

Digital Health Trends 2021



INNOVATION, EVIDENCE, REGULATION, AND ADOPTION

JULY
2021

Introduction

Innovation in digital health tools, including mobile health apps and wearable sensors, bring new approaches to the management of health conditions. Digital therapeutics to treat human disease are being approved by regulatory agencies around the world and routes to reimbursement are being established as developers generate and submit high-quality data on effectiveness to payers and employers. Further, new digital biomarkers are being created using consumer wearables, with the intent to track elements of patient health remotely. As these digital tools begin to have a fundamental impact on patient care and influence clinical trial design, it is important to assess the innovation and evidence they contribute as well as the barriers to and facilitators of their adoption.

This study of digital health covers trends in four areas — innovation, evidence, regulation, and adoption — to assess how these new tools are becoming an entirely new therapeutic modality alongside traditional medicines and medical devices.

We analyze health-related mobile applications that are available to consumers on top app stores, along with shifts in the types of apps available. We further examine trends in the overall body of clinical evidence on app effectiveness, including the types of studies published over time, and use cases where high-quality evidence exists and select apps can be considered for inclusion into guidelines.

A pipeline of digital therapeutic products has also emerged, and we review aspects of their development, evidence generation and commercialization. Shifts in policy intended to encourage innovation and make these accessible to populations, including the new routes to approval and reimbursement being created around the world, are also explored.

Wearables that enable patient self-care and remote monitoring of patient health in real time as digital biomarkers are discussed, along with connected sensors used in clinical trials that are enabling decentralized trial designs.

Finally, we examine the roles of life sciences companies, payers, employers, and app developers in the commercialization of these products, as well as barriers to reimbursement and adoption.

The study was produced independently by the IQVIA Institute for Human Data Science as a public service, without industry or government funding. We gratefully acknowledge contributions of content from Andrea Girardello at 42matters, Marc Sluijs at DigitalHealth. Network; information provided by Megan Coder at DTX Alliance, Erik Henricson at UC Davis, Damiano Zanotto at SIT; and written and data contributions from Zuheir Jebawi, Julia Kern, Ann Skye, Michael Krupnick, Sara Pawley, Ashlea Pedersen, Katy Preciado, Burhan Shawl, David Tripi and many others at IQVIA.

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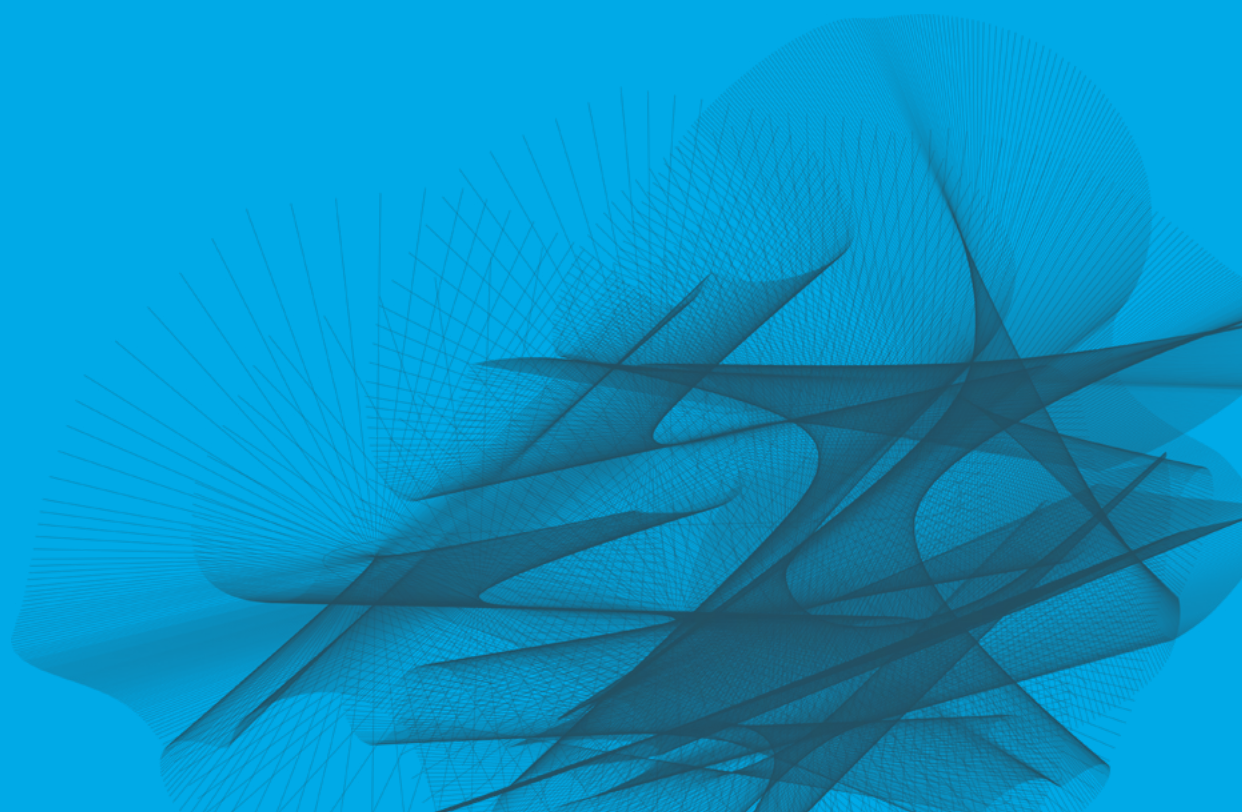
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Executive summary

The proliferation of digital health tools, including mobile health apps and wearable sensors, holds great promise for improving human health, bringing new approaches to the management of health conditions and advancing human data science. Multiple types of digital health tools contributed to mitigating the impact of the pandemic and are now an established part of the digital health landscape.

Accelerating innovation in digital health tools:

Health-related mobile applications available to consumers on top app stores worldwide now surpass 350,000, with more than 90,000 digital health apps added in 2020 — an average of more than 250 apps per day. Consumer apps are the most widely available and used digital health tools, shifting increasingly toward disease-specific uses, but downloads and use are heavily skewed and average quality is middling, so careful selection by consumers is required. While the majority of mobile health apps available are general wellness apps, across a sample of high-quality apps, the number of apps for health condition management are increasing and many are being developed for narrower disease segments. Mental health, diabetes and cardiovascular disease-related apps now account for almost half of disease-specific apps.

This rapid introduction of apps, alongside a consumer wearables market building new abilities to detect digital biomarkers of health and remotely monitor patients, provides evidence of digital health's accelerating innovation. While 55% of consumer wearables still focus on activity and fitness monitoring, the remainder of devices enable data generation and capture across a broad range of health parameters, some offering significant health impact. For instance, during the pandemic people self-monitored their oxygen saturations using pulse oximeters, and spikes in downloads of health apps tied to those devices occurred in waves around the globe, coinciding with peaks in virus cases and lockdowns.

Sensors and digital biomarkers are also being incorporated into the design of clinical trials for pharmaceuticals and medical devices; enabling decentralized and hybrid trials incorporating home visits, reducing the burden on patients participating in clinical trials and accelerating clinical trial timelines. Digital biomarkers to remotely monitor patient health are being validated by feasibility studies with the intent to incorporate them into clinical trials and patient care. At least 438 feasibility studies have examined 933 distinct biomarkers, and 96 clinical trials have used digital biomarkers as endpoints. More than half of feasibility trials are in neurology, musculoskeletal disorders, and sleep.

Advancing regulatory approval and commercialization:

Digital therapeutics (DTx) and digital care (DC) products and tools — which incorporate software as a means to treat, prevent or manage specific diseases or conditions — have been proliferating, and more than 250 such products are now identified, including about 150 products that are commercially available. DTx typically focus on a narrow clinical indication and generate evidence of clinical efficacy, following a development path that normally requires market authorization by a regulatory body and sometimes a prescription from a provider. DC products, almost 100 of which are now available commercially, include care platforms and tools which typically address broadly-defined clinical conditions such as diabetes and can be tailored or personalized to individual needs, requiring active involvement from providers or coaches. As regulators recognize the role DTx and DCs can play in patient care, the creation of regulatory and reimbursement pathways for approved apps is increasing globally, enabling them to play a growing role impacting human health. At least 25 DTx products have been granted market authorization through regulatory processes and another 23 are commercially available, with indications predominantly in the mental health and behavior modification areas, and an additional 89 are in earlier stages of development and evidence generation. Many of these rely on a digital

version of cognitive behavioral therapy as part of their therapy. By offering care beyond traditional in-person interactions, these mental health apps are likely to make mental healthcare more accessible. Although only an intermediate level of adoption has yet occurred, government policies around the world have become more supportive of digital therapeutics, and payers are being challenged to ensure routes to reimbursement.

Growing maturity of clinical evidence:

The overall body of clinical evidence on app effectiveness has grown with more than 2,000 studies published since 2007, including almost 1,500 published in the past five years. Although the annual number of studies published on digital health began to slow in 2018 and continued to decline through 2020, the number of systematic reviews and meta-analyses notably have both continued to grow, jointly reaching 14% of published studies in 2020 and indicating a growth in the maturity of evidence and a consolidation of thinking about the use of apps. Indeed, evidence now supports the inclusion of digital health tools in treatment guidelines for an expanded set of health indications; these include cardiovascular applications (e.g., screening for atrial fibrillation and cardiac dysrhythmias, CHF management, cardiac rehabilitation, and hypertension), use tied to behavioral modification (e.g., medication management, exercise, healthy eating and weight management, and smoking cessation) and management of some chronic conditions (e.g., pain and infectious and parasitic diseases, including HIV/AIDS). However, independent organizations continue to highlight the need for larger and more robust randomized controlled trials (RCTs) that follow patients for longer times and report between-group differences in benefit, assessments of usability, and user-retention to determine the durability of their clinical effect, and evidence of cost-effectiveness that can be analyzed versus standard of care.

Overcoming barriers to adoption:

Multiple commercialization pathways now exist for digital health tools, providing more opportunities to app manufacturers to realize an economic return on investment for those tools supported by robust evidence and user demand. Four broad commercial models are now in place and being used to generate payment or reimbursement for digital tool developers: direct-to-consumer, value-based contracting, “device-like” reimbursement, and “drug-like” reimbursement models. While software developers of digital health apps initially commercialized through public app stores under a direct-to-consumer business model, apps providing the most significant health benefits focus increasingly on payers and employers. In the midst of COVID-19, employers have built relationships with digital health app developers either directly or through payers to safeguard the wellness and mental health of their employees. Self-insured employers have also begun to incorporate digital health apps into their health benefits, looking to offset the key drivers of their health costs. However, the lack of a standardized contracting and app-assessment process is a barrier for employers, making the process time-consuming. A framework to accelerate employer adoption identifies steps toward an ideal state.

In response to growing interest from employers and members, some payers have built digital formularies. However, a number of barriers still exist to widespread adoption and are slowly being tackled, including integration into physician workflows, a lack of standard approaches to app assessment and ratings, guidance and templates for DTx formulary submissions, standards for the prescribing and dispensing of DTx through the pharmacy benefit, as well as reimbursement by Medicare. As medical and regulatory bodies around the world see growing value in these treatments, they are creating novel policies to encourage innovation and make them accessible to their populations. Reimbursement is a final frontier, where payers are being challenged to, and in some countries are advancing policies to, ensure routes to reimbursement.

Digital apps in the health experience

- + **Multiple types of digital health tools contributed to mitigating the impact of the pandemic and are now established part of the digital health landscape.**
- + **Consumer apps remain the most widely available and used digital tool with over 90,000 new digital health apps added in 2020 — an average of more than 250 apps per day — resulting in over 350,000 apps currently available.**
- + **Apps are increasingly focused on health condition management rather than wellness management, with the former now accounting for 47% of all apps in 2020, up from 28% in 2015, and with mental health, diabetes and cardiovascular disease-related apps accounting for almost half of disease-specific apps.**
- + **Downloads and use of apps are heavily skewed with 83% of apps being installed fewer than 5,000 times and collectively accounting for less than 1% of total downloads, while a cohort of 110 apps have each been downloaded more than 10 million times and in aggregate make up almost 50% of total downloads.**
- + **The COVID-19 pandemic had significant impacts on the apps individuals downloaded and used in 2020, including telemedicine apps such as Doximity, where downloads increased 38x, along with exercise apps that helped patients stay healthy, mental health apps to manage depression, anxiety or suicidal thoughts, and blood pressure apps.**
- + **Across a sample of apps, quality varies widely but more than two-thirds of app use categories now include apps of the highest quality, including those for managing most chronic conditions, although average app quality is often middling, suggesting careful app selection by consumers is required.**

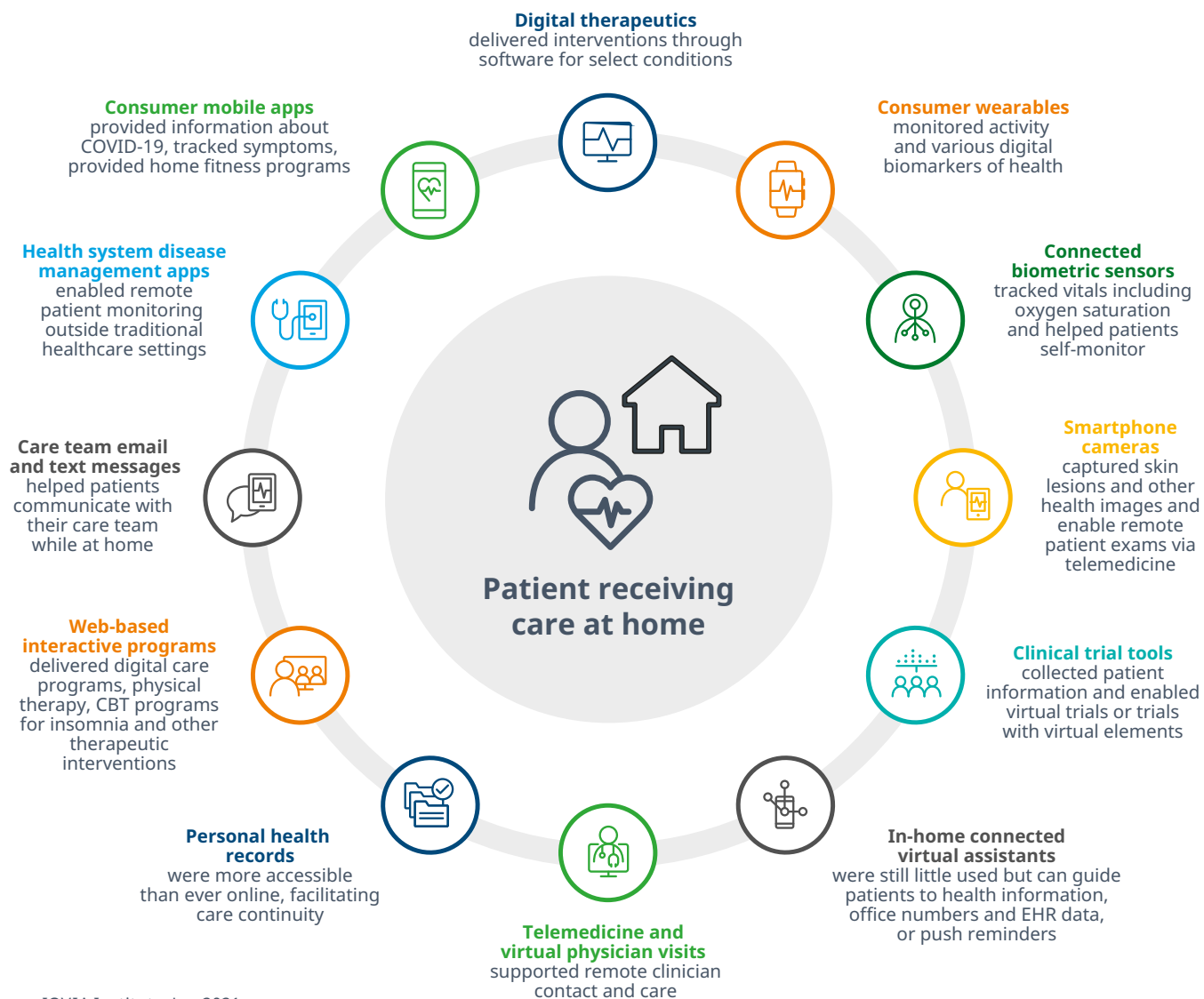
Digital health can be defined in varying ways, but for the purposes of this report, it refers to the use of connected mobile devices — such as mobile phones, tablets, consumer wearables, connected biosensors, virtual reality devices, and in-home virtual assistants — to improve health. The value of these tools typically derives from their abilities to communicate information through the internet, web, Bluetooth or text messaging, to provide continuous monitoring of human health metrics or display health data more clearly.

THE IMPACT OF COVID-19

The COVID-19 pandemic has rapidly thrust patients and physicians into a world of digital health tools. By severing patients from face-to-face physician interaction for periods, it has shifted care provision dramatically to telemedicine for remote or virtual visits.¹ At the same time, a concerned public turned to digital media on their smartphones as a source of information on COVID-19 and sought advice to keep themselves safe. They similarly turned to apps, wearables and digital media to help them exercise and maintain their health (see Exhibit 1).

Digital health had been slowly becoming part of the therapeutic paradigm alongside traditional medicines before COVID-19, and this process has been somewhat accelerated by regulatory agencies adapting to unprecedented times. For instance, in the U.S. during the pandemic, the U.S. Food and Drug Administration (FDA) recognized that digital therapeutics could provide value in addressing mental health and wellbeing during quarantine and isolation, and waived some requirements to enable their distribution and use.² Overall, the pandemic has amplified the need for care provision and remote patient monitoring outside traditional healthcare settings, patient self-monitoring using various connected devices, and digital therapeutics that can deliver interventions via apps.

Exhibit 1: Digital Health Tools in the Patient Journey During the COVID-19 Pandemic



Source: IQVIA Institute, Jun 2021

*"In the context of the COVID-19 public health emergency, the use of digital health technologies, including software as a medical device or other digital therapeutics solutions, may improve mental health and well-being of patients with psychiatric conditions during periods of shelter-in-place, isolation, and quarantine. In addition, by reducing patient contact with, and proximity to, healthcare providers, [they] can ease the burden on hospitals, other healthcare facilities, and healthcare professionals who are experiencing increased demand due to the COVID-19 public health emergency."*²

— U.S. Food and Drug Administration

INVESTMENT IN DIGITAL HEALTH

With this growing importance, the digital health space has seen an increase in investment, with a record \$24 billion of investments in digital health in 2020, and a new monthly record in December 2020 of \$3.4 billion, driven by continued acceleration of mergers and acquisitions and a growing impact of private equity investors (see Exhibit 2).³ Average deal sizes have also been reported as increasing significantly to \$45.9 million — up from an average of \$31.7 million in 2020.⁴ These trends are likely to continue as opportunities expand for mobile technologies to intervene in patient health.

INNOVATION IN MOBILE APPS

App trends

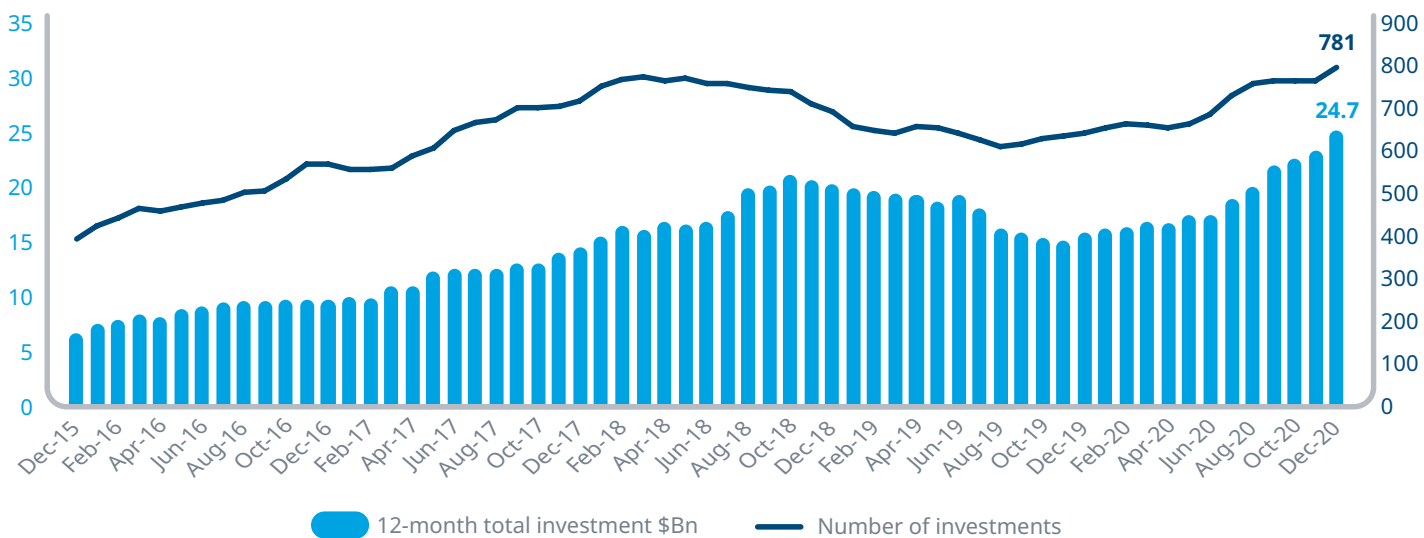
Digital health apps continue to proliferate, with more than 350,000 health and fitness or medical apps now available to consumers worldwide from the Apple Store and Google Play. However, there has been a leveling off of app growth since 2017, with only a 10.3% increase in the number of apps available compared to nearly four years ago (see Exhibit 3). However, this number

significantly understates the dynamics in this period. In 2020 alone, more than 91,000 new apps were introduced to the stores — an average of 251 apps per day.

The net gain of 32,736 apps in the period between July 2017 and June 2021 reflects a release of over 351,000 new apps during that period, with over a third of these (n=116,481) already removed from the store, and the removal of nearly twice as many older apps (released prior to 2017) during this same period. Between app stores more actively purging bad apps that don't function as intended, don't follow guidelines, or are out-of-date, and the ongoing cost for app developers to continually update their apps to new operating systems, many apps that are not making money or are seeing only a few installs eventually drop from the store (see Exhibit 4).^{5,6} Indeed, the attrition of health apps released from 2010-2018 in stores is much more significant than those from recent years, with the loss of about 50-75% of all apps released in those years.

Among apps pulled from app stores, 51% had under 100 downloads, while apps with large numbers of downloads were less likely to be removed, indicating that developers

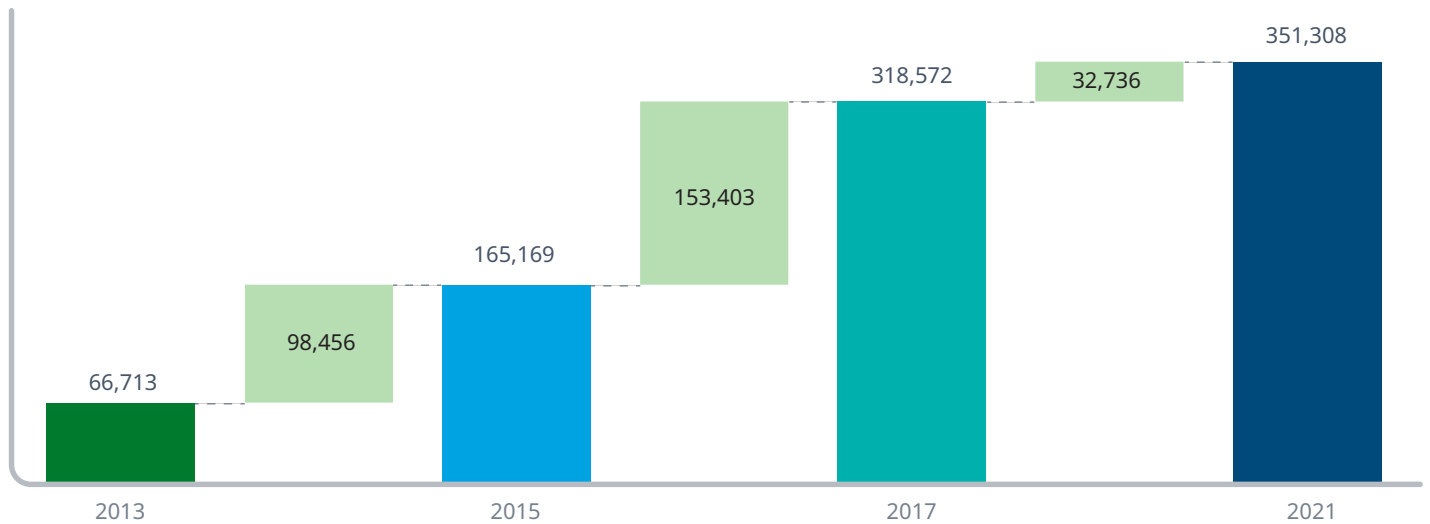
Exhibit 2: Investment in Digital Health Over Five Years Based on 12-month Rolling Totals, \$Bn



Source: Sluijs M. DigitalHealth.Network. \$24Bn invested: Don't look back! Digital Health MarketScan 118th Ed Dec 2020

Notes: Chart displays global data (including US/EU/APAC) and 12 month rolling totals in each period since 2015. Includes Digital Health broadly ranging from connected sensors, analytical technology, patient facing solutions including digital therapeutics, life science information technology (IT) and clinical trial data collection technology, healthcare IT. Includes Venture Capital Investment in private companies with a value above \$1M and excludes private equity buyouts and IPOs.

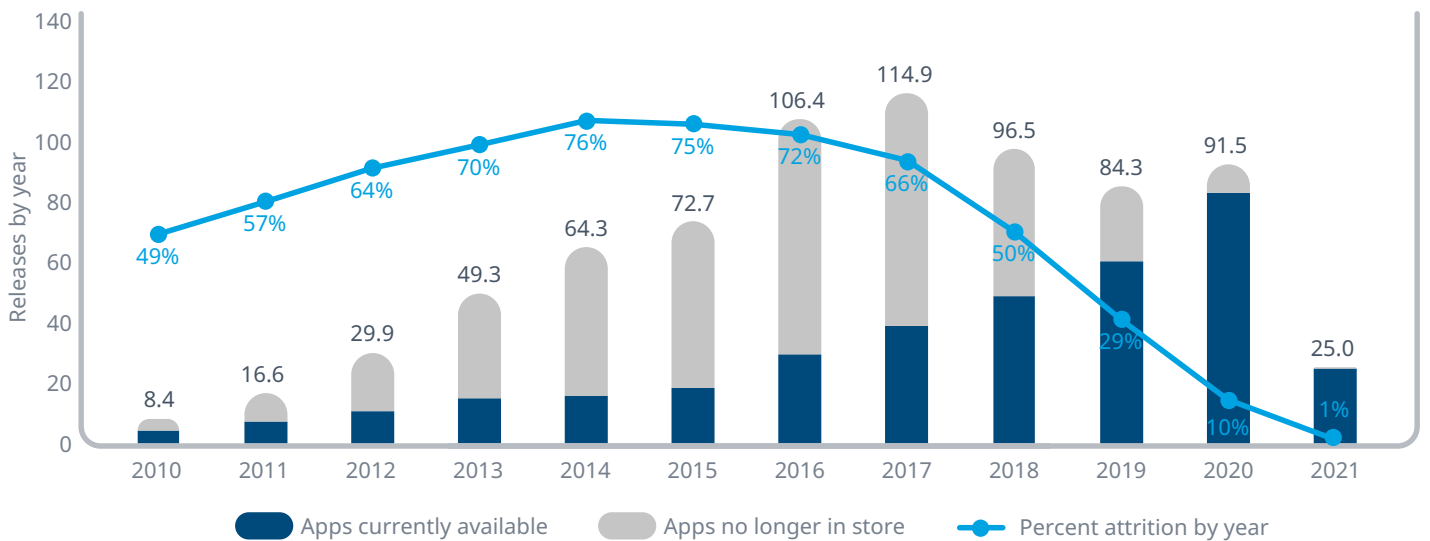
Exhibit 3: Number of Digital Health Apps 2013–2021



Source: 42 Matters, Jun 2021 and Jul 2017; Mevvy, Jun 2015; IQVIA AppScript App Database, Jun 2021; IQVIA Institute, Jun 2021

Notes: Includes digital health apps that are publicly available to consumers and categorized as Health & Fitness or Medical. Apps that have been removed from stores are not included.

Exhibit 4: The Release and Removal of Health Apps from Stores Over Time



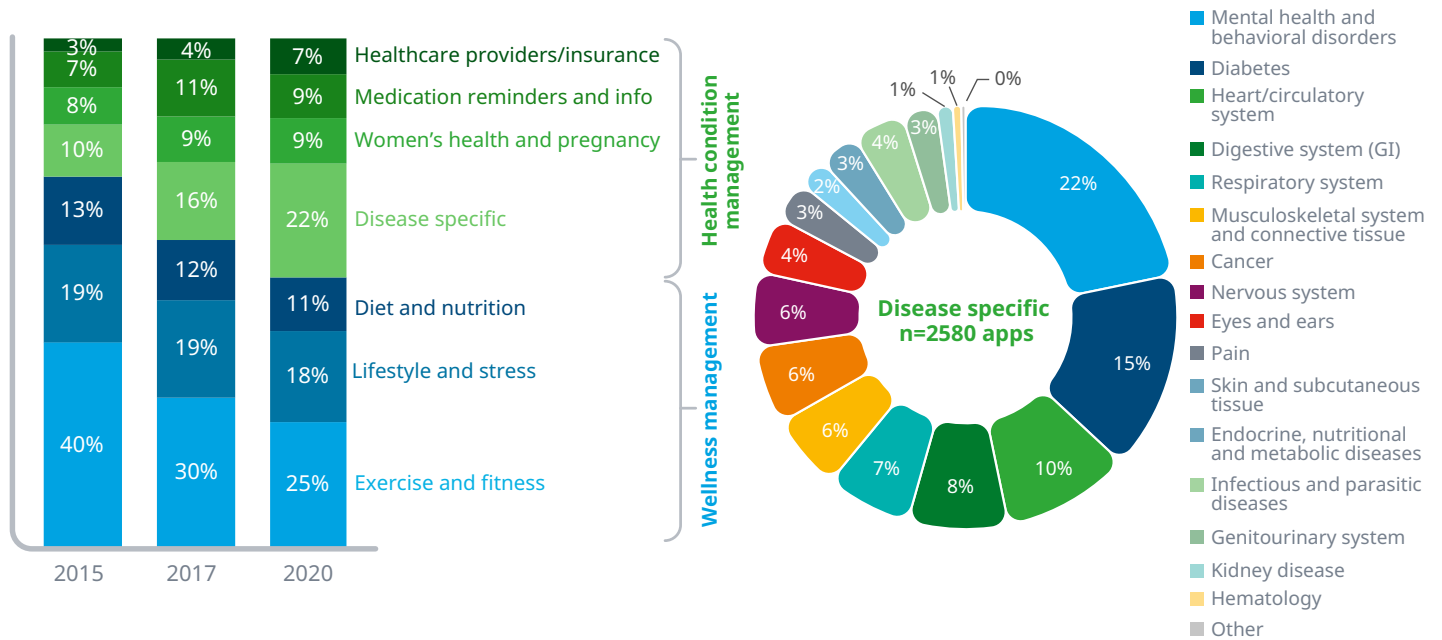
Source: 42 Matters, Jun 2021 and Jul 2017; Mevvy, Jun 2015; IQVIA AppScript App Database, Jun 2021; IQVIA Institute, Jun 2021

Notes: Includes digital health apps that are publicly available to consumers and categorized as Health & Fitness or Medical.

not only need to build apps but also create a plan to drive uptake and differentiate from the noise. Additionally, 61% of all removed health apps were never updated, with another 25% of apps being updated only for a year-period prior to removal, indicating both that apps rapidly succeed or fail, and that some developers cease to update

them, causing them to fall into disrepair. Ultimately, this indicates that developers need a plan to maintain and iterate on the apps they build to be successful — listen to user feedback, make improvements, improve usability, fix bugs, and support new OS versions. Indeed, 70% of the apps that remain on the store have been updated,

Exhibit 5: Digital Health Apps by Category and Disease State in 2021



Source: 42 Matters, Jun 2021 and Jul 2017; Mevvy, Jun 2015; IQVIA AppScript App Database, Jun 2021; IQVIA Institute, Jun 2021
 Notes: Chart displays percent of categorizations. Numbers may not sum due to rounding; 2020 data includes 11,543 unique apps with 11,569 categorizations. 2017 data includes 11,216 unique apps with 11,249 categorizations. 2015 data includes 24,012 apps with 24,088 categorizations. 2020 view removes apps pending review.

and of the 30% that haven't, 90% were released no more than three years ago, indicating they are still relatively up-to-date. For those apps on the store that have issued updates, 56% of those updated within the past year and 85% within the last three years, thereby keeping the app fresh and usable.

Apps present in the AppScript App Database (representative of the most widely used Digital Health apps by consumers, see Methodology) were analyzed by use category to understand the current landscape of digital health apps. Across the patient journey, digital health apps can be divided into two main categories: those focused on "wellness management," which facilitate tracking and modification of fitness behaviors, lifestyle and stress and diet, and those which specifically focus on "health condition management," which supply information on diseases and conditions, enable access to care, and aid treatment such as through medication reminders. The mix of apps has shifted since 2015, with 47% of apps now focused on health condition management, up from 27% in 2015, and wellness

management (especially exercise and fitness apps) declining in relative representation (see Exhibit 5). The relatively lower investment by developers in exercise and fitness apps in this category may reflect the emergence of established apps in these categories and, indeed, among the top consumer apps.

Among the health condition management apps, the largest categories continue to focus on chronic conditions such as mental health and behavioral disorders, which account for 22%, followed by diabetes (15%) and heart and circulatory system apps (10%). Though mental health and behavioral disorders are the leading category, its 22% represents a decline from 28% in 2017, and apps for autism and "augmentative and alternative communication" (AAC), and panic, depression and anxiety continue to dominate. Digestive system, respiratory, musculoskeletal system, cancer and nervous system disorders also account for a significant proportion of health condition management apps, with digestive system apps among the top categories for the first time (shifting from 4% to 8%).

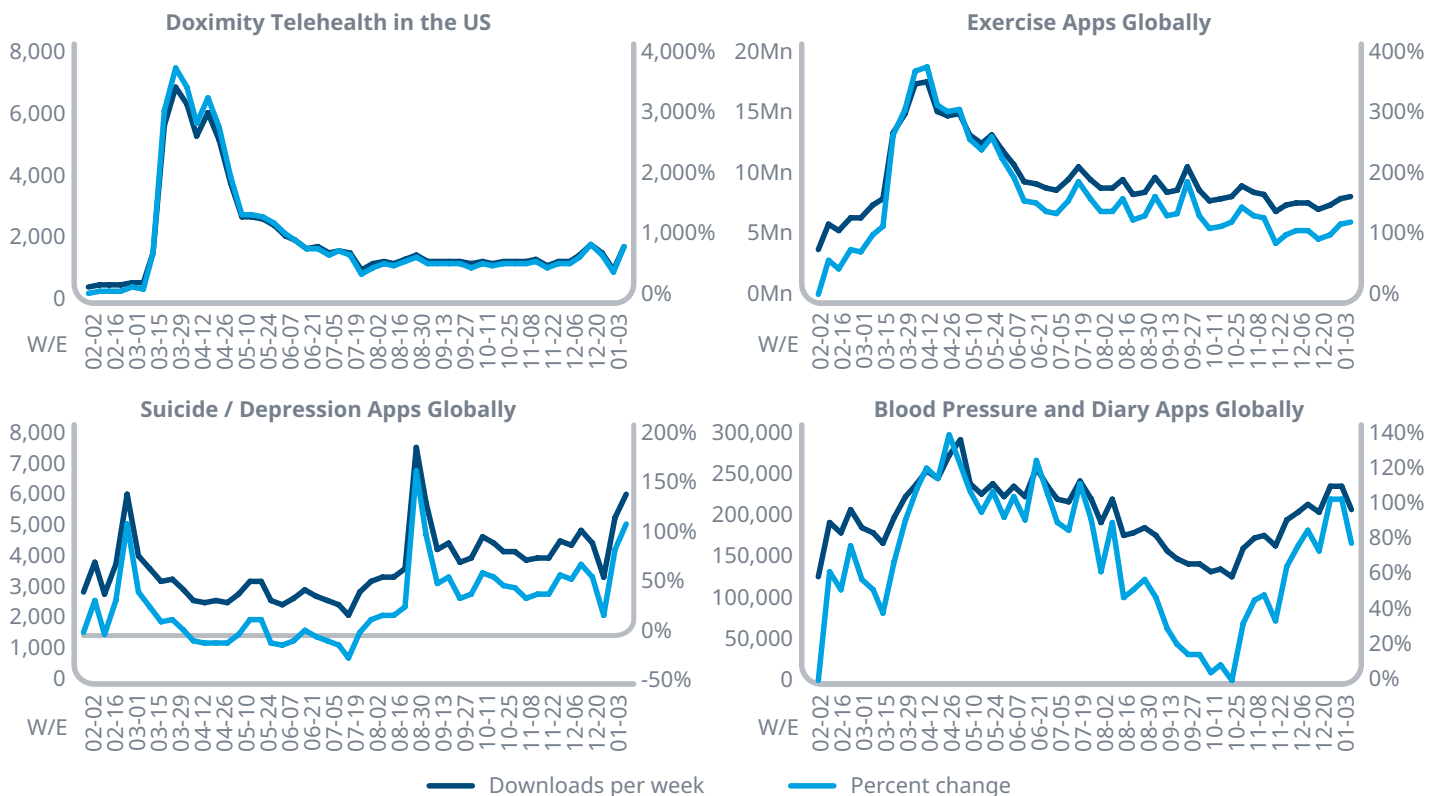
The significant growth seen for digestive system disorder apps was driven in part by apps to help patients adjust their diet to aid irritable bowel syndrome (IBS) and celiac disease. Respiratory apps also grew as a category from 5% to 7% of all apps, with growth seen in those focusing on asthma, COPD and inflammatory respiratory illness. Smaller categories such as apps for genitourinary system, kidney disease and infectious and parasitic diseases also more than doubled in representation over the past few years. Among these, a quarter of all infectious and parasitic disease apps in the AppScript data were COVID-19-focused, with no apps other than COVID-19 apps released into the category in 2020, revealing the extent to which the pandemic predominated that year.

Mobile apps during COVID-19

The COVID-19 pandemic had significant impacts on the apps individuals chose to download and use in

2020, driven by widespread health anxiety, the search for health information, and the need to manage one’s health during the pandemic and periods of lockdown. This trend occurred across a number of health app categories, including telemedicine app downloads such as Doximity in the U.S., which surged 38x from baseline to approximately 7,000 downloads per week on just the Google Play Store (see Exhibit 6), while a set of four communication apps including Microsoft Teams and Zoom that were also used in part for telemedicine increased 23x — from 140,000 downloads to greater than 3.3 million downloads per week. Globally, exercise apps that helped patients stay healthy saw weekly downloads increase 5x from an already high baseline of 3.7 million, while apps specific to condition management such as suicide apps that helped those in need manage suicidal thoughts and depression, and blood pressure apps, increased more modestly, more than doubling.

Exhibit 6: Percent Change Over Baseline in Health App Downloads During COVID-19 2020–2021



Source: 42 Matters, Jan 23, 2021; IQVIA Institute, Feb 2021

Notes: Install data shown is from the Google Play app store only. Shows percent change versus week ending Feb 2, 2020. W/E = Week Ending.

App popularity

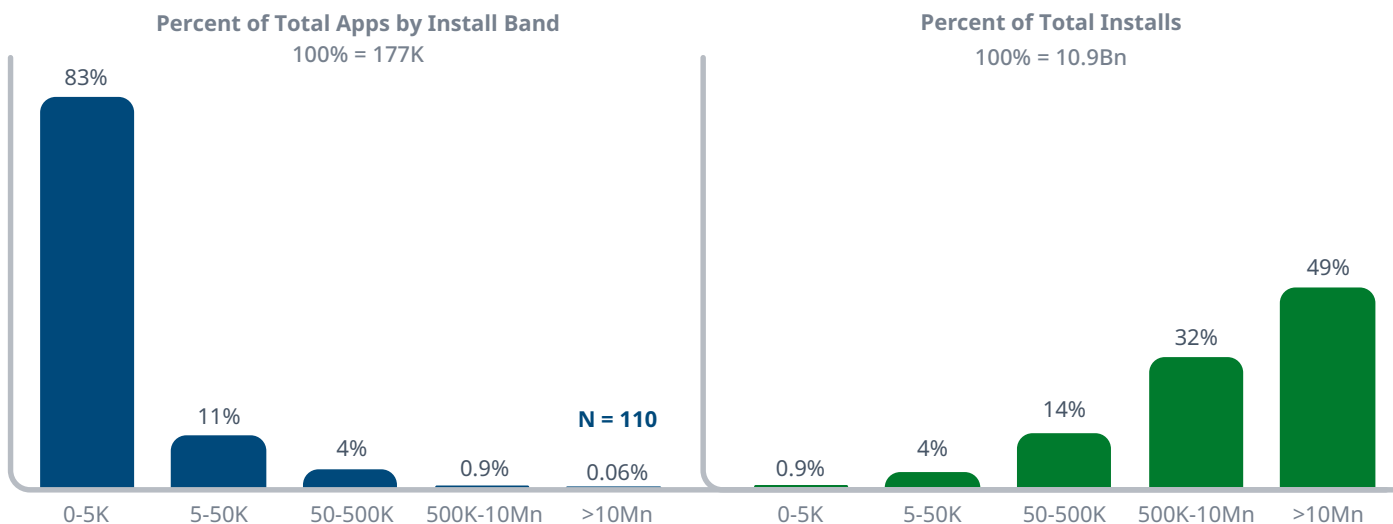
Most health and medical apps available on app stores have relatively few downloads and a small number are disproportionately popular. A full 83% of apps have been installed fewer than 5,000 times and account for less than 1% of total downloads (see Exhibit 7). A group of 110 apps have each been downloaded more than 10 million times and, in aggregate, account for almost 50% of total app downloads. These most popular apps include leaders in the health and fitness space that help users track their activity or connect to wearable devices like Fitbit, Mi Fit, Huawei Health, Google Fit, and Adidas Running App by Runtastic, many of which have been around since 2014, as well as other health tracking apps like Calorie Counter — MyFitnessPal and Home Workout and exercise apps. They also include women’s health ones including Period Tracker - Period Calendar Ovulation Tracker and Flo Period Tracker & Ovulation.

There is also another category that has emerged among top-downloaded apps, which are COVID-19 apps put out by governments or whose installation was supported nationally. For instance, an app released in India for COVID-19 called Aarogya Setu attained more than 100 million downloads in a short period as it was

broadly encouraged and its installation was required by the Indian Government as mandatory for all public and private sector office employees.^{7,8} Other national coronavirus-related apps also attained over 10 million downloads; these include Bluezone for contact detection (Vietnam), Corono-Warn-App (Germany), CoronApp — Colombia, Cuidar COVID-19 Argentina, Hayat Eve Siğar (Turkey), Tawakkalna (COVID-19 KSA, Saudi Arabia), and NHS COVID-19 (UK), among others.

Among medical apps, the most downloaded with more than 10 million installs include WebMD, which helps patients learn about conditions and their symptoms, and GoodRx, which helps patients find a pharmacy with the best drug price. They also include a number of government health system and reimbursement apps, including Mobile JKN, an app of the national healthcare insurance in Indonesia that connects patients with providers throughout Indonesia, MHRS Mobil which is a centralized hospital appointment system in Turkey, and Ameli, L'assurance Maladie in France. Similarly, 1mg - Online Medical Store & Healthcare App, an online pharmacy and healthcare app in India, facilitates telemedicine appointments with doctors, the booking of lab tests, and home delivery of medication.

Exhibit 7: Digital Health App Total Downloads in 2021



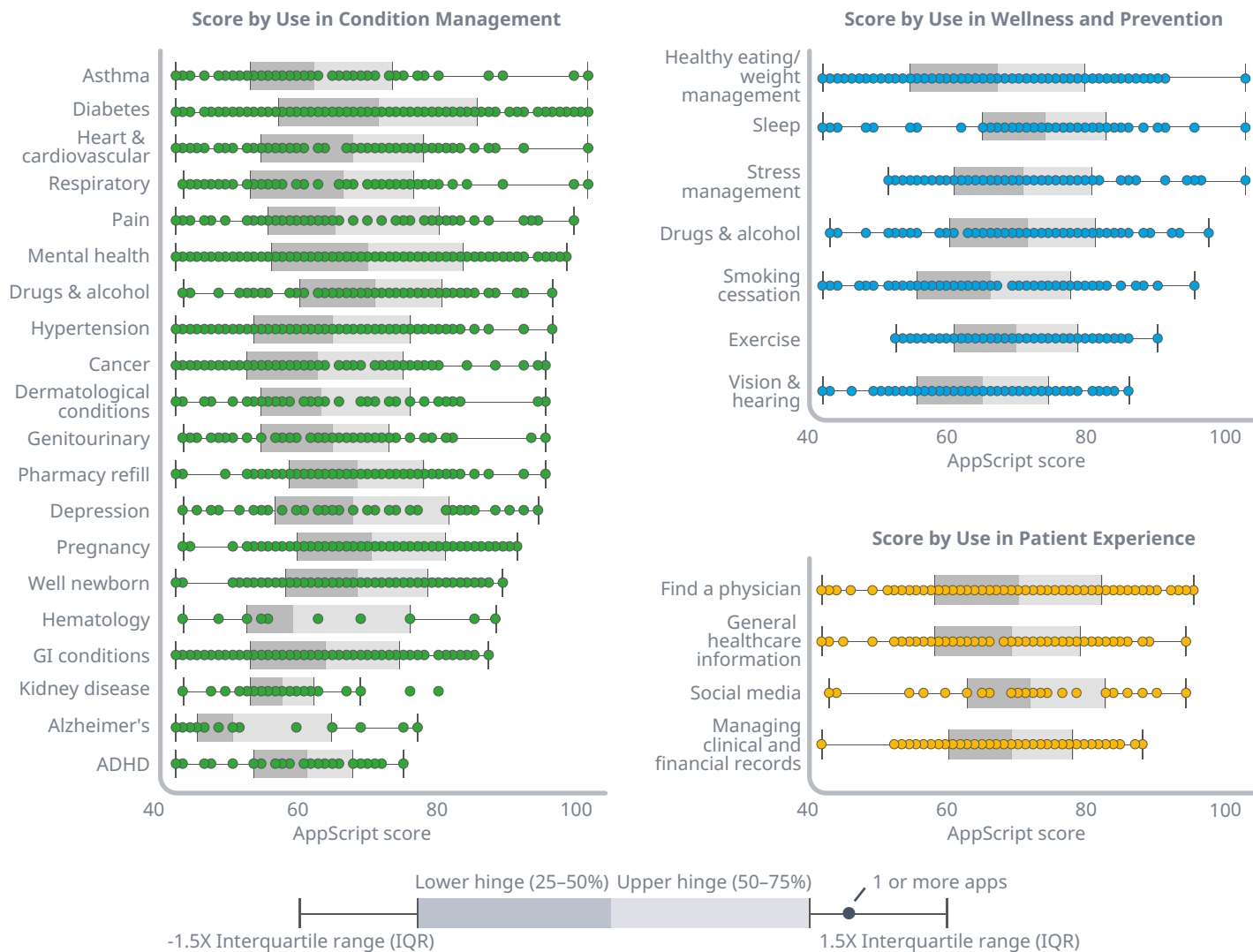
Source: 42 Matters, Jun 2021, Sep 2017; IQVIA AppScript Database, Jun 2021, Sep 2017; IQVIA Institute, Sep 2017
 Notes: Install data shown is from the Google Play app store only. App Store install data not available.

Assessing app quality

While these publicly-available apps assist patients across multiple domains — maintaining their health and wellness, understanding symptoms, seeking care, obtaining information post-diagnosis, and monitoring health conditions and prescriptions — most of these apps are not regulated by the FDA.⁹ Though app developers are not allowed to make claims in the United States and other geographies to treat, cure or diagnose disease without first gaining market authorization as a medical device, the quality of apps across these domains range significantly.

One approach that has therefore been developed to measure the quality of apps is the AppScript Score (see Methodology section and Exhibit 35 for quality rating methodology). While a large number of apps of varying quality are available in each category, more than two-thirds (22/31) of displayed app categories (see Exhibit 8) now include apps of the highest-quality, with an AppScript Score >90. These include most chronic conditions such as respiratory disorders and asthma, diabetes, heart and cardiovascular conditions, hypertension, pain management, mental health and depression, cancer, dermatology, and genitourinary

Exhibit 8: Distribution of AppScript Scores by Digital Health App Category



Source: IQVIA AppScript App Database; Jun 2021

conditions. Indeed, only nine of the use categories fall short of this highest bar — notably including apps for the management of ADHD, Alzheimer's and kidney disease as well as newborn care — although all use categories now include high-quality apps (with an AppScript Score >75). Although each category generally has at least one high-quality app, average app quality is often middling. This implies that while high-quality apps exist, careful app selection is required to ensure quality.

Top apps in select categories

Among the categories with highest scoring apps is diabetes, where both stand-alone apps and those integrated with regulated medical devices exist. Among the top apps in the category is OneTouch Reveal (AppScript Score=100), which helps patients manage their diabetes by tracking blood glucose averages, food consumption, medication use, and activity data. It further synchronizes data automatically with the OneTouch Verio Flex blood glucose meter and provides alerts for high/low glucose readings.¹⁰ Some stand-alone apps, such as mySugr (AppScript Score=100), have focused on 'gamification' to encourage patients to adopt long-term behaviors that increase the time they spend in the optimal glycemic range by earning points redeemable for benefits.¹¹

Spurred on by the COVID-19 pandemic, increased investment in the mental health and behavioral disorders space¹² will help high-quality apps continue to emerge, and lead to growth in access for populations in need of mental health services, particularly as employers begin to pick these up for their employees. Top apps in this space include Mindshift (Score=93), which helps individuals to relax, think positively, and cope with panic, stress, and anxiety by employing Cognitive Behavioral Therapy (CBT) strategies,¹³ and Headspace (AppScript Score=100), which guides individuals to employ meditation and mindfulness techniques to reduce stress and anxiety and achieve improved sleep.¹⁴ Such apps have helped many people since the onset

of the COVID-19 pandemic. Another leading app in the mental health and behavioral category is Proloquo2Go (Score=95), an augmentative and alternative communication (ACC) app that translates picture symbols entered by an individual to speech, or provides text-to-speech capability for individuals with speaking difficulties, including some on the autism spectrum.¹⁵

The pandemic has also accelerated the need and adoption of digital therapeutics for pain.¹⁶ Kaia Health (AppScript Score=98), a digital therapeutic app of physical therapy exercises sits among these and offers AI-assisted motion coach (using a smartphone's camera to track movement along with a mobile app) to treat chronic musculoskeletal pain including neck, hip, knee, shoulder, hand/wrist, and foot/ankle pain treatment.¹⁷

Aging of the population and a rise in polypharmacy have furthered growth among mobile health solutions for medication management.^{18,19} Among such apps is the MediSafe Medication Management app (AppScript Score=100), which allows individuals to enter their medications and dosing schedule (showing the appearance of each medication so patients don't get confused), provides prescription reminders and enables users to track medicines for dependents. The app can also notify a caregiver or other selected party when a dose was missed and provides drug interaction warnings and refill alerts.²⁰

Recent scientific research also suggests the effectiveness of diet-tracking apps to promote successful patient engagement in weight loss programs and losing weight.²¹ Perhaps the most notable highly-rated app in the healthy eating/weight management category is the diet manager/calorie counter, MyFitnessPal, that helps users set calorie intake goals and then track daily consumption against it. In addition to making it easy for individuals to track individual food items consumed and their calorie calculations, it also has a barcode scanner to find food details in its system, remembers previously

eaten foods, and calculates calories of recipes found elsewhere. By integrating and syncing data with fitness tracking devices, it keeps an exercise log, allowing exercise to impact daily calorie allotments.²²

Finally, FDA-cleared Propeller Health (AppScript Score=100) stands out in the respiratory space for asthma and chronic obstructive pulmonary disease (COPD). Using sensors that attach to existing inhalers, it records and monitors medication use (where, when and how often) and sends this information to its app. It further tracks patient symptoms and can connect to health systems and a patient's care team to share relevant info. For instance, clinicians can be alerted when a patient's disease becomes poorly controlled in order to provide proactive outreach and care/guidance. Clinical trials have shown it has a positive impact on adherence, asthma control, and symptoms and outcomes, which have helped lead to its reimbursement/coverage by CMS as an "other related item" for a drug.²³

Wellness apps versus software as a medical device (SaMD)

Under the current FDA General Wellness Policy, many of these digital health apps are considered low risk general wellness products rather than medical devices and can market directly to consumers without review. On the other hand, Mobile Medical Applications (MMA) or software as a medical device (SaMD) — which is defined as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device"²⁴ — typically need to gain market authorization (e.g., approval, clearance, etc.) as a medical device, before they can be marketed. These apps may treat, cure or diagnose disease and aim to make claims to that effect. Depending on the risk profile of the SaMD, the FDA may allow for enforcement discretion or exempt the SaMD from market authorization requirements, e.g., low risk SaMD, but moderate risk SaMD would likely require market authorization. For instance, apps that treat an

eating disorder, anxiety disorder or muscle atrophy; computer games that treat autism; or apps that restore a function impaired by a disease/condition would go beyond the scope of general wellness apps and would meet the definition of a medical device, regulated by the FDA.

Among these fall digital therapeutics (DTx), which help treat, manage, and prevent various diseases. Notably, such DTxs are increasingly seeking and gaining reimbursement by various stakeholders, enabling them to play a growing role in impacting human health, and are becoming a more widely available therapy option.



Consumer apps are the most widely available and used digital health tools, shifting increasingly toward disease-specific uses, but downloads and use are heavily skewed and quality is inconsistent so careful selection by consumers is required.

Digital therapeutics, their proliferation and regulation

- + Digital Therapeutics (DTx), and Digital Care (DC) products — incorporating software as a means to treat, prevent or manage specific diseases or conditions — have been proliferating and over 250 such products are now identified, including about 150 products that are commercially available, and the rest in development.
- + Digital therapeutics, which typically focus on a narrow clinical indication and generate evidence of clinical efficacy, follow a development path that typically requires market authorization by a regulatory body and sometimes a prescription from a provider, though some may be exempt.
- + At least 25 DTx products have been granted market authorization through regulatory processes and 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.
- + Digital care products, almost 100 of which are now available commercially, include care platforms and tools which typically address broadly-defined clinical conditions and can typically be tailored or personalized to individual needs, requiring active involvement from providers or coaches.
- + Neurologic and psychiatric conditions are a key focus of both DTx and DCs, making up over two-thirds of all DTx indications and over 40% of DCs, respectively, with DCs also used by patients suffering from endocrinology, oncology and cardiovascular conditions. Many of these rely on cognitive behavioral therapy (CBT) as part of their therapy.

- + As regulators recognize the role that DTx and DCs can play in patient care, the creation of reimbursement pathways for approved apps is increasing globally, enabling them to play a growing role impacting human health.

Among digital health apps and tools being developed, a subset has set a higher bar by clinically evaluating software as a means to treat, prevent or manage specific diseases — thereby adding a new therapeutic modality to the healthcare toolbox. These have become known as digital therapeutics and digital care products, depending on their function and structure.²⁵ Since the emergence of digital health, there has begun to be a codification of subcategories in this space, and it is worth noting that these are still in flux. For the purposes of this report, we broadly discuss two therapeutic categories below.

Digital therapeutics are typified by their focus on addressing a narrow clinical indication, leveraging fixed content and generating high-quality evidence on clinical effectiveness. Their beneficial effects are the result of a software program itself, more so than the input or involvement of physicians and motivational health coaches, although there may be communication with such parties. They typically follow a development path to secure market authorization as a medical device, such as the FDA in the United States or Notified Bodies in the European Union, and most of these (though not all and not in all countries) require a prescription from a provider for the product to be dispensed and/or reimbursed.

Alongside these exist **digital care** products, including digital care platforms that typically address broadly-defined clinical conditions such as diabetes, and digital care tools — both of which are typically tailored or personalized to individual needs.²⁵ Similar to DTx, these often use an app as a health tool to supply educational content, but also rely on active involvement from providers or coaches to set and shift care targets, track patient progress against those targets, customize treatment, or remotely monitor patients and their symptoms by using connected devices and/or eCOA/

ePRO/data captured by an app to influence care. With both DTx and DCs, the apps are typically used in conjunction with medications and the standard of care for the disease and have run clinical trials.

Some parties consider both of these categories as digital therapeutics, as both include digital health solutions that have proven to advance health outcomes; however, due to the differences between approaches and the role of a care provider, we distinguish between the two in this report.

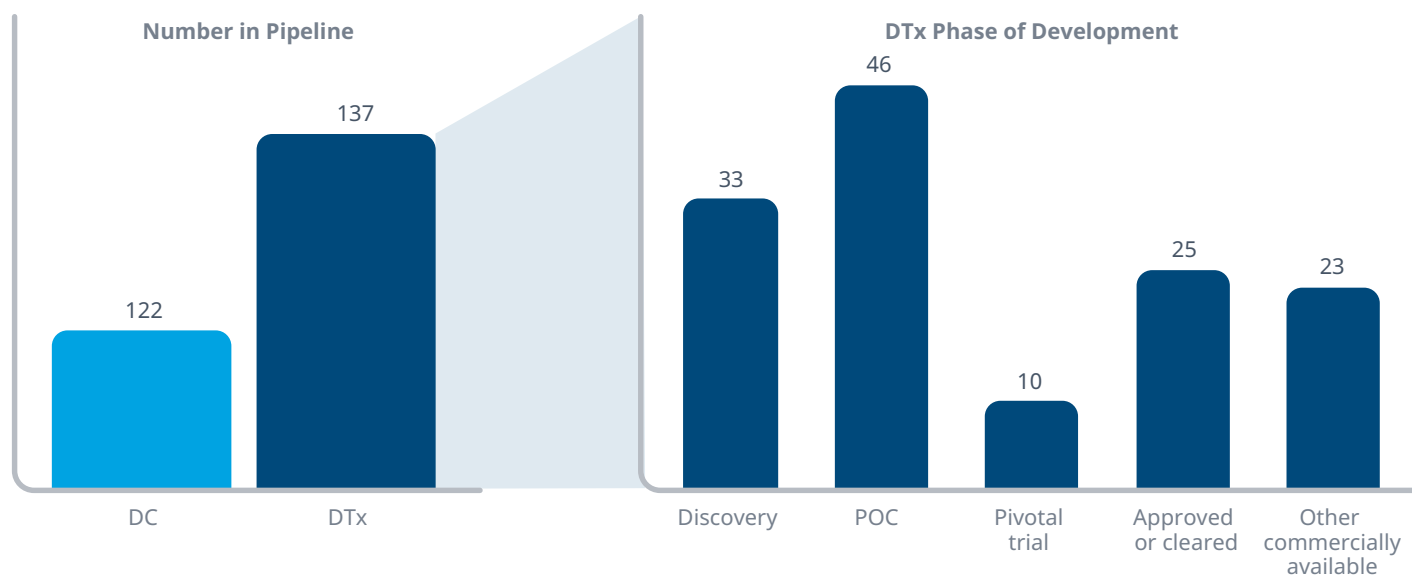
Beyond these exist other categories discussed elsewhere in the report, such as **digital diagnostics**, which use sensors to diagnose disease; **digital medicine products**, which include devices that regulate or monitor the delivery of medicines or stimulation such as continuous glucose monitors or insulin pumps, or track use;²⁶ **device-driven digital solutions** where an external or implantable medical device is guided by an app for biofeedback or another purpose but what the main treatment does is not derived from the software; **device connected apps** that monitor and visualize data coming from a connected sensor; **telemedicine programs** facilitated by apps, and others.

According to the IQVIA Digital Solutions Database, which tracks various types of digital health solutions, a total of 259 digital therapeutics (DTx) and digital care (DC) products were in any phase of development as of June 2021. Among these are 137 digital therapeutic (DTx) apps, games, and virtual reality and 122 digital care (DC) products, care platforms and care tools. Among these, at least 48 DTx and 99 DCs were available commercially, with the rest in development (see Exhibit 9).

“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...”

— Digital Therapeutics Alliance²⁷

Exhibit 9: Pipeline of Digital Therapeutics (DTx) and Digital Care (DC) Programs and Tools



Source: IQVIA Digital Solutions Database, Jun 2021; IQVIA Institute, Jun 2021

Notes: May underestimate the number of EU CE Marked devices that haven't gone through established reimbursement processes. Other commercially available.

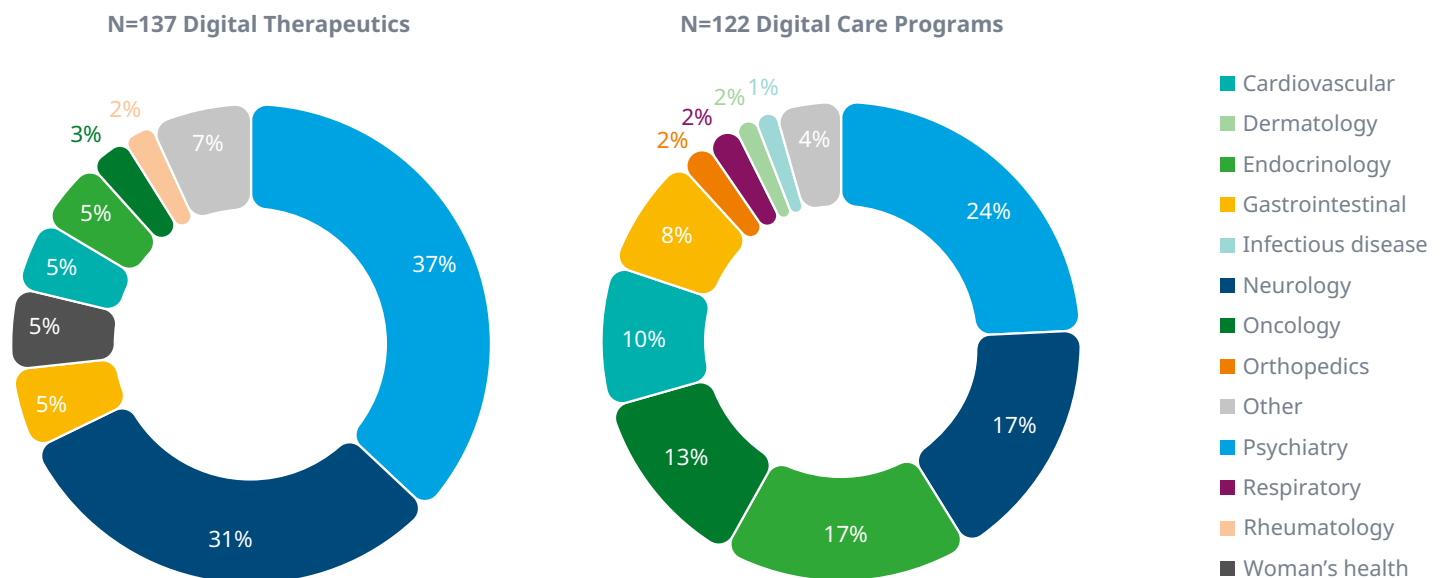
Among DTx, 25 secured market authorization and became available for marketing through regulatory processes — with indications predominantly in the mental health and behavior modification space, including PTSD, ADHD, substance/nicotine use, pain, and insomnia, among others — and an additional 23 became commercially available after either being deemed exempt from regulatory oversight in various countries as low risk devices or “wellness” apps, or through enforcement discretion. Some of these exempt apps are likely to consider seeking further regulatory approval to be able to make effectiveness claims. Another 89 DTx are in the clinical development pipeline, where they are building evidence of technical and clinical feasibility, acceptability, and usability, through proof of concept trials (POCs) and evidence of effectiveness and safety through pivotal trials.

Neurologic and psychiatric indications are a key focus of both DTx and DCs, making up two-thirds (68%) of all DTx indications and 41% of DCs (see Exhibit 10). However digital care products that include health providers or coaches focus more strongly on endocrinology, oncology,

and cardiovascular interventions, which typically have a need for more tailored care and patient monitoring and may be part of rehabilitation programs. Among approved digital care tools in the oncology space, for instance, are apps for patient remote monitoring and symptom management such as Moovcare, Cankado Pro-React Onco, and Oleena, which diary or track the emergence and severity of symptoms in cancer patients with the intent of guiding care team interaction. In the endocrinology space fall a number of digital care programs such as Livongo, Omada and Lark, and DC therapy support tools for diabetes and other conditions, such as the prescription medication management/personalization apps Insulia, Diabeo, Bluestar and iSage, which require a physician to set medication dose and titration schedules so people with diabetes can manage their diabetes therapy based on the app’s AIML programming and calculations.

Though DTx are unique in their direct use of apps or games to treat conditions, digital care products are also critical tools to improve health outcomes. One such program, Moovcare, has been clinically shown in Phase III

Exhibit 10: Therapeutic Focus of DTx and DCs Across All Phases of Development, 2021



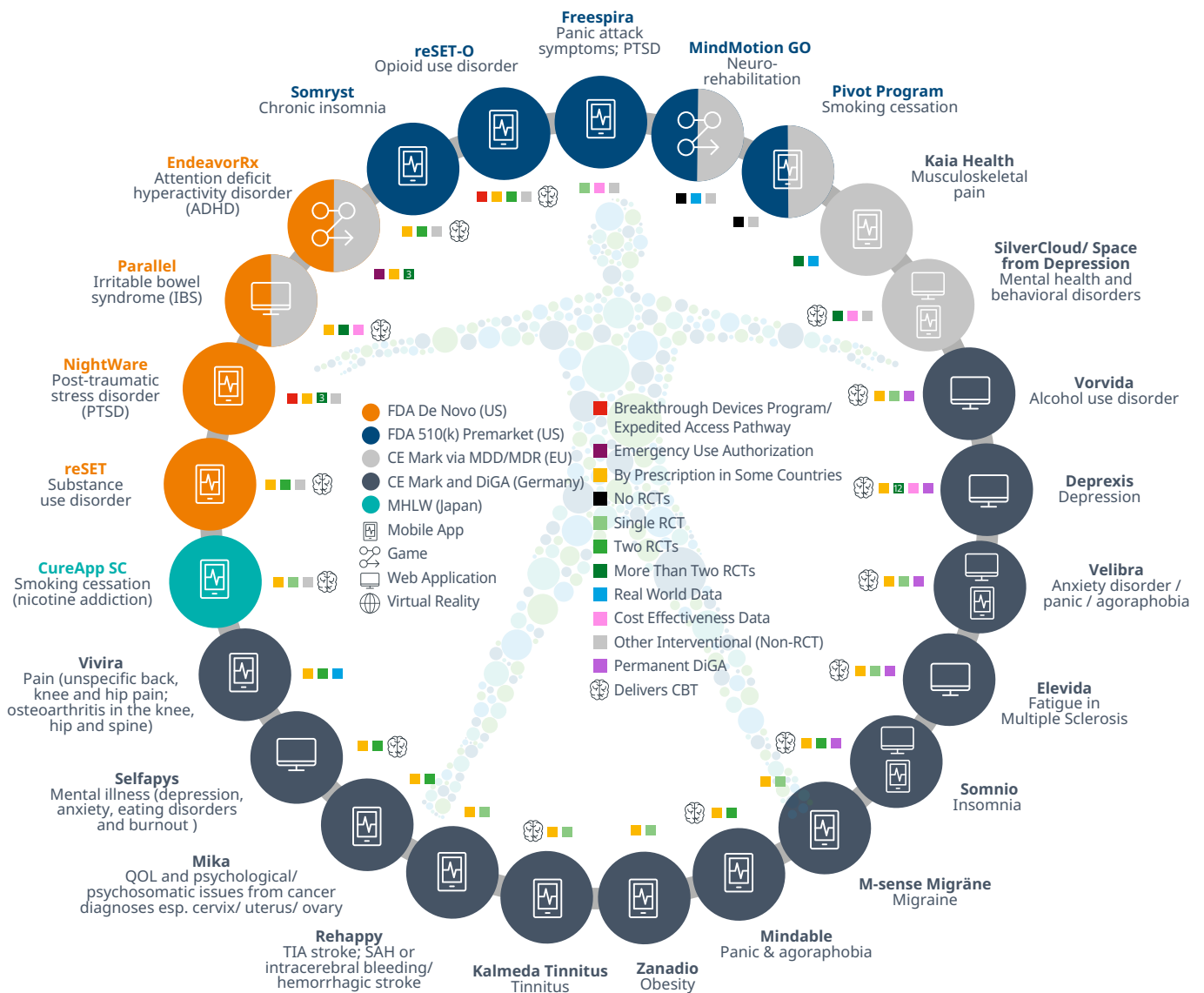
Source: IQVIA Digital Solutions Database, Jun 2021; IQVIA Institute, Jun 2021

Notes: Other DCs include rheumatology, hearing disorder, urologic disease, women’s health / sexual health. Other DTx includes dermatology, liver disease, metabolic disorder, movement disorder, ophthalmology, orthopedics, respiratory, transplantation, vision disorders. DTx and DCs that treat multiple therapy areas are counted in each, such that DTx were mapped 146 times and DCs 136 times.

RCT to extend the life of lung cancer patients in remission, providing a 7.6 month increase in overall survival. By monitoring symptoms that lung cancer patients report on a weekly basis using mobile surveys, it can detect relapse or complications early and alert the prescriber/physician.²⁸ It is also the first digital app to have gained reimbursement in France (1000€ per patient every six months).

Among the 25 DTx with market authorization from at least one country (see Exhibit 11, colored bubbles), nine are in the U.S., 19 are in Europe, and one is in Japan, with some overlap. A notable set of 20 are currently available by prescription in some of the countries they market (yellow squares), along with six digital care tools... whether by stipulation of their authorization, or

Exhibit 11: Digital Therapeutics with Market Authorization through Select Pathways and their Features



Source: IQVIA Digital Solutions Database, Jun 2021; IQVIA Institute, Jun 2021

Notes: Data as of Feb 28 except for DiGA updated May 14th date. Trials listed are Trials to Date; * Yellow with dot indicates sometimes by Rx. FDA Enforcement Policy refers to Enforcement Policy for Digital Health Devices For Treating Psychiatric Disorders During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency Guidance for Industry and Food and Drug Administration Staff. Apr 2020 Available at: <https://www.fda.gov/media/136939/download> TIA = Transient ischemic attack; SAH = subarachnoid hemorrhage. Note: Vorvida also available in the U.S. under FDA Enforcement Policy implemented during COVID-19. In order to be reimbursable, DiGA must be certified as a medical device and bear the CE mark. Excludes medication management apps classified as DCs. May underestimate EU CE Marked devices. Kaia is also commercially available in the U.S. as it is 510K exempt class I/II device, but may further be pursuing regulatory clearance. Not all approved DiGA are displayed as Invirtio and Cankado were considered DCs for this study.

as a requirement for reimbursement. These are typically known as “prescription digital therapeutics (PDTs)” and the requirement for prescribed dispensing typically ties to apps making “medium to high risk claims,” such as to apps treating or improving symptoms of disease. On the other hand, apps with low-risk claims intended broadly to improve health or a health function may be considered low risk medical devices (e.g., Class I) in some regions such as the U.S. and EU and may become available without market authorization.^{29,30}

Notable among prescription digital therapeutics are four that have gained market authorization with claims of effectiveness through the De Novo Classification pathway in the U.S.: EndeavorRx for ADHD in children, which improves attention (sustained and selective) using a video game;³¹ NightWare to reduce sleep disturbance related to nightmares for nightmare disorder or related PTSD in adults;³² Parallel, which is a CBT treatment for adults to reduce symptoms of irritable bowel syndrome;³³ and Reset, which uses CBT and fluency training as an adjunct to contingency management to treat substance abuse, increase abstinence and improve patient retention in outpatient treatment programs.³⁴

While most DTx are apps or web applications, two of the approved DTx are therapeutic video games: EndeavorRx to treat ADHD and MindMotion GO to provide NeuroRehabilitation in a home setting. Such games require the user to take physical actions that typically challenge mental capabilities or stimulate damaged areas of the brain to improve cognitive or physical performance. A further 23 DTx and DC games exist in the pipeline, with nearly all addressing neurological conditions (AD, PD, Stroke, brain injury), and some addressing cognition and musculoskeletal issues. Virtual reality programs (n=18) are also growing in the pipeline, with a slant toward psychiatric disorders addressed by exposure therapy.

Digital therapeutics, by accompanying the patient at home, may offer access to care and support beyond the reach of traditional in-person interactions. DTx mental health apps, for instance, often offer a digital version of

cognitive behavioral therapy, iCBT, likely to make mental healthcare more accessible and potentially reaching individuals in rural settings or overcoming stigma, thereby contributing to health improvements beyond standard of care. Over half, or 14 out of the 25 approved/cleared DTx utilize cognitive behavioral therapy (CBT) to treat the conditions they target (see Exhibit 11), along with 42 more pipeline DTx (56/137 or 39% of all DTx) and at least 22% (27/122) pipeline DCs, though sometimes the latter require accompanying therapy hours. Some challenges exist in classifying these as DCs versus DTx as some appear to offer dual modes with or without care or coaching by a therapist (possibly Silver Cloud, Space from Depression), and some others are intended to bridge individuals for a time until a slot for treatment by a therapist becomes available.

Although the clinical data generated by developers of digital therapeutics varies, the trials they run (green squares) typically include at least one randomized controlled trial, and many include several. While all approved DTx have run some interventional trials, nearly half (n=12) have run two RCTs and five have run more than two clinical trials.

Maturation of regulatory and reimbursement pathways for DTx

DTx are increasingly seeking and gaining both market authorization and reimbursement by various stakeholders, enabling them to play a growing role impacting human health, and are becoming a more widely available therapy option. Many DTx have come through device market authorization pathways where they are either required to submit evidence to support effectiveness claims, such as to the Ministry of Health, Labour and Welfare (MHLW) in Japan or the FDA in the U.S. to obtain effectiveness claims, and when applying for CE Mark under applicable legislation.

United States

One of the 25 apps cleared by regulatory agencies, Somryst, notably was the first PDT to have gone through the FDA’s traditional 510(k) pathway while

simultaneously being reviewed through FDA's (Pre-Cert) Software Precertification Pilot Program,³⁵ in which Pear Therapeutics participates. In the Pre-Cert program, attention is primarily brought onto the developer of the digital health technology and/or software, with the intent of enabling manufacturers that demonstrate a culture of quality and organizational excellence (CQOE) and monitor real-world software-based medical device performance, effectiveness and safety, to face a streamlined premarket review.³⁶ It is important to note that the Pre-Cert Program is still in pilot stage and available only to those companies who were selected to participate in the pilot.

Other DTx were also able to enter the U.S. healthcare market during the pandemic without approval when the FDA waived some regulatory requirements to allow digital health devices treating psychiatric disorders (or "computerized behavioral therapy devices") to market their products without the need to submit a 510(k) premarket notification filing under the Emergency Use Authorization program.³⁷ These include PEAR-004 to improve core symptoms and depression in people living with schizophrenia, as well as Orexo's Deprexis for depression and Vorvida for alcohol misuse — both also currently approved in Europe and reimbursed under Germany's DiGA pathway, where they gained a permanent listing.

Beyond direct approval processes, the FDA has also recently established the Digital Health Center of Excellence (DHCoE) in September 2020 — a central authority intended to manage its approach to digital innovation (including software as a Medical Device (SaMD), wearables, mobile health devices, artificial intelligence and machine learning (AI/ML) that may be built into SaMD and medical applications).³⁸ The intent is to speed innovation of safe and effective digital technologies.^{39,40} In addition to innovating regulatory approaches "to provide efficient and least burdensome oversight while meeting the FDA standards for safe and effective products," the center of excellence's stated mission is also to help connect and build partnerships, and encourage knowledge sharing to advance best practices."

MARKET AUTHORIZATION

European Union — CE Mark via the EU Medical Device Regulation (MDR)

While some market authorization agencies regulating DTx, including the FDA, are attempting to simplify submissions for SaMD and reduce the burden on DTx developers, in Europe the burden may be increasing for some DTx manufacturers. Under the former Medical Device Directive (MDD 93/42/EEC) regulatory framework, devices that were classified as IIa and IIb, as are most DTx, could technically get to market without trials, and some could claim equivalence to prior products.



"The new Medical Device Regulation (MDR) will reclassify some digital technologies from the lowest risk class I to class II+ devices. That will increase the standard of evidence required to receive a CE mark, which is a prerequisite for use and reimbursement in Europe. Companies will need to invest heavily in generating clinical data if they want to market digital therapeutics after 2020."

— Jörg Land, Managing Director of Sonormed GMBH, a DTx company, from Science Business⁴¹

However, under the new EU Medical Device Regulation (MDR 2017/745) implemented in Europe in May 2021, safety, effectiveness, and performance measures will be needed to obtain a CE mark for most such devices. Except for Class I devices that can still self-certify with a Notified Body, DTx will therefore have to do clinical work and submit a clinical evaluation report to get from start to market, as well as submit a notably larger file to regulatory bodies. Since MDR will further require that all devices approved under MDD will need to bring needed clinical data within five years of receiving a certificate, or when it is up for approval, this is likely to increase the burden on digital therapeutic apps already on the market, while also elevating the level of evidence these apps are bringing to the EU market.

UK

Driven in part by the UK's departure from the EU and the MDD/MDR regime, the current regulatory process in the UK is also likely to change. Although there currently exists no dedicated review pathway through which all digital solutions pass to gain regulatory approval and/or reimbursement, NICE announced early in 2021 that it would work with NHSX⁴² to drive the digital transformation of care, and with the Medicines and Healthcare products Regulatory Agency (MHRA) to develop a streamlined regulatory-to-access pathway in England for digital health technologies.⁴³ It further announced a new office for digital health in Q4 2021 to provide rapid, robust, and responsive technology evaluation.⁴⁴ It is unclear whether this new approach will assess clinical evidence for all therapies, but the first step of assessment in addition to regulatory approval (via a CE mark, or UKCA marking after June 30, 2023), will employ a new national criteria or "baseline assessment" launched in February 2021 known as Digital Technology Assessment Criteria for Health and Social Care (DTAC) to determine suitability of digital health technologies to be incorporated into the NHS England and Department of Health and Social Care.⁴⁵ DTAC consists of a set of criteria that has to be met by the technology across a number of domains — clinical safety, data protection, technical assurance, interoperability, and usability⁴⁶ — and is intended to guide developers and commissioners on what "good" digital health technologies look like. As

DTAC also collects, but reportedly does not assess,⁴⁷ information on clinical value proposition, the intent may be for NICE to gather evidence "for subsequent re-evaluation" by reimbursing bodies.⁴³

Other global approval pathways

In Asia, where **Japan** has already approved the DTx, CureApp, through its Ministry of Health, Labour and Welfare (MHLW), **South Korea** is also laying down the groundwork necessary to speed up its commercialization of digital therapeutics, with the release by the Ministry of Food and Drug Safety in November 2020 of a *Guideline on Review and Approval of Digital Therapeutics*.⁴⁸ The guideline includes a definition of DTx; examples of digital therapeutics that specify use for prevention, management or treatment of a medical condition; methods for review and approval (including the technical documents to prepare); and its criteria for judgment. Specifically, when applying for review and approval, SaMD digital therapies are required to submit materials to compare it with already approved/reviewed product(s) as well as provide materials on the intended use (i.e., targeted patients and disease), the evidence-based mechanism of action used to achieve outcomes (scientific/clinical principle), data supporting product performance and clinical trials (to prove both safety and effectiveness), and info on use of the product in other countries.⁴⁸ Although no DTx have yet been approved under this pathway, some DTx such as Nunaps' Nunap Vision, a digital virtual reality therapeutic which provides perception training for patients to help treat visual field defects caused by brain damage, such as from strokes, are actively running trials in Korea and are likely to submit through this pathway.^{49,50}

Current and evolving reimbursement pathways

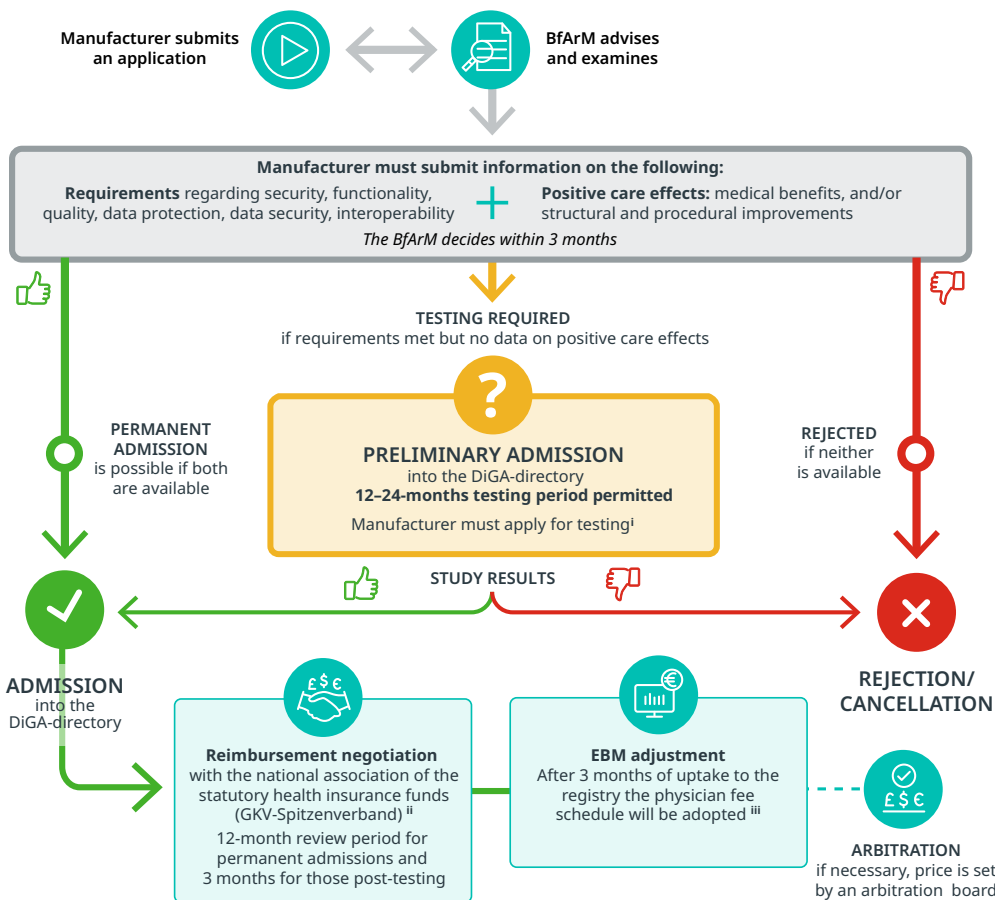
While many countries/regions have worked to set up regulatory pathways, within the EU and UK, there is a parallel effort to take CE marked digital therapeutics that may have been approved under MDD and have them work through additional screenings with clinical evidence reviews to gain reimbursement. Across all these effort runs the intent to hold DTx up to internationally recognized best practices, privacy standards, and evidence requirements, and assess their value.

DiGA

Many of the 25 market authorized DTx (in dark gray in Exhibit 11) were both granted the CE mark and approved for reimbursement under Germany’s new digital health law — the Digital Healthcare Act (*Digitale-Versorgung-Gesetz — DVG*).⁵¹ This fast-track process for digital health applications (DiGA) came into effect on December 2019 to enable doctors to prescribe digital health applications that can then be reimbursed by health insurance companies, and the first app was approved into its directory in September 2020 (see Exhibit 12).^{52,53} In order to gain access to the market, developers must register their CE-marked device (class I or IIA) at the Federal Institute for Drugs and Medical Devices (BfArM), and complete a 122-item criteria relating to app security,

quality, functionality, data security, and data protection through the DiGA approval process, as well as to provide clinical evidence. If clinical evidence is not already available, the manufacturer must then also provide “a plausible justification” for its contribution to improving healthcare and then create a 12-24 month clinical plan to demonstrate “positive care effects.” To gain permanent listing into the DiGA directory (DiGAV), the developer must submit such evidence and undergo review. Although during the testing period the manufacturer sets the price, after final approval, the G-KV (National Pricing Committee) negotiates price. So far, while 15 DTx and DCs have gained temporary approval through DiGA, only five are listed permanently in the directory having produced enough evidence to pass that stage.

Exhibit 12: Germany’s Reimbursement Pathway — Procedure for Admission into the DiGA Directory



Notes:

i. Preliminary admission

12-24-months testing period to prove a plausible justification of the positive care effects, concept for evaluation. Evidence is generated to show positive care effects. During the testing period the app can be prescribed by physicians if the indication is appropriate and manufacturer sets the price, but a price ceiling can be set based on similar apps and price should reflect the extent of the medical benefit. The manufacturer bears the costs of the studies and evaluation.

ii. Reimbursement negotiation

The national association of the statutory health insurance funds (GKV-Spitzenverband) negotiates reimbursement prices for digital health applications with the manufacturers of digital health applications with effect for all health insurance companies. Negotiations are based on the available evidence and the amount of actual remuneration from self-payers and other European countries. Final framework expected August 2021 may impact this process. Manufacturer sets the price during this period.

iii. EBM adjustment

After 3 months of uptake to the registry the physician fee schedule will be adopted. The physician fee schedule defines the remuneration of the outpatient physician, which takes place using a remuneration (EBM-code) and is modified by this process.

Source: BfArM, Available from: https://www.bfarm.de/SharedDocs/Downloads/EN/MedicalDevices/DiGA_Guide.pdf; IQVIA expertise, Jul 2021; IQVIA Institute, Jul 2021

Notes: BfArM = Bundesamt für Arzneimittel und Medizinprodukte (Federal Ministry for Drugs and Medical Devices)

Belgium

While some other countries like the Netherlands have simply put forward digital health app stores like the GGD AppStore⁵⁴ intended to provide an overview of relevant and reliable health apps based on an assessment framework,⁵⁵ similar to the DiGA process, Belgium has also moved to create a centralized reimbursement pathway with its mHealth Belgium platform, requiring information on CE marking, communication security, data protection, interoperability with other systems, and app financing.⁵⁶ Created in 2018, mHealth Belgium is a multi-stakeholder joint initiative between the federal government and medical and industry stakeholders to assess mobile apps that are CE-marked medical devices. The new process was initiated as of January 2021 and framed as a pyramid with three levels of validation to enable reimbursement of mHealth mobile apps. Manufacturers progress through these levels, with level 1 requiring information on base criteria for apps including proof of being a CE certified medical device and compliance with the European Union Data Protection Regulation (GDPR). Level 2 includes requirements of app interoperability and connectivity to eHealth platform's basic services (Belgium's federal network for secure exchange of health data), an independent risk assessment of authentication, security and the use of local e-health services by means of standardized tests,⁵⁷ followed by submission of socio-economic, clinical and budgetary impact evidence to gain reimbursement. Attainment of level 3 means the app has shown social-economic evidence and has been granted reimbursement by the National Institute for Health and Disability Insurance (NIHDI/RIZIV). As of May 25, 2021, a total of 30 mobile applications entered the validation process, with eight having passed to Level 1 (M1) and 22 reaching Level 2 (M2). However, no apps have yet reached Level 3 (M3), though apps that attained the first stages can now submit data for that purpose.⁵⁸ Under this framework, a special working group submits advice (positive/negative) to the insurance committee based on criteria including clinical evidence, the app's potential for healthcare system integration, likelihood of improving or complementing clinical practice or care, and cost.

UK

The reimbursement process to bring digital therapeutics and digital care programs into practice in the UK is slightly different, as it is decentralized. Currently various healthcare providers and types can incorporate digital technologies into their care provision once they receive appropriate regulatory approval (via a CE mark, or UKCA marking after June 30, 2023)^{59,60} and have met NICE's evidence standard framework for digital health solutions, which serves as a guideline for general digital health solution commissioning and reimbursement.⁶¹ Assessments of value and reimbursement/adoption decisions are mostly made at a local level by Clinical Commissioning Groups (CCGs) — purchasing bodies responsible for commissioning primary care services for their local community who select among NHS-vetted service providers. While NICE guidance on clinical assessments can be used to support CCGs in their evaluations, ultimately CCGs are the key decision-makers for the clinical assessment of digital health solutions (DHS) including DTx. This decentralization proves to be a major hurdle to adopting a wide range of clinically effective digital health solutions.

CCGs require evidence be submitted to gain adoption and reimbursement, and the evidence submissions they require may vary. However, as CCGs must make decisions of what to offer based on expected impact to their own allocated general clinical budgets,⁶² they typically look at one main criteria for including them into their services formulary — savings opportunities — making data generation on cost-effectiveness by DTx manufacturers critical to adoption. Moreover, CCG commissioners often require a pilot study to collect real-world evidence (RWE) on the impact of digital health solution on their population. For example, in 2016 the impact on the population of a first national digital care intervention program, the NHS Diabetes Prevention Program, was assessed by the NHS (see Callout Box), and in other disease areas, such as mental health, a small number of CCGs have contracted for pilots to be conducted at their sites with digital health solutions free of charge.

One of the pilots in mental health that has progressed the farthest is Space from Depression from SilverCloud, for treating adults with depression. This digital therapeutic has received widespread adoption across mental health service in the NHS, in part because it has progressed farther along in a process set up to identify high-quality, evidence-based digital therapies for use by mental health service providers under the *NHS Improving Access to Psychological Therapies (IAPT) services*.⁶⁴ That process assesses the effectiveness, content, digital standards and resource impact of digital solutions (delivering an 'IAPT assessment briefing' or IAB), and for those who progress, has an expert panel review and recommend whether to evaluate them in practice by IAPT services. This in-practice evaluation can then take up two years before a final 'IAPT evaluation in practice report', or IEPR is published.⁶⁴ Fourteen therapies have so far seen an IAB published,⁶⁵ while only one has seen a published IEPR — Space from Depression.⁶⁶ While feedback on the app was generally positive and showed that it was an effective treatment for some users and should be part of stepped-care, the top line assessment stated the case for adoption was only

“partially supported” and it was deemed hard to identify which individuals would benefit, and thus patient engagement should be monitored by a therapist.⁶⁶ The positive outcome assessment of the IAPT, and ultimately a guidance published by NICE,⁶⁷ enabled the adoption of the digital therapeutic across the NHS.

Still, app developers face some reimbursement headwinds in the UK. For instance, despite its positive IAPT results and NICE recommendations, the manufacturer of Space from Depression had to build a business model, which consists of selling licenses to services providers at a local level, due to the lack of a centralized reimbursement model for digital therapeutics. Further, very few of the CCGs that conducted pilot programs in other areas continued with paid membership at the end of the pilot program. Despite that, manufacturers and digital health solutions developers use the data collected in pilot programs in their submission dossiers to other CCGs to get their solutions commissioned, and a more centralized path to reimbursement may be on its way with the creation of the new office for digital health.

THE NHS DIABETES PREVENTION PROGRAM: THE FIRST AND ONLY NATIONAL DIGITAL INTERVENTION PROGRAM IN THE UK

In 2016, the Healthier You: NHS Diabetes Prevention Program (NHS DPP) launched, with the aim of supporting people who are at high risk of developing Type 2 diabetes. The program included wearable technology to monitor exercise and online peer groups with five digital health app solution partners chosen via tender (Oviva, Second Nature “formerly Ourpath”, Changing Health and Liva Healthcare, Buddi Nujjer and Hitachi). As part of the program, 5,000 patients were enrolled across eight participating CCGs in various locations. Individuals initially referred to a face-to-face program received bespoke, individualized help, such as advice on weight loss and healthier eating habits, tailored physical activity programs and education on lifestyle choices, which together have demonstrated a reduction in the risk of developing Type 2 diabetes. However, if patients were non-compliant with weekly face-to-face meetings, they were referred to a fully digital intervention from the five providers, which allow users to manage their lifestyle and set and monitor goals electronically, and also access health coaches. The pilot aimed at establishing whether digital interventions are effective in supporting behavior change in those with non-diabetic hyperglycemia (NDH) and overweight and/or obese individuals who have not been diagnosed with NDH. With a combined 132,000 lbs. lost by the end of the pilot, and an average of seven-and-a-half pounds lost per participant,⁶³ the value of digital care programs was demonstrated, and the NHS Diabetes Prevention Program is now rolled out as a long-term NHS program accessible across the UK.

Wearables, digital diagnostics and digital biomarkers

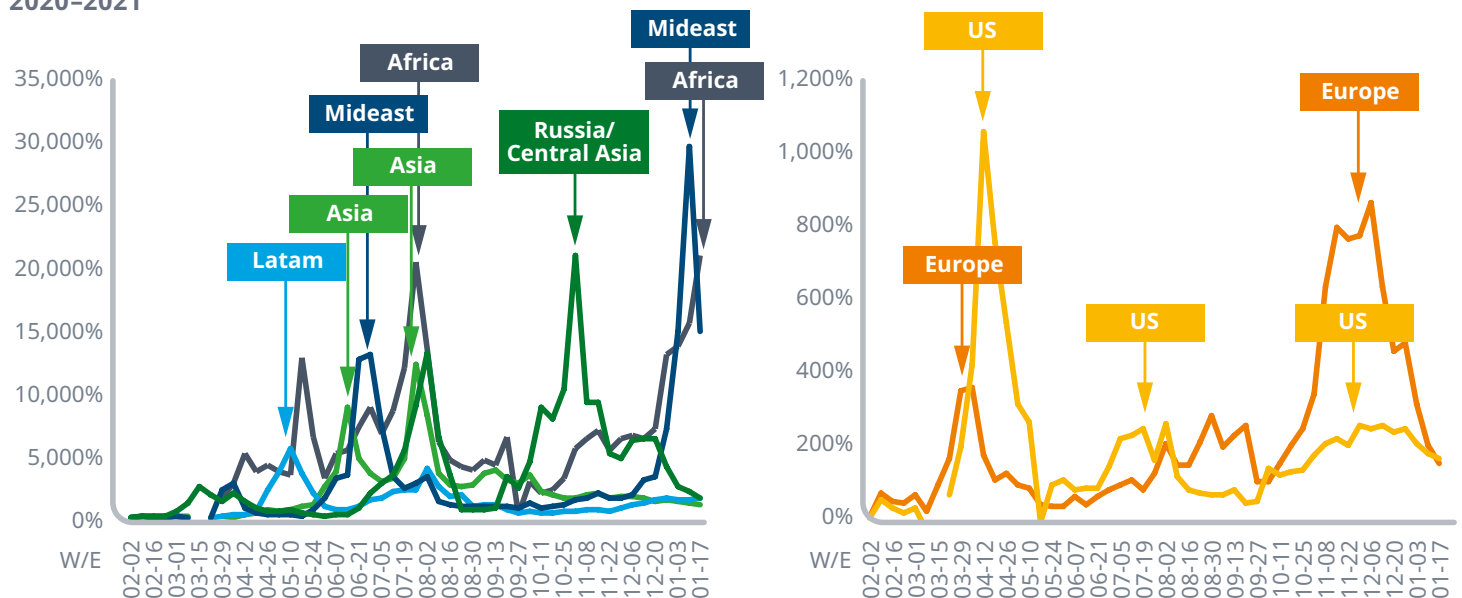
- + Of the 384 currently-marketed consumer wearable devices, activity monitoring devices that measure heart rate, steps taken, distance traveled, and calories burned account for about 55% of these, while the remainder enable data generation and capture across a broad range of health parameters.
- + During the pandemic, a scramble to download health apps tied to devices occurred in waves around the globe, with spikes in downloads coinciding with peaks in virus cases and lockdowns as people self-monitored their health and oxygen saturations.
- + Novel methods and strategies to identify early signs of cancer and respiratory disease in a minimally obtrusive way, including “electronic nose” technology, are noteworthy examples of advances in remote sensor technologies that are enabling digital diagnostics.

+ Digital biomarkers to remotely monitor patient health are being validated by feasibility studies with the intent to incorporate them into clinical trials and patient care. In total, 438 studies have examined 933 distinct biomarkers, with more than half of trials in neurology, musculoskeletal disorders and sleep. Among these are digital biomarkers for neuromuscular disease to track muscular dystrophies and motor neuron diseases.

CONSUMER WEARABLES

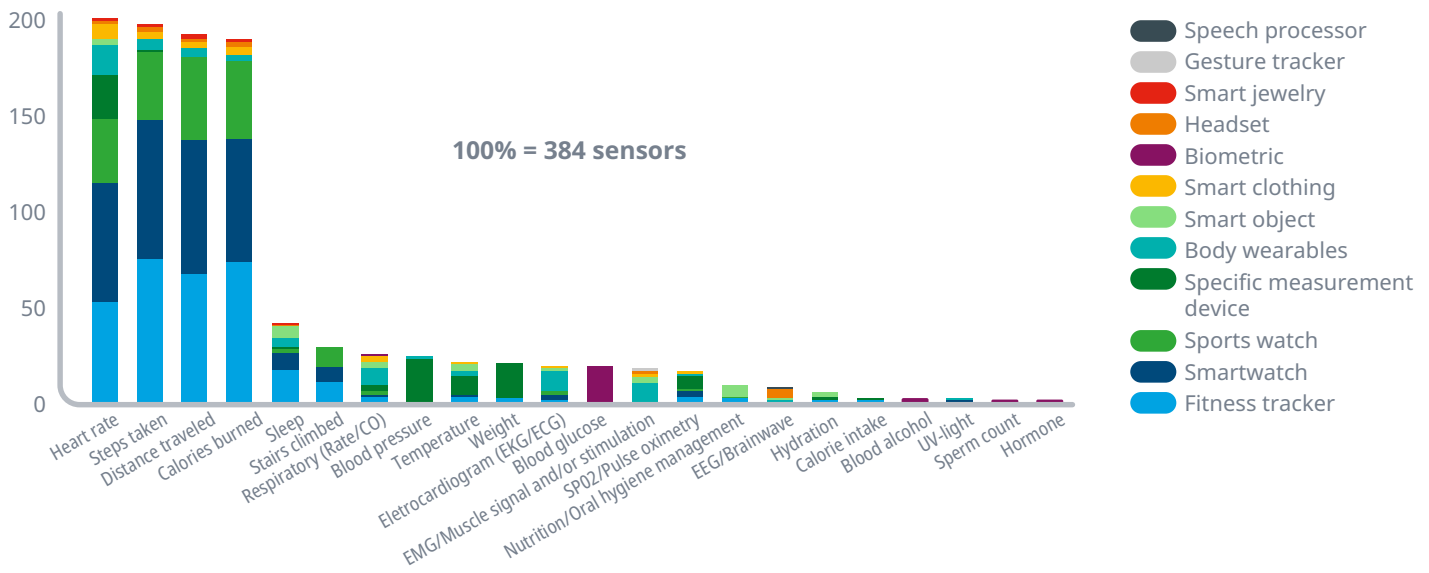
The use of consumer wearable devices that enable individuals to track their activity (such as fitness trackers, smartwatches, sleep trackers and actigraphy devices) as well as parameter-specific biosensors that track various health measures such as temperature, glucose levels or blood pressure, has increased over the years. These sensors, along with apps to display and interpret their data, have become an important element supporting patient wellness efforts.

Exhibit 13: Percent Change Over Baseline in Oximetry App Downloads by Region Tied to COVID-19 Virus Peaks 2020–2021



Source: 42 Matters, Jan 23, 2021; IQVIA Institute, Feb 2021; Data from Wikimedia Foundation, Wikipedia, used to validate peaks, ‘COVID-19 pandemic in X’ where X is various country names. https://en.wikipedia.org/wiki/COVID-19_pandemic_in_X, accessed Feb 8. Russia includes Central Asia. Notes: Install data shown is from the Google Play app store only. Shows percent change versus week ending Feb 2, 2020. W/E = Week Ending.

Exhibit 14: Parameters Measured by Consumer Digital Health Devices by Type



Source: IQVIA AppScript Device Database, Mar 2021; IQVIA Institute, Jun 2021

Notes: Chart includes data from 384 sensors. Total exceeds 384 due to multiple measures being tracked by a single sensor. Specific measurement devices include vitals measurement.

Although many individuals use these devices to monitor and maintain health over time, they also found a more acute role this past year in response to the COVID-19 pandemic. As many people with COVID-19 were found to have low levels of oxygen in their blood even when feeling well, pulse oximeter devices that allow patients to monitor their oxygen saturation (SpO2), were recommended as a way to track the emergence of low oxygen levels that could be an early warning sign that medical care is needed.⁶⁸ As these were available at some pharmacies and stores without a prescription, the use of pulse oximeters increased and the downloading of health apps associated with these devices notably spiked in waves around the globe, coinciding with rising virus cases in various geographies (see Exhibit 13). Installs of these device-associated apps increased by 10x-12x for periods and then fell in the U.S. and Europe, while in other regions including Latin America and Africa, where the baseline use was lower, downloads increased by 50-300x.

The growing demand and need for telehealth are likely to drive this trend further, as use of remote patient monitoring sensors increases. However, at present, the

most measured parameters of consumer wearables are heart rate, steps taken, distance traveled, and calories burned, which are heavily linked to activity monitoring devices, used primarily for maintaining health and wellness. These devices, which include smartwatches, sport watches, and fitness trackers, together account for 55% of the 384 currently-marketed wearable devices but represent 75% of the measures tracked across all devices (see Exhibit 14).

Specific measurement devices (measuring vitals, heart rate, blood pressure, SpO2, temperature and weight) represent around 15% of overall devices, demonstrating the increasing importance of personalized health monitoring in the digital health space, and hold similar health value as devices that take biometric measurements, such as glucose meters. Overall, as the need for remote patient monitoring grows, such FDA-approved devices are likely to proliferate in the upcoming years.⁶⁹ Other body wearables, including ECG devices, muscle EMG sensors, breathing monitors, seizure detectors, and TENS muscle stimulation and vibration wearables for pain relief, represent about

10% of devices. While other categories are smaller and many are unique, such as those performing gesture tracking and speech processing, including SmokeBeat's Somatix, a smoking cessation tool that pairs itself with an individual's smartwatch to detect smoking behavior by tracking hand-to-mouth gestures.

Areas of recent growth include the sleep device market⁷⁰ and infant monitoring devices.⁷¹ In the sleep space, the Withings Sleep Analyzer is an FDA and EU-approved under-mattress pad/sleep tracker with an app to monitor results that tracks sleep duration, phases, and quality⁷² as well as sleep apnea (in Europe, only as pending FDA approval).⁷³ Wearable infant monitoring systems have seen the arrival of textile-integrated sensors to monitor heart rate and oxygen SpO2 (Owlet Smart Sock), temperature sensors as pacifiers (Pacifi Bluetooth Thermometer), and smart bottle feeding systems (BlueSmart Mia) that track milk intake, as well as monitors that track beathing movements such as MonBaby, the Nanit Breathing Band and the Mimo Smart Baby Monitor.

DIGITAL DIAGNOSTICS

Among these sensor devices are some digital diagnostics that, like traditional ones, can detect health conditions using sensors — some located directly on smartphones and other mobile devices, and some on portable external devices. Sometimes powered by artificial intelligence (AI), these broaden patient access to validated diagnostic tools at home. Notable in the cardiovascular space is AliveCor's KardiaMobile (Appscript Score=100), a digital diagnostic that recently received "Breakthrough Device Designation" status from the FDA.⁷⁴ Using a medical-grade personal single or 6-lead ECG device that users put their fingers on, connected to the Kardia mobile app, it provides AI-based ECG-recording and analysis to detect the most common heart arrhythmias. Evidence has demonstrated that it can accurately detect atrial

fibrillation (AF) and shows it to be noninferior to an external loop recorder (ELR) device for detecting arrhythmias in the outpatient setting,⁷⁵ thereby making it an ideal technology for community screening programs to detect silent AF.⁷⁶

Novel methods and strategies are also being developed to identify early signs of cancer and respiratory diseases in a minimally obtrusive way. With chronic obstructive pulmonary disease (COPD), lower respiratory infections, and trachea/bronchus/lung cancers accounting for three out of the six leading causes of death globally in 2019 and affecting almost eight million people,⁷⁷ the global need for diagnostic and monitoring tools in this space is substantial. One digital diagnostic strategy being pursued is to use 'electronic nose' technology that mimics a dog's highly sensitive sense of smell⁷⁸ to detect volatile organic compounds (VOCs) in human breath and elsewhere. More than 3,000 VOCs have been discovered in the human breath, and the concentration of some VOCs notably increases when someone is ill, leading to a specific "breath print" for different diseases.⁷⁹ In one published study of 475 individuals, an 'electronic nose' showed a 96% accuracy in detecting lung cancer in patients and 90-92% specificity,⁸⁰ suggesting this technology may eventually help lead to earlier diagnosis and improved treatment monitoring. Such digital sensors would also be more convenient and accessible than a traditional method of computed tomography screening used to detect lung cancers, especially for low-income countries,⁸¹ and might enable accurate detection of some serious respiratory diseases.

These tools are consequentially being purposed for the mobile/community detection of respiratory diseases, including COVID-19. With technology coming out of the Technion Israeli Institute of Technology, two products are being developed to bind to VOCs in gases — Nanose Medical's DiaNose to detect COVID-19⁸² and Technion's

Na-nose (Sniffphone and Breath Screener) for cancer detection.⁸³ These products are in clinical development, while another product from NASA, the E-Nose Breath Analyzer, is earlier in development for COVID-19 and a variety of other abnormalities, including respiratory illnesses, infectious disease, and cardiovascular conditions.⁸⁴ That device includes a smartphone app that processes, displays, and transmits sensor data for on-the-spot community screening.⁸⁵

Other new digital diagnostics for respiratory diseases include digital stethoscopes such as LungPass, ResApp and Hyfe.⁸⁶ While LungPass⁸⁷ is an external sensor device that records, analyzes, and classifies sounds from the lungs to help monitor (and help providers diagnose) a variety of respiratory conditions, notably pneumonia and chronic obstructive pulmonary diseases (COPD), ResAppDX, is an app that uses a smartphone's built-in microphone to analyze signatures in coughing sounds to diagnose respiratory diseases. As an approved medical device in Europe and Kenya with effective clinical trials, the app offers to provide low-cost and accurate respiratory diagnostic tests in home settings.^{88,89}

DIGITAL BIOMARKERS

By leveraging physiological and behavioral data from wearables or other digital sensors, digital biomarkers are being created to track patient health across a range of diseases — both with the intent to improve patient care by deploying them in the community setting and to use them in clinical trials to assess drug safety and effectiveness. Similar to clinical measurements, disease assessment scales, and other clinical trial endpoints, the intent with digital biomarkers is to provide sources of objective and quantitative measures of an individual's health status across multiple diseases. While traditional clinical methods may capture health data or assess performance at a single point in time, digital biomarkers offer to collect such data more continuously in real

time from wearables or other continuous measurement devices. For patients with chronic conditions, they offer the possibility of improving quality of life by reducing the need for in-person visits. They also offer to better track shifts in health status, patient response to interventions and reduce the subjectivity of self-reported measures typically captured in patient diaries.

Though the initial intent of some wearables, such as activity monitors, was to leverage information from various technical sensors such as an accelerometer and gyroscope to calculate wellness measures such as steps or sleep, scientists soon realized that if individuals were continually wearing such devices, algorithms could be written on the same data to interpret more nuanced aspects of health. Based on the technical sensors and features of the mobile/wearable devices used, biomarkers can shed light on similar aspects of patient health as traditional clinical ones, including aspects of executive function and neuropsychiatric behavioral disruptions in the neurology space (see Exhibit 15), or even provide more natural assessments of patient performance across a number of these domains.

Like other standard endpoints, biomarkers can be leveraged for various purposes that tie to disease processes. They can detect patient susceptibility/ risk, serve to aid in diagnosis (diagnostic biomarkers), monitor the course of disease, be prognostic or predictive of outcomes, track health outcomes as the result of interventions, or be used to personalize care.

Digital biomarkers provide objective and quantitative measures of an individual's health status across multiple diseases.

Digital biomarkers to track patient symptoms, risk and function are being developed across a range of diseases. In the case of neuromuscular diseases, digital biomarkers focus on the muscle weakness that emerges over time, leading to diminished mobility and respiratory difficulties. These include conditions such as Duchenne muscular dystrophy (DMD), some motor neuron diseases including ALS, and spinal muscular atrophy (SMA).⁹²

As new drugs have emerged for both SMA and DMD, patients, payers and other stakeholders have become more interested in gauging their effect on motor performance in the real world. Additionally, the COVID-19 pandemic revealed the restrictive nature of existing clinical measurements, which failed to reach the patient at home and turned manufacturer interest to new biomarkers based on wearables to maintain continuity of their clinical studies.

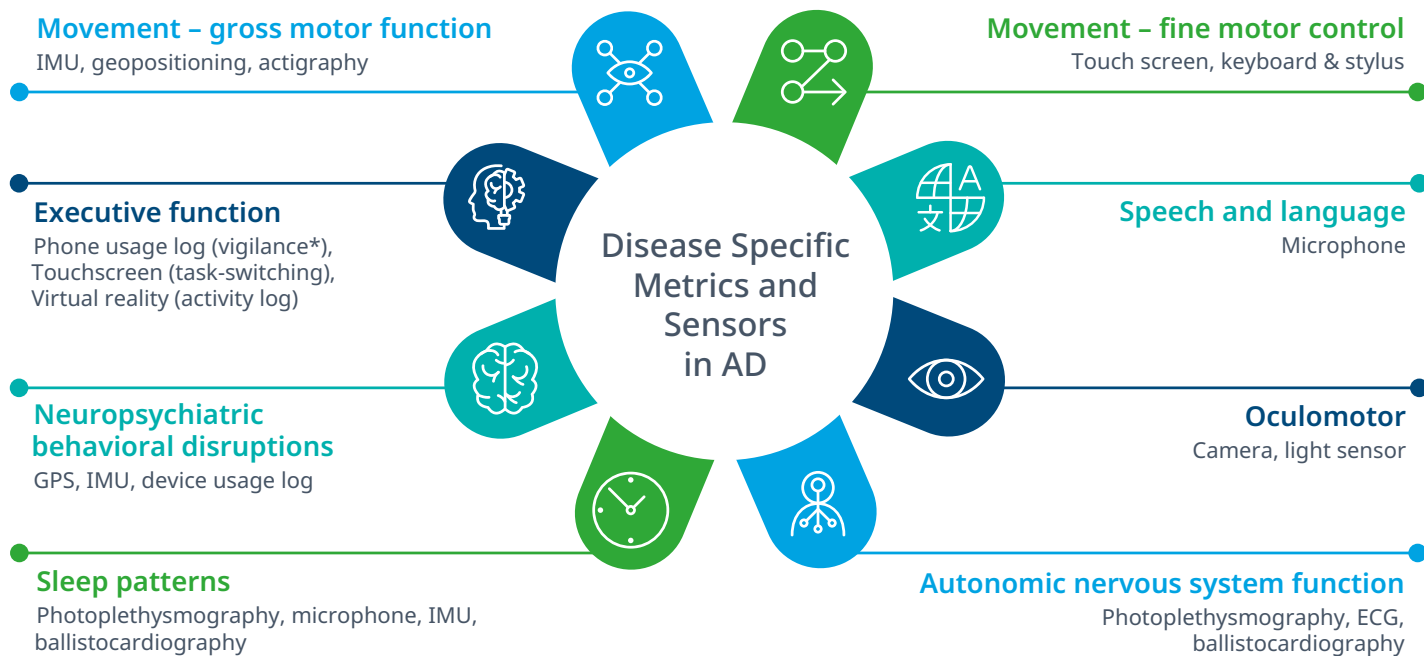
Biomarker proof-of-concept trials have used on-foot sensors that could eventually be deployed in the real world as insoles to assess walking ability and the gait of SMA and DMD patients.⁹³ These use inertial and non-inertial sensors to measure the center of pressure (forces acting on the foot), and gait parameters⁹⁴ like foot displacement, stride length, cadence, and double support time (when both feet contact the ground). Others biomarkers have used unobtrusive belt-worn sensors to estimate distances traveled and to determine typical and atypical walking patterns, or small coin-like movement sensors (currently placed on the body but eventually for use in mobile phones) that are being used in children and babies to define a “typical” toddler gait versus one showing muscle weakness.

The benefits of digital biomarkers are their ability to follow patient performance and progression in a community setting and detect a change when patients begin to lose strength in NMD. To monitor respiratory decline, for instance, some marketed devices such as SanThera and NuvoAir home spirometers are demonstrating their value in the community setting. Others gait sensors may be able to provide differential diagnosis, distinguishing DMD from other disorders such as Charcot-Marie-Tooth disease (CMT) and SMA, or predict which patients are developing a risk for falling. Still others may be able to identify children who are starting to develop gait abnormalities in order to refer them to a specialist early and help speed diagnosis. These innovative biomarkers have the potential to improve SMA and DMD patients’ quality of life by obviating the high-burden of visits to hospital motion labs, and also reduce costs to the healthcare system and patients by helping to reduce secondary medical and pulmonary events.

Although a variety of parties are incorporating wearables in disease research studies, there is a debate on whether to try and extract conventional parameters currently used by clinicians from sensors and wearables — such as those captured by motion capture systems and electronic walkways — or leverage the unique abilities of these wearables to create new measures. Re-creating known parameters of mobility and motion would facilitate adoption by health, medical and academic professionals who easily recognize their value, but existing consumer wearables that tend only to measure high-impact motions are unlikely to be useful in this pursuit. Researchers face other challenges with validated research-grade devices such as Medilogic, Pedar, Moticon, and F-Scan 64 insoles, as these don’t come with measures that correlate to NMD performance parameters and are proprietary systems that typically make it impossible to write new algorithms.

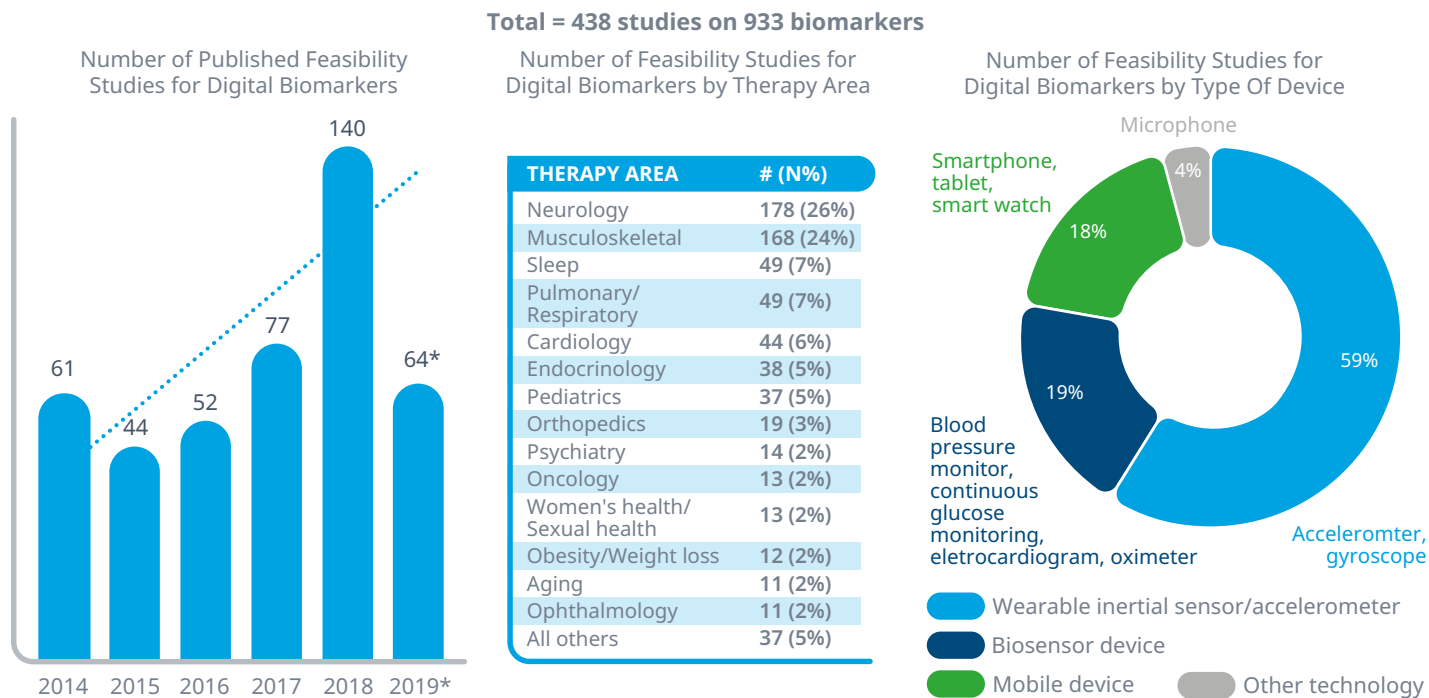
For this reason, researchers are increasingly focused on developing dedicated neuromuscular wearables from prototype up. Such unique gait-focused devices may also deliver benefits to other patient populations with mobility disorders, strokes, age-related muscle wasting, children with neurodevelopmental disorders with gait impairment, or the elderly population, where biomarkers can assess their balance and risk of falling. Even in Parkinson’s patients they may be able to identify symptoms before they become severe enough to identify visually. After these biomarkers are tested in validation and effectiveness studies, they are likely to be used to track the impact of physical therapy interventions, and also to develop clinical trial endpoint measures for drug development.

Exhibit 15: Digital Biomarkers: Use of Sensors to Capture Various Functional Domains — Neurology Examples



Source: Kourtis, L.C., et al. Digital biomarkers for Alzheimer’s disease: the mobile/wearable devices opportunity. npj Digital Med 2, 9 (2019)
 Notes: *Vigilance refers to the ability to sustain attention on a task and is a measure of overall attention. IMU = Inertial measurement unit, ECG = Electrocardiogram, GPS = Global positioning system.

Exhibit 16: Feasibility Studies on Digital Biomarkers Since 2014 and by Therapy Area and Device Type⁹⁵



Source: CTTI, Nov 2020, <https://feasibility-studies.ctti-clinicaltrials.org>. IQVIA Institute, Jun 2020
 Notes: Database includes a systematic search of scientific literature indexed in PubMed and published between January 2014 and June 2019. The term “pilot” was not in the original search from January 2014–May 2018 dataset but was included in the review from June 2018–June 2019. One study from 2013 removed and one duplicate title. * Indicates data and values shown are for partial year through June 2019.

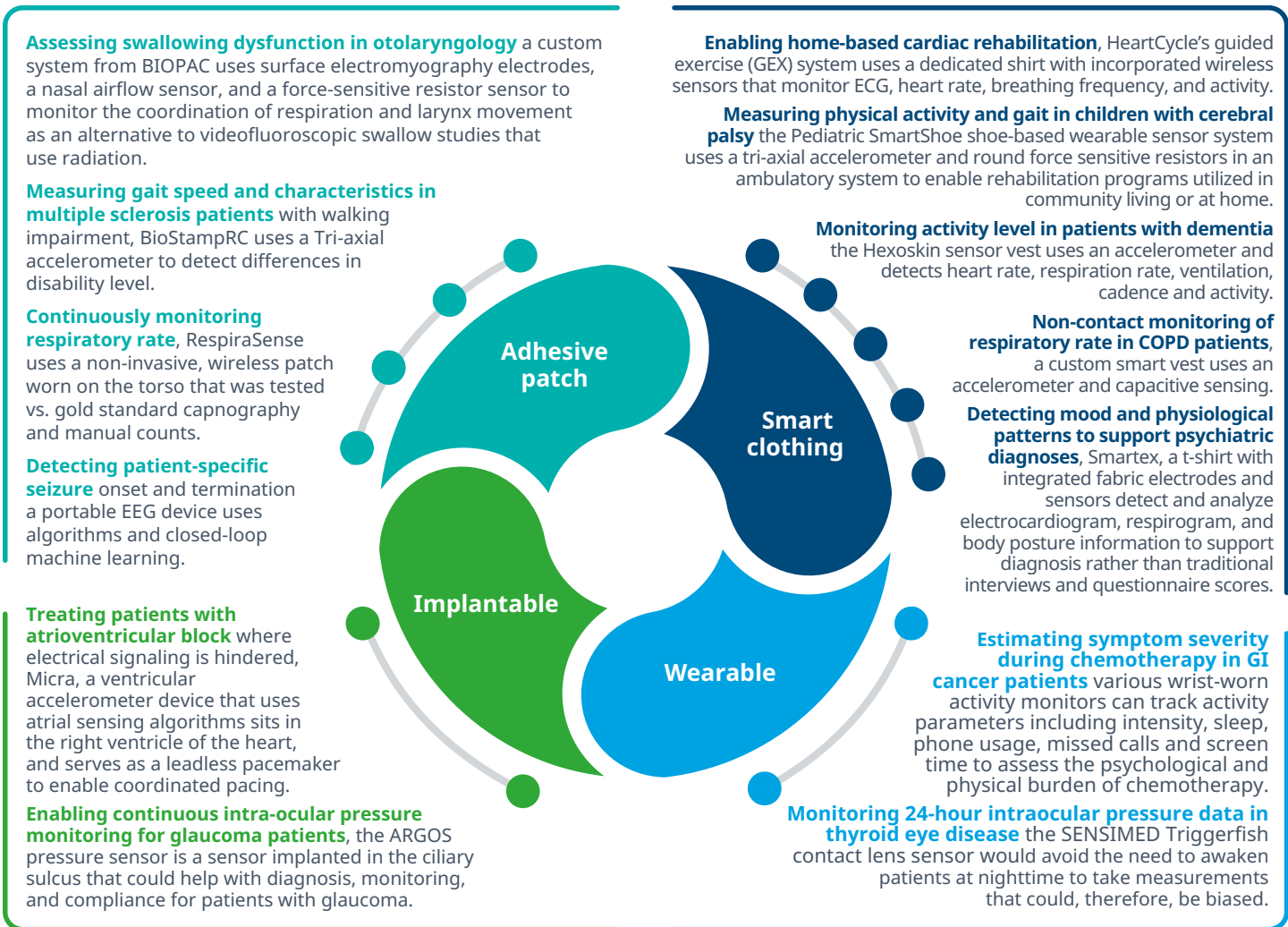
Validating digital biomarkers

Improvements in the sensitivity of these devices, and the creation of dedicated clinical-grade wearables to capture specific measures, are driving innovation in clinical care and clinical trials by offering new methods of remote patient monitoring, giving clinicians the ability to track patient wellbeing and outcomes in the real world. In clinical trials they are gradually enabling the adoption of new endpoints. However, in order to use these new digital biomarkers in either care or research, they must proceed through feasibility/validation trials to assess performance versus comparators, data completeness and user acceptability, usability, and persistence. The number of feasibility studies on digital health

technologies to capture data in clinical research or care settings has been growing since 2014, with neurology, musculoskeletal disorders, and sleep accounting for over half of studies (See Exhibit 16). In total, 438 studies have been done examining 933 distinct biomarkers.

Many devices (e.g., actigraphy) historically have been used in research. However, emerging devices, such as smart-clothing and adhesive patches show the evolution of methods to remotely monitor specific patient populations (see Exhibit 17). Such biomarkers offer to capture measures uniquely tied to disease, and therefore are much more valuable to clinicians.

Exhibit 17: Focus of Biomarkers Tested in Feasibility Studies by Type



Source: CTTI, Nov 2020, <https://feasibility-studies.ctti-clinicaltrials.org>. IQVIA Institute, Jun 2021
 Notes: COPD = Chronic Obstructive Pulmonary Disease.

Digital devices and their role in clinical trials

- + **Sensors and digital biomarkers are being incorporated into the design of clinical trials for pharmaceuticals and medical devices and are enabling decentralized and hybrid trials with home visits, reducing patient and investigator burdens, and accelerating clinical trial timelines. This trend accelerated during the pandemic, when healthcare facility access was restricted, and trial participants were subject to movement restrictions.**
- + **Since 2016, the percentage of trials using connected medical device technologies doubled and is now 8%, with 10% of Phase II and III trials now including connected devices.**
- + **Advances in sensors and the emergence of digital biomarkers are propelling their application in clinical trials.**
- + **Digital biomarkers have gradually gained adoption in clinical trials to track patient outcomes, and more than 193 unique digital biomarkers have been used as endpoints in 96 clinical trials.**
- + **Hybrid decentralized trials are expected to reduce the number of on-site visits required of patients in Phase II and III trials by 44-61%, depending on the therapy area, as visits shift offsite.**
- + **As trials in various therapy areas including oncology, neurology and cardiology often compete for patients, decentralized and hybrid trials that may increase the eligible pool of trial participants may thereby accelerate clinical development and make room for more trials to be run in these areas.**

DIGITAL TECHNOLOGIES IN CLINICAL TRIALS

Beyond their use in the wellness space and for development of novel digital endpoints, clinical-grade sensors and digital biomarkers are also being incorporated into the design of clinical trials intended to test the safety and efficacy of drugs or devices. This can range from the use of portable and connected devices to collect health measurements in traditionally-designed trials, to the emerging use of these devices for remote patient monitoring in the format of decentralized trials — those with semi-offsite execution or even completely home-based or offsite trials.

Connected devices

In clinical trials, connected and portable devices are used to measure the safety and efficacy profile of experimental medicines and devices, and ensure the wellbeing of subjects as they undergo testing. ECG devices have been used for the longest time to measure effects of drugs on the heart to catch signs of cardiac toxicity and disruption of heart rhythms, but the past three-and-a-half years have increased use of CGMs to track the impact of experimental therapies on blood glucose metabolism, spirometry devices to track any effects on pulmonary function or signs of toxicity, as well as the use of ambulatory and home blood pressure monitors to check for hypertensive or anti-hypertensive effects (see Exhibit 18).

During the pandemic, devices to monitor a range of vital signs were also incorporated rapidly into infectious disease trials, among others, to monitor whether a subject enrolled in the trial may have been affected by COVID-19. The future will bring increased use of very-sensitive mobile actigraphy devices, devices for voice/ audio and facial image capture, ambulatory EEG devices, and the miniaturization of various larger devices, such as imaging tools, so they may be increasingly used at the patient side in trials.

Novel uses of these devices will come in the form of digital biomarkers using algorithms and computational models to make sense of incoming signals. By tracking

Exhibit 18: Waves of Connected Medical Device Technology Adoption in Clinical Trials



Source: IQVIA Institute, Jun 2021

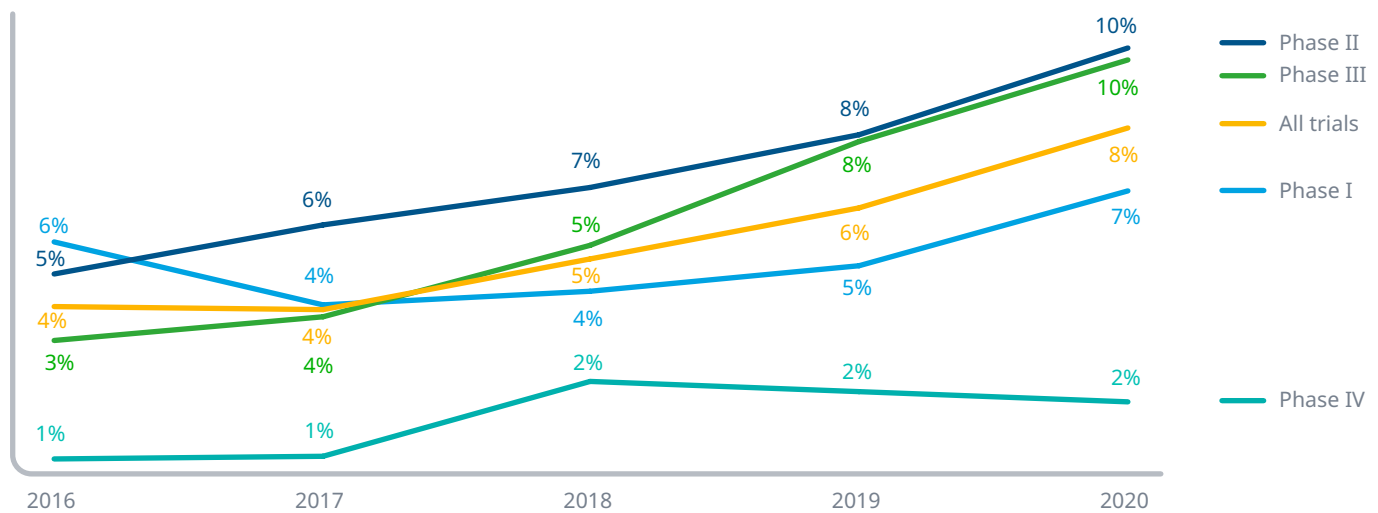
Notes: Includes devices used for safety as well as efficacy evaluations . ¹ = MDPI. How to Select Balance Measures Sensitive to Parkinson’s Disease from Body-Worn Inertial Sensors—Separating the Trees from the Forest. Available from: <https://www.mdpi.com/1424-8220/19/15/3320/html>.

nanced movement using actigraphy, digital biomarkers can track neurodegenerative processes and symptoms of neurological diseases such as Parkinson’s (PD) and Alzheimer’s to indicate symptom progression or even detect trembling, indicating various seizure-types. In PD, for instance, measures such as turning velocity, foot strike angle, arm swing range of motion, and first step length⁹⁶ may be useful to track severity of disease and patient-related outcomes. Voice/audio capture devices using sensitive microphones may be used to detect breathing abnormalities or cough type in the respiratory and infectious disease space, or to detect pauses in

speech that can correlate with depression and mental health or cognitive disorders. Altered facial behavior and emotional expressivity captured remotely using smartphones or other video devices can be used to detect shifts in cognitive function and mental health.

The use of connected medical device technologies has seen significant growth over time, with the percentage of all trials using these rising from 4% in 2016 to 8% of all trials in 2020. Use in Phase II and III trials similarly doubled over the period, and now includes connected devices 10% of the time (see Exhibit 19).

Exhibit 19: Trials Using Connected Medical Devices as a Percentage of All Trials



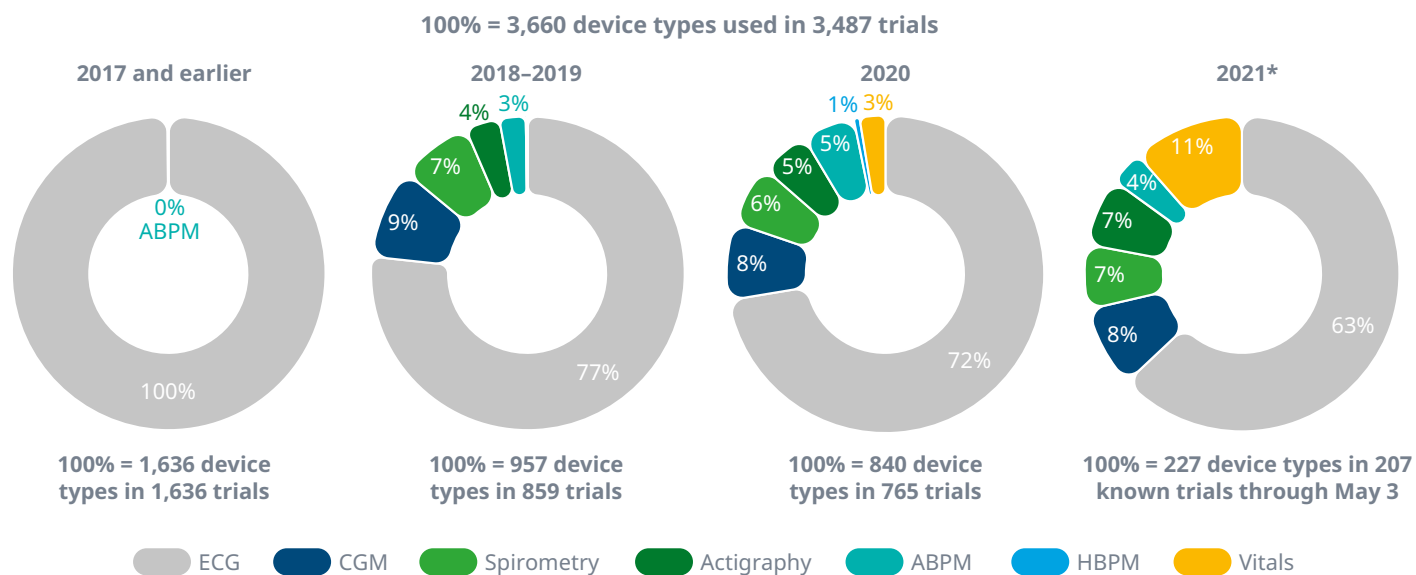
Source: IQVIA Institute, Jun 2021

Notes: Slide shows trials IQVIA is aware of in each year. Connected device trials include those for ECG, vital sign capture, actigraphy, spirometry, blood pressure and glucose monitoring, where a life sciences company intends to outsource the device trial component in Phase I-IV. Excludes trials where the company is directly insourcing devices.

The past three-and-a-half years have also seen a significant diversification in the types of devices being incorporated into trials. Whereas in 2017 and earlier, ECG devices accounted for nearly 100% of all devices included in clinical trials across phases, for trials that are currently starting up in 2021, other device types now make up 37% of devices used. Vital sign monitors grew to 11% of devices used in connected device trials, with CGMs to detect fluctuations in blood glucose levels, spirometry and actigraphy accounting for more than 7% (see Exhibit 20).

Each device can be used across trials of various therapy areas (see Exhibit 21). Just as ECGs are used across all therapy areas as a key measure of cardiac toxicity, which can derail development of new medicines, the other device types are also increasingly being used across trials in many therapy areas including actigraphy devices, CGMs, spirometry, ambulatory blood pressure monitors (ABPM) and vitals sensors. Notably, the top therapy areas for actigraphy are neurology, psychiatry, and cardiovascular trials where it is important to track

Exhibit 20: Connected Device Types and Their Percent Representation in Trials by Year



Source: IQVIA Institute, Jun 2021

Notes: Slide shows trials IQVIA is aware of since 2006 date where a life sciences company intends to outsource the device trial component in Phase I-IV. Excludes trials where the company is directly insourcing devices. Large imaging devices were excluded. *2021 data shows Jan-May 3.

the physical activity and mobility of individuals, but these also are included in dermatology trials. Likewise, CGMs are predominantly used in endocrinology trials but are also included in neurology and respiratory trials where the subject's age may be a factor, and spirometry is used in the respiratory space, as would be expected, but also in neurology and GI trials. ABPM, on the other hand, is used more evenly across therapy areas.

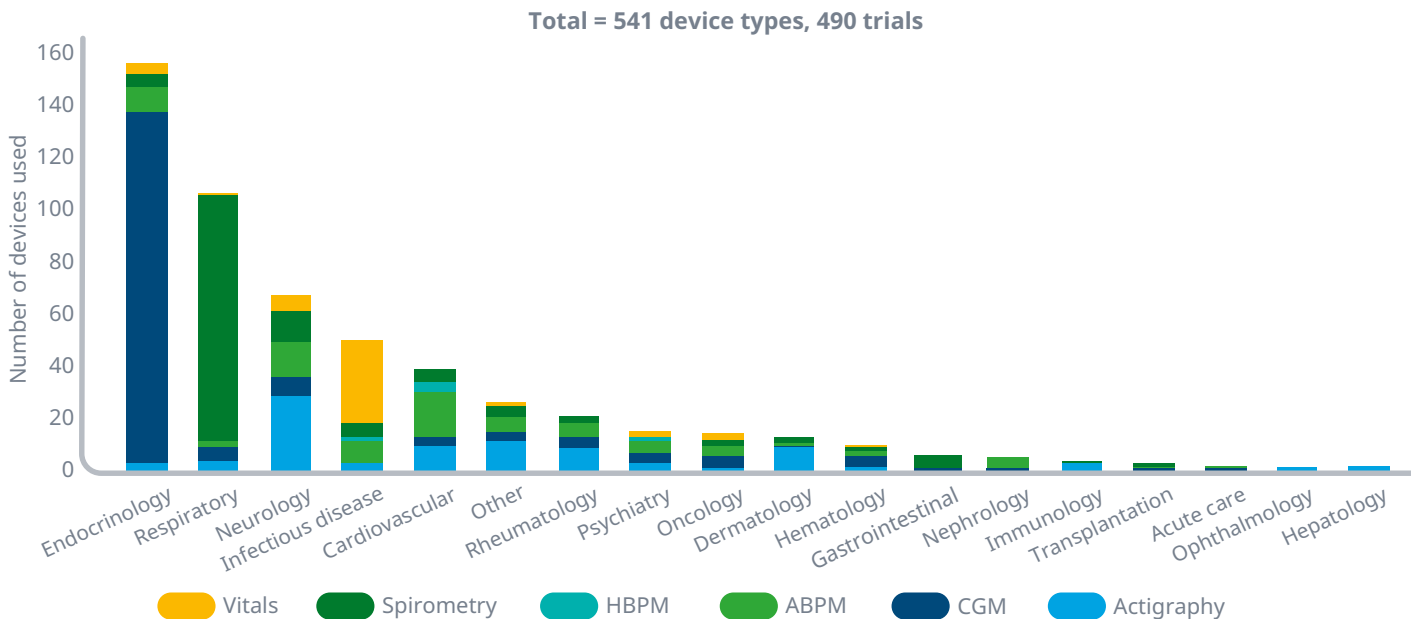
Digital biomarkers as endpoints in trials

The digital biomarkers enabled by both clinical-grade sensors and consumer wearables are also finding their way into clinical trials, enabling biopharma companies to better understand aspects of a patient's health and gain a continuous understanding of disease progression and patient-reported outcomes. Improvements in the sensitivity of devices, and the creation of dedicated clinical-grade wearables to capture specific measures are driving innovation in clinical trials by allowing the inclusion of digital biomarkers as endpoints. Looking at the Digital Medicine Society (DiMe) Library of Digital

Endpoints, which covers industry-sponsored studies of new medical products using digital biomarkers, more than 193 unique digital endpoints have been used in 96 trials, mostly testing drugs and devices. Neurology, endocrinology (i.e., diabetes) and respiratory trials have made the greatest use of digital endpoints (see Exhibit 22) and account for 60% of digital endpoints measured. Among the neurologic conditions being tested are pain, restless leg syndrome and other sleep disturbances, Alzheimer's, and Parkinson's, while in the respiratory space, asthma, COPD, and pulmonary arterial hypertension are key focuses.

Among the health concepts tracked by digital biomarkers, most assessed physical activity and various aspects of sleep — uses that are already well established — followed by biomarkers measuring glucose levels, such as Time in Range, which is starting to become more conventional using continuous glucose monitors, and glycemic variability.^{97,98}

Exhibit 21: Connected Device Types Excluding ECG Used in Trials by Therapy Area, 2017–2021*

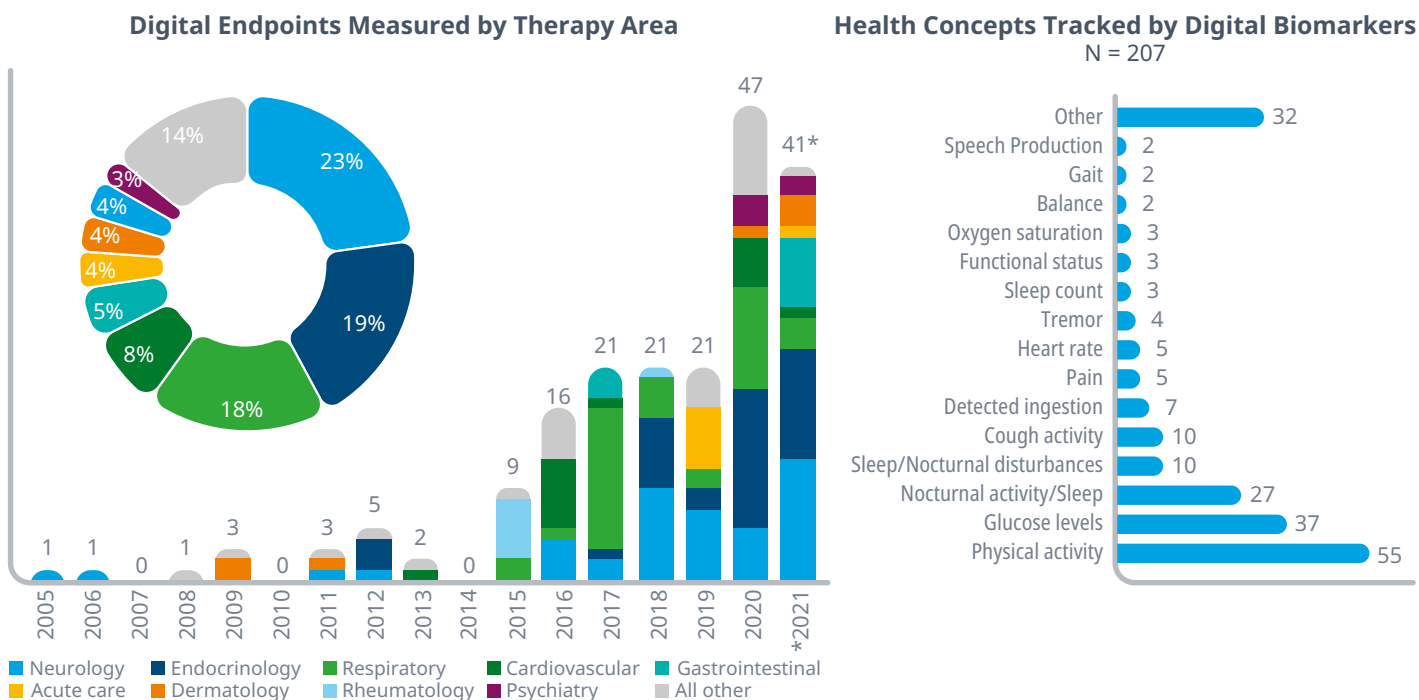


Source: IQVIA Institute, Jun 2021

Notes: Slide shows trials IQVIA is aware of since 2017 where a life sciences company intends to outsource the device trial component in Phase I-IV. Excludes trials with ECG. Excludes trials where the company is directly insourcing devices. Large imaging devices were excluded. *Data as of May 5, 2021.

Exhibit 22: Trials with Digital Biomarkers as Endpoints by Therapy Area and Measure

N = 96 Distinct Trials with 193 Distinct Digital Endpoints



Source: Digital Medicine Society (DiMe) Library of Digital Endpoints. Available from: <https://www.dimesociety.org/index.php/knowledge-center/library-of-digital-endpoints>, Apr 2021

Notes: *2021 Data only through April. DIME Library of Digital Endpoints is a crowdsourced library specifically focused on self-reported, industry-sponsored studies of new medical products (including devices and drugs) or new applications of existing medical products, from 2005 to 2021. Counts all entries in database. Totals may not sum due to rounding.

DECENTRALIZED AND HYBRID TRIALS

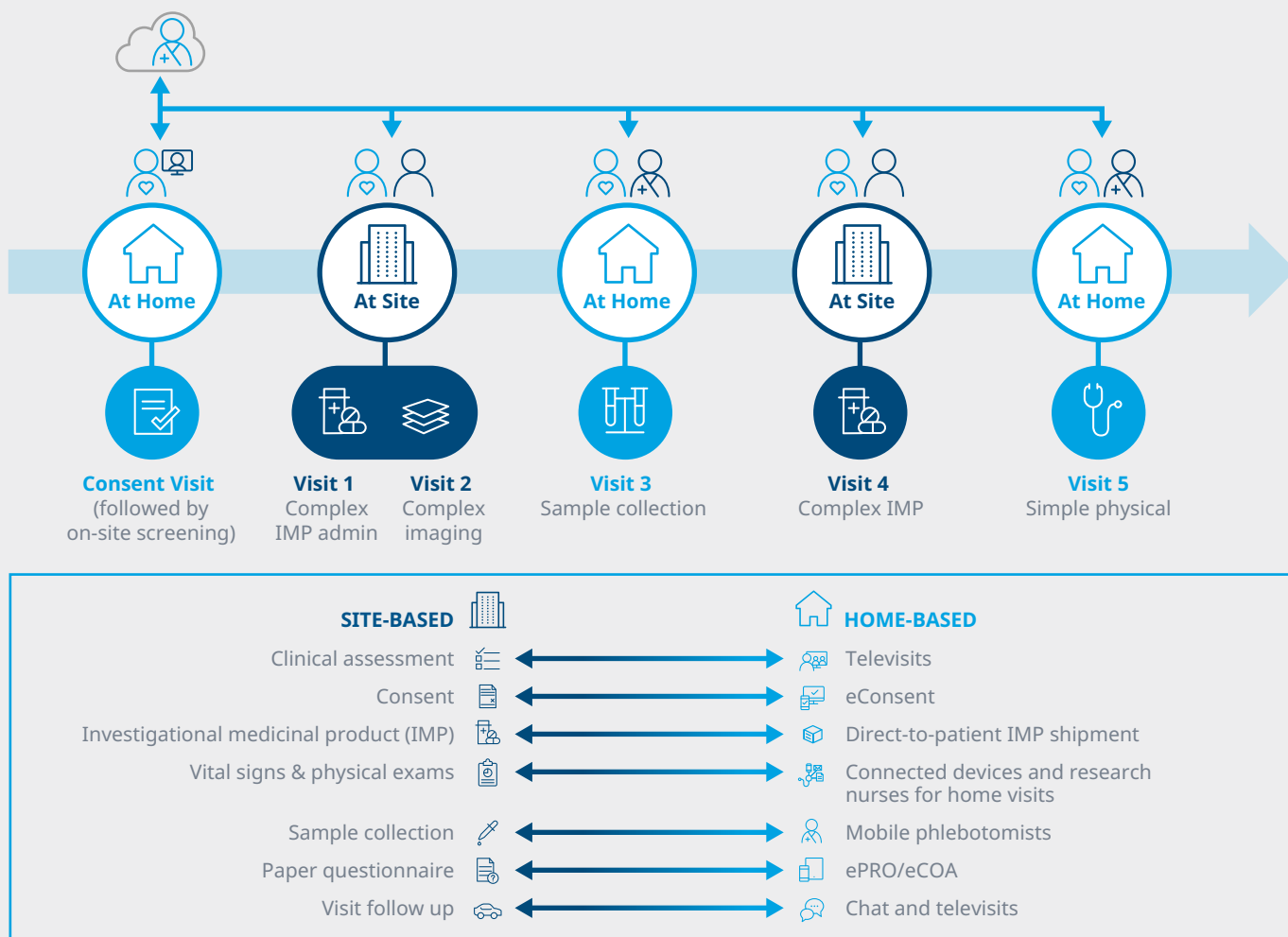
The use of clinical grade connected devices to remotely monitor patient symptoms and health status, along with novel uses of digital biomarkers to detect unique endpoints of interest, are changing the face of clinical

development projects. Combined with the use of telemedicine and even the ability of home health nurses or mobile phlebotomists to visit patients at home, the feasibility of running clinical trials away from a centralized hospital or other research location has

WHAT IS A DECENTRALIZED TRIAL

For the purpose of this report, decentralized trials are defined as trials focused on “bringing the trial to the patient”¹⁰⁰ by utilizing: a platform or technology to communicate with remote study participants and collect data through means such as telemedicine, mobile or local healthcare providers, and mobile technologies such as connected devices.¹⁰¹ Remote patient visits are typically conducted at home through visits from clinical research nurses and mobile phlebotomists and occasionally at nearby medical facilities, and help reduce the burden on patients of participating in clinical trials. Much of the data collection is facilitated by digital devices, such as iPads to provide eConsent, mobile video to confirm medication use, and connected devices to collect vitals (see Exhibit 23).

Exhibit 23: Hybrid trial: A Site-Based Study with Decentralized Components



Source: IQVIA, Jan 2021; IQVIA Institute, Jun 2021

grown. Such hybrid trials combine remote, home-based visits along with traditional site visits to reduce patient burden and streamline operational execution. One key use is likely to be long-term observational extension studies tracking safety after an interventional phase, that can therefore be in a light-touch hybrid design.

Hybrid trials are expected to reduce the number of on-site visits patients need to make while participating in a trial. Between 44-61% of visits in Phase II and III trials are being shifted offsite in hybrid trials, depending on the therapy area, with 51% on average in Phase III and 58% in Phase II trials across therapy areas.⁹⁹ Such home-based trial visits include both induction and safety visits as well as treatment visits, and typically combine a telemedicine interaction with a trial investigator with either a visit by a home health nurse or mobile phlebotomist.

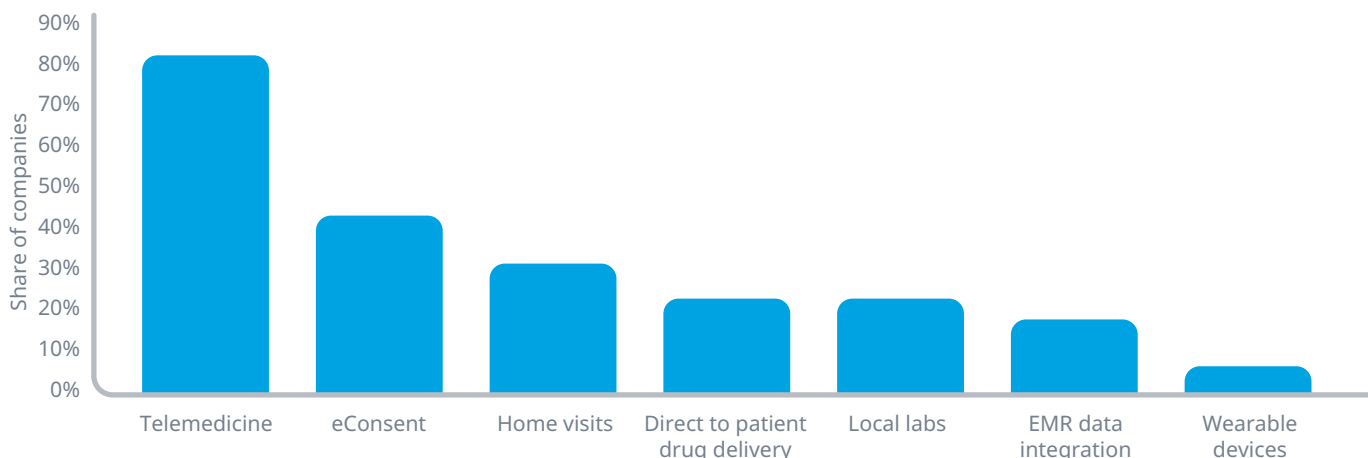
While remote patient monitoring has been discussed and gradually increasing both in the standard clinical environment and within the research space, it has truly been the impact of the COVID-19 pandemic that has accelerated the shift to decentralized and partially-offsite “hybrid” trials. Whereas technology was initially used in the pre-COVID-19 period to ease the burden of recruitment and data management, technologies enabling hybrid and virtual clinical trials have quickly

become essential during COVID-19 and will continue to be in the post-COVID-19 era. This shift has been facilitated by guideline updates issued by regulatory authorities to mitigate the damage caused by the onset of the COVID-19 pandemic and its disruption to clinical trials. For instance, the FDA issued guideline in March 2020 recommending alternative methods, such as phone contacts, virtual visits, and the use of alternative locations for assessments, including local labs or imaging centers, and similar steps were taken by the UK MHRA and others in Europe.^{102,103}

During the COVID-19 pandemic, clinical trials rapidly shifted to decentralized (30%) or partially-decentralized “hybrid” models, with more than half (54%) of active trials using some remote monitoring during the pandemic, with various technologies being adopted by the 50 largest pharmaceutical companies, including telemedicine among more than 80% (see Exhibit 24).^{104,105}

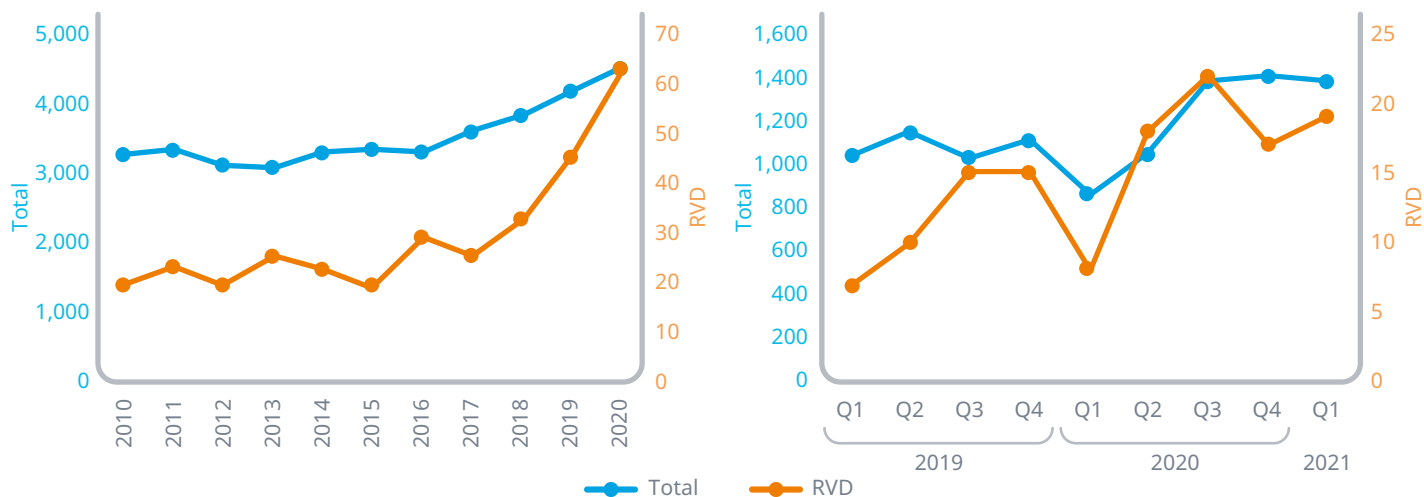
With 60% of investigative sites reporting no experience with remote processes before the pandemic, and smaller pharmaceutical firms similarly lacking experience running offsite trials, much of this work has fallen to contract research organizations to help support the shift, and still 25% of active trials were delayed or suspended.¹⁰⁴ In at least one case, a manufacturer

Exhibit 24: Remote and Virtual Clinical Trial Support Adopted Specifically During the Pandemic



Source: Tufts Center for the Study of Drug Development (CSDD.tufts.edu)

Exhibit 25: Trial Starts for All Trials and Remote, Virtual or Decentralized Trials (RVD)



Report: Global Trends in R&D: Overview through 2020. Report by the IQVIA Institute for Human Data Science.

Source: Citeline Trialtrave, Apr 2021; IQVIA Institute, Apr 2021

Notes: This analysis includes remote, siteless, virtual and decentralized trials, but also trials including a single element typically included in these, such as telemedicine, home health interactions, remote and virtual visits, mHealth, remote sensors (that might collect) digital endpoints and digital biomarkers, eCOA and ePRO, eConsent, medication use tracking devices, as well as those trials using medical event monitoring systems or medication event monitoring systems.

conducting a trial with a dual-format design — where some patients had opted for fully-onsite engagement and others opted for fully decentralized engagement — found only the latter was able to continue through the pandemic. Investments by pharmaceutical companies are therefore likely to continue as they try to “future-proof” their trials for such exceptional events as future pandemics. Already, trials which use technological elements for remote patient monitoring (such as telemedicine or digital health devices) or decentralized formats have been increasing and accelerated during the COVID-19 pandemic (see Exhibit 25).

THE IMPACT OF DECENTRALIZED (DCTs) AND HYBRID TRIALS ON STAKEHOLDERS

The shift to decentralized and hybrid trials is likely to continue and will have an impact on clinical trial staff and participants alike. Participants in trials are likely to benefit most greatly as research becomes a more convenient and participant-centered experience, with more home-based visits and offsite lab work.¹⁰⁶ Compared to traditional RCTs, which could require many on-site study visits, a participant’s time burden, including travel time, in hybrid or fully-decentralized trials can be significantly reduced to

few-or-no on-site visits. This is likely to make participation in trials less prohibitive and improve participant study retention. Instead of going through an in-person informed consent process at the beginning of the first in-person visit, for instance, participants may instead go through a remote eConsent process and be consented by telephone or video conference call with the study’s principal investigator (PI) or clinical research coordinator (CRC), and may receive documents in advance of their remote visits through digital platforms that permit electronic review and digital signature. In addition, participants benefit from various eConsent platforms, which have improved educational components and therefore support greater comprehension.

Overall, the hybrid format is likely to reduce challenges for some participants who otherwise wouldn’t be able to participate, making trials more inclusive and expanding the eligible pool of trial participants. As pharmaceutical and life science companies and their hired contract research organizations (CROs) face a challenge in recruiting participants,¹⁰⁷ expanding the pool of eligible volunteers to those that may have been excluded by various challenges such as lack of access to clinical

sites, geographic challenges, and potential financial and transportation burdens to get to the study sites, is likely to aid recruitment. Along with a separate trend of direct to participant recruitment (DTP) through social media, websites, registries, optimal search engines and mobile devices, research trials are increasingly able to extend their reach to audiences who would have otherwise not known about the trial, enhancing enrollment. As trials in various therapy areas including oncology, neurology and cardiology often compete for participants, such trends that increase the eligible pool of trial participants may thereby accelerate clinical development and make room for more trials to be run in these areas.

At trial sites, the use of hybrid trial designs may require the adoption of new technologies to execute them, resulting in sponsors, CROs, and DCT technology companies needing to invest time in training staff and oversee the implementation of the new model. The adoption of telemedicine by more than 80% of companies during COVID-19¹⁰⁵ likely ties to the speed and need of its implementation, compared with other elements of trial design becoming remote. Other concerns for the site are that sponsors using decentralized and hybrid trials might limit a site's use and overhead payments and reduce site staff allocation (e.g., a nurse or phlebotomist or even the site coordinator) or contract amount per grant, however any reduced staff time commitments may also allow for the uptake of more grants and thus more studies to be run in addition to being compensated for other DCT elements such as home health nurse oversight or technology training.

The shift to hybrid trials will particularly affect site staff. To make their studies completely pandemic proof in the future, sponsors have focused on managing shipments of drugs to participants with lower costs, however these remain one of the key cost-drivers of hybrid trials and are often avoided. When the vendor decides to use direct-to-patient (DTP) shipments — where study drugs are shipped directly to participants via medical delivery services (e.g., Medspeed), curbside or valet medication pickup — pharmacists and supporting staff may be

completely replaced or activities reduced in their study involvement. However, DTP may not be permitted in some countries, and in those cases, pharmacists will still be necessary to dispense the study drugs from the site itself,¹⁰⁸ though the COVID-19 pandemic has pushed countries to reassess their stand on the matter.

The growing need for mobile phlebotomists and home health personnel during the pandemic has also modified specimen collection, allowing for the collection of vitals, blood draws, urine and/or stool samples to be sent from the participant's home to the study's central lab, or to local labs reducing the scope of related activities for site staff. With the rise of DCTs, CROs have rapidly invested and built up their home-health nurse and clinical research nurse services to enable offsite sample collection, with Icon acquiring Symphony,¹⁰⁹ Covance purchasing Globalcare,¹¹⁰ and Syneoshealth acquiring Illingworth Research Group back in December 2020.¹¹¹ Other CROs are building complete sets of solutions around such home health/clinical research nursing.

For sites with data now feeding in from wearable and mobile devices, ePROs, mobile research nursing, telehealth, local labs, and digital biomarkers as eSource data, along with traditional data still coming from clinical medical assessments and medication checks, this process can be challenging. In an analysis by Tufts Center for the Study of Drug Development, nearly half of sponsor companies reported that taking in data captured directly from participants, specialty labs and assessment providers (some for the first time during the pandemic) was more difficult to access and integrate into the study database.¹⁰⁴ For this reason, the ability of new technologies like Electronic Data Capture (EDC) software and eSource to help site staff take in data obtained remotely along with those collected in-person, while making data collection more efficient and standardized in quality, has become all the more essential. With hybrid trials relying increasingly on eSource platforms and data like ePRO and other participant gathered data, CRCs may ultimately find they spend less time collecting data via manual methods.

E-SOURCE DATA

As decentralized trial data collection strategies have matured, a dramatic percentage of data is now being captured using fully electronic methods directly into the trial database, reducing the risk for human error. Data from patient reported outcomes (PRO) and clinical outcome assessments (COA) can be collected electronically and entered into the same digital platform as eSource data from connected devices, resulting in improved speed and accuracy of trials. Platforms enabling a combined data strategy from various sources including connected devices and facilitating data aggregation, cleansing and analysis, will be an accelerator of this trend.

For clinical research associates (CRAs), with hybrid trials that are fully eSource, their data monitoring and review time may be reduced by software that embeds validation checks (e.g. for vitals values). The shift of data storage to the cloud in hybrid trials also means their required travel may be minimized, with less travel from site to site (particularly if multiple trials are being run hybrid at the same site).

Finally, the increased use of remote monitoring is likely to improve participant safety through alerts and other robust information sent to the Principal Investigator.¹¹² With the use of real-time data from continuous connected devices and ePRO collection feeding into study platforms that can provide alerts as well as reports, these tools are helping to improve their ability to care for participants. For instance, participants can login to platforms like IQVIA's Study Hub to complete their electronic patient-reported outcomes (ePRO) regarding possible symptoms, side effects, drug timing and other questions, contributing to the efficiency of the study's data collection and management.¹¹³ Although continuous connected devices may require more data to be reviewed, they offer to yield better participant care. In the CRO world, the access of study concierges and contract research staff to real-time data from remote monitoring devices (e.g., telemedicine) and advanced analytics facilitates the assessment adverse reaction alerts.

Much is to be gained and explored from transitioning clinical trials to hybrid or even completely decentralized trials, yet, much remains to be solved regarding remote communication and remediation, data coordination and integration. Additionally, issues regarding the expected discrimination between those technology-savvy to those that are not, notably a generational and aging population, may only further the gap between eligible and non-eligible participants.¹¹⁴ Numerous efforts remain to be made to use the transformative nature of clinical trials to its full potential.

Hybrid trials combine remote, home-based visits along with traditional site visits to reduce patient burden and streamline operational execution.

The maturity of evidence on digital health

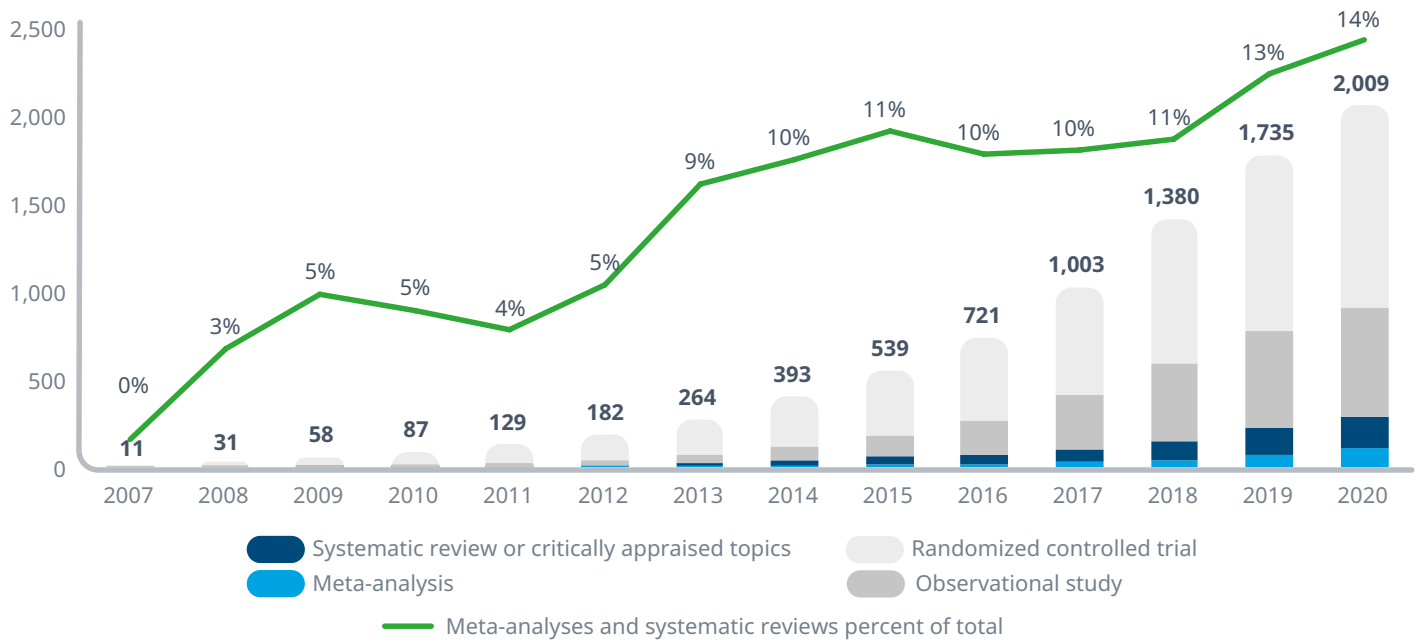
- + The evidence base continues to grow on the effectiveness of digital health apps with more than 2,000 studies published since 2007, including almost 1,500 published in the past five years.
- + The number of systematic reviews and meta-analyses has notably continued to grow, indicating a growth in maturity and a consolidation of thinking about the use of apps across various applications.
- + Evidence now supports the inclusion of digital health tools in treatment guidelines for an expanded set of health indications. These include cardiovascular applications (e.g., screening for atrial fibrillation and cardiac dysrhythmias, CHF management, cardiac rehabilitation, and hypertension), use tied to behavioral modification (e.g., medication management, exercise, healthy eating and weight management, and smoking cessation) and management of some chronic conditions (e.g., pain and infectious and parasitic diseases, including HIV/AIDS).
- + Independent organizations continue to highlight the need for growth in high-quality evidence, larger and more robust RCTs that follow patients for longer times and report between-group differences in benefit, assessments of usability, and user-retention to determine the durability of their clinical effect and evidence of cost-effectiveness that can be analyzed versus standard of care.

EVIDENCE OF DIGITAL HEALTH EFFECTIVENESS

As the developers of digital solutions seek to prove the value of their products and organizations seek to leverage such apps and incorporate them into practice, both parties have run clinical trials, driving continued growth of the evidence base on digital health app effectiveness. According to the IQVIA AppScript Digital Health Evidence Database (see Methodology), the number of digital health effectiveness studies published since 2007 now exceeds 2,000, with nearly three-quarters (n=1,470) of all evidence produced within the past five years. Despite the continued growth, the number of studies published per year on digital health began to slow in 2018 and continued to decline through 2020 (from 377 to 274 publications), though this did not occur across all study types. The number of systematic reviews and meta-analyses notably have both continued to grow, jointly reaching 14% of published studies in 2020, indicating a growth in the maturity of evidence and a consolidation of thinking about the use of apps across various applications (see Exhibit 26). Notably, there were no negative meta-analyses published in the 2018–2020 period. While this is likely indicative of a positive publication bias, it also indicates that as app uses mature, there are successful leading apps and technologies in most areas proving they can have impact, even as emerging players may still be refining their approaches or exploring new ones.

The body of evidence around digital health app effectiveness is now substantial with more than 2,000 studies published since 2007.

Exhibit 26: Cumulative Number of Published Digital Health Efficacy Studies and Percentage of Meta-analyses and Systematic Reviews



Source: AppScript Clinical Evidence Database, Jan 2021

Notes: Only includes studies that evaluated the interventional value of a digital health solution (mobile or web app, connected device, or other mobile intervention such as texting) on patient outcomes such as activity levels, lab results, or healthcare resource utilization. 'Observational Study' includes all trials examining the interventional value or impact of an app excluded from the other three categories regardless of design.

By mapping the studies that have been published on apps to the use cases they support and their level of positive evidence, it is clear that the growing evidence base also now supports clinical or widespread real-world use across more use categories. A significant number of use categories now can be considered ripe for inclusion in clinical guidelines, with multiple positive meta-analyses supporting that use, and many others can now

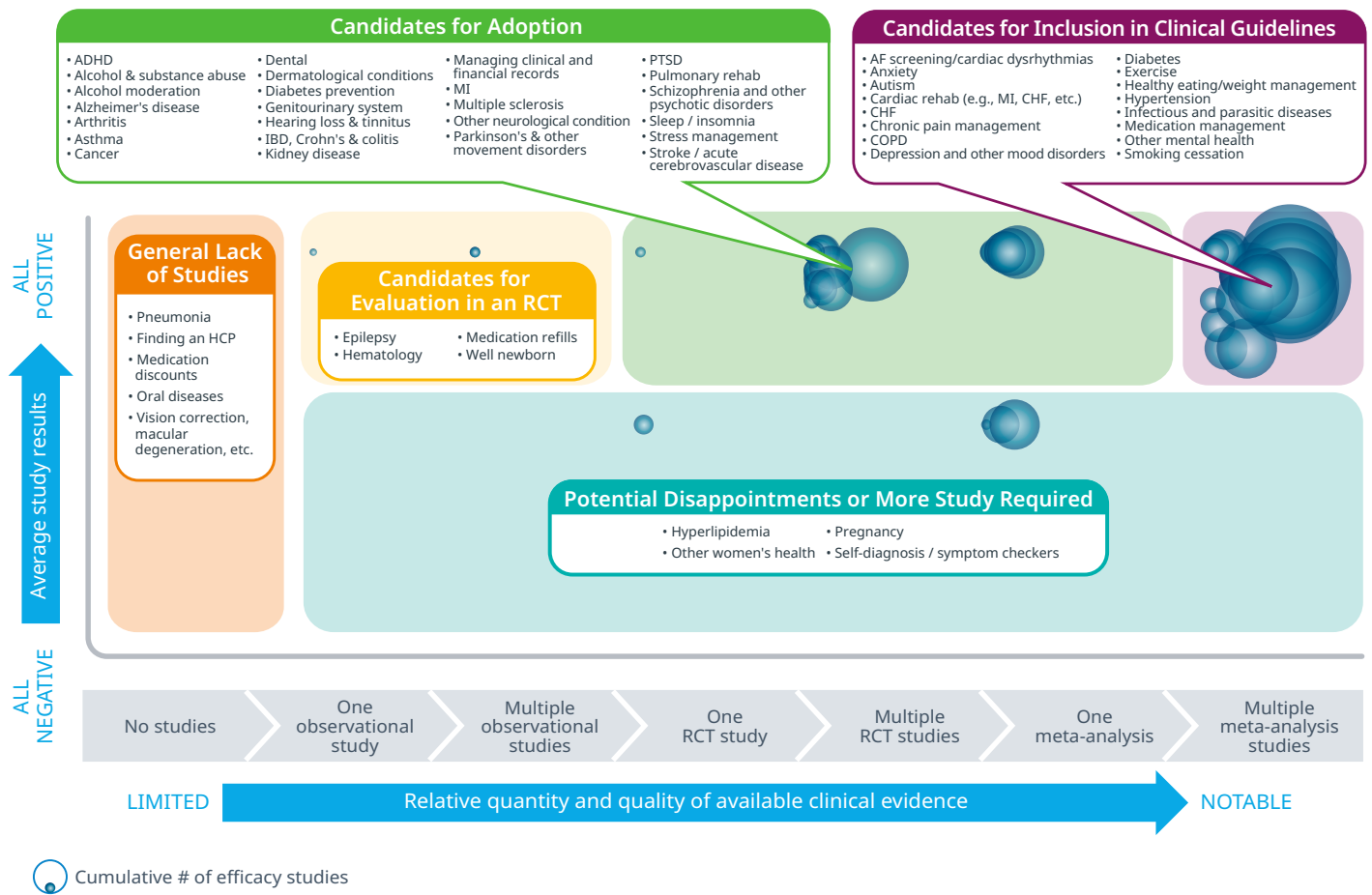
be considered Candidates for Adoption into practice, with randomized controlled trials (RCTs) supporting use (see Exhibit 27).

Still, there remain some categories that lack studies (orange) and others that still have seen no RCT studies performed (yellow), while some have shown neutral or mixed results and are tagged as Potential Disappointments or More Study Required (teal).



There has been a consolidation of thinking about the use of apps across various applications... the growing evidence now supports clinical or widespread real-world use for an expanded set of health indications.

Exhibit 27: Maturity of Digital Health Effectiveness Studies by Use Category, 2020



Source: IQVIA AppScript Clinical Evidence Database, Jan 2021

Notes: Only includes studies that evaluated the interventional value of a digital health solution (mobile or web app, connected device, or other mobile intervention such as texting) on patient outcomes such as activity levels, lab results, or healthcare resource utilization. Shows the average of study results for the highest quality evidence available (i.e., meta-analysis > RCT > observational). ADHD = attention deficit hyperactivity disorder, AF = atrial fibrillation, IBD = irritable bowel disease, MI = myocardial infarct, CHF = chronic heart failure, COPD = chronic obstructive pulmonary disorder, PTSD = post-traumatic stress disorder.

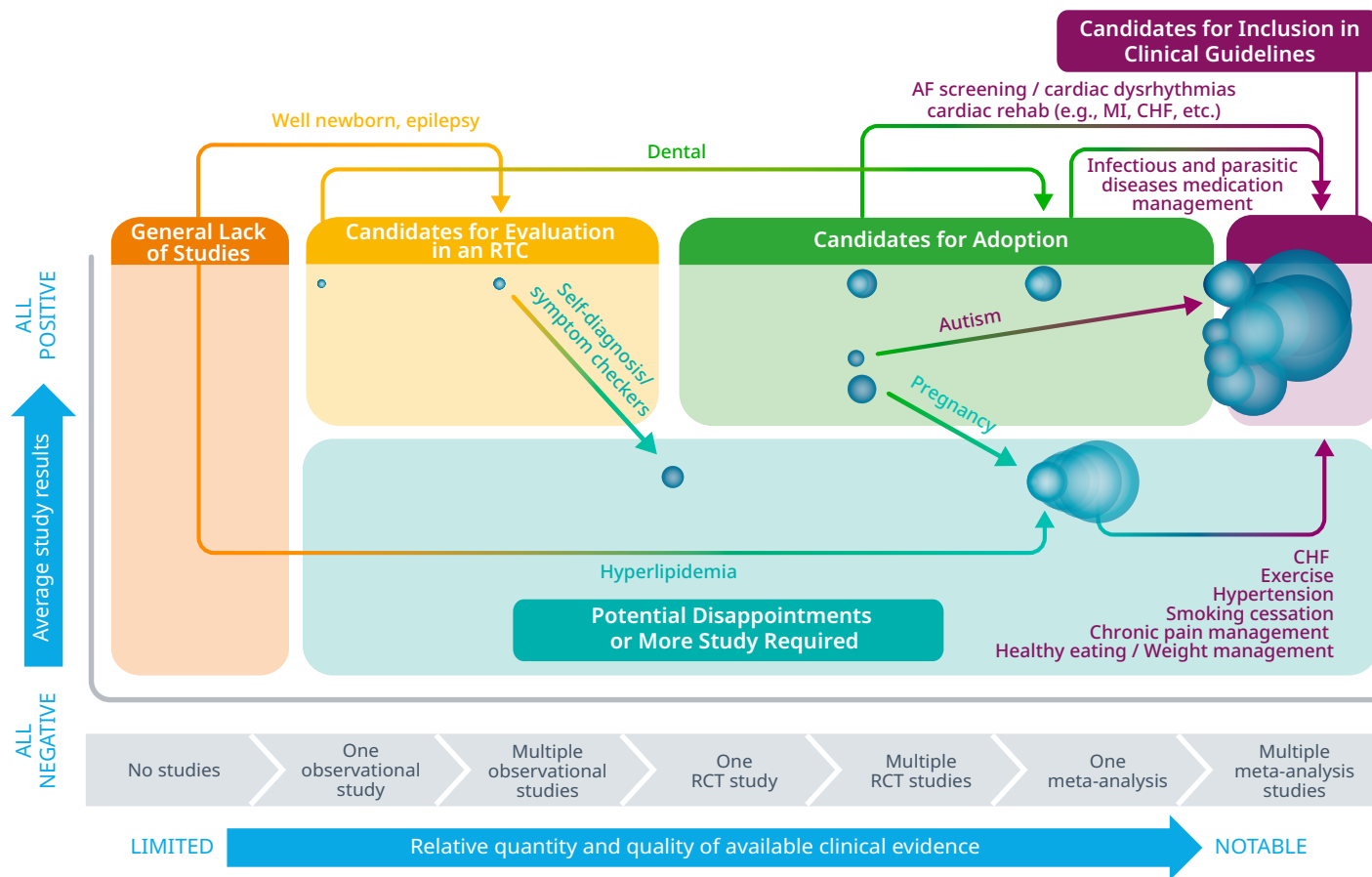
For instance, apps in the categories of hyperlipidemia, self-diagnosis/symptom checking, and women's health and pregnancy require more study to be able to find their place in practice, most having neutral results calling for more study, or having mixed results. For instance, in hyperlipidemia, a recent study saw effects in LDL and total cholesterol but not triglycerides;¹¹⁵ while in women's health, comparatively few effectiveness studies were noted.¹¹⁶ In pregnancy, there was little reported evidence of the effectiveness of exclusively digital interventions; however, programs showed greater success when encouraging a healthy diet, physical activity, or weight management during pregnancy if they had higher user

engagement, such as from proactive reminders to engage in behavior change techniques and feedback on progress.¹¹⁷

RECENT SHIFTS IN EVIDENCE

Among the app categories that that have shifted maturity level (see Exhibit 28) and are newly Candidates for Inclusion in Clinical Guidelines are cardiovascular applications (e.g., screening for atrial fibrillation and cardiac dysrhythmias, CHF management, cardiac rehabilitation, and hypertension), uses tied to behavioral modification (e.g., medication management, exercise, healthy eating and weight management, and smoking

Exhibit 28: Evidence on the Move: Significant Changes in the Maturity of Digital Health Effectiveness Studies by Use Category, 2017–2020



Cumulative # of efficacy studies

Source: IQVIA AppScript Clinical Evidence Database, Jan 2021

Notes: Only includes studies that evaluated the interventional value of a digital health solution (mobile or web app, connected device, or other mobile intervention such as texting) on patient outcomes such as activity levels, lab results, or healthcare resource utilization. Significant movers defined as switching category. Shows the average of study results for the highest quality evidence available (i.e., meta-analysis > RCT > observational). MI = myocardial infarct, CHF = chronic heart failure.

cessation) and management of some chronic conditions (e.g., pain and infectious and parasitic diseases, including HIV/AIDS), where apps can improve retention to care and prevention. These join use categories such as diabetes, depression, and anxiety, which had earlier attained that level of evidence.

The overall amount of evidence supporting these categories (bubble size) has also grown. Taking a

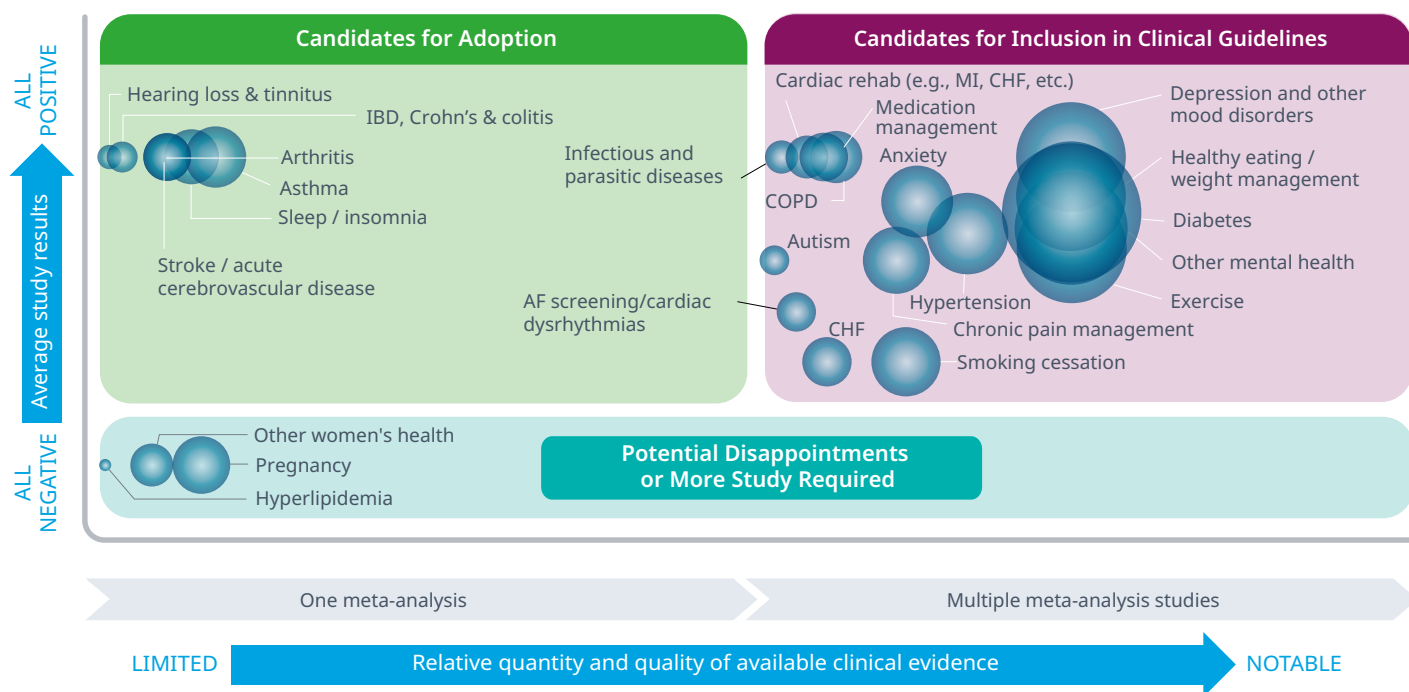
look at use cases with one or more meta-analyses (see Exhibit 29), there has been further growth in the number of positive publications in established categories such as diabetes and mental health (anxiety, depression and other mood disorders, other mental health), along with continued growth in behavioral change uses such as exercise, healthy eating and weight management, medication management, and hypertension.

Exhibit 28: Evidence on the Move: Significant Changes in the Maturity of Digital Health Effectiveness Studies by Use Category, 2017–2020 — continued

Use	2017 Status	Key Publications Since 2017	2020 Status
Exercise	Potential disappointments	Seven meta-analysis studies published by Gal et al (2018), Romeo et al (2019), Chaudhry et al (2019), Shin et al (2019), Kim et al (2019), Ganesan et al (2020) and Laranjo et al (2020) showed that wearables and smartphone applications significantly increase physical activity.	Candidates for inclusion in clinical guidelines
Healthy eating / Weight management	Potential disappointments	Seven meta-analysis studies published by Beleigoli et al (2019), Hwang et al (2019), Shin et al (2019), El Houry et al (2019), Villinger et al (2019) and Islam et al (2020) showed that digital interventions led to a short-term effect on weight loss and BMI and can improved physical health and fitness among adolescents. A recent study by Cavero-Redondo et al (2020) showed that smartphones were the most effective mHealth approach to achieve weight management and the effect of behavioral weight management interventions was more pronounced when compared to usual care and in the short-term (less than six months).	Candidates for inclusion in clinical guidelines
Smoking cessation	Potential disappointments	Meta-analysis published by Uthman et al (2019) indicated that mHealth interventions can improve smoking cessation rates.	Candidates for inclusion in clinical guidelines
Hypertension	Potential disappointments	Three meta-analysis studies published by Lu et al (2019), Liu et al (2020) and Xu et al (2020) showed that interactive intervention leads to a reduction in blood pressure and an increase in medication adherence for people with hypertension.	Candidates for inclusion in clinical guidelines
CHF	Potential disappointments	Meta-analysis published by Kitsiou et al (2019) showed that mHealth interventions are associated with reducing mortality and Heart Failure-related hospitalizations, and improving HF self-care.	Candidates for inclusion in clinical guidelines
Chronic pain management	Potential disappointments	Two meta-analysis studies published by Du et al (2020) and Pfeifer et al (2020) showed that apps-based treatment can be helpful in reducing pain and disability for chronic low back pain patients.	Candidates for inclusion in clinical guidelines
Infectious and parasitic diseases	Candidates for adoption	Meta-analysis published by Qu et al (2019) showed that eHealth interventions reported significant positive effects on antiretroviral therapy (ART) adherence of people living with HIV.	Candidates for inclusion in clinical guidelines
Medication management	Candidates for adoption	Two meta-analysis studies published by Armitage et al (2019) and Wang et al (2019) showed that app-based medication adherence interventions may have a positive effect on patient adherence.	Candidates for inclusion in clinical guidelines
AF Screening / Cardiac dysrhythmias	Candidates for adoption	Meta-analysis published by Prasitlumkum et al (2020) indicated that smart/ wearable devices have similar diagnostic accuracies in terms of atrial fibrillation detection methods.	Candidates for inclusion in clinical guidelines
Cardiac rehab (e.g., MI, CHF, etc.)	Candidates for adoption	Two meta-analysis studies published by Xu et al (2019) and Murphy et al (2020) showed that mobile applications for improving adherence of the cardiac rehabilitation might be effective, convenient and easily show merit in exercise promotion in patients with established coronary artery disease (CAD).	Candidates for inclusion in clinical guidelines
Autism	Candidates for adoption	Two meta-analysis studies published by Khan et al (2019) and Moon et al (2019) showed that available studies for children and young people with neurodevelopmental disorders are mainly for individuals with autism spectrum disorder (ASD) and they have promising results for the use of mobile apps for treatment of individuals with ASD.	Candidates for inclusion in clinical guidelines
Dental	Candidates for evaluation in an RCT	Study published by Patil et al (2020) showed that mobile applications have a significant short-term effect in the improvement of oral hygiene when measured using plaque index and gingival index scores.	Candidates for adoption
Well newborn	General lack of studies	Observational study published by Kwong et al (2018) showed that mobile apps can be an alternative method for collecting newborn and children's physiological data.	Candidates for Evaluation in an RCT
Epilepsy	General lack of studies	Observational study published by Le Marne et al (2018) evaluated an app for epilepsy and showed that the app significantly improved epilepsy knowledge and medication management.	Candidates for Evaluation in an RCT
Hyperlipidemia	General lack of studies	Meta-analysis published by Akbari et al (2019) showed that mHealth interventions can improve the total- and LDL-cholesterol levels but no significant effect on triglycerides and HDL-cholesterol.	Potential disappointments
Self-diagnosis / Symptom checkers	Candidates for evaluation in an RCT	Observational study published by Winn et al (2019) suggested that the use of online symptom checkers are associated with patients' intended behavior when seeking care based on triage questions.	Potential disappointments
Pregnancy	Candidates for adoption	Meta-analysis published by Rhodes et al (2020) showed that there is little evidence of the effectiveness of digital interventions to encourage a healthy diet, physical activity, or weight management during pregnancy.	Potential disappointments

Source: IQVIA AppScript Clinical Evidence Database, Jan 2021

Exhibit 29: Categories with One or More Meta-analysis



Source: IQVIA AppScript Clinical Evidence Database, Jan 2021

Notes: Only includes studies that evaluated the interventional value of a digital health solution (mobile or web app, connected device, or other mobile intervention such as texting) on patient outcomes such as activity levels, lab results, or healthcare resource utilization. Shows the average of study results for the highest quality evidence available (i.e., meta-analysis > RCT > observational). AF = atrial fibrillation, IBD = irritable bowel disease, MI = myocardial infarct, CHF = chronic heart failure, COPD = chronic obstructive pulmonary disorder.

There was also significant publication growth among candidates for adoption, which have RCTs but no meta-analyses yet (not shown). These include apps for cancer, neurological disorders (ADHD, Alzheimer's disease, multiple sclerosis, and other neurological conditions), schizophrenia and other psychotic disorders, as well as stress management, alcohol moderation, dermatological conditions, kidney disease, and diabetes prevention.

While the AppScript Digital Health Evidence Database shows a significant growth in maturity across use cases, likely powered by the leading apps within each use case, a similar review of evidence was performed by the Agency for Healthcare Research and Quality (AHRQ) across 11 chronic conditions and 114 controlled studies — though more narrowly focused on interventions where devices collect and transmit patient-generated health data (PGHD). Similarly to our app analysis, they

found a “possible positive effect” on health outcomes within coronary artery disease, heart failure, and asthma.¹¹⁸ However, for other use categories reported here as ‘Candidates for Inclusion in Clinical Guidelines,’ including obesity (Appscript category: Healthy Eating/ Weight Management), hypertension and cardiac arrhythmias, the report classified the health outcome data from PGDH interventions as unclear. Looking at surrogate outcomes rather than health outcomes data, the report concludes that hypertension and cardiac arrhythmias also showed an effect on blood pressure and time to arrhythmia detection, respectively, but for the other conditions examined — chronic obstructive pulmonary disease, diabetes prevention, sleep apnea, stroke, and Parkinson's disease — evidence on both health outcomes and surrogate outcomes were reported as unclear.

Within the IQVIA AppScript Digital Health Evidence Database, similar negative studies — RCTs and others — have been captured across uses, with many of these cases reporting specific apps failing their feasibility or impact trials (e.g., looking at user compliance, usability, measurement, accuracy, etc.). This suggests there are a number of newcomers still working their way through testing to improve treatment format and content preference.

Many are also apps plagued with low user engagement. Among these were a diabetes app to help support young people's self-management of type 1 diabetes, where app use declined rapidly and failed to improve glycated hemoglobin (HbA1c).¹¹⁹ Similarly, an observational study of a mobile phone intervention in adolescents to improve snack choices failed 'due to low reach and exposure',¹²⁰ and smartphone apps to reach pregnant smokers averse to face-to-face support similarly failed due to low app engagement, such that the app did not increase smoking abstinence during pregnancy.¹²¹ Another self-guided, web-based treatment for postpartum anxiety was experienced as not user-friendly and the content deemed too long, resulting in high patient attrition.¹²²

In other cases, apps have needed to find the specific niches where they can be successful. For instance, although exercise apps have certainly proven their value, some subgroups may fail to benefit, either due to the engagement strategy or the appeal of the app itself. One intervention to promote an active lifestyle in lower-educated working young adults at a high risk of low activity levels found low continuous user engagement with the app was perceived as not adequately tailored to the population, and therefore failed to impact daily physical activity.¹²³

CRITICAL REVIEWS OF EVIDENCE

Though the potential for digital health tools to improving self-management of chronic conditions is significant, independent organizations continue to highlight the need for growth in high-quality evidence — larger and more robust RCTs that follow patients for longer times

and report between-group differences in benefit.¹²⁴ They also stress the importance of usability and user-retention assessments to determine the durability of their clinical effect, and evidence of cost-effectiveness that can be analyzed versus standard of care.

Faced with the increasing number of digital health technologies in an unregulated space, several organizations and associations have taken it upon themselves to review app evidence generation and value in specific disease areas. This past year, the Institute for Clinical and Economic Review (ICER)¹²⁵ and the European Association for the Study of Diabetes (EASD) jointly with the American Diabetes Association (ADA) Diabetes Technology Working Group released reports calling for standards and growth in evidence generation and coverage/reimbursement, while making recommendations to digital tech developers and other stakeholders. Both reports stress the lack of evidence from longer-term randomized clinical trials (RCTs), the need for larger and more diverse study samples, and the necessity for assessments of app usability by the clinicians and patients themselves to determine the durability of their clinical effect and cost-effectiveness. With perspectives incorporated into the reports from disease associations, research organizations, and multiple stakeholders including payers, what permeates is a call for evidence and regulation of digital therapies across diseases (see Exhibit 30).

The ICER's December 2020 final report assessed and compared the clinical effectiveness and value of three digital health technologies to treat opioid use disorder (OUD): reSET-O, Connections, and DynamiCare.¹²⁶ While these three apps were commended for having drawn on established methods of OUD treatment already proven in randomized trials — including such psychosocial interventions as Therapeutic Education System (TES), Computer-Based Cognitive Behavioral Therapy (CBT4CBT), Addiction Comprehensive Health Enhancement Support System (ACHESS), peer support, and contingency management — the ICER report¹²⁶ highlighted that these three apps did not themselves

Exhibit 30: Gaps in Evidence and Barriers to Adoption as Expressed by Professional Associations

Diabetes Mobile Health Apps	Opioid Use Disorder (OUD) Digital Health Technologies
<p>Positive aspects of current state</p> <ul style="list-style-type: none"> • Studies show promise in disease management and promotion of health-related behaviors • Interventional studies show improvement in short term outcomes • First steps already taken in testing diabetes apps for accuracy of medical calculations and establishing quality assurance mechanisms • Processes exist to transmit data from diabetes health apps to other platforms 	<p>Positive aspects of current state</p> <ul style="list-style-type: none"> • Interventions use proven evidence from RCTs of psychosocial interventions (TES, CBT4CBT, A CHES, peer support, contingency management) • Evidence the apps are based on highlight differences in treatment outcomes for various subgroups of patients
<p>Gaps</p> <ul style="list-style-type: none"> • Evidence better identifying differences in response among populations (e.g., based on age/generation, language, socio-economic status) • More rigorous evidence of clinical validity, effectiveness, accuracy, safety through longer-term RCTs with larger study samples • Further assessment of technological issues, useability, and quality • More rigorous quality assurance mechanisms • Greater interoperability and standardized data collection for sharing with HCPs 	<p>Gaps</p> <ul style="list-style-type: none"> • Direct proof that apps deliver the same effectiveness as the established methods • Trials identifying subgroups of patients who benefit most and least to help personalize treatment, such as patients with OUD treated with medication-assisted treatment (MAT) • Studies tracking measures which matter most to patients like ER visits and hospitalization • Need for studies on clinical effectiveness that use observational designs with control arm, and/or sham controlled RCTs with a minimum duration of 6 months to 1–2 years • Assessment of the durability of beneficial clinical effects, impact on health care use and clinician productivity, and clinician and patient usability • Ways to avoid ineffective use
<p>Stakeholder actions suggested</p> <ul style="list-style-type: none"> • Explore, and evaluate medical data security, privacy, and determine cybersecurity regulation of diabetes mobile health apps • Train and update Health Care Professionals (HCPs) with adequate information on app utility • Increased impact and role of professional organizations such as the ADA, EASD, AMA, and IDF in addressing digital health technology issues in diabetes • Increased involvement of the Center for Medicare & Medicaid Services (CMS) 	<p>Stakeholder actions suggested</p> <ul style="list-style-type: none"> • Progress FDA's taxonomy and regulatory requirements of DHTs • Design alternative payment models • Educate providers about availability • Aid implementation • Measure impact of deployed technology

Source: European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) Diabetes Technology Working Group and the Institute for Clinical and Economic Review (ICER)¹²⁵⁻¹²⁷

Notes: AMA = American Medical Association, IDF = International Diabetes Federation (IDF).

prove their value and effectiveness delivering those benefits directly, as had the established methods, nor did they demonstrate a continued benefit to patients with OUD.

Similarly, while prior studies from psychosocial interventions had also identified differences in outcomes between patient subgroups, such as those having previously undergone MAT treatment showing better

outcomes from TES than treatment-naïve patients, the digital apps did not adequately consider these potential differences regarding their use. The report, therefore, highlights a need for trials to consider the significant heterogeneity in people with OUD, to identify potential subgroup of patents who benefit most and least from each digital health technology, and to develop peer-reviewed data supporting a tailored impact on such subgroups to help personalize treatment, such as those

with OUD being treated with MAT. To track measures which matter most to patients, they also suggest studies looking at impact on MAT retention, ER visits and hospitalization rates, and to further minimize bias, recommend observational studies with control arms and/or sham controlled RCTs (with a minimum of six months to one to two years).

Further, to determine the true benefit and clinical effectiveness of app use, the report recommends developers going beyond patient-related outcomes to look at the durability of beneficial clinical effects (i.e., long-term user retention), the impact on a patient's healthcare use and clinician productivity, and usability from a clinician and patient perspective — all of which are needed for payers and providers to make decision on adoption for OUD — as well as aspects of IT security, patient privacy, and generalizability to a larger diverse population.¹²⁵ Among the three apps assessed, only reSET-O was identified as presenting enough evidence of cost-effectiveness for analysis; however, upon analysis, it was determined to represent low value for money at its current price, and would have to be significantly discounted to align its value comparatively with outcome levels characteristic of standard of care.¹²⁶

Finally, the report calls for other actions to support the app ecosystem, including for the FDA to create a taxonomy and regulatory requirements for digital therapies by risk level and type, greater provider education to increase awareness of digital therapy availability and implementation, and the design of alternate payment models (outcomes-based or subscription-based contracts).¹²⁶

A similar report released in January 2020 discusses the perspective of the EASD and ADA Diabetes Technology Working Group on stand-alone diabetes digital health apps. While acknowledging that studies on diabetes mobile apps hold promise in managing disease, promoting health-related behaviors, and improving short term outcomes through 'gamification,' they noted

a need to generate more rigorous evidence of clinical validity, effectiveness, accuracy, safety, and quality assurance, as well as to target age group suitability. It also calls for increased quality and quantity of evidence generation to determine sustainable clinical effectiveness over time, including RCTs and long-term studies as well as increased exploration of technological issues facing diabetes digital health apps to ensure their useability and quality, and to ensure interoperability and standardization of data collection for sharing with healthcare professional (HCPs).¹²⁷

The report also identified a lack of evidence identifying differences among diabetes populations as an issue to ensure accessibility/usability for all subpopulations. For instance, young type 1 diabetes patients tend to be more adept with smartphone use compared to their older counterparts, the predominate use of English language among popular apps poses challenges to non-native speakers, and smartphone and app costs may affect individuals differently based on socio-economic status, thus determining the impact of such variations is critical.¹²⁷ The report further suggests a range of actions that can be taken by various stakeholders to improve use and adoption (see Exhibit 30).

+

Independent organizations continue to highlight the need for larger and more robust RCTs that follow patients for longer times and report between-group differences in benefit, as well as durability of their clinical effect.

Trends in commercialization and adoption

- + **Multiple commercialization pathways now exist for digital health tools, providing more opportunities to provide an economic return on investment for those tools supported by robust evidence and user demand.**
- + **Four broad commercial models are now in place and being used to generate payment or reimbursement for digital tool developers: direct-to-consumer, value-based contracting, “device-like” reimbursement, and “drug-like” reimbursement models.**
- + **While software developers of digital health apps initially commercialized through public app stores under a direct-to-consumer business model, apps providing the most significant health benefits focus increasingly on payers and employers.**
- + **Self-insured employers have begun to incorporate digital health apps into their health benefits, looking to offset the key drivers of their health costs and to ensure staff wellness and mental health during the pandemic.**
- + **The lack of a standardized contracting and app-assessment process is a barrier for employers, making the process time-consuming. A framework to accelerate employer adoption identifies steps toward an ideal state.**
- + **In response to growing interest from employers and members, some payers have built digital formularies, with Omada and Livongo digital care programs for diabetes, Hinge Health for musculoskeletal pain and SilverCloud, Whil, Learn to Live and myStrength for mental health among the most represented.**

COMMERCIAL MODELS

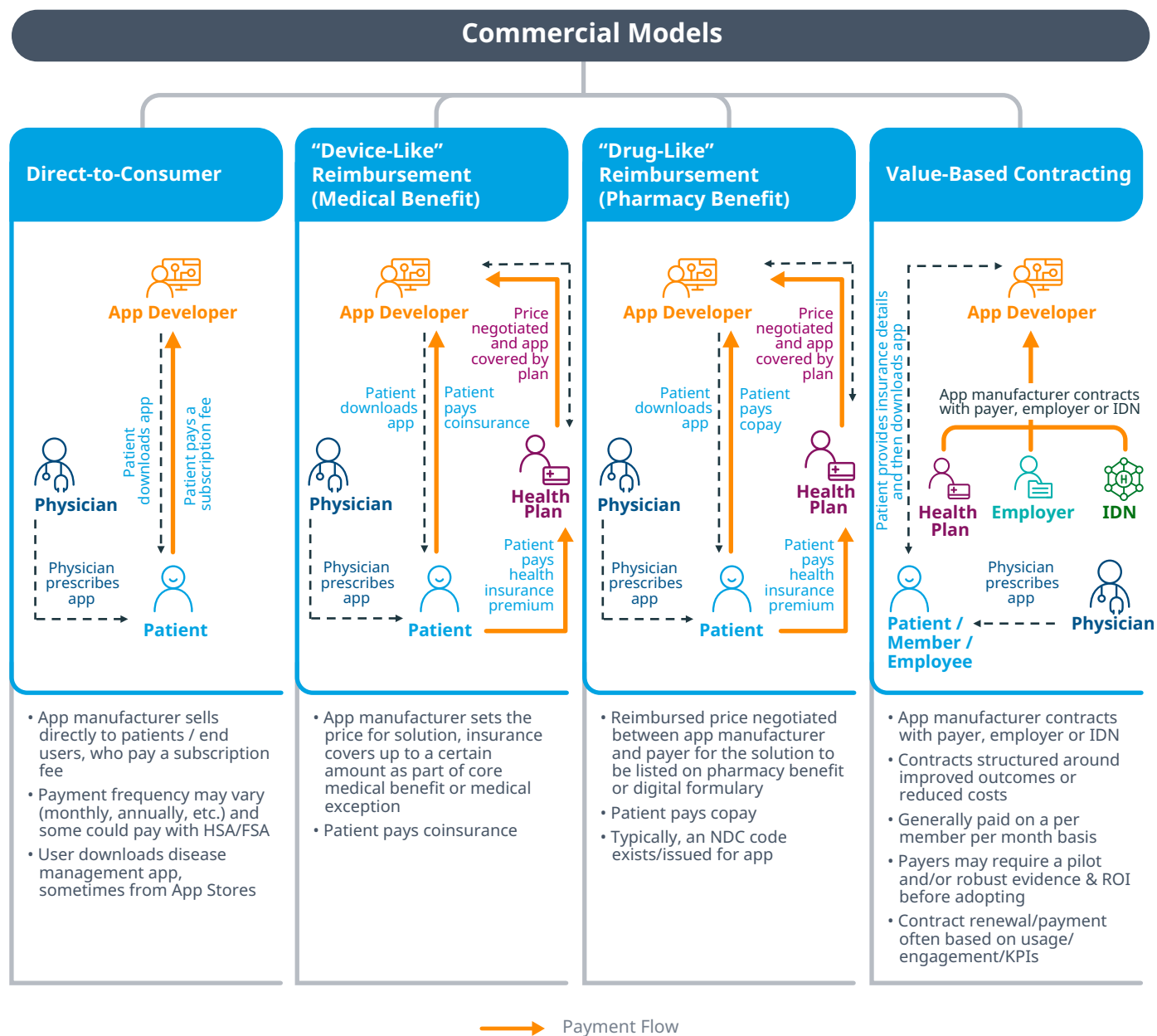
The use of DTx and DCs is growing but remains limited by low but rising levels of awareness and reimbursement of DTx and DCs. This may change as trends in reimbursement shift across markets. With Germany now having direct reimbursement for prescribed apps, the United States beginning to experience increased reimbursement by payers and employers, and the United Kingdom adopting app reimbursement under a federated system of purchasing by Clinical Commissioning Groups (CCGs) and NHS Trusts, developers may gradually shift their commercial models away from direct-to-consumer and instead focus on employers and payers who offer a broader consumer or patient base.

While most app software developers initially sought early financial return from a consumer audience via public app stores under a direct-to-consumer business model, apps providing the most significant health benefits are increasingly turning to employers and payers as routes to commercial success. Based on the evidence they have generated, apps may seek to obtain reimbursement through three other models: device-like reimbursement, drug-like reimbursement, or value-based contracting, which flow through payers, employers, providers, or health systems (see Exhibit 31). In all of these cases, stakeholders are motivated by their responsibility to manage population health costs and risk among a pool of individuals, while providing health benefits to individuals.

The four commercialization pathways that now exist for digital health tools provide increased opportunities for manufacturers to see an economic return on investment, especially for those tools supported by robust evidence and user demand. These include:

1. **Direct-to-consumer**, where a patient downloads a typically unregulated app sometimes from an app store to help them manage aspects of their health. The individual may pay a subscription fee on a

Exhibit 31: App Commercialization Pathways



Source: IQVIA, Mar 2021; IQVIA Institute, Jun 2021

Notes: NDC — National Drug Code, HSA — Health Savings Account; FSA — Flexible Spending Account; IDN — Integrated Delivery Network; KPI — Key Performance Indicator.

monthly or annual basis to the developer. An HCP may also act as an intermediary, sharing a QR code with a patient following a visit as part of a non-insured payment model. In this situation, the patient would pay the cost of the treatment to the clinical practice and the practice would pay the manufacturer for the cost of the treatment.

2. Device-like reimbursement, where fixed coverage for the app is included as part of a health plan’s medical benefit or as part of a medical rider. When an app is prescribed by a physician, the app may be covered under that benefit. The app developer sets the price for a solution and the insurance provider agrees to cover up to a certain amount with the

patient paying a coinsurance, and then the patient can download the app. This applies only to insured individuals paying a health insurance premium to negotiated payers.

App reimbursement under this model may involve both CPT codes and reimbursement codes relating to the SaMD device itself. HCPs may also be reimbursed by CPT codes associated with SaMD treatment.

Within this model, the digital health manufacturer typically negotiates a per-member-per-month (PMPM) amount for each patient treated. The manufacturer is reimbursed directly by the payer based on number of patients treated.

3. Drug-like reimbursement, where fixed coverage for the app is included as part of a health plan's pharmacy benefit — possibly negotiated by the PBM — and may be part of its digital formulary. The reimbursed price is negotiated between developer and payer and typically the patient pays a copay. This applies only to insured individuals paying a health insurance premium to the negotiated payers. In the case of some DTx apps, developers may be reimbursed using an NDC code. As digital solutions mature, such health plan reimbursement may become more common under digital health formularies.

4. Value-based contracting, where an app manufacturer contracts with a payer, employer or IDN and structures payment around improved outcomes or reduced costs. The developer would typically provide evidence of such benefit through studies they have run such as RCTs (or occasionally pilot studies) and demonstrate ROI that can be extrapolated to various populations. A fee would generally be paid on a per-member-per-month basis, with milestones typically structured around improved clinical outcomes for the population or individual (i.e., weight loss or pain reduction), reduced costs, or performance outcomes (i.e., duration of use, number of times on app). In some cases milestone payments are tiered based on the extent of user (member/employee/

patient) benefit achieved, with none offered if a decline in user health is seen, and in other cases, may be based on the extent to which users continue to use or engage with the app. The patient typically provides eligibility details to the app developer and then can download the app.

Employers

As health and wellness apps have generated outcomes data, many self-insured employers have begun to incorporate digital health apps into their health benefits, looking to ensure staff wellness and offset the key drivers of their health costs. Those typically include chronic conditions such as musculoskeletal disorders (that can lead to expensive back surgeries), diabetes, obesity, anxiety, and depression, as well as cancer. Although in prior years, employers were approached to incorporate physical activity programs into their benefits, during the COVID-19 pandemic, behavioral health offerings have exploded — most using digital health technology to deliver programs aimed at improving sleep, anxiety, depression, and other emotional and mental health issues.

The robust nature of the data these providers are bringing to prove their value is also furthering

“Unsolicited pitches to HR by app providers have increased over the past three years and there has been a shift now to focus on stress and coping... the data being provided by digital health companies in the stress and anxiety world are shifting and are very compelling.”

— HR Manager

adoption. The level of evidence has shifted, with many more bringing data from randomized controlled trials, especially in the musculoskeletal space, and for diabetes, stress, and anxiety. Currently there are at least three different models under which health apps with established evidence are bringing their products to employers, and in all cases, app costs are typically frontloaded, with 70–80% of total costs billed at user enrollment and the rest billed periodically thereafter at various milestones according to patient outcomes or other measures. However, depending on the model, assessing such apps and contracting with them can be a very challenging and time-consuming process for employers, with involvement from HR, legal, and data privacy functions to perform due diligence and ensure privacy protections are in place for employees. The pace of contracting for both companies suffers from lack of a framework or standardization for such contracting.

As employers typically want to be blinded as to which employees are users of the app or meet disease criteria for privacy and confidentiality reasons, some of these models are intended to get around this barrier. For instance, disease screening surveys may be sent directly from the digital health provider to identify eligible employees and, in at least one case, an app provider contracted with a lab testing provider to identify individuals meeting criteria.¹²⁸

1. Apps integrated into a payer's medical benefit with prebuilt data integration — Both payers, and benefit managers know that certain therapy areas are key drivers of cost for employers and they have recently been seeking ways to respond using digital health as an added benefit. Under this model, use of a digital health app may be allowed by the payer to substitute for existing provider codes, such as office visits and physical therapy claim codes, or otherwise bill for services. Among these so far are some telemedicine, behavioral health, diabetes prevention and care, and dermatology offerings. Apps may be added to the payer's digital formulary as part of this integration. If an employee or patient qualifies for use of an app

through a self-assessment conducted through an email or webpage, then the payer would include an initial claim for their use in their next invoice and periodically thereafter based on the contract.

There are several benefits of this model. Since the digital health provider has been vetted and contracted by the payer, there is an assurance of quality and no need for the employer to initiate a separate contract with the app developer. The employer's human resources function also avoids receiving monthly invoices that would hit separate wellness budgets, thereby making it possible to avoid additional finance set ups and ongoing invoice management; instead, costs are included in their ongoing medical accrual. This often allows for more efficient corporate approval based on the ROI data presented, if cost-offsets are expected that will avoid a spike in medical accrual spend. A final benefit is that the payer may have already arranged to set up data pathways to measure app performance or be further along developing these. Over time, it is likely that payers will set up distinct billing codes for apps on their digital formularies.

2. Direct employer contracting for user licenses: In this more transactional business model, digital health companies contract directly with employers for user licenses. Usually top apps in their class, they approach employers directly looking to offset costs — such as in the areas of behavioral health and wellness — and employers may directly purchase a number of licenses and set up a landing page for employees to investigate potential use of one or more apps. Typically, the data provided in these cases is less robust or compelling than the prior model, sometimes because the digital app delivers a broader wellness offering such as relaxation or lifestyle management rather than targeted disease management. In these situations, rather than delivering ROI data, the digital health provider may focus on delivering monthly engagement reports, often through a dashboard, on aggregate employee activity and use of the app.

Exhibit 32: Framework to Accelerate Employer Adoption through Data and Integration

Domain	Remaining Needs/ Gaps	Current State	Ideal State
Evidence Presented	A standardized evidence base	<ul style="list-style-type: none"> Some evidence presented based on user engagement, satisfaction, outcomes, case studies 	<ul style="list-style-type: none"> Evidence based outcomes from at least 3 RCTs
Budget Impact / Financial Ease of Use	Payer integration of apps into their claims process Claims integration	<ul style="list-style-type: none"> Employer company must generally figure out how to integrate the solution into their benefit 	<ul style="list-style-type: none"> Payer has an integrated solution to address top 5 cost drivers Claims integration, thus no invoices from vendor
Ease of Contracting	Standardized contracting language and Scope of Work templates tailored to digital health genre	<ul style="list-style-type: none"> Contracting requires major revisions from templates offered by vendors Several rounds of review needed to come to consensus Privacy, procurement and legal typically involved 	<ul style="list-style-type: none"> Payer has master service agreement with vendor Only a simple scope of work is needed to initiate digital health program
Value/Return Estimates	Realistic expectations from company decision makers Broader lens of Value on Investment (VOI) needed versus Return on Investment (ROI)	<ul style="list-style-type: none"> ROI data is frequently missing Inconsistent ROI methodologies 	<ul style="list-style-type: none"> Vendors are transparent about ROI methodology Stakeholders let go of expectation of cash ROI and shift to thinking about VOI Quarterly program-specific statements
Cost/ Billing	Pay for performance/ outcomes Performance guarantees	<ul style="list-style-type: none"> As negotiated in contract, often PEPM or PEPY, requiring PO approvals, vendor set up, monthly invoices 	<ul style="list-style-type: none"> Initial claim amount at registration with subsequent claim amounts related to outcomes
Reporting on KPI's	Standardized reporting	<ul style="list-style-type: none"> Delayed reporting (3-month lag) Some reporting on engagement, satisfaction, outcomes 	<ul style="list-style-type: none"> Realtime metrics dashboards Quarterly aggregate reports including engagement, satisfaction, outcomes, ROI/VOI
Data Flows	Standardized data fields	<ul style="list-style-type: none"> Heavy lift for employer company to set up customer centric process 	<ul style="list-style-type: none"> Customer centric process Only collect what is necessary
Ratings by Independent Organizations	Assessments of independent organizations	<ul style="list-style-type: none"> Sparse assessments by such organizations 	<ul style="list-style-type: none"> Meaningful ratings by independent organizations to guide adoption
Rankings Across App Value Elements	Visibility to app scoring methodology and elements	<ul style="list-style-type: none"> App ratings agencies are sparse like AppScript, ORCHA 	<ul style="list-style-type: none"> App scores that are differentiated from app store customer star reviews Patient attrition included in ranking
Vendor Relationship	Ease of contact	<ul style="list-style-type: none"> Employer may have many separate points of contact, dealing initially with salesperson, then set-up staff, ongoing account rep and finance 	<ul style="list-style-type: none"> One responsive contact Short, frequent, regular meetings

Source: IQVIA Institute; Jun 2021

3. Apps partnered with third-party providers who are not payers

— In some cases, app providers are seeking to partner with third parties. For instance, in one case a lab testing company, Quest, partnered with Omada to find employees that could be good candidates for its digital care program.¹³¹ Through voluntary biometric health screenings or surveys with

company employees, the lab testing service would be able to identify individuals with or at risk of chronic conditions and invite them to participate in the digital program. By having a third party to share relevant and permitted employee data including lab values to the digital health provider, this model allows the employer to have an accurate assessment of their

risk at baseline and the risk reduction achieved, at an aggregate level, while maintaining a separation from employee data. The benefits to the employer are not as expansive as in the first model because the human resources department needs to participate in contracting, setting up data feeds to enable employee biometric screening, enrollment, and registration with the third party and managing invoices.

Of these three models, the first, where apps become integrated into payer medical benefits, may be preferable for employers, and there is growing recognition by payers that integration is appealing. Further, the most reassuring business model for employers are ones where continuing payment milestones are clearly linked to patient outcomes, sometimes in a tiered fashion, with continual reporting on risk mitigation for the entire enrolled patient population. App providers that can extrapolate ROI estimates to each company's population data — typically based on their apps ability to reduce risk as shown in case studies and RCTs — are at an advantage, along with those that can provide case studies at large or similarly-sized companies to look at real-world impacts on spend. For instance, bringing a pre-built risk model extrapolating from actual reductions seen at a case study company to the reduction likely to be seen at the prospective company is helpful, especially if it uses matched cohorts of patients and their typical outcomes. This lets an employer understand the expected outcomes for their population and reduction in claims and anticipated savings.

While employer adoption of digital technologies for their employees has clearly increased over the past year, there still remain barriers across a number of domains that are slowing this process (see Exhibit 32). As various stakeholders are all working to tackle these, it is likely that adoption will accelerate.

PAYER AND PBM DIGITAL HEALTH FORMULARIES

To enable access to digital health technologies for their members and build a greater level of integration and endorsement that employers need, a number of payers have set up digital health formularies of high-performing apps. These stretch across a number of applications, such as diabetes management, musculoskeletal pain, mental health, and heart health (see Exhibit 33). Some of the apps used by multiple payers include Omada and Livongo digital care programs in diabetes care, Hinge Health in musculoskeletal pain and SilverCloud, Whil, Learn to Live and myStrength in mental health. Other payers including United Healthcare are alternatively creating their own digital health program for members, in addition to partnering with DC providers, in this case Level2 for Type 2 diabetes, among others.¹²⁹ For those that already have formularies, included therapeutics are typically clinically reviewed and evaluated by experts that may include pharmacists, physicians, user experience experts, and health research PhDs, thereby facilitating adoption by employers and other parties.

PHARMACEUTICAL COMPANIES

Although manufacturers were once thought of as the main way for DTx apps to gain a foothold in the market, many of the digital therapeutics highlighted in this report are pursuing commercialization independently through value-based contracting and national reimbursement pathways. However, for some pharmaceutical companies, digital health tools are still a focus as they seek to augment the value of their products. Some manufacturers have launched simple companion apps, while others have made investments in digital therapeutics intended to treat conditions (see Exhibit 34). For instance, Click Therapeutics and Boehringer Ingelheim penned a \$500M agreement in the schizophrenia space to jointly develop and commercialize a DTx mobile app, CT-155, for patients with schizophrenia built on Click's platform. Others, including AstraZeneca's

Exhibit 33: Examples of Digital Health Formularies

Cigna

Evernorth Digital Health Formulary

Pulmonary Care

Propeller Health – Asthma & COPD

Quit Genius — CBT for Nicotine Dependence Tobacco/Vaping Cessation with NRT and coaching

Diabetes Care

Omada / Livongo — Pre-diabetes prevention and obesity

Omada / Livongo / Lifescan — Types 1&2 diabetes

Cardiovascular Care

Omada / Livongo - Hypertension

Behavioral /Mental Health

SilverCloud Health CBT /Learn to Live CBT- Depression, Anxiety, Insomnia

Ginger — Access to behavioral health coaches

Women's Health

Wildflower — Family planning, pregnancy, post-partum

Musculoskeletal Care

Hinge Health, Omada MSK by Physera, and RecoveryOne™— chronic muscle and joint pain — provides on-demand, at home physical therapy, and personalized coaching

Caregiver Care

Prevail Health — Caregiver stress and wellness

COVID-19 Care

Buoy — Symptom checking and workplace clearance

UnitedHealthcare

Diabetes Care

Level2 — Type 2 diabetes

Virtual Behavioral Care

AbleTo — Therapist and coach access for CBT

Patient-monitoring

Vivify Health — At-home patient monitoring program (vital measurement, track changes, virtual triage activities)

Physical Activity

UnitedHealthcare Motion — Program designed to promote physical activity with compatible activity trackers enabling members to earn incentives for meeting certain daily walking goals.

Women Health

UnitedHealthcare Healthy Pregnancy App — Personalized content, helps determine risks, and facilitates maternity nurses' support and care during pregnancy

Hearing Care

Right2You — Virtual care and custom-programed hearing aids

Anthem

Chronic Disease and Diabetes

Lark Health (via Anthem's Sydney app) — Prevention and management via CBT framework and personalized care

Aetna

PreferredOne and other plans

PLAN OFFERINGS:

Behavioral/Mental Health

Learn to Live — CBT for mental health

Wysa — Emotionally intelligent chatbot

Diabetes Care

Omada / Livongo

Musculoskeletal Care

Hinge Health — Chronic muscle, back and joint pain

APP DISCOUNTS PROVIDED:

Pain Management

Kaia — Manage pain with exercises

Mental Health

myStrength — Mental and emotional health

Peak — Mental games

Quoo — Wellbeing, anxiety, depression

Behavioral Health/ Smoking Cessation

Smoke Free — Evidence-based techniques to be smoke free.

Sleep

Pzizz —Helps quiet the mind, fall asleep, stay asleep

CVS Health

Point Solutions Management

Behavioral Health

Daylight CBT — Worry, anxiety

Sleepio — Poor sleep

Whil — Digital mindfulness training

Cardiovascular Care

Hello Heart — Heart health and hypertension

Musculoskeletal Care

Hinge Health — Chronic muscle, back and joint pain

Weight Management and Chronic Disease Prevention

Kurbo by Weight Watchers — Healthier choices and lifestyle changes

Wondr Health — Healthier choices and lifestyle changes

Vida — Nutrition and behavioral skills development

Caregiver Care

Torchlight — Caregiver stress and wellness

Kaiser Permanente

Behavioral/Mental Health

Calm/ Headspace/ Whil — Mindfulness and meditation to reduce stress and anxiety and improve sleep

myStrength/ SilverCloud Health/ Thriv — CBT for mental health through interactive activities and/or coaching

Patient Monitoring

KP Health Ally — Self-management of blood pressure, weight, diabetes for patients in a diabetes or hypertension program

Source: Primary data collection from various public sources.¹³⁰⁻¹³⁸

Notes: Data gathered from multiple sources when a single digital formulary page was unavailable and likely not comprehensive. Excludes health benefit, cost savings, and medicine ordering & delivery apps. CBT = Cognitive behavioral therapy.

Exhibit 34: Shifts by Biopharma Companies Into the Digital Health Space in 2020

Digital Therapeutics or Technology Company	Biopharma Company	Diseases/ Indications	Scope
Click Therapeutics	Boehringer Ingelheim	Schizophrenia	Boehringer Ingelheim and Click Therapeutics will jointly develop and commercialize a digital treatment for patients with schizophrenia. The treatment, referred to as CT-155, will be a mobile app built on Click's tech platform.
smartpatient	Novartis	Wet macular degeneration (AMD)	Will launch a new app feature on the MyTherapy app for patients with wet macular degeneration (AMD) focused on educating patients and caregivers about treatment and management.
SidekickHealth	Pfizer	Multiple disease	Partnership to launch a digital therapeutics platform giving patients a tool to help them maintain healthy lifestyles, improve their disease management and improve quality of life. App will provide guidance and resources to facilitate easier and faster communication with healthcare professionals.
NuvoAir	Roche	Cystic fibrosis (CF)	NuvoAir entered a partnership with Roche Italy to make its platform available in selected cystic fibrosis (CF) centers that help patients conduct lung function assessments at home. They can use it to answer questionnaires that look at specific symptoms, track the progression of their disease, and share data with those caring for them.
Holmusk	Merck & Co	Diabetes	Holmusk announced a collaboration with Merck to support patients with prediabetes and diabetes and physicians in Asia-Pacific with GlycoLeap, a mobile digital therapeutics platform that delivers personalized dietary feedback, interactive educational lessons, and 1-1 guidance with a qualified health coach. The goal is to help patients achieve weight loss and improve blood glucose control.

Source: Multiple press releases; IQVIA Institute, Mar 2021.¹⁴⁰⁻¹⁴⁴

collaboration with Kardia, demonstrates the wide range of partnerships involving digital health, stretching also to digital diagnostics that could help patients with chronic kidney disease.¹³⁹ While manufacturers are increasingly seeing a range of value that digital health can bring, including DTx and biomarkers to accelerate clinical trials for their medicines and create new endpoints, a true shift to including DTx in their portfolios would require a redefinition of what a biopharma company is — from a company that develops and deliver drugs to one that delivers improvements in health outcomes through a variety of means. For now, it is unclear how many companies will pursue that route.

OVERCOMING BARRIERS TO USE

Although in the United States 44% of physicians express interest in prescribing medical apps for patients,¹⁴⁵ as do 70% of formulary decision-makers within hospitals, IDNs, MCOs and PBMs — who either currently provide coverage for DTx (25%) or have expressed interest in providing coverage (45%),¹⁴⁵ it is clear that barriers continue to exist to the adoption of these apps.

Standards and ratings

In part, regulation has been a barrier, but continues to evolve. There have been international efforts made to standardize the quality criteria used to assess digital health and wellness apps and pave the way

for more rapid and consistent adoption by various parties. For instance, the International Organization for Standardization (ISO), an international standard-setting body composed of representatives from various national standards organizations, has put forth a standard on the requirements and technical specifications for the development, testing, release and updating of health and wellness apps that is currently pending approval. Made to meet the needs of patients, caregivers, and healthcare professionals, among others, the ISO/TS 82304-2¹⁴⁶ is expected to be published sometime in 2022.⁷

More specifically, the standard puts forth a method to evaluate the app's quality of health and wellness using a set of questions for app developers and manufacturers around four topics: health and safety; ease of use; data security; and robustness of build.¹⁴⁷ The results are used to calculate a score for the quality label and its color code, enabling users to compare apps and select the best one that suits their needs.¹⁴⁸ Questions relating to health and safety, for instance, include ones on claimed health benefits of using the health app, whether or not the app makes clinical judgments, if there are measures in place to detect and prevent incorrect clinical judgements of the health app, and applicable evidence of approval by an independent medical ethics board for clinical research. Overall, the standard offers to pave the way for a form of standardization in quality criteria used to assess health and wellness apps as well as provide a trusted rating system.¹⁴⁴ The standard is likely not only to impact technology companies and national health regulators but also healthcare providers, consumers, advocacy organizations, and researchers.¹⁵⁰

Formulary submissions and pharmacy fulfillment

On a national level in the United States, the professional association Academy of Managed Care Pharmacy (AMCP)¹⁵¹ representing pharmacists, physicians,

nurses, and professionals in the life sciences and biopharmaceutical companies convened a multi-stakeholder meeting in September 2019 to examine the systems and processes that will support the adoption and utilization of digital therapeutics (DTx) to make it easier for patients to get the care they need at an affordable cost. They specifically discussed where DTx should fit within a covered benefit, the evidence requirements needed to cover DTx, how managed care organizations (MCOs) should evaluate their value, and how MCOs and payers can best use DTx for patient engagement and care.¹⁵² Of the notable recommendations made was the use of the NICE evidence standards framework for assessing DTx as well as the development of a system to support decision making for DTx similar to the AMCP's formulary dossier submission system for biopharmaceutical products.

The AMCP Format for Formulary Submissions dossier, originally launched in 2000, provides guidance and templates to biopharmaceutical manufacturers to submit safety, effectiveness, and value data to healthcare decision makers when they are considering products for coverage and formulary placement. In response to the growing need for information relevant to formulary and medical policy decisions on nonpharmaceutical products, including diagnostics and medical devices such as digital health, AMCP released their Format 4.1 in January 2020. The new dossier defines information needed throughout the distinct phases during a product's lifecycle — pre-approval assessments and budgeting for unapproved products near the end of product development pipeline as well as for unapproved uses of existing products that are pending FDA approval.¹⁵³

At the end of 2020, the National Council for Prescription Drug Programs (NCPDP), a standards development organization for the pharmacy services industry,

also released *Background and Guidance for Using the NCPDP Standards for Digital Therapeutics*.¹⁵⁴ Similar to AMCP, the NCPDP's MC Digital Therapeutics (DTx) Task Group evaluated existing NCPDP industry standards originally developed for the prescribing and dispensing of prescription drugs through the pharmacy benefit in order to analyze their applicability in digital therapeutics. The document published proposes how to adapt for DTx the NCPDP standards pertaining to billing units ("each," mL, or GM), product identifiers, SCRIPT transaction data, and telecommunication transactions (eligibility verification, billing, pre-determination of benefits, prior authorization inquiry, information reporting transactions) to support data exchange among DTx participants. The NCPDP guide is among the first in its effort to update its original standard to incorporate digital therapeutics, demonstrating a great need in clarifications and insight regarding digital therapeutics from various stakeholders and a will to find a solution.¹⁵⁵

Medicare Reimbursement Process

Finally, legislative efforts and advances by Congress and the Centers for Medicare & Medicaid Services (CMS) to establish a clear reimbursement process for these new technologies remain slow. Senate bill S.3532 Prescription Digital Therapeutics to Support Recovery Act, introduced in March 2020, would "provide Medicare and Medicaid coverage of prescription digital therapeutics that use behavioral treatments to prevent, manage, or treat mental health or substance use disorders."¹⁵⁶ However, it is still pending approval, delaying the setting of a precedent for the reimbursement of digital therapeutics. Some further hope for policy supporting reimbursement was attributed to the "Medicare Program; Medicare Coverage of Innovative Technology (MCIT) and Definition of 'Reasonable and Necessary'" rule published in the Federal Register in January 2021, establishing a Medicare coverage pathway for innovative

medical devices, including digital therapeutics, designated as breakthrough by the U.S. Food and Drug Administration (FDA). The pathway would result in four years of Medicare coverage starting on the date of FDA market authorization or a manufacturer's chosen date within two years thereafter. To the dismay of many stakeholders, CMS recently announced to further delay the MCIT rule and its coverage until December 2021, slowing the speed of digital therapeutic regulatory advances.¹⁵⁷

Methodology

MOBILE APP DATA

Global mobile application data was sourced from 42Matters and AppScript in June 2021 and obtained via the AppScript App Database. As of June 10, 2021, when the data was pulled, there were 351,308 health apps available with 173,982 in the Apple Store and 177,326 in the Google Play Store. Although some apps are available in both stores, their unique instances may offer different functionality, and are therefore counted as distinct. Although our 2015 report made use of mobile application data supplied by Mevvy rather than 42Matters, these data sources are believed to be substantially similar, as both suppliers source data directly from the relevant app stores. Significant differences are not expected, but minor trend breaks may exist and may have minor impact on longitudinal trends. The analysis only includes apps available for download in the Apple Store and Google Play Store. Other digital health apps, including web apps and closed distribution model apps, are not included in the various analyses of app quantity and category but are included in various clinical evidence assessments.

PATIENT HEALTH APP DATA

Mobile application data sourced from 42Matters was reviewed and supplemented with primary research by IQVIA AppScript to create the curated AppScript App Database of widely available consumer mobile health apps. As of June 10, 2021, when the data was pulled for the 2021 study, a total of 11,543 unique healthcare consumer mobile apps were included in the dataset, including iOS apps from the Apple Store and Android apps from the Google Play Store. This dataset prioritizes review of apps in the “Health and Fitness” and “Medical” categories, as well as the most downloaded apps, to define a set of the digital health apps most widely used by consumers. Under AppScript curation methods, app store apps with greater than 1,000 user ratings are prioritized for in-depth examination, as are apps that

have already been reviewed and have a version or price update. A thorough examination of the content of apps enables exclusion of apps from further analysis that are considered irrelevant to normal healthcare use (e.g., salons, apps with gimmicks, etc.), unavailable in English language, or for healthcare providers as opposed to patients. The remaining included apps are considered genuine digital health apps for patients. For the purpose of counting apps, an app may be counted twice if it is available from both the Google Play Store and the Apple App Store; however, differences exist between platforms regarding functionality and download volume.

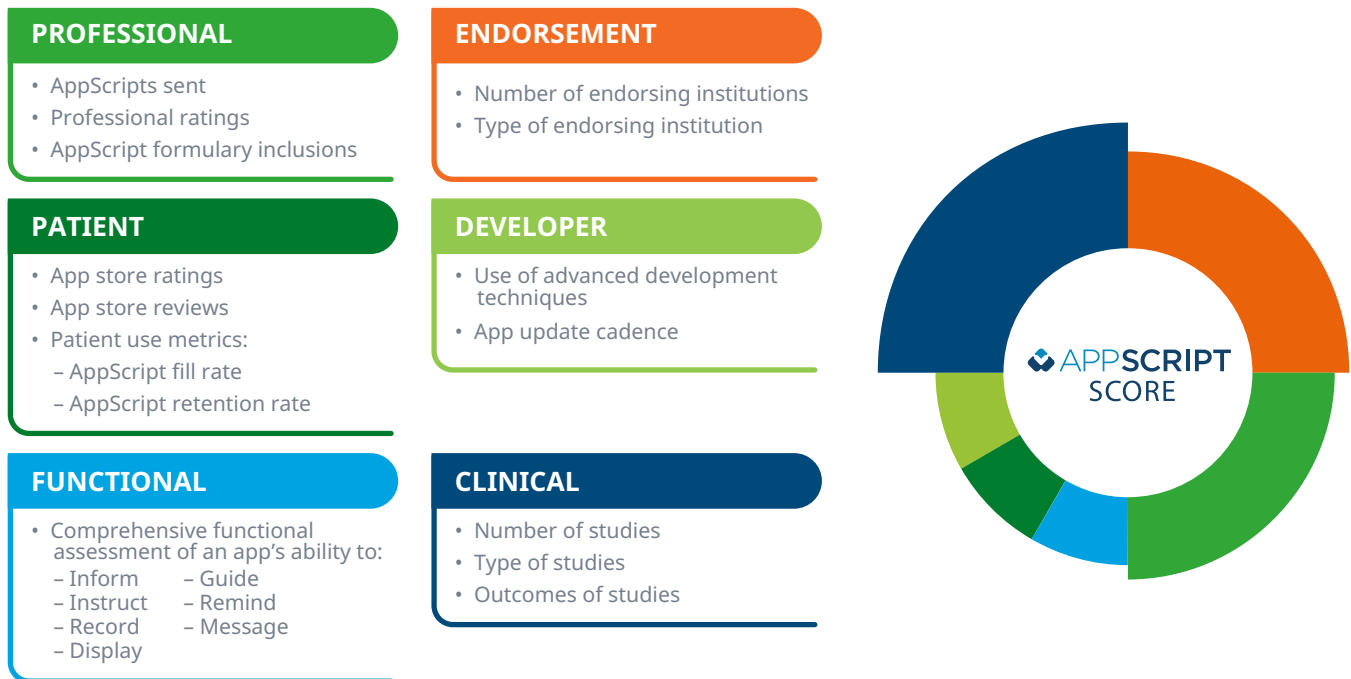
APPSCRIPT SCORE

The AppScript Score discussed in the analysis provides a comprehensive method for all stakeholders to assess digital health app quality and may be predictive of a given app’s value to human health and the overall health system. The AppScript Score is derived from six sub-scores, or “ratings,” across the following dimensions: Patient, Professional, Functional, Developer, Endorsement, and Clinical ratings (see Exhibit 35). More than 70 individual metrics are considered across the six ratings. Some metrics leverage data from the AppScript distribution platform, which enables clinicians to electronically recommend apps, connected devices and digital content to their patients. AppScript Score components are weighted and combined to generate a consolidated score of 1-100.

Within this framework, **Patient** rating leverages commodity Apple Store and Google Play Store ratings and rating counts as well as well as proprietary AppScript “fill rate” and “retention rate” data pertaining to the number of AppScript app recommendations that are downloaded and retained for at least a 30-day period, respectively.

Professional rating is derived from the number of times a given app is recommended to patients by healthcare

Exhibit 35: IQVIA AppScript Score Overview – A Way to Measure the Quality of Apps



Source: IQVIA AppScript, Jun 2021

professionals using the AppScript platform and the number of times a given app has been included in an institution's digital health formulary using the AppScript platform.

Functional rating measures the feature-set of apps (more detail in Exhibit 4), representing the unique investment by the developer and functionality available to users.

Developer rating determines the professionalism and dedication of a developer to deliver high-quality apps that leverage the most recent technologies. Key metrics assessed as part of the Developer rating include the most recent update date of the app and whether the app interoperates with sensors directly or through a data sharing hub (e.g., HealthKit).

Endorsement rating is based on the number of times a given app has been positively endorsed by credible

healthcare organizations such as regulators (e.g., the FDA through a clearance), healthcare provider institutions (e.g., Joslin Clinic), and health content publishers (e.g., HealthLine).

Clinical rating is an evidence-based medicine approach to rating apps focused on the review and scoring of peer reviewed publications. All peer-reviewed publications are scored based on their design qualities and results. Study quality is based on the underlying study design; for example, an RCT is scored higher than an observational study. Study result is based on whether the study found that the underlying app provided a statistically significant benefit on a primary endpoint or was otherwise found favorable by the study's authors (positive result), showed no statistically significant benefit (neutral result), or was significantly worse than a comparator or was otherwise found unfavorable by the study's authors (negative result). An app's Clinical

Methodology

rating is the average score of all available peer reviewed publications that have assessed its content, usability, accuracy, effectiveness, safety, or underlying health economics.

Apps with the highest scores typically have key quality characteristics such as exceptional patient ratings, connectivity to sensors, and rapid update cadence, thereby ensuring that apps are reliable, incorporate the latest technologies and have endorsements from at least digital publishers and often from providers or government authorities (e.g., the FDA).

ANDROID INSTALL DATA ANALYSIS

As of June 10, 2020, Google Play data contained in the AppScript App Database included information on volume of downloads, where downloads were quoted in the following ranges: 10 million to 50 million; 5 million to 10 million; 500,000 to 1 million; 100,000 to 500,000; 50,000 to 100,000; 10,000 to 50,000; 5,000 to 10,000; 1,000 to 5,000; 500 to 1,000; 100 to 500; 10 to 50; 5 to 10; 1 to 5. The median number of downloads was taken for each range, from which a total number of downloads was estimated.

COVID-19 DOWNLOAD TRENDS FROM 42 MATTERS

42Matters data was used separately to map the impact of COVID-19 on app use. All app install data was pulled from the Google Play Store in the Health & Fitness or Medical categories. As an example, suicide apps had the word suicide in the developer name or title or description as well as 5,000+ total downloads and 100+ monthly downloads. The Movember app was excluded. These included Moodtools – Depression Aid, Don't Panic – Depression, Stay Alive, Beyond Now Suicide Safety, Psychiatry Pro-Diagnosis, Info, Treatment, CBT & DBT, Adolescent Suicidal Test, CESD Depression Test, Suicide Safety Plan, Suicide Safe, Mental Health and Psychiatric Care Plans, Mental Health and Psychiatric Nursing Care Plans, Better Stop Suicide and DistrACT. The exercise

request was “workout OR fitness NOT diet NOT water NOT medicine NOT ovulation” in developer name or title or description with more than 10,000,000+ downloads and 50,000+ monthly downloads. Depression/anxiety include apps with “depression OR anxiety” in the title, 100,000+ total downloads and 5,000+ monthly downloads. Oximetry apps included “oximeter” in description or title, 10,000+ total downloads, 5,000+ monthly downloads. The blood pressure app request had “blood pressure” OR hypertension NOT diabetes NOT sugar NOT test in the title with more than 100,000+ downloads and 10,000+ monthly downloads. Fake apps were manually removed. And finally, other app data was requested to track the trend among apps used for telemedicine including ZOOM Cloud Meetings, Zoom for Intune, Microsoft Teams, and Doximity — Medical Network.

DIGITAL THERAPEUTICS AND DIGITAL CARE DATA

The IQVIA Digital Solutions Database includes in-depth information digital therapeutic apps, games, and virtual reality, as well as digital care programs across a range of diseases, and captures information opportunistically on a range of digital diagnostics, digital medicine products, digital health products, telemedicine solutions involving an app, and wearable-driven digital solutions. As of January 2021, there were at least 440 solutions recorded, with comprehensive data on 137 digital therapeutics and 122 digital care programs in any phase of development — a total of 259 therapy products — and 181 products captured non-comprehensively in the other categories. For digital therapeutics, the database captures information across a wide range of indications, pipeline progress, features, dates, and evidence generation conducted. It is updated on a quarterly basis. The capture rate of digital therapeutics is known to be higher than that of digital care programs, and therefore the early stage pipeline of digital care products in the database is likely to be understated.



DEVICE DATA

Data on available consumer wearable sensors was built using primary research by IQVIA AppScript, to form the AppScript Device Database. As of March 2021 when the data was pulled, a total of 384 unique patient sensors were included in the curated AppScript Device Database.

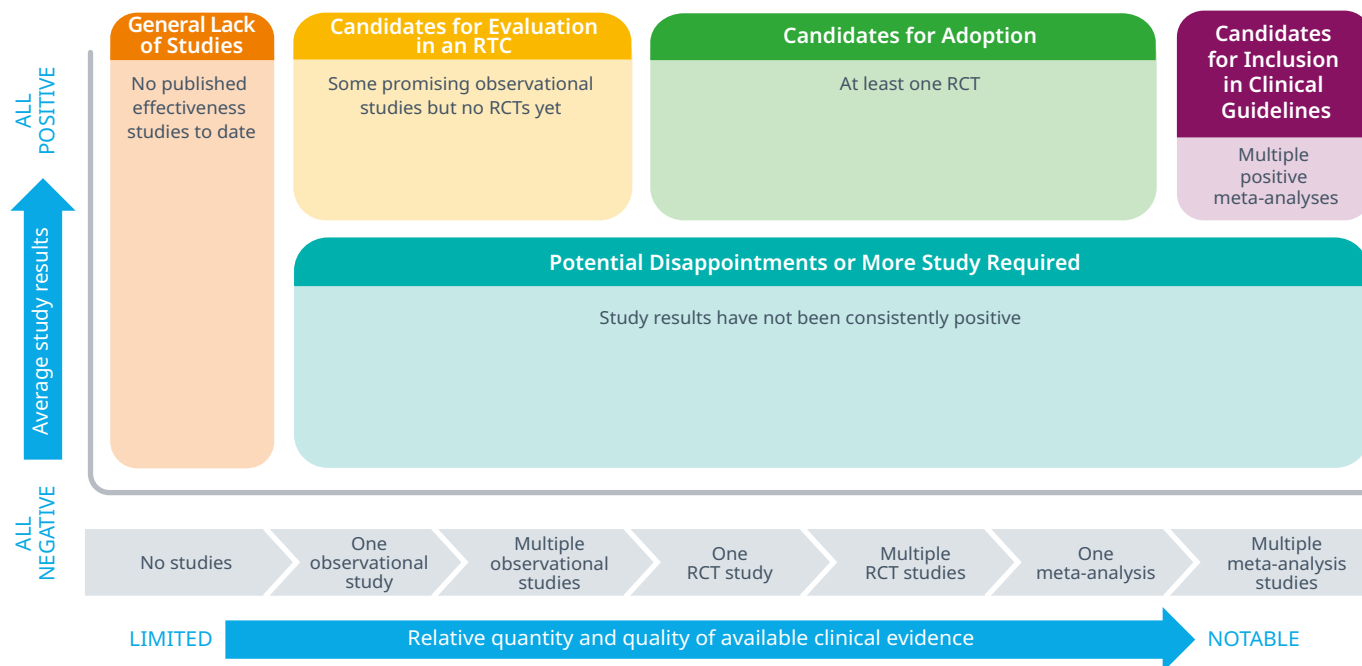
CLINICAL EVIDENCE MATURITY ASSESSMENT USING THE APPSCRIPT DIGITAL HEALTH EVIDENCE DATABASE

To examine trends, clinical evidence produced by apps were assessed using the AppScript Digital Health Evidence Database. The number and types of effectiveness studies published on digital health over time were examined. Peer-reviewed publications are identified and included in the AppScript Digital Health Evidence Database on a rolling basis, leveraging database search as well as manual search

methodologies. Google Scholar and PubMed databases are searched on relevant keywords across therapeutics areas, study types and technology categories. The AppScript team also monitors relevant trade publications and industry contacts for new studies which occasionally requires manual entry above and beyond database search methodologies.

The Digital Health App Clinical Maturity Assessment included app effectiveness studies across dozens of app use categories ranging from individual conditions (e.g., diabetes) to prescription management categories (e.g., filling prescriptions). Many types of peer-reviewed publications were not included in the analysis presented as there were no direct and quantitative implications for improved human health, including content review studies, usability studies, technical and clinical accuracy

Exhibit 36: Digital Health Clinical Maturity Matrix



Sources: IQVIA AppScript Clinical Evidence Database, Jan 2021

Notes: Only includes studies that evaluated the interventional value of a digital health solution (mobile or web app, connected device, or other mobile intervention such as texting) on patient outcomes such as activity levels, lab results, or healthcare resource utilization. Shows the average of study results for the highest quality evidence available (i.e., meta-analysis > RCT > observational)

Methodology

studies, and pure health economic studies (i.e., those based on pre-existing effectiveness data). Effectiveness studies were categorized by study type (observational, RCT, systematic review or meta-analysis study), outcome (positive, negative, neutral) and primary use category (e.g., therapeutic area/medical condition). Positive study outcomes reflect study results demonstrating statistically significant findings of clinical change. Studies were summarized via a “Digital Health Clinical Maturity Matrix” (see Exhibit 36).

Values for the x-axis, Relative Quantity and Quality of Available Clinical Evidence, were derived via a tiered assessment of the available clinical evidence. The first tier of the assessment was the most heavily weighted and focused on the highest quality study designs currently available for the digital health app use category. The study quality point system was scored as follows: No Studies = 0 points, One Observational Study = 1, Multiple Observational Studies = 2, One RCT = 3, Multiple RCTs = 4, One Meta-Analysis Study = 5, and Multiple Meta-Analysis Studies = 6. The second tier of the quantity and quality assessment was a minor factor focused on study quantity. Total effectiveness studies were counted in each digital health app use category, with categories with the most studies receiving close to an additional point and all other studies receiving a fraction of a point based on their relative study counts. Values for the y-axis, Average Study Results, are based on averaged individual study result scores, where each individual study is scored a 1.0 (positive), 0.5 (neutral), or 0.0 (negative). For the Average Study Results assessment, only the highest quality available studies were considered. For example, if a given use case category had many observational studies and two RCTs, only the results of the RCTs were considered. Apps were divided into five clinical maturity groupings based on typical evidence thresholds across the health system.

Digital health app use categories featuring multiple meta-analysis studies and generally positive results were grouped as “Candidates for Inclusion in Clinical Guidelines” as this level of clinical maturity has likely produced studies that meet the explicitly stated requirements of clinical guideline writers. Categories with at least one RCT and generally positive results were grouped as “Candidates for Adoption” as health plans, healthcare providers and individual clinicians generally regard RCT data as a gold standard evaluation. Categories with only observational studies were grouped as “Candidates for Evaluation in an RCT” as they may be considered sufficiently de-risked to invest in a robust, gold-standard RCT study. Categories without any effectiveness studies were grouped as “General Lack of Studies.” Categories with average results of ~0.6 or lower (i.e., at best, closer to neutral than positive) were grouped as “Potential Disappointments or More Study Required” as key health system stakeholders generally expect new healthcare interventions to consistently demonstrate significant clinical value when studied. This being said, given the broad capacity of digital health to improve human health outcomes demonstrated in this report, it is likely that many of these “Potentially Disappointing” categories will ultimately find the appropriate functionality, delivery models and patient sub-populations where consistently favorable results are possible.

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Murray Aitken is Executive Director, IQVIA Institute for Human Data Science, which provides policy setters and decisionmakers in the global health sector with objective insights into healthcare dynamics. He led the IMS Institute for Healthcare Informatics, now the IQVIA Institute, since its inception in January 2011. Murray previously was Senior Vice President, Healthcare Insight, leading IMS Health's thought leadership initiatives worldwide. Before that, he served as Senior Vice President, Corporate Strategy, from 2004 to 2007. Murray joined IMS Health in 2001 with responsibility for developing the company's consulting and services businesses. Prior to IMS Health, Murray had a 14-year career with McKinsey & Company, where he was a leader in the Pharmaceutical and Medical Products practice from 1997 to 2001. Murray writes and speaks regularly on the challenges facing the healthcare industry. He is editor of Health IQ, a publication focused on the value of information in advancing evidence-based healthcare, and also serves on the editorial advisory board of Pharmaceutical Executive. Murray holds a Master of Commerce degree from the University of Auckland in New Zealand, and received an M.B.A. degree with distinction from Harvard University.



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About the Institute



The IQVIA Institute for Human Data Science contributes to the advancement of human health globally through timely research, insightful analysis and scientific expertise applied to granular non-identified patient-level data.

Fulfilling an essential need within healthcare, the Institute delivers objective, relevant insights and research that accelerate understanding and innovation critical to sound decision making and improved human outcomes. With access to IQVIA's institutional knowledge, advanced analytics, technology and unparalleled data the Institute works in tandem with a broad set of healthcare stakeholders to drive a research agenda focused on Human Data Science including government agencies, academic institutions, the life sciences industry and payers.

Research Agenda

The research agenda for the Institute centers on 5 areas considered vital to contributing to the advancement of human health globally:

- Improving decision-making across health systems through the effective use of advanced analytics and methodologies applied to timely, relevant data.
- Addressing opportunities to improve clinical development productivity focused on innovative treatments that advance healthcare globally.
- Optimizing the performance of health systems by focusing on patient centricity, precision medicine and better understanding disease causes, treatment consequences and measures to improve quality and cost of healthcare delivered to patients.

- Understanding the future role for biopharmaceuticals in human health, market dynamics, and implications for manufacturers, public and private payers, providers, patients, pharmacists and distributors.
- Researching the role of technology in health system products, processes and delivery systems and the business and policy systems that drive innovation.

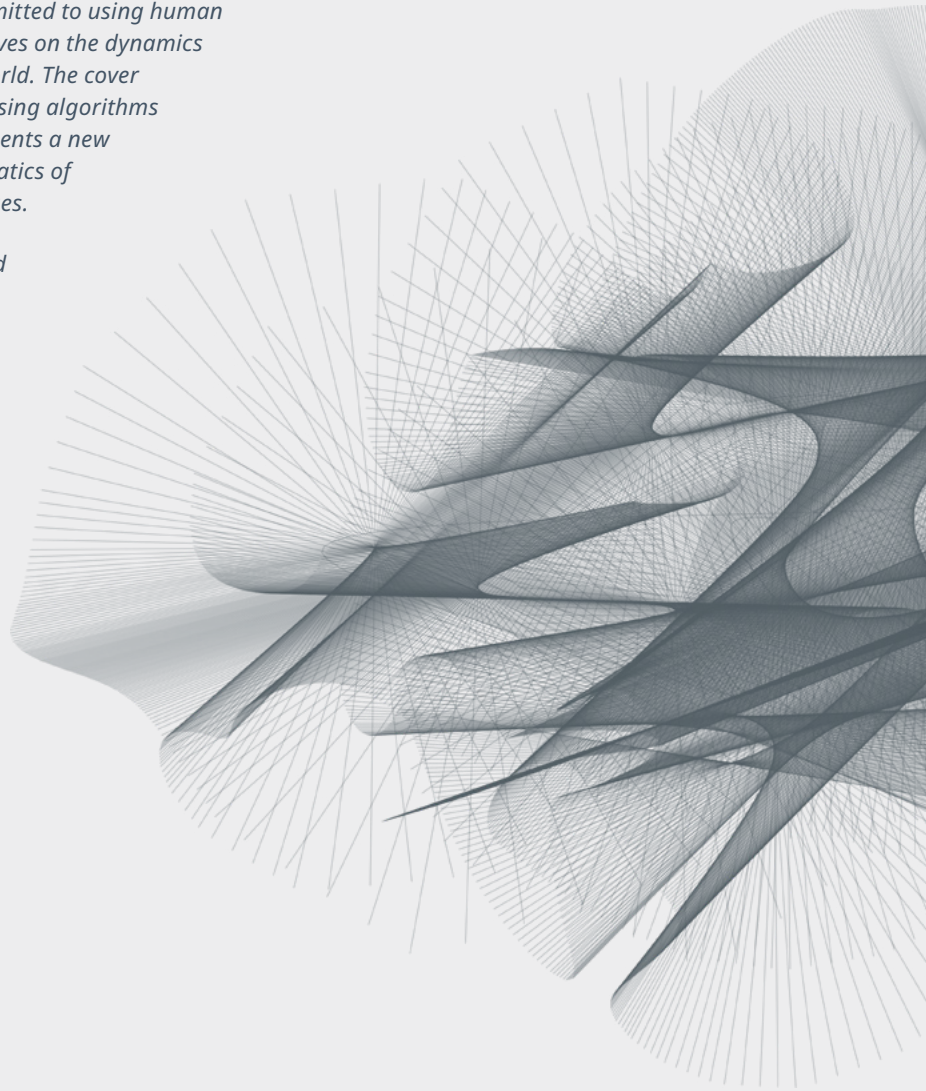
Guiding Principles

The Institute operates from a set of guiding principles:

- Healthcare solutions of the future require fact based scientific evidence, expert analysis of information, technology, ingenuity and a focus on individuals.
- Rigorous analysis must be applied to vast amounts of timely, high quality and relevant data to provide value and move healthcare forward.
- Collaboration across all stakeholders in the public and private sectors is critical to advancing healthcare solutions.
- Insights gained from information and analysis should be made widely available to healthcare stakeholders.
- Protecting individual privacy is essential, so research will be based on the use of non-identified patient information and provider information will be aggregated.
- Information will be used responsibly to advance research, inform discourse, achieve better healthcare and improve the health of all people.

The IQVIA Institute for Human Data Science is committed to using human data science to provide timely, fact-based perspectives on the dynamics of health systems and human health around the world. The cover artwork is a visual representation of this mission. Using algorithms and data from the report itself, the final image presents a new perspective on the complexity, beauty and mathematics of human data science and the insights within the pages.

The algorithmic art for this report cover was derived from a dataset describing features of mobile apps that have each been downloaded more than 10 million times. These most popular apps include global leaders in the health and fitness space, many of which have been around since 2014, as well as COVID-19 apps. Data reflects installs from GooglePlay that were sourced from 42Matters via the IQVIA AppScript app database in June 2021.



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