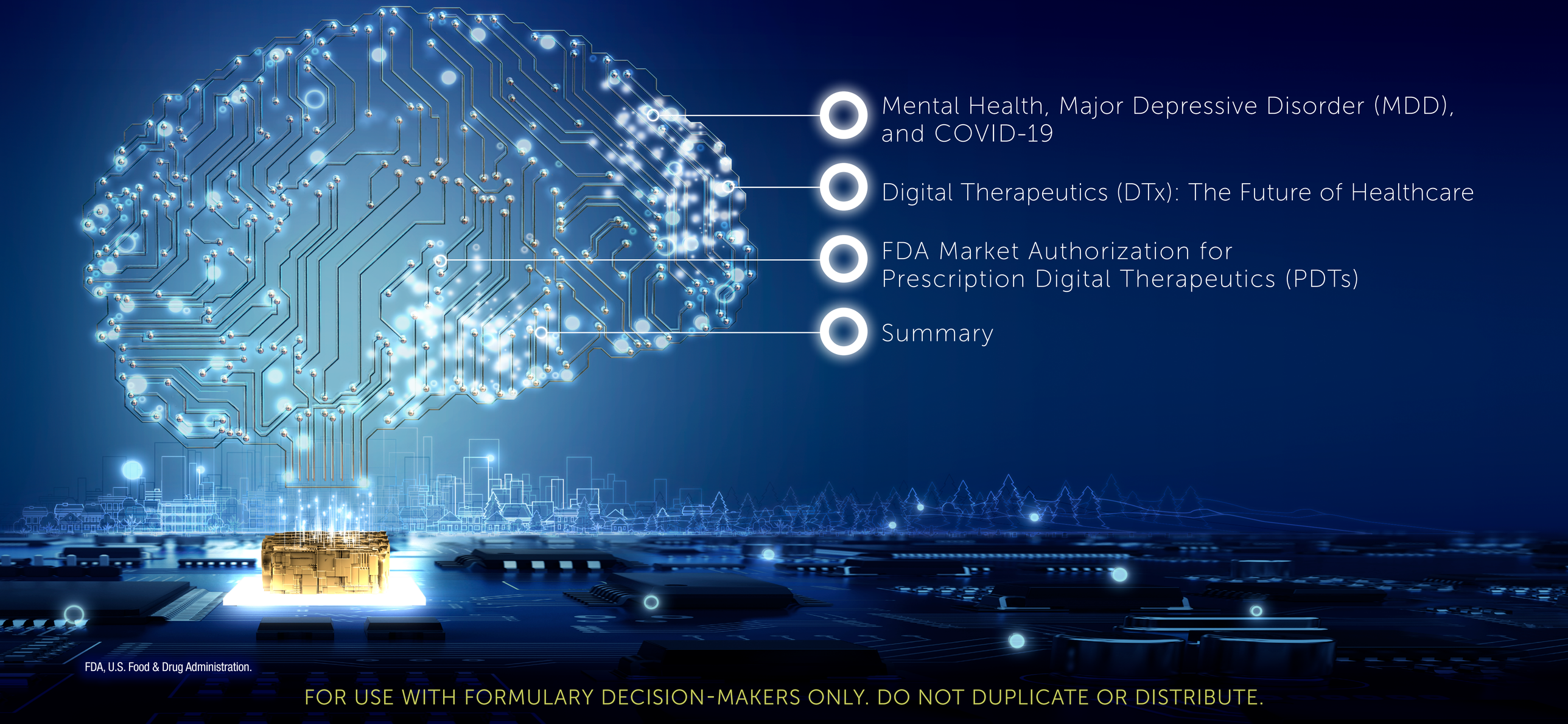
February 2022 20US22EUY0001



FDA, U.S. Food & Drug Administration.

Mental Health, Major Depressive Disorder (MDD), and COVID-19

The COVID-19 pandemic has worsened mental health in the United States

Before COVID-19, US adults struggled with mental health issues.

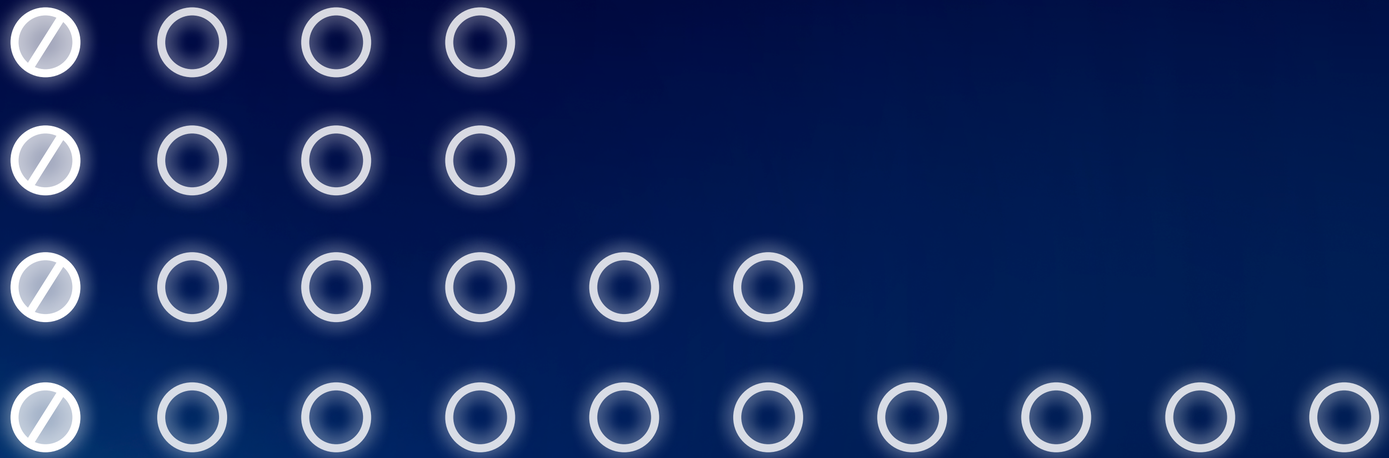
In the Kaiser Family Foundation (KFF) nationally representative survey of 1862 adults, those seeking mental health services unrelated to COVID-19 reported[1,2]

~ 1 in 4 couldn't afford the cost

~ 1 in 4 was unable to access a provider

~ 1 in 6 was unable to access services or medications

1 in 10 experienced limitations in coverage

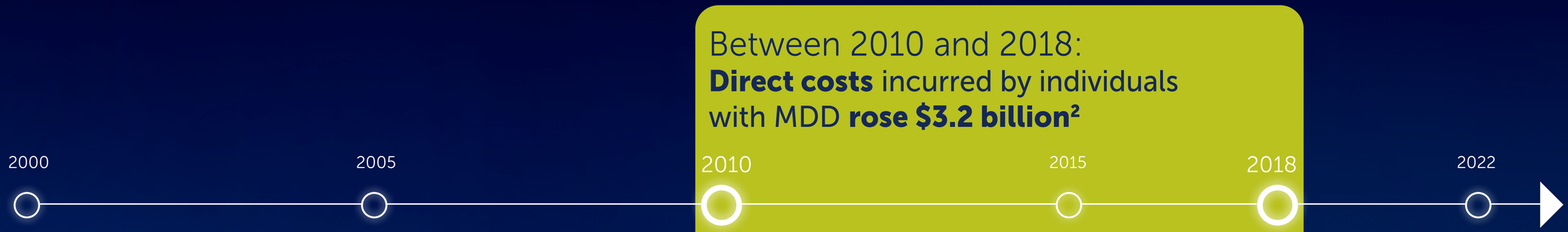


3x increase in the prevalence of **depression symptoms** during the COVID-19 pandemic[3]

REFERENCES: 1. Kearney A, et al, Kaiser Family Foundation. Mental health impact of the COVID-19 pandemic: an update. https://www.kff.org/coronavirus-covid-19/poll-finding/mental-health-impact-of-the-covid-19-pandemic/. Published 2021.Accessed November 3, 2021. **2.** Kearney, et al . Mental health impact of the COVID-19 pandemic: An update - methodology. KFF. https://www.kff.org/report-section/mental-health-impact-of-the-covid-19-pandemic-an-update-methodology/.Published April 14, 2021. Accessed February 8, 2022. **3.** Ettman CK, et al. Prevalence of depression symptoms in US adults before and during the COVID-19 Pandemic. JAMA Netw Open. 2020;3(9):e2019686.doi:10.1001/jamanetworkopen.2020.19686

MDD is common and increasingly costly

- An estimated 19.4 million adults in the United States had at least one major depressive episode in 2019[1]



Between 2010 and 2018:
Direct costs incurred by individuals with MDD **rose $3.2 billion**[2]

Total number of adults with MDD rose **12.9%**[2]

The direct costs for adults with MDD increased[2]

74% aged 18-25

41% aged 26-35

REFERENCES: 1. National Institute of Mental Health (NIMH). Major depression. https://www.nimh.nih.gov/health/statistics/major-depression. Published 2021. Accessed October 17, 2021. **2.** Greenberg PE, et al. Pharmacoeconomics. 2021;39(6):653-655.

Patients encounter barriers at every step of the treatment journey

1 DIAGNOSIS OF MDD

Of the estimated 7.8% of US adults that are affected by MDD every year[1]

31% of adults did not seek treatment due to stigma[2]

Among racial and ethnic minority groups these rates vary from 29.4% to 47.4%[2]

Other obstacles to diagnosis included fear and hesitancy that may affect treatment access[3]

2 PHARMACOLOGIC INTERVENTION

Patients were ~5 times more likely to experience problems obtaining medications when step-therapy or fail-first protocols were required[4]

Patient were ~8 times more likely to experience problems obtaining medications when prior authorizations were required[4]

3 PSYCHOTHERAPY

2 out of 5 Americans live in areas with a shortage of mental health professionals[5]

42% of US adults saw cost and poor insurance coverage as top barriers to mental healthcare[6]

25% of Americans reported having to choose between mental health treatment and daily necessities[6]

4 ACUTE CARE

Mood disorders were the most common cause of hospitalization for all people in the United States under age 45, excluding hospitalization relating to pregnancy and birth[7]

Cost to Payer

Every $1 invested in prevention could yield an estimated $2.3-$2.6 in saved costs[8]

Direct healthcare costs significantly increased with each successive line (up to 3 lines) of therapy highlighting the need for rapid and effective treatment options[9]

As of 2018, an estimated 54% of US counties do not have a single psychiatrist[10]

REFERENCES: 1. National Institute of Mental Health (NIMH). Major depression. https://www.nimh.nih.gov/health/statistics/major-depression. Published 2021. Accessed October 17, 2021 **2.** Substance Abuse and Mental Health Services Administration. Racial/ethnic difference in mental health service among adults and adolescents 2015-2019. https://www.samhsa.gov/data/report/racialethnic-differences-mental-health-service-use. Published 2021. Accessed December 2, 2021. **3.** Stigma and Discrimination. Psychiatry.org. https://www.psychiatry.org/patients-families/stigma-and-discrimination. Published 2022. Accessed January 13, 2022. **4.** West J, et al. Medicaid prescription drug policies and medication access and continuity: findings from ten states. https://ps.psychiatryonline.org/doi/10.1176/ps.2009.60.5.601?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed. Accessed November 30, 2021. **5.** Hostetter, et al. *In Focus: Leveraging Technology to Expand Access to Behavioral Health Care for Medicaid Beneficiaries.* Published 2019. Accessed January 5, 2022, from https://www.commonwealthfund.org/publications/2019/jun/focus-leveraging-technology-expand-access-behavioral-health-care-medicaid?redirect_source=/publications/newsletter-article/2019/jun/focus-leveraging-technology-expand-access-behavioral **6.** The National Council. New study reveals lack of access as root cause for mental health crisis in America. https://www.thenationalcouncil.org/press-releases/new-study-reveals-lack-of-access-as-root-cause-for-mental-health-crisis-in-america/. Published 2018. Accessed November 30, 2021. **7.** Mental Health by the Numbers | NAMI: National Alliance on Mental Illness. Nami.org. https://www.nami.org/mhstats. Published 2021. Accessed December 20, 2021 **8.** American Heart Association. Mental Health: A workforce crisis. American Heart Association CEO Round Table 2018. https://ceoroundtable.heart.org/mental-health-a-workforce-crisis-report/. March 2019. Accessed February 1, 2021. **9.** Arnaud, et al.The increasing economic burden with additional steps of pharmacotherapy in major depressive disorder. Pharmacoeconomics. 2021;39(6):691-706. https://doi.org/10.1007/s40273-021-01021-w **10.** Beck A. *Estimating The distribution of the U.S. psychiatric subspecialist workforce.* School of Public Health Behavioral Health Workforce Research Center University of Michigan; 2018. https://www.behavioralhealthworkforce.org/wp-content/uploads/2019/02/Y3-FA2-P2-Psych-Sub_Full-Report-FINAL2.19.2019.pdf. Accessed November 30, 2021.

Groups that are less likely to obtain or receive mental healthcare[1]

The rate of underdiagnosis or misdiagnosis is higher in diverse and underserved populations,
which may be due to a lack of cultural understanding, language barriers, and cultural presentations of symptoms[1]

PSYCHIATRIC DEMOGRAPHICS IN THE US (2018)[2]

- **64%** White
- **18%** Asian
- **10%** Hispanic or Latino
- **5%** Black or African-American

The diversity profile of mental health patients does not match that of the provider base

Only 33% of African Americans who need mental healthcare received it[3]

American Indian/ Alaskan Natives reported higher rates of PTSD and alcohol dependence than any other ethnic/ racial group[1]

Only 19% of Hispanic adults with a mental illness were likely to use outpatient mental health services[4]

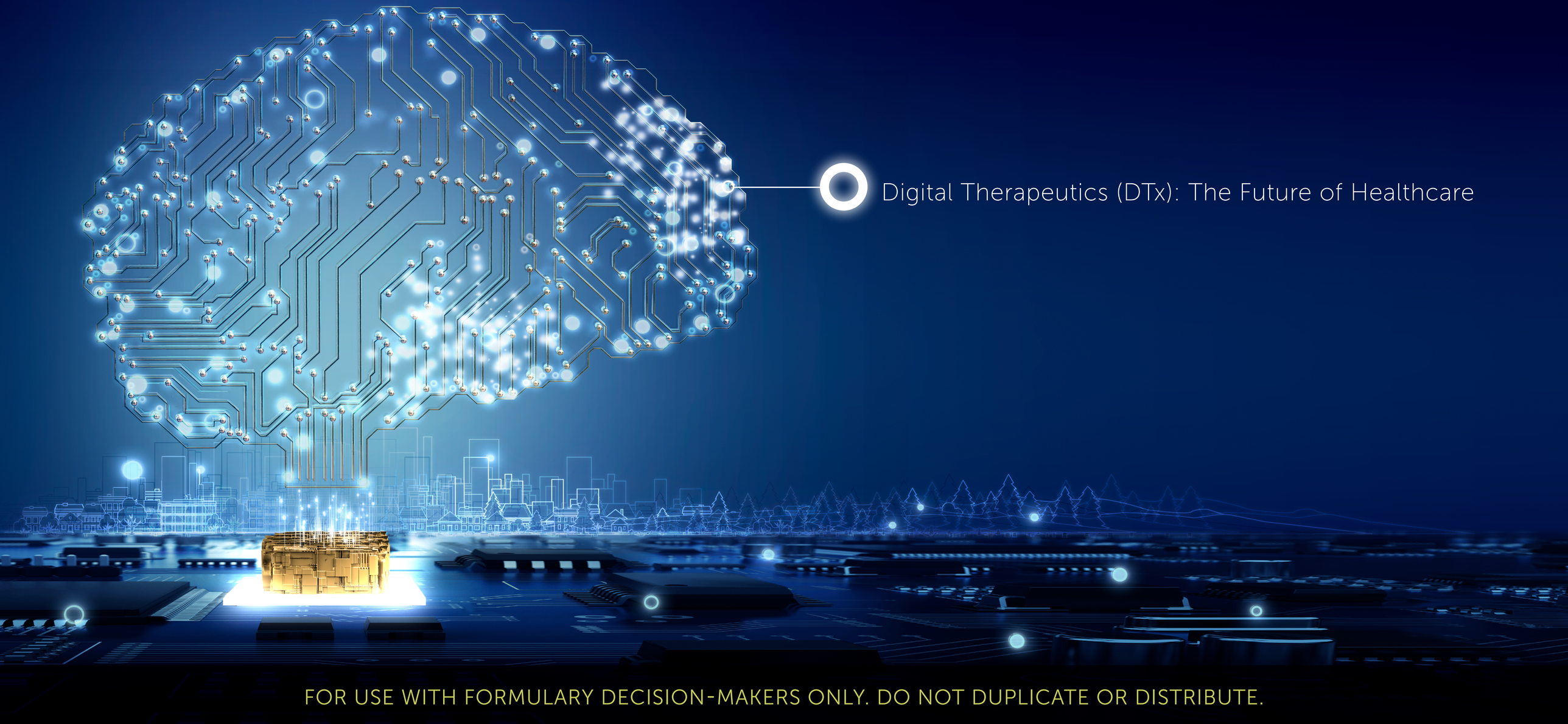
Transgender and nonbinary individuals were twice as likely to experience depression[5]

6 million men are affected by depression per year, but are less likely to acknowledge it[6]

This information is intended to bring awareness to diverse and underserved populations , but is not meant to be exhaustive

PTSD, post-traumatic stress disorder.

REFERENCES: 1. Pyschiatry.org. Mental health disparities: diverse populations - mental health facts for diverse populations. https://www.psychiatry.org/psychiatrists/cultural-competency/education/mental-health-facts. Published 2021. Accessed December 2, 2021. **2.** Psychiatrist demographics and statistics in the US. Zippia. https://www.zippia.com/psychiatrist-jobs/demographics/. Accessed February 28, 2022. **3.** Psychiatry.org. Mental health disparities: diverse populations - African Americans. https://www.psychiatry.org/psychiatrists/cultural-competency/education/mental-health-facts. Published 2021. Accessed December 2, 2021. **4.** Substance Abuse and Mental Health Services Administration. Racial/ethnic difference in mental health service among adults and adolescents 2015-2019. https://www.samhsa.gov/data/report/racialethnic-differences-mental-health-service-use. Published 2021. Accessed December 2, 2021. **5.** Price-Feeney M, et al. Understanding the mental health of transgender and nonbinary youth. https://www.jahonline.org/article/S1054-139X(19)30922-X/fulltext. Published 2020. Accessed December 3, 2021. **6.** Mental Health America. Infographic: mental health for men. https://www.mhanational.org/infographic-mental-health-men. Published 2021. Accessed November 17, 2021.



Digital Therapeutics (DTx): The Future of Healthcare

Digital health may be an extension to conventional medicine

GENERAL MEDICINE

1986 — FDA approves first statin (Mevacor)[1]

1988 — Becton Dickinson introduces the BD Safety-Lok, the first safety-engineered syringe[2]

SPECIALTY MEDICINE

1994 — Palmaz-Schatz releases Balloon Expandable Stent[3]

1995 — First HIV patient starts highly active antiretroviral therapy (HAART)[4]

1998 — Approval of Herceptin for HER2+ breast cancer[5]

PERSONALIZED MEDICINE

2000 — Next-Generation Sequencing becomes commercially available[6]

2003 — Roche launches AmpliChip CYP450[7]

2014 — FDA approves Lynparza with CDx[8]

2016 — FDA approves Medtronics' artificial pancreas[9]

DIGITAL MEDICINE

2017 — FDA approves first digital medicine system[10]

FDA clears Pear Therapeutics' reSET®[11]

REFERENCES: 1. Drugs@FDA: FDA-Approved Drugs. Accessdata.fda.gov. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Published 2022. Accessed January 18, 2022. **2.** Becton Dickinson Takes A Plunge With Safer Needles By gearing up to make devices like these, the company is giving its profits a shot in the arm. - October 1, 2001. Money.cnn.com. https://money.cnn.com/magazines/fortune/fortune_archive/2001/10/01/310912/index.htm. Published 2022. Accessed January 18, 2022. 3. Ourstory.jnj.com. https://ourstory.jnj.com/palmaz-schatz-balloon-expandablestent#:~:text=PALMAZ%2DSCHATZ%20Balloon%2DExpandable%20Stent%2C%201994&text=The%20tube%2Dshaped%20coronary%20device,to%20and%20from%20the%20heart. Published 2022. Accessed January 18, 2022. **4.** Global HIV/AIDS Timeline. KFF. https://www.kff.org/global-health-policy/timeline/global-hivaids-timeline/. Published 2022. Accessed January 18, 2022. **5.** Drugs@FDA: FDA-Approved Drugs. Accessdata.fda.gov. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=103792 Published 2022. Accessed January 18, 2022. 6. Barba M, Czosnek H, Hadidi A. Historical perspective, development and applications of next-generation sequencing in plant virology. Viruses. 2014;6(1):106-136. Published 2014 Jan 6. doi:10.3390/v6010106 **7.** https://www.sec.gov/Archives/edgar/vprr/0302/03024076.pdf. Published 2022. Accessed January 18, 2022. **8.** Accelerated Approval for Olaparib for Advanced Ovarian Cancer, along with Companion Diagnostic Test, Oncology Times: January 25, 2015 - Volume 37 - Issue 2 - p 14 doi: 10.1097/01.COT.0000460541.71340.08 **9.** FDA approves first automated insulin delivery device for type 1 diabetes. U.S. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-approves-first-automated-insulin-delivery-device-type-1-diabetes. Published 2022. Accessed January 18, 2022. 10. Drugs@FDA: FDA-Approved Drugs. Accessdata.fda.gov. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process Published 2022. Accessed January 18, 2022. **11.** PEAR Obtains FDA Clearance of the First Prescription Digital Therapeutic to Treat Disease - Pear Therapeutics. Pear Therapeutics. https://peartherapeutics.com/fda-obtains-fda-clearance-first-prescription-digital-therapeutic-treat-disease/. Published 2022. Accessed January 18, 2022.

DTx are increasingly available

> Digital therapeutics (DTx) deliver medical interventions directly to patients **using evidence-based, clinically evaluated software** to treat, manage, and prevent a broad spectrum of diseases and disorders.[1]
>
> - DTx Alliance

Globally, as of 2020,

25 DTx products
have been granted market authorization.

Another 23 are commercially available, with indications predominantly in the **mental health** and **behavior modification** areas.

An additional 89
are in earlier stages of development and evidence generation.[2]

REFERENCES: 1. Digital Therapeutics Alliance. Understanding DTx: a new category of medicine. https://dtxalliance.org/understanding-dtx/. Published 2021. Accessed December 23, 2021. **2.** IQVIA. Digital health trends 2021. https://www.iqvia.com/insights/the-iqvia-institute/reports/digital-health-trends-2021. Accessed December 20, 2021.

The National Institute of Mental Health (NIMH) has recognized the need to integrate technology into mental healthcare

Strategic goals established by the NIMH for 2021-2026 include:

Increasing access to evidence-based interventions through the expanded use of technology

Expanding access to care through technology is a key goal of the NIMH, specifically:

- Developing psychosocial device-based therapeutic candidates

REFERENCE: 1. Professional Coalition for Research Progress/National Institute of Mental Health. The NIMH strategic plan for research outlines the institute's research goals and priorities over the next five years. https://www.nimh.nih.gov/about/strategic-planning-reports. Accessed August 10, 2021.

Digital solutions differ in their levels of regulatory validation

MEDICAL PROFESSIONAL AND CAREGIVER USE:

DIGITAL PHARMACIES
Solutions that offer prescription sorting, packaging, and same-day prescription delivery services.

DIAGNOSTIC TOOLKITS
Guided medical exams with a remote physician/healthcare professional from anytime and anywhere.

DIGITAL BIOMARKERS
Physiological and behavioral measures, generated by patients and collected through a variety of digital tools.

REMOTE MONITORING
Devices and software that help patients self-manage conditions and allow healthcare professionals to monitor patients remotely.

CARE COMPANIONS
Digital solutions designed to support the care needs of patients during treatment and rehabilitation.

TRIAGE TOOLS
Software that guides patients on their care pathway and provides support for frontline workers.

CAREGIVER TOOLS
Digital solutions designed to help caregivers perform daily operations more effectively in their workplace.

Level of regulatory validation & scrutiny >

PATIENT USE:

PRESCRIPTION
DIGITAL THERAPEUTICS (PDTs)

FDA authorized software as medical device (SaMD), evaluated and clinically validated for safety and efficacy. Delivers disease-specific, evidence-based treatment. **By Rx Only.**

NONPRESCRIPTION
DIGITAL THERAPEUTICS

Non-FDA authorized SaMD, with limited clinically validated safety and efficacy. Delivers **disease-specific** treatment.

WELLNESS
APPS

Nonregulated solutions designed to coach, educate, and provide feedback to help people lead healthier lives and avoid stress-related illness.

Rx, medical prescription.

REFERENCE: 1. Dtxalliance.org. https://dtxalliance.org/wp-content/uploads/2021/01/DTA_FS_DTx-Product-Categories_010521.pdf. Published 2022. Accessed January 18, 2022.

PDTs are clinically validated tools designed to support treatment engagement

Level of regulatory validation & scrutiny

DIGITAL MENTAL HEALTH TOOLS (DMHTS)

PRESCRIPTION
DIGITAL THERAPEUTICS (PDTs)

FDA authorized software as medical device (SaMD), evaluated and clinically validated for safety and efficacy. Delivers disease-specific, evidence-based treatment. **By Rx Only.**[1]

NONPRESCRIPTION
DIGITAL THERAPEUTICS

Non-FDA authorized SaMD, with limited clinically validated safety and efficacy. Delivers **disease-specific** treatment.[1]

WELLNESS
APPS

Non-regulated solutions designed to coach, educate, and provide feedback to help people lead healthier lives and avoid stress-related illness.

PROVIDER-DRIVEN INITIATIVES

- Clinician training in behavioral and primary care
- Patient content (pamphlets, web sites,publications, etc.)
- Electronic medical record (EMR) functionality to support workflow integration

Patient use of DMHTs was **2 to 3 times** the expected rate of similar apps downloaded from general app stores. Up to **1/3** of clinician-referred DMHT users were still actively **using apps 3 months after initiation**[2]

REFERENCES: 1. Dtxalliance.org. https://dtxalliance.org/wp-content/uploads/2021/01/DTA_FS_DTx-Product-Categories_010521.pdf. Published 2022. Accessed January 18, 2022. **2.** Histon, T. Delivering health care through digital mental health ecosystems. Accessed January 3, 2022, from https://www.psychiatrictimes.com/view/delivering-health-care-through-digital-mental-health-ecosystemsRx, medical prescription

PDTs may help overcome a variety of patients' obstacles to treatment

1 DIAGNOSIS OF MDD

Innovative treatment tools may enable patients with MDD to access treatment more quickly

2 PHARMACOLOGIC INTERVENTION

PDTs may bridge the gap between patient and provider

3 PSYCHOTHERAPY

PDTs may be beneficial to patients who cannot easily access providers

4 ACUTE CARE

Innovative interventions may have potential cost-savings with improved treatment outcomes

Innovative interventions may increase the percentage of patients successfully treated for MDD[2]

How do **YOU** anticipate this will impact you and your plan?

The above is a representation of how PDTs may support overcoming treatment obstacles, identified in the previous section

ER, emergency room.

REFERENCES: 1. Ta J. et al. Health Care Resource Utilization and costs associated with nonadherence and nonpersistence to antidepressants in major depressive disorder. *Journal of Managed Care & Specialty Pharmacy.* 2021;27(2):223-239. doi:10.18553/jmcp.2021.27.2.223
2. Greenberg PE, et al. *Pharmacoeconomics.* 2021;39(6):653-655.

SaMDs must follow one of these regulatory pathways to obtain marketing authorization

WITHOUT PREDICATE
FOLLOWS THE DE NOVO PATHWAY

If a predicate device with the same intended use cannot be identified, or if the new device's different technological characteristics raise different questions of safety or effectiveness, a manufacturer may submit a De Novo request, either after receipt of a "Not Substantially Equivalent" (NSE) letter or by directly requesting classification through the De Novo process.[1]

The De Novo review standard is the reasonable assurance of safety and effectiveness.

Marketing authorization via the De Novo classification process is referred to as... **GRANTED**

WITH PREDICATE
FOLLOWS THE 510(k) CLEARANCE PATHWAY

When the FDA determines that a new device is substantially equivalent (SE) to a legally marketed, and previously approved (predicate) device, the new device is subject to the same requirements as the predicate device.[2]

The 510(k) review standard is comparative. Nonetheless, the principles of safety and effectiveness underlie the substantial equivalence determination.

Marketing authorization obtained via the 510(k) process is referred to as... **CLEARED**

REFERENCES: 1. Fda.gov. https://www.fda.gov/media/72674/download. Published 2021. Accessed January 11, 2022. **2.** Fda.gov. https://www.fda.gov/media/82395/download. Published 2014. Accessed January 11, 2022.

Prescription Digital Therapeutics (PDTs) are subjected to FDA regulation and can be authorized as a device

Software as a Medical Device

Software intended to be used for one or more medical purposes, intended to perform these purposes **without** being part of a hardware medical device[1]

PDTS ARE CONSIDERED SOFTWARE AS A MEDICAL DEVICE (SaMD) AND NEED TO MEET GENERAL CONTROLS

These controls are the basic authorities of the Medical Device Amendments that provide the FDA with the means of regulating devices to ensure their safety and effectiveness.

Additional **special controls** must also be met, as general controls are considered insufficient to classify these devices.

The special controls for SaMD are[2]:

- **Clinical data describing and validating** the device and its purpose
- **The label must include** instructions for use, list of compatible devices, and a warning that the device is not intended for use as a standalone therapy and does not represent a substitution for the patient's medication
- Physician and patient **labeling must include** a summary of the clinical testing with the device
- **Software description** including verification, validation, and hazard analysis

REFERENCES: 1. Software as a medical device (SaMD): Key definitions. International Medical Device Regulators Forum. https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf. Published December 18, 2013. Accessed February 2, 2022.
2. Title 21--Food and Drugs Chapter I--Food and Drug Administration Department of Health and Human Services Subchapter H - Medical Devices. CFR - Code of Federal Regulations Title 21. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=882.5801. Published December 27, 2017. Accessed January 7, 2022.

Summary

PDTs may hold promise in the treatment of MDD

Despite advances in treatment, MDD remains a costly and growing population health issue

- Some patients experience less than optimal response to current treatments
- Psychotherapy may be difficult to access due to time constraints or coverage limitations, and may be impractical for some patients
- Provider shortages create significant barriers to treatment

THINK ABOUT DIGITAL

PDTs are FDA-authorized SaMD, evaluated and clinically validated for safety and efficacy

- PDTs may offer a feasible, stigma-reducing option for patients
- Flexible provider engagement may lead to more access to treatment
- PDTs are designed to address current barriers to treatment
- Consistent in approach and practical, this alternative may increase treatment participation

How could Prescription Digital Therapeutics add value for your members?

HCP, healthcare professional.

Otsuka

February 2022 20US22EUY0001