National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

（NCCN腫瘍学臨床診療ガイドライン）

乳癌
検診と診断

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乳癌　検診と診断

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Þ 内科学（家庭医療、予防管理を含む）	¥ 患者擁護団体
	¶ 外科学/腫瘍外科学
	* 考察セクション執筆委員会

臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

NCCN加盟施設における臨床試験のオンライン検索は こちら：nccn.org/clinical_trials/clinicians.aspx

NCCNのエビデンスとコンセンサスによるカテゴリー：特に指定のない限り、すべての推奨はカテゴリー2Aである。
NCCNのエビデンスとコンセンサスによるカテゴリーを参照

NCCN乳癌検診ガイドライン2018年第3版から2019年第1版への更新内容は以下の通りである：

BSCR-1
乳癌リスク群：
・2番目の項目が変更された：「大部分が家族歴に基づくモデルで定義された生涯リスクが20%以上の女性」
・5番目の項目が変更された：「LCISまたはADH/ALHの病歴を有し、*生涯リスクが20%を超える*女性」
・6番目の項目の最初の下位項目が変更された：「まだ実施していない場合は遺伝カウンセラー*または同様の訓練を受けた医療従事者*への紹介」
脚注：
・「b」が変更された：「Medicareおよび保険者は、患者が*検診*マンモグラフィのスケジュール調整に直接アクセスすることを許容している。」
・「c」が変更された：「最低限の既往歴と家族歴を聴取すべきであり、外来受診時には、継続的なリスク評価、リスク低減カウンセリング、ならびに*資格を有する医療従事者による*問診・視触診を行うべきである。定性的および定量的評価の詳細については、NCCN乳癌リスク低減ガイドラインを参照のこと。」（BSCR-2、BSCR-3についても同様）
・「i」が変更された：「問診・視触診と検診なしを比較するランダム化試験は実施されていない。外来受診を推奨する根拠は、乳癌を可能な限り早期で発見できる可能性を最大限に高め、*施行中のリスク評価を確実なものにすること*にある。」（BSCR-2、BSCR-3についても同様）
・「l」が変更された：「トモシンセシスを用いることで要精査率を*低減でき、癌の発見率が改善されるが、疾患特異的死亡率を改善するか否かを判断するには十分な研究が行われていない。*」（BSCR-2、BSCR-3についても同様）
BSCR-2
検診と経過観察：
・外来受診の下、最初の下位項目が変更された：「乳癌リスク群であることが確認された時点で開始するが、*21歳未満では開始しない*」
・2番目の下位項目が変更された：「まだ実施していない場合は遺伝カウンセラー*または同様の訓練を受けた医療従事者*への紹介」
・年1回の検診の下、最初の下位項目が変更された：「近親者で*乳癌*を発症した最低年齢の10年前から開始するが、30歳未満では開始しない」

脚注：
・「m」が変更された：「高品質の乳房MRI~~の限界として~~には、乳房専用コイル~~の必要性~~、MRIガイド下生検~~の施行能力~~が可能な体制、乳房MRIに精通した放射線科医、地域的利便性が~~挙げられる~~*必要である*。閉経前女性では、乳房MRIは月経周期7～15日目に行うのが望ましい。MRIは他の乳房画像検査の方法と~~総合的に~~*関連付けて*診断すべきである。」
・「年1回の乳房MRI」に対して「n」が新たに追加された：「*適応はあるがMRIを受けられない女性には乳房全体の超音波検査を考慮する。*」（BSCR-3についても同様）
BSCR-3
乳癌リスク群：
・下の診断手順が変更された：「*LCISまたはADH/ALHの病歴を有し、生涯リスクが20%を超える*女性」
・3番目の項目が変更された：「年1回の*乳房*MRIを考慮」
BSCR-4
・「外来受診時に症状あり」からの新たな診断手順：
  - *「インプラント挿入後1年以上経過後の乳房インプラントに関連する症状（体液貯留、腫大、大きな潰瘍）」*
  - *「BIA-ALCLなどのインプラント関連の問題について豊富な経験を有する集学的チームへのコンサルテーション」*
  - 「BIA-ALCLの診断精査については、NCCN T細胞リンパ腫ガイドラインを参照」
脚注：
・「o」が新たに追加された：「*乳房インプラントを有する個人は乳房インプラント関連未分化大細胞型リンパ腫（breast implant-associated anaplastic large cell lymphoma：BIA-ALCL）の発生リスクが高い（インプラント挿入から平均8～10年後）。大多数の症例がテクスチャードタイプのインプラントで発生している。*」
BSCR-5
診断的評価：
・「診断マンモグラム」に「＋*超音波検査*」が追加された。
・3列目が大きく変更された。
精査：
・「針生検後~~の経過観察~~（BSCR-8を参照）」に変更された。

NCCN乳癌検診ガイドライン2018年第3版から2019年第1版への更新内容は以下の通りである：

BSCR-5 （続き）
脚注：
・「p」が変更された：「臨床的に悪性の疑いが弱い腫瘤や単純性嚢胞が疑われる腫瘤など、一部の臨床状況では*初回の画像検査法として*超音波検査が望ましく、30～39歳の女性には超音波検査で十分となる場合もある。 考察を参照のこと。」

BSCR-6
・充実性腫瘤の上の診断手順が変更された：「~~画像上の~~変化を評価するための身体診察±超音波検査および/または*診断*マンモグラムを6ヵ月毎に1～2年間」
・「濃縮嚢胞の疑い」からの下の診断手順が変更された：「~~短期経過観察~~*おそらく良性と判断できる所見* BI-RADS®カテゴリー3
  ▸以下が含まれるように変更された：「内容物の視認可能な可動性による濃縮嚢胞の確認 *（BI-RADS®カテゴリー2、良性）*」

脚注：
・「濃縮嚢胞の疑い」からの「穿刺吸引」の枝に対応して「x」が新たに追加された：「*症状または膿瘍の可能性を調べるために嚢胞の性質の確認を考慮してもよい。*」

BSCR-7
・30歳以上の診断手順が変更された：臨床的に悪性の疑いが弱い病変に対する経~~過観察~~*問診・視触診*±~~画像上の~~変化を評価するためのマンモグラム、超音波検査を1～2年間

BSCR-8
・上の診断手順が変更された：「~~画像上の~~変化を評価するための身体診察±超音波検査および/またはマンモグラムを6または12ヵ月時点（1年間）で行う」。（BSCR-12についても同様）
・明確化のために「LCISまたはALH」からの下の診断手順が変更された。

脚注：
・以下の脚注が新たに追加された。
  ▸「y」：「*病理学的所見が画像所見と合致する。*」上の診断手順「良性かつ画像所見と一致」に対応する。
  ▸「z」：「*大半は年1回のスクリーニングのために再来院することになるが、身体診察±更なる画像検査が選択肢となる。*」検診の2列目、上の診断手順に対応する。
  ▸「aa」：「ALH」に対応して変更された：「選択された患者では、外科的切除の代わりにモニタリングが適切となる場合がある（例、平坦型上皮異型［FEA］、*異型を伴わない*乳頭腫、*線維腺腫を支持する*線維上皮性病変、*十分に検体が採取されているか偶発的に発見された*放射状瘢痕）。」
  ▸「dd」：「*多形型LCISには断端陰性での完全切除を考慮してもよい。ただし、多形型LCIS患者の治療に関する治療成績のデータはなく、LCISの組織型について組織学的な分類が不十分であることがその理由の1つになっている。*」で「外科的切除」の下の診断手順に対応した。（BSCR-9についても同様）。

BSCR-9
・「外科的切除」から「*多形型LCIS*」が新たに追加された。
・「外科的切除」の下の診断手順が変更された：悪性~~（多形型LCISを含む）~~

BSCR-10
・「腫瘤が消失せず」からの上の診断手順が変更された：「超音波検査＋画像誘導下*針*生検」
・2列目、「穿刺吸引後」からの中間の診断手順が変更された：「腫瘤が消失したが、外傷性ではない~~と考えられる~~血性の穿刺液を認める」
  ▸2列目、「穿刺吸引後」からの下の診断手順が変更された：「腫瘤が消失し、嚢胞液が~~正常~~非血性」

経過観察評価：
・「細胞診で陰性」からの診断手順が変更された：「~~腫瘤の再発に対する評価のための臨床的な経過観察＋超音波検査~~検診（BSCR-1を参照）」

脚注：
・「ff」：「腫瘤が消失したが、外傷性ではない血性の穿刺液を認める」に対して「*マーキング用クリップを留置し、細胞診に送る。*」が新たな脚注として追加された。

BSCR-11
診断的評価：
・3列目が変更された：「濃縮嚢胞~~BI-RADS®カテゴリー3~~」

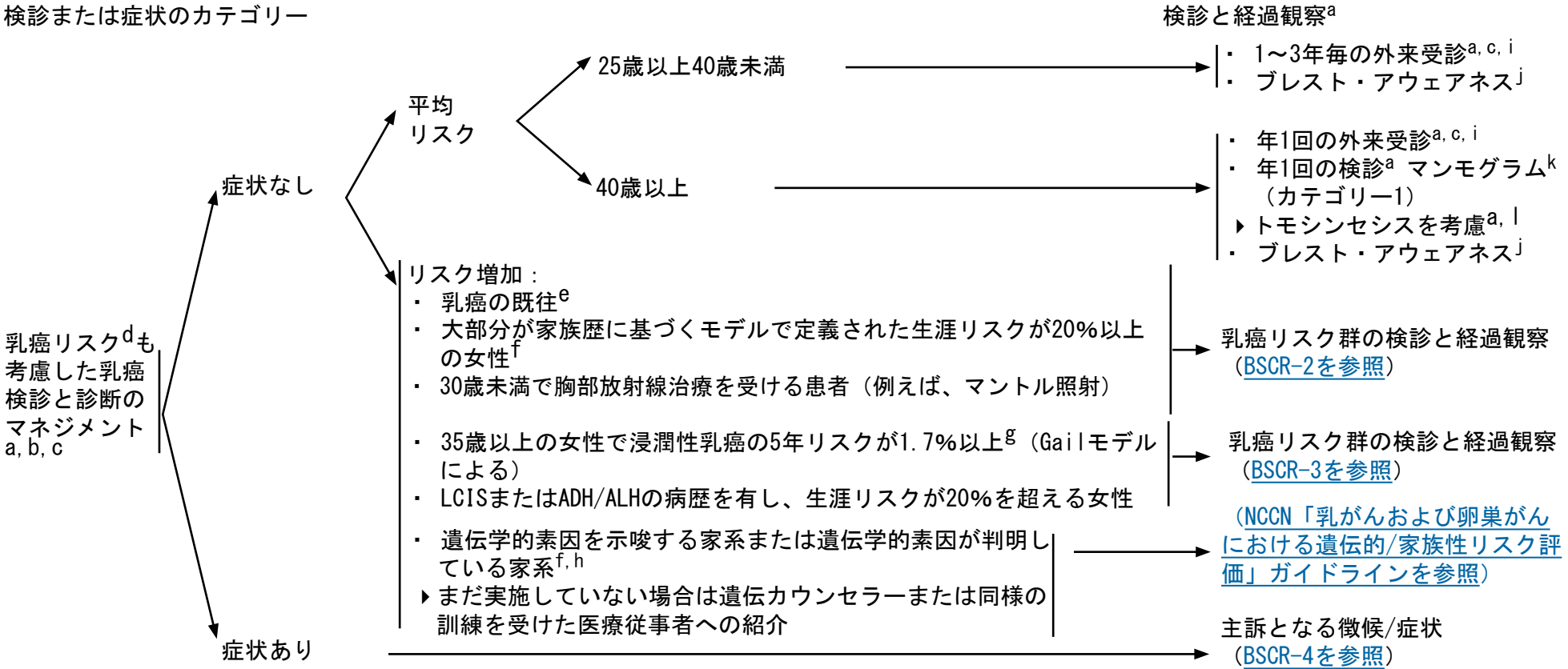
BSCR-12
・「BI-RADSカテゴリー4～5」からの診断手順が以下のように変更された：針生検~~後の経過観察~~（BSCR-8を参照）」

BSCR-13
脚注：
・「jj」：1列目の「異常乳頭分泌（触知可能な腫瘤なし）」に対して、「*腫瘤が触知可能な場合*、BSCR-5またはBSCR-7を参照のこと。」が新たに追加された。

BSCR-14
・このページは変更された。

NCCN乳癌検診ガイドライン2018年第3版から2019年第1版への更新内容は以下の通りである：

BSCR-15
・ このページは大幅に変更された。
脚注：
・「p」が変更された：「臨床的に悪性の疑いが弱い腫瘤や単純性嚢胞が疑われる腫瘤など、一部の臨床状況では*初回の画像検査法として*超音波検査が望ましく、30～39歳の女性には超音波検査で十分となる場合もある。考察を参照のこと。」（BSCR-16についても同様）
・ 脚注全体から参考文献が削除された。
BSCR-17
・「診断マンモグラムおよび/または超音波検査による経過観察、6ヵ月毎に1～2年間」から新たな診断手順が追加された：「不変」から「検診（BSCR-1を参照）」へ、「*有意なサイズの増大または癌を疑う所見の出現*」から「*針生検*」へ
BSCR-18
・「評価」の下の3列目が変更された：「*臨床的*~~全身~~評価」
・「経過観察」の下の5列目が変更された：「*適切な*臨床的管理」または「悪性の場合は該当する悪性腫瘍に関するNCCN乳癌ガイドラインを参照」
脚注：
・「ww」：「臨床的評価」に対して「*他部位のリンパ節腫脹および乳房以外にあるリンパ節腫脹の潜在的原因を評価するための詳細な臨床的評価。*」が新たに追加された。
BSCR-19
・ アルゴリズムに「*男性の臨床像*」のページが新たに追加された。
BSCR-20
・「経過観察」の下、3列目、「BI-RADSカテゴリー4」および「5」の先が変更された：「*完全な画像評価後に画像誘導下針生検による組織採取*」
BSCR-A 1 of 2
・ 2番目の項目が変更された：「十分な問診・視触診としては、直立位および仰臥位での視診と乳房（*外側-内側：中腋窩線から胸骨まで；頭側-尾側：鎖骨から乳房下の隆起部まで*）、腋窩および鎖骨リンパ節領域の全要素の触診などを行う。診察の触診部分にかける時間は触知可能な異常の検出増加と関連している。乳頭からの*時計軸上/4分割*の位置および距離により画像検査所見との位置的な相関の評価が容易になる。」
・ 5番目の項目が変更された：「マンモグラフィで高濃度乳房（不均一高濃度乳房または極めて高濃度乳房）を認める女性に対しては、補助的検診検査の追加に伴うリスクおよび利益に関するカウンセリングを推奨する。」
・ 6番目の項目が変更された：「高濃度乳房はマンモグラフィの感度を低下させる。*マンモグラフィ*での高濃度乳房は乳癌リスクの増加と関連している。」
・ 8番目の項目が変更された：「複数の研究から、トモシンセシスを用いることで要精査率を低減でき、癌の発見率が改善される~~ようである~~ことが示されている。注目すべき点として、ほとんどの研究では2倍の線量の放射線が用いられている。線量は合成2次元再構成画像を用いることで最小限に抑えることが可能である。」
・ 9番目の項目が変更された：「高濃度乳房の女性ではハンドヘルド（用手的）による超音波検査や自動超音波検査によって癌の発見率を向上させることが可能であるが、要精査や良性病変に対する乳房生検が増加する可能性がある。」
・ 10番目の項目が変更された：「現在のエビデンスは、検診としての分子イメージング（例、breast-specific gamma imaging、セスタミビシンチグラフィ、陽電子放出マンモグラフィ）のルーチンな使用を支持していないが、これらの検査法により、マンモグラフィで高濃度乳房を認める女性における早期乳癌の発見率が改善される可能性があることを示したエビデンスが新たに得られている。しかしながら、これらの検査法で全身に照射される実効線量はマンモグラフィよりも~~20～30倍~~著しく高い。
・ 12番目の項目が変更された：「……~~これらの~~限定された集団における年1回のMRIを……」
参考文献：
・ 1～4が考察セクションに移動した。
BSCR-A 2 of 2
・「年1回のMRI検診を推奨する（エビデンスに基づく）」の下、最初の項目が変更された：「~~BRCA~~*乳癌遺伝子変異*保持者の未検査の第一度近親者……」
・「MRI検診の賛否に関するエビデンスは不十分である」の下、3番目の項目が削除された：「乳癌（非浸潤性乳管癌［DCIS］を含む）の既往を有する女性」
BSCR-B
・ 4番目の項目が変更された：「*女性の*第一度近親者の乳癌発症者数」
脚注：
・ 3番目の参考文献が変更された：「現在のGailモデルは、非白人、非アジア人、非アフリカ系の米国人女性の乳癌リスクを正確に評価できない可能性がある。*乳癌および関連する癌の強い家族歴を有する女性の生涯リスクの評価には適切なモデルではない。*」



[a] 乳癌検診の注意事項（BSCR-A）を参照のこと。
[b] Medicareおよび保険者は、患者が検診マンモグラフィのスケジュール調整に直接アクセスすることを許容している。
[c] 最低限の既往歴と家族歴を聴取すべきであり、外来受診時には、継続的なリスク評価、リスク低減カウンセリング、ならびに資格を有する医療従事者による問診・視触診を行うべきである。定性的および定量的評価の詳細については、NCCN乳癌リスク低減ガイドラインを参照のこと。
[d] 定性的および定量的評価の詳細については、NCCN乳癌リスク低減ガイドラインを参照のこと。
[e] NCCN乳癌ガイドラインの「サーベイランス」の節を参照のこと。
[f] 大部分が家族歴に基づくリスクモデル（例、Claus、BRCAPRO、BOADICEA、Tyrer-Cuzick）NCCN乳癌リスク低減ガイドラインを参照のこと。
[g] 改変Gailモデルに採用されている危険因子（35歳以上）（BSCR-B）を参照のこと。
[h] 個々の遺伝性症候群に対して推奨される検診の開始条件は様々である。NCCN「乳癌および卵巣癌における遺伝学的/家族性リスク評価」ガイドラインを参照のこと。
[i] 問診・視触診と検診なしを比較するランダム化試験は実施されていない。外来受診を推奨する根拠は、乳癌を可能な限り早期で発見できる可能性を最大限に高め、施行中のリスク評価を確実なものにすることにある。
[j] 女性は自身の乳房のことをよく知っておき、変化があれば速やかに病院を受診すべきである。
[k] マンモグラフィによる評価(BSCR-20)を参照のこと。
[l] トモシンセシスを用いることで要精査率を低減でき、癌の発見率が改善されるが、疾患特異的死亡率を改善するか否かを判断するには十分な研究が行われていない。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

検診または症状のカテゴリー　　検診と経過観察

乳癌リスク群：
乳癌の既往歴
または
→ NCCN乳癌ガイドラインの「サーベイランス」の節を参照のこと。

大部分が家族歴に基づくモデルで定義された生涯リスクが20%以上の女性[f]
→
- 6～12ヵ月毎の外来受診[a, c, i]
  - 乳癌リスク群であることが確認された時点で開始するが、21歳未満では開始しない
  - まだ実施していない場合は遺伝カウンセラーまたは同様の訓練を受けた医療従事者への紹介
- 年1回の検診[a]マンモグラム[k]
  - 近親者で乳癌を発症した最低年齢の10年前から開始するが、30歳未満では開始しない
  - トモシンセシスを考慮[a, l]
- 年1回の乳房MRIを推奨[m, n]
  - 近親者で乳癌を発症した最低年齢の10年前から開始するが、25歳未満では開始しない
- リスク低減戦略を推奨（NCCN乳癌リスク低減ガイドラインを参照）
- ブレスト・アウェアネス[j]

または

10歳から30歳までに胸部放射線治療を受ける患者

現時点で25歳未満 →
- 年1回の外来受診[a, c, i]
  - 放射線治療の10年後から開始
- ブレスト・アウェアネス[j]

現時点で25歳以上 →
- 6～12ヵ月毎の外来受診[a, c, i]
  - 放射線治療の10年後から開始
- 年1回の検診[a]マンモグラム[k]
  - 放射線治療の10年後から開始するが、30歳未満では開始しない
  - トモシンセシスを考慮[a, l]
- 年1回の乳房MRIを推奨[m, n]
  - 放射線治療の10年後に開始するが、25歳未満では開始しない
- ブレスト・アウェアネス[j]

[a] 乳癌検診の注意事項（BSCR-A）を参照のこと。
[c] 最低限の既往歴と家族歴を聴取すべきであり、外来受診時には、継続的なリスク評価、リスク低減カウンセリング、ならびに資格を有する医療従事者による問診・視触診を行うべきである。定性的および定量的評価の詳細については、NCCN乳癌リスク低減ガイドラインを参照のこと。
[f] 大部分が家族歴に基づくリスクモデル（例、Claus、BRCAPRO、BOADICEA、Tyrer-Cuzick）NCCN乳癌リスク低減ガイドラインを参照のこと。
[i] 問診・視触診と検診なしを比較するランダム化試験は実施されていない。外来受診を推奨する根拠は、乳癌を可能な限り早期で発見できる可能性を最大限に高め、施行中のリスク評価を確実なものにすることにある。
[j] 女性は自身の乳房のことをよく知っておき、変化があれば速やかに病院を受診すべきである。
[k] マンモグラフィによる評価(BSCR-20)を参照のこと。
[l] トモシンセシスを用いることで要精査率を低減でき、癌の発見率が改善されるが、疾患特異的死亡率を改善するか否かを判断するには十分な研究が行われていない。
[m] 高品質の乳房MRIには、乳房専用コイル、MRIガイド下生検が可能な体制、乳房MRIに精通した放射線科医、地域的利便性が必要である。閉経前女性では、乳房MRIは月経周期7～15日目に行うのが望ましい。MRIは他の乳房画像検査の方法と関連付けて診断すべきである。
[n] 適応はあるがMRIを受けられない女性には乳房全体の超音波検査を考慮する。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

検診または症状のカテゴリー	検診と経過観察
乳癌リスク群： Gailモデルによる浸潤性乳癌の5年リスクが1.7%以上の35歳以上の女性[g]	・ 6～12ヵ月毎の外来受診[a,c,i] ▸Gailモデルにより乳癌リスク群と確認された時点で開始 ・ 年1回の検診[a]マンモグラム[k] ▸Gailモデルにより乳癌リスク群と確認された時点で開始 ▸トモシンセシスを考慮[a,l] ・ リスク低減戦略を考慮（NCCN乳癌リスク低減ガイドラインを参照） ・ ブレスト・アウェアネス[j]
または LCISまたはADH/ALHの病歴を有し、生涯リスクが20%を超える女性	・ 6～12ヵ月毎の外来受診[a,c,i] ▸LCISまたはADH/ALHの診断時から開始 ・ 年1回の検診[a]マンモグラム[k] ▸LCISまたはADH/ALHの診断時から開始するが、30歳未満では開始しない ▸トモシンセシスを考慮[a,l] ・ 年1回の乳房MRIを考慮[m,n] ▸LCISまたはADH/ALHの診断時から開始するが、25歳未満では開始しない（得られつつあるエビデンスに基づく） ・ リスク低減戦略を考慮（NCCN乳癌リスク低減ガイドラインを参照） ・ ブレスト・アウェアネス

[a] 乳癌検診の注意事項（BSCR-A）を参照のこと。
[c] 最低限の既往歴と家族歴を聴取すべきであり、外来受診時には、継続的なリスク評価、リスク低減カウンセリング、ならびに資格を有する医療従事者による問診・視触診を行うべきである。定性的および定量的評価の詳細については、NCCN乳癌リスク低減ガイドラインを参照のこと。
[g] 改変Gailモデルに採用されている危険因子（35歳以上）（BSCR-B）を参照のこと。
[i] 問診・視触診と検診なしを比較するランダム化試験は実施されていない。外来受診を推奨する根拠は、乳癌を可能な限り早期で発見できる可能性を最大限に高め、施行中のリスク評価を確実なものにすることにある。
[j] 女性は自身の乳房のことをよく知っておき、変化があれば速やかに病院を受診すべきである。
[k] マンモグラフィによる評価(BSCR-20)を参照のこと。
[l] トモシンセシスを用いることで要精査率を低減でき、癌の発見率が改善されるが、疾患特異的死亡率を改善するか否かを判断するには十分な研究が行われていない。
[m] 高品質の乳房MRIには、乳房専用コイル、MRIガイド下生検が可能な体制、乳房MRIに精通した放射線科医、地域的利便性が必要である。閉経前女性では、乳房MRIは月経周期7～15日目に行うのが望ましい。MRIは他の乳房画像検査の方法と関連付けて診断すべきである。
[n] 適応はあるがMRIを受けられない女性には乳房全体の超音波検査を考慮する。

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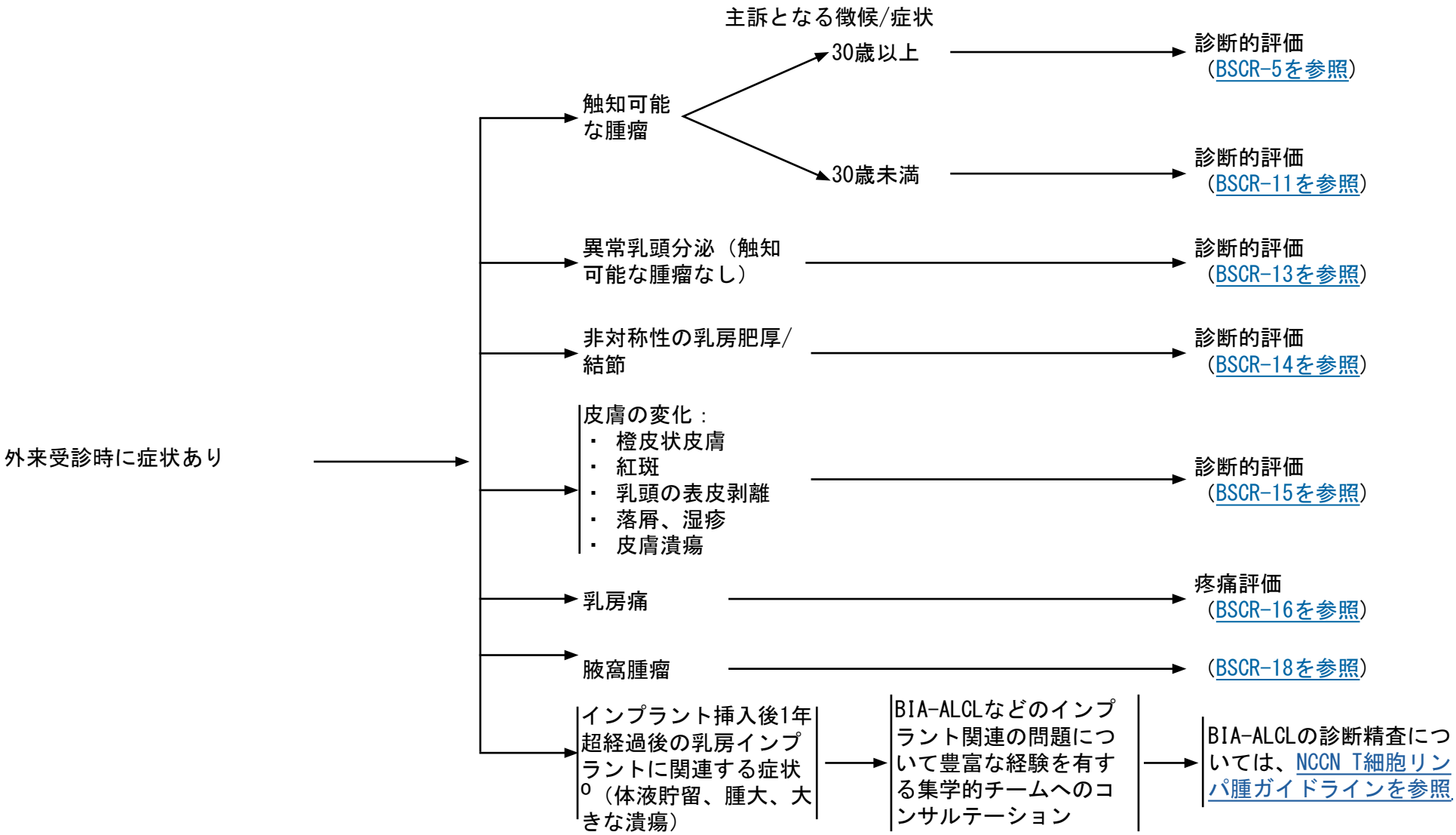
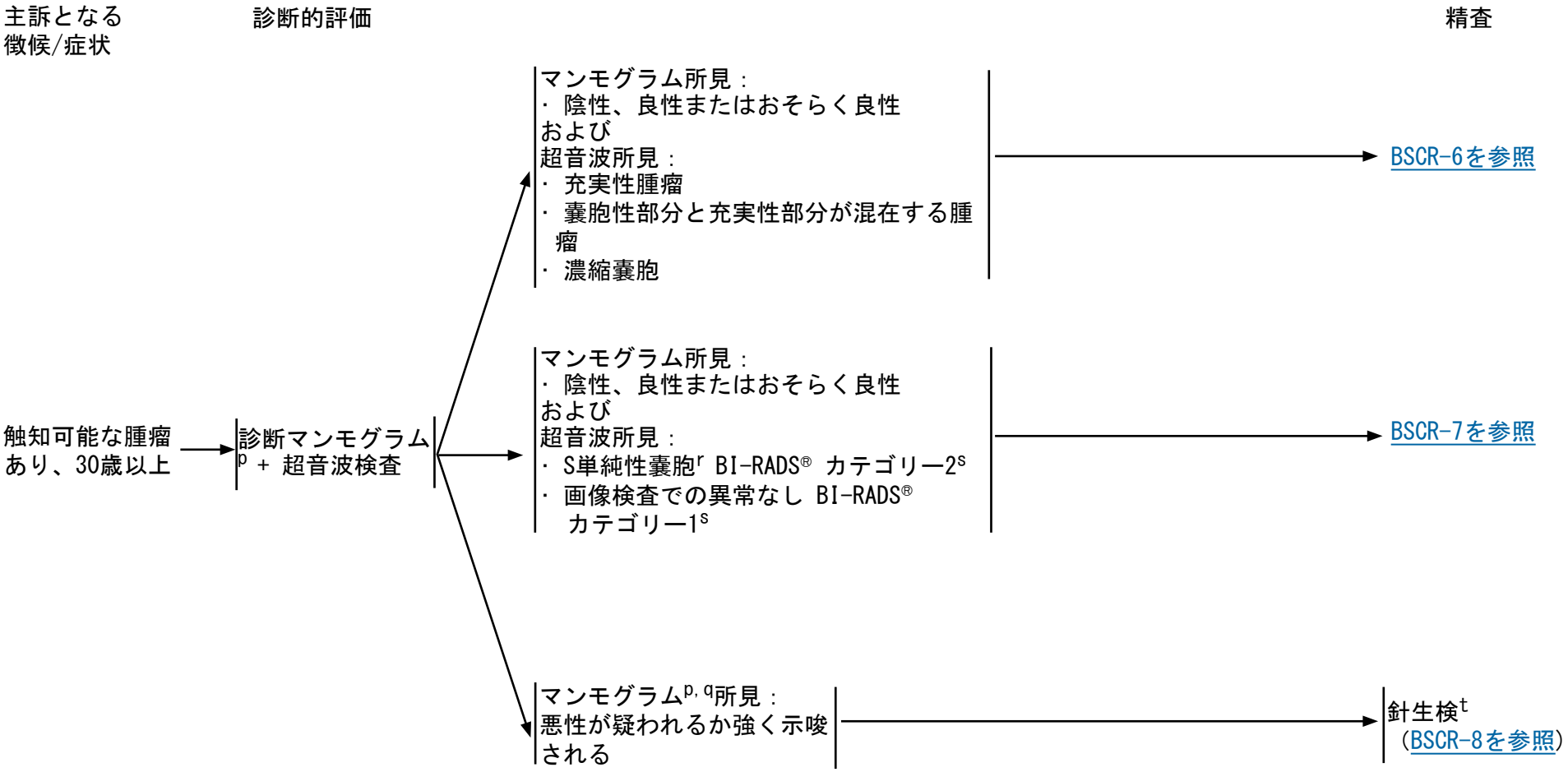
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。



[o]乳房インプラントを有する個人は乳房インプラント関連未分化大細胞型リンパ腫（breast implant-associated anaplastic large cell lymphoma：BIA-ALCL）の発生リスクが高い（インプラント挿入から平均8～10年後）。大半の症例がテクスチャードタイプのインプラントで発生している。

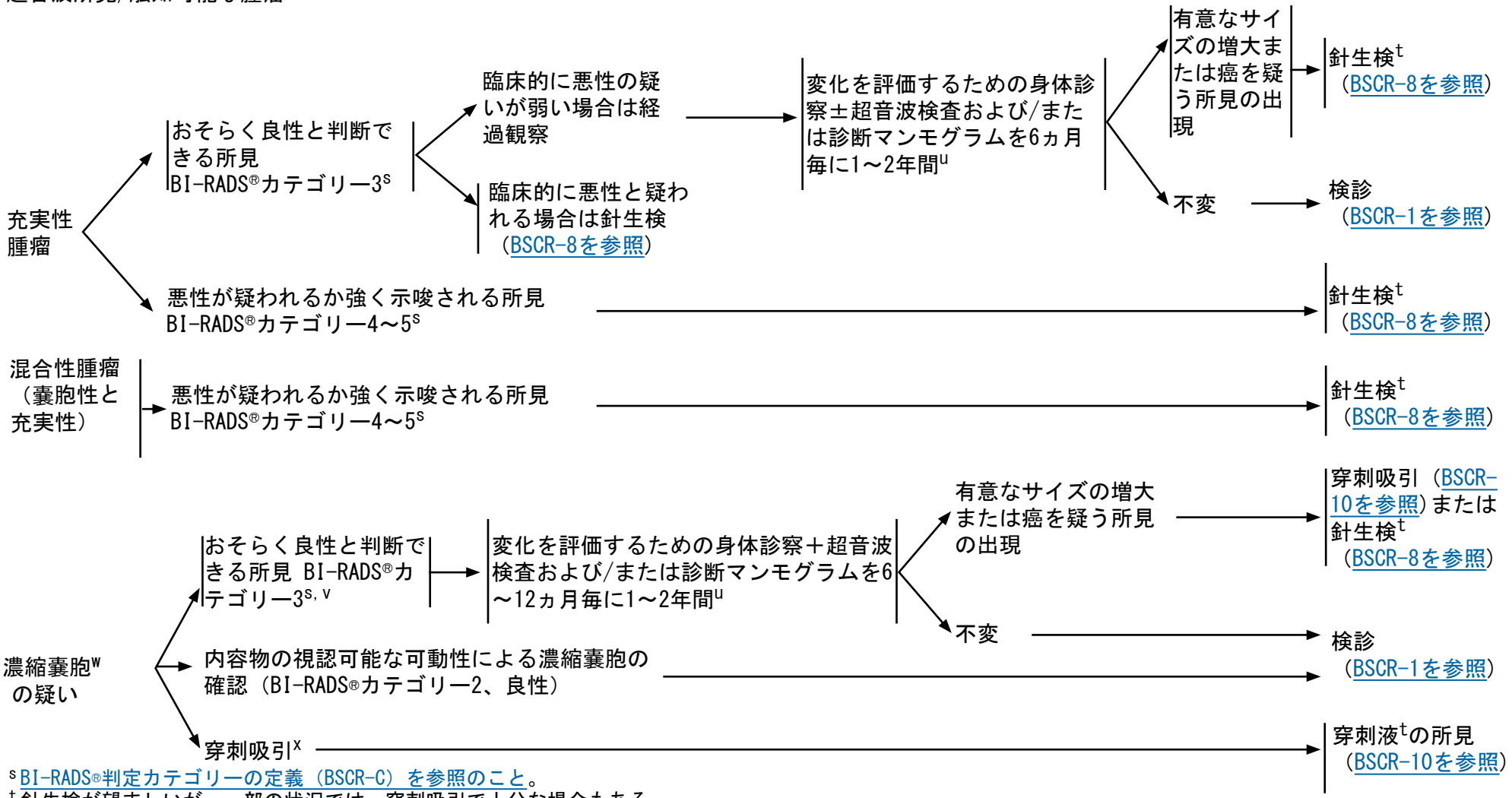
注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。



[p] 臨床的に悪性の疑いが弱い腫瘤や単純性嚢胞が疑われる腫瘤など、一部の臨床状況では初回の画像検査法として超音波検査が望ましく、30～39歳の女性には超音波検査で十分となる場合もある。考察を参照のこと。
[q] 臨床所見と画像所見の位置的な相関を評価する。相関がみられない場合は「マンモグラム所見：陰性、良性またはおそらく良性」まで戻り、触知可能な病変に対して更なる精査を行う。画像所見と触知可能な所見の間に相関がみられる場合は、その後の精査によって問題に対する答えが得られる。
[r] 問診・視触診の結果と画像検査の結果が一致する必要がある。持続する臨床症状には治療目的の穿刺吸引を考慮する。
[s] BI-RADS®判定カテゴリーの定義（BSCR-C）を参照のこと。
[t] 針生検が望ましいが、一部の状況では、穿刺吸引で十分な場合もある。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

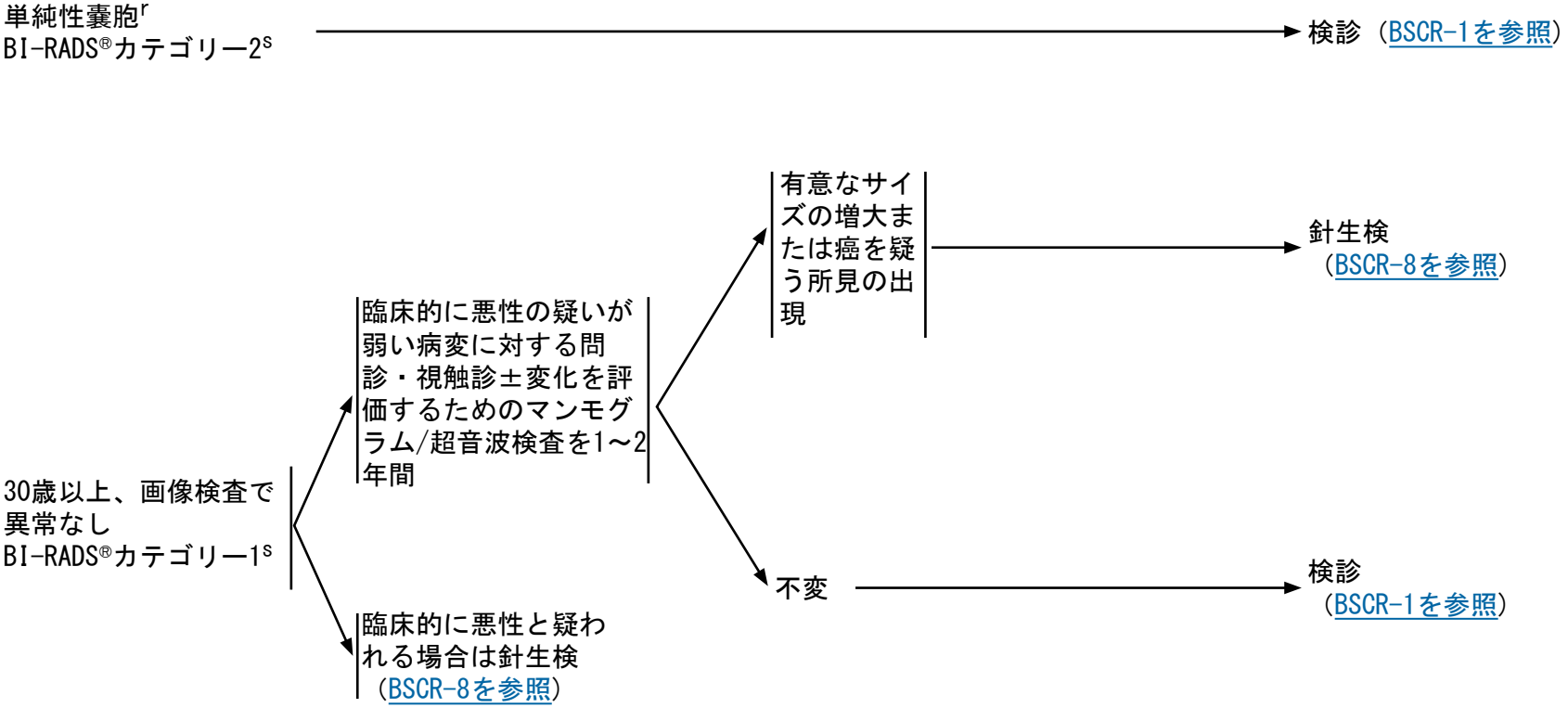
超音波所見/触知可能な腫瘤



[s] BI-RADS®判定カテゴリーの定義（BSCR-C）を参照のこと。
[t] 針生検が望ましいが、一部の状況では、穿刺吸引で十分な場合もある。
[u] 経過観察の間隔には、疑いの強さに応じたばらつきがあってもよい。
[v] 多数の単純性嚢胞が認められる状況では、濃縮嚢胞は良性所見とみなされる場合がある。
[w] 血流のない低エコー部分を含む境界明瞭な円形または卵円形の腫瘤、単純性嚢胞の基準の大半を満たすが、すべてを満たすわけではない。
[x] 症状または膿瘍の可能性を調べるために嚢胞の性質の確認を考慮してもよい。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

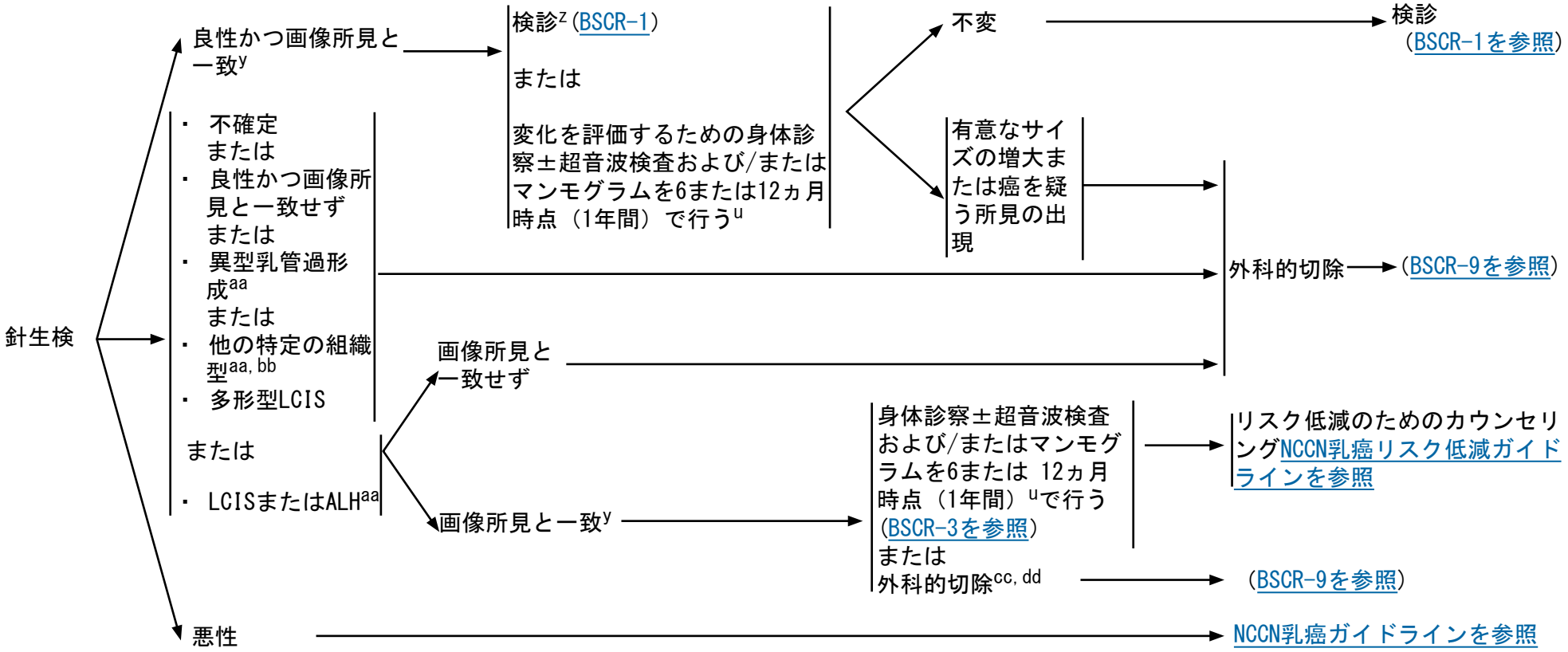
超音波所見/触知可能な腫瘤



[r] 問診・視触診の結果と画像検査の結果が一致する必要がある。持続する臨床症状には治療目的の穿刺吸引を考慮する。
[s] BI-RADS®判定カテゴリーの定義（BSCR-C）を参照のこと。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

針生検後の経過観察評価



[u] 経過観察の間隔には、疑いの強さに応じたばらつきがあってもよい。

[y] 病理学的所見が画像所見と合致する。

[z] 大半は年1回のスクリーニングのために再来院することになるが、身体診察±更なる画像検査が選択肢となる。

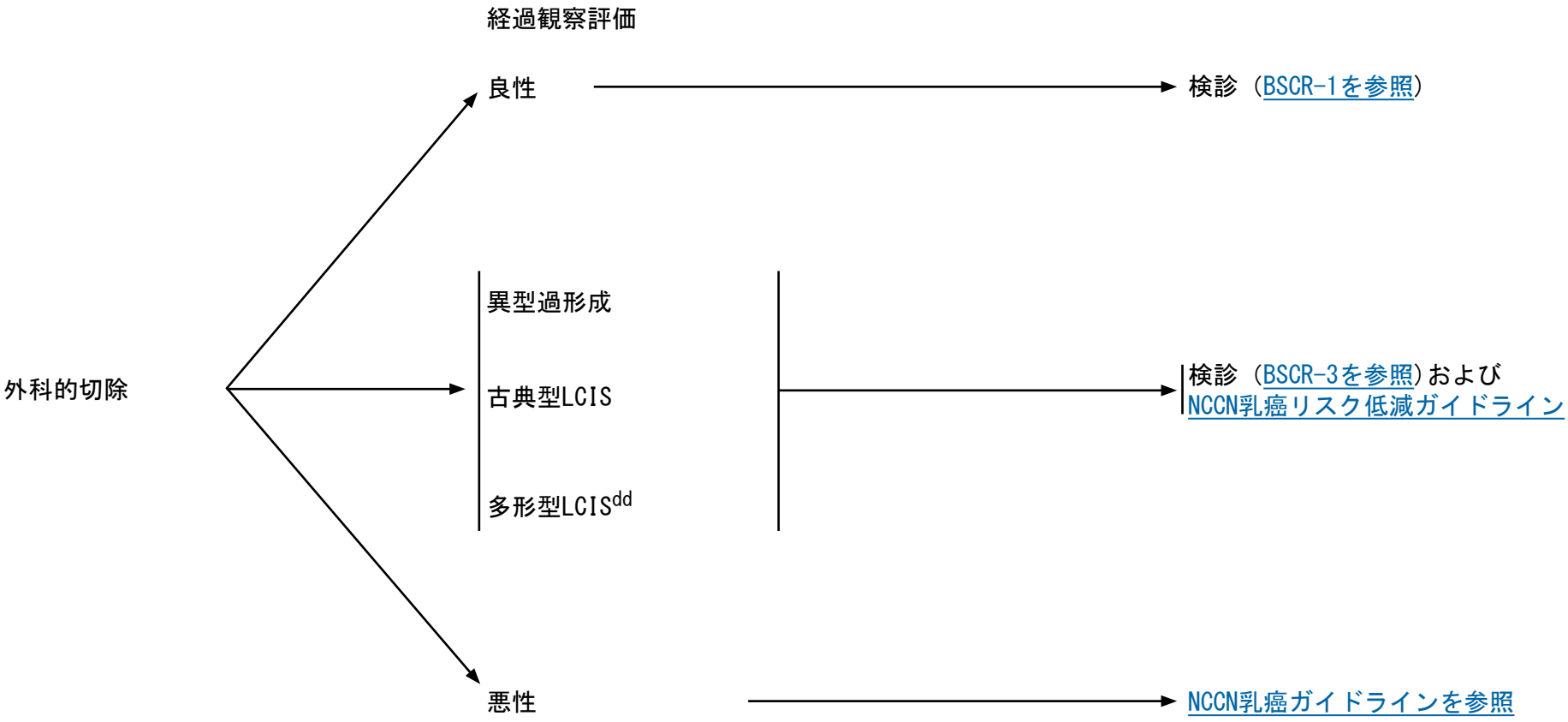
[aa] 選択された患者では、外科的切除の代わりにモニタリングが適切となる場合がある（例、平坦型上皮異型［FEA］、異型を伴わない乳頭腫、線維腺腫を支持する線維上皮性病変、十分に検体が採取されているか偶発的に発見された放射状瘢痕）。

[bb] 追加の組織採取が必要になる場合がある他の組織型：ムチン産生病変、葉状腫瘍の可能性、乳頭状病変、放射状瘢痕、または病理医にとって懸念となる組織型。

[cc] 針生検で4つを超える終末乳管小葉単位に浸潤した多病巣性/広汎性のLCISを認める場合には、外科的切除標本で浸潤癌と診断されるリスクが高い可能性がある。（Rendi MH, Dintzis SM, Lehman CD, et al.Lobular in-situ neoplasia on breast core needle biopsy: imaging indication and pathologic extent can identify which patients require excisional biopsy.Ann Surg Oncol 2012;19:914-921.以下で入手可能：http://www.ncbi.nlm.nih.gov/pubmed/21861212）。

[dd] 多形型LCISには断端陰性での完全切除を考慮してもよい。ただし、多形型LCIS患者の治療に関する治療成績のデータはなく、LCISの組織型について組織学的な分類が不十分であることがその理由の1つになっている。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。



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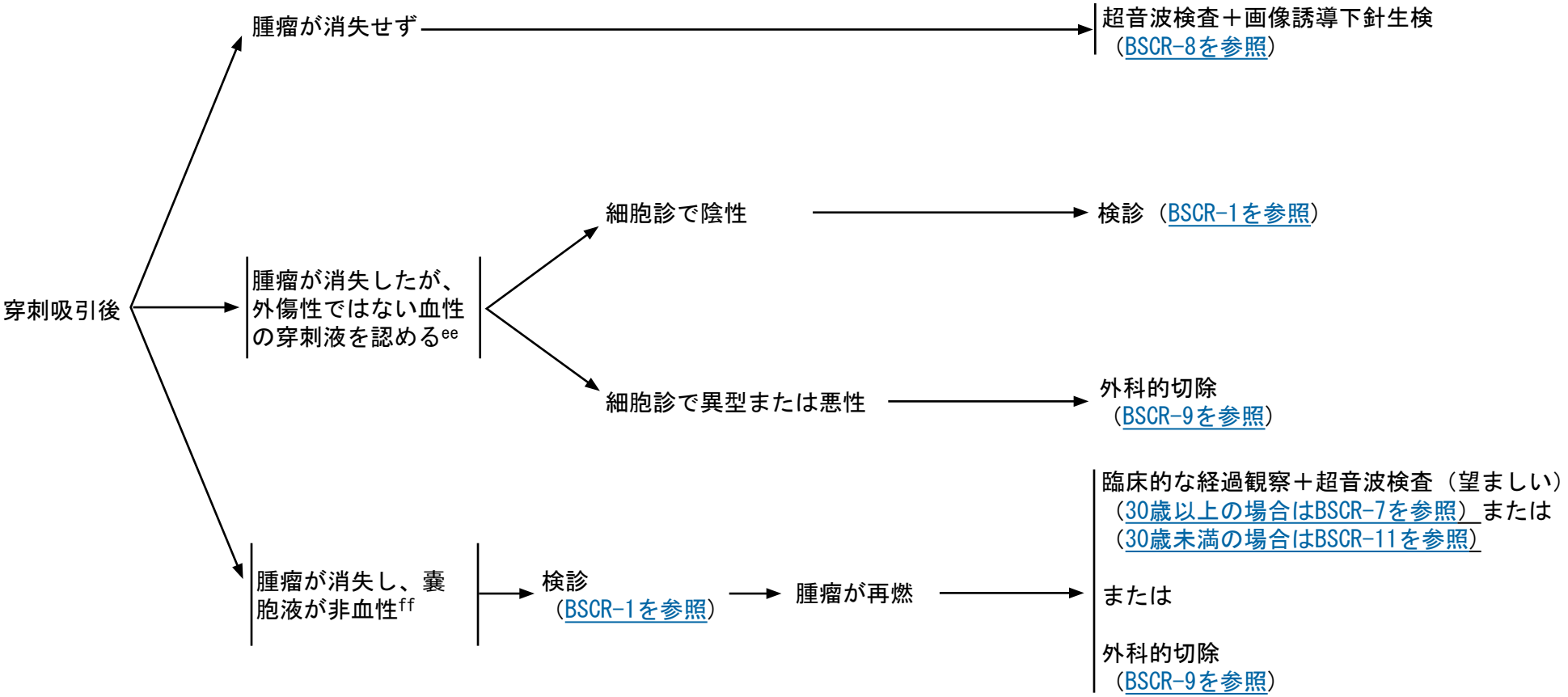
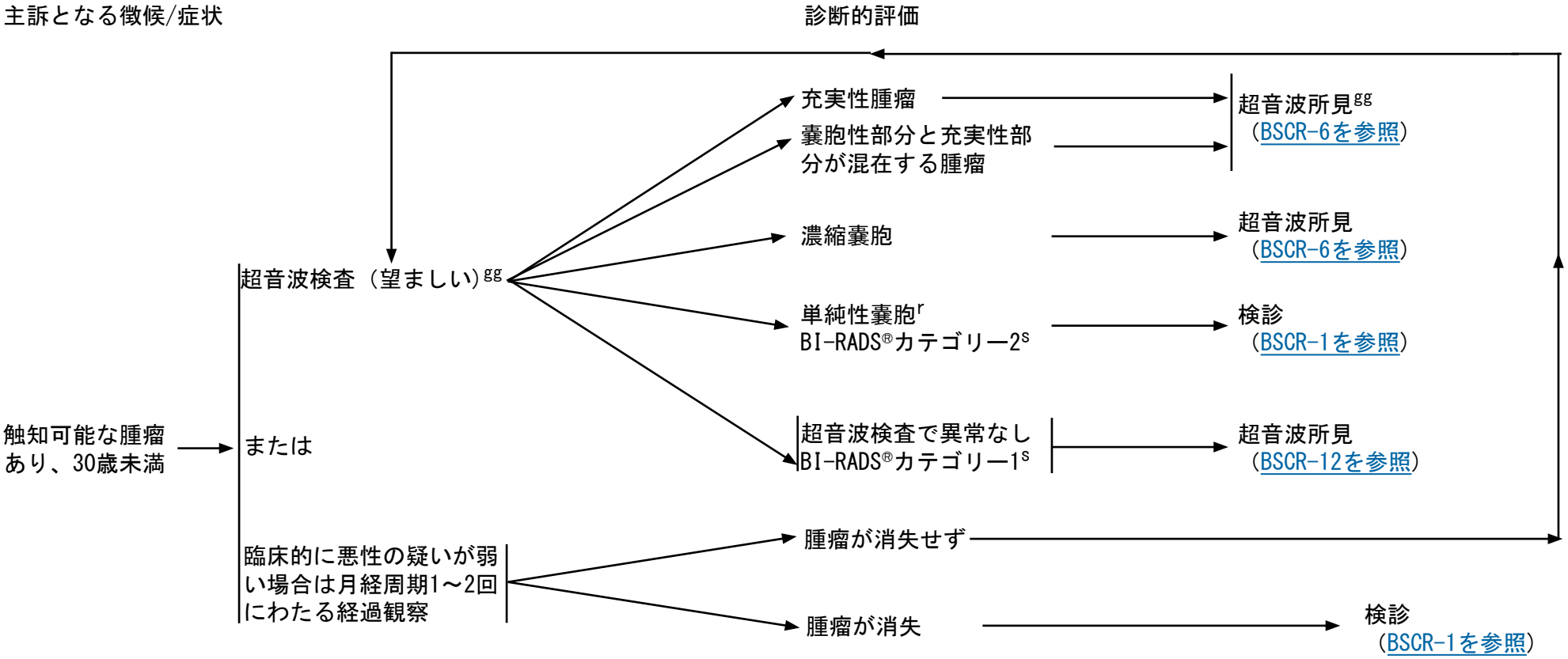
穿刺液所見/触知可能な腫瘤



経過観察評価

eeマーキング用クリップを留置し、細胞診に送る。
ffルーチンの細胞診は推奨されない。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

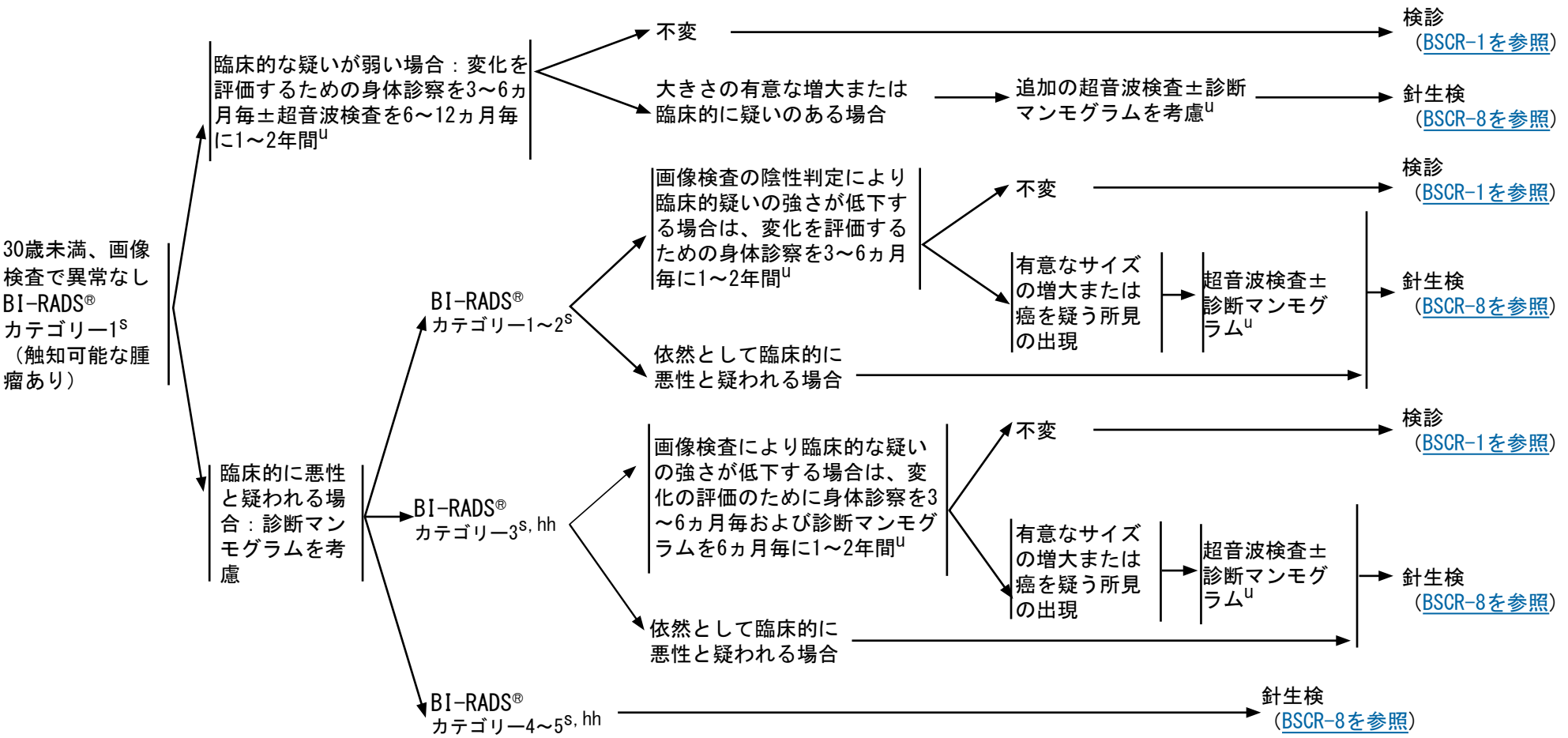


r 問診・視触診の結果と画像検査の結果が一致する必要がある。持続する臨床症状には治療目的の穿刺吸引を考慮する。
s BI-RADS®判定カテゴリーの定義（BSCR-C）を参照のこと。
gg悪性が疑われるか強く示唆される場合は、マンモグラムを施行する。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

超音波所見/触知可能な腫瘤

経過観察評価



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u経過観察の間隔には、疑いの強さに応じたばらつきがあってもよい。
hh臨床所見と画像所見の位置的な相関を評価する。相関がみられない場合は「BI-RADS®カテゴリー1～2」まで戻り、触知可能な病変に対して更なる精査を行う。画像所見と触知可能な所見の間に相関がみられる場合は、その後の精査によって問題に対する答えが得られる。

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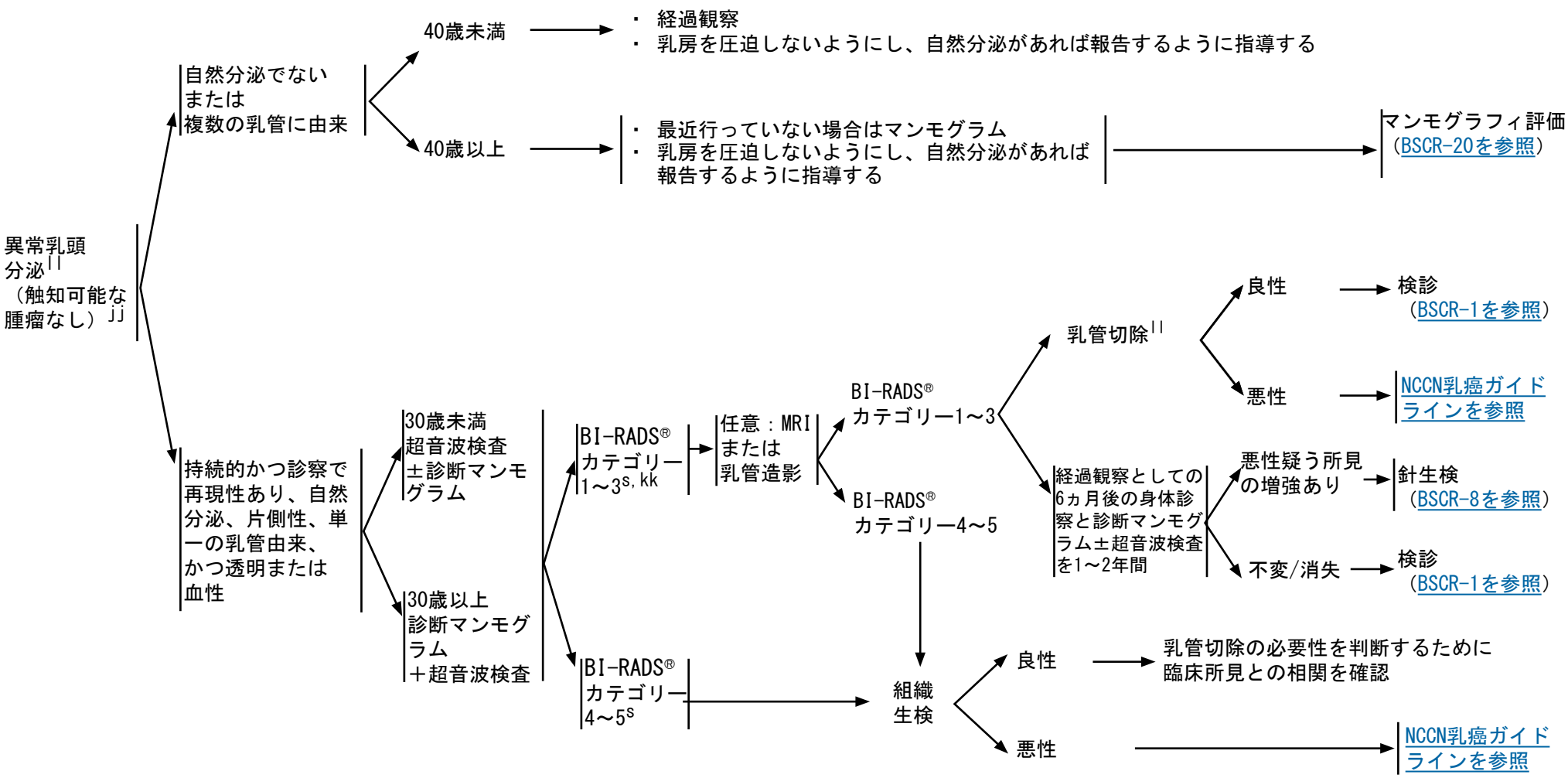
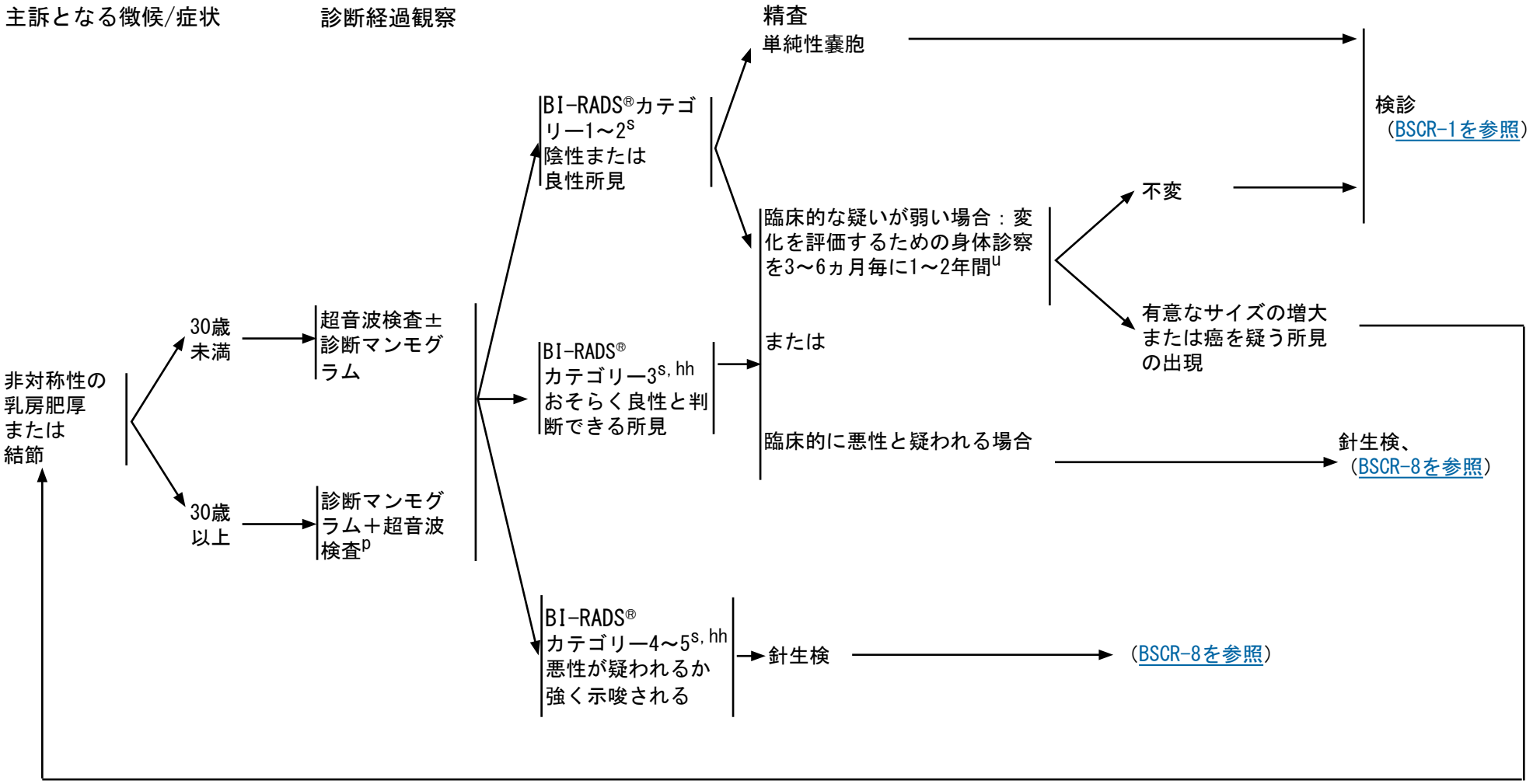
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

主訴となる徴候/症状　　診断経過観察



[s] BI-RADS®判定カテゴリーの定義（BSCR-C）を参照のこと。
[ii]異常乳頭分泌を引き起こす可能性がある薬剤の一覧（すべてを網羅しているわけではない）：向精神薬、降圧薬、オピオイド、経口避妊薬、エストロゲン。
[jj]腫瘤が触知可能な場合、BSCR-5 または BSCR-7を参照のこと。
[kk]BI-RADS®カテゴリー3の所見が異常乳頭分泌と無関係な場合は、BSCR-20に従ってマンモグラフィ所見に対応する。
[ll]臨床的な疑いと患者の意向に基づく。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

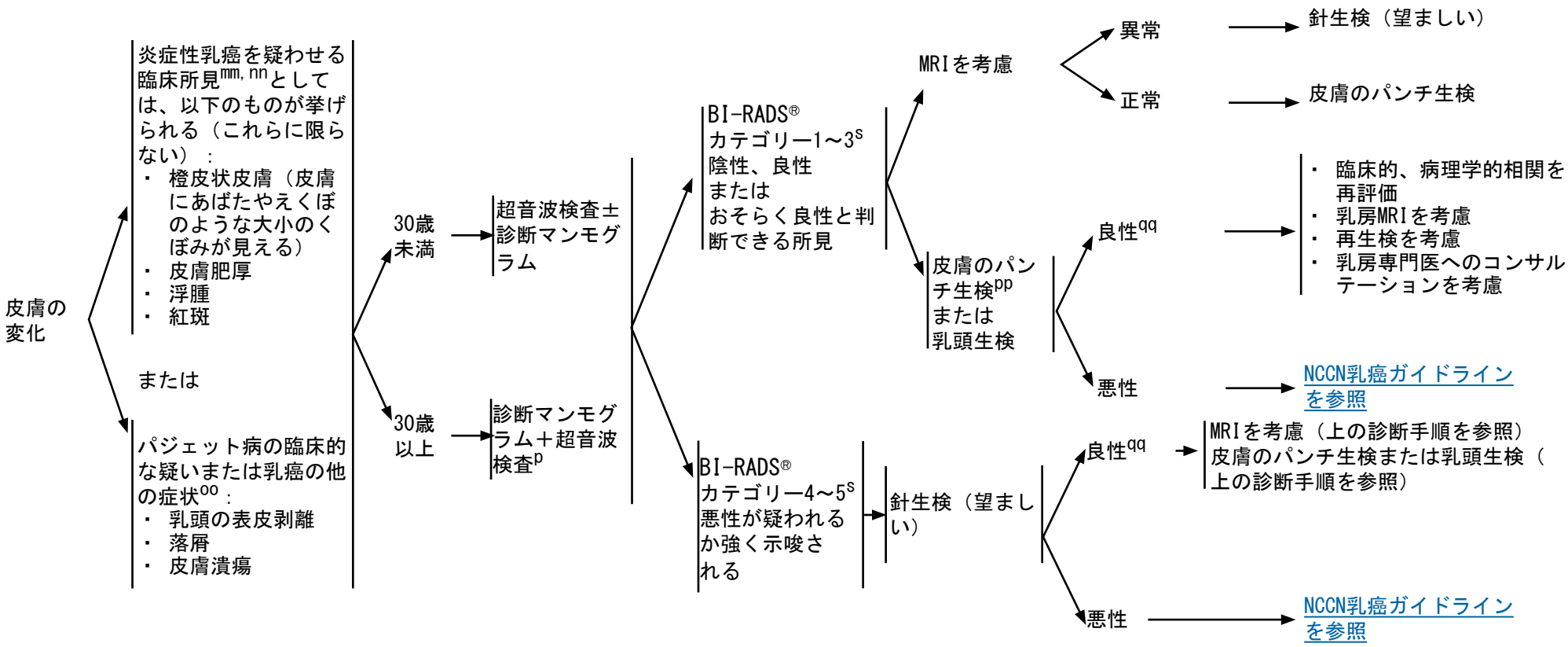


[p] 臨床的に悪性の疑いが弱い腫瘤や単純性嚢胞が疑われる腫瘤など、一部の臨床状況では初回の画像検査法として超音波検査が望ましく、30～39歳の女性には超音波検査で十分となる場合もある。考察を参照のこと。
[s] BI-RADS®判定カテゴリーの定義（BSCR-C）を参照のこと。
[u] 経過観察の間隔には、疑いの強さに応じたばらつきがあってもよい。
[hh] 臨床所見と画像所見の位置的な相関を評価する。相関がみられない場合は「BI-RADS®カテゴリー1～2」まで戻り、触知可能な病変に対して更なる精査を行う。画像所見と触知可能な所見の間に相関がみられる場合は、その後の精査によって問題に対する答えが得られる。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

主訴となる徴候/症状

診断経過観察



[p] 臨床的に悪性の疑いが弱い腫瘤や単純性嚢胞が疑われる腫瘤など、一部の臨床状況では初回の画像検査法として超音波検査が望ましく、30～39歳の女性には超音波検査で十分となる場合もある。考察を参照のこと。

[s] BI-RADS®判定カテゴリーの定義（BSCR-C）を参照のこと。

[mm] これは乳房の重篤な疾患を反映している場合があり、評価が必要である。（Dawood S, Merajver SD, Viens P, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011;22(3):515-523. https://www.ncbi.nlm.nih.gov/pubmed/20603440で入手可能）。

[nn] 臨床的に乳癌の疑いが弱いか感染症の疑いが強い場合は、乳腺炎に対する抗菌薬の短期使用（例、7～10日）が適応となる場合がある。

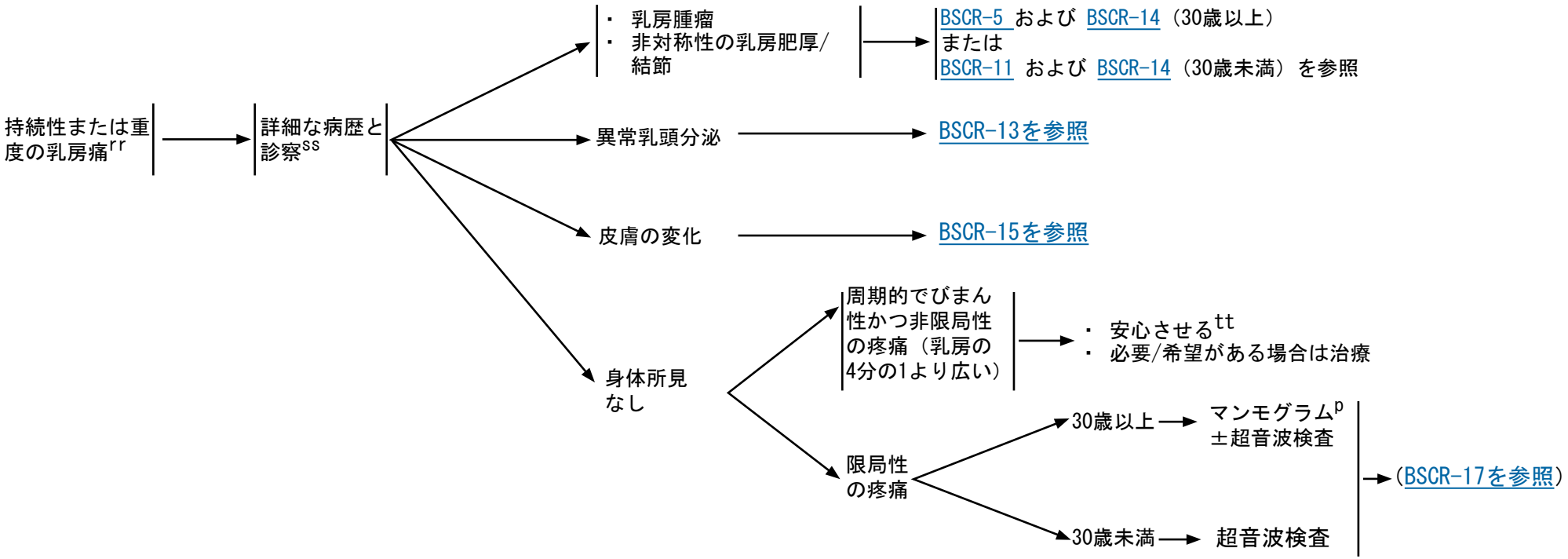
[oo] 臨床的にパジェット病の疑いが弱いか湿疹の疑いが強い場合は、外用ステロイドの短期使用が適応となる場合がある。

[pp] 炎症性乳癌は臨床診断であり、パンチ生検での陽性所見は必要ない。

[qq] 炎症性乳癌が臨床的に疑われる患者では、皮膚のパンチ生検の所見が良性であっても、悪性腫瘍は除外されない。更なる評価が推奨される。

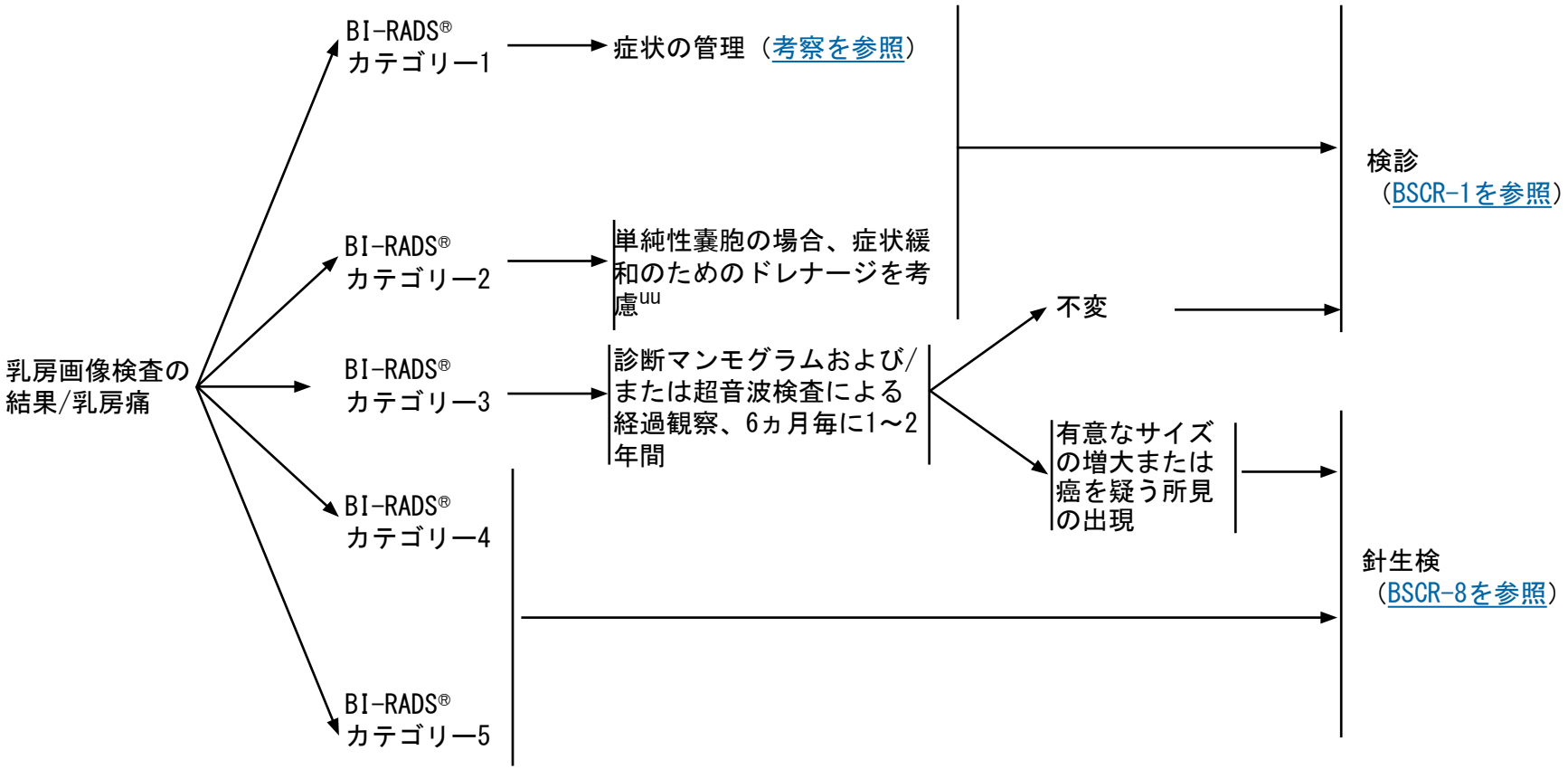
注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

主訴となる徴候および症状　　経過観察評価



[p] 臨床的に悪性の疑いが弱い腫瘤や単純性嚢胞が疑われる腫瘤など、一部の臨床状況では初回の画像検査法として超音波検査が望ましく、30～39歳の女性には超音波検査で十分となる場合もある。考察を参照のこと。
[rr] その症状に対する管理の前の4～6週間として定義される。
[ss] 十分な問診・視触診としては、直立位および仰臥位での視診と乳房、腋窩、および鎖骨リンパ節領域の全要素の触診などを行う。診察の触診部分にかける時間は触知可能な異常の検出増加と関連している。乳頭からの位置および距離により画像検査所見との位置的な相関の評価が容易になる。（BSCR-1を参照）。
[tt] 乳房画像検査による検診が現在行われている場合。

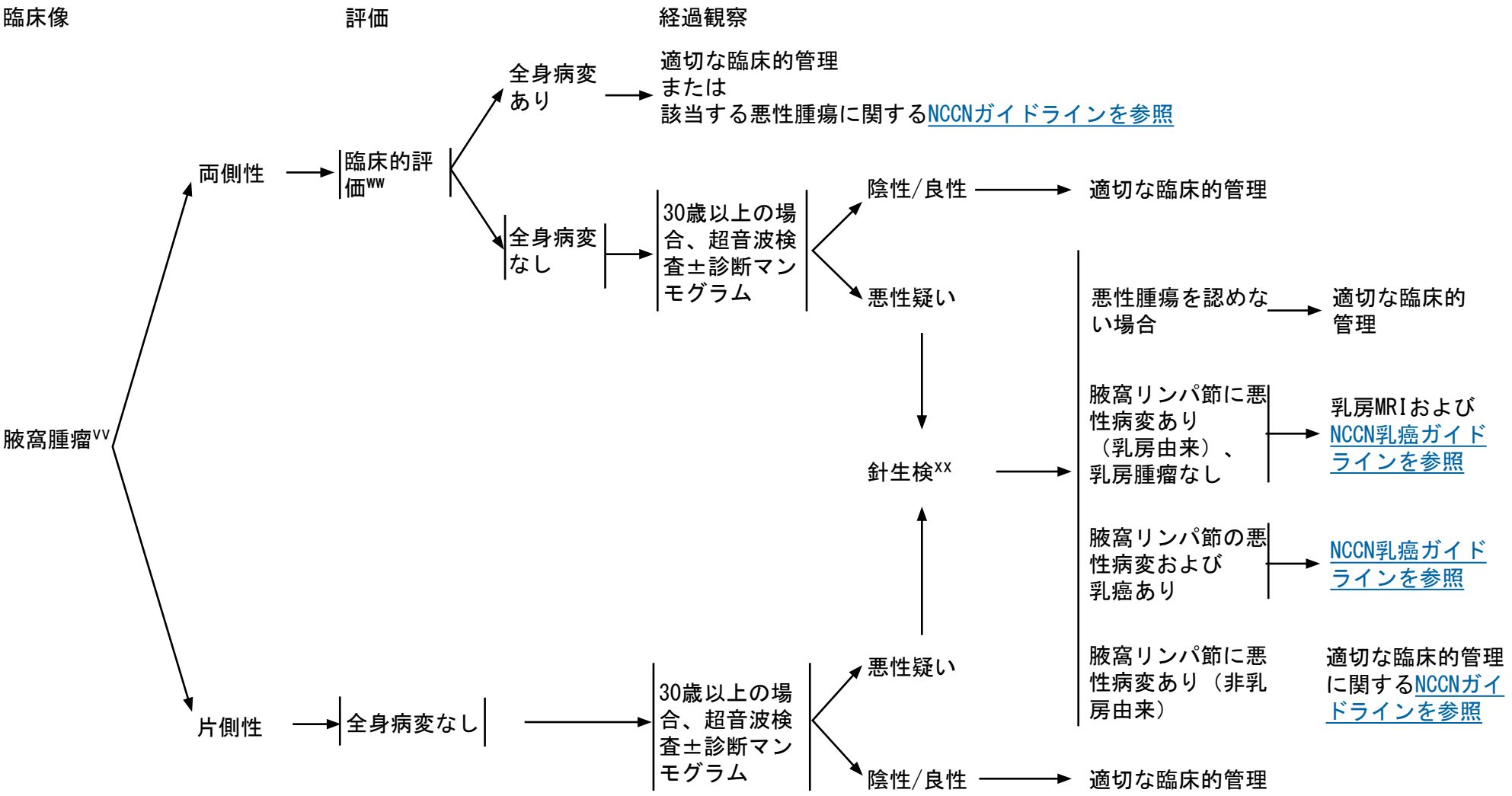
注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。



[s] BI-RADS®判定カテゴリーの定義（BSCR-C）を参照のこと。
[uu]濃縮嚢胞の場合は、穿刺吸引を考慮する。

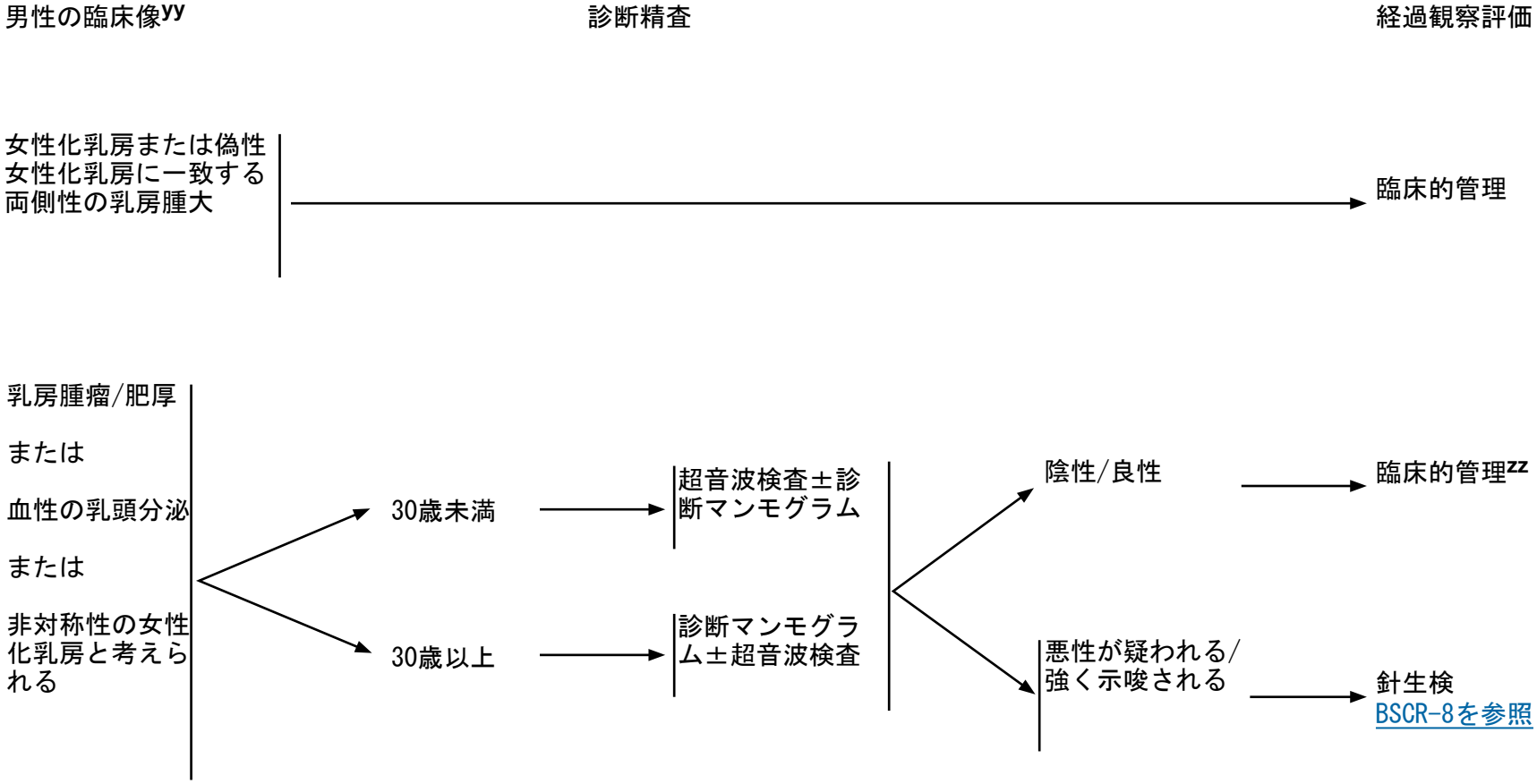
注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

腋窩腫瘤の経過観察に関する推奨



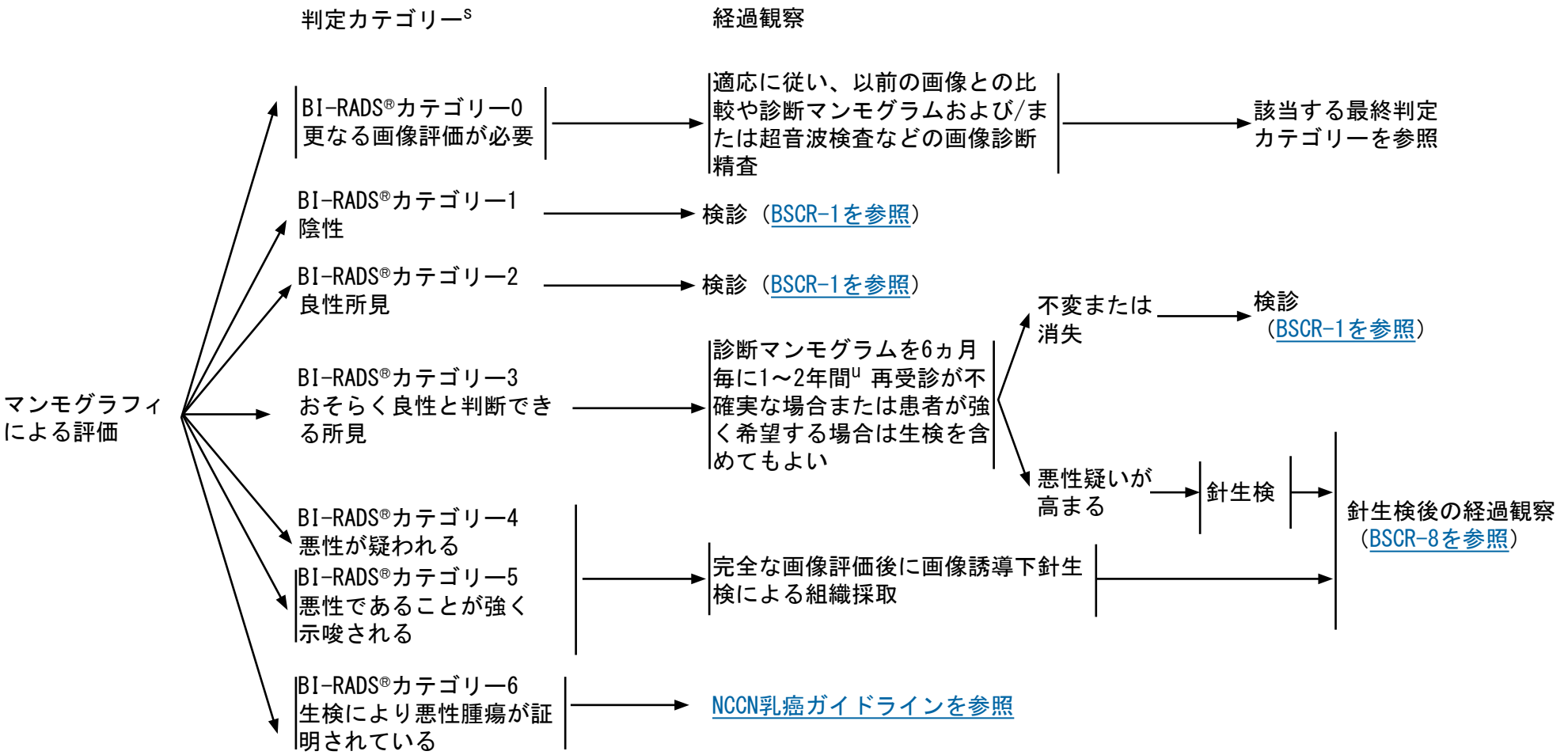
[vv]腋窩に限局しており、悪性リンパ腫の徴候を認めない。
[ww]他部位のリンパ節腫脹および乳房以外にあるリンパ節腫脹の潜在的原因を評価するための詳細な臨床的評価。
[xx]悪性リンパ腫が疑われる場合は、特別な病理学的処理および/または外科的切除が必要になることがある。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。



yyNCCN乳癌ガイドラインの「男性乳癌に関する特別な考慮点」の節を参照のこと。
zz疑わしい臨床所見があれば外科への紹介を考慮する。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。



[s] BI-RADS®判定カテゴリーの定義（BSCR-C）を参照のこと。
[u] 経過観察の間隔には、疑いの強さに応じたばらつきがあってもよい。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

乳癌検診の注意事項

- 女性に対して乳房検診の潜在的利益、リスク、限界に関してカウンセリングを行うべきである。女性の価値観と意向に基づく共同意思決 定が推奨される（考察を参照）。
- 十分な問診・視触診としては、直立位および仰臥位での視診と乳房（外側-内側：中腋窩線から胸骨まで；頭側-尾側：鎖骨から乳房下の隆起部まで）、腋窩および鎖骨リンパ節領域の全要素の触診などを行う。診察の触診部分にかける時間は触知可能な異常の検出増加と関連している。乳頭からの時計軸上/4分割の位置および距離により画像検査所見との位置的な相関の評価が容易になる。
- 期待余命を限定する（例えば10年以下）重度の併存疾患と治療介入が計画されているかどうかを考慮する。
- 検診の実施年齢の上限はまだ確立されていない。
- マンモグラフィで高濃度乳房（不均一高濃度乳房または極めて高濃度乳房）を認める女性に対しては、補助的検診検査の追加に伴うリスクおよび利益に関するカウンセリングを推奨する。
- 高濃度乳房はマンモグラフィの感度を低下させる。マンモグラフィでの高濃度乳房は乳癌リスクの増加と関連している。
- フルフィールドデジタルマンモグラフィは若年女性と高濃度乳房の女性にとって有益となるようである。
- 複数の研究から、トモシンセシスを用いることで要精査率を低減できることが示されており、癌の発見率が改善されるようである。注目すべき点として、ほとんどの研究では2倍の線量の放射線が用いられている。線量は合成2次元再構成画像を用いることで最小限に抑えることが可能である。
- 高濃度乳房の女性ではハンドヘルド（用手的）による超音波検査や自動超音波検査によって癌の発見率を向上させることが可能であるが、要精査や良性病変に対する乳房生検が増加する可能性がある。
- 現在のエビデンスは、検診としての分子イメージング（例、breast-specific gamma imaging、セスタミビシンチグラフィ、陽電子放出マンモグラフィ）のルーチンな使用を支持していないが、これらの検査法により、マンモグラフィで高濃度乳房の女性における早期乳癌の発見率が改善される可能性があることを示したエビデンスが新たに得られている。しかしながら、これらの検査法で全身に照射される実効線量はマンモグラフィよりも著しく高い。
- 現在のエビデンスは、検診としてのサーモグラフィや乳管洗浄のルーチンな使用を支持していない。
- 乳癌ハイリスク群においては、現在のエビデンスとFDAの安全声明[1]（ガドリニウム造影剤）を考慮し、当委員会はこれらの限定された集団における年1回のMRIを引き続き推奨する。

[1] FDA Drug Safety Communication:FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue:https://www.fda.gov/Drugs/DrugSafety/ucm559007.htm.

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

続く

乳癌検診の注意事項

マンモグラフィの補助としての乳房MRI検診に関する推奨[2,3]
（後述の場合を除く検診開始年齢について：BSCR-2を参照）

年1回のMRI検診を推奨する（エビデンスに基づく）：
- 乳癌遺伝子変異保持者の未検査の第一度近親者：MRIの前に遺伝学的検査を勧める。遺伝子変異を有する個人については、NCCN 「乳癌および卵巣癌における遺伝学的/家族性リスク評価」ガイドラインを参照のこと。
- 大部分が家族歴に基づくモデルによる定義で生涯リスクが20%以上。第一度近親者に対する遺伝学的検査を勧める。検査を拒否された場合は、MRIを推奨する。

年1回のMRI検診を推奨する（専門家の統一見解に基づく）：
- 10歳から30歳までに胸部に対する放射線照射

生涯リスクが20%以上の場合は、新たなエビデンスに基づき、LCISおよびALH/ADHに対するMRI検診を考慮する[4]

MRI検診の賛否に関するエビデンスは不十分である：
- 大部分が家族歴に基づくモデルによる定義で生涯リスクが15～20%
- マンモグラフィ上で不均一高濃度乳房または極めて高濃度乳房

MRI検診を受けないよう推奨する（専門家の統一見解に基づく）：
- 生涯リスクが15%未満の女性

[2] John Wiley and Sonsの許可を得て改変。Copyright ©2007 American Cancer Society.Saslow D, Boetes C, Burke W, et al.American Cancer Society Guidelines for Breast Cancer Screening with MRI as an Adjunct to Mammography.CA:Cancer J Clin 2007;57:75-89.
[3] 乳癌の既往があり、これらの危険因子を有する女性には、追加の検診を考慮すべきである。
[4] Tyrer-Cuzickモデルを用いてLCISの生涯リスクを推定することができる。Mayo Clinic Absolute Risk Dataを参照のこと。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

改変Gailモデルに採用されている危険因子（35歳以上）[1]

- 現在の年齢
- 初経年齢
- 第一子の出産年齢または未経産
- 女性の第一度近親者の乳癌発症者数
- 過去に乳房生検で良性と判定された回数[2]
- 過去の乳房生検での異型過形成
- 人種[3]

リスクの計算については、改変Gailモデルに基づく（http://www.cancer.gov/bcrisktool/Default.aspxを参照）。

[1] 詳細については、http://www.cancer.gov/bcrisktool/Default.aspxを参照のこと。
[2] Gailモデルでは針生検も生検回数にカウントする。
[3] 現在のGailモデルは、非白人、非アジア人、非アフリカ系の米国人女性の乳癌リスクを正確に評価できない可能性がある。乳癌および関連する癌の強い家族歴を有する女性の生涯リスクの評価には適切なモデルではない。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

マンモグラフィにおける判定カテゴリーの定義（訳注：BI-RADS®判定）[1,2]

BI-RADS®マンモグラフィ所見

A. 判定が未完了：
カテゴリー0：未完了：追加の画像評価および/または比較のための過去のマンモグラムが必要である：
追加の評価を要する所見が存在する。このカテゴリーは、ほぼ常に検診の状況で用いられる。超音波検査の装置またはスタッフをすぐに手配できない場合や、患者がすべての診断検査の完了を待つことができない、あるいは待つ意思がない場合など、一定の状況下では、この判定カテゴリーが診断マンモグラフィの報告書で用いられることがある。追加の画像評価に関する推奨には、スポット圧迫（拡大の有無は問わない）、特殊なマンモグラフィ像、および超音波検査の利用が含まれる。カテゴリー0は、MRIによる追加評価の必要性を示した診断乳房画像検査での所見に対して用いるべきではない。むしろ、読影を行う医師はMRIが施行される前に作成された報告書で最終的な判定を下すべきである。ほとんどの状況で、また実行可能であれば、マンモグラフィで陰性または良性と判定されない場合には、直近の検査結果を過去の検査結果と比較すべきである。読影を行う医師は、過去の検査結果を入手するのにどれだけの努力を払うべきかについて、そのような試みが成功する可能性とその比較が最終判定に影響を及ぼす可能性を踏まえて、判断すべきである。この状況においては、所見が本質的に悪性を疑わせるものである場合には、過去の検査結果との比較が適当でない可能性があるということに注意する必要がある。

カテゴリー0は、最終判定を行うために過去の画像との比較が必要な場合に限り、その比較のために用いるべきである。比較のための過去の検査結果を待つ状況でカテゴリー0を用いる場合には、たとえ過去の検査結果が入手できなくとも、最終判定が30日以内（早いほど望ましい）に行われることを100%の信頼性で保証する追跡手順を整備しておくべきである。乳房画像検査を実施している医療機関の中には、100%信頼できる追跡手順が整備されていないという理由で、過去の検査結果を待つ状況ではカテゴリー0を決して採用しないという妥当な対応をとっている施設もある。マンモグラフィ検査の結果が過去の検査結果を待つ状況でカテゴリー0と判定され、その後に過去の検査結果が入手できた場合には、変更された判定結果を含める形で、最初のマンモグラフィ報告書に対する補遺を発行すべきである。監査のため、変更された判定結果で当初の判定を置き換えるべきである。

[1] マンモグラフィの結果は、最終判定カテゴリーを用いて報告することが義務づけられている（Quality Mammography Standards:Final Rule.Federal Register.1997;62:55988）。
[2] この表の用語にはAmerican College of Radiology（ACR）の用語が反映されている。ACR-BI-RADS®--5th Edition.ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas; BI-RADS.Reston VA.American College of Radiology, 2014.詳細については、www.acr.orgを参照のこと。American College of Radiologyの許可を得て転載。American College of Radiologyの明示の書面による許諾なく、本文書を他の形態で提示することは認められない。

続く

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

マンモグラフィにおける判定カテゴリーの定義（訳注：BI-RADS®判定）[1,2]

BI-RADS® – マンモグラフィ所見

B. 判定が完了—最終判定カテゴリー：
カテゴリー1：陰性：
特記事項なし。これは検査結果が正常な場合である。

カテゴリー2：良性：
カテゴリー1と同様に、これも「正常」の判定であるが、この場合、読影者はマンモグラフィ報告書に良性所見を記載することを選択する。退縮した石灰化線維腺腫、皮膚の石灰化、金属性異物（針生検、外科クリップなど）、脂肪含有病変（オイル嚢胞、脂肪腫、乳瘤、混合密度の過誤腫など）は、いずれも特徴的な良性の様相を呈し、自信をもって記載できる場合もある。読影者は乳房内リンパ節、血管石灰化、インプラント、または過去の手術と明白に関連する構築の乱れなどを記載する一方、依然としてマンモグラフィ上に悪性所見は認められないと結論づけることを選択する場合もある。一方で読影者は、そのような所見を記載しないよう選択することも可能であり、その場合は検査結果は陰性と判定すべきである（カテゴリー1）。

カテゴリー1とカテゴリー2の判定は、ともにマンモグラフィ上で悪性所見が認められないことを意味するという点に注意すべきである。どちらの場合も、定期的なマンモグラフィ検診の続行の推奨に従うべきである。両者の違いは、カテゴリー2が報告書に具体的な良性のマンモグラフィ所見を記載する場合に用いるのに対し、カテゴリー1はそのような所見を記載しない場合（たとえそのような所見が存在する場合でも）に用いるという点にある。

[1]マンモグラフィの結果は、最終判定カテゴリーを用いて報告することが義務づけられている（Quality Mammography Standards: Final Rule. Federal Register. 1997;62:55988）。
[2]この表の用語にはAmerican College of Radiology（ACR）の用語が反映されている。ACR-BI-RADS®--5th Edition. ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas; BI-RADS. Reston VA. American College of Radiology, 2014. 詳細については、www.acr.orgを参照のこと。American College of Radiologyの許可を得て転載。American College of Radiologyの明示の書面による許諾なく、本文書を他の形態で提示することは認められない。

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注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

マンモグラフィにおける判定カテゴリーの定義（訳注：BI-RADS®判定）[1,2]

BI-RADS® – マンモグラフィ所見

カテゴリー3：おそらく良性：
このカテゴリーを用いて評価された所見は、悪性の可能性が2%以下である。しかし、その特徴的な良性所見の悪性の可能性が実質的に0%よりも高い場合にこのカテゴリー3を使用すべきである。おそらく良性と判断できる所見は、画像検査によるサーベイランスについて提案される期間中に変化しないと予想されるが、読影を行う医師は、定期的なマンモグラフィ検診に限定される管理方針を推奨する前に、その所見の不変を確認することを望む。具体的なマンモグラフィ所見について、生検の代わりとしてのマンモグラフィによる定期的なサーベイランスの安全性および有効性を検証する前向き臨床研究がいくつか実施されている。
3つの具体的な所見について、おそらく良性と判断できる所見としての妥当性が確認されている（石灰化のない境界明瞭な充実性腫瘤、限局的な非対称性陰影、孤立性に集簇する点状石灰化）。これまで引用されてきた研究ではいずれも、おそらく良性（カテゴリー3）の判定を下す際には事前に診断目的の画像評価を完了しておくことの必要性が強調されているため、検診マンモグラフィ検査の読影ではそのような判定を行わないよう推奨される。検診検査から直接カテゴリー3の判定を下すと、以下のような有害な結果につながることも示されている。1）迅速に良性と判定することができたはずの多くの病変に対する不必要な経過観察、2）そうしなければより小さく、進行していた可能性が低かったであろう少数の癌に対する診断の遅れ。また、これまで引用されてきた研究ではいずれも、触知可能な病変が除外されていたため、触知可能な病変に対するおそらく良性の判定については、触知可能な病変について良好な転帰を報告した単一施設研究が2つあるものの、頑健な科学的データに裏づけられているわけではない。最後に、これまで引用されてきた研究で得られたエビデンスは、おそらく良性と判断できる所見の大きさや範囲が増大した場合には、サーベイランスの継続ではなく、生検が必要であることを示唆しているため、他の点で画像上「おそらく良性」の基準を満たす所見が新たに生じたか、その大きさまたは範囲が増大した場合に、カテゴリー3の判定を下すことは賢明ではない。

おそらく良性と判断できる所見の大多数は、長期的（2年または3年）な不変が示されるまで、短期間隔の初回経過観察（6ヵ月）検査とその後の追加検査により管理されるが、代わりに生検が施行される状況（患者の意向や優先される臨床的懸念）も考えられる。

[1]マンモグラフィの結果は、最終判定カテゴリーを用いて報告することが義務づけられている（Quality Mammography Standards:Final Rule.Federal Register.1997;62:55988）。
[2]この表の用語にはAmerican College of Radiology（ACR）の用語が反映されている。ACR-BI-RADS®--5th Edition.ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas; BI-RADS.Reston VA.American College of Radiology, 2014.詳細については、www.acr.orgを参照のこと。American College of Radiologyの許可を得て転載。American College of Radiologyの明示の書面による許諾なく、本文書を他の形態で提示することは認められない。

続く

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

マンモグラフィにおける判定カテゴリーの定義（訳注：BI-RADS®判定）[1,2]

BI-RADS® - マンモグラフィ所見

カテゴリー4：悪性の疑い：
このカテゴリーは、典型的な悪性腫瘍の様相を呈していないものの、生検の推奨を正当化するだけの疑いがある所見に適用される。カテゴリー3の判定では悪性の可能性の上限が2%以下であり、カテゴリー5の判定では下限が95%であることから、カテゴリー4の判定は、悪性の可能性がこれらの間という広い範囲をカバーしている。このため、乳房に対する介入処置に関する推奨は、ほぼすべてがこのカテゴリーを用いて行われた評価に由来するものである。ガイダンスの節にある推奨に従い、そこに提示されたカットポイントを用いてカテゴリー4[3]を4A、4B、4Cに細分することにより、患者と紹介する医師が最終的な行動方針について十分な情報に基づく判断をより確実に行うようになると期待される。

カテゴリー5：悪性であることが強く示唆：
この判定は悪性である確率が非常に高い（95%以上）場合に適用される。このカテゴリーは当初、ワイヤーによる術前の位置同定が乳房に対する最初の介入手技であった時代に、予備的な生検を行わない一期的な外科的治療を考慮してもよい病変を対象とするために確立された。現在では、画像誘導下の経皮的生検が広く受け入れられているため、一期的な手術は行われるとしてもまれとなっている。むしろ、現在の腫瘍管理方針では、センチネルリンパ節の画像診断を外科的管理に含める場合や手術前に術前化学療法を行う場合など、治療選択肢を実施しやすくするために、ほぼ常に経皮的な組織検体の採取による悪性腫瘍の組織診断が行われている。このため、カテゴリー5の判定を採用することの現在の根拠は、悪性ではないと判定された経皮的な組織診断が適切ではないと考えられ、そのため再生検（通常は外科的）が推奨される病変を同定することにある。

カテゴリー6：生検により悪性腫瘍が証明：
このカテゴリーは、追加評価が必要と考えられる既知の癌以外にマンモグラフィ上で異常が認められない状況下で、生検による悪性腫瘍の証明後に施行された検査（経皮的生検後から外科的切除までに施行された画像検査）に適用される。

[1]マンモグラフィの結果は、最終判定カテゴリーを用いて報告することが義務づけられている（Quality Mammography Standards:Final Rule.Federal Register.1997;62:55988）。
[2]この表の用語にはAmerican College of Radiology（ACR）の用語が反映されている。ACR-BI-RADS®--5th Edition.ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas; BI-RADS.Reston VA.American College of Radiology, 2014.詳細については、www.acr.orgを参照のこと。American College of Radiologyの許可を得て転載。American College of Radiologyの明示の書面による許諾なく、本文書を他の形態で提示することは認められない。
[3]悪性腫瘍のリスクに関するBI-RADS®の新しいカットポイントを以下に示す：4A（＞2%～≦10%）、4B（＞10%～≦50%）、4C（＞50%～＜95%）。

続く

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

超音波検査における判定カテゴリーの定義（訳注：BI-RADS®判定）[1,2]

BI-RADS® -超音波所見

A. 判定が未完了：

カテゴリー0：未完了：追加の画像評価が必要である：
追加の画像評価を要する所見が存在する。このカテゴリーは、ほぼ常に検診の状況で用いられる。この状況での追加の画像評価には、検診検査で記録された標準的な画像を補完するための（非標準的な）超音波検査画像の記録が含まれる。追加の画像が記録されない限り、これには読影を行う医師および/または他のスタッフによる再度のリアルタイムスキャンは含まれないという点に注意すべきである。これは超音波検査に特有のリアルタイムの性質を尊重するものであり、その使用を低く評価しているわけではない。

必要とされる同時的な診断マンモグラフィ検査を施行するための装置またはスタッフをすぐに手配できない場合や、患者がすべての診断検査の完了を待つことができない、あるいは待つ意思がない場合など、一定の状況下では、診断超音波検査の報告書でカテゴリー0が用いられることがある。カテゴリー0は、MRIによる追加評価の必要性を示した診断乳房画像検査での所見に対して用いるべきではない。むしろ、読影を行う医師はMRIが施行される前に作成された報告書で最終的な判定を下すべきである。

ほとんどの状況で、また実行可能であれば、検診超音波検査で陰性または良性と判定されない場合には、直近の検査結果（存在する場合）を過去の検査結果と比較すべきである。読影を行う医師は、過去の検査結果を入手するのにどれだけの努力を払うべきかについて、そのような試みが成功する可能性とその比較が最終判定に影響を及ぼす可能性を踏まえて、判断すべきである。この状況においては、所見が本質的に悪性を疑わせるものである場合には、過去の検査結果との比較が適当でない可能性があるということに注意する必要がある。

カテゴリー0は、最終判定を行うために過去の画像との比較が必要な場合に限り、その比較のために用いるべきである。比較のための過去の検査結果を待つ状況でカテゴリー0を用いる場合には、たとえ過去の検査結果が入手できなくとも、最終判定が30日以内（早いほど望ましい）に行われることを100%の信頼性で保証する追跡手順を整備しておくべきである。乳房画像検査を実施している医療機関の中には、100%信頼できる追跡手順が整備されていないという理由で、過去の検査結果を待つ状況ではカテゴリー0を決して採用しないという妥当な対応をとっている施設もある。超音波検査の結果が過去の検査結果を待つ状況でカテゴリー0と判定され、その後に過去の検査結果が入手できた場合には、変更された判定結果を含める形で、最初の超音波検査報告書に対する補遺を発行すべきである。監査のため、変更された判定結果で当初の判定を置き換えるべきである。

適切な管理方針を決定するために過去の検査結果が必要であることから、最終判定が一時的に延期される場合もある。

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超音波検査における判定カテゴリーの定義（訳注：BI-RADS®判定）[1,2]

BI-RADS® -超音波所見

B. 判定が完了—最終判定カテゴリー：
カテゴリー1：陰性：
特記事項なし。これは検査結果が正常な場合である。

カテゴリー2：良性：
カテゴリー1と同様に、これも「正常」の評価であるが、この場合、読影者は超音波検査報告書に良性所見を記載することを選択する。例えば読影者は、単純性嚢胞、乳房内リンパ節、術後の体液貯留、乳房インプラント、または少なくとも2～3年間変化のない濃縮嚢胞/線維腺腫（推定）などの所見を記載する一方で、依然として超音波画像上、悪性腫瘍を示唆する所見は認められないと結論づけることができる。一方で読影者は、そのような所見を記載しないよう選択することも可能であり、その場合は検査結果は陰性と判定すべきである（カテゴリー1）。

カテゴリー1とカテゴリー2の判定は、ともにマンモグラフィ上で悪性所見が認められないことを意味するという点に注意すべきである。どちらも、年齢に応じた定期的な検診の続行の推奨に従うべきである。両者の違いは、カテゴリー2が報告書に具体的な良性の超音波所見を記載する場合に用いるのに対し、カテゴリー1はそのような所見を記載しない場合（たとえそのような所見が存在する場合でも）に用いるという点にある。

[1]マンモグラフィの結果は、最終判定カテゴリーを用いて報告することが義務づけられている（Quality Mammography Standards:Final Rule.Federal Register.1997;62:55988）。
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超音波検査における判定カテゴリーの定義（訳注：BI-RADS®判定）[1,2]

BI-RADS® -超音波所見

カテゴリー3：おそらく良性：
判定カテゴリー3（おそらく良性）は、放射線科医が良性（BI-RADS®カテゴリー2）または悪性疑い（BI-RADS®カテゴリー4）のいずれと判定すべきか不確かな場合にのみ採用する不確かな判定を表すカテゴリーではなく、悪性の可能性が0%ではないものの2%以下であることが判明している特定の画像所見に対して用いるものである。超音波検査では、辺縁が境界明瞭で卵円形で縦横比の小さい充実性腫瘤（線維腺腫が最も多い）と孤立性の濃縮嚢胞は、悪性である可能性がおそらく良性と判断できる規定の範囲内（2%以下）にあり、短期間隔（6ヵ月）の経過観察超音波検査とその後の定期的な超音波検査によるサーベイランスが適切な管理方針となる場合がある。集簇性の微小嚢胞についても同様のデータが報告されているが、対象とされた症例数がはるかに少ないため、このデータはあまり強固なものではない。これら3つ以外の超音波所見に対する判定カテゴリー3の適用は、担当する放射線科医に慎重な経過観察のアプローチを正当化するだけの個人的経験（望ましくは、悪性である可能性がおそらく良性と判断できる規定の範囲内［2%以下］にあると示唆される追加の超音波所見について十分な症例数の経過観察の経験）がある場合にのみ考慮すべきである。

この版のBI-RADS®Atlasでは、カテゴリー3の判定は検診時には行わず、診断のための乳癌画像検査がすべて完了して初めて行うべきであるという推奨も強調されている。この推奨は、通常一度にまとまった量の読影を行う検診マンモグラフィに適しており、それは、この状況では検診検査の読影を行う前に診断精査を完了する機会がないためである。一方、検診超音波検査は、ほぼ常にオンラインで読影が行われるため、患者が乳房画像検査を受ける施設に留まっている間に一連の診断検査も完了し、検査の検診と診断目的の両側面の所見を統合した単一の乳房画像診断報告書が発行される可能性がある。このため、診断精査が同時に完了するであろうことから、検診超音波検査時にカテゴリー3の判定を行うべきではないとする推奨は適切でない。監査においては、カテゴリー3と判定された検診超音波検査の検診要素は監査陽性となるが、その理由は追加で非標準的（診断目的の）画像が記録されることだけでなく、検診時のカテゴリー3の判定が監査陽性と定義されているためでもあることに注意すべきである。

[1]マンモグラフィの結果は、最終判定カテゴリーを用いて報告することが義務づけられている（Quality Mammography Standards:Final Rule.Federal Register. 1997;62:55988）。
[2]この表の用語にはAmerican College of Radiology（ACR）の用語が反映されている。ACR-BI-RADS®--5th Edition.ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas; BI-RADS.Reston VA.American College of Radiology, 2014.詳細については、www.acr.orgを参照のこと。

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超音波検査における判定カテゴリーの定義（訳注：BI-RADS®判定）[1,2]

BI-RADS® -超音波所見

カテゴリー3の判定について、最初の短期の経過観察間隔は通常6ヵ月であり、おそらく良性と判断できる所見が認められた乳房を対象とする。この6ヵ月後の検査で不変が認められたとすると、再びカテゴリー3の判定が下されるとともに、6ヵ月後に短期間隔の2回目の経過観察検査を行う管理方針が推奨される。さらに、この2回目の短期間隔の経過観察検査でも不変が認められたとすると、その検査は再びカテゴリー3と判定されるが、この場合に推奨される経過観察間隔は、すでに12ヵ月間の不変が認められているため、通常は1年間まで延長される。1年後の経過観察は米国における定期的な検診間隔と一致するが、カテゴリー3の判定は画像検査によるサーベイランスの期間がなおも進行中であることを示すために下されるということに注意すべきである。マンモグラフィを用いるサーベイランスと同様に、2～3年間にわたる不変が認められたならば、最終判定カテゴリーを良性（BI-RADS®カテゴリー2）に変更すべきである。読影者の見解として、悪性の所見である可能性がなく、そのためカテゴリー2である場合は、カテゴリー3の分析が完了する前（訳注：即ち、2～3年間の経過観察終了をまたずに）に良性の判定を下してもよい。

カテゴリー4：悪性の疑い：
このカテゴリーは、典型的な悪性腫瘍の様相を呈していないものの、生検の推奨を正当化するだけの疑いがある所見に適用される。カテゴリー3の判定では悪性の可能性の上限が2%以下であり、カテゴリー5の判定では下限が95%であることから、カテゴリー4の判定は、悪性の可能性がこれらの間という広い範囲をカバーしている。このため、乳房に対する介入処置に関する推奨は、ほぼすべてがこのカテゴリーを用いて行われた評価に由来するものである。カテゴリー4[3]を4A、4B、4Cに細分することにより、患者と紹介する医師が最終的な行動方針について十分な情報に基づく判断をより確実に行うようになると期待される。BI-RADS®の判定カテゴリーを管理方針の推奨から分離する例の1つは、BI-RADS®2として正しく評価された単純性嚢胞に対して疼痛管理のために嚢胞穿刺を行う場合である。

[1]マンモグラフィの結果は、最終判定カテゴリーを用いて報告することが義務づけられている（Quality Mammography Standards:Final Rule.Federal Register.1997;62:55988）。
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[3]悪性腫瘍のリスクに関するBI-RADS®の新しいカットポイントを以下に示す：4A（＞2%～≦10%）、4B（＞10%～≦50%）、4C（＞50%～＜95%）。

続く

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BI-RADS® -超音波所見

カテゴリー5：悪性であることが強く示唆：
この判定は悪性である確率が非常に高い（95%以上）場合に適用される。このカテゴリーは当初、ワイヤーによる術前の位置同定が乳房に対する最初の介入手技であった時代に、予備的な生検を行わない一期的な外科的治療を考慮してもよい病変を対象とするために確立された。現在では、画像誘導下の経皮的生検が広く受け入れられているため、一期的な手術は行われるとしてもまれとなっている。むしろ、現在の腫瘍管理方針では、センチネルリンパ節の画像診断を外科的管理に含める場合や手術前に術前化学療法を行う場合など、治療選択肢を実施しやすくするために、ほぼ常に経皮的な組織検体の採取による悪性腫瘍の組織診断が行われている。このため、カテゴリー5の判定を採用することの現在の根拠は、悪性ではないと判定された経皮的な組織診断が適切ではないと考えられ、そのため再生検（通常は吸引式組織生検または外科的）が推奨される病変を同定することにある。また、第4版では、カテゴリー5の判定に対する管理方針として「適切な措置を講じるべき」であることが示唆されただけであったのに対し、第5版では「臨床的な禁忌がなければ生検を施行すべき」というより具体的な管理方針に関する推奨が記載されていることに注意すべきである。この新しい文言は、カテゴリー5の判定について読影を行う医師の管理方針に関する推奨として組織診断を明確に規定しており、この推奨に対する禁忌の確認の負担を紹介側の医師に適切かつ有効に移すものである。

カテゴリー6：生検により悪性腫瘍が証明：
このカテゴリーは、追加評価が必要と考えられる既知の癌以外に異常が認められない状況下で、生検による悪性腫瘍の証明後に施行された検査（経皮的生検後から外科的切除までに施行された画像検査）に用いられる。

[1]マンモグラフィの結果は、最終判定カテゴリーを用いて報告することが義務づけられている（Quality Mammography Standards:Final Rule.Federal Register.1997;62:55988）。
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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 10/04/18

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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Overview

The average lifetime risk of breast cancer for a woman in the United States has been estimated at 12.3% (ie, 1 in 8 women).[1] For 2018, the American Cancer Society (ACS) estimates that 63,960 cases of female carcinoma in situ of the breast and 268,670 cases of invasive breast cancer (266,120 women and 2,550 men) will be diagnosed in the United States.[2] About 41,400 deaths are estimated for 2018.[3] The good news is that death rates have been falling an average of 1.8% each year over the course of 2006 through 2015.[4] This decrease has been attributed to mammographic screening and treatment advances.[5]

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for Breast Cancer Screening and Diagnosis are for facilitating clinical decision-making. The general public and health care providers need to be aware that mammography or any other imaging modality is not a stand-alone procedure. Neither the current technology of mammography or other imaging tests nor the subsequent interpretation of such tests is foolproof. Clinical judgment is needed to ensure appropriate management. The patient's concerns and physical findings must be taken into account along with imaging results and histologic assessment.

Literature Search Criteria and Guidelines Update Methodology

Before the update of this version of the NCCN Guidelines for Breast Cancer Screening and Diagnosis, an electronic search of the PubMed database was performed to obtain key literature using the following search terms: breast cancer screening; screening mammography; breast cancer diagnosis. The search results were narrowed by selecting studies in humans published in English. An updated search was carried out before the publication of this document. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.

Search results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The potential relevance of the PubMed search citations over the past year was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and/or discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Any recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the development and update of the NCCN Guidelines are available at www.NCCN.org.

Breast Screening Components

Breast screening is performed in women without any signs or symptoms of breast cancer so that disease can be detected as early as possible, which allows early treatment to reduce the mortality and morbidity associated with the disease. A diagnostic breast evaluation differs from breast screening in that it is used to evaluate an existing problem (eg, palpable mass, discharge from the nipple).

The components of a breast screening evaluation are dependent on age and other factors such as medical and family history, and can include breast awareness (ie, patient familiarity with her breasts); regular clinical encounters, which include breast cancer risk assessment and clinical breast exam (CBE); breast imaging with screening mammography; and, in selected cases, breast MRI.

Clinical Encounter

The starting point of these guidelines for screening and evaluating breast abnormalities is a clinical encounter, which includes a complete medical history followed by breast cancer risk assessment and a CBE. The frequency of the clinical encounter depends on the age and risk assessment of the patient.

In a review of controlled trials and case-control studies that included CBE as part of the screening modality, sensitivity of CBE was found to be 54% and specificity 94%.[6] Randomized trials comparing CBE versus no screening have not been performed. Rationale for recommending the clinical encounter is to maximize the earliest detection of breast cancers. Overdiagnosis and overtreatment is not a significant issue with CBE, as the majority of palpable cancers found on a CBE are invasive cancers. CBE is an important component of a clinical encounter and is important in order to detect early-stage palpable cancers, especially those that are mammographically occult (eg, lobular carcinomas). According to the NCCN Panel, inspection of the breasts should be performed with the patient in both upright and supine positions. Positioning may be done so as to elicit any subtle shape or contour changes in the breast.[6]

Breast Awareness: Women should be familiar with their breasts and any changes to them.[7,8] Data from a large randomized trial of breast self-examination (BSE) screening have shown that instruction in BSE has no effect on reducing breast cancer mortality. In this study, 266,064 Chinese women who were not undergoing routine mammographic screening were randomized to either receive instruction in BSE or not.[9] Compliance was encouraged through feedback and reinforcement sessions. After 10 to 11 years of follow-up, 135 breast cancer deaths in the group that received instruction and 131 in the control group were observed. The cumulative breast cancer mortality rates were not significantly different between the two arms (relative risk [RR], 1.04; 95% CI, 0.82–1.33; P = .72). The number of benign breast lesions detected in the BSE instruction group was higher than that detected in the control group. Nevertheless, women should be encouraged to be aware of their breasts since this may facilitate detection of interval cancers between routine screenings. The NCCN Panel recommends breast awareness, specifically that all women should be familiar with their breasts and promptly report any changes to their health care provider.

Breast Cancer Risk Assessment

If the physical examination is negative in an asymptomatic woman, the next decision point is based on risk stratification. Women are stratified into two basic categories of risk for the purpose of screening recommendations: average risk and increased risk. Risk assessment is outlined in the NCCN Guidelines for Breast Cancer Risk Reduction. The increased risk category consists of six groups: 1) women with a prior history of breast cancer; 2) women ≥35 years of age with a 5-year risk of invasive breast cancer ≥1.7% (per Gail Model); 3) women who have a lifetime risk >20% based on history of lobular carcinoma in situ (LCIS) or atypical ductal hyperplasia (ADH)/atypical lobular hyperplasia (ALH); 4) women who have a lifetime risk >20% as defined by models that are largely dependent on family history; 5) women between the ages 10 and 30 years with prior thoracic RT (eg, mantle irradiation); and 6) women with a pedigree suggestive of or known genetic predisposition.

Breast Imaging Modalities

Screening Mammography

Of the various imaging modalities, mammography remains the most important as it is the only one to demonstrate a mortality reduction. A screening mammogram typically involves two x-ray images of each breast (ie, one taken from the top [craniocaudal] of the breast and the other from the side [mediolateral oblique]). Technical aspects of mammography can affect the quality of screening results. Digital mammography, which has

replaced film-screen mammography in the United States, generates an electronic image of the breast and allows for computer storage and processing of the image, thereby increasing the ability to detect subtle abnormalities.[10,11]

In a study of 49,528 women who underwent both film and digital mammography, no difference was seen in the overall accuracy of the two procedures.[12,13] However, digital mammography was significantly more accurate in younger women with dense breasts, and there was a nonsignificant trend toward improved accuracy of film mammography in women aged 65 years and older. In another trial of women aged 45 to 69 years randomly assigned to film or digital screening mammography, the latter procedure was shown to result in a higher rate of cancer detection.[14]

More recently, combined use of digital mammography (two-dimensional, 2D) in conjunction with digital breast tomosynthesis (DBT) improves cancer detection and reduces false-positive call-back rates.[15-25] Tomosynthesis allows acquisition of three-dimensional (3D) data using a moving x-ray and digital detector. These data are reconstructed using computer algorithms to generate thin sections of images. The combined use of 2D and DBT results in double the radiation exposure compared with mammography alone. However, this increase in radiation dose falls below dose limits of radiation set by the U.S. Food and Drug Administration (FDA) for standard mammography. The radiation dose can be minimized by newer tomosynthesis techniques that create a synthetic 2D image, which may obviate the need for a conventional digital image.[16,26,27]

The presence of dense breast tissue decreases the sensitivity of mammography to detect small lesions and may obscure visualization of an underlying cancer. In addition, dense breast tissue as measured by mammography is increasingly recognized as an important risk factor for breast cancer.[28-31] About half of all women of screening age have “dense” breast tissue referred to as “heterogeneously dense” or “extremely dense” by American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS®) nomenclature. The presence of dense tissue is not abnormal and can change over time. Many states have passed legislation mandating patient notification of breast density, but few have required insurance coverage for supplemental screening.[32] The NCCN Panel recommends counseling on the risks and benefits of supplemental screening for women with heterogeneously dense and extremely dense breast tissue.[33] Different supplemental imaging modalities may be considered based on risk and patient values/preference.[34]

Screening Ultrasound

Due to limitations of mammographic screening, especially in women with dense breasts, other imaging modalities are being explored to supplement mammography, most commonly ultrasound and MRI. Unlike mammographic screening, both technologies lack evidence from randomized controlled trials (RCTs) of screening efficacy, although ultrasound is widely used in the diagnostic setting. Most clinical ultrasound screening studies have found increased cancer detection to be incremental to screening mammograms in women with dense breasts; however, they may increase recall and benign breast biopsies. For example, a large prospective study in women with dense breasts and elevated risk for breast cancer found that adding screening ultrasound to mammography identified an additional 4.3 cancers per 1000 women screened (95% CI, 1.1–7.2 cancers per 1000) but increased the number of false-positive results.[34] Subsequent follow-up studies showed similar results.[35,36] However, in women with dense breasts, the mammographic sensitivity was found to be 50% (95% CI, 33.8%–66.2%) and the sensitivity of mammography plus ultrasound was 77.5% (95% CI, 61.6%–89.2%).[34] Application of screening ultrasound to women with dense breasts in clinical populations has produced similar results.[37]

Although there is increasing evidence that breast ultrasonography can be useful in the incremental detection of breast cancer as an adjunct to screening mammography in the evaluation of women with dense breasts,[34,35,38-40] the routine use of ultrasound as a universal supplemental *screening* test in women with average risk is *not* recommended by the NCCN Panel at this time. Ultrasonography is commonly used for *diagnostic* follow-up of an abnormality seen on screening mammography and palpable clinical concerns.

Screening MRI

The sensitivity of contrast-enhanced breast MRI at detecting breast cancer is higher than the sensitivity of mammography, although the specificity of the former procedure is often lower, resulting in a higher rate of false-positive findings.[41] In addition, microcalcifications are not detectable with MRI.[42,43] Similar to screening ultrasound, whether MRI screening impacts survival has not been addressed in randomized clinical trials. Therefore, careful patient selection for additional screening with MRI is needed. Although current evidence does not support the use of breast MRI to screen women at average risk of breast cancer, the benefits of screening MRI for early detection of breast cancer in women with high risk, such as those ages 10 through 30 years with a history of prior thoracic radiation, a known genetic predisposition for breast cancer, or a strong family history of the disease have been demonstrated in multiple studies.[44-52] The ACS has published guidelines recommending use of breast MRI as an adjunct to screening mammography in certain populations of women at high risk of breast cancer.[53] Nevertheless, a high false-positive rate for screening MRI was identified in several studies. For example, in one study of high-risk women, many of whom were young and had very dense breast tissue, screening MRI led to 3 times as many benign biopsies as mammography.[54]

A single retrospective study of asymptomatic women with atypical hyperplasia or LCIS enrolled in a high-risk screening program has evaluated use of MRI in this population.[55] Approximately half of the women underwent screening with mammography and MRI, whereas the other half was screened with mammography alone. For those undergoing both types of screening, MRI detected breast cancer in 4% of patients with LCIS who had negative mammogram results. MRI screening did not affect the rate of cancer detection in women with atypical hyperplasia. Women who underwent screening with MRI were more likely to be younger and premenopausal, and to have a stronger family history of breast cancer than those who were evaluated by mammography alone. However, only one woman with cancer detected by MRI following a negative mammography finding had reported a family history of breast cancer, and no difference was seen in the percentages of patients who ultimately developed cancer in the two groups.

Studies have reported that deposits of gadolinium, a component of MRI contrast agents, remain in the brain of some patients who undergo 4 or more contrast MRI scans, long after the last administration.[56-59] Retention of gadolinium has also been seen in the bone.[60,61] The clinical significance and practice implications of these observations are unclear and are being investigated. In 2015, the FDA issued a safety warning alerting that investigations were ongoing for the risk associated with gadolinium deposits in the brain following its repeated use with MRI. In 2017, the FDA issued an update stating that its review of available data had not identified adverse health effects from gadolinium retained in the brain.[62] Patients will be asked to read a medication guide prior to receiving gadolinium.

In women with a history of thoracic radiation between ages 10 and 30 years, a known genetic predisposition to breast cancer, or a lifetime risk of >20% based on models such as Claus or Tyrer-Cuzick, based on current evidence, the NCCN Panel continues to recommend an annual MRI as an

adjunct to mammography. Women with LCIS or ALH/ADH with a lifetime risk of ≥20% should be considered for breast MRI based on emerging evidence of the benefits.

Criteria for the performance/interpretation of high-quality breast MRI include a dedicated breast coil, radiologists experienced in breast MRI, and the ability to perform MRI-guided needle sampling and/or wire localization of MRI-detected findings. The ACR has published guidelines for the performance of contrast-enhanced MRI of the breast.[63]

Other Breast Imaging Modalities

There is emerging evidence that breast scintigraphy and contrast-enhanced mammography may improve detection of early breast cancers among women with mammographically dense breasts;[64-67] current evidence does *not* support their routine use as alternative screening procedures. Thermography and ductal lavage are *not* recommended by the NCCN Panel for breast cancer screening or diagnosis. The FDA has issued a safety alert stating that ductal lavage should not be a replacement for mammograms.[68]

Screening Recommendations for Women at Average Risk

The NCCN Panel recognizes that the primary purpose of screening women with average risk for developing breast cancer is to detect breast cancer early, which allows treatment to decrease mortality and morbidity associated with breast cancer.

Women with Average Risk Between the Ages of 25 and 39:

The NCCN Panel recommends a clinical encounter, which includes ongoing breast cancer risk assessment, risk reduction counseling, as well as a CBE every 1 to 3 years, and encouraging women to be aware of their breasts and promptly report any changes to their health care provider.

Although the screening CBE by itself does not rule out disease, the high specificity of certain abnormal findings by highly qualified clinicians increases the probability of finding certain breast cancers (eg, lobular carcinoma). The NCCN Panel believes that a clinical encounter provides an opportunity for providers to perform a CBE, conduct a breast cancer risk assessment, provide risk reduction recommendations, and counsel on healthy lifestyles.

Women with Average Risk 40 Years and Older:

The NCCN Panel recommends annual clinical encounter, which includes ongoing breast cancer risk assessment, risk reduction counseling, as well as a CBE, and encourages women to be aware of their breasts and promptly report any changes and annual screening mammography (category 1 recommendation) with the *consideration* of tomosynthesis. Women electing to undergo screening mammography should be counseled regarding its potential benefits, risks, and limitations. The NCCN Panel is in agreement with ACS and other organizations that annual screening mammograms in average-risk women aged 40 years and older should be covered by health care payers without additional cost-sharing or copayments.

Mammographic screening and subsequent treatment have been shown to decrease breast cancer mortality beginning at age 40 years.[69,70] Meta-analysis of invitational RCTs, observational studies, and computer modeling of mammographic screening consistently show benefit, although the magnitude of benefit has varied in part due to the diversity of study designs and screening frequency. However, the RCTs are now old and may not reflect current mammography technology, interpretation, and oncologic care. Therefore, effectiveness may be better estimated in more modern observational studies.

The mammography screening guidelines put forth by various organizations vary with respect to age to initiate screening, the frequency of screening, and when to stop screening.[69,70] The assessment of the benefits of mammography versus the risks based on age are weighed on different scales by different organizations.

The NCCN Panel continues to support its long-standing recommendation of *annual* screening mammography beginning at age 40 years (category 1 recommendation), as it results in the greatest mortality reduction, most lives saved, and most life years gained.

The NCCN Panel has not established an upper age limit for screening. According to the panel, if a patient has severe comorbid conditions limiting her life expectancy and no further intervention would occur based on the screening findings, then the patient should not undergo screening, regardless of her age.

Rationale for Mammographic Screening Starting at Age 40:
Reduction in breast cancer-related mortality is the major benefit of mammographic screening for breast cancer. This benefit is evident across studies, including RCTs, case-controlled observational studies, and computer modelling studies.

While breast cancer screening guidelines put forth by all the organizations acknowledge mortality reduction benefit from current studies of mammography screening in women 40 to 49 years of age, those recommending breast cancer screening to begin at age 50[70] view the benefits of screening as being balanced by the harms of screening during this decade. Other organizations, who have recommended screening commencement at age 45 as a "strong" recommendation, have shown the absolute benefit of ages 45 to 49 to be very similar to ages 50 to 54.[69] While showing there is benefit of screening for ages 40 to 44, a "qualified" rather than a "strong" recommendation is given for the younger age group due to the lower absolute benefit. However, the "qualified" recommendation means "most" women would want the earlier screening and only a "small proportion" would not.[69]

Benefits of Mammographic Screening:
Systematic reviews of RCTs have generally shown a reduction in breast cancer mortality with mammography screening.[71]

The UK Age trial specifically studied the effect of film-screen mammographic screening starting at age 40 years.[72] A mean of 10.7 years of follow-up showed a non-statistically significant breast cancer mortality reduction in women invited to screening (RR, 0.83; 95% CI, 0.66–1.04).[72] A follow-up of the UK AGE trial was carried out to study breast cancer mortality and incidence at a median of 17.7 years of follow-up, an increase of 7 years from the previous analysis.[73] There continued to be a non-significant overall reduction in risk of breast cancer mortality (RR, 0.88; 95% CI, 0.74–1.04) during a median of 17 years of follow-up. However, the reduction in breast cancer mortality noted in the first 10 years after diagnosis was now significant in the group that underwent screening compared with the control group (RR, 0.75, 0.58–0.97).[73] Other trials included women who were up to age 49 years at the time of entry into the trial, who were therefore in their 50s during the screening intervention. The results of the UK Age trial support the importance of annual mammography screening in women ages 40 to 49 years of age to reduce breast cancer-related mortality.[73]

A Swedish study compared breast cancer mortality rates in women 40 to 49 years of age living in different counties. Counties included those that invited women for screening starting at age 40 and others that did not invite women to be screened at age 40 and started screening at age 50.[74] After an average 16 years of follow-up, the investigators observed an overall 29% mortality reduction (RR, 0.71; 95% CI, 0.62–0.80). For age

groups 40 to 44 and 45 to 59 years, the RR estimates were 0.82 (95% CI, 0.67–1.00) and 0.63 (95% CI, 0.54–0.75).[74] Although the estimated reduction in breast cancer mortality was smaller for ages 40 to 44 compared with ages 45 to 49, the reduction in mortality seen for ages 40 to 44 was still substantial.[74]

It is important to note that the RCTs studying the benefits of screening mammography used screen film mammography, sometimes using only a single view. Therefore, they may not reflect results obtained with modern advances in imaging. Digital mammography has been shown to detect more breast cancers in women with dense breasts, which is common in younger women. The more recent observational studies better quantify the effectiveness of screening in the context of improved imaging techniques.

Case-control observational studies have shown benefits of reduction in breast cancer mortality ranging from 40% to 45%.[75,76] A meta-analysis of observational case-control studies found a significant reduction in breast cancer mortality with mammographic screening for women aged 40 to >79 years of age with a 48% mortality reduction (odds ratio [OR] 0.52; 95% CI, 0.42–0.65) after adjustment for self-selection.[77] Relevant to the North American population, data from a Canadian study showed a mortality reduction of 44% (CI, 33%–55%) among screened women ages 40 to 49 years, which was similar to the overall reduction in mortality of 40% (CI, 33%–48%) found among women ages 40 to 79 years.[76]

A retrospective analysis evaluating the benefits of mammographic screening of women aged 40 to 49 years found that mammography-detected breast cancer coincides with lower-stage disease at detection, resulting in reduced treatment morbidity and lower rates of recurrence.[78] A population-based study of data from the Netherlands Cancer Registry estimated the impact of tumor size in women with breast cancer in two time intervals: 1999 to 2005 and 2006 to 2012. The year 2005 was used to divide the data into two-time intervals studies, because trastuzumab and other effective adjuvant therapy were introduced after this year in the Netherlands. The analysis found that tumor size remained a critical component of survival even with the availability of new and effective systemic therapy options.[79] These findings reiterate the fact that diagnosing breast cancer at an early stage is important.

The Cancer Intervention and Surveillance Modeling Network (CISNET) models from 2009 demonstrate a 29% to 54% (mean 39%) mortality reduction for annual screening for women ages 40 to 84 years.[80] The CISNET models from 2015, based on digital screening mammography, show greater mortality reduction benefit.[81] Benefits of screening younger women (in their 40s) are more favorable when considered from the perspective of life years saved compared exclusively to mortality reduction.[82] Women in their 40s have the highest number of life years at risk to be lost due to longevity even though their breast cancer risk is smaller. Breast cancer is the second leading cause of deaths for women in their 40s, trailing only poisonings.

Women should be informed of the evidence demonstrating the value of detecting breast cancer early, before symptoms develop. The benefits of early detection include mortality reduction, less aggressive treatment, and a wide range of treatment options. Screening also identifies women with atypical hyperplasia or LCIS who may be candidates for risk reduction therapy to reduce their chance of developing breast cancer.

Harms of Mammographic Screening:
The harms or risk profile for breast cancer screening is weighted differently by different organizations.[69,70] This is a very subjective rating as there are limited data regarding a woman's perspective of the harms of screening. The clinical practice guidelines that recommend delaying screening to age 50 and older[69] place a greater emphasis on the risks of screening mammography, specifically false-positive results and

overdiagnosis. Most women highly value the reduction in breast cancer mortality, whereas many women do not consider false positives and potential overdiagnosis to be a "harm."[83] In this study, 63% of women thought 500 or more false positives per life saved was acceptable.[83]

The NCCN Panel believes that the harms analysis of mammographic screening is most informative if it includes the net harms of mammographic screening in individuals who underwent screening versus those who did not. According to the NCCN Panel, the major harm related to *not performing* any screening for breast cancer is diagnosis of later-stage breast cancer, which may prove to be lethal or require therapy that is more extensive. There is evidence showing that women diagnosed with breast cancer who did not undergo screening had substantially more need for chemotherapy and more extensive surgery than women who underwent routine screening.[84]

Furthermore, absence of mammographic screening for breast cancer does not mean absence of breast-related problems. Non-screened women develop signs and symptoms leading to diagnostic investigation, false-positive biopsies, or potential diagnosis of non-lethal conditions.

A mammogram result is often considered a false positive when it prompts additional imaging tests and/or biopsy in an abnormality that is not cancerous. False-positive results can occur at any age. It is important to distinguish between recalls from screening and biopsies that result in a false-positive outcome. Recalls are defined by the FDA as "incomplete" and not positive. Recalls are resolved by obtaining incremental diagnostic mammographic imaging and/or ultrasound with the vast majority of recalls proving negative and not requiring biopsy. The frequency of recalls from screening are the same per decade whether screening begins at age 40 or age 50.[70] While recalls are commonly thought to be higher in younger women, this primarily reflects higher recall rates at the prevalent or initial screen when prior mammograms are not available for comparison and not the age at which screening commences. Initiating screening mammography at age 50 would shift this "prevalent" false positive to that decade. Furthermore, the decade-long false-positive biopsy recommendation rate is somewhat lower when screening begins at age 40 compared to age 50. Less than 1% of screened women per year will be recommended for a biopsy that proves benign, whether annual screening commences at age 40 or 50. The vast majority of false-positive biopsies are now performed as outpatient image-guided needle biopsies using local anesthesia and are generally well-tolerated and acceptable to women.

Those considering false positives as one of the harms of screening note psychosocial consequence as one of the negative consequences of false positives.[85] However, a cross-sectional survey of women's attitudes toward false positives found that women consider false positives as an acceptable consequence.[83]

Overdiagnosis is the detection of a condition by screening that would not have become apparent by usual care absent screening. Overdiagnosis may lead to overtreatment, which is the more significant problem. It is important to understand that overdiagnosis would not influence the age to initiate screening or the screening interval. The mammographic abnormality that leads to a potential overdiagnosis does not go away without treatment. If the age to initiate screening is raised from 40 to 45 or 50 years, or the screening interval is lengthened to biennial, the potential overdiagnosis would occur at the next mammogram that showed the imaging abnormality.

Overdiagnosis is difficult to measure, because neither the clinician, pathologist, nor the patient can be sure whether the abnormality detected by screening would be harmless or life threatening to the patient. Furthermore, overdiagnosis assumes that the level or amount of diagnosis by symptomatic usual care is optimal. The estimates of overdiagnosis vary widely between various studies (from almost none to up to 54%[69,71,86-88])

due to methods and parameters used for estimation and whether ductal carcinoma in situ (DCIS) is included or excluded. Furthermore, overdiagnosis estimates vary by age and duration of follow-up.

The most reliable estimates of overdiagnosis would be from RCTs in which there was no formal screening offered to the control group for a long period at the end of the screening period. The Malmo randomized trial, in which the older-age invited cohort group was not routinely screened at the end of the trial,[89] showed an overdiagnosis rate of 10% after an average of 15 years follow-up, which included invasive cancer and DCIS. The rate was 7% for invasive cancer.[89] The National Breast Screening Studies in Canada conducted two randomized trials that included a control group that did not receive routine screening at the end of the trial. The follow-up period was 13 years. In the first trial, in which women were aged 40 to 49 years at recruitment, the estimated overdiagnosis was 14%. In the second trial, in which women were aged 50 to 59 years at recruitment, the estimated overdiagnosis rate was 11%.[90,91] Using these 3 studies, the UK review estimated overdiagnosis (including DCIS) to be 10.7%.[92] Yet, these studies are limited by their age and differing use of diagnostic mammography among non-screened women. However, analysis of the UK AGE trial, which included women aged 40 to 49 years, showed a very low rate of overdiagnosis of 1%,[93] a value similar to estimates from Sweden for women in their 40s.[74] A recently reported population-based screening study showed a rate of only 0.3% overdiagnosis after 12 years of follow-up in either invited or uninvited women (n = 988, 090) and a 46% reduction in breast cancer mortality among attenders.[94] Direct estimates of type 1 overdiagnosis for screened U.S. women show marked differences depending on age of diagnosis, with less than 1% among premenopausal women and 22% among women aged 80 years.[95]

Prevention of cancer death is highly valued compared with false-positive results/overdiagnosis by most women.[83] Current science cannot predict which breast cancer may be overdiagnosed or be potentially lethal in any one individual. Personalized treatment programs are recommended and advances in personalized treatment will diminish the risk of overtreatment and significance of overdiagnosis. The treatment of cancer may cause suffering and anxiety, but that suffering is likely worth the gain from the potential reduction in breast cancer mortality. According to the NCCN Panel, the risk of overdiagnosis and false positives are outweighed by the benefit of mortality reduction in determining the age to recommend starting screening.

The NCCN Panel emphasizes adopting strategies and research to reduce the harms of screening (false positives and overdiagnosis) rather than raising the age to initiate screening to potentially delay these issues. This includes newer imaging modalities that improve the detection of breast cancer with fewer recalls (eg, tomosynthesis). Research to better define the biology of breast cancer is needed so that lesions that are not destined to progress are either not treated or are treated less aggressively.

Screening Interval and Rationale for Annual Mammogram Screening: Another consideration is the time interval between screening exams. Performing screening mammography annually versus every other year remains controversial. Most studies and models suggest incremental benefit with annual screening, especially among younger women and premenopausal women.[69,70,80,96] The evaluation of benefits versus risk strongly supports the value of screening and the importance of adhering to a schedule of regular mammograms.

The NCCN Panel believes that the benefits of annual mammography outweigh the risks. Breast cancer mortality is estimated to be lower with annual compared to biennial screening mammograms.[80] Additionally, mammograms can often detect a lesion 2 years before the lesion is discovered by CBE. Interval cancer rates are lower among annually

screened women. To reduce mortality from breast cancer, yearly screening is thought to be more beneficial. The panel also acknowledges that incomplete compliance will alter the outcome of any recommendation.

An evaluation of the CISNET modeling of benefits of screening women between 40 to 49 years found that using *annual* digital mammography saves 30% more lives and 34% more life-years than *biennial* digital mammography.[97] Also, with annual digital screening mammography, the deaths averted (0.6/1000) are similar for ages 40 to 44 *and* 45 to 49 years (0.7/1000).[96,98]

A decline in breast cancer specific-mortality was observed in a cohort of women for every additional annual mammogram performed 5 years prior to breast cancer diagnosis; this further emphasizes the importance of annual mammography.[99] The results of a primary analysis to estimate the association between incidence of DCIS detected by screening and subsequent invasive interval cancer incidence showed a DCIS detection rate of 1.5 per 1000 screened and a reduction of one invasive interval cancer per 1.5 to 3 DCIS cases detected.[100]

While the risk of false positives is greater with annual compared to biennial mammograms,[70] the panel believes that the lower mortality and morbidity of annual screening outweighs this harm.

Age to Stop Mammographic Screening:
There are limited RCT data regarding screening of elderly women, because most trials for breast screening have used a cutoff age of 65 or 70 years.[101-103] However, observational studies and computer models show mortality benefit to age 80 to 84.[69,80] Considering the high incidence of breast cancer in the elderly population, the screening guidelines used for women who are age 40 or older are recommended in the elderly as well. Clinicians should always use judgment when applying screening guidelines. The mortality benefit of screening mammography is often delayed for 5 to 7 years in RCTs that emphasize the importance of life expectancy and overall health when considering age to stop screening. Mammography screening should be individualized, weighing its potential benefits/risks in the context of the patient's overall health and estimated longevity.[104] If a patient has severe comorbid conditions limiting her life expectancy and no intervention would occur based on the screening findings, then the patient should not undergo screening, regardless of her age.[104,105]

Screening Recommendations for Women at Increased Risk

Women with Prior History of Breast Cancer: These women are treated according to the recommendations outlined in NCCN Guidelines for Breast Cancer.

Women Aged 35 Years or Older with a 5-Year Risk of Invasive Breast Carcinoma Greater Than or Equal to 1.7% by the Modified Gail Model: For women aged 35 years and older, a risk assessment tool is available to identify those who are at increased risk. The National Cancer Institute (NCI) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) Biostatistics Center has developed a computerized interactive risk-assessment tool based on the modified Gail model[106-110] that can be accessed at: http://www.cancer.gov/bcrisktool/Default.aspx, which provides risk projections on the basis of several risk factors for breast cancer. The modified Gail model assesses the risk of invasive breast cancer as a function of age, menarche, age at first live birth or nulliparity, number of first-degree relatives with breast cancer, number of previous benign breast biopsies, atypical hyperplasia in a previous breast biopsy, and race. The model calculates 5-year and lifetime projected probabilities of developing invasive breast cancer and can be used to identify women who are at increased risk. The Gail model should not be used for women with a predisposing gene mutation, a strong family history of breast or

ovarian cancer suggestive of a genetic predisposition, women with a prior history of thoracic radiation, or for those with LCIS.

The Gail model was updated using combined data from the Women's Contraceptive and Reproductive Experiences (CARE) study and the SEER database, as well as causes of death from the National Center for Health Statistics, to provide a more accurate determination of risk for African-American women.[111] It has also been updated using the data from the Asian American Breast Cancer Study (AABCS) and the SEER database to provide a more accurate risk assessment for Asian and Pacific Islander women in the United States.[112]

Increased risk of developing breast cancer is defined by the modified Gail model for women ≥35 years of age as a 5-year risk of 1.7% or greater. This is the average risk for a 60-year-old woman, which is the median age of diagnosis of breast cancer in the United States. The 5-year predicted risk of breast cancer required to enter the NSABP Breast Cancer Prevention Trial of tamoxifen versus placebo, as well as the Study of Tamoxifen and Raloxifene (STAR) trial, was 1.7% or greater. As previously mentioned, the modified Gail model risk assessment tool also provides an estimate of a woman's lifetime risk of breast cancer. However, this estimate is based on the Gail model risk criteria, which differ from criteria used in risk assessment models predominantly based on family history (see below). Lifetime breast cancer risk as determined by the Gail model is not used in these guidelines to determine whether a woman is eligible for screening breast MRI.

For a woman aged 35 years or older with a 5-year risk ≥1.7%, the NCCN Panel encourages breast awareness and recommends a clinical encounter every 6 to 12 months and annual digital mammography, with the consideration of tomosynthesis, to begin at the age identified as being at increased risk by the Gail model. In addition, according to the NCCN Panel, women in this group should be counseled for consideration of risk-reduction strategies in accordance with the NCCN Guidelines for Breast Cancer Risk Reduction.

Women Who Have a Lifetime Risk >20% Based on History of LCIS or ADH/ALH: A diagnosis of LCIS or ADH/ALH is associated with high risk of development of cancer in either breast.[113-118]

For women with a history of LCIS or ADH/ALH, the NCCN Panel encourages breast awareness and recommends a clinical encounter every 6 to 12 months beginning at the age of diagnosis and annual digital mammography, with the consideration of tomosynthesis, beginning at the age of diagnosis of LCIS or ADH/ALH but not less than 30 years of age. In addition, according to the NCCN Panel, annual MRI should be considered beginning at the age of diagnosis of LCIS or ADH/ALH but not before age 25 (based on emerging evidence).[55] Women in these groups should also be considered for risk reduction strategies in accordance with the NCCN Guidelines for Breast Cancer Risk Reduction.

Women with a Lifetime Risk of Breast Cancer >20% Based on Models Largely Dependent on Family History: A lifetime risk of breast cancer of >20% as assessed by models based largely on family history is another risk threshold used in the guidelines to identify a woman as a potential candidate for risk reduction strategies, as well as to direct screening strategies. According to the ACS guidelines for breast screening, MRI may be performed as an adjunct to mammography[53] in a high-risk woman if her lifetime risk of breast cancer is approximately 20% or greater based on models that rely mainly on family history. A cancer genetic professional should be involved in determining the lifetime risk of the individual based on models dependent on family history. These include Claus,[119] Tyrer-Cuzick,[120] and other models.[121-123] BRCAPRO[124] and Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)[125] are more commonly used to estimate the risk of *BRCA*

mutations. Strong genetic association between breast and ovarian cancer has been demonstrated in some families by linkage analyses.

For a woman with a >20% lifetime risk of breast cancer based on models largely dependent on family history, the NCCN Panel encourages breast awareness and clinical encounter every 6 to 12 months to begin at the age identified as being at increased risk. The NCCN Panel recommends annual digital mammography, with the consideration of tomosynthesis starting from 10 years prior to the youngest family member but not less than age 30. In addition, in accordance with the ACS guidelines,[53] the NCCN Panel recommends annual breast MRI to begin 10 years prior to the youngest family member diagnosed but not less than 25 years of age for women who have a lifetime risk of breast cancer >20% based on models that rely mainly on family history. According to the NCCN Panel, women in this group should be asked to consider risk reduction strategies in accordance with the NCCN Guidelines for Breast Cancer Risk Reduction.

Women Who Have Received Prior Thoracic Irradiation Between the Ages of 10 to 30 Years: Results from several studies have demonstrated that women who received thoracic irradiation in their second or third decade of life have a substantially increased risk of developing breast cancer by age 40 years.[126-131] For example, in the Late Effects Study Group trial, the overall risk of breast cancer associated with prior thoracic irradiation at a young age was found to be 56.7-fold (55.5-fold for female patients) greater than the risk of breast cancer in the general population.[127,130] The RR of female breast cancer according to follow-up interval was 0 at 5 to 9 years; 71.3 at 10 to 14 years; 90.8 at 15 to 19 years; 50.9 at 20 to 24 years; 41.2 at 25 to 29 years; and 24.5 at >29 years.[130] Results from a case-control study of women treated with thoracic radiation at a young age for Hodgkin lymphoma indicated that the estimated cumulative absolute risk of breast cancer at 55 years of age was 29.0% (95% CI, 20.2%–40.1%) for a woman treated at 25 years of age with at least 40 Gy of radiation and no alkylating agents.[132] Although there is a concern that the cumulative radiation exposure from mammography in a young woman may itself pose a risk for cancer, it is felt that the additional radiation in this population is negligible compared to overall radiation exposure. Findings from a survey of breast screening practices in this population of patients suggest that a sizable segment of this group is not undergoing regular mammographic screening.[133]

For women aged 25 years and older who have received prior thoracic irradiation, the NCCN Panel recommends encouraging breast awareness, and recommends a clinical encounter be initiated every 6 to 12 months 10 years after radiation exposure.[134] Breast imaging assessments with annual digital mammograms, with the consideration of tomosynthesis, are recommended 10 years after RT but not prior to age 30, and annual MRI[44] is recommended to begin 10 years after radiation exposure but not prior to age 25.

For women younger than 25 years who have received prior thoracic irradiation, the NCCN Panel recommends encouraging breast awareness, counseling on risk, and an annual clinical encounter starting 10 years after radiation therapy.

Women with a Pedigree Suggestive Of or With a Known Genetic Predisposition: Accurate family history information is needed to adequately assess a woman's breast cancer risk. Familial cancers share some but not all features of hereditary cancers. For example, although familial breast cancers occur in a given family more frequently than expected based on statistics, they generally do not exhibit inheritance patterns or onset age consistent with hereditary cancers. Familial breast cancers may be associated with chance clustering, genetic variations in lower-penetrance genes, a shared environment, small family size, and/or other factors.

The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian include recommendations for referral to a cancer genetics professional for further evaluation for individuals who have either a personal history or a close family history meeting certain criteria and also list screening recommendations for common hereditary syndromes that confer increased risk for breast and ovarian cancer. (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian).

Diagnostic Evaluation

Breast symptoms are common among women. A retrospective study of women aged 40 to 70 years showed that 16% (total visits of 23 per 100 women) of women will present with symptoms to their provider during a decade with higher frequency among women ages 40 to 59 years compared to older women.[135] Pain is found to be the most common symptom followed by palpable mass. In addition, palpable areas of concern are identified during a breast physical exam. Breast clinical findings are not specific and there is variability in interpretation. Each symptom is associated with a risk of malignancy and warrants diagnostic evaluation; however, most symptoms will be determined to be benign in etiology. Women younger than age 40, who are not usually recommended for routine breast screening, also frequently present with breast symptoms.

Unlike imaging for screening, which is used to detect cancer in asymptomatic women, diagnostic evaluation is used to characterize a clinical finding or possible abnormality found during screening. There is confusion regarding the term “diagnostic” imaging, as it is applied to two very different situations: 1) imaging for clinical finding such as a palpable mass; and 2) incremental imaging after a possible abnormal screening mammogram in an asymptomatic woman (also referred to as recall or callback). To add further confusion, insurance carriers may consider a routine mammogram to be “diagnostic” in certain asymptomatic women (eg, in women with prior cancer). Diagnostic evaluation in this review will be restricted to the former two situations.

Diagnostic evaluation may include physical examination and diagnostic imaging for symptomatic women and diagnostic imaging for women recalled from screening. Diagnostic imaging may include diagnostic mammography, ultrasonography, and at times diagnostic breast MRI. The eventual decision regarding need for tissue sampling is based on level of suspicion on imaging and/or clinical examination. Biopsy is needed in situations where imaging is negative but clinical findings are suspicious, since imaging is not completely sensitive for cancer detection.

While the term “diagnostic” implies diagnosis, imaging results are often not specific enough to be truly “diagnostic.”

Diagnostic Imaging After Screening Mammography Recall

Diagnostic Mammography

Screening mammography consists of two standard x-ray images of each breast, whereas a diagnostic mammogram includes additional views, such as spot compression views or magnifications views, to investigate the finding in question. Diagnostic mammography is associated with higher sensitivity but lower specificity as compared to screening mammography. DBT may replace traditional diagnostic mammographic imaging in certain situations.[136-138]

Frequently, especially for masses or asymmetries, diagnostic ultrasound is also performed. Each imaging modality may be positive or negative, which allows four outcomes: both imaging modality results are negative; both are positive; mammogram is positive and ultrasound is negative; and mammogram is negative and ultrasound is positive. In general, a “final” combined imaging assessment category is rendered after a “recall’

from screening, which is the most suspicious imaging outcome assessment.

The mammographic final assessments are mandated by the Mammography Quality Standards Act and Program (MQSA) and are reported using wording similar to the ACR BI-RADS® assessment categories, which classify likelihood of the breast findings into 6 final assessment catergories.[139] The BI-RADS® assessment categories (which include words and numbers) help to standardize both the reporting of mammographic findings and the recommendations for further management. The assessment wording and numbers are often used interchangeably. The definitions of the mammogram assessment categories are outlined in *Mammographic Assessment Category Definitions* in the algorithm. Importantly, the same imaging terms are used for screened (asymptomatic) recalled women and symptomatic women, which can create confusion regarding recommendations.

NCCN Recommendations for Screening Mammogram BI-RADS® Assessment Categories 1, 2, 3, 4, 5, and 6 are listed below. The NCCN recommendations following evaluation of symptomatic diagnostic women can be found in the next section. Importantly, Negative or Benign BIRADS® imaging assessments, in the setting of symptoms, rely upon correlation of clinical finding, which may indicate need for biopsy even with negative imaging. Conversely, suspicious imaging findings for women with clinical findings of very low suspicion still warrant biopsy.

For BI-RADS® category 1 (negative finding) or category 2 (benign), the panel recommends resuming routine screening.

For BI-RADS® category 3 (probably benign), the panel recommends diagnostic mammograms at 6 months, then every 6 to 12 months for 1 to 2 years as appropriate. If the lesion remains stable or resolves mammographically, the patient resumes routine screening intervals for mammography. If, in any of the interval mammograms, the lesion increases in size or changes its benign characteristics, a biopsy is then performed. The exception to this approach of short-term follow-up is when a return visit is uncertain or the patient strongly desires or has a strong family history of breast cancer. In those cases, initial biopsy with histologic sampling may be a reasonable option.

For BI-RADS® categories 4 and 5 (suspicious or highly suggestive of malignancy), tissue diagnosis using core needle biopsy (preferred) or needle localization excisional biopsy with specimen radiograph is necessary. When a needle biopsy (aspiration or core needle biopsy) is performed, concordance between the pathology report and the imaging finding must be obtained.[140,141] For example, a negative needle biopsy associated with a spiculated category 5 mass (highly suggestive of malignancy) is discordant and clearly would not be an acceptable diagnosis. When the pathology and the imaging are discordant, the breast imaging should be repeated and/or additional tissue sampled or excised; surgical excision is recommended when pathology/image remains discordant. Women with a benign result exhibiting pathology/image concordance should be followed with mammography every 6 to 12 months for 1 to 2 years before returning to routine screening.

For BI-RADS® category 6 (proven malignancy), the patient should be managed according to the NCCN Guidelines for Breast Cancer.

Breast Ultrasonography

Imaging by ultrasound is an important adjunct for diagnosing breast cancer.[142] However, breast ultrasonography does not detect most microcalcifications.[34,45,143-145] The definitions of the ultrasound assessment categories are outlined in *Ultrasonographic Assessment Category Definitions* in the algorithm.

Diagnostic Breast MRI

MRI can also play a role in the diagnostic setting. For patients with skin changes consistent with serious breast disease, consideration of breast MRI is included in the guidelines for those with benign biopsy of skin or nipple following BI-RADS® category 1-3 assessment. Since a benign skin punch biopsy in a patient with a clinical suspicion of inflammatory breast cancer (IBC) does not rule out malignancy, further evaluation is recommended. There is evidence that certain MRI features may facilitate diagnosis of IBC.[146] MRI may be used for suspicious nipple discharge when mammography and ultrasound are not diagnostic.[147-149]

Breast Tissue Biopsy

Breast biopsy is recommended if diagnostic imaging findings or clinical findings are suspicious (BI-RADS® 4) or highly suggestive of malignancy (BI-RADS® 5).

Fine-Needle Aspiration (FNA) Biopsy

An FNA biopsy involves use of a smaller-bore needle to obtain cytologic samples from a breast mass. Advantages of FNA biopsy include its minimally invasive methodology and low cost,[150,151] whereas the need for pathologists with specific expertise in the interpretation of test results and the necessity of performing a follow-up tissue biopsy when atypia or malignancy is identified are disadvantages of the procedure. FNA of nonpalpable lesions can be performed under imaging guidance (eg, ultrasound), although there is evidence to indicate that both core needle biopsy and excisional biopsy are more accurate than FNA in the evaluation of nonpalpable breast lesions.[152,153]

Core Needle Biopsy

A core needle biopsy, also called percutaneous core breast biopsy, is a procedure that typically involves obtaining multiple cores of solid tissue using standard techniques.[154,155] It can be performed under imaging guidance (eg, stereotactic [mammographic] ultrasound or MRI) or directed by palpation. Advantages of breast core needle biopsy include: 1) increased accuracy over FNA when the procedure is performed in situations where no mass is palpable; and 2) an ability to obtain tissue samples of sufficient size so as to eliminate the need for a follow-up biopsy to confirm malignancy.[156] In some situations, the core needle biopsy is performed under vacuum assistance, which can facilitate collection of adequate tissue from a breast lesion without the need for multiple needle insertions.[157-159] Marker clip placement is done at the time of core needle biopsy so that the radiologist can identify the location of the lesion in the event that it is entirely removed or disappears during neoadjuvant treatment of a breast cancer.[160] With a few exceptions, core needle biopsy is preferred in the NCCN Guidelines over surgical excision when tissue biopsy is required. Sensitivity for core needle biopsy directed by ultrasound or stereotaxis is 97% to 99%.[98] According to the NCCN Panel, surgical excision is appropriate if unable to perform core needle biopsy.

Excisional Biopsy

An excisional biopsy involves removal of the entire breast mass or suspicious area of the breast by a surgeon in an operating room setting. Needle or wire localization is done by the radiologist immediately prior to an excisional biopsy of a nonpalpable mammographic or sonographic finding to direct surgical excision. The wire localization may bracket a lesion that had a clip placed in it at the time of the core needle biopsy.[160] Newer localization methods using radionucleotide seeds, reflector devices, or magnetic devices are being explored.

Excisional biopsy is included in the NCCN Guidelines as an option when tissue biopsy is required. Although excisional biopsy is a more invasive method than core needle biopsy and requires needle localization when lesions are not palpable, there are situations where larger tissue samples

may be needed. Excisional biopsy is recommended if the diagnosis by core needle biopsy is an indeterminate lesion, a benign lesion that is not concordant with imaging, ADH or other specific histologies that require additional tissue including mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scars, or other histologies of concern to the pathologist.[151,156,161,162] Support for this recommendation includes results of studies demonstrating an underestimation of cancer when atypical hyperplasia and LCIS are diagnosed by core needle biopsy.[163-168] However, there are situations (eg, select cases of LCIS or ALH such as those concordant with imaging, papillomas, fibroepithelial lesions, and radial scars) where close observation may be substituted for excisional biopsy in select patients.[151,161,169-176]

Diagnostic Evaluation for Symptomatic Findings on Physical Examination

In general, the breast imaging evaluations after physical exam include mammography and ultrasound. The addition of ultrasound to diagnostic mammography significantly increases cancer detection and detection of specific benign findings such as cysts. Imaging for women younger than age 30 begins with ultrasound, while older women generally have both studies unless a cyst is likely.[177,178 ,179-182] Combined negative imaging results place a patient in a very low risk of malignancy (generally less than 3%) category; however, clinical judgment is necessary as some women with negative imaging may warrant biopsy that may identify a malignant mass.[177,183-185] The recommendations for subsequent management follow imaging assessments and clinical level of suspicion. Imaging should precede biopsy in most situations due to potential alteration of imaging findings by the biopsy. BIRADS imaging assessments, even if negative, must be correlated with the clinical findings prior to final clinical recommendations and do not stand alone as in the screening situation. There are clinical situations where biopsy is warranted even with negative imaging results.

Symptomatic or positive findings on physical examination include palpable mass in the breast, nipple discharge without a palpable mass, asymmetric thickening or nodularity, skin changes, axillary mass, and breast pain.

Palpable Mass in the Breast

A palpable mass is a discrete lesion that can be readily identified during a physical exam. The NCCN Guidelines separate the evaluation of women with the palpable mass into two age groups: women aged 30 years or older and women younger than 30 years of age.

Women with Palpable Mass Aged 30 Years or Older:

The main difference in the guidelines for evaluating a palpable mass in women aged 30 years or older compared with younger women is the increased degree of suspicion of breast cancer. The initial evaluation begins with a diagnostic mammogram and ultrasound. Ultrasound should be geographically correlated with the palpable mass in question. Observation without further evaluation is not an option in these women. There are some clinical circumstances, such as mass with low clinical suspicion or suspected simple cyst, in which ultrasound would be preferred and may suffice for women 30 to 39 years of age due to the high sensitivity of ultrasound alone.[180,181,186] After the diagnostic imaging assessment, the abnormality is placed into one of the following categories: negative or benign; probably benign; or suspicious or highly suggestive of cancer with management following BIRADS final assessment recommendations.

If there is a lack of geographic correlation between clinical and imaging findings, further evaluation is recommended. Sensitivity of combined mammography and ultrasound for evaluation of palpable masses is high for cancer detection, although specificity may be relatively low.

For women with mammographic findings that are suspicious or highly suggestive of breast cancer, the NCCN Panel recommends ultrasound to determine lesion size and to guide tissue biopsy. The NCCN Panel notes that FNA and core needle biopsy are both valuable. However, FNA requires cytologic expertise. When a needle biopsy is utilized, concordance between pathology, imaging, and clinical findings must be obtained.

Ultrasound Findings:

Solid Mass:

If the solid mass found on the ultrasound is suspected to be probably benign (ie, BI-RADS® category 3), the options are: 1) observation, if clinical suspicion for breast cancer is low; or 2) tissue (core needle) biopsy, if the mass is clinically suspicious. Observation may be elected for those with low clinical suspicion; a physical examination follow-up with or without ultrasound or diagnostic mammogram is recommended every 6 months for 1 to 2 years to assess stability of the solid mass. There may be variability on the follow-up interval based on the level of suspicion. Numerous clinical studies now support the ability of ultrasound to accurately characterize palpable solid masses as probably benign with risk of malignancy generally less than 2%. However, these same studies have shown that many such masses will eventually warrant biopsy and compliance with follow-up may be low.[178,180,187-191] Progression of size or suspicion on follow-up studies warrants tissue biopsy. The NCCN Panel recommends a tissue (core needle) biopsy for solid masses with a BI-RADS® 4-5.

Cystic Masses:

Breast cysts are classified as simple, complicated, or complex based on the characteristics identified by ultrasound evaluation (see Table 1 for definitions).

Simple Cyst

A cyst meeting all criteria of a simple cyst is considered to be benign (ie, BI-RADS® 2)[34,192] if the clinical findings and ultrasonographic results are concordant. In a retrospective analysis of women (n = 14,602) with benign breast biopsies developing subsequent breast cancer, it was noted that simple cysts were not associated with subsequent breast cancer development.[193] Therefore, these patients then can be followed with routine screening.

Complicated Cyst

A complicated cyst is associated with a low risk of malignancy (<2%) (BI-RADS® 3).[34,194-196] Options for managing complicated cysts are either aspiration or short-term follow-up with physical examination and ultrasonography with or without mammography every 6 to 12 months for 1 to 2 years to assess stability. There may be variability on the follow-up interval based on the level of suspicion. Complicated cysts that increase in size or suspicion should be biopsied. Those that are stable or confirmed to be a complicated cyst with visible mobility of internal components can be followed with routine screening.

Complex (Cystic and Solid) Mass:

A complex cystic and solid mass has both cystic and solid components. Complex cysts have a relatively high risk of malignancy (eg, 14% and 23% in 2 studies).[34,162,195-197] The NCCN Panel recommends a tissue (core needle) biopsy for complex (cystic and solid) masses (BI-RADS® 4-5).

No Imaging Abnormality:

If no ultrasonographic or mammographic abnormality is detected (BI-RADS®) 1), tissue biopsy (core needle biopsy) should be carried out for suspicious clinical findings; and 2) those with low clinical suspicion observation with or without mammogram and ultrasound should be considered for 1 to 2 years to assess stability. The negative predictive

value of negative imaging is high, >96%.[177,181,184 Soo, 2001 #674,185] If the clinical lesion increases in size or suspicion, tissue biopsy should be performed, whereas routine breast screening is recommended if the lesion remains stable.

Follow-up after Core Needle Biopsy

If the biopsy result indicates benign mass, and this finding is concordant with the imaging results, the NCCN Panel recommends either routine screening or a physical examination at 6 or 12 months, with or without ultrasound or mammogram, for 1 year to ensure that the lesion is stable. Routine breast screening is recommended if the lesion is stable. If the lesion increases in size, the NCCN Panel recommends surgical excision.

If the diagnosis by tissue biopsy is an indeterminate lesion, a benign lesion that is not concordant with the imaging findings, or ADH, the NCCN Panel recommends surgical excision. Mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scars, or other histologies of concern to the pathologist may also require excisional biopsy. Select patients (ie, some patients with flat epithelial atypia, papillomas, fibroepithelial lesions, radial scars) may be suitable for monitoring in lieu of surgical excision. For patients with classic LCIS or ALH that is concordant with imaging, the NCCN Panel recommends physical exam with or without imaging for 6 to 12 months along with risk reduction therapy according to the NCCN Guidelines for Breast Cancer Risk Reduction or surgical excision. Multiple-foci LCIS involving greater than 4 terminal ductal units on core biopsy is associated with increased risk of being invasive cancer.[174] Patients with pleomorphic LCIS or LCIS/ALH that is non-concordant with imaging are treated with surgical excision.

Any malignant findings with biopsy or surgical excision should be treated according to the NCCN Guidelines for Breast Cancer.

Women with Palpable Mass Younger Than 30 Years of Age:

The preferred option for initial evaluation of a palpable mass is to proceed directly to ultrasound.[180] Mammogram may be considered if ultrasound or CBE results are highly suspicious or suggestive of cancer or if the patient is identified as having a high risk for breast cancer based on personal and family history. From this point, the decision tree for women younger than 30 years of age is almost identical to the pathway for older women. The main difference is consideration of a diagnostic mammogram in only some situations for the younger women. Because the incidence of malignancy in women who are younger than age 30 is low, observation of the mass for one or two menstrual cycles is also an option in cases with low clinical suspicion. If observation is elected and the mass resolves or is stable after one or two menstrual cycles, the patient may return to routine care. If there is significant increase in size or increase in clinical suspicion, ultrasound should be performed. Needle sampling prior to imaging is not recommended.

If no ultrasonographic abnormality is found (negative, BI-RADS® 1), a mammogram is recommended in cases where there is clinical suspicion. Based on the mammogram results, from this point the management is identical to the pathway for older women. If the clinical suspicion is low, physical examination every 3 to 6 months for 1 to 2 years is recommended with or without ultrasound. If the mass increases in size during the observation period, diagnostic mammogram may be considered followed by tissue (core needle) biopsy. If the mass remains stable, routine breast care is recommended.

Nipple Discharge Without a Palpable Mass

Nipple discharge is common, and, in many cases, unrelated to breast pathology.[198-204] For example, non-spontaneous discharge from multiple breast ducts in a non-lactating woman can occur during pregnancy,

following breast stimulation, in women with certain thyroid conditions, and in those taking certain medications, such as estrogen, oral contraceptives, opiates, and particular antihypertensive agents.[198]

Suspicion of underlying pathology (eg, ductal carcinoma, papilloma) is raised when nipple discharge is persistent and reproducible on examination, spontaneous, unilateral, from a single duct, serous, sanguineous, or serosanguineous.[205]

In patients with a nipple discharge but no palpable mass, an evaluation of the characteristics of the nipple discharge is the first step. The appropriate follow-up of a non-spontaneous, multiple-duct discharge in women younger than age 40 is observation, coupled with education of the patient to stop compression of the breast and to report the development of any spontaneous discharge. In women aged 40 years or older, mammography and a further workup based on the BI-RADS® category along with education similar to that for younger women is recommended. Evaluation of this type of nipple discharge is based on the overall BI-RADS® category of the diagnostic mammogram, if not done previously.

Women presenting with no palpable mass but with persistent, spontaneous, unilateral, single-duct, and clear or bloody discharge are imaged with age-appropriate diagnostic mammography and ultrasound. Several clinical studies have established a very low risk of malignancy when these tests are negative.[206,207] In certain situations, MRI or ductogram may play an adjunctive role, aiding in identifying a possible abnormality and its location. Several studies have shown that breast MRI aids in the diagnosis of suspected ductal disease.[147-149,208,209]

According to the NCCN Panel, when an overall imaging BI-RADS® assessment is category 1-3 (negative, benign, or probably benign), either a ductogram or MRI are optional to guide the duct excision. The management options include duct excision[210] or follow-up with physical exam after 6 months and imaging with diagnostic mammogram with or without ultrasound for 1 to 2 years. If clinical suspicion increases during follow-up, tissue biopsy is recommended.

For BI-RADS® category 4 or 5 (suspicious or highly suggestive of malignancy), the NCCN Panel recommends a tissue biopsy. If the biopsy findings are benign, a ductogram is optional, but surgical duct excision would still be necessary. If findings are indicative of malignancy, the patient should be treated according to the NCCN Guidelines for Breast Cancer.

Asymmetric Thickening or Nodularity

Thickening, nodularity, or asymmetry is distinct from a palpable mass in that the finding is ill-defined and often vague on physical breast examination. Factors to consider include whether the thickening is a new or previous finding, and whether or not it appears to be representative of normal asymmetry. Imaging evaluation follows that of a palpable mass.[177] If the patient is younger than age 30 years and has no high risk factors, ultrasound evaluation is appropriate followed by consideration of diagnostic mammography. Diagnostic mammograms for this age group are low in yield because of the density of the breast and low risk of breast cancer. In a woman aged 30 years or older, a diagnostic mammogram and an ultrasound evaluation should be obtained.

If the overall imaging findings are classified as BI-RADS® category 1-3 (negative, benign, or probably benign) *and* the clinical assessment is benign, the patient should be clinically reexamined with imaging as needed in 3 to 6 months to assess stability. Age-appropriate diagnostic mammogram and/or ultrasound may be performed every 6 to 12 months for 1 to 2 years to assess stability. If the findings on physical exam and/or imaging are stable, routine screening can be resumed. If either or both

findings indicate progression, it should be investigated as previously described for palpable mass.

If a clinically suspicious change is noted or the overall imaging findings are classified as BI-RADS® assessment category 4-5 (suspicious or highly suggestive of malignancy), a tissue biopsy is recommended.

Skin Changes

Any type of unusual skin changes around the breast may represent serious disease and needs evaluation. IBC should be considered when dermal edema (peau d'orange) and breast erythema are present, and nipple excoriation, scaling, and eczema should increase clinical suspicion of Paget's disease. IBC is a rare, aggressive form of breast cancer estimated to account for 1% to 6% of breast cancer cases in the United States. IBC is a clinical diagnosis that requires erythema and dermal edema of a third or more of the skin of the breast with a palpable border to the erythema.[211,212] Paget's disease of the breast is a rare manifestation of breast cancer characterized by neoplastic cells in the epidermis of the nipple areolar complex. It most commonly presents with eczema of the nipple or areola, bleeding, ulceration, and itching of the nipple. The diagnosis is often delayed because of the rare nature of the condition and confusion with other dermatologic conditions.[213,214] Pure Paget's disease is frequently occult on mammography[215] and a negative mammogram does not exclude Paget's disease, which requires skin biopsy.

The initial evaluation of a patient with breast skin changes begins with a bilateral diagnostic mammogram with or without ultrasound imaging. If the imaging results are abnormal, the evaluation proceeds based on the imaging findings. If the breast imaging results are normal, further workup is still needed.

Punch biopsy of the skin or nipple biopsy should be performed following imaging findings consistent with an overall BI-RADS® assessment category 1-3 (negative, benign, or probably benign). Antibiotics may or may not be given, depending on the clinical suspicion for breast infection, but should not delay diagnostic evaluation. If biopsy results are benign, clinical and pathologic correlation should be reassessed. In addition, a breast MRI, a repeat biopsy, and consultation with a breast specialist should be considered. If the skin biopsy is malignant, the patient should be treated according to the NCCN Guidelines for Breast Cancer.

A tissue biopsy should be performed if imaging findings are consistent of an overall BI-RADS® assessment category 4-5 (suspicious or highly suggestive of malignancy). According to the NCCN Panel, core needle biopsy is the preferred option with or without punch biopsy, although surgical excision is also an option. A benign biopsy result should be followed by a punch biopsy of the skin, if not previously performed, or nipple biopsy, with reassessment as described above for BI-RADS® category 1-3. A biopsy showing a malignant finding should be managed according to the NCCN Guidelines for Breast Cancer.

Breast Pain

Breast pain is the most common symptom in the breast. Individuals presenting with breast pain fear that this is a symptom of breast cancer, therefore causing significant anxiety. The risk of cancer in a woman presenting with breast pain as the only symptom is low, between 1.2% and 6.7%.[6,135,216,217]

Evaluation of persistent and severe breast pain includes comprehensive history, type of pain, relationship to menses, duration, location, impact on activities of daily living, factors that aggravate/alleviate pain, any other medical problems and comorbidities, and a thorough CBE. If CBE fails to identify any physical abnormality such as palpable mass, asymmetric thickening, nipple discharge, or skin changes; the pain is cyclic; or diffuse and non-focal and screening mammograms are current and negative, the

NCCN Panel recommends providing reassurance to the patient and treating the pain with symptomatic management (eg, over-the-counter pain medications, if needed; use of a good support bra; ice packs or heating pads). Cyclical breast pain may often spontaneously resolve. Reassurance alone has shown to help resolve the symptom in 86% of women with mild pain and in 52% of women with severe pain.[218] If the breast pain is focal in nature, the NCCN Panel recommends age-appropriate diagnostic imaging (diagnostic mammogram with or without ultrasound for those ≥30 years of age; and ultrasound for those <30 years of age).

For those with BI-RADS® assessment category 1 (negative findings), the panel recommends appropriate symptom management of breast pain. For a simple cyst (benign or BI-RADS® assessment category 2) geographically correlated with focal pain, drainage may be considered for symptom relief. For complicated cysts (probably benign or BIRADS 3), the panel recommends appropriate imaging every 6 months for 1 to 2 years along with symptomatic management of the breast pain, if desired. A tissue (core needle) biopsy should be performed if imaging findings are consistent of an overall BI-RADS® assessment category 4-5 (suspicious or highly suggestive of malignancy).

Axillary Mass

Localized axillary masses are more often related to benign disorders than malignancy.[219] Masses may relate to axillary lymph nodes, accessory breast tissue in the axilla, or other soft tissue abnormality. Infections, inflammation, and malignancy can cause lymphadenopathy. Breast implants can also cause benign axillary lymphadenopathy.[220] However, when cancer is identified in the axillary lymph nodes, breast cancer is the most common cause of axillary lymphadenopathy. In a study evaluating 31 patients with isolated axillary masses, 9 of the 17 cases with cancer had occult breast cancer (5 in the contralateral breast) [221]

For an individual presenting with unilateral or bilateral localized axillary mass and no signs of lymphoma, the NCCN Panel recommends complete clinical evaluation to assess for other sites of adenopathy and potential non-breast etiologies of adenopathy. If no systemic disease is found, the NCCN Panel recommends age-appropriate diagnostic imaging (ultrasound with mammogram for those ≥30 years of age; and ultrasound for those <30 years of age). Palpable axillary mass with negative/benign imaging results should be clinically managed, as appropriate depending on level of clinical suspicion. A core needle biopsy is recommended for palpable axillary mass that is suspicious or highly suggestive on imaging. However, suspicion of lymphoma in axillary lymph nodes may require special pathologic evaluation and/or surgical excision of the axillary mass.

If the core needle biopsy results indicate malignancy of breast origin in the axillary lymph node but no breast abnormality is evident with ultrasound or mammogram, the panel recommends performing MRI and then following the NCCN Guidelines for Breast Cancer as needed for management of the axillary mass. For malignant axillary node with confirmed malignant breast mass or for other types of malignant axillary lymph nodes, the panel recommends referring to the appropriate NCCN Guidelines for management.

Summary

The intent of the NCCN Guidelines for Breast Cancer Screening and Diagnosis is to give health care providers a practical, consistent framework for screening and evaluating a spectrum of clinical breast lesions. Clinical judgment should always be an important component of the optimal management of the patient.

Table 1: Breast Cysts - Types and Definitions	
Simple	Anechoic (cystic), well-circumscribed, round, or oval with well-defined imperceptible wall and posterior enhancement.
Complicated	Has most but not all elements of a simple cyst. Complicated cysts do not contain solid elements, intracystic masses, thick walls, or thick septa. This type of cyst may contain low-level echoes or intracystic debris, and can be described as a round, circumscribed mass containing low-level echoes without vascular flow, fulfilling most but not all criteria of a simple cyst.
Complex	Has some discrete solid component, which may include thick walls, thick septa, and/or intracystic mass. Complex cysts have both anechoic (cystic) and echogenic (solid) components.
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