Introduction

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Abstract Genetics evolved rapidly in the past decade, characterising genes that directly cause specific traits in monogenic diseases, as well as modifier genes that are associated with specific disorders but are not sufficient for causality, rather work in concert with additional gene and environmental factors to elicit the disease, mostly referred to as susceptibility genes. The science has also evolved from bench and lab discoveries to bedside implementations and further gathered momentum as knowledge acquired about allele and genotype frequencies in specific populations (via epidemiological studies) resulting in effective genetic disease prevention programmes. In parallel, numerous polymorphisms have by now been characterised and often formulated into drug labels, which play a role in the pharmacokinetics and pharmacodynamics of available therapeutics, predicting the efficacy of drugs in patients, and minimising the occurrence of drug adverse reactions.

The main two fronts of genetic contribution to personalised medicine address the preventive and the predictive aspects of medicine. Preventive genetics plays a major role in the characterisation of specific genetic disorders through populations-wide policies. Preventive programmes include population screening for carriers of rare, fully penetrant alleles that cause monogenic diseases, prenatal diagnosis of specific syndromes, and genotyping of susceptibility genes within families with high risk of developing a specific disease, providing the basis of Public Health Genetics. Carrier testing programmes go beyond the science and empirical testing, accompanied by premarital counselling aiming to provide necessary information to prevent the occurrence of disease, as well as support effective therapy and improved quality of life when such diseases are expressed. Preventing clinical manifestations by early

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G. Grech, I. Grossman (eds.), *Preventive and Predictive Genetics: Towards Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 9,
DOI 10.1007/978-3-319-15344-5_1

diagnosis and intervention provides another level of preventive strategies that are not directed towards the prevention of the genetic defect, but avoiding emergence of symptoms by excluding exposure to exacerbating specific allergens/nutrients in disorders such as Glucose-6-Phosphate Dehydrogenase deficiency and phenylketonuria. Other strategies include the prevention of secondary complications of a disease, such as the use of antibiotics to prevent life-threatening bacterial infection in sickle cell disease. Overall, the multi-faceted approaches to newborn screening programmes are essential to prevent clinical manifestations or secondary complication of disease.

In complex diseases, genetic testing provides a means for measuring risk of manifesting disease given demographic and environmental risk factors. A "high risk" individual is then provided with recommendations for risk reduction interventions and/or access to screening and monitoring programmes at an earlier age, to prevent the occurrence or to delay onset of the disease. The efficiency of genetic testing to prevent disease depends on the weight of evidence, the predictive value of the variant(s) screened in the programme and the frequency of such alleles and genotypes in a specific population.

Another area of predictive genetics deals with the efficacy and toxicity of drugs in individuals. Pharmacogenomics is defined as the impact of the individual's genetic and genomic make-up on the body's response to drug therapy. This response depends on various factors additional to genotype and genomic expression, including environment, lifestyle and demographics (e.g. age and gender). Currently, the use of genetic information to treat patients is still in its early stages, with some clear success mostly in the oncology and infectious diseases therapeutic areas. Some successful examples include the targeting of tailored pharmaceuticals developed for the treatment of patients with a particular disease subtype or according to a specific genetic make-up pertaining to the drug's mode of action (e.g. zelboraf). In other examples, genetic information is being used to help determine the effective and safe dose of specific pharmaceuticals (e.g. warfarin). However, implementation of this pharmacogenetic knowledge to the clinic has proven to be challenging and to require collaboration between the various stakeholders throughout the discovery, development and validation stages so as to ensure the utility of actionable genetic testing in a cost-effective manner. Targeted therapy and reliable prediction of expected outcomes offer patients access to better healthcare management, by way of identifying the therapies effective for the relevant patient group, avoiding prescription of unnecessary treatment and reducing the likelihood of developing adverse drug reactions.

In accordance with the main themes that define preventive and predictive genetics and its utility and wide-spread adoption world-wide, the chapters of this book walk the reader through the principles of this discipline and the state of the art across key therapeutic areas. To this end, the second chapter (i.e. the one preceding the introduction) discusses the broad definition of public health and the specific role that genetic testing plays in advancing population-level health outcomes. Indeed, preventive genetics has demonstrated utility as a crucial component in the success of population-wide health policies that promote improved health outcomes. The

identification of subjects at risk at the earliest age possible provides opportunities for tailoring actionable medical solutions when needed. Principles of preventive genetic programmes are outlined in details, and specific examples reviewed, including phenylketonuria, MCADD, homocystinuria, maple syrup urine disease, glutaric aciduria type 1, cystic fibrosis, haemoglobinopathies, hereditary haemochromatosis, familial hypercholesterolaemia, familial adenomatous polyposis and familial cancer predisposing syndromes. In addition, while complex traits are mostly yet to have been fully characterised in terms of the exact proportion explained by genetics on a population basis, characterisation of monogenic subtypes within complex diseases can be easily taken up into genetic testing programmes, as exemplified in detail by BRCA1 and BRCA2 for risk of breast and ovarian cancers, as well as other relevant cases. The chapter also touches on the practical, ethical and clinical aspects associated with biobanking of the required samples that facilitate the research, as well as application of screening genetics over time.

In the third chapter Bishop et al. describe the use of pharmacogenetics to the development of safer, more effective and differentiated therapies. This chapter describes the principles and requirements of an efficient and valuable pharmacogenetic strategy throughout the course of developing innovative medicines. This strategy combines a proven methodology with rigorous genetic science to create a "Pipeline Pharmacogenetic Program". By describing the pharma industry and the market forces shaping its drivers, pharmacogenetic applications are portrayed as aides to reduce attrition and enhance the scientific rigor, and over all benefit/risk profile of novel therapies. The authors review the scientific requirements, as well as sample collection and practical decision making perspectives that must be taken into account during R&D. Specific examples are shared throughout the drug development continuum and across a variety of therapeutic areas, including Alcohol Dependence, Oncology and Rare Diseases. Finally, unique features associated with the contemporenous development of drug and companion diagnostic are reviewed by way of describing an example dealing with Alzheimer's disease management.

The type of data and design of pharmacogenetic studies is a requirement to provide the necessary outcome and define actionable markers. In Chap. 4 Flynn et al. summarise the key statistical consideration required for successful and meaningful pharmacogenetic programmes. As a scientific discipline pharmacogenomics must demonstrate rigor of study design and significance of statistical findings, additional to biological and clinical relevance of variants identified. In addition, consideration of statistical factors unique to pharmacogenetics must be examined over the course of biomarker studies aspiring to implement prospective analyses. Furthermore, the nature of the biomarkers studied, whether predictive or prognostic, dictates a different suit of statistical considerations, as examplified by Flynn et al. This chapter provides the elements of good statistical practices in the pharmacogenomic space, spanning the entire field, from study design, source of variability, dimensionality, confirmation, model building, bioinformatics and ultimate development of diagnostics.

In Chap. 5 Mifsud et al. summarise decades of pharmacogenetic research dedicated to the various pharmacokinetics processes that drugs are subject to *in vivo* i.e.

absorption, distribution, metabolism and elimination. Examples span the earliest reports on succinylcholine from the 1950s through to the latest advances. In addition, authors provide a window into regulatory perspectives world-wide, which contribute to the adoption of existing knowledge, as well as dissemination of ADME genetics into novel drug development.

The critical role of genetics in predicting adverse drug reactions is described in Chap. 6 by Turner et al. Paradigm setting examples of the high predictive value of genetic variations for Immune-Mediated Adverse Drug Reaction are described in detail. However, the authors provide ample evidence that genetics can be a key determinant of adverse drug reactions associated with virtually any disease area and any drug mode of action, including analgesia, coagulation, cancer and cholesterol levels. These seminal examples have affected the medical profession in a profound fashion, ushering an industry of diagnostics that is widely accepted world-wide.

Chapter 7 builds on the insights revealed in the previous chapters and adds the first example of applied pharmacogenomics, describe the state of research and utility of pharmacogenomics in prescription of haemoglobinopathies therapeutics. Here, Gravias et al. describe the available treatment options and the genetic factors that have thus far been linked mostly to the β-globin gene cluster. These are believed to act by modulating HbF levels. The authors' analysis is concluded by the observation that the use of pharmacogenomics for haemoglobinopathies therapeutics are currently very limited, requiring larger studies in ethnically diverse patients groups.

Cacabelos et al. review the state of research and applicability of pharmacogenetics to neurodegenerative diseases in Chap. 8. The five categories of genetic variants associated with this field are defined as: (i) genes associated with disease pathogenesis (pathogenic genes); (ii) genes associated with the mechanism of action of drugs (mechanistic genes); (iii) genes associated with drug metabolism; (iv) genes associated with drug transporters; and (v) pleiotropic genes involved in multifaceted cascades and metabolic reactions. The role of each of these categories is then examined within the prototypic neurodegenerative diseases, i.e. Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis and Huntington's disease. The authors conclude by postulating future areas of focus for pharmacogenomic research, as well as overall policies associated with chronic, debilitating, late-onset diseases that affect the nervous system and expected to affect significant proportions of the aging world population.

The genetics and pharmacogenetics of asthma is reviewed in Chap. 9. Current approaches to asthma management call for clinical severity assessments, with regular re-evaluations of treatment, that is subsequently often redosed or switched. Specific pharmacogenetic considerations are provided which address the major drug classes in current use for asthma and/or chronic obstructive pulmonary disease (COPD), including leukotriene modifiers, glucocorticoids and anti-muscarinic agents. The evolving use of pharmacogenetic tools in novel drug development in respiratory indications in further details, providing great promise for patients.

Patel et al. provide an overview on the pharmacogenetics of antineoplastics in Chap. 10. In this context, the authors explain the unique attributes associated with germ-line versus somatic mutations, and the associated prognostic versus predic-

tive value of the reported biomarkers within each category. Specifically, examples are shared which directly address clinical decision making for a variety of solid and liquid tumour types, including the use of 6-mercaptopurine (6-MP), irinotecan, tamoxifen, fluorouracil, crizotinib, imatinib, ATRA, vemurafenib. erlotinib, herceptin, panitumumab and cetuximab. With the reduction in sequencing technology cost it is expected that tumour profiling will be used for patient classification and drug development, as well as for identification of driver mutations that define causality, diagnosis, prognosis and life-saving treatment choices.

Chapter 11 entails the utility of pharmacogenomics to anticoagulant therapy. Here, van Schie et al. describe both the basic science and clinical evidence associated with multi-marker testing for coumarin anti-coagulant therapy. Furthermore, the authors expand the scope of their analysis to coumarin derivatives, clinical trials investigating the effectiveness of pre-treatment genotyping and the cost-effectiveness of pharmacogenetic-guided dosing. These are critical studies required for adoption of pharmacogenetics to common practice and serve as precedents for the entire field.

Having reviewed each therapeutic area separately, Chap. 12 serves to provide a common vision to lessons learned and remaining challenges associated with the practice of genomic medicine. Here, Grech et al. focus on the needs and recommendations to promote patient molecular classification; stratification of well-defined subgroups of predicted responders to specific therapies; the development of technologies and integrative information systems to provide the healthcare system with optimised and sustainable genetic testing protocols; the need of harmonised guidelines for the proper selection of patient groups for clinical trials; and advances in research to generate evidence based knowledge that can be smoothly translated for healthcare use. Key gaps in the uptake of Genomic Medicine in the Health Care System are attributed by the authors to insufficient education of the Healthcare professionals and lack of mechanisms for appropriate dissemination of genomic information within the healthcare system. Lastly, the research community is still lagging behind in providing real-world, validated evidence to the validity of pharmacogenomic findings.

The book is concluded by Ellul, summarising ethical considerations associated with pharmacogenomics. The chapter focuses on ethical issues affecting the individual patient through his or her experience undergoing pharmacogenetic testing for personalised treatment, enrolling in clinical trials, participating in genomic research or donating biological material for biobanking and research. Core concept leading the ethical discussion center around perceived and actual benefits and risks, and the relative relationship between the two. The ubiquitously acceptable tool of informed consent is presented, including its variable applications and its existing and evolving guiding rules. Aspects of discrimination, ethnicity, privacy, confidentiality and the responsibilities of each of the associated stakeholders is detailed as well, providing a rounded account of the complexities and opportunities associated with pharmacogenomic utilisation.

In summary, this book collates a comprehensive account of the state of the pharmacogenomic science and its application to the management of most common dis-

ease areas, as pertaining to available therapies as well as those in development for future, better patient use. The book provides an outstanding didactic content in both preventive and predictive genetics and intended for use in postgraduate courses in Molecular Biology and Genetics, Bioinformatics and other life sciences programmes that focus on applied Genetics for future medicine. The common theme concluded by each of the expert authors converges into the vision that targeted therapies will become mainstay across all disease areas. Further, with the exponential growth of omics Big Data, our ability to translate sequence variation into useful tools for drug development and utilisation will ensure a speedy, safe and efficaceuos drug development process for future generations.