

---

# PERSONALIZED MEDICINE AT FDA

The Scope & Significance of Progress in 2021



# 2021 MILESTONES

1. Approval of 17 personalized medicines representing approximately 35 percent of all newly approved therapeutic molecular entities. Personalized medicines have now accounted for more than a third of new drug approvals for four of the last five years.
2. Approval of two new chimeric antigen receptor (CAR) T-cell-based immunotherapies including a fully integrated CD19-directed genetically modified autologous treatment indicated for patients with refractory large B-cell lymphoma and a B-cell maturation antigen (BCMA)-directed genetically modified autologous treatment indicated for patients with refractory multiple myeloma. These approvals expand the frontiers of CAR T-cell therapy, an evolving personalized treatment paradigm that promises to dramatically improve care for certain patients by genetically re-engineering a patient's own immune cells to combat cancer.
3. Approval of a new therapy for adult patients with non-small cell lung cancer whose tumors have a KRAS G12C genetic mutation. Such mutations account for approximately 13 percent of mutations in non-small cell lung cancers. As the first targeted therapy for tumors with a KRAS mutation, long considered resistant to drug therapy, the approval spotlights the expanding scientific boundaries of personalized medicine.
4. Recognition of a partial listing of the Memorial Sloan Kettering Cancer Center's Oncology Knowledge Base (OncoKB) containing curated research and real-world information regarding specific alterations in 682 cancer-associated genes. OncoKB is the first tumor mutation database to be included in FDA's *Public Human Genetic Variant Databases*. As a clearinghouse for genetic variants with agency-acknowledged disease correlations, the *Public Human Genetic Variant Databases* promise to enhance the efficiency with which test developers can develop premarket submissions for tumor profiling tests underpinning personalized cancer care.
5. Clearance or approval of several significant new or expanded indications for nine in vitro diagnostic testing systems that can inform targeted therapeutic decisions, including the approval of the first Ki-67 cell companion diagnostic for breast cancer and a new tumor-agnostic indication to identify advanced cancer patients with solid tumors of all types that have deficient mismatch repair (dMMR). The approval of the dMMR test further expands 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.
6. Approval of two personalized therapies to treat certain patient populations with familial hypercholesterolemia, a potentially life-threatening condition characterized by severely high cholesterol levels. The newly approved therapies include a small interfering RNA-based therapy that gives patients with primary familial hypercholesterolemia a new treatment to address the root cause of their disease.

# INTRODUCTION

Despite the Covid-19 pandemic, 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 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 17 new personalized medicines in 2021, personalized medicines now account for more than a quarter of the new drugs the agency has approved in the past seven years. This figure represents a sharp recent increase. Just a decade ago, personalized medicines accounted for less than 10 percent of the new therapies approved each year.

In 2021, FDA also expanded the indications for several existing personalized therapies; approved two new cell-based immunotherapies for the treatment of difficult-to-treat cancers; granted recognition of the first tumor mutation database, thereby allowing test developers to use real-world data to support the clinical validity of new diagnostic tests; and approved several new diagnostic indications that will allow for targeted treatment decisions for various health conditions. These new technologies and policies will help innovators and physicians develop safer and more efficacious treatments and prevention regimens based on the principles of patient-centered care.

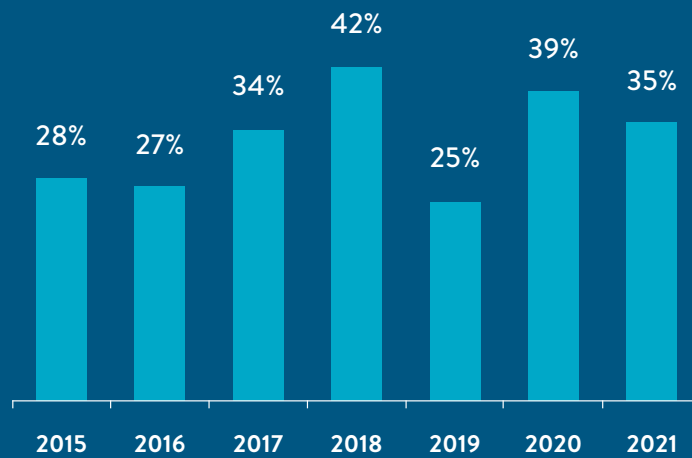
# A CONSISTENT TREND

## 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 50 new molecular entities (NMEs) in 2021. All but two of these NMEs are therapeutic products (the others were diagnostic agents). Of the 48 therapeutic NMEs, 17 of them (35 percent) are personalized medicines as classified by the Personalized Medicine Coalition. In 2020, personalized medicines accounted for 39 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 four of the last five years.

In addition, FDA's Center for Biologics Evaluation and Research (CBER) approved two new cell-based therapies in 2021. These approvals represent 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. FDA has now approved eight cell-based or gene therapies.

## Personalized Medicines Accounted for More Than 25% of FDA Approvals for Each of the Last Seven 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.

# 2021 APPROVALS

**17 of the 48 new therapeutic molecular entities FDA approved in 2021 – as well as two new cell-based therapies – are personalized medicines.**

## **Newly Approved Therapeutic Molecular Entities**

1. **Cabenuva (cabotegravir and rilpivirine)** – for the treatment of human immunodeficiency virus (HIV) infection in adults with virologically suppressed HIV-1 infection. The use of this product can be informed by HIV-1 expression levels in patients.
2. **Tepmetko (tepotinib)** – for the treatment of metastatic non-small cell lung cancer (NSCLC). The decision to use this product is informed by the status of the mesenchymal-epithelial transition (MET) exon 14 biomarker in the tumors of patients.
3. **Evkeeza (evinacumab-dgnb)** – approved as an adjunct therapy for the treatment of familial hypercholesterolemia (FH). The use of this product is informed by the hoFH (homozygous FH) status in patients.
4. **Amondys 45 (casimersen)** – for the treatment of Duchenne muscular dystrophy. The decision to use this product is informed by the status of the DMD gene exon 45 biomarker in patients.
5. **Nulibry (fosdenopterin)** – for the treatment of molybdenum cofactor deficiency (MoCD). The use of this product is informed by the MoCD Type A status in patients.
6. **Jemperli (dostarlimab-gxly)** – for the treatment of recurrent or advanced endometrial cancer. The decision to use this product is informed by the status of the mismatch repair deficient (dMMR) biomarker in the tumors of patients and can be further informed by the PD-L1 biomarker expression levels in the tumors of patients.

7. **Rybrevant (amivantamab-vmjw)** – for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC). The decision to use this product is informed by the status of the epidermal growth factor receptor (EGFR) exon 20 biomarker in the tumors of patients.
8. **Lumakras (sotorasib)** – for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC). The decision to use this product is informed by the status of the KRAS G12C biomarker in the tumors of patients.
9. **Truseltiq (infigratinib)** – for the treatment of locally advanced or metastatic cholangiocarcinoma. The decision to use this product is informed by the status of the fibroblast growth factor receptor 2 (FGFR2) biomarker in the tumors of patients.
10. **Bylvay (obevoxibat)** – for the treatment of pruritis in patients with progressive familial intrahepatic cholestasis (PFIC). The use of this product can be informed by the status of the ABCB11 biomarker in PFIC Type 2 patients.
11. **Nexviazyme (avalglucosidase alfa-ngpt)** – for the treatment of Pompe disease. The use of this product selectively targets the lysosomal acid alpha-glucosidase (GAA) deficiency biomarker in patients.
12. **Welireg (belzutifan)** – for the treatment of adult patients with von Hippel-Lindau (VHL) disease. The dosage and use of this product can be informed by the status of the UGT2B17 and CYP2C19 pharmacogenetic biomarkers in patients.
13. **Exkivity (mobocertinib)** – for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC). The decision to use this product is informed by the status of the epidermal growth factor receptor (EGFR) exon 20 biomarker in the tumors of patients.
14. **Tavneos (avacopan)** – approved as an adjunct therapy for the treatment of active severe vasculitis [granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)] in combination with standard therapy including glucocorticoids. The decision to use this product is informed by the status of the antineutrophil cytoplasmic autoantibody (ANCA) biomarker in patients.

15. **Scemblix (asciminib)** – for the treatment of chronic myeloid leukemia (CML) in chronic phase (CP). The decision to use this product is informed by the Philadelphia chromosome (Ph+) and the T315I mutation biomarker statuses in the patient’s leukemia.
16. **Vyvgart (efgartigimod alfa-fcab)** – for the treatment of generalized myasthenia gravis (gMG). The use of this product is informed by the status of the anti-acetylcholine receptor (AChR) antibody biomarker in patients.
17. **Leqvio (inclisiran)** – for the treatment of heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD). This product is a small interfering RNA (siRNA) that selectively targets the proprotein convertase subtilisin kexin type 9 (PCSK9) mRNA biomarker in patients.

## Two Newly Approved Cell-Based Therapies

18. **Breyanzi (lisocabtagene maraleucel)** – for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B. The treatment is a fully integrated CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of adult patients with the indicated B-cell lymphomas.
19. **Abecma (idecabtagene vicleucel)** – for the treatment of relapsed or refractory multiple myeloma. The treatment is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of adult patients with refractory multiple myeloma.

---

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 2021 does not provide the whole picture of the growing list of personalized medicines available to doctors and their patients. In addition to the 17 personalized NMEs and the new cell-based therapies, FDA approved many significant new personalized medicine indications for existing drugs and combinations of drugs in 2021. These approvals redefine the drugs' intended populations and often provide patients with more effective personalized treatment options. The list of new personalized medicines in 2021 should therefore be complemented with reference to newly approved indications and combinations for Keytruda (pembrolizumab), Ayyakit (avapritinib), Tepezza (teprotumumab-trbw), Tazverik (tazemetostat), Xalkori (crizotinib), Enhertu (trastuzumab deruxtecan), Opdivo (nivolumab), Cabometyx (cabozantinib), Ukoniq (umbralisib), Libtayo (cemiplimab-rwlc), Lorbrena (lorlatinib), Sarclisa (isatuximab-irfc), Kesimpta (ofatumumab), Trodelvy (sacituzumab govitecan-hziy), Tysabri (natalizumab), Ultomiris (ravulizumab-cwvz), Padcev (enfortumab vedotin-ejfv), Lenvima (lenvatinib), Tibsovo (ivosidenib), Brukinsa (zanubrutinib), Tecartus (brexucabtagene autoleucel), Tecentriq (atezolizumab), Rituxan (rituximab), and Oxbryta (voxelotor).

Significant among these expanded indications, FDA approved a new indication for Tecartus for use in patients with refractory B-cell precursor acute lymphoblastic leukemia (ALL). Previously approved for mantle cell lymphoma (MCL), the expanded indication makes Tecartus the first CAR T-cell therapy approved for adults with ALL. There is a high unmet need, as half of this patient population has been shown to relapse after previous treatments, and the median overall survival for relapsed patients is low.

### Continued Emergence of siRNA Treatments

The approval of Leqvio marks the fourth 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. Leqvio can be used to treat familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD).

# IMPACT

## Personalized Treatments Approved in 2021 Address a Spectrum of Health Conditions Including Rare Diseases, Cancer, and Some Common and Infectious Diseases

### Reversing the Root Causes of Disease

Seven of the 17 newly approved NMEs are designed to reverse root causes of certain rare diseases. Many patients with Duchenne muscular dystrophy, molybdenum cofactor deficiency, Pompe disease, von Hippel-Lindau disease, rare types of active severe vasculitis, and generalized myasthenia gravis (gMG) now have treatments available that target the underlying molecular mechanisms of their diseases.

Evkeeza provides a new add-on treatment option for certain patients with familial hypercholesterolemia, a genetic condition that causes severely high cholesterol. The rare population of patients that have the homozygous form of the disease (hoFH) have two mutations in a small group of genes that control the way the body clears cholesterol. As a result, patients have extremely high circulating levels of low-density lipoprotein cholesterol (LDL-C), known as “bad cholesterol,” which can lead to premature cardiovascular disease, including heart attack and heart disease before the age of 30. Many hoFH patients do not improve with other cholesterol-lowering drugs. Without aggressive treatment, patients may die before age 30. Evkeeza binds to and slows the activity of certain dysfunctional enzymes associated with the condition, allowing faster break down and clearance of fats that would otherwise lead to greatly elevated levels of cholesterol. The approval of the drug underlines how personalized medicine tailored to patients’ genetic characteristics can help physicians and patients get ahead of a rare form of this devastating chronic disease.

### A New Treatment for Common Forms of Familial Hypercholesterolemia

The FDA approval of Leqvio provides a first-in-class therapy for patients living with the more common heterozygous form of familial hypercholesterolemia (heFH) or with clinical atherosclerotic cardiovascular disease (ASCVD).

Patients with heFH generally have cholesterol levels two to three times higher than normal. These individuals are at increased risk of cardiovascular events, such as heart attack, stroke, and coronary artery disease. HeFH occurs in approximately 1 in 250 individuals.

ASCVD involves the buildup of cholesterol plaque in arteries. Approximately 18.3 million American adults (8 percent) have ASCVD.

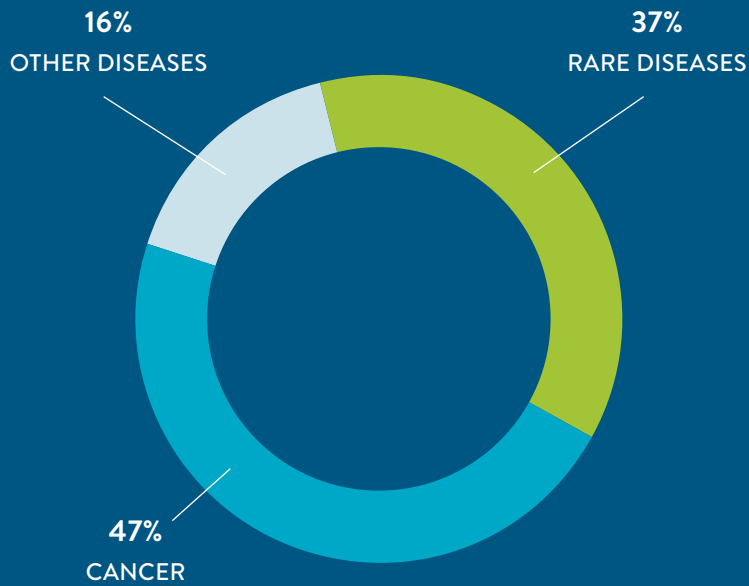
Leqvio is the first siRNA therapy to lower LDL-C among these cohorts of patients. It reduces the amount of LDL-C in the bloodstream by improving the liver's natural ability to prevent the production of a protein that plays a role in keeping circulating cholesterol levels high. Leqvio is delivered as a subcutaneous injection given every six months. This approach may help those who have trouble sticking to medicines that are self-administered.

## Combatting Cancer

Seven of the 17 newly approved molecular entities, two new cell-based therapies, 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 Lumakras for patients with KRAS G12C mutated advanced or metastatic non-small cell lung cancer (NSCLC) marks the first approved targeted treatment for tumors with a KRAS mutation, which account for approximately 25 percent of mutations in lung cancers. KRAS G12C mutations represent about 13 percent of mutations in NSCLC. KRAS mutations have long been considered undruggable, meaning that it was believed that targeted therapies could not be developed for this major genetic driver of cancers. The Lumakras approval demonstrates that this molecular pathway can indeed be targeted, addressing an unmet need for patients with certain types of cancer. The approval represents a significant step towards a future of personalized medicine in which more patients have a targeted treatment option that can improve their clinical outcomes and increase survival rates with fewer side effects than traditional chemotherapy.

### Newly Approved Personalized Medicines Are Indicated for Treatment of Cancer, Rare Diseases, and Common/ Infectious Diseases



- | ■ Cancer     | ■ Rare Diseases | ■ Other Diseases |
|--------------|-----------------|------------------|
| 1. Abecma    | 10. Amondys 45  | 17. Bylvay       |
| 2. Breyanzi  | 11. Evkeeza     | 18. Cabenuva     |
| 3. Exkivity  | 12. Nexvazyme   | 19. Leqvio       |
| 4. Jemperli  | 13. Nulibry     |                  |
| 5. Lumakras  | 14. Tavneos     |                  |
| 6. Rybrevant | 15. Vyvgart     |                  |
| 7. Scemblix  | 16. Welireg     |                  |
| 8. Tepmetko  |                 |                  |
| 9. Truseltiq |                 |                  |

# 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 2021, FDA's Center for Devices and Radiological Health (CDRH) approved or cleared several significant new or expanded indications within nine in vitro diagnostic testing applications that underpin personalized medicine strategies. New approvals and expanded indications associated with the nine tests listed below will help inform targeted treatment decisions to improve drug safety and efficacy.

### Significant New Approvals/Indication Expansions

1. **Agilent Ki-67 IHC MIB-1 pharmDx (Dako Omnis)** – Approved as a companion diagnostic (CDx) to measure Ki-67 cell signatures to guide decisions regarding the use of Verzenio (abemaciclib) for breast cancer in combination with endocrine therapy. This is the first approved CDx for the Ki-67 score, a proteomic biomarker.
2. **Promega OncoMate MSI Dx Analysis System (OncoMate MSI)** – Cleared as an in vitro diagnostic (IVD) testing kit to detect microsatellite instability (MSI) as an aid in the identification of Lynch syndrome in colorectal cancer patients. This is the first cleared PCR (polymerase chain reaction)-based IVD for MSI characterization
3. **VENTANA PD-L1 (SP263) Assay** – Approved as a companion diagnostic to measure PD-L1 expression to guide decisions regarding the use of Tecentriq (atezolizumab) for adjuvant treatment in certain non-small cell lung cancers (NSCLC).

4. **VENTANA MMR Rx Dx Panel** – Indication expanded as a companion diagnostic test for mismatch repair deficiency (dMMR) to guide decisions regarding the use of Jemperli (dostarlimab-gxly). This is the first approved immunohistochemistry (IHC)-based companion diagnostic test of dMMR in patients with solid tumors.
5. **VENTANA ALK (D5F3) CDx Assay** – Indication expanded to include detection of ALK mutations to guide decisions regarding the use of Lorbrena (lorlatinib) for non-small cell lung cancer (NSCLC).
6. **Oncomine Dx Target Test** – Two significant indication expansions, as follows:
  - Indication expanded as a tissue-based companion diagnostic to include detection of EGFR exon 20 insertion mutations to guide decisions regarding the use of Exkivity (mobocertinib) for non-small cell lung cancer (NSCLC).
  - Indication expanded to include detection of single nucleotide variants in IDH1 to guide decisions regarding the use of Tibsovo (ivosidenib) for cholangiocarcinoma.
7. **FoundationOne® CDx** – Three significant indication expansions, as follows:
  - Indication expanded to include detection of MET exon 14 skipping mutations to help guide decisions regarding the use of Tabrecta (capmatinib) for non-small cell lung cancer (NSCLC).
  - Indication expanded to include detection of FGFR2 rearrangements to help guide decisions regarding the use of Truseltiq (infigratinib) for cholangiocarcinoma.
  - Indication expanded to include detection of BRAF V600E mutations to help guide decisions regarding the use of BRAF inhibitor drugs that have been approved by FDA, and BRAF V600E and V600K mutations to help guide decisions regarding the use of BRAF/MEK inhibitor combinations approved by FDA for metastatic melanoma.

8. **Guardant360 CDx** – Two significant indication expansions, as follows:
  - Indication expanded to include blood-based detection of EGFR exon 20 insertions to help guide decisions regarding the use of Rybrevant (amivantamab-vmjw) for non-small cell lung cancer (NSCLC).
  - Indication expanded to include blood-based detection of KRAS G12C to help guide decisions regarding the use of Lumakras (sotorasib) for non-small cell lung cancer (NSCLC).
9. **Therascreen KRAS RGQ PCR Kit** – Indication expanded to include detection of KRAS G12C to help guide decisions regarding the use of Lumakras (sotorasib) for non-small cell lung cancer (NSCLC).

### A New Diagnostic Testing Platform for Risk Detection

FDA's CDRH also authorized the Helix<sup>®</sup> Laboratory Platform, a whole exome sequencing platform to support the detection of germline variation, and provided clearance for the Helix<sup>®</sup> Genetic Health Risk App for late-onset Alzheimer's disease for over-the-counter use on the Helix<sup>®</sup> Laboratory Platform.

### The Significance of Tissue-Agnostic Oncology

Historically, FDA has approved oncology drugs for a specific type of cancer based on the cancer's location in the body (e.g., breast cancer, lung cancer). Tissue-agnostic drugs are instead designed to treat cancers based on the genetic mutations that they display. In 2021, FDA approved the VENTANA MMR RxDx Panel as a new diagnostic test to identify advanced cancer patients with solid tumors of all types that have deficient mismatch repair (dMMR). The approval of the dMMR test further expands the frontiers of the tumor-agnostic treatment paradigm, which proponents of personalized medicine have long envisioned.

# POLICY PRECEDENT

## Continued Progress in the Consideration of Information From External Databases of Genetic Variants

Policymakers continue to explore ways to use the vast amounts of data available in public databases that may be able to support the development of new genetic tests. In 2021, FDA granted recognition to a partial listing of the [Memorial Sloan Kettering Cancer Center’s Oncology Knowledge Base \(OncoKB\)](#) as the first tumor mutation database to be included in the FDA’s [database recognition program](#). Test developers can use information in the OncoKB database to support the clinical validity of tumor profiling tests in premarket submissions.

In oncology, vast amounts of data are important for understanding a patient’s prognosis or cancer subtype and are often necessary to understand the predictive response to FDA-approved and experimental therapies. OncoKB provides an expertly curated database of the biologic and clinical implications of thousands of cancer-associated mutations. The database collates information from various publicly available resources including scientific literature, government agencies, medical professional groups, and clinical trials.

By signaling FDA’s recognition of the gene-disease correlations outlined in the recognized portion of the OncoKB database, the agency’s inclusion of the database in its list of *Public Human Genetic Variant Databases* will provide additional sources of information for test developers as they develop premarket submissions for tests that can further advance personalized medicine, thereby bringing more tests to market, faster.



# CONCLUSION

## Reshaping Health Care and Sustaining the Promise of Personalized Medicine

As evidenced most prominently by the fact that personalized medicines accounted for more than a third of new drug approvals in 2021, personalized medicine continues to reshape the health care landscape, bringing forth novel technologies that improve outcomes for patients and have 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 2021 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 patient outcomes and make health care more efficient.

But continued progress cannot be taken for granted. To ensure that scientists and innovators continue to develop groundbreaking personalized medicine tests and treatments for the benefit of patients and health systems, 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.



PERSONALIZED  
MEDICINE COALITION

[www.PersonalizedMedicineCoalition.org](http://www.PersonalizedMedicineCoalition.org)

202-589-1770

@PerMedCoalition