IVT NETWORK
INSTITUTE OF VALIDATION TECHNOLOGY | an informa business
Unlimited Validation Knowledge Awaits...
Published on *IVT Network* (http://www.ivtnetwork.com)

Crest of a wave? Innovations with personalized medicine

By **Tim Sandle**

Jan 21, 2021 8:00 am EST

Introduction

Medicine and healthcare is undergoing considerable change in terms of the end of the idea of mass production (‘Fordist’) when it comes to certain treatments. In its place, niche drugs are merging in an era of more flexible pharmaceutical production. While it is wrong to draw too precise parallels between wat has occurred in industrialized sectors, like the car industry, with medicine, we are seeing an emerging field of personalized medicine. This includes diagnostic devices (like laboratory tests to measure genetic factors) and therapeutic products.

In recent years there is a trajectory towards positioning medicine and health practices to meet the needs of the individual patient. This means rather than condition x needing drug y, diagnostic testing would be used to select the appropriate therapy for an individual person based on that person’s unique genetic makeup and physical characteristics. There is another reason why personalized medicines could be important. Not only could treatments be more effective, focused treatments could avoid the misuse of medicines or the risks associated with patients being given general treatments not necessarily intended for their particular condition.

Prescription drugs are the third most common cause of death after heart disease and cancer, for which psychiatric drugs (triggering falls) and non-steroidal, anti-inflammatory drugs (primarily by causing bleeding stomach ulcers and myocardial infarction) are most closely associated with fatalities.

Aside from direct risks, genetic medicines will not work with everyone. Examples include: attention deficit hyperactivity disorder medicine only works for one of 10 preschoolers; cancer drugs are effective for around 25 percent of patients; and anti-depression drugs work with just six of 10 patients.

In this IVT Network blog we take a look at personalized medicines, citing some examples, and considering some of the technologies that help to make them happen.

Precision medicine

Precision, or personalized medicine, is about the customization of healthcare. With this concept, medical decisions, practices, and drug products are tailored to the individual patient. In these circumstances medical laboratory testing would be used to select the appropriate therapy for an individual person based on a given person's individual genetic make-up and particular physical characteristics.

Applying advanced technologies

Advances in genomics have helped make personalized medicine a clinical reality, and several patients have benefitted from the tailor-made approach. However, for the gains to be fully realized, 'big data' analysis is needed.

Biomarkers

Big data assessments can aid with the development of personalized medicines. Typical health screens tend to miss the types of biomarkers that are necessary to match patients with specific medicines. Biomarkers can be anything from blood pressure to increasingly complex networks of individual traits. By using big data approaches, medical researchers can locate biomarkers for certain diseases and seek new molecular markers for specific disease risks. This means that biomarkers can help in the assessment of disease targets and identification of suitable patient populations for the development program, as well as providing early signs of safety issues and efficacy in order to facilitate "go/no-go" decisions. The use of biomarkers in the development stage can also provide early indications of real-world effectiveness, which will be helpful for evaluation of the commercial viability of a drug early on (1).

Genomics

To make personalized medicines a reality, further advances need to take place with genomics and with understanding the influence of the microorganisms that reside within the human body (the microbiome) have on the way medicines are processed. Biological research runs the risk of being undermined by the poor design of the digital identifiers that tag data. To improve analysis of genetic material, for example, requires pragmatic guidelines to create, reference and maintain web-based identifiers to improve reproducibility, attribution, and scientific discovery.

Big data analytics

Gathering key patient and drug information requires big data analytics via computer analysis in order to make more accurate treatment decisions and to develop appropriate medicines. As an example, pharmaceutical scientists can a conduct a genome-wide association study to examine one disease, and then sequence the genome of many patients with that particular disease. Automation and artificial intelligence can assist with this. For example, an AI-powered genomic analysis platform can automate the labor-intensive parts of the geneticist's workflow. This means interpreting a patient's genetic test takes less time and effort, and accuracy is not compromised. The goal of such platforms is to scale the genetic testing interpretation in healthcare systems, so they can offer personalized care to a broader population.

This innovation allows the scientist to scan for shared mutations in the genome and then to select an appropriate treatment. Furthermore, with some types of cancer, computer modelling allows for the screening of combination treatments, which could involve more than one immunotherapeutic agent or a combination of immunotherapy and chemotherapy. This is far faster and probably more effective than is possible using traditional methods. However, to safeguard the patient it is important that data is rendered anonymous and the privacy of the patient is assessed at all times (2).

3D printing

Advanced technologies are aiding the development of personalized medicines. An example is with 3D printing, which has been used in the medical field for the past few years. Across healthcare, 3D printing is being used to produce low-cost, made-to-measure implants including jaws, pieces of skulls, hearing aids, and hips.

In pharmaceuticals, the area where 3D printing is likely to have the greatest impact is with tablet production. While the technology is currently prohibitively expensive for mass produced tablets (such as common pain killer drugs), there is a market for 3D printing and the production of personalized medicines. This overcomes the need to purchase large and expensive machinery that will only be used to produce small runs of a niche medicine; in contrast one 3D printer can produce a range of personalized medicines through different software codes being activated (3).

The first 3D-printed approved medicine was in 2015, when the U.S. FDA (Food and Drug Administration) approved the

medicine Spritam, which is a reformulation of the anti-epileptic seizure drug levetiracetam. Since Spritam if formed from a layered, highly porous structure that takes in liquid quickly, it cannot be made using traditional tablet manufacturing methods. This is where 3D printing provided a solution. Additive manufacturing was key to creating the medicine in the form of lattice. The process used takes a powder containing the drug. A powder layer is placed onto a surface, which moves along a conveyor belt and the moves underneath an inkjet printhead. This produces a binding liquid at specific locations along the powdered sheet, functioning to bind the powdered layer together. After this, a second layer of powder is laid down and printed for a second time at the same location. In the case of Spritam, this was undertaken up to 40 times. The advantage of this that when the latticework touches a sip of water it disperses in the mouth rapidly, enabling the medicine to take effect quickly.

A further innovation with tableting and 3D printing is with the production of polypills. These are single tablets containing multiple drugs (in order to reduce the number of different tablets a patient takes). The complication with this is considerable, based on compatibility issues relating to how active pharmaceutical ingredients and incipient materials interact and the rate at which different active ingredients need to be released once the tablet has been ingested and has reached the digestive system.

The solution presented by 3D printing is with containing multiple drugs in a compartmentalized form within the single tablet. To overcome the release process, this is controlled by where a particular medicine is located within the tablet. Tests show that ingredients located in the center of the tablet are released first, with ingredients towards the edges of a tablet released second. This happens by varying the concentration gradient of the different ingredients through the use of paste extrusion 3D printing technology. These types of 3D printers are different to the fused deposition modelling types used to create thermoplastics molds in different shapes and sizes.

Fused deposition 3D printers can also play a role in the production of medicines. It is possible to embeds a drug into a plastic using hot-melt extrusion (where drug molecules are mixed with polymers under mechanical pressure). The resulting filament can be loaded into a print head and then printed. The degree to which this technology can be used depends on the type of drug and its thermal degradation properties. For example, some anticancer drugs can be produced this way, whereas no antibiotic could.

In relation to antimicrobials, an alternative 3D printing process based on stereolithography has proven to be more successful. This form of 3D printing involves taking the active ingredient and positioning.

Quantum computing

Quantum computing, although in its infancy (putting aside the discussion about whether ‘true’ quantum computing exists) is aiding drug discovery. Quantum computing use elements of quantum mechanics to complete previously impossible calculations in a fraction of a second. Such computing power can be used to determine how, where and why drug molecules match, thus adding greater precision and a level of understanding. This deeper understanding is core to drug development. An additional enhancement for the drug discovery process will also arise through machine learning algorithms, which will further speed up the drug molecule screening process. The types of quantum computers likely to achieve this are adiabatic quantum computers. Adiabatic quantum computation is a form of quantum computing that utilizes the adiabatic theorem to perform calculations. This is a complex mathematical approach which means a quantum mechanical system when subjected to gradually changing external conditions adapts its functional form; however, when it is subjected to rapidly varying conditions there is insufficient time for the functional form to adapt. This means the spatial probability density remains unchanged, which relates to the way the machine solves problems.

The process steps for Adiabatic quantum computation are (4):

- Encode your problem (in terms of a Boolean SAT problem),
- Prepare initial state of qubits (program your problem),
- Annealing process (slowly change from initial to final state),
- Measure the answer.

This type of quantum computer could be fully-functional within the next two to five years.

Examples of personalized medicines

To show how progress is being made in developing personalized diagnoses and treatments, some examples are presented below.

Example 1: Cancer treatments

New technology can accurately provide a two-year breast cancer risk estimate that is truly personalized for each woman. This represents a significant step forwards with precision medicine and shift away from generic solutions. For example, with breast cancer screening platforms can now bring together an assessment of different risk factors in order to help to improve breast cancer diagnosis. The factors assessed include age, breast density and subtle mammographic features. By applying such technology, medics can draw an accurate assessment based on each individual patient who is presented for an examination. The personalized approach is more in-tune with each individual and this contrasts with a more generic approach to make diagnoses (5).

An alternative approach is with technologies to detect circulating tumor DNA based on liquid biopsy. This enables medics to track the progression of breast cancer at its earliest stages. Furthermore, the method also assist with real-time analysis for the blood test can track the efficacy of drug therapies better than current imaging techniques. This not only can avoid unnecessary surgical procedures it can help to ensure the most appropriate treatments are delivered (6).

Example 2: Combatting errant RNAs

As one example, researchers at The Scripps Research Institute in Florida have devised broad methods to design precision medicines against diseases caused by RNA. RNA stands for ribonucleic acid. It is an important molecule with long chains of nucleotides and vital for a health organism. When RNA acts erratically this can lead to diseases occurring (7).

To combat such genetic diseases medical researchers have attempted to develop drugs to combat the errant RNAs. Much of this research has been unsuccessful because of sufficient effectiveness and due to side effects. However, now a breakthrough has been achieved. As well as this increased precision, researchers have developed novel chemical approaches to use a disease-causing RNA to help make its own drug. This is by using that RNA as a catalyst for drug synthesis at the needed site.

Trials have taken place on myotonic dystrophy type 1 (progressive muscle wasting and weakness). This disease is caused by an error in the RNA genetic code. A designer molecule can selectively recognize larger, disease-associated repeats over shorter, normal ones and alter the coding. This was advanced through fluorescence imaging to spot the errant code.

Example 3: Other applications

Other examples of the personalized medicine approach include regenerative medicine, which is a branch of translational research in tissue engineering and molecular biology. This works to heal tissue and organ damage. Applications include developing cell therapies for treating conditions like pattern baldness, aging and sun-damaged skin, and chronic tendon degeneration. In a different area, pharmacists are beginning to use pharmacogenomics to guide patients to safer and more effective medications. Pharmacogenomics is a rapidly emerging field that analyzes an individual’s genes to predict his or her response to medications.

Furthermore, cell therapies are being used. These are centered around the premise of transplanting human cells (either from the patients themselves or from a donor) to replace or repair damaged cells, tissue or organs. Currently, approved applications for cellular therapy include treatments for certain blood cancers, damaged cartilage and severe burns. There are a larger number of applications within the clinical phase, such as for the treatment of an expanded number of blood cancers, solid tumors, autoimmune conditions, cardiac disorders, and a wide range of inherited genetic disorders.

Complications

Despite these successes, not every treatment area will prove to be a success. For instance, some therapies based on tumor genomics may well take too long to prepare to be helpful (in that many patients would have died before treatments could be manufactured). Another consideration is how the process will be regulated. Bodies like the U.S. Food and Drug Administration (FDA) can more readily inspect, sample and review processes relating to the production of millions of pills. This becomes more difficult when small numbers of items are being manufactured.

Summary

Personalized or precision medicine concerns moving away from genetic drugs to treat diseases to developing drugs for smaller numbers or individual patients, often by assessing the genetic make-up of people. The healthcare system as a whole is demanding more personalized prescriptions in an effort to improve care and reduce costs. To deliver this, advances in patient screening and new technologies in drug discovery are required, including artificial intelligence. As methods and technology advances, personalized patient treatments, at least for the more serious genetic diseases, should, in time, become commonplace.

References

1. Schwaederle M, Zhao M, Lee JJ, et al. (2016) Association of Biomarker-Based Treatment Strategies With Response Rates and Progression-Free Survival in Refractory Malignant Neoplasms: A Meta-analysis. JAMA Oncol.;2(11):1452–1459. doi:10.1001/jamaoncol.2016.2129
2. Sandle, T. (2020) Personalized medicines and big data, Digital Journal, September 20th 2020, at: http://www.digitaljournal.com/life/health/op-ed-personalized-medicines-a...
3. Sandle, T. (2020) 3D printing is leading to novel, personalized medicines, Digital Journal, August 18th 2020, at: http://www.digitaljournal.com/tech-and-science/science/3d-printing-is-le... d
4. Sandle, T. (2017) Quantum computing initiative advances drug discovery, Digital Journal, 29th June 2017, at: http://www.digitaljournal.com/tech-and-science/technology/quantum-comput...
5. Sandle, T. (2020) Breakthrough in personalized breast cancer medicine, Digital Journal, 20th July 2020, at: http://www.digitaljournal.com/life/health/breakthrough-in-personalized-b...
6. McDonald, B. et al (2019) Personalized circulating tumor DNA analysis to detect residual disease after neoadjuvant therapy in breast cancer, Science Translational Medicine, 11 (504). DOI: 10.1126/scitranslmed.aax7392
7. Velagapudi, S., Gallo, S. & Disney, M. Sequence-based design of bioactive small molecules that target precursor microRNAs. Nat Chem Biol 10, 291–297 (2014). https://doi.org/10.1038/nchembio.1452
