GUIDANCE TO INDUSTRY:
Classification of Digital Health Technologies

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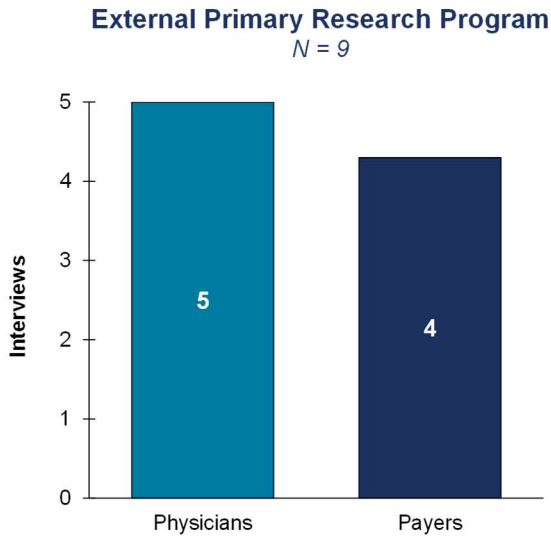
PREFACE: PROJECT CONTEXT, OVERVIEW, AND METHODOLOGY

The digital transformation of healthcare is in full swing. With this rapid pace of innovation comes a complicated and overlapping array of digital technologies that is difficult for patients, clinicians, payers, and policymakers to differentiate, evaluate, and ultimately benefit from. As the leading international organization on digital therapeutic thought leadership and education, the Digital Therapeutics Alliance (DTA) has partnered with Health Advances, a life sciences strategy consulting firm, to assist in defining and classifying the full spectrum of digital health technologies (DHTs). By offering robust categorizations and precise definitions, this guidance aims to foster a unified and consistent understanding of the digital landscape for all stakeholders interacting with and hoping to benefit from digital products.

We performed comprehensive external benchmarking of how DHTs are currently defined and classified. Our research was informed by the latest publications from regulatory bodies (e.g., the United States Food and Drug Administration (FDA), the United Kingdom's National Institute for Consumer Education (NICE)), trade organizations (e.g., DTA, Digital Medicine Society (DiME)), analysts and investors (e.g., Rock Health), as well as the global landscape of innovative digital health companies crafting their own definitions and messaging (Figure A). By identifying key points of differentiation across DHTs, we revised the DTA's classification framework to better reflect the landscape of DHTs today and one that better services where the industry is headed. We then pressure tested the revised classifications with US physicians, US commercial and government payers, and DTA member companies to arrive at this guidance for industry (Figure B).

Given the rapid development of digital products and pioneering companies in this space, we aim to consistently revisit and update this guidance to consider novel technologies and incorporate feedback from the broader healthcare industry.

Figure A: Health Advances Secondary Research Program



DIGITAL THERAPEUTIC ALLIANCE

115+
Members

Figure B: Health Advances Secondary Research Program

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EXECUTIVE SUMMARY

Digital Health Technologies (DHTs) represent an exciting and wide array of products used across the healthcare ecosystem. From patient-facing wearables to electronic medical record (EMR) software and digital clinical trial (DCT) tools, DHTs are either directly used by or impact nearly every stakeholder in healthcare, including patients, healthcare professionals (HCPs), administrators, payers, regulators, and industry professionals. It is more important than ever to ensure there is a consistent understanding of these significantly impactful technologies. To achieve this goal, the combined efforts of the Digital Therapeutics Alliance and Health Advances have sought to classify DHTs into clearly defined and actionable categories.

While several categorizations have been attempted in the past, none have sought to broadly categorize technologies across what we believe are the most important criteria. A deep understanding of how the technologies will be used, what benefits they claim to make, the rigor by which they support their claims, and how they ultimately deliver value are paramount to implementing digital products and realizing their clinical and economic potential. As such, we have developed our categorization based on the following segmentation criteria:

- End User / Beneficiary
- Intended Benefits / Claims
- Regulatory Scrutiny
- Strength of Evidence
- Product / Intervention Type

Such criteria have led us to structure our classification around eight major categories, ranging from patient-facing Digital Therapeutics (DTx) to a host of software products for hospitals, health systems, payers, industry players (e.g., pharmaceutical and medical device companies), and other stakeholders in the healthcare industry. This classification includes:

1. Digital Therapeutics
2. Digital Diagnostics
3. Care Support
4. Patient Monitoring
5. Health & Wellness
6. Health System Clinical
7. Health System Operational
8. Non-Health System Solutions

The goal of this report is to provide stakeholders with a better understanding of DHTs and create actionable categories that will accelerate the awareness, assessment, and ultimate adoption of various digital products. We intend for this guidance to be used by the variety of stakeholders in the ecosystem who are currently evaluating, buying, using, and benefiting from DHTs. While they may vary in practice, some potential use cases may be to:

1. Patients / Caregivers
    - Discover and adopt new DHTs that can be used for self-management of various diseases and/or general health and wellness
    - Better understand the role of DHTs they may already be using

    - Better support a loved one and their use of DHTs to manage their health
2. Healthcare Providers and Health Systems
    - Identify gaps in the DHT ecosystem and find new products to fill them, both to meet clinical and operational / financial goals
    - Assess DHT offerings for overlaps or potential consolidation
3. Payers
    - Refine or develop internal coverage requirements and policies specific to DHT categories to accelerate the review of technologies and allow industry to understand the requirements needed for coverage
    - Evaluate DHTs for coverage against the intended value proposition and best practices of their category
4. Original Equipment Manufacturers (OEMs) / Digital Health Companies / Biopharma
    - Identify gaps in the DHT ecosystem and find new products to fill them to support clinical, operational, and financial goals
    - Self-identify DHTs in portfolio to clarify body of evidence, claims, and competitors
    - Develop more comprehensive DHT ecosystems through business development and partnerships in categories not covered

As new technologies and products are developed, we hope to evolve our understanding of these categories to fit the ever-changing landscape. Additionally, we encourage an open dialogue with all stakeholders regarding the defining criteria of these DHT categories. By doing so, we aim to foster a more comprehensive understanding of the field and promote widespread adoption of digital products.

GLOSSARY

BioMeTs	Biometric measuring technologies
CDMO	Contract development and manufacturing organization
CRO	Contract research organization
DCT	Digital clinical trial
DHT	Digital health technology
DH	Digital health
DiME	Digital Medicine Society
DTA	Digital Therapeutics Alliance
DTx	Digital Therapeutics
EMA	European Medicines Agency
EMR	Electronic medical record
ePRO	Electronic patient reported outcomes
FDA	United States Food and Drug Administration
FTC	United States Federal Trade Commission
GDPR	General Data Protection Regulation
HCP	Healthcare professional
HIPAA	Health Insurance Portability and Accountability Act
HIT	Health information technology
IMDRF	International Medical Device Regulators Forum
IT	Information technology
mHealth	Mobile health
NICE	United Kingdom National Institute for Consumer Education
OEM	Original equipment manufacturer
PHI	Protected health information
PMA	Premarket Approval
RCT	Randomized clinical trials
rPCT	Randomized pragmatic clinical trial
RWE	Real-world evidence
SaMD	Software as a medical device

CHAPTER ONE: DIGITAL HEALTH TECHNOLOGY CATEGORIZATION

SECTION 1.1 – WHAT ARE DIGITAL HEALTH TECHNOLOGIES?

Digital Health Technologies (DHTs) are defined by the US FDA as "computing platforms, connectivity, software, and sensors [used] for health care and related uses."[1] The definition is broad and can include technologies that serve a variety of purposes including facilitating low-acuity patient wellness, operationalizing patient data, and even delivering a standalone intervention. Early categorizations of DHTs took various approaches, though none sought to fully characterize the broad spectrum of DHTs across the most meaningful criteria healthcare stakeholders and users care about. For example, the FDA organizes DHTs based on format: mobile health (mHealth), health information technology (IT), wearable devices, and telehealth / telemedicine.[2] Ultimately, however, categorizing by format is unhelpful in understanding the purpose of each DHT and how they should be used or evaluated. Meanwhile, other categorizations, such as 'Digital Health' versus 'Digital Medicine' versus 'Digital Therapeutics' are at such a high level they cannot be actionable for stakeholders.

SECTION 1.2 – DHT CATEGORIZATION

As a first step to defining DHT categories, we developed a set of DHT differentiation criteria. By doing so, we believe the resulting categories are broad enough to encompass the vast array of products on the market today as well as descriptive enough to enable the categories to be actionable (e.g., consistent coverage and review policies applied to specific categories).

- End User / Beneficiary
- Intended Benefits / Claims
- Regulatory Scrutiny
- Strength of Evidence
- Product / Intervention Type

The first factor considered in our classification is the end user of the DHT. The end user is of primary importance as there is a significant gulf in adoption, validation, and regulation between DHTs intended for patients and those intended to be used by other healthcare stakeholders to impact clinical, operational, and/or financial outcomes. The next three classification factors are inherently linked to the claims a DHT is making (be it clinical or non-clinical) that directly result in the level of regulatory scrutiny to which a product is subject, and the resulting strength of evidence required to meet regulatory requirements. These three criteria are extremely important for all stakeholders to understand given the massive impacts on what a product can and cannot do when utilized in the real world. Lastly, the final classification factor focuses on the unique mechanisms by which products can directly provide or impact the delivery of care.

[1] U.S. Food and Drug Administration, "What Is Digital Health?," September 22, 2020, https://www.fda.gov/medical-devices/digital-health-center-excellence/what-digital-health.
[2] U.S. Food and Drug Administration.

Accounting for the most important criteria differentiating products and based on our review of the DHT landscape, industry definitions, government guidance, and numerous other inputs, we have identified eight categories by which to classify DHTs (Figure 1.1).

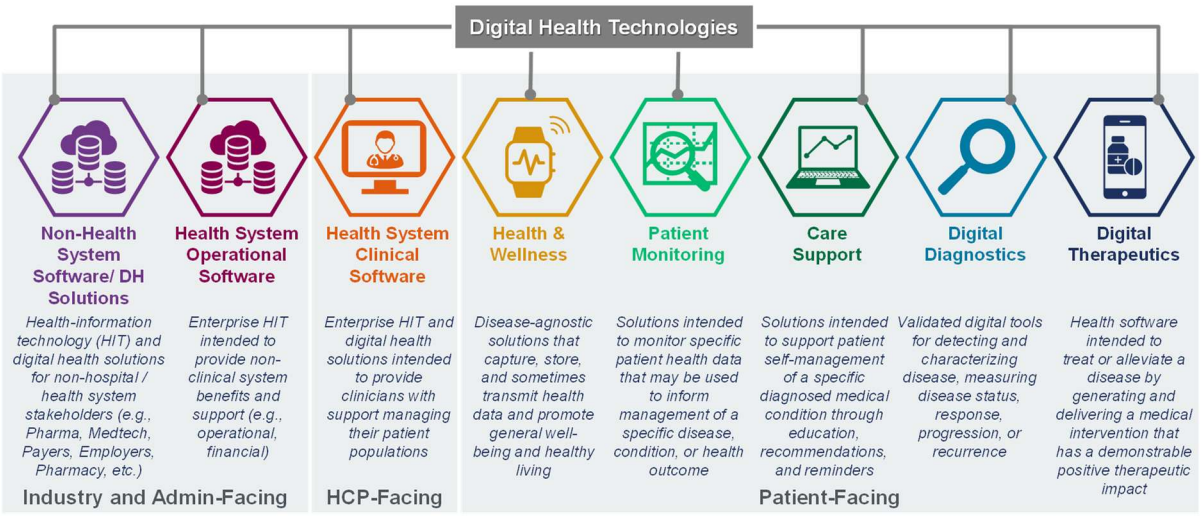

Figure 1.1: Digital Health Technology Categorization

On the left side of Figure 1.1, we have identified three additional categories that primarily service non-patient stakeholders, including healthcare providers, health system and hospital administration, and other stakeholders in the healthcare industry (e.g., original equipment manufacturers, biopharmaceutical companies, employers, and payers). While these solutions may also contain patient-facing elements (e.g., Electronic Medical Record (EMR) patient portals like Epic's myChart), the majority are more akin to enterprise software since they are often centrally adopted and indirectly impact patient care.

On the right side of Figure 1.1, we have identified five categories of patient-facing DHTs. These are products that are primarily intended for a patient to use and will have patient-facing features (e.g., mobile app, computer software, wearable), even though these products can also incorporate features that are physician-, payer-, or health system-facing. This subset of products is presented from left to right in order of increasing impact on clinical management, which is a core orienting principle for how patient0facing DHTs are evaluated, regulated, and paid for. Along with increased impact on clinical management comes a higher bar for evidence required for adoption, greater regulatory scrutiny, and increased stakeholder willingness to pay—all of which are secondary concepts examined in this report.

SECTION 1.3 – PATIENT-FACING DHTs

Figure 1.2 describes how patient-facing DHTs are differentiated based on four key aspects: Label Claims, Intervention Delivery, Evidence Requirements, and Regulatory Implications.

1. **Label Claims**: The product's intended use and claimed benefits, including what the product can and cannot do
2. **Intervention Delivery**: The means by which a product delivers on its label claims, either through direct medical diagnosis or intervention or impact on other interventions
3. **Evidence Requirements**: The rigor and type of evidence a product needs for regulatory approval or authorization
4. **Regulatory Implications**: The extent to which the product is subject to regulatory oversight

DHT Category	Health & Wellness	Patient Monitoring	Care Support	Digital Diagnostics	Digital Therapeutics
Overview	• Disease-agnostic digital health solutions that primarily capture and store general health data and promote healthy living	• Digital solutions intended to monitor specific health data, which may be interpreted by physician for clinical management	• Digital solutions intended to help patients better manage their care of a specific disease or medical condition	• Validated digital tools and software that deliver a diagnosis or prognosis of a specific disease or medical condition	• Health software intended to treat or alleviate a specific disease or medical condition by generating and delivering a medical intervention
Claims	✗ No claims to treat, improve, or diagnose a medical condition	~ May make non-clinical claims to assess patient data	~ May make non-clinical claims to improving health-adjacent measures (e.g., adherence)	✓ Make a clinical claim to diagnose or assess a specific disease or medical condition	✓ Make a clinical claim to treat or alleviate a specific disease or medical condition
Intervention Delivery	✗ Does not deliver a medical intervention	~ Collects health data to inform HCP decision making around medical intervention	~ May recommend actions for patients to better manage care or inform HCPs but does not deliver medical intervention	✓ Software drives medical intervention through a formal diagnosis or assessment	✓ Software itself generates and delivers a medical intervention
Evidence Requirements	✗ Not required	~ Non-clinical claims to assess patient data, must be validated and meet a regulatory agency's quality requriements	~ Any non-clinical claims (e.g., adherence) must be validated and meet a regulatory agency's quality requirements	✓ Diagnostic accuracy must be validated and meet a regulatory agency's quality requirements	✓ Efficacy claims must meet a regulatory agency's quality requirements
Regulatory Implications	✗ No regulatory oversight	~ May require regulatory approval and labeling	~ May require regulatory approval and labeling	✓ Regulated solution with label for indication, usage, evidence, warnings, etc.	✓ Regulated solution with label for indication, usage, evidence, warnings, etc.

Figure 1.2: Patient Facing DHT Differentiation

Patient-facing DHTs are primarily differentiated by their proximity to the patient and their potential to directly impact clinical outcomes. Patient-facing technologies, through marketing and/or labeling, will state a variety of claims on their impacts on outcomes and other measures. It is the presence of these claims, and their specific language, that directly confers a product's potential value and also the various regulations they had to meet to legally make such statements. Across patient-facing DHTs, we see three dimensions of claims: those with clinical claims, those with non-clinical claims, and those without any specific clinical or non-clinical claims at all (Figure 1.2).

- **DHTs with clinical claims** are intended to be used in the context of patient care, are regulated, and are more likely to seek reimbursement by payers or health systems due to the value they offer to the patient. Clinical benefits covered in the product claims are directly attributable to the DHT itself.
- **DHTs with non-clinical claims** may still be used in the context of patient care and reimbursed by payers or health systems as these claims can still provide value to these stakeholders (e.g., improved medication adherence, enable monitoring of key health measures like blood pressure). Since these products do not make explicit claims of clinical improvement, any outcomes are considered indirect and not attributable to the DHT.
- **DHTs without claims** are largely consumer-based products. While these products may promote general wellness or patient experience, any clinical outcomes are not attributable to the DHT itself.

The method by which DHTs influence care or the delivery of care to generate value directly ties to claims (Figure 1.2). This not only determines where stakeholders should look to evaluate causality of outcomes,

but also where OEMs can refine their approaches to improve outcomes. Only two categories of products deliver medical interventions – Digital Therapeutics and Digital Diagnostics, which respectively generate interventions and diagnoses directly through their software. While Care Support tools can make clinical recommendations, they do not serve as interventions themselves. Likewise, while Patient Monitoring and Health & Wellness DHTs can provide patients and/or HCPs with information that can indirectly improve health and well-being, these products do not deliver medical diagnoses or interventions on their own.

- **DHTs that do not impact medical interventions** are largely used in a consumer context and do not aim to deliver health outcomes, but instead aim to arm patients with information about their health and general wellbeing to promote healthier living.
- **DHTs that indirectly impact medical interventions** may be used in the context of patient care to monitor patients or make standard of care recommendations for patients to take, but improved outcomes are delivered indirectly and are dependent on integration with an HCP's clinical practice model and/or a patient taking step to better manage their care.
- **DHTs that serve as medical interventions** inherently improve outcomes through the efficacy of the intervention delivered – Digital Therapeutics are the only category that deliver a medical intervention directly by the software / product.
- **DHTs that drive medical interventions** are a subset of Digital Therapeutics that directly impact and drive a medical intervention (e.g., real-time diabetes monitoring product impacting the amount and timing of insulin delivery).

In order to make the claim that DHTs are directly responsible for their outcomes, OEMs must provide evidence in the form of either randomized-controlled clinical trials (RCTs), randomized pragmatic clinical trials (PCT), real-world evidence (RWE), or a combination of the three. Evidence requirements are regional and set by local regulatory bodies based on the claims made by a DHT. The International Medical Device Regulators Forum (IMDRF) lays out a framework for regulation based on claims and disease severity that has, to date, been in line with the approaches of regulatory bodies across the world. As the evidence requirements directly stem from the claims made by a DHT, those that make no claims require no evidence relating to regulatory, while those that make non-clinical and clinical claims must provide evidence to support those claims (Figure 1.2).[3] It is also important to note that, while evidence requirements for DHTs represent a floor for validation, physicians and payers may impose higher evidence requirements to garner adoption and reimbursement, respectively. Accordingly, OEMs may collect additional layers of evidence to strengthen the value of their DHTs.

SECTION 1.4 – NON-PATIENT-FACING DHTs

Since the advent of the internet, hospitals, health systems, and other players across the healthcare industry have explored ways for digital technologies to improve care, efficiency, and costs. Spurred on by legislation, the rapid adoption of electronic medical records created an ever-expanding amount of data and potential for insights. While not primarily patient facing, the subset of DHTs used by hospital,

[3] International Medical Device Regulators Forum, "'Software as a Medical Device': Possible Framework for Risk Categorization and Corresponding Considerations," September 14, 2014, https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-140918-samd-framework-risk-categorization-141013.pdf.

health system, and industry stakeholders can still significantly impact care for entire populations of patients, as well as individuals.

In hospitals and health systems, digital technologies can be divided into Clinical and Operational buckets based on the expected outcomes each type of product aims to achieve.

Health System Clinical Software (e.g., EMR, clinical decision support, telehealth platforms) is primarily used by physicians and other healthcare professionals to assist in the delivery of clinical care. To date, less regulation has been applied to hospital- and health system-adopted clinical software as their impact on care is typically filtered through the guidance of a licensed healthcare provider. Solutions that arm healthcare providers with enhanced views of their patients, supported by data, to enable better clinical decision-making stop short of making specific care decisions on their own. However, these solutions still go through rigorous screening and validation processes by health systems to ensure they perform appropriately in practice.

Health System Operational Software is less likely to directly impact patient care and less likely to be used day-to-day by physicians but are essential for hospitals and health systems to operate efficiently and minimize costs of delivering care. Operational solutions include Integration/Interoperability Engines, Security/Data Management, Business Analytics, Data Management, and Revenue Cycle Management. The stakeholders involved in evaluating and using operational solutions include non-clinical administrators (e.g., Chief Operating Officer, Chief Financial Officer, Chief Information Officer, Chief Technology Officer) who evaluate solutions based on a variety of criteria, including the ability to return financial value to the organization.

Finally, a last subset of technologies in this category exists that supports non-hospital stakeholders involved in the healthcare ecosystem, such as payers, employers, and industry – **Non-Health System Solutions**. These DHTs can include real-world data aggregation and analytics for pharma companies and payers, stakeholder engagement and support for medical device companies, population health technologies for employers, digital clinical trial solutions for contract research organizations (CROs) and pharmaceutical companies, and many other tech-enabled services and solutions.

SECTION 1.5 – BLURINESS OF MULTI-FEATURE DHTs

Figure 1.2 depicts five clearly differentiated product categories: **Health & Wellness, Patient Monitoring, Care Support, Digital Diagnostics,** and **Digital Therapeutics**. However, given the complexity of DHTs and market demand for end-to-end products, a growing number of DHTs contain multiple features that, if they stood on their own, would fit within different DHT categories.

While it is possible for standalone DHT products to have only one component and function, DHT products are increasingly incorporating multiple components and functions into a single solution. It is therefore important for end users, policymakers, and payers to clearly understand which components are embedded in multi-feature DHTs.

Figure 1.3 depicts six hypothetical products and the components that each one contains. As demonstrated below, the highest risk component in each product determines the product's level of risk and hence, the level of review that is needed to ensure it is safe and effective. Manufacturers should therefore acknowledge the multi-feature nature of their DHTs. This will enable regulators to understand

which features a DHT contains and regulate according to those features, and for other stakeholders to evaluate, disseminate, and utilize multi-feature DHTs more appropriately.

Further work is necessary to standardize the list of potential components that may be incorporated into multi-feature DHTs and the respective standards and expectations affiliated with each component.

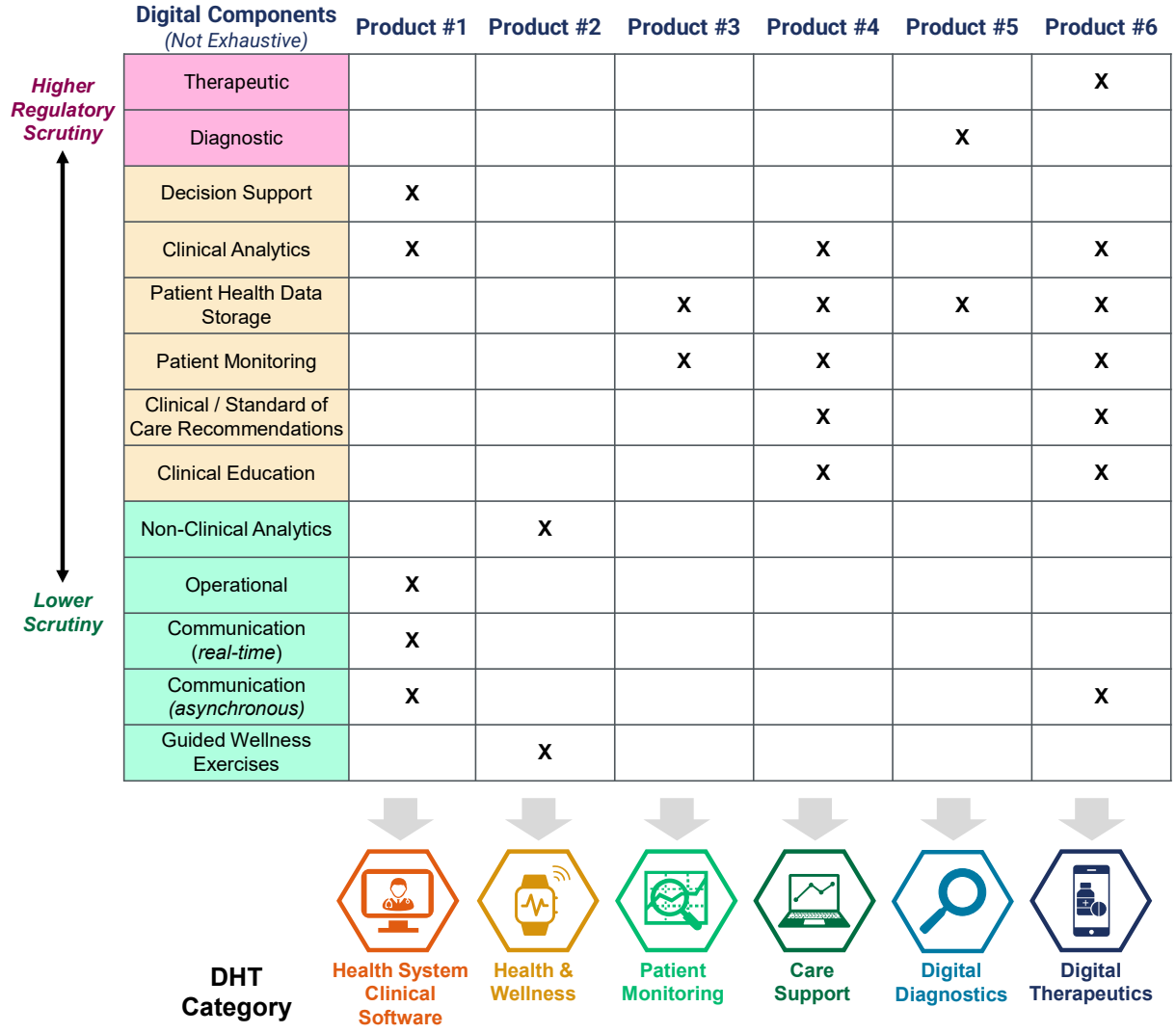

Figure 1.3: Multi-Feature DHTs and Corresponding Categories

CHAPTER TWO: DIGITAL HEALTH TECHNOLOGY DEEP DIVES

SECTION 2.1 – HEALTH & WELLNESS

Health & Wellness products provide non-clinical guidance and education on overall well-being rather than any specific disease states. As such, these DHTs are generally not regulated and have the lowest bar for validation of all DHTs on the market. Although these tools do not make specific medical claims or contain medical records, many of these products still capture, store, and transmit patient data like weight or heart rate that users may consider sensitive or health related. As a result, many companies work to ensure their technology is secure and in some cases Health Insurance Portability and Accountability Act (HIPAA) or General Data Protection Regulation (GDPR) compliant, though this is not guaranteed. Overall, the lack of regulation has provided these tools with a rapid path to market as free or low-cost services, facilitating broader adoption when compared to other DHTs today. Notable entrants such as Calm, MyFitnessPal, Samsung Health, and Apple Health have acquired particularly large user bases.

2.1.1: Definition

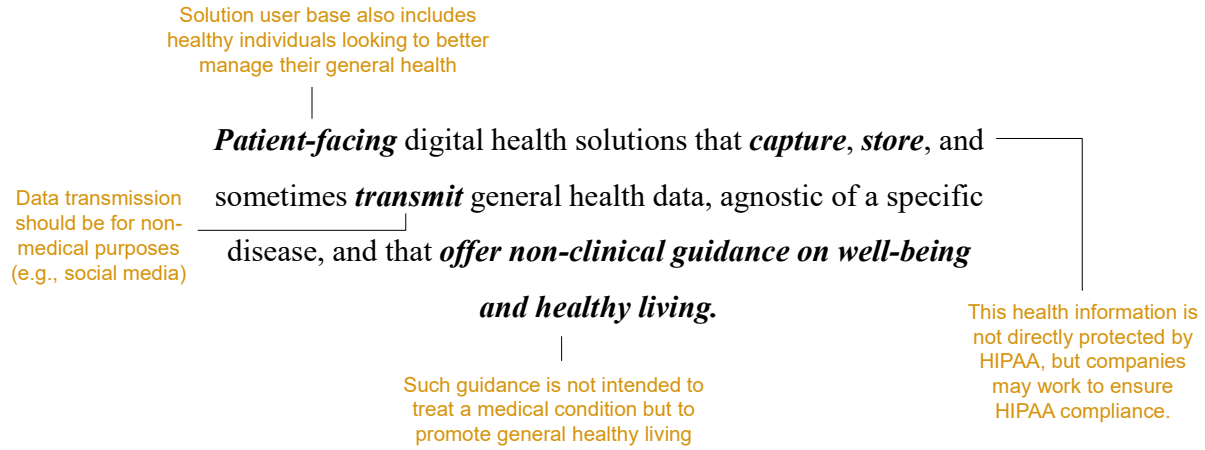

Figure 2.1: Health & Wellness Definition

2.1.2: Defining Characteristics

Points of Differentiation

- **Health & Wellness vs. Care Support:** Unlike **Care Support** tools, **Health & Wellness** products are not intended to relate to a specific diagnosed medical condition as they make no medical claims and should be disease-agnostic. It should be noted that many wellness solutions on the market do indirectly or loosely align with various disease states, though it is still true that they make no medical claims to treating said disease state. **Health & Wellness** products may offer educational content that helps users achieve a healthier lifestyle but any benefit that this content has on a patient's specific medical condition is considered indirect.
- **Health & Wellness vs. Patient Monitoring:** While some **Health & Wellness** products may collect biometrics such as heart rate, total daily steps, or hours of sleep, the methods of collection are not validated, the biometrics are not intended for use in disease management, and data generated by the solution are not considered to be protected health information (PHI) under

HIPAA. **Patient Monitoring** tools typically collect a wider variety of biometrics related to specific disease states, are validated to accurately capture biometrics, and may be required to manage data in a HIPAA-complaint manner.

- **Health & Wellness vs. Digital Therapeutics: Health & Wellness** tools are not themselves an intervention. Further, even though **Health & Wellness** tools may choose to generate evidence to support their health-rated functions, they fall short of making specific-medical claims. Indeed, **Digital Therapeutics** generate evidence and also make disease and/or disorder-specific medical claims. Digital Therapeutics also inherently are an intervention in and of themselves.

Evidence Requirements

Health & Wellness DHTs have no evidence requirements since they do not make specific medical claims. Some companies may choose to develop supporting evidence to showcase their product's potential health benefits and build towards making medical claims, but this is not a requirement, and these studies may lack the rigor of randomized clinical trials or formal real-world evidence studies.

Regulatory

Because **Health & Wellness** products do not make medical claims or cover specific diseases, they are not considered to be medical devices and do not require regulation. The FDA's Wellness Guidance indicates that Health & Wellness products are intended for only general wellness use and present a low risk to safety of users and other – as such, does not intend to examine low risk general wellness products to determine whether they are medical devices. Even though users may consider some data captured, stored, or transmitted to be health data, it is not considered protected health information under HIPAA in the United States as the applications are not intended for use in a medical context and the data is not being collected on behalf of a covered entity such as a healthcare provider or insurer.[4] As such, these products only incorporate basic consumer privacy and security features as mandated by the Federal Trade Commission (FTC), and though some companies work to ensure HIPAA compliance, this is ultimately not required. [5]

2.1.3: Examples: Features & Common Themes

Health & Wellness products typically leverage at least one or several of the features outlined below to provide various levels of guidance, education, and feedback for their target population.

Educational Materials

Educational content highlights best practices for healthy living agnostic to specific clinical conditions. These materials may be shared with patients through different mediums, such as articles, audio, or video and contain content such as healthy recipes or recommendations to sleep better.

Health Diaries

Health diaries store and capture patient-reported information on physical fitness, mood, diet, and sleep patterns. For example, the wellness app MyFitnessPal allows users to track their physical activity during the day and provides a diary to log what a user has eaten in a day.

[4] U.S. Department of Health & Human Services, "Health App Use Scenarios & HIPAA," February 1, 2016, https://www.hhs.gov/sites/default/files/ocr-health-app-developer-scenarios-2-2016.pdf.
[5] U.S. Federal Trade Commission, "Mobile Health App Interactive Tool," December 1, 2022, https://www.ftc.gov/business-guidance/resources/mobile-health-apps-interactive-tool.

Activity and Event Trackers

As opposed to Health Diaries, Activity and Event Trackers operate in the background, passively collecting data via smartphone or wearable sensors. This may include metrics such as daily step count or number of times a user stood up, providing insights into a user's daily movement. The Apple Health and Samsung Health apps provide this feature when paired with their smartwatches and smartphones.

Motivational Tools

Motivational Tools include automatically generated reminders or notifications that prompt a user to engage with the DHT, such as to review educational materials or input data in the health diary.

Health Coaching

Health Coaching is a variation on educational materials that are intended to be interactive, enabling users to provide feedback on the content they are consuming and for the content to direct their health and wellness behaviors. The app Down Dog, for example, provides customizable guided yoga sessions.

Community and Social Networking

Community and Social Networking allows for non-clinical communication between users and their peers often via social media to create a community amongst those leveraging the tool. This often looks like sharing workouts with friends or progress towards health goals.

SECTION 2.2 – PATIENT MONITORING

Patient Monitoring products represent an important building block for DHTs, opening a window into a patient's health between formal healthcare visits. These products are intended to monitor patient data to inform management of a specific disease, treatment regiment, medical condition, or health outcome (Figure 2.2.1). In many cases, these products may be used as an adjunct monitoring tool to help healthcare professionals make clinical decisions. Unlike Digital Diagnostics, Patient Monitoring products do not interpret data in the context of a patient's disease or health status to make definitive diagnoses or prognoses. They instead collect highly valuable data (e.g., patient reported, biometrics) and make said data available to patients and HCPs to inform patient self-management and HCP clinical decision-making. Additionally, Patient Monitoring products do not provide any recommendations to the patient, caregiver, or healthcare provider regarding the management of the disease or medical condition.

2.2.1: Definition

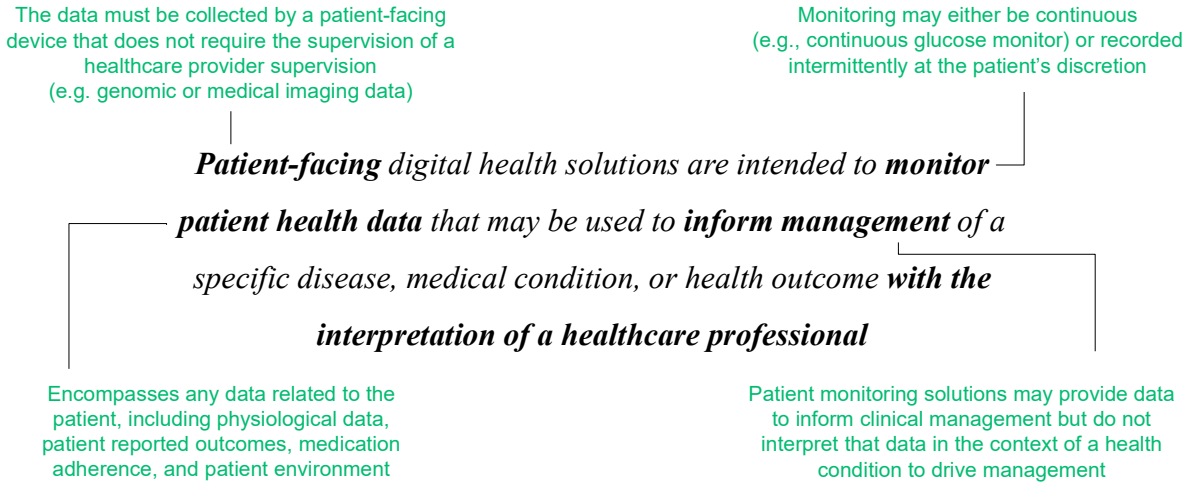

Figure 2.2.1: Patient Monitoring Definition

2.2.2: Defining Characteristics

Points of Differentiation

- **Patient Monitoring vs. Health & Wellness: Patient Monitoring** tools collect disease-specific data for the purpose of informing clinical management by healthcare professionals. While **Health & Wellness** apps may also collect health data, the data is generally not disease-specific and these tools have not been validated to inform clinical management like **Patient Monitoring** products have.
- **Patient Monitoring vs. Care Support: Patient Monitoring** tools measure biometrics and PROs to inform the management of a disease or medical condition, however they do not provide a closed-loop translating measured data to specific educational resources, recommendations, and/or self-management tools to act on the data that characterize **Care Support** tools.
- **Patient Monitoring vs. Digital Diagnostics:** A Digital Diagnostic is a validated tool for detecting disease and/or characterizing disease status, response, progression, or recurrence based on inputted biometrics. A **Patient Monitoring** tool, on the other hand, deals with the underlying health data but the tool itself does not offer any interpretation – rather, the data must be transmitted to a healthcare professional for analysis and any potential diagnoses.

- **Patient Monitoring vs. Digital Therapeutics:** While a **Patient Monitoring** product may inform a healthcare professional's management of a disease, medical condition, or health outcome, the product itself does not deliver a medical intervention to treat or alleviate that condition like a **Digital Therapeutic** does.

Intended Benefits & Claims

Patient Monitoring products are intended to accurately monitor patient data related to a diagnosed medical condition and may be used to relay this data to healthcare providers to inform clinical decision-making.

Evidence Requirements

Patient Monitoring products collect a wide variety of data but do not interpret this data in the context of disease, which means that evidence requirements focus on the accuracy and precision of the product. For products that collect patient reported outcomes, this can look like basic usability and analytical validation of the software; however, for sensor-based biometric measuring technologies (BioMeTs), Goldsack et al. (2020) have proposed a more robust three-component "V3" validation framework. The framework is comprised of (1) verification, (2) analytical validation, and (3) clinical validation. As Patient Monitoring products do not interpret biometrics in the context of disease, the requirement for clinical validation is reduced, with (1) verification and (2) analytical validation being the most important standards to achieve.[6]

(1) Verification refers to the ability of a Patient Monitoring product to demonstrate it can capture sample-level data with reasonable accuracy, precision, consistency, and uniformity, which is especially critical for sensor-based Patient Monitoring products.[7] The verified sample-level data eventually serves as the foundation for algorithms that can process the raw sensor signal into behaviorally or physiologically meaningful biometrics, such as heart rate variability or movement during sleep. The performance of such algorithms is then subject to (2) analytical validation, or the process of discerning whether an algorithm can accurately and precisely measure the biomarker in the clinical population of interest. The final component of the V3 framework Patient Monitoring tools are not subject to, (3) clinical validation, consists of determining whether the biometric collected by a digital tool is clinically meaningful in a specified patient population and context of use.[8]

Regulation of Patient Monitoring products varies depending on potential role in providing patient care. Those that "collect, analyze, or display medical information to diagnose, monitor, or treat medical conditions" are considered software as a medical device (SaMD) and are subject to regulation, while those intended for patient self-monitoring are typically exempt from regulation.[9]

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[6] Jennifer C. Goldsack et al., "Verification, Analytical Validation, and Clinical Validation (V3): The Foundation of Determining Fit-for-Purpose for Biometric Monitoring Technologies (BioMeTs)," *Npj Digital Medicine* 3, no. 1 (April 14, 2020): 55, https://doi.org/10.1038/s41746-020-0260-4.

[7] *Note: While the V3 framework from Goldsack et al. (2020) was designed to evaluate evidence from biometric monitoring tools, verification and analytical validation can be used to evaluate evidence for sensor-based Other Data Monitoring products as well.*

[8] Goldsack et al., "Verification, Analytical Validation, and Clinical Validation (V3)."

[9] U.S. Food and Drug Administration, "Software as a Medical Device (SaMD)," December 4, 2018, https://www.fda.gov/medical-devices/digital-health-center-excellence/software-medical-device-samd#:~:text=Software%20as%20a%20Medical%20Device%20(SaMD),-Your%20Clinical%20Decision.

IMDRF SaMD Risk Categorization Framework

State of Healthcare Situation or Condition	Significance of information Provided by SaMD to Healthcare Decision		
	Treat or Diagnose	Drive Clinical Management	Inform Clinical Management
Critical	IV	III	II
Serious	III	II	I
Non-Serious	II	I	I

Figure 2.2.2: IMDRF SaMD Risk Categorization Framework[10]

Note: Reproduced from IMDRF Final Document "Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations.

To ensure that SaMD are reviewed with the same rigor worldwide regardless of the regulatory body, the International Medical Device Regulators Forum (IMDRF) established a framework to further categorize potential risk (Figure 2.2.2). Depending on the severity of the underlying condition and whether the Patient Monitoring product is used to drive or inform clinical management, these products may be considered anywhere from Category I to III, with higher ranking products likely to encounter a greater degree of regulatory scrutiny. Currently, the regulatory burden for certain Category I SaMD is reduced in the US under FDA enforcement discretion for lower-risk SaMD.[11]

Patient Monitoring tools are also often used for clinical development where they are colloquially referred to as *digital biomarkers.* Within the context of clinical development, regulatory requirements vary based on whether the collected data is intended as an exploratory, secondary, or primary endpoint. There are no explicit rulings as to whether Patient Monitoring products used as exploratory endpoints require regulatory clearance. Thus, while many studies use FDA-cleared products such as ActiGraph's CentrePoint Insight Watch or iRhythm's ZioPatch, others use devices that hold a CE-mark but are not FDA-cleared such as the Oura Ring. For secondary and primary endpoints, such as 95th percentile stride velocity in Duchenne Muscular Dystrophy, the European Medicines Agency (EMA) has stated that a 'suitable device' should be CE-marked.[12] To date, the only FDA-endorsed primary endpoint, Moderate-to-Vigorous Physical activity in Pulmonary Hypertension and Interstitial Lung Disease, is assessed via an FDA-cleared device, but no explicit recommendations have been made by the FDA.[13]

[10] International Medical Device Regulators Forum, "'Software as a Medical Device': Possible Framework for Risk Categorization and Corresponding Considerations."
[11] U.S. Food and Drug Administration, "Examples of Software Functions for Which the FDA Will Exercise Enforcement Discretion," September 29, 2022, https://www.fda.gov/medical-devices/device-software-functions-including-mobile-medical-applications/examples-software-functions-which-fda-will-exercise-enforcement-discretion.
[12] European Medicines Agency, "Draft Qualification Opinion for Stride Velocity 95th Centile as Primary Endpoint in Studies in Ambulatory Duchenne Muscular Dystrophy Studies," February 20, 2023, https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/draft-qualification-opinion-stride-velocity-95th-centile-primary-endpoint-studies-ambulatory_en.pdf.
[13] ActiGraph. "Case Study: Digital Outcome Measures of Physical Activity Approved as Primary Endpoint in Pivotal Cardiopulmonary Study," May 10, 2023, https://landing.theactigraph.com/promos/case-study/mvpa.

2.2.3: Examples: Categories & Common Themes

The **Patient Monitoring** category may be divided into three subcategories based on the type of data a product captures: **Physiologic Monitoring**, **Patient Reported Outcomes Monitoring**, and **Other Data Monitoring**.

Physiologic Monitoring

Physiologic Monitoring tools constitute perhaps the most recognizable class of Patient Monitoring products, consistent with the American Medical Association's definition of remote Patient Monitoring digital products.[14] Such tools are used to capture physiologic data related to a diagnosed medical condition that may or may not be actively managed by a healthcare professional. This subcategory does not include data collected from tools that are not patient facing, such as those used in genomics, in vitro diagnostics, or medical imaging. Physiologic data collection may either be continuous (e.g., continuous glucose monitor, actigraphy for sleep monitoring), through which multiple data points are automatically collected for an extended duration, or intermittent, through which data points are collected on an ad hoc basis at the patient, caregiver, or healthcare provider's discretion (e.g., connected blood pressure cuff or a connected scale). Physiologic monitoring data may be automatically transmitted to the patient's healthcare provider to support the clinical management of a disease, medical condition, or health outcome.

Patient Reported Outcomes Monitoring

The **Patient Reported Outcomes Monitoring** subcategory consists of tools that enable monitoring via electronic patient reported outcomes (ePROs), or health outcomes that are directly reported by the patient and/or caregiver. Examples of ePROs include presence of symptoms, functionality, health-related quality of life, and self-reported medication adherence. Cankado PRO-React-Onco, for example, enables breast cancer patients to record their symptoms and observations via mobile and web applications. The app allows patients to export their ePRO documentation for physician review.

Other Data Monitoring

As the name suggests, **Other Data Monitoring** encompasses other types of data monitoring that are not physiologic in nature nor reported by the patient in the form of an ePRO, yet still provide context that may be used to inform clinical management of a disease, medical condition, or health outcome. Smart inhaler systems such as Teva's Digihaler, for example, have built-in sensors that record how often a patient uses an inhaler. While the Digihaler also measures inhalation airflow, a method of Physiologic Monitoring, the built-in sensors measuring medication adherence principally qualify as Other Data Monitoring since such data is not strictly physiologic in nature nor reported by the patient. Smart pill dispensers similarly use sensors to track pill-based medication adherence. Lastly, tools that monitor the environment around the patient, such as weather, also represent **Other Data Monitoring**. Such tools are particularly relevant for helping allergy patients and their healthcare providers identify potential triggers for flares.

[14] American Medical Association, "Remote Patient Monitoring Playbook," 2022, https://www.ama-assn.org/system/files/ama-remote-patient-monitoring-playbook.pdf.

SECTION 2.3 – CARE SUPPORT

Care Support products include some of the lowest-acuity disease-specific tools to help patients better manage their care. One of the more diverse categories of DHT, Care Support products can include disease education, care coordination, as well as strategies for patient self-management of symptoms. Unlike Health & Wellness products, these products often combine elements of patients monitoring, analytics, and the ability to close the loop and provide disease specific guidance. These products do not go so far to make disease-specific treatment claims, and thus have more limited validation to produce health outcomes, which can lead to potential challenges in traditional fee-for-service reimbursement. Existing products such as Livongo, Biogen's Aby/Cleo, and others have harnessed alternative business models such as use in population health management and multidisciplinary care centers to drive broader adoption.

Figure 2.3.1: Care Support Definition

2.3.2: Defining Characteristics

Points of Differentiation

- **Care Support vs. Digital Therapeutics:** Unlike **Digital Therapeutics** products**, Care Support** tools make no claims to directly treat or alleviate a disease or medical condition. They can make claims to improve various factors important in the management of a disease (e.g., improved adherence), but any benefits on disease outcomes are considered indirect. Even though **Care Support** tools do not make claims of disease treatment, they can have a compelling body of evidence demonstrating improvements in care and care delivery that should indirectly help a patient better self-manage their disease.
- **Care Support vs. Patient Monitoring**: As seen in Figure 2.3.2, **Patient Monitoring** tools measure biometrics to inform the management of a disease or medical condition, but do not provide the educational resources, recommendations, or self-management tools that are core to **Care Support** tools. Care support has closed feedback with a user to provide actionable recommendations as opposed to patient monitoring which simply presents users with data.

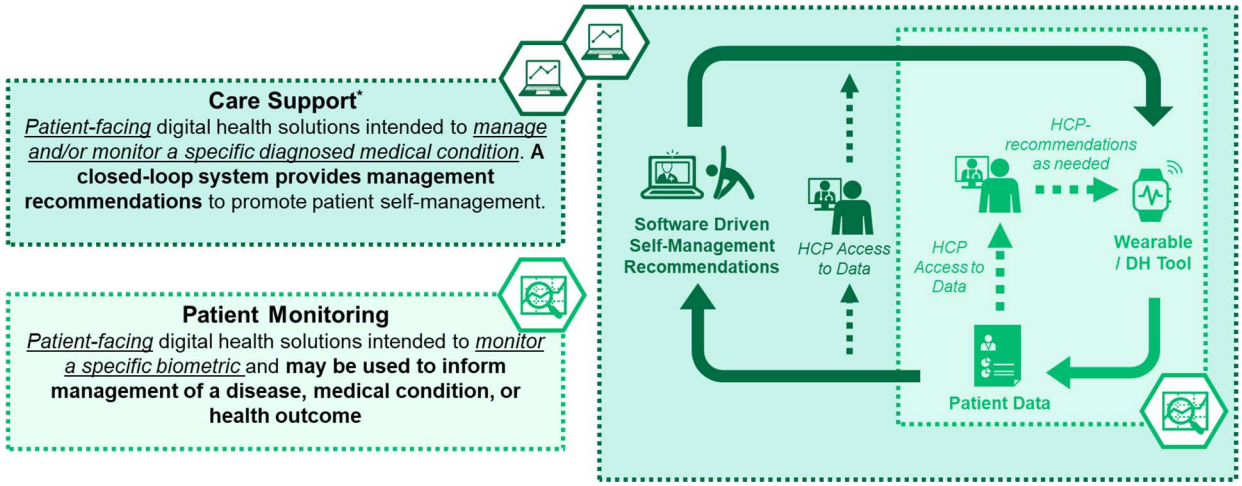

Figure 2.3.2: Care Support versus Patient Monitoring

** Digital therapeutics may contain some of these aspects of care support programs.*

Intended Benefits and Claims

Care Support tools aim to help patients, caregivers, and/or providers manage a medical disorder or disease but make no specific claims of clinical efficacy. These tools may make claims to improve non-clinical outcomes such as medication adherence.

Evidence Requirements

While the Care Support tool itself does not make any product-specific claims, any educational resources or self-management techniques provided must have a foundation in peer-reviewed literature. Biogen's Aby application for multiple sclerosis (MS), for example, does not have any evidence supporting the efficacy of the app itself. However, Aby includes exercise and wellness programs that incorporate techniques that are part of an evidence-based protocol for MS patients.

While a company may conduct studies to validate the basic accuracy of a Care Support tool's data collection or the functionality of its algorithm, such evidence generation is not a prerequisite for a product to be part of the Care Support category.

On the other hand, as soon as a product begins to make claims about the efficacy of the product itself, then it will be subject to additional regulatory scrutiny. For instance, if a Care Support tool claims to improve adherence to medication or adherence to a rehab program, the product will have to produce robust data demonstrating said improvement. If a Care Support tool wanted to make disease-specific treatment claims, it would enter Digital Therapeutics territory (see Digital Therapeutics section) and could be classified as such should it meet DTx requirements.

Regulatory

Like Patient Monitoring products, regulation of Care Support products varies depending on the potential role in patient care. Many Care Support products such as educational apps or patient self-management tools are not intended to collect, analyze, or display medical information to diagnose, monitor, or treat medical conditions and are thus not considered medical devices. Those that directly play a role in care decisions (e.g., diagnosing, monitoring, or treating medical conditions) such as a symptom tracker that can escalate to a healthcare provider are considered SaMD and are subject to regulation by local

regulatory bodies based on their placement in the IMDRF framework.[15] Depending on the severity of the underlying condition and whether Care Support software drives or informs clinical management these products are considered Category I – III, with higher ranking products likely to encounter a greater degree of regulatory scrutiny. Currently, many Category I Care Support SaMD devices carry reduced regulatory burden in the US under FDA enforcement discretion for lower-risk SaMD.[16]

2.3.3: Examples: Features & Common Themes

With highly varying form factors, levels of acuity, and features, Care Support tools constitute one of the most diverse DHT categories. Broadly, Care Support features can be divided into two primary subcategories depending on the type of information that forms the basis for the DHT's recommendations: Static Care Support and Responsive Care Support.

Static Care Support Features

Static Care Support features offer patient educational resources and/or recommendations that are exclusively based on standard of care procedures. Static Care Support features are disease-specific, which differentiates them from Health & Wellness solutions. Static features are static – there is no patient-specific data informing any recommendations or informing which resources are displayed to a patient and when. As a result, static Care Support resources are not personalized or tailored. For example, AbbVie's Complete – Medication Tracker application provides medication reminders to HUMIRA, SKYRIZI, and RINVOQ patients based on standardized dosing protocols. Likewise, Biogen's Aby app provides general resources for MS patients.

Dynamic Care Support Features

Dynamic Care Support features, on the other hand, analyze patient-specific data to tailor self-management resources and recommendations to the end user. The patient-specific data can come in a variety of forms, such as passively collected physiologic data (e.g., Ava fertility tracker), actively transmitted physiologic data (e.g., Livongo, Hinge Health), questionnaire-based patient reported outcomes, and medication utilization (e.g., via smart hardware such as CapMedic). Personalization of Dynamic Care Support products using these data sources is typically driven by an algorithm. Some products may trigger virtual care through a 1:1 connection at opportune times with a non-medical professional (e.g., Livongo) or medical professional (e.g., Hinge Health).

Dynamic Care Support tools have more ability to impact care and patient's ability to better self-manage their disease. Many products in this category aim to make claims of improvement across non-clinical outcomes.

[15] International Medical Device Regulators Forum, "'Software as a Medical Device': Possible Framework for Risk Categorization and Corresponding Considerations."
[16] U.S. Food and Drug Administration, "Examples of Software Functions for Which the FDA Will Exercise Enforcement Discretion."

SECTION 2.4 – DIGITAL DIAGNOSTICS

Digital Diagnostics are clinically validated diagnostics for measuring disease presence, grading, status, response, progression, or recurrence. Similar to in-vitro diagnostics, Digital Diagnostics will have clear sensitivities and specificities that inform how HCPs can interpret and message the findings to patients. Digital Diagnostics can make three primary categories of claims: screening or diagnostic claims, monitoring or treatment response claims, or prognostic claims (Figure 2.4.3). Digital Diagnostics' software algorithms can include a variety of digital inputs, as discussed in **Patient Monitoring,** to make diagnostic and prognostic determinations that will impact clinical care directly. Said solutions may also incorporate inputs from traditional in-vitro diagnostics or imaging to make a conclusion about a patient's health status and/or disease progression. Like traditional in-vitro diagnostics, these products are likely categorized as medical devices as their intent is to be used in driving clinical management of patients. To date there are few marketed Digital Diagnostics, however given that these products are validated to drive clinical decision making, payers are more likely to cover use of these products should they demonstrate strong evidence and utility.

2.4.1: Definition

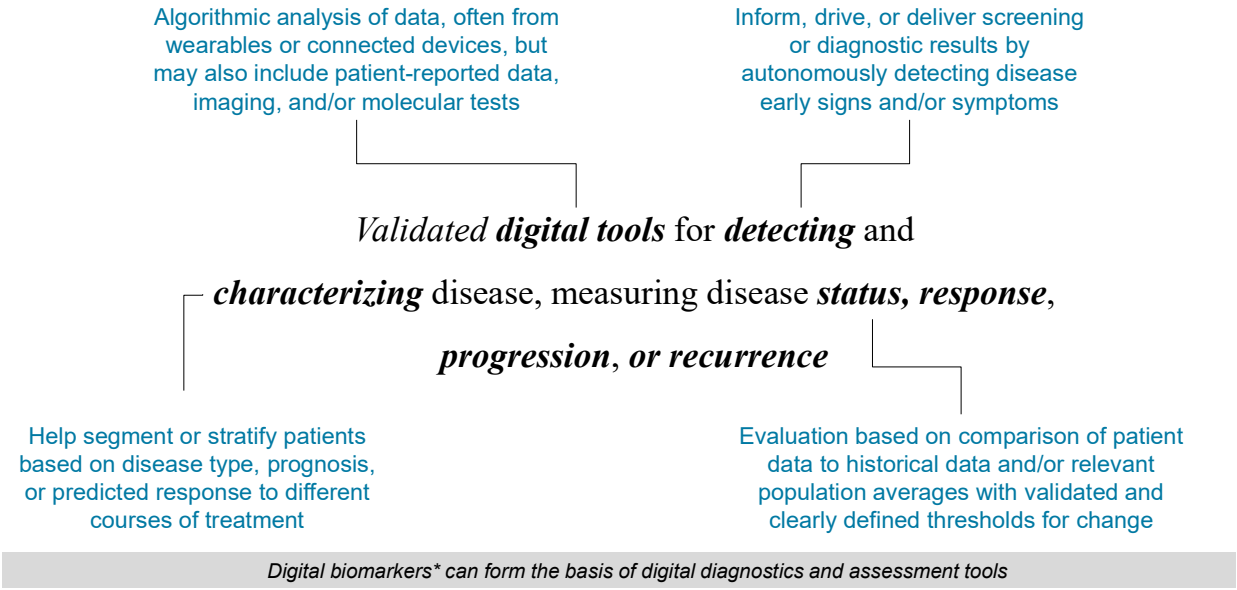

Figure 2.4.1: Digital Diagnostics Definition

** Physiological and behavioral measures passively collected through sensors via wearables, smartphone, or other connected devices in a natural setting.*

2.4.2: Defining Characteristics

Points of Differentiation

- **Digital Diagnostics vs. Patient Monitoring and Clinical Decision Support:** Unlike Patient Monitoring or clinical decision support technologies, Digital Diagnostics are validated to provide a standalone conclusion about a patient's health status that does not require an HCP to further interpret the result. While the other product categories can inform clinical decision-making, a digital diagnostic is able to drive clinical decision-making by making a diagnoses with clear

thresholds for sensitivity and specificity. As such, the evidence and regulatory requirements for Digital Diagnostics are far higher, requiring clinical validation and regulatory clearance (Figure 2.4.2).

- **Digital Diagnostics vs. Digital Therapeutics and Care Support**: Unlike Care Support or Digital Therapeutics, Digital Diagnostics do not offer any actionable recommendations to follow-up on the results presented. Digital Therapeutics may include a Digital Diagnostic that allows for 'closed loop' functionality, where the Digital Therapeutic independently evaluates a patient's prognosis and customizes the intervention based on the result.

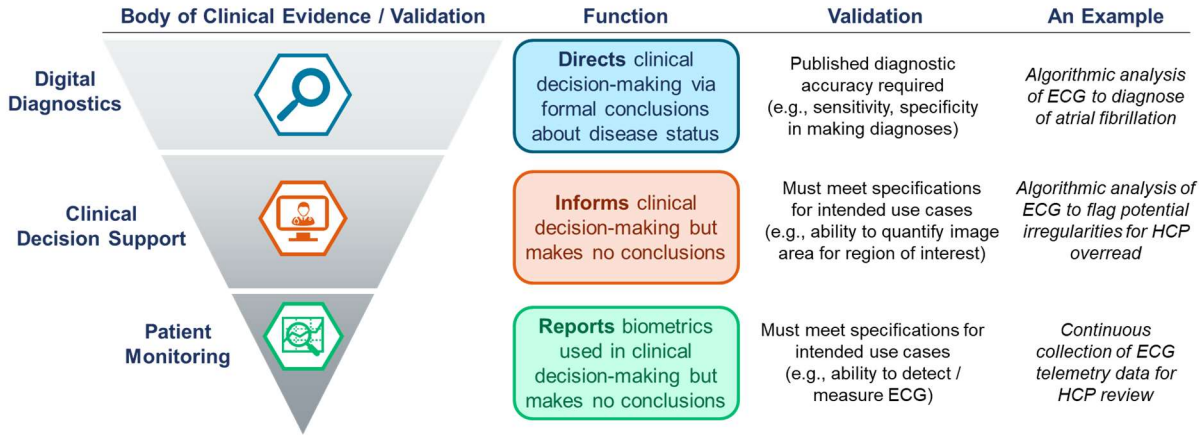

Figure 2.4.2: Evidence for Digital Diagnostics, Clinical Decision Support, and Patient Monitoring

Intended Benefits and Claims

Digital Diagnostics can make three primary categories of claims: screening or diagnostic claims, monitoring or treatment response claims, or prognostic claims (Figure 2.4.3). DHTs with screening or diagnostic claims identify disease-specific signals to make a disease diagnosis. Monitoring or pharmacological response claims include tools that monitor patient disease status and can be used to indicate whether a patient's disease is controlled or requires additional intervention, or if a therapy is effective and should be continued. Prognostic claims include tools that provide insight into a patient's future course of disease, such as response to a specific type of therapy, or risk of disease flare or recurrence.

Evidence Requirements

Given the variety of claims made by Digital Diagnostics, these tools must have a body of supporting evidence specific to the claims being made prior to marketing. As discussed within the Patient Monitoring section, the "V3" validation framework for biometric monitoring technologies also applies to Digital Diagnostics, with these products requiring clinical validation in addition to verification and analytical validation of all input measures.[17] The general experimental design of satisfactory clinical validation for each claim is outlined in Figure 2.4.3; however, given the wide range of input data and use cases possible for Digital Diagnostics satisfactory evidence is likely to be judged on a case-by-case basis.

In addition to common diagnostic statistics such as sensitivity and specificity, the Agency for Healthcare Research and Quality outlines four additional domains across which diagnostics should provide evidence

[17] Goldsack et al., "Verification, Analytical Validation, and Clinical Validation (V3)."

for: risk of bias, consistency, directness, and precision.[18] Of these domains, risk of bias and directness are of particular interest for Digital Diagnostics based on the behavioral and/or novel aspects of biometrics used in many potential diagnostics. For example, assessments of Alzheimer's disease based on speech should be validated across a broad sample of languages to avoid this potential for bias. Additionally, with the expanded variety of biometrics accessible through technology, novel measures such as finger rigidity in Parkinson's Disease may require more extensive clinical validation against health outcomes rather than surrogate outcomes like change in physician rating scales.[19]

These additional validation requirements pose a significant set of challenges to bringing Digital Diagnostics to market and to date most Digital Diagnostics contain a disclaimer that they are not intended to be used as the primary factor in medical therapy decision making or for stand-alone monitoring.

Regulatory

Digital Diagnostics are used to drive clinical decision making and therefore are considered SaMD subject to regulation by most national regulatory bodies. The degree of regulatory scrutiny is guided by the digital diagnostic's categorization in the IMDRF framework, which would be Categories II - IV depending on (1) the severity of relevant disease and (2) whether the diagnostic directly indicates diagnosis or treatment or if it is used to drive clinical management.[20]

2.4.3: Examples: Categories & Common Themes

Digital Diagnostics are primarily segmented by type of claim being made, whether they be for **Diagnosis or Screening**, **Monitoring or Pharmacological Response**, or **Prognosis.** Given the significant validation barrier to develop and market Digital Diagnostics, we have also included some DHTs as examples that currently lack proper validation as Digital Diagnostics and are intended for research use only.

[18] Agency for Healthcare Research and Quality, "Chapter 7: Grading a Body of Evidence on Diagnostic Tests," in *Products*, 2012, https://effectivehealthcare.ahrq.gov/products/methods-guidance-tests-grading/methods.
[19] Andrea Park, "Verily Loses FDA Bid to Add Parkinson's Assessments to Clinical Research Smartwatch," *Fierce Biotech* (blog), June 8, 2021, https://www.fiercebiotech.com/medtech/verily-loses-fda-bid-to-add-parkinson-s-motor-function-assessment-to-clinical-research.
[20] International Medical Device Regulators Forum, "'Software as a Medical Device': Possible Framework for Risk Categorization and Corresponding Considerations."

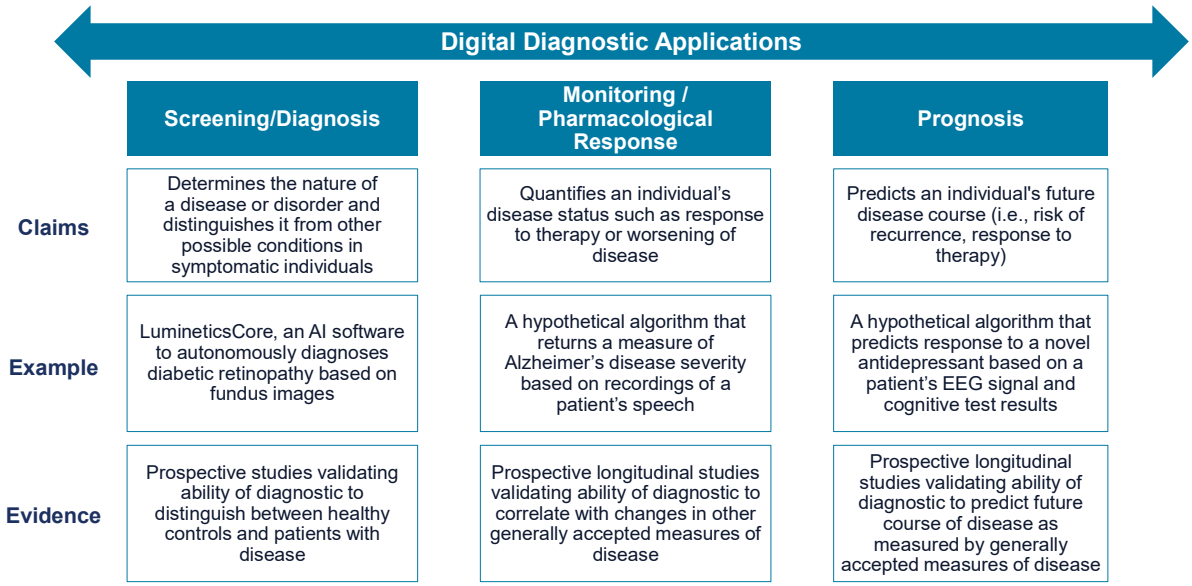

Figure 2.4.3: Digital Diagnostic Applications

Diagnosis or Screening

Diagnosis or Screening tools primarily work to reduce the burden of identifying relevant patients for treatment. As such development of these tools to date have focused on large indications presenting in primary care such as Digital Diagnostics' LumineticsCore diagnostic for diabetic retinopathy.

Monitoring or Pharmacological Response

Monitoring or Pharmacological Response tools are intended to provide more continuous insight into patient health across the course of disease. Many of these tools are intended for patients with chronic illness that may flare or progress such as Empatica's Embrace2 seizure monitoring watch or Winterlight Labs' Alzheimer's speech assessment (research use only).

Prognosis

Prognostic tools provide insight into a patient's future disease course, whether that be response to therapy or rate of progression. These tools are most useful for diseases with significant heterogeneity and are some of the most difficult to validate due to the need for long-term health outcomes data. Hypothetical examples could include a diagnostic to predict the severity of major depressive disorder in response to a prescribed monoamine antidepressant regiment or a diagnostic that predicted rate of disability progression in ALS patients.

SECTION 2.5 – DIGITAL THERAPEUTICS

Digital Therapeutics (DTx) are among the most clinically validated and regulated DHTs today. Specifically, DTx are health software intended to treat or alleviate a disease, disorder, condition, or injury by generating and delivering a medical intervention that has demonstrable positive therapeutic impact on a patient's health. These products can function independently or integrate with ancillary software and medical intervention components to form a DTx ecosystem. Since DTx make disease-specific medical claims, the evidence and regulation requirements for these products is stringent. DTx must be clinically validated either through a randomized controlled clinical trial (RCT), real world evidence (RWE), or ideally a combination of the two, to demonstrate product efficacy. Furthermore, DTx are regulated as medical devices in the US and abroad.

2.5.1: Definition

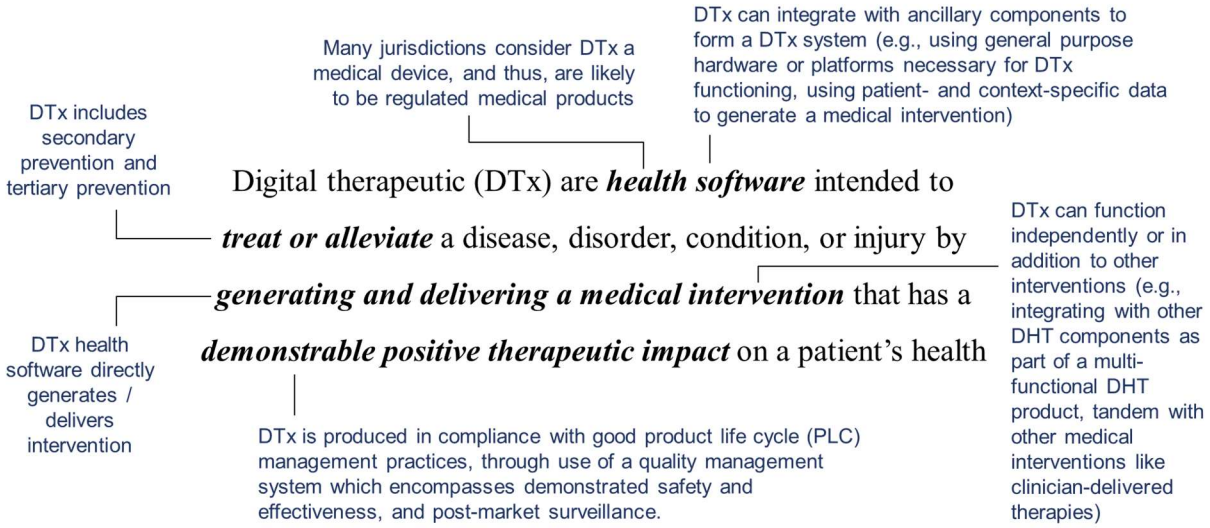

Figure 2.5.1: Digital Therapeutics Definition

2.5.2: Defining Characteristics

Points of Differentiation

- **DTx vs. Care Support: DTx** are differentiated from **Care Support** tools by their evidence-backed claims to function independently of the patient's care team (inclusive of patient self-management) as a standalone medical intervention.
- **DTx vs. Digital Diagnostics**: While **DTx** products are intended to deliver an intervention that treats or alleviates a disease or medical condition, **Digital Diagnostics** are intended to provide a diagnosis or assessment of a disease or medical condition.

Evidence Requirements

DTx are required to have clinical evidence to support their efficacy claims. However, unlike conventional therapeutics, there is a greater variety of acceptable evidence given the lower-risk nature of digital interventions, specifically in their safety profiles. While randomized clinical trials (RCTs) have long been the gold standard of clinical evidence for pharmacotherapies, real-world evidence (RWE) is also highly valuable for DTx given the potential impact of culture, language, socioeconomic class, and method of

DTx implementation on real-world effectiveness. Many companies developing DTx pursue a combination of RCT and RWE, an approach which is generally regarded as best practice.

Ultimately, the safety, efficacy, and value of a DTx will be judged first by regulators and next, externally validated by the variety of users and buyers/payers benefiting from DTx; thus, the evidence presented must support the chosen regulatory pathway and claims. Evidence that establishes safety, efficacy, and value should be published in peer-reviewed journals and analyzed on an ongoing basis as DTx products reach a broader audience. Furthermore, many DTx products will collect, analyze, and apply RWE and/or product performance data to bolster its medical claims.

Regulatory

DTx must adhere to guidelines put forward by regulatory bodies to support their product claims. Since DTx are health software that deliver medical interventions, the majority are considered SaMD and regulated according to their place in the IMDRF framework. Certain DTx may also be regulated as software in a medical device (SiMD). As DTx are intended as interventions to actively treat patients, they are considered Category II – IV based on the severity of the relevant disease.[21]

Regulatory bodies leverage the IMDRF categorization to understand how to regulate DTx within their own country.

US

In the US, the FDA classifies DTx as medical devices in line with the IMDRF's SaMD framework. Certain DTx may also go through the SiMD pathway. However, the nuances of the FDA's classification are continually shifting. Recent years have seen certain DTx categories benefit from enforcement discretion and reduced regulatory burden, particularly those that are considered lower-risk DTx (i.e., for non-serious conditions).[22] DTx for mental health conditions were also given special consideration during the COVID-19 public health emergency from 2020 to 2023.[23] Despite these exceptions, DTx primarily leverage one of the three paths for approval/clearance:

1. **Class II SaMD, De Novo**: Namely for novel devices of low to moderate risk that do not have a valid predicate device. The clinical evidence presented is more closely examined with this path.
2. **Class II SaMD, 510k:** Must demonstrate that the DTx is marked as safe and effective, substantially equivalent, to a legally marketed device that is not subject to a Premarket Approval (PMA). This is typically regarded as the most straightforward path even though it requires a predicate device to build evidence against.
3. **Class III SaMD, PMA:** Most stringent market submission application to demonstrate safety and effectiveness for DTx, making it the least used. A prospective clinical trial is generally required.

[21] International Medical Device Regulators Forum.
[22] U.S. Food and Drug Administration, "Policy for Device Software Functions and Mobile Medical Applications: Guidance for Industry and Food and Drug Administration Staff," September 28, 2022, https://www.fda.gov/media/80958/download.
[23] U.S. Food and Drug Administration, "Enforcement Policy for Digital Health Devices For Treating Psychiatric Disorders During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency," April 1, 2020, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enforcement-policy-digital-health-devices-treating-psychiatric-disorders-during-coronavirus-disease.

EU + UK

In the EU and UK, DTx are regulated as medical devices and thus must be CE marked (UKCA in the UK beginning in 2025). In most countries, DTx manufacturers must complete a self-assessment risk classification to determine which level of CE Mark is necessary and will eventually be reviewed by country-specific regulatory bodies. In the UK, this is largely done by the Medicines and Healthcare products Regulatory Agency (MHRA), in Germany, the Federal Institute for Drugs and Medical Devices (BfArM), and in France, the National Agency for the Safety of Medicines and Health Product (ANSM). There is no EU-equivalent of enforcement discretion as we have seen in the US.

APAC

Japan, South Korea, and Australia have formal DTx regulatory processes where DTx are classified as SaMD. In Japan, DTx are subject to regulatory oversight by the Pharmaceuticals and Medical Devices Agency (PMDA) and Ministry of Health, Labor, and Welfare (MHLW), in South Korea, the Ministry of Food and Drug Safety (MFDS), and in Australia, the Therapeutic Goods Administration (TGA). In China, no formal processes exist yet for DTx, though they are considered medical devices and are evaluated by the National Medical Products Association (NMPA).[24]

	DTx Intended Uses	Description	Impact	*Example Product*
1	**DTx designed to produce behavioral change**	• Digital product that employs various mechanisms by which to change or alter a patient's behavior	• Changes in behavior impact or are themselves a clinical outcome	• *Cognitive-behavioral therapy delivered via a patient app designed to improve patient attention, a key outcome for ADHD patients*
2	**DTx designed to produce physiologic change**	• Digital product that employs various mechanisms by which to directly change a patient's physiology	• Changes in physiology impact or are themselves a clinical outcome	• *Video and audio stimuli directly alter brain chemistry and serotonin production to reduce depressive symptoms*
3	**DTx designed to help with disease and/or condition management**	• Digital product that helps patients self-manage their disease	• Changes in self-management impact clinical outcomes	• *Connected device and app designed to support patients and their self-management of diabetes and lower A1c levels*

Figure 2.5.2: DTx Intended Uses

Note: Digital Therapeutics may have more than one intended use.

2.5.3: Examples: Mechanism Types & Delivery Routes

DTx can employ a range of mechanisms and intervention types to deliver medical intervention and therapeutic benefits to patients. The mechanisms outlined below are some of the most popular types leveraged by DTx.

Digital Therapeutics' intended use can be classified broadly into the following categories based on the outcome they intend to achieve:

[24] Digital Therapeutics Alliance, "Understanding DTx / DTx By Country," 2023. https://dtxalliance.org/understanding-dtx/dtx-by-country/.

Mechanisms that digital therapeutics utilize to achieve intended uses include, but are not limited to:

	DTx Mechanisms	Description	*Example Products*
1	**Behavioral therapy**	• Clinically validated behavioral therapy delivered digitally as opposed to in person	• *Cognitive Behavioral Therapy (CBT) delivered via an app* • *Immersive bio-psycho-social approach delivered via app*
2	**Biofeedback**	• Direct sensing of and feedback on patient biometrics via connected device or app	• *Breathing pattern recognition via connected device* • *Psychophysiological feedback via connected device*
3	**Cognitive training**	• Clinically validated mental exercises delivered digitally as opposed to in person	• *Sensory stimuli and simultaneous motor challenges designed to target neural systems in the brain via connected device* • *Pattern recognition and response via app*
4	**Neurological stimulation**	• Direct neurostimulation tailored via digital solution in response to patient, patient state, biometric, etc.	• *Non-invasive neuromodulation via connected device* • *Auditory-motor entrainment via connected device*
5	**Physiologic stimulation**	• Direct physiological stimulation tailored via digital solution in response to patient, patient state, biometric, etc.	• *Audio stimulation via connected device* • *Visual stimulation via connected device* • *Vibrotactile feedback via connected device*
6	**Software-determined medication dose modification**	• Software-based solution that provides prompts on or directly adjusts to a recommended dose of medication	• *Insulin dose recommendations via connected device and app* • *Trigger-initiated inhaler recommendations via connected device and app*
7	**Software-directed disease management**	• Software-based solution that provides prompts, reminders, and recommendations to support patients in self-management of their disease and/or condition	• *Cancer treatment symptom management recommendations via app* • *Respiratory disease trigger management recommendations via connected device and app*
8	**Software-led, disease-specific clinical coaching / rehabilitation**	• Software-based solution that guides patients through clinically-validated exercises and techniques digitally as opposed to in person	• *Physical therapy rehabilitation via software-program and connected device* • *Optometry rehabilitation via software-program* • *Pelvic floor muscle training (PFMT) via software-program*

Figure 2.5.3: DTx Mechanisms.

Note: Digital Therapeutics may incorporate one or more mechanisms to achieve their intended use(s).

SECTION 2.6 – HEALTH SYSTEM CLINICAL SOFTWARE

Health System Clinical Software are clinician-facing health information technology (HIT) and digital health enterprise solutions intended to provide clinicians with support managing their patient populations. These solutions can range from platforms that capture and visualize data to solutions that support clinical decision-making. While patients may interact with these solutions to an extent, health facilities (e.g., health systems, hospitals) and clinicians are the primary beneficiaries, users, and buyers as these tools are designed to optimize clinical care. Furthermore, these solutions can have various degrees of direct patient impact, ranging from the minimal impact of Clinical Documentation & Image Archiving and Communication Support to the more substantial impact of Clinical Decision Support and Telehealth tools.

2.6.1: Definition

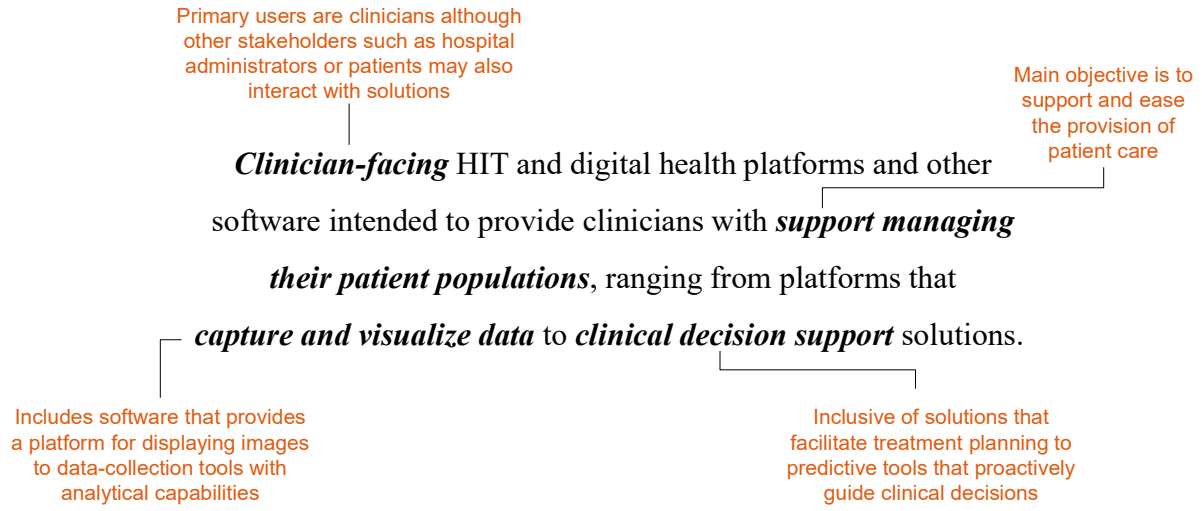

Figure 2.6.1: Health System Clinical Software Definition

2.6.2: Defining Characteristics

Points of Differentiation

- **Health System Clinical Software vs. Operational Software:** While Clinical Software is clinician-facing and intended to have a clinical function or outcome, Operational Software manages non-clinical functions from a hospital of health system business perspective.
- **Health System Clinical Software vs. Non-Health System Software/DH Solutions**: **Clinical Software** is differentiated from **Non-Health System Software** because its primary users are clinicians within hospitals and health systems. Non-Health System Software solutions are for a wider range of stakeholders such as Biopharma, Medtech, and Payors.

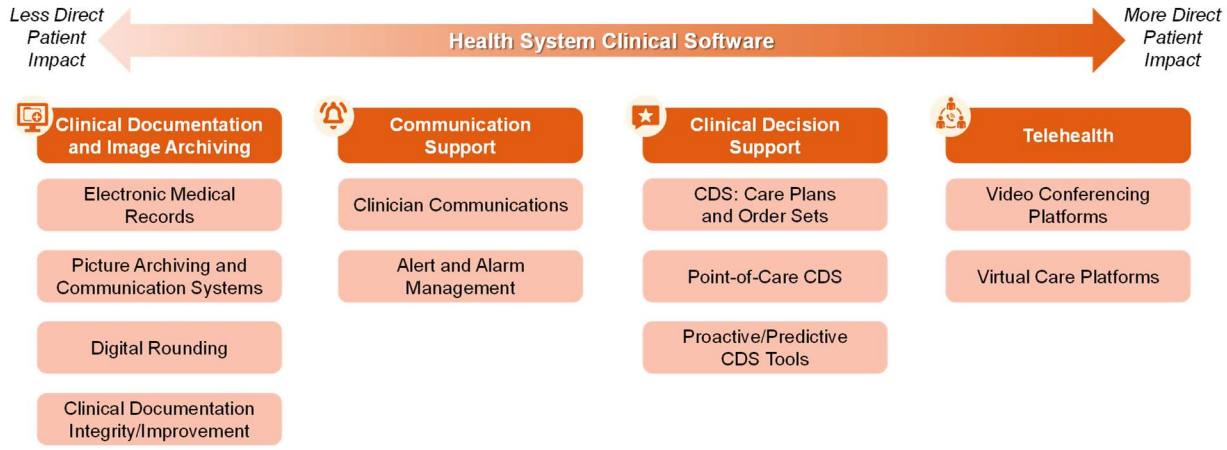

Figure 2.6.2: Health System Clinical Software Categorization (part 1)

Note: Not an exhaustive list.

2.6.3: Subcategories

Health System Clinical Software can be segmented into four key buckets that each possess their own capabilities: Clinical Documentation & Image Archiving, Communication Support, Clinical Decisions Support, and Telehealth (Figures 2.6.2 and 2.6.3). These buckets and their features are defined below and ordered by the level of impact on patients.

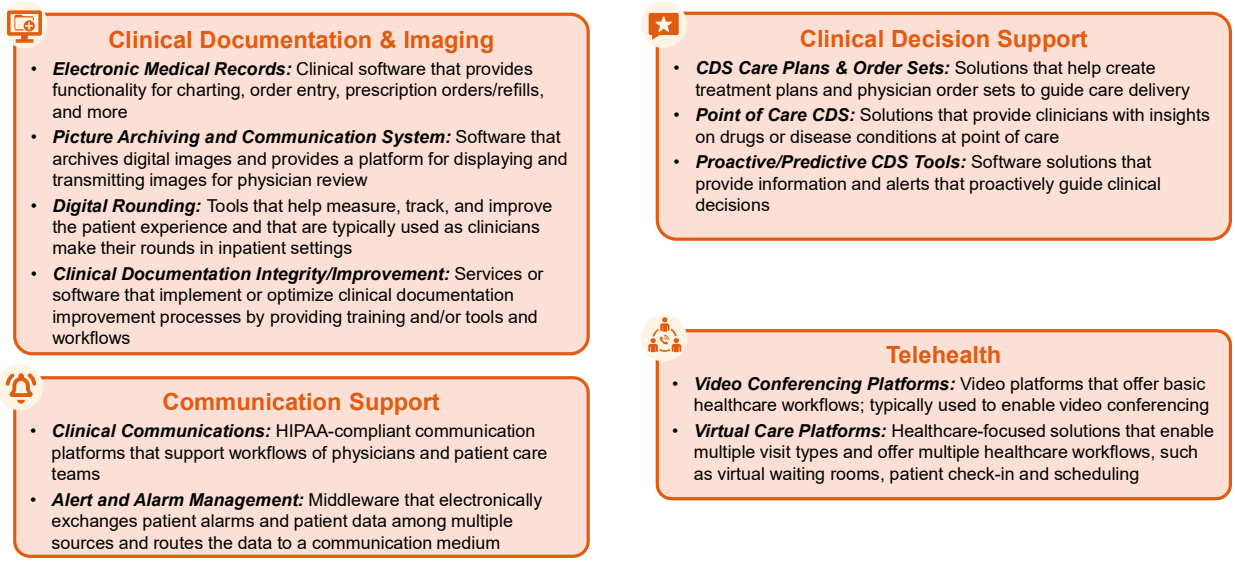

Figure 2.6.3: Health System Clinical Software Categories (part 2)

Note: Not an exhaustive list.

SECTION 2.7 – HEALTH SYSTEM OPERATIONAL SOFTWARE

Health System Operational Software solutions manage non-clinical but critical operational functions. Operational tools often ingest sets of clinical and non-clinical data to improve Operations at healthcare facilities, primarily to drive workflow, efficiency, and economic benefits. While these solutions do not directly interact with patients and often not with clinicians, they do follow similar design principles of security and validation, similarly to Health System Clinical Software.

2.7.1: Definition

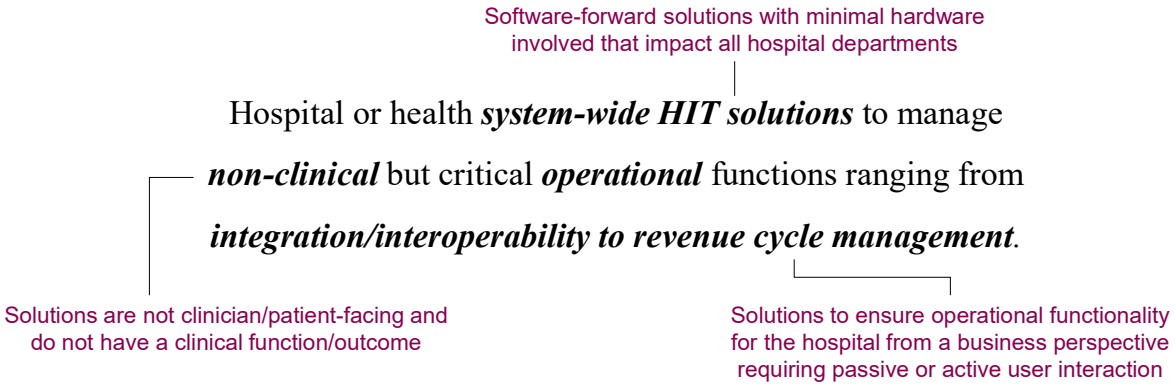

Figure 2.7.1: Health System Operation Software Definition

2.7.2: Defining Characteristics

Points of Differentiation

- **Health System Operational vs. Health System Clinical Software:** Whereas Health System Clinical Software is clinician facing and intended to provide support in managing patients, Health System Operational Software solutions do not have clinical functions or outcomes. Rather, these solutions are intended to ensure operational functionality from a hospital or health system business perspective.
- **Health System Operational Software vs. Non-Health System Software/DH Solutions:** The key difference between Non-Health System Software and Health System Clinical Software is the intended end user. Whereas the former is intended to be used by organizations and corporations that are not directly involved in clinically managing patients, the latter is intended to be used by those who are directly involved in patient care.

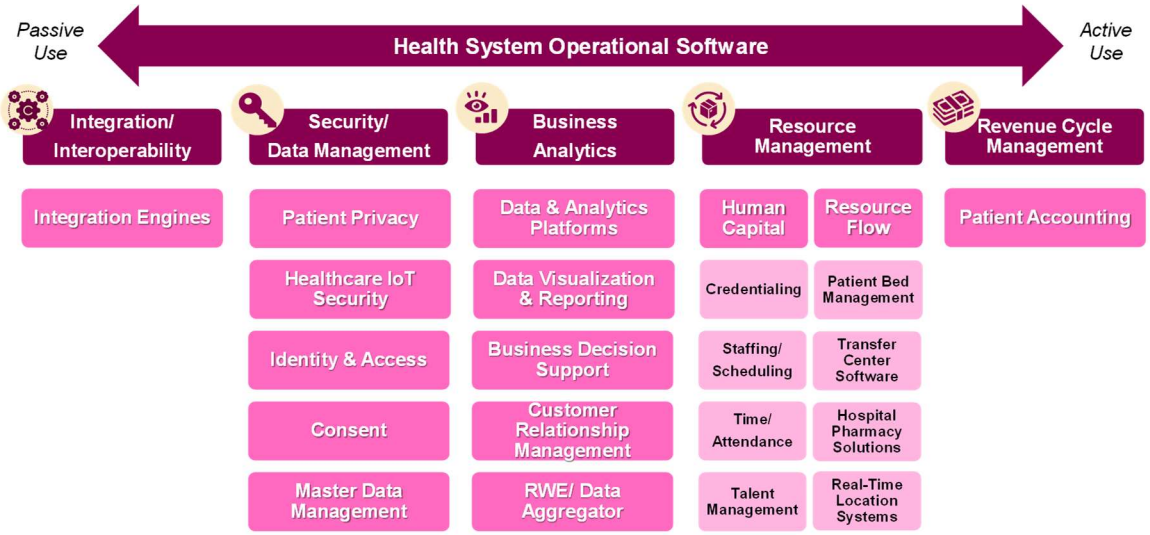

Figure 2.7.2: Health System Operational Software Categories (part 1)

Note: Not an exhaustive list.

2.7.3: Subcategories

Health System Operational solutions span the gamut of passive back-end integration engines to active use in revenue cycle management. Five key buckets help define the range of operational software capabilities: Integration/interoperability, Security/Data Management, Business Analytics, Resource Management, and Revenue Cycle Management (Figures 2.7.2 and 2.7.3).

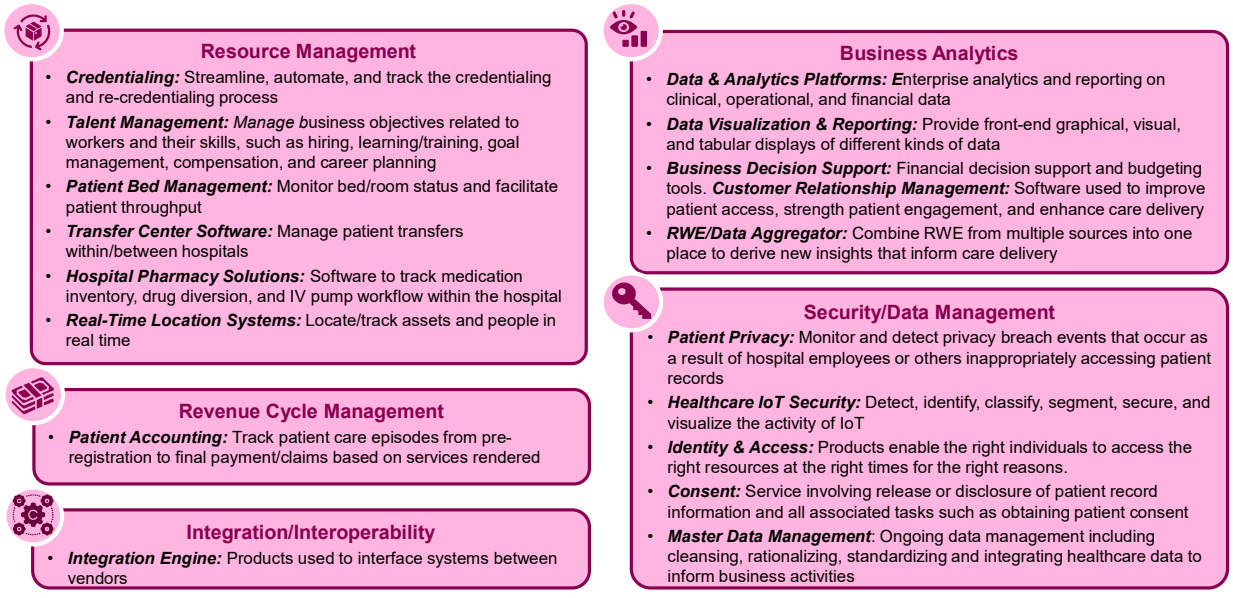

Figure 2.7.3: Health System Operational Software Categories (part 2)

Note: Not an exhaustive list.

SECTION 2.8 – NON-HEALTH SYSTEM SOFTWARE / DH SOLUTIONS

Non-Health System Software solutions encompass a large variety of tools intended for use by non-health system stakeholders such as OEMs, contract development and manufacturing organizations CDMOs, biopharmaceutical companies, payers, employers, pharmacies and more. Such software can be offered as a standalone product or as part of a suite of tools combined into one system. This category includes tools that aim to help users streamline operations, analyze real-world data, optimize sales and marketing efforts, ensure quality and compliance, and facilitate customer engagement.

2.8.1: Definition

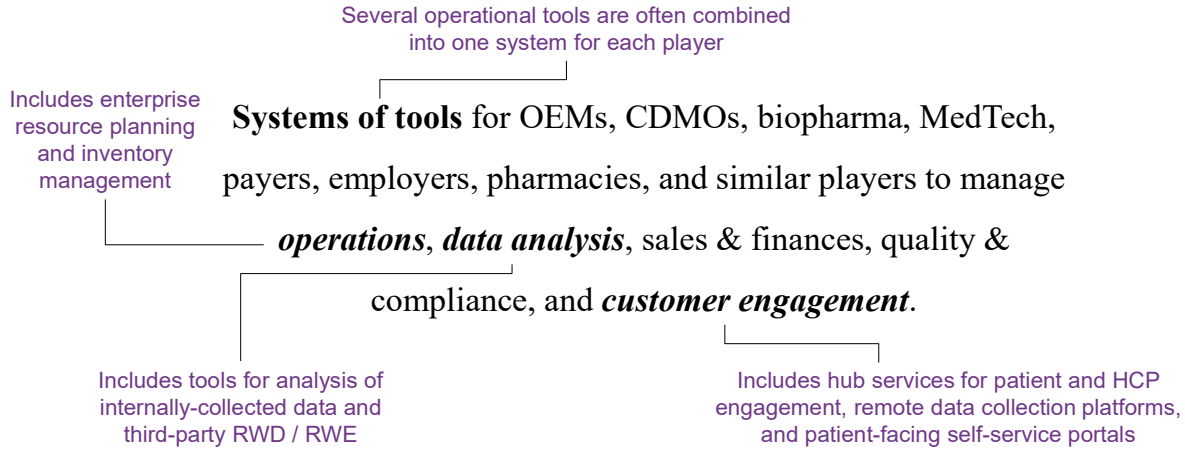

Figure 2.8.1: Non-Health System Software / DH Solutions Definition

2.8.2: Defining Characteristics

Points of Differentiation

- **Non-Health System Software vs. Health System Clinical Software**: The key difference between Non-Health System Software and Health System Clinical Software is the intended end user. Whereas the former is intended to be used by organizations and corporations that are not directly involved in clinically managing patients, the latter is intended to be used by those who are directly involved in patient care.

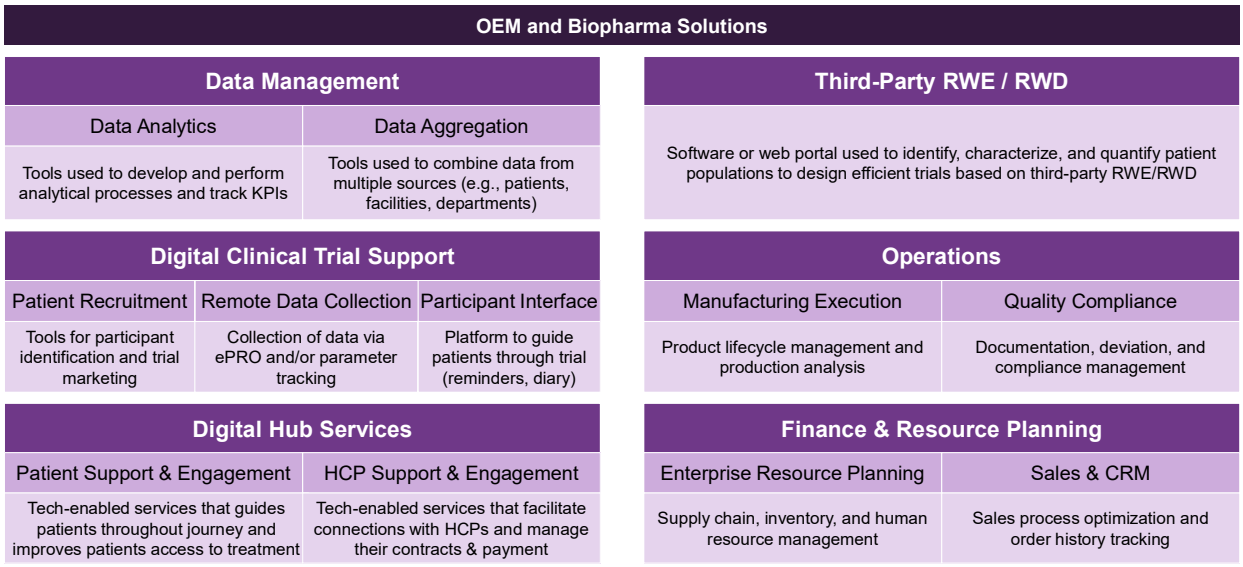

Figure 2.8.2: Non-Health System Software Categorization (part 1)

Note: Not an exhaustive list. KPI = key performance indicator. ePRO = electronic patient reported outcomes. HCP = healthcare provider. RWE / RWD = real world evidence / data. CRM = customer relationship manager.

2.8.3: Subcategories

Given the large range of solutions encompassed under Non-Health System Software, the category is most efficiently subcategorized by the intended end user. Software for OEMs (medical device and biopharmaceutical companies), for example, includes solutions that support stakeholder engagement, data aggregation and analytics, digital clinical trial logistics, enterprise resource planning, and so on (Figure 2.8.2).

Software systems for traditional payers and employers are used to promote population health, manage patient policies, automate billing, and offer member self-service platforms (Figure 2.8.3). Retail pharmacy solutions, on the other hand, use various digital tools to organize, control, and monitor medication expensing; scan prescriptions; manage inventory; support point of sales; and facilitate tech-enabled care.

Traditional Payer and Employer Solutions			
Care & Policy Management	Solutions used to track and manage patient policies, inform care, and improve patient outcomes	**Data & Analytics**	Tools used to perform value, pricing, and risk analyses and/or manage value-based contracts
Accounting	Consolidates financial transactions across multiple departments and facilities and automates billing	**Patient Portal**	Self-service platform for patients to view benefits and access claims
CRM	Software used to manage potential partnerships	**RWE / RWD**	Inform utilization management and cost/value analysis
Compliance	Documentation tools to ensure compliance with patient privacy (e.g., HIPAA) or other regulations	**Claims Management**	Electronically streamline claims and remittance process and appeals

Retail Pharmacy Solutions	
Patient Management	Manage automatic refills and e-prescriptions from provider
Pharmacy Automation	Products used to organize, control, and monitor medication dispensing
Rx Image Scanning	Scan, read, and store hard copies of prescriptions electronically
Inventory Management & Analytics	Optimize and manage inventory levels based on customer behavior
Point of Sales	Allows cashiers to charge, adjust inventory, print receipts; may be augmented by AI
Tech-Enabled Enhanced Care	Allows cashiers to charge, adjust inventory, print receipts; may be augmented by AI

Figure 2.8.3: Non-Health System Software Categorization (part 2)

Note: Not an exhaustive list. RWE / RWD = real world evidence / data. CRM = customer relationship manager.

Source: Health Advances interviews and analysis, KLAS Research, ARI MS..

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Brandon works with digital, biopharma, and medtech clients to develop transformative corporate, franchise, and product growth strategy that is able to meet the needs of stakeholders in the evolving marketplace. Understanding the challenges from all angles and the needs of clients across sectors, Brandon is well-positioned to work with clients to develop innovative commercial and growth strategies as well as evaluate specific investment opportunities. His clients range from small digital start-ups to some of the largest biopharmaceutical companies and private equity firms in the world. While knowledge across multiple therapeutic areas, Brandon has targeted clinical expertise in cardiovascular, metabolic, renal, oncologic, respiratory, mental health, and orthopedic diseases.

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Jeff Abraham co-leads the Digital Health and Health IT Practice at Health Advances. His 15-year career in healthcare spans digital health and therapeutics, medtech, biopharma, and healthcare services. He holds extensive expertise related to commercialization, global market access, product development, and evidence generation.

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Megan founded DTA in 2017 and remains instrumental in developing the foundations for this quickly evolving industry. She leads DTA's efforts related to thought leadership, global policy, international standard development, and the Alliance's DTx Value Assessment & Integration Guide.

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