

Advances in Predictive, Preventive and Personalised Medicine
Series Editor: Olga Golubnitschaja

Godfrey Grech
Iris Grossman *Editors*

Preventive and Predictive Genetics: Towards Personalised Medicine



 Springer

Preventive and Predictive Genetics: Towards Personalised Medicine

Advances in Predictive, Preventive and Personalised Medicine

Volume 9

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Editors

Preventive and Predictive Genetics: Towards Personalised Medicine



Springer

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Current Book Series, published by Springer in collaboration with EPMA, overview multidisciplinary aspects of advanced bio/medical approaches and innovative technologies. Integration of individual professional groups into the overall concept of PPPM is a particular advantage of this book series. Expert recommendations focus on the cost-effective management tailored to the person in health and disease. Innovative strategies are considered for standardisation of healthcare services. New guidelines are proposed for medical ethics, treatment of rare diseases, innovative approaches to early and predictive diagnostics, patient stratification and targeted prevention in healthy individuals, persons at-risk, individual patient groups, sub/populations, institutions, healthcare economy and marketing.



Prof. Dr. Olga Golubnitschaja

Book Series Editor

Dr. Golubnitschaja, Department of Radiology, Medical Faculty of the University in Bonn, Germany, has studied journalism, biotechnology and medicine and has been awarded fellowships for biomedical research in Paediatrics and Neuro-sciences (Medical Centres in Austria, Russia, UK, Germany, the Netherlands, and Switzerland). She is well-cited in the research fields of “gene hunting” and “subtractive hybridisation” applied to predictive prenatal and postnatal diagnostics published as

O. Labudova in years 1990–2000. Dr. Golubnitschaja is an expert in molecular diagnostics actively publishing in the fields of perinatal diagnostics, Down syndrome, diabetes mellitus, hyperhomocysteinemia, cardiovascular disease, neurodegenerative pathologies and cancer. She is the *cofounder* of the theory of multi-pathway organ-related blood fingerprinting with specific molecular patterns at epi/genomic, transcriptional and post/translational levels and author of fundamental works in *integrative medicine*. Dr. Golubnitschaja holds appointments, at the rank of Professor, at several European Universities and in International Programmes for Personalised Medicine and is author of more than 300 international publications in the field. Awards: National and International Fellowship of the Alexander von Humboldt-Foundation; Highest Prize in Medicine and Eiselsberg-Prize in Austria; She is *Secretary-General* of the “European Association for Predictive, Preventive and Personalised Medicine” (EPMA in Brussels, www.epmanet.eu), Editor-in-Chief of *The EPMA-Journal* (BMC in London); Book Editor of *Predictive Diagnostics and Personalized Treatment: Dream or Reality*, Nova Science Publishers, New York 2009; Book Co-editor *Personalisierte Medizin*, Health Academy, Dresden 2010; Book Series Editor *Advances in Predictive, Preventive and Personalised Medicine*, Springer 2012; *European Representative* in the EDR-Network at the NIH/NCI, <http://edrn.nci.nih.gov/>; and *Advisor and Evaluator* of projects dedicated to personalised medicine at the EU-Commission in Brussels, NIH/NCI, Washington, DC, USA, and at Foundations and National Ministries of Health in several countries worldwide.

Preface

Traditionally, medical research comprised of the identification of the pathological causes of a disease, its epidemiology and empirical investigation of treatment response. Intensive genetic research, marked by the completion of the human genome project in 2003, heralded a new era in medical research. While epidemiology and gross pathology are still mainstay useful tools, genetics and genomics have gradually been shown to increase the resolution of drug response research, showing great potential in also informing and identifying the role of genes and their encoded products in the pathophysiology of diseases. This information is already being applied to effective early diagnosis, better risk assessment (prognosis), as well as targeted effective and safe treatment allocation (prediction and monitoring).

Genetic testing and genomics support personalised medicine by translating genome-based knowledge into clinical practice, offering enhanced benefit for patients and health-care systems at large. Current routine practice for diagnosing and treating patients is conducted by correlating parameters such as age, gender and weight with risks and expected treatment outcomes. In the new era of personalised medicine the healthcare provider is equipped with improved ability to prevent, diagnose, treat and predict outcomes on the basis of complex information sources, including genetic and genomic data. The support of regulatory bodies and policy makers internationally has been critical for the rapid translation of personalised medicines into the clinic. Notwithstanding, inequality in the utilisation of targeted therapies in different health care systems across the world exists, and ethical considerations, as well as economic cost-effectiveness analyses are in need to inform decision making. In addition to the benefits of pharmacogenomics in diagnosis and treatment, prevention of illness using genomic information is important to reduce the burden on the healthcare system, a methodology proven effective in many therapeutic areas, but, paradoxically still facing challenges in others. In current settings screening programmes (e.g. BRCA1/2 screening) address this by identifying susceptible families and preventive measures or ensuring appropriate treatment at the earliest stages of disease, hence increasing health management effectiveness.

The integration of pharmacogenomics into the various health care systems have been the responsibility of the respective national health authorities, which in turn follow recommendations by leading regulatory bodies such as the European

Medicines Agency and the US FDA. The dynamics and logistics of this integration therefore vary substantially across the globe. To this end, implementation of pharmacogenomics is an important component of PPPM (Predictive, Preventive and Personalised Medicine), which is the main focus of the European Association for Predictive, Preventive and Personalised Medicine (EPMA). Since 2009, EPMA (<http://www.epmanet.eu/>) embarked on various initiatives to promote PPPM including the launch of the EPMA Journal to ensure dissemination of current aspects of PPPM, and the organisation of the first World Congress in September 2011 bringing together participants from over 40 countries to discuss education, policy and implementation of PPPM. In addition, EPMA took the initiative to publish a series of books in advances in PPPM, including the present one entitled “**Preventive and Predictive Genetics: Towards Personalised Medicine**”. The editors take this opportunity to thank all contributing authors and trust that the content meets the expectation of all readers.

The Editors

Godfrey Grech, PhD
and Iris Grossman, PhD

Acknowledgement of Reviewers

The Editors wish to acknowledge the reviewers for their generous contribution in assessing the Chapters providing constructive critique and recommendations. The reviewers provided the means to enhance the quality of the book and hence we sincerely are grateful.

Beena Koshy, Peter Shaw, Ann Daly, Anderson Wayne H, Dr Alex Gatt, Aruna Bansal, Michael Barnes, Godfrey Grech, Joseph Borg, George Patrinos, Christian Scerri.

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About the Editor



Godfrey Grech, PhD

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Dr. Godfrey Grech is Senior Lecturer at the University of Malta. Since 2006, Dr. Godfrey Grech is responsible for the coordination of an MSc in Biomedical Sciences and currently runs the Molecular Pathology laboratory at the University of Malta. Following his doctorate studies at Erasmus Medical Centre, Rotterdam, he published in high impact journals and presented in International conferences such as the American Society of Hematology, the EPMA Congress and the European Pathology Congress. In the last few years, Dr. Godfrey Grech was selected to lead the research arm of the National Transfusion Centre and was given the role of a Principle Investigator on the National Breast Cancer Research Project. In addition, he is highly recognised by the clinical sector and runs numerous projects with Mater Dei Hospital and was instrumental to set up infrastructures that allow the use of fresh surgical sections in molecular pathology research. Currently he runs various collaborative projects with International Institutions including Erasmus Medical Centre and the Molecular Medicine Institute in Leeds. The main research topic aims to identify biomarkers to classify breast cancer patients into a specific therapeutic group that shall benefit from activation of phosphatases as a main therapeutic option.

Dr. Godfrey Grech was nominated and is elected on international scientific committees including the International Scientific Council of the European Group for Molecular Pathology (EMP); Global Leader at the Genomic Medicine within the National Human Genome Research Institute (NHGRI) of the U.S. National Institutes of Health (NIH); member of the Pharmacogenomics Working Group of the Global Genomic Medicine Consortium (G2MC); Leader of the Cancer Position Paper at the European Association for Predictive, Preventive & Personalised Medicine (EPMA); and national contact point for the Pharmacogenetics for Every Nation Initiative (PGENI).



Iris Grossman, PhD

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Dr. Iris Grossman is CEO and president of the pharmacogenetics management consultancy IsraGene Ltd., as well as VP, global head of the Personalized Medicine and Pharmacogenomics (PMP) unit for Teva Global R&D. She has dedicated her research career, in both industry and academia, to the advancement of the field of personalised medicine. Dr. Grossman is currently charged with defining and implementing the global PMP strategy for Teva, a top-10 global pharmaceutical company, covering both discovery and development R&D programmes. Israel's leading financial magazine, Globes Magazine, selected Dr. Grossman as one of the country's top 40 professionals under 40 years of age in 2013.

This followed several years of spearheading pipeline pharmacogenetic programmes for industry and academia as director of pharmacogenetics at Cabernet Pharmaceuticals Inc. Dr. Grossman moved into consultancy having been responsible for running large-scale pharmacogenetic programmes at GlaxoSmithKline, with an emphasis on infectious and neurological diseases.

In academia, Dr. Grossman was a key member of Professor David Goldstein's team at the Center for Population Genomics and Pharmacogenetics, Institute for Genome Sciences and Policy, at Duke University. Dr. Grossman received her PhD from the Technion – Israel Institute of Technology, where her research project, conducted in collaboration with the Weizmann Institute for Science, investigated pharmacogenetic markers of multiple sclerosis treatment response.

Introduction

Godfrey Grech and Iris Grossman

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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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 contemporaneous 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 exemplified 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 efficacious drug development process for future generations.

Preventive and Predictive Genetics: A perspective

Godfrey Grech, Christian Scerri, Jeanesse Scerri and Tomris Cesuroglu

Abstract Public Health practices focus on the implementation of programmes for health improvement and disease prevention (Khoury et al., Am J Prev Med 40(4):486–493, 2011). Public health initiatives in diseases were initially targeted to prevent infectious diseases. Partly due to the availability of vaccines and anti-microbial therapy and partly due to better standard of living, the world is free of diseases such as small pox, almost free of polio and the prevalence of infections such as malaria and HIV is steadily on the decline. This has meant that the human race is living longer with the result that non-communicable diseases have become a global public health priority. Preventing non-communicable diseases is a more logical approach than treating them, even more so when modifiable, common lifestyle risk factors share a role in the onset and progression of the disease. Preventive genetics plays a crucial role in the identification of subjects at risk at a very early age, which would thus give public health officials the necessary time to take appropriate action.

Genetic tests can be classified into carrier, diagnostic and predictive testing. In carrier testing, the tests are directed towards the identification of carriers of autosomal recessive or X-linked genetic disorders to prevent disease. Preventive genetics can be defined as using genetics for the prevention of a future disease that has a genetic component either in the individual tested or in future offspring. Diagnostic testing is the process that identifies the current disease status of the subject and includes, among others, prenatal and newborn screening. The implementation of screening programmes allow the detection of genetic disorders at an early stage, so as to prevent these conditions or their serious consequences. Predictive testing

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determines whether a subject with a positive history but no symptoms of the disease, is at risk of developing the disorder at a future date. In this chapter, we will discuss the application of genetic screening tests to monogenic disorders and complex disorders with monogenic subsets, in view of the current practices. The multifactorial aetiology of complex disorders involves multiple gene effects and gene-lifestyle interactions that cannot be singled out to give a strong predictive value. However, a subset of the complex disorders are caused by highly penetrant genetic mutations. Hence, in this chapter we shall also address predisposing syndromes with high predictive value. In addition, the need of biobanks will be discussed.

Keywords Public health genomics · Preventive genetics · Predictive genetics · Screening programmes · Monogenic disorders · Monogenic syndromes · Biobanks

1 Screening Programmes

According to the UK National Health Services, the term *screening* signifies a public health service aimed at identifying individuals that, though apparently healthy, are at risk of or are already affected by a particular disease or its complications. This identification could be through a particular medical or biochemical test or a questionnaire. Once identified, the affected individuals could then be offered further information, complementary tests or treatment in a bid to reduce their risk of developing the disease or its complication. The use of genetic testing to improve healthcare, requires implementation of programmes as part of public health practice [1]. In their 2004 paper on the history of medical screening, Morabia and Zhang [2] identified the US army's 1917 screening programme, aimed to exclude individuals with clear psychological disorders from joining the army, as the first reported instance of a "screening programme." This programme consisted of the administration of psychological tests to officers, drafted and enlisted soldiers. Since this early example of a screening programme, other initiatives mostly directed towards the general public and aimed at the prevention or early treatment of important health conditions, have spread across the world.

There are three main types of organised screening programmes, namely population screening, newborn screening (NBS) and cascade screening. Population-based screening involves testing the majority of the population, which may either be defined as the whole population of a country or a specific population at risk (such as Ashkenazi Jews for Tay-Sachs disease, or women over a specific age for breast cancer screening). A highly targeted population for screening of genetic disorders is that of women at the prenatal or pre-conception stage, due to their high accessibility and ease of retraceability. Whereas pre-conception screening allows a wider choice of reproductive options than prenatal screening (i.e. opting to have no children, using a sperm donor, or pre-implantation genetic diagnosis (PGD) and selective implantation of embryos created through in-vitro fertilisation (IVF) in the former, against elective termination of pregnancy in the latter), antenatal groups are easier to target.

Meanwhile, NBS involves screening of all newborns in order to detect (generally and preferably) early-onset diseases before the occurrence of overt symptoms. Several genetic metabolic disorders, diagnosed through biochemical tests rather than genetic tests, constitute the core group of disorders for which established newborn screening programmes exist worldwide. These include phenylketonuria (PKU), for which the first NBS programme was set up in the early 1960s, maple syrup urine disease (MSUD) and congenital hypothyroidism (CH). Other specific disorders that are tested for within certain regions or ethnic groups include the haemoglobinopathies (by isoelectric focusing [IEF] and high-performance liquid chromatography [HPLC]) and Cystic Fibrosis (CF; by immunoreactive trypsinogen [IRT]). Cascade screening starts with an index case showing symptoms (the proband) and testing family members for mutations predisposing them to the same disease. Unlike the other forms of screening, cascade screening specifically targets individuals considered at high risk of acquiring the disease due to family history and is restricted to genetic (i.e. DNA) tests.

In the late 1960s, technological advances in medicine enabled the spread of screening in various fields of medicine but, at the same time, brought forward topics of controversy as well as ethical implications. Under this scenario, the World Health Organisation commissioned a report on screening from James M. G. Wilson and Gunner Jungner. In their 1968 report, Wilson and Jungner [3] recounted their pre-occupation that, while the “central idea of early disease detection and treatment is essentially simple”, achieving its success of “bringing to treatment those with previously undetected disease”, as opposed to “avoiding harm to those persons not in need of treatment”, is not as easy as it might appear. In an attempt to simplify the process of screening, Wilson and Jungner proposed a set of criteria that has been adopted as the gold standard in the establishment of all screening programmes. According to these criteria, screening programmes should be considered for conditions fitting in within the following:

1. The condition should be an important health problem.
2. There should be a treatment for the condition.
3. Facilities for diagnosis and treatment should be available.
4. There should be a latent stage of the disease.
5. There should be a test or examination for the condition.
6. The test should be acceptable to the population.
7. The natural history of the disease should be adequately understood.
8. There should be an agreed policy on whom to treat.
9. The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole.
10. Case-finding should be a continuous process, not just a "once and for all" project.

However, these criteria were targeted towards screening for diseases of significant burden in general and did not take into account certain aspects pertaining to genetic diseases, such as the serious debilitating nature of certain rare genetic conditions and the inheritable nature of these disorders. The accelerated rate of discovery of

new disease-causing genes has opened up a whole new dimension of diagnosis by using genetic testing to detect diseases before the first clinical signs and/or symptoms appear, even before the disease starts its pathological course. Conversely, these advancements have also caused public health to lag behind in the introduction or expansion of genetic screening programmes, mostly because the decision-making process requires extensive risk-assessments and the implementation of pilot studies, as well as control and standardisation of such programmes [4]. This has resulted in different countries applying different criteria, most of which are based on the original ones by Wilson and Jungner but which take into account the mentioned additional factors, leading to a lack of standardisation or consensus. In the following sections, disorders for which screening programmes are either already in place or may be considered in the near future will be described, with the application of screening criteria to the decision-making process. In addition, the use of next-generation sequencing for newborn screening will be discussed as a future strategy in public health genomics.

2 Monogenic Disorders

Monogenic disorders are mainly rare disorders, caused by single-gene modifications that are present in all the cells of the body and following Mendelian modes of inheritance, i.e. dominant, recessive or X-linked [5]. Though the phenotype in monogenic disorders is almost dependent on a single genetic component, it is also influenced by the individual's genome (modifier genes), as well as environmental and lifestyle factors. Rare, or orphan, disorders are most commonly defined as disorders affecting 5/10,000 persons or less, but collectively they contribute to a significant degree of morbidity and mortality. Furthermore, eighty percent of rare disorders have genetic origins [6], and the advent of next-generation sequencing has brought about the accelerated discovery of new causative mutations [7]. There are also several monogenic disorders which are relatively common, either worldwide or in specific populations. Being easier to identify, either by biochemical or genetic tests, these disorders were the first genetic conditions for which population screening programmes were established.

2.1 *Inborn Errors of Metabolism*

An important subset of monogenic disorders consists of the inborn errors of metabolism. Neonatal screening for inborn errors of metabolism has been in place since the early 1960s, following the development of a fast and cheap blood test for phenylketonuria (PKU) [8]. After the success of the first newborn screening programme, maple syrup urine disease (MSUD) screening by the Guthrie ("heel prick") method was soon added. Up to the introduction of tandem mass spectrometry (MS/MS) technology in newborn screening, individual diseases were tested on a one test,

one disorder system that is both expensive and relatively inefficient. The use of MS/MS has expanded the number of inborn errors of metabolism disorders that can be tested from a single dried blood spot, in one single analytical run. To date, MS/MS can identify 45 different disorders, including amino acid disorders, fatty acid oxidation disorders, and organic acidemias, from a single blood spot taken in the neonatal period [9]. Almost all of the national newborn screening programmes in the world include PKU, with medium-chain acyl-coA dehydrogenase deficiency (MCADD) found in a majority of programmes. Other disorders that are actively being added to the list are homocystinuria (HCU), maple syrup urine disease (MSUD) and glutaric aciduria type 1 (GA1).

2.1.1 Phenylketonuria (PKU)

PKU is an autosomal recessive disorder with a reported prevalence as high as 1 in 4500 in Ireland [10] to as low as less than 1 in 100,000 in Finland [11]. In its typical form, it is a result of a mutant phenylalanine hydroxylase (PAH) enzyme, which catalyses the conversion of phenylalanine to tyrosine. Reduced activity of PAH results in an accumulation of phenylalanine and its metabolite phenylpyruvate. This accumulation of phenylalanine leads to intellectual disability, seizures and other symptoms. The major problem is an inability of the brain to utilise other large neutral amino acids (LNAA), such as tryptophan and tyrosine, since the large quantities of phenylalanine block the blood-brain barrier's large neutral amino acid transporter (LNAAT). Thus, the brain is starved from amino acids that are essential for proper synthesis of neurotransmitters. Management of PKU consists in low phenylalanine diet and possibly the oral administration of tetrahydrobiopterin that is a cofactor in the oxidation process of phenylalanine. To be successful in achieving normal brain development, the diet needs to be initiated as early as possible and continued throughout life.

2.1.2 Medium-Chain Acyl-coA Dehydrogenase Deficiency (MCADD)

Medium-chain acyl-coA dehydrogenase deficiency (MCADD) is a disorder of fatty acid oxidation, in particular the conversion of medium chain fatty acids (MCFA) into acetyl-CoA. It is most prevalent in individuals of Northern European Caucasian descent, with reported worldwide prevalence of between 1:10000 and 1:27000 [12]. The inability to convert MCFA into Acetyl-CoA results in a deficiency of fatty acid breakdown during periods of metabolic stress, such as a period of fasting or illness. The presenting symptoms include hypoglycaemic attacks, vomiting and encephalopathy that can lead to coma and sudden death. As studies have shown that over 25% of undiagnosed children die during their first attack, with 16% of the survivors having severe neurological deficiencies [13], early diagnosis and start of treatment is essential. The latter consists of a diet which is high in carbohydrates and low in fatty acids, in particular during periods of risk, and avoidance of fasting [14].

2.1.3 Homocystinuria (HCU)

Homocystinuria (HCU) is another rare, autosomal recessive condition, where the body is unable to convert homocysteine (derived from methionine) into cystathionine due to the reduced activity of the enzyme cystathionine beta-synthase. Thus, in a similar way to phenylketonuria, homocysteine and to an extent methionine, accumulate in the body while there is a deficiency of cystathionine. The reported worldwide prevalence is of 1 in 344,000, with certain countries such as Ireland (1: 65000) reporting comparatively very high rates [15]. The symptoms of HCU include developmental delay of the brain, behavioural changes such as mood and personality disturbances, dislocation of the lens of the eye, disproportionate length of limbs compared to the body, osteoporosis and higher risk of vascular thrombosis. Treatment consists of vitamin B6 (a cofactor of cystathionine beta-synthase) and a low methionine diet. In addition, the administration of oral betaine helps to convert homocysteine back into methionine and thus reduce the levels of homocysteine.

2.1.4 Maple Syrup Urine Disease (MSUD)

Maple syrup urine disease (MSUD) gets its name from the presence of a distinctive sweet smelling urine reminiscent of maple syrup. The condition can be the result of mutations in any one of the four genes that code for the 4 subunits ($E_1\alpha$, $E_1\beta$, E_2 , and E_3) of the branched-chain alpha-keto acid dehydrogenase complex (BCKDC). The lack of BCKDC leads to a gradual increase of the branched-chain amino acids isoleucine, leucine and valine, resulting in a build-up of toxic ketoacids in the blood and consequently in the urine. Like most of the other inborn errors of metabolism, the condition is inherited in an autosomal recessive way. As the disorder can be due to the lack or reduced activity of any one of the 4 subunits, its clinical picture and prognosis is variable, but brain damage with mental problems as well as physical problems, such as lethargy, hypotonia, seizures, pancreatitis and ketoacidosis, are common events. The management of MSUD requires a life-long diet where the level of these essential branched chain amino acids is kept under strict control and at the barest minimum. If well managed from early years, those afflicted are usually able to live a normal life with little or no neurological damage. The prevalence of this disorder is reported to be approximately 1 in 200,000 [9], with increased incidence in persons of Amish, Mennonite, and Ashkenazi Jewish descent [16–18].

2.1.5 Glutaric Aciduria Type 1 (GA1)

Glutaric aciduria type 1 (GA1) is another inherited error of metabolism involving the reduced capability of the breakdown of amino acids. Its worldwide prevalence is reported as 1:100,000 [19]. GA1 is caused by mutations within the *GCDH* gene that encodes for the enzyme glutaryl-CoA dehydrogenase. The enzyme is required for the metabolism of the amino acids hydroxylysine, lysine and tryptophan. This reduction of effective enzyme activity results in a build-up of intermediate me-