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"What Goes Around Comes Around": Lessons Learned from Economic Evaluations of Personalized Medicine Applied to Digital Medicine

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Abstract

Two key trends that emerge from the growth of "Big Data" and the emphasis on patient-centered healthcare are the increasing use of personalized medicine and digital medicine. In order for these technologies to move into mainstream health care and be reimbursed by insurers, it will be essential to have evidence that their benefits provide reasonable value relative to their costs. However, these technologies have complex characteristics that present challenges to assessment of their economic value. Previous work has identified these challenges for personalized medicine and thus this work can inform the more nascent topic of digital medicine.

Our objective is to examine the methodological challenges and future opportunities for assessing the economic value of digital medicine, using personalized medicine as a comparison. We focus specifically on "digital biomarker technologies" and "multigene tests". We identified similarities in these technologies that can present challenges to economic evaluation: multiple results, results with different types of utilities, secondary findings, downstream impact (including on family members), and interactive effects. Using a structured review, we found that there are few economic evaluations of digital biomarker technologies, with limited results. We conclude that more evidence on effectiveness of digital medicine will be needed but that the experiences with

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personalized medicine can inform what data will be needed and how such analyses can be conducted. Our study points out the critical need for typologies and terminology for digital medicine technologies that would enable them to be classified in ways that will facilitate research on their effectiveness and value.

Keywords

Personalized Medicine; Individualized Medicine; Digital Medicine; Cost-Benefit Analysis Methods

INTRODUCTION

The growth of “Big Data” and the increasing emphasis on patient-centered healthcare and consumer engagement have contributed to the emergence of two key technologies: (1) personalized medicine (also known as precision or genomic medicine – the use of genetic information to target health care interventions) and (2) digital medicine (also known as mhealth – the digital transmission of information and various combinations of telecommunications, hardware, and software to deliver healthcare services). It has been said that we are entering the “Information Age” for health care, where everything is connected and where the integration of “Big Data” – characterized by high velocity, volume, and variety – is becoming increasingly important.(1–3) Both personalized and digital medicine are emerging into mainstream health care and away from being narrowly focused only on limited conditions (such as genetic testing for rare childhood disorders) or solely “entertainment” devices that are not intended to impact health outcomes (such as free phone applications (“apps”)).

The emergence of personalized medicine and digital medicine into mainstream healthcare has accelerated in recent years because of the growing availability of these technologies, often at decreasing costs. There are now over 60,000 genetic tests available for more than 4000 disorders,(4) and the cost of multigene panel tests such as whole genome sequencing has dropped dramatically.(5) The use of smartphones is now almost ubiquitous in the US – 80% of US adults have a smartphone, and 30% of these phones have at least one health-related app.(6)

The intersections between personalized medicine and digital medicine are increasing.(7) Eric Topol, in his seminal book on how the digital revolution will create better health care, noted that personalized and digital medicine technologies are converging,(8) and digital health has been defined as the “convergence of the digital and personalized revolutions with health, healthcare, living, and society.”(9) A recent report noted funding for digital health personalized medicine companies comprised half of overall genomics funding in three of the five years, and that delivering on the promise of genomics is dependent on factors that are within the purview of digital health: (1) ensuring broad access to diverse data sets used to deliver insights; (2) removing barriers to clinical workflow incorporation; and, (3) advancing technology, both in the lab and in the cloud.(10) Importantly, digital technologies will play a key role in the recently funded National Institutes of Health Precision Medicine Initiative, with data from mobile health devices and apps integrated with data from genetic tests,

surveys, and electronic health records in what has been termed the “most ambitious medical research program in the history of American medicine.”(11)

However, in order for personalized medicine and digital medicine to be adopted more widely as a routine part of health care services and to be reimbursed by insurers, it will be essential to have evidence that these technologies have been evaluated for their accuracy, clinical effectiveness, economic value, and ethical implications.(12) Many have noted the hope that personalized medicine and digital medicine will transform health care by improving outcomes and decreasing costs.(13, 14) However, many have also noted that more evidence on the value of these technologies will be needed, particularly for digital medicine given that it has more recently started entering mainstream healthcare relative to personalized medicine.(15–20)

Our objective is to examine the methodological challenges and future opportunities for assessing the economic value of digital medicine, using personalized medicine as a comparison, and focusing specifically on digital biomarker technologies and multigene tests. We begin by identifying how these technologies share several characteristics that present similar challenges for economic evaluation. We then draw on prior work identifying methodological challenges for economic evaluation of complex technologies and assess how they are applicable to multigene tests and digital biomarker technologies. We follow with a structured review of cost and outcome studies of digital biomarkers. We conclude with an assessment of future steps needed to facilitate assessing the economic value of these new technologies.

CHARACTERIZING AND COMPARING PERSONALIZED MEDICINE AND DIGITAL MEDICINE

Before we can examine the economic issues, we need to first characterize personalized medicine and digital medicine and describe how they are similar. Both personalized medicine and digital medicine include a wide range of technologies and thus comparing “personalized medicine” and “digital medicine” in their entirety would be too diffuse. We begin by defining the scope of personalized medicine and digital medicine and the focus of this paper – digital biomarkers and multigene tests. We then compare the technologies in terms of challenges to economic evaluation.

- Personalized medicine includes genetic tests and targeted interventions. These technologies can be used for a range of purposes (e.g., risk prediction, treatment decisions, and prenatal screening) and can be focused on either the individual’s genetic make-up or the genetic variation that is acquired, e.g., cancer tumors. Genetic tests also range from tests for a single gene to tests for the entire genome. The scope of personalized medicine is now often considered to include more than genetic information, to include any disease prevention or treatment approach that takes into account differences in people’s genes, environments and lifestyles.(21). (For the purposes of this study, we do not distinguish between genomic medicine, personalized medicine, and precision medicine.)

- Digital medicine includes a wide range of technologies ranging from consumer-oriented monitoring apps to telemedicine and electronic health records. Monitoring apps and devices range from simple activity trackers to more complex technologies such as respiratory monitors to monitor asthma, electrocardiograms to monitor heart conditions, and glucose monitors for diabetes control. An example of a complex, emerging digital technology is the "smart" contact lens with embedded sensors for conditions such as glucose monitoring being developed by Google's Verily.

One scheme classified digital medicine into the following categories:(22)

1. Wearables and Biosensors – wearable or accessory devices that detect specific biometrics and are designed for consumers, with data transmission to providers as relevant
2. Analytics and Big Data – data aggregation and/or analysis to support a wide range of healthcare use cases
3. Healthcare consumer engagement – consumer tools for the purchasing of healthcare products and services or health insurance
4. Telemedicine – delivery of healthcare services (synchronous or asynchronous) through nonphysical means (e.g. telephone, digital imaging, video)
5. Enterprise Wellness – services designed to improve general well-being of employees
6. EHR and clinical workflow – electronic health records and surround applications, including clinical workflow support/augmentation

Within these broad categories, two technologies that are most relevant for the purpose of this study are: (1) "multigene tests" and (2) "digital biomarker technologies" (Box). These technologies are relevant because they both measure "biomarkers", which is a general term for any physiological characteristic that is objectively measured and evaluated to indicate a disease state; both technologies can produce enormous amounts of data that have to be integrated in order to provide meaningful results; and both technologies are complex because they include multiple measures and results, which may include clinically actionable results as well as results that provide only information of personal utility to the consumer or that have no known significance.

An example of the intersection between multigene tests and digital biomarker technologies was noted in a recent report.(6) This report noted that the "most promising" consequence of digital biomarkers is the ability to create digital biomarker panels – and that a parallel is seen in the example of gene expression signatures that serve diagnostics, prognostic, and predictive roles. Health care panels with multiple measures have proven to be clinically useful in other areas of medicine, e.g., 10 year cardiovascular risk is best predicted by a set of measurements including age, gender, cholesterol levels, smoking and medication status, and blood pressure.(6) There are currently a limited number of technologies that directly integrate genomic data with digital technologies for consumer use. Examples are apps that combine behavioral/phenotypic data captured via an iPhone or Apple Watch and genetic

data from 23andMe to identify novel genetic correlations,(10) and the Pathway Genomics OME™ app that “merges cognitive computing and deep learning with precision medicine and genetics to enable Pathway Genomics to provide consumers with genomic wellness information.”(23)

METHODOLOGICAL CHALLENGES OF MEASURING THE VALUE OF COMPLEX TECHNOLOGIES

Our work and that of others has examined the challenges of examining the economic value of complex technologies such as personalized medicine.(24–32) Because of the similarities between personalized medicine and digital medicine – particularly between multigene tests and digital biomarker technologies – reviewing the challenges identified for personalized medicine can provide insights into how similar challenges may be relevant to digital medicine.

Table 1 summarizes test characteristics that have been identified as presenting challenges to economic evaluations: multiple results, results with different types of utilities, secondary findings, downstream impact (including on family members), and interactive effects. For each of these characteristics, we noted the implications for conducting economic analyses, including a need for more complicated analyses and more in-depth analyses of utilities and impacts. The table then describes how multigene tests and digital biomarker technologies illustrate each of these challenges. For example, as noted above, a key advantage of multigene tests and digital biomarker technologies is their ability to integrate results from multiple biomarkers into panels where the sum is greater than the parts. However, this can present a challenge to economic evaluation because data on costs and effectiveness may only be available for each individual biomarker and thus the interactive effect would not be incorporated in value calculations. Similarly, both technologies produce large amounts of information that may not be clinically actionable and may produce unexpected harms such as unexpected results or results that produce anxiety or lead to unwarranted interventions.

COMPARISON OF ECONOMIC EVALUATIONS

We first conducted a structured review of economic evaluations of digital biomarker technologies to assess what is known about their economic value and discuss how these results illustrate some of the methodological challenges for measuring the value of complex technologies. We then compared these results to previously published reviews of economic evaluations of personalized medicine.

Structured Review of Economic Evaluations of Digital Biomarker Technologies

Since there are no specific MeSH terms for “digital medicine”, we used a combination of keyword and MeSH terms to identify economic evaluation studies of digital biomarker technologies (for the past five years through April 2016):

- (((((((((fitbit) OR activity monitor) OR consumer-wearable) OR trackers) OR digital) OR ((((“Computers, Handheld”[Mesh] OR “Cell Phones”[Mesh] OR “Smartphone”[Mesh]) OR “Mobile Applications”[Mesh]) OR

"Telemedicine"[Mesh]))))) AND (("Cost-Benefit Analysis"[Mesh]) OR "Costs and Cost Analysis"[Mesh]) NOT “telemedicine”)

We included studies of technologies that met our definition of digital biomarkers and that included a comparison of costs and outcomes (cost-consequence analysis, cost-effectiveness analysis, or cost-benefit analysis). We excluded studies of technologies that did not collect data from individuals but provided individuals with a one-way communication (e.g. text message) and studies of digital services such as telemedicine. We excluded studies that only examined costs or that used the term “cost-effectiveness” but did not calculate a cost-effectiveness ratio. We identified 281 studies in our initial search. We then excluded 258 studies based on a review of their titles or abstracts and 18 studies based on a review of the full text, leaving five included studies. Studies were coded by two authors.

Two key findings emerge from our review (Table 2). First, we only found five relevant articles.(33–37) None of these studies were conducted in the US, which is surprising given that digital medicine is a major focus in the US. These results suggest that digital biomarker technologies are only beginning to be formally evaluated for their costs/outcomes. Second, we found that only two of the five studies concluded that the digital intervention was cost-effective or that the costs were reasonable relative to the outcomes, with two more studies concluding that the results were equivocal.

This review suggests several ways in which the measurement of the economic value of digital biomarker technologies is likely to be challenging. The included analysis of a digital technology for atrial fibrillation (35) illustrates several of the challenges noted in Table 1. One of the similar challenges found in personalized medicine and digital medicine is the method of addressing the downstream impact on costs and outcomes, including impact on family members that the technologies may present. For example, recent studies suggest that up to 30 percent of people with atrial fibrillation (AF) may have familial AF and thus have a higher chance of having a relative with the condition.(38) Because AF can be inherited, an AF diagnosis can result in a cascade of costs and outcomes not only for the individual (e.g., warfarin therapy) but also for their family members (e.g. risk/diagnostic testing and possible warfarin therapy). The analysis included in our review focused on detecting AF using an ECG; however, they did not consider the fact that AF can be inherited and they did not address downstream costs such as risk/diagnostic testing of family members or treatment for afflicted family members.

Comparison of Economic Evaluations of Digital Biomarker Technologies to Personalized Medicine

There are few published cost-effectiveness analyses specifically focusing on multigene tests.(25, 32, 39–41) We thus used prior reviews of personalized medicine more generally for comparisons. In our prior review of cost-utility analyses of personalized medicine published between 1998 – 2011,(24) we found that 80% of studies (N=59) concluded that genetic testing had favorable cost-effectiveness ratios (cost per QALY gained less than $100,000 or cost-saving). In a review covering studies of personalized medicine published between 2010 – 2014, 84% of studies (N=38) reported that their findings indicated favorable cost-effectiveness.(42) These results are similar to those for other medical interventions.(24) In

comparison, our review of digital biomarker technologies suggests that these technologies may be less likely to be cost-effective than personalized medicine or other technologies although the small number of studies found precludes any definitive conclusions.

CONCLUSIONS

We found only a few economic evaluations of digital biomarker technologies, consistent with reports suggesting that few digital medicine technologies have been evaluated for their costs/outcomes. This is not surprising given that economic value is difficult to examine without first establishing effectiveness of the technology in improving outcomes, and effectiveness data are generally lacking for digital medicine technologies. For example, authors of a recent prospective, randomized trial of individuals using smartphone-enabled biosensors for chronic disease management noted that this was the first randomized trial to examine costs as well as outcomes.(20) This study found no evidence of differences in health care utilization or costs although they found some limited evidence that the use of the technology improved the perception of control over health status. On the one hand, such results assuage concerns that digital monitoring will lead to unwarranted health care utilization and costs; on the other hand, they provide little evidence that such technologies will improve health outcomes.

The current lack of effectiveness evidence will be a hindrance to conducting economic evaluations of digital medicine. However, the experience with personalized medicine suggests how economic analyses can be useful even when such evidence is lacking, e.g., by identifying variables that are particularly important for data collection, estimating the range of possible conclusions, and development of innovative modeling approaches.(2, 24–26, 32)

Our list of challenges suggests what type of data may be needed to conduct economic analyses, such as the interactive effect across multiple measures. Given the small number of economic evaluations of digital biomarker technologies identified we did not attempt to assess their quality. However, in searching for these studies we found many instances where standard methodologies and terminology were not used, e.g., a study was described as being a “cost-effectiveness analysis” when there was no incremental cost-effectiveness analysis ratio presented.

Our study points out the critical need for typologies of digital medicine technologies that would enable them to be classified in ways that will facilitate research on their effectiveness and value. We were unable to locate any detailed categorizations or taxonomies of digital medicine, including in the gray literature. Taxonomies would enable better identification of technologies and their relevant comparators, costs, and outcomes.

A similar need is for standardized subject heading terms in PubMed for digital medicine. There is currently no Major Exact Subject Headings (MeSH) for digital or digital medicine and thus there is variability in how studies are coded and it is difficult to locate relevant studies. It is not surprising that a rapidly developing field such as digital medicine requires an evolution in terminology, but given that smartphones have been available for a decade,

there's an urgent need to develop consistent and timely terminology and categorizations of studies.

Our study has limitations that should be addressed in future research. Given that this is the first study to our knowledge that has begun to lay out the challenges for economic evaluation of digital medicine, this should be considered an initial overview of the topic. Our review of economic evaluations only focused on one specific type of digital medicine and we may have missed some studies because PubMed coding is not yet well-standardized, but we think that our illustrative analyses portend what we would have found with a broader, more comprehensive search. Lastly, we did not attempt to derive inferences from cost/outcome studies of multigene tests, given that few have been published.

In conclusion, we have described an initial approach to considering how the economic value of digital medicine can be examined. We suggested several steps that could facilitate these needed analyses. Digital medicine offers great potential to improve outcomes and increase patient engagement, but evidence on its value is needed.

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Box

Definitions

Multigene tests include: (a) “panels” - tests that analyze multiple genes including newly recognized genes and/or for multiple syndromes and (b) “whole exome/genome sequencing” - tests that analyze the exome or the whole genome.

Digital biomarker technologies, which fall into the category of “wearables and biosensing devices”, use consumer-generated physiological and behavioral measures collected through connected digital tools that can be used to explain, influence, and/or predict health-related outcomes.(6) These technologies may focus on measurements for consumer use only, or clinical measurements that are transmitted to clinicians for health care decisionmaking. They may passively monitor ongoing activities (such as steps taken) or be used to actively collect specific measurements (such as blood glucose).

Table 1

Characteristics of Technologies, Challenges for Economic Evaluations, and Application to Multigene Tests and Digital Biomarker Technologies

Characteristics of Technologies	**Challenges for Economic Evaluations**	**Multigene Testing Examples**	**Digital Medicine Examples**
Measures multiple biomarkers, thus providing multiple results	Complicated analyses are required that may be infeasible due to large number of possible pathways and outcomes	Whole genome sequencing can provides multiple results, with multiple clinical pathways, costs, and outcomes	Activity monitors can provide multiple types of data (steps, heart rate, sleep patterns, etc.) with multiple clinical pathways, costs, and outcomes
Results have different utilities: clinically actionable, personal utility only, harmful, and/or unknown significance	Personal utility is difficult to value; costs of harmful results and/or results with unknown significance may not be incorporated into analyses	Multigene tests may provide information with personal utility or disutility only (e.g., knowing that one is at risk for a non-preventable condition) or that has unknown significance leading to unwarranted interventions (e.g., a genetic variation that has not been validated but leads to further testing)	Activity monitors may provide information that is unlikely to be clinically actionable, e.g., whether you move during the night, and technologies that encourage physical activity such as pedometers may produce unexpected harms (e.g., joint injury)
Results may include secondary findings (potentially actionable findings unrelated to the reason for using the technology)	Complicated analyses required to capture potentially low probability events and associated utilities; often lack of data on costs and outcomes of secondary findings	Multigene testing for one inherited condition (e.g., cardiovascular risk) may reveal previously undiagnosed risk for another condition (e.g., *BRCA1/2*, which confers a high risk of breast and ovarian cancer)	Technologies for measuring continuous blood pressure may provide results on heart disease but could also indicate unrelated findings (e.g., mood and emotion)
Downstream impact on costs and outcomes, including impact on family members	Complicated analyses required to examine impact over time; impact on family members may not be incorporated into analyses	Costs and outcomes for multigene panels for inherited conditions, such as Lynch Syndrome, depend to a large extent on downstream follow-up by family members, e.g., increased colorectal cancer screening	Technologies used to diagnose Atrial Fibrillation (AF) may impact family members (30% of individuals with AF have a family member with the condition)
Results may have interactive effects such that the “sum is greater than the parts”	Complicated analyses required to estimate interactive effects	Tumor profiling measures multiple genes that together may provide a more comprehensive assessment of a tumor and treatment options than if testing were done individually	Technologies such as smart watches provide multiple types of seemingly unrelated data (e.g. standing time, walking/steps, heart rate, weight) and the sum valuation of these on outcomes such as preventing obesity is likely greater than each individual measurement

Table 2

Economic Evaluations of Digital Biomarker Technologies

Condition	Intervention (what is tool and what used for)	Comparator	Population Included (sociodemographic characteristics, N)	Type of Cost Analysis and Results	Key Economic Conclusions from Articles (direct quote from manuscript)	Did Authors Conclude that Cost-Effective or Reasonable Costs?	Source
Atrial Fibrillation (AF)	Screening for AF using iPhone iECG by pharmacists for stroke prevention	Diagnosis of AF in an unscreened population	General Population (65–84 yo), Australia, N=1000	Cost-Utility Analysis: $4,066 per QALY gained; $20,695 for preventing one stroke	"Screening with iECG for AF in pharmacies with an automated algorithm is both feasible and cost-effective."	YES	(35)
Heart Failure	CardioManager App to allow heart disease patients to self – manage their conditions	No use	Heart failure patients, Spanish communities (Castile and Leon), N=2000	Cost-Utility Analysis: $11,300 per QALY gained	"CardioManager may generate 33% reduction in cost of management and treatment… may be able to save more than $10,940 per patient to the local Health Care System"	YES	(33)
Asthma Control	t+ Asthma App for monitoring & transmission of symptoms, drug use, & peak flow w/ immediate feedback to	Standard paper based monitoring strategies	Asthma Patients, UK, N=288	Cost-Consequence Analysis: Telemonitoring cost difference was significant ($108 per patient). Mean cost	"The t+ Asthma App was more expensive because of the expenses of telemonitoring and was not cost-effective."	NO	(36)

Condition	Intervention (what is tool and what used for)	Comparator	Population Included (sociodemographic characteristics, N)	Type of Cost Analysis and Results	Key Economic Conclusions from Articles (direct quote from manuscript)	Did Authors Conclude that Cost-Effective or Reasonable Costs?	Source
	improve asthma control			of care $382 intervention group vs. $380 comparison group.			
Physical activity and health-related quality of life	Pedometer-based activity instructions to increase daily # of steps	Time-based Instructions (initial clinical consultation, written advice w/ time-based personal activity goals, 3 telephone sessions)	Low physical activity, adults aged 65 years and over, Auckland, NZ, N=330	Cost-Utility Analysis: Intervention vs. comparator, per 30min of weekly walking/per QALY: (i) community care costs $115/ $3105 (ii) exercise and community care costs $1300/$3500 (iii) all costs $185/$4999	"There were no significant between-group differences in costs. Outcomes suggest intervention may be cost-effective in increasing physical activity and health-related quality of life over 12 months."	MAYBE	(34)
Physical Activity	2 interventions: - Minimal (normal walking w/ minimal instruction) - Maximal (using pedometer to increase walking to 15,000	Normal Walking Behavior	Low physical activity individuals, Glasgow, Scotland, N=79	Cost-Effectiveness Analysis: QALY $143 (minimal) and $917 (maximal) per person achieving 15,000 steps/week	"Pedometer based walking interventions may be considered cost-effective and suitable for implementation within the wider community."	MAYBE	(37)

Condition	Intervention (what is tool and what used for)	Comparator	Population Included (sociodemographic characteristics, N)	Type of Cost Analysis and Results	Key Economic Conclusions from Articles (direct quote from manuscript)	Did Authors Conclude that Cost-Effective or Reasonable Costs?	Source
	steps)						

QALY, Quality adjusted life-year; iECG, iPhone electrocardiogram – an instrument that attaches to an iPhone that is used to take an electrocardiogram; Cardio Manager App – a disease management app for patients with heart disease that includes sections for disease information, for recording the user's activities and health measurements, and for registering the users' medications and the hours that they should have them; t+ Asthma App - enables twice daily recording and transmission of symptoms, drug use, and peak flow. The recorded peak flow was displayed within the traffic light zones and the patient was prompted to follow their agreed action plan. Incursion into the red or amber zones triggered contact by an asthma nurse; Pedometer, an instrument for estimating the distance traveled on foot by recording the number of steps taken.