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Pharmaceutical Innovation and its Implications for Nursing, Medical Records, and Diagnostics Practice

NOURA ABDULLAH ALKHARJI , NORA MOHAMMED ALDOSARY , WEJDAN AMEIN ABDULLAH, JEHAN KHELAIF ALANAZI, DOAA ALI ALYAMI, MUBARAK SAUD ALANAZI, REHAM MOHAMMAD ALSOULAIMI,NOOR FAHAD ALSHURAIM, AFAF SNITAN AL-OTAIBI, NAHID AHMAD LAMFON,JEHAD HASSAN ALSHAIKH , ABDULLAH ALHUMAIDI ALHARBI, Asma Saad Al-Qahtani, WAEL IBRAHIM AL GHANIM , JUMANA SAUD ALGHAMDI , MARIAM ADNAN ALKHADRAWI

Abstract

Background: Patient-generated health data (PGHD) refers to health-related information collected directly from patients to address health issues. In the field of cancer, PGHD is increasingly utilized to inform regulatory decisions and assess treatment quality. This data includes self-reported health and treatment records, patient-reported outcomes (PROs), and biometric sensor data. Advances in wireless technology, mobile devices, and the Internet of Things have facilitated the collection of PGHD both during clinical visits and in everyday life. Regulatory and scientific entities, including the US Food and Drug Administration and the Institute of Medicine, have recognized the importance of PGHD.

Aim of Work: The objective of this study is to provide a comprehensive summary of the clinical, regulatory, technical, and analytic aspects of PGHD in cancer research and healthcare. The study aims to evaluate the evidence supporting the use of PGHD for monitoring symptoms, with a particular focus on patient-reported outcomes (PROs).

Methods: The assessment includes a review of existing literature and frameworks surrounding PGHD. It discusses the current methods for digital phenotyping, which involves the real-time collection and analysis of biometric, behavioral, self-report, and performance data using electronic devices. Additionally, the study explores the analytical potential of PGHD within the context of big data and artificial intelligence in medicine.

Results: The findings highlight the benefits of integrating PGHD into clinical treatment, including improved symptom monitoring and enhanced patient engagement. However, challenges remain in integrating PROs and biometric data into electronic medical records, analyzing complex biometric datasets, and redesigning clinical workflows. The evidence supporting the use of biometric data is currently more limited compared to that of PROs.

Conclusion: Despite the existing difficulties, the potential advantages of PGHD suggest that it is likely to be increasingly incorporated into cancer research and clinical treatment. The study emphasizes the need for continued exploration of solutions to overcome the challenges associated with PGHD integration.

Correspondence to:

Key Words: *Patient-Generated Health Data (PGHD) – Patient-Reported Outcomes (PROs) – Digital Phenotyping Cancer Research – Big Data and Artificial Intelligence.*

Introduction

OVER the last ten years, there has been significant advancement in converting biology findings into novel cancer therapeutics, including targeted treatments, immune checkpoint inhibitors, and adaptive cellular therapies. The impact of each new therapy is gradual, but when combined with prior advancements in early identification, their cumulative effect on survival rates has been unparalleled. While patients may still suffer feelings of isolation and dread during diagnosis and treatment, it is becoming common for cancer to be managed as a chronic illness rather than a terminal disease (Fig. 1). Consequently, ensuring the preservation of the quality of life has emerged as a progressively significant objective in therapeutic practice **[1-4]**.

Patient-generated health data (PGHD) refers to health-related information collected directly from patients to address their health concerns. This data includes self-reported health and treatment histories, patient-reported outcomes (PROs), and biometric data. PROs are reports on a patient's health condition provided by the patient themselves, without interpretation by a clinician or anyone else. PROs can cover disease-related symptoms, treatment side effects, and quality of life, which assesses how symptoms and side effects affect daily functioning. While self-reported health and treatment histories and PROs are commonly used in clinical and research settings, the use of biometric PGHD

data is still in the early stages of development **[5-7]**. Biometric data encompasses both passively obtained data from wearable sensors, such as a physical activity tracker, and actively gathered data by patients using other tools, such as a wireless blood pressure cuff. The progress in wireless technology, cellphones, and the Internet of Things has made it easier to gather Patient-Generated Health Data (PGHD) both during clinic visits and in everyday activities. This article examines the potential advantages and difficulties of Patient-Generated Health Data (PGHD) in order to provide information for regulatory decisions, research, and the provision of cancer treatment.

Fig. (1): Examples of Patient-Generated Health Data, as defined by the US Department of Health and Human Services.

The Importance of Patient-Generated Health Data in Cancer Care:

The rising interest in Patient-Generated Health Data (PGHD) in the field of oncology both reflects and strengthens the growing influence of patient advocates in shaping regulatory priorities. In 2009, the FDA published a preliminary guidance document that emphasized the importance of incorporating patient perspectives in the evaluation of drug benefits and risks. This approach, known as patient-focused drug development, has primarily involved the inclusion of Patient-Reported Outcomes (PROs) as secondary measures in phase 3 clinical trials. However, the adherence to implementation guidelines for this approach has been less than ideal. Apart from one study that collected blood pressure readings from patients at home, the remote collection of biometric data has been limited **[8-10]**. However, the gathering of patient-reported outcomes (PROs) is significant due to the abundance of evidence indicating that PROs provide information that is supplementary to, although distinct from, adverse events assessed by clinicians. Despite physicians' medical training, their estimates of adverse events often underestimate patients' accounts of symptomatology. Studies have shown that clinical trials often underestimate the severity of symptoms by as much as 76% **[11-13]**.

On the other hand, patient-reported outcomes (PROs) are more effective in detecting differences in treatment-related side effects compared to assessments made by clinicians. It is important to note that patients participating in clinical trials are typically younger, healthier, and have higher socioeconomic status compared to those receiving standard care outside of clinical trials. Therefore, adverse events reported in clinical trials may not be representative of the experiences of patients receiving the same treatment in real-world settings **[14]**. On the other hand, patient-reported outcomes (PROs) allow patients to express their opinions. Without PRO data from reliable studies, patients may have to rely on anecdotal information from the internet to understand what to expect from a specific disease and treatment. However, this anecdotal information may not be accurate or applicable to everyone. PRO data become especially crucial when patients have to choose between multiple treatments that offer similar or modest benefits in terms of survival. PRO data may enhance decision making in this scenario by providing valuable information on the quality of life, including the capacity to fulfill one's obligations and duties while undergoing treatment (e.g., remaining employed), which can also provide substantial emotional and financial advantages **[15]**.

PGHD also signifies a growing recognition of the significance of proactive symptom management in providing excellent cancer treatment **[16-18]**. This approach aligns with the Institute of Medicine's (IOM) recommendation to include patients in order to enhance the quality of care. As recently as 1999, PROs were framed in terms of understanding trade-offs between quantity and quality of life **[19]**. 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 **[20-22]**. These and other studies showed that early palliative care also improved quality of life and reduced distress in both patients and caregivers **[20, 22-24]**. 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 chemother-

apy for a longer time [25, 26]. 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 [27]. Thus, it has become evident that improving quality of life can also lengthen quantity of life.

There are several opportunities available to enhance the treatment of symptoms. Cancer Care Ontario has extensively documented the symptoms experienced by oncology patients through the systematic use of the Edmonton Symptom Assessment Scale since 2007 [28]. In a study involving 120,745 patients diagnosed within a year, the most frequently reported moderate to severe symptoms were tiredness (59%), low overall well-being (55%), anxiety (44%), lack of appetite (43%), and pain (37%). Factors such as having a diagnosis of respiratory or oropharyngeal cancer, being younger, female, having a lower income, more comorbidities, and living in an urban area were associated with a higher likelihood of experiencing a significant symptom burden. These findings align with meta-analyses that have estimated the prevalence of commonly reported symptoms by patients. For example, the prevalence of pain is estimated to be 55% during anticancer treatment; 39% after curative treatment; 66% in advanced, metastatic, or terminal disease; and 50.7% in all cancer stages [29].

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 [30-32]. 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 [33, 34]. In contrast, the estimated prevalence of depression in noncancer controls assessed similarly is 10% [34]. 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. [35, 36]. 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. The prevalence of these symptoms highlights a notable lack of adequate monitoring and treatment, especially in patients undergoing active therapy and those with advanced disease.

The manifestation of symptoms is often not fully acknowledged in therapeutic practice, which might lead to its widespread occurrence. Outside of the field of oncology, it has been observed that 31% of patients who reported chest pain, 38% of those who reported difficulty breathing, and 45% of those who reported coughing on a clinical visit form did not have their symptoms documented in the electronic medical record (EMR). A comprehensive study conducted across multiple medical centers revealed that oncologists underestimated the prevalence of patients' symptoms, especially among those with a low Karnofsky performance status or a poor Mini-Mental State score, as well as those who were recently diagnosed, hospitalized, or undergoing opioid titration. Even in a palliative care inpatient unit, nurses' assessments of patients' symptoms did not align significantly with the patients' own assessments. It is worth noting that healthcare providers' perceptions of symptoms not only differ from those of patients but also from those of other providers. The study found that there was a low to moderate agreement between pairs of providers when assessing symptoms such as neuropathy, dyspnea, diarrhea, nausea, constipation, fatigue, and vomiting. This highlights the importance of effective communication and proper documentation of patient-reported outcomes (PROs) among patients, providers, and the treatment team [37-39].

PROs, or patient-reported outcomes, are linked to significant clinical events during the course of an illness [40,41]. 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 [42]. 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 (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, multiple myeloma, early-stage colorectal cancer, advanced breast cancer, metastatic castration-resistant prostate cancer, metastatic renal cell carcinoma, advanced cancers, and a variety of tumor types [48-50]. In fact, some data suggest that PROs predict survival better than provider-rated performance status [51].

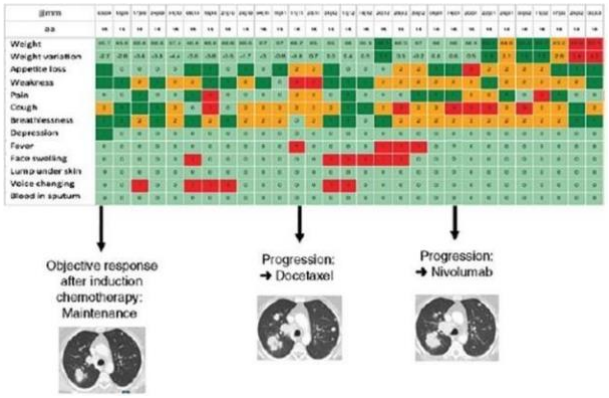

Fig. (2): A case study conducted by Denis et al that illustrates the alterations in Patient-Reported Outcomes (PROs) during the treatment and progression of Stage IV Lung Adenocarcinoma.

An Examination of the Scientific Foundation for the Clinical Monitoring of Patient-Generated Health Data (PGHD):

There is an increasing body of literature indicating that integrating Patient-Generated Health Data (PGHD) into clinical care can enhance outcomes compared to standard care. The evidence supporting the use of PGHD in clinical settings primarily comes from studies on interventions that monitor symptoms and Patient-Reported Outcomes (PROs). These interventions aim to improve communication between patients and healthcare providers regarding the 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 **[52-55]**. As noted above, these benefits are consistent with additional studies suggesting that symptom management or palliative care improves survival **[25, 26]**. 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 **[25,56]**.

Velikova et al **[63]** 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. Carlson et al. **[35]** also found a similar result, showing that the combination of distress screening with telephone triage and resource referral had the greatest impact on the percentage of lung cancer patients experiencing high distress levels, compared to screening alone. Contrarily, patients with breast cancer did not show any differences in the percentage of those reporting high distress levels. These patients initially had lower levels of distress compared to patients with lung cancer. Additionally, McLachlan et al. **[67]** found that in their randomized trial, patients who reported moderate to severe depression at the beginning experienced greater reductions in their depression scores when they received clinic-based screening for unmet needs with care coordination, as opposed to those who received conventional clinical care. Therefore, monitoring symptoms in a clinic setting may be particularly advantageous for patients with severe symptoms, especially when the obtained data are reviewed and discussed during the clinical visit. The existing body of literature aligns with various quality-of-care initiatives, such as the Quality Oncology Practice Initiative by the American Society of Clinical Oncology (ASCO) or Electronic Clinical Quality Measures by Medicare. These initiatives emphasize the importance of Electronic Medical Record (EMR) documentation of screening and management of Patient-Reported Outcomes (PROs) such as pain and distress as indicators of exceptional cancer care quality **[68,69]**.

The outcomes of randomized studies on remote symptom monitoring of patient-reported outcomes (PROs) have been inconclusive. Remote symptom monitoring interventions refer to strategies aimed at enhancing the exchange of information between patients and healthcare professionals about the symptoms experienced by patients when they are not physically present at the clinic or hospital. Remote symptom monitoring frequently employs ecological momentary assessment, which refers to the real-time reporting of patient-reported outcomes (PRO). This method is less prone to recall bias compared to retrospective questionnaires completed during clinic visits. While certain trials have shown enhancements in symptoms and quality of life, others have not. The inconsistent results may be attributed to variations in remote monitoring techniques, patient-provider communication, and the characteristics of the patient population. Remote monitoring methodology has included study-initiated calls from an automated telephone system, patient-initiated calls to an automated telephone system, study-initiated online questionnaires, patient-initiated smartphone-based or online questionnaires, study-initiated telephone calls from a nurse or nurse practitioner, study-initiated calls from a research coordinator,87 or a paper symptom diary **[70-73]**.

Digital Phenotyping: Utilizing mobile technology for the collection of Patient-Generated Health Data (PGHD):

The underutilization of the extensive aggregation of Patient-Generated Health Data (PGHD) for clinical and scientific objectives is quite unexpected, considering the many options available for data collecting. The slow adoption of these data may be attributed to difficulties in evaluating them, as explained below. However, there has been a significant increase in the number of device-based programs (apps) that may monitor many aspects of health and behavior, such as digital phenotyping. Presently, around 81% of individuals in the United States possess a smartphone, while 17% own a smartwatch. Those who own smartphones and smartwatches are typically younger and have a higher socioeconomic standing compared to those who do not own these devices. Consequently, there is apprehension that relying on Personal Generated Health Data (PGHD) from these devices could worsen health inequalities. This is a matter that needs to be acknowledged and dealt with as the collection of PGHD becomes more prevalent. However, commercially accessible devices provide a strong possibility to improve the gathering and examination of PGHD, which often have reliability and validity similar to medical-grade biometric sensors.

Data mining, natural language processing, and artificial intelligence (AI) applied to big data provide a promising approach for analyzing patient-generated health data (PGHD):

The term AI was first introduced in 1956, defining it as the belief that every aspect of learning or any other characteristic of intelligence can be precisely described in a way that a machine can imitate it. At the same time, it was acknowledged that algorithmic decision making could potentially surpass human judgment in terms of accuracy and reliability. This idea was famously proposed by psychologist Paul Meehl in 1954 and has been supported by a substantial amount of data. Despite being dismissed by the New England Journal of Medicine in 1987 due to the complexity of the medical field, AI experienced a resurgence in the early 2010s. The emergence of this phenomenon can be attributed to the convergence of three significant trends: 1) advancements in computational capabilities; 2) the creation of novel artificial intelligence algorithms; and 3) the proliferation of extensive and high-quality datasets for training purposes. These first two trends enabled scientists to construct and train deep neural networks that were significantly larger and more intricate.

The dimensions and caliber of the training data, on the other hand, enabled these networks to attain exceptional precision in several specialized jobs. An initial use case involved the categorization of images, which was soon followed by the identification and delineation (semantic segmentation) of multiple objects within images. These advancements were then adopted and utilized by biomedical researchers for the categorization of medical images and the identification of skin cancer. Additionally, there has been a growing implementation of machine learning in the analysis of patient-generated health data (PGHD). Two recent studies have shown that Patient-Generated Health Data (PGHD) in the form of internet search logs of symptoms can help identify cases of pancreatic cancer and lung cancer at an early stage **[74-76]**. Additionally, machine learning techniques have been used to analyze Patient-Reported Outcomes (PROs) and predict the progression of multiple sclerosis (as well as the recovery process after hip and knee replacement surgeries.

Artificial intelligence is undergoing fast evolution. In late 2018, Google scientists created and released a highly effective algorithm called Bidirectional Encoder Representations from Transformers (BERT) for natural language processing. BERT surpassed previous performance records in almost all natural language processing tests and, for the first time, achieved a level of performance comparable to that of humans in several of these tests. BERT and similar technologies are now being used to analyze unstructured biomedical and clinical texts. The use of these new technologies in the clinical field is still in its early phases, but advancements are being made at an increasing pace. In 2018, the FDA established an expedited approval process for medical technologies that utilize artificial intelligence. By the end of 2019, the FDA had authorized the use of 26 AI-based tools for marketing and implementation in the United States. While there are currently no known commercially available AI tools specifically designed for collecting and analyzing patient-generated health data (PGHD) in the context of cancer, we anticipate the emergence of such tools in the near future. Ample computational capacity and methods are readily accessible. These tools will enable scientists to find and extract novel information from patient-reported outcomes (PROs), wearable sensors, and electronic medical record (EMR) notes **[77]**.

Summary and Prospects for the Future:

In the last ten years, there has been remarkable advancement in the battle against cancer, particularly in the areas of treatment and technology. Currently, we may combine these achievements

by developing novel, data-centric methods using patient-generated health data (PGHD) to detect and address critical events like toxicity and cancer advancement at an early stage. This, in turn, has the potential to decrease the number of emergency department visits and hospital admissions. Simultaneously, technology enables enhanced communication with patients outside the clinical setting to support the adoption of good lifestyle habits, effective symptom control, and consistent drug use. Nevertheless, there are several technical, analytic, and procedural obstacles that must be surmounted in order to integrate patient-generated health data (PGHD) into regular research and cancer care **[13, 16].** The available evidence supporting the use of biometric data is limited compared to that for patient-reported outcomes (PROs). Furthermore, the use of Patient-Generated Health Data (PGHD) should be executed in a manner that effectively mitigates the worsening of health inequalities in the provision of cancer treatment. However, similar to the way treatment advancements work, PGHD-based interventions, while each one is small, may collectively have a significant impact on improving both the quality and duration of life.

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الابتكار الصيدلاني وتداعياته على ممارسات التمريض والسجلات الطبية والتشخيص

الخلفية: تشير بيانات الصحة التي ينتجها المرضى (PGHD) إلى المعلومات المتعلقة بالصحة التي يتم جمعها مباشرة من المرضى لمعالجة القضايا الصحية. في مجال السرطان، يتم استخدام PGHD بشكل متزايد لإبلاغ القرارات التنظيمية وتقييم جودة العلاج. تشمل هذه البيانات سجلات الصحة والعلاج التي يبلّغ عنها المرضى، ونتائج المرضى المبلّغ عنها (PROs)، وبيانات المستشعرات الحيوية. لقد ساعدت التطورات في التكنولوجيا اللاسلكية، والأجهزة المحمولة، وإنترنت الأشياء في تسهيل جمع PGHD خلال الزيارات السريرية وفي الحياة اليومية. وقد اعترفت الوكالات التنظيمية والعلمية، بما في ذلك إدارة الغذاء والدواء الأمريكية ومعهد الطب، بأهمية PGHD.

الهدف: الهدف من هذه الدراسة هو تقديم ملخص شامل للجوانب السريرية والتنظيمية والتقنية والتحليلية المتعلقة بـ PGHD في أبحاث السرطان والرعاية الصحية. تهدف الدراسة إلى تقييم الأدلة التي تدعم استخدام PGHD لمراقبة الأعراض، مع تركيز خاص على نتائج المرضى المبلّغ عنها (PROs).