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Relevance of Personalized Health Care in Patients with Arterial Hypertension: Where are we now?

Carmen Binder, Hans Hendrik Schäfer,
Edelgard Kaiser, Martin Hund and Thomas Dieterle

Additional information is available at the end of the chapter

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Abstract

Personalized health care (PHC) or precision medicine is a new medical concept that aids in treatment decisions for patients by tailoring them to their individual needs. It often employs genetic testing to select appropriate and optimal therapies (pharmacogenomics). Although this concept is widely applied in oncology, the field of hypertension is still in the early stages and "personalization" is currently limited to tailoring antihypertensive treatment according to age, comorbidities, and ethnicity. Despite the fact that incomplete/lack of treatment response occurs in 10–30% of hypertensive patients for angiotensin-converting enzyme (ACE) inhibitors and in 15–25% for β-blockers, major continental guidelines still recommend the use of antihypertensive agents in a "one-size-fits-all" approach, neglecting the 1977 postulation of the Joint National Committee that "all patients must receive individualized therapy programs." The arrival of molecular testing offers new possibilities to differentiate monogenetic from polygenetic disorders and to identify associations between hypertension and drug response to corresponding genes. Up to 50% of the variation in blood pressure (BP) is attributable to genetic factors. Polymorphisms have been identified and studied in genes for BP-modifying receptors, such as ADBR (β-adrenergic receptors), and pharmacological pathways (GNB3, RAAS system). Approximately, one-quarter of the currently analyzed gene polymorphisms demonstrate significant pharmacogenetic effects (ADD1 Gly460Trp and the insertion/deletion [I/D] polymorphism in intron 16 of the ACE gene). Several large screening studies are currently ongoing to assess the impact on efficacy of antihypertensive medication of variants in hypertension-susceptibility genes. The GenHAT substudy of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) assessed the predictive validity of the ACE I/D genotype for coronary heart disease. The Family Blood Pressure Program included 11,079 participants to map genetic variants associated with hypertension. In this review chapter, we display the current body of knowledge regarding PHC in the treatment of hypertension. In particular, we highlight genetic variants associated with hyperten-

sion and response/non-response to antihypertensive substance classes. Second, we describe technological aspects of PHC and display the most recent example of a PHC marker used in preeclampsia (PlGF/sFlt-1/PlGF). We then present the results of a guideline review, which included six international guidelines (the European Society of Cardiology/the European Society of Hypertension (ESC/ESH), the Joint National Committee (JNC)8, the Canadian Hypertension Education Program (CHEP), the National Institute for Health and Care Excellence (NICE) and the American Heart Association (AHA)/the American College of Cardiology (ACC)/the Centers for Disease Control and Prevention (CDC) and the American Society of Hypertension (ASH)/the International Society of Hypertension (ISH)) on recommendations regarding PHC in arterial hypertension and address contemporary governmental health agency perspectives on PHC. Finally, we present the view of physicians on the development of PHC.

Keywords: personalized health care, arterial hypertension, customer, technologies, genes

1. Introduction

The history of personalized medicine is as old as humankind. Attempts to identify which patients are prone to a particular disease and which patients will benefit from a particular treatment reach back to Hippocrates, who stated: "It is far more important to know what person the disease has than what disease the person has."

1.1. The term personalized health care

Personalized health care (PHC) describes attempts to tailor medical treatment to the characteristics of the individual patient. This creates a setting in which individuals can be allocated into subpopulations. PHC aims to allocate therapeutic and preventive interventions to that section of the population that is likely to respond [1]. Adequate treatment may lead to a significant reduction in disease burden by preventing a number of long-term problems, for example, caused by untreated hypertension including cerebrovascular disease, renal insufficiency, and coronary artery disease [2]. PHC can also reduce the response time to treatment and visit frequency. Drug intake itself can lead to adverse effects—a burden that is usually balanced against the beneficial effects of therapy [3]. Adverse events are a secondary source of costs and they increase the likelihood of therapy withdrawal and the risk of non-compliant behavior. PHC allows adverse events associated with ineffective treatment to be avoided and can reduce health-care costs significantly. **Table 1** exhibits the conceptual components of PHC. **Figure 1** displays the effects of PHC on the health-care environment.

1.2. Treating arterial hypertension

Hypertension is a major public health problem [4] and is the most common modifiable risk factor for vascular disease [5]. It affects around 992 million people worldwide [6] and has a high prevalence in Europe [7]. The response to antihypertensive therapy is very heterogeneous

and this has driven much interest in the pharmacogenomics, which combines the fields of pharmacology and genomics to establish how a person's genetic makeup influences their response to drugs. In pharmacotherapy, on average only 50% of patients receiving a given drug will experience the expected therapeutic benefit [8]; the remaining 50% experience either insufficient effects or no effects at all [9]. In patients with hypertension, the rate of incomplete or absent responses ranges from 10 to 30% for angiotensin-converting enzyme inhibitors (ACEIs) and 15–25% for β-blockers reaching 30–70% for statins, and 40–70% for β2-agonists [10]. Overall, it is assumed that only approximately 30% of patients respond adequately to antihypertensive drugs [11].

Personalized Healthcare in arterial hypertension			
Detailed Assessment	**Comprehensive Assessment**	**Morphological Assessment**	**Functional Assessment**
Genomic Testing	Family History	Intima-Media Thickness	Endothelial Function
	Laboratory Testing		Heart Rate Variability
	Evidence on Gender/Age/Ethnicity		Stress Testing
	Risk Factors/Scores		

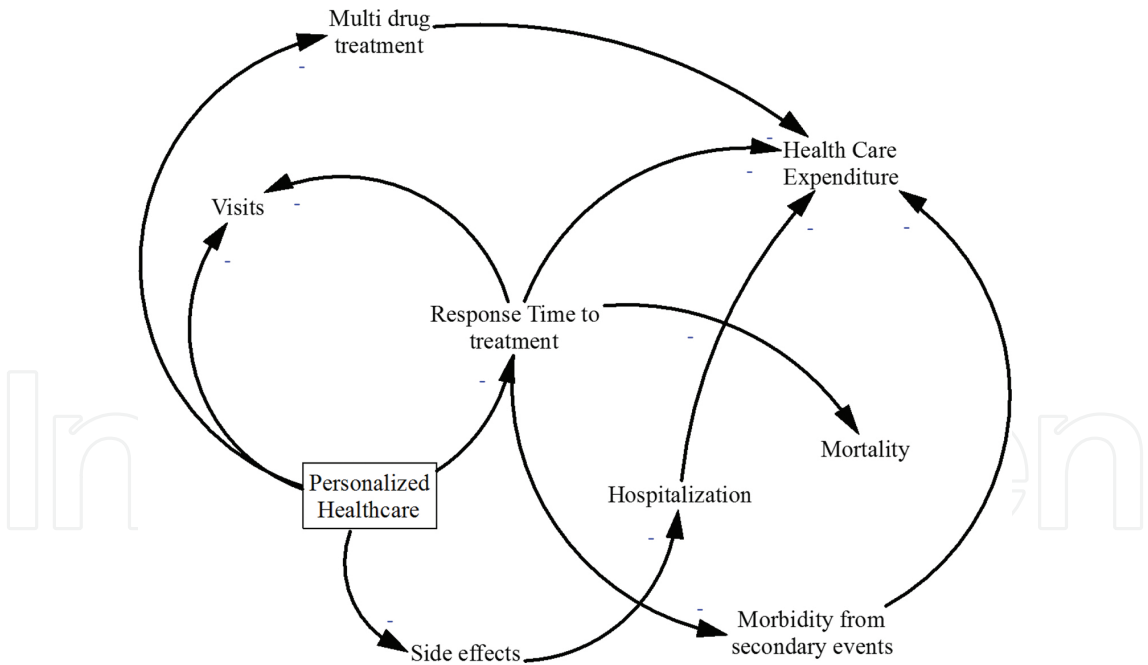**Table 1.** Overview of components of PHC.

Figure 1. Effects of PHC on the health-care environment (causal loop).

1.3. Guideline recommendations and clinical practice

Individualized treatment approaches for patients with arterial hypertension have been recommended for several decades [12]. As early as 1977, the Joint National Committee (JNC)

Reports on the Detection, Evaluation, and Treatment of High Blood Pressure (BP) [13] stated predictively that "all patients must receive individualized therapy programs." In reality, this recommendation was replaced with a standardized advocacy of diuretics [14] and the only individualized component of contemporary blood pressure treatment remains clustering patients according to gender [15], race [16], end-organ damage, or comorbidities.

1.4. Genetic factors for blood pressure variability

The completion of the Human Genome Project [17] revolutionized medicine. Advances in the understanding of the human genome have enabled physicians to pursue optimal preventive health-care strategies instead of the rather reactive health-care approaches used in the past [18]. For the first time, it conclusively mapped all human genes, including those that may account for hypertension. Up to 50% of BP variation can be explained by either monogenetic or polygenetic factors [19]. However, it was disappointing that the influence of single gene polymorphisms was less than expected (<5%) while the impact of race and sex was considerably higher [20]. BP differences of <0.5 mmHg are normally associated with a single nucleotide polymorphism (SNP) [10].

1.5. Demand for better technologies

Parallel with these discoveries, breakthrough technologies came on the market, including the automated high-throughput sequencer [21], as well as new methodologies allowing less invasive diagnostics such as liquid biopsy [22]. These technologies were primarily driven by the need for better diagnostics in the oncology field and made the handling of genomic information more established and accepted.

1.6. Health economic aspects of PHC

Over the last couple of years, payers, health economists, and policy makers evolved as a new stakeholder group in the health-care landscape articulating an interest in a more cost-efficient treatment. Genomic investigation allows not only the early diagnosis of diseases but also the identification of disease sub-entities. Both components have an impact on the health-care expenditures. In recent years, other fields of medicine (e.g., neonatal diagnostics) have started using genetic information for patient management. Due to fairly low costs for antihypertensive therapy, PHC has been slow in entering this field of medicine. Thus, overall, the use of individualized treatment approaches in hypertension remains low (at around 7% in the USA [23]). A McKinsey ranking from 2010 [24] regarding the scientific and economic potential of companion diagnostics, which was based on expert interviews and other quantitative factors, yielded low values for antihypertensive assays (<1.7 on a scale from 0 to 2.7 for the economic potential and 1.1 on a scale from 0.4 to 2.8 for scientific potential), putting them in a "no-go" area for company investment. Not surprisingly, the analysis showed high values for oncology, anti-infectives, and autoimmune drugs. However, what is very often forgotten is the fact that a test, particularly one that is able to show high per-patient savings in a highly prevalent disease, can be a very attractive opportunity. Thus a test that can prevent or drastically delay an ischemic cardiac or a cerebral event can be considered as a favorable asset. In addition, PHC

tests in hypertension are less likely to create microeconomic incentives for prescribing physicians. This is because the treatment of hypertension is a predominantly conservative discipline and not associated with costly procedures.

1.7. Pharmacogenetics

In more recent years, the International Haplotype Project contributed to better understanding of genetic polymorphisms by developing a map locating genes affecting health, disease, and responses to drugs (HapMap) [25]. However, in 2010 only around 10% of all Food and Drug Administration (FDA)-approved drugs include pharmacogenomic information in their labels [26], and a total of 39 FDA-approved drugs demanded genetic testing at that time [27]. By contrast, another study of 200 top-prescribed drugs showed that pharmacogenetic data were available for up to 71.3%, although only 24% of all cardiovascular drugs in the 200 top-prescribed drugs had pharmacogenetic data [28]. Of these, approximately 23 and 18% of pharmacogenetic data in the cardiovascular and hormone/hormone-modifier classes, respectively, were related to drug-metabolizing enzyme and drug transporter genes (i.e., pharmacokinetics) [28]. Trials investigating variants in hypertension-susceptibility genes and their interaction with antihypertensive therapy, for example, GenHat [29], have been initiated as well as biobanks and registries to assess information about pharmacogenomics of hypertension, including the Family Blood Pressure Program [30] and the Pharmacogenetics Knowledge Base (PharmGKB; https://www.pharmgkb.org/).

The following chapters review various aspects of PHC in arterial hypertension, namely genes in arterial hypertension, technologies used in PHC, guideline recommendations on PHC, and physician views on PHC. Finally, a case study of PHC displays the impact of a medical value assay on the management of preeclampsia.

2. Genes in arterial hypertension

BP is a complex physiological trait that is affected by complex interplays between genetic and environmental factors. Gene variants may affect BP variability by acting on gene and protein expression. Thus, the characterization of genes associated with BP may provide not only a deeper understanding of the cellular processes involved in BP regulation but also how transcripts mediate genetic and environmental effects.

Many trials have demonstrated a substantial heritability of BP. Adoption, twin, and family studies document a significant heritable component to BP levels and hypertension [31–33]. Estimates of the heritability of resting systolic and diastolic BPs, based on family studies, are thought to be generally in the range of 30–60% [34]. A heritable component to salt sensitivity of BP has been described in black Americans [35]. A large proportion of the phenotypic variation in BP appears to be inherited as a polygenic trait [36, 37]. A wide variety of approaches, such as linkage and candidate gene studies (CGSs) or studies of families with rare Mendelian high or low BP syndromes, were used for the search for genes associated with BP

variability [38–42]. Nevertheless, the majority of genetic contribution to BP variation remained unexplained.

Systolic blood pressure			Diastolic blood pressure			Hypertension		
SNP	Chr.	Nearest gene	SNP	Chr.	Nearest gene	SNP	Chr.	Nearest gene
rs12046278	1	CASZ1	rs13423988	2	GPR73/ARHGAP25	rs17806132	2	PMS1
rs7571613	2	PMS1	rs13401889	2	MSTN	rs305489	3	SYN2
rs448378	3	MDS1	rs9815354	3	ULK4	rs7640747	3	ITGA9
rs2736376	8	MTMR9	rs7016759	8	EFCAB1	rs11775334	8	MSRA
rs1910252	8	EFCAB1	rs11014166	10	CACNB2	rs899364	8	FAM167A/BLK
rs11014166	10	CACNB2	rs11024074	11	PLEKHA7	rs11014166	10	CACNB2
rs1004467	10	CYP17A1	rs2681472	12	ATP2B1	rs2681472	12	ATP2B1
rs381815	11	PLEKHA7	rs3184504	12	SH2B3	rs278126	12	CIT
rs2681492	12	ATP2B1	rs2384550	12	TBX3/TBX5	rs11612893	12	FZD10/PIWIL1
rs3184504	12	SH2B3	rs6495122	15	CSK/ULK3	rs16982520	20	ZNF831/EDN3

SNP, single nucleotide polymorphism; Chr., chromosome.

Table 2. Meta-analysis of CHARGE and Global BPgen of top 10 loci for systolic and diastolic BP and hypertension (adapted from Levy et al. [43]).

It is conceivable that BP variation in the general population may be a reflection of the sum of multiple variants with small effects. Thus, very large studies might be needed to identify such effects. In fact, large-scale genome-wide association studies (GWAS) have identified numerous gene loci that are associated with BP [43–45]. As an example, the top 10 loci for systolic and diastolic BP as well as for arterial hypertension derived from the Cohorts for Heart and Aging Research in Genome Epidemiology (CHARGE) Consortium [46] and the Global BPgen Consortium [43] are summarized in **Table 2**.

The study of the genetic background of an individual may be helpful to analyze the intrinsic and extrinsic susceptibility for a disease as well as the effects of the disease on the individual. The potential of such a personalized, particularly genome-based approach to arterial hypertension is summarized in **Figure 2**. Obviously, the treatment of chronic conditions would not start before the earliest possible time of point detection. In many cases, it will only start with substantial delays after this time point and many chronic conditions, including hypertension, will only be detected when acute or chronic end-organ damage becomes clinically overt resulting in deleterious consequences for the patient [47]. In these conditions, genome-based information across the continuum of health and disease may complement and improve the current approach by early identification of individuals at risk for a disease and, at the same time, enabling early preventive and/or therapeutic interventions [48, 49].
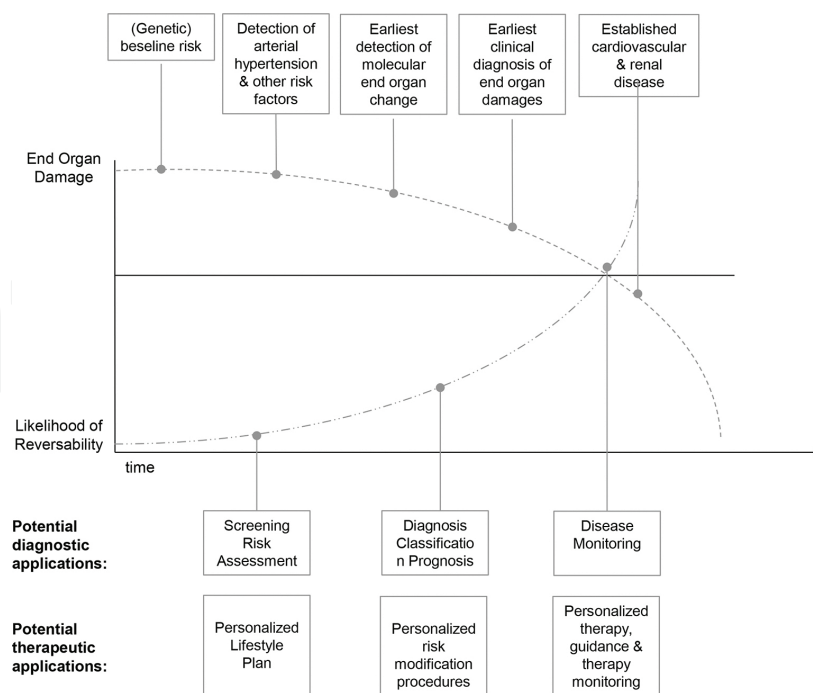
Figure 2. Opportunities for PHC in hypertension.

2.1. Potential application of genomics in risk stratification in arterial hypertension

Associations between genes and hypertension identified by GWAS or CGS are limited by small effect sizes limiting the ability of individual genes to predict the development of hypertension. This limitation can be overcome by constructing genetic risk scores that combine the effects of multiple genetic variants into a single variable. A potential application of genetic risk scores can be the early identification of patients at risk for developing hypertension. Published examples include a genetic risk score derived from data from the British Genetics in Hypertension (BRIGHT) study and a genetic risk prediction model derived from the Wellcome Trust Case Control Consortium (WTCCC) study [50–52]. Unfortunately, genetic risk scores for hypertension only have a very limited predictive power [51] and therefore add little additional information compared to non-genetic risk prediction models.

2.2. Potential application of genomics in therapy guidance

More promising applications of genetic testing are expected from the field of pharmacogenomics (i.e., the study of genetic predisposition to drug response). It is estimated that 1.56 billion adults worldwide will be diagnosed with arterial hypertension by 2025 [6]. Being a chronic condition, hypertension usually requires lifelong therapy. However, despite a wide variety of available antihypertensive drugs, BP is controlled in only approximately 50% of patients. Moreover, therapeutic strategies in the general population have not been as effective as expected from clinical trial results [53]. These data indicate that the optimal approach to antihypertensive therapy has not yet been established and that further improvements in patient care and treatment efficacy need to be achieved.

Drug class	Gene	Population	Drug	Data source	Reference
Diuretics	*YEATS4*	White-/African-Americans/Others	Hydrochloro-thizide	GWAS, CGS	[56, 57]
	PRKCA	Swedish/Norwegian, Finnish		GWAS	[58]
	NEDDL4	Swedish/Norwegian, White-/ African-Americans/Others, White-/African-Americans/ Hispanics		CGS	[59, 60]
	FGF5 SH2B3 EBF1	White-/African- Americans/Others		CGS	[61]
	CLIC5 RUNX2	Finnish		GWAS	[62]
	TET2 CSMD1	Italian		GWAS	[63]
ACE Inhibitors / Angiotensin II Receptor Blockers	*AGT*	Chinese, Indian	Enalapril/ Inidapril, Benazepril	CGS	[64–66]
	AGTR1 NR3C2	Chinese	Enalapril	CGS	[67]
	ABCC9 YIPF1	Japanese	Not specified	GWAS	[68]
	FUT4	White-/African- Americans	Candesartan	GWAS	[69]
	GPR83 SCNN1G CYP11B2	Not specified		CGS	[70]
	STK39	Finnish	Losartan	GWAS	[71]
	CAMK1D	Italian		GWAS	[72]
	GRK4	Japanese	Losartan, Candesartan, Telmisartan	GCS	[73–75]
Beta-Blockers	ADRB1	White-/African- Americans Hispanics	Metoprolol	CGS	[76]
	FGF5 CHIC2 MOV11 HFE	White-/African- Americans/Others	Atenolol	CGS	[61]
	GNB3	Italian		CGS	[77]
	GRK4	White-/African- Americans/Hispanics		CGS	[78]
	LPL PPARA	Europe, Africa, Asia		CGS	[79]

Drug class	Gene	Population	Drug	Data source	Reference
	TNFRSF11B				
	APOB				
	ADRA1A				
	CACNB2				
	LIPC				
	CASR				
Calcium Channel Blockers	PICALM TANC2 NUMA1 APCDD1	Japanese	Not specified	GWAS	[68]
	KCNMB1	White-/African-Americans/Hispanics	Verapamil	CGS	[80]
	CACNA1C	White-/African-Americans/Hispanics		CGS	[81]
	PLCD3	Swedish/Norwegian	Diltiazem	CGS	[82]

GWAS, genome-wide association study; CGS, candidate-gene study.

Table 3. Pharmacogenetics/genomics studies in arterial hypertension by drug class.

In this respect, pharmacogenomic approaches have the potential to lead to the development of diagnostic tools for predicting the most effective therapeutic approach to hypertension. In fact, an increasing number of studies have revealed and continue to reveal genetic variants that are associated with response or non-response to antihypertensive drug classes such as diuretics, β-blockers, calcium channel blockers (CCBs), ACE inhibitors, and angiotensin II receptor blockers (**Table 3**). While parameters obtained from anthropometric, biochemical, or technical examinations are helpful for the adequate selection of drug classes that will provide optimal end-organ protection, they are of limited value for predicting the individual response to antihypertensive therapy [54, 55]. Unfortunately, despite promising data, information on interactions between gene variants and antihypertensive drug efficacy is not yet part of the routine evaluation of hypertensive patients. This may be due to confounding factors (e.g., environmental or epigenetic factors). Their effect is far less well understood and more research is needed to further clarify the interplay between genes, environment, and response to antihypertensive therapy.

3. Technologies for PHC in essential hypertension

BP has a significant genetic component, but only a minority of cases is attributed to genetic variants identified to date [83]. There is a general belief, however, that by further understanding these interactions, there is high potential in PHC for the prevention and treatment of

essential hypertension. While most studies focus on the types of analytes that could be relevant, such as nucleic acids and proteins, here we investigate the technologies currently in use and those with the biggest potential for PHC in hypertension.

3.1. Real-time quantitative PCR and digital PCR

Polymerase chain reaction (PCR) has become an indispensable tool in biomedical research. Real-time quantitative PCR (qPCR) allows measurement of the amplification of a targeted DNA molecule in real time based on fluorescence [84]. The resulting PCR curve is used to define the exponential phase of the reaction, which is a prerequisite for the accurate calculation of the initial copy number at the beginning of the reaction [84, 85]. One study developed a screening test based on six multiple SNP loci associated with essential hypertension and was able to demonstrate significant correlation between one SNP and patients with hypertension [86].

Although qPCR is still the technology of choice, the latest PCR technology—the so-called digital PCR (dPCR)—now offers measurement of nucleic acids with generally superior precision, sensitivity, and reproducibility over qPCR [87, 88]. In dPCR, the sample is separated into a large number of partitions, allowing for simultaneous template amplification separately in each partition. The latest development of dPCR technology employs thousands to millions of reaction partitions, thus providing a scalable multiplexing environment [89]. The advantages in terms of sensitivity and reliability demonstrate the potential of dPCR for molecular diagnostics, for example, in the cell-free DNA fraction of blood plasma, but the technology has not yet been introduced into mainstream clinical practice, and hence no reference was found for the use of dPCR with regard to genetic testing for hypertension.

3.2. Next-generation sequencing (NGS)

In the past decade, there has been extraordinary progress in our ability to sequence the human genome and the price of sequencing an average human genome has dropped from approximately US$10 million to below US$1000 [90, 91]. Most sequencing technologies use similar protocols with common methods for template preparation (building and amplifying a library of nucleic acids), nucleic acid sequencing using library fragments as template from which a new complementary DNA fragment is synthesized, and imaging and data analysis [92]. The actual sequencing occurs through a cycle of washing and flooding the fragments with known nucleotides in a sequential order, and digital recording of incorporated nucleotides [92]. Raw sequencing data then undergo several layers of data analysis to rebuild the sequence from a multitude of DNA fragments, after which the compiled sequence can be analyzed [93]. Targeted sequencing, such as whole-exome sequencing, allows us to investigate the coding part of the genome, which represents only about 1.5% of the genetic code. The exome can be sequenced at a much lower cost compared with the whole genome, and with deeper coverage (>100× vs. 30–40× coverage), which increases accuracy [94]. Technological advances in high-throughput genomic sequencing enabling genome-wide association studies and whole-exome sequencing are expected to bring greater insights into the genetic causes of essential hypertension and will eventually bring those technologies into clinical practice [79]. Numerous

companies are working on the development of high-throughput genomic technologies in order to make genomics information universally available.

Examples include Genia, with its nanopore technology for single molecule sequencing, and Illumina Inc., which has developed large-scale whole-genome sequencing on the HiSeq X Series and Thermo Scientific (http://www.pacb.com/products-and-services/; https://www.thermofisher.com/ch/en/home.html) [95, 96].

To fully reveal the potential of NGS, it is important to consider multiple sources of genetic information, such as inheritance and association studies, and bioinformatics. For example, the application of next-generation linkage and association methods to hypertension demonstrated that OSBPL10—a disease-susceptibility gene for dyslipidemia—might also influence systolic BP [97]. A novel statistical approach to detect genetic associations between a trait and SNP regions across the entire genome (whole-genome sliding-window-based optimal weighted approach) revealed three highly susceptible windows across chromosome 3 for diastolic BP and identified 10 of 48,176 windows as the most promising for influencing both diastolic and systolic BP [98]. A recent analysis of functional differences in hypertension pharmacogenes was conducted by investigating human genomic variation using data from the 1000 genomes project, coupled with a functional prediction analysis [79]. Results indicated significant interpopulation differences depending on geographical origin, giving insights into interindividual differences in antihypertensive drug response and suggesting that rare variants mainly determine the functionality of hypertension pharmacogenes [79]. However, there have been few of these studies and more research based on NGS technologies is necessary to further understand hypertension pharmacogenomics and to fully leverage them for PHC [79].

3.3. Bioinformatics

The above examples underline the fundamental role played in PHC of the ability to process and analyze huge volumes of data, such as electronic medical records, in vivo imaging, genomics, and other "-omic" technologies [94, 99]. Millions of genetic polymorphisms are identified with NGS technology; but in order to find an association between a polymorphism and a phenotype, a large number of statistical tests have to be performed and then require correction for multiple testing [100]. A methodology was recently proposed for unified analysis of NGS data. A pipelined series of statistical and bioinformatics methods was used to analyze associations between genetic polymorphisms and a disease phenotype, using hypertension as the example, and to identify statistically significant pathways of genes that may play a role in the disease [100].

3.4. Epigenomics

Rather than just being affected by variations in the coding genome, epigenetic mechanisms, including microRNAs, histone modification, and methylation, are increasingly seen to play a role in the development of hypertension [101]. Non-coding areas of the human genome, which make up almost 99% of it, were long regarded as "junk DNA" [102]. In contrast, the Encyclopedia of DNA Elements (ENCODE) project has shown that non-coding DNA is a critical

element of gene function regulation across cell, tissue, and organ types [103, 104]. The ENCODE project systematically mapped regions of transcription, transcription factor association, chromatin structure, and histone modification, which enabled them to assign biochemical functions for 80% of the genome [103]. Regulatory elements, such as transcription-factor-binding sites, histone modification, chromatin structure, and DNA methylation, are highly cell-type specific. Those non-coding regions are extensively transcribed into non-coding RNAs, such as microRNAs and long-non-coding RNAs (lncRNA), with various functions including the influence of the pathophysiology of hypertension [102]. For example, micro-RNAs seem to be associated with hypertension via sympathetic nerve activity, ion transporters in the kidney, endothelial function, vascular smooth muscle phenotype transformation, and communication between cells [102]. In another study, expression levels of microRNAs implicated in vascular smooth muscle cell phenotypic modulation were assessed in patients with hypertension and healthy controls. Changes in vascular smooth muscle cells play a critical role in the pathophysiology of arterial remodeling in essential hypertension. Levels of hsa-miR-143, hsa-miR-145, and hsa-miR-133a were downregulated, and hsa-miR-21 and hsa-miR-1 upregulated in peripheral blood mononuclear cells of patients with hypertension compared with normotensive subjects [105]. There also seems to be potential for clinical use of non-coding RNAs to identify or treat patients with cardiovascular diseases [106, 107]. As non-coding RNAs are a relatively new field of research for hypertension, the number of supporting studies is small, and further research is needed [107].

3.5. Other "omic" studies and technologies

Despite the leading role of genomics, other new "omics" technologies have been developed that allow us to bridge between genotype and phenotype [92].

3.5.1. Transcriptomics and differential gene expression

Transcriptomic approaches allow us to study the complete set of RNA transcripts, for example, through microarray or RNA sequencing. Microarray chips can hold tens of thousands of genes and can be used to compare gene expression levels in certain disease states [108, 109]. However, our literature review did not reveal any transcriptome studies addressing PHC in essential hypertension.

3.5.2. Proteomics

Proteomics gives a snapshot of the proteins present at a given time in a cell or an organism and might help to reveal novel diagnostic and therapeutic approaches in hypertension. A study aiming to identify urinary proteins involved in the pathogenesis of hypertension and salt sensitivity revealed different uromodulin protein levels in individuals with hypertension versus healthy individuals [110]. Patients with higher levels of uromodulin were homozygotes for specific UMOD gene variants and displayed a decreased level of salt excretion [110]. Another study assessing the correlation between hypertension with γ-glutamyltransferase (GGT) and alanine aminotransferase (ALT) levels in a Chinese population revealed that elevated GGT was associated with hypertension but not ALT [111].

3.5.3. Metabolomics

Metabolomics studies the metabolites resulting from biochemical degradation processes and allows conclusions to be drawn on the prevalence of such processes. Several studies highlighted distinctions in the metabolic footprint of patients with hypertension and hence the potential in its analysis (e.g., through gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry) [112–114]. One study pointed out that the metabolic perturbation associated with alcohol abuse may contribute to the development of hypertension, probably by a shift in the ratio of the oxidized:reduced forms of nicotinamide adenine dinucleotide (NADH:NAD$^+$) [112]. Other results suggest that disorders in amino acid metabolism might play an important role in the pathogenesis of juvenile hypertension and circulating levels of uridine adenosine tetraphosphate are strongly associated with the disease [113, 115]. In another study, sex-steroid pattern was significantly associated with the risk of incident hypertension [116]. However, more clarity about the different metabolic influences is needed to translate these findings into clinical practice.

3.6. Importance of mobile technologies

With the omnipresence of new mobile technologies and connected devices, patient self-monitoring is becoming an increasingly important and promising topic across various diseases. Despite a large number of mobile apps and devices designed to track general health and well-being and also BP specifically [117], formal clinical research on such self-monitoring devices still seems to be limited. Some initial studies focused on patient education in patient-centered hypertension care [118, 119]. The FDA has cleared some mobile apps for BP and cardiac monitoring (e.g., the Withings BP Monitor) [120]. Initial studies dealing with patients' self-monitoring conclude that in order to motivate patients to self-manage their hypertension, engage with their devices, and communicate through them with health-care providers, it is crucial that the technology is both flexible and secure [119].

In the following chapter, we compare the content of important international guidelines regarding PHC in hypertension.

4. Guidelines on PHC in arterial hypertension

4.1. Status quo and guidance in hypertension on personalized medicine: hypertension guideline perspectives

In this section, we review the content of six international hypertension guidelines regarding evidence and recommendations on how to execute PHC in the management of high blood pressure. While the majority of guidelines still emphasize the importance of comprehensive PHC, only little evidence is displayed on detailed PHC. The guidelines reviewed here are summarized in **Table 4**.

Guideline	Specific condition	Treatment				Notes
		Initial	2nd line	3rd line	4th line	
ESC/ESH	**Asymptomatic organ damage**					
	LVH	ACE inhibitor, calcium antagonist, ARB				
	Asymptomatic atherosclerosis	Calcium antagonist, ACE inhibitor				
	Microalbuminuria	ACE inhibitor, ARB				
	Renal dysfunction	ACE inhibitor, ARB				
	Clinical CV event					
	Previous stroke	Any agent effectively lowering BP				
	Previous MI	BB, ACE inhibitor, ARB				
	Angina pectoris	BB, calcium antagonist				
	HF	Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists				
	Aortic aneurysm	BB				
	Atrial fibrillation, prevention	Consider ARB, ACE inhibitor, BB, or mineralocorticoid receptor antagonist				
	Atrial fibrillation, ventricular rate	BB, non-dihydropyridine calcium antagonist				
	ESRD/proteinuria	ACE inhibitor, ARB				
	Peripheral artery disease	ACE inhibitor, calcium antagonist				
	Other					
	Isolated systolic hypertension (elderly)	Diuretic, calcium antagonist				
	Metabolic syndrome	ACE inhibitor, ARB, calcium antagonist				
	Diabetes mellitus	ACE inhibitor, ARB				
	Pregnancy	Methyldopa, BB, calcium antagonist				
	Blacks	Diuretic, calcium antagonist				
JNC8	Nonblacks, including T2D	Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination				
	CKD ± diabetes, all races	Initiate ACE inhibitor or ARB, alone or in combination with other drug class				
	Blacks, including T2D	Initiate thiazide-type diuretic or CCB, alone or in combination				
CHEP 2015	Diastolic hypertension ± systolic hypertension (target BP <140/90 mmHg)	Thiazide/thiazide-like diuretics, BBs, ACE inhibitors, ARBs, or long-acting CCBs (consider ASA and statins in selected patients). Consider initiating therapy with a combination of first-line drugs if the BP is 20 Hg	Combinations of first-line drugs			Not recommended for monotherapy: α-blockers, BBs in those 60 years of age, ACE inhibitors in black people. Hypokalemia should be avoided in those prescribed diuretics. ACE inhibitors, ARBs, and direct renin inhibitors are

Guideline	Specific condition	Treatment				Notes
		Initial	2nd line	3rd line	4th line	
		systolic or 10 mmHg diastolic above target				potential teratogens, and caution is required if prescribing to women with child-bearing potential. Combination of an ACE inhibitor with an ARB is not recommended
	LVH (target BP <140/90 mmHg)	ACE inhibitor, ARB, long-acting CCB, or thiazide/thiazide-like diuretics	Combination of additional agents			Hydralazine and minoxidil should not be used
	Nondiabetic CKD (target BP <140/90 mmHg)					
	Renovascular disease	Does not affect initial treatment recommendations. Renal artery stenosis should be primarily managed medically	Combinations of additional agents			Caution with ACE inhibitors or ARB if bilateral renal artery stenosis or unilateral disease with solitary kidney. Renal artery angioplasty and stenting could be considered for patients with renal artery stenosis and complicated, uncontrolled hypertension
	Cardiovascular disease (target BP <140/90 mmHg)					
	Past stroke or TIA	ACE inhibitor and a thiazide/thiazide-like diuretic combination	Combination of additional agents			Treatment of hypertension should not be routinely undertaken in acute stroke unless extreme BP increase. Combination of an ACE inhibitor with an ARB is not recommended
	Recent MI	BBs and ACE inhibitors (ARBs if ACE inhibitor intolerant)	Long-acting CCBs if BB contraindicated or not effective			Nondihydropyridine CCBs should not be used with concomitant HF
	CAD	ACE inhibitors or ARBs; BBs for patients with stable angina	Long-acting CCBs. When combination therapy is being			Avoid short-acting nifedipine. Combination of an ACE inhibitor with an ARB is specifically not

Guideline	Specific condition	Treatment				Notes
		Initial	2nd line	3rd line	4th line	
			used for high-risk patients, an ACE inhibitor/dihydropyridine CCB is preferred			recommended. Exercise caution when lowering SBP to target if DBP is ≤ 60 mmHg
		For patients with stable angina, BBs are preferred as initial therapy (Grade B). CCBs may also be used (Grade B)				
	HF	ACE inhibitors (ARBs if ACE inhibitor intolerant) and BBs. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be added for patients with a recent cardiovascular hospitalization, acute MI, increased BNP or NT-proBNP level, or NYHA class II -IV symptoms	ACE inhibitor and ARB combined. Hydralazine/isosorbide dinitrate combination if ACE inhibitor and ARB contraindicated or not tolerated. Thiazide/thiazide-like or loop diuretics are recommended as additive therapy. Dihydropyridine CCB can also be used			Titrate doses of ACE inhibitors and ARBs to those used in clinical trials. Carefully monitor potassium and renal function if combining any of ACE inhibitor, ARB, and/ or aldosterone antagonist
	Nondiabetic CKD with proteinuria ** (target BP <140/90 mmHg)	ACE inhibitors (ARBs if ACE inhibitor-intolerant) if there is proteinuria, diuretics as additive therapy	Combinations of additional agents			Carefully monitor renal function and potassium for those receiving an ACE inhibitor or ARB. Combinations of an ACE inhibitor and ARB are not recommended in patients without proteinuria
	Peripheral arterial disease	Does not affect initial treatment recommendations	Combinations of additional agents			Avoid BBs with severe disease
	Isolated systolic hypertension without other compelling indications (target BP for age	Thiazide/thiazide-like diuretics, ARBs, or	Combinations of first-line drugs			Same as diastolic hypertension ± systolic

Guideline	Specific condition	Treatment				Notes
		Initial	2nd line	3rd line	4th line	
	<80 years is <140/90 mmHg; for age ≥ 80 years: target SBP is <150 mmHg)	long-acting dihydropyridine CCBs				hypertension
	Dyslipidemia	Does not affect initial treatment recommendations	Combinations of additional agents			
	Diabetes mellitus (target BP <130/80 mmHg) Diabetes mellitus with microalbuminuria,* renal disease, cardiovascular disease, or additional cardiovascular risk factors	ACE inhibitors or ARBs	Addition of a dihydropyridine CCB is preferred over a thiazide/thiazide-like diuretic			A loop diuretic could be considered in hypertensive CKD patients with extracellular fluid volume overload
	Diabetes mellitus not included in the above category	ACE inhibitors, ARBs, dihydropyridine CCBs or thiazide/ thiazide-like diuretics	Combination of first-line drugs. If combination with ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic			Normal urine microalbumin to creatinine ratio <2.0 mg/mmol
	Blacks	ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients				
	Overall vascular protection	Statin therapy for patients with 3 or more cardiovascular risk factors or atherosclerotic disease. Low-dose ASA in patients 50 years of age. Advise on smoking cessation and use pharmacotherapy for smoking cessation if indicated				Caution should be exercised with the ASA recommendation if BP is not controlled
NICE 2011	Aged <55 years, non-black: target BP below: 140/90 mmHg in people aged <80	Step 1: ACE inhibitor or ARB	Step 2: CCB in combination with	Step 3: Step 2 optimal or best	Step 4: Low-dose	BBs not preferred initial therapy, maybe in

Guideline	Specific condition	Treatment				Notes
		Initial	2nd line	3rd line	4th line	
	years (http://www.nice.org.uk/guidance/cg127)		ACE inhibitor or ARB	tolerated doses or combination of ACE inhibitor or ARB, CCB, and thiazide-like diuretic	spironolactone (25 mg/d) if blood potassium level ≤4.5 mmol/L; higher-dose thiazide-like diuretic if blood potassium level >4.5 mmol/L. If further diuretic therapy not tolerated, contraindicated, or ineffective: α-blocker or BB	younger people '... with intolerance or contraindication to ACE inhibitor or ARB '... women of child-bearing potential or '... increased sympathetic drive Initial therapy with BB + second drug CCB not thiazide-like diuretic reduce risk of developing diabetes NICE new evidence uncertainties: 'Different antihypertensive strategies in patients with diabetes, nephropathy and a history of MI for the treatment of hypertension and prevention of HF'
	Diabetes and kidney disease: BP target <130/80 mmHg (nice.org.uk/guidance/ng28, nice.org.uk/guidance/cg182)	RAS antagonist to: '- patients with CKD and diabetes and ACR ≥3 mg/mmol '- patients with CKD and hypertension and ACR ≥30 mg/mmol '- all patients with ACR ≥70 mg/mmol (irrespective of hypertension or CVD) In patients with CKD, hypertension and ACR <30 mg/mmol but no diabetes treat according to hypertension guidelines				Do not offer a combination of RAS antagonists to people with CKD [new 2014]
	Diabetes and cerebrovascular damage: BP target <130/80mmHg					

Guideline	Specific condition	Treatment				Notes
		Initial	2nd line	3rd line	4th line	
	(nice.org.uk/guidance/ng28) HF (nice.org.uk/guidance/cg108; http://www.nice.org.uk/guidance/cg127)	Amlodipine Step1: to people aged > 55 years and to black people of African or Caribbean family origin of any age. If there is edema or intolerance, or evidence of HF or a high risk of HF, offer a thiazide-like diuretic	If a CCB is not suitable for step 2 treatment, for example because of oedema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.			Verapamil, diltiazem or short-acting dihydropyridine agents should be avoided
	BP <140/80 mmHg (nice.org.uk/guidance/ng28)	ACE or if intolerant ARB African or Caribbean family origin ACE inhibitor + plus either diuretic or CCB.	CCB or diuretic (thiazide or thiazide-related diuretic)	Add the other drug (ie CCB or diuretic)	α-blocker, a BB or a potassium-sparing diuretic (caution if already taking ACE inhibitor or ARB)	not combine ACE inhibitor with ARB
	Women of child-bearing potential	BBs or see hypertension guidelines in specific situations (eg preeclampsia, diabetes (CCB) etc.) (nice.org.uk/guidance/cg107)				
	Black people of African or Caribbean family origin, age >55 years	CCB If CCB not suitable, eg edema or intolerance, HF, or high risk of HF: thiazide-like diuretic	Black people of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with CCB			
	Age >80 years: BP target 150/90 mmHg	same antihypertensive drug treatment as age >55 years, taking into account any				

Guideline	Specific condition	Treatment				Notes
		Initial	2nd line	3rd line	4th line	
AHA/ACC/CDC	Diabetes and eye: BP target <130/80 mmHg (nice.org.uk/guidance/ng28)	comorbidities				
	Systolic 140–159 or diastolic 90–99 mmHg	Thiazide	Thiazide for most patients or ACE inhibitor, ARB, CCB or combination	Optimize dosage or add medications		
	Systolic >160 or diastolic >100 mmHg	Thiazide and ACE inhibitor, ARB, or CCB or consider ACE inhibitor and CCB				
	Kidney disease	ACE inhibitor, ARB				
	Stroke and TIA	Thiazide, ACE inhibitor				
	CAD/post MI	BB, ACE inhibitor				
	Systolic HF	ACE inhibitor or ARB, BB, aldosterone antagonist, thiazide				
	Diastolic HF	ACE inhibitor or ARB, BB thiazide				
	Diabetes	ACE inhibitor or ARB, thiazide, BB				
ASH/ISH	Nonblack, stage 1, age <60 years	ACE inhibitor or ARB	CCB or thiazide	CCB + Thiazide + ACE inhibitor or (ARB)	spironolactone, centrally acting agents, BBs	
	Stage 2	Start with 2 drugs: CCB or thiazide + ACE inhibitor or ARB		CCB + thiazide + ACE inhibitor or (ARB)	spironolactone, centrally acting agents, BBs	
	CAD	BB + ACE inhibitor or ARB	CCB or thiazide	CCB or thiazide		
	Stroke	ACE inhibitor or ARB	Thiazide or CCB	CCB or thiazide		
	HF	ACE inhibitor or ARB + BB + diuretic + spironolactone regardless of BP	Dihydropyridine CCB			
	CKD	ACE inhibitor or ARB, in blacks ACE inhibitor	CCB or thiazide	Thiazide or CCB		
	Diabetes	ARB or ACE inhibitor, in blacks CCB or thiazide	CCB or thiazide, in blacks ACE inhibitor or ARB	Thiazide or CCB		
	Blacks, stage 1, all ages	CCB or thiazide	ACE inhibitor or ARB or combine CCB + thiazide	CCB + thiazide + ACE inhibitor or (ARB)	spironolactone, centrally acting agents, BBs	
	Non-black, age ≥60 years	CCB or thiazide	ACE inhibitor or ARB	CCB + thiazide + ACE inhibitor or (ARB)	spironolactone, centrally acting agents, BBs	

*Microalbuminuria defined as persistent ACR > 2.0 mg/mmol;** Proteinuria defined as urinary protein > 500 mg per 24 hours or ACR > 30 mg/mmol in 2 of 3 specimens. ACC = American College of Cardiology; ACE = angiotensin-converting enzyme; ACR = albumin:creatinine ratio; AHA = American Heart Association; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; ASH = American Society of Hypertension; BB = β-blocker; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CDC = Centers for Disease Control and Prevention; CHEP = Canadian Hypertension Education Program; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; ESRD = end-stage renal disease; ESC = European Society of Cardiology; ESH = European Society of Hypertension; HF = heart failure; ISH = International Society of Hypertension; JNC = Joint National Committee; LVH = left ventricular hypertrophy; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; RAS = renin–angiotensin system; T2D = type 2 diabetes; TIA = transient ischemic attack.

Table 4. Summary of hypertension treatment guidelines.

4.1.1. European Society of Cardiology/European Society of Hypertension

The European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines [121] categorize patients with hypertension according to their BP, medical history, physical

examination, and laboratory parameters. The ESC/ESH guideline recommends that physicians detect causes of secondary hypertension, record cardiovascular risk factors, and identify other cardiovascular diseases. It further advises the evaluation of familial (genetic) predisposition to hypertension and cardiovascular disease and alludes to 29 SNPs that are associated with systolic and/or diastolic BP and could be useful contributors to risk scores for organ damage. Methodologies to detect asymptomatic organ damage in the individual patient are described. The focus for the heart is on left ventricular hypertrophy; for the vessels, it is on arterial stiffness and carotid plaque load; for kidney function, on glomerular filtration rate and the existence of established renal parenchymatous disease on proteinuria. For the brain, the guidelines refer to silent infarctions, white matter hyperintensities, and microbleeds.

In general, the ESC/ESH guideline concludes that the main benefits of antihypertensive treatment are due to lowering of BP per se and are largely independent of the drugs employed. Thus, all drug classes are suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in combination. The guideline discusses the hypotheses behind BP recommendations (i.e., the "lower the better" vs. J-shaped curve theories) and suggests that targeted BP will have to be revisited with additional data concerning associated organ damage and evaluating different end points (left ventricular hypertrophy, new-onset microalbuminuria, renal failure, cardiovascular events, etc.). Despite this uncertainty, the ESC/ESH guideline recommends continued monitoring for asymptomatic organ damage. It suggests therapy stratification of antihypertensive drugs for specific conditions and organ damage types (e.g., with some organ damage certain hypertension medications are discouraged because of contraindications, while others are recommended, as they show a greater effectiveness). Monitoring of end-organ damage with (bio)markers (e.g., serum creatinine level, electrocardiograph, echocardiograph, ankle-brachial index, etc.) to detect regression with treatment, progression of hypertension-dependent abnormalities, as well as the appearance of conditions requiring additional therapeutic interventions (such as arrhythmias, myocardial ischemia, stenotic plaques, and heart failure) is valued in the ESC/ESH guidelines. Further detail is given on the combinatory possibilities of the drug classes.

4.1.2. US Eighth Joint National Committee

The US Eighth Joint National Committee (JNC8) guideline [122] presents an evidence-based approach for the management of hypertension in adults to recommend treatment thresholds, goals, and medications. JNC8 stratifies its blood-pressure-lowering therapy recommendations based on age, ethnicity (black vs. non-black), diabetes, and chronic kidney disease (CKD).

JNC8 gives eight recommendations based on systematic review of the literature. A ninth recommendation was developed by the panel members based on expert opinion to aid physicians in implementing JNC8. It includes an algorithm summarizing recommendations 1–8 and advice on combining antihypertensive drugs. JNC8 acknowledges that recommendation 9 has not been validated with respect to achieving improved patient outcomes and there will likely be no supporting evidence from well-designed randomized controlled trials.

The JNC8 dosing regimen proposes three strategies:

- Start one drug, titrate to maximum dose, and then add a second drug.

- Start one drug and then add a second drug before achieving maximum dose of the initial drug.

- Begin with two drugs at the same time, either as two separate pills or as a single pill combination.

If BP goals are not achieved, then JNC8 urges that second and third drugs are added from the list. Continuous monitoring of BP is advised to adjust the treatment regimen until target BP is reached. The combination of an ACEi and angiotensin receptor blocker should not be used. If an antihypertensive drug is not effective in a specific situation or has an adverse effect, it can be replaced.

4.1.3. Canadian Hypertension Education Program guideline

The Canadian Hypertension Education Program (CHEP) treatment guidelines [123] provide recommendations for the indication of drug therapy, therapy goals, and detailed patient categorization according to their organ damage or comorbidities. For individuals with diastolic and/or systolic hypertension, no rigid specification is provided for initial therapy. The physician can chose from β-blocker, thiazide/thiazide-like diuretic, long-acting calcium channel blocker (CCB), or ACEi/ARB taking into consideration patient age (β-blocker only in patients aged <60 years) and ethnicity (ACEi in non-black patients).

In isolated hypertension, β-blockers are no longer part of first-line therapy if patients are aged ≥60 years.

In general, the CHEP guideline recommends global vascular protection therapy for adults with hypertension without compelling indications for specific agents, including statin therapy in hypertensive patients with ≥3 cardiovascular risk factors and acetylsalicylic acid therapy in hypertensive patients aged ≥50 years.

Additional hypertension treatment categories are ischemic heart disease (coronary artery disease or a recent myocardial infarction), heart failure, stroke (acute and non-acute management), left ventricular hypertrophy, non-diabetic CKD, renovascular disease, and diabetes mellitus. The specific and detailed BP targets and pharmacological recommendations specifying initial therapy, second-line therapy, and notes and/or cautions for hypertension are summarized.

4.1.4. UK National Institute for Health and Care Excellence hypertension guideline

The UK National Institute for Health and Care Excellence (NICE) hypertension guideline (http://www.nice.org.uk/guidance/cg127) uses patient age as the starting point for their recommendations, with treatment escalation in a stepwise fashion if BP is not adequately controlled. If the patient is aged <55 years, step 1 antihypertensive treatment is an ACEi or a low-cost ARB. In patients aged ≥55 and black people of African or Caribbean family origin of

any age, NICE recommends a CCB. A thiazide-like diuretic (chlorthalidone, indapamide) can be selected instead of a CCB if the patients present with edema, intolerance, heart failure, or a high risk of heart failure.

In step 2, NICE recommends the addition of a CCB to the ACEi or ARB. Alternatively, a thiazide-like diuretic can be used. In step 3, the combination of ACEi (ARB), CCB, and thiazide-like diuretic should be used. Resistant hypertension is treated at step 4 by adding diuretics (low-dose spironolactone, higher-dose thiazide-like diuretic) or a β-blocker or an α-blocker to the treatment regimen.

NICE recommends that patients aged ≥80 years should receive the same antihypertensive regimen as people aged >55, taking into account any comorbidities. Patients with isolated systolic hypertension (systolic BP ≥160 mmHg) should be treated with the same regimen as those with both raised systolic and diastolic BP. β-Blockers are not preferred for initial therapy in hypertension, but could be considered in younger patients with evidence of increased sympathetic drive, intolerance, or contraindication to ACEi and ARB, or for women of child-bearing potential. If β-blockers are required, then a CCB rather than a thiazide-like diuretic should be added to reduce the risk of developing diabetes.

BP targets and therapy recommendations for hypertensive patients with diabetes and/or CKD are not given in the NICE hypertension guideline but appear separately in the NICE guidelines for type 2 diabetes (NG28; http://www.nice.org.uk/guidance/ng28) and CKD (CG182; chronic-kidney-disease-in-adults-assessment-and-management-35109809343205). Since publication of the hypertension guidelines in 2011, there has been an evidence update (https://www.nice.org.uk/guidance/cg127/evidence/evidence-update-248584429).

In brief, current NICE treatment recommendations for patients with diabetes (http://www.nice.org.uk/guidance/ng28) comprise first-line treatment with an ACEi or an ARB. If the patient is of African or Caribbean family origin, an ACEi/ARB should be combined with a diuretic or a CCB. Second and third steps could be a CCB and/or a diuretic. BP targets are 140/80 mmHg (or 130/80 mmHg if there is kidney, eye, or cerebrovascular damage). Patients with CKD (albumin:creatinine ratio (ACR) ≥30 mg/mmol) and hypertension should be started on an ACEi/ARB. Patients with CKD and an ACR <30 mg/mmol and no diabetes should follow NICE hypertension guideline recommendations (http://www.nice.org.uk/guidance/cg182). Patients with diabetes and an ACR ≥3 mg/mmol or an ACR ≥70 mg/mmol (irrespective of hypertension or cardiovascular disease) should also be treated with an ACEi/ARB. In patients with CKD, target systolic BP should be <140 mmHg and diastolic <90 mmHg (unless they also have diabetes, see above).

4.1.5. American Heart Association/American College of Cardiology/Centers for Disease Control and Prevention treatment algorithm

The AHA, American College of Cardiology, and CDC hypertension management algorithm recommends stratifying treatment according to hypertension stages [124]. Patients with stage 1 hypertension should start with lifestyle modification and treatment with a thiazide diuretic should be considered. Patients with stage 2 hypertension should immediately start a thiazide

with either an ACEi or ARB or a CCB. Alternatively, an ACEi and CCB combination could also be used. If BP cannot be controlled, they recommend a thiazide for most patients or an ACEi, ARB, or a CCB, or a combination. The next treatment step involves using the highest tolerated dose or adding another antihypertensive.

The AHA/ACC/CDC algorithm recommends different medications depending on the medical conditions associated with hypertension as follows:

- Coronary artery disease/post-myocardial infarction: β-blockers, ACEi.

- Systolic heart failure: ACEi or ARB, β-blockers, aldosterone receptor blocker, thiazide.

- Diastolic heart failure: ACEi or ARB, β-blockers, thiazide.

- Diabetes: ACEi or ARB, thiazide, β-blockers, CCB.

- Kidney disease: ACEi or ARB.

- Stroke or transient ischemic attack: thiazide, ACEi.

4.1.6. American Society of Hypertension/International Society of Hypertension clinical practice guidelines

In the American Society of Hypertension and International Society of Hypertension clinical practice guidelines, the BP targets are defined according to age and comorbidities [125]. The target is 140/90 mmHg in the general hypertensive population. In older patients (aged >80 years), the goal is <150/90 mmHg unless these patients have CKD or diabetes, in which case <140/90 mmHg can be considered. With most patients requiring more than one drug, the increase of the dose and/or adding a new drug to achieve BP control is required. If the untreated BP is ≥20/10 mmHg above the target BP, treatment should be started with two drugs simultaneously. The choice of drug is dependent on age, ethnicity/race, and other clinical characteristics and comorbid conditions (e.g., diabetes, coronary artery disease, etc.) of the patient.

4.2. Government health agencies' perspectives on personalized medicine

The European Health Research Directorate of the European Commission defined PHC as a medical model using molecular profiling for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention with fewer side effects. In support of the 2020 vision for PHC in Europe, the Health Research Directorate of the European Commission started with a series of four preparatory workshops (http://ec.europa.eu/research/health/pdf/towards-personalised-medicine-leaflet_en.pdf; http://ec.europa.eu/research/health/index.cfm?pg=policy&policyname=personalised, PerMed: http://www.permed2020.eu/) on personalized medicine covering

- The role of "-omics" technologies for personalized medicine (http://ec.europa.eu/research/health/pdf/summary-report-omics-for-personalised-medicine-workshop_en.pdf).

- Stratification biomarkers (http://ec.europa.eu/research/health/pdf/biomarkers-for-patient-stratification_en.pdf).

- Clinical trials and regulatory aspects.

- Opportunities and challenges for European health care (http://ec.europa.eu/research/ health/pdf/13th-european-health-forum-workshop-report_en.pdf).

This was followed by a conference entitled "European Perspectives in Personalized Medicine" in 2011, acknowledging the huge potential for PHC and the multitude of challenges (http:// ec.europa.eu/research/health/pdf/personalised-medicine-conference-report_en.pdf). In 2013, the Commission developed a staff working document on "-omics" technologies in PHC (http:// ec.europa.eu/research/health/pdf/2013-10_personalised_medicine_en.pdf). In 2014, an additional workshop for Regulatory Aspects and Early Dialogue EHFG Forum 4 "Personalised Medicine 2020" – October 2, 2014, Bad Hofgastein, Austria (http://www.permed2020.eu/ _media/2_EMA_02-10-14_Ehmann.pdf), was held.

As part of the Horizon 2020 program, a call for a proposal has been issued for "Coordinating personalized medicine research" (http://ec.europa.eu/research/participants/portal/ desktop/en/opportunities/h2020/topics/2449-sc1-hco-05-2016.html). Thus, the European Commission attributes great importance to the topic of PHC in general.

Expectations regarding potential benefits for patients, clinicians, and health-care systems are as follows:

- Ability to make better-informed medical decisions,

- Higher probability of desired outcomes owing to better-targeted therapies,

- Reduced probability of adverse reactions to medicines,

- Focus on the prevention and prediction of disease rather than on reaction to it,

- Earlier disease intervention than has been possible in the past, and

- Improved health-care cost containment.

4.3. Assessment of guideline content

Although some therapy guidance is provided by the guidelines, the method of selection for antihypertensive therapy is largely empirical [126] and an individual cardiovascular and renal event risk assessment is yet not possible. In the various guidelines, different approaches have been taken to stratify patients and integrate BP with either age and ethnicity or other risk factors. Some guidelines (e.g., NICE) focused primarily on the age and ethnicity most likely associated with differences in plasma renin activity, while others provide specific recommendations to integrate different asymptomatic organ damage, metabolic conditions, and cardiovascular and renal comorbidities to establish an individual patient regimen (e.g., CHEP 2015). This approach is based on the finding that BP reduction is not considered to be the only mechanism acting to reduce cardiovascular risk, as BP-independent, probably class-specific effects seem to contribute to the effects of risk reduction with BP-lowering drugs. In a recent meta-analysis, the evidence of risk reduction for congestive heart disease and heart failure, and particularly mortality, was found with some drug classes only [127].

There are efforts to understand the molecular underpinnings of BP regulation. The hope is that this will improve the prediction of cardiovascular susceptibility and thus could in the future offer insight into personalized hypertension treatment. As hypertension is a difficult phenotype to access, owing to its variability and susceptibility to other environmental factors and physiological pathways, another approach could be to search for predictors of antihypertensive drug responses. If robust predictors of BP response are available, therapy stratification will be feasible, which could facilitate treatment success.

The available data on genetic markers have been promising in terms of defining genetic determinants of response to antihypertensive drugs. However, no studies to date have been sufficiently powered with an effect size large enough to allow genetic markers of antihypertensive drug responses to be included in the guidelines to inform individualized antihypertensive treatment decisions. Despite a lack of pharmacogenomics for personalized antihypertension treatment-guided approaches, Clinical Pharmacogenetics Implementation Consortium guidelines [128] are available for other cardiovascular drugs (i.e., clopidogrel [129], warfarin [130], and simvastatin [131]).

To overcome the challenges (small sample sizes in available studies with well-characterized BP responses and genetic data, replication of genomic signals in independent cohorts, identification of the biological basis for the genetic association, etc.), the International Consortium for Antihypertensive Pharmacogenomics Studies was formed in 2012. In addition, the US President Barack Obama has announced a research initiative that aims to accelerate progress toward a new era of precision medicine ([132], www.whitehouse.gov/precisionmedicine) and the National Institutes of Health and other partners are implementing this vision (http://www.nih.gov/precision-medicine-initiative-cohort-program).

5. PHC from a physician's perspective

Despite advances in research and technologies, the PHC concept is still new for a number of physicians and it remains unclear how quickly the adoption of PHC into routine practice will occur.

5.1. Warfarin and statins: a field study on genetic testing

There is wide variation in inter-individual responses to anticoagulants, such as clopidogrel, as well as to statin therapy with underlying genetic differences assumed to be responsible [133, 134]. In fact, of patients with an acute myocardial infarction treated with clopidogrel, those carrying CYP2C19 loss-of-function alleles had a higher rate of subsequent cardiovascular events than non-carriers of that allele [135]. The FDA even published a black-box warning regarding clopidogrel administration, as 2–14% of the population are poor CYP2C19 metabolizers and hence require alternative clopidogrel dosing in order to effectively prevent clotting, heart attacks, and strokes [136].

Also for the target molecule of statins, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, it is known that, compared with individual homozygous for the major allele of one of the SNPs,

individuals with a single copy of the minor allele had up to 22% less reduction in total cholesterol levels [133].

Genetic screening to guide selection of anticoagulation and lipid-lowering therapy has been limited to date, because solid clinical data to support its use are not yet available [133, 137, 138]. However, it is believed that the formal integration of genetic testing to optimize warfarin dosage would reduce over- or under-coagulation of patients. In the US alone, optimal coagulation has been estimated to translate into an annual reduction of 85,000 serious bleeding events and 17,000 strokes, leading to a reduction in health-care spending of about $1.1 billion [139]. In order to investigate the current use and evolution of genetic testing in clinical practice, interviews with cardiologists in the USA and Germany have recently been conducted.

In a substudy of a recently published analysis [140], we interviewed 39 cardiologists in private practices, community hospitals, and academic centers in the USA and Germany about their use of genetic testing for diagnosis and treatment, and treatment guidance. Physicians were initially asked about how frequently they order genetic (genotyping) tests for cardiovascular risk factors in patients with heart failure: (i) before prescribing warfarin or clopidogrel and (ii) before prescribing statin drugs or hydralazine. They were also asked (iii) how frequently they order genetic tests to diagnose or assess the risk of long QT syndrome and various cardio-myopathies or to monitor transplant rejection in heart-transplant patients. In conclusion, the cardiologists were asked (iv) how they expect the use of personalized medicine tests to change in the area of heart failure and hypertension. These interviews were conducted by three neutral, interview-experienced researchers employed by Enterprise Analysis Corporation (EAC; Stamford, CT, USA), all of whom had strong diagnostic knowledge (one MD, one PhD, and one BS, MBA).

The results of our interviews are summarized in **Table 5** and **Figure 3**. Only one US cardiologist routinely ordered genotyping tests to determine patient response to clopidogrel or warfarin. The majority of interviewees indicated that they never or rarely ordered these tests in cases of non-response to treatment, with numbers being close to equal in the USA and Germany. Functional thrombocyte tests were ordered as they were reimbursed. In the case of statins, only one cardiologist in the USA and two in Germany ordered genetic tests frequently for all patients to assess responsiveness to statin drugs or for inheritance of familial hypercholesterolemia. About 10% of interviewees ordered these tests occasionally but more than 80% never or rarely ordered these types of tests. Limited clinical benefit, cost, and reimbursement were mentioned as the main reasons for not using these tests. Although patients with cardiomyopathies, such as long QT syndrome, and transplant patients, were rare compared with anticoagulation patients, physicians seem to be aware of the genetic tests that have been developed for those conditions. Fifteen percent of the physicians mentioned that they ordered these genetic tests occasionally when they see such a case, but 44% said that they never ordered these tests. Physicians in private practice often indicated that they referred their patients to an academic center for specialized evaluation.

	never	rarely	occasionally	frequently	all patients	total
Warfarin / Plavix						
Germany	12 (60%)	7 (35%)	1 (5%)	0 (0%)	0 (0%)	20 (100%)
USA	10 (53%)	7 (37%)	1 (5%)	0 (0%)	1 (5%)	19 (100%)
Total	**22 (56%)**	**14 (36%)**	**2 (5%)**	**0 (0%)**	**1 (3%)**	**39 (100%)**
Statins						
Germany	10 (50%)	6 (30%)	2 (10%)	1 (5%)	1 (5%)	20 (100%)
USA	10 (53%)	6 (32%)	2 (10%)	0 (0%)	1 (5%)	19 (100%)
Total	**20 (51%)**	**12 (31%)**	**4 (10%)**	**1 (3%)**	**2 (5%)**	**39 (100%)**
Cardiomyopathies / long QT						
Germany	9 (45%)	4 (20%)	3 (15%)	2 (10%)	2 (10%)	20 (100%)
USA	8 (42%)	6 (32%)	3 (16%)	2 (10%)	0 (0%)	19 (100%)
Total	**17 (44%)**	**10 (26%)**	**6 (15%)**	**4 (10%)**	**2 (5%)**	**39 (100%)**

Table 5. Physician responses concerning the use of genetic testing for warfarin/clopidogrel prescription, statin prescription, and in cardiomyopathies such as long QT syndrome.

Legend:

GER = Germany, USA = United States of America,

Filling:

Black: never, black with white dots: rarely, horizontal stripes: occasionally, diagonal stripes: frequently, white with black dots: all patients
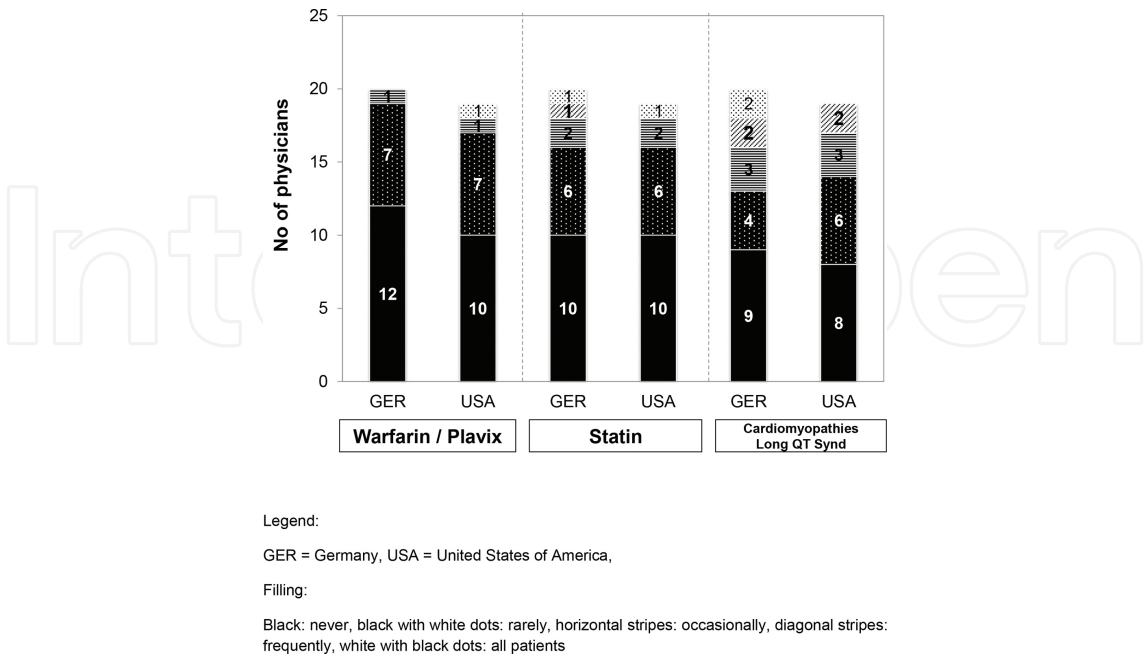
Figure 3. Physicians' responses concerning the use of genetic tests in cardiology.

Despite the fact that currently most cardiologists barely use PHC tests, most believe that the use of such tests will increase over the next decade. In the USA, 89% anticipate growth in the use of these tests, with 37% expecting a slight, 47% a moderate, and 5% a substantial growth. In Germany, 85% of physicians predict an increased usage of personalized medicine in cardiology, with 20% expecting a substantial, 60% a moderate, and 5% a slight growth. Only 15% of the German cardiologists and 11% of the US cardiologists do not anticipate any change in the use of these tests (see **Table 6**).

Country	Expected change, No. of responses (%)			
	Substantial	Moderate	Slight	No change
Germany (n=20)	4	12	1	3
	(20%)	(60%)	(5%)	(15%)
USA (n=19)	1	9	7	2
	(5%)	(47%)	(37%)	(11%)
Total (n=39)	**5**	**21**	**8**	**5**
	(13%)	**(54%)**	**(21%)**	**(13%)**

Table 6. Expected change in the use of personalized medicine in cardiology.

Despite the fact that the concept of personalized medicine has been discussed in cardiology for over a decade, our study has confirmed that there is still no regular use of genetic tests for pharmacogenomic-guided treatment in cardiovascular disease [139]. Although cardiologists are known to order general in vitro diagnostic (IVD) tests in 60% of their consultations with the results of these tests influencing diagnosis or treatment decisions in 70% of cases [140], the use of genetic testing is still rare in routine cardiology. Our study has shown that only one to three cardiologists out of 39 ordered genetic tests on a regular basis before prescribing anticoagulation or statins. For long QT syndrome and other rare cardiomyopathies, physicians indicated more frequent use of genetic testing, with 15% of cardiologists using them occasionally.

One reason for the limited use of genetic testing for pharmacogenomics in cardiology seems to be a lack of sufficient clinical evidence. Physicians often indicate that there is no adequate benefit to be gained from these tests, which has been mentioned in earlier studies [139]. Even though newer studies have demonstrated the value of genetic testing (e.g., identifying CYP2C19*2 carriers for antiplatelet treatment with prasugrel rather than with clopidogrel to reduce high on-treatment platelet reactivity after percutaneous coronary intervention [141]), larger clinical utility studies might be needed. Another reason stated by the physicians is the cost of these tests or the lack of reimbursement. Both reasons highlight little awareness of the value of genetic testing in terms of economic benefits, which would equal clinical utility and cost-effectiveness [142]. This indicates that more studies are needed to generate clinical evidence and proof of economic value for genetic testing in patients with cardiovascular diseases.

To showcase a successful example of how PHC is used in a sub-entity of HT, the next chapter focuses on the development of the sFlt-1/PlGF ratio, used to guide treatment decisions in patients with preeclampsia. Despite being a secondary form of hypertension, its prevalence is associated with the existence of chronic hypertension in women. While in the general population the risk of preeclampsia is 3–5%, around 17–25% of women with chronic hypertension develop superimposed preeclampsia [143].

6. PHC in preeclampsia

6.1. Hypertension in pregnancy

Hypertension is the most common complication of pregnancy [144]. Although many pregnant women with high BP have healthy babies, hypertension during pregnancy can be dangerous for both mother and fetus. Hypertensive disorders of pregnancy can be classified as follows: (a) chronic hypertension (high BP that either precedes pregnancy, is diagnosed within the first 20 weeks of pregnancy, or does not resolve by the 12-week postpartum checkup), (b) gestational hypertension (transient hypertension of pregnancy or chronic hypertension identified in the latter half of pregnancy), (c) preeclampsia-eclampsia, or (d) preeclampsia superimposed on chronic hypertension [144]. Effects of high BP range from mild to very severe, with serious cases causing maternal and fetal harm. Preeclampsia and eclampsia, in particular, can be life-threatening for mother and baby.

6.2. What is preeclampsia?

Preeclampsia is a heterogeneous, multi-organ disorder, which affects 3–5% of pregnancies worldwide and is a leading cause of maternal death [145–148]. It is associated with placental dysfunction and can result in adverse outcomes for mother and child. Maternal adverse outcomes include eclampsia (seizures), HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), early delivery, placental abruption, renal failure, and death [149–151]. Adverse outcomes for the child include intrauterine growth restriction (IUGR), intraventricular hemorrhage, necrotizing enterocolitis, and perinatal death.

The clinical features of preeclampsia are often variable and non-specific. Hypertension is often present, and is associated with convulsions and other severe cerebral manifestations, but it is not easily differentiated from gestational hypertension or undiagnosed pre-existing chronic hypertension. Other signs include headache, proteinuria, visual disturbances, abdominal pain, edema, sudden weight gain, and vomiting. It is difficult to predict which women who present with these signs and symptoms during pregnancy will develop preeclampsia. There has been an unmet medical need to improve current predictive tools in order to better tailor the provision of specialized management and care to those women who require it.

6.3. Management of preeclampsia

Currently, there is no cure for preeclampsia, other than delivery of the baby. Available pharmacological interventions are limited and are generally aimed at treating the complications of the syndrome. Such treatments include anticonvulsive medication (magnesium sulfate [152]) and antihypertensive medications (e.g., labetalol), and the use of corticosteroids to promote fetal lung maturation ahead of preterm delivery. Clinical experience suggests that early detection, monitoring, and supportive care are important to improve maternal and fetal outcomes in this progressive syndrome, by allowing expeditious decision making and referral to specialist perinatal care centers [153–155]. This requires a reliable model of preeclampsia prediction in order to appropriately tailor management plans.

6.4. Clinical benefits of preeclampsia prediction: tailoring health care

The use of a clinical measurement (a biomarker) for the prediction of preeclampsia in women with signs of preeclampsia could facilitate PHC, and ensure that the right patients are identified for monitoring, for referral to specialist perinatal centers (if required), and to receive appropriate interventions. Furthermore, the ability to accurately rule out a diagnosis of preeclampsia could help prevent unnecessary hospitalization and the emotional stress for patients and their families that this entails. Targeted monitoring and management could also provide economic benefits for health-care providers, by reducing the level of monitoring required for those women unlikely to develop the syndrome. Advances in the understanding of preeclampsia pathogenesis have enabled the identification of potential biomarkers.

6.5. Pathology of preeclampsia

Historically, preeclampsia was defined by the new onset of hypertension and proteinuria during pregnancy. However, the definition of preeclampsia has recently been revised to include women with new-onset hypertension without new-onset proteinuria, provided that there are other new-onset manifestations (e.g., IUGR or maternal renal, hepatic, or neurologic dysfunction) [156]. In fact, preeclampsia is part of a wider spectrum of conditions, which involve placental dysfunction, decreased perfusion of the placenta, and inflammation (**Figure 4**).

In preeclampsia, incomplete remodeling of maternal spiral arteries can lead to intermittent placental hypoperfusion and oxidative stress, which in turn leads to an exaggerated maternal inflammatory response [157]. Immune factors (e.g., AT1-AA), oxidative stress, natural killer cell abnormalities, and other factors may cause placental dysfunction, leading to the release of anti-angiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sENG). Conversely, circulating maternal serum concentrations of pro-angiogenic placental growth factor (PlGF) are decreased (relative to normotensive pregnancies) [157]. This angiogenic imbalance is thought to cause vasoconstriction and generalized endothelial dysfunction, which may lead to preeclampsia and fetal growth restriction [158–160]. PlGF has been investigated as a potential diagnostic and predictive biomarker for preeclampsia [161–163]. The ratio of circulating maternal serum levels of sFlt-1 and PlGF has also been proposed as an

indicator of preeclampsia; a high sFlt-1/PlGF ratio is associated with an increased risk of preeclampsia [164–170], and the ratio is elevated in pregnant women 4–5 weeks before the clinical onset of preeclampsia [166]. There has been evidence to suggest that the sFlt-1/PlGF ratio (which reflects the in situ balance of an anti-angiogenic factor and a pro-angiogenic factor) may be a better indicator of preeclampsia than either sFlt-1 or PlGF alone [171].
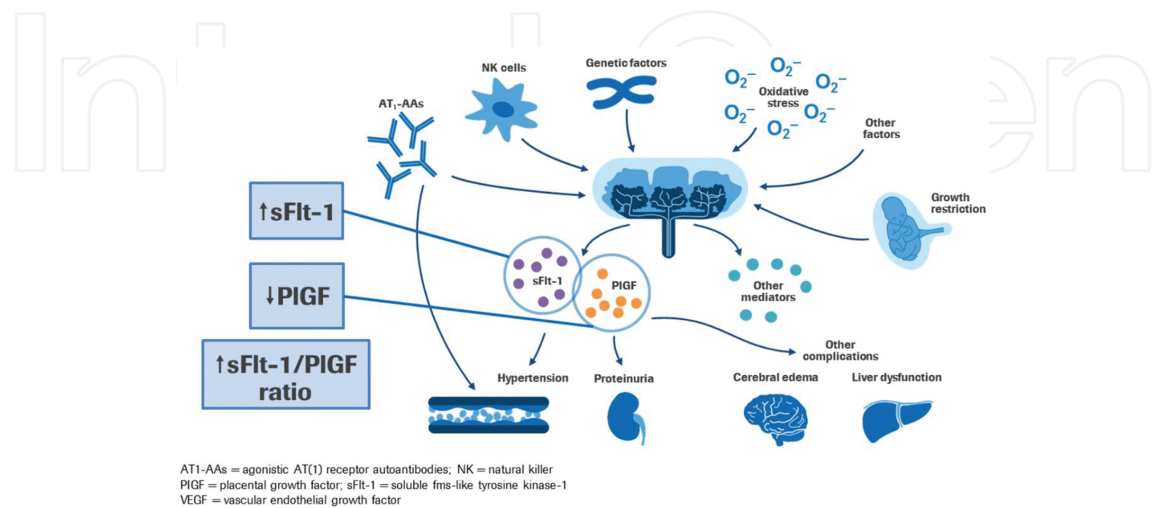

AT1-AAs = agonistic AT(1) receptor autoantibodies; NK = natural killer
PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1
VEGF = vascular endothelial growth factor

Figure 4. Pathophysiological features of preeclampsia (adapted from Wang A, Rana S, Karumanchi SA. Preeclampsia: the role of angiogenic factors in its pathogenesis. Physiology [Bethesda]. 2009;24:147–158).

6.6. Measurement of sFlt-1, PlGF, and the sFlt-1/PlGF ratio

There are a variety of commercially available tests for PlGF, which include the Elecsys® PlGF immunoassay (cobas e platform; Roche Diagnostics, Mannheim, Germany, **Table 7** [172]), Triage® PlGF test (Alere International, Waltham, MA) [173], DELFIA® Xpress PlGF 1-2-3 test (Perkin Elmer, Waltham, MA) [162, 163], and the BRAHMS PlGF Kryptor™ (Thermo Fisher Scientific, Waltham, MA) [174]. There are two sFlt-1 assays available: the Elecsys®sFlt-1 (cobas e platform; Roche Diagnostics) and the BRAHMS sFlt-1 Kryptor™ (Thermo Fisher Scientific) [175]). These are automated assays that use maternal serum.

	Elecsys® sFlt-1	**Elecsys® PlGF**
Assay time	18 min	18 min
Sample material	Serum	Serum
Sample volume	20 μL	50 μL
Detection limit	Approx. 6 pg/ml	< 2 pg/ml
Measuring range	10–85 000 pg/ml	3–10 000 pg/ml
Imprecision	< 5%	< 5%

Table 7. Product characteristics of the Elecsys® sFlt-1 and PlGF assays [172, 175].

The sFlt-1/PlGF ratio can be calculated using the Roche Elecsys® test or the BRAHMS Kryptor™ assays. It is important to note that the testing methods from different companies are not interchangeable, and the cutoff levels established with a one-assay ratio are not applicable to the other assays.

6.7. PlGF and the sFlt-1/PlGF for preeclampsia diagnosis

An Alere Triage® PlGF level of <36 pg/mL supports a diagnosis of preeclampsia [173]. In a method comparison study the Elecsys® immunoassay sFlt-1/PlGF ratio showed improved diagnostic utility over the Triage® PlGF assay with improved specificity as a diagnostic aid of preeclampsia [176].

For the Elecsys® sFlt-1/PlGF ratio, the reference median values during an uneventful pregnancy have been published (**Figure 5**). The analysis of elevated Elecsys® sFlt-1/PlGF ratios in women with preeclampsia has been used to establish recommended cutoff levels for preeclampsia diagnosis by gestational age [177]. For the early gestational phase (week 20 + 0 days to week 33 + 6 days), women with an sFlt-1/PlGF ratio of ≤33 had the lowest likelihood of a positive preeclampsia diagnosis (sensitivity/specificity of the test: 95/94%), and women with a ratio of ≥85 had the highest likelihood of a positive preeclampsia diagnosis (sensitivity/specificity: 88/99.5%). For the late gestational phase (week 34 to delivery), a cutoff of ≤33 to rule out diagnosis and a cutoff of ≥110 to rule in diagnosis has been recommended (sensitivity/specificity of 89.6/73.1% and 58.2/95.5%, respectively) [172, 175]. The Elecsys® sFlt-1/PlGF ratio is CE-IVD (Conformité Européenne–In Vitro Diagnostics) approved for use as an aid in the diagnosis of preeclampsia in conjunction with other diagnostic and clinical information.
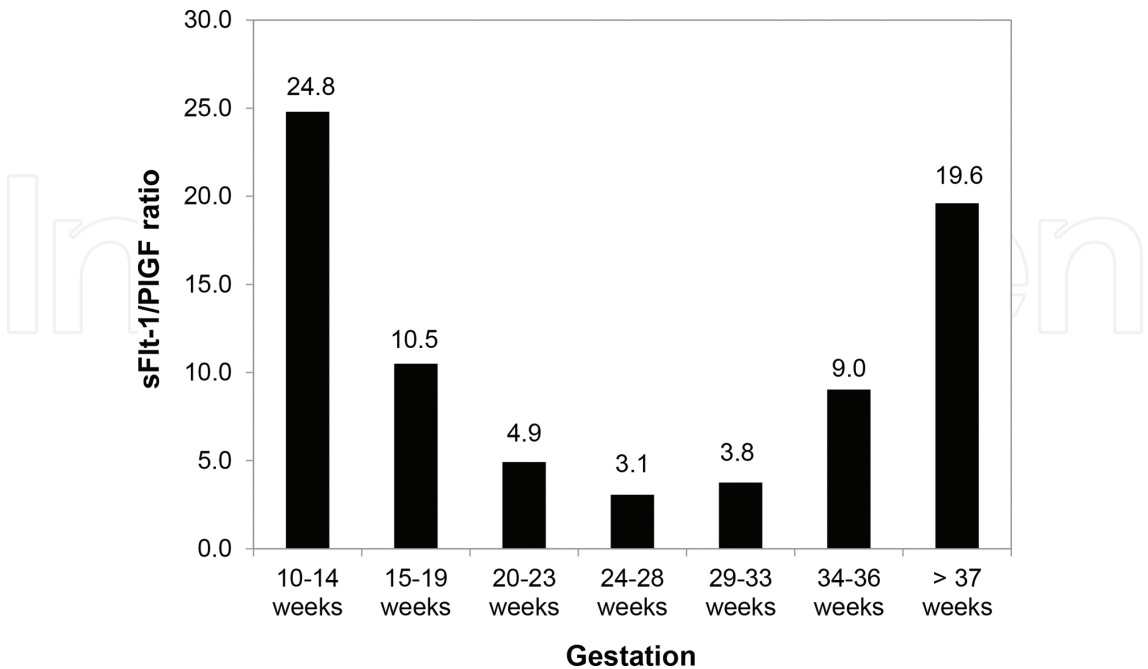

Figure 5. Median values of the Elecsys® sFlt-1/PlGF ratio in uneventful pregnancies [177].

The BRAHMS Kryptor™ sFlt-1/PlGF ratio was assessed for preeclampsia diagnostic utility in a recent small study (*n* = 39 women who developed preeclampsia including *n* = 30 women with late-onset preeclampsia; 76 controls). To diagnose preeclampsia (rule in preeclampsia), a BRAHMS Kryptor™ sFlt-1/PlGF ratio of >110 had a 67.7% specificity (late-onset preeclampsia), compared with the Roche Elecsys® sFlt-1/PlGF ratio showing 85.5% specificity [178].

6.8. The sFlt-1/PlGF ratio and preeclampsia prediction

To date, the BRAHMS sFlt-1/PlGF ratio has been assessed only for the diagnosis of preeclampsia [174, 178]. By contrast, the Elecsys® sFlt-1/PlGF ratio has been validated for both the diagnosis and the prediction of preeclampsia [172, 175]; it is the *predictive* role of the biomarker that is anticipated to guide PHC for preeclampsia, and so the results of studies examining the Elecsys® sFlt-1/PlGF ratio for preeclampsia prediction are discussed subsequently.

The Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia Study (PROGNOSIS) was a large, non-interventional, multicenter study, designed to derive and validate a cutoff-based prediction model for the short-term prediction of the absence or the presence of preeclampsia using the sFlt-1/PlGF ratio [171]. In this study, 1050 women with singleton pregnancies between 24 + 0 and 36 + 6 weeks of gestation, and one or more symptoms of preeclampsia (but no confirmed diagnosis), were enrolled and split into two cohorts. Data from the first cohort of 500 women (development cohort) were used to develop a model and identify the optimum sFlt-1/PlGF cutoff level of 38, which was independent of gestational age (**Table 8**). The second cohort (validation cohort, *n* = 550) was used to validate this proposed optimum level.

	Development Cohort	Validation Cohort
Preeclampsia within 1 week, % (95% CI)		
Negative predictive value (rule out)	98.9 (97.3–99.7)	99.3 (97.9–99.9)
Sensitivity	88.2 (72.5–96.7)	80.0 (51.9–95.7)
Specificity	80.0 (76.1–83.6)	78.3 (74.6–81.7)
Preeclampsia within 4 weeks, % (95% CI)		
Positive predictive value (rule in)	40.7 (31.9–49.9)	36.7 (28.4–45.7)
Sensitivity	74.6 (62.5–84.5)	66.2 (54.0–77.0)
Specificity	83.1 (79.3–86.5)	83.1 (79.4–86.3)

Calculations of sensitivity were defined based on participants who developed preeclampsia within 1 or 4 weeks. Calculations of specificity were defined based on participants who did not develop preeclampsia within 1 or 4 weeks. CI denotes confidence interval.

Table 8. Validation of a sFlt-1/PlGF ratio cutoff of 38 for rule out and rule in in preeclampsia ([171]; From New England Journal of Medicine, Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, Olovsson M, Brennecke SP, Stepan H, Allegranza D, Dilba P, Schoedl M, Hund M, Verlohren S, Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia, 374, 34–42. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society).

To rule out preeclampsia within 1 week, the negative-predictive value (NPV) of the selected level of ≤38 was 99.3%, with a sensitivity and specificity of 80.0 and 78.3%, respectively. To rule in preeclampsia within 4 weeks, an Elecsys® sFlt-1/PlGF ratio of >38 had a positive-predictive value (PPV) of 36.7%, with a sensitivity and specificity of 66.2 and 83.1%, respectively. This PPV is high compared with other predictive tools that have historically been employed: standard clinical and laboratory information (e.g., proteinuria and BP measurements) have PPVs of 20–26% in detecting preeclampsia-related adverse outcomes [179–181]. An Elecsys® sFlt-1/PlGF ratio of ≤38 was also predictive of the absence of fetal adverse outcomes within 1 week (NPV of 99.3% in the validation cohort); a ratio of >38 was associated with a PPV of 47.5% for these outcomes at 4 weeks. The sFlt-1/PlGF ratio is also CE-IVD approved for use as an aid in short-term prediction of preeclampsia in pregnant women with suspicion of preeclampsia in conjunction with other diagnostic and clinical information.

6.9. Tailoring preeclampsia health care using the sFlt-1/PlGF ratio

The Elecsys® sFlt-1/PlGF ratio has only recently been validated for the prediction of preeclampsia, and so its value in tailoring the management of preeclampsia in clinical practice remains to be fully seen. The use of the sFlt-1/PlGF ratio for the short-term prediction of preeclampsia in women with suspected preeclampsia could guide PHC and ensure that the right patients are monitored or referred, and receive appropriate interventions. The ability to rule out preeclampsia could, in theory, prevent the unnecessary hospitalization with economic benefits for health-care providers, although further analyses are needed to establish this [182].

Studies are currently underway to assess the value of the sFlt-1/PlGF ratio in clinical practice. The Preeclampsia Open Study (PreOS), for example, aims to establish whether knowledge of the Elecsys® sFlt-1/PlGF ratio influences a physician's decision making, by assessing intended procedures before and after knowledge of the sFlt-1/PlGF ratio [183].

The utilization of the sFlt-1/PlGF ratio could be used to guide future treatment options. A pilot study examined the safety and efficacy of therapeutic apheresis to remove circulating sFlt-1 in 11 pregnant women (20–38 years of age) with very early-onset preeclampsia. In this study, apheresis reduced the circulating levels of sFlt-1 by 18% (a range of 7–28%). In women who received a single treatment or multiple treatments of apheresis, pregnancy continued for a further 8 days (range 2–11 days) and 15 days (range 11–21 days), respectively. In control patients with preeclampsia ($n = 22$), pregnancy continued for a further 3 days (range 0–14 days). No adverse effects of apheresis were observed in the infants [184]. Further trials are needed to confirm these results; if successful, knowledge of the sFlt-1/PlGF ratio could be used to help identify women who are most likely to benefit from such therapy.

6.10. Current recommendations for the use of preeclampsia biomarkers

In the UK, the National Institute for Health and Care Excellence (NICE) has recommended (as of May 2016) the use of the Elecsys® immunoassay sFlt-1/PlGF ratio and Triage® PlGF test, in combination with standard clinical assessment, to help rule out preeclampsia in women of week 20 + 0 days to 34 weeks + 6 days gestation [174]. NICE suggest that further research is

needed before the DELFIA® Xpress PlGF 1-2-3 test and BRAHMS sFlt-1 Kryptor™/BRAHMS PlGF plus Kryptor™ PE ratio can be recommended [174]. In Germany, the sFlt-1/PlGF ratio has been incorporated into guidelines on preeclampsia as a diagnostic aid [185].

A consensus statement has recently been published, providing guidance on the use of the Elecsys® immunoassay sFlt-1/PlGF ratio in women with singleton pregnancies who have signs or symptoms of preeclampsia [154]. According to this guidance, if the ratio is <38, the patient is unlikely to develop preeclampsia within 1 week and further management is at the clinician's discretion. If the ratio is >85 (in women of early gestation) or >110 (in women of late gestation), preeclampsia or placental dysfunction is present, and the patient should be managed according to local guidelines (severely elevated ratios may indicate the need for fetal lung maturation and delivery). If the sFlt-1/PlGF ratio is 38–85 (early gestation) or 38–110 (late gestation), a diagnosis of preeclampsia cannot be definitively made, but the patient is highly likely to develop the condition within 4 weeks. If this occurs in early gestation, a follow-up test within 1–2 weeks should be considered. If this occurs during late gestation, the health-care team should consider lowering the threshold for the induction of delivery.

6.11. Medical value

The sFlt-1/PlGF ratio is a typical example for a medical value test, consisting of two established markers. The medical value component in this case has been established by analyzing how this ratio can contribute to a better patient management. Without this analysis, the clinical value of both markers alone would be somewhat lower. Therefore, the "value" term arises around patients and payers simultaneously describing a framework for performance improvement in health care [186]. The medical value component consists of two pivotal factors and follows a stringent definition:

i.   A medical value test must show improved patient outcomes, derived through algorithms, validated in clinical utility studies addressing an unmet medical need.

ii.   Deliver actionable and medically relevant information enabling support and guidance in decision making.

Ultimately, such tests may justify a change of the current disease management and thus can help to reduce direct and indirect health-care costs. Medical value is added, when, for example, a test allows patient stratification into responders/non-responders for a given medical treatment or allows a more efficient/more effective allocation of patients to a certain treatment or disease management [187].

7. Closing remarks (summary)

Owing to a complex interaction between genes and proteins in combination with environmental factors that lead to hypertension [188, 189], and despite an increasing body of knowledge regarding genes involved in the pathophysiology of essential hypertension, the commercialization of PHC biomarkers in clinical practice is still at an early stage.

Technologies such as NGS together with computational methods allow us to analyze relationships between genetic and epigenetic factors influencing essential hypertension [188]. Up to now, these technologies have been used mainly for research [79], but in the future such technologies could be used to optimize treatment and primary prevention by combining comprehensive and detailed PHC. Knowing an individual's sequencing data might help to assess the risk for hypertension, while the use of a biosensor to continuously monitor changes in BP would allow physicians to make the treatment decisions at the earliest time point possible and hence avoid organ damage [94]. Arrays of genetic markers, along with clinical factors and/or other biomarkers, could be utilized for the development of mathematical algorithms predicting BP response to a given antihypertensive drug, similar to that used for warfarin pharmacogenetic dosing [190]. "Risk scores" for genetic markers may guide the prediction of the "best drug" avoiding long-term cardiovascular complications (e.g., stroke, atrial fibrillation, etc.).

Contemporary guidelines for the treatment of hypertension mention the potential of pharmacogenomics. An increased uptake of the use of personalized treatments is expected in upcoming years, although more studies are needed to generate a body of clinical evidence before genetic testing can be fully introduced in the treatment of cardiovascular diseases. For the first time, a new scientific statement from the ACC, AHA, and ASH on the treatment of hypertension in patients with coronary artery disease [191] refers to genetic-susceptibility variants for atherosclerotic disease and/or BP response to antihypertensive treatment. The guidelines discuss that the determination of genetic variants may be of some use for selecting appropriate antihypertensive agents to reduce both BP and the risk for coronary artery disease [192]. Thus, with the emergence of pharmacogenetics and other potential "-omics" biomarkers to guide antihypertensive treatment, guidelines are needed for biomarker qualification and clinical validation and to allow translation into clinical tools for clinical application.

The sFlt-1/PlGF ratio is a predictive and diagnostic tool in maternal care that could support the shift toward PHC in preeclampsia management. Measurement of this biomarker ratio in women with suspected preeclampsia can aid physician decision making, and help ensure that the right women receive the monitoring and specialist perinatal care that they require, while avoiding unnecessary hospitalizations.

PHC and pharmacogenomic testing has the potential to predict the response to antihypertensive therapy and to adequately select the appropriate dose that may ensure maximal efficacy, especially in patients with end-stage hypertensive disease, malignant hypertension, or treatment-refractory hypertension. This concept reduces the utilization of cost-intensive drugs in non-responders and avoids costs related to the treatment of side effects or due to the withdrawal of drugs [193]. While physicians must be trained in the handling and interpretation of test results, patients and payers must also be educated on the benefits and limitations of PHC. However, broad acceptance of such tests can only be obtained with a trained clinical workforce and compelling economic evidence for payers that pretreatment testing is efficient.

Acknowledgements

Author details

Carmen Binder[1], Hans Hendrik Schäfer[2,5], Edelgard Kaiser[3], Martin Hund[3] and Thomas Dieterle[4*]

*Address all correspondence to: Thomas.Dieterle@ksbl.ch

1 Diagnostics Information Solutions, F. Hoffmann-La Roche Ltd., Diagnostics Division, Basel, Switzerland

2 Divisional Medical and Scientific Affairs, F. Hoffmann-La Roche Ltd., Basel, Switzerland

3 Centralized and Point of Care Solutions, Medical and Scientific Affairs, Roche Diagnostics International Ltd., Rotkreuz, Switzerland

4 Kantonsspital Baselland, Liestal, Switzerland

5 Institute of Anatomy II, University Hospital Jena, Friedrich Schiller University, Jena, Germany

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