Towards decision-making using individualized risk estimates for personalized medicine: A systematic review of genomic classifiers of solid tumors

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Abstract

Recent advances in the understanding of the genetic underpinnings of cancer offer the promise to customize cancer treatments to the individual through the use of genomic classifiers (GCs). At present, routine clinical utilization of GCs is uncommon and their current scope and status, in a broad sense, are unknown. As part of a registered review (PROSPERO 2014:CRD42014013371), we systematically reviewed the literature evaluating the utility of commercially available GCs by searching Ovid Medline (PubMed), EMBASE, the Cochrane Database of Systematic Reviews, and CINAHL on September 2, 2014. We excluded articles involving pediatric malignancies, non-solid or non-invasive cancers, hereditary risk of cancer, non-validated GCs, and GCs involving fewer than 3 biomarkers. A total of 3,625 studies were screened, but only 37 met the pre-specified inclusion criteria. Of these, 15 studies evaluated outcomes and clinical utility of GCs through clinical trials, and the remainder through the use of mathematical models. Most studies (29 of 37) were specific to hormone-receptor positive breast cancer, whereas only 4 studies evaluated GCs in non-breast cancer (prostate, colon, and lung cancers). GCs have spurred excitement across disciplines in recent decades. While there are several GCs that have been validated, the general quality of the data are weak. Further research, including prospective validation is needed, particularly in the non-breast cancer GCs.

Introduction

Over the past 30 years, there have been substantial advances in our knowledge of the genetic underpinnings of cancer. The increase in this knowledge, and in the technology to evaluate it, has generated tremendous excitement because of its potential to customize therapies at the patient-specific level and deliver on the promise of personalized medicine. There is an increasing emphasis on "precision oncology" or "genomics-driven oncology" [1,2], with individualized therapy strategies driven by molecular "-omics" information.
A genomic classifier (GC) offers the opportunity to select patients most likely to respond to therapy, based on stratification of probability of a clinical outcome according to a DNA or RNA expression signature [3,4]. This provides the potential to intensify therapy in patients with high-risk disease, improving cure rates, and avoid the ‘overtreatment’ of patients with biologically low-risk disease that historical, clinical, or histopathologic criteria cannot otherwise distinguish. Since the mid-2000s, several commercially available breast cancer GCs have been approved for coverage by Medicare & Medicaid [5]. Population-based research has identified increasing utilization rates of GCs among breast cancer patients, with concordant reduction in the proportion of women with hormone receptor positive cancer receiving chemotherapy [6]. Recent series estimate that 18% of women with breast cancer in the U.S. undergo the 21-gene recurrence score assay, which is only one of many [7]. Comparatively, there has been surprisingly little clinical implementation of GCs for other solid tumors.

Additional research is needed to deliver on the promise of GCs for solid tumors [2,8]. Despite the promise of genomics-driven cancer medicine, its clinical implementation is limited by a relative lack of prospective evidence regarding genomic assay validation and clinical performance [9]. The availability of strong evidence from well-designed, prospective trials is a significant challenge and rate-limiting step in the development of GCs [3].

Our purpose was to describe the current state of GCs and delineate areas of research that could validate their routine use in clinic. We systematically review and report the current evidence evaluating the utility of commercially available GCs for solid tumors of adults. Our study describes the outcomes and clinical utility measure of GCs as studied through clinical trials or the use of mathematical models.

Methods and materials

As part of a registered, PROSPERO International prospective systematic review (PROSPERO 2014:CRD42014013371), we conducted literature database searches of Ovid Medline (PubMed), EMBASE, the Cochrane Database of Systematic Reviews, and CINAHL on September 2, 2014. The MeSH search criteria are provided in the supporting information (S1 File), but generally includes terms associated with genomic and/or personalized cancer care. We restricted search criteria those reported in English. This resulted in 3,815 articles with 190 duplicates (3,625 unique articles, Fig 1). The PRISMA checklist is provided in the supporting information (S2 File).

Two investigators independently reviewed manuscript titles and abstracts to identify original data studies that involved the use of validated GCs to demonstrate clinical utility. Clinical utility is demonstrated when the test is shown to improve clinical outcomes and/or alter clinical decisions. Studies were required to involve solid tumors, adult patients (≥ 18 years old), and GCs with 3 or more biomarkers. Manuscripts involving pediatric malignancies, non-solid or non-invasive tumors (e.g., leukemia, ductal carcinoma in situ, etc.), hereditary risk of cancer, non-validated GCs, and GCs involving less than 3 biomarkers were excluded (Fig 1). In addition, manuscripts were reviewed independently by the two investigators for quality by applying the general principles of the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) checklist items [11]. A third investigator served to resolve all coding disagreements. Each included manuscript was assessed for clinical site, assay(s) used, number of patients or simulated patients, the specific clinical population the results apply to, the methodology, the main contribution of the study, and the country of origin. Data extraction was completed using a pre-defined spreadsheet; one investigator performed the data extraction while a second investigator reviewed the spreadsheet to confirm correct data extraction. We present a figure to show the timeline of when the studies were published, number of patient
Results

We identified 3,625 manuscripts for title review according to the above methods. As shown in Fig 1, this was reduced to 2,302 manuscripts for abstract review and 1,119 studies for full text review. After this final review, 37 manuscripts were included [18–54]. A total of 273 abstracts and 55 manuscripts needed a third investigator to resolve coding disagreements. Tables 1 and 2 depict the key characteristics of each included study. Table 1 provides a summary of the breast cancer studies while Table 2 presents studies for all other types of cancer. Of the 37 studies, 15 studies evaluated outcomes and clinical utility of GCs through clinical trials, and the remainder through the use of mathematical models.

Fig 2 depicts the timeline of the publication of the studies and the date relevant GCs became commercially available [12–17]. Each dot represents a study, with green dots for modeling studies and orange dots for clinical studies. The dot diameter for clinical studies corresponds to the number of patients in the study. In general, breast cancer GCs were developed and commercially available earlier than GCs for other cancers.

Breast cancer

Thirty-three (89%) of studies evaluated breast cancer, and of these, 29 (89%) were specific to hormone-receptor positive breast cancer, and 31 (94%) concerned the Oncotype DX GC (Table 1). Among the trials concerning breast cancer GCs, 13 (39%) concern the clinical
validation of GCs, mostly through the testing of prospectively collected tissue banks and evaluation of various clinical outcomes (overall survival, cancer recurrence, pathologic response to neoadjuvant therapy, etc.).

Two studies presented comparisons of multiple GCs. Iwamoto et al. compared six distinct assays for breast cancer (MammaPrint, Oncotype DX®, a 76-gene signature assay, mitotic kinase prognostic score, MKI67 mRNA expression, and molecular subtype). They demonstrated that the assays generally performed similarly in their abilities to predict 5-year overall survival, progression-free survival, and pathologic complete response [25]. Kelly et al. compared the Oncotype DX® GC to the PAM50 Breast Cancer Intrinsic Classifier™ and demonstrated general agreement between the two [28].

Of the breast cancer GC articles, 20 (61%) are based in mathematical models and generally concern cost-effectiveness. The main type of mathematical model used is a Markov model, a state-transition model used to simulate the health outcomes and costs for a cohort of patients. Each article included demonstrated that the use of GCs in breast cancer was cost-effective in a variety of reimbursement models (Table 1). In addition, 4 articles demonstrated that the use of GCs in breast cancer altered decisions regarding the recommendation for or against adjuvant therapy.
## Table 1. Papers evaluating breast carcinoma.

| Year | Site | Assay                        | n   | Population                             | Methodology                              | Main Conclusion                                                                 | Country         |
|------|------|------------------------------|-----|----------------------------------------|------------------------------------------|---------------------------------------------------------------------------------|-----------------|
|      |      | **Clinical Outcomes**        |     |                                        |                                          |                                                                                  |                 |
| 2008 | Breast | Oncotype DX                  | 72  | HR+, locally advanced breast cancer    | Retrospective analysis of clinical outcomes | GC predicts pathologic complete response to neoadjuvant chemotherapy           | USA [18]        |
| 2008 | Breast | Oncotype DX                  | 465 | HR+ breast cancer                      | Case control study                       | GC predicts cancer control/survival                                              | USA [19]        |
| 2008 | Breast | Oncotype DX                  | 58  | HR+, early stage breast cancer         | Retrospective analysis of clinical outcomes | GC affects adjuvant therapy decision making                                     | USA [20]        |
| 2009 | Breast | Oncotype DX, 78-gene profile, Two-Gene-Index | 246 | HR+, early stage breast cancer         | Retrospective analysis of clinical outcomes | GC predicts cancer control/survival                                              | Netherlands [21]|
| 2010 | Breast | Oncotype DX                  | 367 | HR+, node-positive, postmenopausal breast cancer | Retrospective analysis of clinical outcomes | GC predicts cancer control/survival                                              | USA [22]        |
| 2010 | Breast | Oncotype DX                  | 1,231 | HR+, postmenopausal breast cancer      | Retrospective analysis of clinical outcomes | GC predicts cancer control/survival                                              | UK [23]         |
| 2010 | Breast | MammaPrint                   | 168 | HER2+, early stage breast cancer       | Retrospective analysis of clinical outcomes | GC predicts cancer control/survival                                              | Netherlands [24]|
| 2011 | Breast | MammaPrint, Oncotype DX, 76-gene signature | 228 | Breast cancer                          | Retrospective analysis of clinical outcomes | Each GC performed similarly                                                    | USA, Japan, and Italy [25] |
| 2011 | Breast | Oncotype DX                  | 154 | HR+, early stage breast cancer         | Prospective GC vs. expert opinion         | Experts tend to overestimate risk of recurrence compared to GC                 | USA [26]        |
| 2011 | Breast | Oncotype DX                  | 133 | Breast cancer                          | Retrospective analysis of clinical outcomes | GC predicts cancer control/survival among ER+ tumors                           | USA [27]        |
| 2012 | Breast | PAM50, Oncotype DX           | 151 | HR+, node negative breast cancer       | Retrospective analysis of clinical outcomes | Each GC agreed except in low risk patients                                       | USA [28]        |
| 2012 | Breast | Oncotype DX                  | 853 | HR+, early stage breast cancer         | Retrospective analysis of clinical outcomes | GC less utilized among African Americans and demonstrated higher recurrence scores | USA [29]        |
| 2013 | Breast | Oncotype DX                  | 665 | HR+, early stage breast cancer         | Retrospective analysis of clinical outcomes | GC predicts cancer control/survival                                              | USA [30]        |

| Year | Site | Assay                        | n   | Population                             | Methodology                              | Main Conclusion                                                                 | Country         |
|------|------|------------------------------|-----|----------------------------------------|------------------------------------------|---------------------------------------------------------------------------------|-----------------|
|      |      | **Modeled Outcomes**         |     |                                        |                                          |                                                                                  |                 |
| 2005 | Breast | Oncotype DX                  | 100 | HR+, node-negative breast cancer       | Cost-effectiveness, Markov Model         | GC is cost effective                                                         | USA [31]        |
| 2007 | Breast | Oncotype DX                  | 688 | HR+, early stage breast cancer         | Cost-effectiveness, Markov Model         | GC is cost effective                                                         | USA [32]        |
| 2010 | Breast | MammaPrint                   | 427 | Early stage breast cancer              | Cost-effectiveness, Markov Model         | GC is cost effective                                                         | USA [33]        |
| 2010 | Breast | Oncotype DX                  | 368 | HR+, early stage breast cancer         | Cost-effectiveness, Markov Model         | GC is cost effective                                                         | Israel and USA  [34] |
| 2010 | Breast | Oncotype DX                  | 89  | HR+, early stage breast cancer         | Prospective pre/post GC decision making  | GC affects adjuvant therapy decision making                                     | USA [35]        |
| 2010 | Breast | MammaPrint                   | 305 | HR+, node negative breast cancer       | Cost-effectiveness, Markov Model         | GC is cost effective                                                         | Netherlands and Austria [36] |
| 2010 | Breast | Oncotype DX                  | 665 | HR+, HER2-, early stage breast cancer | Cost-effectiveness, Markov Model         | GC is cost effective                                                         | Canada [37]     |
Non-breast cancer

As demonstrated in Table 2, 4 studies (11%) evaluated GCs in non-breast cancer. Hornberger et al. demonstrated that the ColoPrint GC predicted clinical outcomes in stage II colon cancer [53], and Maak et al. went on to demonstrate its cost-effectiveness in this setting [51]. Cooperberg et al. provided retrospective clinical evidence supporting the Decipher GC [52]. While Roth et al. demonstrated the cost-effectiveness of a 14-gene GC for early stage non-small cell lung cancer following surgery [54], other articles regarding this classifier did not meet our predefined inclusion criteria.

Discussion

Our results provide a summative analysis of the current state of the clinical research supporting the validation of GCs in patients with some solid tumors. While there are several commercially available GCs, the bulk of the existing published data are evaluations of breast cancer GCs.

While breast cancer is a common malignancy that usually requires multimodality therapy, cure rates for most women with breast cancer is already high. Regardless, there is a subset of patients with breast cancer that go on to die from their disease, and GCs are poised to identify these patients and potentially cure them. The development of GCs regarding more commonly...
fatal diseases such as locally advanced lung cancer or glioblastoma multiforme may have limited clinical utility, since most patients with poor-prognosis cancers will receive the most intensively validated therapy and a decision aid may not be clinically relevant for personalized decisions.

Interestingly, all of the articles in this systematic review regard the decision for (or against) adjuvant chemotherapy following definitive surgical resection. For most cancers however, there are multiple therapies that could be informed through GCs. In head and neck cancer, for example, many patients undergo definitive surgical resection and adjuvant therapy while others are receive definitive chemoradiotherapy (without surgery) without clear existing evidence as to which (if either) improves outcomes for patients. As another example, it is unlikely that the superiority (or inferiority) of radical prostatectomy over radiotherapy will ever be established, but it is possible that GCs could serve to define a subset of patients that would be better served with either therapy.

GCs have positioned themselves in a gap in cancer care that has obsessed researchers for decades. On one side are diseases that have targetable, gene-specific mutations (e.g., ALK-rearranged non-small cell lung cancer) and on the other side are markedly heterogeneous diseases where only non-discriminatory therapies have effect. GCs have the ability to fill this gap by analyzing numerous genes and weighting them based on their ability to drive cancer recurrence and metastasis, keying physicians in that more intensive or alternative therapy is warranted.

There are several trends across GCs that should be noted including that the majority of patients included in these studies are Caucasian. Baseline genetic heterogeneity between racial groups could have an impact on the external validity of these tests, and further research in this area is needed before broad application of any genetic test is appropriate across a diverse population. Finally, relatively few of the studies included comparisons of multiple GCs; as noted by Hunter [55], more research is needed to compare how risk categorizations differ between GCs.

**Conclusion**

GCs promise an era of precise, personalized cancer care. While there are several GCs that have been accepted for clinical use (particularly in breast cancer), our review demonstrates that there are a relatively limited number of studies available to provide supportive evidence of clinical utility. We await the prospective validation of several of the alternative GCs for other solid
tumors. Further research, including prospective validation is needed, particularly for non-breast cancer GCs.

Supporting information
S1 File. MeSH search criteria.
(PDF)
S2 File. PRISMA 2009 checklist.
(DOC)

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References
1. Garraway LA, Verweij J, Ballman KV. Precision oncology: an overview. J Clin Oncol. 2013; 31: 1803–1805. https://doi.org/10.1200/JCO.2013.49.4799 PMID: 23589545
2. Garraway LA. Genomics-driven oncology: framework for an emerging paradigm. J Clin Oncol. 2013; 31: 1806–1814. https://doi.org/10.1200/JCO.2012.46.8934 PMID: 23589557
3. Simon R, Wang S. Use of genomic signatures in therapeutics development in oncology and other diseases. 2006; 6: 166–173.
4. Golub TR, Slonim DK, Tamayo P, Huard C, Gaasenbeek M, Mesirov JP, et al. Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. Science. 1999; 286: 531–537. PMID: 10521349
5. Dinan MA, Mi X, Reed SD, Hirsch BR, Lyman GH, Curtis LH. Initial trends in the use of the 21-gene recurrence score assay for patients with breast cancer in the Medicare population, 2005–2009. 2015; 1: 158–166. https://doi.org/10.1001/jamaoncol.2015.43 PMID: 26181015
6. Hassett MJ, Silver SM, Hughes ME, Blayney DW, Edge SB, Herman JG, et al. Adoption of gene expression profile testing and association with use of chemotherapy among women with breast cancer. 2012; 30: 2218–2226. https://doi.org/10.1200/JCO.2011.38.5740 PMID: 22585699
7. Oruccevic A, Heidel RE, Bell JL. Utilization and impact of 21-gene recurrence score assay for breast cancer in clinical practice across the United States: lessons learned from the 2010 to 2012 National Cancer Data Base analysis. Breast Cancer Res Treat. 2016; 157: 427–435. https://doi.org/10.1007/s10549-016-3833-9 PMID: 27206678
8. Khoury MJ, Clauser SB, Freedman AN, Gillanders EM, Glasgow RE, Klein WM, et al. Population sciences, translational research, and the opportunities and challenges for genomics to reduce the burden of cancer in the 21st century. Cancer Epidemiol Biomarkers Prev. 2011; 20: 2105–2114. https://doi.org/10.1158/1055-9966.EPI-11-0481 PMID: 21795499
9. Simonds NI, Khoury MJ, Schully SD, Armstrong K, Cohn WF, Fenstermacher DA, et al. Comparative effectiveness research in cancer genomics and precision medicine: current landscape and future prospects. J Natl Cancer Inst. 2013; 105: 929–936. https://doi.org/10.1093/jnci/djt108 PMID: 23661804
10. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. 2009; 6: e1000097. https://doi.org/10.1371/journal.pmed.1000097 PMID: 19621072
11. McShane LM, Altman DG, Sauerbrei W, Taube SE, Clark GM, et al. Reporting recommendations for tumor marker prognostic studies (REMARK). J Natl Cancer Inst. 2005; 97: 1180–1184. https://doi.org/10.1093/jnci/dij257 PMID: 16106022
12. OncotypeDx. OncotypeDx Breast Recurrence Score: FAQs for Physicians. 2016. Available: http://breast-cancer.oncotypedx.com/en-US/Professional-Invasive/Resources/FAQs.aspx.
13. Agenda. Agenda: Company Overview. 2015. Available: http://www.agendia.com/about/company-overview/.
14. PRNewswire. Clarient Launches Insight® Dx Mammostrat® Breast Cancer Recurrence Test. 2010. Available: http://www.prnewswire.com/news-releases/clarient-launches-insight-dx-mammostrat-breast-cancer-recurrence-test-111586344.html.
15. NanoString Technologies. NanoString Launches Its First Commercial Diagnostic Product in the European Union and Israel. 2013. Available: http://www.nanosting.com/company/corp_press_release?id=74.
16. Agenda. Agenda: Milestones. 2015. Available: http://www.agendia.com/about/milestones/.
17. PRNewswire. GenomDx Biosciences Closes Series B Financing. 2013. Available: http://www.prnewswire.com/news-releases/genomdx-biosciences-closes-series-b-financing-225783691.html.
18. Chang JC, Makris A, Gutierrez MC, Hilsenbeck SG, Hackett JR, Jeong J, et al. Gene expression patterns in formalin-fixed, paraffin-embedded core biopsies predict docetaxel chemosensitivity in breast cancer patients. Breast Cancer Res Treat. 2008; 108: 233–240. https://doi.org/10.1007/s10549-007-9590-z PMID: 17468949
19. Goldstein LJ, Gray R, Badve S, Childs BH, Yoshizawa C, Rowley S, et al. Prognostic utility of the 21-gene assay in hormone receptor–positive operable breast cancer compared with classical clinicopathologic features. 2008; 26: 4063–4071. https://doi.org/10.1200/JCO.2007.14.4501 PMID: 18678838
20. Rayhanabad JA, Difronzo LA, Haigh PI, Romero L. Changing paradigms in breast cancer management: introducing molecular genetics into the treatment algorithm. Am Surg. 2008; 74: 887–890. PMID: 18942607
21. Kok M, Linn SC, Van Laar RK, Jansen MP, Van den Berg, Teun M, Delahaye LJ, et al. Comparison of gene expression profiles predicting progression in breast cancer patients treated with tamoxifen. Breast Cancer Res Treat. 2009; 113: 275–283. https://doi.org/10.1007/s10549-008-9939-y PMID: 18311582
22. Albain KS, Barlow WE, Shah S, Hortobagyi GN, Livingston RB, Yeh I, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. 2010; 11: 55–65. https://doi.org/10.1016/S1470-2045(09)70314-6 PMID: 20005174
23. Dowsett M, Cardoso F, Wesseling J, Bedard PL, Linn S, Rutgers E, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. 2010; 28: 1829–1834.
24. Knauer M, Cardoso F, Wesseling J, Bedard PL, Linn S, Rutgers E, et al. Identification of a low-risk subgroup of HER-2-positive breast cancer by the 70-gene prognosis signature. Br J Cancer. 2010; 103: 1788–1793. https://doi.org/10.1038/sj.bjc.6605916 PMID: 21081926
25. Iwamoto T, Lee J, Bianchini G, Hubbard RE, Young E, Matsuoka J, et al. First generation prognostic gene signatures for breast cancer predict both survival and chemotherapy sensitivity and identify
overlapping patient populations. Breast Cancer Res Treat. 2011; 130: 155. https://doi.org/10.1007/s10549-011-1706-9 PMID: 21833625

26. Joh JE, Esposito NN, Kiluk JV, Laronga C, Lee MC, Loftus L, et al. The effect of Oncotype DX recurrence score on treatment recommendations for patients with estrogen receptor-positive early stage breast cancer and correlation with estimation of recurrence risk by breast cancer specialists. Oncologist. 2011; 16: 1520–1526. https://doi.org/10.1634/theoncologist.2011-0045 PMID: 22016474

27. Lee JJ, Shen J. Is the Oncotype DX assay necessary in strongly estrogen receptor-positive breast cancers? Am Surg. 2011; 77: 1364–1367. PMID: 22127090

28. Kelly CM, Bernard PS, Krishnamurthy S, Wang B, Ebbert MT, Bastien RR, et al. Agreement in risk prediction between the 21-gene recurrence score assay (Oncotype DX(R)) and the PAM50 breast cancer intrinsic Classifier in early-stage estrogen receptor-positive breast cancer. Oncologist. 2012; 17: 492–498. https://doi.org/10.1634/theoncologist.2012-0007 PMID: 22418568

29. Lund MJ, Mosunaj M, Davis KM, Gabram-Mendola S, Rizzo M, Bumpers HL, et al. 21-Gene recurrence scores: racial differences in testing, scores, treatment, and outcome. Cancer. 2012; 118: 788–796. https://doi.org/10.1002/cncr.26180 PMID: 21720988

30. Sgroi DC, Sestak I, Cuzick J, Zhang Y, Schnabel CA, Schroeder B, et al. Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: a prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. 2013; 14: 1067–1076. https://doi.org/10.1016/S1470-2045(13)70387-5 PMID: 24035531

31. Hornberger J, Cosler LE, Lyman GH. Economic analysis of targeting chemotherapy using a 21-gene RT-PCR assay in lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer. Am J Manag Care. 2005; 11: 313–324. PMID: 15898220

32. Lyman GH, Cosler LE, Kuderer NM, Hornberger J. Impact of a 21-gene RT-PCR assay on treatment decisions in early-stage breast cancer. Cancer. 2007; 109: 1011–1018. https://doi.org/10.1002/cncr.22506 PMID: 17311307

33. Er Chen M, Tong KB, Malin JL. Cost-effectiveness of 70-gene MammaPrint signature in node-negative breast cancer. Am J Manag Care. 2010; 16: e333–e342. PMID: 21291290

34. Klang SH, Hammerman A, Liebermann N, Efrat N, Doberne J, Hornberger J. Economic implications of 21-gene breast cancer risk assay from the perspective of an Israeli-managed health-care organization. 2010; 13: 381–387.

35. Lo SS, Mumby PB, Norton J, Rychlik K, Smerage J, Kash J, et al. Prospective multicenter study of the impact of the 21-gene recurrence score assay on medical oncologist and patient adjuvant breast cancer treatment selection. 2010; 28: 1671–1676. https://doi.org/10.1200/JCO.2008.20.2119 PMID: 20065191

36. Retèl VP, Joore MA, Knauer M, Linn SC, Hauptmann M, van Harten WH. Cost-effectiveness of the 70-gene signature versus St. Gallen guidelines and Adjuvant Online for early breast cancer. Eur J Cancer. 2010; 46: 1382–1391. https://doi.org/10.1016/j.ejca.2010.02.035 PMID: 20359886

37. Tsol DT, Inoue M, Kelly CM, Verma S, Pritchard KL. Cost-effectiveness analysis of recurrence score-guided treatment using a 21-gene assay in early breast cancer. Oncologist. 2010; 15: 457–465. https://doi.org/10.1634/theoncologist.2009-0275 PMID: 20421264

38. Hornberger J, Chien R, Krebs K, Hochheiser L. US insurance program’s experience with a multigene assay for early-stage breast cancer. 2011; 7: e33s–e45s. https://doi.org/10.1200/JOP.2011.000303 PMID: 21886510

39. Vanderlaan BF, Broder MS, Chang EY, Oratz R, Bentley TG. Cost-effectiveness of 21-gene assay in node-positive, early-stage breast cancer. Am J Manag Care. 2011; 17: 455–464. PMID: 21819166

40. Hall PS, McCabe C, Stein RC, Cameron D. Economic evaluation of genomic test-directed chemotherapy for early-stage lymph node-positive breast cancer. J Natl Cancer Inst. 2012; 104: 56–66. https://doi.org/10.1093/jnci/djr484 PMID: 22138097

41. Hannouf MB, Xie B, Brackstone M, Zaric GS. Cost-effectiveness of a 21-gene recurrence score assay versus Canadian clinical practice in women with early-stage estrogen-or progesterone-receptor-positive, axillary lymph-node negative breast cancer. BMC Cancer. 2012; 12: 447. https://doi.org/10.1186/1471-2407-12-447 PMID: 23031196

42. Lamond NW, Skedgel C, Rayson D, Lethbridge L, Younis T. Cost-utility of the 21-gene recurrence score assay in node-negative and node-positive breast cancer. Breast Cancer Res Treat. 2012; 133: 1115–1123. https://doi.org/10.1007/s10549-012-1989-5 PMID: 22361999

43. Yang M, Rajan S, Issia AM. Cost effectiveness of gene expression profiling for early stage breast cancer. Cancer. 2012; 118: 5163–5170. https://doi.org/10.1002/cncr.27443 PMID: 22359236

44. de Boer RH, Baker C, Speakman D, Chao CY, Yoshizawa C, Mann GB. The impact of a genomic assay (Oncotype DX) on adjuvant treatment recommendations in early breast cancer. Med J Aust. 2013; 199: 205–208. PMID: 23909545
45. Holt S, Bertelli G, Humphreys I, Valentine W, Durrani S, Pudney D, et al. A decision impact, decision conflict and economic assessment of routine Oncotype DX testing of 146 women with node-negative or pN0mi, ER-positive breast cancer in the UK. Br J Cancer. 2013; 108: 2250–2258. https://doi.org/10.1038/bjc.2013.207 PMID: 23695023

46. Paulden M, Franek J, Bedard PL, Trudeau M, Krahn M. Cost-effectiveness of the 21-gene assay for guiding adjuvant chemotherapy decisions in early breast cancer. 2013; 16: 729–739. https://doi.org/10.1016/j.jval.2013.03.1625 PMID: 23947965

47. Reed SD, Dinan MA, Schulman KA, Lyman GH. Cost-effectiveness of the 21-gene recurrence score assay in the context of multifactorial decision making to guide chemotherapy for early-stage breast cancer. 2013; 15: 203–211. https://doi.org/10.1038/gim.2012.119 PMID: 22975761

48. Retèl V, Joore M, Drukker C, Bueno-de-Mesquita J, Knauer M, Van Tinteren H, et al. Prospective cost-effectiveness analysis of genomic profiling in breast cancer. Eur J Cancer. 2013; 49: 3773–3779. https://doi.org/10.1016/j.ejca.2013.08.001 PMID: 23992641

49. Ward S, Scope A, Rafia R, Pandor A, Harnan S, Evans P, et al. Gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in breast cancer management: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2013; 17.

50. Mislick K, Schonfeld W, Bodnar C, Tong KB. Cost-effectiveness analysis of Mammostrat(R) compared with Oncotype DX(R) to inform the treatment of breast cancer. Clincioecoon Outcomes Res. 2014; 6: 37–47. https://doi.org/10.2147/CEOR.S53142 PMID: 24470765

51. Maak M, Simon I, Nitsche U, Roepman P, Snel M, Glas AM, et al. Independent validation of a prognostic genomic signature (ColoPrint) for patients with stage II colon cancer. Ann Surg. 2013; 257: 1053–1058. https://doi.org/10.1097/SLA.0b013e31827c1180 PMID: 23295318

52. Cooperberg MR, Davicioni E, Crisan A, Jenkins RB, Ghadessi M, Karnes RJ. Combined value of validated clinical and genomic risk stratification tools for predicting prostate cancer mortality in a high-risk prostatectomy cohort. Eur Urol. 2015; 67: 326–333. https://doi.org/10.1016/j.eururo.2014.05.039 PMID: 24998118

53. Hornberger J, Lyman GH, Chien R, Meropol NJ. A multigene prognostic assay for selection of adjuvant chemotherapy in patients with T3, stage II colon cancer: impact on quality-adjusted life expectancy and costs. 2012; 15: 1014–1021. https://doi.org/10.1016/j.jval.2012.07.012 PMID: 23244802

54. Roth JA, Billings P, Ramsey SD, Dumanois R, Carlson JJ. Cost-effectiveness of a 14-gene risk score assay to target adjuvant chemotherapy in early stage non-squamous non-small cell lung cancer. Oncologist. 2014; 19: 466–476. https://doi.org/10.1634/theoncologist.2013-0357 PMID: 24710309

55. Hunter DJ. Uncertainty in the era of precision medicine. N Engl J Med. 2016; 375: 711–713. https://doi.org/10.1056/NEJMp1608282 PMID: 27557298