Clinicians’ Expectations for Gene-Driven Cancer Therapy

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ABSTRACT: A new era of medicine is rapidly approaching, which will change not only pathological diagnosis but also medical decision-making. This paper raises the question of how well prepared doctors are to address the new issues that will soon confront them. The human genome has been completely sequenced and general understanding about cancer biology has increased enormously with understanding that unregulated gene function and complicated changes in signal pathways are related to uncontrolled cell growth. Thus, gene-driven therapy involving alterations to genes are recognized to present new therapy options. This advance will necessitate major changes to the decision-making aspect of physicians. This article focuses on defining the pertinent changes and addressing what they mean for practicing physicians.

KEYWORDS: gene alteration, medical decision, individualized medicine

Introduction

Today cancer patients are more likely to inquire about genetics than ever before. They would like to know the origin of their cancer, the prognosis for the cancer, and whether their children are at risk of getting cancer. Thus, the need for genetic counseling is increasing all the time.1-3 When whole gene exon maps and the complete genetic makeup are available to everyone, genetic counseling would be needed to explain the implications and importance of the findings. There is also a potential risk that mutation carriers may be subject to different forms and degrees of genetic discrimination.4 Genetic responsibility for oneself and others is a strongly debated implication of genetic testing for cancer and demands broad consideration of the boundaries between individual and community rights.4 Similarly, until gene maps are available from primary tumors and from each relapse, it would not be possible to provide a picture of the cancer or of the genes involved its development. Even when the gene maps are available, it will still always have to be supplemented by the clinical events connected to genes. All the data need to be understood and interpreted for the benefit of a patient seeking help. Genetic knowledge can be perceived as enhancing the control that individuals have over their lives or as paralyzing the decision process of an individual who may feel predestined to suffer a serious disease.5 As research continues to unveil more drug–gene and disease–gene associations and clinical practice moves toward the concept of personalized medicine, it is critical that clinicians understand which pharmacogenetic assays are available to identify differences between individuals, as they predict the safety and efficacy of anticancer drugs.6 The mapping of the human genome and technological developments in DNA sequencing, gene expression profiling, and proteomics have raised expectations of implementing genotype–phenotype data into the clinical decision process and have also multiplied the complex interaction of genetic and other laboratory parameters that can be used for therapy adjustments.7

New data produced for clinical purposes, including genetic testing, differ from old data that lack genetic testing.3
This increases the gap between old and new drugs, which is based on the availability of DNA sequencing data. However, with efficient research efforts, it is possible to reach the required level of knowledge with existing chemotherapy drugs. This makes it possible to rely on old drugs and continue using them in the course of therapy decisions, which are increasingly based on new data from gene maps. All old clinical trial materials should be reassessed, and if samples exist, the trials should be rerun to extract gene-related information. New, faster, and cheaper methods, eg, the Exome Variation Analyzer, make broadly focused whole genome sequencing possible. Such an action would probably rewrite some of the major phase 3 trial results. If this is not done, there may not be enough data to determine the best way to use existing drugs, and so will use them according to the old treatment guidelines that lack gene-related elements. In that case, only the new trials with new targeting agents will have these essential new elements, and this will extremely widen the gap between old and new trials. This in turn will create obstacles to develop work in combinations. Drug companies find it difficult enough to get their new molecules through approval processes and will not have a financial incentive to accomplish something with old, non-patentable, low-priced alternative products in their drug portfolios. Re-running the clinical trials would be highly beneficial for ordinary clinicians, and thus, governments should take the responsibility for doing so. Furthermore, it should be the role of the government to define the financing required to analyze biomaterials with the complete patient records already available.

International research teams supported by public funding agencies, such as the National Institutes of Health, and by private foundation, such as the Wellcome Trust, are rapidly enlarging the catalog of genetic changes associated with neoplasia and other ailments, using ever faster, ever cheaper sequencing methods and heavy-duty bioinformatics. The main inhibitory element is not the low volume of samples available, but poor or non-existent clinical data combining clinical cases with findings in tumor samples. This problem is well recognized from chemotherapy trials and this is one of the reasons why open-label phase III studies are so strongly acknowledged in clinical oncology. Retrospective data, especially routinely written patient records, are imperfect sources of background information on gene results. Clinical patient records should be redesigned to have a structure that supports automatic data extraction and to make it possible to have real-life reference material for particular therapy options. This article will discuss new elements related to genetic testing focusing on defining changes and evaluating what they would mean for practicing physicians.

**Methods**

This review is based on a PubMed search, which was performed with the terms medical decision and gene (Table 1). Publications in languages other than English and trials involving non-human subjects were excluded. Abstracts of 171 publications were reviewed and the classification was performed with the predetermined variables listed in Tables 2 and 3. Trialcom was searched using the term individualized medicine cancer (Table 4). The number of publications and trial protocols cited are as researched in November 2014.

**Results**

A search of the term gene on PubMed produces almost two million hits (1,971,971). Within clinical oncology, there were 189,328 hits, a number that then decreased dramatically, when the search was conducted for both clinical oncology and gene or for genome terms (Table 1). A search for terms including both gene and clinical oncology offers relatively few hits (9,224) and a search for medical decision offers even fewer hits (1,253). Combining clinical oncology, medical decision, and gene in a search term produced 171 hits (Table 2). These 171 articles were targeted for further analysis (Table 2). There were 68 reviews and 87 original articles. In fact, 154 articles were about clinical situations, and 17 articles, despite the presence of the search term hits, were preclinical papers. BRCA1 and 2 dominated with 28 articles. Breast cancer was the most frequent indication with 63 articles. Of the original articles with all indications, abstract analysis revealed 25 articles dealing with driver mutations, 25 with multiple gene analysis including 9 on 21-gene assay, and 16 on the Oncotype DX test. Gene profiling, either DNA or RNA, was dealt in 17 abstracts. The following cancer topics were the subject of fewer than seven articles: colon (3), leukemia (5), brain (3), prostate (2), bladder (1), thyroid (1), liver (2, Her-2 (6), Kras (2), EGFR (2), radiotherapy (2), and pediatric (2). In 17 articles, the original study was based on surveys and counseling was examined in eight articles. There were 68 review articles, of which 23 mainly focused on driver mutations, while profiles were addressed in 26 articles. The indications most frequently examined in articles were breast (24), colorectal (10), and lung cancer (7), and other cancers were addressed just a few times; these included ovarian (3), prostate (3), sarcoma (2), gastric (1), and testis (1). Gene profiles were central to 26 review articles, with proteomics in three and large-scale genomics in three, and multiple gene tests were reviewed in 17 articles, 21-gene assays

| SEARCH TERM                          | NUMBER OF HITS |
|--------------------------------------|----------------|
| Gene                                 | 1,971,971      |
| Clinical oncology                     | 189,328        |
| Gene-driven therapy                   | 4,499          |
| Clinical oncology genome              | 9,224          |
| Clinical oncology gene-driven therapy | 247            |
| Medical decision                      | 66,397         |
| Clinical oncology medical decision    | 2,814          |
| Medical decision gene                 | 1,253          |
| Clinical oncology medical decision gene| 171            |
Table 2. Classification of publications by the term “Clinical oncology medical decision gene” based on abstract content analysis.

| ABSTRACT TOPICS                                           | NUMBER OF PUBLICATIONS |
|-----------------------------------------------------------|------------------------|
| Clinical oncology medical decision gene/non clinical      | 171/17                 |
| Original/Review articles                                  | 87/68                  |
| Original: driver mutations/multigene/BRCA/gene profiles   | 25/25/23/17            |
| Original: breast/surveys/counseling                       | 39/17/8                |
| Review: driver mutations/multigenes/gene profiles         | 23/17/26               |
| Review: breast/BRCA/Her2/ colorectals/Ras/lung/EGFR       | 24/5/2/10/7/7/3       |

Note: This table shows the number of articles to certain topic determined by abstracts.

Table 3. Distribution of topics.

| ALL DRIVER MUTATIONS | MULTIPLE PROFILES COUNSELING |
|----------------------|------------------------------|
| 1996–2001 75         | 28                           |
| 2002–2007 32         | 17                           |
| 2008–2013 20         | 6                            |
| 2014 32              | 5                            |

Notes: The PubMed search gave abstracts from 1996 to November 2014. Distribution of topics driver mutations, profiles, and counseling are shown.

Table 4. Number of trial protocols reported in ClinTrials.com side by November 2014 to indicated search terms.

| SEARCH TERMS               | NUMBER OF PROTOCOLS |
|----------------------------|---------------------|
| Individualized medicine cancer | 149                 |
| Lung                       | 28                  |
| Breast                     | 18                  |
| Colorectal                 | 14                  |
| Renal                      | 11                  |
| Pancreas                   | 7                   |
| Melanoma                   | 5                   |
| Prostate                   | 5                   |

Data. Before investing in full-scale exon testing for all patients, methods should be standardized. Quality issues should be addressed by an extensive monitoring and auditing function.

Discussion

In this study, literature was searched using PubMed research with a defined set of terms: “clinical oncology and medical decision and gene”. By doing this, it was possible to follow the development of the area, as reflected in a number of articles (Table 3). The bibliographical approach was utilized to give a solid perspective and overview of an area that is developing so rapidly. Of course, one set of search terms cannot pick up everything in a broad research field, but it may illuminate the study area. The search term used provided 171 hits, which represent only 0.0000867% of PubMed articles defined under the term gene (Table 1). There was a clear and steady increase in numbers. A review of articles spanning 20 years reveals a move from individual driver mutation articles and counseling papers toward multiple genes and gene profile papers (Table 3). However, in the past five years, only 17 original papers published could be classified as focused on gene profiles.11-27 A similar slow development can be seen in the number of clinical trial protocols dealing with individualized medicine and cancer (Table 4). It was concluded in 2012 that as a rule the molecular data on gene-driven therapies and specifically on breast cancer gene profiles were not sufficiently mature to include them in decision-making algorithms determining treatment recommendations for individual patients.18 In many ways, the promise of a new era of gene-driven therapies relies on all tumor genes being taken into account at one time and making a difference to patient therapy.28 However, development is proceeding slowly and is likely to advance stepwise through the application of the classical logic of the natural sciences. This process is typified by focusing on one question at a time, and obtaining a near complete picture depends on first resolving a sufficient number of sub questions. This thinking is closely linked to technical improvements and new innovations. The clinical necessity of considering one patient at a time and collecting all the problems of that patient in a table at once present a considerable challenge for genetic science.
Much has been written about the concept of the magic bullet of antibody applications. It was suggested that the discovery of the magic bullet was close and that once identified it would resolve the clinical question of how to successfully treat metastasized cancer. Monoclonal antibodies offer the promise of cancer-specific drug targeting (Paul Ehrlich’s “magic bullet”), but a modest number of anticancer antibodies have been approved for clinical use only during the past decade. It took three decades to get bioscience knowledge to the level where it was possible to announce some magic bullets, the magical antibody era has not yet occurred. Instead, antibody technology has provided similar answers to other technology areas, and the promise of a rapid revolution has failed to materialize. At the time of writing, there are still more than 400 such antibody molecules awaiting clinical trials, so the revolution is far from becoming reality. Gene-driven therapies have been proposed to have a major impact on future drug developments and also on oncologists’ therapy decisions. This time, the possibility of radical change happening in a short space of time is stronger than it proved to be with antibodies.

Gene-driven therapies have already started to change routine clinical decision-making. The simplest change occurs when a certain driver mutation known to be a predictive factor is recognized. Luckily, there are now a few drugs that will work on limited patient populations, eg, Her-2 and trastuzumab and Kras wild-type and cetuximab. The availability of these drugs will offer new treatment options. Traditionally, treatments are defined to suit the largest number of people, usually resulting in 10–40% of treated patients receiving some benefit, while the remainder is actually treated for nothing. The fundamental rationale has been to generalize the treatments offered in clinical trials to all patients. The current demand to demonstrate efficacy in the form of large phase III trials is based on the principle of expanding treatment results to general patient populations. The limitations are understood, as it is not always possible to access the same patient profile in real life as it is in clinical trials. However, the new thinking provides an opportunity to enrich the treatment effect by selecting patients based on genetic alterations. Instead of giving a standard consensus treatment to everyone, gene-driven therapy assesses the patient’s gene status to select treatments to suit that individual patient. Success in cancer treatment should no longer be measured in terms of a percentage of patients responding to a certain treatment, but should extend to include the overall success in terms of the number of healed patients given various treatments guided by gene alterations.

Of course, this new decision-making culture is just started to form, and to significantly advance, it will require access to data covering clinically usable treatments. The idea would be to use data on certain types of patients with definite genes and gene variations relating to predictable treatment results. Doing so would mean that all individually crafted treatments could be based on some, if not many, pieces of data from treatment already carried out. The data could then be accessed to inform treatment decisions for new patients. DNA analysis of the patient will give information on probable drug interactions and possible metabolic issues before starting a patient on medication. During the past 10 years, cancer medicine has experienced technological advances, now allowing rapid and inexpensive sequencing of the entire human genome. The adoption of genome-wide association studies on responses to drugs, genome sequencing from drug development, and treatment programs are the most striking short-term opportunity to improve the drug candidate pipeline and to boost the efficacy of medication already in use. On the other hand, patient DNA would be needed to establish the differences in tumor DNA and could also be used in the evaluation of the therapeutic index, for example, in measuring the pharmacokinetic characteristics of the patient. Tumor samples will provide prognostic information on a particular cancer type; moreover, multiple genes tools are objective and reproducible in terms of the analysis of proliferation, but these approaches may still overlook the biological heterogeneity with tumors evidenced by distinct cell subpopulations with different genomic patterns and functions. In addition, there could also be a predictive side discovering how the efficacy of a therapy is related to gene alterations over the course of the follow up. This body of information is expanding all the time. These new diagnostic tools are adding prognostic and predictive elements to the ordinary diagnosis; in particular, they address the relationship between clinical judgment and clinical decision-making, as the biological and clinical components are realigned.

Predictive connections need solid and accurate clinical data, which are not normally available from patient records. The use of patient records retrospectively will be constrained by considerable volumes of missing data and could markedly reduce the value of large sample banks. It is becoming increasingly apparent that it may not be the volume of samples but that the completeness of patient clinical data will define the actual value of a sample bank. The U.S. Federal Drug Administration has approved a 2,000 gene test for working diagnoses and management of metastatic and poorly differentiated cancers, which encompasses over 4% of cancers of unknown origin. Following the test results, the recommendation for guideline-consistent chemotherapy increased from 42 to 65% of patients, and the recommendation for non-guideline-consistent regimens declined from 28 to 13%. For patients with difficult-to-diagnose cancers, the test changed the working diagnosis and given therapy for the majority of patients.

It can be stated that there is a conceptual limitation to the current genome decision-making, as it is based on whether a certain individual factor is found or not. Therefore, single exon changes termed driving mutations are currently in focus, while a complete gene cluster analysis or complete gene profiling for everyone could only be performed experimentally and theoretically. Clinical data combining gene changes and clinical patient data are still lacking, and it is not possible to take into account more than a small fraction of gene alterations.
However, future data will be based primarily on the extraction of problems and focusing on a single gene mutation at a time. This will restrict results, and it is likely that a considerable amount will be missed.

Validated molecular tests assessing tumor tissue or patient germ line DNA already inform decision-making; however, many theoretical and regulatory challenges must be overcome before the promise of personalized molecular medicine can be fully realized. An analysis capable of including all genes is still some way in the future, and a complete genome analysis, which could also take into account introns and DNA remaining outside known gene structures, is even further away. It is calculated that only around 5% of DNA could be defined as genes and the remainder is noncoding or “junk” DNA. It may well be that only 20,000–30,000 genes affect the functioning of the DNA, but the whole DNA molecule may function together to produce the end effect. This means that introns and junk DNA may have a distinct but as yet unknown role in DNA. It is not unreasonable to think that DNA, despite being constructed from simple pieces (including four nucleosides), will possess multilayer complexity with interactions and network effects. Many genes can be involved when DNA works, but they exert their effect through sum effects in which all genes operate as a network, and only when all genes have had their input is the direction in which the DNA function moves determined. The gene network is complex and creates a sum effect, so that all genes have an impact on the end function but in a variable way.

There are in fact several examples of somatic mutations in tumors driving therapies by predicting responses. This has sparked the active development of targeted therapies with predictive factors. There is also a realization that germ line DNA variants can help optimize cancer drug dosing and predict the susceptibility of patients to the adverse side effects of these drugs – knowledge that can ultimately be used to improve the benefit/risk ratio of cancer treatment for individual patients. The number of pharmacogenetic assays available is continuously expanding as more molecularly targeted anticancer drugs begin their clinical development. Analysis of germ line DNA mutations can often help to predict pharmacokinetics and pharmacodynamic responses, whereas somatic DNA mutations are particularly useful in predicting tumor response. It is considered essential for clinicians to understand the molecular pathways for anticancer drugs, the therapeutic implications of mutations within these pathways, and the clinical assays available to test for pharmacogenetic differences.

The use of individualized medicine may increase differences among institutions, as there would be no single correct treatment that could be used universally. In principle, treatment guidelines will only define approaches to how gene alterations could be interpreted to understand their usefulness in a patient’s therapy. Massive databanks will have records of gene-based therapy decisions, and physicians will track their treatments and success against a certain patient’s cancer. There will be distinct and unique treatments based on the interpretation of existing data. However, the unifying feature will be the number of healed patients with a number of treatments. Finally, patient populations will be acknowledged to be different, and instead of the patients, the treatment focus will be on the genes used that drove the therapy.

The Canadian regulatory body, the Medical Advisory Secretariat (MAS), has begun work on evidence-based reviews of published literature and published a thorough review of gene expression profiling to guide adjuvant chemotherapy decisions in women with early breast cancer. It was an evidence-based economic analysis, following which the MAS concluded that there are methodological and statistical limitations that affect both the generalizability of the currently available evidence, as well as the magnitude and statistical strength of the observed effect sizes. They found low-quality evidence of the prognostic value of an Oncotype-DX test and only very low-quality evidence of its predictive value. The test was not recommended for widespread use, but the MAS did request more evidence be sought.

An ordinary patient visit process to an oncologist in the future might involve the patient presenting a gene card, which would be scanned and all specific information transferred to a server to make it available to the oncologist. The doctor would then check for recorded interactions between the patient’s genes and the available drugs, and also screen the risk levels revealed by the family’s medical history and predisposing genes found in the DNA of family members. The tumor and metastases would already have been analyzed in gene analysis centers, producing genome exon results ready to be inserted into programs linking existing data to the therapy options. Following a clinical examination and diagnosis, the doctor would decide on the medicine to be administered. The integrated gene program would propose cytostats and biostats (targeted biological agents with moderate treatment effect) according to published data in descending order of calculated efficacy, while simultaneously screening for side effects against the patient’s medical history and family gene records. Only once that process is completed would a final proposal for treatment be made by the computer program. Despite the upcoming changes in decision-making related to gene-driven therapies, the doctor–patient relationship will undoubtedly remain and must be supported by an overarching sense of trust. Doctors cannot hide behind perfectly functioning test programs: patients want to know that their own doctor is responsible for the decisions involving the treatment of their cancer. That element of there being one doctor interpreting the patient’s situation and treating them is what will remain. For an oncologist, this genomic workout will provide the most efficient tool to support the understanding of the development of a particular cancer and its peculiar characteristics and to prioritize therapies accordingly.

**Author Contributions**
Conceived and designed the experiments: AJ. Analyzed the data: AJ. Wrote the first draft of the manuscript: AJ.
Contributed to the writing of the manuscript: AJ. Agree with manuscript results and conclusions: AJ. Jointly developed the structure and arguments for the paper: AJ. Made critical revisions and approved final version: AJ. The author reviewed and approved of the final manuscript.

REFERENCES

1. Kuschel B, Lux MP, Goeeke TO, Beckmann MW. Prevention and therapy for BRCA1/2 mutation carriers and women at high risk for breast and ovarian cancer. *Eur J Cancer Prev*. 2000;9(3):139–50.

2. Klemm JR, O’Dea A, Chamberlain C, Fabian CJ. Patient satisfaction of BRCA1/2 genetic testing by women at high risk for breast cancer participating in a prevention trial. *Fam Cancer*. 2005;4(4):279–84.

3. Azad N, Zahnow CA, Rudin CM, Baylin SB. The future of epigenetic therapy in solid tumours – lessons from the past. *Nat Rev Clin Oncol*. 2013;10(5):256–66.

4. Surbone A. Social and ethical implications of BRCA testing. *Ann Oncol*. 2013;24(suppl 9):160–6.

5. Surbone A. Cultural competence: why? *Ann Oncol*. 2004;15(5):697–9.

6. Patel JN, Mandock K, McLeod HL. Clinically relevant cancer biomarkers and pharmacogenetic assays. *J Oncol Pharm Pract*. 2014;20(1):65–72.

7. Nestingi J, Borst L, Schmiegelow K. Challenges in implementing individualized medicine illustrated by antimitabolite therapy of childhood acute lymphoblastic leukemia. *Clin Proteomics*. 2011;8(1):8.

8. Courant S, Cabot C, Lefebvre A, et al. EVA: exome variation analyzer, an efficient and versatile tool for filtering strategies in medical genomics. *BMC Bioinformatics*. 2012;13(suppl 14):59.

9. Jekunen A. Decision-making in product portfolios of pharmaceutical research and development – managing streams of innovation in highly regulated markets. *Drug Des Deliv Ther*. 2014;8:2009–16.

10. Steenma DP. The beginning of the end of the beginning in cancer genomics. *Nat Rev Genet*. 2004;11(1):51–9.

11. Albanell J, González A, Ruíz-Borrego M, et al. Prospective transGEICAM study of the impact of the 21-gene recurrence score assay and traditional clinical-copathological factors on adjuvant clinical decision making in women with estrogen receptor-positive (ER) node-negative breast cancer. *Ann Oncol*. 2012;23(3):625–31.

12. Berchuck A, Iversen ES. Patterns of gene expression that characterize long-term survival in advanced stage serous ovarian cancers. *Clin Cancer Res*. 2005;11(10):3686–96.

13. Holdsworth C, Kim M, Liao J, Phillips MH. A hierarchical evolutionary algorithm for multiobjective optimization in IMRT. *Med Phys*. 2010;37(9):4986–97.

14. Lancaster JM, Dressman HK, Whitaker RS, et al. Gene expression patterns that characterize advanced stage serous ovarian cancers. *J Soc Gynecol Investig*. 2004;11(1):51–9.

15. Li A, Beldag S, Kotliarov Y, Fine HA. GliomaPredict: a clinically useful tool for stratification of glioma patients to specific molecular subtypes. *BMC Med Inform Decis Med*. 2010;10:38.

16. Li LF, Xu XJ, Zhao Y, et al. Integrated gene expression profile predicts prognosis of breast cancer patients. *Breast Cancer Res Treat*. 2009;113(2):231–7.

17. Oratzi R, Kim B, Chao C, et al. Physician survey of the effect of the 21-gene recurrence score assay results on treatment recommendations for patients with lymph node-positive, estrogen receptor-positive breast cancer. *J Oncol Pract*. 2011;7(2):94–9.

18. Schwartz GP, Reis-Fihlo J, Puxatra L, Consensus Committee, et al. Adjuvant therapy in stage I carcinoma of the breast: the influence of multigene analyses and molecular phenotyping. *Cancer*. 2012;118(8):2031–8.

19. Sulayman N, Spellman E, Graves KD, et al. Psychosocial and quality of life in women receiving the 21-gene recurrence score assay: the impact of decision style in women with intermediate RS. *J Cancer Epidemiol*. 2012;2012:728290.

20. Terczyk KP, Hensley Alford S, Emmons KM, Lipkus IM, Wilfond BS, McBride CM. Parents’ attitudes toward pediatric genetic testing for common disease risk. *Pediatrics*. 2011;127(5):e1288–95.

21. Trosman JR, Van Bebber SL, Phillips KA. Coverage policy development for personalized medicine: private payer perspectives on developing policy for the beginning of the end of the beginning in cancer genomics. *J Natl Cancer Inst*. 2004;105(10):701–10.

22. Varadhachary GR, Spector Y, Abbruzzese JL, et al. Prospective gene signature study using microRNA to identify the tissue of origin in patients with carcinoma of unknown primary. *Clin Cancer Res*. 2011;17(12):4063–70.

23. Cheung FS, Tong AC, Leung KC, Kwan WH, Yau TC. Initial experience with the Oncotype DX assay in decision-making for adjuvant therapy of early oestrogen receptor-positive breast cancer in Hong Kong. *Hong Kong Med J*. 2014;20(5):401–6.

24. Miao R, Luo H, Zhou H, et al. Identification of prognostic biomarkers in hepa-titis B-virus-related high-risk liver carcinoma and stratification by integrative multiomics analysis. *J Hepatol*. 2014;61(4):840–9.

25. Drukker CA, van den Hout HC, Sonke GS, et al. Risk estimations and treatment decisions in early stage breast cancer: agreement among oncologists and the impact of the 70-gene signature. *Eur J Cancer*. 2014;50(6):1045–54.

26. Elias MH, Baha AA, Azlan H, et al. BCR-ABL kinase domain mutations, including 2 novel mutations in imatinib resistant Malaysian chronic myeloid leu-kemia patients–frequency and clinical outcome. *Leuk Res*. 2014;38(4):454–9.

27. Pritchard CC, Salipante SJ, Koehler K, et al. Validation and implementation of targeted capture and sequencing for the detection of actionable mutation, copy number variation, and gene rearrangement in clinical cancer specimens. *J Med Diagn*. 2014;16(1):56–67.

28. Collisson EA, Cho RJ, Gray JW. What are we learning from the cancer genome? *Nat Rev Clin Oncol*. 2012;9(11):621–30.

29. Deckert FM. Current constructs and targets in clinical development for anti-body-based cancer therapy. *Curr Drug Targets*. 2009;10(2):158–75.

30. Hudis CA. Trastuzumab – mechanism of action and use in clinical practice. *N Engl J Med*. 2007;357(13):39–51.

31. Messersmith WA, Ahnen DJ. Targeting EGFR in colorectal cancer. *Nat Rev Gastroenterol & Hepatol*. 2008;5(9):479–89.

32. Hofstatter EW, Bale AE. The promise and pitfalls of genomics-driven cancer medicine. *Virtual Mentor*. 2013;15(8):681–6.

33. Harper AR, Topol EJ. Pharmacogenomics in clinical practice and drug develop-ment. *Nat Biotechnol*. 2012;30(11):1117–24.

34. Oakman C, Santarpia L, di Leo A. Cancer assessment tools and optimiz-ing adjuvant therapy. *Nat Rev Clin Oncol*. 2010;7(12):725–32.

35. Solin LJ, Gray R, Baehsner F, et al. Multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. *J Natl Cancer Inst*. 2013;105(10):701–7.

36. Bourtou P, Keating P, Cambrosio A. Regulating diagnosis in post-genomic med-icine: re-aligning clinical judgment? *Sci Med*. 2011;73(6):816–24.

37. Hornberger J, Alvarado MD, Rebecca C, Gutierrreiz HR, Yu TM, Gradishar WJ. Clinical validity/utility, change in practice patterns, and economic implications of risk stratifiers to predict outcomes for early-stage breast cancer: a systematic review. *J Natl Cancer Inst*. 2012;104(14):1068–79.

38. Soon WW, Harirhan M, Snyder MP. High-throughput sequencing for biology and medicine. *Mol Syst Biol*. 2013;9:60.

39. Tsimberidou AM, Ringborg U, Schilsky RL. Strategies to overcome clinical, regulatory, and financial challenges in the implementation of personalized medicine. *Ann Soc Clin Oncol Educ Book*. 2013:118–25.

40. Alexander RP, Fang G, Rozovsly J, Snyder M, Gerstein MB. Annotating non-coding regions of the genome. *Nat Rev Genet*. 2010;11(8):559–71.

41. Castellano-Davis CI. The evolution of noncoding DNA: how much junk, how much functional? *Trends Genet*. 2005;21(10):533–6.

42. McLeod HL. Cancer pharmacogenomics: early promise, but concerted effort needed. *Science*. 2013;339(6217):1563–6.

43. Health Quality Ontario. Gene expression profiling for guiding adjuvant che-motherapy decisions in women with early breast cancer: an evidence-based and economic analysis. *Ont Health Technol Assess Ser*. 2010;10(23):1–57.