Digital Therapeutics: The Integral Cog of Digital Innovation in Drug Development

Vivek Vikram Singh (PhD),
Associate Director,
Healthcare R&A, WNS

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It is well acknowledged that the traditional drug development paradigm has been changing rapidly in the 21st century, with greater focus being placed on delivering personalized medicine solutions. This has been fueled by the development of social networks, smartphones, wearable devices and cloud-based data platforms, which have enabled the collection, storage and analysis of ever-increasing amounts of clinically relevant data. Furthermore, the expansion of digital analytical tools and advances in Machine Learning (ML) have empowered researchers to transform data into knowledge and aid clinical decision-making.

This new-age armamentarium permits a broad range of activities in digital health, including in mobile health (mHealth), Health Information Technology (HIT), wearable devices, telehealth / telemedicine and personalized Digital Therapeutics (DTx).

The Field of Digital Therapeutics

In simple terms, DTx are a health discipline and treatment option that utilize digital and often online health technologies to treat a medical condition. It is however different from, say, a wellness app in that a DTx must undergo clinical validation / trial to prove its efficacy as a bona fide therapeutic.

DTx thus form an independent category of evidence-based products within the broader digital health landscape. It is distinguished through its primary function of delivering software-generated therapeutic interventions directly to patients to prevent, manage or treat a medical disorder or disease. The individual treatment strategy is 'optimized' (for instance, by applying ML techniques to the individual's observed data), thereby realizing the principle of personalized medicine. DTx are validated by regulatory bodies, as required, to support product claims regarding risk, efficacy and intended use.

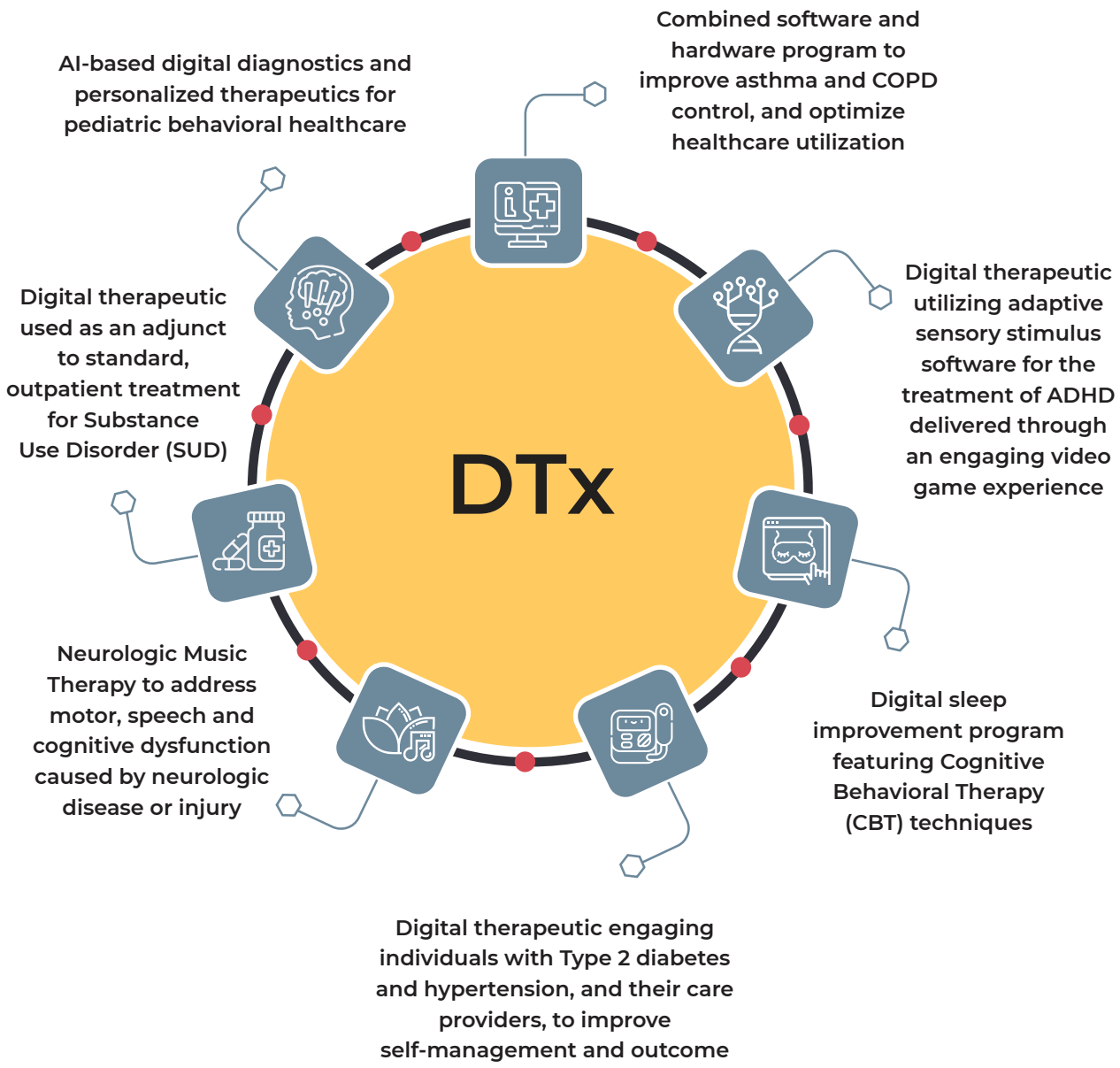
Megan Coder, executive director of the Digital Therapeutics Alliance (DTA), a non-profit organization, which is responsible to set standards and integrate DTx into healthcare, says, "Digital therapeutics are part of the broader digital health landscape, but in order to be called one, a product has to be software driven and evidence based, and make a claim to prevent, manage, or treat a medical disease or disorder. A digital therapy can be used alone, or with other therapies to optimize outcomes."

DTx are considered distinct from pure-play adherence, diagnostic and telehealth products. However, while their key focus is on delivering direct therapeutic interventions, DTx products possess the unique ability to incorporate additional functionalities into its comprehensive portfolio. Integration with mHealth platforms; ability to provide complementary diagnostic or adherence interventions; compatibility with digital devices, sensors, or wearables; remote delivery of intervention; and integration into electronic prescribing, dispensing, and EMR platforms, are the key additional features that can be part of a DTx solution.

The types of interventions being delivered / developed by DTx products across the industry are as diverse as the disease states being addressed. In September 2017, Pear Therapeutics' lead product, reSET®, was the first DTx to receive market authorization from the US FDA to work in conjunction with conventional outpatient clinician-delivered care (face-to-face therapy) for Substance Use Disorder (SUD). It's a mobile-based medical application system for a patient use and has a clinician dashboard interface. With reset®, patients can get Cognitive Behavioral Therapy (CBT), to teach them skills that aid in the treatment of SUD. Its purpose is to increase abstinence from substance abuse and retention of prescribed behavior in an outpatient therapy programs. Soon thereafter, Pear's second product candidate, reSET-O®, for the treatment of Opioid Use Disorder (OUD) received Breakthrough Designation (BTD) and was authorized by the US FDA in December 2018.

With the burgeoning of DTx platforms and applications, patients, providers and payers can expect increasing comprehensive network of therapy modalities for physical, mental and behavioral disease states. As per a market report analysis from ResearchAndMarkets, the global DTx market is expected to grow at a CAGR of 31.4 percent, from USD 3.4 Billion in 2021 to USD 13.1 Billion by 2026. Theincreasing focus on preventive healthcare, emerging R&D trends, technological advancements, importance of patient convenience and user-friendliness, and launch of novel products with enhanced efficiency are key factors contributing to the high CAGR in the forecast period.

Examples of DTx in the market or currently under development

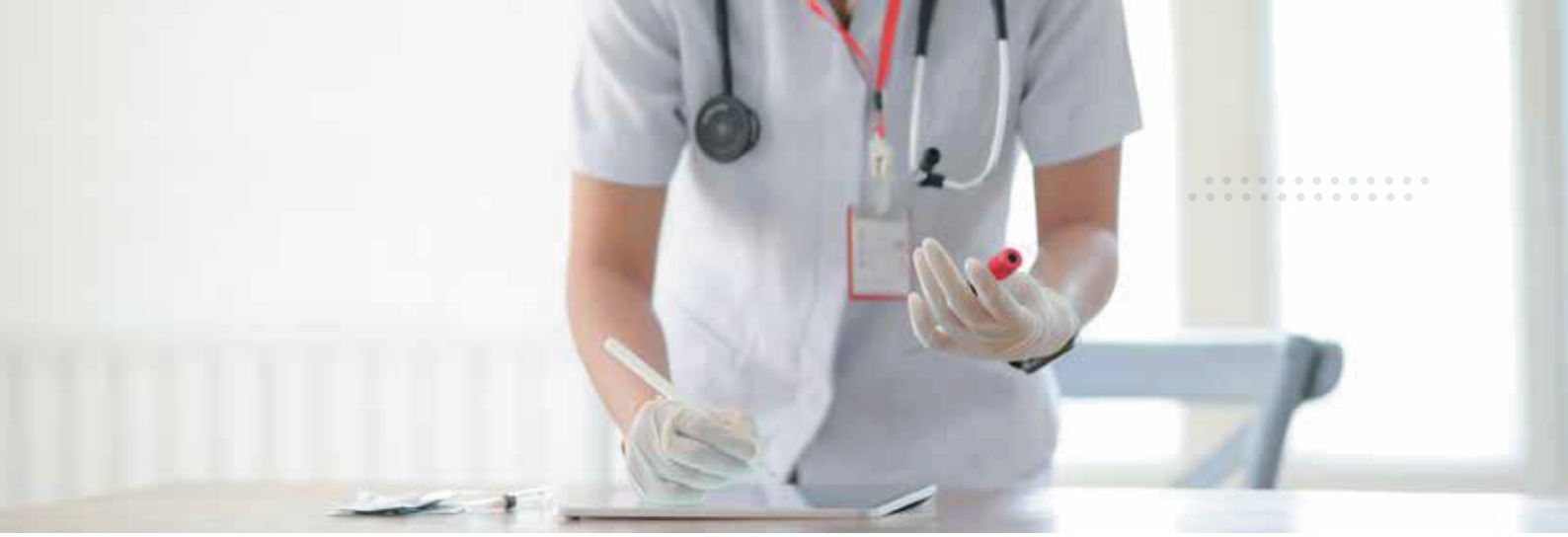


In essence, every DTx product corresponds to one of the four categories based on its intended use and official product claims:

- Address a medical condition
- Manage or prevent a medical condition / disease
- Optimize an individual medication
- Treat a medical condition or disorder

Each category of DTx displays varying degrees of product claims, requirements for regulatory oversight, patient and provider access and integration with concurrent therapies.

	Primary Purpose of DTx Product			
	Address a Medical Condition	**Manage or Prevent a Medical Condition / Disease**	**Optimize Medication**	**Treat a Medical Condition / Disorder**
Level of Product Claims (Related to Medical Disorder or Disease)	No efficacy claims regarding a medical disorder or disease	Low to medium risk (e.g. reduce rate of disease progression)	Medium to high risk (e.g. improve efficacy of adjunctive therapies)	Medium to high risk (e.g. direct efficacy claims on clinical outcomes)
Clinical Evidence Requirement	Clinical trials required	Clinical trials required	Clinical trials required	Clinical trials required
Level of Support for Product Claims	Regulatory enforcement discretion (without explicit oversight)	Third-party validation of efficacy / safety claims by regulatory or equivalent national body	Third-party validation of efficacy / safety claims by regulatory or equivalent national body	Third-party validation of efficacy / safety claims by regulatory or equivalent national body
Patient Access to DTx	Direct-to-consumer (prescription not required)	OTC or prescription required	OTC or prescription required	Prescription required
Association to Concurrent Therapies	Works independently or indirectly supports another therapy	Monotherapy or directly supports a concurrent treatment	Directly supports a concurrent treatment	Monotherapy or directly supports a concurrent treatment



Regulatory Perspectives on Digital Therapeutics

The US Food and Drug Administration (FDA) and regulatory agencies of other regions have been undertaking considerable effort to streamline their respective regulatory frameworks to support the development, evaluation and, when warranted, clearance of novel DTx. As digital treatments proliferate, scrutiny of the various medical claims being made becomes more important. DTx come under the purview of the Software as a Medical Device (SaMD) framework, developed by the International Medical Device Regulators Forum (IMDRF), though not everything reviewed by the SaMD is a digital therapeutic.

The IMDRF, conceived in February 2011 as a medium to deliberate directions in medical device regulatory harmonization. It is a voluntary group of medical device regulators from around the world, to build on the robust foundational work of the Global Harmonization Task Force (GHTF) to fast-track international medical device regulatory harmonization. In 2013, IMDRF formed the Software as a Medical Device-Working Group (WG) to provide guidance for supporting global innovation and quick access to safe and effective SaMD. Chaired by the FDA, the SaMD-WG outlined the key definitions, framework for risk categorization for SaMD, quality management for SaMD and guidance for the clinical evaluation of SaMD for the industry and FDA.

The precise path prescribed in the SaMD framework that DTx must take, and the level of clinical evidence its maker must provide, is dependent on the novelty of the product and how great a risk it poses should it malfunction. Pear's reSET®, for instance, had to submit results of a randomized controlled trial through the FDA's De Novo approval pathway. The FDA approved it as a prescription-only product, a designation that is independent of the level of regulatory control DTx require. Nonetheless, regardless of the type of claim being made, the FDA can exercise 'enforcement discretion' waiving regulatory oversight if it decides a product is low risk.

In 2017, the FDA outlined a pilot scheme for a 'pre-certification' program to assess companies rather than products. Pre-certified companies, deemed to have demonstrated excellence in software development and validation, could market lower-risk devices without further oversight or through a more streamlined process. Real-world performance data, which is generally much easier to collect for DTx than for pharmaceuticals, could then be used to affirm a product's regulatory status as well as support its evolution. The idea is being tested in a pilot scheme involving nine companies that are undergoing the new process alongside conventional review, to check that they produce the same decision.

Novel Business Models for Digital Therapeutics

Conceptually, DTx can be prescribed with or without combinations with a pharmacotherapy. Although DTx as a monotherapy has been the pivotal approach in its development, the use of a digital therapeutic prescribed along with a pharmacotherapy is potentially a more interesting strategy. Such interaction is not only limited to digital and pharmacological treatments targeting the same indication, but could also pertain to co-indications.

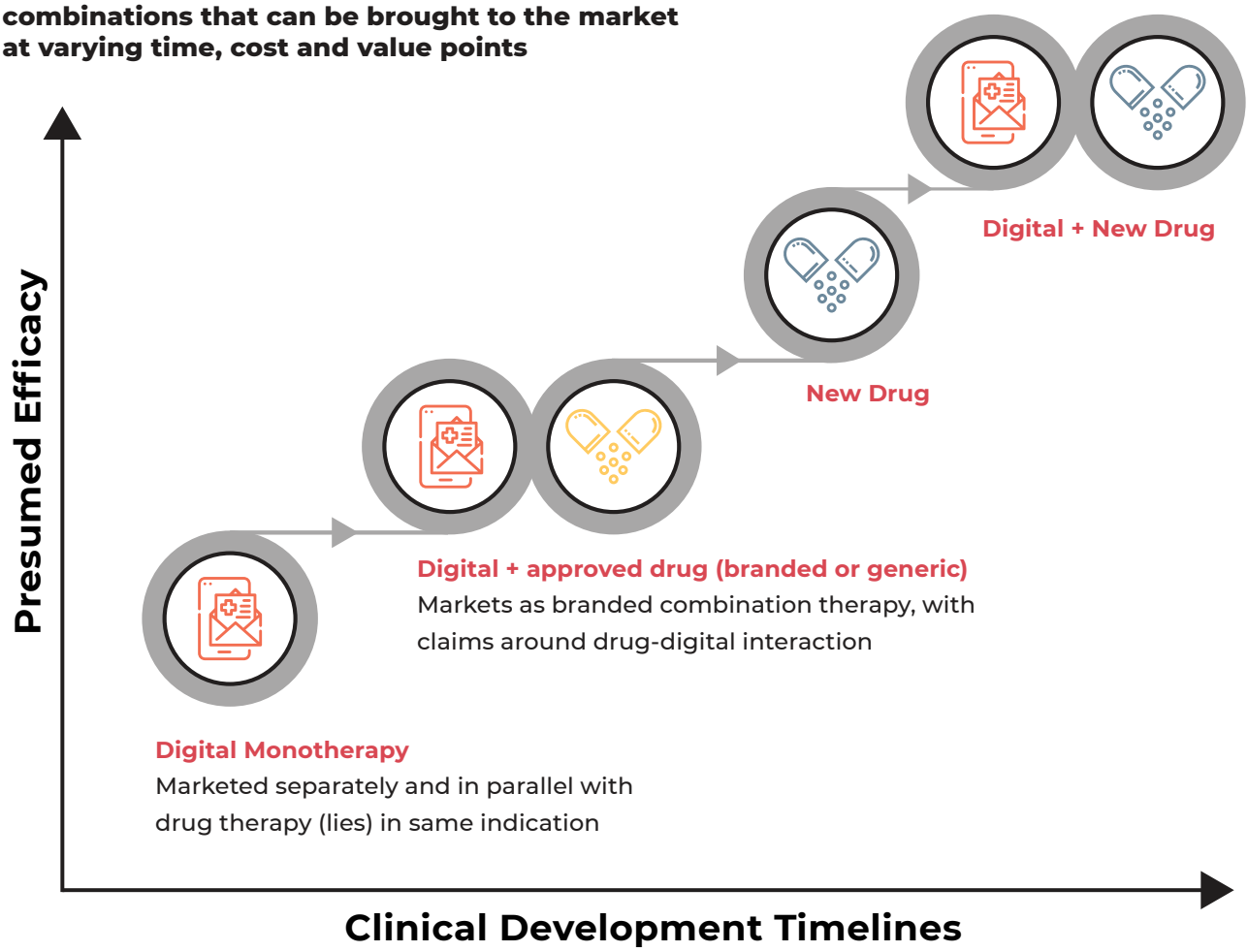
For instance, anxiety co-occurs with a number of chronic conditions, including inflammatory, respiratory and oncological disorders. Whereas a lot of pharmacological therapies exist for the treatment of inflammation, respiratory distress and cancers, and while behavioral therapies have proven to be greatly effective in the treatment of anxiety, much less is understood about the synergistic effect of treating both at the same time.

Arguably, when compared with the development of new molecular entities, the development of a DTx monotherapy as well as the combination of a DTx with a known pharmacotherapy have faster and more cost-effective paths to patients and medical value creation. Therefore, it could be an interesting opportunity for the biopharmaceutical industry to explore capabilities of these novel DTx technologies to enhance overall outcomes of pharmacological treatment.

On a more protracted level, one could also imagine the development of a new molecular entity combined with a DTx technology, planned from the onset as part of a combined 'drug-device' therapy. This could potentially create more medical value for patients than bringing the new molecule to the market by itself.

However, the current market dynamics of new drug development may not be conducive to assuming such additional risk in the development of the new molecule, even if the addition of the innovative technology could create incremental medical value. It may be for future visionaries to explore how DTx technologies may be incorporated into core drug development without significantly adjusting the classical pharma business model, which focuses primarily on new molecular entities.

Figure: A model depicting various 'drug-digital' combinations that can be brought to the market at varying time, cost and value points



Conclusion and Outlook

Digital therapeutics provide a new approach to treatment and disease management, wherein digital systems help patients manage their own health and disease conditions. DTx utilize the infrastructure of the Internet, mobile phone and the novel gains in AI, ML and big data analytics to optimize treatment for a given individual, thereby echoing true principles of personalized medicine. As the distribution of the global population shifts towards older age groups, prevention and effective management of chronic diseases is more relevant than ever. DTx may provide safer and less expensive options than traditional treatment, which, in turn, may save hundreds of billions of dollars in healthcare.

Similar to pharmaceuticals, DTx necessitate rigorous investigation in randomized controlled clinical trials to provide reliable evidence of safety and effectiveness. However, unlike regular drug development, the timelines can be substantially reduced because some steps, such as toxicity studies, are not applicable. Although, clinical trials to assess digital interventions pose new logistical, statistical and ethical challenges, DTx provide unique opportunities for implementing innovative research designs and big data analytical techniques. Novel models of unison between bio / pharma and tech companies is bound to expedite development of innovative digital medicinal products.

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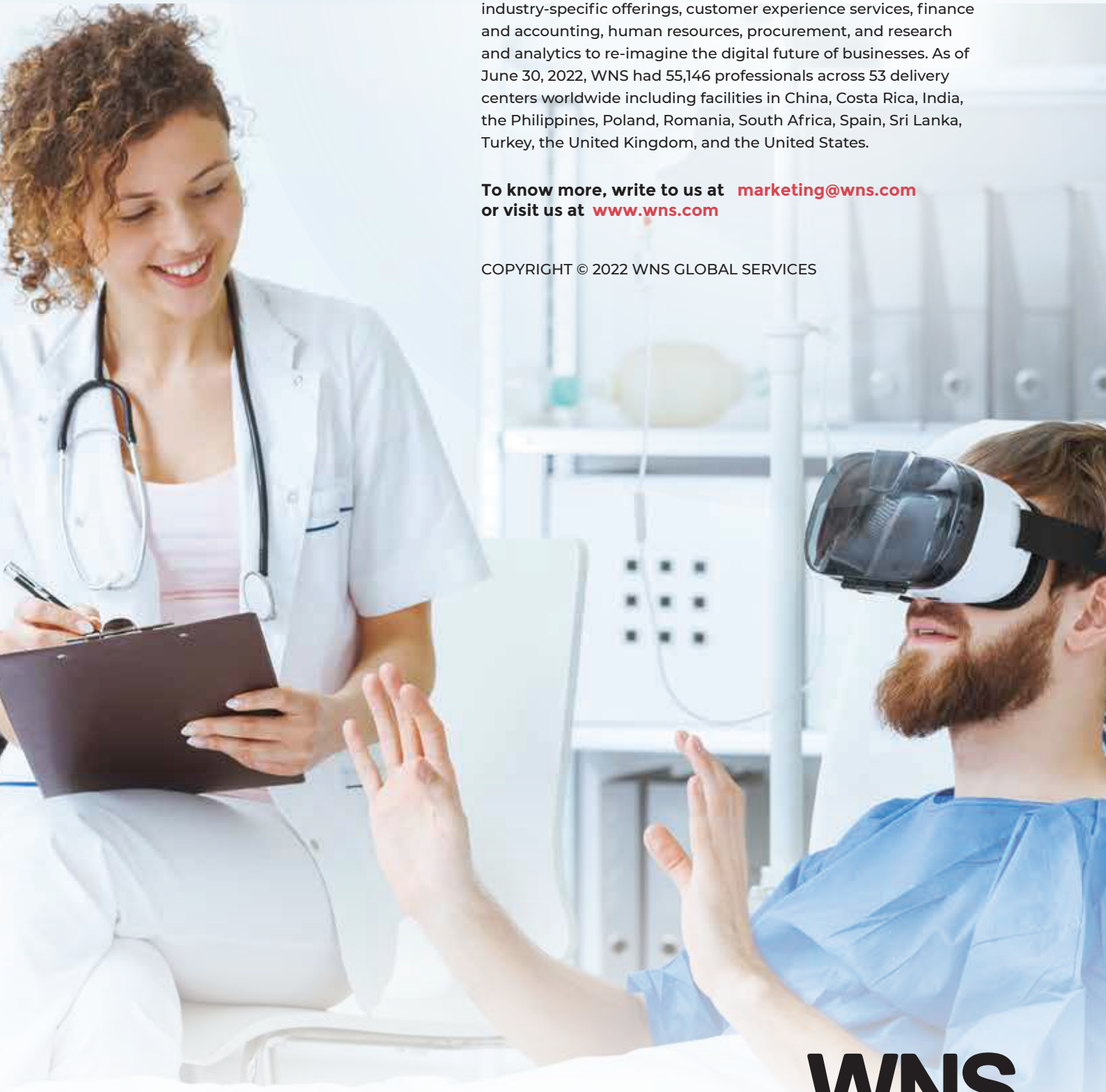

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