TITLE: **Oncotype DX in Women and Men with ER-Positive, HER2-Negative Early Stage Breast Cancer who are Lymph Node Negative: A Review of Clinical Effectiveness and Guidelines**

DATE: 20 February 2014

CONTEXT AND POLICY ISSUES

For patients with estrogen receptor-positive (ER+) and lymph node-negative (LN-) early stage breast cancer (ESBC), the decision to initiate adjuvant chemotherapy (ACT) after surgery has traditionally been guided by clinical and pathological factors (i.e., characteristics of the patient and the tumour), in conjunction with clinician and patient preferences. In the absence of ACT, 15% of these patients will have a cancer recurrence within 5 years yet up to 90% receive ACT.[1] Unfortunately, many patients are therefore exposed to ACT toxicity and cost with little or no clinical benefit, and identifying those who do benefit remains a challenge.[1] The dilemma has pushed researchers to seek additional methods to evaluate cancer recurrence risk in order to support better decision-making about ACT. Gene-expression profiling (GEP) is an emerging clinical strategy which proposes to meet this need by using genomic information to inform risk prediction and treatment selection one patient at a time.[1]

Oncotype DX (ODX) (Genomic Health, Inc., Redwood City, CA) is a serum GEP test that was first marketed in the United States (US) in 2004. It was designed to measure the 10-year risk of tumor recurrence in ESBC at the time of initial diagnosis.[2] Risk is reported as a 21-gene signature or recurrence score (RS) on a scale of 0-100. The RS is then translated into one of three categories of risk: low (RS<18), intermediate (RS 18-30), or high (RS>30).[2] ODX aims to complement traditional prognostic information via better risk stratification, and thus help to identify patients most likely to benefit from ACT. ODX was initially developed in women with ER+ LN- ESBC (65% of patients at diagnosis), although its use has since been explored for the lymph node-positive (LN+) population.[2-5] This report explores the evidence available to date on the use of ODX in patients with ER+ LN- ESBC,,the clinical utility of the test, and its impact on treatment decisions.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of Oncotype DX in women and men with ER positive, HER2 negative early stage breast cancer who are node negative?

2. What are the guidelines associated with Oncotype DX in women and men with ER positive, HER2 negative early stage breast cancer who are node negative?

KEY FINDINGS

An OncotypeDX (ODX) recurrence score aims to (a) provide prognosis with respect to 10-year recurrence of breast cancer, and (b) guide the need for adjuvant chemotherapy (ACT) treatment. The evidence base for the use of ODX in women with ER+ HER2- LN- early stage breast cancer (ESBC) to guide ACT treatment decisions includes four recent examples of secondary research (health technology assessments [HTAs] and systematic reviews [SRs]) and four additional primary studies. There is no evidence related specifically to men. Results consistently show about 30% of treatment plans are affected, primarily being lower rates of ACT for patients determined to be at low recurrence risk. For a smaller proportion determined to be at higher risk, ACT is suggested where initial treatment planning did not include ACT. The most uncertainty relates to the intermediate risk category where evidence is unclear; a large 7-country study (TAILORx) is focussing on the treatment of this group with study completion planned for late 2017.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international HTA agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and December 18, 2013. The grey literature search was conducted on January 31, 2014.

Selection Criteria and Methods

Publications were selected if they reported on women and men with ESBC that was ER+ HER2- and LN- who received ODX testing for ACT planning and / or disease prognosis, according to the selection criteria outlined in Table 1. The focus for the evidence review was on secondary research (HTAs and SRs) with primary studies sought if they were more recent than those included in the secondary research. Of interest was the clinical effectiveness of the testing. Place in therapy of ODX testing in clinical practice guidelines (CPG) was also explored. One

reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection.

Table 1: Selection Criteria

Population	Women and men with ER+ HER2- LN- ESBC
Index Test	Oncotype DX
Comparator	None
Outcomes	Clinical effectiveness (validity and utility), including patient safety
Study Designs	• HTAs / systematic reviews / meta-analyses; recent primary research if necessary • Clinical practice guidelines

Exclusion Criteria

Studies were excluded if, in the event of a mixed population (i.e., LN- and LN+), results were not presented separately for LN- patients. Likewise, to be considered for inclusion in this review, clinical validity or utility had to be specified as outcomes.

Critical Appraisal of Individual Studies

The AMSTAR instrument[6] was used to guide the critical appraisal of the methodological quality of the HTAs and systematic reviews included in this report. For the four recent prospective studies, attention was paid to study size and design, blinding, possible sources of bias, and funding and potential conflicts-of-interest. For the CPGs, AGREE II[7] was used as a guide with particular attention paid to CPG scope (including specific patient population and intended users); funder and potential conflicts-of-interest of the developers; and aspects of CPG methodology such as extent and reporting of the literature search, types of included evidence, types of clinical outcomes tracked, and grading of evidence and recommendations.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 222 citations. After screening titles and abstracts, 190 articles were excluded and 32 potentially relevant articles were selected for full-text review. Four relevant citations were identified from the grey literature and six by hand-searching. Of the 42 reports, 28 did not meet the inclusion criteria and were excluded, leaving a total of eight relevant reports for the clinical review and six clinical practice guidelines. Of the eight articles identified for the clinical review, four articles were secondary research (HTAs or SRs)[1,2,8,9] and the other four were primary studies published after the secondary research completed literature searching.[10-12] On-going clinical trials of relevance to this topic area are provided in Appendix 1. The study selection process is outlined in the PRISMA flowchart in Appendix 2. The evidence for each research question is reported separately.

What is the clinical effectiveness of ODX in women and men with ER+ HER2- LN- ESBC?

Summary of Study Characteristics

Four secondary reviews were included – two HTAs[2,8] and two SRs[1,9] – and four clinical studies published more recently.[3,10-12] See Appendix 3 for study detail. The secondary research originated in Canada, Spain, the UK and the US and each included from four to 23 studies. Included studies were generally retrospective, either retrospective analyses of data from previous randomized controlled trials or retrospective cohort studies with the Spanish report[9] being the exception as it only allowed prospective studies conducted in Europe. The recent primary studies were from Australia, Canada, Germany and Japan and all were prospective, enrolling consecutive women. All included evidence was published in 2012 or 2013 with the secondary research reporting recent literature cut-off dates (2011-2013). All research focused on patients with ER+ HER2- LN- ESBC comparing the recommendations for treatment before and after revealing the ODX RS. Two publications included LN+ patients but reported data for this population separately. Initial treatment planning was generally based on current clinic-pathologic factors although the UK review[2] included the use of additional prognostic tools such as Adjuvant! Online and / or the Nottingham Prognostic Index. Research focused on the impact of ODX RS on treatment planning, particularly the switch from ACT to no ACT or vice versa based on patient RS.

Summary of Critical Appraisal

One review was available as a conference abstract[9] only but was included as it focused on prospective European studies (with three of the four included studies also published as conference abstracts). The remaining three reviews were limited to the evidence available which did not include prospective studies of the use of RS followed by changes in treatment with long-term follow-up to determine outcomes. Three of the reviews reported rigorous methodology such as descriptions of comprehensive literature searches and use of two independent data extractors; the fourth review[9] was reported only in abstract form and therefore methodological detail was limited. One of the reviews reported industry funding.[9] The four recent examples of primary research were similar - all were prospective cohort studies of clinical utility enrolling consecutive cohorts of women with ER+ HER2- LN- ESBC and all were funded by Genomic Health Inc. with conflicts-of-interest reported by a number of the researchers. All tracked treatment recommendations (ACT or no ACT) before and after ODX RS results were known and then reported the differences attributed to knowledge of RS; however, the prospective studies did not report long-term follow-up as to actual patient treatment or outcomes. Details of the critical appraisal of individual studies are provided in Appendix 4.

Summary of Findings

All publications reported that ODX RS changed treatment recommendations for many patients – generally at least 30%. Of patients for whom a change was suggested, more than half (up to 79% in one study[10]) had an ACT recommendation dropped as their RS showed them to be at

low risk of recurrence. A smaller proportion had a recommendation for ACT added if the RS score showed them to be at high risk. A consistent approach appeared be that the advice for treating patients at low risk and high risk is clear; it is the group deemed to be at intermediate risk where there is uncertainty. Clarity will come with the 2017 completion of the TAILORx trial that is prospectively investigating this patient group (see Appendix 1). Details of individual study findings are reported in Appendix 5.

What CPGs are associated with ODX in women and men with ER+ HER2- LN- ESBC?

Six sets of guidance were reviewed and included here.[13-18] This included materials from Ontario, Canada;[16] Europe;[14] a large international collaboration;[15] the United Kingdom;[18] and the US.[13,17]

Summary of Guideline Characteristics

Overall, the guidance is very recent with only one set of CPGs issued more than one year ago.[13] Generally, the guidance appeared to be for physicians although in two cases patients were identified as potential users.[16,17] Included patient populations varied with two narrowing the group from patients with breast cancer to patients with ESBC.[15,16] While three of the CPGs covered management of breast cancer,[14,15,17] three focused specifically on genetic testing.[13,16,18] Details of individual guideline characteristics are provided in Appendix 6.

Summary of Critical Appraisal of Guidelines

With respect to reported CPG methodology, descriptions were poor in all but one document.[19] Two CPGs reported the details of their literature searches[13,16] with one including an evidence synthesis as a support for the recommendations.[16] In addition, the CPGs from NICE referred to an extensive HTA that was used as an evidence base.[18] Underlying evidence for the recommendations was cited by all CPGs although only two assigned levels to the evidence[13,14] and one also assigned grades to the recommendations.[14] Funding for CPG development was reported by three initiatives,[15,16] and potential conflicts-of-interest were reported by five with four including some involvement of Genomic Health, Inc.[13-15,18]

Summary of Guideline Recommendations

All guidance was supportive of the value of ODX testing for both prognosis and ACT planning (except the work by Cancer Care Ontario [CCO] that was not meant to provide advice about when to use the test). Three of the CPGs specifically suggested ODX as an option for patients with ER+ HER2- LN- disease. Often the CPG developers recommended ODX over competitor technologies due to a larger body of evidence available for ODX. This was particularly true in the document developed by the CCO that focused on differences among tests. Details of the recommendations from the included CPGs are provided in Appendix 7.

LIMITATIONS

A significant limitation is the fact that the main outcomes of available studies relate to changes in decision-making and treatment, and the impact of those changes on patient outcomes is not reported. Furthermore there is no true reference standard to which ODX can be compared, and the use of the technology in a male population remains a research gap. An additional limitation of the evidence is a reliance on retrospective studies that used archived blocks of breast tumour tissue for ODX RS testing. However, a number of prospective studies are underway including a very large US-led clinical trial (TAILORx) of 11,000 women with ER+ HER2- LN- in seven countries, in which hormone therapy alone is being compared with standard care (i.e. hormone therapy + ACT) in a randomized sub-study of women classified at intermediate risk for tumour recurrence by ODX testing. The TAILORx study is funded by the Breast Cancer Research Foundation. Other prospective studies are underway or have been recently reported, with Genomic Health Inc. playing a major role in both study funding and support for researchers.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The evidence for the contribution of ODX RS to both disease prognosis (tumour recurrence within 10 years) and treatment planning (the value of adding ACT or not, depending on RS) is accumulating with all identified primary and secondary research supporting some benefits of the technology. However, the extent of the benefit is still unclear, as differences in patient clinical outcomes as a result of changes in treatment decision-making remain unknown. An outstanding issue awaiting clarity is the recommended course of action for patients classified as being at intermediate risk. In addition, there are a number of competitive technologies available including risk stratifiers available at no cost. The patented ODX RS test is exclusively performed by a California laboratory at a cost of at least $4000 and currently Canadian patients who are able to access the test appear to be paying privately. Expanded use of the test will require adequate education for providers and patients, observation about what choices providers and patients actually make once the ODX information is obtained, and how this technology impacts health outcomes and health system costs. Decision-makers will be interested in economic analyses that examine the costs of testing versus the traditional costs of treatment.

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APPENDIX 1: List of On-going Clinical Trials

1. Ontario Trial:

   ClinicalTrials.gov [Internet]. Bethesda (MD): NLM; 2000 Feb 29 -. Identifier NCT01423890. A prospective cohort study to evaluate the Oncotype DX® test in early stage breast cancer (ONCOTYPEDX); 2013 Aug 6 [cited 2014 Feb 4]. Available from: http://www.clinicaltrials.gov/ct2/show/record/NCT01423890?term=oncotype+DX+node+negative&rank=2

   Sponsored by the Ontario Clinical Oncology Group with the Ontario Ministry of Health and Long Term Care as a collaborator, the study started in January 2012 with results anticipated in March 2014. Enrolled are 1000 women and men with ER+ HER2- LN- ESBC on endocrine therapy who are candidates for ACT. The primary outcomes are changes in oncologist treatment recommendations and patient treatment preferences based on ODX.

2. TAILORx US Trial:

   ClinicalTrials.gov [Internet]. Bethesda (MD): NLM; 2000 Feb 29 -. Identifier NCT00310180. Hormone therapy with or without combination chemotherapy in treating women who have undergone surgery for node-negative breast cancer; 2013 Nov 4 [cited 2014 Feb 4]. Available from: http://www.clinicaltrials.gov/ct2/show?term=oncotype+DX+node+negative&rank=1

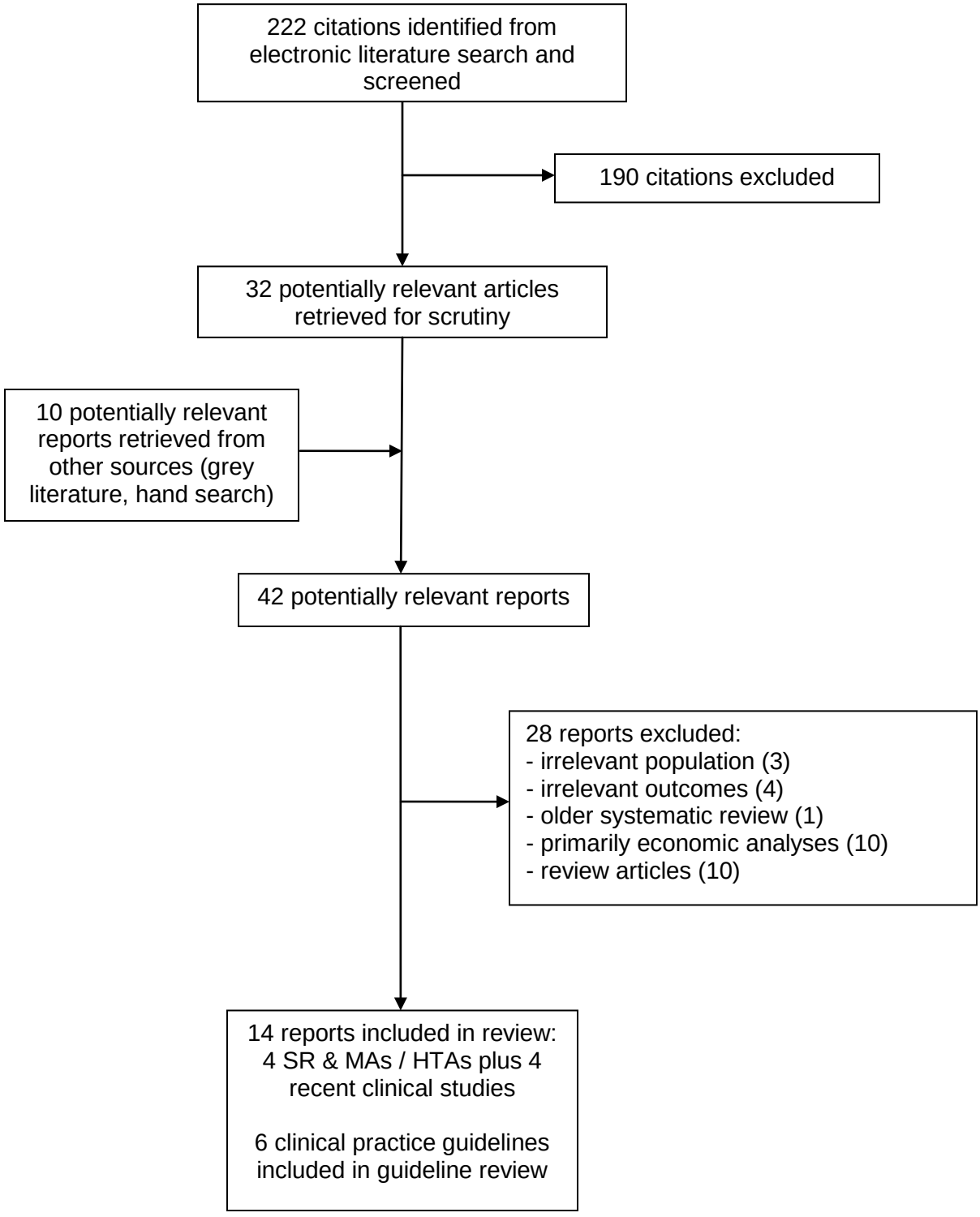
   Sponsored by the US National Cancer Institute, the study started in April 2006 with study completion anticipated in December 2017. Enrolled are > 11,000 women with ER+ and/or PR+ HER2- LN- ESBC in Australia, Canada, Ireland, New Zealand, Peru, Puerto Rico and US who had breast-conservation surgery plus radiotherapy. Patients were divided into three experimental groups depending on the RS: Group 1 (low risk) receive hormone therapy only and Group 3 (high risk) receive ACT followed by hormone therapy. Those in Group 2 (intermediate risk) are randomized to receive either hormone therapy alone (as for Group 1) or combination ACT and hormone therapy (as for Group 3). Follow-up is planned for up to 20 years. The primary outcome measure is disease-free survival at up to 10 years.

3. French Trial

   ClinicalTrials.gov [Internet]. Bethesda (MD): NLM; 2000 Feb 29 -. Identifier NCT01446185. Treatment decision impact of OncotypeDX™ in HR+, N- breast cancer patients (SWITCH); 2013 Apr 17 [cited 2014 Feb 4]. Available from: http://www.clinicaltrials.gov/ct2/show/study?term=oncotype+DX+node+negative&rank=3

   Sponsored by Genomic Health®, Inc., the study at six centres in France started in January 2011 and ended in May 2012 but no study results appear to be available. Enrolled were 100 women with ER+ HER2- LN- (or pN1(mi)) ESBC. The study's primary objective was to determine the impact of the ODX RS on ACT treatment recommendation with a desire to assess test performance specifically in France.

APPENDIX 2: Selection of Included Studies



APPENDIX 3: Summary of Clinical Study Characteristics

Table A1: Summary of Characteristics of Included Clinical Reviews

First Author, Publication Year, Country	Study Design	Patient Characteristics, Sample Size (n)	Index test	Comparator(s)	Clinical Outcomes
HTAs / Systematic Reviews / Meta-analyses					
Albanel,[9] 2012, Spain [conference abstract]	SR & MA	ESBC ER+ HER2- LN- patients. Analysis included 4 prospective studies from Europe (France, Germany, Spain, UK) (n=565 patients)	ODX	"Traditional parameters" for decision making	Clinical utility of ODX to impact ACT decisions
Carlson,[1] 2013, USA	SR & MA	ESBC ER+ LN- patients. SR included 23 studies (8 in abstract form) with a literature search up to March 2012	ODX	Treatment based on clinic-pathological factors	Clinical utility of ODX in community practice (impact on ACT)
Tiwana,[8] 2013, Canada (Alberta)	HTA	ESBC ER+ LN- and LN+ (reported separately for some analyses). HTA included 14 studies with a literature search up to December 2012	ODX	Treatment based on clinic-pathological factors	Clinical utility of ODX to (a) predict survival, disease-free survival and risk of distant recurrence; and (b) impact ACT decisions
Ward,[2] 2013, UK	HTA	ESBC in ACT setting (majority ER+ LN-). HTA included 12 studies (2 in abstract form) with a literature search up to May 2011	Nine GEP or expanded IHC tests, including ODX	Current UK clinical practice (i.e., Adjuvant! Online and/or Nottingham Prognostic Index)	Clinical validity; clinical utility

ACT=Adjuvant chemotherapy; ER=Estrogen receptor; ESBC=Early stage breast cancer; GEP=Gene expression profiling; HER2=Human epidermal growth factor receptor 2; HTA=health technology assessment; IHC= immunohistochemistry; LN=Lymph node; MA=Meta-analysis; ODX=Oncotype DX; SR=Systematic review; UK=United Kingdom

Table A2: Summary of Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics, Sample Size (n)	Index test	Comparator(s)	Clinical Outcomes
Davidson,[12] 2013, Canada (2 BC Cancer Centres)	Prospective cohort study of clinical utility	150 consecutive women with ER+ HER2- LN- ESBC; mean age 53 (range 23-78) years; 54% pre-menopausal	ODX	Treatment based on clinic-pathological factors (using locally developed CPGs)	Clinical utility of ODX to impact ACT decisions
deBoer,[3] 2013, Australia (3 centres)	Prospective cohort study of clinical utility	101 consecutive women with ER+ HER2- LN- ESBC; mean age 57	ODX	Treatment based on clinic-pathological factors	Clinical utility of ODX to impact ACT decisions
Eiermann,[11] 2013, Germany (15 sites)	Prospective cohort study of clinical utility	244 consecutive women with ER+ HER2- LN- ESBC; mean age 56 years	ODX	Treatment based on clinic-pathological factors (using local treatment algorithms)	Clinical utility of ODX to impact ACT decisions
Yamauchi,[10] 2013, Japan (2 centres)	Prospective cohort study of clinical utility	104 consecutive women with ER+ HER2- LN- ESBC; mean age 50 years	ODX	Presumed to be treatment based on clinic-pathological factors (not stated)	Clinical utility of ODX to impact ACT decisions

ACT=Adjuvant chemotherapy; BC=British Columbia; CPG=clinical practice guideline; ER=Estrogen receptor; ESBC=Early stage breast cancer; HER2=Human epidermal growth factor receptor 2; LN=Lymph node; ODX=Oncotype DX

APPENDIX 4: Summary of Critical Appraisal

Table A3: Summary of Critical Appraisal of Included Clinical Reviews

First Author, Pub. Year	Strengths	Limitations
Albanel, [9] 2012 [conference abstract]	• Only prospective clinical studies were included. • All included patients had ER+ HER2- LN- ESBC with ODX performed and RS recorded.	• Material only reported in abstract form. • Methods description limited, e.g., no detail about literature search or data extraction manpower. • Three of four included studies reported in abstract form only – all funded by Genomic Health, Inc. • Across studies, patient ages were similar but significant variation in tumor size and grade. • All authors had potential conflicts-of-interest related to relationships with Genomic Health, Inc.
Carlson, [1] 2013	• Research question and inclusion criteria established *a priori.* • Comprehensive literature search. • Two independent data extractors. • Contacted corresponding authors if data were incomplete. • Assessed heterogeneity and publication bias.	• Literature search limited to English language. • About 1/3 of included studies were abstracts. • List of excluded studies not provided although PRISMA diagram provided. • Methodological quality of included studies not assessed. • Unable to adjust for patient-level confounders in the pooled analysis as the data were at study level. • Included studies primarily from US academic centres (may not generalize).
Tiwana, [8] 2013	• Research question and inclusion criteria established *a priori.* • Comprehensive literature search with no language restrictions. • Two independent data extractors. • Quality of non-randomized studies assessed. • Research / authors declared no COI.	• Not always clear what the LN status of patients was (multiple analyses performed). • Unable to adjust for patient-level confounders in the pooled analysis as the data were at study level.
Ward,[2] 2013	• Update of two earlier high-quality SRs (2008 and 2010) with 12 additional studies (9 retrospective). • Research question and inclusion criteria established *a priori.* • Comprehensive literature search. • A listing of included and excluded studies was provided. • Quality assessment of studies. • Declarations of interest and sources of financial support were reported.	• Study selection and data extraction performed by single reviewer (uncertainty or discrepancies resolved with second or third reviewer). • Literature search limited to English language articles (unless no other comparable publications).

AB=Alberta; ACT=Adjuvant chemotherapy; AHRQ=Agency for Health Research and Quality; COI=Conflict of interest; ER=Estrogen receptor; ESBC=Early stage breast cancer; HER2=Human epidermal growth factor receptor 2; LN=Lymph node; MoH=Ministry of Health; ODX=Oncotype DX; RS=Recurrence score

Table A4: Summary of Critical Appraisal of Included Primary Clinical Studies

Author, Pub. Year	Strengths	Limitations
Davidson, [12] 2013	• Prospective design / consecutive recruitment. • ODX results not shared until initial treatment planning was complete.	• Cohort study. • Study funded by Genomic Health, Inc. • Three of 18 researchers had potential COI related to Genomic Health, Inc.
deBoer, [3] 2013	• Prospective design / consecutive recruitment. • ODX results not shared until initial treatment planning was complete (before and after design)	• Cohort study. • Study funded by Genomic Health, Inc. • Four of 6 researchers had potential COI related to Genomic Health, Inc.
Eiermann, [11] 2013,	• Prospective design / consecutive recruitment. • ODX results not shared until initial treatment planning was completed by the tumour board.	• Cohort study. • Study funded by Genomic Health, Inc. • Six of 16 researchers had potential COI related to Genomic Health, Inc.
Yamauchi, [10] 2013	• Prospective design / consecutive recruitment.	• Cohort study. • Small sample size (planned for 200 but enrollment stopped after benefit was found). • Patients had to pay for the assay costs themselves (cost generally about $4000); likely skewed types of patients participating but no data provided on patients who declined enrollment. • Unclear whether initial planning was completely blind to ODX results. • Study funding not reported; 6 of 10 researchers had potential COI related to Genomic Health, Inc.

COI=Conflict of interest; ODX=Oncotype DX

APPENDIX 5: Summary of Clinical Study Findings

Table A5: Summary of Study Findings and Authors' Conclusions for Included Reviews

Author, Yr	Main Study Findings	Authors' Conclusions
Albanel, [9] 2012 [conference abstract]	• ODX results changed the clinical-pathological recommendation in 32% of patients (including those with intermediate RS where change was 31%). • Of patients to originally receive ACT, 48% were recommended HT alone after RS result; of patients to originally receive HT alone, 18% were recommended ACT after RS result. • 26% relative reduction in numbers of patients to receive ACT after RS score.	• *"… [ODX] testing has a significant and similar impact on adjuvant treatment decisions despite differences in therapeutic traditions, with an overall change rate of 32%."* (Pg. 1) • *"[RS] category predicted, independently of age group, tumor size category, or tumor grade, the likelihood of changing adjuvant treatment recommendations."* (Pg. 1) • *"The consistency of the results from different countries underlines the utility of [ODX]."* (Pg. 1)
Carlson, [1] 2013	• ODX results changed the clinical-pathological ACT recommendation in 33% of patients. • In patients receiving ODX, receipt of ACT were: 28% overall, 6% low risk, 37% intermediate risk, and 83% high risk. • Low RS patients were significantly more likely to follow the treatment suggested by ODX versus high RS patients.	• *"…there is good supporting evidence for [ODX testing] for both accurate risk stratification and the prediction of chemotherapy benefit, but further prospective evidence is desired to fully evaluate the clinical utility."* (Pg. 19) • *"the use of GEP testing holds the promise of improved risk stratification, treatment selection, and the commensurate clinical and economic benefits that follow. However, our enthusiasm should be measured and proceed in step with the generation and evaluation of high-quality supporting evidence, such that our decisions are based not on promise, but on the critical evaluation and rational assessment of the evidence."* (Pg. 20)
Tiwana, [8] 2013	• Ability to predict 10-year survival: Cited a NICE report that concluded ODX was "*an independent predictor of survival, DFS and risk of distant recurrence*." • With respect to recommended changes due to ODX results: (a) changed recommendation in 32% of patients; (b) 18% reduction in ACT recommendation; (c) 42% of patients with ACT recommendation moved to no ACT; (d) 15% of patients with recommendation for no ACT moved to ACT.	• *"The survival difference between those treated with [ACT[and those treated with hormones is greater in those with a high risk [ODX] score than those with a low risk score [but] limited, low quality evidence supports the clinical utility of [ODX] to predict benefit from chemotherapy."* (Pg. 26) • *'All studies reported a change in practice supporting the pooling of results and conclusion that [ODX] does result in a clinical change"* [although a high degree of heterogeneity among studies] (Pg. 76)
Ward, [2] 2013	• Clinical validity: [As compared with previous SRs], further larger studies now exist that support the prognostic capability of [ODX]. • Clinical utility: Although studies document changes in decision-making for 32% to 38% of patients, many have methodological flaws and only one was UK-based.	• *"[ODX] was shown to be a better predictor of distant recurrence at 10 years than traditional clinic-pathological predictors ... [ODX] evidence is the furthest along the validation pathway compared with other similar tests, and the evidence base, in particular in relation to the prognostic ability of the test, was reasonably sound."* (Pg. 40) • *"There are no prospective studies reporting the impact of ODX on long-term outcomes such as overall survival."* (Pg. 153)

ACT=Adjuvant chemotherapy; DFS=Disease free survival; ER=Estrogen receptor; ESBC=Early stage breast cancer; HT=hormone therapy; LN=Lymph node; NICE=National Institute for Health and Care Excellence; ODX=Oncotype DX; SR=Systematic review; UK=United Kingdom

Table A6: Summary of Study Findings and Authors' Conclusions for Primary Clinical Studies

First Author, Year	Main Study Findings	Authors' Conclusions
Davidson, [12] 2013	With respect to recommended changes due to ODX results: (a) changed recommendation in 45 patients (30%; 95%CI: 22.8-38.0%); (b) in 67% of these patients, the recommendation for ACT changed to no ACT; (d) in 33%, the recommendation for no ACT moved to ACT.	"*Within the context of a publicly funded health care system, the [ODX RS] significantly affects adjuvant treatment recommendations*." (Pg. 2470)
deBoer,[3] 2013	With respect to recommended changes due to ODX results: (a) changed recommendation in 24 patients (24%); (b) in 12 of 30 patients, the recommendation for ACT changed to no ACT (a drop of 40%); (d) in 12 of 71, the recommendation for no ACT moved to ACT (an increase of 17%).	• *"[ODX RS] had a major impact on ACT decision-making."* (Pg. 205) • *"Our data suggest that use of the assay can spare patients potentially unnecessary treatment as well as identify patients for whom potentially lifesaving therapy might otherwise be omitted."* (Pg. 207)
Eiermann, [11] 2013	With respect to recommended changes due to ODX results: (a) changed recommendation in 74 patients (30%; 95%CI: 24.6-36.5%); (b) in 60% of these patients, recommendation for ACT changed to no ACT; (d) in 40% of these patients, recommendation for no ACT moved to ACT.	• *"RS-guided chemotherapy decision-making resulted in a substantial modification of [ACT] usage."* (Pg. 618) • *"[The impact of the RS on decision-making] resulted in a substantial reduction of [ACT] usage and should thus support efforts to improve the access for patients."* (Pg. 623)
Yamauchi, [10] 2013	With respect to recommended changes due to ODX results: (a) changed recommendation in 34 patients (33%; 95%CI: 24-43%); (b) in 79% of these patients, recommendation for ACT changed to no ACT; (d) in 21% of these patients, recommendation for no ACT moved to ACT.	• *"In ER+ LN- disease, results consistently show a revision of treatment recommendations in approximately 35% of cases and a predominant shift of recommendations from ACT to hormonal treatment alone."* (Pg. 7) • *"Results from this prospective study in a Japanese population confirm an effect of [ODX] on adjuvant treatment decision-making, consistent with reported experiences from the United States and Europe."* (Pg. 1)

ACT=Adjuvant chemotherapy; CI=Confidence interval; DFS=Disease free survival; ER=Estrogen receptor; LN=Lymph node; ODX=Oncotype DX; RS=Recurrence score

APPENDIX 6: Summary of Guideline Characteristics

Table A7: Summary of Characteristics of Included CPGs (listed alphabetically)

Org., Year, Country	Scope of CPG	Intended CPG Users	Patient Population	CPG Development Methods	Funder; COI
ASCO,[13] 2007, USA (updated from 2000)	Use of tumor markers in breast cancer (13 markers considered)	Physicians	Patients with breast cancer	Literature searches were performed (details included). The 9-members committee's review focused on SRs. Significant outcomes (e.g., overall survival, disease-free survival, and CEA) supported recommendations.	CPG funding was not reported; one author disclosed a relationship with Genomic Health, Inc.
CCO,[16] 2013, Canada (Molecular Oncology Advisory Committee	To compare ODX with other prognostic tests available in ON (i.e., not to recommend test indications as it was assumed clinicians had this knowledge)	Clinicians, patients and funding bodies	Patients with ESBC	Developed as a quality initiative of the CCO PEBC. Methods included an extensive literature search of CPGs, SRs and primary literature (search strategy presented) and a 25-page qualitative synthesis of the evidence (28 studies) as a support for the recommendations.	Funded by Ontario MOHLTC; no authors declared COI
ESMO,[14] 2013, Europe (8 countries)	Primary breast cancer: diagnosis, treatment and follow-up	Presumed physicians	Patients with breast cancer	Methodology not discussed although the supporting evidence was classified (I to V) and the grade of each recommendation was classified (A to E).	CPG funding was not reported; one author disclosed a relationship with Genomic Health, Inc.
NCCN,[17] 2014, USA	Breast cancer: diagnosis, treatment and follow-up	Physicians (version for patients also)	Patients with breast cancer	Methodology not discussed within this extensive document (180 pages; 570 references; 28 panel members)	CPG funding and participant COI were not reported
NICE,[18] 2013, UK	GEP and IHC tests (n=4) to guide ACT in management of ESBC	Presumed physicians	Patients with breast cancer (esp. ER+ HER2- LN-)	Methodology not discussed within the guideline except that the underlying evidence was the detailed HTA performed by Ward et al.(2011)[2]	CPG funding and participant COI were not reported. Genomic Health and the 3 other manufacturers participated as stakeholders.
St. Gallen, [15] 2013, International	Treatment of women with ESBC	Presumed physicians	Patients with ESBC	Expert Panel reviewed questions developed by iterative consultation over the months preceding the conference. Voting was" yes, no or abstain" (the latter for COI or insufficient evidence or knowledge).	Conference funded by registration fees and a grant from the USA NCI; COI tables included for participants; 4 of 77 listed Genomic Health, Inc.

ACT=adjunct chemotherapy; ASCO=American Society of Clinical Oncology; CCO=Cancer Care Ontario; CEA=Cost-effective analysis; COI=Conflict of interest; CPG=Clinical practice guideline; ESBC=Early stage breast cancer; ESMO=European Society of Medical Oncologists; GEP=Gene expression profiling; IHC=Immunohistochemistry; MoH=Ministry of Health and Long-term Care; NCCN=National Comprehensive Cancer Network; NCI=National Cancer Institute; NICE=National Institute for Health and Clinical Care; ODX=Oncotype DX; ON=Ontario; PEBC=Program in Evidence-based Care; QOL=Quality of life; SR=Systematic review; UK=United Kingdom; USA=United States

APPENDIX 7: Summary of Clinical Study Characteristics

Table A8: Relevant Recommendations from Included CPGs (listed alphabetically)

Organization, Publication Year, Country	CPG Recommendations Related to OPX Testing
ASCO,[13] 2007, USA	"*In newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer, [ODX] can be used to predict the risk of recurrence in patients treated with tamoxifen. ODX may be used to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy. In addition, patients with high recurrence scores appear to achieve relatively more benefit from adjuvant chemotherapy than from tamoxifen."* (Pg. 5289)
CCO,[16] 2013	• *"In cases of breast carcinoma where Oncotype DX is indicated for clinical prognosis and treatment decisions, other assays should not currently be considered equivalent with respect to data generated or risk stratification." (Recommendation #1)* (Pg. 2) • *"In cases where it is unclear whether or not Oncotype DX is indicated for clinical prognosis and treatment decisions, Adjuvant! Online may be used as a no-cost method …these assays should not be considered equivalent to Oncotype DX if the latter is indicated." (Recommendation #2)* (Pg. 3) • *"Given the preliminary status of much of the available evidence, periodic reassessment… is recommended. (Recommendation #3)* (Pg. 4)
ESMO,[14] 2013, Europe	*"In case of uncertainty regarding indications for adjuvant chemotherapy (after consideration of other tests), gene expression assays such as MammaPrint® or Oncotype DX® may be used where available to determine the individual recurrence risk and predict the benefit from chemotherapy [IV, A]"* (Pg. vi15) [Note: Level of Evidence IV is defined as 'retrospective cohort studies or case-control studies' and Grade of Recommendation A is defined as 'strong evidence for efficacy with a substantial clinical benefit, strongly recommended'.]
NCCN,[17] 2014, USA	*"Pending the results of prospective trials, the Panel considers [ODX] an option when evaluating patients with primary tumors characterized as 0.6-1.0 cm with unfavorable features or >1 cm and ER+ HER2- LN-. In this circumstance the RS may be determined to assist in likelihood of recurrence and benefit from chemotherapy…RS should be used in the context of other elements of risk stratification for an individual patient."* (Pg. MS-24)
NICE,[18] 2013, UK	*"[ODX] is recommended as an option for guiding ACT decisions for people with ER+ LN− HER2- ESBC if (a) the person is assessed as being at intermediate risk and (b) information on the biological features of the cancer provided by ODX is likely to help in predicting the course of the disease and would therefore help when making the decision about prescribing ACT, and (c) the manufacturer provides ODX to NHS organisations according to the confidential arrangement agreed with NICE."* (Pg. 10)

Organization, Publication Year, Country	CPG Recommendations Related to OPX Testing
St. Gallen,[15] 2013, International	*"[ODX] is accepted as providing not only prognostic, but also predictive information regarding the utility of ACT in addition to endocrine therapy for patients with luminal disease…[it] can help define a group of patients for whom chemotherapy is futile because the biological nature of the tumour is such that it is substantially unresponsive to such agents. The Panel considered that only [ODX] was predictive of chemotherapy responsiveness [versus competitor technologies]."* (Pg. 2207)

ACT=adjunct chemotherapy; ASCO=American Society of Clinical Oncology; CCO=Cancer Care Ontario; COI=Conflict of interest; CPG=Clinical practice guideline; ESBC=Early stage breast cancer; ESMO=European Society of Medical Oncologists; HER2=Human epidermal growth factor receptor 2; MoH=Ministry of Health; NCCN=National Comprehensive Cancer Network; NHS=National Health Service; NICE=National Institute for Health and Clinical Care; ODX=Oncotype DX; ON=Ontario; PEBC=Program in Evidence-based Care; RS=Recurrence score; SR=Systematic review; UK=United Kingdom; USA=United