The Influence of Chemistry on Personalized Medicine

Jack Kushner H1* and Christopher Kinter2
1Professor of Medicine, USA
2Associate Professor of Chemistry, US Naval Academy, USA
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*Corresponding author: Jack Kushner H, Professor of Medicine, USA, Email: jkaopental@comcast.net

Abstract
The medical profession, patients, and third party payers of healthcare have greeted personalized medicine with a wave of enthusiasm worldwide. While genetics, pharmacology, neurology, pediatrics, psychiatry, oncology, biotechnology, infectious disease departments, and public health have received the majority of the well-deserved recognition, developments within chemistry have been responsible for many of the significant contributions to the possibilities envisioned in the future of medicine. This article demonstrates just how chemistry has unraveled the mysteries of what we now call genomic medicine.

Keywords: Chemistry; Personalized medicine; Genetics; Glutamate; Aptamers; Pharmacogenomics; Drug delivery systems; RNA sequencing; CRISPR

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Personalized medicine or genomic medicine has been popularized by the progresses made in sequencing the genetic composition of patients. There have also been advances in microarrays and computing. Researchers can sequence RNA transcriptomes, identify SNP haplotypes, rare variants, splice exon boundaries, and accomplish germline gene editing [1]. Just as personalized medicine has grown, so too have chemistry and genetics contributed to the delivery of healthcare. Personalized medicine is not limited to genes, diseases, and drugs, but also has applications in agriculture, animal health, and husbandry [2]. Additional benefits of personalized medicine have to include the identification of genetic predisposition, the employment of disease preventive measures, the improvement of diagnostic assessments, more timely therapeutic interventions, and more efficacious medications with fewer adverse effects.

The fields of chemistry and genetics have benefited from the increased interest in personalized medicine. Professor Anton Maximov at the Srippts Research Institute has discovered that neurons in various brain regions that store memory can form networks without synaptic activity [3]. Education engenders the growth of new synapses in the brain and these synapses are driven by chemical neurotransmitters that relay signals from one neuron to another [4]. Glutamate is a neurotransmitter that activates neurons when memory is formed. Additional research demonstrates that genomic integrity requires that branched nucleic acid molecules be processed to produce double-helical DNA [5-7]. In the past, antibodies were the dominant source for biomarker research. Because of their instability and potential immunogenicity, researchers have been seeking alternative approaches to rival antibodies as molecular probes. Accordingly, aptamers have become more attractive. Aptamers are single-stranded synthetic oligonucleotides composed of DNA or RNA, with a length of 20-100 nucleotides. These aptamers have a remarkable binding affinity to a variety of targets such as metal ions, small molecules, proteins, and intact cells. Aptamers are generated by an in vitro selection process called Systematic Evolution of Ligands by Exponential Enrichment (SELEX). Aptamers depend on chemical artistry [8-10]. Aptamers are chemically synthesized and can be tailored to conjugate with other molecules such as bioaffinity molecules, chemical linkers and nanomaterials. These attributes make aptamers valuable molecular tools for biomarker studies [11].

Besides promoting individualized disease diagnosis and risk prevention, patients are empowered by personalized medicine to become more involved in their own medical decisions and to make healthcare more predictive. Now patients aid in the preemption of diseases via early detection and prevention and they have assumed more responsibility for their own healthcare. There has been a shift from disease treatment to disease prevention which lowers the cost of healthcare [12,13]. This logic can be extended to the use of genetic testing as a method...
to prevent the expression of a genetic disease in an individual or “phenotypic prevention”. Testing can prevent intergenerational disease transmission or “genotypic prevention”. An alternative to periodic uncomfortable colonoscopy exams screening for cancer has recently been developed. Now patients might choose to have a Cologuard noninvasive colon cancer screening test which is based on the latest advances in stool DNA science [14].

There has been an increase in personal genome testing on the basis of genetic profiling; i.e. the testing of multiple genetic variants simultaneously for the prediction of common multifactorial disease. There are four test characteristics of personal genome testing: a non-targeted type of testing, high analytical validity, low clinical validity, and problematical clinical utility. The low level of clinical validity raises questions about societal risks and regulatory requirements. Multifactorial diseases, such as cardiovascular diseases, macular degeneration, type 2 diabetes, depression, and many types of cancer might be caused by multiple genetic factors and non genetic factors. Clinical utility requires that the test provide patients with actionable options for preventing or treating a problem. Current personal genome testing does not pass this test.

The largest personalized medicine example implemented in the USA is the newborn screening public health program [15,16]. Most of the genetic conditions included in the screening panels are autosomal recessive disorders and some are assays that identify heterozygote carriers (e.g. hemoglobinopathies). Additional screening may include X-linked conditions (e.g. Duchenne muscular dystrophy) and autosomal dominant conditions. Some newborn tests include identification of both acquired and hereditary hearing loss. The American College of Medical Genetics recommends allowing all pregnant women a chance to select diagnostic or screening approaches for the detection of fetal aneuploidy. The College also suggests educating everyone that diagnostic testing is an option for the detection of chromosome abnormalities.

Genetic tests can identify those individuals who are at a high risk of developing certain cancers. For example, genetic testing can be employed to identify breast cancer patients who are most likely to benefit from the drug Herceptin. Another genetic test is being used to determine the initial dose of Mercaptopurine, in order to prevent severe side effects. This medication is used to treat leukemia and autoimmune diseases. The American College of Medical Genetics and Genomics has published a list of 59 genes which should help identify and manage risks for selected genetic disorders, thus leading to the prevention of morbidity and mortality [17]. Some genetic tests can measure gene expression in breast cancer tissue and predict which women will have the highest risk of cancer recurrence and might benefit from chemotheraphy. The TGFβ1 gene is associated with a small increase in breast cancer whereas the BRCA1 gene and the BRCA2 genes have a 50-85% lifetime risk of developing breast cancer. This risk is high enough incidence to merit the prophylactic removal of both breasts and the ovaries. Recently Dr. Yongcho Ma at the Stanley Manne Children’s Research Institute in Chicago, Illinois, found that the UBQLN4 gene variant interferes with a pathway involved in breaking down a certain protein called beta catenin. An accumulation of this protein leads to defects in the motor neuron structure. This discovery identifies another potential target treatment for amyotrophic lateral sclerosis (ALS) [18]. Researchers at Loyola University of Chicago have studied how misfolded protein clumps invade a healthy brain cell. Previous research has found that in patients with Alzheimer’s disease, Parkinson’s disease, and Huntington’s chorea all have proteins that are folded abnormally in clumps inside the brain cells. Different proteins are implicated in each of the diseases: tau in Alzheimer’s disease, alpha-synuclein in Parkinson’s disease, and huntingtin in Huntington’s disease. Once the proteins enter the cell, they also enter the vesicles which are small compartments encased in membranes. The proteins rupture the vesicles and invade the cytoplasm [19].

Immune cell-mediated tumor cell killing can involve the components of both the innate and adaptive immune systems including:

- a) Natural killer (NK) cells,
- b) Cytotoxic T cells (MHC-dependent),
- c) Antibodies secreted by B lymphocytes,
- d) Engineered antibodies such as bispecific antibodies and bispecific T cell engagers (bites),
- e) Genetically engineered T cells targeting specific tumor antigens (e.g. CAR-T; MHC-independent), and
- f) Macrophage-mediated phagocytosis [20-22]. Tumor cells typically acquire extensive mutations in their genomes, including the genes of key regulatory and signaling proteins. When cleaved, processed, and presented by MHC molecules on the surface of antigen presenting cells, these mutated proteins can elicit a cellular immune response. It is for this reason that T lymphocytes can be found inside tumors.

T cells can be genetically engineered to express a tumor antigen-specific T cell receptor (TCR) or a chimeric antigen receptor [23,24]. Kite Pharma CAR-T cancer therapy shows strong, a durable result in lymphoma patients. CART, or chimeric antigen receptor T-cells, is a new form of cancer immunotherapy in which a patient’s own T cells are removed and then engineered to identify and kill the malignant blood cancer cells. In their pivotal study, 77 patients with advanced diffuse large B-cell lymphoma (DLBCL) were treated with Kite’s KTE-C19. The response rate was between 31%-33% after three months [25]. Patients respond to drugs in a variety of ways. Pharmacogenomics testing can be done to help improve drug treatment [26].

A Yale research team headed by Dr. W.M. Saltzman has modified the surface properties of drug-loaded nanoparticles and can potentially direct these particles to specific cells in the
the ability for nanoparticles to deliver drugs to specific areas of the body will help fight cancer and will minimize the side effects of drugs which often are toxic. They covered a group of particles with polymers rich in aldehydes which bind to amines that are found in many proteins. The modified particles could be tailored to specific therapies and to improve efficacy in target cells without causing any toxicity to the cells not being targeted [27]. Nanoparticles have been employed for other malignant tumors including liposomes, polymeric nanoparticles, dendrimers, magnetic and other inorganic nanoparticles. Researchers have demonstrated that there is the potential utility for an anti-body-targeted, intracellular delivery system with peptides/proteins that antagonize targets [28].

There are now diagnostic panels for cardiovascular disease, appendicitis, and pneumonia/respiratory diseases. The company named True Bearing addresses this enormous market for human disease diagnostics and identifies new drug targets using the latest single molecule RNA sequencing techniques. One product, TruCad, is a “liquid angiogram” which senses immune imbalances in the blood with great accuracy. This is a first in a collection of comprehensive RNA based diagnostics to guide precision care. According to Dr. Timothy McCaffrey at The George Washington University Medical Center, this technique increases the accuracy of diagnosing coronary artery disease with a 80% accuracy compared with other clinical tests which have a 54% accuracy. Considerable research has been directed toward the Glutamatergic System. Glutamate is the major excitatory neurotransmitter in the nervous system. Glutamate receptors are found throughout the brain and spinal cord in neurons and glia. There are at least 30 proteins in the glutamate synapse control system. These proteins are situated in various cell types: pre and post synaptic neurons, astrocytes, and neurons that use Gamma Aminobutyric acid or GABA, the chief inhibitory neurotransmitter in the brain. GABA is synthesized by the enzyme L-glutamic acid decarboxylase [29]. Only three medications target glutamate or glutamate receptors; namely, Memantine, Ketamine, and D-Cycloserine. Other drugs modulate other neurotransmitters such as Dopamine, Serotonin, and Acetylcholine.

Some of the genetic screening tests that are presently available can indicate whether or not the patients have a propensity or possibility for developing various diseases such as Alzheimer’s disease, Parkinson’s disease, Multiple Sclerosis, or even schizophrenia [30]. Dr. Roger Rosenberg, Director of Alzheimer’s Disease Center at the University of Texas Medical Center, has announced that a new DNA vaccine will prompt an immune response that produces antibodies which might protect against toxic proteins associated with Alzheimer’s disease. Two studies in animals demonstrate how the vaccine elicits a response which hopefully will be safe when used in humans [31] Dr. Auriel Willette of Iowa State University says that TOMM40 (translocase of Outer Mitochondrial Membrane-40kD) elucidated a difference in the gene’s impact on memory, cognitive function and risk, based on a family history of Alzheimer’s disease and the length of a specific section of the gene [32,33].

Along with the great hopes and dreams for the place of personalized medicine in the practice of clinical medicine, some aspirations have not completely materialized [34]. Although genes are known to influence obesity, hypertension, and cancer, there are many diseases that are caused and influenced by environmental, behavioral, and social factors. One of the major promises of personalized medicine has been that the identification of the predictors of disease would help in the intervention of that disease. This may be true regarding some cancers, but this is not the case regarding many other diseases. It was hoped that large populations would change their behavior when they realized that they are in a high-risk group. Unfortunately, some individuals do not change their behavior. There is still a need to focus on social, economic, and environmental factors when dealing with poverty, obesity, and education. If genomic medicine does not live up to the promises, then funding either from the government or private sources could dry up [35]. Dr. Kelly Ormond and Dr. M.K. Cho have warned that DNA sequencing for genome-wide genetic testing has been yielding huge amounts of information and still the clinical implications are not fully understood. We still need to develop technical standards for measuring sequence accuracy [36]. We should consider ethical principles such as informed consent, privacy, data ownership and sharing, technological regulation, access issues of potential stigma, and perceptions of disability. There must be regulation of genomic testing in clinical settings, and direct-to-consumer settings. There has to be more protection against genetic discrimination and misuse of genetic data. Biobanks need to be established but then this raises questions about sample collection storage, sharing sample, re-identification, privacy and confidentiality. And finally, the cost of gene-based therapies and genetic testing are significant obstacles for personalized medicine.

The cost of developing drugs for personalized medicine is growing and is spread over smaller groups of patients. It is not unusual to hear of drugs costing more than $500,000 a year. Who can afford this cost? The drugs may not be effective [37]. Greater legal risks will also become more of a problem such as failure to warn of a genetic predisposition to cancer once identified, failure to refer for genetic testing for gene-drug interaction, failure to use a genetic marker to tailor treatment, premature use of a genetic test to tailor treatment, failure to disclose genetic risk to a patient’s family, and breach of confidentiality with unauthorized disclosure of a patient’s data [38].

Recently the Food and Drug Administration has recently approved ten of the personal genomics company 23 and Me screening tests for genetic health risks including one for Alzheimer’s disease. This is a turning point toward empowering people to monitor their own health. Patients no longer have to go through a physician to have a genetic test done [39]. The Human Fertilisation and Embryology Authority granted regulatory
approval for mitochondrial DNA transfer and approved genetic modification for research purposes in healthy human embryos. This opens up the opportunity for such techniques as CRISPR/Cas 9 to be used. CRISPR is an acronym for Clustered Regularly Interspaced Short Palindromic Repeats. This is part of the immune system of bacteria which helps to ward off attacks by viruses. Drs. Jennifer Doudna and Emmanuelle Charpentier have demonstrated a tool that includes Cas9- which targets and edits DNA in a test tube [40]. Some ethicists are concerned about using nontherapeutic genetic enhancement and designer babies. CRISPR/Cas 9 is an RNA guided nuclease system of bacterial origin that can be engineered to target a specific sequence in the genome where the CAS 9 protein causes a precise double strand break. The American College of Medical Genetics Board of Directors believes genome editing in the human embryo is premature and should be subject to vigorous ethical debate and further refinement of technological issues [41].

Conclusion

The role of chemistry is crucial to the importance of personalized medicine. Chemical transmitters which relay signals from one neuron to another include Glutamate, Dopamine, Serotonin, and Acetylcholine. DNA is now being used as a diagnostic test in Cologuard screening for colonic cancer. DNA is being used as a vaccine by some researchers. Some proteins are definitely associated with specific diseases such as tau in Alzheimer’s disease, alpha-synuclein in Parkinson’s disease, and huntingtin in Huntington’s disease. The protein catenin leads to defects in Motor Neuron Disease. There was a discussion about the use of Herceptin in breast cancer and the catenin reveals important role of genetics.

23. Vietnam National University, Vietnam CAR; composed of an intracellular signaling domain that is linked to an extracellular domain derived from a tumor-specific antibody.

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