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A viewpoint from the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy

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Abstract

Pharmacogenomics promises to advance cardiovascular therapy, but there remain pragmatic barriers to implementation. These are particularly important to explore within Europe, as there are differences in the populations, availability of resources and expertise, as well as in ethico-legal frameworks. Differences in healthcare delivery across Europe present a challenge, but also opportunities to collaborate on PGx implementation. Clinical work force upskilling is already in progress but will require substantial input. Digital infrastructure and clinical support tools are likely to prove crucial. It is important that widespread implementation serves to narrow rather than widen any existing gaps in health equality between populations. This viewpoint supplements the working group position paper on cardiovascular pharmacogenomics to address these important themes.

Challenges in clinical implementation

Across Europe there have been multiple Government funded initiatives to embed genomics into healthcare. These have largely focused on cancer and rare diseases but many also include pharmacogenomics (PGx)[1]. Aside from the technical aspect of testing, common barriers to implementation are differing healthcare delivery across European populations, workforce capacity and capability, the development of digital infrastructure and clinical systems to interpret and integrate data, and limited evidence of clinical benefit and/or cost-effectiveness[2]. The Ubiquitous Pharmacogenomics Consortium, funded by the H2020 programme, is currently evaluating the use of a multi-gene panel in a cluster design, across 7 countries, for clinically relevant end-points and cost-effectiveness.

Differences in delivery of European Healthcare

Only European Union member states are subject to EU guidelines related to use of medicines. Even among member states, adoption of guidelines related to healthcare and education is not uniform, often relying on local policy. Additionally, across Europe there are differences in the level of healthcare expenditure and approach to funding. Finally, populations across Europe vary significantly in terms of ethnicity, cultural and religious beliefs.

Workforce capacity and capability

Clinical geneticists are experts in understanding genetic variation but are a limited resource, with numbers of Clinical Genetics consultants varying from 1 per ~140,000 to 1,150,000 per head of population across Europe[3]. Furthermore, they may be less familiar with other diagnostics and complex prescribing encompassed by PGx. Thus, in order to facilitate the implementation of PGx, the wider workforce needs to be upskilled. This needs to involve at least enough basic genetic literacy to use clinical decision support tools, which will need to be developed to support translation of data to clinical action.

At present PGx rarely features in European higher specialty medical training programmes, undergraduate medical education, pharmacy or nursing programmes across Europe and it is vital that this is addressed for the successful implementation of pharmacogenomics. There is some encouraging evidence of increased curricular inclusion as compared with 15 years ago[4]. However, the amount of time dedicated to PGx training is often minimal and the quantity of actionable PGx information is likely to increase over time, presenting further challenges.

Short courses on advanced training in genomics in medicine are available for healthcare professionals through the European School of Genetic Medicine. In England, the Genomics Education Programme supports a postgraduate Master's degree in Genomic Medicine. The impact of these programmes is yet to be determined. Although these bespoke programmes will increase training of a minority of individuals, they are unlikely to impact the majority of the workforce where training as part of continual professional development is needed.

Systems and infrastructure

Across Europe, most healthcare information technology systems are poorly equipped to deal with the volume and complexity of genetic data; therefore, expanding digital infrastructure across the healthcare sector is key. To support clinicians with limited knowledge in PGx, clinical decision support software is particularly important and may be facilitated by electronic healthcare systems.

Due to geographical variation in provision of genetic services, countries such as France and the UK have created regional hubs in centres of excellence to ensure standardised testing, data collection and equitable access to services for patients.

Clinical and cost-effectiveness

One of the major barriers to the implementation of PGx has been the paucity of evidence demonstrating improved efficacy, safety or cost-effectiveness. Examples of where there is evidence are included in the accompanying position paper, and this evidence base is growing. Thus far the majority of studies support PGx as cost effective[5]. Longer-term data demonstrating positive clinical outcomes and cost-effectiveness is vital to gain support from governmental policy makers.

There are currently recommendations for more than 80 drugs (https://cpicpgx.org/); PharmGKB curates a database of pharmacogenetic variants (https://www.pharmgkb.org/). Most are based on genetic studies done in Caucasian European ancestry populations. Interpretation, and any necessary reclassification, of variants of unknown significance (VUS) may be a challenge given the spectrum of ancestries across Europe and admixing of populations.

Importance of collaborative networks

Many of the challenges related to the implementation of PGx across Europe have begun to be addressed by the development of national and international collaborative networks between healthcare professionals, academic researchers, industry and regulatory bodies. This enables sharing of clinical and research data from differing populations, educational resources and begins to address the legal, social and ethical concerns arising across Europe. These collaborations will enable rapid expansion of knowledge, improving the care for patients and minimising resource waste and duplication. Governmental, academic and regulatory cooperation will be required, and such a unified approach will make possible data sharing opportunities, which will in turn require infrastructure to be built.

Ethical, legal and cultural considerations

Legal and regulatory framework

Legislation - European laws relating to the use of genetic testing in healthcare systems, applicable to but not specific to PGx testing, are heterogenous and designed for diagnostic purposes rather than PGx. The framework for diagnostic

genetic testing may be inappropriately stringent in a PGx setting and pose an unnecessary barrier to PGx implementation[6].

European Medicines Agency (EMA) stance on PGx– The EMA endorses best-practice in genetic testing analysis and actionability of results: product information includes up-to-date PGx data[7]. Currently individual medications contain PGx data as endorsed by EMA licensure rather than an enveloping EMA comment on PGx panel testing. 15% of all EMA licensed pharmaceutical agents contain PGx information in the summary of product characteristics[8]. As PGx testing and intervention move to an integrated panel approach, concurrent evolution in regulatory guidance is likely to be needed.

Direct-to-consumer (DTC) genetic tests regulation– A description of the regulatory framework in Europe from experts across the EU showed that while some nations restrict genetic testing to the purview of medical practitioners, other nations allow DTC testing, while a third model exists with provision to refuse license for tests that are not scientifically sound[9]. Legislation is often not specific to DTC[10]. In the current context of Intra-European movement, it may thus be prudent to standardize access to PGx test results and interface with national health service access.

The *in vitro* diagnostic (IVD) framework applies to commercial diagnostic devices, via the Communauté Européenne (CE) mark. The role of the CE label, which denotes that the commercial product "has been assessed *by the manufacturer* and deemed to meet EU safety, health and environmental protection requirements", should be clarified**;** it may be misconstrued as a quality standard from a scientific or medical perspective[11].

Ethical concerns and implications

Confidentiality and genetic data – Individuals and relationships are increasingly identifiable from increased coverage in genetic panels and sequencing. This is particularly relevant with PGx as testing would likely be polymorphism or gene panel based rather than based on an individual single nucleotide polymorphism (SNP) test. Police investigations have made use of genetic data processed by DTC companies. This raises questions about the extent to which forensic access to genomic databases stored in clinical systems may be broached in the future (presumably under court order).

Privacy and data protection – PGx testing is likely to generate an enormous quantity of data. How will this be managed and who can have access under what circumstances? If someone dies can this data be accessed by clinicians or shared with next of kin in case of clinically actionable and genetically transmissible variant identifications? Existing consensus is to treat any genetic data like all other sensitive data contained within electronic health records from an information governance perspective, though some have queried a need for extended legislative protection for genetic data[12].

Informed consent with imperfect information – Informed consent (IC) is a cornerstone of ethical clinical practice. In the context of incomplete and evolving information

regarding variant classification and actionability in prescribing, participants may be consenting to treatment based on a rapidly evolving interpretation of the information base. Current consent practices vary and should be standardized at a minimum content level[13]. IC for ongoing research from PGx data mining should be addressed separately.

Transparency and provisions to action an evolving knowledge base – The uncertainty around VUS and emerging PGx variants, and the rapid evolution of genetic knowledge, make transparency paramount and necessitate viable plans to keep patients appraised of changes in variant classification. The European Society of Human Genetics framework for next generation sequencing recommends that the laboratory is responsible to re-issuing reports and contacting referring clinicians when a variant changes categories[14].

Responsibility – Clinical decision making with limited gold standard RCT evidence and an enormous number of variables may open up clinicians to criticism in case of an adverse event and retrospective cherry picking of data. How will responsibility in PGx decisions be shared between government, health care organizations, clinical practitioners and patients? Further clarity is needed. This should include consultation with all stakeholders to assess acceptability. There are clearly legal implications in terms of prescriber liability if any standard practice PGx is not integrated.

Distributional justice –PGx will have to prove worthy of the substantial investment to justify propelling PGx forward at the opportunity cost of other public health care initiatives.

Social justice – As touched on above, most genetic studies do not include representation from a full cross section of society, limiting variant detection, clinical validity and PGx applicability. Worldwide Ancestry-based research should therefore be encouraged. Furthermore, relations of the mainstream research community and medical establishment with several ethnic minority groups, such as indigenous people, has been fraught with mistrust[15]. There is therefore a concern raised as the most historically privileged ethnic group, Caucasian Europeans, will be even more privileged as personalised medicine advances care tailored to this group. This is an example of the Matthew effect, a phrase taken from the biblical adage describing an age old *rich get richer* phenomenon of perpetuated privilege and inequality. The social justice implications of this pattern must be made explicit and rectified by initiatives encouraging expansion in this area of research.

In summary, differences in healthcare delivery across Europe, as well as workforce and infrastructure shortfalls, represent barriers to implementation of evidence based cardiovascular PGx within the EU. Collaboration and adequate consideration of ethical issues can help PGx to advance cardiovascular care for all strata of society, across the EU.

Conflicts of interest

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References:

1. Stark Z, Dolman L, Manolio TA, Ozenberger B, Hill SL, Caulfied MJ, Levy Y, Glazer D, Wilson J, Lawler M, Boughtwood T, Braithwaite J, Goodhand P, Birney E, North KN. Integrating Genomics into Healthcare: A Global Responsibility. *Am J Hum Genet* 2019;**104**:13–20.
2. Pearce C, Goettke E, Hallowell N, McCormack P, Flinter F, McKevitt C. Delivering genomic medicine in the United Kingdom National Health Service: a systematic review and narrative synthesis. *Genet Med* 2019;**21**:2667–2675.
3. Lynch SA, Borg I. Wide disparity of clinical genetics services and EU rare disease research funding across Europe. *J Community Genet* 2016;**7**:119–126.
4. Karas Kuželički N, Prodan Žitnik I, Gurwitz D, Llerena A, Cascorbi I, Siest S, Simmaco M, Ansari M, Pazzagli M, Resta C Di, Brandslund I, Schwab M, Vermeersch P, Lunshof JE, Dedoussis G, Flordellis CS, Fuhr U, Stingl JC, Schaik RH van, Manolopoulos VG, Marc J. Pharmacogenomics education in medical and pharmacy schools: conclusions of a global survey. *Pharmacogenomics* 2019;**20**:643–657.
5. Berm EJJ, Looff M de, Wilffert B, Boersma C, Annemans L, Vegter S, Boven JFM van, Postma MJ. Economic Evaluations of Pharmacogenetic and Pharmacogenomic Screening Tests: A Systematic Review. Second Update of the Literature. Bruns H, ed. *PLoS One* 2016;**11**:e0146262.
6. Roses AD. Pharmacogenetics and the practice of medicine. *Nature* 2000;**405**:857–865.
7. Committee for Medicinal Products for Human Use (CHMP). Guideline on good pharmacogenomic practice. 2018.
8. Ehmann F, Caneva L, Papaluca M. European Medicines Agency initiatives and perspectives on pharmacogenomics. *Br J Clin Pharmacol* 2014;**77**:612–617.
9. Borry P, Hellemondt RE van, Sprumont D, Jales CFD, Rial-Sebbag E, Spranger TM, Curren L, Kaye J, Nys H, Howard H. Legislation on direct-to-consumer genetic testing in seven European countries. *Eur J Hum Genet* 2012;**20**:715–721.
10. Kalokairinou L, Howard HC, Slokenberga S, Fisher E, Flatscher-Thöni M, Hartlev M, Hellemondt R van, Juškevičius J, Kapelenska-Pregowska J, Kováč P, Lovrečić L, Nys H, Paor A de, Phillips A, Prudil L, Rial-Sebbag E, Romeo Casabona CM, Sándor J, Schuster A, Soini S, Søvig KH, Stoffel D, Titma T, Trokanas T, Borry P. Legislation of direct-to-consumer genetic testing in Europe: a fragmented regulatory landscape. *J Community Genet* 2018;**9**:117–132.
11. Your Europe EU. CE marking. https://europa.eu/youreurope/business/product-requirements/labels-markings/ce-marking/index_en.htm (27 June 2020)
12. McGuire AL, Fisher R, Cusenza P, Hudson K, Rothstein MA, McGraw D, Matteson S, Glaser J, Henley DE. Confidentiality, privacy, and security of genetic and genomic test information in electronic health records: points to consider. *Genet Med* 2008;**10**:495–499.
13. Haga SB, Mills R. A review of consent practices and perspectives for pharmacogenetic testing. *Pharmacogenomics* 2016;**17**:1595–1605.
14. Matthijs G, Souche E, Alders M, Corveleyn A, Eck S, Feenstra I, Race V, Sistermans E, Sturm M, Weiss M, Yntema H, Bakker E, Scheffer H, Bauer P. Guidelines for diagnostic next-generation sequencing. *Eur J Hum Genet* 2016;**24**:2–5.
15. Claw KG, Anderson MZ, Begay RL, Tsosie KS, Fox K, Garrison NA. A framework for enhancing ethical genomic research with Indigenous communities. *Nat Commun* 2018;**9**:2957.