survival rate [32]. Patients that are carrying the *HER-2* gene amplified have distinctive molecular signature that can distinguish these type of cancers from other breast cancers [28]. A lot of studies were conducted in order to reverse these adverse effects of the *HER-2* gene overexpression and eventually achieved with the use of monoclonal antibodies targeting the tyrosine kinase receptor [29]. A great example is the antibody trastuzumab that inhibits tumor growth when used as monotherapy, also when used with cisplatin, carboplatin, docetaxel and ionising radiation have synergistic effects and when used with doxorubicin, cyclophosphamide, methotrexate, and paclitaxel has additive effects [33].

Since that time, several clinical trials have proved the efficacy of trastuzumab resulting also in establishing routine HER-2 testing in breast cancer patients and changing dramatically the

therapeutic approach to those carrying the mutation. [28]. *This gene is a great milestone of applied personalised medicine clearly showing that the right choice of a drug, based on the genetic background of a patient, can have positive effects on their life.*

From the aforementioned, the impact of personalised medicine on the health care community is obvious. There is an important value in understanding the cause of the problem and making health better by solving it.

2. Limitations of today's medicine – The case of COVID-19

The limitations of personalised medicine have come to the foreground nowadays due to the pandemic of coronavirus disease 2019 (COVID-19) that emerged in December 2019 in China and managed to spread rapidly in multiple countries at the beginning of February 2020 [34]. Despite all the worldwide recognised advances and discoveries that have been achieved, modern medicine still cannot provide a treatment with current therapeutic approaches. It is widely recognised that the genetic background of each patient in the case of COVID-19 pandemic is one of the major contributors of drug effectiveness and toxicity [35]. Thereby, the challenge of COVID-19 virus made physicians and healthcare staff to realise the problems that the global healthcare system faces and to acknowledge the crucial role of applied personalised medicine.

2.1.1. Treatment difficulties

Scientists believe that this virus causes pneumonia by interacting with the ACE2 receptors. But are we sure that the COVID-19 virus attacks the respiratory system and not the circulation of oxygen?

Due to the limitations of existing experimental methods, the pathogenesis of the virus is not clear yet. According to literature, decreased levels of haemoglobin, neutrophil, and increased levels of serum ferritin, erythrocyte sedimentation rate, C-reactive protein, albumin, and lactate dehydrogenase were observed in patients with COVID-19 pneumonia. Haemoglobin is a protein contained in red blood cells and it is responsible for the transportation of oxygen to the tissues. It consists of four units of haem. Therefore, the aforementioned observations indicate that haem also increases [36] as a result of haemoglobin oxidation [37] and causes, in turn, the accumulation of many detrimental iron ions [36]. The haem release can cause inflammation in two ways: (1) by "intercalating in the membrane and altering cellular structures" and (2) by "activating immune responses and inflammatory reactions which act as the pro-oxidant in endothelial cells, neutrophils, and macrophage" [37]. Consequently, heam accumulation in the respiratory system results in increased permeability in the membranes of endothelial cells, facilitating, thus, the COVID-19 virus to

enter into the endothelial cells of the lung and cause secondary inflammation resulting in pneumonia. The hypoxia that low levels of haemoglobin causes in the lungs can be a co-factor that ultimately leads also to pneumonia. The maintenance of satisfactory levels of heamoglobin is hereby essential for the oxygenation of tissue and decreased levels of the latter in infected patients result in a limited capacity of red blood cells to transfer oxygen to the tissues.

So far, there are no specific drugs that can be effective in controlling the disease. Due to the global spread of the virus and the non-existent vaccine the global health community has been focused on finding the best antiviral agent to control the disease. Many clinical trials are ongoing in order to establish a course of treatment and prevent the numerous deaths happening daily. Several drugs are being tested for their activity against the COVID-19 virus and almost 30 agents have been revealed [38].

According to the National Health Commission (NHC) of the People's Republic of China 7th edition interferon α (IFN-α), lopinavir/ritonavir, chloroquine phosphate, ribavirin, and arbidol are recommended for empirical therapy against COVID-19 virus (latest edition March 4, 2020) [39-41]. On the 7th of March the NHC reported that tocilizumab (TCZ) also has been included in the treatment guidelines as an antiviral agent [42]. Other drugs such as azithromycin, an anti-biotic, or corticosteroids act in support of the above antiviral agents helping the overall treatment as concomitant agents [41, 43]. Details about these drugs are shown in figure 1.

The aforementioned guidelines include 6 drugs as principal antiviral agents for the COVID-19 therapy. IFN-a is a broad-spectrum antiviral agent that is described as an inhibitor of the *in vitro* reproduction of the COVID-19 virus [38]. Lopinavir/ritonavir is an aspartate protease inhibitor used as medication in the human immunodeficiency virus (HIV). Due to its in vitro anti-viral activity [38] lopinavir/ritonavir have been suggested as second-line treatment for COVID-19 according to the only one existing today therapeutic algorithm from Hellenic government [44]. However, its effect on eliminating COVID-19 virus is still controversial [45, 46]. Chloroquine phosphate (or hydroxychloroquine), a widely used anti-malaria drug, might also have positive effects on treating the COVID-19 virus [38]. Studies suggest that its potential anti-viral activity can be attributed to an increase in the endosomal pH required for virus/cell fusion and the disruption of the glycosylation of cellular receptors of the COVID-19 virus [47]. Due to its antiviral and anti-inflammatory effects, chloroquine phosphate is utilised in the first line of COVID-19 treatment along with azithromycin according to the therapeutic algorithm of the Hellenic government [44, 47, 48] (Figure 2). However, its use should be considered with caution due to its potential cardiotoxicity (e.g. QT prolongation and drug-drug interactions) [44, 49] as well as its adverse effects on people with G6PD deficiency. The administration of chloroquine phosphate in patients with G6PD deficiency can cause hemolytic anemia proving once again that genes influence responses to drugs and highlighting the vital

importance of personalised medicine. Chloroquine phosphate has also been suggested for prophylaxis in areas with high COVID-19 incidences but results are inconclusive and further investigation is needed [50]. Although it is proposed as a treatment against the COVID-19 virus its benefits have not been proven yet [51].

Another anti-viral agent suggested on the guidelines is ribavirin. Ribavirin inhibits the replication of multiple viruses and because of its use in emergency clinical management it has also been suggested for the management of COVID-19 virus. However, its clinical effectiveness has not yet been established [52]. Ribavirin is used in combination with IFN-a or lopinavir/ritonavir for the treatment of COVID-19 virus [38]. Arbidol is another anti-viral drug that is approved for influenza treatment. Arbidol has promising anti-viral activity regarding the COVID-19 pandemic [53] and it is potentially more effective as a monotherapy compared to lopinavir/ritonavir compound [40]. In any case, the drugs described above are not suggested to be administered for more than 10 days [38].

A new addition to the guidelines was TCZ as studies mention a positive effect on controlling the COVID-19 virus. So far, findings support that TCZ is effective in preventing or treating the cytokine storm, observed in patients affected by the COVID-19 virus [41]. TCZ has been chosen instead of corticosteroids due to its fewer side effects on patients. It is an anti-IL-6 receptor (interleukin-6 receptor) antibody that in combination with glucocorticoid could potentially improve the condition of critically ill patients [41]. TCZ alone or in combination with anakinra, siltuximab alone, or in combination with anakinra as well as anakinra alone are currently being tested for their ability to improve the lung function by inhibiting the cytokine storm (expected completion December 2020) [54].

Besides the drugs already included in the guidelines, there are several other drugs worth mentioning. Favipiravir and remdesivir are two promising agents that are currently being tested for their anti-viral effect against COVID-19 [38]. Favipiravir, an RNA-polymerase inhibitor, is in an ongoing clinical trial that is expected to end in July 2020 [55] and remdesivir, a nucleoside analog, in an ongoing clinical trial expected to finish in May 2020 [56]. Another promising drug is bevacizumab that will be further discussed in the next chapter.

Given that a lot of COVID-19 patients are already on treatment for other chronic diseases, concerns have been raised about the potential synergistic effect of commonly used therapeutic agents (Figure 3) along with the COVID-19 therapy. Such agents known as concomitant agents are the Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs), HMG-CoA Reductase Inhibitors, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and corticosteroids. ACE inhibitors and ARBs are used globally from numerous people for various diseases such as hypertension, heart failure, coronary artery disease, or kidney disease [57]. Due to considerations of biological plausibility and a large percentage of COVID-19 patients with cardiovascular disease having

a poor disease progression, speculation exists about the worse outcome of patients on long term therapy with these agents. However there is still a lack of clinical evidence regarding their effects on the COVID-19 infection and further investigation is being conducted [58]. HMG-CoA Reductase inhibitors (or statins) might lower cardiovascular morbidity related to COVID-19 reducing thus the progression of the disease [58, 59]. Furthermore, the use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) seems to be controversial. Several reports suggested that NSAIDs might worsen the outcome of the virus by inhibiting antibody production. However, FDA counteracted this belief highlighting that there is no adequate evidence [58] (Figure 3). Another concomitant agent is ascorbic acid. Given its involvement in the immune response to viral agents, it has been suggested that ascorbic acid might have additional benefits to COVID-19 patients. Thus, intravenous ascorbic acid administration is being tested in an ongoing clinical trial investigating its potential anti-inflammatory and antioxidant activity [60].

As the novel COVID-19 pandemic continues, the research community works extensively to suggest the best treatment approach. In this regard, WHO launched a promising international clinical trial called “Solidarity”, that aims at finding drug combinations for the COVID-19 management [61]. Other clinical trials are also being conducted in order to finally determine the right treatment for COVID-19 patients [5]. Although a lot of effort has been done from the health care community, treatment guidelines are still changing every day worsening thus the circumstances and conditions that physicians have to face. Until now, there is not an effective treatment approach suitable for everyone. Furthermore, disease severity and progression seem to vary even among people with similar phenotypes. This global pandemic proves once again the necessity for personalised medicine and genetic sequencing for detecting potential adverse effects attributed to drugs used for virus treatment. In this regard, the case of chloroquine for malaria in patients with G6PD deficiency, previously described, should be taken as an example.

2.1.2. Obstacles in diagnostic test development

Although new technological advances have helped scientists to move a step forward in the development of novel diagnostic tools, there are still major problems regarding the reliability, sensitivity and specificity of diagnostic testing. As it is above mentioned, the world faces a pandemic disease, the coronavirus disease 2019 (COVID-19) [34]. Scientists struggle to balance between urgency and the sensitivity of diagnostic testing to achieve applied effectiveness in any medical diagnostic tool.

So far, several regulatory authorised diagnostic tests have been used to detect the existence of the COVID-19 virus. One of the most utilised is the RT-PCR test (real-time reverse transcription-

polymerase chain reaction) [62-64]. Designed for the qualitative detection of nucleic acids from the COVID-19 virus [63], this test uses samples taken from nasopharyngeal and oropharyngeal swab or sputum of patients that their symptoms suggest the existence of the COVID-19 virus (e.g. fever, tiredness and dry cough and/or symptoms of acute respiratory illness) [63, 64].

However, despite the supply challenges due to the increasing demand currently, there are also concerns regarding the performance of the different technologies used [65]. The RT-PCR test lacks the necessary accuracy and sensitivity due to the substantial percentage of "false-negative" results [62-64]. Hence, depending on the kit's label, the number of samples used and the RT-PCR machine there is a great percentage of error when using the RT-PCR test [63, 64]. According to WHO negative results do not necessarily exclude the possibility of COVID-19 infection and RT-PCR assay should not be the only criterion for COVID-19 diagnosis [63]. Literature suggests adopting chest CT (computed tomography) as an additional diagnostic tool in parallel with the RT-PCR test. Chest CT is a non-invasive diagnostic test with great efficiency that can minimise the false-negative cases from RT-PCR assay [62].

Nevertheless, the RT-PCR test is suggested to be used in severe cases to determine the need for hospitalisation. Due to lack of resources, this test cannot be applied widely and people with less severe symptoms are recommended to stay at home without testing.

Rapid antibody testing has also been authorised by WHO according to the Emergency Use Listing (EUL) for the identification of IgM/IgG antibodies in patients. It is well known that the presence of IgM antibodies signals the first line of defense when a patient is infected and the presence of IgG antibodies signals immunity for an individual [66]. This type of assay is different from the RT-PCR test, as it focuses on the proteins (antibodies) produced by the immune system as a response to a viral infection. Despite that it is a simple, rapid and highly sensitive test, it lacks specificity [66], as IgM and IgG antibodies can be detected in various infections and not only in the case of COVID-19 virus. Even though, antibody testing is probably the test that can provide the most accurate results there are not such tests provided at the moment.

Consequently, with the current diagnostic tools several people could be misdiagnosed or mistreated and hence, it is evident that there is a need for more specificity in diagnosis resulting in a better therapeutic outcome.

3.The ***"next generation of treatment"***

Nowadays, research community and health care providers try to improve not only the treatment strategies but also the *in vitro* diagnostics including the identification of novel biomarkers or the study of clinical phenotypes for a better disease prediction, response to drugs, etc. [67]. In this

regard, significant progress has been accomplished in the field of biomarkers. The term biomarker exists since the 1950s and has been widely used during the 1980s [68]. It is defined as a measurable characteristic that can indicate physiological and/or pathophysiological processes or pharmacologic responses to treatment [69]. In the past decade, the field of biomarker research and especially in cardiovascular diseases and cancer has been developed rapidly [68]. A great example for the revolutionary application of biomarkers in personalised medicine is the vascular endothelial growth factor A (VEGF-A), which is described as an endothelial cell-specific mitogen. Produced by many cell types including tumor cells, macrophages, platelets, keratinocytes, and renal mesangial cells [70], the VEGF family and their receptors have a key role in angiogenesis , in tumor growth [71] and physiological functions such as hematopoiesis, wound healing, etc. [70].

In 1993, Kim and colleagues were the first who identified monoclonal antibodies that can target and neutralise VEGF-A, inhibiting thus tumor growth in preclinical studies. This triggered the production of numerus anti-VEGF drugs such as the recombinant humanised VEGF-A specific monoclonal antibody bevacizumab, which was approved in 2004 by the US Food and Drug Administration (FDA) as the first-line treatment for metastatic colorectal cancer [72]. A new era of treatment, the VEGF-A anti-therapy, has come to light, resulting in better therapeutic outcomes in patients and approaching the ultimate goal, personalised medicine.

As described above hypoxia and inflammation are two interrelated conditions. Hypoxia causes inflammation in several lung diseases such as acute lung injury (ALI) and infection and vice versa [73]. Hypoxic stress can induce VEGF-A activity in the lungs. [73]. Nowadays, regarding the COVID-19 pandemic, it has been observed that COVID-19 patients have higher VEGF levels compared to healthy population and hypothesised that VEGF-A anti-therapy might be applicable in this case as well. Thereby, a Clinical trial is being conducted in order to investigate the effect of bevacizumab on disease control and treatment, especially on the acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) associated with COVID-19 virus. (estimated study completion: May 2020) [74].

Biomarkers and especially VEGF-A family are important tools for personalised medicine that can assist the diagnosis as well as the selection of patients for specific treatments. Unfortunately, the majority of them are not yet clinically used. Given the disputable efficacy of various chronic disease prevention strategies, new, stringent biomarkers, including the genetic predisposition ones, should be urgently identified and established in the clinical practice.

4. Personalised medicine starts with the patient

Personalised medicine is an ancient vision of rising challenges for healthcare systems and the research community throughout the years. It aims at confronting every obstacle on the prevention,

diagnosis, and treatment of diseases by targeting each patient individually. Advances in both science and technology have already contributed to significant improvements regarding disease management and clinical outcomes prediction [75].

In figure 4 the journey of personalised medicine through time is depicted. Forty-seven centuries passed between two very serious pandemics and the reasonable query is what it really happened over these years. From 2700BC until the Hippocratic period medicine developed rapidly to reach a level that even today we face difficulties to attain [1]. After the Hippocratic period, a significant gap appeared. Eighteen centuries passed without the patient being considered as an individual and with the “one size fits all” approach being the center of attention. This gap , that inevitably slowed down the evolution of personalised medicine, resulted in patients exposure to a health care system that did not considered them as different entities [2]. After the 1950s personalised medicine gained traction again with impactful discoveries starting shaping the future of medicine. Since 2005, although a lot of discoveries and technological advances have been accomplished, minor applications have been observed.

Nowadays, fifteen years later, personalised medicine still struggles to be applicable. There is no need to leave another fifteen years to pass until we understand the necessity of this field in medicine. Overcoming the application obstacles immediately will be an important step towards a new more personalised beginning on medicine. However, this cannot be achieved without providing both to the healthcare community and the public the necessary information and awareness regarding this field.

The outbreak of the COVID-19 infection is the right occasion and challenge for both research and healthcare professionals to change towards a more personalised approach taking into account individuals’ needs. Efficient therapeutic regimens should be discovered and tested in a very short period to minimise the consequences of this infection. New diagnostic tools with increased sensitivity and specificity should be applied and might be the next generation of diagnosis. The combination of new and already established biomarkers could be the key to improve diagnostics tools and treatments, as it happened in the case of VEGF and bevacizumab.

Consequently, the COVID-19 pandemic acknowledged the limitations that health care is facing, underlining the important issues that medicine is forced to encounter. Thus, the COVID-19 urged the health care system to change adapting a new reality of tailored therapy. A lot of advances are expected to be accomplished and a lot of current limitations to be overpassed in the next years. Personalised medicine, having the patient at the center of attention, is going to shape the future in medicine.

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