表9　Bevacizumab+PTXレジメン投与時の注意点　（パクリタキセルについては表7参照）

ベバシズマブ	◎分子標的薬（モノクローナル抗体） ◎主な毒性：高血圧、鼻出血、タンパク尿。まれに、腸管穿孔などが出現 ◎注意点 ・ベバシズマブはバイアルとなっており、必要量を抜き取り生理食塩液に希釈して点滴静注する ※10mg/kgの場合は「抜き取り量（mL）＝体重（Kg）×0.4（mL／Kg）」となる

対象

◎手術不能または再発乳がん

投与法

◎転移性乳がんの場合、ベバシズマブは10mg/kg（体重）を1・15日目、パクリタキセルは80～90mg/m²を1・8・15日目に投与し、28日を1クール（3投1休）とする（図4、表8）。

ケアのポイント（表9）

1．ベバシズマブ投与時の注意点

◎ベバシズマブで多く見られる副作用は、高血圧、鼻出血、タンパク尿である。まれに腸管穿孔などが起こりうるため、注意が必要である。

◎約1.8%の患者でインフュージョンリアクション（蕁麻疹、呼吸困難、口唇浮腫、咽頭浮腫など）が出現するとされている。通常、症状は軽度～中等度である。初回投与時に現れやすいため、初回は90分以上かけて投与し、十分に観察する。初回投与の忍容性が良好であれば、2回目の投与は60分間で行ってもよい。2回目の投与においても忍容性が良好であれば、それ以降は30分間投与に短縮できる。

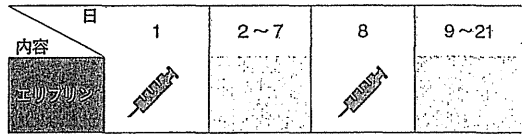
◎症状出現時には、副腎皮質ステロイドや抗ヒスタミン薬などを投与する。

⑤Eribulin（エリブリン）

◎エリブリン（ハラヴェン®）を単剤で投与するレジメンである。エリブリンは、クロイソカイメンから精製・抽出された微小管（チューブリン）阻害薬である。

◎再発治療として、3次以降となる患者を対象にした臨床試験において、主治医選択治療群*2と比較して全生存期間が有意に延長したことから、最近、日米欧で承認された薬剤である。

図5　Eribulinレジメン



◎3週（21日）クール

対象

◎既治療（アントラサイクリン系薬剤あるいはタキサン系薬剤）の手術不能または再発乳がんに対して実施される。

投与法

◎エリブリン1.4mg/m²を1・8日目に投与し、21

日ごとに繰り返すレジメン（2投1休）で用いられている（図5、表10）。

ケアのポイント（表11）

◉副作用は、骨髄抑制とそれに伴う感染症、末梢神経障害（末梢性ニューロパチー）が主である。また、約半数に脱毛が見られる。

◉まれであるが、重症な肝機能障害や間質性肺炎の出現が報告されている。

◉血管漏出時の合併症については不明だが、臨床試験での血管漏出をきたした1例では潰瘍形成などはなかったと報告されている。

表10　Eribulinレジメンの投与例

使用する薬剤

◉エリブリン（ハラヴェン®）
・補液（生理食塩液など）

投与方法

投与日	投与順	投与内容（投与量）		投与時間
1日目	①	生理食塩液（50mL）	メイン 点滴	15分
	②	ハラヴェン®（1.4mg/m²）＋生理食塩液（50mL）	側管 静注	2～5分
	③	生理食塩液（50mL、ルート内フラッシュ用、残量破棄可）	側管 静注	適宜
2～7日目	投与なし			
8日目	1日目と同様			
9～21日目	投与なし			

表11　Eribulinレジメン投与時の注意点

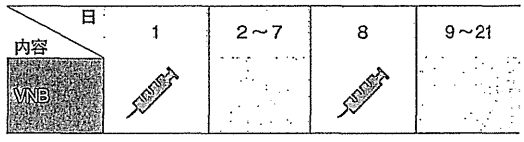
エリブリン	◉微小管（チューブリン）阻害薬 ◉主な副作用：骨髄抑制とそれに伴う感染症、末梢神経障害（末梢性ニューロパチー） ◉注意点 ・希釈する場合は、日本薬局方生理食塩液を使用し、0.02mg/mL未満の濃度に希釈しない ・エリブリンを5%ブドウ糖注射液で希釈しない（反応生成物が発生する） ・併用禁忌・併用注意薬は知られていないが、投与されたエリブリンの大部分は未変化体として尿・便中に排泄され、他の薬剤に及ぼす影響や受ける影響については少ないと考えられている

⑥VNB（ビノレルビン）

◉ビノレルビン（ナベルビン®）を単剤で投与するレジメンである。

◉HER2陽性乳がんに対しては、トラスツズマブとの併用療法が行われている。

図6　VNBレジメン



◉3週（21日）クール

対象

◉既治療（アントラサイクリン系薬剤あるいはタキサン系薬剤）の手術不能または再発乳がんに対して実施される。

投与法

◉現在、ビノレルビン 25mg/m² を1・8日目に投与し、21日ごとに繰り返すレジメン（2投1休）が、標準的に用いられている（図6、表12）。

ケアのポイント（表13）

◉副作用は、骨髄抑制が主である。脱毛も、ほとんど見られない。

◉患者が自覚する副作用は比較的少なく、QOLにすぐれた薬剤といえる。

文献
1. 医薬品医療機器総合機構：医薬品医療機器情報提供ホームページ（http://www.info.pmda.go.jp/）.
2. 日本乳癌学会編：乳癌診療ガイドライン1 治療編2011年版. 金原出版, 東京, 2011.
3. 日本癌治療学会編：制吐剤適正使用ガイドライン第1版. 金原出版, 東京, 2010.

*1 蓄積性心毒性：薬剤の総投与量に応じて心筋障害やうっ血性心不全のリスクが高まる。
*2 主治医選択治療群：「対象患者に対して最良」と前もって医師が判断した治療法（化学療法、内分泌療法、生物学的製剤、緩和治療のいずれか）を実施した群。

表12 VNBレジメンの投与例

使用する薬剤

◉VNB：ビノレルビン（ナベルビン®）
・補液（生理食塩液など）

投与方法

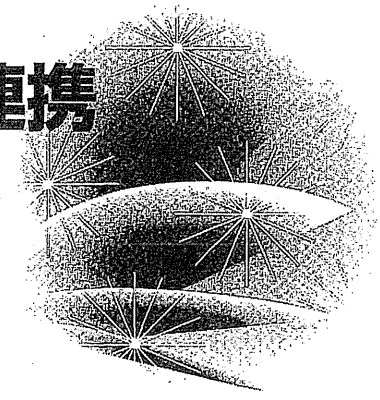
投与日	投与順	投与内容（投与量）		投与時間
1日目	①	生理食塩液（50mL）	メイン 点滴	15分
	②	ナベルビン®（25mg/m²）＋生理食塩液（50mL）	側管 静注	10分以内
	③	生理食塩液（50mL、ルート内フラッシュ用、残量破棄可）	側管 静注	適宜
2～7日目	投与なし			
8日目	1日目と同様			
9～21日目	投与なし			

表13 VNBレジメン投与時の注意点

ビノレルビン（VNB）	◉ビンカアルカロイド系抗がん剤 ◉主な副作用：骨髄抑制 ◉注意点 ・血管炎、静脈炎を起こすことがあるので、約50mLの生理食塩液・5%ブドウ糖注射液・乳酸リンゲル液で希釈し、開始から10分以内に投与を終了するのが望ましい ・併用注意：ベンゾジアゼピン系薬剤（ジアゼパム、トリアゾラム、ミダゾラム等）、アゾール系抗真菌薬、マクロライド系抗生物質、カルシウム拮抗薬（VNBの代謝が阻害され血中濃度が上昇して副作用を増強させる可能性がある）

PART. 6 ● 乳がんとともに生きる

乳がん診療と医療連携



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わが国の乳がん患者は年々増加しており，最近は年間6万人を超える人が新たに乳がんと診断されています。また，継続的な医療を受けている乳がん患者は19万人で，1日あたり2万人以上が医療施設を受診していると推定されています（平成23年患者調査）。

一方で，医療提供側の不足や偏在により医療水準に地域格差のあることや，専門病院への患者の一極集中などが問題となっています。実際，乳がん患者の9割が診療所ではなく病院を受診しています（同調査）。このような状況を改善するための方法として，診療連携パス（以下，パス）を用いた医療連携の取り組みが開始されています[1)2)]。本稿では，がん対策推進基本計画からみた乳がんの診療と医療連携について，東京都の取り組みを含め説明します。

乳がんの診療と医療連携

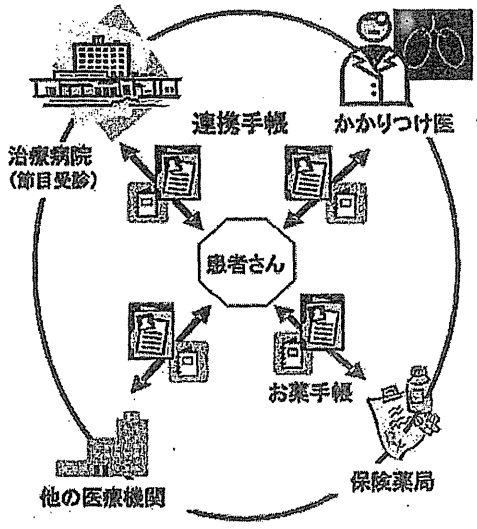
乳がんと診断された場合，初期治療として集学的治療（手術，放射線療法，薬物療法など複数の治療法を必要に応じて組み合わせる治療）が行われます。このうち，手術，放射線療法，化学療法は短期間で終わりますが，ホルモン療法は5～10年間行われます。また，手術後5年以降に再発することがあるため，長期にわたる経過観察が必要となります。

乳がんは慢性疾患ですが，手術，放射線療法，化学療法が行われる時期は合併症，副作用などで日々刻々と容態が変化するため，急性期型の診療が必要となります。一方，その後のホルモン療法と経過観察の時期は病状が安定しているため，慢性期型の診療が中心となります。現在行われている医療連携の多くは，後者の慢性期型の診療を対象としています。

このような医療連携の場合，専門病院は急性期型の診療と年に一度の定期検査を担当し，地域の医療施設（以下，かかりつけ）は慢性期型の診療を担当することになり，患者は一つの病気に対して2人の主治医をもつことになります。このときにパスを使用すると，それぞれの主治医と患者が治療経過を共有でき，より適切な診療を行うこと/受けることが可能となります（図1）。また，病状に変化があり，専門病院を受診する際やほかの医療施設を受診する際にもパスがあると安心です。さらに，看護師，薬剤師などの医療スタッフも情報を共有することができます。同時に，「いつ」「どこで」「どのような」診察・検査を受ければよいかがわかります。このように，パスは情報を伝達するツール・診療計画書としてチーム医療の要となります。

一方，高血圧，糖尿病など，がん以外の慢性疾患の診療においては，その病気によって

図1　診療連携パス（連携手帳）を用いた医療連携のイメージ



〔出典：『東京都医療連携手帳』より〕

おこる合併症を予防することが，生活の質を保ちながら長生きするために重要になります。医療連携の最大の利点は，がん以外の病気を早期に診断し，その合併症を予防できることにあります。かかりつけ医はこのような慢性疾患の管理に長けています[2]。

がん対策と医療連携

1）国のがん対策

国の本格的ながん対策は1984年の「対がん10カ年総合戦略」にはじまりますが，当初はがんに関する研究の推進に力が注がれていました。一方，2001年ごろよりがん患者団体の要求・請願活動がさかんになり，がん医療の均てん化（どこでも標準的な医療を受けられるよう医療技術などの格差をなくすこと）や，がん患者の生活の質の向上など，患者の視線からのがん対策が求められるようになりました。これらの活動がしだいに国会議員を動かし，06年に「がん対策基本法」が成立し，翌年6月には「がん対策推進基本計画（以下，推進基本計画）」が閣議決定されました。

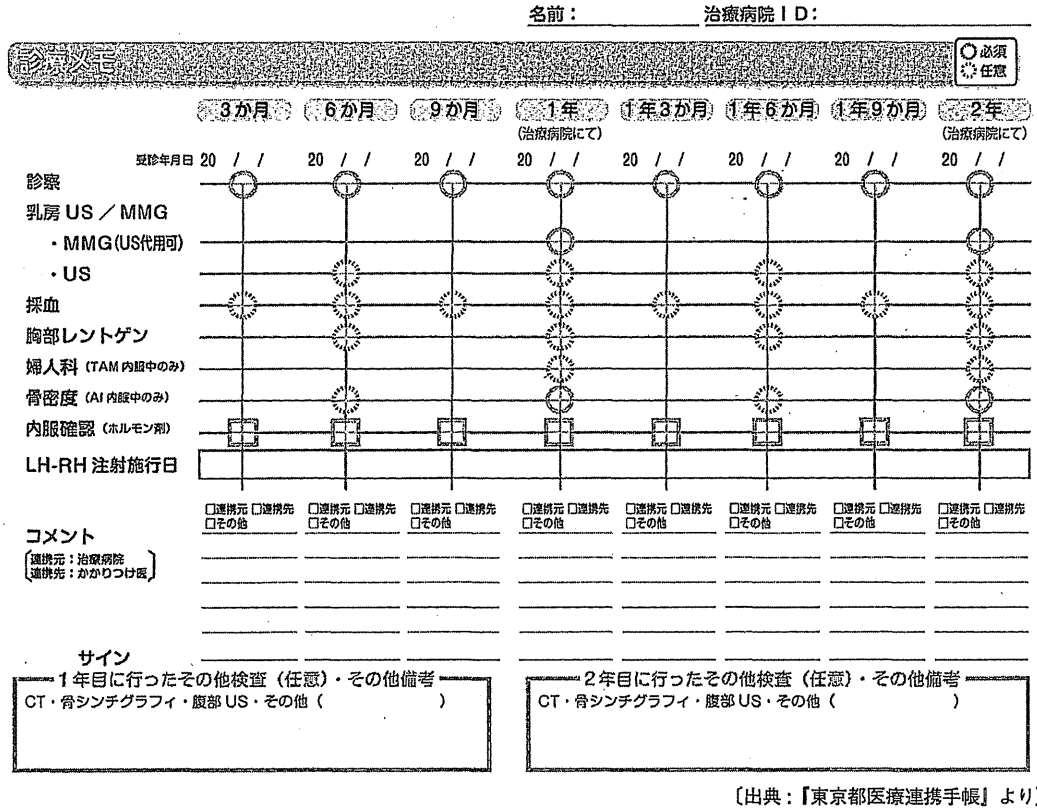
この推進基本計画は2007年から11年までの5年間を対象とするもので，がん医療の質の保証・均てん化を目ざして，すべての二次医療圏（一般的な医療サービスを提供するために指定された複数の市町村からなる地域）にがん診療連携拠点病院（以下，拠点病院）を整備し，五大がん（胃，大腸，肝，肺，乳がん）のパスを作成することなどが決められました。これを受けて，各都道府県は地域のがん医療の現状をふまえた都道府県がん対策推進計画を策定しました。

2）東京都の取り組み

東京都は2008年3月に「東京都がん対策推進基本計画」を策定し，4月に都道府県拠点病院2施設，地域拠点病院12施設を認定しました[1)2)]。都道府県拠点病院については通常1施設が指定されていますが，東京，宮城，京都，福岡では2施設体制がとられており，都道府県拠点病院としての機能を分担しています。さらに，東京都にはセンター・オブ・センターとしての機能を担っている国立がん研究センター中央病院があります。

一方，東京都の場合，人口が多いことから二次医療圏に一つの拠点病院では負担が大きいため，拠点病院と同等の機能をもつ病院を，東京都認定がん診療病院（以下，認定病院）として独自に認定しています。これ以外にも東京都には，それぞれのがん種ごとに集学的治療などを積極的に行っている医療施設が多く存在しています。このため，2012年からはがん種ごとに専門的ながん診療を行っている医療施設を「東京都がん診療連携協力病院（以下，協力病院）」として認定しています。現時点で，東京都の拠点病院は25（国立がん研究センター中央病院を含む），認定病院は10，協力病院は15（乳がんは4施設）あり，これらの医療施設が医療連携の計画を策定，すなわちパスを発行する病院（以下，計画策定病院）となります。

図2　東京都の乳がん診療連携パス（手術後2年までの経過観察）



〔出典：『東京都医療連携手帳』より〕

東京都のパス

1）基本コンセプト

東京都においてはパスの整備に向けて，2009年より拠点病院，認定病院，国立がん研究センター中央病院および東京都医師会が協力し，がん種ごとに連携パス委員会を組織して作成を開始しました[1)2)]。この際，東京には多数の医療施設があることや，交通網が発達しているために二次医療圏を超えた患者の受診が多いなどの地域特性があるため，都内の医療施設が共通に使用できる統一様式のパスを作成すること，計画策定病院とかかりつけのあいだを患者が定期的に行き来する循環型とすること，エビデンスを重視したシンプルで使いやすいものにすることを基本的なコンセプトとしました。

さらに，疾患名が表から直接みえないようにするため，がん種を明記せず表紙の色とシンボルマークで区別できるようにしました。また，携帯や利用のしやすさを考えA5サイズの手帳とし，名称を東京都医療連携手帳（以下，連携手帳）としました。2010年2月からの試験運用と改訂を経て，12年6月から正式運用を開始しています。

2）乳がんの連携手帳

乳がんの連携手帳は，対象を急性期型の診療が終了した患者とし，手術後10年までは少なくとも年1回，手術を受けた計画策定病院を受診することを前提として作成しています。表紙はピンク色で，シンボルマークとしてピンクリボンをあしらっています。内容は見開きを原則とし，経過観察の間隔は，術後3カ

表1　乳がん手術後の経過観察

	項　目	推　奨
必須のもの	問診・視触診	手術後1～3年　3～6カ月ごと 手術後4～5年　6～12カ月ごと 手術後6年以降　年1回
	マンモグラフィ	年1回
任意のもの	血液検査，腫瘍マーカー 各種画像検査*	必要に応じて行う
	婦人科受診	タモキシフェン内服中に不正出血などがある場合（閉経後の場合）
	骨塩量測定	アロマターゼ阻害剤を内服している場合などで骨粗鬆症の危険のある場合は年1回（閉経後の場合）

＊胸部X線，CT，腹部超音波（US）検査，MRI，PET，骨シンチグラフィ
〔日本乳癌学会編：科学的根拠に基づく乳癌診療ガイドライン　2011年版，金原出版；患者さんのための乳がん診療ガイドライン　2012年版，金原出版より改変〕

月めから術後5年までは3カ月ごと，術後5～10年までは6カ月ごとを予定しています（図2）。

診療内容としては，診察とマンモグラム（エコー検査でも可），採血，胸部X線検査，婦人科受診，骨密度測定，ホルモン剤の内服確認，LH-RHアゴニスト注射日をあげ，それぞれのチェック欄と日付やコメントの記入欄を作成しています。これらの項目ついては乳癌診療ガイドラインを参考に実施時期を示し，必須（毎回の診察・内服確認と年1回のマンモグラム）のものを実線，任意のものを点線で区別しています[3)4)]（表1）。婦人科受診と骨塩量測定は，ホルモン療法の副作用を考慮して項目としてあげています。

なお，この連携手帳で想定しているのは乳がん手術後の経過観察です。そのため，ほかの病気の診療や副作用のチェックのための検査や，健診・ドック・検診は適宜受けていただく必要があります。ただし，手術後に定期的な経過観察を受けている場合には，あらためて乳がん検診を受ける必要はありません。

東京都における医療連携の現状と問題点

現在の制度では，計画策定病院が連携するかかりつけの一覧と使用するパスを，地方厚生局に届け出ることが必要になっています。東京都では50の計画策定病院と2000を超える医療施設が届け出ていますが，すべてのかかりつけが届け出ているわけではありません。一方，計画策定病院以外にも乳がんの診療を行っている医療施設はたくさんありますが，現在の制度では計画策定病院として届け出ができません。また，すでに別の疾患でかかりつけに通院していても，そのかかりつけが届け出を行っていないと推進基本計画上の医療連携の対象とはなりません。

さらなる問題として，退院後30日までにパスを作成することが求められていることがあります。すなわち，手術が終了したばかりでまだ急性期型の診療計画が立てられない時期に，慢性期型の診療計画を立てて医療連携を開始することになります。

このように種々の障壁が立ちはだかっているため，医療連携の実績はまだ十分にあがっていません。本来，パスの役割は安全で安心な医療の提供を切れ目なく行うためのツールであることを考えると，より柔軟な制度が望まれます。

また，医療連携とパスの認知度も低い状況にあります。今後の課題として，認知度を上げ医療連携に参加する医療施設と患者を増す

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必要があります。これらの対策の一つとして，東京都では乳腺専門医のいるクリニックとセンター病院の両者がTokyo Breast Consortium（http://www.breastcons.com/）を組織し，顔のみえる連携を目ざして活動を行っています。

一方，切れ目のないスムーズな連携を行うためには，各医療施設に連携についての相談や調整を行う部署や，連携コーディネーターあるいは連携マネージャーを配置し，医療連携を行いやすい環境をつくることも必要です。実際，四国がんセンターでは連携コーディネーターを配置し，パスの説明，情報提供，施設間の交渉を行うことにより，円滑な医療連携が行われています[5]。乳がんの場合，もともとかかりつけのない患者が多いため，このような取り組みはきわめて大切です。

同時に，医療連携のシステムやパスを社会情勢の変化や診療ガイドラインの改訂にあわせて更新しながら，IT化も含めて柔軟に運用していく必要があります。また，現在の医療連携は地域が前提ですが，地域を超えた受診が少なくないことを考慮すると，地方さらには全国での運用が可能となるシステムの構築が望まれます。同時に，急性期型の診療や緩和ケア，検診の医療連携についても検討していく必要があります。そして，医療連携が真に患者の安全，安心につながっているかどうかを評価していくことも大切です。

がん対策基本法，推進基本計画には国民，患者の努力の必要性が指摘されています。とくに，推進基本計画においては，正しい知識をもち，予防に努め，がん検診を受けることや，患者や家族も病態や治療内容などについて理解し，医療従事者との信頼関係を構築するよう努めること，がん対策に参加し，がん医療や患者と家族に対する支援を向上させるという自覚をもって活動することが求められています。これまでの医療が病院中心の病院完結型であったのに対し，医療連携は患者中心のチーム医療による地域完結型を目ざしています。このためには医療，行政の関係者と患者・家族のあいだで意識のギャップをなくし，三位一体として協力していくことが望まれます。

*

推進基本計画は2012年6月に見直しが行われ，現在，各都道府県で新たな推進基本計画が策定されつつあります。このなかでパスを用いた医療連携はますます重要になると考えられます。本稿では東京都の取り組みを紹介しましたが，全国の取り組みと共通する部分も多いと思います。今後，パスがより効率的な連携のツールとして磨きあげられ，患者が中心に参加するチーム医療としての医療連携が定着することを祈って稿を終えます。

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［くろい・かつまさ／乳腺外科］

the evidence-based antiemetic guidelines.[9,10] We need to build on the state-of-the-art knowledge about CINV to improve the management of our patients. Palonosetron and aprepitant offer significant advantages compared with older agents, and this is reflected in recently updated international guidelines.[9,10] If the ultimate goal in CINV research is no nausea and vomiting in patients undergoing chemotherapy, a more appropriate and reliable efficacy end point for future trials would be complete protection (defined as no vomiting, no rescue antiemetics, and no nausea) during the 5 days after chemotherapy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Antipsychotics-Containing Regimen As an Alternative to Standard Antiemetics for Delayed Nausea Induced by Highly Emetogenic Chemotherapy

To the Editor: Roscoe et al[1] recently presented data from a double-blind randomized clinical trial to determine the efficacy of the addition of dexamethasone on days 2 and 3, a second-generation 5-hydroxytryptamine receptor antagonist (5-HT RA; palonosetron), and a neurokinin-1-receptor antagonist (aprepitant) for delayed nausea. This study failed to show the benefit of palonosetron and aprepitant compared with a standard regimen that included prochlorperazine. The authors commented that most randomized trials reporting the efficacy of aprepitant did not use effective alternative medication, such as prochlorperazine, for delayed nausea. Among the 5-HT RAs, the effects of palonosetron and granisetron for controlling delayed nausea are similar, provided that prochlorperazine is used.[1] Prochlorperazine, an antipsychotic, acts on dopaminergic receptors at the chemoreceptor trigger zone, possibly at other CNS centers, and peripherally. Prochlorperazine may be most frequently used for nausea and vomiting.[2]

Another antipsychotic, olanzapine (OLN), blocks receptors of multiple neurotransmitters: dopamine receptors (as with prochlorperazine), serotonin receptors, alpha-1 adrenergic receptors, muscarinic receptors, and H_1 receptors.[3] OLN was shown in a randomized phase III trial to be as effective as aprepitant for antiemesis during highly emetogenic chemotherapy (HEC).[4] We retrospectively reviewed consecutive patients with early breast cancer who underwent adjuvant or neoadjuvant chemotherapy with HEC and were refractory (mostly because of grade 3 nausea or vomiting) to the standard antiemetic regimen as determined after the first cycle of chemotherapy at our hospital from January 2009 to December 2010 (before aprepitant became available in our institution). For the second cycle, the patients received 2.5 to 10 mg OLN per day, from days 1 to 3, in addition to the standard antiemetic regimen (5-HT RAs and dexamethasone 20 mg intravenously on day 1, and 4 mg dexamethasone orally or intravenously per day on days 2 and 3). Of the 12 women who received HEC and OLN, grade 3 nausea and vomiting was reduced from 42% to 8% and from 67% to 0%, respectively. Surprisingly, 42% of patients required no breakthrough antiemetic treatment despite poor control during the preceding cycle. No grade 3 or 4 adverse events

thought to be related to OLN were noted, but 67% and 33% of patients complained of grade 1 to 2 drowsiness and dizziness, respectively. These events prompted a reduction in dose or duration of OLN; nevertheless, efficacy was retained.

In Japan, the per-cycle cost of OLN used in the trial was approximately ¥2,000 (equivalent to approximately $22), and that of aprepitant was about ¥15,000 ($167). The cost of prochlorperazine per cycle in the study by Roscoe et al[1] was about ¥120 ($1.3). In line with the cost of standard chemotherapy—for example, the cost of doxorubicin and cyclophosphamide per cycle is about ¥20,000 ($222)—the medication for supportive care is as expensive as the antineoplastics. Therefore, antipsychotics such as prochlorperazine and OLN are not only effective for prevention of chemotherapy- induced nausea and vomiting, but also highly cost-effective.

Reconsideration of the antiemetics guideline may be important, especially when pharmacoeconomics for developing countries are concerned. With the use of inexpensive antipsychotics in addition to dexamethasone and a first-generation 5-HT RA, palonosetron and a neurokinin-1 receptor antagonist add little other than expense. Large randomized clinical trials with a placebo are difficult to conduct without financial support from pharmaceutical companies. Therefore, clinical trials that are designed to study noninferiority of cost-saving strategies are rarely conducted. Until the data clearly indicate that the next-generation 5-HT RAs and/or neurokinin-1-receptor antagonists are superior to the more cost-effective regimen, which uses dexamethasone, a first-generation 5-HT RA, and antipsychotics, this regimen may serve as an alternative, especially for a medically underserved population.

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Reply to L. Celio et al and H. Ishiguro et al

We are pleased to have the opportunity to address the concerns with our article[1] that were raised by Celio and Aapro.[2] First, we agree with them that the article would have been strengthened by inclusion of the data on vomiting in the published article rather than in the online appendix. Journal space constraints combined with the fact that delayed nausea (DN), not vomiting, was our primary outcome dictated this choice. The data we provided online directly address the concerns of Celio and Aapro regarding control of vomiting and nausea on day 1. In brief, 39% of subjects reported acute nausea (any level) on day 1, and there were no significant differences between groups with respect to average acute nausea ($P = .827$), maximum acute nausea ($P = .834$), nor incidence of acute nausea ($P = .819$). Ten percent of subjects reported vomiting on day 1. Using logistic regression that controlled for chemotherapy regimen and Community Clinical Oncology Program site, there were no significant differences between treatment groups ($P = .501$). Sixteen percent of the patients vomited at least once during days 2 or 3 (group 1, 18%; group 2, 24%; group 3, 8%; group 4, 14%). We conducted comparisons between groups 1 and 2, groups 1 and 4, and groups 3 and 4 on incidence of delayed vomiting (DV) using logistic regression. The P values for these three comparisons were .216, .218, and .031, respectively, with none meeting the Bonferroni corrected criterion for statistical significance of .017.

With respect to the concern over the case-mix of moderately emetogenic chemotherapy and highly emetogenic chemotherapy, we note that combined anthracycline and cyclophosphamide regimens were reclassified as highly emetic in the 2011 update of the American Society of Clinical Oncology antiemetic guidelines.[3] Under this reclassification, 59% of our patients received highly emetogenic chemotherapy, including all in the subgroup analyses of patients with breast cancer referred to by Celio and Aapro.[2]

Celio and Aapro[2] are correct in stating that there was no significant difference in DN rates among patients receiving prochlorperazine compared with those receiving prochlorperazine plus

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EPIDEMIOLOGY

Economic evaluation of the 70-gene prognosis-signature (MammaPrint®) in hormone receptor-positive, lymph node-negative, human epidermal growth factor receptor type 2-negative early stage breast cancer in Japan

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Abstract The 70-gene prognosis-signature is validated as a good predictor of recurrence for hormone receptor-positive (ER+), lymph node-negative (LN−), human epidermal growth factor receptor type 2-negative (HER2−) early stage breast cancer (ESBC) in Japanese patient population. Its high cost and potential in avoiding unnecessary adjuvant chemotherapy arouse interest in its economic impact. This study evaluates the cost-effectiveness of including the assay into Japan's social health insurance benefit package. An economic decision tree and Markov model under Japan's health system from the societal perspective is constructed with clinical evidence from the pool analysis of validation studies. One-way sensitivity analyses are also performed. Incremental cost-effectiveness ratio is estimated as ¥3,873,922/quality adjusted life year (QALY) (US$43,044/QALY), which is not more than the suggested social willingness-to-pay for one QALY gain from an innovative medical intervention in Japan, ¥5,000,000/QALY (US$55,556/QALY). However, sensitivity analyses show the instability of this estimation. The introduction of the assay into Japanese practice of ER+, LN−, HER2− ESBC treatment by including it to Japan's social health insurance benefit package has a reasonable chance to be judged as cost-effective and may be justified as an efficient deployment of finite health care resources.

Keywords Adjuvant therapy · Breast cancer · Cost-effectiveness · Gene diagnosis · 70-gene prognosis-signature

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Introduction

Oestrogen receptor-positive (ER+) diseases have a large share in breast cancer, which amount to 76.9% in Japan [1]. And among those, 61.0% of them are node-negative (LN−) and human epidermal growth factor receptor type 2-negative (HER2−) diseases [1]. After the primary surgery on these cases, a difficult clinical decision must be made about whether to add systemic chemotherapy to standard adjuvant endocrine therapy. Whereas the effectiveness of adjuvant endocrine therapy has been established [2], the use of adjuvant chemotherapy in ER+, LN−, HER2− diseases is still under debate [3].

The 70-gene prognosis-signature (MammaPrint®) is a prognostic tool, which was developed to predict the recurrence in LN− diseases [4] and individualise adjuvant therapy for early stage breast cancer (ESBC) patients. The usefulness of the tool has been validated in several studies of retrospective patients [5–7] including Japanese patients [8]. Patients classified as at low risk of recurrence by the assay may need adjuvant endocrine therapy only, while those at high risk may require additional treatment with chemotherapy. The assay was cleared for younger patients by the US Food and Drug Administration in 2007, of which age indication has been later extended to older patients [9].

And it has been included in St Gallen consensus statement since 2009 [3].

One of the notable attributes of the assay is its high cost: ¥380,000 (US$4,222; US$1 = ¥90). Coupled with its potential cost-saving effect by avoiding expensive and highly toxic chemotherapy, the economic evaluation of the assay has aroused great interests among health managers and oncologists. A cost-effectiveness analysis regarding ER+, LN− diseases among younger and older patients was reported from The Netherlands [10], which found the use of the assay cost-effective to guide adjuvant treatment decision compared to both St Gallen consensus and Adjuvant! Online software (http://www.adjuvantonline.com). Another cost-effectiveness analysis regarding ER+, LN− diseases among younger patients was reported from the US [11], which also found the use of the assay cost-effective compared to Adjuvant! Online software. However, no cost-effectiveness study has been reported from Japan or Asian countries, although the clinical utility of the assay has been validated in corresponding population [8].

In this study, we analyse the cost-effectiveness of introducing the assay into Japanese practice of ER+, LN−, HER2− ESBC treatment. In the current Japanese context, an introduction with limited indication such as ER+ and HER2− diseases is an agendum for health managers and oncologists, since ER− and HER2+ diseases may have clearer indication for adjuvant chemotherapy and anti-HER2 therapy, respectively, without the use of 70-gene prognosis-signature. The results would be of help in considering the inclusion of the assay in the benefit package of Japan's social health insurance, as well as interesting to health managers and oncologists in Asian countries.

Methods

We conduct a cost-effectiveness analysis of introducing the 70-gene prognosis-signature into the current Japanese practice of ER+, LN−, HER2− ESBC treatment with decision tree and Markov modelling including sensitivity analysis from the societal perspective. Since we have already developed an economic model depicting the courses followed by the target patients elsewhere [12, 13], which are economic evaluations of the 21-gene signature (Oncotype DX®), we combine this model with clinical evidence depicting treatment decision changes among target patients. We also carry out a deliberate literature survey to find out the best available clinical evidence. The PubMed database and Igaku Chuo Zasshi (Japana Centra Revuo Medicina), a Japanese medical literature database, are accessed with combinations of relevant terms such as 70-gene prognosis-signature, MammaPrint, etc.

Treatment decision change and recurrence

We assume that the current Japanese practice of ESBC treatment is according to St Gallen 2009 criteria without the use of multigene assays based on a survey of Japanese experts practice [14] and current consensus guidelines [15], in which the use of Adjuvant! Online software is not recommended. Then we search for reports on clinical outcomes of target patients to make a comparison between St Gallen criteria-guided treatment without multigene assays and the 70-gene prognosis-signature-guided treatment. We assume 100% usage of the gene signature when it is included into the Japanese social health insurance benefit package. However, data of such comparison is not available in the Japanese validation study [8]. It reports the distant metastasis-free survival rates according to the 70-gene prognosis-signature, but not according to St Gallen 2009 criteria. And we have no access to the data to implement further analysis for our economic modelling. However, Retèl et al. [10] is a unique report of the comparison, which presents the results of a pooled prognosis analysis of three validation studies [5–7, 10]. Table 1 shows the 5-year distant recurrence rates by St Gallen criteria-guided treatment and the 70-gene prognosis-signature-guided treatment. In St Gallen criteria-guided treatment, 89.84% of the patients are classified as at high risk of distant recurrence and are given adjuvant chemotherapy, while 10.16% are classified as at low risk and are treated with adjuvant endocrine therapy only. Their 5-year incidence rates of distant recurrence for the first 5 years and the second 5 years are 10.95 and 7.79% in patients at high risk and 3.23 and 10.0% in patients at low risk, respectively. In the 70-gene prognosis-signature-guided treatment, 46.23% of the patients are classified as at high risk and are given adjuvant chemotherapy, while 53.77% are classified as at low risk and are treated with adjuvant endocrine therapy only. Their 5-year incidence rates of distant recurrence for the first 5 years and the second 5 years are 17.73 and 10.35% in patients at high risk and 3.66 and 6.33% in patients at low risk, respectively. The reduction of the use of chemotherapy using the 70-gene prognosis-signature instead of St Gallen criteria is 43.61%.

Patient cohort

ER+, LN−, HER2− ESBC patient cohort at the age of 55 is targeted for our base-case analysis. The age, 55 years old, is chosen according to the average age of equivalent patient population in a Japanese nationwide cancer registry [1].

Decision tree and Markov model

Our economic model shown in Fig. 1 incorporates clinical courses followed by ER+, LN−, HER2− ESBC patients,

Table 1 5-Year incidence rates of distant recurrence

Treatment	Risk classification	Probability (95% CI)	Adjuvant therapy	1–5 Years (95% CI)	6–10 Years (95% CI)	Source
St. Gallen criteria-guided	High	0.8984 (0.8643 to 0.9325)	Chemotherapy	0.1095 (0.0723 to 0.1467)	0.0779 (0.0440 to 0.1117)	[5–7, 10]
	Low	0.1016 (0.0675 to 0.1357)	Endocrine therapy alone	0.0323 (−0.0336 to 0.0981)	0.1000 (−0.0139 to 0.2139)	
The 70-gene prognosis-signature-guided	High	0.4623 (0.4060 to 0.5186)	Chemotherapy	0.1773 (0.1135 to 0.2411)	0.1035 (0.0472 to 0.1597)	
	Low	0.5377 (0.4814 to 0.5940)	Endocrine therapy alone	0.0366 (0.0075 to 0.0656)	0.0633 (0.0249 to 0.1017)	

CI confidence interval

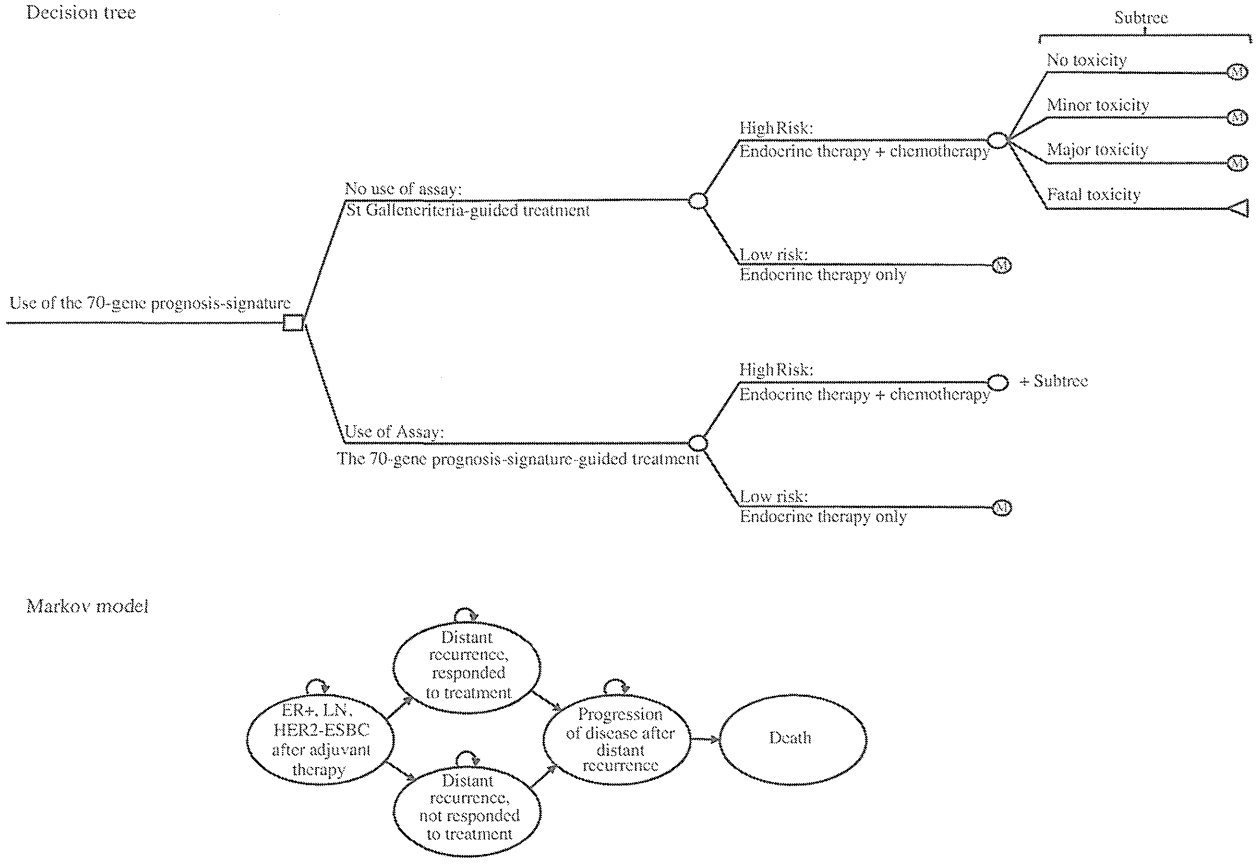

Fig. 1 Decision tree and Markov model

which is adopted and modified from our past studies [12, 13].

The decision tree corresponds to the comparison between St Gallen 2009 criteria-guided treatment versus the 70-gene prognosis-signature-guided treatment. The decision node of the tree is a decision whether to use the assay or not. Following chance nodes portion out the cohort to different adjuvant therapies depending on the risk classification. Here, we consider two types of adjuvant therapies: endocrine therapy plus chemotherapy for patients classified as at high risk of recurrence, and endocrine therapy alone for patients classified as at low risk of recurrence. Branches following 'plus chemotherapy' lead to subtrees via chance nodes, which portion out the cohort to different toxicities.

The Markov model shows the clinical course followed after the completion of adjuvant therapy. Five stages are modelled here: (1) ER+, LN−, HER2− ESBC after adjuvant therapy, (2) distant recurrence responded to treatment, (3) distant recurrence not responded to

treatment, (4) progression of disease after distant recurrence, and (5) death. Transitions between stages are indicated with arrows. Patients follow various courses after recurrence, and situations other than these five stages and transitions described here may be possible. However, we model the course this way based on the available reports of prognosis model of metastatic breast cancer, which is calibrated with the results of several randomised trials [12, 13, 16, 17]. So here, patients with recurrence undergo drug treatment with endocrine therapy or/and chemotherapy depending on their status.

The span of each stage is set at 1 year. Markov process is repeated up to 10 years, since the transition probabilities of recurrence are calculated by the 5-year incident rates of distant recurrence up to 10 years, and most of the recurrences are known to occur within this time horizon. After 10 years, a patient survived with no recurrence are assumed to have a life expectancy of 65-year-old Japanese female population [12, 13, 18], and those with recurrence are assumed to have a life expectancy of 2 years [12, 13, 19].

Outcomes estimation

Outcomes of each scenario in terms of life years (LYs) and quality adjusted life years (QALYs) are estimated by assigning probabilities and utility weights to the decision tree and Markov model from the literature.

Probabilities of risk classification, attached to the first chance node, are adopted from the results of a pooled prognosis analysis of three validation studies [5–7, 10] shown in Table 1. Table 2 shows other probabilities, utility weights, and costs used. Probabilities of adjuvant chemotherapy toxicity, which are attached to the chance node in the subtree, are assumed to be 60% for minor toxicity, 5% for major toxicity, and 0.5% for fatal toxicity according to the report of efficacy and cost-effectiveness of adjuvant chemotherapy in breast cancer [12, 13, 20].

In regards to the Markov model, transition probabilities of recurrence are calculated from the 5-year incident rates of distant recurrence depending on patients' status in Table 1. As mentioned above, transition probabilities between stages after recurrence are adopted from the prognosis model of metastatic breast cancer [12, 13, 16, 17]. Probabilities of the response to treatment for recurrence are fixed at 38.0% [12, 13, 17]. Probabilities of the progression of disease after recurrence are also fixed at: 59.7% if responded to the treatment and 98.3% if not responded to the treatment [12, 13, 16]. Probabilities of death after the progression of disease are fixed at 40.0% [12, 13, 16].

In order to estimate the outcomes in terms of QALYs, utility weights are chosen for various health states during the clinical course that patients follow. A weight for health states after adjuvant therapy without any toxicity or distant recurrence is chosen to be 0.98 [12, 13, 21]. Weights for toxicities are 0.90 for minor toxicity, and 0.80 for major toxicity [12, 13, 20], of which duration is assumed at 6 months. The health states during chemotherapy in preventing distant recurrence or the progression of disease weighs 0.50 [12, 13, 22], of which duration is assumed at 6 months. Health states after chemotherapy weigh 0.84 if responded to the treatment, 0.70 if stable, and 0.49 if the disease progressed [12, 13, 17].

Outcomes are discounted at a rate of 3% [23].

Costing

From the societal perspective, costing should cover the opportunity cost borne by various economic entities in the society. In the context of this study, costs borne by social insurers and patients are considered, since these two entities are the major payers to health care providers in Japan's social health insurance system. The amount of direct payments by these entities, according to the national medical care fee schedule, is estimated as costs, while costs of sector other than health and productivity losses are left uncounted in this study.

Cost items are identified along the decision trees and Markov model: the assay, adjuvant therapies, treatments for toxicity, monitoring, treatments for distant recurrence, and end-of-life treatments as shown in Table 2. The cost of the assay is ¥380,000 (US$4,222) according to the price offered by the Japanese supplier of MammaPrint®. Costs of treatments except the end-of-life treatments are estimated by combining a model of breast cancer care and the national medical care fee schedule. The care model is developed based on both a nationwide survey of Japanese expert practice and the consensus guidelines [12–15, 24].

Adjuvant endocrine therapy includes outpatient care with tamoxifen, aromatase inhibitors, and LH–RH analogues depending on patient's status, and it is assumed to continue up to 5 years, which costs ¥534,610/year (US$5,940/year) [12, 13]. Adjuvant chemotherapy includes various regimens. Anthracycline-based combination chemotherapy is used in about a half of all cases, and oral fluorinated pyrimidine and CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) therapy are frequently used among other regimens. These cost ¥343,001/year (US$3,811/year) [12, 13].

There are three levels of toxicity in the decision tree. However, only the cost of major toxicity is estimated as

Table 2 Probabilities, life expectancies, utility weights, and costs

	Base case value	Source
Probabilities		
Adjuvant chemotherapy toxicity		
Minor	60.0%	[12, 13, 20]
Major	5.0%	
Fatal	0.5%	
Responded to treatment for distant recurrence	38.0%	[12, 13, 17]
Progression of disease after distant recurrence		
Responded to treatment	59.7%	[12, 13, 16]
Not responded to treatment	98.3%	
Death after progression of disease	40.0%	[12, 13, 16]
Life expectancy at 10 year		
No distant recurrence	12.3	[12, 13, 18]
Distant recurrence	2.0	[12, 13, 19]
Utility weights		
After adjuvant therapy with no distant recurrence	0.98	[12, 13, 21]
Toxicity		
Minor	0.90	[12, 13, 20]
Major	0.80	
Distant recurrence		
Chemotherapy, 6 months only	0.50	[12, 13, 21]
If respond to treatment	0.84	[12, 13, 17]
Stable	0.70	
Progression of disease	0.49	
Costs		
The 70-gene prognosis-signature (MammaPrint®)	¥380,000	Local supplier
Adjuvant therapy		
Endocrine therapy (per year)	¥534,610	[12, 13]
Chemotherapy	¥343,001	
Treatment for toxicity		
Major	¥173,352	[12, 13, 25, 26]
Monitoring		
After adjuvant therapy with no recurrence (per year)	¥25,340	[12, 13]
Treatment for distant recurrence		
Endocrine therapy and chemotherapy (per year)	¥558,458	[12–15, 24]
End-of-life (per year)	¥1,315,143	[12, 13, 27]

¥173,352 (US$1,926). This includes an unplanned hospitalisation for 1 month in two-fifths of the cases, and rescue treatment at outpatient clinic in three-fifths of the cases [12, 13, 25, 26]. For minor toxicity, from which 60% of patients suffer, the cost is included in the cost of adjuvant chemotherapy, since prophylactic use of antiemetic, for example, is routinely applied these days. And the clinical course of fatal toxicity is so diverse and not fit to costing by the modelling here, therefore, its cost is assumed to be the same as the end-of-life treatments cited from the literature [12, 13, 27].

After the completion of adjuvant therapy, patients are assumed to visit their physician twice a year for the purpose of monitoring, of which cost is ¥25,340/year (US$282/year) [12, 13].

There are various options of treatments for distant recurrence depending on regimens used in the adjuvant therapy. Yet, we assume crossover hormonal treatments followed by capecitabine within the first year as a typical first line and second line therapies for our hypothetical cohort, which cost ¥558,458/year (US$6,205/year) [12–15, 24]. We further assume that this cost is applicable to the second year and thereafter.

The cost of the end-of-life treatments are ¥1,315,143/year (US$14,613/year)[12, 13, 27], which is also used as the cost of treating fatal toxicity.

Table 3 Results of cost-effectiveness analysis

Outcomes	Treatment	Cost	Incremental cost	Effect	Incremental effect	Incremental cost-effectiveness ratio
LY	St. Gallen criteria-guided	¥3,793,824		18.60 LY		
	The 70-gene prognosis-signature-guided	¥4,025,209	¥231,385	18.65 LY	0.048 LY	¥4,820,813/LY
QALY	St. Gallen criteria-guided	¥3,793,824		17.96 QALY		
	The 70-gene prognosis-signature-guided	¥4,025,209	¥231,385	18.02 QALY	0.060 QALY	¥3,873,922/QALY

LY life year, *QALY* quality adjusted life year

Costs are also discounted at a rate of 3% [23].

Comparison

Incremental cost-effectiveness ratios (ICER) are calculated:

$$\mathrm{ICER} = \frac{\mathrm{Cost}_{\text{The 70-gene prognosis-signature-guided treatment}} - \mathrm{Cost}_{\text{St Gallen criteria-guided treatment}}}{\mathrm{Effect}_{\text{The 70-gene prognosis-signature-guided treatment}} - \mathrm{Effect}_{\text{St Gallen criteria-guided treatment}}}$$

Although there is no established threshold value to interpret the ICER in Japan, some suggest social willingness-to-pay for one QALY gain from an innovative medical intervention in Japan as ¥5,000,000/QALY (US$55,556/QALY) [28]. We refer to this value in judging the cost-effectiveness.

Sensitivity analysis

In order to appraise the stability of ICERs against assumptions made and uncertainty of adopted values of probabilities, utility weights, and costs in our economic model, one-way sensitivity analyses are performed. The age of cohort is changed to 45 and 65 years old. Probabilities of risk classification and the 5-year incidence rates of distant recurrence shown in Table 1 are changed by 95% confidence interval. Probabilities and life expectancies shown in Table 2 are changed by ±50%. Utility weights shown in Table 2 are changed by ±20%. And costs shown in Table 3 are changed by ±50%. Discount rate is also changed from 0 to 5%.

Results

Cost-effectiveness

Table 3 shows the result of the cost-effective analysis of the 70-gene prognosis-signature. The cost of the 70-gene prognosis-signature-guided treatment, ¥4,025,209 (US$44,725), exceeds that of St Gallen criteria-guided treatment, ¥3,793,824 (US$42,154), which results in a positive incremental cost of ¥231,385 (US$2,571). The effect in terms of LYs of the 70-gene prognosis-signature-guided treatment, 18.65 year, exceeds that of St Gallen criteria-guided treatment, 18.60 year, which results in a positive incremental effect of 0.048 year. The ICER is calculated as ¥4,820,813/LY (US$53,565/LY). Similarly, the effect in terms of QALYs of the 70-gene prognosis-signature-guided treatment, 18.02 QALY, exceeds that of St Gallen criteria-guided treatment, 17.96 QALY, which results in a positive incremental effect of 0.060 QALY. The ICER is calculated as ¥3,873,922/QALY (US$43,044/QALY). According to the suggested social willingness-to-pay for one QALY gain, ¥5,000,000/QALY (US$55,556/QALY) [28], this is judged as cost-effective.

Stability of ICER

Table 4 shows the results of one-way sensitivity analyses.

The ICER is found very sensitive to clinical evidence depicting the treatment decision changes and the following 5-year incident rates of recurrence. Negative gains in outcomes are found in: increasing the probability of high risk guided by the 70-gene prognosis-signature; decreasing the probability of low risk guided by the 70-gene prognosis-signature; decreasing the 5-year incident rates after the St Gallen criteria-guided treatment; and increasing the 5-year incident rates after the 70-gene prognosis-signature-guided treatment. Cost-ineffective ICERs are found in: decreasing the probability of high risk guided by the St Gallen criteria; increasing the probability of low risk guided by the St Gallen criteria; and decreasing the 5-year incident rate from 1 to 5 year after the St Gallen crieteria-guided treatment for low-risk patients.

Table 4 Results of sensitivity analysis

	Range tested in sensitivity analyses	Incremental cost-effectiveness ratio (¥/QALY)	
		− Change	+ Change
Probabilities of risk classification			
St Gallen criteria-guided, high	Change by 95% CI	15,696,389	1,974,969
St Gallen criteria-guided, low		1,974,969	15,696,389
The 70-gene prognosis-signature-guided, high		729,324	Cost more, gain less
The 70-gene prognosis-signature-guided, low		Cost more, gain less	729,324
5-Year incidence rate of distant recurrence			
St Gallen criteria-guided, high, 1–5 years		Cost more, gain less	74,972
St Gallen criteria-guided, high, 6–10 years		Cost more, gain less	635,546
St Gallen criteria-guided, low, 1-5 years		147,550,296	1,968,870
St Gallen criteria-guided, low, 6–10 years		Cost more, gain less	1,920,488
The 70-gene prognosis-signature-guided, high, 1–5 years		123,080	Cost more, gain less
The 70-gene prognosis-signature-guided, high, 6–10 years		811,354	Cost more, gain less
The 70-gene prognosis-signature-guided, low, 1–5 years		588,308	Cost more, gain less
The 70-gene prognosis-signature-guided, low, 6–10 years		842,462	Cost more, gain less
Probabilities and life expectancies			
Adjuvant chemotherapy toxicity			
Minor	Change by ±50%	4,244,799	3,562,494
Major		3,970,536	3,780,250
Fatal		5,947,033	2,884,531
Responded to treatment for distant recurrence		3,873,334	3,874,347
Progression of disease after distant recurrence			
Responded to treatment		3,870,181	3,873,468
Not responded to treatment		3,873,493	3,873,832
Death after progression of disease		3,857,505	3,874,406
Life expectancy at 10 year			
No distant recurrence		5,211,728	3,084,132
Distant recurrence		3,868,265	3,879,420
Utility weights			
After adjuvant therapy with no distant recurrence	Change by ±20%	10,288,306	2,386,140
Toxicity			
Minor		2,780,389	6,384,768
Major		3,764,178	3,990,067
Distant recurrence			
Chemotherapy, 6 months only		3,873,184	3,875,130
If responded to treatment		3,873,849	3,873,498
Stable		3,873,498	3,873,849
Progression of disease		3,871,240	3,876,428
Costs			
The 70-gene prognosis-signature (MammaPrint®)	Change by ±50%	700,218	7,047,447
Adjuvant therapy			
Endocrine therapy (per year)		3,864,105	3,883,576
Chemotherapy		5,116,591	2,631,073
Treatment for toxicity			
Major		3,905,391	3,842,274
Monitoring			
After adjuvant therapy without recurrence (per year)		3,868,877	3,878,788
Treatment for distant recurrence			
Endocrine therapy and chemotherapy (per year)		3,876,226	3,871,438
End-of-life (per year)		3,875,557	3,872,125
Other assumptions			
Discount rate	0%/5%	2,606,613	4,448,622
Age of cohort	45/65 years old	3,456,614	4,536,315

QALY quality adjusted life year, *CI* confidence interval

The ICER is found relatively insensitive to probabilities, life expectancies, utility weights, costs, and other assumptions. However, cost-ineffective ICERs are found in: decreasing the utility weight after adjuvant therapy with no distant recurrence; increasing the cost of the 70-gene prognosis-signature; increasing the utility weight for minor toxicity; decreasing the probability of fatal toxicity; decreasing the life expectancy at 10 year with no recurrence; and decreasing the cost of adjuvant chemotherapy.

Discussion

We evaluate the cost-effectiveness of introducing the 70-gene prognosis-signature into Japanese practice of ER+, LN−, HER2− ESBC treatment. Our economic model indicates that the use of the signature gains more in terms of outcomes but costs more at the same time. The estimated ICER, ¥3,873,922/QALY (US$43,044/QALY) is not more than a suggested social willingness-to-pay for one QALY gain from an innovative medical intervention in Japan, ¥5,000,000/QALY (US$55,556/QALY) [29]. However, our sensitivity analysis shows the instability of this estimation as well. Changing the value of some variables results in negative gains in outcomes, or produce ICERs that is above the threshold. Therefore, we conclude that the introduction of the 70-gene prognosis-signature into Japanese practice of ER+, LN−, HER2− ESBC treatment has a reasonable, but not riskless chance to be judged as cost-effective and justified as an efficient deployment of finite health care resources.

In the sensitivity analysis, the prognosis prediction capacity of the assay is found most influential. This is plausible from the viewpoint of model construction. The range tested in regards to these variables is 95% confidence interval of the base-case values. So for this assumption, a larger patient pool of validation studies would reduce the instability. The costs of the assay and adjuvant chemotherapy are also found influential, which are as anticipated. Relative costs of these are a key factor for economic implication of the assay.

Since the Markov model used in this study is similar to our economic evaluation of another gene signature, the 21-gene signature, for similar patient population [12], a straightforward comparison can be made between the results. While the 21-gene signature predicts the benefits from chemotherapy in addition to the prognosis, which is modelled in our previous evaluation, this model is comparable in a way that we assume the predictable benefits of chemotherapy of the 70-gene prognosis-signature is zero. Regarding ER+, LN−, HER2− diseases, the introduction of the 21-gene signature has more favourable ICER, ¥434,096/QALY (US$4,823/QALY), than the results of this study. However, due caution is needed to interpret this comparison because the breadth of indication for other patient population or other setting such as the prediction of response to neoadjuvant therapy is different from each other, which inevitably affect the value for money of the assay on every count. And the differences in clinical validation studies of these gene signatures make the comparison profoundly complicated. For example, the difference of simplified patient characteristics in each economic model may have a substantial relevance. The choice of clinical endpoint in the economic modelling, such as between local recurrence response and overall survival, may also be significant.

Although no direct comparison can be made between economic evaluations conducted under different health systems [29, 30], the cost-effectiveness of the 70-gene prognosis-signature for ESBC patients found in this study is consistent with the findings of past reports from The Netherlands [10] and the US [11], which found the use of assay cost-effective in each context.

This study has its own limitations. First of all, the clinical evidence depicting the treatment decision change and prognosis to recurrence is adopted from a pooled study of validation studies overseas. Its representativeness of Japanese patient population targeted in this study is inevitably questionable and racial differences should exist. Although we justify our approach taken as the best available evidence to date, further analyses based on Japanese clinical data are awaited. Our previously conducted economic evaluations of the 21-gene signature were analysed in two phases: early analysis using clinical evidence overseas [13] and late analysis using data from Japanese validation study [12]. This experience suggests that there is a room for different results as to the 70-gene prognosis-signature as well. Second, the quotation of an established economic model of courses followed by the target patients [12, 13] may fail to catch up with the latest developments in breast cancer treatments. For example, our Markov model assumes the so-called second generation adjuvant chemotherapies. But the use of third generation adjuvant chemotherapies is still limited in Japan [31], and no remarkable change has been made about adjuvant endocrine therapies in the Japanese consensus guideline [15] since our previous study. And therefore, we think that the quotation from the past model is still acceptable for the purpose of this study. Third, utility weights adopted are also derived from western countries due to the unavailability of data from Japan. Fourth, due to the same reason, our model does not include potentially costly clinical stages such as local recurrence or contralateral breast cancer. In regards to these shortcomings, reports that allow us to refine our model are awaited.

In considering the routine use of expensive biomarkers such as gene signatures, the appraisal of cost-effectiveness is imperative [32] with growing concerns globally about financing medical advancements [33]. The results of this study imply that the diffusion of the assay is potentially acceptable under Japan's health system from the viewpoint of health economics.

However, there is also a concern about the novelty of such biomarkers under severe health care resources constraints. Biomarkers for individualised treatments imply more 'cost-saving' by avoiding unnecessary care than expensive new drugs, while its approval process is often different from pharmaceuticals. Some health managers in Japan and elsewhere may intuitively think their routine use is financially acceptable only when 'cost-saving' results are reported in economic evaluations. However, from the viewpoint of economic evaluation, it is not justifiable to set different thresholds between biomarkers and pharmaceuticals. For example, an expensive drug therapy, adjuvant trastuzumab treatment, is included in Japan's social health insurance benefit package, although it has been found cost-effective but not cost-saving [34]. Exploration of financing strategy beyond the conventional cost-effectiveness analysis may be needed.

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Conflict of interest All authors declare that there is no possible conflict of interest.

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