# RAISING THE BAR: FDA ACCELERATES THE PUSH TOWARD PERSONALIZED MEDICINE

by Daryl Pritchard, Ph.D., and Christopher J. Wells, M.P.A.

The U.S. Food and Drug Administration (FDA) set a new record in 2018 by approving 59 new molecular entities (NMEs), 25 of which are classified as personalized medicines because biomarker information is included in their labels that can be used to identify which patients are most likely to benefit or be at a higher risk of severe side effects from their use (see **Table 1**). These 25 personalized medicine approvals — which account for 42 percent of the NMEs approved last year — represent a new high-water mark for personalized medicine, capping a five-year period during which personalized medicines have accounted for more than 20 percent of new medicines each year (see **Figure 1**).

The growing prominence of personalized treatment approvals at FDA highlights several emerging trends at the agency. It also underlines the importance of maintaining an environment that encourages innovation while resisting policies that threaten to slow the development of personalized medicine treatments and the diagnostics that guide them.

## Expedited Review

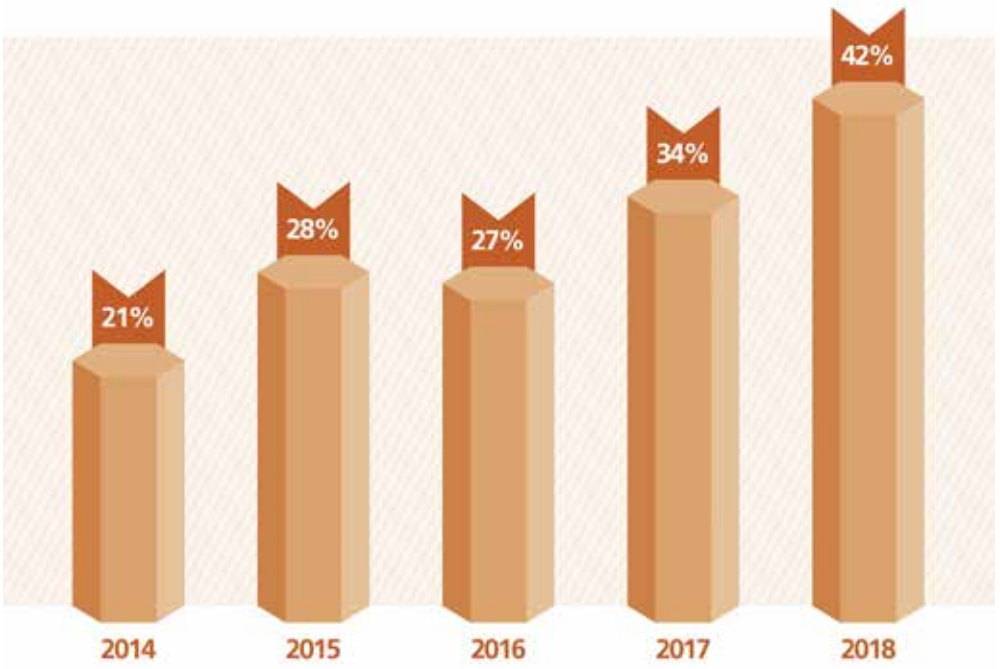
Over the past five years, an increasing number of NMEs have gone through some form of expedited review before being approved — and this trend is accelerating the pace at which personalized medicines are coming to market. Of the 25 new personalized medicines approved last year, 24 were subject to some form of expedited FDA review through either orphan drug, priority review, fast-track or breakthrough therapy programs. This demonstrates the agency's commitment to bringing new personalized treatments to patients rapidly.

## Expanding Indications

Even the large number of new therapies classified as personalized medicines in 2018 does not provide the whole picture, however, on the growing list of personalized medicines available to doctors and their patients. In addition to the 25 personalized NMEs, FDA approved many significant new personalized medicine indications and/or drug combinations for previously existing drugs in 2018. These approvals redefine the therapies' targeted populations and provide patients with more effective personalized treatment options. The list of new personalized medicines in 2018 should therefore be complemented with reference to newly approved indications for Lynparza (olaparib), Gilotrif (afatinib), Verzenio (abemaciclib), Imfinzi (durvalumab), Blincyto (blinatumomab), Rubraca (rucaparib), Opdivo (nivolumab), Yervoy (ipilimumab), Tagrisso (osimertinib), Tafinlar (dabrafenib), Mekinist (trametinib), Kymriah (tisagenlecleucel), Xalkori (crizotinib), Venclexta (venetoclax), Keytruda (pembrolizumab), Kisqali (ribociclib), Tecentriq (atezolizumab), Imbruvica (ibrutinib), Rituxan (rituximab), Hemlibra (emicizumab-kxwh), and Adcetris (brentuximab vedotin) for new molecularly defined subsets of patients.

**"EVEN THE LARGE NUMBER OF NEW THERAPIES CLASSIFIED AS PERSONALIZED MEDICINES IN 2018 DOES NOT PROVIDE THE WHOLE PICTURE"**

**Figure 1:** Personalized Medicines Have Topped 20 Percent of FDA Approvals for Five Straight 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, identified by diagnostic tools, that help guide decisions and/or procedures for their use in individual patients.

## A New Kind of Personalized Treatment

The approval last year of Onpattro (patisiran) marks the first 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. Onpattro can be used to treat peripheral nerve disease (polyneuropathy) caused by hereditary transthyretin-mediated amyloidosis (hATTR).

## Tissue-Phenotype Agnostic Indications in Oncology

Of the 25 new personalized treatments approved in 2018, 10 deliver more impactful treatment options for patients with cancer. These include Vitrakvi (larotrectinib), which is only the second personalized therapy the agency has ever approved to treat all tumors with certain molecular characteristics regardless of where in the body the tumors are

**Table 1:** FDA Approved a Record Number of 25 Personalized Treatments in 2018

**Medicines Listed in Chronological Order by Date of Approval**

**Methodology:** When evaluating new molecular entities, PMC categorizes personalized medicines as those therapeutic products for which the label includes reference to specific biological markers, identified by diagnostic tools, that help guide decisions and/or procedures for their use in individual patients.

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|---|---|---|---|
| 1. | **Lutathera (lutetium Lu 77 dotatate)** for the treatment of gastroenteropancreatic neuroendocrine tumors. The decision to use this product is informed by the somatostatin receptor (SR+) biomarker status in the tumors of patients. | 14. | **Galafold (migalastat)** for the treatment of Fabry disease. The decision to use this product is informed by the GLA variant status in patients. |
| 2. | **Biktarvy (bictegravir; emtricitabine; tenofovir alafenamide)** for the treatment of HIV-1 infection. The decision to use this product is informed by the HIV-1 expression levels in patients. | 15. | **Takhzyro (lanadelumab-flyo)** for the treatment of types I and II hereditary angioedema. The decision to use this product is informed by the C1-inhibitor biomarker levels and function in patients. |
| 3. | **Symdeko (tezacaftor; ivacaftor)** for the treatment of cystic fibrosis. The decision to use this product is informed by the F508del mutation and CFTR mutation biomarker statuses of patients. | 16. | **Pifeltro (doravirine)** for the treatment of HIV-1 infection. The decision to use this product is informed by the HIV-1 expression levels in patients. |
| 4. | **Trogarzo (ibalizumab-uiyk)** for the treatment of HIV-1 infection. The decision to use this product is informed by the HIV-1 expression levels in patients. | 17. | **Vizimpro (dacomitinib)** for the treatment of advanced non-small cell lung cancer (NSCLC). The decision to use this product is informed by the EGFR biomarker status in the tumors of patients. |
| 5. | **Crysvita (burosumab-twza)** for the treatment of x-linked hypophosphatemia (XLH). The decision to use this product can be informed by the PHEX mutation biomarker status in patients. | 18. | **Libtayo (cemiplimab-rwlc)** for the treatment of cutaneous squamous cell carcinoma (CSCC). The decision to use this product can be informed by the PD-L1 expression levels in the tumors of patients. |
| 6. | **Doptelet (avatrombopag)** for the treatment of thrombocytopenia in patients with chronic liver disease. The use of this product can be informed by the Factor V Leiden, Prothrombin 20210A, Antithrombin, or Protein C or S biomarker statuses in patients. | 19. | **Revcovi (elapegademase-lvlr)** for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID). The decision to use this product is informed by the ADA mutation biomarker status in patients. |
| 7. | **Palynziq (pegvaliase-pqpz)** for the treatment of phenylketonuria (PKU). The decision to use this product can be informed by the PAH mutation biomarker status in patients, and the use of this product is informed by the phenylalanine biomarker concentration in patients. | 20. | **Tegsedi (inotersen)** for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis. The decision to use this product is informed by the TTR biomarker status in patients. |
| 8. | **Mektovi (binimetinib)** for the treatment of metastatic melanoma. The decision to use this product is informed by the BRAF biomarker status in the tumors of patients. | 21. | **Talzenna (talazoparib)** for the treatment of advanced breast cancer. The decision to use this product is informed by the BRCA mutation biomarker status in patients. |
| 9. | **Braftovi (encorafenib)** for the treatment of metastatic melanoma. The decision to use this product is informed by the BRAF biomarker status in the tumors of patients. | 22. | **Lorbrena (lorlatinib)** for the treatment of advanced non-small cell lung cancer (NSCLC). The decision to use this product is informed by the anaplastic lymphoma kinase (ALK) biomarker status in the tumors of patients. |
| 10. | **Tibsovo (ivosidenib)** for the treatment of relapsed or refractory acute myeloid leukemia (AML). The decision to use this product is informed by the IDH1 mutation biomarker status in the tumors of patients. | 23. | **Vitrakvi (larotrectinib)** for the treatment of solid tumor cancers with a specific gene fusion. The decision to use this product is informed by the neurotrophic receptor tyrosine kinase (NTRK) gene fusion biomarker status in the tumors of patients. |
| 11. | **Krintafel (tafenoquine)** for the treatment of Plasmodium vivax malaria. The decision to use this product is informed by the G6PD biomarker status in patients. | 24. | **Firdapse (amifampridine)** for the treatment of Lambert-Eaton Myasthenic Syndrome (LEMS). The use of this product can be informed by the N-acetyltransferase 2 (NAT2) biomarker status in patients. |
| 12. | **Mulpleta (lusutrombopag)** for the treatment of thrombocytopenia in patients with chronic liver disease. The use of this product can be informed by the Factor V Leiden, Prothrombin 20210A, Antithrombin, or Protein C or S biomarker statuses in patients. | 25. | **Xospata (gilteritinib)** for the treatment of relapsed or refractory acute myeloid leukemia (AML). |
| 13. | **Onpattro (patisiran)** for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis. The decision to use this product is informed by the TTR biomarker status in patients. | | |

A complete list of the 59 new molecular entities FDA approved in 2018 can be accessed at: https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm592464.htm.

located. Tissue-phenotype agnostic indications anticipate a new paradigm in oncology care based entirely on targeting the molecular characteristics of a patient's underlying disease, rather than traditional care strategies that base treatment decisions on the cancer's tissue of origin.

## Personalized Medicine Biosimilars

Two new biosimilars for existing personalized oncology medicines were also approved in 2018, including Truxima (rituximab-abbs), the first biosimilar to Rituxan (rituximab) for the treatment of adult patients with CD20-positive, B-cell non-Hodgkin's lymphoma (NHL), and Herzuma (trastuzumab-pkrb), as a biosimilar to Herceptin (trastuzumab) for the treatment of human epidermal growth factor receptor 2 (HER2) over-expressing breast cancer and metastatic gastric cancer. The availability of biosimilars for the targeted treatment of biomarker-positive patients should help improve access to personalized medicine for these types of cancers.

## Beyond Oncology

A close look at the newly approved treatments also reminds us that personalized medicine's applications go beyond oncology.

### Rare Diseases

Personalized medicine is having an outsized impact for patients with certain rare diseases, as evidenced by the nine new treatments FDA approved in this area last year.

For example, in 2018, FDA approved a personalized medicine called Symdeko (tezacaftor/ivacaftor) that helps cystic fibrosis patients with certain genetic mutations produce more functional copies of the CFTR protein, thereby addressing the molecular mechanism of the disease. Like other targeted therapies for cystic fibrosis patients, Symdeko can dramatically improve the quality of life for these patients by reducing infections and other complications associated with excess mucus in the lungs. Around 90 percent of patients with cystic fibrosis now have access to personalized medicines such as Symdeko, and these treatments are expected to help patients live longer lives and breathe freely.[1]

**"DECISION-MAKERS IN THE PUBLIC AND PRIVATE SECTORS NEED TO MAINTAIN COLLABORATIONS TO OVERCOME THE REIMBURSEMENT CHALLENGES ASSOCIATED WITH PERSONALIZED TESTS AND TREATMENTS"**

### Pharmacogenomics

FDA also approved four new therapies with pharmacogenomic indications in 2018. These drugs come with labels specifying certain genetic mutations that, if present in the patient's genome, may increase the risk of side effects associated with the drug. These labels allow physicians to recommend alternative treatment approaches or adjust the prescribed dose of the drug accordingly.

## Conclusion

More than ever, these trends in the development of new technologies demonstrate 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 continued progress cannot be taken for granted.

To ensure that industry leaders continue to develop groundbreaking personalized medicine tests and treatments, policymakers must continue to favor policies that encourage the advancement of the field. It is especially important that policymakers establish a predictable funding environment for FDA's activities at levels sufficient to support its work. In addition, decision-makers in the public and private sectors need to maintain collaborations to overcome the reimbursement challenges associated with personalized tests and treatments that can turn increased up-front costs into downstream benefits for patients and health systems. Doing so will help ensure that patients will have ever-greater access to critical, innovative products. ■


### Reference

1. Joseph, A. (2019, February 4). 'We're Still Waiting.' As Cystic Fibrosis Drugs Deliver New Hope, Not Everyone is Being Swept Up by Scientific Progress. *STAT*. Retrieved from https://www.statnews.com/2019/02/04/cystic-fibrosis-patients-nonsense-mutations/.



**Daryl Pritchard, Ph.D.,** is Senior Vice President of Science Policy at the Personalized Medicine Coalition, where he leads the Coalition's efforts to develop and promote optimal science-related policies and to increase awareness and understanding of personalized medicine among health care providers, patients, policymakers and other stakeholders.

**Christopher J. Wells, M.P.A.,** is Vice President of Public Affairs at the Personalized Medicine Coalition, where he oversees the development of PMC's marketing and communications messages and leverages a comprehensive portfolio of digital and traditional communications tools to increase awareness and understanding of the field.