
PERSONALIZED MEDICINE AT FDA

The Scope & Significance of Progress in 2020



2020 MILESTONES

1. Approval of 19 personalized medicines representing approximately 39 percent of all newly approved therapeutic molecular entities. Personalized medicines have now accounted for more than a third of new drug approvals for three of the last four years.
2. Approval of the first chimeric antigen receptor (CAR) T-cell-based immunotherapy for patients with refractory mantle cell lymphoma whose prior treatments either did not work or stopped working. This approval expands the frontiers of the CAR T-cell treatment paradigm, which holds tremendous promise for improving cancer care.
3. Release of seven guidance documents on the manufacturing and clinical development of gene and cell-based therapeutic products. These guidance documents will help streamline the development of potentially curative therapeutics.
4. Clearance or approval of eight significant new in vitro diagnostic test indications that can inform targeted therapeutic decisions, including the approval of the first two tumor-agnostic indications to identify advanced cancer patients with solid tumors of all types that have NTRK gene fusions or are tumor mutational burden-high (TMB-H). The approvals of the NTRK and TMB-H indications further expand the frontiers of the tumor-agnostic treatment paradigm, which focuses on using biomarkers as the basis for treatment decisions as opposed to a tumor's location in the body.
5. Approval of a new small interfering RNA-based therapy that gives patients with primary hyperoxaluria type 1 (PH1), a rare genetic metabolic disorder that primarily causes progressive kidney failure and can lead to damage of other organs, including the heart, bones, and eyes, the first treatment to address the root cause of their disease.
6. Approval of the first comprehensive pan-tumor liquid biopsy next-generation sequencing-based test as a companion diagnostic device for multiple biomarkers detected in cell-free DNA isolated from plasma specimens. This test allows physicians to detect actionable biomarkers in patients' blood, mitigating the need for more invasive tissue biopsies in certain patient populations.

INTRODUCTION

Two-thousand twenty will always be remembered as the year in which the world was gripped by the COVID-19 pandemic. The variability of disease severity and response to treatments for patients infected with SARS-CoV-2 has reinforced the recognition that health care needs to evolve from one-size-fits-all, trial-and-error medicine to a targeted approach utilizing each patient's molecular and other health-related information. Against this backdrop, the pace of progress in personalized medicine 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 the field.

Personalized medicine, sometimes called individualized or precision medicine, is 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 that impact health. By combining data from diagnostic tests with an individual's medical history, circumstances and values, health care providers can develop targeted treatment and prevention plans with their patients.

With the approval of 19 new personalized medicines last year, personalized medicines now account for more than a quarter of the new drugs the agency has approved in the past six years. This figure represents a sharp increase since a decade ago, when personalized medicines accounted for less than 10 percent of the new therapies approved each year.

In 2020, FDA also expanded the indications for several existing personalized therapies; approved a new cell-based immunotherapy for the treatment of a difficult-to-treat cancer; released several guidance documents for developers of cell-based and gene therapies; and approved the first liquid biopsy next-generation sequencing-based testing platforms in oncology. These new technologies and guidance documents will help innovators and physicians develop safer and more efficacious treatments and prevention regimens based on the principles of human heterogeneity.

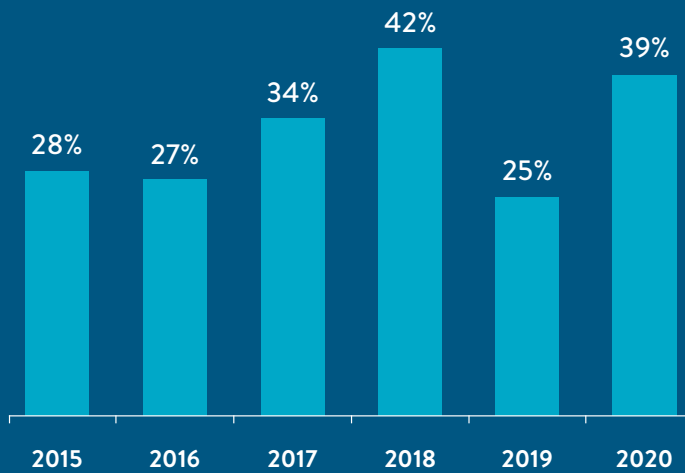
A CONSISTENT TREND

Personalized Medicines Account for More Than a Quarter of All New Therapeutics Approved Since 2015

FDA's Center for Drug Evaluation and Research (CDER) approved 53 new molecular entities (NMEs) in 2020. All but four of these NMEs are therapeutic products (the others were diagnostic agents). Of the 49 therapeutic NMEs, 19 of them (39 percent) are personalized medicines as classified by the Personalized Medicine Coalition. This is the highest percentage since 2018, when personalized medicines accounted for 42 percent of newly approved NMEs. Personalized medicines now account for more than a quarter of the new therapeutics approved since 2015. They have comprised more than a third of new drug approvals for three of the last four years.

FDA's Center for Biologics Evaluation and Research (CBER) also approved a new cell-based therapy in 2020. This 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 modify specific cellular functions. The FDA has now approved six cell-based or gene therapies.

Personalized Medicines Accounted for More Than 30% of FDA Approvals for Three of Last Four Years



Methodology: When evaluating new molecular entities, 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.

2020 APPROVALS

19 of the 49 new therapeutic molecular entities FDA approved in 2020 – as well as a new cell-based therapy – are personalized medicines.

Newly Approved Therapeutic Molecular Entities

1. **Ayvakit (avapritinib)** – for the treatment of metastatic gastrointestinal stromal tumor (GIST). The decision to use this product is informed by the PDGFRA exon 18 biomarker status in the tumors of patients.
2. **Nexletol (bempedoic acid)** – for the treatment of adults with familial hypercholesterolemia who require additional lowering of LDL-C. The use of this product can be informed by the FH biomarker (LOLR, APOB, PCSK9) status in patients.
3. **Tukysa (tucatinib)** – for the treatment of metastatic breast cancer. The decision to use this product is informed by the HER2 biomarker status in the tumors of patients.
4. **Pemazyre (pemigatinib)** – for the treatment of cholangiocarcinoma. The decision to use this product is informed by the FGFR2 biomarker status in the tumors of patients.
5. **Trodelvy (sacituzumab govitecan-hziy)** – for the treatment of metastatic triple-negative breast cancer. The decision to use this product is informed by the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) biomarker statuses in the tumors of patients.

6. **Tabrecta (capmatinib)** – for the treatment of non-small cell lung cancer (NSCLC). The decision to use this product is informed by the MET exon 14 biomarker status in the tumors of patients.
7. **Retevmo (selpercatinib)** – for the treatment of lung and thyroid cancers. The decision to use this product is informed by the RET fusion biomarker status in the tumors of patients.
8. **Uplizna (inebilizumab-cdon)** – for the treatment of neuromyelitis optica spectrum disorder. The decision to use this product is informed by the AQP4 biomarker status in patients.
9. **Rukobia (fostemsavir)** – for the treatment of human immunodeficiency virus (HIV) infection in adults with multidrug-resistant HIV-1 infection. The use of this product can be informed by the HIV-1 expression levels in patients.
10. **Evrysdi (risdiplam)** – for the treatment of spinal muscular atrophy. This product selectively targets the SMN2 biomarker in patients.
11. **Olinvyk (oliceridine)** – for the management of acute pain. The use of this product can be informed by the CYP2D6 biomarker status in patients.
12. **Viltepsa (viltolarsen)** – for the treatment of Duchenne muscular dystrophy. This product selectively targets, and its use is informed by, the DMD gene exon 53 biomarker in patients.
13. **Enspryng (satralizumab-mwge)** – for the treatment of neuromyelitis optica spectrum disorder. The decision to use this product is informed by the AQP4 biomarker status in patients.
14. **Gavreto (pralsetinib)** – for the treatment of non-small cell lung cancer (NSCLC). The decision to use this product is informed by the RET fusion biomarker status in the tumors of patients.
15. **Zokinvy (lonafarnib)** – for the treatment of progeroid laminopathies. The decision to use this product is informed by the LMN4 and/or ZMPSTE24 biomarker statuses in patients.

16. **Oxlumo (lumasiran)** – for the treatment of hyperoxaluria type 1. This product selectively targets the hydroxy acid oxidase 1 (HAO1) biomarker in patients.
17. **Imcivree (setmelanotide)** – for the treatment of obesity due to pro-opiomelanocortin (POMC) deficiency. The decision to use this product is informed by the POMC, PCSK1, or LEPR biomarker statuses in patients.
18. **Orladeyo (berotralstat)** – for the treatment of hereditary angioedema types I and II. The use of this product can be informed by the C1-INH biomarker status in patients.
19. **Margenza (margetuximab-cmkb)** – for the treatment of breast cancer. The decision to use this product is informed by the human epidermal growth factor receptor 2 (HER2) biomarker status in the tumors of patients.

Newly Approved Cell-Based Therapy

20. **Tecartus (brexucabtagene autoleucel)** – for the treatment of mantle cell lymphoma (MCL). The treatment is a fully integrated CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of adult patients with refractory MCL.

Methodology: When evaluating new molecular entities, 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 2020 does not provide the whole picture of the growing list of personalized medicines available to doctors and their patients. In addition to the 19 personalized NMEs and the new cell-based therapy, FDA approved many significant new personalized medicine indications for previously existing drugs and combinations of drugs in 2020. These approvals redefine the drugs' intended populations and often provide patients with more effective personalized treatment options. The list of new personalized medicines in 2020 should therefore be complemented with reference to newly approved indications for Opdivo (nivolumab), Yervoy (ipilimumab), Imfinzi (durvalumab), Nerlynx (neratinib), Cyramza (ramucirumab), Braftovi (encorafenib), Zejula (niraparib), Lynparza (olaparib), Rubraca (rucaparib), Alunbrig (brigatinib), Bavencio (avelumab), Tecentriq (atezolizumab), Keytruda (pembrolizumab), Darzalex (daratumumab), Kesimpta (ofatumumab), Tagrisso (osimertinib), Erbitux (cetuximab), Avastin (bevacizumab), Tarceva (erlotinib), Mylotarg (gemtuzumab ozogamicin), and Tazverik (tazemetostat) for new molecularly defined subsets of patients.

Among these expanded indications, FDA approved a second tissue-agnostic indication for Keytruda, this time for use in all advanced cancer patients with solid tumors that are tumor mutational burden-high (TMB-H), an important measure of the number of somatic mutations per coding region within a tumor's genome.

Continued Emergence of siRNA Treatments

The approval of Oxlumo (lumasiran) marks the third 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. Oxlumo can be used to treat the rare genetic disorder primary hyperoxaluria type 1.

The Approvals of New Biosimilars in Personalized Medicine

Several biosimilars for personalized medicines were also approved in 2020, to include biosimilars for Rituxan (rituximab), Herceptin (trastuzumab), and Avastin (bevacizumab), which were first approved in the U.S. in 1997, 1998, and 2004, respectively.

IMPACT

Seven of the Personalized Treatments Approved in 2020 Address the Root Causes of Devastating Rare Diseases; One is a First-of-its-Kind Anti-Retroviral for Patients with HIV; Others Provide New Options for Cancer Patients.

Reversing the Root Causes of Disease

Seven of the 19 newly approved NMEs are designed to reverse previously unmitigated root causes of certain congenital diseases. Many patients with neuromyelitis optica spectrum disorder (NMOSD), spinal muscular atrophy (SMA), Duchenne muscular dystrophy, progeria, pro-opiomelanocortin (POMC) deficiency, and primary hyperoxaluria now have treatments available that target the underlying molecular mechanisms of their diseases.

Uplizna (inebilizumab-cdon) and Enspryng (satralizumab-mwge) provide new treatment options for many patients with NMOSD, a rare, lifelong and debilitating autoimmune disorder of the central nervous system that primarily damages the optic nerves and spinal cord, causing blindness, muscle weakness and paralysis. Uplizna targets immune cells that are responsible for the production of autoantibodies directed against AQP4, a biomarker that is specific to some NMSOD patients, thereby ameliorating symptoms of the disease. Enspryng targets interleukin-6 (IL-6) receptor activity, which is believed to play a key role in the inflammation associated with NMOSD. Enspryng provides the first treatment option to prevent disease-related relapses that can be administered at home by patients or their caregivers. For people with NMOSD, relapses can cause devastating, irreversible and disabling neurological effects. Having these new treatment options will make a meaningful difference for those living with NMOSD and their loved ones.

First-of-Its-Kind Treatment for Patients with HIV

The approval of Rukobia (fostemsavir) provides a first-in-class therapy for patients living with HIV who cannot manage the disease with available anti-retroviral medications due to resistance, intolerance or safety considerations. Many patients living with HIV who have tried multiple HIV medications but whose infection could not be successfully treated now have a new kind of treatment option that may allow them to finally keep their disease in check.

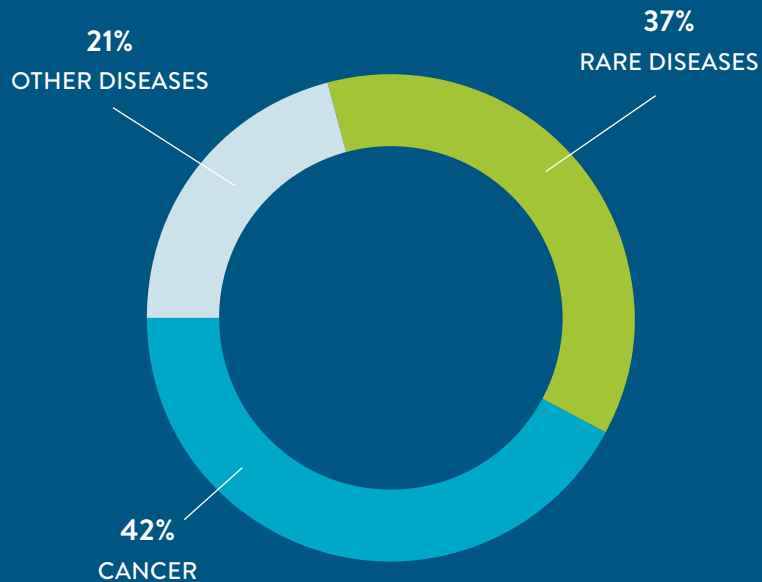
Combatting Cancer

Nine of the 20 newly approved personalized treatments and more than 20 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.

The approval of Pemazyre (pemigatinib) marks the first targeted treatment for patients with cholangiocarcinoma, a cancer of bile ducts. Most cholangiocarcinoma patients are diagnosed after the cancer has already spread and can't be treated with surgery. The progression free survival rate for patients receiving standard chemotherapies is therefore very low. Pemazyre provides patients with certain types of advanced cholangiocarcinoma with a targeted treatment option that may improve their clinical outcomes and increase survival rates.

Keytruda (pembrolizumab), originally approved for use in patients with advanced non-small cell lung cancer in 2014, was approved for a new tissue-agnostic indication in 2020. Now patients with metastatic TMB-H solid tumors, which are typically identified through genomic testing, can receive Keytruda as their second line of treatment. The TMB genomic signature can help determine a patient's likelihood of responding to Keytruda, which often produces longer survival timelines and reduced adverse side effects for these patients as compared to standard chemotherapy.

New Molecular Entities Are Indicated for Treatment of Cancer, Rare Diseases, and Common/Infectious Diseases



- | ■ Cancer | ■ Rare Diseases | ■ Other Diseases |
|-------------|-----------------|------------------|
| 1. Ayvakit | 9. Enspryng | 16. Incivree |
| 2. Gavreto | 10. Evrysdi | 17. Nexletol |
| 3. Margenza | 11. Orladeyo | 18. Olinvyk |
| 4. Pemazyre | 12. Oxlumo | 19. Rukobia |
| 5. Retevmo | 13. Uplizna | |
| 6. Tabrecta | 14. Viltepso | |
| 7. Trodelvy | 15. Zokinvy | |
| 8. Tukysa | | |

NEW DIAGNOSTICS

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

An important consideration for personalized medicine is the use of diagnostics to discern biomarker statuses to guide drug use. In 2020, FDA's Center for Devices and Radiological Health (CDRH) approved or cleared eight significant new or expanded in vitro diagnostic testing indications that underpin personalized medicine strategies. New approvals and expanded indications associated with the five tests listed below will help inform targeted treatment decisions to improve drug safety and efficacy.

Significant New Approvals/Indication Expansions

1. **Oncomine Dx Target Test** – Indication expanded to include RET fusion-positive genetic mutations to help guide the decision to use pralsetinib for non-small cell lung cancer patients.
2. **FoundationOne® CDx** – Three significant indication expansions, as follows:
 - Indication expanded for use of the F1CDx test to include certain genomic signatures indicating TMB-H to help guide the decision to use pembrolizumab for patients with solid tumors of all types.
 - Indication expanded for use of the F1CDx test to include certain genetic mutations in the NTRK1/2/3 gene to help guide the decision to use larotrectinib for patients with solid tumors of all types.
 - Indication expanded for use of the F1CDx test to include certain genetic mutations in the FGFR2 gene to help guide the decision to use pemigatinib for patients with cholangiocarcinoma.

3. **FoundationOne® Liquid CDx** – Approved to detect certain genetic mutations and genomic signatures from liquid biopsies to help inform treatment decisions for all solid tumors.
4. **Guardant360® CDx** – Approved and expanded as follows:
 - Approved to detect certain genetic mutations and genomic signatures from liquid biopsies to help inform treatment decisions for all solid tumors.
 - Indication expanded for use of the Guardant360 test to include certain genetic mutations in the EGFR gene to help guide the decision to use osimertinib for patients with non-small cell lung cancer.
5. **Cobas® EZH2 Mutation Test** – Approved to detect genetic mutations in the EZH2 gene to help guide the decision to use tazemetostat for advanced follicular lymphoma (FL).

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 2020, FDA approved Foundation Medicine’s FoundationOne Liquid CDx and Guardant Health’s Guardant360 CDx (see above) as liquid biopsy-based diagnostics to identify certain genetic mutations in patients with solid tumors of all types. The liquid biopsy capacity of these tests provides new options for many patients with advanced cancers. Although not yet approved for non-advanced cancer cases, the technology also may have the potential to impact earlier detection, when cancer is generally more treatable, if applied to patients in early stages of cancer progression and/or high-risk people who may be asymptomatic.

POLICY PRECEDENTS

The Continued Development of Gene Therapies

This is a pivotal time in the field of gene therapy as innovators continue to explore and develop new gene therapy-based medical products, which involve the transplantation of normal genes into a patient's own cells to replace missing or defective genes or modify specific cellular functions. In 2020, FDA released six final guidance documents on gene therapy manufacturing and clinical development as well as a draft guidance on orphan drug policy for gene therapies:

1. [*Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations; Draft Guidance for Industry*](#)
2. [*Chemistry, Manufacturing, and Control \(CMC\) Information for Human Gene Therapy Investigational New Drug Applications \(INDs\); Guidance for Industry*](#)
3. [*Long Term Follow-up After Administration of Human Gene Therapy Products; Guidance for Industry*](#)
4. [*Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up; Guidance for Industry*](#)
5. [*Human Gene Therapy for Hemophilia; Guidance for Industry*](#)
6. [*Human Gene Therapy for Rare Diseases; Guidance for Industry*](#)
7. [*Human Gene Therapy for Retinal Disorders; Guidance for Industry*](#)

CONCLUSION

Sustaining the Promise of Personalized Medicine

The global COVID-19 pandemic did not slow the extraordinary pace of scientific innovation in personalized medicine, which is leading to improved outcomes for patients and having a tremendous impact on the efficacy and efficiency of health care. Despite ongoing challenges in the areas of scientific discovery, diagnostic regulatory policy, coverage, reimbursement, and clinical adoption, the developments at FDA in 2020 show that 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.

But as the COVID-19 crisis reminds us, continued progress cannot be taken for granted.

To ensure that scientists and innovators 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.

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 health systems.



www.PersonalizedMedicineCoalition.org

202-589-1770

@PerMedCoalition