Abstract: Patient-generated health data (PGHD), or health-related data gathered from patients to help address a health concern, are used increasingly in oncology to make regulatory decisions and evaluate quality of care. PGHD include self-reported health and treatment histories, patient-reported outcomes (PROs), and biometric sensor data. Advances in wireless technology, smartphones, and the Internet of Things have facilitated new ways to collect PGHD during clinic visits and in daily life. The goal of the current review was to provide an overview of the current clinical, regulatory, technological, and analytic landscape as it relates to PGHD in oncology research and care. The review begins with a rationale for PGHD as described by the US Food and Drug Administration, the Institute of Medicine, and other regulatory and scientific organizations. The evidence base for clinic-based and remote symptom monitoring using PGHD is described, with an emphasis on PROs. An overview is presented of current approaches to digital phenotyping or device-based, real-time assessment of biometric, behavioral, self-report, and performance data. Analytic opportunities regarding PGHD are envisioned in the context of big data and artificial intelligence in medicine. Finally, challenges and solutions for the integration of PGHD into clinical care are presented. The challenges include electronic medical record integration of PROs and biometric data, analysis of large and complex biometric data sets, and potential clinic workflow redesign. In addition, there is currently more limited evidence for the use of biometric data relative to PROs. Despite these challenges, the potential benefits of PGHD make them increasingly likely to be integrated into oncology research and clinical care.

Innovations in Research and Clinical Care Using PGHD

The past decade has seen remarkable progress in the translation of biological discoveries into new cancer treatments, such as targeted therapies, immune checkpoint inhibitors, and adaptive cellular therapies. The effect of each new treatment is incremental but, cumulatively, their impact on survival rates, together with previous advances in early detection, has been unprecedented. Although diagnosis and treatment can still be a lonely and fearful experience for patients, in many cases, cancer is becoming a chronic condition rather than a fatal disease. The result is that maintenance of quality of life has become an increasingly important clinical goal.

Quality of life is one aspect of patient-generated health data (PGHD), or health-related data gathered from patients to help address a health concern.1,2 PGHD include self-reported health and treatment histories, patient-reported outcomes (PROs), and biometric data (see Fig. 1).1 PROs are defined by the US Food and Drug Administration (FDA) as “reports of the status of a patient’s health condition that come directly from the patient, without interpretation of the patient’s response by a clinician or anyone else.”2 PROs can be categorized as disease-related symptoms, side effects of treatment, and quality of life (ie, how symptoms and side effects impact daily functioning).4

Keywords: neoplasms, patient-generated health data, quality of life, telemedicine
Whereas self-reported health and treatment histories are well established in the clinical setting, as are PROs in the research setting, the use of biometric PGHD data is still in early development. Biometric data can include passively collected data from wearable sensors (eg, a physical activity tracker) as well as data actively collected by patients through other instruments (eg, a wireless blood pressure cuff). Advances in wireless technology, smartphones, and the Internet of Things have facilitated new ways to collect PGHD during point-of-care clinic visits and in routine daily life. In the current article, we review the opportunities and challenges of PGHD to inform regulatory decisions, research, and cancer care delivery.

The Need for PGHD in Cancer Care
Growing interest in PGHD in oncology both reflects and reinforces an increasing role for patient advocates in directing regulatory priorities. In 2009, the FDA released a draft guidance document encouraging patient-focused drug development to ensure that the patient experience is sufficiently represented in benefit-risk assessment. Patient-focused drug development has primarily taken the form of collecting PROs as secondary outcomes in phase 3 clinical trials, although adherence to guidelines for implementation has been suboptimal. With the exception of one trial that collected home-based blood pressure readings, the remote collection of biometric data has been limited. Nevertheless, the collection of PROs is important because there are extensive data suggesting that PROs provide information that is complementary to, but different from, clinician-rated adverse events. Although clinicians’ ratings of adverse events are informed by medical knowledge, they tend to significantly underestimate patients’ reports of symptomatology. It has been demonstrated that severe symptomatology is underreported in clinical trials by up to 76%. In contrast, data suggest that PROs are more sensitive to treatment-related differences in toxicity than clinician-rated adverse events. Notably, patients treated on clinical trials tend to be younger, healthier, and have higher socioeconomic status than patients treated outside of clinical trials in the community setting. Thus adverse events reported on clinical trials may not be generalizable to patients receiving the same treatment as standard of care. In contrast, PROs give a voice to patients. Without PRO data from high-quality studies, patients instead may rely on anecdotal information from the internet about what to expect for a given disease and treatment. This anecdotal information may be inaccurate or ungeneralizable. PRO data are particularly important when patients must decide between 2 or more treatments that demonstrate similar or modest benefits regarding survival. PRO data can inform decision making in this situation by providing insight into quality of life, such as the ability to maintain one’s roles and responsibilities during treatment (eg, continuing to work), which can also have significant emotional and financial benefits.

PGHD also reflect increased awareness of the importance of proactive symptom management in high-quality cancer care. Proactive symptom management is part of a larger trend recommended by the Institute of Medicine (IOM) of engaging patients to improve quality of care. As recently as 1999, PROs were framed in terms of understanding tradeoffs between quantity and quality of life. However, a series of studies published starting in 2010 demonstrated that early palliative care improved survival by an average of 4.6 months in patients with advanced cancer. These and other studies showed that early palliative care also improved quality of life and reduced distress in both patients and caregivers. Findings were extended in a recent high-visibility study demonstrating that clinic-based symptom monitoring and management improved quality of life and extended survival by 5 months in patients with cancer who received chemotherapy, perhaps because they received chemotherapy for a longer time. Notably, the survival benefits of symptom management compare favorably with anticancer agents that were approved by the FDA between 2009 and 2013, which demonstrated a median survival benefit of 2.7 months. Thus it has become evident that improving quality of life can also lengthen quantity of life.

Opportunities abound to improve symptom management. Symptomatology has been chronicled most comprehensively by Cancer Care Ontario through systematic administration of the Edmonton Symptom Assessment Scale to oncology patients since 2007. In a study of 120,745 patients within 12 months of diagnosis, the most commonly endorsed moderate to severe symptoms were tiredness (59%), low overall well-being (55%), anxiety (44%), lack of appetite (43%), and pain (37%). A diagnosis of respiratory or oropharyngeal...
cancer, younger age, female sex, lower income, greater comorbidities, and urban residence were associated with significantly higher odds of elevated symptom burden. These findings are consistent with meta-analyses estimating the prevalence of common patient-reported symptoms. For example, the prevalence of pain is estimated to be 55% during anti-cancer treatment; 39% after curative treatment; 66% in advanced, metastatic, or terminal disease; and 50.7% in all cancer stages. The estimated prevalence of fatigue is from 14% to 27% among breast cancer survivors, 78% among older patients receiving palliative care, and 7% in the general population. The estimated prevalence of depression is 27% during treatment, 21% during the year after diagnosis, 15% 1 year after diagnosis, and 12% >2 years after diagnosis. In contrast, the estimated prevalence of depression in noncancer controls assessed similarly is 10%. The estimated prevalence of anxiety is 18% in long-term cancer survivors versus 13% in noncancer controls assessed similarly. A large study found that the prevalence of distress was 46% across the cancer continuum in 55 cancer centers in North America, which was similar to rates reported in Europe. Thus, although symptoms of depression and anxiety returned to normative levels in long-term survivorship, the prevalence of pain and fatigue remained high across the survivorship continuum. Rates of these symptoms demonstrate a significant unmet need for symptom monitoring and management, particularly during active treatment and in patients with advanced cancer.

Symptomatology tends to be underrecognized in clinical care, which may contribute to its high prevalence. Outside of the context of oncology, it has been noted that 31% of patients reporting chest pain, 38% of those reporting dyspnea, and 45% of those reporting cough on a clinical visit information form did not have documentation of the symptom in the electronic medical record (EMR). A large multicenter study found that oncologists underestimated rates of patients’ symptoms, particularly among patients with a poor Karnofsky performance status or a poor Mini-Mental State score or among those who were hospitalized, recently diagnosed, or undergoing opioid titration. Even on a palliative care inpatient unit, nurses’ ratings of patients’ symptoms were not significantly correlated with patients’ own ratings of their symptoms. Providers’ perceptions of symptoms differ not only from those of patients but also from those of other providers. In a study of symptoms assessed by pairs of providers approximately an hour apart, intraclass correlations were fair to poor across a range of symptoms, including neuropathy, dyspnea, diarrhea, nausea, constipation, fatigue, and vomiting. These findings demonstrate the need for clear communication and documentation of PROs between patients and providers as well as among members of the treatment team.

PROs are associated with clinically important events across the disease trajectory. A meta-analysis of 21 studies reported that PROs in which symptoms and quality of life were included were significantly associated with radiographic tumor response to chemotherapy, radiotherapy, and/or targeted therapy. Regarding progression, Denis et al have published a series of studies demonstrating that patient-reported symptoms of lung cancer (eg, fever, cough) can identify cancer...
progression early (see Fig. 2).43-46 A randomized trial showed that screening for these symptoms was associated with a 7-month survival advantage over usual care, which in part may have been because patients in the intervention group had better performance status at progression and thus were more likely to receive optimal treatment.46,47 Finally, several studies have shown that PROs enhance prediction of survival in myelodysplastic syndromes,48 multiple myeloma,49 early-stage colorectal cancer,50 advanced breast cancer,51 metastatic castration-resistant prostate cancer,52 metastatic renal cell carcinoma,53 advanced cancers,54,55 and a variety of tumor types.56,57 In fact, some data suggest that PROs predict survival better than provider-rated performance status.58

The Evidence Base for Clinical Monitoring of PGHD

There is a growing literature base suggesting that incorporating PGHD into clinical care can improve outcomes over standard care.59 Evidence for the clinical collection of PGHD comes primarily from studies of symptom monitoring interventions of PROs, which are defined for the purposes of this review as those intended to improve communication between patients and providers regarding patients’ symptoms. Numerous randomized trials have shown that clinic-based symptom monitoring improves patient-provider communication and increases the concordance of their ratings of symptoms and quality of life.60-68 As noted above, these benefits are consistent with additional studies suggesting that symptom management or palliative care improves survival.25,26,60-69 The mechanisms by which these benefits occur are currently unclear, although they may due to better medication adherence and/or physical functioning, such that patients are able to receive more therapy.46 Notably, improvements in outcomes have generally occurred without lengthening clinic visits.61,63 Findings are less consistent regarding whether clinic-based symptom monitoring improves PROs, although several studies have demonstrated a beneficial effect on quality of life and/or symptomatology.25,63,66,70,71 Velikova et al63 found greater improvement in quality of life for patients in their intervention group when PRO data were explicitly discussed in the clinical encounter than for corresponding patients whose PROs were not explicitly discussed. A similar finding was reported by Carlson et al,72 who observed that the proportion of patients who had lung cancer with high distress levels were affected most when distress screening was combined with telephone triage and
resource referral, as opposed to screening alone. In contrast, there were no group differences in the percentage reporting high distress levels among patients with breast cancer, who reported less baseline distress than patients with lung cancer. Similarly, McLachlan et al.\textsuperscript{73} reported that, for patients in their randomized trial who reported moderate to severe depression at baseline, patients who received clinic-based screening for unmet needs with care coordination exhibited greater reductions in their depression scores compared with those who were randomized to conventional clinical care. Thus clinic-based symptom monitoring may be most beneficial in patients with high symptomatology and when the data collected are discussed during the clinical encounter. Current literature is consistent with numerous quality-of-care initiatives, such as the Quality Oncology Practice Initiative from the American Society of Clinical Oncology (ASCO) or Electronic Clinical Quality Measures from Medicare, in which EMR documentation of screening and management of PROs such as pain and distress are indicators of high-quality cancer care.\textsuperscript{74,75}

Results from randomized trials of remote symptom monitoring of PROs have been more equivocal. We define remote symptom monitoring interventions as those intended to improve communication between patients and providers regarding patients’ symptoms when patients are away from the clinic or hospital. Remote symptom monitoring often uses ecological momentary assessment, defined as real-time PRO reporting, that may be less subject to recall bias than retrospective questionnaires completed in the clinic.\textsuperscript{76} Although some trials have reported improvements in symptoms and quality of life,\textsuperscript{77-79} others have not.\textsuperscript{80-85} Mixed findings may be because of high study heterogeneity in terms of remote monitoring methodology, patient-provider communication, and the patient population. Remote monitoring methodology has included study-initiated calls from an automated telephone system,\textsuperscript{79} study-initiated online questionnaires,\textsuperscript{24,81} patient-initiated smartphone-based or online questionnaires,\textsuperscript{82,86} study-initiated telephone calls to a nurse or nurse practitioner,\textsuperscript{83,85} study-initiated calls from a research coordinator,\textsuperscript{87} or a paper symptom diary.\textsuperscript{78} Some studies incorporated automated alerts about severe or worsening symptoms to providers,\textsuperscript{77,79,80,84,88,89} whereas others encouraged patients to discuss symptoms with their providers.\textsuperscript{81} Most studies focused on patients who were receiving chemotherapy or radiation\textsuperscript{77,80,82,83,89} or on post-surgical patients,\textsuperscript{79,83,88} although some focused instead on patients with advanced cancer\textsuperscript{78,84} or posttreatment cancer survivors.\textsuperscript{81} Notably, although some trials reported on process variables such as patient uptake of the intervention and provider responses to alerts,\textsuperscript{79,80,84} no studies systematically examined important health system factors such as the type of clinic or provider workflows. Nevertheless, in general, efficacious remote monitoring interventions were those that focused on patients with high unmet needs amenable to intervention, high response rates by providers to alerts, and structured provider responses that focused on symptom reduction. Taken together, these data suggest that thoughtfully designed remote symptom monitoring interventions may improve outcomes in patients with cancer. In addition, numerous studies have shown that remote symptom monitoring is feasible and acceptable to patients and providers.\textsuperscript{80,84,86,88-93} However, more work is clearly needed to identify characteristics of health systems, patient populations, and intervention designs to ensure that remote symptom monitoring is maximally efficacious.\textsuperscript{94,95}

**Digital Phenotyping: Mobile Technology to Collect PGHD**

The limited use of the large-scale collection of PGHD for clinical and research purposes is somewhat surprising given the abundance of opportunities to collect such data. Slow uptake may result from challenges in analyzing these data, as described below. Nevertheless, there has been a proliferation of device-based applications (apps) to track almost any aspect of health and behavior (ie, digital phenotyping). Currently, approximately 81% of Americans own a smartphone, and 17% own a smartwatch.\textsuperscript{96} Smartphone and smartwatch owners tend to be younger and have a higher socioeconomic status than non-owners.\textsuperscript{96} Thus there is concern that reliance on PGHD from these devices could exacerbate health disparities,\textsuperscript{97,98} an issue that must be considered and addressed as PGHD collection increases. Despite this concern, commercially available devices provide a robust opportunity to refine the collection and analysis of PGHD, which in many cases have reliability and validity comparable to those of medical-grade biometric sensors. Device-based biometric, behavioral, real-time reporting, and performance measurement approaches are described below.

**Biometrics**

The field of device-based biometric sensors is rapidly expanding. Examples include wireless scales, blood pressure cuffs, thermometers, pulse oximeters, heart rate monitors, and blood glucose meters. These devices typically transmit data to a smartphone app that records the readings. Smartwatches are also increasingly incorporating these capabilities, such as electrocardiograms. Initial published studies have shown good accuracy in comparisons with gold-standard ambulatory electrocardiograms, making them useful for screening of atrial fibrillation and other cardiac issues.\textsuperscript{99-101} Additional features in development are smartphone-based spirometry, video plethysmography, and detection of seizures.\textsuperscript{102-104} With the exception of blood glucose monitors, which face higher regulatory scrutiny, most products are regulated by the FDA as class II medical devices, indicating that they are safe to use but not verifying their accuracy. In light of the increasing demand for device-based health monitoring, it is clear that biometric monitoring will continue to evolve in terms of accuracy and functionality.
Physical Activity

Accelerometers have been used to quantify human physical activity in the context of research since the 1980s. However, commercially available wrist-worn activity trackers have only recently caught up with research-grade devices in terms of data accuracy. The increasing ubiquity of smartwatches provides new opportunities for passive monitoring of physical activity as a remote indicator of overall health and well-being in patients with cancer. Accelerometers located in smartphones can also be used to detect a variety of physical activities, including walking, jogging, going up and down stairs, and sitting. Notably, it has been demonstrated that the acceptability of smartphones is superior to that of wrist-based activity trackers. Several observational studies have shown that higher levels of physical activity are associated with a reduced risk of all-cause mortality and/or cancer-specific mortality in patients with local or regional breast cancer, colorectal cancer, locally advanced non–small cell lung cancer, and other cancer types. Higher levels of physical activity are also associated with a reduced risk of several of these cancers, whereas sedentary time is associated with higher risk, independent of physical activity. In addition, in a meta-analysis of over 1 million adults from the general population, higher levels of physical activity mitigated the negative association between sitting time and all-cause mortality. Thus remote monitoring using accelerometers could be used clinically to encourage physical activity among patients with cancer.

In contrast, decreases in physical activity may indicate new-onset mental or physical health concerns among patients with cancer. For example, physical slowing is a symptom of depression. Research shows that, among individuals without cancer, depression is associated with subsequent sedentary behavior and activity disruption. Sedentary behavior and smartphone use have also been identified as sensitive indicators of stress and depressive mood in noncancer populations, such as college students. Sedentary behavior, together with longer screen time on a smartphone, was found to identify symptom burden among patients with cancer with an accuracy of 88%. Moreover, sudden decreases in physical activity during active treatment may indicate acute toxicities, such as renal insufficiency, pneumonitis, and gastritis, although more research needs to be conducted on these relationships.

Location

Patients’ community mobility may also indicate overall mental and physical well-being. Several methods have been developed to measure location using smartphones, including the global positioning system (GPS), Wi-Fi, and Google Location History. Location may be a proxy for a diversity of daily activities outside the home that indicate good quality of life, including social, leisure, and work activities as well as activities of daily living (eg, shopping). Regarding mental health, in a study of adults without cancer, depression was detected with an accuracy of 87% using GPS measurements of movement, mobility between favorite locations, and movement independent of location. Another study found that GPS monitoring, in combination with location data from the search-and-discovery app Foursquare, identified depression and anxiety with 88% accuracy, which was better than either method alone. Regarding physical health, better physical quality of life and less pain have been associated with the number of trips outside the home in patients recovering from stroke and spinal surgery, respectively. GPS can also be used to track outdoor physical activity, such as walking, which has been found to occur less often in patients with non–small cell lung cancer compared with similar individuals without cancer. Outdoor walking capacity using GPS has been strongly associated with clinic-based physical performance measures such as the 6-minute walk test. Thus there is significant potential to use location data as a way to remotely monitor the quality of life in patients with cancer.

Diet

Dietary habits have been notoriously difficult to accurately capture because of the use of long retrospective questionnaires that can be susceptible to recall bias and social desirability bias. Because of participant burden, dietary habits are typically measured relatively infrequently in epidemiologic studies, which may affect study findings. Web-based and app-based dietary measures offer opportunities for improved measurement. Participant burden can be reduced through the use of branching logic for question presentation. In addition, accuracy of recall may be improved through the use of photos of portion sizes that would be difficult to present on paper-and-pencil–based measures. Accuracy of recall may be improved through the use of photos of portion sizes that would be difficult to present on paper-and-pencil–based measures. Although not fully developed yet, the use of a smartphone camera together with machine-learning algorithms to identify foods and portions may be a less burdensome way to collect dietary information in the future. Nevertheless, studies of device-based measurement of dietary habits tend to suffer from high rates of attrition, which itself may bias results. Assessment of diet is clinically important, however. A diet that is low in saturated and trans fats and high in fiber, vegetables, fruits, and other nutrients may reduce the risk of all-cause and cancer-specific mortality after a diagnosis of breast or colorectal cancer, although evidence is limited in patients with other cancer types. Interestingly, patients who improved their diet after a colorectal cancer diagnosis also demonstrated lower cancer-specific mortality, suggesting that web-based and app-based dietary measurements could be used in the context of clinical intervention to improve cancer outcomes.

Sleep

There is a large body of literature to support the reliability and validity of sleep assessment using research-grade,
wrist-worn accelerometers. Outputs include the amount of time awake after sleep onset, sleep efficiency (ie, the percentage of time in bed spent sleeping), and total sleep time. Traditionally, assessing sleep stages (eg, rapid-eye-movement sleep) required polysomnography in sleep laboratories. Over time, the validity of consumer-grade wearable devices has improved, and some devices now include a heart rate sensor, which enables detection of some sleep stages. Some of the more recent devices also demonstrate similar agreement with gold-standard polysomnography and research-grade devices. However, one drawback of wrist-worn devices is that they will likely need to be recharged during the assessment period. Project Baseline (Verily Life Sciences LLC) has instead used a piezoelectric sensor placed under the mattress to detect sleep, which has demonstrated high validity and does not require recharging. A less accurate, but very low-burden, detection method is to use smartphone screen interaction to approximate bedtimes and waking times. Smartphones have also shown promise for the evaluation of perceived sleep quality using patient reports as well as detection of sleep–disordered breathing using built-in microphones. In addition, the MyHeart Counts study from Apple uses smartphones to detect ambient light. Nevertheless, until battery life and sleep sensor technology improve in commercially available wearables and smartphones, alternate measures of sleep may need to be used.

Real-Time Reporting
Mobile devices provide an outstanding opportunity to capture real-time patient-reported data. There is a large literature base focused on the ecological momentary assessment of symptoms such as pain, fatigue, and depression in real time. Although it is burdensome for patients relative to passive monitoring of behaviors, ecological momentary assessment can provide important information regarding daily and intraday variability in symptoms without recall bias. For example, using real-time, validated, smartphone-based brain games Small et al demonstrated significant intraday cognitive variability in patients with breast cancer. Cognitive variability may be a more sensitive indicator of cancer-related cognitive impairment than office-based neuropsychological assessment, as it precedes cognitive decline in normal aging. Smartphone-based cameras are increasingly used to remotely assess dermatologic conditions or surgical complications and have the potential to identify complications early, providing better, lower cost care. Real-time reporting can facilitate just-in-time interventions or microinterventions, which are cognitive-behavioral interventions that can be delivered by smartphone or smartwatch to deliver interventions personalized to an individual’s current circumstances or environment. Examples include reminders to exercise during periods of inactivity or smoking-cessation texts to suggest coping strategies during reported nicotine cravings. Finally, an innovative clinical trial has used smartphone-based real-time symptom reporting to manage dose-limiting toxicities of cediranib and olaparib for ovarian cancer, a regimen that can cause rapid-onset hypertension and diarrhea. There is untapped potential for remote symptom monitoring in clinical trials to keep patients on drug longer, with potential survival benefits.

Functional Status
A sizable body of research has demonstrated that smartphones can reliably detect gait, physical performance, range of motion, and falls. A smartphone placed in a pants pocket can detect stride times, a clinically meaningful metric of locomotor control, with accuracy comparable to that of gold-standard, clinic-based instrumentation. Interestingly, measurement of gait parameters is equally reliable and valid regardless of whether the smartphone is worn on the body, on a belt, or in a pocket or purse. Two-minute and 6-minute walk tests can be administered remotely via smartphone with results comparable to those of clinic-based tests. The same is true for the Timed Up and Go test, in which a patient is asked to stand up from a chair without using their arms, walk a set distance, return, and sit down again. Range of motion in the wrist and ankle can also be captured reliably via smartphone. In addition, falls can be distinguished from daily actions with an accuracy of 90% using a smartphone-based accelerometer and gyroscope. Similar to gait detection, the accuracy of fall detection does not appear to differ based on placement of the smartphone on a belt or in a pocket. The use of a smartwatch together with a smartphone can significantly decrease the rate of false-positive results when detecting falls. Remote monitoring of functional status may be particularly useful for telemedicine visits and in geriatric populations.

Big Data: Untapped Potential for PGHD
Digital phenotyping can yield very large data sets that are amenable to big data analytics. The term big data is defined by Google as extremely large sets of data that may be analyzed by computer to uncover patterns, trends, and associations, particularly those related to human interactions and behavior. Initial forays into big data in the context of health care have been limited primarily to analyses of clinical information, payment and billing data, genomics, and biomarkers. Little has been done specifically in PGHD. Historically, a primary concern regarding sharing of health data has been patient privacy. The US Healthcare Insurance Portability and Accountability Act of 1996 and later laws focused on regulating the electronic storage, transmission, disclosure, and reporting of security breaches of identifiable health information, as well as enforcement mechanisms for health care systems that did not comply. The US Health
Information Technology for Economic and Clinical Health Act of 2009 developed a system of incentives and penalties for health care systems to implement EMR systems. The widespread implementation of EMR systems has enabled large-scale pooling of deidentified data from patients outside the context of a clinical trial. Concurrently, it has become increasingly clear that very large data sets would be required to detect and understand the complex genetic and biological mechanisms of cancer.

At the same time, a consensus emerged that the field of medicine had an ethical obligation not just to protect patients’ privacy but also to aggregate and learn from their data. This position was articulated in 2006 in a publication from the IOM entitled The Learning Healthcare System. Alarmed at the rising costs of health care, the IOM recognized an urgent need for data to optimize the effectiveness and value of medical decisions. The existing framework of randomized clinical trials and regulatory approvals was too slow and costly to provide evidence for more than a sliver of decisions made by health care providers on a daily basis. As a result, the IOM proposed using real-world evidence to fill in knowledge gaps in the fast-changing health care landscape. The IOM recognized that progress toward this goal would rely on “the emergence of linked clinical information systems that might allow information about safety and effectiveness to emerge naturally in the course of care.” A follow-up IOM conference set forth a rapid-learning systems model specifically for oncology. The 2009 conference provided a more detailed vision of an iterative process in which clinical data are systematically collected and analyzed, with the resulting insights implemented into clinical care. Changes in outcomes are then measured and form the basis for new hypotheses, analyses, and adjustments to care. Although rapid-learning systems were described with a focus on clinical data, it is not difficult to envision the incorporation of PGHD as well. The vision of a rapid-learning system relies heavily on advancements in large-scale data aggregation, harmonization, and analysis that are only now starting to be realized.

Recent large-scale data collection initiatives can be seen across government, advocacy, and academic sectors. Regarding government, in 2015, President Obama announced a new Precision Medicine Initiative, one focus of which was to create infrastructure for open data sharing. The 21st Century Cures Act in 2016 provided $1.8 billion in funding to support the Cancer Moonshot Initiative to build a national cancer data infrastructure, establish networks for patients to directly contribute tumor profile and PRO data, and analyze biospecimens from past clinical trials to predict future patient outcomes. The National Institutes of Health is also directing the All of Us research program, an ambitious cohort study of a million or more individuals of diverse backgrounds living in the United States. Participants will be followed for 10 years; data collected include patient-reported surveys, clinical data from the EMR, and biospecimens. The National Institutes of Health also maintains a wide variety of additional federal health databases of clinical, genomic, imaging, and epidemiological data from federally funded research projects. These federal initiatives are consistent with those launched by advocacy groups. One example is ASCO’s CancerLinQ, a platform for sharing and analyzing oncology data from health care information technology (IT) systems. Currently consisting of over 1 million records from 2000 oncology care providers, the goals of CancerLinQ are to improve quality of care and facilitate research. Other advocacy groups, such as the GO2 Foundation for Lung Cancer, have patient registries in which patients can share data with researchers. Indeed, patients with cancer express willingness to provide PGHD to cancer registries if data are kept confidential. Academic institutions are also undertaking large data collection efforts. An example is the Oncology Research Information Exchange Network (ORIEN), a partnership among 19 academic cancer centers to collect and aggregate deidentified molecular, clinical, and epidemiological data.

The private sector has launched parallel initiatives. For example, Flatiron Health created a computing platform to provide EMR, billing, analytics, and clinical trial screening capabilities for community oncology practices. Curated clinical data from the platform flow into a data warehouse, which can be mined to monitor quality of care, examine patterns of real-world treatment utilization, and create in silico control groups for clinical trials. Another example from the private sector is Verily’s Project Baseline Health Study, a 4-year longitudinal study of 10,000 individuals living in the United States. Data to be collected include biometric data (e.g., electrocardiogram data, electrodermal data, heart rate, sleep quality) from Google Watch; genetic information, blood samples, clinical data from annual in-person study visits with health care providers; and PROs. This project has recognized the vast analytic possibilities engendered by mobile and wearable devices. Google has also partnered with health care providers such as Ascension, an organization consisting of 2600 hospitals, physicians’ offices, and other facilities, to aggregate patients’ health histories. The goal of this initiative, called Project Nightingale, is to design new artificial intelligence (AI) algorithms to support patient care. Similar initiatives are underway at Apple, Microsoft, Amazon, and other companies. An example is the Apple Health Records application programming interface (API), which is under development as part of HealthKit, an app that aggregates and presents health information from iPhone, Apple Watch, and third-party apps. Health Records can link to the EMR or patient portal and display information on health conditions, laboratory results, immunizations, medication, procedures, and other data from participating medical providers.
Apple also allows users to share health data with researchers. More broadly, APIs allow for data from devices and wearable sensors to be uploaded to the EMR or data warehouses with the patient’s permission. Thus preliminary infrastructure resources needed for large-scale PGHD collection have been established from which additional APIs can be developed. In the meantime, most large, aggregated data sets are typically comprised of clinical and molecular data with little to no PGHD.

Data Mining, Natural Language Processing, and AI Using Big Data: A Promising Approach for Analysis of PGHD

The term AI was first coined in 1956 as “the conjecture that every aspect of learning or any other feature of intelligence can in principle be so precisely described that a machine can be made to simulate it.” Concurrently, there was recognition that algorithmic decision making might actually surpass the accuracy and reliability of human judgment, an assertion famously proposed by the psychologist Paul Meehl in 1954, which has been supported by an impressive array of data. Although AI was dismissed by the New England Journal of Medicine in 1987 because “the field of medicine is so broad and complex that it is difficult, if not impossible, to capture the relevant information in rules,” it experienced a resurgence in the early 2010s. This development was caused by the convergence of 3 major trends: 1) improvements in computing power; 2) development of new AI algorithms; and 3) increases in the number and quality of big data sets for training. The first 2 trends allowed scientists to construct and train dramatically larger and more complex deep neural networks. The size and quality of training data, meanwhile, allowed these networks to achieve high accuracy at several narrow-domain tasks. One early application was the classification of images, followed shortly by labeling and outlining (semantic segmentation) of multiple objects within images. These developments were transferred and applied by biomedical scientists to the classification of medical images and the detection of skin cancer. There has also been increasing application of machine learning to PGHD. For example, 2 recent studies have demonstrated that PGHD in the form of internet search logs of symptoms facilitate the early identification of cases of pancreatic cancer and lung cancer. Machine learning has also been applied to PROs to predict the course of multiple sclerosis and recovery after hip and knee replacement.

AI is rapidly evolving. For example, in late 2018, scientists at Google developed and published a powerful new algorithm for natural language processing: Bidirectional Encoder Representations from Transformers (BERT). BERT set new performance records across nearly all natural language processing benchmarks and, for the first time, achieved human-level performance on several of these. BERT and related technologies are being applied to unstructured biomedical and clinical texts. Translation of these new technologies into the clinical domain is still in the early stages, but progress is accelerating. In 2018, the FDA developed a fast-track approval process for AI-based medical technologies. By late 2019, the FDA had cleared 26 AI-based tools for marketing and use in the United States. Although there are no commercial AI tools to our knowledge focused on PGHD in the context of cancer, we expect such tools to appear shortly. Sufficient computing power and algorithms are widely available. These should allow scientists to identify and extract new information from PROs, wearable sensors, and EMR notes.

Challenges and Opportunities for Clinical Integration of PGHD

Although advancements in technology have the potential to revolutionize medicine through the collection and analysis of PGHD, clinical integration of PGHD has lagged behind. Challenges to clinical integration include data linkage and scaling across health care systems, provider engagement, and actionability. A significant barrier to data linkage and scaling across health care systems is the inflexibility of most EMR platforms. Although commonly used EMR systems in oncology such as Epic (Epic Systems Corporation) are starting to incorporate PRO measures, uptake of both PROs and biometric data has been limited by usability issues of the EMR platforms themselves. As the IOM noted in 2013, “Originally designed for billing and coding purposes, health IT systems have not been integrated efficiently into clinical care, do not facilitate the coordination of care, and the need to customize local systems has created a situation where health IT systems cannot communicate with each other. Many of these systems are inflexible and thus are unable to adapt to the changing needs of a modern health care system.” When collected as part of clinical care, PGHD may be buried in the clinical record, with poor visibility and interpretability. For example, Rotenstein et al reported barriers to the use of PRO data in a large radiation oncology clinic, including difficulty accessing data in the EMR (60%), difficulty bringing the data into the treatment note (48%), too much data (38%), and difficulty interpreting data (26%). Notably, these barriers also apply to remotely collected biometric data and could be addressed through better EMR integration and visualization. In recognition of such barriers to clinical integration, the National Cancer Institute’s Center for Strategic Scientific Initiatives included in its 2020 “provocative questions” the need to identify new ways to integrate PGHD into the EMR. The development of the Fast Healthcare Interoperability Resources (FHIR) data standard and APIs provides opportunities to flexibly...
create software that securely pulls discrete data from the EMR into third-party software. FHIR could be used to improve the presentation and visualization of PGHD in the form of both PROs and remotely collected biometric data, although EMR companies must enable FHIR capability. Recent trends in IT define FHIR as an approach suitable for citizen developers in which applications are developed by nonexperts with the support and approval of cooperating IT experts.221 Driving this trend is the development of low-code/no-code solutions, which enable users with little to no programming background to create and interact with the applications they need. Numerous potential benefits include rapid development, elimination of the need to wait for developers, and solutions that solve the problem at hand. There are also potential drawbacks, including security, scalability, and limited use for complex applications. These IT trends may improve the access to and impact of the collected data for patients, researchers, and physicians. Developers of such software should draw heavily from research in the fields of user-focused design and human-computer interaction to create intuitive data visualizations that focus on important clinical information and allow providers to identify patterns of data that provide important clinical insights. Although some initial research has been conducted on the visualization of PGHD,224-227 transdisciplinary collaborations, including citizen developers, graphic designers, cognitive scientists, bioinformaticians, biostatisticians, data scientists, and computer scientists, will be needed to create the frictionless user experience necessary for optimal uptake.

Despite challenges with EMR integration, the clinical collection of PROs in oncology results in high provider satisfaction.222,228-230 High rates of satisfaction have been reported despite initial provider concerns. These initial concerns commonly focus on the time required to collect and address PROs in the clinic, lack of training regarding the interpretation and management of some PROs, patient burden, and liability issues if PROs are overlooked.231-233 Thus an important aspect of the successful clinical implementation of PROs is addressing provider concerns, including appropriate provider training and clinical decision support.13,14,16,234,235 Concerns may also be ameliorated in part by communicating observed benefits of PROs reported by other providers. PROs can contribute to shared decision making and strengthen rapport between patients and providers by facilitating better communication.230 Interestingly, PROs may also reduce provider burnout by contributing to more efficient clinical workflow.230 Because providers arrive to the clinical encounter with information regarding patient concerns, they can spend more time addressing these concerns in a meaningful way rather than running through checklists of questions.230 PRO data may also be less vulnerable than traditional clinical assessments to white coat syndrome, in which patients are less likely to report symptoms during an interview than on paper.236 After clinical rollout of PROs in a radiation oncology setting, over one-half of the 53 providers surveyed reported no or only the rare impact of PROs on their ability to see patients on time, and a majority would recommend PROs to a colleague at another institution.222

Several steps can be taken to address actionability concerns as well. Perhaps most importantly, collection and use of PGHD to drive clinical decisions should be incorporated into medical boards and continuing education. Training should be extended to physicians, advanced practice professionals, nurses, and medical assistants. Training should include both management of PROs and use of PGHD to support shared decision making. For example, Thomas Jefferson University has a graduate certificate program in digital health. Organizations such as ASCO and the National Comprehensive Cancer Network provide detailed, evidence-based guidelines for the management of PROs, including nausea and vomiting, fatigue, distress, and general supportive care. Some PRO data collection apps, such as Carevive (Carevive Systems Inc), use algorithms based on these guidelines to suggest self-management strategies.237 Measure-specific algorithms for identifying severe symptoms and clinically significant worsening of symptoms have been well articulated.238,239 The necessary elements are in place to determine the actionability of PROs. Better provider education and well integrated clinical decision support remain to be addressed, however. Payer reimbursement for symptom management, particularly in the realm of telehealth and digital therapeutics, is also needed. Efforts to address these issues should include the perspectives of multiple stakeholders, including patients, families, providers, payers, EMR companies, and IT developers.240

Summary and Future Directions
The past decade has seen unprecedented progress in the war on cancer in both the therapeutic and technological domains. We now have the opportunity to integrate these accomplishments by creating new, data-driven approaches using PGHD to identify and intervene early on in clinically significant events such as toxicity and cancer progression, which, in turn, may reduce emergency room visits and hospitalizations. At the same time, technology allows closer contact with patients outside of the clinical encounter to facilitate healthy lifestyle behaviors, symptom management, and medication adherence. However, there are still many technological, analytic, and workflow challenges that need to be overcome to incorporate PGHD into routine research and cancer care.13,16,240-242 The evidence base to support the use of biometric data is sparse relative to that for PROs.
In addition, the use of PGHD must be implemented in a way that prevents exacerbation of health disparities in oncology care. Nevertheless, as with treatment discoveries, although each intervention is incremental, together, PGHD-based interventions can dramatically improve both quality and quantity of life. ■

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