Summary

Biomarkers have been used in clinical medicine for decades. With the rise of genomics and other advances in molecular biology, biomarker studies have entered a whole new era and hold promise for early diagnosis and effective treatment of many diseases. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention. They can be classified into five categories based on their application in different disease stages: 1) antecedent biomarkers to identify the risk of developing an illness, 2) screening biomarkers to screen for subclinical disease, 3) diagnostic biomarkers to recognize overt disease, 4) staging biomarkers to categorise disease severity, and 5) prognostic biomarkers to predict future disease course, including recurrence, response to therapy, and monitoring efficacy of therapy. Biomarkers can indicate a variety of health or disease characteristics, including the level or type of exposure to an environmental factor, genetic susceptibility, genetic responses to environmental exposures, markers of subclinical or clinical disease, or indicators of response to therapy. This chapter will focus on how these biomarkers have been used in preventive medicine, diagnostics, therapeutics and prognostics, as well as public health and their current status in clinical practice.

Introduction

Health sciences have been experiencing a shift from population-based approaches to individualized practice. The focus on individuals could make public health strategies more effective by allowing practitioners to direct resources towards those with the greatest need. However, the success of these efforts will largely depend on the continued identification of biomarkers that reflect the individual’s health status and risk at key time points, and successful integration of these biomarkers into medical practice. To be clinically useful, tests for biomarkers must have high predictive accuracy, and be easily measurable and reproducible, minimally invasive, and acceptable to patients and physicians. Once a proposed biomarker has been validated, it
can be used to assess disease risk in a general population, confirm diagnosis of disease in an individual patient, and tailor an individual's treatment (choice of drug treatment or administration regimes). In evaluating potential drug therapies, a biomarker may be used as a surrogate for a natural endpoint, such as survival or irreversible morbidity. If a treatment alters the biomarker, which has a direct connection to improved health, the biomarker serves as a surrogate endpoint for evaluating clinical benefit. More recently, with rapid advances in the molecular approaches to biology, genetics, biochemistry and medicine, and in particular with the rise of genomics, transcriptomics, proteomics and metabolomics, molecular biomarkers appear to hold the promise of transforming medical practice into personalized medicine—the right treatment at the right dose for the right person at the right time for the right outcome.

Context and public health significance

Clinical medicine covers disease prevention, diagnosis and treatment. Biomarkers play a critical role in all these aspects. There are three major types of biomarkers: biomarkers of exposure, effect and susceptibility. A biomarker of exposure is an exogenous chemical or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism. Specific markers of exposure include the presence of a xenobiotic compound or its metabolites in body tissues or fluids and in excretory products. For example, blood lead concentration has been used as a marker for lead exposure; saliva cotinine (a metabolite of nicotine) level has been used as a marker in investigating adolescents' cigarette consumption. A biomarker of effect is a measurable alteration of an endogenous factor that is shown to be linked with impairment or disease resulting from exposure to an exogenous agent. For example, the alteration in pulmonary function tests in children after exposure to environmental tobacco smoke is a biomarker of effect (3). Somatic mutations have been used as biomarkers of effect after exposure to carcinogens. A biomarker of susceptibility indicates individual factors that can affect response to environmental agents. These reflect variations between individuals in genetic structure, some of which make the individual more susceptible to health effects from environmental exposures (4). For example, skin cancer is related to excessive sun exposure, but not everyone develops skin cancer even with the same amount of exposure. Three recent studies revealed that genetic variants associated with three sections of genes were found to be linked with increased risk of skin cancer: 1) the variant of the TYR gene that encodes a R402Q amino acid substitution, previously shown to affect eye colour and tanning response, was associated with increased risk of developing cutaneous melanoma (CM) and basal cell carcinoma (BCC); 2) variations in a haplotype (set of closely associated genes) near the ASIP gene, known to affect pigmentation traits, conferred significant risk of CM and BCC; and 3) an eye colour variant in gene TYRP1 was also associated with risk of CM (5–7). The relationship between these biomarkers and their relationship with clinical medicine are illustrated in Figure 17.1.

Figure 17.1. Simplified flowchart of classes of biomarkers (indicated by boxes) representing a continuum of changes. Solid arrows indicate progression, if it occurs, to the next class of marker. Dashed arrows indicate that individual biomarker influences and/or indicates the rates of progression

![Figure 17.1](image)

Source: Adapted from (106)
Biomarkers have been used in routine monitoring activities (8). Validated and are widely used in cholinesterase activities have been and organophosphate effects on haemoglobin synthesis of renal effects of cadmium, lead changes of exposure. Biomarkers carcinogens and as indicators of to identify workers exposed to adducts and mutagenicity in urine years to identify exposed individuals. For example, macromolecule adducts and mutagenicity in urine have been successfully applied to identify workers exposed to carcinogens and as indicators of changes of exposure. Biomarkers of renal effects of cadmium, lead effects on haemoglobin synthesis and organophosphate effects on cholinesterase activities have been validated and are widely used in routine monitoring activities (8).

Antecedent and screening biomarkers have been used in preventive medicine for several decades to: screen before birth for genetic disorders, such as Down syndrome; screen newborn babies for genetic diseases, such as phenylketonuria (PKU) (9); check whether an individual is a carrier for a recessive disorder (where abnormal genes must be inherited from both parents to lead to the condition), such as cystic fibrosis; and indicate whether someone with a family history of a late-onset disease, such as Huntington’s, is likely to develop the disease. These tests are aimed largely at single-gene disorders that have Mendelian patterns of inheritance. The identification of genetic variants responsible for diseases, in these single-gene disorders can lead directly to clinically helpful and reasonably accurate predictions and diagnosis of disease. Early diagnosis and proper treatment can make the difference between lifelong impairment and healthy development.

Common, complex diseases such as cancer, heart disease and diabetes contribute to the major disease burden and mortality both in developed and developing countries. These common diseases are caused by genetic and environmental factors (e.g. lifestyle and diet, and the interaction between them). Therefore, it is very difficult to define a single biomarker that could identify the risk of developing a particular disease. Although there are some rare subtypes of common diseases, such as breast and colorectal cancer, with a clear hereditary pattern, biomarkers for a single or several defective genes could indicate a lifetime risk of developing these cancers (e.g. overexpression of HER2/neu oncogene and loss of function mutations in BRCA1 and BRCA2 tumour suppressor genes for breast cancer (10–12), and activating mutation in Ras oncogene and loss of function mutations in APC and p53 tumour suppressor genes for colon cancer) (12). Subtypes of these cancers and most other common diseases are less deterministic; even apparently simple Mendelian disorders may prove to have widely variable clinical phenotypes. For example, thalassaemia, an apparently simple genetic disease, has substantial complexities (13). Individuals with exactly the same globin mutations may suffer either from a severe life-threatening disorder or be relatively unaffected. Despite this, great efforts have been made towards simultaneous, systematic analysis of larger numbers of biomarkers for disease prediction, although these approaches are more suited to research than routine diagnostic activity. Biomarkers may help predict those individuals more susceptible to common disorders, so that specific attention can be directed towards them (e.g. enrolment in a screening programme). However, translating these biomarkers into clinical medicine to help prevent people having these common diseases still has a long way to go. As Kofi Annan, the former Secretary General of the United Nations, said, “We are under no illusion that preventive strategies will be easy to implement. For a start, the costs of prevention have to be paid in the present, while its benefits lie in the distant future. And the benefits are not tangible—when prevention succeeds, nothing happens. Taking such a political risk when there are few obvious rewards requires conviction and considerable vision.” (14).

Biomarkers in diagnostics

Biomarkers have been used in disease diagnosis for over a century, beginning when the ABO blood
group system was first discovered and used to detect ABO haemolytic disease of the newborn (HDN) and transfusion reactions. The four basic ABO phenotypes are O, A, B and AB. After it was found that blood group A’s red blood cells (RBCs) reacted differently to a particular antibody (later called anti-A1), the blood group was divided into two phenotypes, A1 and A2. RBCs with the A1 phenotype react with anti-A1 and account for about 80% of blood type A. RBCs with the A2 phenotype do not react with anti-A1 and makeup about 20% of blood type A. HDN, caused by ABO antibodies, occurs almost exclusively in infants of blood group A or B who are born to group O mothers (15). This is because the anti-A and anti-B formed in group O individuals tends to be of the IgG type (and therefore can cross the placenta), whereas the anti-A and anti-B found in the serum of group B and A individuals, respectively, tends to be of the IgM type. Although uncommon, cases of HDN have been reported in infants born to mothers with blood group A2 (16) and blood group B (17). The most common cause of death from a blood transfusion is clerical error, in which an incompatible type of ABO blood is transfused. If a recipient who has blood group O is transfused with non-group O RBCs, the naturally occurring anti-A and anti-B in the recipient’s serum binds to their corresponding antigens on the transfused RBCs. These antibodies fix complement and cause rapid intravascular haemolysis, triggering an acute haemolytic transfusion reaction that can cause disseminated intravascular coagulation, shock, acute renal failure and death. Routine biomarker tests can confirm the diagnosis.

Another important use of biomarkers in clinical medicine is the early detection and diagnosis of chromosome and single-gene disorders. Both cytogenetic and molecular genetic biomarkers have been used to accomplish this. Conditions caused by a change in the number (e.g. aneuploidy) or structure of chromosomes (e.g. translocation, inversion, deletion, and duplication) are known as chromosome disorders. Biomarkers used in the chromosome analysis developed in 1956 soon led to the discovery that several previously described conditions were due to an abnormality in chromosome number. For example, in Turner syndrome, only one intact X chromosome is present (45, X); all or part of the second X is deleted. Patients with Down syndrome have an extra chromosome 21 (47, XX/XY, +21). Patau syndrome is the result of trisomy 13, while trisomy 18 causes Edwards syndrome. The biomarker test in this case is assessment of chromosome numbers.

Microdeletion/microduplication syndromes are a group of chromosome disorders that could be detected by biomarker copy number variation (CNV). “Micro” represents submicroscopic, meaning that these deletions, normally smaller than 3Mb, cannot be detected using a microscope. New technologies, especially array comparative genomic hybridization (array-CGH), enabled many malformations and syndromes to be recognized. Figure 17.2 shows recently detected or confirmed microdeletions/duplications collected in DECIPHER (DatabasE of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources) (https://decipher.sanger.ac.uk/).

Applications of new biomarkers in these disorders have generated particular interest. For example, most Angelman and Prader-Willi syndromes are related to microdeletion involving the proximal part of the long arm of chromosome 15q (15q11–12). It is now known that if the deletion occurs de novo on the paternally inherited number 15 chromosome, the child will have Prader-Willi syndrome; a deletion occurring at the same region on the maternally inherited number 15 chromosome causes Angelman syndrome. Non-deletion cases also exist and are often due to uniparental disomy (i.e. both homologues of a chromosome pair are inherited from only one of the parents), with both number 15 chromosomes being paternal in origin in Angelman syndrome and maternal in origin in Prader-Willi syndrome. This “parent of origin” effect is referred to as genomic imprinting and methylation of DNA. Here, CNV and methylation biomarkers, coupled with clinical observations, have helped identify new underlying genetic mechanisms (18).

The most widely used biomarkers identified during the last few decades are for the diagnosis of single-gene disorders. More than 10 000 human diseases are believed to be caused by defects in single genes, affecting 1–2% of the population (18). The disease can be relatively trivial in its effects (e.g. colour blindness), or lethal like Tay-Sachs (a fatal inherited disease of the central nervous system; babies with Tay-Sachs lack an enzyme called hexosaminidase A (hex A) which is necessary for breaking down certain fatty substances in brain and nerve cells). Other disorders, though harmful to those afflicted with them, appear to offer some advantage to carriers. For example, carriers of sickle cell anaemia and thalassemia appear to have enhanced resistance to malaria. Some other examples of single-gene diseases are cystic fibrosis, Marfan syndrome,
Huntington disease and hereditary haemochromatosis. Early detection and diagnosis of these disorders rely on rapidly developed biomarkers, especially molecular biomarkers. For example, phenylketonuria (PKU) is a common genetic disorder (1 in 12,000 births) which results from a deficient enzyme required for the metabolism of the amino acid phenylalanine. Failure to recognize the disorder early in life results in mental retardation. Routine biochemical screening of newborn infants for PKU was recommended by the Ministry of Health in the United Kingdom in 1969, after it had been shown that a low phenylketonuria diet could prevent the severe learning disabilities. Cystic fibrosis is another example of a single-gene disorder where molecular biomarkers play an important role in diagnosis. Cystic fibrosis is the most common life-threatening autosomal recessive disorder in Caucasians, affecting 1 in 2500 newborns. The disease results from a defect in the cystic fibrosis transmembrane conductance regulator (CFTR). Diagnosis of cystic fibrosis is based on the combination of suggestive clinical symptoms, elevated chloride levels on a standardized sweat test, family history and genetic testing to identify the presence of CFTR mutations. Over 1000 CFTR mutations have been identified, with the ΔF508 being the most common in all ethnic groups. Mutation panels using PCR to detect the most common mutations are widely available in clinical DNA diagnostic laboratories (19).

To date, approximately 20,000 chromosomal abnormalities have been registered on laboratory databases, and over 10,000 single-gene traits and disorders have been identified. While on an individual basis most of these are very rare, collectively they make a major contribution to human morbidity and mortality. Screening biomarkers have been used to help early detection and diagnosis of these disorders. Current nationally managed screening programmes in the United Kingdom include: antenatal screening for Down syndrome, sickle-cell disease and thalassemia; newborn screening for PKU, congenital hypothyroidism, sickle-cell disease, thalassemia, cystic fibrosis and hearing impairment; and adult screening for breast cancer, cervical cancer and sight-threatening diabetic retinopathy. Applications of biomarkers in these screening programmes have greatly helped people with early intervention (e.g. diet), decision-making (e.g. marriage and childbearing) and early treatment.

Many of our most common diseases run in families, but they lack the simple inheritance patterns characteristic of single-gene disorders. In complex disorders, pedigrees reveal no Mendelian inheritance patterns, and gene mutations are often neither sufficient nor necessary to explain the disease phenotype (20). The more complicated nature makes genetic analysis for early diagnosis much more difficult than for single-gene or chromosomal disorders. There has been significant activity in the development of biomarkers for the diagnosis and prognosis of common diseases such as heart disease and cancer. Since the start of the 21st century, there...
has been an explosion of high-throughput genomic, proteomic and metabolomic technologies that have furthered our understanding of molecular mechanisms that underlie these common diseases. These technologies are forming the basis for more advanced molecular diagnostics in which DNA, RNA, protein and metabolite data are integrated with traditional clinical profiles to give clinicians the ability to accurately diagnose diseases (21–24). To date, although a large number of candidate biomarkers have been identified which have the potential to be used for both early diagnosis and therapeutic guidance in cancer, heart disease, Alzheimer’s disease, rheumatoid arthritis and asthma, only a fraction have been approved in tests by the US Food and Drug Administration (FDA) (Table 17.1) (25). Even among those biomarkers approved by FDA tests, few of them have lived up to their initial promise. For example, the carcinoembryonic antigen (CEA) test for colon cancer initially claimed to have 100% sensitivity and specificity (26); later investigations found much lower levels of discrimination (27). The cancer antigen 125 (CA125) test was also hailed as a groundbreaking diagnostic test for ovarian cancer, but it is now considered less reliable, as only 50% of women with treatable, early-stage ovarian cancer have increased CA125 levels, while women with other conditions, such as endometriosis, can have increased levels (28). Prostate specific antigen (PSA), currently the best overall serum biomarker for prostate cancer, has high sensitivity (greater than 90%) but low specificity (~25%), which results in many men having biopsies when they do not have detectable prostate cancer (29–32). The serum tumour biomarker for breast cancer (CA15–3) has only 23% sensitivity and 69% specificity, and is only useful in monitoring therapy for advanced breast cancer or recurrence (33). For a biomarker to be valuable in clinical practice, it must have high sensitivity and specificity.

The lack of sensitivity and specificity for single markers is not surprising given the degree of heterogeneity present in both solid tumours and the human population at large. Thus, a prevailing hypothesis is that a panel of biomarkers would cumulatively possess a higher sensitivity and specificity than any single biomarker (34).

**Biomarkers in therapeutics and prognostics**

Biomarkers play an important role in disease treatment, prognosis and management in many different ways. Several common diseases are very heterogeneous, as the same disease may show different phenotypes, may be caused by different genetic mechanisms, and may respond differently to the same treatment. For example, biomarker Philadelphia chromosome, t(9;22) translocation, is found in 95% of cases of chronic myeloid leukaemia (CML) and in some cases of acute lymphoblastic leukaemia (ALL). CML is caused by a chromosomal rearrangement that creates a fusion between two normal proteins producing one abnormal protein, BCR-ABL, that promotes a rapid increase in the number of white blood cells. This biomarker led to the development of Gleevec® (imatinib mesylate), which binds specifically to BCR-ABL and inhibits its action. Appropriate prescription of the drug can be confirmed by a diagnostic test that detects the presence of the BCR-ABL gene. Studies show vastly improved response rates and lower toxicity for CML patients receiving imatinib compared with patients receiving standard chemotherapy (35). Over 90% of patients receiving imatinib respond positively to initial treatment, and many experience complete remission. The presence or absence of this biomarker can also facilitate appropriate application of another drug, Busulfan (Busilvex®, Myleran®). According to the prescribing information, “Busulfan is clearly less effective in patients with chronic myelogenous leukemia who lack the Philadelphia (Ph1) chromosome. Also, the so-called ‘juvenile’ type of chronic myelogenous leukemia, typically occurring in young children and associated with the absence of a Philadelphia chromosome, responds poorly to Busulfan. The drug is of no benefit in patients whose chronic myelogenous leukemia has entered a ‘blastic’ phase.” Therefore, the presence of the Philadelphia chromosome can aid the diagnosis and treatment of these diseases.

Biomarkers can also work as a surrogate endpoint to indicate the treatment response. A clinical endpoint is a characteristic or variable that reflects how a patient feels, functions or survives. A surrogate endpoint is a biomarker intended to substitute for a clinical endpoint. It is expected to predict clinical outcome (benefit or harm, or lack of benefit or harm) based on epidemiological, therapeutic, pathophysiological or other scientific evidence. For example, in cancer treatment, the application of FDG-PET, which is on clinical trial by the US FDA, National Cancer Institute (NCI) and the Center for Medicare Studies (CMS), may have an important role as a surrogate endpoint for assessing the clinical efficacy of oncologic therapies. FDG-PET represents fluorodeoxyglucose positron emission tomography, an imaging method to detect gamma
### Table 17.1. US FDA-published list of valid genomic biomarkers, approved drug labels, and test recommendation (1 = test required, 2 = test recommended, 3 = information only)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Label context</th>
<th>Test</th>
<th>Drug</th>
<th>Other drugs associated with this biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Her2/neu over-expression</td>
<td>Over-expression of Her2/neu necessary for selection of patients appropriate for drug therapy (breast cancer)</td>
<td>1</td>
<td>Trastuzumab (Herceptin®)</td>
<td>Gefitinib</td>
</tr>
<tr>
<td>EGFR expression with alternate context</td>
<td>Epidermal growth factor receptor presence or absence (colorectal cancer)</td>
<td>1</td>
<td>Cetuximab (Erbitux®)</td>
<td></td>
</tr>
<tr>
<td>UGT1A1 variants</td>
<td>UGT1A1 mutation patients, exposure to drug and hence their susceptibility to toxicity (colorectal cancer)</td>
<td>2</td>
<td>Irinotecan (Camptosar®)</td>
<td></td>
</tr>
<tr>
<td>TPMT variants</td>
<td>Increased risk of myelotoxicity associated to thiopurine methyltransferase deficiency or lower activity</td>
<td>2</td>
<td>Azathioprine (Imuran®)</td>
<td></td>
</tr>
<tr>
<td>Protein C deficiencies (hereditary or acquired)</td>
<td>Hemathelial or acquired deficiencies of protein C or its cofactor protein S</td>
<td>2</td>
<td>Warfarin (Coumadin®)</td>
<td></td>
</tr>
<tr>
<td>C-KIT expression</td>
<td>Gastrointestinal stromal tumour c-KIT expression</td>
<td>3</td>
<td>Imatinib mesylate (Gleevec®)</td>
<td>Omeprozole, Pantoprazole, Esomeprazole, Diazepam, Nifedipine, Rabeprazole</td>
</tr>
<tr>
<td>CYP2C19 variants</td>
<td>CYP2C19 variants (poor metabolizers PM and extensive metabolizers EM) with genetic defect leads to change in drug exposure</td>
<td>3</td>
<td>Voriconazole (Vfend®)</td>
<td>Omeprazole, Pantoprazole, Esomeprazole, Diazepam, Nifedipine, Rabeprazole</td>
</tr>
<tr>
<td>CYP2C9 variants</td>
<td>CYP2C9 variants PM and EM genotypes and drug exposure</td>
<td>3</td>
<td>Celecoxib (Celebrex®)</td>
<td>Warfarin</td>
</tr>
<tr>
<td>CYP2D6 variants</td>
<td>CYP2D6 variants PM and EM genotypes and drug exposure</td>
<td>3</td>
<td>Atomoxetine (Strattera®)</td>
<td>Venlafaxine, Risperidone Tiotropium bremide inhalation, Tamoxifen, Timodil Mestolate</td>
</tr>
<tr>
<td>CYP2D6 with alternate context</td>
<td>CYP2D6 PM and EM variants and drug exposure and risk</td>
<td>3</td>
<td>Fluoxetine HCl (Prozac®)</td>
<td>Fluoxetine HCl and Olanzapine, Clozapine hydrochloride, Tolterodine, Terbinafine, Tramadol + Acetaminophen, Clobazepine Aripiprazole, Metoprolol, Propranolol, Cereveldil, Propafenone, Thioridazine, Promazine, Nortriptyline</td>
</tr>
<tr>
<td>DPD deficiency</td>
<td>Severe toxicity (stomatitis, diarrhea, neutropenia and neurotoxicity) associated to deficiency of dihydropyrimidine dehydrogenase</td>
<td>3</td>
<td>Capcictabina (Xeloda®)</td>
<td>Fluorouracil cream, Fluorouracil Topical Solution &amp; Cream</td>
</tr>
<tr>
<td>EGFR expression</td>
<td>Epidermal growth factor receptor presence or absence (NSCLC, pancreas cancer)</td>
<td>3</td>
<td>Erlotinib (Tarcoza®)</td>
<td></td>
</tr>
<tr>
<td>EGFR expression with alternate context</td>
<td>Epidermal growth factor receptor presence or absence (SCLC: squamous cell carcinoma of head and neck)</td>
<td>3</td>
<td>Cetuximab (Erbitux®)</td>
<td>Gefitinib</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>G6PD deficiency (or NADH methemoglobin reductase deficiency) and risk for haemolysis</td>
<td>3</td>
<td>Rasburicase (Elite®)</td>
<td>Dapsonine</td>
</tr>
<tr>
<td>NAT variants</td>
<td>N-Acetyltransferase slow and fast acetylators and toxicity</td>
<td>3</td>
<td>Primaquine (Primaquine®)</td>
<td>Chloropurine</td>
</tr>
<tr>
<td>Philadelphia chromosome deficiency</td>
<td>Philadelphia (Ph1) chromosome presence and efficacy: Busulfin is less effective in patients with CML lacking the Ph1 chromosome</td>
<td>3</td>
<td>Rifampin isoniazid (Rifater® and pyrazinamide)</td>
<td>Isoniazide dimnitrate and hydralazine hydrochloride</td>
</tr>
<tr>
<td>UCD deficiency disorders</td>
<td>Valproate therapy and area cycle disorders interaction</td>
<td>3</td>
<td>Valproic acid (Depakene®)</td>
<td>Sodium phenylacetate and sodium benzoate</td>
</tr>
<tr>
<td>VKORC1 variants</td>
<td>Polymorphisms of vitamin K epoxide reductase complex subunit identify warfarin-sensitive patients who require a lower dose of the drug</td>
<td>3</td>
<td>Warfarin (Coumadin®)</td>
<td>Arsenic oxide</td>
</tr>
<tr>
<td>PML/RAR alpha gene expression (retinoic acid receptor responder and non-responders)</td>
<td>PML/RAR (alpha) fusion gene presence</td>
<td>3</td>
<td>Tretinoin (Aitut®, Retacen®, Retin-A®)</td>
<td></td>
</tr>
</tbody>
</table>

Source: (25)
rays. It measures glucose uptake by tumours using a radioactive form of fluorine incorporated in a sugar molecule. Tissues that accumulate radioactive glucose are visible through positron emission tomography. It is believed that FDG-PET could become a tool for gauging a cancer patient’s response to chemotherapy or radiation by accurately measuring tumour metabolism. Physicians will quickly know whether or not the tumour is responding to therapy and when to switch therapies to provide the best chance for curing or managing the cancer. Cervical tumour uptake of F-18 FDG, measured as the maximal standardized uptake value (SUV<sub>max</sub>) by PET, and its association with treatment response and prognosis in patients with cervical cancer were evaluated. It was found that a higher SUV<sub>max</sub> was associated with an increased risk of lymph node metastasis at diagnosis (<i>P</i> = 0.0027) (36).

Biomarkers can help reduce adverse drug reactions. Studies estimate that over 2 million serious adverse drug reactions (ADRs) occur annually in the United States, and as many as 137,000 deaths are caused by ADRs (37). Using biomarkers to indicate if the patient is suitable for treatment with certain drugs, and what dose is appropriate for the patient, could prevent some of these deaths. Any given drug can be therapeutic to some individuals and ineffective to others, and likewise some individuals suffer from adverse drug effects whereas others experience drug resistance. Often, distinct molecular mechanisms underlie therapeutic and adverse effects. Studies have linked differences in drug responses to differences in genes that code for the production of drug-metabolizing enzymes, drug transporters or drug targets (38–40). These genetic variations could be used as biomarkers to direct a physician’s drug choice for a patient and prevent adverse drug reactions. For example, the anticoagulant drug warfarin, marketed as Coumadin<sup>®</sup> by Bristol-Myers Squibb, is used to prevent potentially fatal clots in blood vessels. Approximately 2 million people start warfarin therapy each year to prevent blood clots, heart attacks and stroke. However, too much or too little of the drug can cause serious, life-threatening bleeding or blood clots. According to the FDA’s adverse events reporting database, complications from warfarin are the second (just after that from insulin) most common reason for patients to go to the emergency department. Variability in the response to warfarin has been linked to mutations in two genes: CYP2C9 and VKORC1. Clinical studies have shown that patients with variations in these two genes may need a lower warfarin dose than patients without those variations. Recently, the FDA cleared the first test to detect gene variants in patients that are sensitive to the anticoagulant warfarin.

Thiopurine methyltransferase (TPMT) is another example of a biomarker being applied to drug treatment. TPMT is responsible for inactivating purine drugs used for treating acute lymphoblastic leukaemia (ALL) and other diseases (41). Variations in the TPMT gene can cause changes in TPMT enzymatic activity and thus drug metabolism. One in 300 patients has TPMT deficiency. In these patients, the normal dose of purine causes an accumulation of active compound, which may lead to a potentially fatal bone marrow reaction resulting in leucopenia, an abnormal lowering of the white blood cell counts. Therefore, if TPMT deficiency is detected, the dose is lowered by 10–15% to keep the systemic level of the drug comparable to that in patients with normal TPMT who have been given a standard dose of the drug (http://www.personalizedmedicinecoalition.org/communications PMC_pub_11_06.php). (More information on genomic biomarkers for drug usage can be found at http://www.fda.gov/Drugs/ ScienceResearch/ResearchAreas/ Pharmacogenetics/ucm083378.htm.)

**Biomarkers in clinical trials and drug discovery**

With rapid advances in the molecular approaches to biology, genetics, biochemistry and medicine, a significant number of new drugs and treatments have been developed. But most of these discoveries still remain in the research field. Efficiently and effectively translating these discoveries into clinical practice is complex and involves the integration of scientific rationale and the regulatory process. Various models depict translational research as a process occurring in two stages (42–44). The first (sometimes referred to as type 1 (T1) translation) uses the findings from basic research, including preclinical studies, to inform the development and testing of an intervention in clinical trials, such as Phase I-III clinical trials. The second (type 2 (T2) translation) involves the translation of findings from clinical research into clinical and public health practice and policy (42,43). This section discusses how biomarkers have been used in clinical trial and drug development, and what changes can be brought about by biomarker application in these fields in clinical medicine.

A clinical trial is defined as a prospective study comparing the effect and value of intervention(s)
against a control in human beings (45). Clinical trials are commonly classified into four phases. Phase I trials select drug dose, schedule and associated toxicities. Phase II trials determine the degree of efficacy and govern admission to Phase III testing. Phase III trials compare a new treatment against the existing standard treatment; if it gives better results, it may become the new gold standard. Phase IV trials are carried out after a drug has been licensed. Information is collected about side-effects, safety and the long-term risks and benefits of a drug (http://www.cancerhelp.org.uk/help/default.asp?page=52). For example, the conventional drug development process will normally proceed through all four stages over many years. A new drug is estimated to cost between US$800 and US$1700 million, and is expected to take anywhere between 7–12 years to be approved and launched. The complexity and duration of clinical trials are determined by the use of a long-term clinical endpoint (e.g. clinical progression, survival) to assess the clinical benefit of a new treatment or drug. Biomarkers have the potential to be used in clinical trials as validated surrogate endpoints to indicate drug efficacy or toxicity, or to make a “go/no-go” decision.

Biomarkers can be influential in every phase of drug development, from drug discovery and preclinical evaluations, through each phase of clinical trials and into post-marketing studies (Figure 17.3). Biomarkers have been used to identify and justify targets for therapy. For example, 95% of CML patients possess a mutation called Philadelphia chromosome, a translocation between chromosome 9 and chromosome 22 that produces a specific tyrosine kinase enzyme, BCR-ABL. Novartis’ Gleevec® (imatinib mesylate) specifically targets this enzyme by attaching to the cancerous cells and stopping them from growing and spreading. But in some patients, the cancer cells mutate just enough to be resistant to imatinib. Bristol-Myers Squibb produced another drug, dasatinib (BMS-354 825), that inhibits five tyrosine kinase proteins, including BCR-ABL and SRC (a protein that may play a role in imatinib resistance). This new agent shows very good response in those who are resistant to imatinib.

Biomarkers play an important role in preclinical studies. Critical proof-of-concept studies typically involve appropriate animal models. In cancer studies, for example, the complexities of modeling human cancer in experimental systems are well known and have impeded cancer drug development over the years (46). Genetically engineered cancer models have improved the situation, but most current models have limited capability for predicting clinical effects. Models that feature biomarker properties, comparable with those seen in patient populations, will enhance their utility as predictive models. Specific effects on biomarkers in such models can, in turn, provide proof-of-concept for therapeutic Figure 17.3. Roles of biomarkers (grey) and their associated technologies (blue) along the different phases of drug development and post-launch (yellow)
approaches (46). For instance, in a preclinical study of dasatinib, biomarkers Phospho-BCR-ABL/ phospho-CrkL were investigated in K562 human CML xenografts grown s.c. in severe combined immunodeficient mice. Results showed that following a single oral administration of dasatinib at a preclinical efficacious dose of 1.25 or 2.5 mg/kg, tumoural phospho-BCR-ABL/phospho-CrkL were maximally inhibited at 3 hours and recovered to basal levels by 24 hours. The time course and extent of inhibition correlated with the plasma levels of dasatinib in mice. Pharmacokinetic/pharmacodynamic modelling predicted that the plasma concentration of dasatinib required to inhibit 90% of phospho-BCR-ABL in vivo was 10.9 ng/mL in mice and 14.6 ng/mL in humans, which is within the range of concentrations achieved in CML patients who responded to dasatinib treatment in the clinic (47).

Use of biomarkers can shorten the clinical trial duration. In diseases with a long natural history, the final result of comparative trials with survival endpoints is often not known for 5–10 years after the study onset. If these clinical endpoints could be replaced by validated surrogate endpoints (biomarkers) that could be measured earlier, more conveniently or more frequently, then new drugs could be validated quicker and administered to patients. In addition, clinical trials could get by with smaller sample sizes, and costs could be lowered by using stratified patients based on molecular biomarkers. Traditional drug development relies on the random assignment of sufficient numbers of participants with a particular condition to investigational drug and control groups to enable detection of statistically significant drug responses. Some patients may be less genetically predisposed to respond to the investigational medication than others. As such, it is typical to enrol large numbers of patients to ensure sufficient power to detect with statistical certainty any true treatment effect among those who are responsive to the medication. In contrast, the application of biomarkers to clinical trials enables targeted selection of subjects and smaller trials by identifying subjects more likely to respond to a drug based on their genotype (48). The use of biomarkers may lead to more precise and effective inclusion and exclusion criteria in clinical trials and can be used at multiple points in the drug development process (49). Biomarkers will be most valuable when genotypes for adverse response and optimal efficacy for a given compound occur at a high frequency in the patient population (50). By applying biomarker-based stratification, based on these genotypes or protein biomarkers to predict and monitor drug response, specific subgroups of subjects examined in Phase III clinical trials would be expected to demonstrate greater response to and/or fewer adverse effects from the drug being studied. These trials would likely decrease drug development time, costs and potentially speed up the approval of drugs (51).

**Examples/case studies**

The goals of using biomarkers in drug treatment are to minimize toxicity and to maximize the effectiveness of therapy. Here are two cases of biomarker applications: UGT1A1 for minimizing toxicity and HER2 for maximizing drug efficiency.

**UGT1A1 and irinotecan**

Irinotecan (Camptosar®), a topoisomerase I poison, is approved for use in combination with 5-fluorouracil (5-FU) and leucovorin chemotherapy for first-line treatment of metastatic colorectal cancer, and also as a single agent in second-line salvage therapy of 5-FU refractory metastatic colorectal cancer. It is also commonly used to treat esophageal, non-small cell lung cancer, breast cancer and other solid tumours in a second- or third-line setting (52). Although it prolongs survival, it also causes severe diarrhoea and neutropenia in 20–35% of patients treated. Fatal events during single-agent irinotecan treatment have been reported (53,54). UDP-glucuronosyltransferase (UGT1A1) is responsible for the clearance by glucuronidation of drugs (e.g. irinotecan) and endogenous substances (e.g. bilirubin). As shown in Figure 17.4, the primary active and toxic metabolite of irinotecan, SN-38, is inactivated by UGT1A1 to form SN-38G, which is eliminated via the bile. It has been determined that variations of the TA repeat length in the UGT1A1*28 gene is located on chromosome 2q37. The polymorphic TA repeat in the 5′-promoter region of UGT1A1 may consist of 5, 6, 7 or 8 repeats. The wild-type allele (UGT1A1*1) has six TA repeats, and the variant allele (UGT1A1*28) has seven TA repeats. Patients who are homozygous for the UGT1A1*28 allele, glucuronidate SN-38, less efficiently metabolize than patients who have one or two wild-type alleles; therefore, homozygous patients are exposed to higher plasma concentrations of SN-38 (52,55). In a meta-analysis,
data presented in nine studies was reviewed that included 10 sets of patients (a total of 821 patients) and assessed the association of irinotecan dose with the risk of irinotecan-related haematologic toxicities (grade III–IV) for patients with a UGT1A1*28/*28 genotype (52). As shown in Table 17.2, the risk of toxicity was higher among patients with a UGT1A1*28/*28 genotype than among those with a UGT1A1*1/*1 or UGT1A1*1/*28 genotype at both medium and high doses of irinotecan; however, risk was similar at lower doses (52).

In 2005, the FDA approved the inclusion of UGT1A1 genotype-associated risk of toxicity on the irinotecan package insert and cites that a clinical test (Invader UGT1A1 Molecular Assay; Third Wave Technologies Inc.) to detect common UGT1A1 alleles is available. The FDA-approved label for the test states that “individuals who are homozygous for the UGT1A1*28 allele are at increased risk of neutropenia following initiation of Camptosar treatment. A reduced initial dose should be considered for patients known to be homozygous for the UGT1A1*28 allele. Heterozygous patients may be at increased risk of neutropenia; however clinical results have been variable and such patients have been shown to tolerate normal starting doses.” (http://www.fda.gov/Drugs/ScienceResearch/ ResearchAreas/Pharmacogenetics/ucm083378.htm).

However, as shown in Figure 17.4, irinotecan interacts with multiple polymorphic drug metabolizing enzymes and transporters (54,56–62), being inactivated by CYP3A4 to APC and requiring conversion by carboxyesterases to the active metabolite SN38. The latter in turn is inactivated by UGT1A1 glucuronidation as the main degradation pathway. In addition, irinotecan and its metabolites serve as substrates for transporters, including the ABC transporters (ATP-drive extrusion pumps) MDR1, MRP2, and BCRP. Each of these factors displays interindividual variability, with functional polymorphisms potentially contributing to variable irinotecan response. Haplotype analysis has provided additional insight into the regulation of gene transcription (54,56,57,62), but a quantitative assessment of all factors is lacking. As a result, use of TA repeat polymorphisms in predicting in vivo UGT activity and SN38 exposure after irinotecan administration has been only partially successful. The Clinical Pharmacology Subcommittee, Advisory Committee for Pharmaceutical Science, reviewing the product, further noted that “...although there is indication to start with a lower dosage, it is not necessarily an indication that sensitive patients will do well with this dosage” (54). This example illustrates that pharmacogenetic (PGx) testing can identify patients who are likely to respond differently to a particular drug and indicate the appropriate dosage, but that testing does not necessarily translate into dosing instructions. Hence, the
value of prospective genotyping for UGT1A1 in irinotecan therapy must be determined empirically in the intended target populations (63).

**HER2 and trastuzumab (Herceptin®)**

Human epidermal growth factor receptor 2 (HER2), also known as ErbB2 and Neu, is a cell surface glycoprotein with intrinsic TK activity that is involved in cell growth and development (46,64). In normal quantities, HER2 promotes normal cell growth, but when a genetic mutation causes HER2 to be overexpressed on the cell surface, certain breast cancer cells are prompted to multiply uncontrollably and invade surrounding tissue (46,65). The cloned HER2, associated with a form of metastatic breast cancer, appeared as a potential monoclonal-antibody target in 1985. It has many of the properties required for such a target; it is overexpressed on the surface of tumour cells and not on normal cells, it has an extracellular domain that is readily accessible, and expression of the receptor is stable in primary tumour tissues and metastatic deposits. HER2 became a potential biomarker with the initial observation that the HER2 gene was amplified in 25% of axillary lymph node-positive breast cancers, and, when present, correlated with poor prognosis (66). Additional studies confirmed that HER2 protein overexpression was also a prognostic biomarker in breast cancer, correlating with decreased relapse-free and overall survival (66–68). Moreover, additional clinical data have shown that HER2 amplification/overexpression is a predictive biomarker for greater or lesser response to certain chemotherapies or hormonal therapies in breast cancer (69–73). The role of HER2 as an oncogenic protein and clinically relevant biomarker led directly to the development of a specific targeted therapy: trastuzumab (Herceptin®; Genentech, South San Francisco, CA), a humanized IgG1 monoclonal antibody with high affinity and specificity for HER2. The clinical trials were started in 1992. In advanced breast cancers with HER2 overexpression, trastuzumab was shown to be active as a single agent in second- and third-line therapy (74,75), and subsequently as first-line therapy (76). Trastuzumab is particularly effective in combination with chemotherapy. In 1998, the drug was approved in the United States by the FDA as Herceptin. This drug was able to get a fast track approval status for two reasons: it demonstrated efficacy in patients previously resistant to more conventional treatments, and a diagnostic test was able to identify the patients that were expected to benefit from it. The HercepTest is the first example of a pharmacogenomic test that is marketed along with a drug. There are two tests to determine HER2 status and select patients for treatment with trastuzumab. The first approved was an immunohistochemistry (IHC) test, the HercepTest, which measures the level of expression of the HER2 protein. The possible outcomes of the test are reported as numbers
from 0 to 3+, with 0 representing no overexpression and 3+ representing high overexpression. Only 3+ is defined as HER2 positive. The most recently approved method, fluorescence in situ hybridization (FISH), detects the underlying gene alteration in the patient's tumour cells. FISH makes the number of HER2/neu gene copies visible. In healthy cells, there are two copies of the HER2/neu gene per chromosome. If FISH detects more than two copies of the HER2 gene, it means that the cell is abnormal and is HER2-positive. This abnormality is also referred to as HER2 gene amplification. The results of the FISH test can be reported as positive or negative.

Recent comparison of FISH and IHC shows that FISH appears to be superior at providing prognostic information with respect to the detection of higher-risk breast cancers (77). Unfortunately, it is expensive and requires additional equipment and training beyond what is commonly found in most laboratories. For this reason, it is recommended that only IHC results of 2+ (which represents a little overexpression of HER2) should be retested with FISH to prevent false-negative outcomes (78), as shown in Figure 17.5.

The HER2 case is one of the most successful applications of biomarkers in drug development and disease treatment. The advantage of this case is the co-development of drugs and diagnostic tests, which greatly reduced the number of patients involved in the clinical trials and facilitated a fast-track approval status. It is known that women with HER2+ breast cancer do not respond well to standard therapy, and that patients whose breast cancers lack HER2 overexpression are highly unlikely to respond to trastuzumab alone (46). Moreover, HER2 positivity could predict the effect of adjuvant treatment of other drugs. For example, it was reported that HER2 positivity was associated with a significant benefit from the addition of paclitaxel to the treatment regimen (79). The interaction between HER2 positivity and the addition of paclitaxel was associated with a hazard ratio for recurrence of 0.59 ($P = 0.01$). Patients with a HER2-positive breast cancer benefited from paclitaxel regardless of estrogen-receptor status, but paclitaxel did not benefit patients with HER2-negative, estrogen-receptor-positive cancers.

The effect of adjuvant trastuzumab in the treatment of HER2-positive early breast cancers has been evaluated in randomized controlled trials and in a meta-analysis of published randomized trials. Results of a study on trastuzumab use after adjuvant chemotherapy in HER2-positive breast cancer patients found that one year of this treatment combination had a significant overall survival benefit after a median follow-up of two years (Figure 17.6) (80).

A meta-analysis of five randomized controlled trials was performed comparing adjuvant trastuzumab treatment for HER2-positive early breast cancer. Pooled results from the trials showed a significant reduction of mortality ($P < 0.00001$), recurrence ($P < 0.0001$), metastases rates ($P < 0.0001$) and second tumours other than breast cancer ($P = 0.007$), as compared to no-adjuvant-trastuzumab patients (81).

However, there are still questions about the HER2 biomarker and

**Figure 17.5. Algorithm for HER2 testing**

Figure 17.6. Exploratory disease-free survival subgroup analysis for one year of trastuzumab versus observation

Source: (80). Reprinted from The Lancet, Copyright (2007), with permission from Elsevier.
trastuzumab treatment. For example, almost half of HER2-positive breast cancer patients are non-responsive to trastuzumab therapy or become drug resistant during treatment. Although other biomarkers have been investigated, and some drugs are in clinical trial, no breakthrough drug has been reported yet. Another unsolved issue is toxicity. In the meta-analysis, they reported more grade III or IV cardiac toxicity after trastuzumab \( \frac{203}{4555} = 4.5\% \) versus no trastuzumab patients \( \frac{86}{4562} = 1.8\% \); therefore, careful cardiac monitoring is warranted (81).

**Strengths, limitations and lessons learned**

Biomarkers have been used in disease prevention, diagnosis, treatment, prognosis and drug development for many years, but have only recently shown the potential to revolutionise the health paradigm into a new era. The successful completion of the human genome sequencing project laid the foundation for identifying mechanism-based biomarkers. Although US$1000 per individual for sequencing is still a ways off, BioNanomatrix and Complete Genomics Incorporated have formed a joint venture to develop a system capable of sequencing the entire human genome in eight hours at a cost of less than $100. By its completion, the proposed technology will have the potential to enable improvements in the diagnosis and personalized treatment of a wide variety of health conditions, as well as the ability to deliver individually tailored preventive medicine (http://nanotechwire.com/news.asp?nid=5087&ntid=130&pg=1).

Recently developed "omics" technologies, such as genomics, transcriptomics, proteomics, metabolomics and other high-throughput technologies, offer useful tools for biomarker discovery. Genomics studies organisms in terms of their genomes (i.e. their full DNA sequences) and the information they contain (an indication of what can happen). Transcriptomics is used to analyse gene expression (what appears to be happening). Proteomics is used to investigate proteins (compounds that make things happen). Metabolomics is used to measure metabolites (substances that indicate what has happened and is happening). It is widely known that early diagnosis and effective treatment of common diseases requires capturing and interpreting information at different levels and using a variety of novel techniques (as shown in Figure 17.3).

Computational technology and bioinformatics play a major role in the discovery of new biomarkers, the validation of potential biomarkers, and the analysis of disease states. For example, Figure 17.7 shows the detail of a subnetwork of the protooncogene MYC. Two types of technologies have made this work possible: the advent of a new wave of high-throughput biotechnology, with its sequencers, gene expression arrays, mass spectrometers and fluorescence microscopes; and information technology for qualitative changes in the way biological knowledge is stored, retrieved, processed and inferred.

Large and well-organized consortia and networks, as well as updated regulatory systems, guarantee the validation of biomarkers and their successful translation into clinical practice. A good example of this is the FDA consortium that includes members of the pharmaceutical industry and academia, and aims to observe how genetic biomarkers contribute to serious adverse events. The consortium launched two projects: to address drug-related liver toxicity; and to study a rare but serious drug-related skin condition called Stevens-Johnson syndrome. The Biomarkers Consortium has launched a web site to encourage researchers to submit biomarker project concepts (http://www.biomarkersconsortium.org/).

In clinical medicine, there are still many challenges that must be met before the full value of biomarkers, especially molecular biomarkers (e.g. cancer biomarkers), can be realized.

First, identification of highly prevalent targets that constitute key master promoters of oncogenesis in specific tumours is still very difficult. For instance, the oncogenic process in malignant gliomas is driven by several signalling pathways that are differentially activated or silenced with both parallel and converging complex interactions. To date, no new molecule seems to be promising enough to justify a large Phase III trial (82).

Second, once a potential target is identified, it is not easy to discover new agents capable of restoring normal cell functions through interaction with the target. A major hurdle is that tumour cells acquire drug resistance. Certain cancers are effectively treated because the targeted drug is applied. But very often patients develop secondary mutations that recruit other kinases that are not affected by the inhibitor to substitute for the pharmacologically impaired kinase, and to restore downstream molecular signalling cascades that contribute to tumour growth (82–84).

Third, there are still many methodological issues to resolve. For example, how to define proper criteria for responsiveness, avoid measurement errors, interpret laboratory results, educate medical staff to accept and use biomarkers in...
their daily medical practice, and how to help the public better understand genetic tests (85).

Finally, ethical and social issues must be considered. Individual, family and societal goals may conflict with current health care practices and policies in regards to genetic testing. Current health care policies do not fully address these concerns. One major barrier is the potential loss of societal benefits, such as employment or insurability, based on one’s genetic characteristics, which is referred to as genetic discrimination (85). Other issues include genetic testing on those who lack the capacity to consent, genetic testing on stored tissue samples and tissue banks, and ensuring appropriate monitoring of genetic tests. These concerns warrant the attention and action of society as a whole.

Future directions and challenges

Multiple targets, prevention and prediction, personalization and cooperation will be the future directions of biomarker applications in clinical medicine. Multiple biomarkers will be more frequently applied in clinical tests, especially for common diseases. “Multiple” could represent many markers from the same profile, or markers from different profiles, such as DNA, mRNA, microRNA or protein and gene expression. In 2007, for example, the FDA approved a gene-based breast cancer test designed to determine the likelihood of early stage breast cancer recurrence within 5–10 years after treatment. The test called MammaPrint™ (Agendia) is a DNA microarray-based diagnostic kit that measures the level of transcription.
of 70 genes in breast cancer tumours. The profiles are scored to determine the risk or recurrence and with it the need for adjuvant therapy (86). There is currently a great deal of research being done on multitargeted therapies, which simultaneously target some of the many signalling pathways involved in tumour development and proliferation. “Mixing cocktails,” as Charles L. Sawyers recently described it (84), will continue to grow, but should be under the appropriate molecular guidance.

Preventive and predictive biomarkers will play a key role in future health care. New agents, such as antiangiogenesis/vascular-targeting drugs, have moved from cancer therapy to cancer prevention. Molecular and epidemiologic studies of cancer risk and drug sensitivity and resistance began ushering in the era of personalized prevention (84,87). Development of new treatments has increased the need for markers that predict outcome and those that direct which treatment options are most likely to be effective for a particular patient with a particular tumour (88).

Personalized medicine is the use of detailed information about an individual’s inherited and/or acquired characteristics and their phenotypic data to select a preventative measure or medication that is particularly suited to that person at the time of administration. This revolution in clinical care is predicated on the development and refinement of biomarkers, enabling disease prevention, and diagnosis and treatment of patients and populations (89). Biomarkers will be used before birth and throughout life. For example, a couple planning to have children could be tested for specific biomarkers to avoid haemolytic disease of the newborn (HDN) and some recessive diseases (carrier parents have a 25% chance of passing on the disease to the baby). Children with a family history of diabetes, heart disease or cancer may take a genetic test to adjust their lifestyle or consider preventive treatment. Therapeutic and prognostic biomarkers should be applied to all kinds of patients, especially cancer patients, to direct their treatment plans and predict the treatment outcomes. Within the foreseeable future, when the US$100 genome sequencer is developed, everybody would be able to have their whole-genome information on their ID card.

In the first decade of the 21st century, the fast-growing application of omics technologies in translational research and clinical medicine have been witnessed. It has accelerated biomarker development, improved the accuracy for diagnosis/treatment, and advanced personalized medicine. One example is the application of omics in reproductive medicine, in particular in vitro fertilization (IVF) treatment, an assisted reproduction. A key step in assisted reproduction is the assessment of oocyte and embryo viability to determine the embryo(s) most likely to result in a pregnancy. Although conventional systems such as morphological charaterization and cleavage rating have been successful in improving pregnancy rates, their precision is far from ideal (90,91). It was reported that two out of three IVF cycles fail to result in a pregnancy, and more than eight out of 10 embryos fail to implant (92). The presence of aneuploidy in embryos frequently causes failed implantation and pregnancy. In a recent study, CGH, a genomics approach, was used in assessment of embryo aneuploidy and achieved implantation and pregnancy rates of 68.9 and 82.2%, respectively (93). Alternatively, using microarray CGH (aCGH) and single nucleotide polymorphism microarray have the potential for further improvement in assessment of embryo aneuploidy at a higher resolution, as they can be used to detect more refined regions (less than megabases, or even less than kilobases of nucleotides) in any chromosome (94,95). Other omics have also been applied to assessing embryo viability, such as metabolomics (96,97), transcriptomics (98) and proteomics (99). These omics technologies present unique advantages as well as their own intrinsic limitations. However, a combined strategy of omics may enhance the thorough screening of gametes and embryos for their viability and reproductive potential. The applications of omics technologies in other medical fields are in different stages of development and ever expanding. It is envisioned that the biomarkers derived from those omics will realize their full potential before long in all fields of clinical medicine.

In summary, biomarkers have been widely used in clinical prevention, diagnostics, therapeutics, prognostics, clinical trials and drug development. With mapping of the human genome complete, rapid development of new technologies and the collaboration of different disciplines, biomarkers promise personalized medicine, though many challenges remain to be overcome.


References


