

Expanding the Frontiers of Precision Medicine

- The Human Genome Project changed the face of modern medicine. As knowledge has grown about genomics and the gene mutations that cause disease, it has become more and more apparent that the traditional one-size-fits-all approach to medicine doesn't work.

Reports suggest that in many disease areas, the percentage of patients who don't benefit from a given drug is extremely high. In cancer, for example, untar- geted drugs are ineffective in as many as 75% of patients, and even in disease areas that are considered to be better understood, such as asthma, untargeted drugs are ineffective for 40% of patients.

It is now well accepted that genetic makeup can affect the safety and effectiveness of a therapy. Recognizing this fact, the FDA publishes a table of pharmacogenetic associations, showing how some drugs can have a severe adverse effect on patients with certain genes or where dosage needs to be adjusted based on a patient's genes. This pharmacogenomic information is not only available for newly approved therapies but also for products that have been on the market for some time and have been updated with biomarker information.

This has propelled efforts toward precision

Biomarkers Explained

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, disease processes, or biological responses to a therapeutic intervention and can be used to reduce uncertainty and guide clinical care.

Molecular biomarkers can include:

DNA, RNA, and proteins

Biomarkers help inform medical

decisions for: prevention measures, diagnosis, to treat or don't treat, and dosing.

How to Detect a Biomarker:

Diagnostics, blood draw, microscopic analysis, gene sequencing, biopsy and protein analysis

Source: Value of Personalized Medicine, PhRMA

medicine — or ensuring the right patient gets the right medicine at the right time. To achieve these objectives, big medicine combines molecular biology and systems biology with big data to find correlations and better target treatment.

The Personalized Medicine Coalition (PMC), which was established by 20 institutions in 2004 and now has 210 members, recently released a paper, titled: "Expanding the Frontiers of Personalized Medicine Through Education, Advocacy and Evidence Development: A Strategic Plan for Advancing the Field in 2021." PMC wants to ensure both decision-makers and consumers are educated

on personalized medicine to, on one hand, advance precision medicine initiatives, and on the other, to help patients discuss tailored treatment plans with the physicians. Another key element of PMC's plan is to help advance the field through "continued investments in biomedical research as well as modernized regulatory, coverage, and payment policies that support access to personalized medicine."

From a research perspective, PMC is focused on developing evidence to support precision medicine's adoption. An important element of this initiative is to address issues of health equity in research for precision medicines through strategies researchers can use to better engage more diverse patient populations. In addition, PMC has programs aimed at evaluating progress made, assessing the clinical and economic value of precision medicine, and looking at clinical integration strategies.

The Benefits of Personalized Medicine

- Shifting the emphasis in medicine from reaction to prevention
- Directing targeted therapy and reducing trial-and-error prescribing
- Reducing the frequency and magnitude of adverse drug reactions
- Using cell-based or gene therapy to replace or circumvent molecular pathways associated with disease
- Revealing additional targeted uses for medicines and drug candidates
- Increasing patient adherence to treatment
- Reducing high-risk invasive testing procedures
- Helping to shift physician-patient engagement toward patient-centered care
- Helping to control the overall cost of healthcare

Source: The Personalized Medicine Report, Personalized Medicine Coalition

Precision Medicine Across Therapies

The area where precision medicine is used most widely is in oncological diseases, which makes sense given that all cancers are caused by genetic changes or mutations. For example, it was discovered that NTRK fusion-driven cancers, which can be present in lung, thyroid, brain, colon, soft tissue, and bone cancers, are best treated with targeted therapies.

Precision medicine plays a key role in cancer diagnosis, through molecular testing to identify hereditary mutations. It's also key to research, since gathering genetic data helps to determine which will be best suited to clinical trials for novel therapies.

Other therapeutic categories where precision medicine is being applied in research include central nervous system diseases such as Alzheimer's and Parkinson's disease.

Large and small companies alike have placed significant emphasis on precision medicine. For example, Merck Group has stated that its "vision for personalized medicine is that every patient takes the type and dosage of

medicine that is best suited for their personal circumstances.”

For example, its product Erbitux (cetuximab), an epidermal growth factor receptor (EGFR) monoclonal antibody (mAb), has been approved for K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer and squamous cell cancer of the head and neck. In colorectal cancer, a predictive biomarker can determine the likely efficacy of the drug, which ensures it is only used on patients who will benefit from the therapy.

“No two cancers are entirely the same on a molecular level,” says Lisa Benincosa, head of global translational medicine at Merck Group. “Personalized medicine will enable a truly patient-centric approach, revolutionizing both clinical research and the way healthcare is delivered to patients.”

Pfizer, meanwhile, describes precision medicine as a philosophy that guides everything it does. Areas where Pfizer is exploring targeted therapies include hemophilia B through a collaboration with Spark Therapeutics; inflammatory disease by way of computational fingerprints to understand disease progression and response to treatment; and novel targets through the Pfizer Functional Genomics Center.

Novartis has a strong precision medicines focus, and its Piqray drug was approved in 2019 to treat patients with HR+/HER2-breast cancer with PIK3CA mutations.

In addition, the company’s Novartis Molecular Diagnostics is focused on developing companion diagnostics and other tests to ensure the right patient is treated with the right therapy.

There are also numerous small companies focused on precision medicine, from those developing platforms to integrate and index disparate data sources, to companies working to make genomic medicine more accessible, to companies developing non-invasive tests based on next-generation sequencing, to companies offering pharmacogenomic testing and services to providers and payers.

Precision Medicine Breakthroughs

One of the barriers to precision medicine has been obtaining samples for testing biomarkers. Typically, this has been an invasive and expensive process since it has required tissue biopsies.

Increasingly, researchers are looking into minimally invasive liquid biopsies to identify biomarkers for a number of cancers. These tests are possible using body fluids such as

blood, urine, and saliva. Combined with biosensor technologies, it’s becoming possible to quickly and simply analyze patient samples. An example of where biosensors are being used is in diabetes, through wearable sensors that measure body fluids for blood glucose testing.

Another technology that is advancing precision medicine is deep phenotyping, which enables a deeper understanding of human physiology and disease. Phenotyping technologies include omics technologies, such as transcriptomics, proteomics, and metabolomics, and microbiome profiling.

Digital biomarkers are also becoming important tools for precision medicine. Examples include mood assessment tools through voice

recording and actigraphs, which measure patient movement in real time using sensors. Actigraphs could potentially be invaluable tools for assessing major depressive disorder and bipolar disorder because of the nature of the conditions, which show notable increases or decreases in energy, goal-directed behavior, movement, and sleep patterns.

“A firm understanding among all health care stakeholders of all the ways in which biomarker testing has clinical utility will be instrumental to overcoming implementation challenges and providing the most efficient and effective personalized healthcare,” the PMC states in its personalized medicine report. ^{PV}

EXECUTIVE VIEWPOINTS



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Big Data as Matchmaker

Big data helps match patients with the best available therapies specific to the molecular and genomic signature of a patient’s tumor. It is also being used to help identify genetic or ethnic correlations with rare adverse events from commonly used therapies. More importantly, big data can expand access to biomarker-driven precision-medicine clinical trials in a decentralized approach by enabling practices or providers to expeditiously enroll a patient in a trial after the qualifying biomarker is identified.

manufacturers might consider synthesizing datasets from various sources, for example market access data, to generate longitudinal insights into the patient journey. Machine learning and predictive analytics can then identify trends and patterns within unique patient personas. Using these personas, manufacturers can provide patients high-touch support to improve adherence. By identifying where the patient is in their treatment journey and maintaining engagement throughout each stage, manufacturers can predict the probability of nonadherence and provide effective corrective actions.

Creating Personalized Engagement

Many therapeutic areas, such as chronic and rare diseases, can benefit from precision medicine, especially when combined with precision treatment of ongoing disease management. Patients not only need assistance with adherence challenges, but with managing required lifestyle, nutritional, or physical modifications that are necessary to improve the overall outcome for the patient. Manufacturers that use predictive analytics and behavioral technology provide patients the personalized engagement they need throughout their journey.



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Synthesizing Various Datasets for Insights

From diagnosis to disease management,