

Opinion

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Support for developing personalized genomic medicine

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How to cite this article: McNamee CJ. Support for developing personalized genomic medicine. *J Transl Genet Genom* 2018;2:20. <https://doi.org/10.20517/jtgg.2018.24>

Received: 8 Aug 2018 **First Decision:** 22 Oct 2018 **Revised:** 30 Oct 2018 **Accepted:** 30 Oct 2018 **Published:** 16 Dec 2018

Science Editor: Sheng-Ying Qin **Copy Editor:** Cui Yu **Production Editor:** Huan-Liang Wu

Abstract

This article discusses the benefits of personalized genomic medicine, some of the challenges of adoption into the clinic, and provides examples of UK and European projects that are developing the practice of personalized genomic medicine. It highlights the work of the UK Pharmacogenetics and Stratified Medicine Network in providing information, developing multidisciplinary collaborations, and organizing events, to support the advancement of personalized genomic medicine.

Keywords: Pharmacogenetics, personalized medicine, genomics, drug development, safety

INTRODUCTION

Traditionally the signs and symptoms of disease determined a patient's treatment, but recent advances in new sequencing technologies, and novel diagnostic techniques, allow clinicians to use genomic data to both diagnose sub-types of disease and predict how each patient will react to a particular drug^[1]. Personalized/precision genomic medicine, also described as stratified^[2]/P4 (predictive, preventive, personalized and participatory) medicine^[3], uses the patient's genomic profile to stratify patients into groups (based on their sub-type of disease and response to drug therapies) then offers each group precise treatment, personalized to the genomic profile of the group. P4 medicine describes how personalized genomic medicine not only predicts patient response to treatment but also predicts their disease risk so they may participate in preventative treatment to reduce the risk.

Genomic personalized medicine enables physicians to offer their patients the most effective drug, at the correct dose, in the right combination with their other medications, from the onset of treatment, to improve



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healthcare outcomes. As the population ages there is a strain on healthcare systems to treat the increasing number of patients suffering with multiple medical conditions that require polypharmacy. Personalized genomic medicine will be at the forefront of improving the prescribing of drug treatments to help meet the challenge of delivering a more efficient modern healthcare system, especially for those patients suffering with multi-morbidities.

The advent of personalized genomic medicine offers an opportunity to maintain a more healthy population by preventing disease. Studying a patient's genomic profile predicts the risk of disease, particularly where there is a family history of disease; for example, variants in the *BRCA* genes increase the risk of breast and ovarian cancer^[4]. Patients with *BRCA* variants have the opportunity to opt for preventative treatment, such as elective surgery or close monitoring, to mitigate their high risk of disease, or adopt changes in life style to minimize the risk. For example, the famous actress Angela Jolie had surgery to prevent breast cancer when she discovered she had inherited the *BRCA1* mutation. Gene sequencing to evaluate the risk of transferring an inherited disease may become part of couple's reproductive decisions to prevent the transfer of a life threatening genetic condition to the next generation.

This move away from basing clinical decisions on the signs and symptoms of disease to offering genomic medicine began at the turn of the century and has attracted worldwide interest. For example, the UK has recently produced a National Health Service (NHS) genomic medicine strategy and an industry life sciences policy^[5] to lead the way in encouraging the development of personalized genomic medicine to improve patient care, president Obama launched the precision medicine initiative in 2015 in the USA.

OPPORTUNITIES FOR PERSONALIZED GENOMIC MEDICINE

Diagnosis of disease

Technological advances at pace have significantly improved the diagnosis of disease and moved the field of personalized genomic medicine forward. For example, whole genome sequencing becoming ever more affordable for research has led to the identification of many different subtypes of disease within each disease category. Whole genome sequencing and gene panel tests are becoming increasingly common as part of the diagnostic process to identify disease subtypes more precisely to offer patients personalized treatment. Novel sequencing techniques, and gene panel tests, have identified how the presence of genomic variants in some patients affect their drug metabolism making pharmacogenomics (the study of how a patient's genetic profile affects the way in which they respond to a particular drug) an essential part of selecting the most appropriate drug to prescribe at the correct dose^[6]. For example, oncology is leading the way in using pharmacogenomics to support clinicians select the safest and most effective medications for patients with cancer from the start of their treatment^[7]. The development and increasing use of these types of genomic diagnostic tests is moving personalized medicine forward. The US Food and Drug Administration (FDA) produces a comprehensive list of information on pharmacogenomic biomarkers found in drug labeling^[8].

The development of companion diagnostics alongside drug development is popular with the pharma industry and is becoming a very lucrative global industry^[9]. Companion diagnostics (for example, a genetic test or *in vitro* biomarker diagnostic assay device) identify which patients will gain benefit from a particular drug so supports the development of personalized medicine. However, issues around who funds the development of companion diagnostics, and once developed how to repay the cost of their use (and use of other genomic tests) to healthcare providers in the clinical setting have yet to be resolved. Resolving these issues and increasing the use of companion diagnostics will enable practitioners to select treatments that are effective from the onset of treatment and so reduce clinical visits ultimately making significant savings on healthcare costs.

Projects using genomic medicine diagnosis

Often patients with rare diseases have no definite diagnosis or specific treatment available for their condition. Genetic variants cause many rare diseases so clinicians are turning to genomics to obtain a diagnosis and to

look for novel ways to offer their patients treatment. There are around 70,000 rare diseases, so as a category rare diseases are not actually so rare and affect 6%-7% of the UK population. This prominence of rare diseases, and their link to genetic variants, led to the initiation of the UK 100,000 genome project^[10]. Genomics England was set up to sequence the whole genomes of 100,000 patients suffering with rare diseases and cancers (along with close family members) to provide a diagnosis for their condition and to potentially offer them some treatment. Genomic Medicine Centers set up across England sequenced participant's samples and collated the data into a central repository to create a rich resource for scientists to investigate the genetic basis to disease and research drug-gene interactions. The legacy of this project is the launch in spring 2019 of a UK wide NHS genomic medicine service (GMS)^[11] that links the established Genomic Medicine Centers with other clinical departments, such as clinical pharmacologists, geneticists, *etc.* A panel of experts will review the scientific evidence for drug-gene interactions and develop a central directory for the GMS that lists all the variants proven to relate to drug efficacy (the directory constantly updated as knowledge of drug-gene interactions increases). The GMS will offer a range of sequencing and panel tests to general practitioners (and other hospital clinicians) to diagnose disease genotype, and use algorithms to interrogate the test data to identify any genetic variants listed in the directory known to be associated with drug-gene interactions. Computerised drug decision software will interrogate patient results and alert clinicians when variants that pose a prescribing risk are detected, allowing patients to be prescribed either a lower dose or alternative drug treatment.

The Ubiquitous Pharmacogenetics (UPGx) consortium pre-emptive pharmacogenomics testing for preventing adverse drug reactions study^[12] is another project evaluating the effectiveness of implementing testing into various healthcare systems across Europe. In a similar way to the GMS, UPGx is investigating if applying a selected group of pharmacogenomics markers into the diagnostic process improves prescribing and saves on healthcare costs. Pharmacogenomics data on drug-gene interactions linked into electronic clinical decision support systems will alert prescribers/pharmacists when a patient's electronic health record contain a pharmacogenomics variant that puts the patient at risk of an adverse drug reaction to the drug they are prescribing.

The practice of personalized genomic medicine is worldwide and these are just a couple of examples of projects that are leading the introduction into the clinic. The percentage of precision medicine drugs approved by the FDA annually has already increased from 5% in 2015 to 35% in 2017^[13]. Almost 50% of the drugs approved were for treatment for conditions other than oncology demonstrates how widespread the use personalized genomic medicine is becoming across all sectors of medicine.

Drug safety

Most drugs are only effective on average for between 50%-75% of the general population and there are examples of oncology blockbuster drugs where efficacy is as low as 25%^[14]. Whilst many patients may simply have no response to a drug, genetic variants in metabolic pathways are responsible for causing adverse drug reactions which can be life threatening for some patients. For example, the effect of such a variant caused catastrophic hypersensitivity to the drug abacavir in some HIV patients^[15]. Pre-emptive genotyping of patients prior to prescribing abacavir has significantly reduced the number of patients suffering this life threatening adverse drug reaction.

In the UK alone approximately 8000 hospital beds are occupied at any one time with patients suffering from adverse drug reactions, placing a huge £2 billion burden on the healthcare system^[16]. Furthermore, there is a significant cost to the pharmaceutical industry when a drug has to be withdrawn post marketing due to safety concerns. Incorporating pharmacogenetics data into the prescribing and drug development processes is crucial to support delivering patients safer and more effective treatments^[17]. Currently there are only a few genetic variants linked to drug-gene interactions compared to the number of drugs on the market, but as more pharmacogenetics data becomes available this number will steadily increase.

Drug development

Advances in genomic medicine allow the pharma industry to move away from the development of blockbuster drugs that are only effective for a proportion of the population. Drug development has remained relatively unchanged over the last 50 years but the cost (~\$2.87 billion) and length of time it takes from discovery to launch (12-15 years) of a new drug is no longer sustainable. The pharmaceutical industry is using genomics to identify novel drug targets, and help create companion diagnostics, to identify those patients most likely to benefit from a novel drug potentially reducing some of the burden of the financial costs, and development time, to get a new drug to market^[18]. Currently ~46% drugs fail at phase I trials, ~66% at phase II and ~30% at phase III, leaving only ~8% lead compounds ever reaching the market place^[19]. Pre selecting patients based on their genomic profile during phase one clinical trials helps industry reduce the number of patients required to demonstrate drug efficacy and safety, limit the potential of drugs failing at the phase 2/3 hurdle, and help to overcome regulatory hurdles prior to licensing provides a strong case for the use of genomics in drug development.

Drug trials

Genomic medicine has a distinct role to play in developing innovative clinical trials that are more effective than traditional random control trials^[20]. Basket trials have been used for novel cancer drugs, where an individual drug is trialed on a variety of tumors expressing a common single mutation to increase both the scope of the trial and the number of patients eligible to join the trial. Bucket trials pool patients with a single variant expressed in different cancer types into one trial to test a novel drug reduces the number of clinical trials required and the length of time for the trial. Umbrella trials incorporate different treatment arms within a single trial to test the impact of a range of drugs on various mutations within a single cancer type. These innovative clinical trials are of great interest to industry as they reduce the time and costs of launching the novel drugs of the future.

CHALLENGES FOR PERSONALIZED GENOMIC MEDICINE

Patient support

Adoption of genomic medicine into clinical use provides many opportunities to improve healthcare but there are several challenges to overcome before it becomes mainstream for all medical disciplines. Scientists rely on patient samples and data for their research so support from the public and patients is essential to move genomic medicine forward^[21]. Patients have an important role to play in focusing scientific research to areas that will improve their condition to maximize productive research output. Issues around obtaining the most appropriate level of consent to collect patient samples in biobanks, then ethical permission for academic and industry sectors to access those samples and data for research, have to be resolved. Educating the public on how genomic data is collected, securely stored, and ethically utilised will demonstrate transparency, provide patients with confidence to donate their samples and data to researchers, plus raise awareness of the benefits of genomic medicine. This raised awareness of the benefits of genomic medicine will also help clinicians enroll patients in clinical trials to test the novel drugs of the future.

Patients are already bringing direct to consumer genetic test results to clinics and asking physicians to use them to prescribe their medication. The regulators have a role to play in validating both the quality of such tests, and to ensure there is sufficient evidence that the variants identified are clinically relevant and actionable, for these direct to consumer test results to be of use for prescribing.

Multidisciplinary support

Physicians, and other healthcare professionals, require support from a wide range of different disciplines to employ a personalized genomic medicine approach into their clinical practice. For example, bioinformatics experts will have to adapt healthcare data systems to incorporate patient data into electronic records in a suitable interoperable format. Experts in technology will be required to develop the decision support tools

to identify relevant variants in patient's data and their pharmacogenomics effect, then put in place apps to update healthcare systems regularly to incorporate novel gene-drug interactions as academic researchers identify them.

Education of healthcare professionals at all levels will play an important role in raising awareness of how the field of personalized genomic medicine is moving forward. Clinicians may not need in-depth knowledge of the science behind the identification of a variant, or the type of gene variant, but they require an understanding of the effect of the variant on disease and the way a patient metabolises a particular drug. There are several fields leading the practice of personalized genomic medicine but there are some clinicians, particularly in general practice, that would benefit from continued personal development training to keep pace with this fast moving field.

Developing collaborations

Traditionally academics gain their reputation, and attract research funding, through their publication records, whereas industry require confidentiality agreements to protect the development of their novel drugs. Previously this conflict of interest compromised the development of collaborative working partnerships across academic and industrial institutions. Combined expertise from multidisciplinary sectors being required to move personalized medicine forward opens up the opportunity for collaborative partnerships. Academics carry out the basic research into the genetic links to disease and find the molecular targets for industry to go on to develop the much-needed novel drugs of the future. There are opportunities for small medium enterprises (often the commercial spin off from academic research projects) to support large pharma by developing the companion diagnostics to personalize novel drugs. Due to the spiraling costs of drug development large pharma are becoming ever more receptive to partnerships with other sectors to maximize their research and development capacity. Research funding bodies are recognizing the benefits of collaboration so launch multidisciplinary funding calls to encourage the various sectors to come together to make personalized genomic medicine a success.

UK Pharmacogenetics and Stratified Medicine Network

The UK Pharmacogenetics and Stratified Medicine Network^[22] was set up as an overarching organization to provide the opportunity for academic, clinical, industrial and regulatory partners to collaborate with patients (and other minority groups) to move forward the uptake of pharmacogenetics and use of personalized medicine in the clinic [Figure 1]. Members use the web based collaborators database to highlight their interests and promote their organizational expertise, then search the database to locate colleagues from other disciplines to develop partnerships to move their research forward. The network is a non-profit making organization that has attracted almost a thousand members over the last four years. Such organizations as the National Institution for Health Research-Clinical Research Network, Northern Health Science Alliance, UCB Pharma and Innovate UK have sponsored the development of the network. The website also acts as a "one stop shop" providing information on the events taking place, funding and education opportunities, and all the latest news on how the field is progressing. Professor Sir Munir Pirmohamed founded (and chairs) the network, with the support of a steering committee made up of individuals from the key sectors involved in personalized medicine directing network activities. Every year ~250 delegates from across all sectors come together at the open meeting to listen to quality presentations on the developments in personalized medicine and meet up with colleagues from other disciplines. The network also invites leading experts throughout the year to bespoke workshops to debate and propose solutions to the challenge of moving personalized genomic medicine forward. Presentations from these annual open meetings and workshops are down loadable from the website, outcomes from the workshops published in peer-reviewed journals. The UK Pharmacogenetics and Stratified Medicine Network is linking up with similar European organizations, the US Pharmacogenetics Research Network, and representatives from other continents to develop a global consortium dedicated to exchanging knowledge and moving personalized genomic medicine forward.



Figure 1. The UK Pharmacogenetics and Stratified Medicine Network. The network was set up in the UK to develop multidisciplinary collaborations, across academic, industrial, healthcare and regulatory sectors, to encourage research in personalized medicine and promote the use of pharmacogenetics in the clinic to improve patient healthcare outcomes <http://www.uk-pgx-stratmed.co.uk>

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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