RESEARCH PROJECT B

IS INDIVIDUALIZED MEDICINE THE FUTURE OF THE MEDICAL INDUSTRY?

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List of Abbreviations

Abbreviation	Explanation
ALL	Acute lymphocyte leukemia
AML	Acute myeloid leukemia
CCD	Conventional cytogenetic diagnosis
CGH array	Comparative genomic hybridization array
CLL	Chronic lymphocyte leukemia
CML	Chronic myeloid leukemia
CT	Computed tomography
DNA	Desoxyribonukleinsäure
FISH	Fluorescence in situ hybridization
GS	Gleason Score
Gy	Gray
HIV	Humane Immunodeficiency-Virus
ICER	Incremental cost-effectiveness ratio
ICPerMed	International Consortium for Personalised Medicine
LYG	Life years gained
MDG	Molecular genetic diagnosis
mpMRI	Multiparametric magnetic resonance imaging

Abbreviation	Explanation
MRI	Magnetic resonance imaging
PCa	Prostate cancer
PET	Positron emission tomography
PCR	Polymerase chain reaction
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
QALY	Quality-adjusted life years
RNA	Ribonucleic acid

Abstract:

Individual medicine gained increasing popularity in the medical industry in the past years. Especially oncology plays a major role in individual medicine, as significant research has been done in this area in the last decade. In order to provide individual treatment to patients, individualized medicine in cancer therapy uses molecular genetic examination of blood or tumor tissue.

This paper discusses individual treatment approaches for the selected diseases of prostate cancer and leukemia. Individual medicine in prostate cancer is still considered to be in its infancy whereas in leukemia it is already advanced. Conventional treatment in prostate cancer is highly standardized and well-developed and thus, individual approaches in PCa are not yet well-established or well-researched. Therefore, the relevance of individual treatments in prostate cancer is still to be discussed. In contrast to that leukemia has a promising future in the area of individualized medicine. However, individualized treatments are still very expensive and health insurances only cover a limited amount of financial expenses. As genetic testing is becoming more significant and is likely to be used more often in the future, the cost for individual treatments are expected to decrease over time. Also, this paper suggests future implications for the application of individual medicine in Germany in the areas of health care promotion, disease prevention and disease management until the year 2030.

Highlights of the paper:

- Individual medicine in leukemia is already well-established, however necessity of individual approaches in prostate cancer is discussed
- Individual medicine is currently very cost-intensive but increases the quality of life and the lifespan.
- In order to implement individual medicine in the future it is anticipated to improve health care promotion, disease prevention and disease management.

Key words:

Individual medicine; Prostate cancer; Leukemia, Cost-effectiveness; Predictions for 2030 in Germany.

1 Introduction to individualized medicine

Individualized medicine – often interchangeably used with personalized and precision medicine – is currently a highly popular topic in the medical field. The development of individualized medicine is also many times referred to as paradigm shift in health care (Maier, 2019). It emerged from the trend of targeting to offer patients individualized care. Despite its newness, personalized medicine has already offered crucial insights into numerous diseases (Erden, 2015).

As mentioned, there are various terms for the targeting health care concept that suffer from the same disease but have a different set of biomarker and genetic characteristics (Tiriveedhi, 2018). Individualized, personalized and precision medicine are the terms that are mostly used in the literature to describe genetic-based diagnostic testing to stratify and identify patients for targeted delivery of a therapeutic procedure or pharmaceutical medicine. Still, there are minor differences in the precise definition of each of these terms (Tiriveedhi, 2018). In the following, three of the frequently used terms are briefly described.

Individualized medicine targets to improve the quality and effectiveness of treatment by systematic diagnostics, tailor-made therapeutic procedures and targeted prevention, which is designed to the needs of patient groups or individual patients, while increasing cost-effectiveness and reducing side effects in the long term (Acatech, 2017).

Personalized medicine refers to the application, development or selection of specific therapeutic or preventive measure that is based on the patient's individual profile, with the focus on drugs. However, there are different definitions to be found in the literature and many times 'personalized medicine' is used interchangeably with 'individualized medicine' (Acatech, 2017).

Precision medicine is often used as a synonym for 'personalized' and 'individualized medicine' and describes a concept of modern medicine which mainly includes aspects of molecular or genomic medicine (Acatech, 2017).

As the definitions portray, there are only minor differences in the terms, which is why this research uses the terms interchangeably.

The approach of individualized medicine is to treat diseases and protect the health by taking a person's environment, behaviors and especially genes into account. The interventions are individually tailored to a person or a group, rather than everyone receiving the same care by using a one-size-fits all approach. Precision medicine includes the classification of individuals into subpopulations differing in the prognosis or biology of potentially developing diseases, susceptibility to a certain disease and their response to a particular treatment (Maier, 2019). The individualized approach also considers the right treatment at the right time for the right patient. It is a progressing field in medicine that uses resources dedicated to search for predictive, prognostic and diagnostic biomarkers (Jackson and Chester, 2015).

Personalized medicine is a concept that may help patients to find a fitting therapy more quickly and aid to make the health care system increasingly efficient. It is based to a large extent on today's possibilities of modern genetic diagnostics.

In the past, professionals intended to make decisions that offer the best possible therapy for a particular patient, by not only focusing on the diagnosis but also on the personal characteristics of the patient. However, the novelty of introducing modern diagnostics is also the consideration of the molecular, cellular and genetic characteristics, which aid to draw conclusions for advantages or disadvantages in a therapy (vfa, no date). For quite some time, it has been known that not all patients respond equally to therapies, which is due to the fact that every person has individual characteristics and genetic compositions. Thus, the same disease can be caused by different factors and responses to drugs or therapies care differently processed by the individual's body. To identify these particular differences in the disease and to respond with the according treatment is the main goal of individualized medicine (Deutsche Krebsgesellschaft, 2014).

Individualized medicine includes an enthusiasm about the rapidly advancing medical potential of genetic knowledge, which incorporates a shift from individual gene tests (genetics) to an increasing potential for assessing multiple genes simultaneously (genomics). Genomics offer improved approaches in personalized health care by implying that this novel science aids to provide crucial information on an individual's unique health needs (Burke, Brown Trinidad and Press, 2014). Thus, genomics is of great importance in personalized medicine, as it enables "whole exome sequencing to identify rare variants and to use novel exome arrays to genotype these rare variants in

the population” at an acceptable time and cost (Tremblay and Hamet, 2013). Applying genomics in individualized medicine incorporates the potential to enhance prognosis, diagnosis, treatment as well as risk assessment (Tremblay and Hamet, 2013).

Still, individualized medicine is in its early stage in this area of research (Erden, 2015). Even though individualized medicine already has some applications in which it is used routinely, like in the inflammatory bowel disease, it is still in its infancy of application in many other fields (Jackson and Chester, 2015).

2 Individualized medicine in the area of oncology

Individualized or precision medicine is most often referred to the medical specialty of oncology (Maier, 2019). The terms individualized, personalized or targeted in relation to cancer treatment are currently much discussed. They are used as a synonym for evolving and modern cancer medicine and therapies that are precisely tailored to the needs of each individual patient (Deutsche Krebsgesellschaft, 2014).

Available statistics show the high relevance of research in individualized medicine in the area of oncology. When observing the leading causes of death worldwide in the past year, it can be noticed that cancer is the second most common cause for death with 24% just after cardiovascular diseases (Statista, 2020). Subsequently, when examining the most common cancer deaths by type, it can be observed that, among others, types like lung cancer, breast cancer, pancreatic cancer, prostate cancer or leukemia have a very high mortality (Statista, 2019a). Thus, it seems evident that there is an increasing need for improved customized care, especially in the area of oncology. This can also be observed in the precision medicine market worldwide, which showed the highest application in the area of oncology with approximately 38 billion U.S. dollars in 2017 (Statista, 2019b).

Individualized cancer therapy is based on novel diagnostic methods such as the molecular genetic examination of blood or tumor tissue. Subject to research are specific alterations characterizing the tumor cell, which are known as biomarkers. Once the biomarkers have been detected, the tumor cell can be precisely targeted. Biomarkers enable a prediction as to whether a certain treatment method is effective and can consequently be used (Deutsche Krebsgesellschaft, 2014).

Individualized medicine is especially important in the area of oncology that has an increased emphasis on prevention and functional implications that are associated with chemotherapy and surgical management strategies. Developments regarding individualized cancer medicine, that include the recognition of predictive and prognostic biomarkers, enable targeted treatments to patients which are likely to benefit and improve their survival outcomes from individualized therapies (Jackson and Chester, 2015).

In many tumor diseases, such as breast cancer or lung cancer, various cancer cell structures are already identified which then can be targeted. This also differentiates this novel type of therapy from already known treatments such as chemotherapy. With chemotherapy, all fast-growing cells are attacked rather imprecisely, which leads to healthy cells being damaged as well. Targeted therapies, however, are effective against molecules of the tumor cell, which are responsible for tumor growth. This individualized approach in the processes of cancer development is expected to have improved effects on the disease and only few side effects on healthy body cells (Deutsche Krebsgesellschaft, 2014).

Although there is already a number of cancer drugs that have a successful and targeted effect, tumor spread and growth cannot always be delayed or prevented. This is due to the fact that tumors often show numerous variations and that not all of them could be accurately identified. Also, there are not yet appropriate or suitable drugs available for all known variations. In practice, this implies that it is often achievable to block certain cancer-promoting molecules. Still, due to the numerous variations, this is often not sufficient to effectively stop tumor growth, as it is also possible for tumor cells to multiply again via other unknown routes. However, intensive research is currently being conducted on individualized approaches. Experts believe that these approaches could revolutionize cancer medicine, leading to many types of cancer being cured in the future (Deutsche Krebsgesellschaft, 2014). Moreover, regarding the development of personalized medicine, it is considered realistic that genetic stratification approaches can enhance care for individual patient groups (Wäscher *et al.*, 2013).

Individualized medicine has been one of the main focuses and objectives in cancer care in the past years and is likely to continue in the future as well (Alitto *et al.*, 2015).

As oncology is an immensely broad field with various possible applications for individual medicine, it was decided to specify on the disease prostate cancer and

leukemia. These specifications were chosen, due to their progress in research and application for individual medicine. The specification on prostate cancer was chosen as it is only in its infancy of research and therefore has a high development potential. Additionally, leukemia was chosen as it is already well developed in individual therapies and applications. In the following chapters, the conventional and individual treatments of prostate cancer and leukemia are discussed in detail.

3 Methodology

This study's main source of information was secondary literature. However, to receive further insights into this area of research, a qualitative study with expert interviews was conducted.

3.1 Theoretical Background

As mentioned, the basis for information in this research was identified through screenings of databases, as well as public health websites. The findings of the screening of available databases and websites formed the basis of the interview guide, which was prepared for conducting the interviews.

3.2 Primary Data

For primary data, expert interviews were chosen, with the purpose of receiving another quality of information (Aghamanoukjan et al., 2009). The interviews were conducted via telephone, including audio-recordings of the conversation (Saunders et al., 2009). Based on the findings of the secondary research, an interview guide was developed, including general questions for individual medicine, disease-specific questions on prostate cancer and leukemia, future implication related questions, as well as questions concerning the current status quo of individual medicine in Germany (see appendix 1).

3.3 Procedure

To gain additional insights into the topic of individual medicine, it was decided to select three different specialists related to the area of research. The interview partners chosen are a specialist for hematology and oncology, a specialist for laboratory medicine and a specialist for human genetics and internal medicine. It was intended to interview specialists that are exposed to individual medicine from different perspectives. All interviewees were provided with the interview guide before the interview, in order to give well-founded answers. Also, all participants were informed about the use of their provided data in this research. The interviews were conducted between June 23, 2020 and June 29, 2020.

3.4 Processing

Firstly, all recordings of the interviews were transcribed, in order to assure accountability of the obtained data (Aghamanoukjan et al., 2009). For documentation, a summarizing transcription was chosen (Höld, 2009). Afterwards, the obtained data was analyzed and compared to the initial findings in secondary literature. The transcripts were being screened and used to support findings, or conversely, to open up new perspectives and points of discussion, which were not considered in literature.

4 Prostate

Prostate carcinoma (prostate cancer (PCa)) is a malignant tumor of the prostate gland and the most frequent occurring cancer in men in Germany with more than 60,000 new cases every year. Cancer of the prostate gland is rare before the age of 50 and is often distinguished from other malignant tumors by its slow growth (Deutsche Krebsgesellschaft *et al.*, 2019). PCa is “characterized by a remarkable genomic complexity mirrored in the clinically variable behavior of the disease” (Bartucci *et al.*, 2016). North America and Europe are diagnosing over 500,000 cases of prostate cancer each year. Approximately one in six men are diagnosed with prostate cancer in their lifetime, and one in 34 men are estimated to die from metastatic castration-resistant prostate cancer (Fraser *et al.*, 2015).

4.1 Introduction to prostate cancer

The tumor initially spreads within the prostate. However, as it continues to grow, it can break through the connective tissue capsule surrounding the organ and grow into adjacent tissue affecting for example the seminal vesicles, bladder, or rectum. Also, as the duration of the disease increases, the probability that cancer cells will spread in the body and form metastases increases. For this reason, an early detection is of great importance. When the tumor is still small and has not spread into the surrounding organs the chances of treatment and thus cure is greatest (Deutsche Krebsgesellschaft *et al.*, 2019).

The interviewed specialist of laboratory medicine states “[...] if [prostate cancer is] early enough detected it is not life threatening.” (see appendix 3)

The problem is that there are no typical symptoms that indicate prostate cancer in an early stage. In most cases, prostate cancer develops in the outer glandular zone and the consequences as interferences in urination only occur when the tumor is already large and has spread throughout the entire organ. Warning signs of a late, often very advanced stage of prostate cancer can be, for example difficulties with the act of urination, blood in urine or semen, pain during ejaculation or potency disorders (Deutsche Krebsgesellschaft *et al.*, 2019).

There are certain causes and risk factors for prostate cancer. The risk of developing prostate cancer increases with age. Over 80 percent of all men who are diagnosed with prostate cancer are over 60 years old. Another risk factor for prostate cancer is a genetic predisposition. According to estimates, the proportion of genetically caused prostate cancer is between five and ten percent. It has been known for some time: Men whose fathers or brothers have been diagnosed with prostate cancer have twice as high of a risk of developing the disease themselves as the rest of the male population. At the same time, the probability of being affected earlier by cancer of the prostate gland is increasing. Also being overweight and smoking increases the risk of prostate cancer (Deutsche Krebsgesellschaft *et al.*, 2019).

PCa can be divided into low-risk and high-risk cancer. To stratify the cancer risk for clinical and biopsy decision-making, classical prognostic factors, which include the biopsy-based Gleason Score (GS), the prostate-specific antigen (PSA) level, as well as clinical tumor staging, are used. Most low-risk cancer patients may not require any treatment due to the slow-growing and small tumors (Liu, 2017). Conversely, overtreatment of low-risk and indolent cancers can lead to an increased but inappropriate morbidity as a consequence of surgery and radiotherapy.

4.1.1 Detection of prostate cancer

For early detection and if prostate cancer is suspected, the doctor examines the prostate via the rectum (digital-rectal examination). This is because prostate carcinomas mostly develop in the part of the gland that faces the rectum. The doctor looks for irregularities and hardenings that suggest the suspicion of a carcinoma. However, not every prostate cancer can be detected in this way. Especially small tumors are sometimes not noticeable during the palpation (Deutsche Krebsgesellschaft *et al.*, 2019).

Next to the examination by the doctor blood should be taken to determine the PSA level which is seen as a successful detection method by experts “[...] there is a good way for the screening using the PSA as [a] laboratory parameter.” (interview with specialist for laboratory medicine, see appendix 3).

PSA is a protein produced by the glandular cells of the prostate. In small amounts, PSA passes into the blood. The doctor therefore takes blood from the patient, which is then examined in the laboratory. The normal PSA level in healthy men ranges from zero to two and a half nanogram per milliliter (ml) of blood. In the case of prostate carcinoma, the PSA concentration in the blood is usually elevated. But an increase in the PSA level is not a sure sign of cancer. There are many other reasons for an altered PSA level. For example, an inflammation of the prostate (prostatitis), a benign enlargement of the prostate (benign prostatic hyperplasia), a previous palpation or cycling before taking a blood sample can raise the PSA level. Conversely, just as an elevated PSA value does not always indicate prostate cancer and "normal" PSA values do not out rule prostate cancer to one hundred percent. Therefore, in addition to the absolute value, the rate of increase between different PSA measurements is also important. Intensive research is currently being conducted to find improvements or alternatives to the PSA test (Deutsche Krebsgesellschaft *et al.*, 2019).

If there is a well-founded suspicion for a prostate carcinoma, ultimately only a tissue sample (biopsy) can confirm this suspicion. However, a nuclear spin examination (multiparametric magnetic resonance imaging) of the prostate should be carried out before a biopsy takes place. This provides a better indication of whether a malignant prostate cancer, an inflammation or a benign enlargement is present. This has the advantage that some patients, whose prostate changes turn out to be no malignant prostate cancer, can be spared the biopsy. With the MRI examination it is also possible to find the exact location of the tumor within the prostate and from there the samples can be taken with great accuracy (Deutsche Krebsgesellschaft *et al.*, 2019).

If prostate cancer is present, the next step is to determine the size of the tumor, where it may have spread and how malignant the tumor is by using various other diagnostic measures (Deutsche Krebsgesellschaft *et al.*, 2019).

4.1.2 Different stages of prostate cancer

With the help of the TNM classification of Malignant Tumors (TNM), prostate cancer can be classified according to tumor size and spread. Stages T1-T4 describe the size and extent in more detail. The treatment depends on the stage of the prostate cancer.

Locally restricted cancer (T1 and T2):

The cancer is still confined to the prostate and has not formed any metastases. A complete removal and cure of the tumor is possible by surgical intervention or by radiation therapy. In older patients with small, less malignant tumors, it is also possible to simply wait and see whether the tumor grows. However, this procedure, called "active monitoring", requires regular determination of the PSA level, regular palpation and ultrasound examinations of the prostate, as well as taking new tissue samples of the prostate. Often old or sick patients no longer want to be burdened by a surgical intervention or by radiation therapy. These patients can be treated palliatively with medication, but a cure by medication is not possible (Deutsche Krebsgesellschaft *et al.*, 2019).

Advanced prostate cancer (T3 and T4):

The tumor has spread beyond the prostate, for example into the rectum or seminal vesicles, but has not yet formed metastases in lymph nodes or other organs. In this case either surgery or a combination of radiation and hormone therapy can lead to recovery. However, survival rates are better with surgery for these locally advanced tumors (Deutsche Krebsgesellschaft *et al.*, 2019).

Tumor with metastases:

The tumor has already formed metastases in lymph nodes or other organs. The possible treatments in this case are a therapy with anti-hormonal drugs or the removal of the testicles (orchiektonime) followed by chemotherapy after about four months (Deutsche Krebsgesellschaft *et al.*, 2019).

4.2 Traditional prostate cancer treatments

If prostate cancer is detected early enough, it may not be life threatening and therefore could be treated with conventional methods as “the treatment is well established [and] it is highly standardized” (Interview with specialist for human genetics and internal medicine, see appendix 4).

Surgical intervention: If the carcinoma is still confined to the prostate, it is common to remove the prostate by a surgical intervention. There are different possibilities for surgical interventions. One is the open surgery, called open prostatectomy, in which the surgeon makes a vertical 8 to 10-inch incision below the belly button. The prostatectomy is then performed through this incision (Deutsche Krebsgesellschaft *et al.*, 2019).

Another possibility is the laparoscopic prostatectomy. In this case the surgeons make several small incisions into the belly. Through the incisions surgical tools and a camera (laparoscope) are inserted and the prostatectomy can be performed from outside the body. The surgeon can view the field of operation with the help of a video screen. This approach is called a minimally invasive procedure. It has the advantage that the patient is significantly less affected by it than in an open surgery where large access to the operating area is needed. As a result, the patient loses less blood, a smaller dose of narcosis is needed, the risk of infection decreases, minor scars are formed, and the hospital stay is shortened (Deutsche Krebsgesellschaft *et al.*, 2019).

The third option is the robot-assisted laparoscopic prostatectomy. As in the laparoscopic prostatectomy small incisions are made to view the field of operation. During an operation with this approach a surgeon controls an advanced robotic system from a control console outside the body. By using the control console, the surgeon can move the surgical instruments. Natural hand shaking, and the pulse of the surgeon are suppressed thanks to software algorithms and special filter mechanisms. This allows extremely precise cuts. The software allows the doctor a very detailed, three-dimensional view of the surgical field. At the control console, the operator can move the instruments with the help of sticks and the movements are transferred to the surgical instruments. Due to the mobility and the zoom of the camera, the surgeon always has an optimal view of the surgical field. A famous and widely used surgical robot system is for example the Da-Vinci system by Intuitive Surgical (Universitätsklinikum des Saarlandes; Deutsche Krebsgesellschaft *et al.*, 2019).

Radiation therapy: In radiation therapy, high-energy radiation is locally limited to the tumor area. It is intended to kill the malignant cells by damaging their genetic material (DNA). For small tumors limited to the prostate, radiation therapy can be an alternative to surgery. If the tumor is no longer restricted to the prostate, but has spread, radiation

is of great importance in combination with hormone therapy (Deutsche Krebsgesellschaft *et al.*, 2019).

The cell-damaging effect of radiation therapy is not specific, for example healthy body cells are also affected. However, depending on the degree of damage, the cell's' own repair systems can repair the damage to the genetic material. As with scissors, they cut out the spots and replace them with intact ones. This ability to repair the genetic material is better developed in healthy cells than in cancer cells. While the healthy cells regenerate, the cancer cells die and are eliminated by the body's immune cells. To give the healthy cells enough time to repair the genetic damage, the radiation dose that the patient is receiving in total must be divided into several individual sessions (fractions) (Deutsche Krebsgesellschaft *et al.*, 2019).

The doctor selects the radiation dose based on the radiation sensitivity of the tumor. If a cure is to be achieved, the radiation dose is 40 to 70 Gray (Gy). The total dose required to destroy the tumor is normally divided into fractions of 1.8 to 2 Gy each. This ensures good tolerability and reduces the risk of permanent damage and late complications. However, the ability of healthy tissue to repair itself remains the limiting factor for radiation therapy (Schmoll *et al.*, 2006).

4.3 Individual treatment

For many years, research in the field of prostate cancer was mainly dominated by a one-size-fits-all approach, which comprised high numbers of patients without using molecular stratification. This approach lead to clinical prognostic features that reflect disease burdens instead of disease biology (van Soest, 2017). The clinical management of prostate cancer can be very challenging due to the variable pathologic and clinical disease behavior. Therefore, there is an increased need for treatment optimization and specification to each patient, which leads to improved and progressive outcomes (Bouchelouche and Choyke, 2016).

Thus, increased attention is given to the development of individualized or personalized treatment in the field of oncology, where therapies are precisely tailored to particular characteristics of each individual oncology patient. It is also required to accurately characterize and locate the cancer to treat it in the best possible manner (Bouchelouche and Choyke, 2016). Using novel and effective biotechnologies, like

next-generation sequencing, aided to significantly advance “the comprehensive analysis of cancer genomic alterations that has a single-base resolution, is genome-wide and is high-throughput” (Liu, 2017).

The disease can be divided into low-risk and high-risk cancer. Overtreatment of low-risk and indolent cancers can lead to an increased but inappropriate morbidity as a consequence of surgery and radiotherapy. For instance, approximately 66% of low-risk prostate cancer cases could only use active surveillance and thereby prevent treatment-related complications. Therefore, improved predictors of individualized treatment and prognosis are needed for patients receiving intensified and customized PCa treatment. Recent next-generation sequencing developments permit the identification of predictive and prognostic signatures which are grounded on genomic profiles (Fraser *et al.*, 2015). Furthermore, for high-risk cancer patients it is common that individuals have different responses to the standard treatment or the same drug. This standard treatment is not the best option for all patients, when comparing it to choosing an individual and effective treatment for each patient. The genetic variances between patients and their tumors may be the leading cause for differences in drug or treatment responses. Thus, there is an increasing necessity for novel biomarkers targeting genomic aberrations of the cancer, which can be used to improve cancer risk and progression diagnosis, understand oncogenic heterogeneity and aid an effective therapy prediction by using an individualized or personalized approach (Liu, 2017).

Biomarker profiling and oncogenetic testing depicts an increasing requirement to facilitate the optimal drug choice based on observed alterations in individual patients, especially for targeted therapy. Consequently, appropriate treatment could be received by patients already in an early stage to reduce medical costs and the risk of mortality. A drug-diagnostic model co-development model was developed to use novel cancer drugs. Drugs which were developed using the mentioned model aim matched subsets of individual patients and are defined by clinical biomarkers. Moreover, an elevated success rate was demonstrated in clinical trials for drugs that use biomarkers in patients (Liu, 2017).

Additionally, genetic heterogeneity is also of importance regarding to the clinical outcomes diversity in prostate cancer. Numerous genome-wide DNA- and RNA-based prognostic signatures were introduced in the past (Fraser *et al.*, 2015). Deep and targeted DNA sequencing offers an in-depth assessment of low-frequency and

clinically relevant genetic variations. This targeted RNA sequencing permits an analysis of complex gene fusions and transcriptomes (Liu, 2017). The current whole-genome sequencing technology development of DNA submicrogram quantities can be especially informative (Fraser *et al.*, 2015). Progressive technologies may aid to "detect the genomic alterations of tumor cells in circulation and continue to improve the investigation of challenges in field of personalized cancer therapy" (Liu, 2017).

4.3.1 Future Predictions

The recent developments regarding patient specific therapies that target the numerous vulnerabilities of cancer can aid to achieve a complete transformative impact of cancer precision and individualized medicine (Bartucci *et al.*, 2016). This concept of precise and individualized medicine driven by genomics can offer numerous advantages in prostate cancer treatment. However, this concept is only in its infancy in prostate cancer treatment and there is a need of continuously collecting genomic information that correlate with a therapeutic response. It can be useful to develop catalogues of cancer-related genes, as well as assessments of pathway activation that may enable an improved identification of additional drivers. Moreover, activated protein networks and genomic landscapes of tumors have to be characterized to guide towards therapies with optimized therapeutic effects. Lastly, operational challenges and logistics have to be addressed in the future as well (Mullanea and Van Allen, 2016).

However, as the one-size-fits-all approach dominated the treatment of prostate cancer (PCa) for many years, the introduction of personalized medicine or individualized treatment remains challenging. Still, it can be argued that the general approach in PCa treatment already has individual aspects, as a specialist for hematology and oncology (see appendix 2) reasoned that

> *"it is not totally accurate to say prostate doesn't allow for individualized treatment. [...] They evaluate the patients and for each patient they develop the best treatment plan which is taking into account how advanced the cancer is and what is the best approach to potentially cure the patient. And then they put together a package of treatment approaches like surgery, hormone therapy or radiation therapy to give the patient the best option to tackle the problem".*

4.3.2 PSMA Therapy

An example for individualized treatment of prostate cancer (PCa) can be the PSMA therapy. Recently, an increasing focus on the prostate-specific membrane antigen (PSMA) has been observed and serves as a target for therapy and imaging (Bouchelouche and Choyke, 2016).

The prostate-specific membrane antigen (PSMA) “is a type II membrane protein originally characterized by the murine monoclonal antibody (mAb) 7E11 - C5.3 and is expressed in all forms of prostate tissue, including carcinoma” (Chang, 2004). The protein has a 3-part structure, which consists of a 24-amino-acid transmembrane portion, a 19-amino-acid internal portion, as well as a 707-amino-acid external portion. The prostate-specific membrane antigen gene can be found in the chromosome 11 in an area that is not commonly removed in prostate cancer (Chang, 2004). PSMA is exceedingly expressed by PCa, and its appearance increases with metastatic disease, tumor aggressiveness and disease recurrence. Consequently, the prostate-specific membrane antigen (PSMA) serves as an excellent target for therapy and imaging of prostate cancer. In the past years, there has been an increased number of works that developed an elevated affinity PSMA ligand for therapy and imaging. The strategy of ‘image and treat’ with radionuclides has shown potential of becoming of great importance in the PCa management (Bouchelouche and Choyke, 2016).

In the past, there was a number of PSMA PET/CT studies conducted which have shown promising results, leading to an increased number of clinical uses in institutions (Bouchelouche and Choyke, 2016). The PET/CT combination consists of two different imaging procedures, which are the positron emission tomography (PET) and the computed tomography (CT). Both of these procedures have different functions and therefore offer diverse images and information (Deutschen Gesellschaft für Nuklearmedizin, no date). Moreover, there was only a limited number of publications on PSMA PET/MRI (positron emission tomography–magnetic resonance imaging) (Bouchelouche and Choyke, 2016). In contrast to the PSMA PET/CT imaging, “small molecule binding to PSMA can be linked by a chelator to a therapeutic isotope to treat cancer lesions in a theranostic approach. The most reported treatment using PSMA is 177Lutetium-PSMA-617 radioligand therapy” (von Eyben, Baumann and Baum, 2018). However, there are many clinical trials that currently evaluate the role of PSMA PET/MRI and PET/CT in prostate cancer management. Still, PSMA can be promising

target for therapy in PCa patients. Therefore, PSMA PET molecular imaging is crucial for the development of personalized medicine in PCa (Bouchelouche and Choyke, 2016).

Findings of the past years have consistently proven that PSMA expression can be found in all prostate tissue types and there is also an increased expression of PSMA in cancer tissue. Additional research has demonstrated that PSMA has an internalization signal, which “allows internalization of the protein on the cell surface into an endosomal compartment” (Chang, 2004). This characteristic can also pave the way towards future therapeutic and diagnostic maneuvers in which PSMA can be utilized as an antigenic target (Chang, 2004). Therefore, an immense progress in PSMA therapies for treatment and diagnostics could be observed in recent years. However, it still remains challenging if PSMA can be used for treatment and diagnostics of prostate cancer to postpone death progression and to reduce mortality (von Eyben, Baumann and Baum, 2018).

4.3.3 PSMA in the future

Currently, the role of PSMA in personalized prostate cancer treatment continues to be the subject of various clinical trials (von Eyben, Baumann and Baum, 2018).

Numerous reviews agree on future treatment using Lu-PSMA-617 radioligand therapy (RLT), which is especially effective for end-stage patients. However, there is an increasing need of treatment for patients in the early stage of prostate cancer (PCa). Some studies are already researching on optimizations, which are required for PSMA-based RL, by selecting ideal agents and dosing schedules (von Eyben, Baumann and Baum, 2018).

PSMA, like many receptor-targeting radiopharmaceuticals, aids as a theragnostic agent to offer the opportunity to underline PCa lesions through PET/CT imaging. Subsequently metastatic sites are irradiated with personalized doses of alpha or beta particle emitters in radioligand therapy (Ceci and Fanti, 2019).

Moreover, PSMA is currently considered to be one of the most effective targets for therapy and imaging in the field of nuclear medicine. The prostate-specific membrane antigen is upregulated in prostate cancer cells and can be used as a successful prognostic and diagnostic biomarker of prostate cancer. Research has shown this

overexpression in 90 to 100% of PCa cells. This makes PSMA a reliable and suitable tissue biomarker for functional imaging in prostate cancer. The PSMA expression “is upregulated when tumor becomes androgen independent, and during anti-androgen therapy” (Ceci and Fanti, 2019). Therefore, this characteristic can make the PSMA expression assessment especially attractive and serves as a potential early indicator of tumor heterogeneity and progression of prostate cancer (Ceci and Fanti, 2019).

As can be seen, there are only limited individual treatments available in current prostate cancer treatment. However, this might not be caused by missing research in this field, but due to the well-developed conventional treatments for prostate cancer. This is also indicated by the three interviewed specialists. For instance, the specialist for hematology and oncology (see appendix 2) mentioned “a vast variety of weapons [already] also available to treat patients with hormone therapy with surgical approaches and radiation therapy”. This is also supported by the specialist for human genetics and internal medicine (see appendix 4), as he indicates that PCa is a good treatable cancer, with well-established treatments, which is why there is not a desperate need for improving individual care. The specialist for laboratory medicine (compare appendix 3) states that prostate cancer can be detected in an early stage. This is continued by explaining that “it can be treated with conventional methods, [...] and if early enough detected, it is not life threatening. So, the pressure for a more individualized treatment is not as high” (Interview with specialist for laboratory medicine, see appendix 3).

5 Leukemia

Leukemia is a type of cancer that affects the capability of a human body to produce healthy blood cells. These blood cells are produced in the bone marrow which is the soft center of a bone. Leukemia is the uncontrolled cancerous proliferation of leukocytes. Blood cells contain (Schmidt Robert, Lang Florian, 2010):

- Red blood cells, which help to transport oxygen from the lungs to the body's tissues and organs and transports carbon dioxide to the lungs to be exhaled
- Platelets, which help blood to clot
- White blood cells, which fight infections, viruses, and diseases

Generally, leukemia refers to cancer in the white blood cells. In some rare cases cancer in red blood cells or platelets may occur. It is caused by malignant transformation of

hematopoietic or lymphatic cells and is associated with the proliferation and accumulation of neoplastic cells. These malformations appear primarily in the bone marrow, usually also in the blood and lymphatic tissues, more seldom in other organs (Roche Lexikon Medizin, 2003).

Leukemia reports for 2% of all carcinosis. It is believed that white men are more likely to sicken with leukemia than adults from another ethnic or racial background. Adults, especially elderly people are more likely to sicken than children. When children do get leukemia it usually happens before the age of 10 years (Harvard medical school, 2019).
In this paper only the cancer of the white blood cells will be discussed.

Most commonly the disease affects lymphocytes and granulocytes which are two of the most important white blood cells. The aforementioned cells are circulating through the body to help fight infections, viruses and diseases. Leukemias caused by lymphocytes are called lymphocytic leukemias; those by granulocytes are called myeloid, or myelogenous, leukemias (Leukemia and Lymphoma society, 2014; Schmidt Robert, Lang Florian, 2010).

Moreover, Leukemia is differentiated between acute and chronic leukemia. Characteristic for acute leukemia is that it occurs suddenly and affects both adults and children. Chronic leukemia affects a patient for a longer time and hardly ever affects children (Harvard medical school, 2019). The causes for leukemia differ but are not fully researched yet. However, exposure to chemicals like benzene as well as other hydrocarbons, zytostatika or tumor viruses can cause Leukemia (Roche Lexikon Medizin, 2003). Furthermore, genetic abnormalities like down syndrome or treatments such as radiation are believed to be causes (Roche Lexikon Medizin, 2003).

Leukaemia can be hereditary, as for example in chronic lymphocytic leukemia, but in most cases the family history plays a minor role (Harvard medical school, 2019).

	Acute Leukemias	Chronic Leukemias
Trigger	Occurs when white blood cells multiply too fast in the bone marrow. As they reach a high quantity, they displace healthy cells and are sometimes transferred to other organs causing damages.	appears when the body produces too many blood cells that are only partially evolved. These cells do not work like mature blood cells.
Main variations of the disease	**Acute lymphocytic leukemia (ALL)**. Most commonly appears in children under the age of 10 or elderly people over the age of 50. The disease occurs if primitive blood-forming cells, lymphoblasts, multiply without evolving into normal blood cells. These abnormal cells displace healthy blood cells. They can accumulate in the lymph nodes and lead to swelling.	**Chronic lymphocytic leukemia (CLL)** most prevalent type of adult leukemia. Most likely between the age of 60 and 70. This disease develops abnormal lymphocytes and develops from an attained (not present at birth) mutation to the DNA of a single marrow cell that evolves into a lymphocyte (Leukemia and Lymphoma society, 2014). This leads to the result that affected cells are not able to fight infection as well as normal cells. The cancerous cells are located in the bone marrow, blood, spleen, and lymph nodes. This can lead to swollen glands
	Acute myeloid leukemia (AML) is most diagnosed in teenagers and people in their 20's. This disease accounts for half of all diagnosed leukemia sicknesses. This disease appears if primitive blood-forming cells, myeloblasts, multiply without evolving into normal blood cells. Undeveloped myeloblasts multitude the bone marrow and interfere with the production of normal blood cells. This causes anemia (a disease which leads to a person not having enough red blood cells). Another cause may be bleeding and bruising and frequent infections.	**Chronic myeloid leukemia (CML)** develops most likely in people between the age of 25 and 60 years. During this disease abnormal blood cells develop so called myeloid cells.

Table 1: Characteristics of different types of Leukemia (Harvard medical school, 2019)

The symptoms of the disease are very variable in different forms of Leukemia as the table above clarifies. Both bone marrow and all other organs can be penetrated by the

malignant cells. The functional failure of blood cells leads to an insufficiency of oxygen transport, also called anemia, reduction of the defense function (tendency for infections) and hemostasis (easier to bleed when hurt). Enlargement and functional impairment of affected organs can occur as well (Roche Lexikon Medizin, 2003). In Appendix 5 the most common symptomatic key findings of the four most common leukemia diseases are described.

Within the leukemia variations AML, ALL, CLL and CML there are different subtypes which require different treatments and have different prognosis. In the following the conventional treatment of acute and chronic leukemia will be discussed.

5.1 Conventional Treatment of Leukemia

The treatment of leukemia is one of the most intense cancer therapies because the disease is located in the bone marrow which is responsible to produce the cells fighting all diseases in the body. However, the chemotherapy of leukemia then destroys the cancer cells as well as the healthy cells. During the treatment, the immune system will be shut down which leads to a diminished ability of the body to fight illnesses or infects. Curing of Leukemia takes a long time and a high effort. Especially during the time of immune suppression, it is advised that patients are treated in medical centers with high experience in the treatment of leukemia (Harvard medical school, 2019).

The conventional treatment of leukemia depends on whether patients have fallen ill with acute or chronic leukemia.

5.2 Treatment of acute leukemia

The treatment of acute leukemia depends on the individual condition of the patient rather than on the stage of the disease or whether it returned after remission.

Treating acute leukemia happens in stages. This treatment is proceeded if patients are diagnosed with ALL or AML. However, concerning AML the overall health status of the patient has to be taken into consideration as well as the blood cell count:

Phase	Treatment
Phase 1 (induction therapy)	Stationary chemotherapy is used in order to control the disease
Phase 2 (consolidation)	The patient returns for further chemotherapy sessions to the hospital but stays at home in time periods where no treatment takes place.
Phase 3 (prophylaxis)	Different drugs are used to prevent the cancer from spreading into brain or nervous system. It might be combined with radiation therapy.
Phase 4 (maintenance)	Different doctor appointments make sure that Leukemia does not return after it has been treated.

Table 2: Phases of treatment of acute Leukemia (Harvard medical school, 2019)

In case ALL or AML returns patients are treated with different chemotherapy drugs. Some patients even receive a marrow transplant. However, the full recovery of ALL/AML may take some years (Roche Lexikon Medizin, 2003)

The incidence of AML increases with age, as the median age at diagnosis is 70 years (Bower *et al.*, 2016).

Treating AML, it is important to reach the complete remission as this prolongs survival significantly. However, there are differences for pediatric or adult ALM (Syndrom, 2018). The standard therapy of AML is called “3+7” (Lichtman, 2013). The method was developed in 1973 and resulted in the administration of drugs for 7 days of continuous intravenous arabinosylcytosine (cytarabine) followed by 3 days of intravenous daunorubicin. If it can be observed that blasts remain aspirated on day 14 after the treatment usually a second course starts. The second course contains 2 days of using an anthracycline and 5 days of ara-C. In case the day 14 marrow has fewer blasts, the marrow is observed and monitored weekly until evidence and response can be seen. Until the evidence of complete remission patients receive further doses of the drugs ara-C and antracyline. The dose or the frequency might be adapted according to the health-status of the patient (Lichtman, 2013).

In order to cure AML a complete remission should be reached. This complete remission is defined as a marrow with more than 5% blasts and peripheral blood with more than 1.000 neutrophils and more than 10.000 platelets (Kantarjian, E., Estey, S., 2008). Complete remission is reached in 70–80% of adults with an average age of 60 years. However, remission rates for older patients are lower and the relapse rates are increasing. This results in very low long-term survival rates among elderly people. An important prognostic factor is age (Bower *et al.*, 2016).

The risk of AML returning during the first two years of remission is high. However, after the third year it strongly declines to a relapse quote of 10%. This allows patients after being in remission for more than three years to consider themselves as cured (Kantarjian, E., Estey, S., 2008).

The success rate of the aforementioned treatment has increased in the past decades. According to a population-based study in Sweden the relative survival ratio between 1973 and 2011 increased for patients < 61 years at diagnosis. A significant improvement of the relative survival ratio was observed in patients aged 61-70 with diagnosis from 16% to 28%. Even after remission, the defeated disease can lead to a reduction in life expectancy. A male 65-year-old patient diagnosed with AML had in 2005 a life expectancy of 25% whereas the same patient in 2011 had a life expectancy of 34%. This increase can be traced back to an improved risk stratification of elderly patients and advancement in supportive care in more recent years. Furthermore, the progress manifested due to a better anti-infectious treatment as well as improved diagnostic methods. However, it is important to mention that other countries like the UK or USA have lower survival rates than Sweden. Taking into account the life expectancy of patients being diagnosed at an age above 80 has not significantly improved (Bower *et al.*, 2016).

5.3 Treatment of chronic leukemia

There are two kinds of chronic leukemia:

- Chronic lymphocytic leukemia (CLL)
- Chronic myeloid leukemia (CML)

According to current research it is not possible to cure patients with CLL, but symptoms can be alleviated which increases the quality of life of the patients. Due to the slow progression of this disease it is common that some patients do not experience any symptoms over a long period of time (Deutsche Krebsgesellschaft, 2018).

However, treating CLL requires a so-called staging before the actual treatment can take place. There are five different stages of CLL known as table 4 depicts:

Stage	Characteristics	Advised treatment
Stage 0	Generally, there are no other symptoms of leukemia than that there are too many lymphocytes in the blood.	Treatment may not be necessary. Patient will be monitored closely.
Stage I	Swelling of the lymph nodes due to too many lymphocytes in the blood.	Close monitoring and potentially chemotherapy.
Stage II	Swelling of the lymph nodes, spleen, and liver due to too many lymphocytes.	Close monitoring and potentially chemotherapy.
Stage III	Development of Anemia due to too few red blood cells in the blood.	Intensive chemotherapy with one or more drugs as well as a potential bone marrow transplant.
Stage IV	Swelling of the lymph nodes, spleen, and liver and probably development of Anemia due to too few platelets in the blood.	Intensive chemotherapy with one or more drugs as well as a potential bone marrow transplant.

Table 4: Stages of CLL cancer (Harvard medical school, 2019)

Patients characterized with stage 0 CLL will be observed closely. Their therapy includes medical testing as well as continuous examinations on whether the disease is stable or begins to break out. In case of fever or other symptoms of infections or illnesses a doctor should be consulted immediately. In case the disease breaks out the treatment is started immediately. Apart of the watch and wait approach chemotherapy is most used to conventionally treat patients with CLL. Drugs used for chemotherapy in combination with anti-CD20 monoclonal antibody target cancer cells as well as healthy cells of the body (John C. Byrd and Joseph M. Flynn, 2014). In some cases,

chemotherapy can cause unpleasant short-term side-effects. However, drugs used for the treatment of CLL like chlorambucil, cyclophosphamide, fludarabine, and bendamustine have mild to modest side-effects such as vomiting, nausea, rash, increasement of infection or lowering of the normal blood counts. Rarely a bone marrow transplant will become necessary for the treatment of the patient. According to the overall health status, the stage of the disease and the age of the patient as well as the availability of a suitable donor, it is possible to have major success with this approach. When a suitable donor is found blood stem cells are extracted and transplanted to the patient. The donor's blood stem cells travel to the bone marrow and anticipate production of new blood stem cells and stimulate growth of the marrow (Leukemia and Lymphoma society, 2014).

The following list states symptoms that make a treatment of CLL necessary (Leukemia and Lymphoma society, 2014):

- Enlarged lymph nodes
- Enlarged spleen
- Severe anemia
- rapidly increasing lymphocyte count (> 300) (this reason alone may not be a trigger to start treatment
- Decreasing platelet count
- Other symptoms like fatigue, night sweats, weight loss or fever

CML is usually characterized by a defective string of DNA, the Philadelphia chromosome. This genetic abnormality is caused by the production of an abnormal protein. Healing CML is usually only possible by utilizing a stem cell transplantation, which is a risky procedure and only partially applicable for a few patients (Deutsche Krebsgesellschaft, 2018). However, more common treatment of CML is inducing tyrosine kinase inhibitors such as imatinib, dasatinib, nilotinib, bosutinib or ponatinib. Medicine like tyrosine kinase inhibitors block the function of this abnormal protein which leads to improving a person's blood counts. This treatment has been approved for CML patients in 2002 and is today the standard treatment for patients diagnosed with CML in the chronic phase. Hemotherapy, immune therapy or allogeneic stem cell transplantation are the more traditional approaches of treating CML (Von Bubnoff and Duyster, 2010).

Using this treatment, cytogenetic remission can be achieved in about 85% of patients. Therapies which involve marrow transplant are only used if the patient does not react positive to the tyrosine kinase inhibition (Leischner, 2017).

Especially with enzyme or kinase inhibitors doctors have reached great success rates as this treatment is usually “well tolerated, and [...] induces remission for most patients which are very durable” states the specialist for hematology and oncology (see appendix 2).

5.4 Individual treatment of Acute Myeloid Leukemia (AML)

For this scientific work, we have chosen the field of leukemia and the focus on AML because it is a pioneer in the development of individualized medicine. In contrast to prostate cancer, it is already common practice to use forms of individualized medicine in AML diagnosis and treatment. One reason for this is that it is relatively easy to get to the tumor cells in AML. This argument is further supported by the specialist for laboratory medicine “[...] the characteristics of the tumor cells can be well investigated and classified. This leads to the possibility to directly target these specific characteristics of the tumor cells” (see appendix 3). In the case of prostate cancer, however, it is only possible to take a biopsy directly from the prostate. Within the following paragraphs the most common forms of individualized diagnosis and therapy forms in Acute Myeloid Leukemia (AML) are presented.

For many years, there have not been other options than the one-size-fits-all approach of chemotherapy or hypomethylating agents for the treatment of AML. But in the past decade a series of technological advances have revolutionized the ability of examining cancer genomes leading to the possibility of whole-genome sequencing. Today it is possible to do a genomic profiling of the tumor cells and thereby define up to 40 genomic subtypes of AML. Each AML genome contains around 400 mutations including 6-26 coding mutations. Most of these mutations are harmless and were acquired during the normal aging of hematopoietic stem cells. The challenge that remains is to identify the “AML driver” mutations. By whole genome sequencing several AML driver mutations have been identified and for these mutations several drugs were approved to target these mutations. As sequencing technologies keep on improving and the costs for sequencing decrease, it is likely that whole-genome sequencing of cancer cells will become common in the diagnostics of patients with AML or other

cancers (Link, 2012). In former times sequencing of human cancer genome was not possible due to the size and complexity of the human genome with about three billion base pairs. Due to two major advances it was possible to overcome these obstacles. A map of the human genome was provided by the Human Genome Project in 2001 and technological advances in DNA sequencing dramatically reduced the cost and time of sequencing genomes (Link, 2012).

AML is a complex form of cancer and within this group there are many subtypes. In addition, AML patients differ very much in their health condition, age and co-morbidities and therapy needs to be adjusted to these conditions. Understanding the individual disease is the key to accessing the right personalized therapy. Today there are different types of genetic test methods for patients with AML. Genetic test methods are already part of the diagnosis routine within AML in cancer centers (Link, 2012).

Within the next paragraphs the different genetic tests will be discussed. The types of genetic tests for patients with AML include karyotype, fluorescence *in situ* hybridization (FISH), polymerase chain reaction (PCR), sequencing, and microarrays. These DNA or RNA assays are the most powerful tools for predicting the behavior of AML in response to therapy. The results of these tests do not only identify disease-specific genetic alterations that are important for diagnosis but also provide a mechanism to monitor tumor burden in response to therapy. The tests can be classified into prognostic tests to assess the likelihood of response to standard therapy and predictive tests to assess response to a nonstandard intervention (Gulley et al., 2010).

A brief description of each genetic technology is given in the following paragraphs.

In the genetic karyotype tests whole chromosomes from cells in the metaphase stage of cell division are stained and visualized by microscopy. The karyotype serves as a genome wide screen for translocations and other defects that are present in about half of the different forms of AML. The findings are further interpreted in the context of the patient's clinical and histopathological features. This helps to diagnose and classify AML. Prognosis can also be impacted by nonspecific karyotypic changes. They are differentiated into a complex karyotype with three or more concomitant defects and a monosomal karyotype defined by two or more autosomal monosomies (Gulley et al., 2010).

Within the Fluorescence in Situ Hybridization (FISH) tests whole chromosomes are hybridized to complementary probes and visualized on a fluorescence microscope.

FISH tests can be applied to either interphase (nondividing) or metaphase (dividing) cells. Its use is to confirm a tumor-related defect that then can be monitored over time in blood or bone marrow. It can also detect cryptic translocation in a tumor suspected of harboring a defect. Next to that it can detect a deletion or duplication that is not recognized by a karyotype test. A typical interphase FISH is performed on 200 cells and reliably detects a leukemic clone when there are at least 5% of cells in that specimen (Gulley et al., 2010).

For a Polymerase Chain Reaction (PCR) DNA is isolated and one specific segment is copied billions of times to ease the detection and for further analysis. PCR has a great analytic sensitivity. After 30 cycles of amplification each DNA target sequence has been copied 2^{30} times, yielding to a billion amplicons. These amplicons then can be further evaluated by using precise real-time instrumentation and/or analytic methods such as sequencing, melt curve analysis or electrophoresis (Gulley et al., 2010).

Determining the order of nucleotide bases by DNA sequencing can be useful for genes like CEBPA that have multiple mutations at different nucleotide positions. To determine the nucleotide sequence one of the DNA strands must be replicated and the order in which labeled nucleotides are added must be monitored (Gulley et al., 2010).

With microarrays it is possible to simultaneously perform many different analyses as gene expression profiling, gene copy number measurement or allele-specific mutation detection. Microarrays generate a massive amount of data that requires bioinformatic tools to present the data in a way that makes the interpretation possible for the doctor. The main challenge are quality assurance and assay validation that are especially challenging when there are so many tests performed at the same time. Two examples for arrays are the comparative genomic hybridization array (CGH array) and the gene expression array. With the CGH array, patient DNA is hybridized to thousands of probes arrayed on a solid surface. The gene dosage is determined for each locus on the array and thereby deletions, duplications and gene amplifications can be identified. Within the gene expression array patient RNA is amplified and labeled and then mixed with control RNA labeled with a different fluorochrome. Following this it is hybridized to thousands of probes arrayed on a solid surface. Scans of each probe followed by data analysis grant evaluation of the gene expression profile in the tissue. The gene expression profile then can be matched to the pattern of normal or diseased tissues.

This can be very useful for the diagnosis or to predict the response to a certain therapy (Gulley et al., 2010).

6 Economic Impact of individual medicine

Regardless whether the individual drugs are paired with high success rates or not, they are expensive. Between 1995 and 2013 Howard et al. analyzed 58 anticancer drugs approved by the FDA. This analysis indicated that launch prices, adjusted for inflation and drugs' survival benefits, increased by 10%, or about $8500, per year (Carrera, Kantarjian and Blinder, 2018). However, most commonly in Germany individual treatments are not covered by insurances. According to the German consumer advice center insurances only cover what is economic, sufficient and necessary from the medical perspective. Everything that goes beyond medical necessity is not covered (Verbraucherzentrale, 2019). However, statutory health insurances in Germany are not allowed to cover individual health services according to German law. A private invoice must be paid by the patients themselves. This does not only account for individual diagnosis or treatment of cancer but starts at individual tests or services at the physician which are not part of the range of service of statutory health insurances (Verbraucherzentrale, 2019).

Apart from that, pricing for targeted medicine plays a crucial role as these drugs are only for a narrow target group (Tiriveedhi, 2018). Experts believe that individual medicine will have a rough start with reduced markets. However, markets will increase if a clear understanding of value addition to customers and patients as well as profit maximization to pharmaceutical companies is clarified. Furthermore, establishing a potential complementary role of clinical laboratories as providers of molecular diagnostics will accelerate development. The value of the respective individual drug has to be justified. It has quickly emerged that individual medicine is not cheaper in comparison to conventional drugs. Prices have been stated as high as US $350,000 per patient per year (Tiriveedhi, 2018). However, in small trials an extremely improved outcome has been observed, in some other areas the benefits were marginal. It is important to assess the value-based pricing in order to convince public funds and other agencies to further invest in that field of research (Tiriveedhi, 2018).

The price definition in the pharmaceutical industry follows systematic rules just like any other industry. The pricing range is determined by the market and competitive

pharmaceutical industries. Especially, considering individual medicine drug prices are further influenced by clinical laboratories and biomarker testing. The demand side of the pricing assessment evaluates the value of the product perceived by the customer assuming there is a competitive and free-trade environment. These arguments usually determine the upper limit of the pricing range of the respective product. The lower price limit of a product, especially of drugs is assessed by companies. They are taking into account cost of production, including research and development, drug development, preliminary phase, trials, return on investment, and net present value. Especially when following the value-based approach it should be considered to seize the potential value that will be created by the drug. An approach to determine the potential value is by summing up the cost of the best alternative or reference price and the differential value of the targeted therapy. It is obvious that the customer base for targeted medicine will be shrinking. However, the added value to the costumer as these drugs are believed to increase the specificity and success regarding treatment of the respective disease will lead to an increase in value perception of customers (Tiriveedhi, 2018) (Nationale Akademie der Wissenschaften Leopoldina, 2014). In order to overcome this challenge of narrower markets Philpson made an approach of a two-part-pricing strategy. He suggests for optimal health care pricing should combine individual diagnosis approaches as well as individual drugs to find an optimal pricing strategy. This enables institutions to scoop out purchasing willingness of patients and the lost profit with the treatment can be offset with the pricing of the diagnosis (Philipson, 2018). Apart from creating additional revenue this leads to an incentive to innovate as more new diagnosis possibilities can be priced accordingly (Tiriveedhi, 2018).

A challenge for implementing personalized medicine in different types of cancer is the complexity of building an infrastructure for appropriate genomic sequencing in cancer, which includes the collection of tissue, testing of genomic alterations, analysis of genome and the report of results back to the patients. However, one of the most crucial challenges for genomic sequencing is the high cost related to it (Fraser *et al.*, 2015). The cost factor is a crucial one and is commented by the specialist for hematology and oncology (see appendix 2): “individualized medicine and all these targeted agents are expensive, and treatments are getting more expensive”. Even though the costs for genomic sequencing have been continuously decreasing, public health insurance companies rarely cover the costs for it, which leads to fewer possible patients of personalized therapies (Fraser *et al.*, 2015). In privatized health insurance systems,

patients also have to assume higher deductibles or possibly have to “cover a treatment that is not validated and therefore not reimbursed by their insurance” (Kasztura *et al.*, 2019).

Another approach of finding the optimum pricing strategy for individual medicine is by utilizing the experience and search goods. Nelson defines search goods “as one whose qualities can be determined by the consumer before purchase” (Leahy and Service, 2005). Likewise, the quality of experienced goods cannot be determined before purchasing (Leahy and Service, 2005).

A paradigm shift from experience goods to search good could reduce healthcare costs strongly. For example, the length of hospital stay may be shortened especially for chronic diseases and cancers. Lengthened hospital stays sustain high costs from perpetuation. Treating patients more efficiently with individualized approaches can therefore reduce inpatient stay at the hospital (Tiriveedhi, 2018).

Moreover, it is common to calculate the incremental cost-effectiveness ratio (ICER). This approach determines the ratio of the difference between the cost of new and current standard therapy to the difference of change in quality-adjusted life years (QALYs) between new and current standard therapy (Tiriveedhi, 2018):

$$ICER = \frac{(Cost\ of\ new\ therapy - cost\ of\ current\ standard\ therapy)}{QALYs\ generated\ by\ new\ therapy - QUALYs\ generated\ by\ current\ standard\ therapy}$$

Personalized medicine has to be evidence-based, which can include a benefit-risk assessment. Stratified medicine can easily be applied to today’s methods. Conversely, highly individualized medicine, including specific therapeutic agents, is in need of analyzing cost units (Broich and Bieber, 2013). Therefore, there are various studies of cost-effectiveness of personalized medicine available. This cost-effectiveness analyzes and evaluates if the clinical outcome improvements, that an intervention offers, are sufficient to validate the increased spending of money. It provides information on which interventions offer greater value for the spending of a constant amount of money, rather than determining if the intervention is reducing costs. Moreover, cost-effectiveness of targeted interventions can depend on numerous factors, like the test accuracy, the prevalence of genes or alleles in populations or the costs for personalized testing and treatment (Kasztura *et al.*, 2019).

From the perspective of a paying patient, cost-effectiveness is usually determined “by comparing cost per quality-adjusted life year (QALY) gained, with a currently accepted

threshold of ‘willingness-to-pay’” (Kasztura *et al.*, 2019). Many studies conclude that the personalized medicine intervention is cost-effective compared to the conventional treatment. However, the ‘willingness-to-pay’ varies between patients in different countries. Also, the amount of money per quality-adjusted life year, a society is ready to spend, is very variable (Kasztura *et al.*, 2019). The aforementioned approach has been used for the evaluation of cost-efficiency of molecular genetic diagnosis for patients sickened with AML. This approach will be discussed in the following.

6.1 Cost-efficiency of AML-treatment

It proved to be difficult to gain insights into the cost efficiency of treatment possibilities for a number of diseases of leukemia. However, Hörster et al. (2017) compare in their research the cytogenetic diagnosis (CCD) with the molecular genetic diagnosis (MDG). This diagnosis methods are used for patients who are ill with AML. The paper gives an economic outlook within the German healthcare context (Hörster *et al.*, 2017). However, it needs to be stated that the conventional cytogenetic diagnosis as mentioned in the aforementioned paper can be considered as an individual diagnosis approach itself. As we are taking into account the results of this paper, we are recognizing the conventional cytogenetic diagnosis as a conventional treatment.

The results show that 27% of patients treated with CCD are still alive and 31% treated with MGD are still alive both after the time of 10 years. The majority of patients in both diagnostic groups died within month two and four. On average the incremental gain in life expectancy is increasing by about seven months for individuals in the MGD group compared to individuals from the CCD group (Hörster *et al.*, 2017).

Regarding the cost-effectiveness MGD generated about USD 32,000 more costs and has an ICER of about USD 4,928 per survived month. Prolongation of life within the MGD group costs USD 15,267. Assuming a lifetime of 42-45 months, costs within the MGD group amount to USD 99,706 per person on average (Hörster *et al.*, 2017).

Furthermore, the main impact on ICER is whether the patient is a high or a low-risk patient which has an impact on the likelihood of needing a stem-cell transplant which increases costs massively. The higher the percentage of low risk-patients, the lower is the ICRE in USD per survived month. The MGD strategy becomes dominated by CCD with 90% of low-risk patients. This leads to average decreasing costs of MGD (Hörster *et al.*, 2017).

Conclusively, the study showed that the evaluated method of personalized medicine (molecular genetic diagnostics) leads to a seven months longer life at USD 32,000 more costs on average in this group of patients and therefore to an ICER of about USD 4,928 per survived month (US$ 59,136/LYG). Thus, based on the approach of the WHO for interpretation of ICER, this method of personalized medicine can be interpreted as cost-effective (Hörster *et al.*, 2017).

In the following the cost-effectiveness of prostate cancer will be discussed.

5.2 Cost effectiveness of prostate cancer

Personalized medicine has been emerging in the treatment of different types of cancer in the past years. However, the treatment of prostate cancer with the help of different individualized therapies remains relatively unexplored. Consequently, economic data on therapies like prostate-specific membrane antigen (PSMA) are hardly available. Thus, there has to be a paradigm shift from conventional therapies towards a more personalized approach with the help of pharmacological research and therapies for the pharmaceutical and biotechnological industry. Therefore, the development of diagnostic markers with the help of a therapeutic agent, as well as the potential economic impacts and cost savings or increases have to be discussed (Broich and Bieber, 2013).

The cost for a personalized therapy may vary depending on how advanced and severe the disease is expressed (Broich and Bieber, 2013). The optimal result would be that the therapy outcomes improve and costs decrease. The worst result would be that the therapy outcomes decrease and costs increase. However, the reality for most personalized medicine interventions is that the therapy outcomes improve, but the costs increase as well (Kasztura *et al.*, 2019).

Conclusively, the economic impact on personalized medicine in the field of prostate cancer is still relatively unexplored. There is a need for further research and cost-effectiveness assessments in individualized medicine in PCa. Still, the conversation around diverse options for financing of personalized therapies in healthcare are ongoing (Kasztura *et al.*, 2019).

In the following the current status of individual medicine in Germany is evaluated and an overview of different institutional activities regarding that topic is given.

7 Current Status quo in Germany

Germany is a country in which research in oncology is advanced (Kohler, 2018).

> *"In general, I would say it's one of the best worldwide, […] particularly on these two issues […] diagnostics and treatments. […] In these two areas diagnostics and treatments its very well established and the clinics will come more and more the better the pathological services in our country will improve"* (Interview with specialist for human genetics and internal medicine, see appendix 4).

Taking into account multiple research centers as well as support from institutions and politics. In the following the current status of individual medicine in Germany will be discussed.

As of now individual cancer medicine is mainly used in academic institutions (Westphalen *et al.*, 2020). However, there are different institutions supporting further research on individual medicine in Germany on different levels. The following list is just an extract of the actions undertaken.

In order to increase the exchange of information between different academic centers and to establish a strategy for further development of individual medicine a project group called 'Molecular Diagnostics and Therapy' with support of "Deutsche Krebshilfe" was established (Westphalen *et al.*, 2020).

According to the Federal Ministry of Education and Research they want to accelerate further research and are therefore taking part in the Europe-wide project "Personalized medicine 2020 and beyond". Led by the Federal Ministry of Education and Research, recommendations have been evolved which have the potential to move health research, medical care, as well as service providers forward. Additionally, the Federal Ministry of Education and Research has provided 360 million euro over the period of 2013 until 2016 to further increase development and research and to be able to invest into respective research and development projects (Bundesministerium für Bildung und Forschung, 2013).

Additionally, there have been four comprehensive cancer centers established since 2015. Those comprehensive cancer centers are in Freiburg, Heidelberg, Tübingen and Ulm in order to establish a coordinated, nationwide supply structure in Baden-Württemberg (Schirmacher, 2019). According to the specialist for human genetics and internal medicine (see appendix 4) "there is only a need of university centers. Or let's

say a few large hospitals where you have thousands of investigations in a year". There are several more research activities in Germany (Schirmacher, 2019).

Even on an international level a consortium for Personalised Medicine (ICPerMed) was founded which connects more than 40 European countries and institutions with the aim to further enhance personalized medicine research. (International Consortium for Personalised Medicine, 2019).

Due to the intense research in the last decade individual medicine is already present in today's medical care. At the end of 2017, a total of 53 personalized drugs have been placed on the German market. Half of those developed drugs for individual medicine have been developed in the last 5 years. Some of them directly due to research in this scientific area and pre-tests; other drugs subsequently after a "regular" drug was able to be personalized. (Roche, 2020; Kohler, 2018).

Furthermore, every sixth drug developed and approved in 2017 has been an individual one. It is believed that more than 40% of all new active substances and over 70% of future oncology medicines are at present being researched and developed in combination with biomarkers. The first personalized drug including a pre-test had been approved in 1996. Since then an average of more than 1 in 13 admitted new drugs have been personalized drugs (Kohler, 2018).

Today in the field of personalized medicine in oncology more than three quarters (41 of 53; 77%) of the admitted drugs are used for (Kohler, 2018):

- 13 for breast cancer (of which 1 active ingredient is also used for stomach cancer)
- 10 for leukemias
- 9 for lung cancer
- 9 for other types of cancer

Furthermore, fields other than oncology are featuring personalized drugs as well like (Deutscher Bundestag, 2016; Kohler, 2018):

- Drug therapy of metabolic diseases (5 out of 53; 9.4 %)
- Epilepsy
- Humane Immunodeficiency-Virus (HIV)
- Immunological diseases (2 out of 53; 3.8 % each)
- musculoskeletal disorders (1 out of 53; 1.9 % each)

Additionally, the German Cancer society states that nowadays many tumor diseases like breast cancer, colon cancer or lung cancer can be dealt with by using individual drugs.

According to the latest research findings, tumor treatment is usually preceded by a molecular genetic analysis of the respective cancer cells. This ensures that the cancer tumor is effectively combated with personalized drugs (Deutscher Bundestag, 2016).

Experts argue that the healthcare system in Germany is quite advanced: “So ideally compared to other countries there are many more options for individualized medicine in Germany. The healthcare system in Germany is generally very well established and provides good healthcare [...]” (see appendix 2).

However, the trend of individual medicine is all-embracing which means it is not only targeting the molecular medicine, but also the human being as a whole. While nowadays treatment with individual prosthetics is part of the state-of-the-art experts believe that it will take up to 30 more years until individual health care is implemented. (Niederlag, Lemke and Rienhoff, 2010). Furthermore, it is believed that the introduction of innovation into the healthcare system in Germany is severely delayed. There is a lack of understanding in regard of the potential of individual medicine among policy makers, regulators as well as the broad stakeholders. The perception of both reduction of harm in the population as well as an increase in quality of life for the patients has to improve significantly (Hogan, 2018). Especially, the enforcement and development of individual medicine of measures that are beyond individual drugs are causing further challenges on the healthcare system (Kohler, 2018).

8 Forecast for individual medicine until 2030

Personalized medicine is already transforming biomedical and clinical research. The goal of personalized medicine is to achieve the optimum outcome for individuals, rather than populations. By employing powerful computational assistance, personalized medicine will enab-le the prediction of future probabilities and guide decisions made by healthcare providers. The changes coming with personalized medicine are a leading focus of activity in health-related science globally and industrialized countries are investing substantially in personalized medicine across different domains. Nevertheless, the investments made into personalized medicine should be

reasonable, focusing on the most promising approaches and exclude unfavorable methods and technologies (Aaviksoo et al. 2017).

Personalized medicine is showing great potential to improve health promotion, disease prevention and disease management, but there are upcoming challenges for this field. Challenges are to translate research results into clinical practice, to facilitate their adaptation by healthcare systems and the development of cost calculations and reimbursement models. The International Consortium for Personalised Medicine (ICPerMed) has developed a vision on how the use of personalized medicine approaches can promote the “next generation” medicine in 2030. ICPerMeds vision aims at concentrating on the personal characteristics of the individual and equitable access of all citizens to personalized medicine. In their perspective this leads to increased effectiveness, economic value, and the best possible healthcare. ICPerMed has created a framework of five perspectives, which shall be observed (Vicente et al. 2019).

The first perspective concerns the citizens and their relationship with the broad availability of medical information and their own health data. For 2030 the first perspective envisions that the health-related data is controlled by the citizens. Also, the health data input and access are controlled, supported, and monitored by the citizens. Next to that the medical information is easily accessible, reliable, and understandable for the citizen (Vicente et al. 2019).

To make perspective one come true the citizens must have the confidence that their data is securely stored and processed. This is, according to a specialist for human genetics and internal medicine (see appendix 4), a particular issue in Germany. The specialist mentions challenges of:

> *“how to deal with assessing the individual risk [and] with whom to share the information. This is by means of this data protection […] in Germany. We have a very specific German kind of challenge you would not want to have your insurance sharing or this risk factors of your life”.*

For this reason, there must be clear regulations on how to store, manage and control the access to the personal data. The regulations must protect the personal rights of the citizen, but at the same time enable data sharing between different healthcare

providers and researchers and support the digitalization and standardization of health data. Next to this citizen's as well as the healthcare professionals should be informed about the benefits and challenges of personalized medicine. Possibilities to spread this information are campaigns to raise awareness and forums with various stakeholders discussing the challenges of personalized medicine (Vicente et al. 2019).

The second perspective concerns the healthcare providers. The implementation of personalized medicine will require engagement and commitment by them. For 2030, the second perspective envisions that the optimal use of health-related information and research will lead to the identification of the best health promotion, disease prevention, diagnosis, and treatment options for each patient. Furthermore, personalized treatment of vulnerable groups with the minimization of adverse effects will be routine. This requires clinical decisions made by multidisciplinary teams. Additionally, the education of healthcare professionals must adopt the interdisciplinary aspects of personalized medicine such as regulatory questions including equity and ethics to utilize all available information. Lastly, the clinicians and research workers must work closely together to support a rapid development and implementation of personalized medicine (Vicente et al. 2019).

Perspective two requires an improvement of digital literacy among the healthcare providers as for example more compatible and interoperable data sharing platforms. Also, in many areas personalized medicine is failing to gain the full confidence of healthcare providers. One reason for this is that the evidence of the potential benefits of personalized preventive approaches is not sufficiently displayed yet. For this the transfer of clinical and biomedical research to routine healthcare needs to be facilitated. Another factor influencing the success of perspective two is that the educational materials for the healthcare providers need to be easily accessible and medical education on personalized medicine technologies must be compulsory (Vicente et al. 2019). The importance of education in individual medicine is also highlighted by a specialist for hematology and oncology (see appendix 2) who mentions that:

> *"if we move into that direction it is coming from new targeting treatments and those are generally developed based on better understanding of the cancer*

biology. Implementing that also requires trained physicians so the educational part is important".

The third perspective concerns the implementation of personalized medicine in the healthcare system. For 2030 the third perspective anticipates that there will be equitable access to personalized healthcare for all citizens independent of their age, gender, ethnicity, and insurance coverage. Also, it envisions fair and reasonable allocations of the resources within the healthcare system. Lastly there will be a secure health data flow from citizens and healthcare systems to regulatory authorities and researchers (Vicente et al. 2019).

To make perspective three come true healthcare systems need to retain access to high-quality healthcare which is affordable to all and ensure access to underserved populations. The specialist for hematology and oncology (see appendix 2) confirms this aspect stating that

"many countries in the world are poor and have poorly developed healthcare systems. And a large proportion of the world's population doesn't have access to more sophisticated cancer medicine which we have available in the US or in Europe".

Personalized medicine depends on state-of-the-art technology for this reason the costs of personalized medicine needs to incorporate the long-term value of innovative ideas with justifiable reimbursement models ensuring access for everyone. Also, healthcare services need to be optimized for the inclusion of personal data in individual healthcare strategies. An option on how this can be achieved is the establishment of centers of excellence in primary care for personalized medicine, centers specialized on diagnostic testing and data centers. The future optimization of healthcare services depends on the resources and the infrastructure. The sustainability of healthcare systems demands a prioritization of resources and investments with a global perspective according to value-based approaches based on economic analysis of personalized medicine approaches. Next to that healthcare systems will make wide use of personal data for primary prevention with more preventive and predictive services for citizens. For this it needs the availability of advanced infrastructures with harmonized databases at the national and international level. This would contribute to appropriate preventive measures and lead to the selection of the optimal therapy. Also,

funding for research will be pivotal and healthcare funders must be encouraged to support research. The benefits and harms of personalized medicine can fully be examined by the engagement of independent research. Furthermore, the research community must engage in health economics studies and look at the impact of personalized medicine on health inequalities (Vicente et al. 2019).

The fourth perspective concerns the availability of high-quality data together with the issue of data privacy. For 2030 the fourth perspective envisions that there will be a combination of imaging, diagnostic, genomic and other molecular data, and information on lifestyle to be used by healthcare providers and researchers for efficient healthcare. Also, harmonized solutions ensuring data privacy and data security are used in a transparent way within the health-data management. This ensures benefits for citizens, while the costs and risks are being minimized (Vicente et al. 2019).

The aspect of increasing data security is further emphasized by the expert of human genetics and internal medicine stating that “So we would need [...] [a new law] which is focusing particularly on this issue by means also of how to deal with information and how to deal with the data protection.” (see appendix 4)

A difficulty for this future perspective becoming true is the complexity of personal health, genetic and lifestyle datasets. Health professionals will have the challenge of interpreting data and produce relevant results from it. There will be a need for appropriate mathematical modeling and computer simulations to interpret the huge amounts of biological and clinical data. But the mathematical models and the computer simulations can only work if the data is of sufficient quality, quantity, and structure. Therefore, there must be data management and data handling protocols compliant with international state-of-the-art standards. Another essential topic is the protection of health-related data. A pan-European study showed that 50% of people were concerned that their data would be abused by non-medical personal and 60% of the people were afraid that their data will be used by private companies (Vicente et al. 2019).

The fifth and last perspective reviews the aspects of economic value for society by implementing personalized medicine. For 2030 the last perspective envisions a balance between investment, profit, and benefit. Also, there will be innovative and

appropriate business models in place and new jobs in the healthcare system will be created (Vicente et al. 2019).

There is a broad range of potential viewpoints to realize this. Options could be a strict development of the private sector or a broad societal perspective. The true value of personalized medicine might come from looking beyond short-term benefits and instead looking at the direct benefit to healthcare costs. This remains a crucial aspect, as “Individualized medicine is very cost intense” and it remains very difficult for the “insurance system to cover these costs” (Interview with specialist for laboratory medicine, see appendix 3).

When a societal perspective is integrated, the benefits beyond personalized medicine may be evaluated and might allow the optimization of the resources dedicated to the healthcare system. With this approach the efficiency of the system and the value to the healthcare investments might be maximized. In order to realize this, there would have to be a shift in the way the systems are currently working. In Europe, the existence of publicly funded healthcare system could facilitate this step. Key is to ensure that structures are in place to extract knowledge from the data and international data sharing to optimize the healthcare systems (Vicente et al. 2019).

9 Conclusion

The main goal of individualized medicine is to tailor treatment to a specific group or person, instead of applying a one-size-fits-all approach. Individual medicine has been an emerging topic within many different fields of application and has a significant impact on different diseases. However, oncology plays a major role in individual medicine, as significant research has been done in this area in the last decade. Personalized medicine in cancer therapy especially uses molecular genetic examination of blood or tumor tissue for targeted treatment. Therefore, oncology has been one of the main focuses for individualized medicine and is likely to continue in the future.

This paper discusses individual treatment approaches of two different diseases. First, prostate cancer (PCa) in which the individual treatment is still in its infancy and has a high development potential. Second, leukemia, especially ALM, in which individual

treatment is already advanced with well-developed targeted therapies and applications.

Conventional treatment in prostate cancer is highly standardized and well-developed, which was also confirmed by the interviewed specialists. This results in individual approaches in PCa that are not well-established yet. Therefore, the relevance of individual treatments in prostate cancer is still to be discussed.

Individualized medicine plays an essential role in the German health care sector. Especially in the area of leukemia individual treatments are promising, as they lead to an increased expectancy of life. However, these treatments are still very expensive and health insurances only cover a limited amount of financial expenses. As genetic testing is becoming more significant and is likely to to be used more in the future, the cost for individual treatments are expected to decrease over time. Thus, the best possible outcome would be that the quality of treatments will increase, whereas the costs will decrease.

Still questionable is how the future of individual medicine will look like. Overall there are five factors that need to be developed for a promising future of individualized medicine. Firstly, a stronger confidence among patients concerning data security has to be established. Secondly, the educational system of healthcare professionals must reflect the interdisciplinary aspects of personalized medicine. Thirdly, the collaboration between clinicians and research workers must be closer to support a rapid development and implementation of personalized medicine. Fourthly, an improvement of digital literacy among the healthcare providers is needed and lastly, all patients must have access to the high-quality healthcare.

10 Limitations

A limitation was that it was not possible to get primary data on the economic assessment from institutions or hospitals. This led to insufficient data regarding the financial realization of individual medicine, for instance the cost of treatment. Furthermore, limited access to literature for individualized treatments of prostate cancer were available. Moreover, concerning individual treatment of leukemia, only diagnostic approaches of AML have been considered. No statements regarding CLL, CML or ALL can be made. Additionally, this paper focuses on individual medicine in

Germany. There might be limitations conveying the information to other parts of the world.

Lastly, this paper is based on extensive literature review by the authors to the best of their ability and current knowledge. As qualitative expert interviews were conducted, the specialists answered according to their experience and understanding of this topic. However, the obtained data from the selected specialists might differ from other specialists in this field and therefore might have subjective elements.

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12 Appendix

Appendix 1: Interview Guideline

General	*What are your experiences with individual medicine? If you have used it, which approach did you use?* *What are the benefits for the patients using individual medicine?*
Specific	*Would you consider individual medicine especially for leukemia as a very much developed treatment method already and why?* *In areas with less developed individual medicine approaches like prostate cancer is there a reason why this has not yet been improved/researched?*
Implications	*In your opinion, what has to change to implement individual medicine more broadly?* *In order to implement individual medicine, the insurance system has to change – how?*
Status Quo	*Would you consider individual medicine well established in Germany?*

Appendix 2: Transcription of the Interview with specialist for hematology and oncology conducted by Johannes Burger on 28.06.2020

Question	Answer
What are your experiences with individual medicine? If you have used it, which approach did you use?	Individual medicine means you see a patient and you take into account individual risk factors and individual preferences as well as the patient's entire living situation. Is it a young or an old patient, what are the expectations from treatment, what are the goals of treatment: is it cure or to improve some symptoms? Always when you approach a patient with a medical diagnosis an individual approach to the patient is useful. As you know I work in cancer treatment in leukemia patients who range in age between 18 up to 90. For each patient we develop an individual treatment plan which takes into account the goals of treatment and preferences of the patient. For example, a patient is in his eighties and is diagnosed with a chronic lymphocytic leukemia. That patient has a life expectancy of maybe another 10 years. For those patient’s aggressive chemotherapy-based treatment has a lot of toxicities and does not improve treatment. For those patients we would rather use a treatment which would not affect the patient’s quality of life and which is allowing patients to continue their daily activities. The situation might be different for a young patient who has acute leukemia where you have to use treatments which are usually based on intensive chemotherapy not just to improve the quality of life of the patient but with the goal of potentially curing. There is a wide range of different diagnosis and different treatments which we have to fit to each patient and to each individual situation.
What are the benefits for the patients using individual medicine?	The benefit is that you take into account each patient’s situation and their individual health status. So, you have to try to get a whole picture of the patient that is not just focusing on the diagnosis but also on other factors. Some patients have

Question	Answer
	preferences for certain treatments or already have another previous disease like diabetes. Some patients have difficulties to come regularly into the hospital and therefore would prefer a treatment which is easy to administer and doesn't require bringing patients into the hospital. So, you can look at all these factors but what is most important is that you find the best treatment which gets the leukemia or whatever the diagnosis is taken care of and gets that in some sort of remission maybe. But you don't always have to use the most active treatment because that can differ between patients that are older or younger or patients that have other diseases which may cause drastic side effects and problems. So, you have to find the right balance between very active treatment but also avoiding, if possible, side effects and toxicities.
Would you consider individual medicine especially for leukemia as a very much developed treatment method already and why?	That is a good question because it depends on which disease you are talking about and for some diseases there might be just limited treatment available. If you talk about cancer treatment, for some cancers the treatment options are limited and therefore you have less options to really offer individualized treatments. For leukemias we fortunately have usually different types of approaches. When we talk about CLL we have a variety of treatment options which we can try to fit to the patients need. And that is where we practice individualized medicine. When we for example treat elderly patients with CLL. This is a leukemia which has an average age of 72. So many of these patients are in their seventies or eighties. Then we don't want to use traditional chemotherapy-based treatment and we now have more targeted treatment approaches with enzyme or kinase inhibitors. Which are usually well tolerated, and which induce remission for most patients which are very durable. But then among the different targeted treatments we have for elderly patients there are different types. There are enzyme or kinase inhibitors which

Question	Answer
	are targeting an enzyme called bruton's tyrosine kinase. There are inhibitors of an anti-apoptosis protein called BCL2 a drug which is called Venetoclax. There are kinase inhibitors which are targeting an enzyme called PI3 kinase and among all these there are settle differences in terms of side effect profiles. For example, the BTK inhibitors have risk for bleeding complication or for arrhythmia which is called atrial fibrillation where the heart beats out of rhythm and too fast. If you have a patient who has a history of heart disease or bleeding complication. You may want to consider rather using one of these other drugs and not a BTK inhibitor. So, you can look at each patient and see which medication might be the best fit and then you discuss the pros and cons with each patient and then you come up with a treatment plan. And as you start treatment you see the patient again frequently in the beginning and less frequent when the treatment works well. But in the beginning, you make sure that the patient is doing well and is feeling well and is satisfied with the treatment. And if that is not the case you change treatment based on either side effects or intolerance of these treatments. But it's not just the decision point when you pick the initial treatment. But if you see the patients over the years you may have to adjust, or you may have to change treatment based on how this individual patient tolerates that treatment.
In areas with less developed individual medicine approaches like prostate cancer is there a reason why this has not yet been improved/researched?	I am not an expert on prostate cancer. I think when you speak to someone who is a prostate cancer expert, they will say our treatments are quite good and we have new development which allow us to move into the same direction. But you are right in general in solid cancers the possibilities are not as diverse, and they don't have as many targeted treatments available. The reason is that in many other cancers other than in leukemias the disease hypogenesis is less well developed. The key to individualized medicine is to understand the

Question	Answer
	cancer biology to develop targeted treatments that are based on disease biology. Once you can hit disease specific abnormalities you have more targeted treatments which then give us more options then those which are currently available. But if you ask specifically about prostate cancer, I think they have a vast variety of weapons also available to treat patients with hormone therapy with surgical approaches and radiation therapy. I think it is not totally accurate to say prostate doesn't allow for individualized treatment. I think they do the same thing. They evaluate the patients and for each patient they develop the best treatment plan which is taking into account how advanced the cancer is and what is the best approach to potentially cure the patient. And then they put together a package of treatment approaches like surgery, hormone therapy or radiation therapy to give the patient the best option to tackle the problem.
In your opinion, what has to change to implement individual medicine more broadly?	I would say if the patient is seen in a cancer center which is specialized in treatment of these kinds of diseases you will already see that individualized treatment is the state of the art. But it's a continuous development where in each cancer the disease biology is studied and where new treatment approaches are developed based on better understanding the disease biology with the goal of moving away if possible from traditional chemotherapy based treatment which have most often a lot of side effects from not targeting cancer cells but from targeting other healthy organs in the patient. If we move into that direction it is coming from new targeting treatments and those are generally developed based on better understanding of the cancer biology. Implementing that also requires trained physicians so the educational part is important. The finances are important. Many countries in the world are poor and have poorly developed healthcare systems. And a large proportion of the world's population

Question	Answer
	doesn't have access to more sophisticated cancer medicine which we have available in the US or in Europe.
In order to implement individual medicine, the insurance system has to change – how?	What is the goal of the healthcare system? The healthcare system should provide best care for all patients and all people living in a society. So that would be the ideal if you want to have an ideal insurance system you would first have to make sure that all people in that society have access to it. That works in some countries better than in others. Of course, healthcare is expensive, and it is difficult to balance the cost and the expense to society as a whole. So, it comes to the question who's paying for these insurance systems and how do you pay for it. And then of course individualized medicine and all these targeted agents are expensive, and treatments are getting more expensive. You either leave that up to the market which is done in the US. Here pharmaceutical companies develop targeted treatments and are able to basically dictate the price of these medications. Or you can have a more controlled approach like what is done in Europe where agencies oversee the negotiations between healthcare system and pharmaceutical companies. It is a very complicated approach where you have to balance the different interests, the pharmaceutical interest wants to maximize their profit so that their shareholders have a benefit. But you have to balance that with society which has limited resources where you want to get the best treatment for each patient. I think the fundamental question is whether the free market is able to regulate that in a reasonable way or whether governments should have some oversight and put some regulation into that system. In an extreme pharmaceutical companies or insurance companies, which both have an interest in making money, they develop their interests at the expense of maybe less patients having access to healthcare systems or just exploding costs for the healthcare system.

Question	Answer
Would you consider individual medicine well established in Germany?	I am not practicing in Germany anymore, but I think Germany has one of the best healthcare systems in the world. So ideally compared to other countries there are many more options for individualized medicine in Germany. The healthcare system in Germany is generally very well established and provides good healthcare to basically all German citizens so that is a big plus. But the healthcare system has been more and more privatized in Germany too. So profit interest have gained more access to daily practice of physicians and the individualized treatment is limited by considerations of how expensive a treatment is or how profitable it is for a hospital or a private practice to treat a patient who has for example a very complicated disease which is very expensive to treat. So, the influence of money and profit of insurance companies and hospital providers is greater than it was a few decades ago which is a concerning development. But nonetheless Germany has quite good individualized medicine options for most of these patients.

Appendix 3: Transcription of the Interview with specialist for laboratory medicine conducted by Johannes Burger on 23.06.2020

Question	Answer
What are your experiences with individual medicine? If you have used it, which approach did you use?	I am a specialist in laboratory medicine. So, I do not have any experience in using individual medicine as a therapy, but diagnostics are usually the key to find out about the individual factors that could lead to therapy. That is for example the detection of a specific genetic mutation in tumor cells that could be a target for a drug that specifically binds to the mutated structure and inhibits further proliferation of tumor cells.
What are the benefits for the patients using individual medicine?	The more individualized a therapy could be the better for the patient. The resulting treatment will hopefully directly target the specific problem and have less negative side effects. In former times for example in cancer treatment drugs were used that kill all cells that have a high turnover. As a negative effect all cells that permanently need to regenerate like blood building stem cells, hair etc. will be killed as well if the tumor cell is killed. With an individualized approach in the best case only the tumor cells would be killed. And as tumor cells are very individual there needs to be very specific diagnostics to be able to detect that specific target of the tumor cell in each individual patient.

Question	Answer
Would you consider individual medicine especially for leukemia as a very much developed treatment method already and why?	Yes, leukemic cells are easy to access as you just need to take peripheral blood or get a bone marrow sample. As blood building with its development from the completely immature stem cell towards the mature cells is well understood and these cells continuously change their phenotype during this maturation process, the characteristics of the tumor cells can be well investigated and classified. This leads to the possibility to target directly these specific characteristics of the tumor cells. In solid tumors this is not as easy to get tumor cells for diagnostics and there is not that much of knowledge on all the specific characteristics of these tumor cells compared to the blood cells.
In areas with less developed individual medicine approaches like prostate cancer is there a reason why this has not yet been improved/researched?	As pointed out it is already an invasive process to get tumor material although it is possible. Prostate cancer has a high incidence in elderly men and there is a good way for the screening (using the PSA as laboratory parameter), so it can be detected in an early stage. Once detected it can be treated with conventional methods (operation, radiation) and if early enough detected it is not life threatening. So the pressure for a more individualized treatment is not as high as in other more aggressive cancers.
In your opinion, what has to change to implement individual medicine more broadly?	There is still a lot of research to be done to be able to find more individualized therapy options in many different medical fields. Finding individual targets is the key for the development of this individual treatment.
In order to implement individual medicine, the insurance system has to change – how?	Individualized medicine is very cost intense. I have no idea how this could be managed that our insurance system could cover these costs.

Question	Answer
Would you consider individual medicine well established in Germany?	I think we are only at the beginning of these new developments in individual medicine so I would not call it “established” but it is well accepted to go this direction. There is growing knowledge and a lot of studies going on which will continue.

Appendix 4: Transcription of the Interview with specialist for human genetics and internal medicine conducted by Johannes Burger on 29.06.2020

Question	Answer
What are your experiences with individual medicine? If you have used it, which approach did you use?	My only experiences are that I see an increasing clinical application of individual medicine in three different areas: in diagnostics, in treatment, and fairly new in risk assessment. Risk assessment by means of management of risks. And this is basically due to the progress in the scientific understanding of pattern mechanism of diseases. And this of the cellular, molecular and genetic level. This has enabled us to have a more causal approach so that we are really focusing on 'what is the cause of the disease' and this does apply for all three of these different options for diagnostics, for treatment and for risk assessment. The focus from a broad picture of the disease let's say for instance breast cancer to the individual personal conditions. Let's say for instance just to make it clear. Breast cancer would be the general broad approach but the particularly situation might be lady of 36 years of age with a breast cancer and a clear family burden of cancer. She might have a particular kind of cancer this is classified by the so called TNN System and also we do with a pathology with a tissue examination we do some molecular profiling and she might have in addition to that other cancers and there might be other cancers in the family and there might be which is kind of a hint for hereditary condition the age of onset is very young. The younger she is so more likely that she has a hereditary condition. This is her personal situation then there is something where we do individualization by means of historical background of spread cancer. So, what is the spread in the body. What is the time when we have caught the cancer? And we have also highly specific biomarkers that are indicating particular risks and also some prediction of response to treatment or even to work effective. All together this is an indication for a very specific individualized treatment. And if we go ahead and see this as a treatment kind of focus, we have also a prophylactic kind of

Question	Answer
	approach because she might be prone or at risk for other kind of cancers if we had done a specific longtime analysis. Maybe a general remark on the term individual medicine: there is a challenge related. There is something… sometimes it does … like a password, like a … in German you would say a “Modewort” with many similar terms. Personalized medicine, precision medicine. These are all terms that are used for sometimes even to create an overdrawn estimation or expectation. That expectation might be too high and you have a term when you have passwords where you have commercialization and that profit oriented companies want to get in this kind of business. So, I think most important is not to understand not to create wrong expectations. And so back to my own Application. I’m a geneticist and I’m a human geneticist and a tumor geneticist. So, I try to establish the personal cancer risk by molecular genetic analysis of individuals risks. So, we are searching for specific mutation in the germ line. You might have heard this in 2014, Angelina Jolie, this American Actress went into public. She had a called BRC1 mutation and as a consequence of that you have a really very focused and individualized kind of not treatment rather than a surveillance, an intensified surveillance, a preventive measurement so you can have even a prophylactic surgery on that. So that to the first point.
What are the benefits for the patients using individual medicine?	First, I think it’s to reduce a burden of the disease by preventing it. And if you have a disease you can focus clearly on a specific kind of molecular profiling of the disease so you have a very focused and high effective treatment. This will all do two things: One is to avoid unnecessary treatment by stratification and this is always based on what I have said already on the molecular profiling of the tumor and something which is important for health care system and for the society for the insurance companies is: it will substantially reduce the cost. Because this treatment is highly focused, highly effective and avoiding unnecessary site or wrong approaches.

Question	Answer
Would you consider individual medicine especially for leukemia as a very much developed treatment method already and why?	I would say NO. I'm a hematologist so I think leukemia is a very, very rare and very rarely hereditary. I mean the stratification of the disease is clearly defined by the disease and in this you could say yes, we have seven different kind of acute molecular leukemias. We have two very different chronic leukemias and they all are kind of treated differently. But this is not really developed in the area of individual medicine and it just traced back to the 19th century to Virchow a very old pathologist. In 18 hundred so and so he was capable of saying the chronic leukemia this is an acute myeloid leukemia and I would not really call this individualization. But it is a highly stratification of the disease. I hope this helps to your question.
In areas with less developed individual medicine approaches like prostate cancer is there a reason why this has not yet been improved/researched?	I think that prostate cancer is very common and fairly good treatable cancer. So, the treatment is well established. Its highly standardized and you might say the individualization/ the standardization because if you have specific makers you will differentiate the treatment. So, it is well developed and I don't see really limited… I do not see any needs to improve that. I mean historically there has been a discussion and these are two important terms not to be mixed up for screening the population by TSA which is a biomarker you want to investigate the huge percentage of the population at a certain age. So, you can say in general the older you are the more likely you will develop cancer. And prostate cancer will let's say six to seven percent of our population will suffer from that. So, you could after a certain age you could argue we do this screening but I as an Oncologist would not really see it as an individualization. Just a population screen. You see you have basically most of these cancers have two different types. One which is clearly indicating a hereditary background. You understand what I mean. You have a germline change and so it's not only the patient by itself but rather the whole family which is kind of at risk by this cancer. And this is easily to be or let's say fairly easily to be distinguished between if

Question	Answer
	you have let's say friends, I don't know whether you know that but I think it was in the internet. Sapper, this artist he had had prostate cancer when he was very, very young. So this is a totally kind of background you would go much more in details to characterize this tumor, to characterize his gene and genetic background and then if you find something which is specifically marking this biomarker for this disease you would want to go to the family and screen patients at risk. And so, I think that should be enough for this question.
In your opinion, what has to change to implement individual medicine more broadly?	Actually, I don't really see a need to change our approach. In these two areas diagnostics and treatments its very well established and the clinics will come more and more the better the pathological services in our country will improve so you need molecular profiling of all tumors. And there is only a need of university centers. Or let's say a few large hospitals where you have thousands of investigations in a year. You need to have a let's say kind of "Flächendeckende Versorgung" so it should cover the whole population. I mean we need to increase our resources on that.
In order to implement individual medicine, the insurance system has to change – how?	Well I think a major particular German issue or challenge is 'how to deal with assessing the individual risk'. With whom to share the information. Is by means of this data protection "Datenschutz" in Germany. We have a very specific German kind of challenge you would not want to have your insurance sharing or this risk factors of your life. On the other hand, if you make it in an appropriate way that there would be a general acceptance in the population by means of balance of checking Balance. We all including the person who is insured might benefit. Let's say for instance what I'm thinking about is, insurance companies know that you have a specific genetic risk in your family and only for those persons at risk which are classified for that they will provide a specific kind of surveys, a specific kind of intensified survey project. And so, by means of focusing their resources on these people that they can benefit of it. Both sides win. It could be a win-win situation. But as

Question	Answer
	far as I experienced in Germany, we have a very, very strong and restricted kind of polling party against this share of Information. I mean they always quote China where you have the social ranking and this is, I mean the other extreme, if you are an autocratic system, but we might have to work on it. But in general, we all would benefit from it. So, the people with increased risk and the insurance companies who might be taking care properly. But you see I'm really focusing on this issue of risk assessment in healthy people. Because I'm doing this as a human geneticist these people were being counseled in my practice. Without having the disease or not yet having the disease but it is an advance and so and let's say the perspective and so. Preventive medicine is an issue in Germany particularly problematic or challenging because the legal basis for all the reimbursement … I have to say it in German because I'm lacking the English term "Soziales Gesetzbuch Number five". And this is made for diseases not for preventing or keeping people healthy. So we would need (I think it has already a number thirteen or something like that) a new "Soziales Gesetzbuch" which is focusing particularly on this issue by means also of how to deal with information and how to deal with the data protection and when you're fair of this data what would be the implication if you are not living healthy enough. So it's really a challenge and the "Bundesministerium für Gesundheit" is always saying this is not our issue it's an issue of society in itself. That's the reason preventive lifestyle. To not use a term of medicine is a challenge in Germany. You could say I want to have a prescription of an apple a day and the health insurance has to pay it because it's healthy and will reduce the cost. So, you see that's a very problematic not at all medical kind of issue, it's a more legal part.
Would you consider individual medicine well established in Germany?	In general, I would say it's one of the best worldwide. But particularly on these two issues what I said diagnostics and treatments. And with a third issue the prevention in general we have this general problem…

Question	Answer
	I think I'm not overdoing it by saying this German system does belong to one of the best in the world. Particularly when we're talking about individual medicine when it comes to these to points diagnostics and treatment. The third part prevention, risk assessment and risk management is basically related to the point I made it some minutes ago about this "Soziale Gesetzbuch Number 13" the prevention and to keep the people healthy. It's a major challenge that we can achieve kind of a general acceptance in the population where this is not only the objective and the goal for the individual than rather for the whole society. And I make, I think few minutes ago, also this quotation that in China you have this social ranking. That you are controlled by the society. Nobody would want to have something like that. On the other hand, if you are very individual and always keeping this hidden for ourselves, we'll never ever be able to improve the whole system. So, I think this issue of prevention of health… prevention of diseases and keeping health is majorly related to other issues. Something like education in the population. And majorly the most important question is 'who is entitled to enforce this keeping of people healthy?'. So, I think this is what I said to the last question.

Appendix 5: Diagnostic key findings of the four most frequent leukemia diseases

* H=High, N=normal, I=increased

	Acute lymphocytic leukemia (ALL).	Acute myeloid leukemia (AML)	Chronic myeloid leukemia (CML)	Chronic lymphocytic leukemia (CLL)
Age	Childhood	Every age	Middle age	Middle and higher age
Leukocyte values	H* in 50% N* & I* in 50%	H* in 60% N* or I* in 40%	H* in 100%	H* in 98% N or I in 2%
White differential blood count	A lot of lymphoblasts	A lot of	Whole row	Small lymphocytes
Anemia	For more than 90% of patients heavy	For more than 90% of patients heavy	For more than 80% mild	For 50% mild
Thrombocytes	I > 80%	I > 90%	H in 60%, I in 10%	I in 20-30%
Enlarged lymph nodes	often	seldom	rare	often
Enlarged Spleen	60%	50%	often and massive	seldom and moderate

Table 5: Diagnostic key findings of the four most frequent leukemia disease (Roche Lexikon Medizin, 2003)