PRECISION ONCOLOGY WITH ELECTRONIC MEDICAL RECORDS

Losiana Nayak, *Rajat K. De

Machine Intelligence Unit, Indian Statistical Institute, Kolkata, India
**Correspondence to rajat@isical.ac.in*

Disclosure: The authors have declared no conflicts of interest.
Acknowledgements: Losiana Nayak acknowledges University Grants Commission, New Delhi, India, for a UGC Post-Doctoral Fellowship (No. F.15-1/2013-14/PDFWM-2013-14-GE-ORI-19068[SA-II]).
Received: 01.09.17 **Accepted:** 12.12.17
Citation: EMJ Innov. 2018;2[1]:64-72.

ABSTRACT

Electronic medical record (EMR)-based precision oncology is a vision that is so far limited to a few pilot and basket studies, with the goal being the design of a proper treatment for cancer patients in real time, based on the panomics knowledge of the patient, and that of similar types of patients. It aims to deliver better treatment outcomes through the design of rational drug combinations, a lower number of futile therapies, reduced patient discomfort, and a healthy human society with a reduced risk of cancer. The concept of precision oncology began with a few cancer awareness programmes and preventative screenings almost a decade ago. However, the technique took an astronomical leap with the start of the Precision Medicine Initiative Cohort Program and Cancer Moonshot programme very recently. Both projects have invested heavily towards several goals, including the merging of cancer registries and EMR to find the best treatment options for a cancer patient, an idea which, if extended globally, will generate unprecedented possibilities for precision oncology. EMR serve as a broad platform merging a variety of patient information and expert advice to facilitate co-ordinated cancer care. In this article, a summary of the recent EMR-based precision oncology practices for prevention, diagnosis, prognosis, prediction, and their associated concerns and limitations is presented. Though the path of precision oncology is unchartered, the usefulness of real-time information derived from EMR or electronic health records will lead to better precision decision-based oncotherapies.

Keywords: Electronic health records (EHR), electronic medical record (EMR), individualised medicine, panomics, precision cancer medicine, precision decision, stratified medicine.

INTRODUCTION

Cancer is a universal phenomenon, yet each cancer type differs from the other variants. In addition, individual human beings differ from one another by a genome difference of approximately 1%. This tiny difference in the genome sequence, in turn, causes a huge discordance in cancer treatment and drug resistance. The dimensionality of cancer networks is much higher compared to other disease systems; cancer is a genomic disease, harbouring a number of mutated oncogenes and tumour suppressor genes that specify the molecular pathways for tumour growth, sustenance, and progression. The network function depends on the individual patient, external factors, and the ability of the network to overcome treatment mechanisms. The treatment of cancer requires a combined effort among a varied team of experts, including counsellors, medical doctors, caregivers, pathologists, radiologists, surgeons, and others. Irrespective of best efforts, a complex disease like cancer is often unmanageable due to the involvement of genetic, lifestyle, and environmental factors. However, with the use of precision medicine, the situation is improving, albeit slowly. Even though a definitive cure for cancer has not been found, the life expectancy of certain cancer patients has certainly increased.

Predictive, preventative, personalised, and participatory (known as P4) treatment of each individual patient, often coupled with population perspective,[1-3] is one of the definitions of precision

medicine,[4] also known as stratified medicine;[5] it tries to impart proper treatment to a patient in real time.[6,7] Identification, risk assessment, and targeted therapy for cancer patients by considering resources like the genomic sequence, the prevalence of rare mutations, and proteomic profile, among others, is known as precision cancer medicine or precision oncology.[8]

In simpler words, precision oncology can be defined as diagnosis, prognosis, prevention, treatment, and follow-up that are tailored specifically to an individual patient based on their genetic profile and supported by the genetic profiles of similar types of patients;[9,10] it is an emerging approach for disease treatment and prevention that takes into account the genetic variability, environment, and lifestyle-related habits of each person.[11]

DISCUSSION

Precision oncology is applicable to various aspects of human health, for example, identification of presymptomatic individuals, detection of disease, patient-specific therapy, the study of disease evolution, the design of effective surveillance, and management techniques, among others; altogether, it focusses on providing a uniform platform for human health management.[8] Traditional evidence-based medical practice along with precision medicine will pave the way for the achievement of such ambitious goals.

The idea of precision oncology gained momentum after a few 'fit for all' solutions, i.e., molecularly driven therapies that have been devised for certain types of cancers. At present, imatinib has dramatically improved the survival of chronic myeloid leukaemia patients[12,13] and HER2-targeted therapies have improved survival rates of women with metastatic HER2-positive breast cancer.[14,15] More detailed applications of precision oncology have been reported by Hyman et al.[16] Precision oncology aims to reduce morbidity and mortality, along with improving clinical outcomes of cancer patients, as each patient and cancer type is unique, and so must be the precision decision for each treatment.

Catalogue maintenance and curation of cancer sequence variants are crucial for precision oncology and have immense clinical relevance.[17] Profiling the somatic mutations of genes may predict tumour evolution, prognostics, and treatment. In this context, Tsang et al.[18] reviewed various functional annotation resources and tools to interpret variants in precision genomic oncology. OncoPaD,[19] a web-based tool, has been developed for the rational design of cancer next-generation sequencing (NGS) panels based on mutational data.[20] Based on 7,298 cancer cases from 29 cancer types, it estimates the cost-effectiveness of the designed panel on a cohort of tumours and provides reports on the importance of individual mutations for oncogenesis and therapy. The tool helps in addressing many translational and basic research questions, including those regarding precision oncology. The advent of this NGS technique has a crucial role in precision cancer therapy, a subject that cannot be covered in the present article's scope, but is well described elsewhere.[21]

However, the idea of large-scale precision oncology is burdened by many hurdles, for example, acquired resistance of tumours, cost-benefit analysis, clinical evaluation, clinical trial design, drug resistance, genetic and genomic analyses of tumours of patients, informatics methods to evaluate genetic variants, liquid biopsy data-related issues, target prioritisation, molecularly targeted drug effectiveness, and tumour heterogeneity, among others.[22,23] Improvement is needed in the areas of genome sequencing of cancer patients, identification of targets, better access to clinical studies, and design of therapies. In addition, involvement of appropriate parties and stakeholders at every step is crucial for progress in precision oncology, starting from the patient, clinician, physician, caregiver, and third-party insurance providers. These issues should be properly addressed before precision oncology becomes a universal phenomenon for cancer treatment.

In this context, electronic medical records (EMR), the digital version of patient health records, play a crucial role in providing a means by which a patient's previous health history or health history of patients with similar cancer types can be studied and used for real-time treatment. EMR serve as a broad platform that merges a variety of patient information and expert advice to facilitate co-ordinated cancer care.[24] They aid in personalised cancer risk management and treatment by taking into account the behavioural and social contexts.[5] An EMR-adapted healthcare system efficiently streamlines day-to-day hospital procedures, along with internal quality control checks, and facilitates easy access to patient data from anywhere around

the globe following proper authentication from a user. EMR are changing the current practice of medicine, as expected almost a decade ago.[11,25,26]

Interestingly, the basket studies into the use of patient EMR for precision oncology[12-15,21-23,26-35] have provided meaningful observations for better clinical outcomes. New knowledge developed from the large range of EMR data, with help from predictive models, has generated confidence for precision oncology-based decisions. Precision oncology is a nascent area of therapy but, gradually, with help from information technology and more EMR data, it will take shape from the variety of heterogeneous cancer-related patient data. Precision medicine alongside patient EMR will aid prevention, diagnosis, prognosis, and prediction of cancer types, often one form of assistance combined with others, for the improvement of cancer treatment. Here, we discuss the research developments, or rather the lack of them, in these specified areas.

Preventive Approach

There is currently little scope for adding any cancer prevention measures to a patient's EMR, as hardly any such measures exist. Mostly, the preventive measures are limited to small cohort screenings[22] but, as a Pre-Cancer Genome Atlas (PCGA)[36] is being developed, it will be important to add information on preventative measures into EMR to help in individualised cancer care. For example, programmes like the Million Veterans Program[37] and the Precision Medicine Initiative Cohort Program[38] are adding EMR data into their repositories as part of their quest for cancer prevention. Similarly, there are many existing cancer data and knowledge-bases (Table 1) that will be necessary to include for the development of preventative, diagnostic, and prognostic approaches for cancer.

Cancer Diagnosis

To date, the conventional method for cancer diagnosis is mostly based on histopathological reports and radiographic findings. However, the essential role of genomics in the form of biomarkers, molecular signatures, and the molecular profiling reports to detect cancer types cannot be negated. This information is now being stored in the EMR of cancer patients and, in the future, can be used for fast cancer categorisation. Precision cancer diagnostics extend beyond the conventional methods of gene expression profiling and EMR-based decisions. In this respect, we herein discuss some innovations that generate standardised onco-data for inclusion in EMR or electronic health records (EHR).

Pyradiomics[39] is a Python programming language-based open-source radiomic quantification platform to extract radiomic features from computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) images. It establishes a reference standard for radiomic analyses with immense significance that will reflect in cancer diagnosis.[40] The Health Level Seven® (HL7) Clinical Genomics group[41] is working towards the standardisation of genome data and harmonisation with EMR. LesionTracker[42] is a web-based open-source image assessment and tracking platform for oncology clinical trial workflows. Tumor Map[43] is an integrated portal for exploration and interrogation of cancer genomics data by using Google's map technology. It can also facilitate identification of cancer subtypes in silico based on common molecular activities in a set of tumour samples.[44] The inclusion of such data with EMR or EHR will be beneficial for further analyses at a later stage for diagnostic purposes.

Prognostic Approach

Nowadays, a few rapid learning health systems[45-48] are in practice for sourcing prognostic and associative factors from text-based cancer EMR. Text-based Exploratory Pattern Analyser for Prognosticator and Associator discovery (TEPAPA)[45] is a feature learning pipeline for identifying disease-associated factors from unstructured EMR narratives. It has already been applied to a cohort of 82 head and neck squamous cell carcinoma patients' EMR for phenotyping. CancerLinQ™,[46] a cancer decision support system, uses more than a million EMR for any kind of precision decision; it stores data from any format including EMR, provides real-time clinical decision support, measures clinical performance, and generates hypotheses from clinical data to provide lessons learned about technical and logistical challenges. Cancer Commons[49] is a non-profit network of patients, physicians, and scientists who help in identifying the best options for treating an individual's cancer. It facilitates rapid learning for precision oncology by gathering panomic and clinical data about individual patients from the Donate Your Data (DYD) registry.

Furthermore, the Melanoma Rapid Learning Utility (MRLU)[47] is an analytical engine and user interface that provides clinical decision support for

melanoma treatment by identifying and analysing cohorts from a database of 237 metastatic melanoma patients. Precision Oncology 3.0[48] advocates the analysis of panomic data to hypothesise the patient-specific cancer molecular pathways and their personalised treatments by combining the targeted therapies, and Watson,[50] an IBM developed machine learning system, recommends trials and individualised therapies based on cancer patient data obtained from various sources, including EMR. The Electronic Medical Records and Genomics (eMERGE) Network[51] is also helping to develop the EMR-guided cancer genomic studies and associated decisions.

In addition, cancer-associated research often reflects important information for the oncology community based on EMR data, a few of which are discussed. Gregg et al.[27] performed a study of 2,352 prostate cancer patients' EMR to automate the determination of risk strata according to the D'Amico Risk Classification, in which prostate cancer patients can be labelled as low, intermediate, or high-risk. The natural language processing (NLP) algorithms developed by Gregg et al.[27] had 91% raw agreement with manual risk categorisation, with a recall of 78% (N=1,833). With proper standardisation, such automating procedures for collecting risk characteristics will reduce the time and effort taken, while integrating the information into the respective EHR or disease registries.

Symmans et al.[28] have assessed the long-term prognostic risk of breast cancer patients by analysing 1,158 patients' EMR belonging to five cohorts after neoadjuvant chemotherapy alone or in conjunction with HER-2-targeted treatment. Patient-specific age, classification of primary cancer (whether multifocal or multicentric), clinical and radiologic characteristics of primary cancer, clinical stage of cancer before treatment, diabetic status (present or absent), follow-up for relapse or death, height, and weight data have been considered from the respective EMR for the prognostic study. The study indicates long-term survival after neoadjuvant chemotherapy in all the considered phenotypic subsets of breast cancer, albeit with a need for further external validation.

Heo et al.[30] performed a study of 44 advanced biliary tract cancer patients' EMR to investigate the significance of the clinical impact of overexpression of the proto-oncogene *c-MET*. Various patient-specific details have been taken from EMR and expression of the c-MET protein has been generated from tumour samples of metastatic patients for this study. In approximately one-third of the patient population, overexpression of c-MET was found, but it cannot be significantly correlated with the other associated variables, generating a need for further studies.

A research study of 99 smokers' EHR performed by Begnaud et al.[22] reflected a randomised electronic promotion of lung cancer screening and Afghahi et al.[47] found the differential use of chemotherapy associated with sociodemographic characteristics by a study of EMR, cancer registry, and genomic data belonging to 293 breast cancer patients. In addition, Rioth et al.[52] created an automated, real-time database of annotated tumour variants of cancer patients to gather data generated during cancer care for secondary use during the precision decision. Schwaederle et al.[33] generated a study using NGS of 439 diverse cancer patients where they integrated the NGS data with age, cancer histology, sex, stage of metastasis at diagnosis (if any), metastatic disease at the time of the biopsy (if any), and race extracted from electronic medical charts, among others, to find actionable aberrations in patients. Lastly, Servant et al.[53] developed a knowledge data interface that facilitates data integration and tracks the processing of individual samples for precision decision in real-time.

As EMR and/or EHR are being considered as a global data source for cancer prognosis, their completeness in accumulating all kinds of patient-related data is necessary. At present, there are many cancer resources (Table 1) and their inclusion or association with the EMR will ensure a more detailed cancer prognosis.

Predicting Cancer Risk

EMR, the data flat files for cancer patients, can be subjected to standard statistical analysis techniques.[22,28,30,47] Symmans et al.[28] used the Kaplan–Meier estimator with 95% confidence intervals estimated using the Greenwood formula with log-log transformation for determination of survival probability. In addition, Heo et al.[30] used the t-test, Fisher's exact test, or one-way analysis of variance, as appropriate, to analyse correlations between expression of the proto-oncogene *c-MET* and the associated clinicopathologic variables. They used the Kaplan–Meier estimator for the analysis of all time-to-event variables.[30]

Table 1: Examples of existing cancer data and knowledge-bases.

Name	URL	Remarks
Cancer Genome Interpreter	https://www.cancergenomeinterpreter.org/home Last accessed: 14 December 2017.	Relies on existing knowledge for the identification of alterations in a cancer and detection of therapeutically actionable alterations.
Cancer Moonshot	www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative Last accessed: 14 December 2017.	The government of the USA has plans for authorising $1.8 billion in funding for the Cancer Moonshot programme over 7 years, starting from 2017. The project is aimed at vaccine development for cancer types.
Cancer Driver Log (CanDL)	https://candl.osu.edu/ Last accessed: 14 December 2017.	An expert-curated database that lists all possible nucleotide positions for each amino acid change along with their associated literature reference and the chromosome locations.
cBIOPortal	http://www.cbioportal.org/ Last accessed: 14 December 2017.	Large-scale cancer genomics data sets can be visualised, analysed, and downloaded from this source.
Clinical Interpretations of Variations in Cancer (CIViC)	https://civic.genome.wustl.edu/ Last accessed: 14 December 2017.	A cost-free source for variant information and cancer-related mutations.
ClinVar	https://www.ncbi.nlm.nih.gov/clinvar/ Last accessed: 14 December 2017.	Human variations and their associated phenotypes are listed in this database.
Genomics Evidence Neoplasia Information Exchange (GENIE)	http://www.aacr.org/Research/Research/Pages/aacr-project-genie.aspx#.WZWgm1EjHIV Last accessed: 14 December 2017.	This project aggregates and links clinical-grade cancer genomic data with clinical outcomes from tens of thousands of cancer patients treated at multiple international institutions.
Georgetown Database of Cancer (G-DOC)	https://gdoc.georgetown.edu/gdoc/ Last accessed: 14 December 2017.	A precision medicine platform containing molecular and clinical data from thousands of patients and cell lines, along with tools for analysis and data visualisation.
International Cancer Genome Consortium (ICGC)	http://icgc.org/ Last accessed: 14 December 2017.	With 89 committed projects, the goal of the ICGC is to obtain a comprehensive description of genomic, transcriptomic, and epigenomic changes for different tumour types, which has great importance across the globe.
My Cancer Genome	https://www.mycancergenome.org/ Last accessed: 14 December 2017.	A tool that matches tumour mutations to therapies, making information accessible and convenient for clinicians.
National Cancer Institute (NCI)'s Molecular Analysis for Therapy Choice (MATCH)	https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match Last accessed: 14 December 2017.	A precision medicine cancer treatment clinical trial for cancer patients with tumours with specific genetic changes.
OncoKB	http://oncokb.org/#/ Last accessed: 14 December 2017.	A precision oncology knowledge base listing 476 genes, 3,701 variants, 65 tumour types, and 97 drugs.
Personalised cancer therapy	https://pct.mdanderson.org/ Last accessed: 14 December 2017.	An integrated research and clinical trials strategy for implementing personalised cancer therapy and improving patient outcomes.
The Cancer Genome Atlas (TCGA)	https://cancergenome.nih.gov/ Last accessed: 14 December 2017.	Maps of the key genomic changes in 33 types of cancer have been generated and stored in this database.
TCGA Pan-Cancer Compendium	http://bioinformatics.mdanderson.org/TCGA/NGCHMPortal/ Last accessed: 14 December 2017.	Stores next-generation clustered heat maps (NG-CHM) covering multiple tumour and data types profiled by TCGA.
Cistrome Cancer	http://cistrome.org/CistromeCancer/CancerTarget/ Last accessed: 14 December 2017.	Predicted transcription factor targets and enhancer profiles in cancers have been collated from TCGA expression and public ChIP-seq profiles and stored in this resource.

Statistical analysis by Begnaud et al.[22] included the Wilcoxon rank sum test for quantitative characteristics and Fisher's exact test for categorical items, and the multivariable logistic regression technique was used by Afghahi et al.[47]

EMR data can also be subjected to advanced machine learning techniques for better retrieval of insightful information.[27,52] Gregg et al.[27] used natural language processing to achieve >90% accuracy for low, intermediate, and high-risk stratification of localised prostate cancer patients. A naïve Bayes classifier was used by Rioth et al.[52] to categorise cancer patient care data into 18 separate clinical groups with 99.37% accuracy, and Schwaederle et al.[33] used linear or binary logistic regression analyses and Spearman's rho coefficients. However, application of these statistical and machine learning techniques in one or more cancer resources (Table 1) is yet to be attempted.

Limitations

Precision oncology has many limitations at the preventive, diagnostic, prognostic, and predictive stages.[54] Molecular profiling of tumours is not yet used for all types of cancer and many of the molecular alterations observed in patients do not respond to drugs; therefore, more research is required regarding the complete characterisation of viable target biomolecules. Diversity also exists among the types of clinical molecular tests and opinions vary among clinical oncologists regarding the interpretation of genomic test results. These inconsistencies will be reflected in the EHR and will diminish confidence in precision oncology-associated therapies.

Most often, DNA-based alterations, such as mutations and gene duplications, among others, are found to be responsible for the development of a typical subtype of cancer in a patient. A large proportion of EMR lack DNA alteration data of cancer patients, since third-party payers rarely reimburse for mutational analysis, and so forms a major bottleneck for progress in precision oncology. Even when the mutations are available, a great diversity arises when EMR for all patients of a population are referred to as a background study. How to overcome such diversity and reach a consensus for treating a real-time patient is a dilemma for many oncologists.[55]

Furthermore, EMR are often erroneous or have incomplete data. Knowledge derived from such error-prone or partial data either misleads the oncologists or prevents the achievement of a consensual opinion regarding cancer treatment in general. Even if the EMR are correct, various protocols and sometimes unbalanced treatments across the globe contribute a lot of variation, and a small sample size and heterogeneous patient population may create more confusion. Automated data collection from EMR cannot guarantee the precision level of manual data extraction by experts and the allowable level of precision in automated data collection is a big debate. However, >90% precision is generally considered high. Overfitting of data must be avoided while aiming for higher levels of precision.[27]

An EMR is a single record of disease instance and, for better cancer care, a properly monitored EHR should be established for a patient. An EHR is an accumulation of multiple EMR over a time period listing the relapse of cancer and retreatment, where applicable; it should list the patient history, family histories, detailed social histories, the testing and imaging results, treatment details, and genomic information to be considered as an ideal cancer EHR.[24] However, there is no universal guideline for criteria of an EHR, except a definition of minimum requirement from the World Health Organization (WHO)[56] for structuring EMR or EHR.

Moreover, searching for a common factor across related EHR may be a daunting and large task due to a lack of interconnections, mutual compatibility, and interoperability.[5] If similar types of EHR cannot be analysed in real time, finding a common clue for a disease will prove difficult. To date, no uniform approach to address all the above-mentioned issues is in place. Altogether, the lack of completeness, consistency, homogeneity, and accuracy of cancer EMR or EHR will reflect in precision oncology-based decisions. Hence, a robust universal format and clear regulations should exist for patient EMR to avoid these caveats and to ensure reliability and efficiency.[57,58]

In developed countries, maintenance of the EHR is a must for the free centralised government healthcare; a report regarding this has been penned by Ben-Assuli.[59] However, in developing and under-developed countries, the maintenance of EHR is performed by third parties, particularly for insurance purposes of the wealthier population who can afford private healthcare facilities. It is often pursued in a very incomplete and sporadic manner. As precision oncotherapies are heavily dependent on population or cohort-based details, EHR data

of developed countries may not help for precision oncology-based treatments in other geographic populations. A lack of proper EHR data will delay and hamper the scope of precision oncology in these countries.

EMR-based precision oncology has provided a large amount of introspection and garnered a lot of focus; however, whether it has generated enough confidence for the decisions to be adopted for clinical and therapeutic purposes is doubtful. A selection of scientists and researchers have already expressed their concerns regarding the performance of precision oncology[60,61] and there are doubts regarding clinical usefulness of targeted therapies derived from EMR.[62] According to these professionals, current precision oncology practices are too simple an approach for a complex disease like cancer. However, there is also another cohort of professionals who strongly believe in it due to a few clinically useful, although unexpected, advances.[63,64] Often, the same researchers are found to sway between feeling hope, optimism, and/or concern regarding precision oncology. Whether the concept of precision oncology will be the next groundbreaking landmark innovation of science, or result in a pseudo-innovation, is not clear.[65-67] However, the authors' opinions favour pragmatic optimism with the advent of the new cloud-based software platforms,[68,69] novel ways for phenotypic representation[70] and stratification,[71] multiomics data analytics platforms,[72] and big data infrastructures[73] for advancement of precision oncology.

CONCLUSION

In this paper, the authors have introduced the emerging area of electronic record (EMR/EHR)-based advances for the improvement of cancer treatment. Moreover, this paper has summarised a few of the recent EMR-based precision oncology practices for prevention, diagnosis, prognosis, prediction, and their associated concerns and limitations.

A cancer patient experiences many emotional and physical hurdles, starting from the initial confirmation and acceptance of their diagnosis. The associated stress, stigma, and sickness looms like a black cloud over the patient. Irrespective of any kind of curative or palliative care, a cancer patient's life expectancy certainly decreases following diagnosis; some patients have a few days of life or a few years, while others live longer, but always with a fear of tumour recurrence. In these scenarios, even a few scientific details derived from EMR and some unexpected advances that aid in oncotherapy become a baton of hope and belief.

The idea of EMR data-derived precision oncology is novel and the path for achieving this idea is unchartered, while the limitations are many. With the increase of lifestyle addictions and disorders coupled with the genetic and environmental factors, cancer is becoming the second leading cause of global death,[74] with 75% of deaths occurring in low and middle-income countries. However, the unbeatable human desire for cancer-free, longer, and healthier lifespans also exists and EMR/EHR will lead the way towards this through precision oncology-based therapies.

REFERENCES

1. Khoury MJ et al. A population approach to precision medicine. Am J Prev Med. 2012;42(6):639-45.
2. Austin ED et al. Translational advances in the field of pulmonary hypertension molecular medicine of pulmonary arterial hypertension. From population genetics to precision medicine and gene editing. Am J Respir Crit Care Med. 2017; 195(1):23-31.
3. Filipski KK et al. Pharmacogenomics in oncology care. Front Genet. 2014;5:73.
4. Nayak L et al. Precision medicine with electronic medical records: From the patients and for the patients. Ann Transl Med. 2016;4(Suppl 1):S61.
5. Beckmann JS, Lew D. Reconciling evidence-based medicine and precision medicine in the era of big data: Challenges and opportunities. Genome Med. 2016;8(1):134.
6. Colijn C et al. Toward precision healthcare: Context and mathematical challenges. Front Physiol. 2017;8:136.
7. Frey LJ et al. Precision medicine informatics. J Am Med Inform Assoc. 2016;23(4):668-70.
8. Bertier G et al. Integrating precision cancer medicine into healthcare-policy, practice, and research challenges. Genome Med. 2016;8(1):108.
9. Bode A, Dong Z. Precision oncology - The future of personalized cancer medicine? npj Precision Oncology. 2017;1:2.
10. Huang B at al. The path from big data to precision medicine. Expert Review of Precision Medicine and Drug Development. 2016;1(2):129-43.
11. Mody RJ et al. Precision medicine in pediatric oncology: Lessons learned and next steps. Pediatr Blood Cancer. 2017;64(3).
12. Druker BJ et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med. 2006;355(23):2408-17.
13. Bower H et al. Life expectancy of

patients with chronic myeloid leukemia approaches the life expectancy of the general population. J Clin Oncol. 2016; 34(24):2851-7.

14. Slamon DJ et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783-92.

15. Swain SM et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372(8):724-34.

16. Hyman DM et al. Implementing genome-driven oncology. Cell. 2017; 168(4):584-99.

17. Ritter DI et al. Somatic cancer variant curation and harmonization through consensus minimum variant level data. Genome Med. 2016;8(1):117.

18. Tsang H et al. Resources for interpreting variants in precision genomic oncology applications. Front Oncol. 2017;7:214.

19. OncoPaD: Web-tool for the rational design of cancer NGS panels based on mutational data. 2016. Available at: http://bbglab.irbbarcelona.org/oncopad/index_p. Last accessed: 13 December 2017.

20. Rubio-Perez C. Rational design of cancer gene panels with OncoPaD. Genome Med. 2016;8(1):98.

21. Xue Y, Wilcox WR. Changing paradigm of cancer therapy: Precision medicine by next-generation sequencing. Cancer Biol Med. 2016;13(1):12-8.

22. Begnaud A et al. Randomized electronic promotion of lung cancer screening: A pilot. JCO Clin Cancer Inform. 2017;1:1-6.

23. Andre F et al. Prioritizing targets for precision cancer medicine. Ann Oncol. 2014;25(12):2295-303.

24. Warner JL. Integrating cancer genomic data into electronic health records. Genome Med. 2016;8(1):113.

25. Electronic medical records: Possibilities and uncertainties abound. J Oncol Pract. 2006;2(2):75-6.

26. Schram A et al. Precision oncology: Charting a path forward to broader deployment of genomic profiling. PLoS Med. 2017;14(2):e1002242.

27. Gregg JR et al. Automating the determination of prostate cancer risk strata From electronic medical records. JCO Clin Cancer Inform. 2017;1:1-8.

28. Symmans WF et al. Long-term prognostic risk after neoadjuvant chemotherapy associated with residual cancer burden and breast cancer subtype. J Clin Oncol. 2017;35(10):1049-60.

29. Kalloger SE et al. A predictive analysis of the SP120 and 10D7G2 antibodies for human equilibrative nucleoside transporter 1 (hENT1) in pancreatic ductal adenocarcinoma treated with adjuvant gemcitabine. J Pathol Clin Res. 2017;3(3):179-90.

30. Heo MH et al. The clinical impact of c-MET over-expression in advanced biliary tract cancer (BTC). J Cancer. 2017; 8(8):1395-9.

31. Stockley TL et al. Molecular profiling of advanced solid tumors and patient outcomes with genotype-matched clinical trials: The Princess Margaret IMPACT/COMPACT trial. Genome Med. 2016;8(1):109.

32. Conley BA, Doroshow JH. Molecular analysis for therapy choice: NCI MATCH. Semin Oncol. 2014;41(3):297-9.

33. Schwaederle M et al. On the road to precision cancer medicine: Analysis of genomic biomarker actionability in 439 patients. Mol Cancer Ther. 2015;14(6):1488-94.

34. Finlayson SG et al. Toward rapid learning in cancer treatment selection: An analytical engine for practice-based clinical data. J Biomed Inform. 2016; 60:104-13.

35. Ford JM. Precision oncology: A new forum for an emerging field. Precision Oncology. 2017;1:1-2.

36. Kensler TW et al. Transforming cancer prevention through precision medicine and immune-oncology. Cancer Prev Res (Phila). 2016;9(1):2-10.

37. Gaziano M et al. Million Veteran Program: A mega-biobank to study genetic influences on health and disease. J Clin Epidemiol. 2016;70:214-23.

38. Hudson K et al. The precision medicine initiative cohort program - Building a research foundation for 21st century medicine. Precision Medicine Initiative (PMI) Working Group report to the Advisory Committee to the Director. 2015. Available at: https://acd.od.nih.gov/documents/presentations/09172015-PMI.pdf. Last accessed: 13 December 2017.

39. Pyradiomics. Welcome to pyradiomics documentation! 2016. Available at: http://pyradiomics.readthedocs.io/en/latest/. Last accessed: 13 December 2017.

40. Van Griethuysen JJM et al. Computational radiomics system to decode the radiographic phenotype. Cancer Res. 2017;77(21):e104-7.

41. Health Level Seven® International. Clinical Genomics. 2009. Available at: http://www.hl7.org/Special/committees/clingenomics/overview.cfm. Last accessed: 13 December 2017.

42. Urban T et al. LesionTracker: Extensible open-source zero-footprint web viewer for cancer imaging research and clinical trials. Cancer Res. 2017;77(21): e119-22.

43. University of California Santa Cruz, Genomics Institute. Tumor Map. 2017. Available at: https://tumormap.ucsc.edu/. Last accessed: 13 December 2017.

44. Newton Y et al. TumorMap: Exploring the molecular similarities of cancer samples in an interactive portal. Cancer Res. 2017;77(21):e111-4.

45. Lin FPY et al. TEPAPA: A novel in silico feature learning pipeline for mining prognostic and associative factors from text-based electronic medical records. Sci Rep. 2017;7(1):6918.

46. Sledge GW et al. ASCO's approach to a learning health care system in oncology. J Oncol Pract. 2013;9(3):145-8.

47. Afghahi A et al. Use of gene expression profiling and chemotherapy in early-stage breast cancer: A study of linked electronic medical records, cancer registry data, and genomic data across two health care systems. J Oncol Pract. 2016;12(6):e697-709.

48. Shrager J, Tenenbaum JM. Rapid learning for precision oncology. Nat Rev Clin Oncol. 2014;11(2):109-18.

49. Cancer Commons. Changing the way the world treats cancer, starting with you. 2017. Available at: https://www.cancercommons.org/. Last accessed: 13 December 2017.

50. Malin JL. Envisioning Watson as a rapid-learning system for oncology. J Oncol Pract. 2013;9(3):155-7.

51. Gottesman et al.; The eMERGE Network. The Electronic Medical Records and Genomics (eMERGE) Network: Past, present, and future. Genet Med. 2013;15(10):761-71.

52. Rioth MJ et al. Pragmatic precision oncology: The secondary uses of clinical tumor molecular profiling. J Am Med Inform Assoc. 2016;23(4):773-6.

53. Servant N et al. Bioinformatics for precision medicine in oncology: Principles and application to the SHIVA clinical trial. Front Genet. 2014;5:152.

54. Berger MF, van Allen EM. Delivering on the promise of precision cancer medicine. Genome Med. 2016;8(1):110.

55. Fiore LD et al. Data sharing, clinical trials, and biomarkers in precision oncology: Challenges, opportunities, and programs at the department of veterans affairs. Clin Pharmacol Ther. 2017;101(5):586-9.

56. World Health Organization. Medical Records Manual: A Guide for Developing Countries. 2006. Available at: http://www.wpro.who.int/publications/docs/MedicalRecordsManual.pdf. Last accessed: 13 December 2017.

57. Hersh WR et al. Caveats for the use of operational electronic health record data in comparative effectiveness research. Med Care. 2013;51(8 Suppl 3):

S30-7.

58. Zulman DM et al. Evolutionary pressures on the electronic health record: Caring for complexity. JAMA. 2016;316(9):923-4.

59. Ben-Assuli O. Electronic health records, adoption, quality of care, legal and privacy issues and their implementation in emergency departments. Health Policy. 2015;119(3): 287-97.

60. Prasad V. Perspective: The precision-oncology illusion. Nature. 2016; 537(7619):S63.

61. Tannock IF, Hickman JA. Limits to personalized cancer medicine. N Engl J Med. 2016;375(13):1289-94.

62. Prasad V. Precision medicine in diffuse large B-cell lymphoma: Hype or hope? Eur J Cancer. 2016;68:22-6.

63. Warner JL. Giving up on precision oncology? Not so fast! Clin Transl Sci. 2017;10(3):128-9.

64. Prasad V, Gale RP. Precision medicine in acute myeloid leukemia: Hope, hype or both? Leuk Res. 2016;48:73-7.

65. Prasad V et al. Precision oncology: Origins, optimism, and potential. Lancet Oncol. 2016;17(2):e81-6.

66. Garraway LA et al. Precision oncology: An overview. J Clin Oncol. 2013;31(15):1803-5.

67. Schwaederle M, Kurzrock R. Actionability and precision oncology. Oncoscience. 2015;2(10):779-80.

68. University of California. New software platform bridges gap in precision medicine for cancer. 2014. Available at: http://cancer.ucsf.edu/element/auje3xj/2014/11/06/new-software-platform-bridges-gap-in-precision-medicine-for-cancer.5685. Last accessed: 13 December 2017.

69. Flatiron. OncoEMR®: More time with your patients, less time in your EHR. 2014. Available at: https://flatiron.com/community-oncology/oncoemr/. Last accessed: 13 December 2017.

70. Miotto R at al. Deep patient: An unsupervised representation to predict the future of patients from the electronic health records. Sci Rep. 2016;6:26094.

71. Beaulieu-Jones et al. Semi-supervised learning of the electronic health record for phenotype stratification. J Biomed Inform. 2016;64:168-78.

72. Schumacher A et al. A collaborative approach to develop a multi-omics data analytics platform for translational research. Appl Transl Genom. 2014; 3(4):105-8.

73. Hinkson IV et al. A comprehensive infrastructure for big data in cancer research: Accelerating cancer research and precision medicine. Front Cell Dev Biol. 2017;5:83.

74. World Health Organization. Cancer: World's health ministers renew commitment to cancer prevention and control. 2017. Available at: http://www.who.int/cancer/media/news/cancer-prevention-resolution/en/. Last accessed: 13 December 2017.