AN ACADEMIC CLINICIAN’S ROAD MAP TO HYPERTENSION GENOMICS: RECENT ADVANCES AND FUTURE DIRECTIONS

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Short running title:

A ROAD MAP TO HYPERTENSION GENOMICS

Emma F Magavern1, Helen R Warren1,Fu L Ng1, Claudia P Cabrera1, Patricia B Munroe1, Mark J Caulfield1

1- William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK.

Word count: 8441 (5492 excluding references and figures)

Corresponding author:

Professor Sir Mark Caulfield

Queen Mary University of London
William Harvey Research Institute
Bart and The London School of Medicine, Clinical Pharmacology, Charterhouse Square
Charterhouse Square
London EC1M 6BQ
UNITED KINGDOM

m.j.caulfield@qmul.ac.uk

+44(0) 20 7882 3403

Abstract

At the dawn of the new decade it is judicious to reflect on the boom of knowledge regarding polygenic risk for essential hypertension supplied by the wealth of genome wide association studies. Hypertension continues to account for significant cardiovascular morbidity and mortality, with increasing prevalence anticipated. Here we overview recent advances in the use of big data to understand polygenic hypertension, as well as opportunities for future innovation to translate this windfall of knowledge into clinical benefit.

**Keywords:**Hypertension, cardiovascular disease, genetics, risk score

**Introduction**

Hypertension (HTN) is one of the most significant chronic medical problems of the current century, affecting both developed and developing countries alike, leading to significant mortality as well as morbidity. HTN contributes to the majority of strokes and up to half of all incidence of coronary artery disease1. Elevated systolic blood pressure (BP) causes more than 10 million deaths per year 2. As the prevalence of metabolic syndrome increases these problems will only heighten, and there are predicted to be 1.5 billion hypertensive people by 2025 without accounting for projections of soaring obesity 3. The current and projected costs associated with this disease burden are staggering, with HTN associated costs in the USA of 131 billion USD annually4,5. Given that the burden of hypertension in developing countries is estimated to be double that of developed countries there is an urgency in reaching affordable intervention globally3.

In clinical practice, hypertension management remains a challenge due to the complex nature of the disorder, the intersection of lifestyle (smoking, alcohol and diet) and genetic risk factors, as well as the many causes of secondary hypertension and the unclear mechanisms of multidrug treatment resistance, which leads to a high prevalence of poorly controlled HTN 6. Though rare forms of heritable monogenic syndromes exist causing extreme high or low blood pressure phenotypes, the large epidemiologic burden remains in essential hypertension, a polygenic condition within the general population 7,8. Complicating our understanding of cardiovascular clinical and genetic risk is the interplay between HTN and other clinical risk factors, commonly referred to as ‘metabolic syndrome’, and postulated common genetic risk pathways9,10.

The mainstay of therapy is lifestyle modification, with weight loss, exercise and reduced intake of salt and alcohol recommended, in addition to antihypertensive medications: angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs), calcium channel blockers, mineralocorticoid receptor antagonist (MRA), diuretics, and anti-adrenergic agents (alpha and beta receptor blockers)11.

To approach the challenges of blood pressure from a genomic perspective, genome wide association studies (GWAS) of increasing scale have been performed since 200712. There have been a crescendo of genetic signals reported for association with BP traits (Figure 1). The proportion of blood pressure trait variance explained by the genetic regions identified for essential hypertension accounts for approximately one-third of BP heritability13. Exploration of genetic signals could provide efficacious targeted therapy and inspire new therapeutic innovation6,8 .

Despite a rapidly increasing number of genetic loci found to have significance in BP regulation, and the promise of genetic risk scores for risk stratification, none of the genomic findings have yet been integrated into clinical practice at the bedside 14,15. It is important to pause and examine if the summation of research to date fulfils the clinical promise anticipated at the dawn of genomic discovery.

As we tentatively approach complex genetic data from a clinician’s perspective, how can we tease out genetic risk from risk attributable to modifiable lifestyle choices? How can we understand what quantity of an individual’s risk for HTN and cardiovascular disease (CVD) is inherited and immutable versus risk incurred from a 40-pack year smoking history, a diet rich in salt and cholesterol, or a BMI >30 and sedentary lifestyle? How much of this is intertwined? This would be important to the patient sitting across the clinic table and can inform optimal clinical interventions and communications.

**Findings from Blood Pressure Genome-wide Association Studies**

Genetic association analyses are performed to detect association of genetic regions with BP traits16. As the association of a single common genetic variant only has a modest effect, significant associations for common variants are more detectable with increasing sample sizes. Interpreting results is not straightforward. A significant hit from a GWAS simply indicates an association signal at a chromosomal region containing many correlated variants in linkage disequilibrium (LD), rather than pinpointing the exact causal gene or functional variant, and does not imply that the nearest gene is the causal gene. For example, in most BP-GWAS papers, the novel locus is reported and named according to its nearest annotated gene. However, further functional or bioinformatics work may suggest that the most likely causal gene is in fact a different gene; either a gene located nearby, mapping to another variant in high LD at the association signal, expressed by a co-localized eQTL (expression quantitative trait loci), or a long-range interacting gene (e.g. candidate genes suggested by Hi-C analyses previously)13. Trans-acting regulatory elements, which can change gene expression at a remote site, are also important to consider 17. Furthermore, a large proportion of significant hits are in non-coding regions of the genome. Changes to non-protein regions of the genome are implicated in many common genetic diseases, via an array of mechanisms.  These include: promotors, enhancers, splice site regulating changes, changes to translation, stability, or localization, and changes to noncoding structural or regulatory RNA18. While prioritization of variants in protein coding regions is common practice, the characterization and prioritization of non-coding variants remains very challenging. The discovery of these functional and regulatory elements may prove pivotal to an improved understanding of BP.

Recent GWAS analyses for BP traits have included increasing numbers of individuals from large biobank studies, contributing to large scale meta-analysis consortium studies. A GWAS analysis in 2018, with a total of >1 million participants comprising discovery data from the UK Biobank (UKB) and International Consortium for Blood Pressure (ICBP), with follow-up in the Million Veteran Program (MVP), and Estonian Genomic Centre of the University of Tartu studies, reported 535 novel loci, increasing known common associations responsible for hypertension from the prior validated 274 loci to a total of 90113. A subsequent study for common and rare BP genomics, using data from MVP and UKB, with follow up in ICBP and BioVU (Vanderbilt University biobank) identified 208 new common variant blood pressure loci and 53 rare variants (defined as minor allele frequency (MAF) <1%)19.

The discovery of thousands of loci associated with BP has increased the complexity of an already challenging task; to analyse the large quantities of genomic and associated phenotypic data. Bioinformatics has a key role to play and can be fine honed through deep machine learning to assist in identification and prioritization of disease associated genetic variants identified through GWAS 20. Furthermore, the critical appraisal of potential drug targets at genetic loci has been increasingly facilitated by databases, which we discuss in detail later in “Target validation”.

*BP Heritability and Environmental Interactions*

Heritability estimates explain how much of blood pressure variation is explained by genetics, though some estimates can also reflect shared environment. Estimates from GWAS data indicate that systolic blood pressure has a heritability of 30%21. However initial genetic findings for all common single nucleotide polymorphisms (SNPs) from early GWAS pre-2015 together only explained less than 3% of the trait variance 6. Researchers have since sought to discover the variants accounting for the disparity, to solve the ‘missing heritability’ problem, with a greater proportion attributable to variants identified in 2018 8,13,15,22. As more loci are discovered with ever larger studies, variants responsible for ever smaller percentages of blood pressure variation are found23. However, a UKB-based GWAS multi-trait heritability study suggests that all of the significant heritability of blood pressure traits has already been accounted for and asserts that prior models of HTN heritability have overestimated genetic contribution, due to under-correction for shared environment 24. This is intriguing and supports a change from family-study based estimates of heritability to SNP-based heritability estimates; though estimates of multi-trait SNP-based heritability vary widely, as they are dataset-specific24,25. There may also be ancestry specific differences in heritability which have not yet been fully explored.

GWAS have also examined gene and environmental exposure interaction. Data from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium identified novel GWAS loci associated with increased blood pressure traits dependent on smoking exposure26,27. Further studies have also examined the effects of genetic interactions with alcohol intake and educational attainment on blood pressure traits28. The results from interaction analyses to date have only provided a limited number of new loci not detected from main effects analyses.These gene-environment interaction (GxE) studies support hypotheses of amplified risk for lifestyle exposure in those with genetic predisposition which is more than the sum of each risk factor separately. Envisioning widespread availability of genomic data in the future, we might be able to identify those in the cardiovascular clinic at a higher risk of HTN from smoking or alcohol intake, and explain that they may benefit more than the average individual from lifestyle modifications.

Epigenetics describes changes in gene expression resulting from environmental exposures, without changing the sequence of the DNA. Examples include DNA methylation and modification of histones, as well as noncoding RNA that regulates gene expression, such as microRNA29,30. Increasing evidence supports an important role of epigenetics in BP, but further research is needed to illustrate a path forward in translating epigenetic advances to clinical gains29.

Another important development is the emerging and increasing overlap of BP loci with other traits**.** This may have clinical relevance to both risk prediction and therapeutic repurposing of pharmaceutical agents (as in the case of SGLT2 inhibitors discussed below).Pleiotropy is a distinct but related concept; that variation in one gene can have multiple discrete phenotypic effects. One of the recurrent themes of cutting edge large genomic studies is the overlap of genetic associations between blood pressure loci and other conditions, some cardiovascular, including metabolic conditions such as obesity and lipid loci, and other non-cardiovascular traits such as Alzheimer’s disease13. Increased discovery of genetic links between schizophrenia and blood pressure, among other cardiovascular associations, has been a particularly intriguing line of investigation31. Further work is needed to elucidate common genetic risk within metabolic syndrome traits.

*Role of Rare Variants*

Although rare monogenic causes of hypertension do not carry a significant epidemiologic burden, studying these disorders can improve our understanding of physiology and pathophysiology of blood pressure regulation6,8. Some of the earliest findings of monogenic variants in familial hypertension, via linkage analysis, have had the largest impact on clinical care to date as the mechanism may guide treatment8. One such example, discovered in the 1990s is the constitutively active epithelial sodium channel (ENaC) sodium channel in Liddle’s disease, due to mutations in 3 genes encoding the different subunits of the *SCNN* gene. ENaC is known to be the target of amiloride and can thus effectively guide therapeutic treatment for dramatic clinical response 32. In the tradition of PCSK9 inhibitor discovery for dyslipidaemia, the hope in further exploration of rare variants in syndromic HTN is to find new targets and inspiration for translation to drug design33. Genomics England research groups, among others, are currently engaged in such rare variant analysis34.

There are also important rare variants beginning to be identified in population-based GWASs for essential hypertension. A recently published BP GWAS study from MVP identified ten rare coding variants (MAF <1%) from exonic analyses associated with systolic BP (SBP), diastolic BP (DBP), or pulse pressure (PP), of which four were in genes without prior reported BP associated SNPs19. The average absolute effect of these alleles on BP (1.5mmHg, 0.6mmHg, and 1.5mmHg for SBP, DBP, and PP) is still minimal from a clinical perspective, but notably larger than that of reported common variants (Figure 2)19. A genome-wide rare variant analysis, including noncoding regions, was also performed, with trans-ethnic and ancestry-stratified discovery analyses from MVP and replication in UKB individuals of European ancestry. A total of 48 rare variants were reported, with much larger average effect sizes: 9.7mmHg for SBP; 2.3mmHg for DBP; 13.9 mmHg for PP19. Unlike common variants or coding variants identified, the magnitudes of BP differences for these single rare variants are clinically significant, although many of these were discovered from smaller sample sizes of Hispanics (N ~ 21,000) or Blacks (N ~ 60,000), so may have ancestry-specific effects, and require further validation in larger samples across other ancestries.

The ICBP consortium has also combined existing and new cohorts to conduct a meta-analysis for rare BP genetic associations in approximately 1.3 million participants; a study that is inclusive of large numbers of Asian and African ancestry participants (unpublished data, Surendranet al, accepted *Nature Genetic*s35) (Figure 1). They identified 87 rare BP associated variants: 32 of these were located in loci that had not been previously linked with BP35. The effects of these rare variants on BP are notably larger than those of identified common BP alleles (Figure 2)35.

Both of these studies show some support for rare variants in the population with larger, clinically meaningful effect sizes, which could benefit therapeutics, and which may in turn hold promise for translational utility of forthcoming whole genome BP studies.

**Target Validation**

After a GWAS identifies a locus as associated with BP, this region is subjected to downstream bioinformatics analyses in search of known disease association, candidate genes and mechanistic relevance. Broadly, genes associated with salt regulation, adrenergic tone, and calcium channels are the most frequent groupings of interest as targets of existing antihypertensive therapies. However, often a GWAS identifies loci in or near genes without prior association with HTN or CVD and the mechanism may be unclear8. Due to the many factors that can cause a correlation where there is no causative effect in population GWAS (most prominently via LD) potential candidate genes should be tested vigorously and validated with bioinformatic and laboratory protocols. The results can then fuel efforts towards rational drug design, which we discuss in further detail below.

*Loci of Interest*

There are numerous loci of interest from recent GWAS discoveries, and we briefly describe some examples here. Candidate genes at discovered loci include *VEGFA*, which stimulates angiogenesis, and induces migration and proliferation of vascular endothelial cells, as well as the *FGF9* gene which is hypothesised to influence BP via regulation of *VEGFA*13,36–38. The *APOE* locus is linked to lipid metabolism, Alzheimer’s disease, and cardiovascular disease; knock out animal models suggest a protective function in atherosclerosis and hypertension, and indicate that serum levels of the protein encoded by this gene (the primary apoprotein of the chylomicron) are correlated with SBP13. The *RAMP2* locus was a novel hit from GWAS13, and the gene has been prior described to modify the affinity of adrenomedullin receptors39. Another new locus of interest maps to the *UTS2R* gene (urotensin-2 receptor), which encodes a G-protein coupled-receptor (GPCR) activated by urotensin II to cause significant vasoconstriction13,40. Relaxin, a protein hormone that contributes, as the name suggests, to vasorelaxation as well as other cardiovascular signal pathways via *PI3K*, another novel BP locus identified, has already been the target of therapeutics in trials for heart failure. This culminated in the recently concluded RELAX-AHF-2 trial which, although negative for significant improvement in hard heart failure outcomes, did show significant BP reductions - unfortunately not desirable during an acute decompensation of heart failure41–43. A large BP GWAS published in 2018 identified the relaxin gene as a novel systolic BP locus of interest, while a GWAS published in 2019 noted a novel BP rare coding variant in RXFP2, which codes for a G-protein coupled receptor, the target of relaxin and serelaxin (a modified recombinant form of relaxin)13,19. These targets are leads for future innovation and necessitate further study.

*Druggable Targets*

Druggability denotes the assessment of GWAS loci for translation to potential BP therapeutics, as well as identifying any current existing drugs targeting the gene product of interest. This may identify known pharmacological agents for BP or perhaps drugs licenced for other conditions which then highlights repurposing potential. There are widely-used open access online resources, which estimate how likely a gene is to provide opportunity for small molecule therapeutic regulation. Chembl is one such searchable database, curated by the European Bioinformatics Institute in the UK, providing information about bioactive molecules44. Drug Gene Interaction database (DGidb) complements and allows a search by gene for “potential druggability” or by Drug-Gene interaction, using compiled information from online resources, existing databases and academic publications45. Output from such resources is not without limitations and should be taken as a starting point of inquiry.

Use of these tools has accompanied GWAS publications, allowing broad identification of GWAS validated loci as either targets of existing therapeutic agents or potential targets of novel therapeutic design13,19,36. However, these algorithms do not consider harms of existing therapeutics for possible repurposing or foreseeable harmful or even lethal effects of alterations at “druggable” genetic loci. For example, the authors of one large scale GWAS note that GJA1, one of those genes identified as “druggable”, has an association with the QT interval, where both short and long QT can cause fatal arrhythmias36,46. There are cohort reports in the literature of sudden infant death attributed to GJA1 gene mutations; therefore there may well be critical safety concerns in assessing this gene as a therapeutic target36,46,47. This case highlights the crucial nature of interdisciplinary application of such data, including statisticians, bioinformaticians, scientists and clinicians, in identifying suitable and promising drug targets.

Using the DGidb database for analysis of novel variants found that one of the loci, *SLC5A1* is targeted by canagliflozin, an approved and widely used medication to treat type 2 diabetes mellitus; it works via sodium-glucose-transport protein 2 (SGLT2) inhibition, causing hyperglycaemic patients to excrete glucose renally thereby lowing blood sugar13. In fact, a randomized controlled clinical trial published a mere 2 months later found that SGLT2 targeted therapy added to an angiotensin II receptor blocker (ARB) therapy in a Japanese diabetic cohort with uncontrolled nocturnal HTN did not alter glycaemic control but did significantly improve hypertension (reduced 24-hour BP by 7.7/2.9 mmHg versus placebo)48. Though the BP lowering effect of SGLT2 inhibitors was not a new finding, having been reported from meta-analysis data in 2014, the magnitude in this study was larger than that prior seen49. To date this class of therapeutics is only used to treat type II diabetes mellitus as a primary indication and is not licenced for primary treatment of hypertension.

From a translational therapeutic perspective, it is interesting to examine variants at BP associated loci known to be targeted by medications for other indications. One example is the *FDFT1* gene which is the target of lovastatin, postulated in the past to have lipid independent mediated impact on BP50,51. To date, there have not been any high-quality clinical trials that have looked past class effect at lovastatin individually. Another interesting find is *PLAU*, which is the target of two different bisphosphonates – zoledronic and alendronic acid – as well as calcitriol, synthetic activated vitamin, and hypothesised to modulate BP in an inverse fashion52. Clinically this could be important as many elderly people with frailty related fractures, who not infrequently also suffer from orthostatic hypotension, are put on “bone protection” therapy, which is a combination of a bisphosphonate and vitamin D. If these therapies contribute significantly to lower BP, either alone or in combination, this may add to falls risk and therefore would merit clinical investigation. The product literature lists both hypo- and hypertension as possible uncommon side effects of zolendronic acid but there is no mention of BP side effects in either alendronic acid or calcitriol.

Several novel BP variants supported by converging lines of evidence from GWAS, *in vitro,* and *in silico* data (*PSMB9*, *PSMB7, PLAU*, *ADK*), are targets for anti-cancer therapies and immune modulators. This potentially sheds some mechanistic light on genetic contribution to side effects of BP dysregulation in patients on relevant cytotoxic and immunomodulating therapy, including bleomycin, sirolimus, oprozomib, marizomib, carfilzomib and bortezomib19.

**Translation to outcomes**

As the sample sizes analysed in GWAS escalate there may be diminishing returns, as larger numbers unearth more and more connections of smaller effect sizes, associating with increasingly diverse traits. The omnigenic theory proposes that complex traits are regulated by most if not all active genes in the relevant tissue, and in fact these genetic loci may not be related to the trait of interest directly, but will influence it in a small way via complex downstream regulatory effect on a core gene53. Evangelou *et al* responded to this theory by emphasizing the BP and cardiovascular specificity of genetic loci and pathways identified13. It would also be hoped that the new rare variant findings with clinically meaningful larger effect sizes would contribute to greater specificity in the BP trait biology. In any case, the authors of the omnigenic theory foresee a continued role for large scale GWAS in stratified risk prediction and as a mechanism of elucidating complex regulatory pathways53.

When assuming a large-scale view of recent gains in the field of BP genomics this prediction seems to hold true. One promising outcome from the recent boom in BP GWAS is the identification of new pathways that haven’t yet been the targets of BP therapeutics (Figure 3). For example, TGF-β and Notch signalling pathways are predicted to be important in SBP, with some prior mechanistic support as gene products within these pathways are known to influence renal sodium excretion and ventricular remodelling13,19,54–56. However, functional studies determining the relationship between the genetic loci and physiologically and clinically relevant mechanistic and molecular pathways have not yet caught up with GWAS discovery. This represents the next hurdle in translation of the genomic gains to the bedside, and further mechanistic advances would facilitate a better platform for targeted therapeutic development.

*Genetic Risk Scores*

As a clinician looking for a bottom line - what can we offer to patients as a result of this genetic data that would change management where a carefully taken clinical and family history, and routine investigations, would not?

Genetic risk scores (GRS) combine together many significant associated genetic variants from GWAS, weighted by their effect sizes to provide predictive risk scores of common polygenic disease traits such as BP57. The GRS for BP constructed from all 901 loci reported in 2018 predicted a three times higher risk of hypertension in the top versus the bottom decile in the UKB cohort13. Even more interestingly, it significantly predicted risk of myocardial infarction, stroke and all incident CV outcomes on the order of 50% increased risk of adverse outcomes in the top decile of risk versus the lowest risk decile (respective odds ratios of 1.47, 1.50, and 1.52)13. Compared to prior GRS, the additional inclusion of the newly identified variants made this more powerful for risk stratification13,58.

GRS may be the most directly clinically applicable use of big data GWAS findings. However, use of a GRS has yet to be trialled in clinical practice to test any potential risk modification, and it is not clear what clinical change would be recommended above current clinical risk stratified indications for primary and secondary prevention.

While published BP GWAS studies have so far only constructed GRS using SNPs of validated genome wide significance, emerging polygenic risk scores (PRS) in other aspects of cardiovascular disease are incorporating either all pairwise-independent genome-wide SNPs or all LD-pruned SNPs meeting a more liberal p-value threshold59. Future BP risk scores are likely to take the form of PRS rather than GRS and aim to compare risk stratification by PRS to a validated clinical risk stratification representative of current clinical practice. If the addition of a PRS can improve on existing gold standard clinical risk stratification to predict future disease, then there is a role for early preventative lifestyle modification and therapeutic use which would need to be prospectively trialled to assess for benefits in hard outcomes.

Though a PRS has not yet been published for HTN there has been recent interest in the use of such risk scores in cardiovascular disease, with two papers published on the same day in February of this year looking at utility of PRSs in coronary artery disease in middle aged cohorts of European descent60–62. Unfortunately, the results were disappointing, showing no clinically significant benefit in risk stratification using PRS above clinical risk stratification in these USA and UK cohorts60–62.

*Mendelian Randomization*

Mendelian randomization (MR) uses genetic variables as a proxy for risk exposure to support causal relationships between risk factors and BP or between BP variation and outcomes. It can support a directional association and attribute cause and effect variables using retrospective observational data, thereby clarifying complex relationships prone to confounding and reverse causation. MR has been gaining ever more traction, with the number of publications using MR multiplying nearly 10-fold in 10 years 63. Observational studies only have the ability to examine associations via correlations between variables and can suffer from the problem of reverse causation. Instead MR can infer causality by using a genetic variable as the instrumental variable, which is known to predict an exposure, but which is not related independently to the outcome/disease of interest. It claims power equivalent to that of a randomized controlled trial by operating under the assumption that there is random assortment in meiosis64. MR can therefore support a causal association from observational data in a context where multiple potential confounders may cloud other forms of observational cohort data analysis. Indeed, the genetic proxies used in MR are not affected by confounders or reverse causation. As BP cohort observational studies require correction for many confounding factors, MR instead offers an appealing way to support causal directional relationships for both genetic predictors of target biomarkers and BP (X🡪BP) as well as genetic predictors of BP and outcomes of interest (BP🡪Y).

Although this genetic technique has been widely used to study various cardiovascular risk factors, it had not been commonly applied to hypertension until recently. In the past two years there have been several studies utilizing MR to examine various aspects of BP, most commonly as an outcome of interest for various exposures (X🡪BP), or, conversely, as the exposure (BP🡪Y) using BP predictive genetic instruments65.

Many initial studies were focused on a causal effect of lifestyle risk factors for HTN (X🡪BP). The translational benefit of lifestyle causal inference by MR is, of course, benefit by lifestyle modification or public policy/public health. Study results include: a causal effect of smoking on heart rate but not on blood pressure66; caffeine intake causing lower blood pressure in non-smokers67; no causal effect of dairy consumption on BP68; a sex dependent relationship between alcohol and hypertension in a Chinese cohort69; and that a hypothesised relationship between lower educational attainment and higher SBP may not remain after adjusting for BMI and smoking70,71.

A MR meta-analysis from 21 different studies (N = 60,028) found a non-statistically significant lowering of systolic BP with a 6.5cm increase in adult height72. Other anthropomorphic parameters explored using MR include obesity (as expected, genetically determined high BMI was associated with higher BP) 73–75. Although lower birthweight was associated in observational studies with higher BP this did not prove causal in the MR 76.

There has also been an increase in studies using MR to look at biomarkers associated with BP. While some results came as no surprise, for example N-terminal prohormone of brain natriuretic peptide (NT-proBNP) association with SBP and DBP, others have not been previously hypothesised including: urokinase-type plasminogen activator (uPA), adrenomedullin (ADM), interleukin-16 (IL16), cellular fibronectin (cFn), and insulin-like growth factor binding protein 3 (IGFBP3)77. Studies have identified β-2 macroglobulin contribution to HTN78, the BP lowering effect of vitamin D79, the effects of increased total and LDL cholesterol, and triglycerides, on raising BP80,81, the effect of increased HbA1C on raising systolic BP82, and support for an incremental causal relationship between homocysteine concentration and BP83, and no evidence of a causal effect of γ-glutamyltransferase (GGT) on BP84, .

MR is an interesting genetic approach to novel biomarker identification and known biomarker validation. In one example of utility, MR was used to test causal relation between genetically determined bilirubin levels and BP (with an instrumental variable responsible for approx. 45% bilirubin variation), finding no causal relation though the prospective trial data showed an association between measured bilirubin and HTN risk, leading the authors to conclude either confounding or reverse causation. This is an example where MR changed the interpretation of clinical data85.

A fascinating novel interdisciplinary MR analysis used genetic determinants of periodontitis and found that periodontitis causes higher systolic BP, which was mitigated by the trialled intensive periodontitis therapy in contrast to standard periodontitis care (mean difference of -11.1 mmHg in systolic BP; 95% CI 6.5-15.8; P < 0.001). This result directly supports clinical translation, as a trial looking for untreated or suboptimal treated periodontitis in HTN patients may identify a cohort for intervention on poorly controlled BP with intensive therapy for periodontitis 86.

In the published literature to date, there are fewer MR studies examining the effect of genetically determined BP on outcomes (i.e. BP🡪Y), likely because they may confirm outcome associations that are already known, such as left ventricle (LV) remodelling due to HTN87. However, such studies may play an important role in the future where rare variants of large effect sizes in essential hypertension, mined from the GWAS discussed, could identify health outcomes that may be modifiable at individual loci.

In a novel application of methodology, a recent study utilized MR to establish the validity of genetic proxy loci for several common classes of antihypertensive therapy; beta-blockers, calcium channel blockers and angiotensin-converting enzyme inhibitors, and propose an unstudied link between calcium channel blockers and diverticulosis 88. While these genetic tools are powerful and contributing much to an evolving understanding of hypertension and its multifaceted predictors, they should be interpreted with caution when applied to diverse populations of different and admixed ancestries.

**Future Directions**

The increasingly sophisticated analytic tools applied to large biobank genomic data inspire optimism regarding a wide range of potential clinical translations.

*Large Biobanks and Sequencing Efforts*

Cohorts likely to produce population scale genomic insights in coming years are FinnGen (a Finnish biobank of 500,000 individuals) the MVP mentioned above (as further samples are forthcoming), and the Accelerating Detection of Disease cohort, a UK initiative aiming to recruit 5 million healthy individuals89–91. The role of imputation will remain significant, with increasing power to impute whole genome sequences as reference numbers grow92. Trans-Omics for Precision Medicine (TOPMed), a consortium that has conducted whole genome sequencing in approximately 155 thousand participants from different studies, is analysing BP traits, and results of this are forthcoming. Together, sequencing technologies and -omics approaches could enable further discovery as well as to provide links to mechanisms and support in target validation and translation of BP genetics.

For translation to clinical impact, deep or enriched phenotyping is desirable. The UK Biobank is a great example of a recent large dataset, which is enabling further network-based, multi-trait, cross-trait type analyses by inclusion of more phenotypic information. Examples of such large scale undertakings in progress are the 100,000 genome project from Genomics England, and the Qatari genome programme, funded by the private non-profit Qatar Foundation, which may prove useful in identifying distinct syndromic BP disorders with stronger heritable risk93. Only 44% of the rare variants from the most recent analysis of rare variants and exome-chip content by Surendran et al. were in coding regions of the genome, emphasizing yet again a need for whole genome studies.

The larger effect sizes of the newly discovered rare variants within a general population (Figure 2) maintains the hope that pharmacogenomics (PGx) may still be able to achieve its goal of progressing BP treatment in the future, by targeting the medication to an individual’s genome (Figure 3).

As illustrated prior, the explosion in MR studies is transitioning to biomarker and therapeutic targets from initial identification of risk factors, a paradigm shift likely to generate a wealth of new hypothesis for therapeutic innovation. It would be interesting to see future trials use such biomarkers within a clinical context to explore translational bedside potential in BP assessment and therapeutics (Figure 3).

The dramatic reduction in costs of genomic profiling with next generation sequencing, and the anticipation of third generation sequencing may make even a small risk reduction from preventative treatment following polygenic risk scoring worthwhile on cost-benefit balance (Figure 3)14. However, this is currently speculative, as such a risk score has yet to be trialled in any interventional prospective clinical setting, so the estimated projection of benefit can only be approximately inferred from existing data13,19,36,94.

*Will the next step come from industry?*

Parallel to the ongoing progress in academia, the multinational pharmaceutical company GlaxoSmithKline (GSK) purchased exclusive access to genetic data for drug design from direct to consumer testing company 23andMe in 2018, for 300 million US dollars95,96. One motivation for this is that medications with mechanisms targeted from genetic data have double the chance of successfully going from phase one clinical trials to approval95,97. This is remarkable as the therapeutic pipeline is extremely porous, with only an estimated 10-14 % of phase 1 clinical trial drugs reaching approval, at a high cost 98,99. More than half of approved drugs with targeted genes are associated with online mendelian inheritance in man (OMIM) reported mendelian traits97. This agreement between a pharmaceutical giant and direct–to-consumer (DTC) genetic testing was hailed with justifiable caution in the public domain amid concerns of privacy of individual genetic data once in the commercial pharmaceutic realm96. Though there are indeed many reasons to view this collaboration from a critical perspective, it is a significant development in escalation and collaboration of corporate resources to investigate novel therapeutic potential from genetic data and may well uncover significant pieces in the puzzle of BP genomics due to the large amount of data collected by DTC testing, combined with the epidemiologic burden of disease, and industry resources and expertise in therapeutic design.

*Ethical considerations in BP Genomics*

There are also health economic considerations, together with ethical and legislative concerns. The greatest need for improved management is in developing countries where the needs are far more basic, and in particular relating to environmental factors. Another ethical concern is that the existing data is largely not validated within either highly admixed populations or populations descendent from non-European ancestry. It is worth noting that existing cohorts are comprised, in the vast majority, of men of European descent, arguably the population least in need of resources from a distributional justice perspective. This is of course by necessity rather than design but remains a limitation. Some recent strides have been made in reference genomes outside of European ancestry, such as the Qatari reference genome and the pan-genome100,101.

What is clear is that tools from genetic data such as PRS could become an actuarial tool if widespread genotypic testing were to make it into the commercial realm, which has recently become a distinct possibility due to the collaboration between GSK and 23andMe. In the 1920s, before the Framingham Heart Study, and before essential hypertension was monitored and treated by the medical community as a standard practice, the Actuarial Society of America had deduced the harm of hypertension from analysing the >10million people they insured (life insurance) and led the way for systematic use of sphygmomanometers102. With regard to ethical and legislative concerns, noted in prior reviews14, although some nations have adopted laws or less formal modes of preventing use of genetic data for life insurance, most have not103. Use of genomic risk stratification for life insurance is likely to be a quandary, and health insurance in non-socialized health care systems could prove even more thorny.

Sources of Funding and Disclosures:

EFM is funded by a NIHR Academic Clinical Fellow award

All authors acknowledge support from the NIHR Barts Biomedical Research Centre.

MC is the Chief Scientist for Genomic England

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**Figure legends**

**Figure 1:** “Advancing Discovery in Blood Pressure Genetics Studies over the Past 10 Years”

From selected major blood pressure genetic studies from the past 10 years, we show the number of novel discoveries reported from primary analyses, distinguishing between novel common loci (with replication from 2-stage designs, or non-replicated from 1-stage designs) and rare variants13,19,35,36,58,104–107. The printed numbers state the total sample size. (\*) indicates studies focusing on Exome-chip content.

**Figure 2:** “Comparing Minor Allele Frequency vs Effect Size of Published Variants Associated with Blood Pressure”

This plot compares Minor Allele Frequency (MAF) on the X-axis vs Effect Sizes (in mmHg) on the Y-axis for reported variants associated with blood pressure (BP). Each variant is only plotted once, according to its primary (most significant) BP trait, with all data taken from the publication they were first reported in. In order to show effect sizes for the three continuous BP traits on the mmHg scale, any variants reported only with results for Hypertension from logistic regression are excluded. For comparison of data, we only consider variants identified as the lead variant from novel loci of primary analyses from main-effect genetic association studies (i.e. excluding results from interaction / stratified / multi-phenotype / conditional analyses) and only from discovery analyses of predominantly European ancestry (i.e. allowing European-only and multi-ancestry results, but excluding data from studies of single non-European ancestries). Hence variants include: the SNPs plotted in Sup Fig 2 of Evangelou et al 2018, plus any variants published since from Giri et al 2019 (MVP) and Surendran et al 2020 (BP-ICE). Rare variants are only plotted if replication data contributed to the genome-wide significant combined meta-analysis results. A y-axis break is used due to one rare variant having a much larger effect size (MVP, Giri et al 2019).

**Figure 3**: “Future progress expected to yield clinical translation”