PERSONALIZED MEDICINE AT FDA

The Scope & Significance of Progress in 2019

PMC

2019 MILESTONES

1. Approval of 11 personalized medicines, representing more than 20 percent of all newly approved therapeutic molecular entities for the sixth year in a row

2. Approval of a gene therapy that gives patients with spinal muscular atrophy the first treatment to address the root cause of their disease

3. Approval of a small interfering RNA-based therapy that gives patients with acute hepatic porphyria the first treatment to address the root cause of their disease

4. Clearance or approval of seven companion or complementary in vitro diagnostic tests that can inform targeted therapeutic decisions to improve the safety and efficacy of treatment regimens

5. Qualification of the first digital technology software designed to accelerate progress in personalized medicine

INTRODUCTION

Expanding Frontiers

The transformation of health care from one-size-fits-all, trial-and-error medicine to a targeted approach utilizing each patient's molecular information continues to accelerate as the U.S. Food and Drug Administration more regularly and rapidly approves diagnostic tools and treatments that expand the frontiers of personalized medicine.

Personalized medicine, sometimes called individualized or precision medicine, is a rapidly evolving field in which physicians use diagnostic tests to determine which medical treatments will work best for each patient or use medical interventions to alter molecular mechanisms, often genetic, that cause disease or influence a patient's response to certain treatments. By combining molecular data with an individual's medical history, circumstances and values, health care providers can develop targeted treatment and prevention plans.

Following the approval of 11 new personalized medicines last year, personalized medicines now account for more than one of every four drugs the agency has approved in the past six years. This figure represents a sharp increase since 2005, when personalized medicines accounted for 5 percent of the new therapies approved each year.

In 2019, the agency also expanded the indications for several existing personalized therapies; approved a new gene therapy for the treatment of a rare disease; and qualified the first digital technology platform via its pre-certification program. These new drugs and technologies will help physicians develop safer and more efficacious targeted treatment regimens.

A CONSISTENT TREND

Personalized Medicines Account for One Out of Every Four New Therapeutics Approved Since 2014

FDA's Center for Drug Evaluation and Research (CDER) approved 48 new molecular entities (NMEs) in 2019. All but four of these NMEs are therapeutic products (the others were diagnostic agents). Of the 44 therapeutic NMEs, 11 of them (25 percent) are personalized medicines as classified by the Personalized Medicine Coalition. These approvals continue a trend that began in 2014, when PMC classified 21 percent of NMEs as personalized medicines. The trend accelerated in 2015, 2016, 2017 and 2018, when the Coalition classified 28 percent, 27 percent, 34 percent, and 42 percent of NMEs, respectively, as personalized medicines.

FDA's Center for Biologics Evaluation and Research (CBER) also approved a new gene therapy in 2019. The approval represents a significant advancement for this class of personalized treatments, which involve the transplantation of normal genes into a patient's own cells to replace missing or defective genes or modify specific cellular functions.

Personalized Medicines Top 20% of FDA Approvals for Sixth Year in a Row

Bar chart showing:
- 2005: 5%
- 2014: 21%
- 2015: 28%
- 2016: 27%
- 2017: 34%
- 2018: 42%
- 2019: 25%
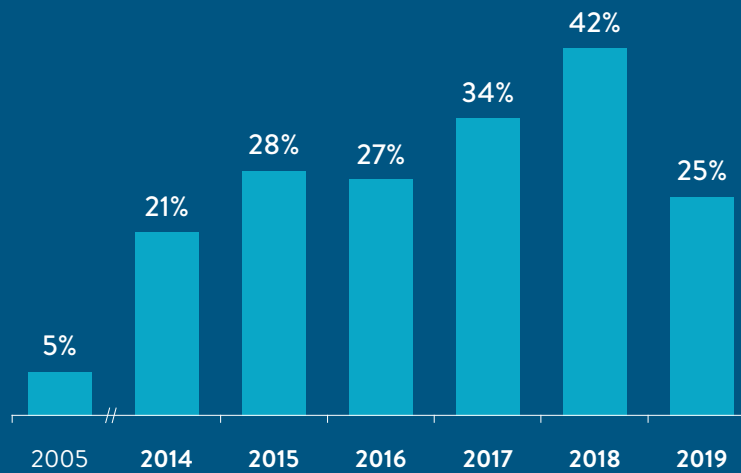
Methodology: When evaluating NMEs, PMC categorizes personalized medicines as those therapeutic products for which the label includes reference to specific biological markers, often identified by diagnostic tools, that help guide decisions and/or procedures for their use in individual patients.

2019 APPROVALS

11 of the 44 new therapeutic molecular entities FDA approved in 2019 — as well as a new gene therapy — are personalized medicines.

Newly Approved Therapeutic Molecular Entities

1. Mayzent (siponimod) for the treatment of relapsing forms of multiple sclerosis. The use of this product is informed by the CYP2C9 biomarker status in patients.

2. Balversa (erdafitinib) for the treatment of locally advanced or metastatic urothelial carcinoma. The decision to use this product is informed by the FGFR3 or FGFR2 biomarker statuses in the tumors of patients.

3. Piqray (alpelisib) for the treatment of advanced or metastatic breast cancer in combination with fulvestrant. The decision to use this product is informed by the HR, HER2, and PIK3CA-mutated biomarker statuses in the tumors of patients.

4. Wakix (pitolisant) for the treatment of excessive daytime sleepiness in adult patients with narcolepsy. The use of this product can be informed by the CYP2D6 biomarker status in patients.

5. Pretomanid (pretomanid) for the treatment of pulmonary extensively drug resistant, treatment-intolerant or non-responsive multidrug-resistant tuberculosis. The decision to use this product is informed by XDR and/or MDR biomarker statuses in patients.

6. Rozlytrek (entrectinib) for the treatment of metastatic non-small cell lung cancer. The decision to use this product is informed by the ROS1 biomarker status in the tumors of patients.

7. Trikafta (elexacaftor/ivacaftor/tezacaftor) for the treatment of cystic fibrosis. The decision to use this product is informed by the CFTR F508del mutation status in patients.

8. Givlaari (givosiran) for the treatment of acute hepatic porphyria. This product selectively targets the aminolevulinate synthase-1 biomarker in patients.

9. Oxbryta (voxelotor) for the treatment of sickle cell disease. This product selectively targets the hemoglobin S (HbS) biomarker in patients.

10. Vyondys 53 (golodirsen) for the treatment of Duchenne muscular dystrophy. This product selectively targets a mutated version of the DMD gene that is amenable to exon 53 skipping in patients.

11. Enhertu (fam-trastuzumab deruxtecan-nxki) for the treatment of meta-static breast cancer. The decision to use this product is informed by the HER2 biomarker status in the tumors of patients.

Newly Approved Gene Therapy

12. Zolgensma (onasemnogene abeparvovec-xioi) for the treatment of spinal muscular atrophy. The treatment is a fully integrated gene therapy to correct bi-allelic mutations in the SMN1 gene.

Methodology: PMC defines personalized medicine as an evolving field in which physicians use diagnostic tests to determine which medical treatments will work best for each patient or use medical interventions to alter molecular mechanisms, often genetic, that cause disease or influence a patient's response to certain treatments. By combining molecular data with an individual's medical history, circumstances and values, health care providers can develop targeted treatment and prevention plans. When evaluating NMEs, PMC defined personalized medicines as those therapeutic products for which the label includes reference to specific biological markers, often identified by diagnostic tools, that help guide decisions and/or procedures for their use in individual patients.

Other Important Trends in Drug Approvals

Expanding Indications

Even the large number of new therapies classified as personalized medicines in 2019 does not provide the whole picture of the growing list of personalized medicines available to doctors and their patients. In addition to the 11 personalized NMEs and the new gene therapy, FDA approved many significant new personalized medicine indications for previously existing drugs in 2019. These approvals redefine the drugs' intended populations and often provide patients with more effective personalized treatment options. The list of new personalized medicines in 2019 should therefore be complemented with reference to newly approved indications for Cyramza (ramucirumab), Zejula (niraparib), Lynparza (olaparib), Tecentriq (atezolizumab), Keytruda (pembrolizumab), Herceptin-Hylecta (trastuzumab/hyaluronidase-oysk), Inlyta (axitinib), Mavyret (glecaprevir/pibrentasvir), Kadcyla (ado-trastuzumab emtansine), Tibsovo (ivosidenib), Venclexta (venetoclax), Xospata (gilteritinib), Symdeko (tezacaftor/ivacaftor), Soliris (eculizumab), and Inrebic (fedratinib) for new molecularly defined subsets of patients.

The Emergence of siRNA Treatments

The approval of Givlaari (givosiran) marks the second FDA approval of a new class of personalized medicine drugs called small interfering ribonucleic acid (siRNA) treatments, which work by selectively targeting and silencing a portion of RNA involved in causing disease. Givlaari can be used to treat acute hepatic porphyria.

The Approvals of Biosimilars in Personalized Medicine

Several biosimilars for personalized medicines were also approved in 2019, to include biosimilars for Rituxan (rituximab) and Gleevec (imatinib), which were first approved in the U.S. in 1997 and 2001, respectively.

AN UNPRECEDENTED IMPACT

Five of the Personalized Treatments Approved in 2019 Are the First to Address the Root Causes of Devastating Rare Diseases; Others Provide New Options for Cancer Patients or Help Patients Avoid Debilitating and Costly Adverse Side Effects

Reversing the Root Causes of Disease

Five of the 12 newly approved personalized treatments are designed to reverse previously unmitigated root causes of certain congenital diseases. Many patients with spinal muscular atrophy (SMA), Duchenne muscular dystrophy, acute hepatic porphyria, cystic fibrosis, and sickle cell disease now have treatments available that target the underlying molecular mechanisms of diseases where there were no options before.

Zolgensma (onasemnogene abeparvovec-xioi) is the fourth fully integrated gene therapy approved by FDA and the first therapeutic option for SMA patients that targets the underlying genetic defect that causes the disease. Children born with SMA rapidly develop debilitating and often fatal muscle weakness and experience difficulty performing essential functions of life. Many do not survive past early childhood due to respiratory failure. Patients with SMA now have a treatment option to minimize the progression of SMA and significantly improve functionality and survival. For SMA patients and their families, the positive impact of Zolgensma cannot be overstated.

The cystic fibrosis triple combination drug Trikafta (elexacaftor/ivacaftor/ tezacaftor) targets the protein made by a mutated CFTR gene, an underlying cause of the disease. Trikafta improves the functionality of the defective protein. Previously available therapies that target the dysfunctional protein have had a remarkable impact on some cystic fibrosis patients, dramatically reducing disease symptoms and extending patients' lives. These previously approved therapies, however, are only available for some cystic fibrosis patients with specific mutations. In contrast, Trikafta is approved for use in cystic fibrosis patients with at least one of several types of CFTR mutations that affect more than 90 percent of all patients with the disease — roughly 27,000 people in the United States.

The remaining personalized medicines approved for rare diseases selectively target underlying molecular abnormalities in acute hepatic porphyria, Duchenne muscular dystrophy and sickle cell disease. Oxbryta (voxelotor), for example, provides new hope for patients with sickle cell disease, an inherited blood disorder in which abnormally shaped red blood cells restrict the flow in blood vessels and limit oxygen delivery to the body's tissues, leading to severe pain and organ damage. Oxbryta is the first drug that selectively targets the hemoglobin S (HbS) defect, which is the central molecular abnormality in sickle cell disease. Sickle cell patients treated with Oxbryta experience an increased hemoglobin response rate, which can lead to fewer episodes of extreme pain, reduced organ damage and fewer health care visits annually.

Combatting Cancer

Four of the 12 newly approved personalized treatments and more than 15 of the newly approved indications for existing personalized medicines provide new treatment options for cancer patients. These treatments can significantly improve the outlook for many patients, reducing disease progression and extending survival.

Keytruda (pembrolizumab), originally approved for use in patients with advanced non-small cell lung cancer in 2014, was approved for several expanded indications in 2019. Many cancer patients who receive Keytruda survive longer and have reduced adverse side effects compared to patients who receive standard chemotherapy. Patients treated with Keytruda also indicate a clinically significant improvement in their quality of life in patient-reported outcomes. The drug, which is more effective for patients whose tumors express relatively high levels of the PD-L1 biomarker, is now available for patients with advanced melanoma, head and neck squamous cell carcinoma, Hodgkin's lymphoma, endometrial carcinoma, esophageal squamous cell carcinoma, bladder cancer and renal cancer.

Avoiding Adverse Side Effects

Two of the 12 newly approved personalized treatments contain information on their labels that will help patients avoid debilitating and costly adverse side effects. Doctors can use genetic testing to ensure that they prescribe Mayzent (siponimod) and Wakix (pitolisant) to those patients who are most likely to benefit from the drug without experiencing substantial negative effects.

NEW DIAGNOSTICS

Newly Approved/Cleared Diagnostics Will Help Target Treatments to Patients Who Will Benefit From Them

An important consideration for personalized medicine is the use of companion and complementary diagnostics to discern biomarker statuses to guide drug use. In 2019, FDA's Center for Devices and Radiological Health (CDRH) approved or cleared seven new or expanded in vitro diagnostic tests that underpin personalized medicine strategies. Each of the diagnostics listed below will help inform targeted treatment decisions to improve drug safety and efficacy.

New Diagnostics

1. Ventana PD-L1 (SP142) Assay to detect PD-L1 status to help guide the decision to use atezolizumab for patients with triple negative breast cancer.

2. Therascreen FGFR RGQ RT-PCR Kit to detect FGFR status to help guide the decision to use erdafitinib for patients with urothelial cancer.

3. Therascreen PIK3CA RGQ PCR Kit to detect certain genetic mutations in the PIK3CA gene to help guide the decision to use alpelisib for patients with advanced breast cancer.

4. PD-L1 IHC 22C3 pharmDx — P150013/S016 and P150013/S014 to detect PD-L1 status to help guide the decision to use pembrolizumab for patients with head and neck squamous cell cancer.

5. LIAISON XL MUREX HCV Ab, LIAISON XL MUREX Control HCV Ab to detect if patients are infected with various subtypes of the hepatitis C virus to help guide treatment decisions.

6. Myriad myChoice CDx to detect the homologous recombination deficiency status to help guide the decision to use niraparib for patients with ovarian cancer.

7. FoundationOne CDx: Indication expanded for use of the F1CDx test to include certain genetic mutations in the PIK3CA gene to help guide the decision to use alpelisib for patients with breast cancer.

The Significance of Liquid Biopsy

In some cases involving personalized cancer care, patients are unable to receive advanced diagnostic testing because they cannot endure a tissue biopsy or they cannot give a sufficient sample. These patients would benefit from the availability of a liquid biopsy, which is a diagnostic test performed on a sample of blood that contains circulating cancer cells or DNA fragments from tumor cells. In 2019, FDA approved Qiagen's Therascreen PIK3CA RGQ PCR Kit (see above) as both a tissue and liquid biopsy companion diagnostic to identify breast cancer patients with PIK3CA mutations. The liquid biopsy capacity of the test provides new options for many patients with advanced breast cancer.

Newly Qualified Digital Technology Software

For the first time in 2019, FDA qualified a digital medical device development tool of a personalized medicine test type. The OsiriX CDE Software Module is the first biomarker test for brain injury and may help innovators more efficiently enroll patients, based on their individual characteristics, in clinical trials of therapeutic medical devices intended to be used to treat mild traumatic brain injury.

CONCLUSION

Sustaining a Promising Paradigm

These significant developments reflect the extraordinary pace of scientific innovation in personalized medicine, which is leading to improved health outcomes and having a tremendous impact on health care delivery efficiency and efficacy. While ongoing challenges in the areas of scientific discovery, diagnostic regulatory policy, coverage and reimbursement, and implementation of new technologies into clinical practice must be addressed, the science is leading the health system away from one-size-fits-all, trial-and-error medicine and toward the utilization of molecular information to improve outcomes and make the health system more efficient. This progress is largely due to the commitment to personalized medicine in the biopharmaceutical and diagnostic industries as well as at FDA.

But continued progress cannot be taken for granted.

To ensure that industry leaders continue to develop groundbreaking personalized medicine tests and treatments and that patients have access to these products, policymakers, as they have in the past, must favor policies that encourage the advancement of the field.

"As the regulators of these novel therapies, we know that the framework we construct for product development and review will set the stage for continued advancement of this cutting-edge field and further enable innovators to safely develop effective therapies for many diseases with unmet medical needs."

— **Peter Marks, M.D., Ph.D., Director, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration**
On the announcement of a new framework for regulatory review of gene therapies in January of 2020

ABOUT US

The Personalized Medicine Coalition (PMC), representing innovators, scientists, patients, providers and payers, promotes the understanding and adoption of personalized medicine concepts, services and products to benefit patients and the health system.