Introduction

Personalized approaches, both genomic and non-genomic can be applied in almost every disorder of the human body. Some minor disorders can be managed by conventional approaches, which may be modified in an individual patient. Full chapters are devoted to cardiovascular, neurological, psychiatric, and respiratory systems. All other disorders are presented briefly in this chapter.

Personalized Management of Ophthalmic Disorders

Management of several ophthalmic disorders can be personalized. Clinical and genetic heterogeneity of ocular disorders makes it difficult to identify compounds that can treat all patients effectively, suggesting that tailored treatments may be necessary. Several genes underlying disease have been identified and sequencing has enabled understanding of these diseases at molecular level and accurate molecular diagnosis. Proteomic analysis of fluid taken from the patient’s eye and analysis of the protein profile may be useful for personalized treatment of idiopathic inflammatory disorders of the eye.

Proteomics-Based Personalized Management of Uveitis

Analysis of expression levels of 200 human cytokines in vitreous samples of patients with posterior uveitis, based on their cytokine expression profile, suggests that certain protein networks and molecular pathways are altered in various forms of uveitis (Velez et al. 2016). Expression of IL-23, IL-1 receptor I, IL-17 receptor, tissue inhibitors of metalloproteinase 1 and 2 (TIMP-1 and TIMP-2), IGF-binding protein 2 (IGFBP-2), NGF-b, PDGF receptor β polypeptide, BMP-4, and stem cell factor (SCF) constituted a common cytokine signature in the vitreous of patients with uveitis. In 1 patient with progressive, idiopathic visual loss, this last-line analysis implicated retinal autoimmunity, a diagnosis that was validated when the serum sample was found to contain antibodies to S-arrestin, a retinal protein and potent cause of autoimmune retinal degeneration. In this case, the analysis identified a common cytokine signature for posterior uveitis and guided the diagnosis of a patient with idiopathic uveitis. Personalized treatment by implantation of a device that continuously releases a steroid into the eye reversed the visual loss, illustrating how proteomic tools may individualize therapy.
Combining Cell and Gene Therapies for Retinal Disorders

Gene therapy of inherited retinal diseases is a form of personalized treatment. Ophthalmic gene therapy has been very successful in both animals and humans and several clinical trials are in progress. Since the eye is an immune privileged organ, only a weak immune reaction is triggered when a viral vector is injected in the eye, reducing the side effects of gene therapy, and increasing transfection efficiency. Gene therapy of various disorders is described in more detail in a special report on this topic (Jain 2020). Gene therapy slows down degeneration in rodent models of primary photoreceptor diseases. The ultimate solution to restoration of vision might be blending both gene therapy and stem cell transplantation. Viral vectors might be used for transfection of stem cells, giving them genes that force them to become photoreceptors. The progress made with such approaches now offers hope to patients with these incurable forms of blindness.

CRISPR (clustered regularly interspaced short palindromic repeats) and iPSCs can be used for interrogation of disease pathophysiology, analysis of gene therapy and as a source of autologous cells for cell transplantation and replacement for retinal degenerative disorders (Wiley et al. 2015). Applications of iPSCs and CRISPR include disease modeling, diagnostics and therapeutics – with an ultimate view towards understanding how these two technologies can come together to address heterogeneity of retinitis pigmentosa in a novel personalized medicine platform (Zheng et al. 2015). Coupled with the ability to generate iPSCs from mature cells and to differentiate them into retinal cells, CRISPR brings within reach the possibility of autologous iPSC-derived retinal cell transplantation, which might not only halt, but also potentially reverse progressive vision loss in retinitis pigmentosa.

Genetic Testing for Personalized Skin Care

Lab 21 (New York) claims that by taking DNA samples from customers it can provide a personalized skin cream based on specific variations of five genes related to skin sensitivity and aging. The only way to get the formula is to visit one of the company’s shops. After answering a 10-minute online questionnaire about their skin, ethnic origins, pore size and hydration, the customers get the inside of their mouths swabbed for a DNA sample. The test and the sample are sent to a laboratory to be analyzed and the customized skin creams are generated based on the results. Some geneticists and dermatologists are rather skeptical about this product. It is not a product that is genetically programmed for their skin. Simply studying a DNA sample, without the knowledge of genes that regulate skin health is unscientific. Another issue is privacy because the swabs taken at the shops contain a complete set of an individual’s genetic information including genes relevant to several diseases. Lab 21 says that it will keep all genetic information private, and their Web site claims the genetic samples are destroyed immediately after the analysis is complete.

GeneLink Inc invented the first genetically designed patentable DNA test for customized skin care products, and in partnership with DNAPrint, is screening millions of candidate biomarkers. Tests are designed to assess genetic risks for certain skin disorders due to nutritional deficiencies and provide a basis for recommending formulations that have been specifically designed to compensate for these deficiencies.

Personalized Management of Skin Disorders

There is an overlap between cosmetics, skin care and therapy of skin disorders. Everything from ancient herbs to sheep placentas has been used to make skin care products.

Management of Hair Loss Based on Genetic Testing

Androgenetic alopecia occurs with increasing phenotypic expression based on advancing age, approximately 65% men and 50% of women will...
be affected by the age of 60. Clinical diagnosis relies largely on the development of a hair loss pattern, and visible areas of thinning or baldness, which is not apparent until ~50% of hair are lost in a given area. Thus, patients will have substantial hair loss prior to initiation of therapy. However, the two FDA-approved medications to combat hair loss, minoxidil and finasteride, are most effective at stabilizing hair loss rather than hair regrowth. Therefore, a screening test for androgenetic alopecia which identifies patients at higher risk for developing it can offer the opportunity for early medical intervention prior to visible signs of hair loss.

An association between male pattern baldness and the androgen receptor gene is well recognized. HairDX (www.hairdx.com) provides genetic tests for both male and female androgenetic alopecia, which are administered in the privacy of a physician’s office using a simple cheek swab. HairDX (RxR) genetic test for finasteride response provides men with a score – CAG repeat score. Smaller CAG test score is associated with an increased response to finasteride for treatment of androgenetic alopecia in men. Among men that had the best response to finasteride, ~70% had a CAG score <22, whereas among men that had a subtle response to finasteride ~70% had a CAG >22. This test helps to personalize treatment of androgenetic alopecia.

**Personalized Urology**

Like any other specialty, personalized medicine has an impact on practice of urology. This is most significant in the management of tumors of the genitourinary tract, particularly bladder and prostate cancers, which are dealt with in Chap. 21. One of the challenges in this area is meaningful translation of the massive amount of data from basic research to clinical practice. Focus in the future is on targeting of tumor stem cells, validated biomarkers, and genetic profiling of urological neoplasms. Several clinical applications are expected, from diagnosis to selection of candidates for different treatment modalities, to modulation of sequential treatment plans, and prognosis (Mancini et al. 2016).

**Personalized Management of Obesity**

**Basics of Obesity**

Obesity affects >500 million people worldwide and contributes to type 2 diabetes, cardiovascular disorders, and cancer. Obesity is the result of a positive energy balance, whereby energy intake exceeds expenditure, resulting in the storage of energy in fat cells or adipocytes, which are brown or white, and in a living organism can be converted from one cell type to the other. White fat cells function mainly as flexible energy stores, which are filled in times of calorie abundance, whereas brown adipocytes specialize in burning energy in the form of fat and sugar to produce heat.

Energy balance is maintained by consumption of food and physical activity, as well as by the dissipation of energy as heat through thermogenesis in mitochondria-rich brown adipocytes and through inducible thermogenesis in white adipocytes. Thermogenesis is triggered by mechanisms within the cells themselves or by the sympathetic nervous system (e.g. through β-adrenergic receptor agonists), in response to exercise, diet, or exposure to cold. Further studies suggest that there are two distinct types of brown fat: classical brown fat derived from a myf-5 cellular lineage and uncoupling protein 1 (UCP1)-positive cells that emerge in white fat from a non-myf-5 lineage. Beige cells resemble white fat cells in having extremely low basal expression of UCP1, but, like classical brown fat, they respond to cyclic AMP stimulation with high UCP1 expression and respiration rates (Wu et al. 2012). Regulators of mitochondrial thermogenesis control the expression of the gene encoding UCP1, which depolarizes the inner mitochondrial membrane, causing proton transfer and heat dissipation.

Incidence of obesity has increased dramatically in the past few years fuelled by a shift in dietary habits owing to the widespread availability of low-cost, hypercaloric foods. However, there are differences in susceptibility to obesity among individuals exposed to the same environmental factors, which implicates genetic risk factors.
**Genetics of Obesity as a Basis for Personalized Management**

Genotype plays an important role in the development of obesity, and recent genome wide association studies have identified multiple loci associated with body mass index and distribution of body fat. However, fat mass and obesity (FTO) associated gene explains the largest amount of the genetic variance in obesity traits over the lifespan.

Examination of epigenomic data, allelic activity, motif conservation, regulator expression, and gene coexpression patterns, have been used to dissect the regulatory circuitry and mechanistic basis of the association between the FTO region and obesity in mice with endogenous CRISPR-Cas9 genome editing followed by validation by directed perturbations in samples from patients (Claussnitzer et al. 2015). The results indicate that the rs1421085 T-to-C SNV underlies the association between FTO and obesity by disrupting ARID5B-mediated repression of IRX3 and IRX5, which leads to a developmental shift from browning to whitening programs and loss of mitochondrial thermogenesis. This could lead to a cell-autonomous shift from white adipocyte browning and thermogenesis to lipid storage, increased fat stores, and body-weight gain. Manipulation of the uncovered pathway, including knockdown or overexpression of the upstream regulator ARID5B, genome editing of the predicted causal variant rs1421085, and knockdown or overexpression of target genes IRX3 and IRX5, had a significant effect on obesity phenotypes. To develop new treatments for obesity, one needs to find methods for converting white into brown adipocytes. Most of the research has focused on identifying precursor cells for brown fat cells, but this is insufficient. A better approach would be manipulation of interconversion process of 2 types of fat by pharmacological or by nutritional means.

**Limitations of Personalized Approach to Management of Obesity**

Although numerous genes have been associated with increased body weight, the extent to which genes determine the ability to lose weight remains unclear. One study represents a substantial step towards answering this, at least for the FTO gene, the allele currently associated with the largest variance in body mass index (Livingstone et al. 2016). This was a systematic review and meta-analysis of randomized trials in overweight or obese adults reporting reduction in body mass index, body weight, or waist circumference by FTO genotype (rs9939609 or a proxy) after dietary, physical activity, or drug based interventions. Gene by treatment interaction models were fitted to individual participant data from all studies included in this review, using allele dose coding for genetic effects and a common set of covariates. Conclusion of this study were that carriage of the FTO minor allele was not associated with differential change in adiposity after weight loss interventions. It adds to the evidence suggesting that environmental factors might dominate over at least common obesity linked genes. These findings of the study show that individuals carrying the minor allele respond equally well to dietary, physical activity, or drug based weight loss interventions and thus genetic predisposition to obesity associated with the FTO minor allele can be at least partly counteracted through such interventions. It is increasingly evident that personalised interventions based on the genome may not suffice in tackling the problem of obesity. The solutions to the obesity crisis must be societal, as well as individual and multi-disciplinary approaches including environmental drivers may be of greater benefit in the long term (Tedstone 2016).

**Personalized Management of Diabetes**

Worldwide prevalence of diabetes mellitus is ~347 million. Historically there are two main types: type 1 diabetes mellitus (T1DM) or insulin-dependent DM affecting 10% of individuals and type II diabetes mellitus (T2DM) affecting the rest, i.e. 90%. Monitoring of diabetes mellitus is rapidly advancing toward fully automated glucose control systems such a personalized glucose advisory system (PGASystem) for management
of DM. Adults with T1DM appear to be enthusiastic about using a PGASystem system for their diabetes management but also have significant concerns affecting their overall willingness to follow such a system’s advice because of the following concerns: (1) how the advice is generated; (2) relinquishing control to automated technology; and (3) inadequate personalization of the system (Shepard et al. 2012).

DM provides an example of chronic disease management with a focus on patient self-management. Despite advances in DM therapy, many affected persons still fail to achieve treatment targets and remain at risk of complications. Personalizing the management of diabetes according to the patient’s individual profile can help in improving therapy adherence and treatment outcomes. A 6-step cycle for personalized DM (self-) management and collaborative use of structured blood glucose data has been described (Ceriello et al. 2012). E-health solutions can be used to improve process efficiencies and enable remote access. Decision support tools and algorithms can help physicians in making therapeutic decisions based on individual patient profiles.

There is a need for technology that can accurately assess β cell death to improve diagnosis of DM, allow for disease staging, and provide improved evaluation of the efficacy of treatment. A PCR-based technology (Islet Sciences) can be used to identify β cell death before the onset of hyperglycemia and soon after the onset of T1DM. The method uses a stepwise detection and analysis of β cell and non-β cell-derived insulin DNA based on the existence of unique DNA methylation patterns in the β cells that are absent from other cells in the body.

**Biomarkers in the Management of Diabetes**

Efforts to prevent DM should be tailored to high-risk individuals rather than populations and will be based on genetic and other new biomarker tests. Accurate biomarker tests to identify people at risk for diabetes could enable targeted and individualized prevention efforts. DNA variants conferring higher risk for T2DM have been identified, but these account for only a small fraction of genetic risk, which limits their practical predictive value (Spiegel and Hawkins 2012). Identification of these variants has not yet led to new, individualized prevention methods. Further research is needed to identify genomic and other types of biomarkers that could accurately predict risk and facilitate targeted prevention.

**Closed Loop Control of type1 DM**

A closed-loop system (also known as an “artificial pancreas”) automates insulin delivery according to needs to the desired glycemic outcomes and shown to be effective in meta-analyses (Karageorgiou et al. 2019). A “hybrid” closed-loop system (Medtronic MiniMed 670G), which modulates basal insulin delivery but does not administer automated boluses is in commercial use. A closed-loop system (Control-IQ, Tandem Diabetes Care) uses an algorithm with a dedicated hypoglycemia safety module, automated correction boluses, and overnight intensification of basal insulin delivery designed to consistently target near-normal glycemia each morning. The 6-month International Diabetes Closed Loop (iDCL) randomized trial showed that use of Control-IQ achieved a greater percentage of time spent in a target glycemic range as compared with a sensor-augmented pump (Brown et al. 2019).

**Personalized Prediction of Postprandial Glycemic Response**

Examination of a cohort of adults without diabetes has shown that a personalized predictive model that considers unique features of the individual, such as clinical characteristics, physiological variables, and the microbiome, in addition to nutrient content is more predictive than current dietary approaches that focus only on the calorie or carbohydrate content of foods (Mendes-Soares et al. 2019). Providing non-diabetic individuals with tools to manage their glycemic responses to food based on personalized predictions of their
post-prandial glycemic responses (PPGRs) may enable them to maintain their blood glucose levels within limits associated with good health. Personalized PPGR predictions are accessible in the form of a mobile or web-based application, enabling real-time assessment of influences of foods and combinations of foods on blood glucose levels of the individual at the time of consumption. This capability adds to strategies already in place that are aimed at decreasing the incidence of diabetes while enabling individuals to better control their nutritional behaviors.

**Personalized Management of Monogenic Diabetes**

Monogenic diabetes (MD) accounts for 1–2% of all diabetes cases. Because of its wide phenotypic spectrum, MD is often misdiagnosed as type 1 DM or type 2 DM. Although clinical and biochemical parameters may suggest MD, definite diagnosis requires genetic analysis. In a sequencing study, the most common mutations were found in the GCK gene, followed by the mitochondrial genome and the HNF1B and HNF1A genes. A new diagnostic panel of 42 genes was developed based on the survey and validated with an independent sample of 9 known MD patients, which confirms the need for a comprehensive analytical instrument for the diagnosis of MD (Kherra et al. 2017). The diagnosis of MD is crucial because it enables personalized treatment and may improve metabolic control as well as reduce long-term complications.

**Selection from Multiple Options for Treatment of T2DM**

T2DM is commonly treated with more than one type of therapy, including oral antidiabetic drugs (OADs) and agents used in the treatment of diabetic complications. Several pharmacological classes of OADs are currently available for the treatment of T2DM, of which insulin secretagogues (i.e., sulphonylureas and meglitinides), insulin sensitizers (thiazolidinediones) and biguanides are the most frequently prescribed. Although many of these OADs have been used for more than half a century in the treatment of T2DM, the pharmacogenomic characteristics of these compounds have only recently been investigated, primarily in retrospective studies. Advances in pharmacogenomics have led to the identification of polymorphisms that affect the expression and function of drug-metabolizing enzymes and drug transporters, as well as drug targets and receptors. Pharmacogenomic data obtained from studies of T2DM treatment, with a focus on polymorphisms in genes affecting pharmacokinetics, pharmacodynamics and treatment outcome of the most commonly prescribed OADs throws some light on the therapeutic response to and side effects associated with OADs (Emami-Riedmaier et al. 2015). Novel ‘omics’ technologies and might aid in the personalized management of T2DM.

**Stratification of Diabetes into 5 Subgroups and Personalized Medicine**

A study reported that diabetes patients in Sweden and Finland fell into 5 clusters, one of which was like T1DM, while the other 4 clusters were “subtypes” of T2DM (Ahlqvist et al. 2018). Classification of 5 clusters of diabetes are shown in Table 18.1. The authors are not suggesting getting rid of type 1 and type 2 diagnoses; rather, they are suggesting that there are subtypes, which had significantly different patient characteristics and risk of diabetic complications. Particularly, individuals in cluster 3 (most resistant to insulin) had significantly higher risk of diabetic kidney disease than individuals in clusters 4 and 5 but had been prescribed similar diabetes treatment. Cluster 2 (insulin deficient) had the highest risk of retinopathy. In support of the clustering, genetic associations in the clusters differed from those seen in traditional T2DM. This new substratification might eventually help to tailor and target early treatment to patients who would benefit most, thereby representing a first step towards personalized medicine in diabetes. The conventional algorithm for treating T2DM is a one-size-fits-all algorithm. Patients are often started on a metfor-
min, and other drugs are added if it does not work. Recognition of subtypes might help physicians more specifically choose a first, second or third medication for their patients.

An important next step will be to translate the new classification described above into the clinic. For this purpose, a clinical decision support system (CDSS) based upon machine learning, has been developed (Prasad and Groop 2019). If the above variables are measured when the patient comes to the clinic, and results are fed into the CDSS (a computer program which can be part of the patient record), there will be a proposal on which subgroup and most appropriate treatment. A key step in this process is that the new subclassification will be approved by authorities and applied to national guidelines. This will require validations in clinical settings and expanding findings to other ethnic groups, work which is in progress. In the future, much more information can be fed into the CDSS, for example genetics. It is anticipated that not in a too distinct future, the genetic code will be a part of patient records to support clinical decisions and personalized medicine.

### Table 18.1 Classification of diabetes into 5 clusters

| Cluster | Synonym | Cause/description |
|---------|---------|-------------------|
| Cluster 1 | Severe autoimmune diabetes like T1DM | Autoimmune disease that prevents production of inulin |
| Cluster 2 | Severe insulin-deficient diabetes like cluster 1 | Inulin deficiency but not due to autoimmune disease but deficiency in the cells that produce inulin |
| Cluster 3 | Severe insulin-resistant diabetes | Overweight and high insulin resistance due to lack of cellular response despite production of enough insulin |
| Cluster 4 | Mild obesity-related diabetes | Milder form of the disease with tendency to be obese with less metabolic problems than in cluster 3 |
| Cluster 5 | Mild age-related diabetes like cluster 4 | Most common form of diabetes affecting ~40% of people who older at their age of diagnosis |

Modified from: Ahlqvist et al. (2018)

#### Personalized Management of Gastrointestinal Disorders

**Role of Microbiome in Personalized Management of Gastrointestinal Disorders**

The human microbiota consists of the 10–100 trillion symbiotic microbial cells harbored by each person, primarily bacteria in the gut; the human microbiome consists of the genes these cells harbor. There is a link between a host’s microbiota, digestion, and metabolism. Gut microbiota also play an important role in obesity. Advances in DNA sequencing technologies have created a new field of research, called metagenomics (environmental genomics), enabling comprehensive examination of microbial communities, even those comprised of uncultivable organisms. Instead of examining the genome of an individual bacterial strain that has been grown in a laboratory, the metagenomic approach enables analysis of genetic material derived from complete microbial communities harvested from natural environments. Integration of microbial ecological theories with computer science algorithms in longitudinal studies has shown that bacterial strains remain stable over time suggesting that microbial signatures may distinguish individuals (Byrd and Segre 2015).

Increasingly powerful tools used to extract meaningful patterns from this wealth of data have been developed or updated as well. Emerging technologies such as stool transplantation, 16S rRNA and whole-genome sequencing on the Illumina platform, the ability to transplant human microbial communities into mice with high efficiency even from frozen samples, and the creation of personalized culture collections raises the prospect of a future in which therapies for individual humans are piloted in a battery of mice that are subjected to different treatments, and where leave-one-out experiments that reveal the effects of the deletion of individual species (Ursell et al. 2012).
**Personalized Therapy of Inflammatory Bowel Disease**

Inflammatory bowel disease (IBD) refers primarily to two diseases — ulcerative colitis and Crohn’s disease — but the cause remains unknown. The incidence and prevalence of IBD varies widely throughout the world; they are considerably higher in the US and Europe than in Asia and Africa. Most studies indicate a range of 4–8 new cases per 100,000 population per year in in the US and Europe. IBD patients are treated by sulfanomidess, steroids and immunosuppressants. For difficult cases, leukocytapheresis, beclo-methasone dipropionate, anticytokines and other new therapies are tried.

IBD First Step SM and IBD Diagnostic System (Prometheus Laboratories) have the potential to decrease the number of diagnostic procedures (including colonoscopies and radiographs) currently used to identify and subtype IBD from non-IBD disorders. Imuran immunosuppressive therapy can be optimized with PRO-PredictRx (Prometheus Laboratories).

Affymetrix GeneChip miRNA Array can identify miRNA biomarker panels that can classify the various forms of IBD to develop a diagnostic test to shed light on how patients are being correctly or incorrectly diagnosed in their respective diseases and to provide information on how they are responding to treatment. This will enable personalized treatment of IBD.

Advances in genome analysis might have an impact on the treatment of inflammatory bowel diseases. Genomic studies have revealed some genetic factors contribute to pathogenesis of IBD such as HLA, IL4, MUC3, IBD1 locus, IBD2 locus. More information about genes concerning IBD will be provided by analyzing dense SNP map using DNA tip. They will open the way to personalized therapy of IBD.

Crohn’s disease is characterized by variation in both location and behavior. Chromosome 16 and the HLA region on chromosome 6 have been implicated in susceptibility to disease. Mutations in the NOD2/CARD15 gene, identified on chromosome 16, have been associated with disease overall but are found in only 25% of patients. The clinical pattern of Crohn’s disease may be defined by specific genotypes. These findings may provide the basis for a future molecular classification of disease.

Genetic and epigenetic studies have revealed 240 risk gene loci associated with IBD, which are mainly involved in regulating innate and adaptive immunity, as well as maintaining intestinal epithelial barrier function. However, the functional consequences of the identified genetic polymorphisms for IBD pathogenesis in vivo are often unknown. Even less is known about the role for epigenetic modifications in IBD pathogenesis. Although several epigenetic events seem to be causatively involved in IBD pathogenesis, the knowledge about the functional relevance of those epigenetic modifications is scanty. Patterns of DNA methylation and histone modifications might serve not only as biomarkers of disease activity or disease course, but also as new targets in therapeutic interventions in IBD patients (Wawrzyniak and Scharl 2018).

There are few proven examples of the importance of pharmacogenetics of serotonin-modifying agents used in functional gastrointestinal or motility disorders. Genetic variations in transporters and translation mechanisms are associated with responses to treatment in IBD. Research on the impact of polymorphisms of key proteins on the pharmacokinetics and pharmacodynamics of drugs that alter serotonin-mediated signalling will assist in explaining diverse responses to those drugs and ultimately improve personalized approach to IBD.

**Personalized Management of Lactose Intolerance**

Lactose intolerance is usually due to insufficient lactase and the patient is unable to break down lactose, the predominant sugar found in milk and other dairy products. This results in lactose intolerance symptoms such as nausea, cramps, bloating, gas, and diarrhea. Between 30 and 50 million Americans are lactose intolerant. Currently, no treatment exists to improve the body’s ability to produce lactase, but symptoms can be controlled through diet and lactase enzyme supplements.
Many other diseases, such as irritable bowel disease and celiac disease, can present with these same symptoms. Improperly diagnosed and unmanaged, these diseases can lead to serious complications. Until now, diagnostic methods used to detect lactose intolerance could not determine the underlying cause, making it difficult for physicians to customize critical patient treatment. A highly specific, proprietary genetic test, PRO-GenoLogix Lactose Intolerance (Prometheus Inc), identifies patients with a certain genetic marker that is associated with lower than normal levels of the lactase enzyme. This genetic test will be especially helpful in differentiating genetic lactose intolerance from other diseases with overlapping symptoms thus eliminating confusion in the diagnostic work-up and therapeutic plan. In addition, this simple blood test does not require patients to undergo fasting, dietary restrictions, or lengthy sample collection and, therefore, will likely be better tolerated by patients. The results of this test will enable physicians to individualize treatment of their patients by discerning whether a patient has a genetic basis for lactose intolerance or if their symptoms are related to another disease or disorder.

Improved Matching of Blood Transfusion

Blood transfusions are among the earliest forms of personalized therapies because the the blood groups of the donor and recipient are matched. Whilst blood transfusions are inherently safe with the compatibility between the donor and the recipient being tested using serological techniques, there is a significant section of the population that suffer serious illness and side affects after receiving multiple transfusions of blood that is not a perfect match. These patients develop antibodies after some time that reject imperfectly matched blood transfusions, a process known as alloimmunization, which can lead to serious illness and life-threatening side effects.

Bloodchip will provide the medical community with a much clearer picture of the many different and often small variations in blood types, thereby allowing more accurate matching of donors and recipients. The new test will be of real benefit to patients who currently receive multiple blood transfusions and require a perfect match in blood types. Bloodchip has been developed by the Bloodgen Consortium, a pan-European group of academic institutions, national blood transfusions services in the UK, Germany, Sweden, Spain, the Czech Republic and the Netherlands, and will be manufactured by Progenika Biopharma. The Bloodchip test will literally be a life saver for those who suffer from illnesses that require multiple blood transfusions such as hemophilia, sickle cell disease and thalassemias by ensuring that the patients receive perfectly matched blood to enable them to better manage their conditions. Bloodchip has already been tested on 3000 patients with the results compared against the traditional serological test and will shortly be awarded the European CE mark and undergo intensive clinical trials. Bloodchip has been widely accepted by the medical community and will become the new standard for the testing of blood types in course of time.

Personalized Approaches to Addiction

Drug addiction, alcoholism and smoking are prevalent problems for which there are no satisfactory universal treatment strategies. Attempts are being made to understand basic mechanisms underlying various types of addiction to provide a more rational mechanism-based approach to each type of addiction. Some examples are given here.

Reversal of Cocaine-Evoked Synaptic Plasticity

Drug-evoked synaptic plasticity is observed at many synapses and may underlie behavioral adaptations in addiction. Mechanistic investigations start with the identification of the molecular
drug targets. Cocaine, e.g., exerts its reinforcing and early neuroadaptive effects by inhibiting the dopamine transporter, thus causing a strong increase in mesolimbic dopamine (D). Among the many signaling pathways subsequently engaged, phosphorylation of the extracellular signal-regulated kinase (ERK) in the nucleus accumbens is of interest because it has been implicated in NMDA-receptor and D1-receptor-dependent synaptic potentiation as well as in several behavioral adaptations. Cocaine potentiates excitatory transmission in D1-receptor-expressing medium-sized spiny neurons (D1R-MSNs) in mice via ERK signaling with a time course that parallels locomotor sensitization (Pascoli et al. 2011). Depotentiation of cortical nucleus accumbens inputs by optogenetic stimulation in vivo efficiently restores normal transmission and abolishes cocaine-induced locomotor sensitization. These findings establish synaptic potentiation selectively in D1R-MSNs as a mechanism underlying a core component of addiction, probably by creating an imbalance between distinct populations of MSNs in the nucleus accumbens. These data also provide proof of principle that reversal of cocaine-evoked synaptic plasticity can treat behavioral alterations caused by addictive drugs and may inspire novel therapeutic approaches involving deep brain stimulation or transcranial magnetic stimulation.

**Pharmacogenetics of Drug Addiction**

Pharmacogenetics provides the tools required to identify genetic predictors of probable drug response, drug efficacy, and drug-induced adverse events—identifications that would ideally precede treatment decisions. Drug abuse and addiction genetic data have advanced the field of pharmacogenetics in general. Although major findings have emerged, pharmacotherapy remains hindered by issues such as adverse events, time lag to drug efficacy, and heterogeneity of the disorders being treated. The sequencing of the human genome and high-throughput technologies are enabling pharmacogenetics to have greater influence on treatment approaches. Genes important in drug abuse pharmacogenetics have been identified, which provide a basis for better diagnosis and treatment of drug abuse disorders.

Since 2007, the National Institute of Drug Abuse (NIDA) has sought SNPs for inclusion in a custom microarray platform to study the genetics and pharmacogenetics of drug abuse, addiction, and related mental disorders. NIDA plans to develop the so-called Neuroarray. and is looking for community input on custom SNPs that provide in-depth coverage of genes with prior knowledge of association with drug addiction and related disorders. It intends to make the array available competitively through standard NIH mechanisms to help researchers study genetic vulnerability to addiction and related disorders, and to develop genetic patient profiles for targeted pharmacotherapies.

**Genetic Polymorphism and Management of Alcoholism**

Several gene variants have been identified as risk or protective factors in alcoholism. The genes coding for dopamine receptors, serotonin transporters, and dehydrogenases represent susceptibility loci for addictive behavior. Polymorphisms of the mu-opioid receptor (OPRM1) and dopamine D4 receptor (DRD4) genes are associated with subjective responses to alcohol and urge to drink. A SNP in the OPRM1 gene has been associated in some studies with the efficacy of naltrexone in reducing drinking, but other studies did not find the same effect. The presence of the L versus the S allele on a serotonin transporter gene has been found to influence responses to ondansetron. Alcoholics with the L-allele have greater alcohol craving than those with the S-allele, and polymorphisms in another receptor result in differences in sensitivity to benzodiazepines used to treat early stage alcohol withdrawal systems.

Alcoholism is a complex psychiatric disorder caused by multiple factors, both genetic and environmental. Furthermore, there are probably
different subtypes of alcoholism each with a distinct genetic background, which require different therapeutic approaches. However, gene polymorphisms are not only responsible for a predisposition to alcoholism, but also for individual responses to treatment. Because of the genetic heterogeneity between alcoholics there is no one drug that works in all patients, which has made it necessary to provide multiple treatment options that clinicians can use to find the ones that work. A personalized treatment that matches specific interventions to the individual, particularly to an individual’s genetic profile, is more efficient.

A randomized study has evaluated the efficacy and tolerability of topiramate in heavy drinkers whose treatment goal is to reduce drinking to safe levels (Kranzler et al. 2014). In a European American subsample of the study, topiramate’s effect on heavy drinking days was significantly greater than that for placebo only in subjects with SNP rs2832407 in gene GRIK1, which encodes the kainate GluK1 receptor subunit. The moderator effect of rs2832407, if validated, would facilitate the identification of heavy drinkers who are likely to respond well to topiramate treatment – a personalized treatment option. Treatment strategies focusing on genes contributing to drug and alcohol dependence, e.g. gene therapy have been examined in animal models and clinical trials have been conducted with drugs. Table 18.2 shows genetic influences on pharmacotherapy of alcohol.

However, further research is required before these developments will considerably change today’s clinical handling of alcoholism on an individual basis. The NIH/National Institute on Alcohol Abuse and Alcoholism (NIAAAA) supports a range of research efforts in this area and fund human and animal studies that can help to determine the full range of genetic variation that affects the pharmacodynamic and pharmacokinetic parameters resulting in altered drug efficacy and toxicity. These studies will include sequencing technologies to identify variations in candidate genes that may play a role in drug responses, use of pharmacogenetic testing to examine genetic variability in side effects from medication, and use of gene expression profiling to determine transcriptomics changes associated with drug response.

### Personalized Therapy for Smoking Cessation

The evidence to date is very consistent with respect to the significance of genetic contributions to smoking behavior. However, attempts to elucidate the role of specific genetic variants have met with mixed success. Explanations for the lack of consistency in the results of genetic association studies include biases in ascertainment, ethnic admixture, lack of attention to covariates or modifiers of genetic risk, and the need for more refined phenotypes. As the field of genetics and smoking research progresses, increasing attention is being devoted to gene-environment interactions, particularly the

| Drug         | Genetic variant       | Effect on outcome                 | References                |
|--------------|-----------------------|-----------------------------------|---------------------------|
| Topiramate   | GRIK1 (rs2832407)     | Heavy drinking days, Adverse events | Kranzler et al. (2014)    |
| Naltrexone   | OPRM1 (Asn40Asp), DRD4 VNTR (rs1799971) | Heavy drinking days, Abstinence rates, Relapse to heavy drinking | Kim et al. (2019)         |
| Ondansetron  | LL/LS/SS (5-HTTLPR) (rs1042173), SLC6A4 (5-HTTLPR) | Drinks per drinking day, Days abstinent | Johnson et al. (2011)     |
| Sertraline   | 5-HTTLPR triallelic SLC6A4 | Heavy drinking days, Drinking days | Kranzler et al. (2011)    |
| Acamprosate  | GATA4 (rs1327367)     | Relapse                           | Kiefer et al. (2011)      |
| Disulfiram   | DBH (rs161115)        | Adverse events                    | Mutschler et al. (2012)   |

Modified from: Batki and Pennington (2014)
identification of genetic variants that may modify the effects of pharmacological treatment of smoking. With advances in molecular biology and genomics technology, individualization of smoking cessation therapy according to genotype is within our grasp. Such research has the potential to improve treatment outcome, thereby reducing morbidity and mortality from smoking-related disease.

**Antidepressant Therapy for Smoking Cessation**

It is known that variant alleles of the dopamine receptor D2 (DRD2) gene may play a role in determining nicotine addiction. Now researchers have demonstrated that a dopamine receptor gene polymorphism appears to influence the response of cigarette smokers to smoking cessation therapy that includes an antidepressant medicine – venlafaxine. Individuals with at least one copy of the A1 allele of the gene have fewer and less-sensitive D2 dopamine receptors than do individuals with two copies of the A2 allele. As part of a smoking-cessation study, half the smokers were given venlafaxine whereas the other half received a placebo. All the smokers were offered standard smoking-cessation counseling and transdermal nicotine. The researchers found no significant difference between the active and placebo treatments for the smokers with the A1 allele in terms of reduction in negative affect during their attempt to quit but those with the A2 allele receiving venlafaxine reported 25% lower score on testing for negative affect. This study demonstrates the value of genotyping in designing a specific smoking cessation therapy for a subgroup of patients.

**DNA Methylation-Based Test for Monitoring Smoking**

A significant barrier to the development of improved intervention and screening measures is the lack of clinically validated biomarkers to detect and measure the extent of tobacco consumption. Smoking can strongly modify DNA methylation and leave a biomarker on the human genome, which persists in DNA even if cigarettes are no longer being consumed. The Smoke Signature® test (Behavioral Diagnostics LLC), a droplet digital PCR (ddPCR) test, can detect this stable epigenetic reprogramming by measuring exact level of DNA methylation to accurately quantify smoking by a patient over time. DNA methylation status at cg05575921, a CpG locus in the aryl hydrocarbon receptor repressor is significantly associated with smoking status. A clinical study has reported that ddPCR assessments of cg05575921 methylation can be used to accurately determine smoking status in adults and lay the groundwork for a better understanding of the dose response relationship of cigarette smoking to demethylation at this locus (Philibert et al. 2018).

The test is specifically designed to test for smoking – not other types of tobacco consumption. This differentiation can help clinicians distinguish between traditional cigarette smoking and the use of e-cigarettes or chewing of tobacco gum. The saliva DNA-based test will enable personalized medicine-based approaches to smoking cessation including incentive-based methods, to be routinely used in all health care settings, including telemedicine, for those with addictive disorders. Sensitive quantitative measurements of cigarette consumption can guide smoking cessation and prevention efforts.

**Effectiveness of Nicotine Patches in Relation to Genotype**

In women the effectiveness of nicotine patches seems to be related to genotype. Women with the variant T allele of the dopamine D2 receptor DRD2 32806 show considerable benefit from patches, whereas those with the more common CC genotype do not. The increased effectiveness reflects a tendency to a higher quit rate with the active patches and a lower quit rate with placebo patches. No significant relation between genotype and patch effectiveness was seen for men. The overall effectiveness of nicotine replacement therapy could be greater if the therapy were targeted at those most likely to respond.
Sex Differences in Smoking as Response to Stress

Women are 31% less likely to quit smoking successfully, in part because nicotine replacement therapy is more effective in male smokers. A study has shown that female smokers experience more stress and craving than men after viewing cellphone-delivered stress-inducing images such as those of violence and war but not smoking cues, which are images such as a photograph of a cigarette or a person smoking (Tomko et al. 2020). Although all smokers making a cessation attempt would likely benefit from interventions to reduce stress, these findings suggest that women could receive particular benefit. Management of nicotine addiction should not only consider sex differences but include strategies for stress management in women.

Personalized Geriatrics

Geriatrics, the branch of medicine dealing with disorders of elderly, is a recognized sub-speciality. There is no separate chapter on geriatrics in this book as many of the diseases described in various chapters of this book occur at various ages from infancy to old age although some occur more commonly in the elderly. Aging is the most significant risk factor for chronic disease in humans as genetic and degenerative changes accumulate throughout life leading to various disturbances in function, e.g., in protein homeostasis, metabolism, and cellular signaling, ultimately resulting in senescence and death of cells or their uncontrolled proliferation, which manifest as degenerative disorders or cancer.

This section will point out some issues to be considered in personalized management of disease in the elderly patients. Prevalence of both therapeutic failures and adverse drug reactions are significantly higher in older than in younger subjects. This might be due to higher use of polypharmacy and multiple co-existing diseases in the elderly. Nevertheless, other explanations must also be sought. There are alterations in metabolism and pharmacokinetics due to impairment of renal and hepatic functions that are common in the elderly. Pharmacogenetics of drug metabolizing enzymes, drug transporters and receptors should not be overlooked.

Chronological Versus Biological Age

In conventional medicine, most of the physiological parameters and laboratory values are based on chronological age of the patient. An elderly patient undergoing pulmonary or cardiovascular investigation that slight impairment of performance is still within the norm for his or age whereas prior to illness, the performance might have been >50% as compared to average persons of his age. People age at different rates depending on several factors including genetic, environmental and lifestyle. A physical active 70-year old may have been performing at the level of a 50-year old prior to onset of disease. Despite slight impairment of function, performance of this person may still be within the normal range for chronological age but may indicate early disease. This factor is often overlooked by the physician, but a personalized approach takes this into consideration as a person is his or her own control even within the span of time.

Pharmacogenetics and Adverse Drug Reactions

Prevalence of both therapeutic failures and adverse drug reactions are significantly higher in older than in younger subjects. This might be due to higher use of polypharmacy and multiple co-existing diseases in the elderly. Nevertheless, other explanations must also be sought. There are alterations in metabolism and pharmacokinetics due to impairment of renal and hepatic functions that are common in the elderly. Pharmacogenetics of drug metabolizing enzymes, drug transporters and receptors should not be overlooked.

Role of Biomarkers and Ageotyping

A study involving longitudinal and multiomics profiling of healthy individuals from 29 to 75 years of age examined how different types of ‘omic’ measurements, including transcripts, proteins, metabolites, cytokines, microbes and
clinical laboratory values, correlate with age (Ahadi et al. 2020). Both known and new biomarkers that associated with age, as well as distinct molecular patterns of aging in insulin-resistant as compared to insulin-sensitive individuals were identified. The authors defined different types of aging patterns in different individuals, termed ‘ageotypes’, based on the types of molecular pathways that changed over time in a given individual, which may provide a molecular assessment of personal aging, indicator of an individual’s lifestyle and medical history, that may eventually be useful for monitoring and intervening in the aging process.

This study identified about 600 so-called biomarkers of aging that predict the functional capacity of a tissue and essentially estimate its “biological age” as well as four distinct ageotypes: immune, kidney, liver and metabolic. Some persons fit squarely in one category, but others may meet the criteria for all four, depending on how their biological systems hold up with age. Each aging “profile” included a combination of traits, mixed and matched from different ageotypes. It is possible that improvements in ageotype can be targeted at the individual pathway level (such as, immune function or metabolic pathways) using selective interventions (such as, drugs) or in aggregate using broad lifestyle changes. The availability of personal time dependent aging markers potentially enables aging to be acted upon at an individual level. The authors aim to develop a simple ageotype test that could be used in a physician’s office to quickly assess a patient’s health status, and potentially point them toward the best possible treatment option for that individual.

**Systems Pharmacology Approach to Disorders of Aging**

Events contributing to age-dependent physiological decline also occur due to hormonal and metabolic changes, affecting interconnected cellular networks. This complexity confounds the development of effective treatments for age-related diseases. In contrast to monotherapy and polypharmacology, a systems pharmacology approach can identify synergistic combinations of drugs that modulate distinct nodes within a network, minimize off-target adverse effects, and improve therapeutic outcomes. G protein-coupled receptors (GPCRs) are particularly good targets for the application of systems pharmacology, because they activate different signal transduction pathways that can culminate in a common response. Such an approach can provide an appropriate drug regimen for the personalized treatment of AMD (Luu and Palczewski 2018).

**Personalized Pediatrics**

**WGS for Personalized Management of Genetic Disorders in Critically Ill Infants**

Genetic disorders and congenital anomalies are the leading causes of infant mortality. Conventional testing in neonatal and paediatric intensive care units (NICU and PICU) is not sufficiently timely to guide acute clinical management for most genetic diseases. The high infant mortality rate indicates a substantial need for rapid genomic diagnoses. A retrospective comparison of STATseq and standard genetic testing in a case series from the NICU and PICU of a large children’s hospital has shown that in selected acutely ill infants, STATseq had a high rate of diagnosis of genetic disorders and altered the management of most infants in the NICU or PICU (Willig et al. 2015). STATseq for infants in NICU and PICU who are diagnosed with genetic diseases can improve outcomes in the setting of framework for personalized medicine.

**Personalized Nephrology**

**Personalized Management of Chronic Kidney Disease**

Chronic kidney disease (CKD) is a major health problem with socioeconomic burden. Acute renal injury due to various causes results in local
inflammation and the production of proinflammatory cytokines, which contribute to the recruitment of inflammatory cells that synthesize and release profibrotic cytokines. This induces the activation and recruitment of matrix-producing cells and epithelial-to-mesenchymal transition EMT, which ultimately leads to renal fibrosis in CKD resulting in end-stage renal disease. Transforming growth factor (TGF)-β1 is both a well-known EMT inducer and profibrotic molecule that participates in the pathogenesis of renal fibrosis. Genetic polymorphisms, and epigenetic as well as transcriptional variations, can increase the risk of CKD.

**Genes and Chronic Kidney Disease**

GWASs have identified genetic variants in CKD, which reveal the pathways and mechanisms, and provide targets for therapeutic interventions. For example, GWASs have identified the variants in the promoter of the UMOD gene, SNP rs4293393, which increased UMOD expression. Uromodulin overexpression leads to salt-sensitive hypertension by upregulating Na-K-Cl transporter (NKCC2) phosphorylation, and contributes to renal damage. This mechanism indicates that pharmacological inhibition of NKCC2 would be more effective in lowering blood pressure in hypertensive patients who were homozygous for UMOD promoter risk variants than in other hypertensive patients, and that uromodulin might be a therapeutic target for lowering blood pressure and preserving renal function (Trudu et al. 2013).

RNA microarrays are used to analyze gene expression profiles in renal glomerular and tubular samples in diabetic kidney disease (DKD). Weighted gene co-expression network analysis has identified 10 modules of genes in tubuli and 12 modules in glomeruli, which indicate that dysregulation of cell proliferation might contribute to the development of DKD, and these genes can be therapeutic targets for DKD (Tang et al. 2012).

Both DNA hypomethylation and hypermethylation occurs in CKD. Hypermethylation downregulates the expression of the renoprotective gene KLOTHO and is associated with CKD progression; thus, KLOTHO might be a potential epigenetic drug target to suppress CKD progression (Young and Wu 2012).

**MicroRNAs and Chronic Kidney Disease**

MicroRNAs (miRNAs) are more stable than mRNA and are found in different body fluids, especially in urine, suggesting that miRNAs could serve as ideal biomarkers of CKD with various pathologies. miRNA-29 regulates the expression of collagen genes and extracellular matrix proteins, which are involved in modulating renal fibrosis, negatively correlating with tubulointerstitial fibrosis in urine exosome. Identifying the regulation and function of these miRNAs in renal pathogenesis might pinpoint them as new therapeutic targets for progressive CKD and renal fibrosis.

**Metabolomics and Chronic Kidney Disease**

Metabolomic biomarkers of diabetes are sugar metabolites, ketone bodies, free fatty acids, and branched chain amino acids. Distinct phospholipids, sphingolipids, and sphingomyelins in serum can identify DN from type 1 and type 2 diabetic patients. Urinary levels of acylcarnitines and hippuric acid are associated with early kidney damage and reflect alterations in β-oxidation and uremic toxin elimination, respectively. Furthermore, increases in γ-butyrobetaine, citrulline, symmetric dimethylarginine, and kynurenine as well as a decrease in azelaic acid (β-oxidation) indicate the progression from micro-DN to macro-DN.

**TGF-β1 as a Target for Therapy of Chronic Kidney Disease**

TGF-β1 is a well-known biomarker of CKD. Its elevated level in both the serum and urine of CKD patients turned out to be positively correlated with the level of estimated glomerular filtration rate, reflecting the activation of renal fibrotic progression. Molecules and drugs regulate, or are
regulated by TGF-β1 via different signal pathways which could influence the expression of fibrotic related genes that might result in renal fibrosis. With the knowledge of TGF-β1-related pathways, CKD might be refined and treated via these underlying molecular mechanisms.

TGF-β antagonists which reduce or block the activation of TGF-β1, including anti-TGF-β antibodies, the TGF-β receptor antagonist, and the targets of inhibiting TGF-β synthesis, might ameliorate renal fibrosis. Fresolimumab, a human MAb that neutralizes all 3 isoforms of TGF-β, is being studied in a phase II clinical trial in patients with steroid-resistant primary focal segmental glomerulosclerosis. LY2382770, an antibody that neutralizes the bioactivity of TGF-β1, is also being investigated in a phase II clinical trial in DN patients. GW788388, a TGF-β receptor antagonist and siRNA for the TGF-β receptor, could also inhibit TGF-β signaling activity. Pirfenidone, with antifibrotic and anti-inflammatory activities via the inhibition of TGF-β1 synthesis, has been demonstrated to be safe and effective in many disorders such as idiopathic pulmonary fibrosis, multiple sclerosis, and liver fibrosis. Clinical trials of pirfenidone in CKD have been performed in patients with focal segmental glomerulosclerosis and DN. The results suggested that pirfenidone might be an effective agent to slow renal function decline in CKD. In addition, the inhibition of TGF-β signaling by Smad7, bone morphogenetic protein-7 agonists, connective tissue growth factor inhibitors, in vivo delivery of siRNA, as well as all other molecules and pathways could be potential therapeutic targets to inhibit or slow the progressive loss of kidney function in patients with CKD (Sun et al. 2017).

Proteomics and Chronic Kidney Disease

Proteomic technologies serve not only to identify potential biomarkers but also to provide diagnostic methods. Microalbuminuria is an early sign of kidney disease in people with diabetes and indicates increased risk of cardiovascular disease. Most of urinary proteins are generated by the kidney and, hence, hold substantial information on renal pathogenesis. The CKD273 classifier, based on 273 urinary peptides, is well suited for the early detection of CKD and prognosis. A multicentre, prospective, observational study with embedded randomized controlled trial (PRIORITY), tested whether CKD273 score was associated with development of microalbuminuria and whether progression to microalbuminuria could be prevented with the mineralocorticoid receptor antagonist spironolactone (Tofte et al. 2020). Results showed that in patients with type 2 diabetes and normoalbuminuria, a high-risk score from the urinary proteomic classifier CKD273 was associated with an increased risk of progression to microalbuminuria over a median of 2.5 years, independent of clinical characteristics. However, spironolactone did not prevent progression to microalbuminuria in high-risk patients.

Podocyte phospholipase A2 receptor (PLA2R) is an antigenic target in autoimmune membranous nephropathy (MN). Anti-PLA2R antibodies in serum and glomerular deposits can serve as diagnostic biomarkers of idiopathic MN and can also differentiate idiopathic MN from secondary MN, with high specificity and sensitivity. Moreover, in anti-PLA2R-associated idiopathic MN, serum titers of anti-PLA2R antibodies can be positively correlated with proteinuria and disease activity to predict the remission and relapse of idiopathic MN. Thus, anti-PLA2R antibody titers could have an important role in the selection of patients for immunosuppressive therapy and for monitoring the response to treatment (Ronco and Debiec 2015).

Personalized Management of Renal Disease Associated with Hypertension

ACE Inhibitors as Renoprotective Agents in Hypertension

Angiotensin converting enzyme (ACE) inhibitors preserve native kidney function in patients with renal disease better than other antihypertensive drugs, most likely because they more effectively reduce proteinuria. The plasma concentration of the ACE inhibitors target is, at
least in part, under genetic control. A polymorphism of the ACE gene based on the presence or absence of a 287 base pair element in intron 16 accounts for 47% of the total phenotypic variance in the plasma ACE levels of healthy individuals. Polymorphisms of the ACE gene account for half the variance in ACE levels in Caucasian but not in Black individuals. Unfortunately, pharmacogenetic studies performed so far do not provide a clear answer as to whether the efficacy of the reduction of proteinuria by ACE inhibitors is influenced by the ACE genotype – probably because these studies were not primarily designed to answer this question. Pharmacogenomics of the ACE inhibitors needs to be examined in a properly designed pharmacogenomic study with a defined endpoint and an appropriately selected control population.

Gene Associated with End-Stage Renal Disease and Hypertension

African Americans have high incidence rates of end-stage renal disease (ESRD) labeled as due to hypertension; they have a 4-fold higher risk of developing all common forms of it than whites in the US. Various studies have shown strong association with idiopathic and HIV-related focal segmental glomerulosclerosis and non-muscle myosin heavy chain 9 (MYH9) gene polymorphisms in this ethnic group. A study has shown that hypertension-associated ESRD in African Americans is substantially related to MYH9 gene polymorphisms and this may explain the poor response to blood pressure control in those diagnosed with hypertensive nephrosclerosis (Freedman et al. 2009). About 70% of African-Americans with non-diabetic forms of kidney disease have the MYH9 gene, and many of them end up on dialysis. Thus, high blood pressure may not be the chief cause common forms of kidney disease in African-Americans. It is possible that many African Americans classified as having hypertension-associated ESRD have occult MYH9-associated segmental or global glomerulosclerosis. This study shows that gene-environment and/or gene-gene interactions may initiate kidney disease in genetically susceptible individuals, because African Americans homozygous for MYH9 risk alleles do not universally develop kidney disease. However, there is no reason to screen all African-Americans for the risk variant of this gene, or even all African-Americans with high blood pressure, because it is common among all African-Americans. Genetic screening would be most useful for people who have close relatives on dialysis, meaning they are at high risk, or individuals who want to donate kidneys.

Personalized Approach to Type I Primary Hyperoxaluria

A personalized approach has been applied to the management of type I primary hyperoxaluria an inherited kidney disorder that can cause organ failure in children and young adults. Early diagnosis is important, as the condition, if not treated early and correctly, can cause kidney stones or kidney failure in half of the patients, and necessitate a transplant. A genetic mutation (c.508) allows certain kidney stone patients to benefit from vitamin B6 and this finding has been used to develop a genetic test to predict which patients are best suited for this treatment. The gene defect responsible for the disorder disrupts production of a key enzyme, alanine: glyoxylate aminotransferase, located in the liver. The enzymatic deficit causes the liver to produce too much oxalate, which is excreted in the urine. High concentrations of oxalate in the urine can cause kidney stones and injury to the kidney, leading to kidney failure.

Personalized Gynecology

The principles of personalized medicine apply to diseases of women. The most import area of application is cancer and personalized/precision management of various cancers affecting women are described in Chap. 21. Examples of some other disorders are mentioned briefly in this chapter.
Female Sexual Dysfunction

Female sexual dysfunction (FSD) is the broad term covering several disorders from menarche to menopause, which result from an interaction of psychosocial and biological factors modulating the expression of sexual symptoms and associated distress. These are dependent on genetic and epigenetic mechanisms, including acquired medical conditions. Personalized management of FSDs requires an understanding of psychological and environmental determinants as well as the genetic basis to select the most effective intervention for an individual. However, there is a paucity of studies of genetic contribution to FSD. Pharmacogenomics is still in its infancy in the field of sexual medicine as most of the data regarding genetic polymorphisms of drug targets associated with susceptibility to sexual dysfunction have been obtained in males. There is a need for pharmacogenomic studies of FSDs to guide an individualized approach by predicting both therapeutic effects at varying dosages of hormonal and nonhormonal agents as well as, adverse drug reactions and drug interactions.

Hormone Replacement Therapy in Women

There is some controversy about the usefulness and risks of hormone replacement therapy (HRT) in postmenopausal women. Sequence variants in the gene encoding estrogen receptor alpha (ER-alpha) may modify the effects of hormone-replacement therapy on levels of high-density lipoprotein (HDL) cholesterol and other outcomes related to estrogen treatment in postmenopausal women. Some clinical trials have shown that postmenopausal women with coronary disease, who have the ER-alpha IVS1-401 C/C genotype, or several other closely related genotypes, have an augmented response of HDL cholesterol to hormone-replacement therapy. This points to the possibility of using genetic screening for tailoring decisions about hormone-replacement therapy for maximizing the health and well being of postmenopausal women. It is conceivable that, ultimately, more comprehensive pharmacogenomic studies of HRT, in conjunction with more detailed phenotypic biomarkers of disease outcome will lead to effective algorithms for individualizing HRT for postmenopausal women.

Lower Urinary Tract Disorders in Women

Lower urinary tract symptoms (LUTS), including urinary incontinence, urgency and nocturia, affect approximately half of women worldwide. Current diagnostic methods for LUTS are invasive and costly, while available treatments are limited by side effects leading to poor patient compliance. A study aimed to identify urine metabolic signatures associated with LUTS using proton nuclear magnetic resonance (1H NMR) spectroscopy (Bray et al. 2017). Despite high variation in the urine metabolome across the cohort, associations between urine metabolic profiles and BMI, parity, overactive bladder syndrome, frequency, straining, and bladder storage were identified using KODAMA (knowledge discovery by accuracy maximization). Four distinct urinary metabotypes were identified, one of which was associated with increased urinary frequency and low BMI. Urine from these patients was characterized by increased levels of isoleucine and decreased levels of hippurate. This study suggests that metabolic profiling of urine samples from LUTS patients offers the potential to identify differences in underlying etiology, which may permit stratification of patient populations and the design of more personalized treatment strategies.

Personalized Surgery

Surgery has been traditionally more personalized than drug therapy. Decision to use surgery and choice of procedure are often tailored to individual patients. Surgery for some conditions, genotype studies may influence the decision for surgery. An example is weight loss surgery. The magnitude of weight loss-induced high-density lipoprotein cholesterol (HDL-C) changes may
depend on genetic factors. Association of SNPs in the gene loci that contribute significantly to plasma HDL-C levels in obese individuals at baseline persist at 10 yr follow-up after bariatric surgery even after considerable weight loss due to bariatric surgery (Sarzynski et al. 2011). The authors did not observe any associations with bariatric surgery-induced changes in HDL-C levels. The results show that the genetic variants contributing to overall HDL-C levels in apparently weight-stable individuals have little effect on inter-individual variation in the changes of HDL-C in response to the weight loss induced by bariatric surgery. A better understanding of the SNP-HDL associations in obesity and after weight loss surgery could be used as an aid for improving risk prediction and in determining the best treatment options for obese patients.

Risks/benefits are carefully weighed before embarking on surgical procedures. Even in standard textbook procedures, the surgeon often modifies the approach according to the findings and other anatomical variables that may be encountered.

Algorithms for patient management may contain medical and surgical alternatives, combination of both, or surgery as the only choice after failure of medical treatment. Understanding the molecular basis of disease with refinements in molecular diagnostics has contributed considerably to the decision-making process as well as prediction of outcome of surgery. Role of surgery, wherever applicable, is described in the personalized management of various diseases in other chapters. Surgery is most frequently integrated with medical management and diagnostics in case of cancer and neurological disorders.

Response to other non-pharmacological methods may be used to make decision about surgery. Some of these methods can also be personalized and may be combined with surgery. Examples are personalized radiotherapy in management of cancer and personalized hyperbaric oxygen (see Chap. 10).

Increasing emphasis on personalized medicine with integration of diagnostics and surgery will likely reduce the need for surgery as well as failed surgical procedures and complications of surgery. Surgery of the future is also being refined with integration of new technologies such as robotics and minimization of the invasive and traumatic process inherent in surgery.

### Personalized Approaches to Miscellaneous Problems

#### Personalized Treatment of Malaria

Worldwide there are an estimated 500 million new cases of malaria per year. Malaria is caused by a protozoan infection of red blood cells with one of four species of the genus plasmodium: *Plasmodium falciparum, P. vivax, P. ovale, or P. malariae* are responsible for up to 2.7 million deaths yearly. Chloroquine, developed in the 1940s, was the mainstay of prevention and treatment at one time. Development of resistance to this drug has limited the efficacy in most parts of the world. Hydroxychloroquine is like chloroquine and is useful in treating several forms of malaria as well as lupus erythematosus and rheumatoid arthritis. There are few effective treatments available. Verpamil, when given in combination with chloroquine, reverses the drug resistance partially. This parallels the ability of verapamil to inhibit drug resistance in cancer cells. Malarone (GlaxoSmithKline), a combination of atovaquone and proguanil), is approved as a treatment of malaria resistant to chloroquine. The focus of research now is development of therapies based on genomic knowledge of the *P. falciparum*.

In the malaria genome sequencing project, DNA sequences of chromosomes 2, 3, 10, 11 and 14 are already determined with several others nearing completion. The US Naval Medical Research Center (Bethesda, MD) and the NIH are major backers of these efforts. The Stanford University (Palo Alto, CA) and The Institute of Genome Research (Rockville, MD) serve as the two principal US sequencing centers, while the Sanger Center (Cambridge, UK) is the main site in the UK for sequencing the DNA of several *P. falciparum* chromosomes.

With some *P. falciparum* chromosomal sequences completed and others nearing completion, considerable effort is going into understanding gene compositions and expression patterns of
the parasite. The aim is to build a comprehensive picture of the parasite’s multi-staged, genetically determined lifestyle in the search for vulnerable points where drugs are most likely to block its host-debilitating actions. The genomic information can be used to develop effective malaria vaccines, each of which is aimed at a different life stage of the parasite. The term “vaccinomics” has been used to describe the comprehensive, genomics-based effort to develop a working vaccine. The gene sequence is providing many new drug targets. For instance, the genome encodes several genes specifying ABC-transporter proteins that are implicated in drug resistance. Currently, the only approved malaria vaccine is RTS, S (commercial name Mosquirix), a recombinant vaccine using genes from the outer protein of \textit{P. falciparum} and a portion of a hepatitis B virus plus a chemical adjuvant to boost the immune response, which is rather weak. A completely effective vaccine is not yet available for malaria, although several vaccines are under development.

There are associations between chloroquine resistance and mutations in mdr-like gene (pfmdr 1) on chromosome 5 that encodes a protein Pgh 1 located in the lysosomal membrane of the parasite. A mutation of pfcr – a gene on chromosome 7 that encodes a transmembrane protein pfCRT in the lysosomal membrane – is required to confer basic resistance before a mutation in pfmdr 1 can increase the resistance. Screening for pfcr mutations in populations at risk can be used to monitor for resistance and this knowledge has major implications for the design of rational new drugs for malaria.

Although several molecular diagnostics are available for detection of malaria, accuracy in diagnosis of malaria and the resilient capacity of the malaria parasite in acquiring resistance to antimalarial drugs are barriers to the control and elimination of this disease. Phenotypic variations are becoming more common and could be based on geographical location or differential transmission setting. Spectroscopic techniques such as nuclear magnetic resonance (NMR), surface enhanced Raman spectroscopy (SERS)), and ultralow cost microfluidic chips can deliver more sensitive and rapid field malaria detection, and reveal unique ‘molecular fingerprint’, to provide rapid phenotyping (rather than genotyping) platform in the field. NMR-based malaria detection is based on recognition of the paramagnetic susceptibility of malaria hemozoin crystals, which conditions a differential proton NMR signature of the infected erythrocyte to enable quantitative determination of the parasitemia. Because parasite survival dependent on hemozoin formation as a by-product of heme detoxification process upon hemoglobin degradation, it is a natural biomarker of presence of parasites in patients’ blood. NMR-based hemozoin detection technologies are not only sensitive diagnostics but can also enable development of a personalized medicine for malaria (Veiga and Peng 2020).

**Personalized Management of Osteoporosis**

Osteoporosis, a disease characterized by reduced bone mass and increased skeletal fragility, affects 10 million Americans; another 34 million are at risk for it. Because of numerous causes as well as risk factors, there are wide variations in course of osteoporosis and response to treatment. Calcium and vitamin D are used commonly for prevention of osteoporosis in those at risk, e.g. postmenopausal women. Once considered to be an inevitable consequence of aging, osteoporosis is both diagnosable and treatable.

Bisphosphonates are widely prescribed for treatment of osteoporosis. Examples include: alendronate, risedronate, ibandronate, and zoledronic acid. All the bisphosphonates that have been approved for the treatment of osteoporosis have shown robust efficacy in preventing fractures in clinical trials lasting 3–4 years, but data on safety have raised concern regarding the optimal duration of use for achieving and maintaining protection against fractures. Current FDA labeling states: “The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.” To optimize the efficacy of bisphosphonates in reducing fracture risk, decisions to continue treatment must be based on individual assessment of risks and benefits. In this regard, patients at low risk for fracture (e.g. younger patients...
without a fracture history and with a bone mineral density approaching normal) may prove to be good candidates for discontinuation of bisphosphonate therapy after 3–5 years, whereas patients at increased risk for fracture (e.g. older patients with a history of fracture and a bone mineral density remaining in the osteoporotic range) may benefit further from continued bisphosphonate therapy. Further investigation into the benefits and risks of long-term therapy, as well as surveillance of fracture risk after discontinuation of bisphosphonate therapy, will be crucial for determining the best regimen of treatment for individual patients with osteoporosis.

**Personalized Care of Trauma Patients**

Traumatic injuries claim hundreds of thousands of lives each year in the US. In addition, millions of patients are hospitalized, at an annual cost to society of more than $200 billion. Patients may face a long and difficult recovery period riddled with many potentially fatal complications along the way.

It is important to understand the genetic features that enhance a patient’s recovery as well as the elements that cause people to die sometimes weeks after an injury occurs. Identifying those factors could help physicians choose the best treatment, a decision that could mean the difference between life and death. Although most of the trauma patients recover, a fraction of them develop complications that lead to infection and multisystem organ failure, which is the most common cause of death after traumatic injury. The goal is to use functional genomics as a tool to identify those patients who, after severe trauma and burn injury, will go on to manifest multisystem organ failure.

Various studies have correlated molecular biomarkers with outcome to identify trauma and burn patients that are most likely to become seriously ill. Certain genes are active in patients with serious infections or traumatic injuries, and the major source of variance in apparent gene expression in the blood compartment is due to interindividual variation. The magnitude of the interindividual variance and the changes in gene expression produced by traumatic injury were somewhat greater than the variance associated with the sample processing and analysis in the same subject. However, prior to adopting this approach in clinical practice, it will be necessary to continue the experimental procedures in larger multicenter trials, following hundreds of patients over time to describe the molecular profile of healing in response to burns and traumatic injury.

**Personalized Medical Care of Astronauts during Space Flights**

Health hazards to which astronauts are exposed as they traverse the space in long journeys include extreme temperatures, high levels of radiation, loss of bone density, diminishing muscle mass and atherosclerosis. State-of-the-art diagnostic technologies are being used to improve our understanding and management of the physically demanding aspects of interplanetary voyages. Astronauts’ health is vigilantly monitored before take-off and using genomic analysis techniques, it is possible to predict the risk of a disease developing in an individual and customize a preventative intervention plan accordingly. Differences among astronauts, as revealed by “Omics” technologies such as genomics, proteomics and metabolomics, can be amplified in extreme conditions, such as space flight. A better understanding of individual differences may enable development of personalized countermeasure packages that optimize the safety and performance of each astronaut. “Omics” will enhance our ability to: (1) more thoroughly describe the biological response of humans in space; (2) describe molecular attributes of individual astronauts that alter the risk profile prior to entering the space environment; (3) deploy Omics techniques in the development of personalized countermeasures; and (4) develop a comprehensive Omics-based assessment and countermeasure platform that will guide human space flight in the future (Schmidt and Goodwin 2013). Selected examples where biochemical individuality might
significantly impact countermeasure development include gene and small molecule variants associated with: (1) metabolism of therapeutic drugs used in space; (2) one carbon metabolism and DNA stability; (3) iron metabolism, oxidative stress and damage, and DNA stability; and (4) essential input (Mg and Zn) effects on DNA repair. Omics profiling should serve as the basis for research in aerospace personalized medicine and explore methodological considerations to advance the field. Personalized medicine may become the standard of care for humans in space in the future. Technologies for personalized medical support for astronauts also contribute to personalized care for patients on Earth.

**Personalized Management of Motion Sickness**

Approximately one in three individuals is highly susceptible to motion sickness but the underlying causes of this condition are not yet well understood. However, it is a heritable disorder and the first genome-wide association study on motion sickness revealed that 35 SNPs are associated with motion sickness (Hromatka et al. 2015). Many of these SNPs are near genes involved in balance, and eye, ear, and cranial development (e.g. PVRL3, TSHZ1, MUTED, HOXB3, HOXD3). Other SNPs may affect motion sickness through nearby genes with roles in the nervous system, glucose homeostasis, or hypoxia. Several of these SNPs display sex-specific effects, with up to three times stronger effects in women. Associations with comorbidities include migraine, postoperative nausea and vomiting (PONV), vertigo, morning sickness, and altitude sickness. Two of these related phenotypes, PONV and migraine, share underlying genetic factors with motion sickness. These results point to the importance of the nervous system in motion sickness and suggest a role for glucose levels in motion-induced nausea and vomiting, a finding that may provide insight into other nausea-related phenotypes like PONV. They also highlight personal characteristics (e.g. being a poor sleeper) that correlate with motion sickness, findings that could help identify risk factors or treatments. In this study, individuals who experienced motion-induced nausea and vomiting had lower levels of insulin than people who did not experience gastrointestinal symptoms. The study further suggested that stable glucose levels might help to relieve motion-induced gastrointestinal upset. Some phenotypic associations might provide clues about the etiology of motion sickness, e.g. poor circulation and experiencing light-headed with exercise, or they might suggest simple remedies for motion sickness such as improving sleep quality. An advantage of web-based phenotypic collection method of 23andMe Inc., the company that conducted the study, is that it can easily investigate whether seemingly related traits have shared underlying genetics. Identification of 4 SNPs simultaneously associated with motion sickness plus PONV or migraines may not only provide clues into the etiology of all three conditions but may also point to overlapping risk factors or treatments.

**Personalized Treatment of Rare Diseases**

Although next-generation sequencing is revolutionizing their diagnosis, the sheer number of rare diseases (RDs) as distinct conditions exceeds 7000 (https://globalgenes.org/rare-list). RDs affect >5% of the world’s population and US alone has >30 million such patients. Many RDs have no effective treatment and lack of knowledge creates delayed diagnosis, making management difficult. Discovery of biomarkers in RDs will enable timely prevention and effective treatment. Since 80% of RDs are of genetic origin, identification of new genes and causative mutations are valuable biomarkers. Furthermore, dynamic biomarkers such as expressed genes, metabolites, and proteins are also important for following prognosis and response the therapy (Gülbakán et al. 2016). Biomarker discovery and their use in diagnosis of RDs is important for developing personalized therapies for RDs. Many RDs have no effective treatment. Except for treatments that gain “orphan drug status”,

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there is no help offered by the regulatory authorities to drug developers for RDs. It is necessary to study the proposed treatment of RDs in relevant animal and cellular models. The understanding of how pathomechanism of RDs overlaps with that of other chronic diseases, may help in getting further support for research in RDs. Advances in omics technologies have enabled identification of pathophysiological pathways that are potential drug targets. Personalized drugs targeting these pathways may be developed for multiple RDs with common underlying molecular aberrations. Suggestions made for improving management of RDs include the following (National Academy of Sciences, Engineering, and Medicine 2017):

- Train clinicians to diagnosis and effectively manage complex diseases.
- Validate common biomarkers for diagnosis and monitoring of disease in subgroups.
- Integrate pharmaceutical, academia, and government resources to lower barriers and channel limited resources into meaningful studies that address disease mechanisms and develop efficacious treatments for distinct disease sub-groups.
- Consider innovative N-of-1 precision trials tailored to each rare disease patient or subgroup.

**Development of Individualized Biological Therapies for Rare Diseases**

Molecular diagnosis in a child with neuronal ceroid lipofuscinosis 7 (CLN7, a form of Batten’s disease, a rare, fatal neurodegenerative condition, was followed by rational design, testing, and manufacture of milasen, a splice-modulating antisense oligonucleotide drug tailored to one patient (Kim et al. 2019). Proof-of-concept experiments in cell lines from the patient served as the basis for launching an “N-of-1” study of milasen within 1 year after first contact with the patient. There were no serious adverse events, and treatment was associated with objective improvement. This study indicates feasibility of rapid development of patient-customized treatments for RDs. This patient and a few others, including one with idiopathic multicentric Castleman’s disease that was refractory to blockade by interleukin-6, led to identification of a specific signaling pathway as a target for the treatment of disease (Fajgenbaum et al. 2019).

These examples show how recently developed technologies enable mapping of disease pathways for individualized drug development. Finding sustainable funding for such interventions may prove challenging, because the cost of production can be quite substantial, particularly for gene therapies. These issues are being addressed at the FDA with input from academic, patient advocate, pharmaceutical industry, and other stakeholders.

**Incidental Findings in Genetic Screening and Clinical Sequencing**

New genome-scale screening tests may lead to a phenomenon in which multiple abnormal genomic findings are incidentally discovered, analogous to the “incidentalomas” that are often discovered in radiological studies. The “Incidentalome” in radiology has some benefits resulting from discovery of unexpected potentially life-threatening conditions that can be treated prior to clinical manifestations. However, the incidentalome resulting from molecular diagnostics threatens to undermine the promise of molecular medicine in at least three ways:

1. Physicians will be overwhelmed by the complexity of pursuing unexpected genomic measurements.
2. Patients will be subjected to unnecessary follow-up tests, causing additional morbidity.
3. The cost of genomic medicine will increase substantially with little benefit to patients.

Given the current limitations of sensitivity and specificity of many genomic tests, application of these for screening of large populations to detect conditions with low prevalence will result in large numbers of false positives. Even if genomic tests were to achieve 100% sensitivity and a false-positive rate of zero, the risk of the incidentalome still remains. Some pathology of disease discovered incidentally never reaches clinical significance and may not influence decision for management. For example, several prostate car-
cinomas accurately diagnosed after the finding of an elevated prostate-specific antigen level in all likelihood would not contribute to an individual’s death and may not be treated.

The role of a genome-wide panel (i.e., a panel of 500,000 genetic polymorphisms all ordered and measured together), however, cost-effective to measure, needs to be compared with a series of more focused genomic-based panels with clear indications for use and proper protocols for workup of unexpected findings. The physicians need to be educated to ensure that there is appropriate clinical justification to perform and interpret these tests in a manner that ushers in the era of personalized medicine and does not allow the incidentalome to block its arrival.

Advances in sequencing technologies have facilitated concurrent testing for many disorders, and the results may provide information about a patient’s health that is unrelated to the clinical indication, i.e., incidental findings. This is a paradigm shift from traditional genetic testing in which testing, and reporting are tailored to a patient’s specific clinical condition. Clinical laboratories and physicians are wrestling with this increased complexity in genomic testing and reporting of the incidental findings to patients.

A report by the Association of Molecular Pathology working group has discussed the pros and cons of next generation sequencing (NGS) technologies, potential benefits, and harms for reporting of incidental findings, including the effect on both the laboratory and the patient, and compares those with other areas of medicine as summarized in Table 18.3 (Hegde et al. 2015).

Table 18.3 Recommendations of the Association for Molecular Pathology on incidental findings

| Recommendation |
|----------------|
| Test advantages and limitations should be clearly stated on the laboratory reports for the physicians. |
| Laboratories should develop a consent form, which clearly explains the test advantages and limitations, and the categories of variants reported (e.g., diagnostic, carrier, pharmacogenetic biomarkers). |
| Choice of opt-in or opt-out be given to patients and their families in the pre-counseling session. |
| Clearly state which genes (American College of Medical Genetics-defined list, laboratory-defined list, or all genes) will be analyzed in incidental findings with the disclaimer that not all regions of all genes are covered. |
| Only known pathogenic or likely pathogenic variants should be reported. |
| Reported pathogenic variants should be confirmed with an alternate technology. The method used for confirmation should be stated under the methodology section in the reports. |
| Laboratories should actively submit the list of pathogenic variants identified in their defined list of genes for which they choose to report incidental findings to public databases such as ClinVar, Human Gene Mutation Database, and Leiden Open Variation Database. |

Patients/families should be counseled on the limitations of exome sequencing. They should understand that there are many genes not amenable to variant detection by NGS. Not all genes or gene regions are analyzable by NGS; therefore, a negative result does not rule out a variant in the list of genes of American College of Medical Genetics (ACMG) or any other expanded list of incidental findings. For example, the ACMG list includes the Lynch syndrome gene, PMS2. Since there are up to 16 pseudogenes for some exons in the PMS2 gene with a high level of extreme sequence similarity, it may not be possible to determine whether variants identified in the PMS2 gene are in the PMS2 gene or a pseudogene. Because of all these problematic genes, the recommendation from this working group is that pathogenic incidental findings should be confirmed by Sanger sequencing before reporting the result. In addition, the common causative mutation in other ACMG genes may be a large deletion, e.g., SMN1, which causes spinal muscular atrophy); large deletions are not amenable to detection by either NGS or Sanger sequencing and require other methods for detection. Laboratories should clearly describe on the consent document the type of variants reported for the primary indication, e.g., pathogenic and likely pathogenic variants, variants of unknown significance identified in genes known to be associated with disease, and variants in genes of unknown function. They should describe how this differs from the types of variants reported for incidental findings, which should be restricted to prior reported known pathogenic variants and
expected pathogenic variants that are of the type expected to be causative for the disorder. The discussion and recommendations presented by the working group underline the need for continued research and discussion among all stakeholders to improve our understanding of the effect of different policies on patients, healthcare providers, and clinical laboratories.

**Personalized Management of DNA Repair Disorders**

DNA maintenance is emerging as a central factor in a multitude of diseases, and loss of genomic integrity leads to severe multisystem syndromes. Monogenic DNA-repair disorders display features of accelerated aging. Most of these diseases are recessive, indicating that a single allele can compensate for loss of the other. Although organ involvement may be similar among diseases, the pathogenesis may be different. Identification of multiple disease-causing genes within specific pathways has increased our molecular understanding and revealed that mutations in the same DNA-repair gene can lead to highly diverse clinical outcomes. For example, mutations in XPF can lead to Fanconi’s anemia, xeroderma pigmentosum, xeroderma pigmentosum with the Cockayne syndrome, and the XFE progeroid syndrome. Molecular evidence linking cellular processes to specific disorders should be followed up in clinical research to enable development of personalized interventions (Keijzers et al. 2017).

**Personalized Preventive Medicine and Public Health**

Genomics and genetics are vital for the development of preventive medicine and public health. Current practice of preventive healthcare involves general advice applicable to population at large, e.g. dietary measures to lower cholesterol. Personalized preventive medicine involves integration of new genetic information into epidemiologic studies to help clarify causal relations between both lifestyle and genetic factors and risks of disease. An example is prevention of atherosclerosis where multiple factors interplay in the etiology. Since atherosclerosis involves arterial inflammation, a polymorphism in the 5-lipoxygenase gene promoter could relate to atherosclerosis in humans and that this effect could interact with the dietary intake of competing 5-lipoxygenase substrates. Inflammatory mediators, leukotrienes, are generated from arachidonic acid (polyunsaturated n-6 fatty acid) by the enzyme 5-lipoxygenase. Variant 5-lipoxygenase genotypes have been found in persons with increased atherosclerosis suggesting that dietary n-6 polyunsaturated fatty acids promote, whereas marine n-3 fatty acids inhibit, leukotriene-mediated inflammation that leads to atherosclerosis in these persons. Genetic risk predictors have important potential implications for clinical medicine because they identify individuals at risk before the condition has manifested, e.g., individuals with a high polygenic score for heart attack derive the greatest benefit from preventive therapy such as cholesterol-lowering medications (Natarajan et al. 2017). Such findings could lead to new dietary and targeted molecular approaches for the prevention and treatment of cardiovascular disease according to genotype.

The significance of risk factors and measures to counteract them vary considerably from one individual to another. General advice to a person to modify all risk factors may not be practical and the compliance is low. By identifying genetic predisposition to disease, the physician could focus on risk assessment and develop a comprehensive personalized plan to modify risk factors and initiate preventive strategies. A practical scenario in preventive medicine practice could be as follows:

A buccal smear sample can be taken in the physician’s office for DNA analysis and analysis may eventually be performed for a very reasonable cost to provide information about predisposition to specific diseases. The physician can use this information and draw up a personalized prevention plan taking into consideration the lifestyle of the individual. However, a systematic review of 9 reviews of 36 primary studies concluded that presenting risk information on its own, even when highly personalized, does not
produce strong effects on lifestyle behaviors or changes which are sustained (French et al. 2017). Future research should consider how best to use personalized risk information to engage people in behavior change programs that are more likely to be effective in producing changes in behavior.

**Personalized Public Health**

Public health, defined as the science of protecting and improving the health of people and their communities, overlaps preventive medicine, which is focused on an individual. Public health promotes healthy lifestyles, researches prevention of disease and injury, and covers detection, prevention, and response to infectious diseases in a population. Personalized/precision public health involves integration of genomic, genetic, and epigenetic information as well as biotechnologies to improve research and applications at a population level. It follows the principles of personalized medicine and allows consideration of other factors such as racial and social inequality. Although the focus is on the community, individuals within the community are also involved.

In 2020, the greatest public health challenge is COVID-19 epidemic. Personalized approach to management of COVID-19 is discussed in Chap. 15. These rapidly accumulating data indicate that it might be better to target interventions for populations, ie, personalized public health like the use of genomic and other personalized patient-specific data to provide the right treatment to the right patient at the right time, personalized public health uses population-specific data to provide the right intervention to the right population at the right time. COVID-19 pandemic provides an opportunity for further evolution of the field of personalized public health, as new tools and technologies begin to complement traditional medical and public health approaches to prevention and control. Careful evaluation of the validity and utility of these new technologies as applied to personalized public health and their effectiveness in reducing COVID-19 cases and decreasing morbidity and mortality will be essential, along with consideration of the ethical, legal, and social implications. These applications will require a strong collaboration among the health care sector, individual clinicians and health centers, private sector, governments, and communities (Rasmussen et al. 2020).

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